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NOVEL APPLICATIONS OF FUNCTIONALISED ORTHOESTERS : TOWARDS THE SYNTHESIS OF VARIOUS NATURAL PRODUCTS

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Research is to see what everybody else has seen, and to think what nobody else has thought.

Albert Szent-Gyorgi (1893-1986)

Success is the ability to go from one failure to another with no loss of enthusiasm.

Sir Winston Churchill (1874-1965)

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"**Connective synthesis of spirovetivanes: Total synthesis of (±)-Agarospirol, (±)-Hinesol and (±)-α-Vetispirene**" (Chapter 3)
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Eur. J. Org. Chem. **2004**, 3962

"Cerium(IV) Ammonium Nitrate (CAN) catalysed highly chemoselective deprotection of ketals and THP ethers in the presence of enol triflates" (Chapter 3)
Nuno Maulide and István E. Markó
Synlett **2005**, 2195

"Stereoselective synthesis of bicyclic lactones by annelation with functionalised orthoesters" (Chapter 5)
Nuno Maulide and István E. Markó
Chem. Commun. **2006**, 1200

"2-(Trimethylsilyloxy)furan as a Dianion Equivalent: A Two-Step Synthesis of Functionalized Spirocyclic Butenolides" (Chapter 5)
Nuno Maulide and István E. Markó
Org. Lett. **2006**, *8*, 3705

Abstract.

For the past years, our laboratory has been interested in the development of a specific class of functionalised orthoester derivatives **8.001**, and their application as annelating reagents. Previous work had demonstrated that these reagents could be used in a two-step procedure to generate interesting spirocyclic ketones **1.018** (Figure 1).

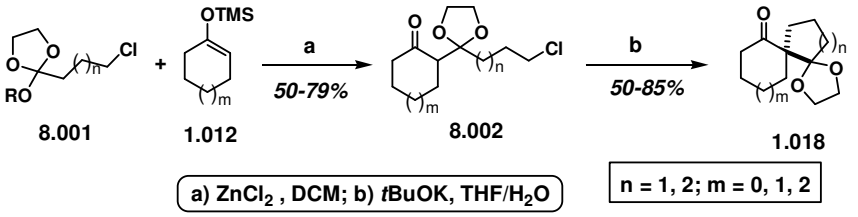


Figure 1

At the onset of our thesis, we devoted our efforts to the study and application of this methodology. This resulted in an improved and more efficient procedure for the spirohexannelation of β-ketoketals **2.102** (Figure 2). During these initial studies, an intriguing and novel transannular cyclisation was discovered.

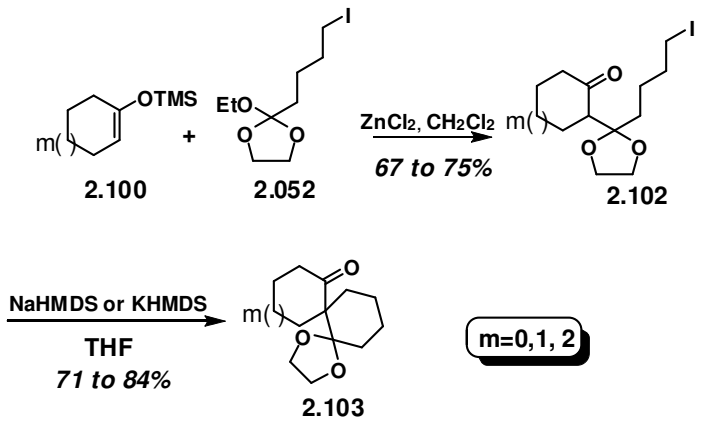


Figure 2

The reactivity of these spirocycles was also briefly examined, laying the ground for an application to the total synthesis of Agarospirol, Hinesol and α-Vetispirene, three naturally occuring sesquiterpenes belonging to the Spirovetivane family. Our approach, summarised in Figure 3, involves a number of interesting key-steps. These include a mild CAN-catalysed deprotection of **3.222**, a chemoselective Fe^{III}-mediated organometallic coupling of **3.268** and an efficient rearrangement to unsaturated ester **3.294**, from which all natural products are readily derived. The applicability of the CAN-catalysed deprotection, in the presence of an enol triflate moiety, to a broader range of compounds was also investigated.

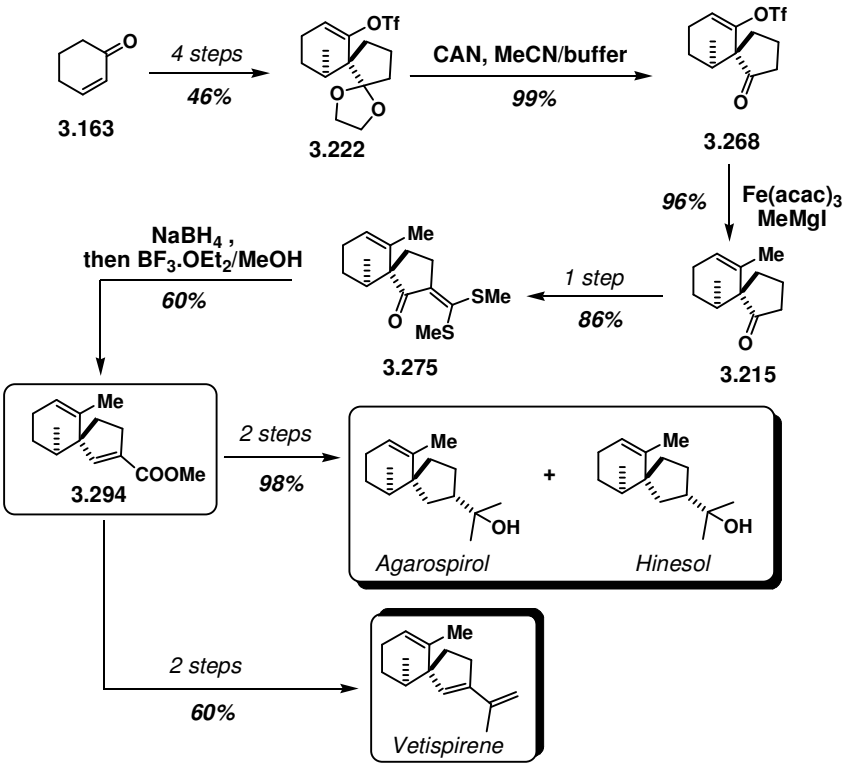


Figure 3

The potential of functionalised orthoesters **8.001** as annelating agents was then further evaluated in the context of other silyl enolethers. The heteroaromatic derivatives of furan **8.008** proved to be excellent coupling partners for our functionalised orthoesters and enabled the efficient preparation of a wide array of butenolides **8.009** (Figure 4).

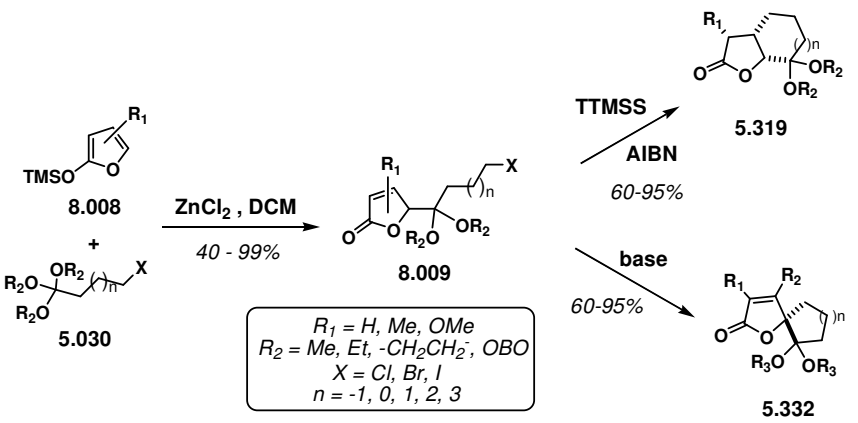


Figure 4

These butenolides could then be elaborated, by radical-mediated cyclisation, into bicyclic lactones **5.319**. Such a cyclisation proved to be a highly stereoselective process, as illustrated in Figure 4 (Cf. **8.009** → **5.319**). Notably, a host of compounds bearing different ring-sizes could be obtained by this method.

Alternatively, treatment with base triggered an efficient spirocyclisation, delivering spirocyclic butenolides **5.332** in good to excellent yields (Figure 4).

The corresponding pyrrole derivative **6.001** was also examinated and exhibited intriguing reactivity (Figure 5). Preliminary work hints at the possibility of readily preparing the aza-analogues of **5.332**, spirocycles **8.014**. Nonetheless, a particularly salient feature of **6.001** is the possibility of rapidly crafting functionalised indolizidine frameworks (such as **6.104**) by using the inherent nucleophilicity of the nitrogenated moiety.

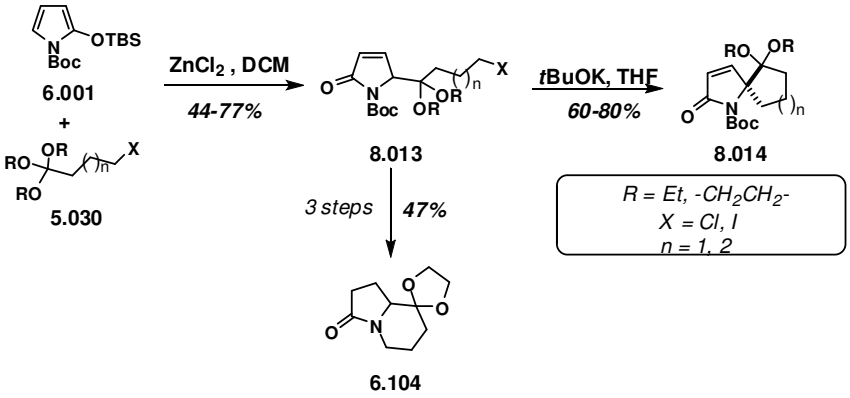


Figure 5

Finally, the evaluation of silylated acyloins as the silyl enolether partners allowed an entry into the chemistry of cyclobutanones. A simple procedure for the synthesis of spirocyclic ethers, featuring a one-pot deprotective cyclisation, was developed (Figure 6).

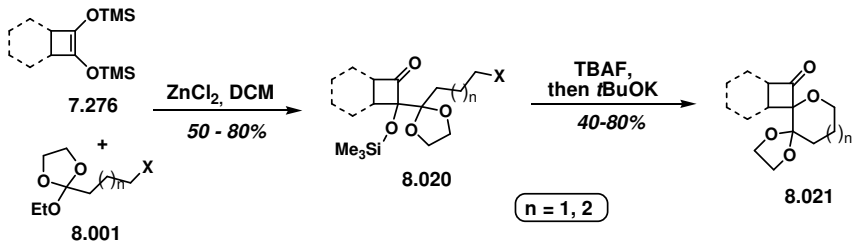


Figure 6

These compounds were further shown to react exquisitely to a number of transformations. For instance, the spirocycloether **7.120** underwent all the

possible methylene- and oxygen- insertions into the cyclobutanone ring with very high selectivity (Figure 7).

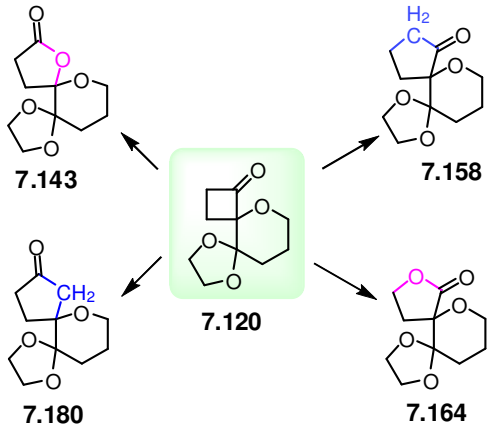


Figure 7

During these investigations, an unexpected fragmentation was serendipitously discovered upon attempted application of the Beckmann rearrangement. As shown in Figure 8, we were able to exploit this process and use it to devise a new procedure for the synthesis of interestingly substituted tetrahydropyrans **7.250**.

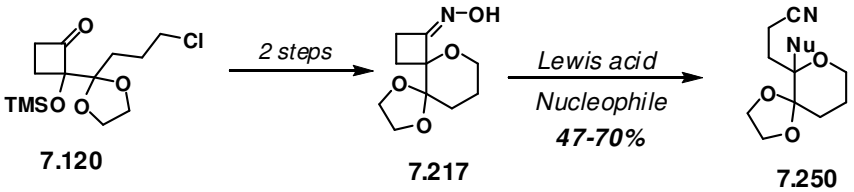


Figure 8

Resumé.

Durant ces dernières années, notre laboratoire s'est interessé au développement et à l'application des orthoesters fonctionnalisés **8.001** en tant qu'agents d'annélation. Des travaux précedents ont demontré que ces réactifs pouvaient être employés pour la préparation de cétones spiranniques telles que **1.018** (Schéma 1).

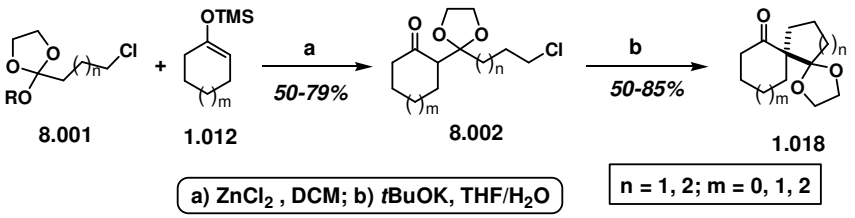


Schéma 1

Au début de notre thèse, nous avons consacré nos efforts à l'étude et aux applications de cette méthodologie de spiroannélation. Nos premières observations nous ont ammené à développer une version ameliorée de cette méthode pour la formation de cycles à 6 chaînons, au départ des β-cétocétales **2.102** (Schéma 2). Durant ces premières études, nous avons également découvert une nouvelle cyclisation de type transannulaire.

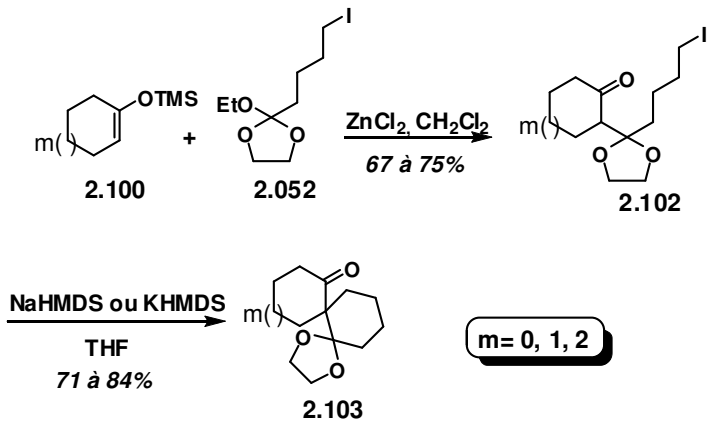


Schéma 2

La réactivité de ces spirocycles a ensuite fait l'objet de notre attention. En effet, leur application dans la synthèse totale de l'Agarospirol, de l'Hinésol et du α-Vétispirène, trois produits naturels issus de la famille des Spirovétivanes, a été réalisée. Notre approche, resumée dans le Schéma 3, repose sur quelques étapes-clés particulièrement intéressantes, notamment une déprotection (de **3.222**) dans des conditions douces, catalysée par le CAN ; un couplage chimiosélectif du vinyl triflate **3.268** promu par le fer (III) et un réarrangement efficace menant à l'ester insaturé **3.294**, à partir duquel les troix produits naturels sont aisément accessibles. Nous avons également pu étudier le champs d'application de cette déprotection, catalysée au CAN, à d'autres substrats possédant la fonction vinyl triflate.

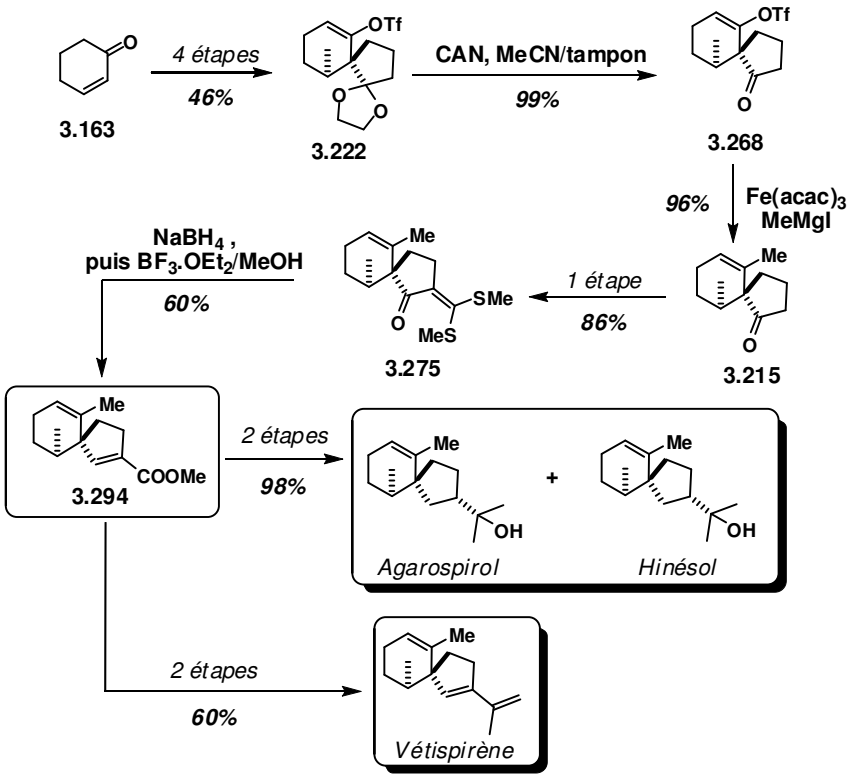


Schéma 3

Le potentiel synthétique des orthoesters fonctionalisés **8.001** en tant qu'agents d'annélation a ensuite été investigué dans le cadre d'autres éthers d'énol silylés. Les derivés du furanne, tels que **8.008**, se sont averés être d'excellents partenaires nucléophiles, conduisant à la préparation de divers buténolides **8.009** (Schéma 4).

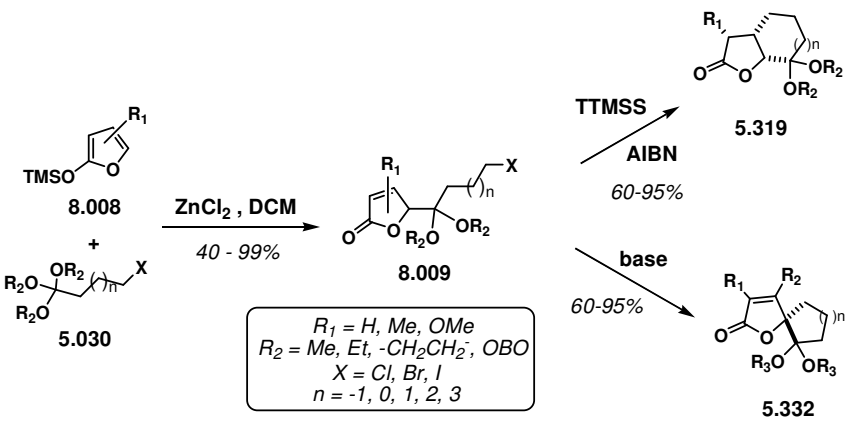


Schéma 4

Lors de leur traitement dans des conditions radicalaires, ces buténolides subissent une cyclisation très efficace, générant ainsi des lactones bicycliques. Nous avons montré que cette cyclisation est en effet hautement stéréosélective, comme illustré dans le Schéma (Cf. **8.009** → **5.319**). Il est à remarquer que des cycles de tailles différentes peuvent être formés par cette réaction.

Alternativement, un traitement basique suffit à proumouvoir une spiroannélation menant aux spirobuténolides **5.332** avec des rendements bons à excellents (Schéma 4).

Le composé **6.001**, dérivé du pyrrole, a aussi été employé dans des processus d'annélation (Schéma 5). Des résultats préliminaires indiquent que les analogues azotés de **5.332**, les azaspirocycles **8.014**, peuvent être preparés d'une façon similaire. Toutefois, la caractéristique la plus frappante du composé **6.001** réside dans la possibilité d'accéder à des noyaux de type indolizidine (tels que **6.104**), grâce à la nucléophilie intrinsèque de l'atome d'azote.

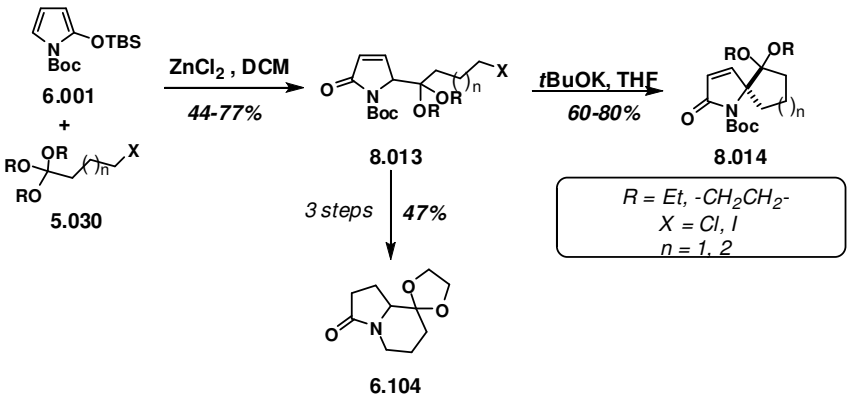


Schéma 5

Enfin, l'évalutation des derivés silylés d'acyloïnes nous a conduit à la chimie des cyclobutanones. Nous avons pu développer une procédure simple pour la synthèse d'éthers spiranniques **8.021**, au moyen d'une déprotection/cyclisation en une étape (Schéma 6).

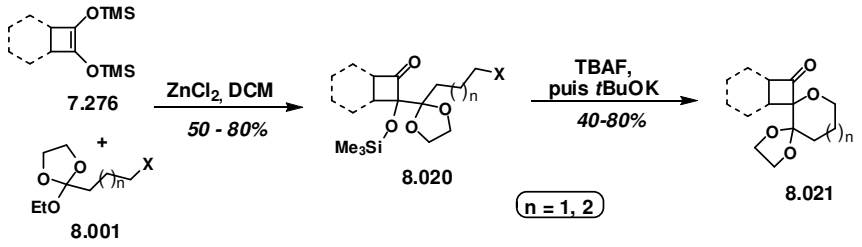


Schéma 6

Les composés obtenus ont fait preuve d'une réactivité fascinante. Par exemple, le spiroéther **7.120** subit toutes les insertions possibles de méthylène- et d'oxygène à travers le motif cyclobutanone avec une selectivité très élevée (Schéma 7).

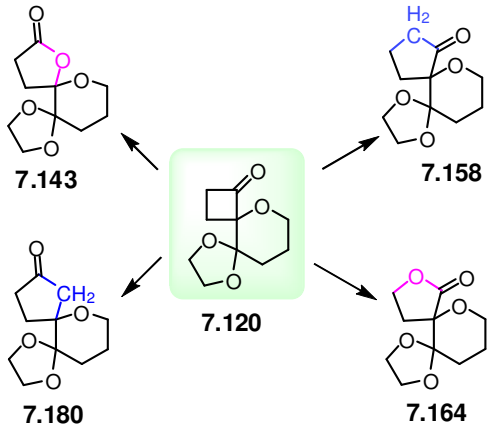
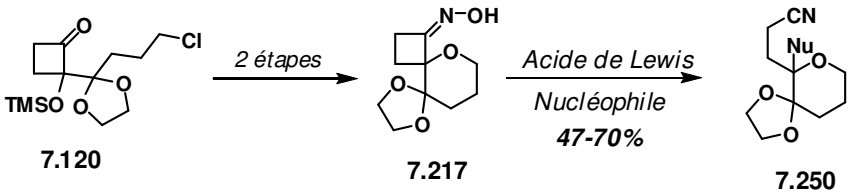


Schéma 7

Durant ces recherches, nous avons découvert une fragmentation inattendue lors de quelques essais d'application du réarrangement de Beckmann. Comme presenté au Schéma 8, nous avons pu exploiter cette réaction dans une nouvelle synthèse de tétrahydropyrannes substitués **7.250**.



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List of abbreviations

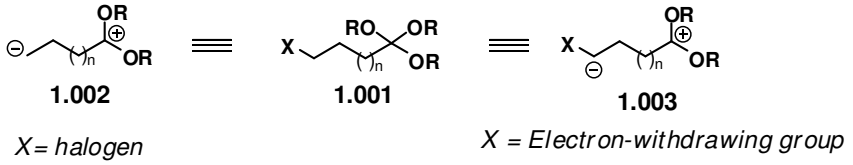
abs	absolute
Ac	acetyl
acac	acetylacetonate
AcOEt	ethyl acetate
Ar	aryl
Bn	benzyl
br	broad
Bu	butyl
***t*Bu**	*tert*-butyl
Bz	benzoyl
°C	Celsius degree
***m*CPBA**	*meta*-chloroperbenzoic acid
CSA	camphorsulphonic acid
D	heating
d	chemical shift
d	doublet
DIBALH	diisobutyl aluminium hydride
DBA	dibenzylidene acetone
DBU	1,8-diaza-bicyclo[5.4]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHP	dihydropyran
DMAP	4-(dimethylamino)-pyridine
DMP	Dess-Martin periodinane
d.e.	diastereomeric excess
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DPPB	diphenylphosphino butane
d.r.	diastereomeric ratio
E^+	electrophile
EDG	electron-donating group
e.e.	enantiomeric excess
Et	ethyl
h	hour
HMDS	bis(trimethylsilyl)amine
HMPA	hexamethylphosphoramide
HRMS	high-resolution mass spectroscopy
IR	infrared spectroscopy

J	coupling constant	**q**	quartet
LDA	lithium di(isopropyl)amide	**rt**	room temperature
min	minute	**s**	singlet
Me	methyl	**sh**	sharp
Mes	Mesityl	**t**	triplet
MOM	methoxymethyl	**TBAF**	tetrabutylammonium fluoride
Ms	methanesulfonyl (mesyl)	**TBHP**	*tert*-butylhydroperoxide
MS	mass spectroscopy	**TBDPS**	*tert*-butyldiphenylsilyl
NMO	N-methyl morpholine N-oxide	**TBS**	*tert*-butyldimethylsilyl
NMR	nuclear magnetic resonance	**TBSOF**	N-Boc-2-*tert*-butyldimethylsilyloxy pyrrole
nOe	nuclear Overhauser effect	**TES**	triethylsilyl
Nu	nucleophile	**TIPS**	triisopropylsilyl
PG	protecting group	**TfO**	trifluoromethanesulfonate (triflate)
Ph	phenyl	**TMEDA**	tetramethyl-ethylenediamine
PCC	pyridinium chlorochromate	**TMS**	trimethylsilyl
PDC	pyridinium dichromate	**TMSOF**	2-trimethylsilyloxy furan
PE	petroleum ether	**TMSOTf**	trimethylsilyl triflate
PMB	*p*-methoxybenzyl	**Ts**	*p*-toluenesulfonyl (tosyl)
***i*Pr**	isopropyl		
ppm	parts per million		
PPTS	pyridinium *p*-toluenesulfonate		
Py	pyridine		

Chapter 1 : Introduction and Objectives

Though orthoesters have mostly been employed as carboxylic acid protecting groups and as acylating agents, their synthetic utility as annelating partners in novel ring forming reactions has been little investigated.

In particular, functionalised orthoesters of the formula **1.001** have been used as linchpin reagents possessing simultaneously a masked carbocation, in the form of an orthoester, and a carbanion such as **1.002** or **1.003** depending upon the nature of X (Scheme 1.1).

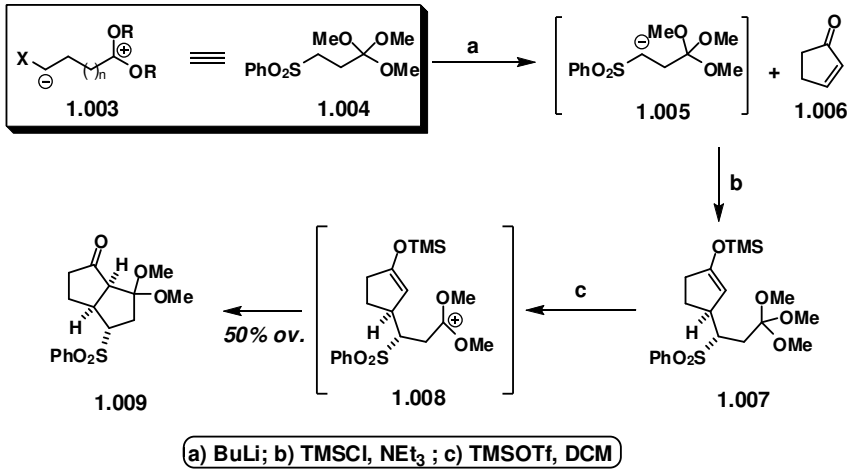


Scheme 1.1

Léon Ghosez and his group have shown that sulphone **1.004** might be considered as an equivalent of the synthon **1.003** (Scheme 1.2).[1] Indeed, the anion **1.005**, generated by BuLi deprotonation, reacts with enones such as **1.006** in the presence of TMSCl, leading to silyl enolethers **1.007**. Treatment

[1] (a) Huart, C.; Ghosez, L. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 634; (b) De Lombaert, S.; Nemery, I.; Roekens, B.; Carretero, J.C.; Kimmel, T.; Ghosez, L. *Tetrahedron Lett.* **1986**, 5099; (c) Renard, M.; Ghosez, L. *Tetrahedron* **2001**, *57*, 2597; (d) Ding, P.; Ghosez, L. *Tetrahedron* **2002**, *58*, 1565. See also: (e) Ghosez, L. *Pure App. Chem.* **1996**, *68*, 15

of this enolsilane compound with a Lewis Acid then generates the stabilised oxonium cation **1.008**, which readily undergoes cyclisation to bicycle **1.009**.

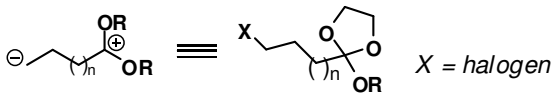


Scheme 1.2

In this sequence, the carbanionic properties of orthoester **1.004** have been employed *prior to* the generation of oxonium **1.008**.

Although this methodology offers an elegant approach towards fused bicyclic compounds of great synthetic interest from readily available enones, our laboratory has been interested in different applications of functionalised orthoesters. This work began more than 10 years ago with Dr. Ali Ates, who focused on the preparation and use of orthoesters of the general formula **1.010** (Scheme 1.3).[2]

[2] (a) Ates, A. *Développement d'une nouvelle stratégie pour la synthèse des cycles de taille moyenne*, Ph. D. Thesis, **1999**, UCL; (b) Ates, A.; Markó, I.E. *Synlett* **1999**, 1033

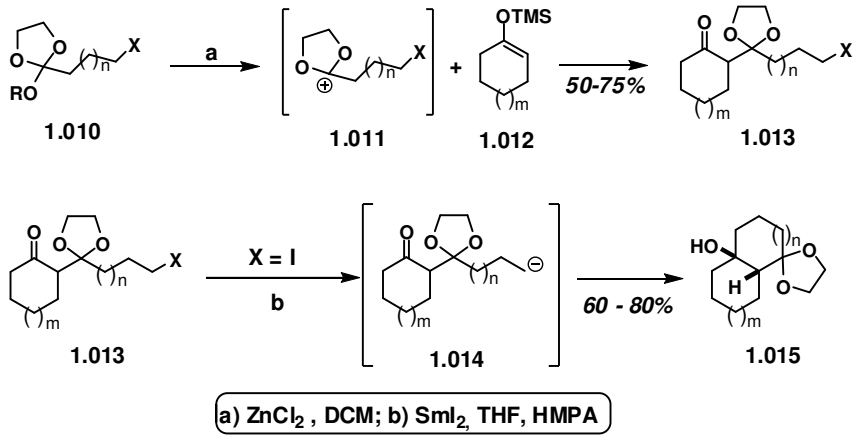


1.002 **1.010**

Scheme 1.3

These ω-halogenated orthoesters now bear a dioxolane bridge connecting two of the alkoxy residues. They can be considered as bifunctional reagents of the type **1.002**.

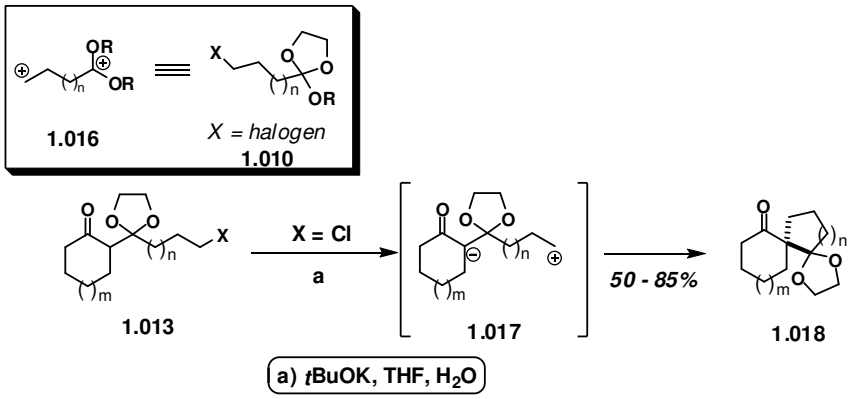
Indeed, our laboratory has developed synthetic sequences which are not only complementary to the chemistry presented above but also of a *reverse* nature (Scheme 1.4). For example, following Lewis-acid promoted *intermolecular* condensation of orthoesters **1.010** with cyclic silyl enolethers **1.012**, β-ketoketals **1.013** can be obtained in good to excellent yields. Ali Ates demonstrated during his Ph.D. that the treatment of the adducts **1.013** with SmI_2 led to the development of a novel methodology for the preparation of bicyclic alcohols **1.015**. He then initiated work, aimed at their fragmentation into medium-sized carbocycles, which was continued by Dr. Corinne DeDobbeleer. In this strategy, it is important to stress that the carbanionic properties of orthoester **1.010** (expressed in **1.014**) have been expressed *subsequently to* its use as a masked carbocation **1.011**.



Scheme 1.4

More recently, Dr. Jean-Christophe Vanherck went on to demonstrate that the orthoesters **1.010** could also behave as bis-electrophiles **1.016** (Scheme 1.5).[3] When adducts **1.013** were treated with base, ring-closure to spirocycles **1.018** ensued. It is interesting to note that in this bis-electrophilic synthon **1.016** both electrophilic centers can be activated independently, since the orthoester moiety usually reacts through an S_N1-like process whereas the halide terminus is typically engaged in S_N2-type displacements.

[3] (a) Vanherck, J.-C. *Etude et application synthétique d'une nouvelle méthode de spiroannélation,* Ph.D. Thesis, **2004**, UCL; (b) Markó, I.E.; Vanherck, J.-C.; Ates, A.; Tinant, B.; Declercq, J.-P. *Tetrahedron Lett.* **2003**, 3333



Scheme 1.5

Remarkably, the spirocycles **1.018** thus obtained possess two distinguishable carbonyl groups. The presence of a free carbonyl on one ring system and of a dioxolanyl ketal on the other is a major asset for further, selective functionalisations.

We have thus joined the "orthoester-adventure" with a number of goals as guiding points in the horizon of our Ph.D..

1) To further study the spiroannelation of simple, cyclic silyl enolethers, to broaden the scope of this methodology and to improve on its weak points;
2) To study the reactivity of the obtained spirocyclic adducts, addressing questions such as selectivity and stereocontrol;
3) To demonstrate the efficiency of the methodology in the stringent context of the total synthesis of some natural products.

Our innate curiosity also sparked an interest in expanding the usefulness of our orthoesters by applying them to the generation of other families of products. Of particular interest to us were heterocyclic oxygenated- and nitrogenated substructures whose prominence in biologically active, naturally occuring substances is particularly ubiquitous. It was expected that the diversification of the reaction manifolds might provide us with unanticipated reactivity features of orthoesters, which may have laid dormant in the pioneering studies mentioned above.

The present document tells the logical story of these and other investigations, with their fair share of success, failure and serendipitous discovery.

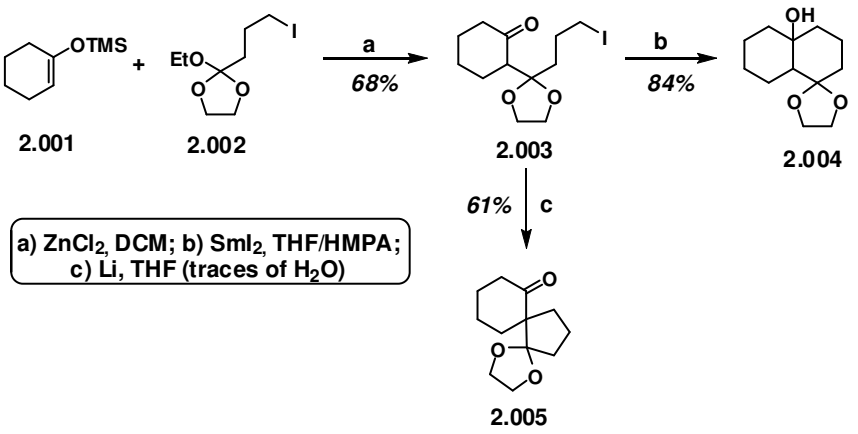
Chapter 2 : Spiroannelations of simple cyclic enolethers

2.1. Introduction and previous results

As mentioned in the preceding Chapter, our laboratory has previously employed orthoesters such as **2.002** as annelating reagents for simple cyclic silyl enolethers. In this section, we shall examine in more detail the spiroannelation methodology developed by Dr. Jean-Christophe Vanherck during his Ph.D. Thesis before presenting the additional modifications and improvements discovered during our own work.

During his studies of the Barbier cyclisation of β-ketoketal **2.003** (obtained by condensation of orthoester **2.002** with silyl enolether **2.001**), Dr. Ali Ates treated this compound with a suspension of Li metal in THF, under sonication.[4] This was expected to induce halogen-metal exchange and trigger nucleophilic attack onto the neighbouring carbonyl, thus generating bicyclic alcohol **2.004**. Whilst no trace of the desired decalin could be detected, he was surprised to observe the formation of spiro-bicycle **2.005**, which was isolated in 61% yield (Scheme 2.1).

[4] Ates, A. *Ph.D. Thesis*, UCL, **1999**



Scheme 2.1

While Dr. Ates eventually succeded in the preparation of bicyclic alcohols such as **2.004**, using a highly efficient SmI_2-mediated reductive cyclisation (Scheme 2.1), attempts to reproduce the preparation of **2.005** in rigorously dried THF met with failure, thus indicating that adventicious moisture had been responsible for the initially successful ring closure. These preliminary observations stimulated Dr. Jean-Christophe Vanherck to undertake a systematic screening of conditions that might provide suitable for this novel spirocyclisation.[5]

Among the bases tested at this stage, potassium *tert*-butoxide in « wet » THF [6] provided the best results (Table 2.1, entry 3). However, the reaction displayed erratic behaviour, suggesting that fine-tuning of the water content was required. After extensive optimisation, it was found that the

[5] Vanherck, J.-C. *Etude et application synthétique d'une nouvelle méthode de spiroannélation*, Ph.D. Thesis, UCL, **2004**

[6] By writing "wet" it should be understood that non-dried and non-distilled analytical-grade THF was employed.

addition of 1 equivalent of water to an anhydrous solution of β-ketoketal **2.003** in THF, prior to the introduction of *t*-BuOK, was optimal (entry 4). Under these conditions, spirocycle **2.005** was obtained in 95% yield within 30 minutes.

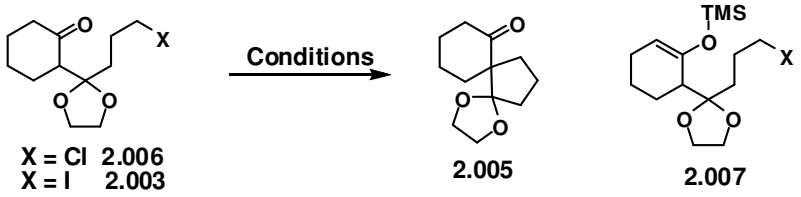


Table 2.1

Entry	*Substrate*	*Conditions*	*Result*
1	**2.003**	Li, H_2O (trace), THF	66% of **2.005**
2	**2.003**	*t*BuOK (1.4 eq), dry THF	0% of **2.005**
3	**2.003**	*t*BuOK (1.4 eq), « wet » THF[a]	80% of **2.005**[b]
4	**2.003**	*t*BuOK (1.4 eq), dry THF, H_2O (1 eq), 30 min.	95% of **2.005**
5	**2.006**	*t*BuOK (1.4 eq), dry THF, H_2O (1 eq), 60 min.	92% of **2.005**
6	**2.006**	*t*BuOH (1 eq), KOH (1 eq), THF	10% of **2.005**
7	**2.006**	KHMDS (1.2 eq), THF	30% of **2.005**
8	**2.006**	LDA (1 eq), THF	0% of **2.005**
9	**2.006**	LDA (1 eq), THF, then TMSCl	68% of **2.007**

[a] - See text. [b]- Average yield for >10 experiments.

Interestingly enough, these conditions were also suitable for the cyclisation of chlorinated derivative **2.006** in similarly high yields, although longer reaction times were needed (entries 5-9).

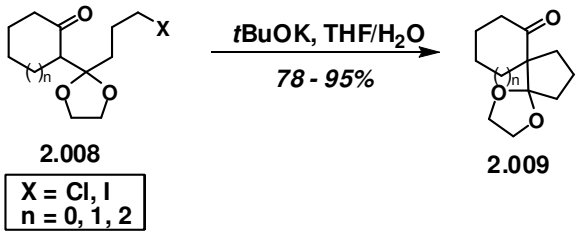
The results obtained can be rationalised by assuming that under the reaction conditions a fast, simultaneous generation of 1 equivalent KOH and *t*BuOH occurs, as strongly suggested by the pKa difference (H_2O: 15.7; *t*BuOH: 19, amounting to an equilibrium constant of $10^{3,3}$). However, control experiments performed in the presence of 1 eq. KOH with or without added *t*BuOH led only to sluggish reactions (≤10% isolated yield after 2h reaction, entry 6). One might therefore consider the possibility of an eventual synergistic effect between *t*BuOK and water, similar to previous observations of Gassman and co-workers,[7] and analogous in nature to systems commonly designated as "unimetallic superbases".[8] Such systems have been widely studied in the case of sodium bases but, to the best of our knowledge, no reports on the potassium counterparts exist in the literature.

Whatever the true nature of the basic entities in solution, these conditions were by far the most effective, especially when compared to the use of nitrogen bases. Whereas KHMDS provided only low yields of spirocycle **2.005** (entry 7), the use of LDA consistently returned unreacted starting material (entry 8). A trapping experiment (TMSCl) provided silyl enol ether **2.007**, thus demonstrating that kinetic enolate generation had occurred. However, no equilibration to the thermodynamic enolate, required for spirocyclisation, was observed.

This protocol was then applied to a range of unsubstituted β-ketoketal intermediates of different ring-sizes (Scheme 2.2). As can be observed, this

[7] Gassman, P.G.; Schenk, W.N. *J. Org. Chem.* **1977**, *42*, 918
[8] Caubere, P. *Chem. Rev.* **1993**, *93*, 2317

novel spirocyclisation is extremely efficient for the assembly of spiro[*n*.4]alkanes.[9] Furthermore, it should be noted that chlorine and iodine behave equally well as leaving groups in this intramolecular S_N2-type reaction. This is most likely a consequence of the rather high rate of cyclisation to form a five-membered ring (*vide infra*). On the other hand, these cyclisations appear to benefit from a moderate Thorpe-Ingold effect provided by the dioxolane moiety, which brings the reactive centers into spatial proximity.



2.008

X = Cl, I
n = 0, 1, 2

2.009

Scheme 2.2

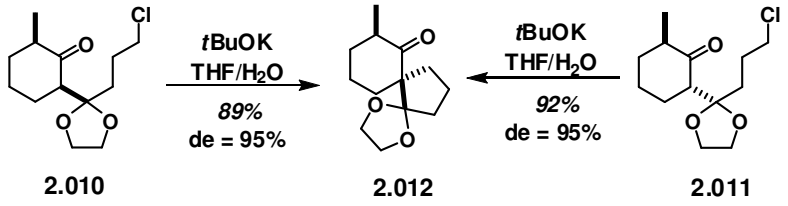
After these initial studies, Dr. Vanherck proceeded to evaluate the stereoselectivity of this methodology when substituted β-ketoketals were employed.

Efforts initially focused on substituted β-ketoketals **2.010**-**2.011**. As both diastereomers of this compound, available through condensation, are readily separable by chromatography, it appeared interesting to probe the stereochemical issue of their spirocyclisation.[10] Remarkably, upon treatment

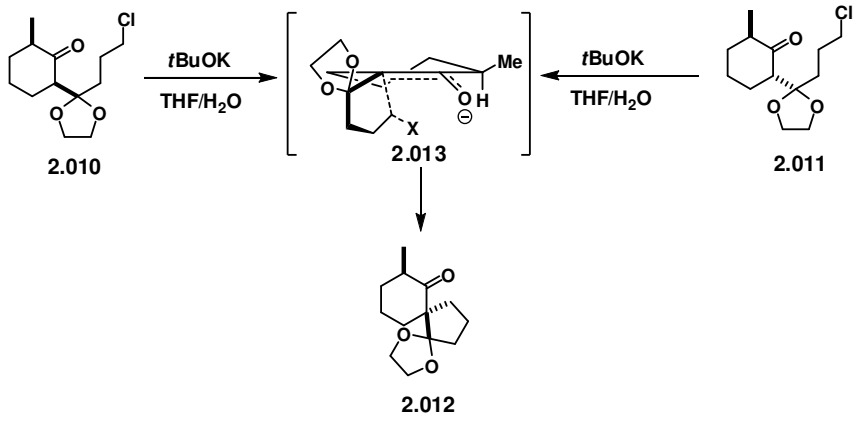
[9] For a preliminary disclosure of these results, see: Markó, I.E.; Vanherck, J.-C.; Ates, A.; Tinant, B.; Declercq, J.-P. *Tetrahedron Lett.* **2003**, 3333

[10] Most of the results in the following discussion are valid for both the iodinated- and the chlorinated β-ketoketals. However, only the results obtained with the chlorinated starting materials will be discussed for conciseness.

with *t*-BuOK in wet THF, the same spirocyclic ketone **2.012** was obtained, and this regardless of which starting stereoisomer was employed (Scheme 2.3). In fact, both compounds should generate the same intermediate enolate **2.013** (Scheme 2.4). According to well-established precedent, alkylation of such an enolate should occur through an axially-directed approach of the incoming electrophile, in the lowest-energy half-chair conformer **2.013** (Scheme 2.4).



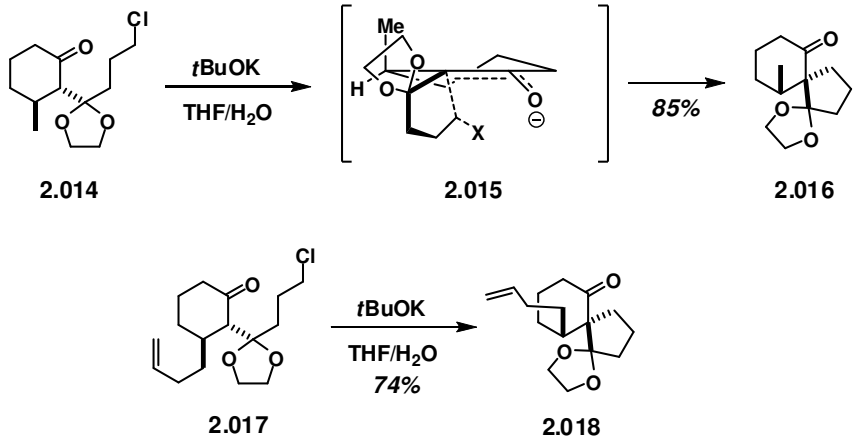
Scheme 2.3



Scheme 2.4

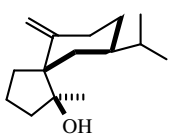
Subsequently, β-substituted ketals were examined. Investigations began with the readily accessible methyl-substituted **2.014**, obtained exclusively as the *trans*-diastereomer (Scheme 2.5). Spiroannelation of this compound provided a single crystalline product in the form of spirobicycle **2.016**, whose structure was unambiguously established through X-ray analysis. A possible explanation for this result arises if one assumes the intermediacy of the half-chair enolate **2.015**, in which the methyl substituent occupies a pseudo-axial position in order to minimise unfavorable *gauche*-interactions with the ketal substituent. This result seems to be in accord with literature precedents (for examples, cf. Chapter 3).

The stereoselectivity and yield of this reaction are not affected by a change in substituent, as the β-ketoketal **2.017** bearing a butenyl side-chain, also provides efficiently the spirocycle **2.018** in greater than 95% diastereomeric excess.

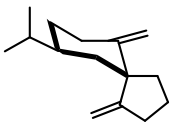


Scheme 2.5

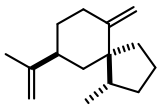
Finally, the effect of γ-substitution in this spiroannelation protocol was evaluated. The importance of γ-substitution is readily acknowledged if, for instance, one considers the structures of Spirojatamol,[11] Erythrodiene[12] or Spirolepechinene[13] (Scheme 2.6). These bioactive natural products would become very attractive synthetic targets in the event that a stereoselective annelation onto a γ-substituted cyclohexanone derivative could be achieved. Given the ready availability of 4-*t*-butylcyclohexanone, the condensation products derived from this ketone were employed as models by Dr. Vanherck. The use of a bulky group in the 4-position was furthermore expected to conformationally lock the substrate and thus provide the highest degrees of stereoselectivity possible, taking in account the remote nature of the substituent.



Spirojatamol
2.019



Erythrodiene
2.020



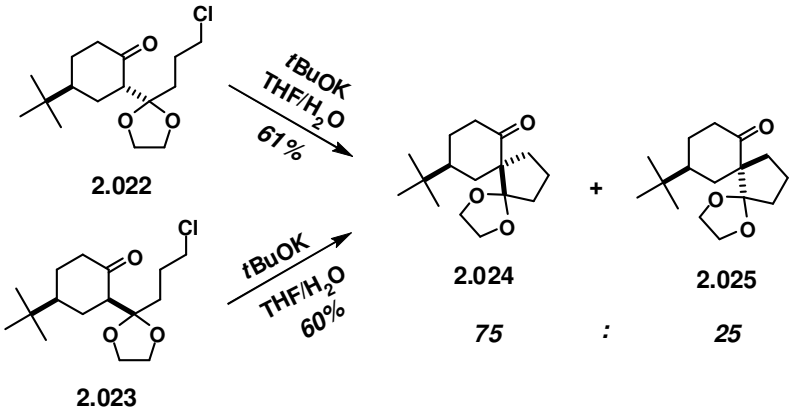
Spirolepechinene
2.021

Scheme 2.6

In the event, β-ketoketals **2.022** and **2.023** were obtained in a 3:2 ratio and were readily separated by column chromatography. Upon spirocyclisation, both diastereomeric ketals afforded the same mixture of products: spirobicycles **2.024** and **2.025** were obtained in a 75:25 ratio. In this case, axially directed cyclisation of an intermediate in which the bulky *t*-

[11] Bagchi, A.; Oshima, Y.; Hikino, H. *Tetrahedron* **1990**, *46*, 1523
[12] Pathirana, C.; Fenical, W.; Corcoran, E.; Clardy, J. *Tetrahedron Lett.* **1993**, *34*, 3371
[13] Eggers, M.D.; Sinnwell, V.; Stahl-Biskup, E. *Phytochemistry* **1999**, *51*, 987

butyl substituent adopts a pseudoequatorial orientation predominates, but is apparently not the only operational pathway (Scheme 2.7).

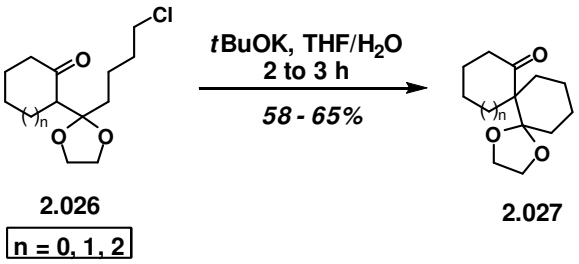


Scheme 2.7

At this stage, the efficient generation of spirobicycles through a 5-*exo*-tet cyclisation of a β-ketoketal precursor had been established and the main stereochemical features of this procedure had been accessed. Given the prominence of spirocyclic systems bearing two 6-membered rings, Dr. Vanherck turned his attention to the study of the related 6-*exo*-tet ring-closure of homologous β-ketoketals.

Dr. Jean-Christophe Vanherck's studies in this area initially focused upon unsubstituted, 5-carbon tethered compounds **2.026** (Scheme 2.8). Through application of the aforedescribed procedure, he observed smooth formation of spirocycles **2.027**, though longer reaction times were required and lower chemical yields were obtained. This is not entirely unexpected, as the chemical literature is densely populated with reports highlighting the rate

difference between 5- and 6- membered ring forming reactions, whether radical or ionic in nature.[14]



2.026

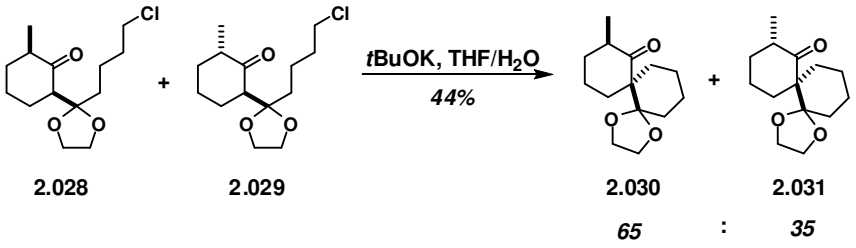
n = 0, 1, 2

2.027

Scheme 2.8

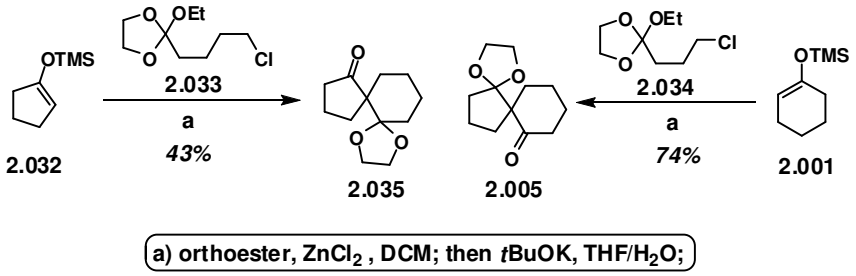
This decreased rate might also be responsible for the lower selectivity observed when substituted β-ketoketals bearing a 5-carbon tether were subjected to the spiroannelation conditions (Scheme 2.9). Indeed, **2.028** and **2.029** (employed as a mixture) provided only a 65:35 ratio of epimeric spirocyclic ketones **2.030-2.031**. Interestingly enough, epimerisation of the diastereomeric spirobicycles is likely to be partially responsible for this, as subjection of pure **2.030** or **2.031** to the reaction conditions effects isomerisation to the same epimeric mixture obtained previously. Probably, the decreased rate of formation of the 6-membered ring renders epimerisation competitive, under these conditions, with the desired cyclisation.

[14] For a representative example, see: Casadei, M.A.; Galli, C.; Mandolini, L. *J. Am. Chem. Soc.* **1984**, *106*, 1051



Scheme 2.9

A particularly useful feature of this cyclohexannelation is that it delivers mono-protected, spirocyclic diketones. This enables the stepwise functionalisation of both rings in the spirocyclic system. Interestingly enough, the fact that either 5- or 6- membered rings can be efficiently grafted onto a pre-existing template allows the efficient synthesis of complementary protected, isomeric spirocyclic compounds **2.005** and **2.035**, simply by the judicious choice of the annelating agent (Scheme 2.10). This type of versatility is likely to prove very useful in synthetic ventures. It would therefore be of paramount importance to increase the efficiency of the ring-closure to form 6-membered rings, in order to fully benefit from this versatility (Cf. overall drop in yield of 30% between **2.005** and **2.035**).



Scheme 2.10

Furthermore, we were also interested in exploring solutions to the lack of stereoselectivity observed in the case of γ-substituted cyclohexanones. We believed that this would be a major asset of the methodology and it could potentially allow us to prepare the natural products shown in Scheme 2.6 in short order. Our results on these endeavours are described in the following subsections.

2.2. Results and discussion

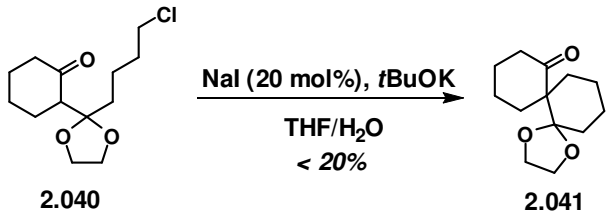
2.2.1. First observations

Our first efforts were aimed at increasing the yields of the 6-*exo*-tet cyclisations. After successfully reproducing the results displayed in Scheme 2.8, we reconsidered the use of the iodinated counterparts of compounds **2.026**. Indeed, the latter derivatives had probably been overlooked, due to the lack of benefit of iodine as a leaving group in the cyclopentannelation reactions.

We thought that this might be due to an enhancement of competitive, decomposition pathways. Indeed, the iodinated β-ketoketals are likely to be somewhat prone to elimination of HI to form alkenes, whereas with the chlorinated adducts such reactions should be considerably slowed in favor of

the intramolecular, spirocyclisation process.[15] Since the 5-membered cyclisation itself is a rapid step, no net gain results from using iodine as the leaving group. When a 6-membered ring-closure is considered, though, the use of iodine as leaving group might provide some improvement (although eliminative pathways remain as potential pitfalls).

At first, we probed this possibility by attempting an *in-situ* exchange of chloride by iodide through addition of substoichiometric amounts of NaI to a THF/H_2O solution of ketal **2.040**, followed by exposure to *t*BuOK. Surprisingly, rapid conversion of the starting material to very polar compounds ensued, with little production of the spirocycle **2.041**.[16]



2.040 **2.041**

Scheme 2.11

Recognising that exchange conditions would not be a useful option, we turned to the preparation of the iodinated analogue of **2.040** in pure form. To this end, a 5-carbon iodinated orthoester reagent was required. Given the central role occupied by orthoesters in our dissertation, we will devote the following paragraphs to describe their preparation in multigram scale.

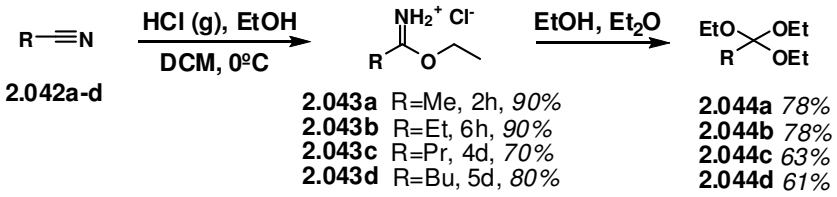
---

[15] For an elimination of HCl from chlorinated condensation adducts akin to **2.026**, cf. Chapter 7.

[16] Decomposition of chlorinated condensation adducts upon addition of NaI under basic conditions appears to be a recurrent trend. Cf. Chapter 5.

2.2.2. Synthesis of orthoesters

A number of different methods have been developed for the synthesis of orthoesters throughout the years.[17] Nevertheless, the conditions reported by Pinner are undoubtedly the most recurrently employed in the literature.[18] Based upon these conditions, McElvain has studied the synthesis of differently substituted triethyl orthoesters **2.044** (Scheme 2.12).[19] These compounds can be prepared from the corresponding nitriles **2.042** in two steps. Transformation of aliphatic nitriles **2.042** in the corresponding imidate salts is accomplished in the presence of hydrochloric acid and ethanol ; the time required for this conversion depends upon the steric environment of the alkyl chain, as shown in Scheme 2.12. Finally, the addition of ethanol to imidate salts **2.043** leads to the formation of orthoesters **2.044**.

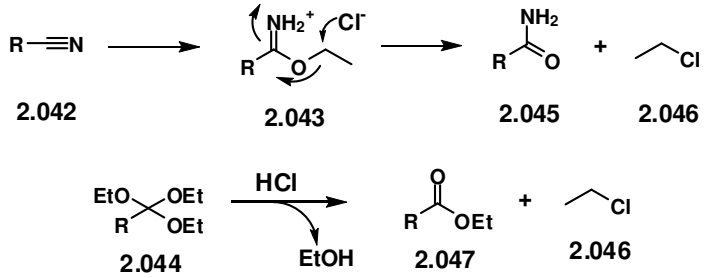


Scheme 2.12

Under these conditions, the preparation of imidate salts **2.043** must be undertaken at low temperature, to avoid their decomposition into the

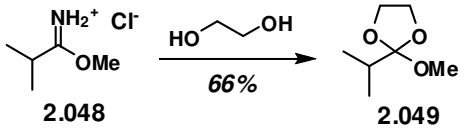
[17] (a) Kantlehner, W. In *Comprehensive Organic Synthesis;* Trost, B.M., Fleming, I., Eds.; Pergamon Press: Oxford, **1991**; Vol. 6, p 485; (b) DeWolfe, R.H. *Synthesis* **1974**, 153
[18] Pinner, A. *Ber.* **1883**, *16*, 356
[19] McElvain, S. M.; Nelson, J. W. *J. Am. Chem. Soc.* **1942**, *64*, 1825

corresponding amide **2.045** and ethyl chloride **2.046** (Scheme 2.13). Furthermore, upon alcoholysis, a second parasite reaction can take place. The remaining imidate salts **2.043**, still present in the medium, can liberate some hydrochloric acid which might promote the hydrolysis of the orthoesters **2.044** (Scheme 2.13).



Scheme 2.13

McElvain has also demonstrated that the addition of ethylene glycol onto excess imidate **2.048** generates the cyclic orthoester **2.049**.[20]

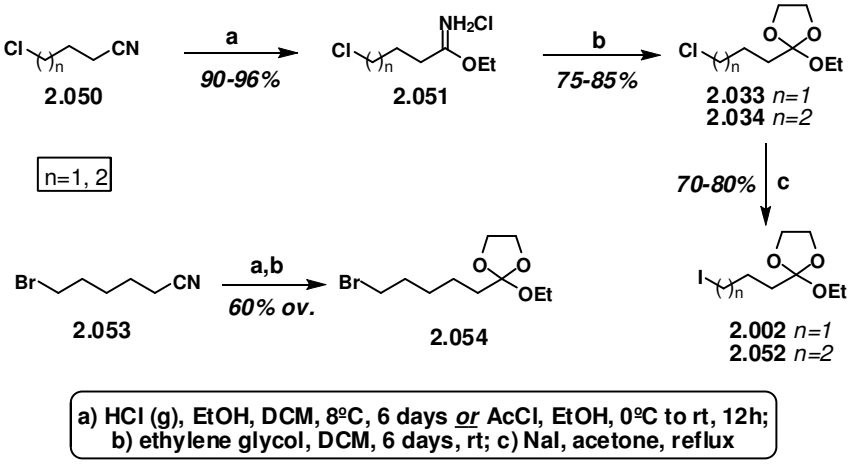


Scheme 2.14

Based essentially upon these precedents, our laboratory has developed a synthesis of the functionalised orthoesters required for our annelation purposes.[4]

[20] McElvain, S. M.; Aldridge, C. L. *J. Am. Chem. Soc.* **1953**, *75*, 3993

Thus, starting from commercially available ω-chloronitriles **2.050**, a two-step Pinner/alcoholysis sequence gives access to dioxolane-containing orthoesters **2.033-2.034** (Scheme 2.15). We have further improved this sequence by replacing the forcing conditions of the classical Pinner reaction (gaseous HCl, EtOH/DCM, 6 days at 8ºC) by an *in situ* generation of HCl in EtOH, through dropwise addition of acetyl chloride.[21] This protocol dramatically reduces the reaction time to less than 12 hours, while producing inocuous ethyl acetate as the only by-product of the reaction.



Scheme 2.15

Finally, whenever iodinated orthoesters were required, a simple Finkelstein exchange (NaI, acetone) delivered the required products. However, it should be noted that in the case of the 5-carbon orthoester **2.052**, residual (<20%) chlorinated **2.034** remained after this exchange reaction.

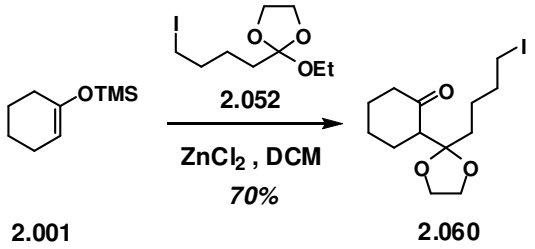
[21] Yadav, V. K.; Babu, K. G. *Eur. J. Org. Chem.* **2005**, 452

Either using a large excess of sodium iodide or switching to higher boiling solvents (butanone, acetonitrile, etc) did not obviate this problem and only contaminated further the mixture by producing considerable amounts of decomposition products.[22] Nonetheless, as will be shown, this fact had no visible consequences on our subsequent uses of orthoester **2.052**.

The same conditions were successfully employed in the preparation of a higher homologue, brominated orthoester **2.054**.

2.2.3. Improving the 6-membered ring formation

Having an access to the iodinated 5-carbon orthoester **2.052**, we then decided to test it in the condensation/spiroannelation sequence. The condensation step proceeded uneventfully to deliver β-ketoketal **2.060** in 70% yield (Scheme 2.16).



Scheme 2.16

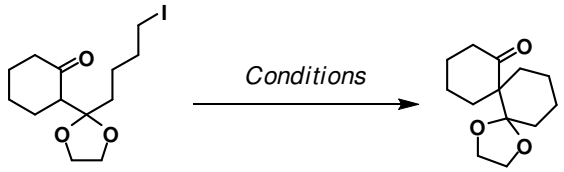
The spiroannelation of **2.060** was studied using different bases (Table 2.2). Unfortunately, the addition of *t*BuOK to a solution of **2.060** in

[22] For the synthesis of other orthoesters, see Chapter 5.

THF/H_2O produced only a 59% yield of spirocycle **2.041** along with 17% recovered starting material (71% yield based on recovered starting material). Moreover, the reaction was extremely sluggish, requiring more than 4 days and additional portions of *t*BuOK to reach an acceptable level of conversion.

However, when NaHMDS was used as the base in dry THF, we were pleased to observe the smooth conversion of **2.060** to spirocycle **2.041** within 12h of reaction. Following chromatographic purification compound **2.041** was obtained in an excellent 84% yield.

KHMDS also proved effective, though the reaction time at room temperature was considerably reduced (12h to 3h)! During this cyclisation, we observed the formation of a white solid (presumably KI). It is possible that the less soluble (as compared to NaI) KI drives the cyclisation forward by precipitating out of solution as it forms.



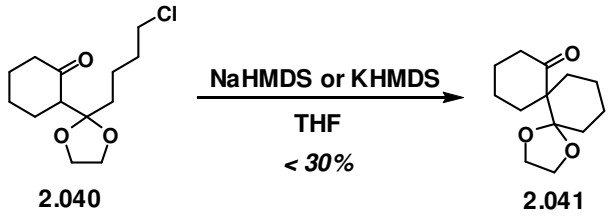
2.060 **2.041**

Table 2.2

Entry	*Conditions*	*Reaction time (h)*	*Yield of **2.041**[a]*
1	*t*BuOK (1.4 eq), H_2O (1 eq.), THF, rt[b]	>96	*59%*
2	NaHMDS (1.5 eq), THF, 0ºC to rt	12	*84%*
3	KHMDS (1.5 eq), THF, 0ºC to rt	3	*75%*

[a] – Yield of pure, isolated product ; [b] – 2 additional portions of *t*BuOK added subsequently.

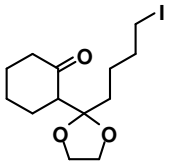
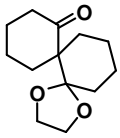
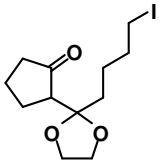
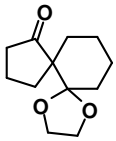
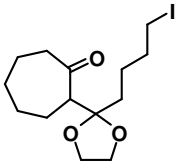
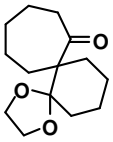
To verify that the observed enhancements in yield and rate of the spirocyclisation were due to the change in the nature of the leaving group, we treated chlorinated **2.040** with the same nitrogen bases (Scheme 2.17). However, only sluggish cyclisations were observed when **2.040** was reacted with either NaHMDS or KHMDS, and less than 30% of the product could be isolated, even after >2 days reaction.



Scheme 2.17

The efficiency of these conditions was then assessed by comparing them with the 6-membered annelations previously described by Dr.Vanherck (Table 2.3). In the case of both cyclopentanone- and cycloheptanone-derived silyl enolethers, the condensation step proceeded in good yields. Importantly, with both substrates, an increase of *ca.* 20% yield was observed for the spirocyclised products **2.035** and **2.063**. NaHMDS and KHMDS proved to be efficient in promoting this otherwise torpid cyclisation, but better yields always ensued with NaHMDS as the base.

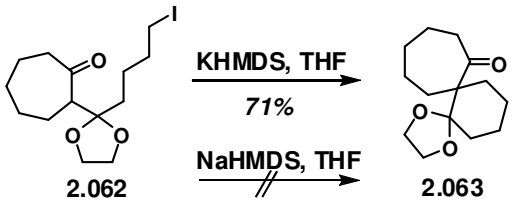
Table 2.3

Entry	*B-ketoketal*	*Yield*[a]	*Spirocycle*	*Yield*[b]
1	 **2.060**	*70%* *(62%)*	 **2.041**	*84%* *(58%)*
2	 **2.061**	*67%* *(67%)*	 **2.035**	*80%*[c] *(65%)*
3	 **2.062**	*75%* *(70%)*	 **2.063**	*71%*[d] *(59%)*

All yields refer to pure, isolated products and to spirocyclisations with NaHMDS in THF unless otherwise stated ; [a]- Yield in parenthesis refers to the analogous ω-chloro-β-ketoketal ; [b]- Yield in parenthesis refers to the spiroannelation from the ω-chloro-β-ketoketal ; [c]- KHMDS afforded only 65% of **2.035** ; [d]- Result obtained with KHMDS.

2.2.4. Discovery of a novel cyclisation mode

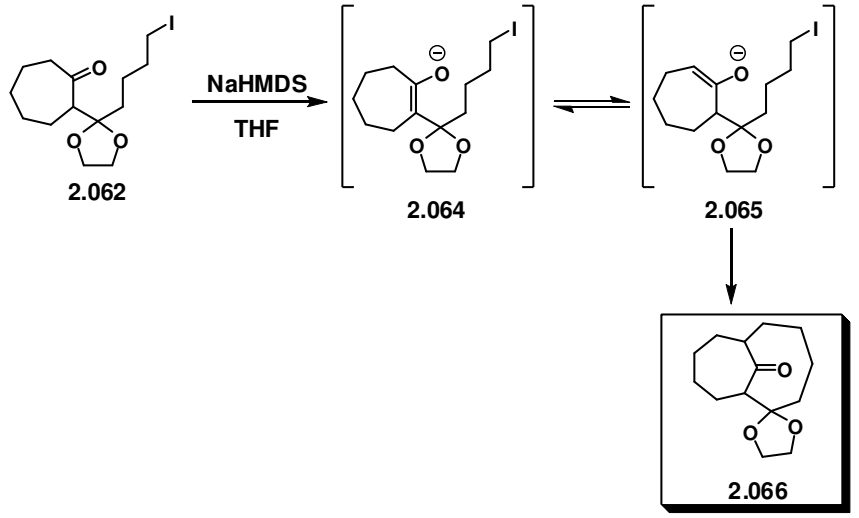
In order to complete the study of the new conditions found for the 6-membered ring-closure, the reaction of cycloheptanone **2.062** (Table 2.3, entry 3) with NaHMDS in dry THF was examined. After 24 h, the formation of a new compound was ascertained. However, this product was *more* polar than the starting material, as opposed to the spirocycles which are typically *less* polar than their β-ketoketal precursors. After purification, we were surprised to obtain a compound whose spectroscopic features were clearly different from those of the spirocycle **2.063** (Scheme 2.18). In particular, 2 new proton resonances between 2.4 and 4.0 ppm were observed in the ^{1}H-NMR spectrum. These signals suggested the presence of two C-H methine protons, which were confirmed through APT-DEPT NMR analysis. This is in stark contrast to the spirocyclic products obtained thus far, which only possess quaternary and methylene (CH_2) carbon atoms.



Scheme 2.18

A combined spectroscopic analysis ruled out the olefin products resulting from direct elimination of HI or cyclisation onto the oxygen atom

of the intermediate thermodynamic enolate. The ensemble of the data collected strongly suggested structure **2.066** for this compound (Scheme 2.19). The formation of **2.066** implies a transannular cyclisation of the *kinetic* enolate **2.065** from precursor **2.062**.

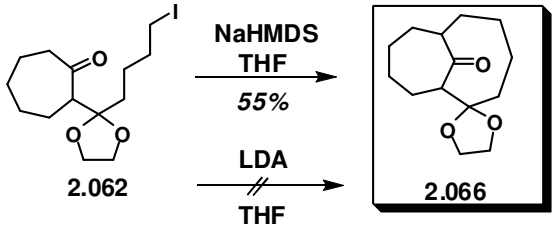


Scheme 2.19

Expecting that direct formation of the kinetic enolate **2.065** might accelerate the reaction, we treated β-ketoketal **2.062** with LDA. To our dismay, even after 2 days of reaction, only the starting material could be recovered along with numerous decomposition products.

NaHMDS is known to induce the formation of thermodynamic enolates from substituted ketones. Thus, we can only assume that equilibration to the kinetic regioisomer must have occurred, as depicted in Scheme 2.19. We currently hold no plausible answer as to why this reaction seems to be specific to a sodic, silylated amide base.

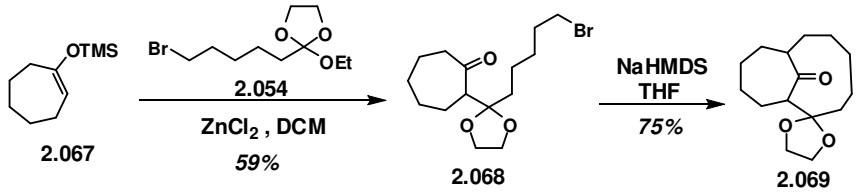
After a brief optimisation of the conditions, we found that the new product **2.066** could be isolated in 55% yield when β-ketoketal **2.062** was treated with 1.3 eq of NaHMDS, in 0.1M THF solution, from 0ºC to rt overnight.



Scheme 2.20

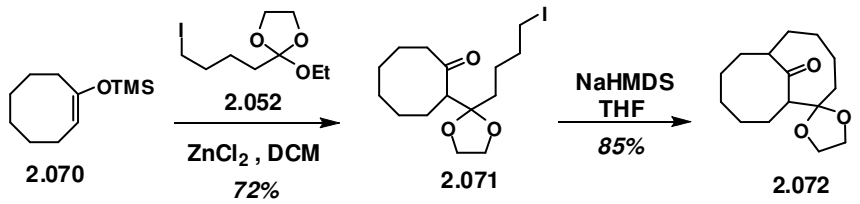
We believe that the higher conformational flexibility of the cycloheptanone ring, along with the longer 5-carbon tether used, might be responsible for this novel reactivity. Therefore, it would be legitimate to assume that orthoester tethers equal or longer than 5 carbons, when grafted onto cycles of 7 or more members, could provide products akin to **2.066** upon exposure to the conditions mentioned above.

The β-ketoketal **2.068**, readily accessible from cycloheptanone silyl enolether **2.067** and the corresponding 6-carbon brominated orthoester **2.054**, would be a suitable candidate for testing this hypothesis (Scheme 2.21). In the event, following treatment of **2.068** with NaHMDS, a smooth cyclisation ensued to provide what seems to be bridged bicycle **2.069** in 75% isolated yield. Bicyclic product **2.069** possesses spectroscopic characteristics similar to its analog **2.066**.



Scheme 2.21

In a similar fashion, we have extended this concept to the cyclooctanone β-ketoketal **2.071**. As for the cases discussed above, transannular cyclisation occured to provide compound **2.072**.



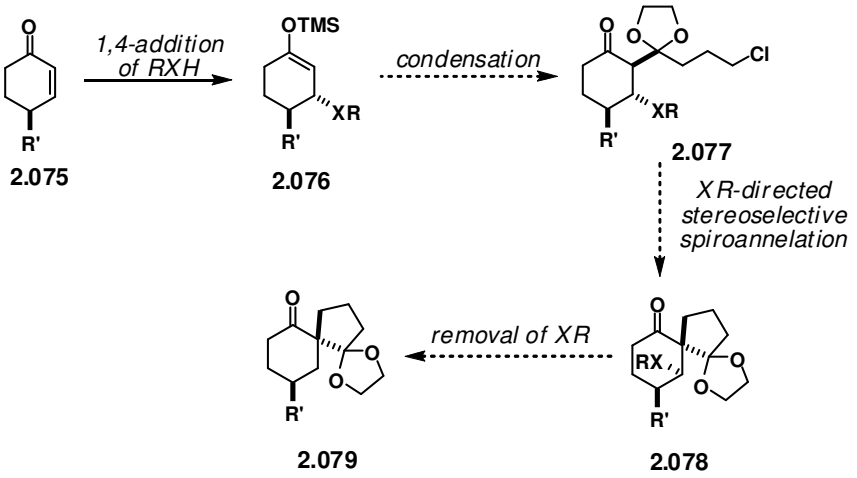
Scheme 2.22

Bearing in mind the counter-intuitive nature of our observations, we have attempted to prepare the oxime of ketone **2.066** with the hope of obtaining a crystalline derivative suitable for X-ray diffraction analysis. Unfortunately, we have not been successful in this endeavour and due to time limitations our investigations on the transannular cyclisation were halted at this point.

2.2.5. Studies on the synthesis of Erythrodiene, Spirojatamol and Spirolepechinene : an evolving approach

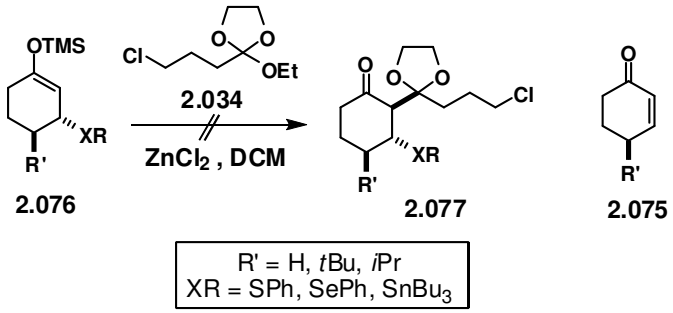
One of our goals was also the development of alternative approaches to the stereoselective 5-membered spiroannelation of γ-substituted cyclohexanones. As might be recalled, these were the least diastereoselective of the 5-membered spiroannelations studied so far (Scheme 2.7) and the configuration of the major diastereomer was opposite to that required for the preparation of Erythrodiene **2.019** and/or Spirojatamol **2.020** (Scheme 2.6).

With an aim of increasing this diastereoselectivity, a number of different approaches were contemplated. Prominent among the multitude of strategies that we have attempted to reduce to practice, the installation of a temporary substituent at the β-position, as in **2.076**, was particularly attractive. Indeed, as we have seen in Section 2.1., almost any appendage at this position should direct the condensation (to **2.077**) and, most importantly, the spiroannelation step to **2.078**. Once a locked intermediate such as **2.078** is reached, simple removal of the temporary substituent –XR would deliver the requisite spirocyclic product **2.079**, bearing the *trans*-relationship (between R'- and the dioxolane-bearing arm) contained in Erythrodiene and Spirojatamol.



Scheme 2.23

As attractive as this might seem, our efforts were consistently thwarted in the application of this plan. We have examined a number of heteroatomic –XR substituents, such as sulphur, selenium and tin derivatives. These should be readily removed at the end of the sequence through tin hydride radical chemistry. Unfortunately, all our attempts to condense the silyl enolethers **2.076** with functionalised orthoester **2.034** led, at best, to trace amounts of the coveted condensation adduct **2.077**. Apparently, under these conditions, retro-Michael addition to **2.075** was the dominant pathway. Screening other Lewis Acids (*e.g.* $BF_3.OEt_2$, $TiCl_4$, TMSOTf, $Sn(OTf)_2$, etc.) proved fruitless.

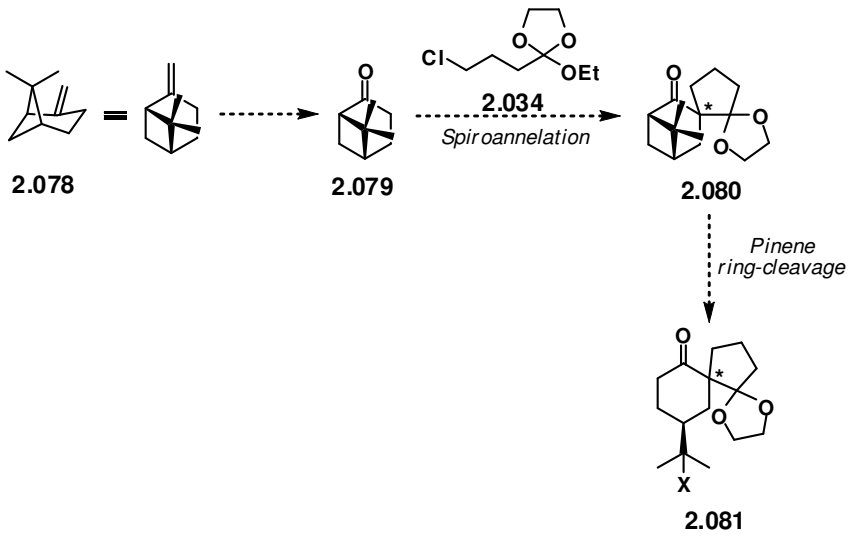


Scheme 2.24

Disheartened by these setbacks, we then considered an alternative approach. Given that the required condensation/spiroannelation would have to occur with high stereoselectivity relative to a remote center (the γ-isopropyl substituent), we hypothesized that a compound that would simultaneously bear a surrogate for this center **and** exist in a locked conformation might prove a valuable template for our plan.

Bicyclic derivatives possessing a *gem*-dimethyl substituent at the bridge carbon are known to display very high levels of facial discrimination in a series of reactions involving nucleophilic and electrophilic attacks. Camphor derivatives have long been used for their inherent chirality and availability in optically pure form **and** for the excellent diastereoselection portrayed upon reaction with external species. Furthermore, pinane derivatives retain all these advantages with the added bonus of undergoing acid-induced ring-cleavage of the bicyclic system with formation of a 4-isopropylcyclohexanone. This is exactly what is required for our synthetic plan !

Thus, as shown in Scheme 2.25, we envisaged to use nopinone **2.079**, readily available from β-pinene **2.078**, as the starting material.[23] Condensation of orthoester **2.034**, followed by spiroannelation, should lead to a spirocyclic pinene derivative **2.080**. The stereoselectivity of the latter step would then irreversibly set the isopropyl-dioxolane relative arrangement to either *cis*- or *trans*-. Such an arrangement would then ideally be revealed through acid-promoted ring cleavage to a cyclohexanone derivative **2.081**.[24]



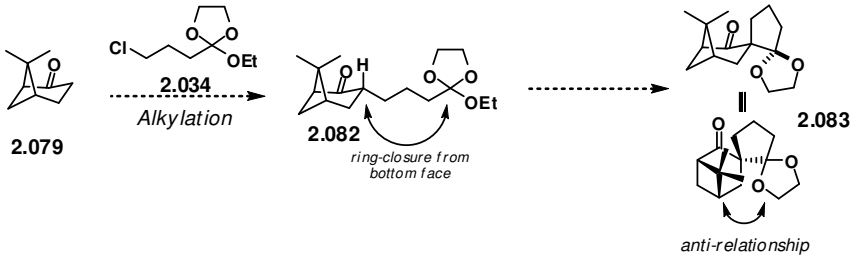
Scheme 2.25

Given the known preference of pinane derivatives to react in an *endo*-fashion (*i.e.*, on the face away from the *gem*-dimethyl substituent), we anticipated that the requisite *anti*-relationship contained in Erythrodiene and

[23] See, e.g. : Hon, Y. S.; Lin, S. W.; Chen, Y. J. *Synth. Comm.* **1993**, *23*, 1543

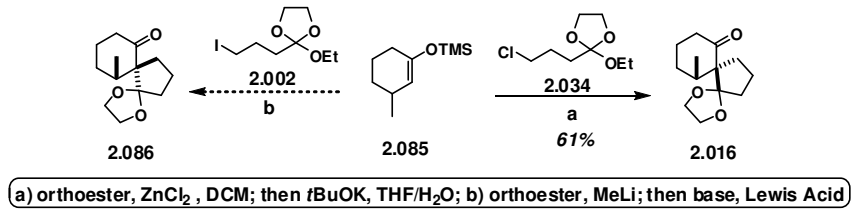
[24] This is amply precedented in the literature. For an elegant, recent example, see: Le Goanvic, D.; Tius, M. A. *J. Org. Chem.* **2006**, *71*, 7800

Spirojatamol could only be attained through a reversal in the order of operations performed (Scheme 2.26). Thus, if alkylation of nopinone with the halide terminus of the orthoester preceded the Mukaiyama-aldol reaction of the orthoester extremity, compound **2.083**, in which the *gem*-dimethyl (and thus the latent isopropyl) and the dioxolane substituent are *anti*-disposed, should be obtained.



Scheme 2.26

Such a « reverse spiroannelation » procedure would be conceptually novel and interesting. Moreover, it would empower us with an extremely high degree of synthetic flexibility. Consider, for example, silyl enolether **2.085** (Scheme 2.27). As shown previously (Scheme 2.5), this compound undergoes condensation/spiroannelation with complete stereoselectivity to afford **2.016**. If our orthoesters could be induced to react in the « reverse » mode, the enolate derived from **2.085** would, at first, provide a compound akin to **2.082** (Scheme 2.26). Upon Mukaiyama-aldol spiroannelation (and admitting that the facial discrimination would remain complete), spirocycle **2.086**, **the spiro-epimer of 2.016**, would be obtained.

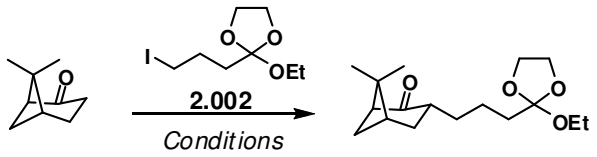


Scheme 2.27

With this additional stimulus, we embarked upon studies aimed at the alkylation of nopinone with orthoester **2.002**, bearing iodine as a more competent leaving group.

From the onset, we recognised that the alkylation adduct **2.082** would be quite difficult to obtain in pure form. Indeed, all our attempts to purify the reaction mixtures by chromatographic methods led to complete decomposition of the desired product. We were thus contrived to estimate the conversion level by ^{1}H-NMR analysis of the mixture.

A selection of our best results is shown in Table 2.4.



2.079 **2.082**

Table 2.4

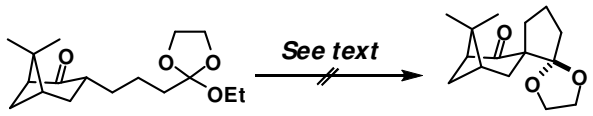
Entry	Ratio **(2.079)/(2.002)**	Concentration of **(2.079)** (M)	Yield (%)[b]
1	1:1	0.5	33
2	1:1	0.2	-
3	1:1	1.0	29
4	2:1	1.0	50
5	1:1.7	0.8	65
6[c]	1:1.6	0.9	>80

(a)-All reactions performed with 1,1 eq. LDA (relative to **2.079**) in THF; (b)- Yields determined by ^{1}H-NMR; (c)-5 eq. DMPU added.

As can be seen, useful conversions (near 80%) could be achieved by the use of excess orthoester and the addition of DMPU to the reaction mixture. An optimal concentration of 0.9M was also an important factor for the success of this reaction.

Having an access to mixtures enriched in alkylation product **2.082**, we turned our attention to the crucial ring-closure step. Initial attempts at forming the silyl enolether of **2.082** led to numerous by-products. For this reason, we reasoned that the direct silylation-activation of compound **2.082** might provide better results (Scheme 2.28).

Unfortunately, all the conditions screened led, at best, to low yields and erratic, irreproducible reactions that afforded complex mixtures of products. A range of Lewis-acids, including silyl derivatives (TMSI, TMSOTf, etc), as well as zinc-, boron- and tin-electrophiles, were tested. In addition, we also considered the addition of a base (*inter alia* NEt_3, iPr_2NEt) to the mixture to facilitate deprotonation to an enol or silyl enolate, alas, to no avail.



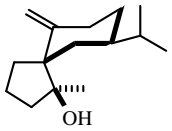
2.082 **2.083**

Scheme 2.28

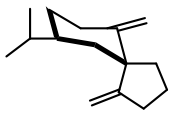
We believe that different factors may be at stake in this unfortunate outcome. On one hand, the presence of orthoester (and orthoester-derived) residues as contaminants in the crude product **2.082** may compete for the Lewis Acid added, thus generating additional electrophilic entities (bound to react in a variety of manners) in solution. On the other hand, under these conditions the bicyclic pinene framework may undergo partial rupture.

Although solutions to this predicament can be foreseen (Cf. last section of this Chapter), other factors forced us to shift our attention to a complementary aspect of this study in the pinene series. Indeed, we became aware of the existence of Spirolepechinene **2.021**, a compound extracted from the leaves of *Lepechinia bullata* and used in folk medicine in Colombia and Venezuela. Most interestingly, although Spirolepechinene possesses the

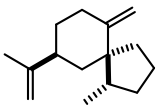
so-called « spirojatamane skeleton »,[25] it is **epimeric** to Erythrodiene and Spirojatamol at the spirannic carbon (Scheme 2.29). Its framework might therefore be accessible by application of the « normal » spiroannelation procedure to nopinone **2.079**.



Spirojatamol
2.019



Erythrodiene
2.020

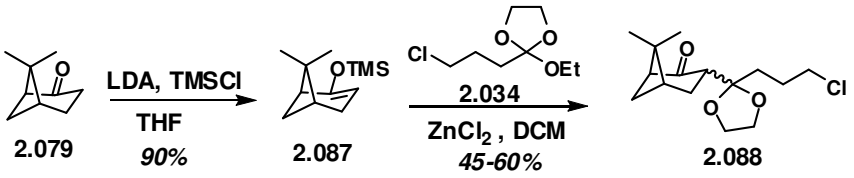


Spirolepechinene
2.021

Scheme 2.29

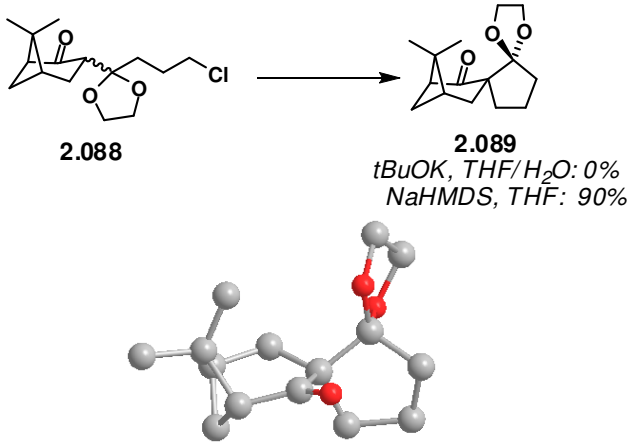
As matters transpired, the reduction of this plan to pratice was not linear. Though condensation of nopinone silyl enolether **2.087** with orthoester **2.034** did provide β-ketoketal **2.088** (as a mixture of epimers), yields were consistently below average for this kind of reaction (45-60%). Varying the relative proportions of the reactants, the nature of the Lewis Acid or using the TES-silyl enolether of nopinone had no positive effect. Nonetheless, synthetically useful amounts of β-ketoketal **2.088** could still be amassed through this procedure.

[25] This term was coined by Forsyth *et al.*: Huang, H.; Forsyth, C. J. *J. Org. Chem.* **1995**, *60*, 2773



Scheme 2.30

A surprise awaited us upon attempted spiroannelation : when **2.088** was treated with *t*BuOK in wet THF, no reaction occurred ! Fortunately, changing the base to NaHMDS smoothly effected ring closure, providing spirocycle **2.089** in good yields. As polycyclic **2.089** was a solid, crystals suitable for X-ray diffraction could be grown and the structure was solved by Dr. Bernard Tinant (Scheme 2.31).



Scheme 2.31

It can be seen that the dioxolane-bearing carbon is oriented *syn* to the *gem*-dimethyl bridge of the pinene system, as anticipated on the premise that this annulation would occur from the least-hindered *endo*-side of the molecule (Scheme 2.31). However, two aspects of this structure are worthy of note. First, it is apparent that the distance between the dioxolane moiety and the gem-dimethyl group (hydrogens omitted for clarity) is relatively small. This raises the possibility that the use of a bulkier ketal as protecting group could provide sufficient bias to gradually reverse the stereochemical outcome of the spiroannulation.

Second, the topology of the system places both the carbonyl and the dioxolane protecting group into chelating distance. Given that one of our long-term objectives is the synthesis of optically pure spiro-ligands benefiting from the rigidity of the spirocyclic center (Cf. Chapter 8), compound **2.089** is an excellent starting point which possesses also considerable potential due to the differential protection of both carbonyls.

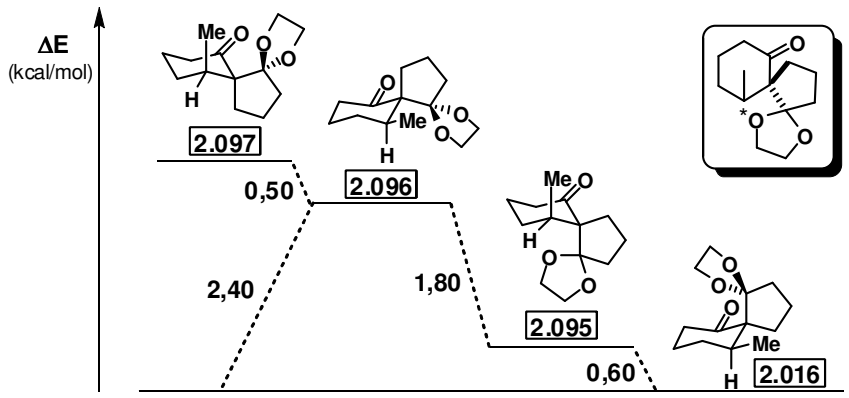
This sequence therefore holds promise for a number of synthetic applications.

2.2.5. Investigation on the origins of the diastereoselectivity of the spiroannelation step

In parallel, we were also increasingly interested in obtaining further information on the exceptional stereoselectivity displayed by the spiroannelation procedure described previously. We were particularly intrigued by the complete diastereocontrol of the cyclisation of β-ketoketal **2.014** to spirocycle **2.016** (Cf. Scheme 2.5).

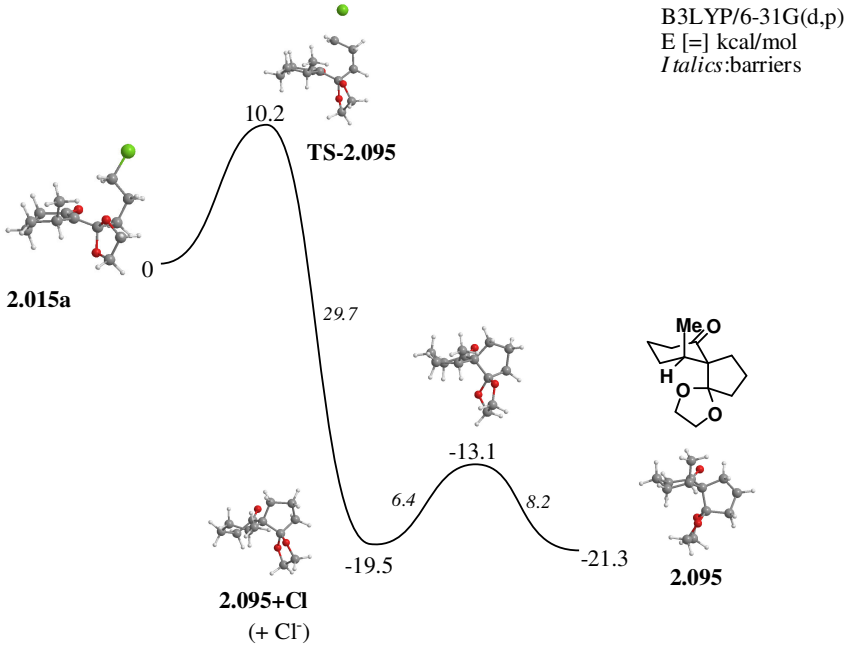
It occurred to us that quantum chemical methods, involving theoretical calculations, might shed some light on the matter. Given our technical limitations in this area, we sought a collaboration with Dr. Luís Veiros at the Instituto Superior Técnico, in Lisbon (Portugal).

The DFT calculations were performed at the B3LYP/6-31G level. Dr.Veiros started by computing all the possible conformations and configurations of the final spirocyclic products and found that **2.016** (the observed product) and **2.095** were the most stable ones (Scheme 2.32). It should be noted that **2.095** is the epimer of **2.016**. Interestingly, the alternative conformer of **2.016** (which is **2.097**), placing the dioxolane substituent in an equatorial position and the methyl substituent in an axial orientation, is predicted to be 2,9 kcal/mol less stable than **2.016**.

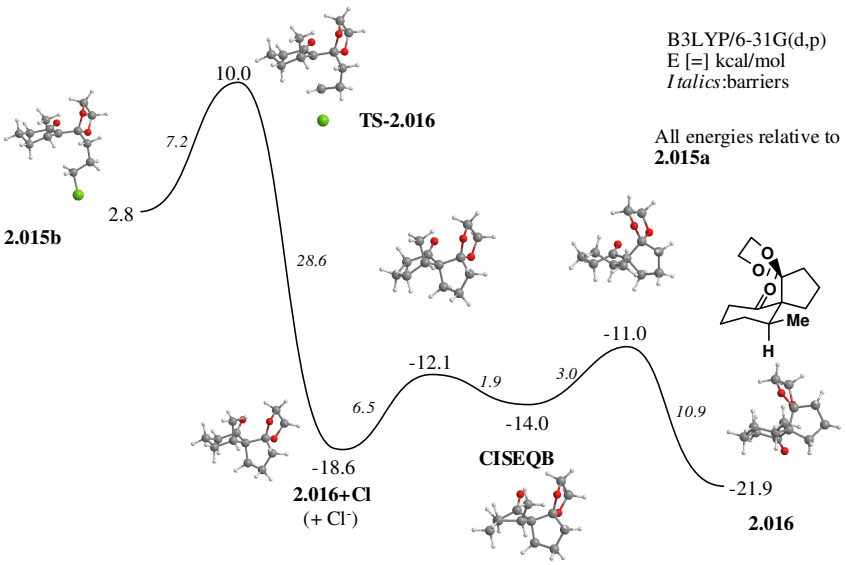


Scheme 2.32

He then proceeded to determine the least-energy pathway for the conversion of the enolate **2.015** into each of these two diastereomeric products. The results are displayed in Scheme 2.33 and Scheme 2.34.


B3LYP/6-31G(d,p)
E [=] kcal/mol
Italics:barriers
10.2
TS-2.095
0
2.015a
29.7
-13.1
6.4
8.2
-19.5
-21.3
2.095+Cl
(+ Cl-)
2.095
Me
O
H
O
O

Scheme 2.33



Scheme 2.34

A number of interesting trends are suggested by the Schemes. For instance, if one compares the transition-state structures for each of the products, it appears that, in terms of absolute energy, **TS-2.016** is only 0.2 kcal/mol more stable than its counterpart **TS-2.095**.[26] This energy difference itself is too small to account for the observed ratio of epimers experimentally obtained, which is >95:5.[27]

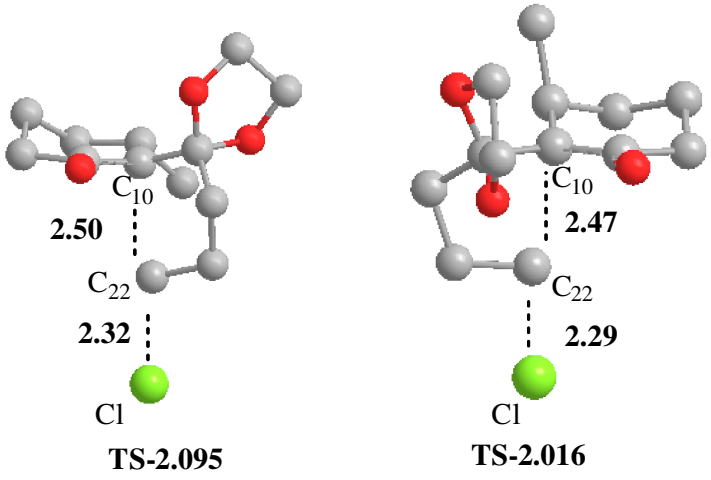
However, it should be noted that the enolate conformers which precede each one of these transition states are also different. Indeed, enolate

[26] When the calculations are performed using a different system, the BPE1BPE functional, this difference increases to 0.5 kcal/mol.

[27] Though a number of intermediates have been determined for each of the reactions, those that lay to the right of the transition state structures **TS-2.016/TS-2.095** correspond to low-energy ring-flip processes and are essentially irrelevant in a discussion of the relative rate of reaction for the formation of both possible stereoisomers.

2.015a, which ultimately leads to the non-observed product **2.095**, is actually more stable by nearly 3 kcal/mol than its analogue **2.015b**. The net result of this is an effective lowering of the activation barrier for the generation of **TS-2.016**, with the same value. Although this seems to suggest a lower-energy pathway leading to **2.016**, inspection of both enolate precursors reveals that they only differ by a number of rotations about the C-C bonds of the β-ketoketal chain. Nonetheless, this situation is reminiscent of the classical acceleration effect observed for the crown-ether-promoted anionic Oxy-cope rearrangement, wherein a *destabilisation* of the ground-state structure leads to a net lowering of the activation energy and, therefore, to an acceleration of the reaction. In our case, as we had anticipated, this corresponds to the methyl substituent adopting a pseudo-axial orientation in the enolate **2.015** (*vide supra*).

Further insight is provided by careful examination of the transition-state structures.



(all distances in Å)

Scheme 2.35

Interestingly, **TS-2.016** is a more "compact" transition-state than its analogue **TS-2.095**. As can be seen, not only the C-C bond to be formed (C_{10}-C_{22}) but also the C-Cl bond which is breaking (C_{22}-Cl) are shorter. This sort of "compact" arrangement usually provides more stable transition state structures. However, if this was the only factor in action, **TS-2.016** should be much more stable than **TS-2.095.**

In fact, the latter factor is partially offset by the particular orientation of the carbonyl and the dioxolane oxygen atoms. Indeed, in **TS-2.016** they are disposed in the same direction. It is, presumably, the dipole-dipole repulsion between these substituents which is responsible for the destabilisation of **TS-2.016**. It is noteworthy that in **TS-2.095**, the dioxolane and the carbonyl oxygen atoms point in opposite directions.

It should be kept in mind that these calculations are done in the gas-phase and without taking the solvent into consideration. This might be too much of a constraint in cases when a charged species gives rise to a neutral molecule and another charged species, such as the current situation.[28]

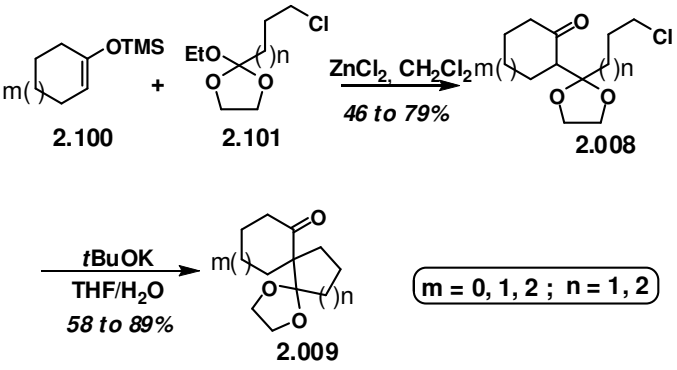
Nevertheless, a number of parameters might be invoked in our favor. For instance, the oxygen atoms appear to define a cavity between them. Though such a cavity would surely be too small to accommodate a K^+ cation, we can speculate that a supramolecular aggregate consisting of, *e.g.*, 3 enolate anions and 1 potassium ion would considerably stabilise this intermediate. Also, one mustn't forget that both H_2O and *t*BuOH are likely to be present in solution. Given that **TS-2.016** is a "closed" structure, hydrogen-bonding to these neutral molecules might be more favorable than in the "open" **TS-2.095**.

Most of the possibilities mentioned should have an influence not only on the relative energy of **TS-2.016** but also on the energy required for interconversion between **2.015a** and **2.015b**. It should be noted that both of these factors are to contribute in similar manner to increase the probability of formation of **2.016**. The calculations described here appear to suggest, however, that the exquisite diastereoselectivity observed in the formation of spirocycle **2.016** does not originate solely from intrinsic, purely electronic factors.

[28] It may, however, be an acceptable limitation for *intramolecular* rearrangements of charged molecules; the accuracy of the results reported in Chapter 3 appears to lend some credence to this assumption.

2.3. Conclusions and perspectives

At the onset of this Chapter, we have presented what can be considered as the primary "driving-force" for this Ph.D. Thesis: a very efficient spiroannelation methodology previously developed by Dr. Jean-Christophe Vanherck. This comprises a two-step procedure involving a condensation and a base-promoted spiroannelation to deliver mono-protected spirocyclic diketones in good yields. High degrees of stereoselectivity, efficiency and simplicity appear to render this cyclisation one of the best methods known for the synthesis of spirocycles.[29]

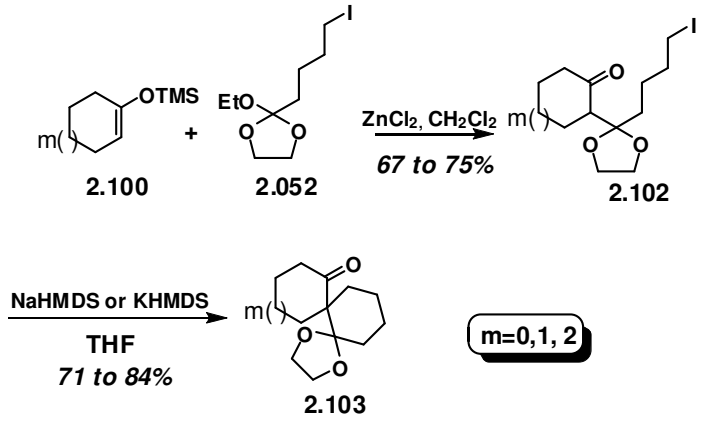


Scheme 2.36

[29] For reviews, see: (a) Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007; (b) Vanderwalle, M.; DeClercq, P. *Tetrahedron* **1985**, *41*, 1767; (c) Krapcho, A.P. *Synthesis* **1976**, 425; (d) Krapcho, A.P. *Synthesis* **1974**, 383; (e) Marshall, J.A.; Brady, St. F.; Anderson, B.H. *Progress in the Chemistry of Organic Natural Products* **1974**, *31*, 283; (f) Reference 5.

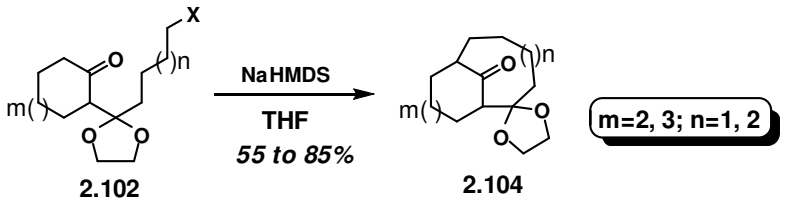
However, no methodology is perfect. Indeed, the ring-closure of compounds **2.008** bearing a 5-carbon tether (n=2) proceeds in low yields under these conditions, effectively hampering the scope of this protocol.

We have addressed this problem by replacing chlorine for iodine as the leaving group and, simultaneously, by modifying the conditions of the spiroannelation step so that 6-membered rings can now be closed in high yields (Scheme 2.37).



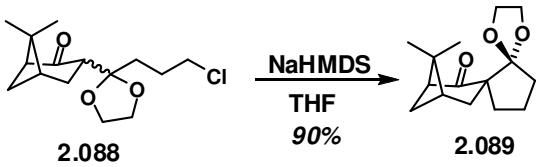
Scheme 2.37

Whilst expanding the scope of this method, serendipity provided us a most interesting discovery: it would appear that, given a tether sufficiently long and a carbocyclic enolate large enough, a new cyclisation mode becomes available (eventually becoming the exclusive pathway) to our β-ketoketal intermediates. Experimental evidence strongly suggests that bridged bicyclic compounds are formed in this event (Scheme 2.38). Further work will be necessary to both confirm the structure of these compounds in an unambiguous fashion and extend the scope of this novel reaction.



Scheme 2.38

Furthermore, an interesting spiropinene derivative was synthesized through application of a modified spiroannelation reaction. This compound possesses great potential for elaboration into both Spirolepechinene and novel ligands that could be used in catalytic reactions.

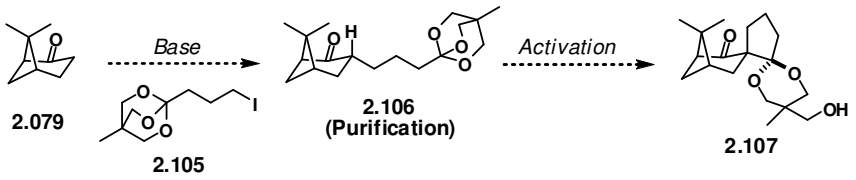


Scheme 2.39

We also believe that the epimer of **2.089** could be prepared by a "reverse spiroannelation" procedure. As shown in Scheme 2.40, we plan to solve the stability problem of the intermediate alkylation product by using a OBO-orthoester **2.105**.[30] These derivatives were introduced and championed by Corey.[31]

[30] For the first use (to the best of our knowledge) of an OBO-orthoester as an *intermolecular* Mukayiama-Aldol condensation partner, cf. Chapter 5

[31] For the original reference see : (a) Corey, E. J.; Raju, N. *Tetrahedron Lett.* **1983**, *24*, 5571



Scheme 2.40

Thus, if the intermediate **2.106** bears a more robust OBO-orthoester moiety, we should be able to purify it and remove all traces of unreacted orthoester (and ketone) by-products. Having access to pure **2.106**, it could be readily ring-closed to **2.107** through either stepwise formation of the silyl enolether/ring-closure or through one of the direct activation procedures that we have tested in Section 2.2.5.

Finally, we attempted to gain insight into the reasons underlying the exceptional diastereoselectivity of our spiroannelation methodology through a multidisciplinary approach, calling the tools of computational chemistry to our aid. The reaction modelled was the ring closure of β-ketoketal **2.014** to **2.016**. The structures of all possible spiroannelation products were computed and the two most stable were retained for further consideration. Then, the putative intermediates were determined, showing that the observed product appears to be not only the thermodynamically most stable compound but also the kinetically prefered product. However, the low differences observed in the activation energies led us to speculate about extraneous factors which might be operative. It would be interesting, from an experimental point of view, to probe some of these speculations. For instance, what might be the outcome of the spiroannelation of **2.014** in the presence of a known chelating

agent for potassium (such as a crown ether)? The relevance of this experiment becomes even more obvious when our results in the novel cyclisation mode of β-ketoketals (Cf. Section 2.2.3) are recalled. What is the true influence of the enolate counterions in solution, that causes such a dramatic shift from Na^+ to K^+? Are the enolate anions monomeric entities or do they exist as supramolecular aggregates of enhanced stability? How can the coordination to the metal ion influence the reactivity of the intermediate enolate as to induce spiroannelation or to force transannular cyclisation? The answers to these and other questions are bound to keep our laboratory busy in this domain for some time to come.

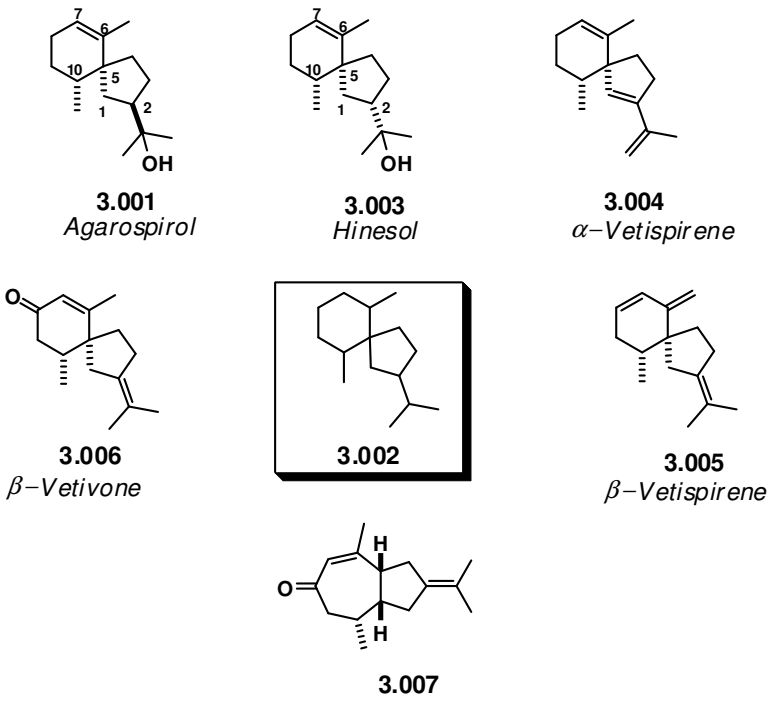
As mysterious as these results might seem, they still provide ready access to spirocycles and bridged bicycles, *at will*. And although we might not yet grasp the full picture in the case of the exquisitely stereoselective annelation of **2.014** to **2.016**, the formation of this (and other) spirocycle(s) in excellent yield bodes well for its(their) application in synthetic ventures. It is one such synthetic *tour-de-force*, employing the annelation to **2.016** as a departure point, that we shall present and discuss in the following Chapter.

Chapter 3 : Total synthesis of Agarospirol, Hinesol and Vetispirene

3.1. Introduction

A highly valued aromatic resin is extracted from agarwood (*Aquilaria agallocha Robx.*), which is employed in Asian traditional medicine as a sedative but also as an incense. In 1965, Agarospirol **3.001** was isolated from this oil (Scheme 3.1).[32] This compound was the first fully characterised sesquiterpene bearing the spirovetivane skeleton **3.002**. This product is the first member of a large family of naturally occuring terpenes with a number of distinctive structural features : a trisubstituted, endocyclic alkene moiety at C_6-C_7, a methyl substituent located at C_{10}, oriented with a *cis* relationship relatively to the C_1-C_5 bond and an isopropyl side-chain protruding from C_2.

[32] Yosioka, I.; Kimura, T. *Chem. Pharm. Bull.* **1965**, *13*, 1430



Scheme 3.1

Other spirovetivanes include Hinesol **3.003** and α- and β-Vetispirene **3.004** and **3.005**. While the former is a secondary metabolite of *Atractylodes lancea*, all of them are minor constituents of vetiver oil, an aromatic oil from vetiver grass (*Vetiveria zizanoides*).[32,33] Recently, it was found that (-)-Hinesol, a spasmolytic[34] and anti-ulcer substance,[35] is a relatively specific

[33] Yosioka, I.; Takahashi, S.; Hikino, H.; Sasaki, Y. *Chem. Pharm. Bull.* **1959**, *7*, 319
[34] Morita, M.; Nakanishi, H.; Morita, H.; Mihashi, S.; Itokawa, H. *Chem. Pharm. Bull.* **1996**, *44*, 1603
[35] Satoh, K.; Nagai, F.; Kano, L. *Biochem. Pharmacol.* **2000**, *59*, 881

inhibitor of H^+, K^+-ATPase and an active ingredient of cerebral circulation and metabolism improvers.[36]

The best-known member of this family and one of the major components of vetiver oil is β-vetivone **3.006**, for which Pfau and Plattner initially proposed, in 1940, structure **3.007**.[37] Nearly 30 years later (1967), Marshall and his group demonstrated this proposal to be incorrect[38] through the synthesis of a degradation product of natural β-vetivone. Eventually they went on to confirm structure **3.006** as the correct one, effectively giving birth to the spirovetivane family of sesquiterpenes.[39]

The currently accepted biogenetic origin of the spirovetivanes has been originally formulated by Andersen in 1970 and is depicted in Scheme 3.2.[40] Thus, a tertiary eudesmyl cation of the general formula **3.009** would suffer ring contraction to **3.010** with formation of a spirocyclic quaternary center. Concomitant elimination of a proton then generates the characteristic double bond mentioned above. Evidence in support of this proposal comes from the chemical degradation of β-rotunol **3.011** (Scheme 4.3). Dehydration of this compound by a combination of $POCl_3$ and pyridine indeed leads to the formation of spirocyclic compound **3.012** (yield not reported).[40]

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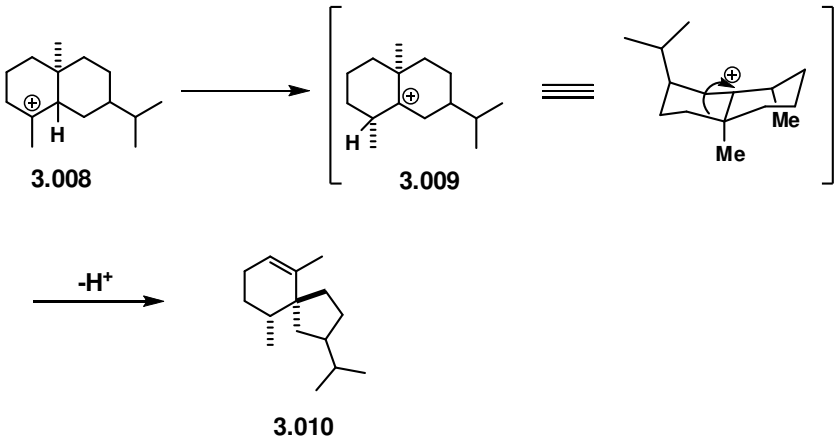
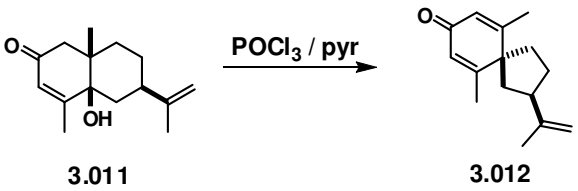
[36] Yamahara, Y. (Tsumura and Co.) Jpn Kokai Tokkyo Koho JP 03232820, 1991; *Chem. Abstr.* **1992**, *116*, 67250p
[37] Pfau, A.S. ; Plattner, P.A. *Helv.Chim. Acta* **1940**, *23*, 768
[38] Marshall, J.A.; Johnson, P.C. *J. Am. Chem. Soc.* **1967**, *89*, 2750
[39] Heathcock, C.H. *The Total Synthesis of Natural Products* ; ApSimon, J., Ed.; Wiley, New York, **1973**, *2*, 466
[40] Andersen, N.H.; Falcone, M.S.; Syrdal, D.D. *Tetrahedron Lett.* **1970**, 1759



Scheme 3.2



Scheme 3.3

We have chosen Agarospirol **3.001**, Hinesol **3.003** and α-Vetispirene **3.004** as benchmarks to illustrate the spiroannulation methodology described previously (Chapters 1 and 2). Before laying down our own strategy, we will briefly review the known syntheses of these spirovetivane sesquiterpenes.

3.2. Literature survey

In this review, we shall cover published syntheses of Agarospirol **3.001**, Hinesol **3.003** and α-Vetispirene **3.004** in chronological order. Aditionally, a small number of historically important syntheses of β-Vetivone will be briefly discussed where appropriate. For each approach, focus will be given to the overall strategies employed to set up the Spirovetivanes' characteristic structural features, rather than to exhaustively detail all of the individual steps.

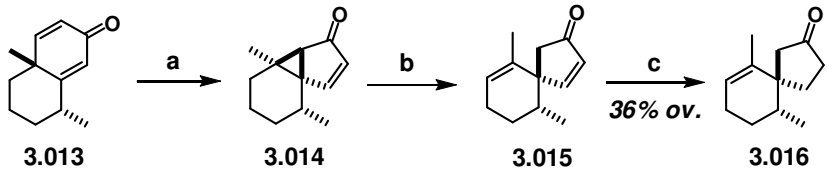
3.2.1. James Marshall : (±)-β-Vetivone and (±)-Hinesol (1970)

Following his earlier demonstration that the original structure **3.007** proposed for β-vetivone was incorrect, Marshall and his group formulated their own proposition as **3.006** and confirmed it through an original synthesis, as depicted in Scheme 3.4.[41]

The Marshall group took advantage of a previously reported procedure leading to spirocycle **3.016**.[42] Therefore, irradiation of dienone **3.013**, prepared in two steps from dimethylcyclohexanone, affords tricycle **3.014**. Solvolysis of this compound under strongly acidic conditions then

[41] Marshall, J.A.; Johnson, P.C. *J. Chem. Soc., Chem. Commun.* **1968**, *391*; Marshall, J.A.; Johnson, P.C. *J. Org. Chem.* **1970**, *35*, 192
[42] Kropp, P.J. *J. Am. Chem. Soc.* **1965**, *87*, 3914

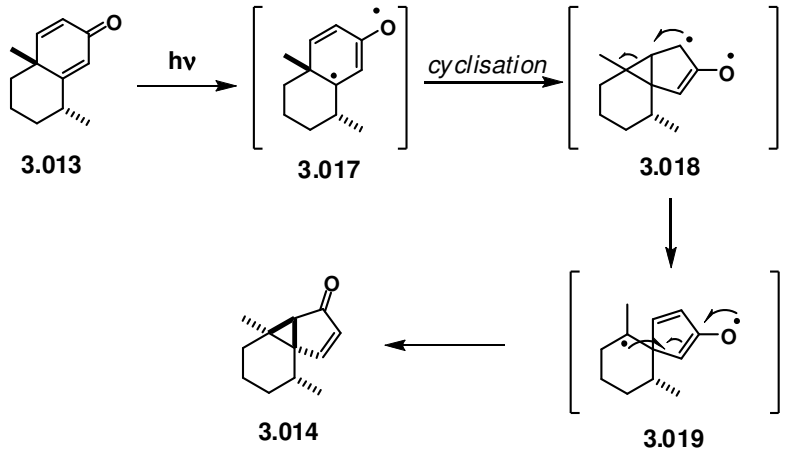
effects cyclopropane cleavage to **3.015**. Selective hydrogenation of the conjugated double bond, in alkaline solution, then provides ketone **3.016**.



Scheme 3.4

This sequence merits further comment. Photochemical isomerisations of compounds akin to **3.013** have been known for a long time due to an analogous process occuring with santonin.[43] A plausible mechanism is depicted in Scheme 3.5. Following excitation of the dienone chromophore, intramolecular cyclisation to fused cyclopropyl di-radical **3.018** occurs. This intermediate then undergoes rearrangement through ring-opening and re-closure, affording the product **3.014** *via* the intermediacy of spirocycle **3.019**.

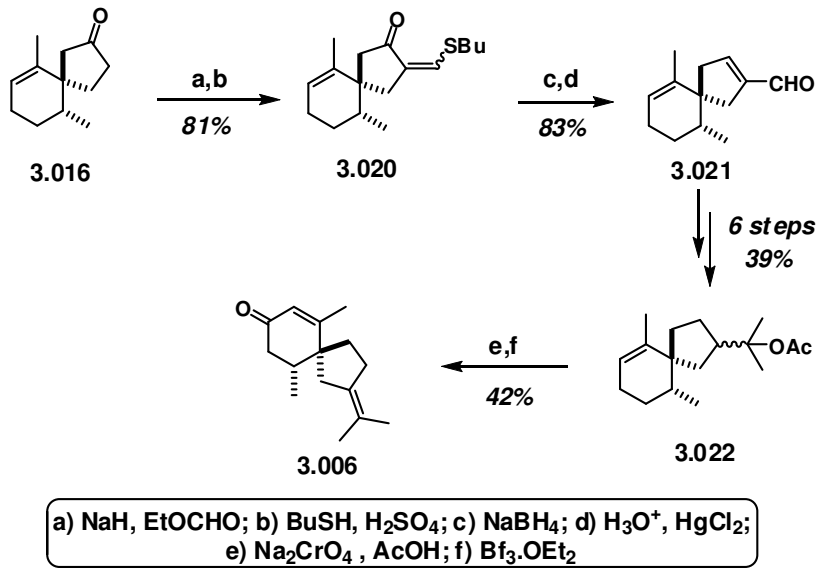
[43] See, *e.g.*: Barton, D.H.R.; de Mayo, P.; Shafig, M. *J. Chem. Soc.* **1958**, 140



Scheme 3.5

Returning to the total synthesis (Scheme 3.6), the authors then exploited the difference in steric hindrance between both positions α- to the carbonyl in **3.016.** Therefore, conventional enolate chemistry enabled the introduction of a β-butylthioenone appendage onto **3.016** in 81% overall yield. Following carbonyl 1,2-reduction with $NaBH_4$, mercury-assisted solvolysis of the resulting alcohol provided enal **3.021** in 83% yield. A series of functional group manipulations then converted this intermediate to a mixture of epimeric acetates **3.022** (5 :3 ratio). Importantly, the major epimer of this mixture was identified as hinesol acetate by comparison with an authentic sample derived from the natural product. Finally, allylic oxidation of this mixture followed by acetate elimination afforded β-vetivone in 42% yield, unambiguously establishing structure **3.006** as that of the natural product.

In summary, Marshall's landmark synthesis produced β-vetivone in 15 steps and 4% overall yield from dienone **3.013**.

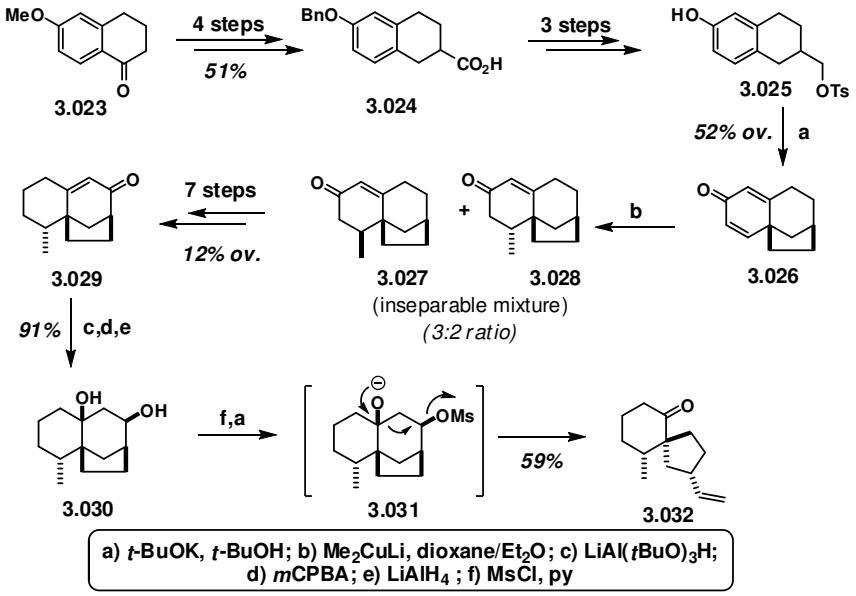


Scheme 3.6

Marshall's plan for the stereocontrolled synthesis of hinesol, published soon thereafter, also featured the fragmentation of a tricyclic system.[44] The key precursor to such a tricycle is tosylate **3.025** (Scheme 3.7). Upon exposure to potassium *tert*-butoxide in *tert*-butanol, the tricyclic dienone **3.026** was obtained in 52% overall yield from carboxylic acid **3.024**. Conjugate addition effected by methyl cuprate in dioxane/ether led to an inseparable mixture of epimeric adducts **3.027** and **3.028**, in a 3 :2 ratio, in favour of the undesired product. A laborious sequence of operations converted this mixture into the enones **3.029**, which, at last, could be

[44] Marshall, J.A.; Brady, S.F. *J.Org. Chem.* **1970**, *35*, 4068

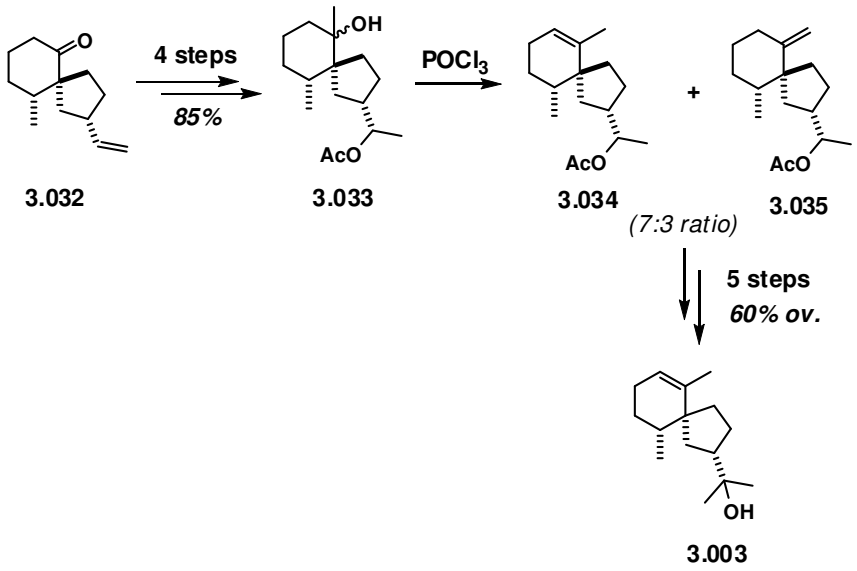
separated by column chromatography. Reduction of the desired diastereomer, followed by OH-directed epoxidation and regioselective epoxide opening with $LiAlH_4$, set the stage for the key-fragmentation reaction. In the event, selective mesylation of the secondary alcohol preceded base-mediated, Grob fragmentation to afford vinyl ketone **3.032** in 59% overall yield (Scheme 3.7).



Scheme 3.7

Although the remaining steps leading to Hinesol are trivial (Scheme 3.8), it should be noted, for reasons that shall become apparent later, that $POCl_3$-induced dehydration of tertiary alcohol **3.033** (generated through adition of MeLi to ketone **3.032**) led to a 7 :3 mixture of endo- and exocyclic

alkene isomers **3.034** and **3.035**. Elaboration of the major component of this mixture eventually afforded Hinesol **3.003**.



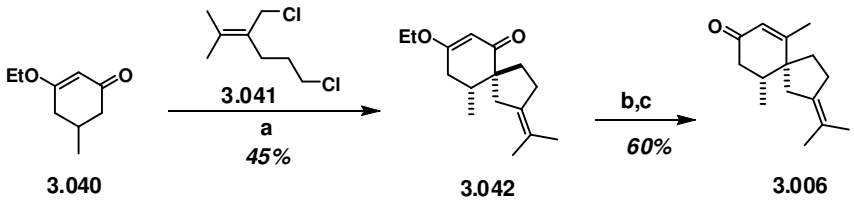
Scheme 3.8

This approach produced Hinesol in 26 steps and 0.6% overall yield from the tetralone **3.023**.

3.2.2. Gilbert Stork : (±)-β-Vetivone (1973)

Paramount among synthetic strategies towards β-vetivone, the Stork-Danheiser-Ganem synthesis, reported in 1973, is probably the most efficient

synthesis of this natural product reported to date (Scheme 3.9).[45] Starting from vinylogous ester **3.040**, kinetic enolate generation is achieved by exposure to LDA/HMPA at low temperature. Addition of the dichloride **3.041**, followed by 2.2 equivalents of LDA and warming to room temperature, led to an elegant one-step linchpin spirocyclisation, which afforded spirocycle **3.042** in 45% yield as a single diastereomer !

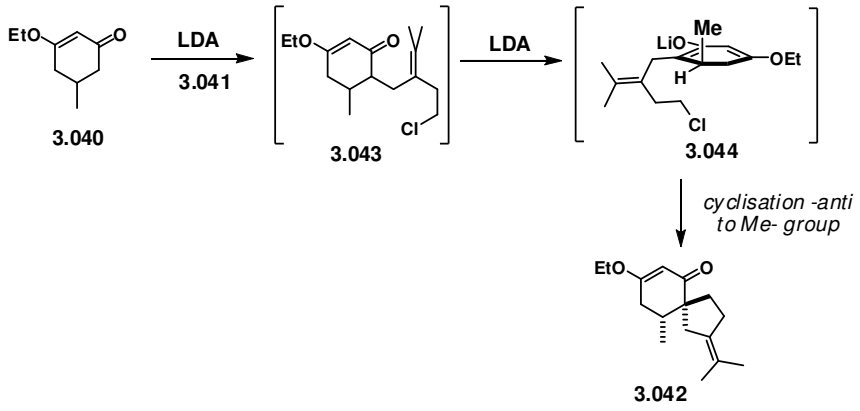


Scheme 3.9

The sequence of operations reported above most likely result in the events depicted in Scheme 3.10. Thus, kinetic enolate formation and alkylation by the more reactive allylic chloride presumably generates monoalkylated ketone **3.043** in solution. The subsequent addition of excess LDA then forms enolate **3.044**. In this quasi-planar intermediate, the lone methyl substituent probably controls the stereoselectivity of the second alkylation, which occurs in an *anti*-fashion.

[45] Stork, G.; Danheiser, R.L.; Ganem, B. *J. Am. Chem. Soc.* **1973**, *95*, 3414

Finally, the well-known nucleophilic addition-acidic reorganisation of vinylogous esters,[46] pioneered by Stork, provided β-vetivone in 60% yield for the two steps (Scheme 3.9).



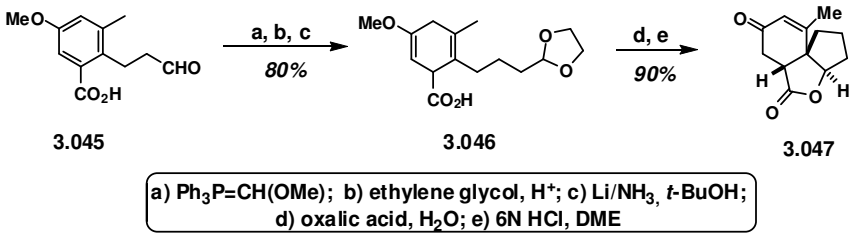
Scheme 3.10

Stork's stereoselective synthesis of β-vetivone is extremely short and convergent, proceeding in only 3 steps from **3.040** and in 27 % overall yield. This strategy has not been employed for any other members of the Spirovetivane family.

[46] Stork, G.; Danheiser, R.L. *J. Org. Chem.* **1973**, *38*, 1775

3.2.3. Kiyoyuki Yamada : (±)- Hinesol and (±)-α-Vetispirene (1973)

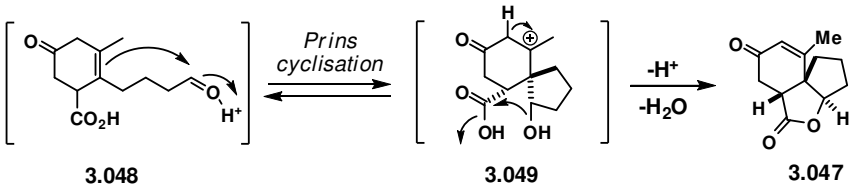
In 1973, Yamada reported the first unified approach to the spirovetivane sesquiterpenes, including β-vetivone (Scheme 3.11).[47] His synthesis began with trisubstituted anisole derivative **3.045**. Homologation of the aldehyde in **3.045**, followed by acetalisation and Birch reduction, provided deconjugated diene **3.046** in 80% overall yield. Non-conjugative hydrolysis of the enol ether (aqueous oxalic acid in DME) then afforded a keto-carboxylic acid which, upon exposure to concentrated HCl, effected bicyclisation affording lactone **3.047** in 90% yield as a single diastereomer.



Scheme 3.11

In this reaction, an initial Prins-cyclisation onto the deprotected aldehyde presumably occurs to generate carbocation **3.049** (Scheme 3.12). Conjugative elimination and γ-lactone formation then account for the observed product.

[47] (a) Yamada, K.; Nagase, H.; Hayakawa, Y.; Aoki, K.; Hirata, Y. *Tetrahedron Lett.* **1973**, 4963; (b) Yamada, K.; Aoki, K.; Nagase, H.; Hayakawa, Y.; Hirata, Y. *Tetrahedron Lett.* **1973**, 4967

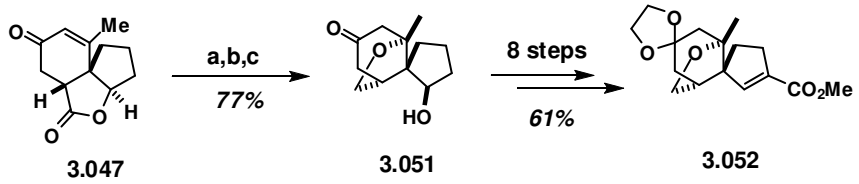


Scheme 3.12

The stereochemical issue of this process merits further comment. Indeed, the Yamada group had determined, through model studies, that if the carboxylic acid substituent was not present the cyclisation was not completely stereoselective (4 :1 ratio of isomers observed). Further experiments by the group suggested that this domino cyclisation was reversible in nature. It is therefore conceivable that, though the formation of the spirocyclic center may not be kinetically stereocontrolled, the final lactonisation step acts as a siphon, funneling towards the product only those reactive intermediates that possess the correct orientation of the hydroxy- and carboxylic acid groups for (irreversible) lactonisation.

From compound **3.047**, a number of transformations were required to attain the desired targets (Scheme 3.13). Following selective protection of the ketone carbonyl, complete reduction of the lactone with $LiAlH_4$ and acidic unravelling of the dioxolane triggered an intramolecular Michael addition, leading to tricyclic ether **3.051** in 77% overall yield. This intermediate was then laboriously progressed to unsaturated ester **3.052**, through an eight-step sequence. It should be noted that introduction of the

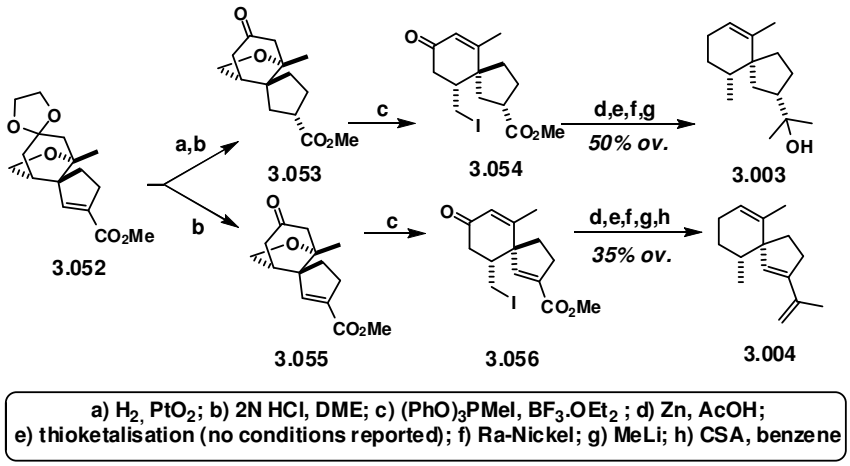
ester moiety was accomplished through a dimethyl carbonate condensation on a ketone enolate.



Scheme 3.13

Tricyclic, unsaturated ester **3.052** is the pivotal intermediate in Yamada's synthetic plan. In the route towards Hinesol (Scheme 3.14), hydrogenation of **3.052** over platinum oxide followed by dioxolane deprotection led, stereoselectively, to **3.053**. Presumably, hydrogenation occurred from the face opposite to the quaternary methyl group. In yet another ring-cleavage step, treatment of tricyclic **3.053** with $(PhO)_3PMeI$ in the presence of $BF_3.OEt_2$ as a Lewis Acid smoothly effected ring cleavage and concomitant formation of iodide **3.054**. After reduction of the iodomethyl substituent, thioketalisation provided a dithiolane which underwent Raney Nickel-promoted desulfurisation. Addition of methyl lithium completed the synthesis of (±)-Hinesol **3.003** in 50% overall yield.

A nearly identical sequence, excluding the initial hydrogenation step of unsaturated ester **3.052**, led to (±)-α-Vetispirene **3.004**.



Scheme 3.14

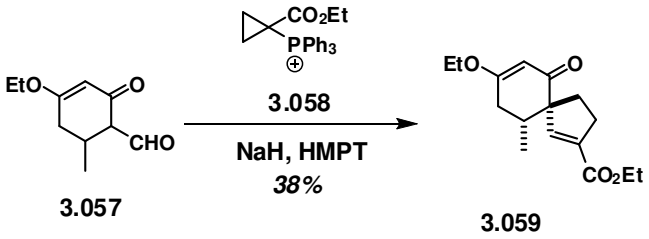
Overall, the Yamada approach provided Hinesol in 23 steps and 17% global yield. As for α-Vetispirene, it was accessed in 23 steps and 12% overall yield.

3.2.4. William Dauben : (±)- Hinesol and (±)-α-Vetispirene (1975)

The Dauben group, at the University of California, Berkeley, pioneered an extremely efficient access to spirocyclic structures, based on the use of cyclopropyl phosphonium salt **3.058**.[48] Their strategy conceptually resembles that of Stork (Cf. Section 3.2.2), and their starting material is

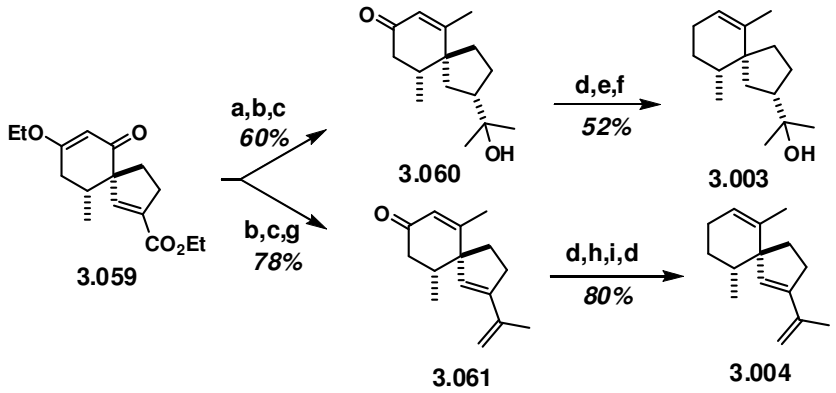
[48] (a) Dauben, W.G.; Hart, D.J. *J. Am. Chem. Soc.* **1975**, *97*, 1622; (b) Dauben, W.G.; Hart, D.J. *J. Am. Chem. Soc.* **1977**, *99*, 7307

actually the α-formyl derivative **3.057** of Stork's departing compound **3.040** (Scheme 3.15). Treatment of this compound with sodium hydride followed by addition of activated cyclopropane **3.058** effected a tandem spiroannelation to give **3.059** in 38% yield, as a single diastereomer. Dauben *et al.* showed this to be a general reaction of α-formylcycloalkanones which, though proceeding in <50% yields, is nevertheless highly convergent. The stereoselectivity of this reaction can be rationalised in similar grounds as in the case of Stork (*vide supra*).



Scheme 3.15

Spirocycle **3.059** was utilised as a key-intermediate to access a variety of natural products, in a manner analogous to the syntheses described above (Scheme 3.16). Thus, in the pathway leading to hinesol, palladium-catalysed hydrogenation of ester **3.059** in ethanol proceeded stereoselectively to afford a single saturated ester. Dauben further mentions that this reaction was critically solvent-dependent : when performed in ethyl acetate, for example, a mixture of products resulting from indiscriminate reduction of both double bonds in **3.059** resulted. It appears that solvation of the highly polarised carbonyl group of the vinylogous ester in **3.059** could create a steric barrier to catalyst binding from that face of the cyclopentene double bond, while simultaneously deactivating the vinylogous double bond for reduction.



Scheme 3.16

MeLi addition, followed by treatment with HCl then provided ketol **3.060** in 60% overall yield from **3.059**. This ketol was subsequently reduced to the diol with $LiAlH_4$, regioselectively acetylated and, finally, reduced to give Hinesol **3.003**.

On the other hand, if the hydrogenation step of **3.059** is supressed, treatment with MeLi and acidic hydrolysis, followed by CSA-promoted elimination of the allylic tertiary alcohol installs the conjugated diene moiety of α-Vetispirene. Reduction of the carbonyl group through a procedure introduced by Corey[49] then led to α-Vetispirene.

The Dauben approach is notable by its flexibility. It provided hinesol in only 8 steps and 12% overall yield from α-formylated **3.057**, whereas α-

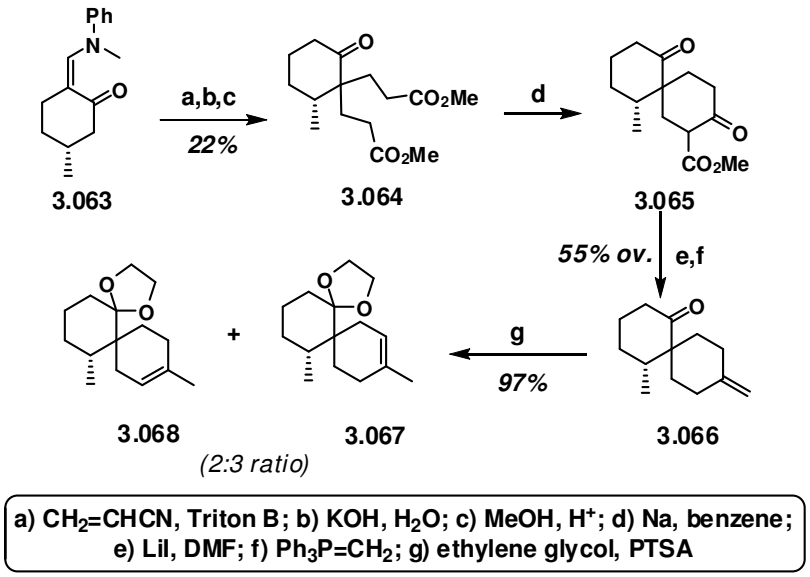
[49] Corey, E.J.; Achiwa, K. *J. Org. Chem.* **1969**, *34*, 3667

vetispirene was prepared in 8 steps and 24% global yield from the same compound.

3.2.5. Robert Ramage : (-)-Agarospirol (1975)

Robert Ramage and his team were the first to synthesize a spirovetivane sesquiterpene in optically active form (Scheme 3.17).[50] Ramage performed a stereospecific synthesis from enantiomerically pure keto-enamine **3.063**. The enamine functionality served the unique purpose of blocking the least-hindered α-position of ketone **3.064**. Thus, double addition of acrylonitrile to **3.063** followed by basic hydrolysis and Fischer esterification provided optically active diester **3.064** in 22% overall yield. Dieckmann condensation of this diester led to β-ketoester **3.065**, which was then subjected to Krapcho decarboxylation and methylenation using a Wittig reagent. The observed selective olefination was most likely due to the inherent steric hindrance of the α-spirocyclic carbonyl.

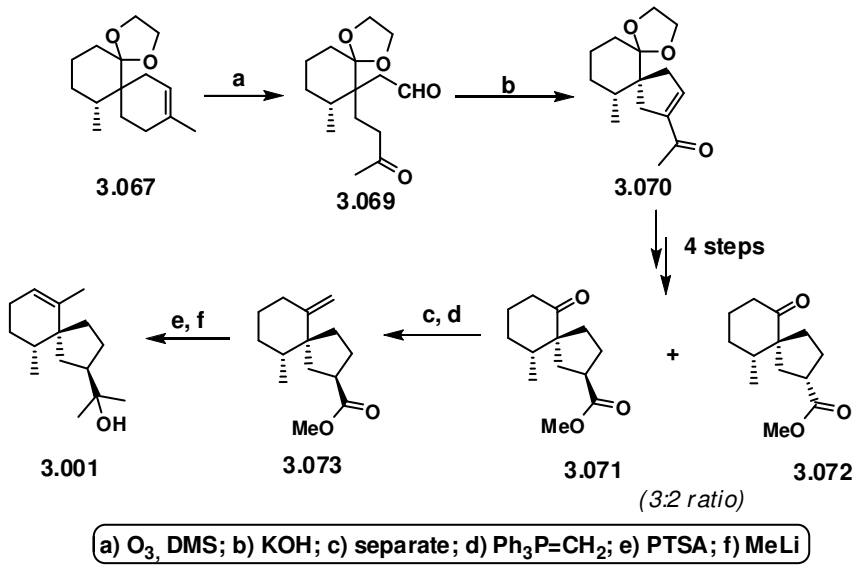
[50] Deighton, M.; Hughes, C.R.; Ramage, R. *J. Chem. Soc., Chem. Commun.* **1975**, 662



Scheme 3.17

Protection of the free ketone as a dioxolane concomitantly produced the isomerized alkenes **3.068** and **3.067** in a 2:3 ratio. Ramage reports that isomer **3.067** was converted to (-)-Agarospirol *via* a ring contration in 7% yield, but no yields for the individual steps were mentioned. This lengthy sequence (abbreviated in Scheme 3.18) includes ozonolytic cleavage of the six-membered ring and aldol-recyclisation as shown, followed by haloform reaction, reduction and esterification (not shown). At this stage, another separation of isomers was required since reduction of the unsaturated ester was not stereoselective. The required epimer, obtained as the major constituent of a 7 :3 mixture, was finally elaborated onto the natural product **3.001** in three additional steps. It is noteworthy that the exocyclic alkene

3.073, obtained from **3.071** by another Wittig olefination, could be completely isomerised to its endocyclic isomer under acidic conditions.



Scheme 3.18

Ramage's asymmetric synthesis proceeds in 16 steps and 0.8% overall yield. Although no comment was made in Ramage's paper, the minor ester diastereomer **3.072** should be amenable to transformation into optically active Hinesol.

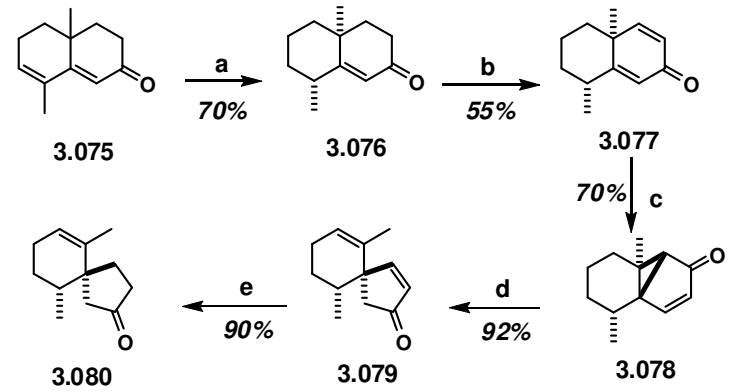
3.2.6. Drury Caine : (±)-α-Vetispirene (1976)

In 1976, Drury Caine reported evolutive approaches to the spirovetivanes.[51] The Caine synthesis originally focused on the preparation of an epimer of Marshall's key-intermediate **3.016**, by a route that closely resembles the one already presented (Cf. Section 3.2.1.). Nevertheless, since the carbonyl group in Caine's intermediate is located at the precise center where functionality exists in the spirovetivanes his approach is complementary in nature to that of Marshall.

Caine's optimised synthesis of ketone **3.080** begins with conjugated decalone **3.075**. Selective γ,δ-reduction with Pd/C in ethanol selectively leads to enone **3.076**, possessing a thermodynamically unstable *cis*-8,10-dimethyl arrangement, epimeric to Marshall's starting material (*vide supra*). The nowadays conventional α-selenoxide elimination method was used for introduction of a second double bond in **3.077**. It should be noted, however, that this procedure had been reported for the first time only one year before (1975) ![52]

[51] (a) Caine, D.; Boucugnani, A.A.; Chao, S.T.; Dawson, J.B.; Ingwalson, P.F. *J. Org. Chem.* **1976**, *41,* 1539; (b) Caine, D.; Boucugnani, A.A.; Pennington, W.R. *J. Org. Chem.* **1976**, *41*, 3632

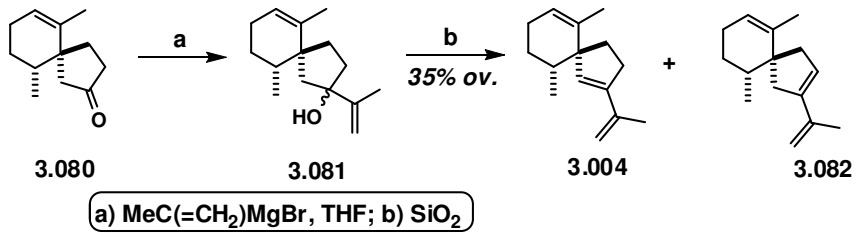
[52] Reich, H.J.; Renga, J.M.; Reich, I.L. *J. Am. Chem. Soc.* **1975**, *97*, 5434



Scheme 3.19

Following the footpath of Marshall, a photoisomerisation/acidic cleavage sequence was used to prepare the spirocyclic framework of **3.079** and a similar enone reduction, by hydrogenation under basic conditions, finally provided **3.080**.

As Caine himself had previously reported, addition of isopropenylmagnesium bromide, followed by chromatography on silica gel, directly afforded α-vetispirene **3.004** and the isomeric triene **3.081** in an approximately 3 : 2 ratio and in 35% yield from **3.080** (Scheme 3.20). Separation of such volatile terpenes was possible by preparative GLC.



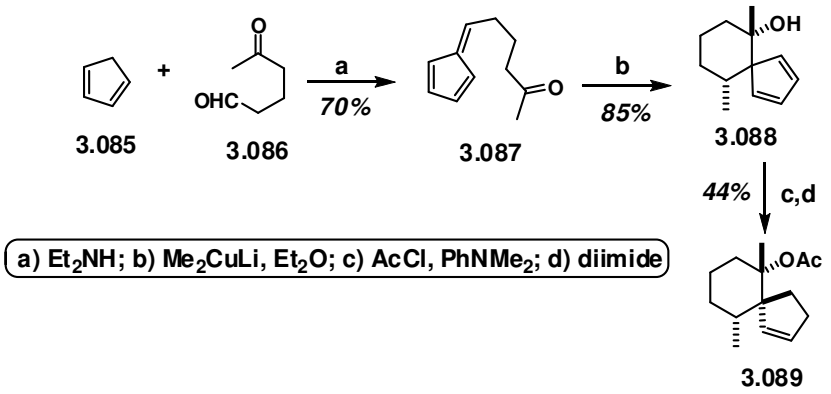
Scheme 3.20

Drury Caine's synthesis of α-Vetispirene took only 7 steps and proceeded in 8% overall yield from **3.075**.

3.2.7. Georg Büchi : (±)-Hinesol and (±)-Agarospirol (1976)

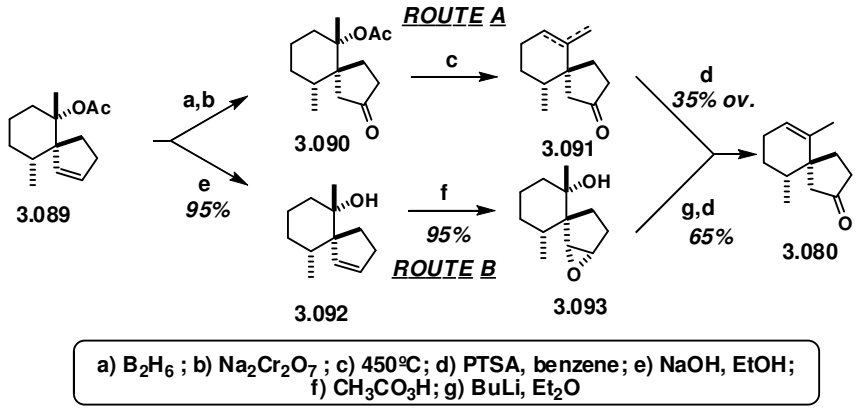
In the same year as Caine's approach was completed, another synthesis of ketone **3.080** was reported by Büchi.[53] In his plan, Büchi employs a direct spiroannelation of fulvene **3.087**, readily available through condensation of cyclopentadiene **3.085** with aldehyde **3.086**. Conjugate addition of dimethylcuprate onto this compound then generated the cyclopentadienyl anion *in situ*, which intramolecularly attacked the pendant ketone carbonyl to form, stereoselectively, the diene-alcohol **3.088**. Acetylation of the tertiary alcohol followed by a diimide-mediated monoreduction then afforded acetate **3.089**.

[53] Buchi, G.; Berthet, D.; Decorzant, R.; Grieder, A.; Hauser, A. *J. Org.Chem.* **1976**, *41*, 3208



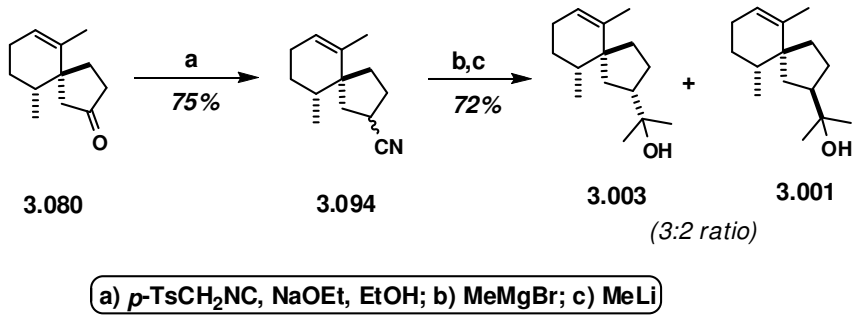
Scheme 3.21

Büchi developed two different pathways for the conversion of **3.089** to ketone **3.080**. In route a, hydroboration/oxidation of the double bond followed by acetate pyrolysis at 450ºC and equilibration of endo and exocyclic olefins with *p*-toluenesulfonic acid in boiling benzene, yielded the more stable endocyclic olefin **3.080**. In route b, an elegant epoxyde rearrangement of **3.093** was employed. In the event, treatment of **3.093** with butyllithium in ether caused isomerisation to a ketone, which was dehydrated to **3.080** under acidic conditions.



Scheme 3.22

The endgame of Büchi's approach featured a TosMiC (the van Leusen reagent)[54] conversion of the ketone **3.080** to the mixture of epimeric nitriles **3.094**, followed by isopropylol generation through sequential additions of methylmagnesium bromide and methyl lithium. This provided a mixture of (±)-Agarospirol **3.001** and (±)-Hinesol **3.003** in a 2 :3 ratio.



Scheme 3.23

[54] Oldenziel, O.H.; van Leusen, A.M. *Tetrahedron Lett.* **1973**, 1357

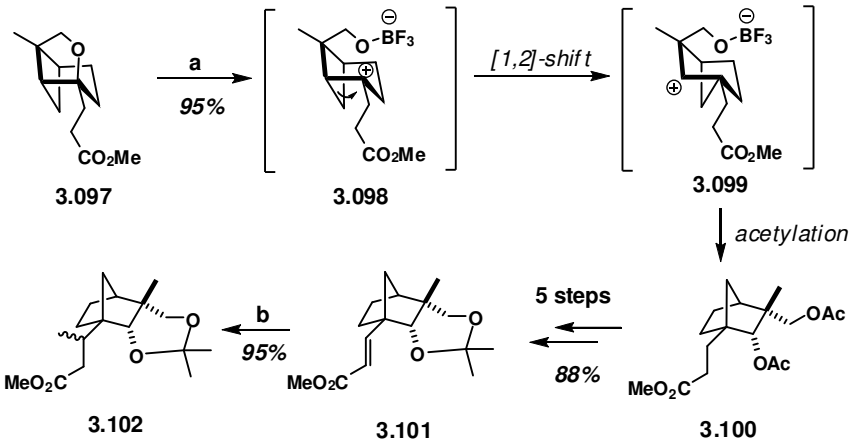
Overall, Büchi's original synthesis proceeds through 11 steps and with a global yield of 8%. Notably, due to Caine's work in the same year, Buchi's synthesis of **3.080** constituted a formal synthesis of α-Vetispirene.

3.2.8. Philip Magnus : (+)-Hinesol (1978)

The first enantiospecific synthesis of (+)-Hinesol (the antipode of the natural product) was reported by the Magnus group, at that time still located at Imperial College, London.[55] Magnus' synthesis is particularly lengthy and, though starting with β-pinene, required no less than 8 steps to produce compound **3.097** from the latter, from which we shall begin our discussion (Scheme 3.24).

Treatment of ether **3.097** with $BF_3.OEt_2$ in acetic anhydride provided bicycle **3.100** in nearly quantitative yield. As depicted, this Wagner-Meerwein rearrangement implies a [1,2]-shift within the pinene cage-like structure, converting it into a norbornane derivative. Oxygen-directed delivery of acetate onto the putative carbocation **3.099** accounts for the observed stereochemical outcome.

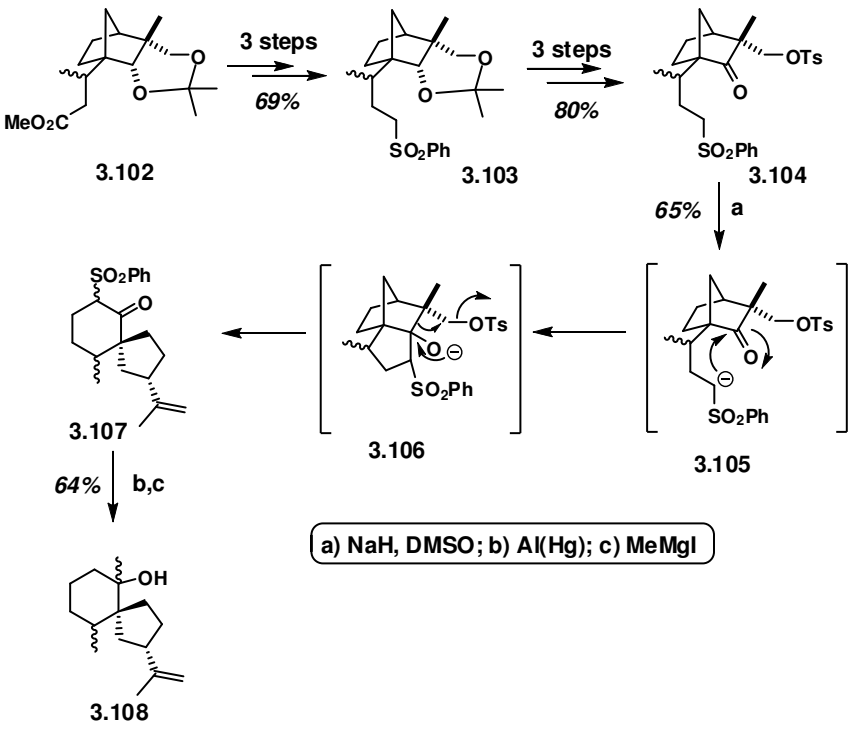
[55] Chass, D.A.; Buddhasukh, D.; Magnus, P. *J. Org. Chem.* **1978**, *43*, 1750



Scheme 3.24

A laborious sequence of 5 steps was then required to transform this compound into unsaturated **3.101**. Dimethyl cuprate addition to **3.101** effects introduction of the characteristic spirovetivane methyl substituent, albeit with no selectivity. The lack of stereocontrol in the formation of **3.102** implies that Magnus will obtain equal amounts of (+)-Hinesol and its C_{10}-epimer (Epi-Hinesol) at the end of the synthesis.

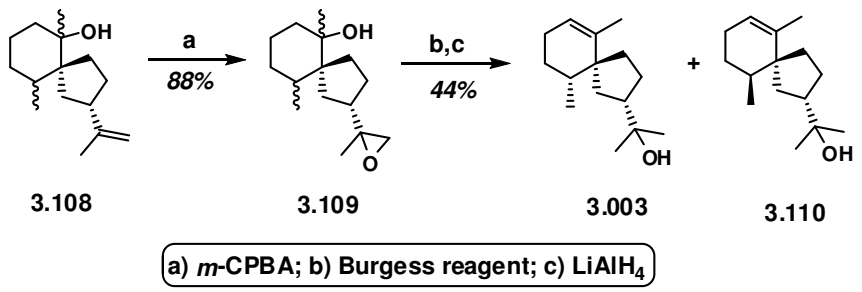
A number of cosmetic operations then advanced this material to ketosulphone **3.103**, setting the stage for the key-step (Scheme 3.25). Upon exposure to NaH in DMSO, ketosulphone **3.102** undergoes an initial intramolecular cyclisation, followed by Grob fragmentation, leading to the spiroderivative **3.107** as a mixture of diastereoisomers. Reduction of the sulphone moiety, followed by addition of methylmagnesium iodide onto the carbonyl function of **3.107** generated tertiary alcohols **3.108**.



Scheme 3.25

Magnus' endgame slightly differs from previous approaches (Scheme 3.26). Indeed, after epoxydation of the olefin **3.108**, Burgess elimination of the tertiary alcohol and $LiAlH_4$ reductive opening of the epoxide provided, still as an inseparable mixture, Hinesol **3.003** and Epi-hinesol **3.110**. It should be noted that the Burgess reagent-mediated dehydration is not selective, affording a nearly equal amount of *exo-* and *endo-* olefinic isomers. Interestingly, Magnus reports that the exocyclic isomer can be converted into its endocyclic counterpart by refluxing with PTSA in

benzene. This is a remarkable result in light of the presence of a tertiary alcohol (or epoxyde) that should dehydrate rapidly under these conditions.



Scheme 3.26

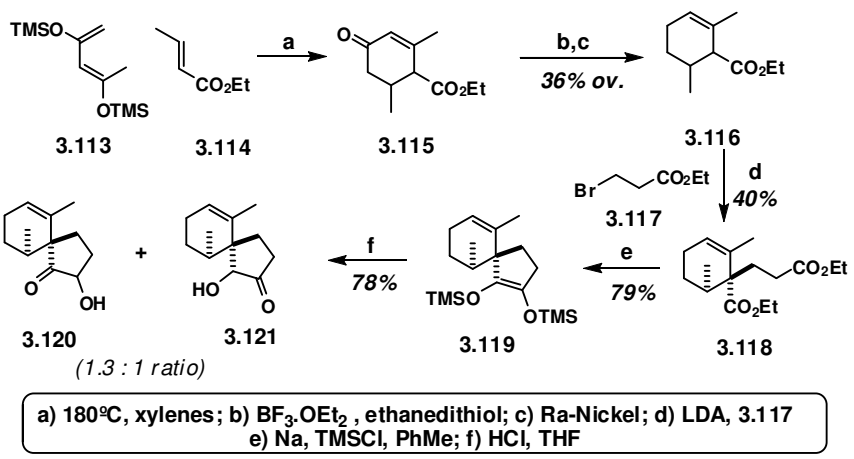
In summary, the Magnus group accomplished a 27 step-synthesis of (+)-Hinesol, with an overall yield of 0.2%.

3.2.9. Toshiro Ibuka : (±)-Agarospirol, (±)-Hinesol and (±)-α-Vetispirene (1979)

As the closing point of a true « golden decade » in the chemistry of spirovetivanes, Ibuka and co-workers in Kyoto reported another connective strategy for the preparation of these natural products.[56] Their synthesis, depicted in Scheme 3.27, began with a Diels-Alder reaction between bis-

[56] (a) Ibuka, T.; Hayashi, K.; Minakata, H.; Ito,Y.; Inubushi, Y. *Can. J. Chem.* **1979**, 1579; (b) Ibuka, T.; Hayashi, K.; Minakata, H.; Inubushi, Y. *Tetrahedron Lett.* **1979**, 159

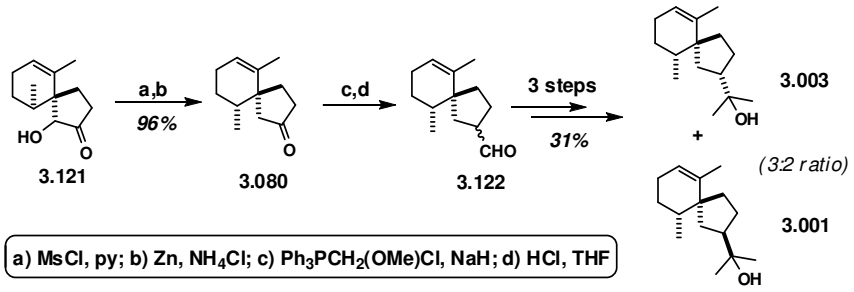
silyloxydiene **3.113** and ethyl crotonate **3.114**, followed by acidic workup to provide γ-ketoester **3.115**. After a two-step carbonyl reduction, Ibuka created the key quaternary center through alkylation of the enolate derived from ester **3.116**. Since the electrophile approaches this enolate from the less-hindered face, product **3.118** is generated as a single diastereomer albeit in moderate yield. Acyloin condensation of diester **3.118**, by exposure to sodium metal and trimethylsilylchloride in toluene, produced the 1,2-bis-silyloxyalkene **3.119** in good yield whilst effecting at the same time the crucial spiro-ring closure.



Scheme 3.27

The elegant preparation of silylated acyloin **3.119** stands in stark contrast with the laborious and low-yielding sequence required for its elaboration into the synthetic targets. Thus, acidic hydrolysis of **3.119** unsurprisingly results in a nearly 1 :1 mixture of α-ketols slightly favoring the undesired regioisomer **3.120**. Two-step reduction of the α-oxygenated

function (Scheme 3.28) followed by homologation of the resulting ketone to the corresponding aldehyde leads, after standard manipulation of the functional groups, to a mixture of Agarospirol **3.001** and Hinesol **3.003** in a 2 :3 ratio.



Scheme 3.28

Intriguingly, ketone **3.080** is the same intermediate obtained by Dauben 3 years before. It is therefore a bit surprising that Ibuka employed a sequence for the transformation of this ketone into the natural products that is 2 steps longer than Dauben's approach !

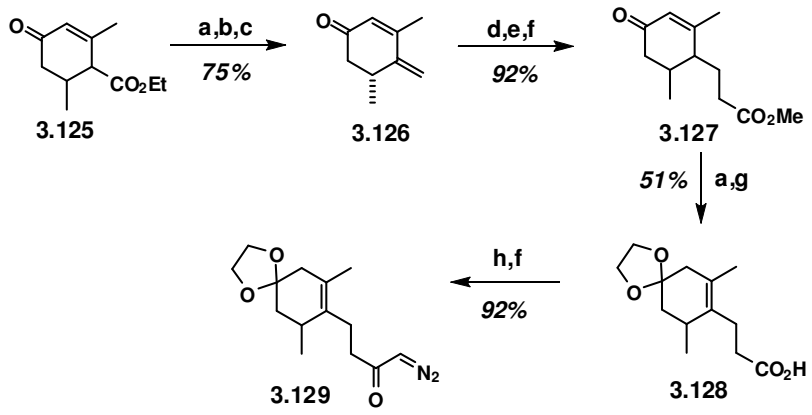
Ibuka's synthesis required 13 steps for the preparation of Agarospirol and Hinesol. Alas, the overall yields are only 0.24% for the former and 0.36% for the latter.

Following the frenetic activity in this field during the 1970's, a considerably smaller body of work, aimed at the spirovetivanes, was reported during the first half of the 1980's. Nevertheless, this period would prove fruitful for the development of original fragmentation-based strategies.

3.2.10. Pierre Deslongchamps : (±)-Agarospirol and (±)-Hinesol (1980)

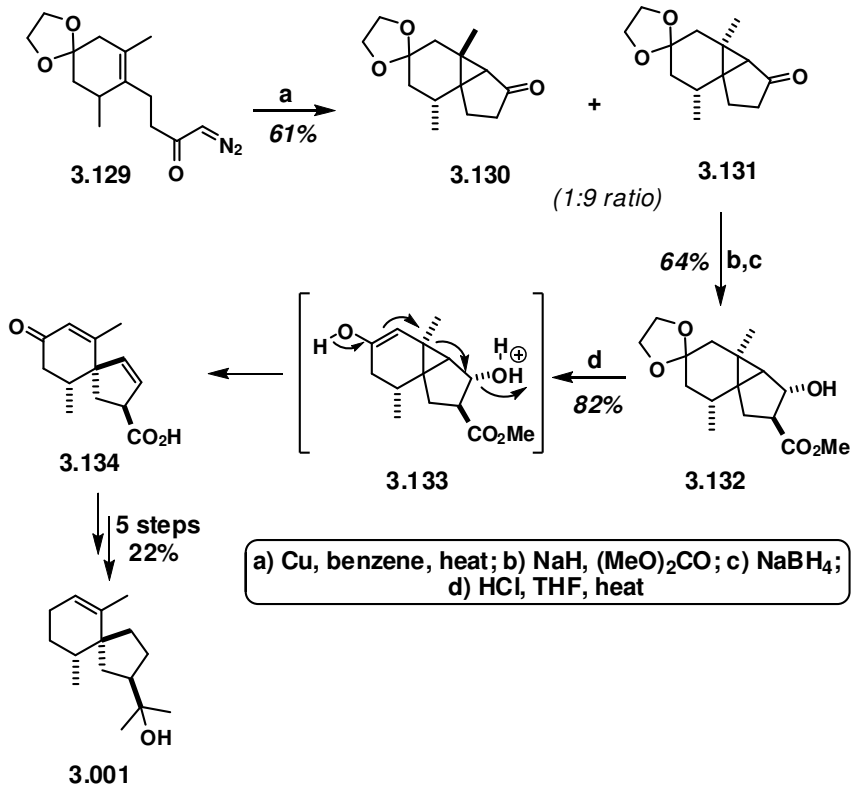
In 1980, Deslongchamps and his team, in Canada, reported another acid-promoted fragmentative approach to the spirovetivanes.[57] Unfortunately, the elaboration of the requisite tricyclic precursor necessitated a high number of steps (Scheme 3.29). Accordingly, ketone **3.125** was converted to dienone **3.126** in three straightforward steps. Though this sequence is apparently trivial in nature, the experimental conditions required for the obtention of **3.126** were surely not. Indeed, if the *exo*-double bond of **3.126** were to isomerise, collapse of the structure to a phenol derivative would surely ensue.

[57] Lafontaine, J.; Mongrain, M.; Sergent-Guay, M.; Ruest, L.; Deslongchamps, P. *Can J. Chem.* **1980**, *58*, 2460



Scheme 3.29

Malonate addition to this Michael-acceptor eventually led to ketoester **3.127**. Protection of the carbonyl function followed by double-bond isomerisation then provided tetrasubstituted alkene **3.128** in moderate yields. Finally, in preparation for the first key-step, the carboxylic acid moiety was uneventfully converted to a diazoketone **3.129**.



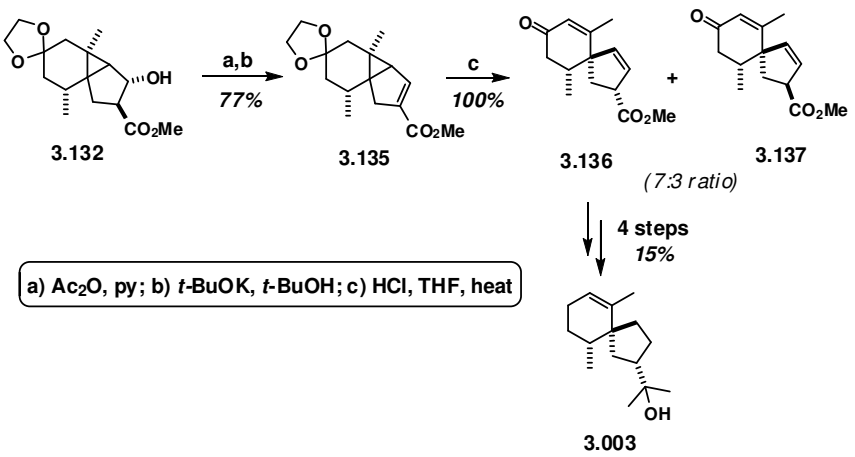
Scheme 3.30

As shown in Scheme 3.30, copper-cataysed diazo decomposition of **3.129** provided tricycles **3.130** and **3.131** in a 1:9 ratio, through intramolecular cyclopropanation. It appears that the future C_{10}-methyl group once again directed the stereochemical course of the spirocyclisation, forcing the carbene to approach preferentially in an *anti*-fashion to generate the observed ratio of products.

After chromatographic separation, ketone **3.131** was progressed to ester **3.132**, setting the stage for the pivotal fragmentation. In the event,

exposure of alcohol **3.132** to HCl in THF triggered a tandem deprotection/dehydrative fragmentation process, generating spiroketoacid **3.134** in 82% yield.

The endgame employed by Deslongchamps for the synthesis of Agarospirol **3.001** closely relates to previously described approaches and will not be described in detail here. It is noteworthy, though, that the same intermediate was also employed in a synthesis of Hinesol, as shown in Scheme 3.31.



Scheme 3.31

Therefore, if elimination to unsaturated ester **3.135** preceded the fragmentation step, a mixture of spirannic esters **3.136** and **3.137** could be obtained in a 7 :3 ratio, in favour of the epimer required for the synthesis of Hinesol. Elaboration of **3.136** to the natural product was carried out along

the same lines as Agarospirol. Obviously, the minor epimer **3.137** could be reintegrated in the route previously presented towards Agarospirol.

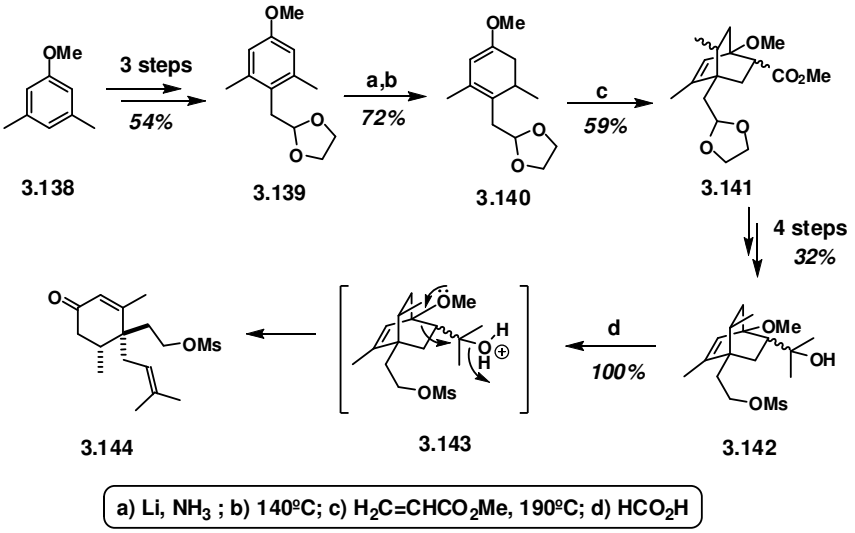
Overall, the approach employed by Deslongchamps was the first to provide Agarospirol and Hinesol separately. Agarospirol required 19 steps, with a global yield of 2.1%, while Hinesol was prepared in a total of 21 steps and 0.9% overall yield from **3.125**.

3.2.11. Tadashi Masamune : (±)-β-Vetivone and (±)-Hinesol (formal) (1981)

Only 1 year after the disclosure of Deslongchamps' strategy, Masamune presented an alternative fragmentation approach to the Spirovetivanes.[58]

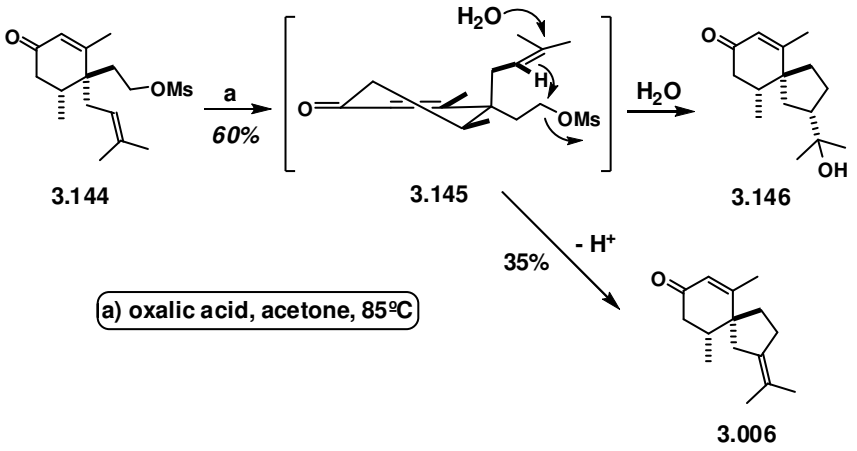
As depicted (Scheme 3.32), the synthesis began with dimethylanisole **3.138**. Through conventional aromatic chemistry, this compound was converted into functionalised derivative **3.139** in three steps. Subsequent Birch reduction and thermal isomerisation then produced conjugated diene **3.140**, a suitable Diels-Alder partner. In the event, reaction of **3.140** with methyl acrylate afforded a mixture of 4 diastereomeric products, from which only the *syn-exo* and *syn-endo* counterparts were advanced through the rest of the synthesis. Four operations were then necessary to convert this mixture of isomers into mesylates **3.142**, setting the stage for two consecutive, elegant processes.

[58] Murai, A.; Sato, S.; Masamune, T. *Tetrahedron Lett.* **1981**, *22*, 1033



Scheme 3.32

In the first key-transformation, treatment of tertiary alcohol **3.142** with formic acid effected quantitative dehydrative fragmentation to **3.144**, which possesses two of the required stereogenic centers of the final target already in place.



Scheme 3.33

In another elegant transformation, heating compound **3.144** in acetone with oxalic acid triggered a stereoselective cationic cyclisation, presumably proceeding through conformer **3.145**, and leading to alcohol **3.146** in 60% yield. As a by-product, β-vetivone **3.006** was also isolated in 35% yield. Since Dauben (Cf. Section 3.2.4) and others had previously deoxygenated the ketone carbonyl of **3.146** to prepare Hinesol **3.003**, this work also constituted a formal synthesis of that natural product.

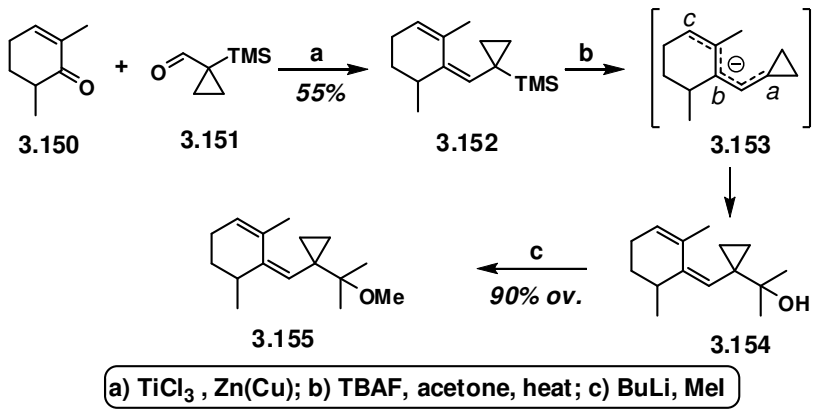
Masamune's synthesis of β-Vetivone proceeds in 12 steps but a modest 2,5% overall yield.

3.2.12. Leo Paquette : (±)-α-Vetispirene (1982) and (±)-Agarospirol, (±)-Hinesol (both formal) (1984)

In 1982, Paquette and Yan reported a thermolytic rearrangement providing one of the most concise syntheses of the spirovetivanes effected thus far.[59] In 1984, the Paquette group expanded this approach to encompass a formal access to Agarospirol and Hinesol.[60]

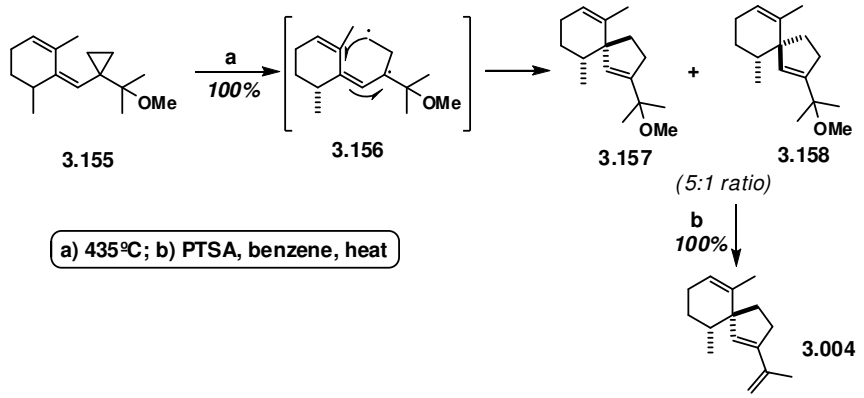
Both pathways relied upon an elegant application of the vinylcyclopropane-cyclopentene rearrangement. McMurry condensation of cyclopropanecarboxaldehyde **3.151** and enone **3.150** provided diene **3.152** in a reasonable yield for this kind of transformation (Scheme 3.34). In the route towards α-Vetispirene, heating **3.152** with anhydrous TBAF in acetone, generated tertiary alcohol **3.154** in excellent yield. In this coupling, the intermediate pentadienyl anion **3.153** presumably undergoes regioselective alkylation at carbon a rather than carbon c in order to avoid the formation of a methylene cyclopropane. Attack at the center marked b, of course, would dispel conjugation in the final product. Methylation of tertiary alcohol **3.154** finally provided the thermolysis substrate, **3.155**.

[59] Yan, T.-H.; Paquette, L.A. *Tetrahedron Lett.* **1982**, 3227
[60] Paquette, L.A.; Yan, T.-H.; Wells, G.J. *J. Org. Chem.* **1984**, *49*, 3610



Scheme 3.34

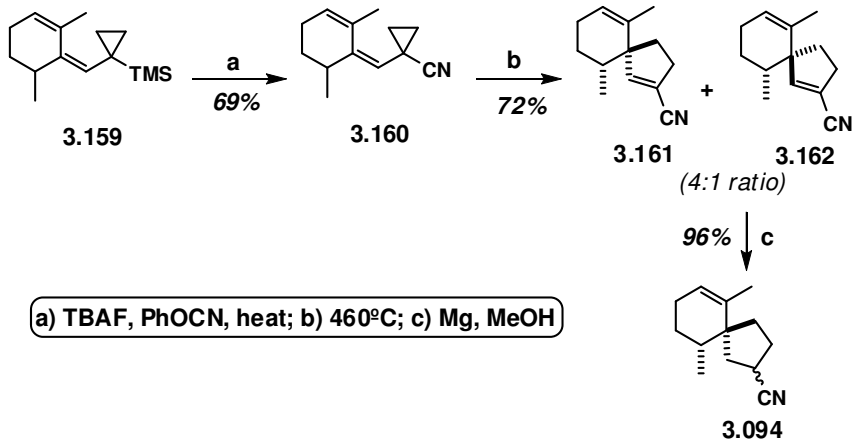
In the event, pyrolysis of the dienyl ether **3.155** at 435-440ºC produced quantitatively a 5 :1 mixture of **3.157** and **3.158**, respectively. The stereoselectivity of this procedure suggests the preferential recombination of the putative intermediate diradical **3.156** from the less-shielded face of the six-membered ring. This is, as the reader now trivially recognises, the face opposite to the methyl substituent.



Scheme 3.35

Finally, demethoxylation of the major isomer, under mild acidic conditions, proceeded smoothly and afforded, once again in quantitative yield, α-Vetispirene **3.004** in 5 steps with a spectacular 38% overall yield from cyclopropane **3.151**!

The sequence employed to access Agarospirol and Hinesol closely resembles the one described for α-Vetispirene (Scheme 3.36). Replacement of the TMS-functionality by a nitrile was effected using phenylcyanate in 69% yield. Thermolysis of this nitrile **3.160** afforded spirocycles **3.161** and **3.162** in good yield and similar stereoselectivity as in the case of α-Vetispirene. Finally, selective reduction of the conjugated double bond with magnesium in methanol provided a mixture of epimeric nitriles **3.094** (diastereomeric ratio not reported), which we have previously encountered in our discussion of Buchi's 1976 synthesis.



Scheme 3.36

The interception of Buchi's synthetic pathway enables a formal synthesis of Agarospirol and Hinesol to be claimed.

3.2.13. Edward Piers : (±)-Agarospirol and (±)-Hinesol (both formal) (1983)

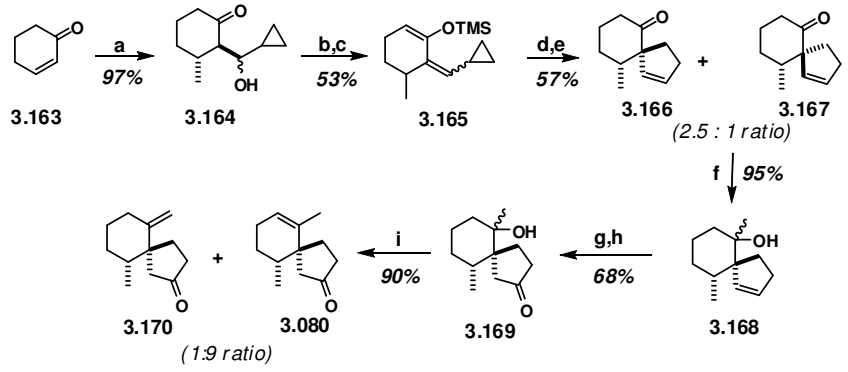
Between Paquette's two syntheses, Piers reported a conceptually identical, albeit longer, approach.[61] His route contains, nevertheless, information deemed important for the discussion of our own results in this area (*vide infra*). It is for this reason that we summarise it briefly hereunder.

Conjugate addition of dimethylcuprate onto cyclohexenone **3.163** followed by capture with cyclopropanecarboxaldehyde leads to alcohols

[61] Piers, E.; Lau, K.C.; Nagakura, I. *Can J.Chem.* **1983**, *61*, 288

3.164 in good yield. Dehydration and enolate silylation then provide dienes **3.165**, the substrates for the vinylcyclopropane-cyclopentene rearrangement.

Analogous to Paquette's route, thermolysis of this compound provides spirocycles **3.166** and **3.167**. It should be noted that, though the temperatures required for rearrangement are slightly lower (380ºC), the stereoselectivity displayed in this transformation is clearly poorer as the desired product **3.166** is obtained as the major component of a 2.5 :1 mixture.



Scheme 3.37

Whereas Paquette's intermediates already contain the endocyclic double bond characteristic of the final products, and additionally possess useful functionality in the five-membered ring, Piers' route provides, in a comparable number of steps, a less decorated intermediate. Addition of MeLi to the ketone provided alcohols **3.168** and a two-step

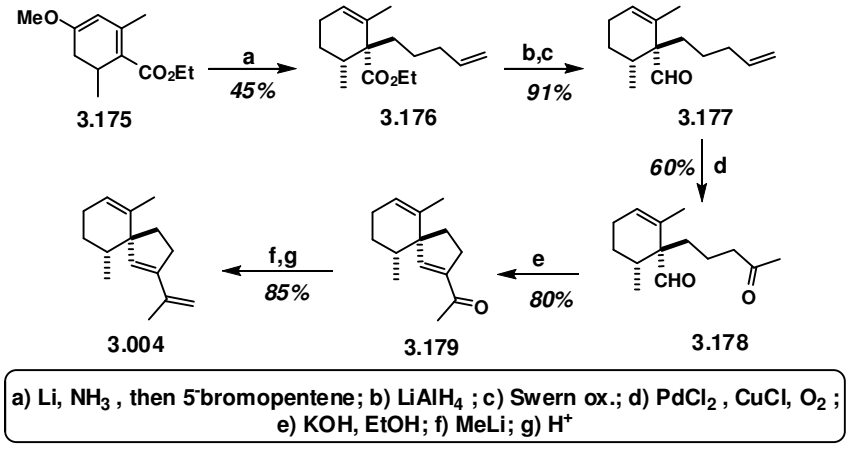
hydroboration/oxidation/oxidation sequence generated the ketone **3.169**. Finally, Buchi and Ibuka's intermediate **3.080** was obtained by dehydration of the tertiary alcohol in **3.169**. Upon treatment with PTSA in benzene, the desired endocyclic alkene **3.080** was produced, accompanied by its exocyclic isomer **3.170,** in a very favorable 9 :1 ratio.

3.2.14. Geneviève Balme : (±)-α-Vetispirene (1985)

The pinnacle of a 15-year period of successive syntheses of the title spirovetivane sesquiterpenes was reached in 1985, when Geneviève Balme single-handedly accomplished a short and stereoselective synthesis of (±)-α-Vetispirene.[62]

Balme's approach began with conjugated ester **3.175** (Scheme 3.38). Upon exposure to 7 equivalents of lithium in THF/ammonia followed by addition of 5-bromopentene, **3.175** undergoes a series of successive transformations : reduction, methoxy elimination, second reduction and stereocontrolled α-alkylation to provide a 45% yield of **3.176**. As we have repeatedly seen in syntheses of the spirovetivanes, the adjacent methyl substituent controls the selectivity of the alkylation step and secures the correct stereochemistry.

[62] Balme, G. *Tetrahedron Lett.* **1985**, 2309



Scheme 3.38

Full reduction of **3.176** followed by Swern oxidation provided **3.177**. Cyclisation to the advanced intermediate **3.179** was effected by Wacker oxidation of the terminal olefin followed by aldol condensation. From this compound, MeLi addition and dehydration provided α-Vetispirene **3.004**.

In summary, Geneviève Balme prepared α-Vetispirene in 7 steps with an overall yield of 17% from **3.175**. Although Balme did not report further on this topic, it is conceivable that this precise route could be easily adapted for the synthesis of Agarospirol and Hinesol. Indeed, conjugate reduction of enone **3.179** would intercept a number of the routes previously described. Interestingly, this would be accomplished by others later on (*vide infra*).

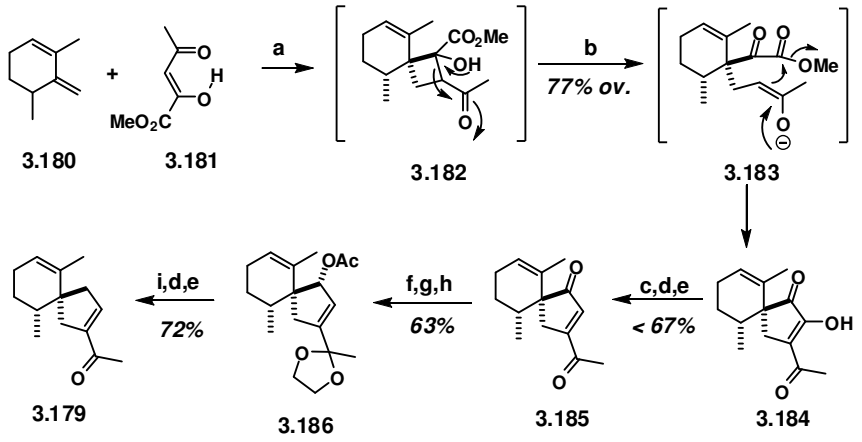
3.2.15. Hitoshi Takeshita : (±)-Agarospirol and (±)-Hinesol (1995)

The Balme synthesis marked a 10-year hiatus in the reports on total syntheses of the spirovetivanes. Takeshita and co-workers were to break the silence with an innovative construction of the spirocyclic framework.[63]

In the event (Scheme 3.39), photocycloaddition of diene **3.180** with pyruvate derivative **3.181** led mainly to the cycloadduct **3.182**. This compound was not isolated but directly treated with Na_2CO_3. This brought about a smooth aldol fragmentation, reminiscent of the DeMayo reaction, to afford **3.184** in an impressive 77% overall yield.

This elegant sequence provided Takeshita with a densely functionalised five-membered ring analogue of the spirovetivanes. Unfortunately, a lot of effort had to be devoted to excise superfluous functionalities. Thus, methylation (under unreported conditions or yields) followed by zinc-mediated reduction and acidic treatment effected removal of the hydroxyl group to provide **3.185**. A second sequence of protection/reduction/acidic treatment was employed for the extrusion of the α-spirannic carbonyl. These operations provided Takeshita with **3.179**, the same intermediate that Balme had obtained 10 years before. It is unfortunate that the 9 synthetic steps just described had to be used for the sole purpose of removing functionalities from the initially obtained spirocyclic product.

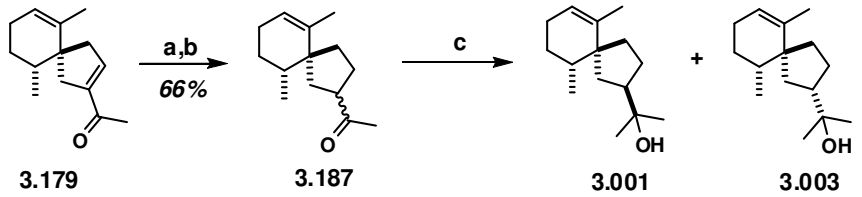
[63] Hatsui, T.; Wang, J.-J.; Ikeda, S.-Y.; Takeshita, H. *Synlett* **1995**, 35



a) hν, EtOAc; b) Na_2CO_3; c) Methylation; d) Zn, AcOH; e) PTSA; f) ethylene glycol, PTSA; g) Ac_2O, py; h) $LiAlH_4$, Et_2O; i) AcOH;

Scheme 3.39

As portrayed in Scheme 3.40, one additional Zn-promoted reduction (a favorite of this synthesis), followed by MeMgBr addition then provided a mixture of (±)-Agarospirol **3.001** and (±)-Hinesol **3.003**, in an unreported ratio and yield. Although Takeshita does not claim it, his approach can also be considered a formal synthesis of α-Vetispirene **3.004**.



a) Zn, AcOH; b) PTSA; c) MeMgBr, Et_2O

Scheme 3.40

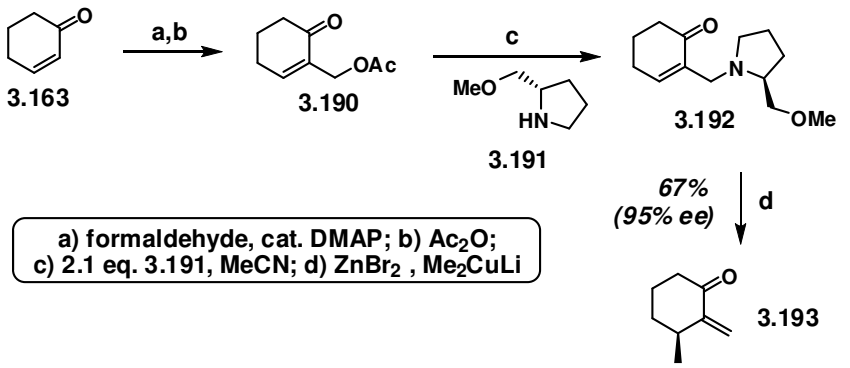
Overall, Takeshita's pathway proceeds in 13 steps and proceeds in less than 15% overall yield, calculated with the only values reported.

3.2.16. Xiyan Lu : (-)-Hinesol (2003)

The 21st century saw a renewed interest in the Spirovetivanes, with three approaches reported during the 2000-2006 period. The earliest, by Lu, was the first synthesis of optically active (-)-Hinesol, the natural enantiomer.[64]

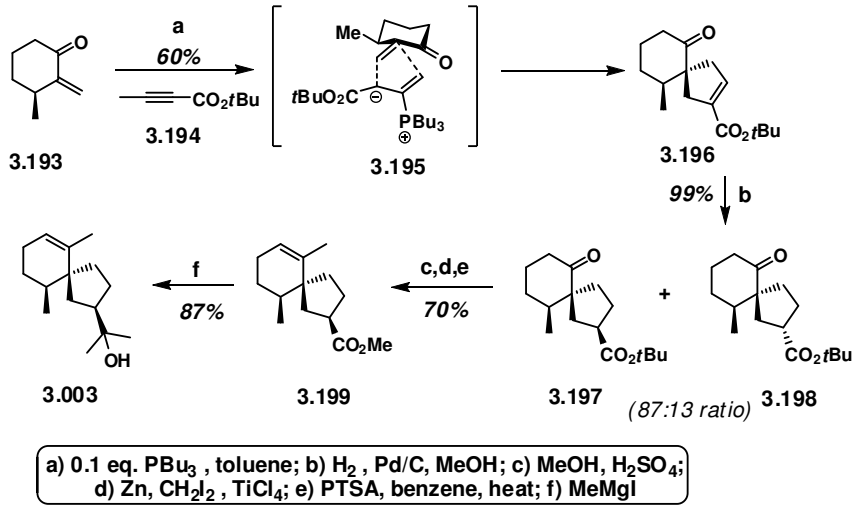
Lu's concise route began with the Baylis-Hillman reaction of cyclohexenone **3.163** and formaldehyde, followed by acetylation (Scheme 3.41). S_N2 displacement by enantiomerically pure pyrrolydine **3.191** provided allylic amine **3.192**, which served as the template for introduction of asymmetry (absolute stereocontrol). Conjugate addition of dimethylcuprate onto this enone proceeded with the concomitant elimination of the chiral auxiliary, generating enone **3.193** with an excellent transfer of chirality (95% ee).

[64] Du, Y.; Lu, X. *J. Org. Chem.* **2003**, *68*, 6463



Scheme 3.41

The pivotal step of this synthesis is shown in Scheme 3.42. Subjection of **3.193** to a PBu_3-catalysed coupling with propiolate **3.194** afforded spirocycle **3.195** in 60% yield and as a single diastereomer. In this interesting reaction, conjugate addition of the phosphine onto the propiolate generates a 1,3-dipole, which undergoes a regio- and stereoselective cycloaddition to the methylene group of **3.193**. Once again, the recurrent stereochemical control provided by the adjacent methyl substituent is responsible for the excellent diastereoselection observed (95 :5 ratio).



Scheme 3.42

Two steps in the elaboration of **3.196** to (-)-Hinesol **3.003** merit further comment (Scheme 3.42). First, the hydrogenation of the unsaturated *t*-butyl ester **3.196** in methanolic solution gave an 87 :13 mixture of epimers in favor of the desired compound **3.197**. Arguments similar to those employed in the discussion of the Dauben synthesis (Cf. Section 3.2.4) can be invoked to rationalise this observation. Finally, the authors chose a different endgame for the installation of the endocyclic double bond. Instead of the now familiar Grignard addition/dehydration sequence, Lu followed the precedent of Ramage *et al.* and prepared the *exo*-cyclic isomer through a Nozaki olefination, only to completely isomerise it to *endo*-**3.199** by exposure to PTSA in refluxing benzene.

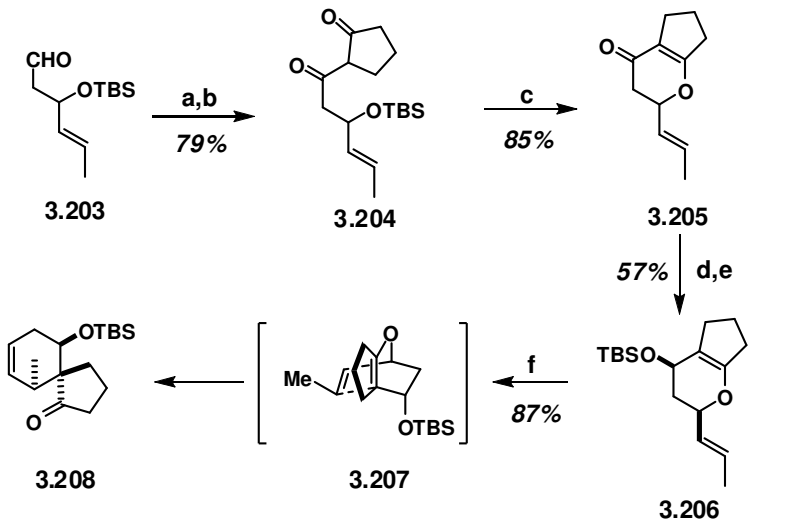
Lu's elegant synthesis provided (-)-Hinesol in 10 steps and 21% overall yield.

3.2.17. Susumu Kobayashi : (±)-Hinesol, (±)-β-Vetivone and (±)-α-Vetispirene (2006)

After we completed our own synthesis of the spirovetivanes (Cf. Section 3.4), Kobayashi and his group at Chiba (Japan) disclosed their original approach, based on the Claisen rearrangement of dihydropyrans.[65]

Treatment of aldehyde **3.203** with the enolate derived from cyclopentanone, followed by Swern oxidation, gave **3.204**. Acid-induced cyclisation afforded dihydropyrone **3.205** and subsequent reduction and protection provided dihydropyran **3.206** as a single diastereomeric product, preluding the crucial Claisen rearrangement.[66]

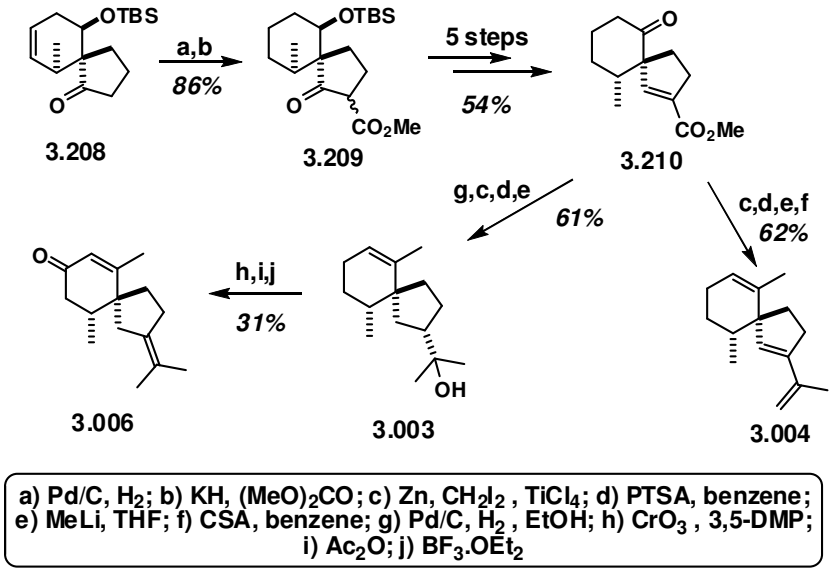
[65] Nakazaki, A.; Era, T.; Numada, Y.; Kobayashi, S. *Tetrahedron* **2006**, 6264. Interestingly, Kobayashi and co-workers used copies of our spectra to confirm their successful synthesis of α-Vetispirene.
[66] For previous studies, see: Nakazaki, A.; Miyamoto, H.; Henmi, K.; Kobayashi, S. *Synlett* **2005**, 1417



Scheme 3.43

Upon thermolysis of **3.206** in toluene (250ºC, sealed tube), a smooth Claisen rearrangement took place, producing spirocycle **3.208** in excellent yield and as a single diastereomer. To explain the observed stereoselectivity, the authors proposed the intermediacy of boat-shaped transition state **3.207**.

Progression of compound **3.208** to advanced intermediate **3.210** was achieved through a laborious route. Of relevance to the subsequent discussion is the fact that introduction of a carbomethoxy substituent was achieved without complications by treatment of the product of hydrogenation of **3.208**, with an excess of KH and dimethyl carbonate.



Scheme 3.44

The endgame in Kobayashi's pathway leading to α-Vetispirene **3.004** draws from previous syntheses (Cf. Section 3.4). The introduction of the endocyclic double bond was done analogously to Lu. As for the appendage of the isopropenyl side-chain, a procedure essentially similar to Yamada's was employed.

Similar considerations can be made concerning the route from **3.210** to Hinesol **3.003** and β-Vetivone **3.006**. As Lu had observed, hydrogenation of ester **3.210** provided an 87 :13 ratio of stereoisomers (not shown). The remainder of the synthesis is a reproduction of Lu's approach. It should be noted, however, that Kobayashi performed a selective allylic oxidation of Hinesol **3.003** into Hinesolone (not shown), which was then converted, *via* Marshall's previously reported procedure[41] (Cf. Section 3.2.1), into β-

Vetivone **3.006** in 31% overall yield. Therefore, Kobayashi's work provides a definitive synthetic link between Hinesol **3.003** and β-Vetivone **3.006**.

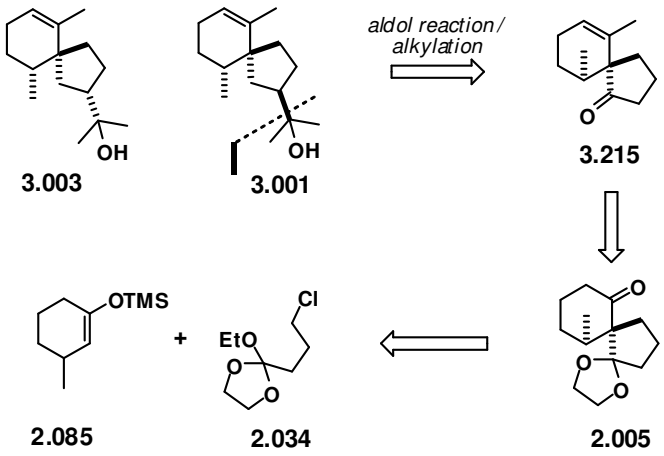
3.3. Conclusions

A large number of interesting syntheses ensued from more than 35 years of research on the spirovetivane sesquiterpenes. The preceding literature survey raises a number of important points. First of all, the majority of the syntheses presented suffer from lengthy sequences of pre- or post-key-step functionalisation. Second, the insertion of the isopropylol side-chain in the five-membered ring usually leads to a mixture of Agarospirol and Hinesol. The ratio between these epimers obviously depends on the strategy employed for the installment of this substituent. Third, a small number of the approaches presented are particularly short and efficient. Among them, the Büchi, Dauben, Paquette, Balme and Lu syntheses are rather concise. However, whilst the first two suffer from low yields in their key-transformations, Paquette's pivotal step employs rather harsh conditions. Lu's (and to a certain extent Balme's) approach probably represents, in our opinion, the highest level of refinement and efficiency from the syntheses discussed in this section.

The spirovetivanes are relatively small molecules, of low molecular weight (< 250 g/mol). In light of what has been presented, it might thus seem as if little new chemistry could still spurge from this field of research. It is our hope that the following section can prove this statement to be utterly premature.

3.4. Our strategy

Resting upon the results obtained by Dr. Jean-Christophe Vanherck during his Ph.D. (Cf. Chapters 1 and 2), and the literature precedent discussed above, our retrosynthetic analysis is presented in Scheme 3.45. It features a late-stage introduction of the isopropylol side chain to reveal ketone **3.215** as an advanced intermediate. This compound should be accessible by functional group manipulations, analogous to those presented before, on the spirannic ketodioxolane **2.005**. This intermediate could derive from the direct application of the methodology presented in Chapters 1 and 2 to β-substituted silylenol ethers such as **2.085**.



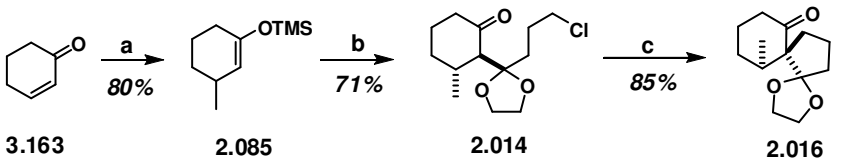
Scheme 3.45

3.5. Preliminary results

During his Ph.D., Jean-Christophe Vanherck made significant progress towards the concretisation of the aforementioned retrosynthetic analysis.[67] His results are described below.

3.5.1. Spiroannelation

The sequence started with the conjugate addition of dimethylcuprate onto cyclohexenone followed by *in situ* trapping of the resulting enolate by TMSCl, providing the β-substituted silylenol ether **2.085** (Scheme 3.46). Condensation of this compound with orthoester **2.034** proceeded uneventfully, affording a diastereomerically pure adduct, which was tentatively assigned as *trans*-**2.014**, in 71% yield.



a) MeMgBr, CuI, TMSCl, THF; b) $ZnCl_2$, 2.034, CH_2Cl_2 ; c) *t*-BuOK, THF/H_2O

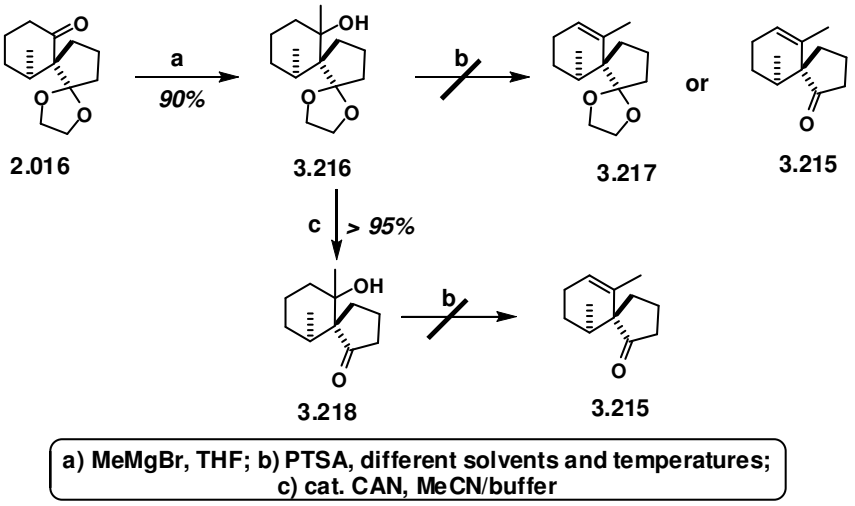
Scheme 3.46

[67] J.-C. Vanherck, *Etude et application synthétique d'une nouvelle méthode de spiroannélation*, Ph.D. Thesis, UCL, 2004

Spiroannelation of **2.014**, by treatment with *t*-BuOK in wet THF as previously described, smoothly delivered spirocycle **2.016** in 85% yield. Once again, a single diastereomer was obtained. The stereochemical outcome of this reaction has been discussed in depth previously (Cf. Chapter 2) and is in agreement with the numerous syntheses described in the preceding section of this chapter.

3.5.2. Installation of the alkene moiety

For the introduction of the endocyclic, trisubstituted double bond, a sequence involving the addition of an organometallic methyl-donor followed by dehydration of the ensuing tertiary alcohol seemed to be the most logical approach (Scheme 3.47). In the event, subjecting **2.016** to the action of MeMgBr smoothly provided alcohol **3.216** in excellent yield. However, upon treatment with catalytic amounts of PTSA in different solvents, complex mixtures of products were obtained that contained neither the desired alkene **3.215** nor its deprotected counterpart **3.217**.

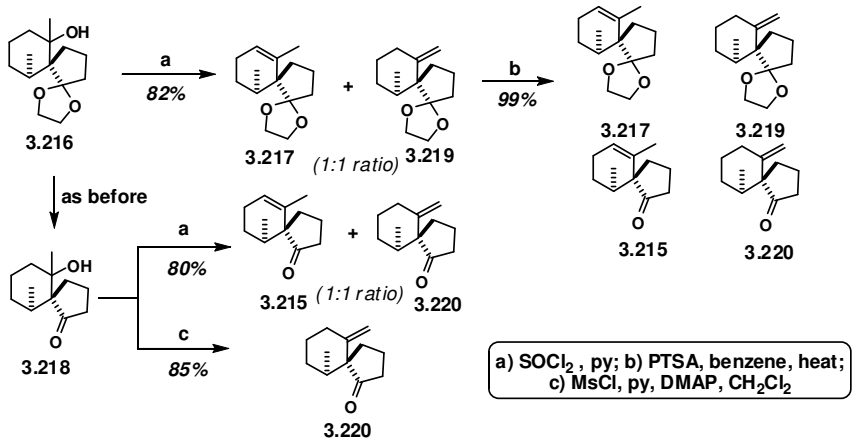


Scheme 3.47

Suspecting that the dioxolane substituent might exert a nefarious effect on the outcome of this dehydration reaction, its deprotection was envisaged. Employing a methodology previously developed in our laboratory, treatment of **3.216** with catalytic amounts of CAN, in buffered acetonitrile, cleanly afforded ketoalcohol **3.218** in high yields (Scheme 3.47). However, this alcohol also proved reluctant to undergo the desired elimination, leading once more to a mixture of decomposition products containing no trace of the coveted olefin **3.215**.

Attention was then turned to the use of base-mediated elimination protocols (Scheme 3.48). Treatment of protected alcohol **3.216** with thionyl chloride and pyridine delivered for the first time the requisite alkene **3.217**, accompanied by an equimolar amount of its exocyclic isomer **3.219**. All efforts towards the isomerisation this inseparable mixture by exposure to catalytic quantities of PTSA in refluxing benzene failed : not only the ratio

of olefin isomers **3.217** and **3.219** remained unchanged, but the mixture was now contaminated with some of the keto-olefins **3.215** and **3.220**.



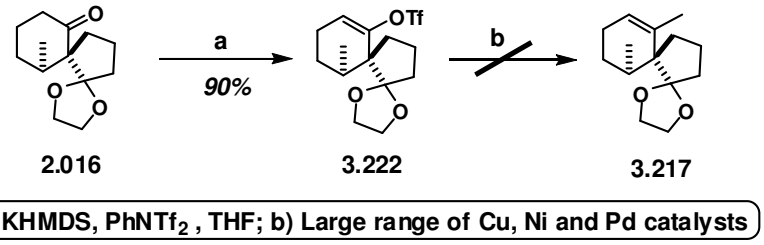
Scheme 3.48

Subjection of the deprotected keto-alcohol **3.218** to the thionyl chloride protocol resulted in similar observations. Moreover, when mesyl chloride and pyridine were used as dehydration agents, only the exocyclic alkene **3.220** was obtained.

These unanticipated, repeated failures in introducing the endocyclic alkene moiety through a dehydration approach contrived a change in strategy. Among possible tactics, the transition metal-catalysed C-C coupling between an enol triflate **3.222** and an organometallic methyl donor emerged as an attractive possibility.

Transformation of the spirocyclic ketone **2.016** into enol triflate **3.222** proceeded without significant problems (Scheme 3.49). Alas, screening of a large variety of copper, nickel and palladium catalysts, under a range of

conditions, for the coupling of **3.222** resulted, at best, in capricious and irreproducible reactions.

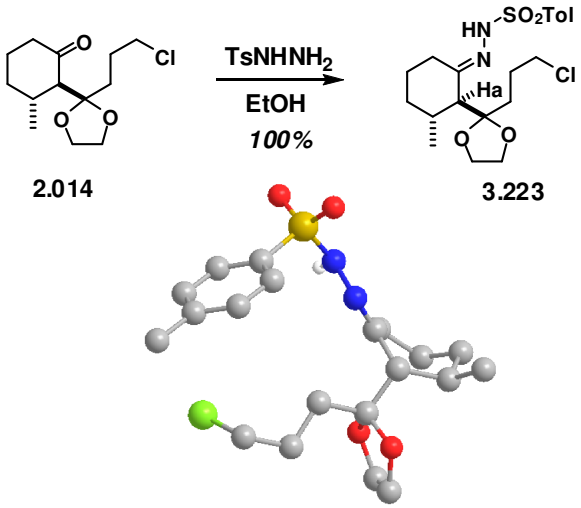


Scheme 3.49

3.6 Results and discussion

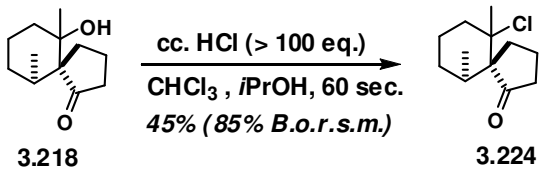
3.6.1. Initial results

We began our work by reproducing the most relevant results described previously by J.-C. Vanherck. The stereochemistry of the condensation adduct **2.014** was unequivocally established through single-crystal X-ray analysis of its tosylhydrazone derivative **3.223** (Scheme 3.50). Though this might seem an academic issue, since the relative configuration is destroyed upon the subsequent enolate formation, it is interesting to note that the sofa-like conformation adopted by **3.223** (and **2.014**) leads to particularly small values of the coupling constant *J* for the proton H_a which might results in erroneous stereochemical assignments. Indeed, this hydrogen resonates as a doublet with *J* = 2.8 Hz.



Scheme 3.50

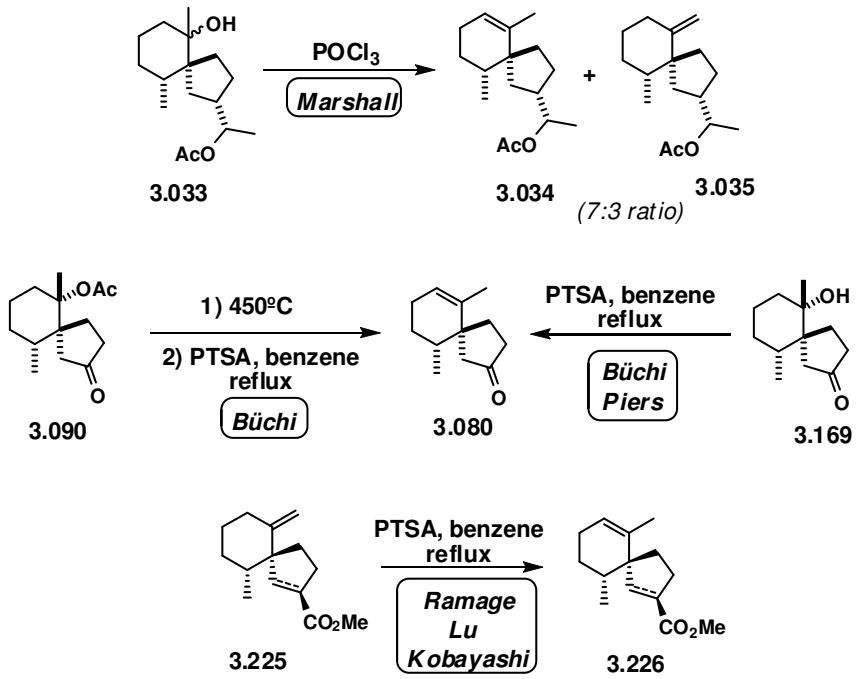
We were not more fortunate than Dr. Vanherck in attempting to selectively dehydrate tertiary alcohol **3.218**, despite numerous attempts under diverse conditions. During such assays (Scheme 3.51), admixing deprotected **3.218** with an overwhelming excess of HCl for a very short time did yield a new product in 45% yield (47% starting material recovered). This compound was rapidly proved to be the tertiary chloride **3.224**, presumably the result of S_N1 displacement of alcohol **3.218**.



Scheme 3.51

3.6.2. Interpretation of phenomena

With a wealth of efforts frustrated at a seemingly forthright transformation, a deeper understanding of the phenomena observed was in demand. Comparison of our results with the ample literature precedent was puzzling, to say the least. To our knowledge, virtually all the syntheses previously, reported either generated a spirocyclic skeleton already bearing the requisite olefin functionality, or introduced it through the elimination of a tertiary alcohol followed by an acid-promoted isomerisation.



Scheme 3.52

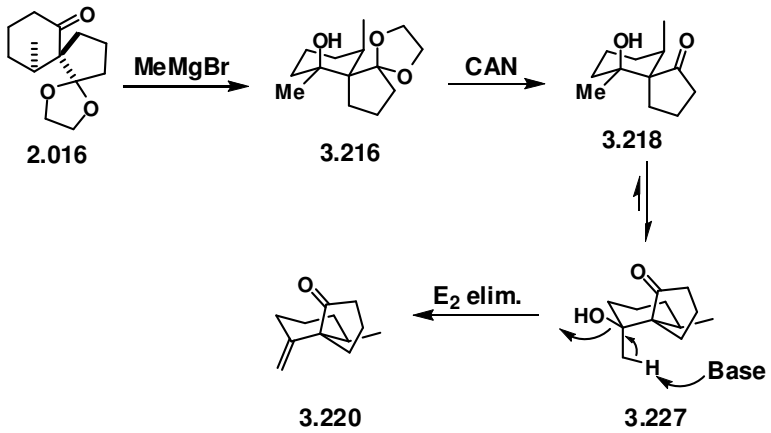
Indeed, as compiled in Scheme 3.52, Büchi, Piers and Magnus (not shown) reported the easy dehydration to « the more stable » endocyclic olefins **3.080**, with isomerisation occuring upon treatment with PTSA in benzene. Ramage, Lu and Kobayashi even went further, as they deliberately prepared the exocyclic alkenes **3.225** and then isomerised them to the « more stable » *endo*-counterparts **3.226** under the aforementioned conditions. Marshall's early and isolated case of poor selectivity seems to be the closest to our own results.

Careful analysis of the data shows that all reports concerned the *acidic* elimination of tertiary alcohols or acetates. Furthermore, we noted that the single disparity, in our system, appears to be the location of functionality in the five-membered ring. Our substrates are unique in that they possess a substituent at the carbon-α (instead of -β) to the spirocenter. The following questions thus arose:

a) Why would base-mediated elimination provide preferentially the exocyclic alkene isomer ?
b) Could the relative thermodynamic stability of the *exo* and *endo* isomers be a function of the substitution in the cyclopentane ring ? and/or
c) Are the α-located, oxygenated substituents in the five-membered cycle diverting the putative cationic intermediates from the desired elimination pathways ?

Question a) can be clarified if one considers the relative stereochemistry of alcohols **3.216** and **3.218** (Scheme 3.53). Our results,

particularly on the synthesis of potential GHB-antagonists (Cf. Chapter 4), as well as Dr. Vanherck's observations strongly suggest that MeMgX addition occurs from the face opposite to the dioxolane substituent, hence yielding compound **3.216**. After deprotection, it is likely that the most favorable chair conformer in solution is **3.227**, placing the hydroxy substituent in an equatorial position.



Scheme 3.53

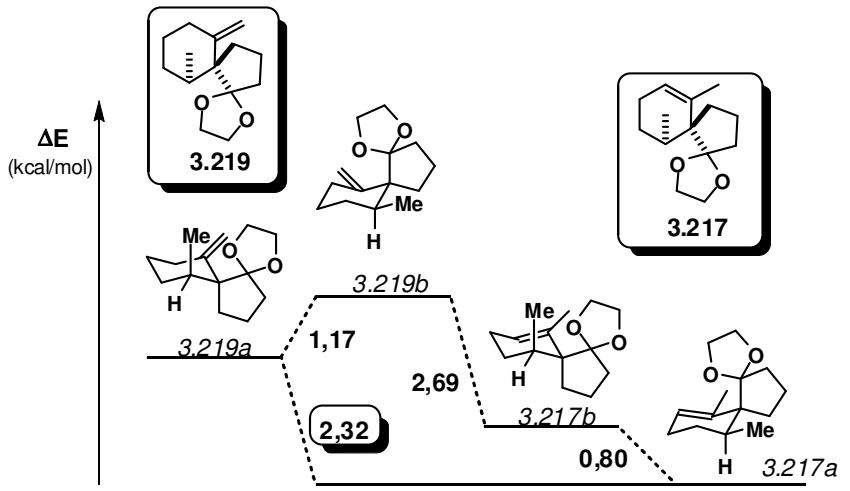
As mentioned above, the mesylate elimination provides only the undesired, exocyclic double bond isomer. Since concerted E_2 elimination requires antiperiplanar alignment of both the leaving group and the abstracted hydrogen, the latter conformation might favor the formation of the *exo* double-bond isomer **3.220**.

Questions b) and c) were seemingly beyond our experimental reach and were best illuminated through recourse to DFT calculations. Once again

(Cf. Chapter 2), this work was done in collaboration with Dr. Luís F. Veiros of the Instituto Superior Técnico, in Lisbon (Portugal).

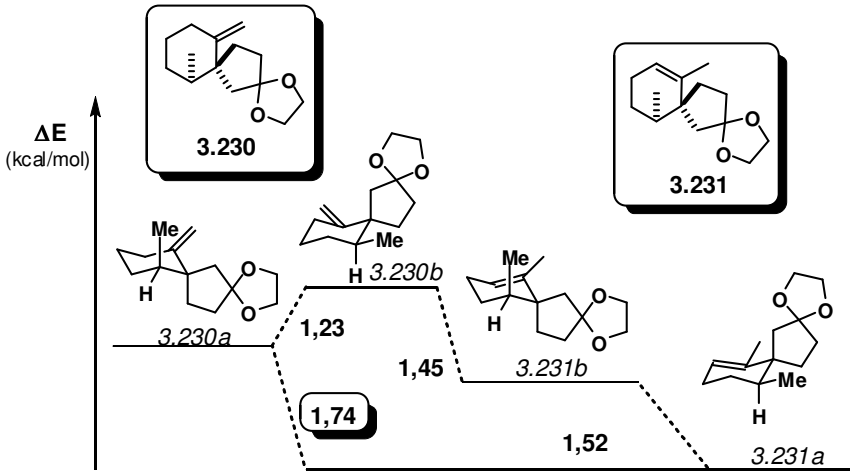
The first step was the optimisation of the geometries of all « our » possible keto- and dioxolanyl-substituted olefin isomers. Subsequently, the relative energies of these compounds were calculated in order to access their relative stability. For the sake of comparison, analogs bearing the keto- and dioxolanyl substituent one carbon atom farther from the spirannic center were also considered. In each case, both chair conformers were analysed, amounting to a total of 16 species studied.

Beginning with α-dioxolanyl compounds (Scheme 3.54), the *endo*-cyclic isomers **3.217a/b** are predicted to be the most stable ones regardless of the conformation of the five-membered ring. The energy difference between the most stable conformers of each pair (encircled value in the Scheme) is higher than 2 kcal/mol.



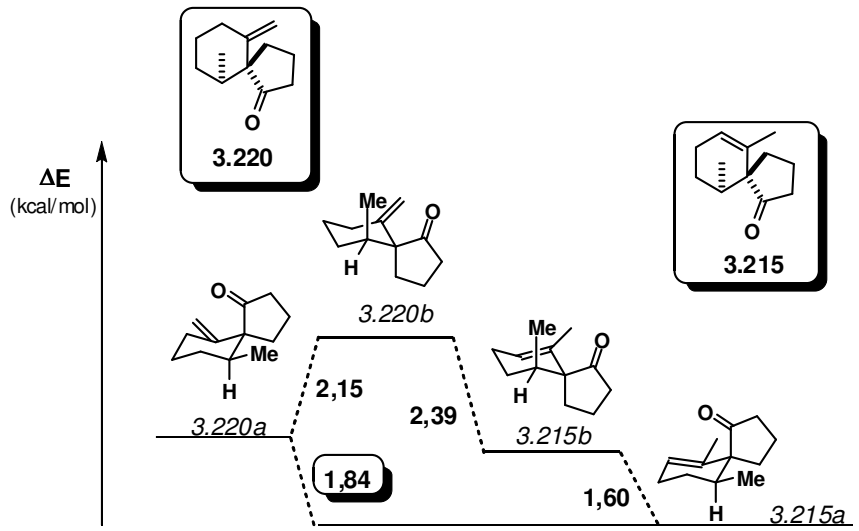
Scheme 3.54

A nearly superimposable trend is observed when the analog olefin isomers **3.230** and **3.231**, bearing a dioxolane at the β-position relative to the spirannic center, are considered (Scheme 3.55).



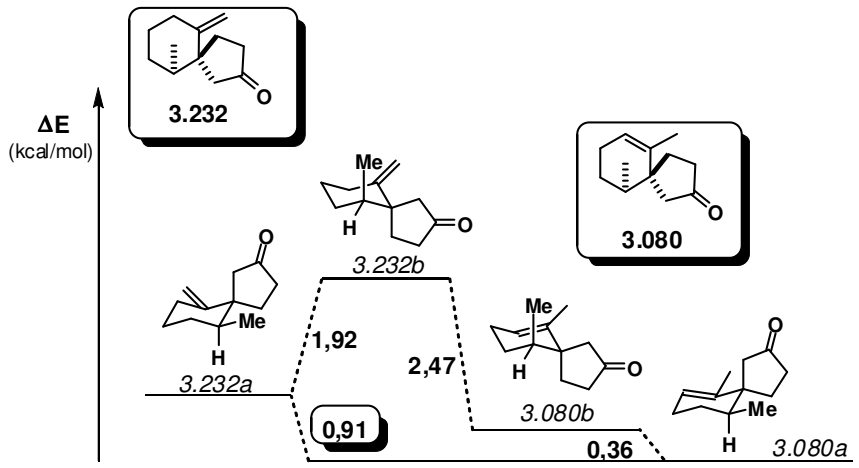
Scheme 3.55

Similar observations ensued when examining the deprotected compounds, with the logical change in relative stability of the conformers : in each pair, the conformers that place the ketone carbonyl in an axial position are now more stable than their equatorial counterparts (Scheme 3.56).



Scheme 3.56

In the case of the β-keto analogues (Scheme 3.57), the calculations are supported by the observations of Buchi, Piers and others on the ease of isomerisation of the *exo*- olefin **3.232** to its *endo*- isomer **3.080**, though the energy difference is smaller than in the previous cases (nearly 1 kcal/mol).

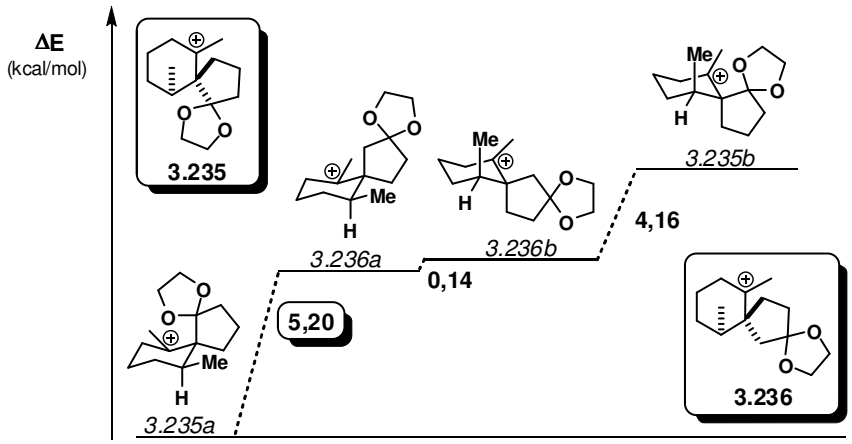


Scheme 3.57

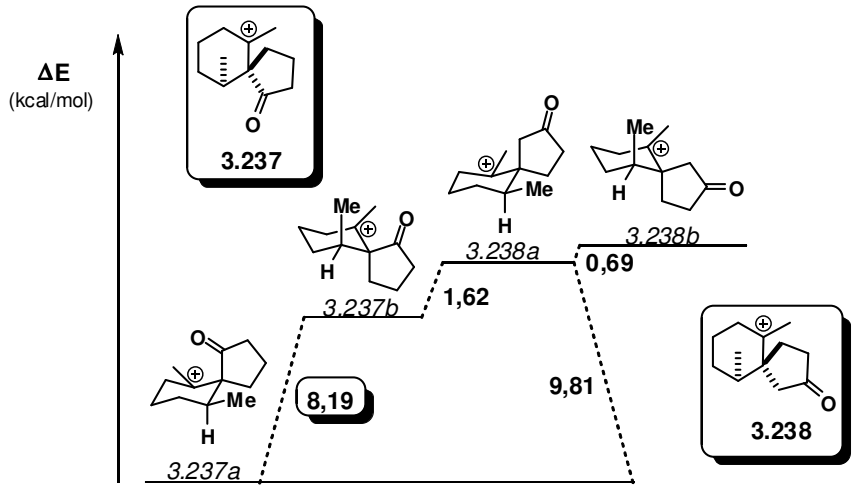
It is clear from these results that intrinsic thermodynamic stability *per se* is not the reason for our repeated failure in obtaining the coveted endocyclic double bond isomer through an elimination process. These preliminary calculations, if anything, lend further credence to the accepted tenet of higher stability of the *endo* isomer. Further data was therefore required to accomodate our results at this stage.

Examination of the putative carbocationic intermediates led to more intriguing observations (Scheme 3.58 and Scheme 3.59). The study was conducted in analogous fashion to that done previously ; tertiary carbocations bearing keto- and dioxolanyl-substituents in both the α- and β-positions relative to the spirocyclic carbon atom were considered and their structures optimised.

In these cases, significant energy differences were detected (up to 9 kcal/mol) between « our » cations **3.235/3.237** and the model compounds **3.236/3.238**. Indeed, all the carbocations that are decorated with oxygenated functionality α- to the carbon atom are much more stable than their analogs. Furthermore, stabilisation by the α-located substituents is higher when they adopt an axial (such as **3.235a** and **3.237a**), rather than equatorial, orientation. This observation suggests that transfer of electron density from the oxygen atoms to the cationic centre might be taking place.

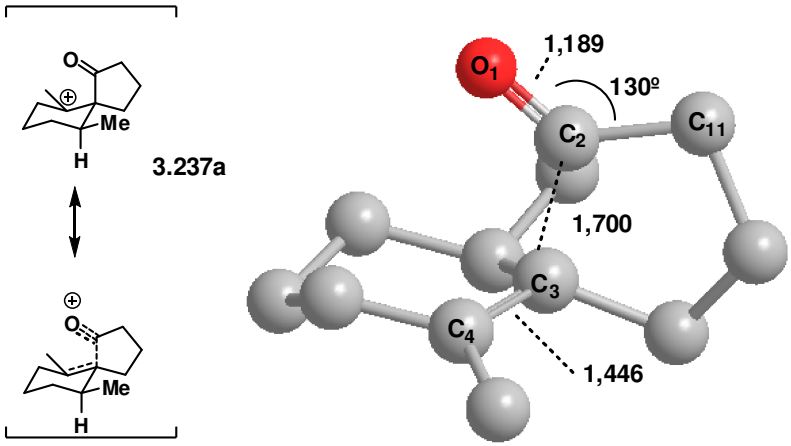


Scheme 3.58

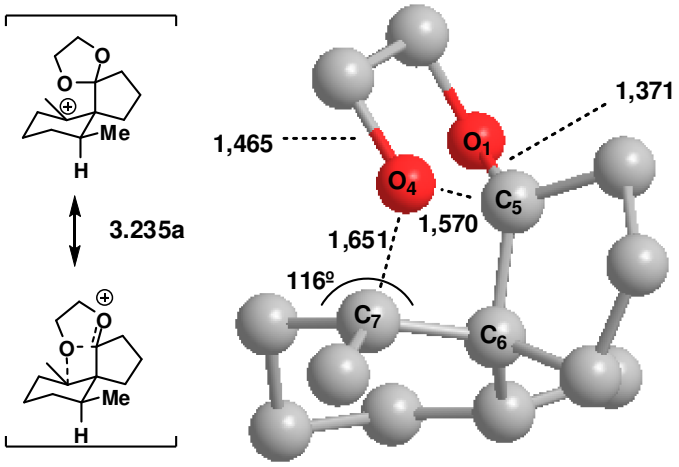


Scheme 3.59

To verify this assumption, the optimised structures of these compounds were analysed (Scheme 3.60 and Scheme 3.61).



Scheme 3.60



Scheme 3.61

NB : All bond distance values are in Å.

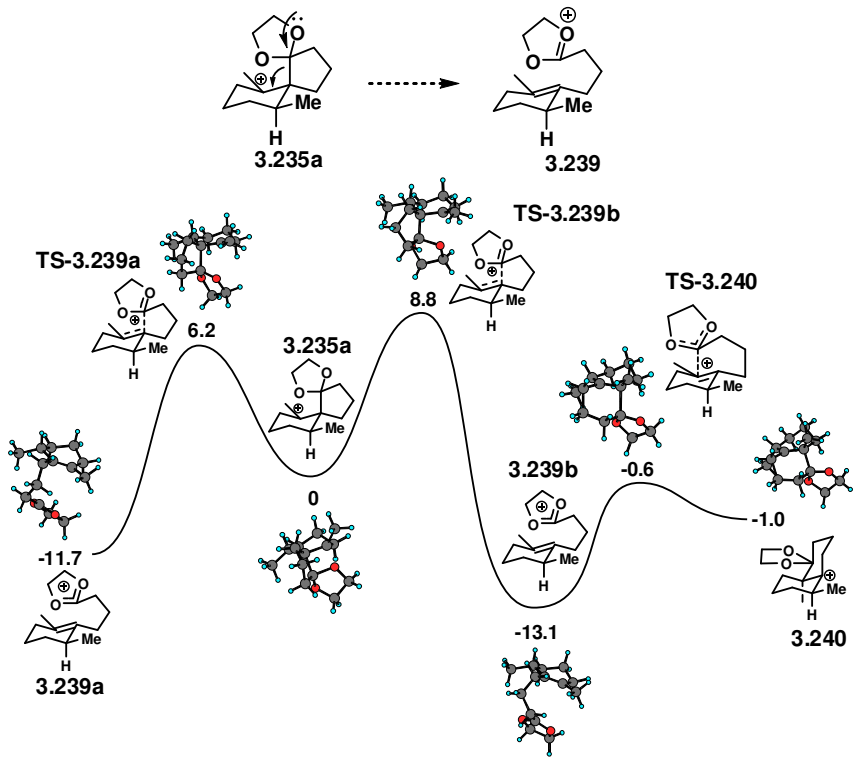
Examination of the optimised structures of **3.235a** and **3.237a** reveals that they correspond in fact to « extreme » resonance structures wherein the positive charge is effectively transfered to oxygen. In Scheme 3.60 there is a considerable elongation of the C_2-C_3 bond in **3.237a**, as confirmed by the high value of 1,700 Å (as opposed to the average 1,5Å). On the other hand, the C_2-O_1 bond is shortened to below 1,2Å and the C_{11}-C_2-O_1 angle shows deviation from sp^2 character as it increased to 130º. In accordance with these facts, the C_3-C_4 bond is of an order higher than 1 and shortened to 1,45Å. This corresponds to the canonic structure drawn, where a development of acylium character occurs on the C=O carbonyl whereas the carbocation is closer to an alkene with partial disruption of the C_2-C_3 bond.

Analogous results can be drawn from consideration of the dioxolanyl-substitued cation **3.235a** (Scheme 3.61). Examination of this structure now shows a considerably short contact distance between O_4 and C_7, indicating a

different kind of stabilisation which not possible in the keto-substituted carbocation (*vide supra*). The calculated distance of 1,65Å strongly suggests partial bonding between these two atoms, and this results in angle shortening to 116°. The electronic donation of the dioxolane oxygen concurs, on the other hand, to a lengthening of the O_4-C_5 bond and considerable shortening of the O_1-C_5 bond (below 1,38Å), leading to a greater double bond character. In this case, back donation from the remote dioxolanyl oxygen « liberates » its neighbour to stabilise cationic character through direct bonding.

Both structures discussed are, to the best of our knowledge, unknown in the context of spirocycles and we believe that they correspond to « non-classical » carbocations in that the positive charge is delocalised through bond-formation and/or rupture.

During this study, an unexpected fragmentation was unveiled, that would confirm our assumptions on the unusual stability of the carbocations discussed above (Scheme 3.62). In this reaction, a dioxolane-assisted ring-cleavage of the five-membered cycle converts the carbon-centered cation in **3.235a** to a highy-stabilised oxonium intermediate **3.239**. The complete reaction profile was determined for this example.



Scheme 3.62

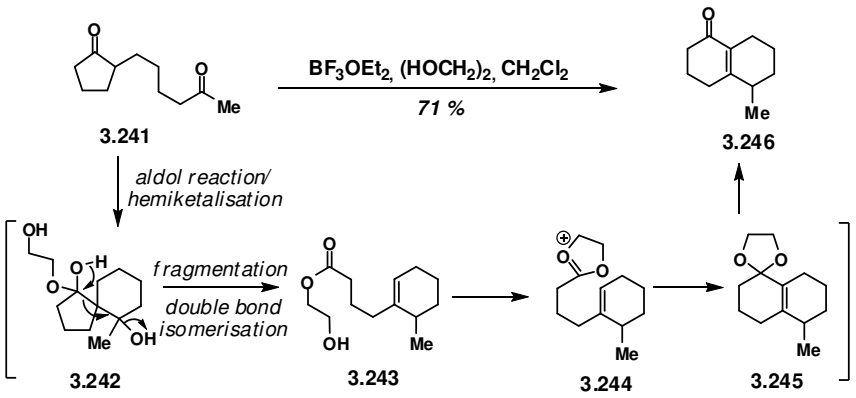
NB : All energy values are in kcal/mol.

Two different transition states **TS-3.239a/TS-3.239b**, separated by less than 3 kcal/mol, were found, leading to two conformers of the oxonium cation **3.239**, which are also of similar energy. Each of these fragmented products corresponds to an energy minimum and render this type of ring-opening a very likely pathway. In one of these conformers (**3.239b**), the side-chain bearing the oxonium is in a geometrically favorable position to suffer addition from the cyclohexene double bond. This leads to a new, decalin-like cation **3.240**. It should be noted, however, that the activation

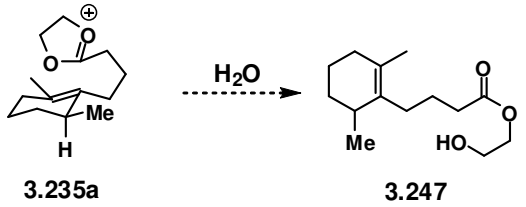
barrier for this process is approximately of 13 kcal/mol. Furthermore, the product of this intramolecular π-cation cyclisation **3.240** is much less stable than its ring-opened precursor **3.239b**. These facts clearly suggest that, though the fragmentation process to **3.239a/b** is a very likely one, these ring-opened cation might have an extended lifetime and only reluctantly undergo cyclisation.

Almost simultaneously, we found a literature precedent related to such a reaction through examination of work by Sakai.[68] In this case (Scheme 3.63), a similar dioxolanyl cation **3.244** is invoked in the conversion of **3.241** to **3.246**. Under the reaction conditions, these intermediates do react by intramolecular π-cation cyclisation affording **3.245**. In our case, such a process probably requires a higher activation energy (Cf. Scheme 3.63), since it would lead to the formation of a crowded quaternary center. Moreover, our elimination attempts were not run under anhydrous conditions. Therefore, interception of the oxonium **3.235a** by water might occur rapidly, leading to the (2-hydroxyethyl)ester **3.247** (Scheme 3.64).

[68] Miyao, Y. ; Tanaka, M. ; Suemune, H. ; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1535



Scheme 3.63

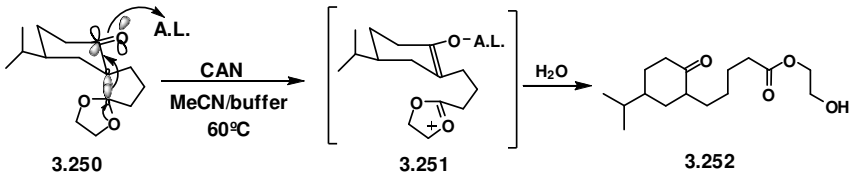


Scheme 3.64

Other results, some of which were obtained by Dr.Vanherck during his Ph.D., hint at the unusual stability of dioxolanyl- and keto-substituted cations and at their propensity to undergo ring cleavage.

Indeed (Scheme 3.65), during his synthetic studies on Erythrodiene and Spirojatamol (Cf. Chapter 4), J.-C. Vanherck observed that, upon exposure of **3.250** to our laboratory's CAN-catalysed deprotection protocol, small amounts (<20%) of ring-opened product **3.252** were formed. In consonance with the preceding discussion, only the diastereomer shown underwent fragmentation ; its epimer bearing the dioxolanyl substituent in

equatorial position (not shown) afforded only the deprotection product. More interestingly, the formation of this by-product could be easily suppressed by performing the deprotection reaction at room temperature instead of 60ºC. This observation now has a double meaning in that it correlates this kind of fragmentation with more forcing conditions, *i.e.* higher temperatures.



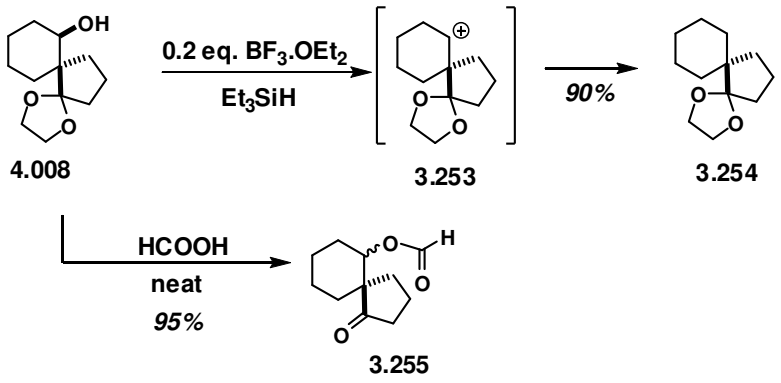
Scheme 3.65

Preliminary experiments aimed at probing the stability of a dioxolanyl-substituted cation were next performed (Scheme 3.66). Alcohol **4.008**, which we have used during our studies towards the synthesis of GHB-analogues (Chapter 4), was chosen as a model substrate. In the event, **4.008** was treated with substoichiometric amounts of $BF_3.OEt_2$ and excess Et_3SiH, from 0ºC to room temperature.

To our surprise, the fully reduced spirocycle **3.254** was produced as the exclusive product of this reaction. In itself, it constitutes a particularly rare example of the direct reduction of a secondary aliphatic alcohol, a process not only difficult but hitherto known to be efficient only in the presence of the very strong Lewis acid $B(C_6F_5)_3$.[69] Similarly, the solvolysis of compound **4.008** in neat formic acid produced the deprotected formate

[69] Gevorgyan, V.; Rubin, M.; Benson, S.; Liu, J.-X.; Yamamoto, Y. *J. Org. Chem.* **2000**, *65*, 6179

esters **3.255** in quantitative yield.[70] Once again, there is little precedent for the direct, uncatalysed formylation of a secondary alcohol in the presence of formic acid alone.



Scheme 3.66

At the end of the day, all the experiments reported served a double purpose :

a) Provide evidence supporting the formation of a highly stabilised carbocation upon ionisation of alcohols such as **4.008** ; this is the most plausible explanation for the outcome of both the reduction and the formylation reactions ;

b) Correlate the fragmentation process with an increase in temperature, suggesting that the putative carbocations can be resistant to fragmentation at room temperature.

[70] We believe that deprotection occured (unsurprisingly) as a consequence of the liberation of 1 equivalent of water in the formic acid medium.

These results did not only fulfill our expectations, but it also should be noted that this unexpected rearrangement could, if properly utilised, be an interesting synthetic tool. Perspectives for its exploitation will be outlined in the final chapter of this Thesis.

3.6.3. A solution for functionalisation of the six-membered ring

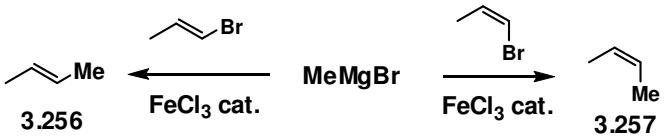
Though a slightly clearer picture of some of the causes for our ailments in installing the endocyclic double bond started to emerge, we were still left with little foreseeable solutions. We did, however, recognise that an organometallic coupling approach might be a powerful « last resort » lifeline.

Lately, iron(III)-catalysed coupling processes are receiving a considerable amount of attention.[71] The use of iron as a non-toxic and cheap metal in C-C bond-forming reactions was first hinted at by Kochi in 1971,[72] but failed to receive further attention as it was overshadowed by the rise of palladium- and nickel-catalysts as superior systems for such transformations. Kochi noticed that alkenyl halides underwent *stereospecific* cross-coupling with alkyl and aryl Grignard reagents, in the presence of catalytic amounts of FeX_3, with retention of the configuration of the substrate (Scheme 3.67).

[71] Recent reviews: a) Shinokubo, H; Oshima, K. *Eur. J. Org. Chem.* **2004**, 2081; b) Bolm, C; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217; (c) Furstner, A.; Martín, R. *Chem.Lett.* **2005**, 624

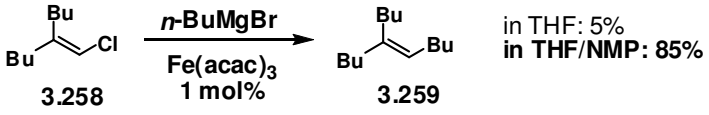
[72] a) Tamura, M.; Kochi, J.K. *J. Am. Chem. Soc.* **1971**, *93*, 1487; b) Neumann, S.M.; Kochi, J. K. *J. Org. Chem.* **1975**, *40*, 599

However, the fact that the alkenyl halide had to be employed in excess constituted a significant drawback in preparative terms.



Scheme 3.67

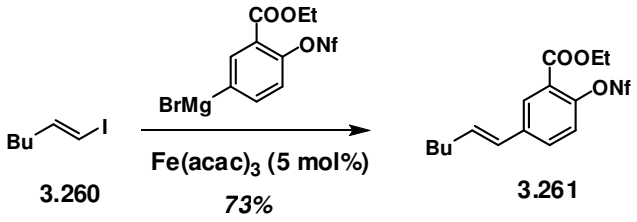
This limitation was overcome by Cahiez *et al.* who showed the beneficial effect of NMP as a cosolvent in such transformations (Scheme 3.68).[73] Under these conditions, the reactions of alkenyl halides (1 equiv., X = I, Br, Cl) proceeded stereo- and chemoselectively even if reactive functional groups, such as amides, esters, ketones, and alkyl chlorides were present in the substrates.



Scheme 3.68

Further flexibility was gained with the advent of functionalized Grignard reagents. A striking example is shown in Scheme 3.69,[74] in which the alkenyl iodide **3.260** reacts in high yield with a Grignard reagent bearing an aryl nonaflate (Nf) moiety that remains intact.

[73] Cahiez, G; Marquais, S. *Pure Appl.Chem.* **1996**, *68*, 53
[74] Dohle,W.; Kopp, F.; Cahiez, G.; Knochel, P. *Synthesis* **2001**, 1901



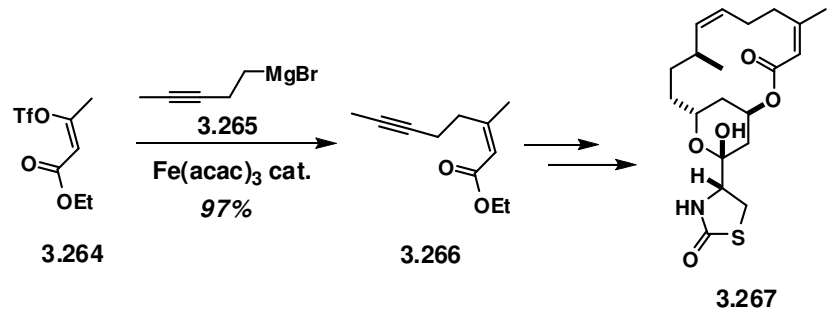
Scheme 3.69

Alkenyl sulfones and -phosphates were also found to be suitable substrates, although formal reduction of the C–X bond occasionally accompanies productive cross coupling.

Furstner and co-workers did a number of mechanistic studies and contributed to the general acceptance of this method within the synthetic community.[75] The Furstner group provided several elegant examples of the use of this reaction in synthesis, though the electrophiles used were apparently limited to aryl- and activated vinyl triflates. For example, in an early manoeuver aimed at the total synthesis of Latrunculin B **3.267**, activated triflate **3.264** coupled smoothly with Grignard reagent **3.265** to form one of the key-fragments of the natural product.[76]

[75] (a) Furstner, A.; Leitner, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 609; (b) Furstner, A.; Leitner, A.; Mendez, M.; Krause, H. *J. Am. Chem.Soc.* **2002**, *124*, 13856

[76] Furstner, A.; De Souza, D.; Parra-Rapado, L.; Jensen, J. *Angew. Chem. Int. Ed.* **2003**, *42*, 5358



Scheme 3.70

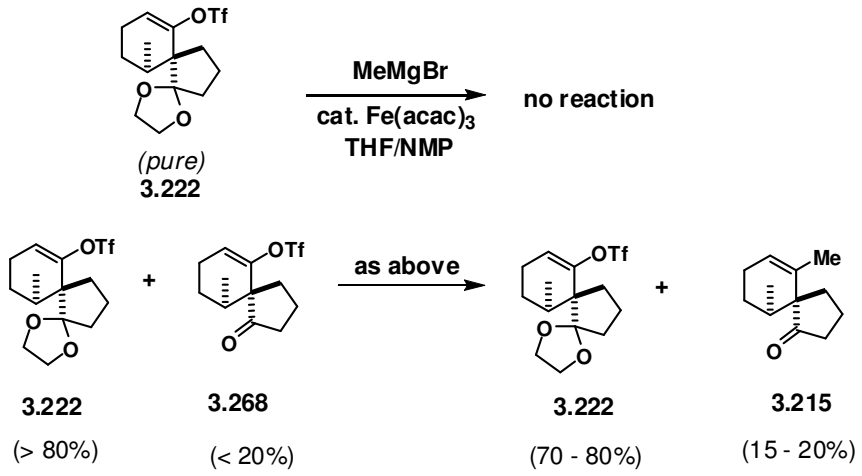
When we began our study (December 2003), there were no reports on the iron-catalysed coupling of *unactivated* alkenyl triflates with Grignard reagents.[77] It was therefore with trepidation that we attempted such a procedure on our substrate **3.222**. Alas, Cahiez's optimised conditions (1-5 mol% $Fe(acac)_3$, MeMgBr, THF/NMP) returned only the starting material (Scheme 3.71).

An unexpected, serendipitous solution to this problem was discovered when an $Fe(acac)_3$-catalysed reaction was performed on an aged sample of **3.222** contaminated by small amounts of ketone **3.268** (Scheme 3.71).[78] Whilst **3.222** was recovered quantitatively, **3.268** reacted smoothly and chemoselectively under these conditions, affording in excellent yield the long-sought after adduct **3215**. These compounds could be easily

[77] Incidentally, such a (detailed) report would appear a few months after we completed our synthesis. See : (a) Seidel, G.; Laurich, D.; Furstner, A. *J. Org. Chem.* **2004**, *69*, 3950.

[78] The deprotected triflate **3.268** was presumably formed due to the presence of traces of TfOH, from the triflation reaction, in compound **3.222**.

distinguished by analysis of the crude H^1-NMR spectrum,[79] and they were readily separated by chromatography on silica gel.



Scheme 3.71

This serendipitous observation prompted us to study the coupling reaction in closer detail and the conditions were optimised as shown in Table 3.1. Pure deprotected triflate **3.268** was initially obtained by purification of our aged sample.

From this study, several interesting conclusions can be drawn. First of all, it appears that the steric hindrance provided by the dioxolane substituent precludes any access to the vinyl triflate by the iron reagent (entries 5 and 6). On the other hand, the reaction appears to have an "optimal" loading of iron

[79] The vinylic proton of triflate **3.222/3.268** resonates as a well-resolved triplet, while its coupled counterpart **3.215** displays a broad singlet in the H^1 NMR-spectrum.

catalyst; higher amounts than 20 mol% inhibit the reaction while lower catalyst loadings prove unable to effect the desired conversion (entries 1 to 3). In every case, the procedure is extremely clean and the only two products detected are the starting triflate and/or the trisubstituted alkene.

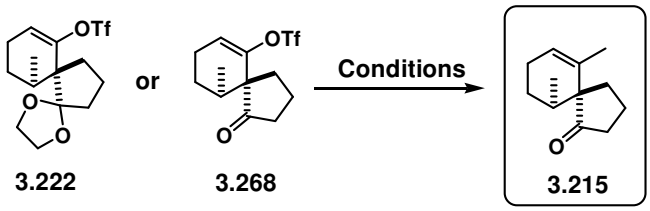


Table 3.1

Entry	Reactant	mol% $Fe(acac)_3$,temperature	Result
1	**3.268**	50%, -42ºC to rt	**3.215** (60%), **3.268** (40%)
2	**3.268**	100%, -42ºC to rt	**3.268**
3	**3.268**	10%, -42ºC to rt	**3.268**
4	**3.268**	20%, -15ºC to 0ºC*	**3.215** (96%)
5	**3.222**	20%, -15ºC to rt	**3.222**
6	**3.222**	50%, -15ºC to rt	**3.222**

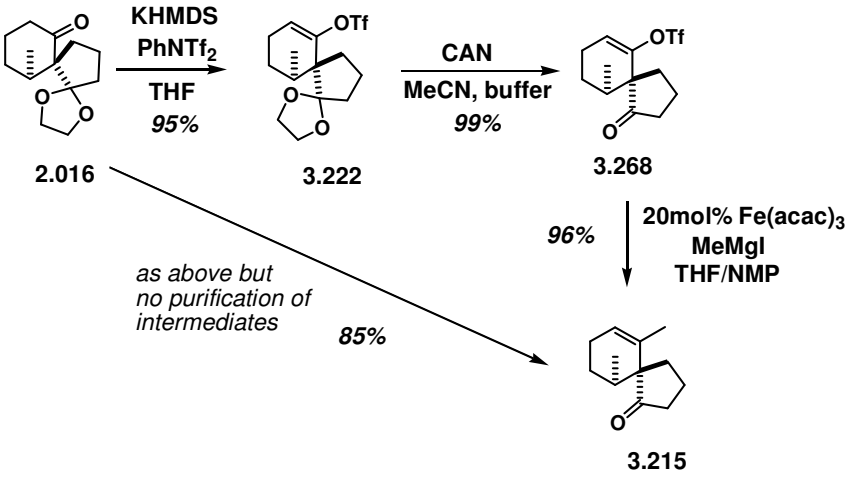
(a) All reactions were performed in THF/NMP with 3 equivalents of methylmagnesium iodide.

* - The reaction is complete within 20 minutes between –15ºC and 0ºC.

The successful implementation of our strategy obviously depended upon delineating a suitable protocol that would selectively unmask the ketone function in **3.222** without hydrolysing the sensitive enol triflate functionality. In the event (Scheme 3.72), treatment of ketal **3.222** under our laboratory's CAN-catalysed deprotection conditions (3% CAN in buffered

acetonitrile, 1 hour, 60ºC), smoothly and quantitavely unveiled the carbonyl function, affording **3.268** in >99% yield.[80] It is noteworthy that the acid-labile triflate moiety is untouched under these conditions. This deprotection step can also be effected at room temperature, but is much slower (after 24 hours, the conversion is only ca. 50%).[81]

Triflate **3.268** was then subjected to the $Fe(acac)_3$-catalysed coupling as described above leading to the endocyclic alkene **3.215** in excellent yield.



Scheme 3.72

The fact that the free ketone carbonyl in **3.268** survives, whilst an excess of MeMgI is employed, is noteworthy. Although it may be speculated that steric hindrance shields the carbonyl functionality from attack by

[80] (a) Markó, I.E.; Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Vanherck, J.-C. *Angew. Chem. Int. Ed.* **1999**, *38*, 3207; (b) Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Vanherck, J.-C.; Markó, I.E. *Tetrahedron* **2003**, *59*, 8989

[81] For a thorough discussion of this step and its generalisation as a useful methodology, cf. Section 3.7.

nucleophiles, we have successfully added a number of Grignard reagents (including MeMgX) to similar α-spirannic ketones, under mild conditions (Cf. Chapter 4). Fürstner suggests that exposure of Fe(III) salts to MeMgBr leads to the formation of « iron-ate » complexes $[Me_4Fe](MgBr)_2$.[71,75] These ate-complexes of Fe(II) are then responsible for the methyl-transfer. However, they will apparently only do so to highly activated electrophiles, such as enol triflates. It is therefore reasonable to assume that the formation of such complexes might be much faster than the uncatalysed attack onto the hindered ketone carbonyl, and that the cross-coupling reaction then becomes the only available pathway.

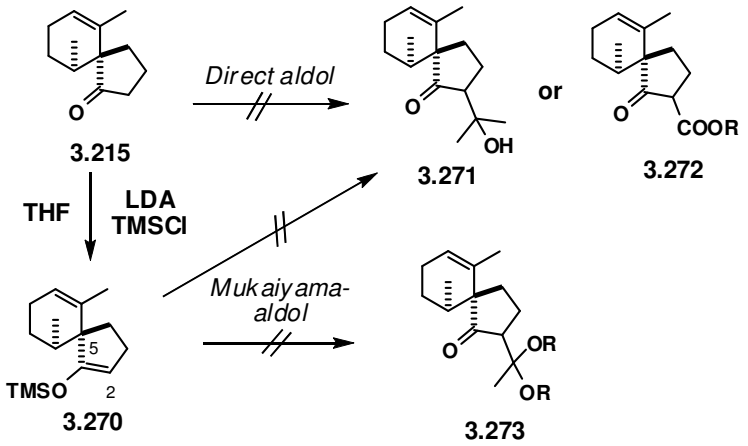
We can also speculate on the possibility that the preceding metal-catalysed C-C coupling reactions using Cu, Ni or Pd were in fact thwarted by the steric hindrance provided by the dioxolane substituent. Subsequent observations during our studies on the histrionicotoxin alkaloids shed more light on this issue (Cf. Chapter 4).

We should note that the entire sequence depicted in Scheme 3.72 (enol triflate synthesis, ketal removal and Fe(III)-catalysed coupling) can be realised successively without chromatographic purification of the intermediates **3.222** and **3.268**. Moreover, it can be easily performed on multigram scale and the overall yields average 85%. It is therefore gratifying that, despite all our setbacks, an efficient procedure to convert ketone **2.016** into olefin **3.215** in 3 steps has been developed. It is also noteworthy that, to the best of our knowledge, this is the first instance in which, during a total synthesis of a spirovetivane sesquiterpene, the characteristic endocyclic, trisubstitued double-bond is installed through a catalytic organometallic reaction.

3.6.4. Final functionalisation and completion of the synthesis

Having successfully secured large quantities of ketone **3.215**, attention was then focused upon the elaboration of the five-membered ring and the introduction of the requisite appendages. In contrast to Kobayashi's work,[65] initial attempts at directly installing the isopropylol side-chain, present in the natural products, by aldol reaction between the anion derived from ketone **3.215** and acetone, chloroformate or cyanoformate[82] esters met with failure. Subsequent efforts employing Lewis acid-mediated condensations of the silyl enolether derivative **3.270** with either an aldehyde, 2,2-dimethoxypropane or an orthoacetate derivative resulted also in recovered starting material **3.215** (Scheme 3.73).[67]

[82] Mander, L.N.; Sethi, P.S. *Tetrahedron Lett.* **1983**, 5245

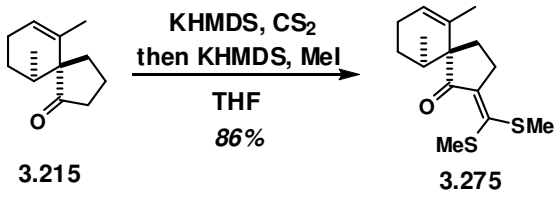


Scheme 3.73

Molecular modeling studies revealed that the presence of the two α-methyl substituents provides sufficient steric hindrance around C_2 as to preclude a proper approach of the incoming electrophile. Only the smallest reagents might be able to reach that centre. The elegant work of Junjappa *et al.* on the preparation and subsequent transformations of α-oxo ketene dithioketals inspired us and provided the ultimate solution to our predicament.[83]

Thus, we were delighted to observe that successive treatment of ketone **3.215** with KHMDS, carbon disulphide, KHMDS and finally methyl iodide led in 86% yield to the desired adduct **3.275** (Scheme 3.74).

[83] (a) Myrboh, B.; Ila, H.; Junjappa, H. *J. Org. Chem.* **1983**, *48*, 5327; (b) Myrboh, B.; Asokan, C.V.; Ila, H.; Junjappa, H. *Synthesis* **1984**, 50; (c) Asokan, C.V.; Ila, H.; Junjappa, H. *Synthesis* **1985**, 163

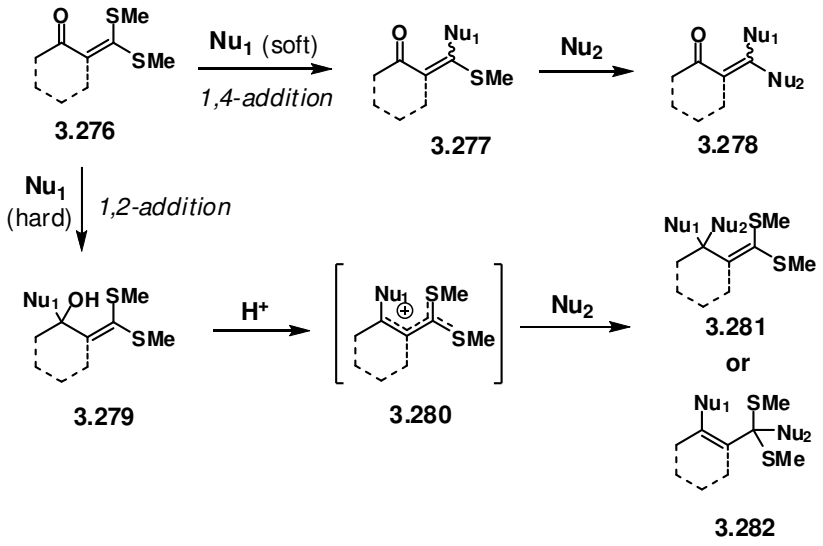


3.215 3.275

Scheme 3.74

Compound **3.275** belongs to the family of α-oxoketene dithioketals. Such compounds display a fascinating chemistry, which has been relentlessly exploited through the past 20 years by Junjappa and by Karl Dieter.[84] As would be expected, α-oxoketene dithioketals such as **3.276** are susceptible to both conjugate- and 1,2-attack by incoming soft and hard nucleophiles, respectively. They are competent Michael acceptors and 1,4-addition can occur with expulsion of one or two alkylthio- residues (Scheme 3.75). But the more interesting features come into play when 1,2-addition is considered. Indeed, the resulting secondary or tertiary allylic alcohols **3.279** are very easily ionised, giving rise to highly stabilised carbocationic intermediates **3.280**. Trapping of such intermediates, which can be performed with appreciable regioselectivity, provides densely functionalised products **3.281** or **3.282**.

[84] See, *e.g.*: (a) Dieter, R. K.; Chang, H. J. *J. Org. Chem.* **1989**, *54*, 1088; (b) Dieter, R. K. *Tetrahedron* **1986**, *42*, 3029; (c) Dieter, R. K.; Silks, L. A., III; Fishpaugh, J. A.; Kastner, M. E. *J. Am. Chem. Soc.* **1985**, *107*, 4679



Scheme 3.75

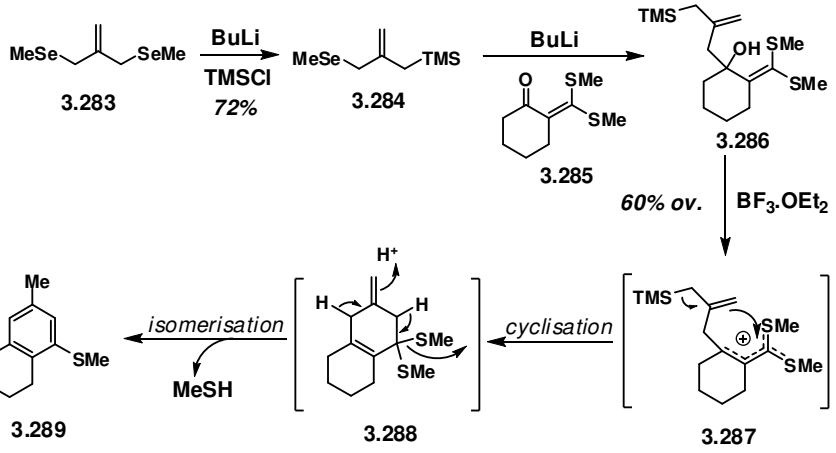
In work carried out in collaboration with Sebastien Brahy, we had the opportunity to tap slightly on the potential of such intermediates.[85] The versatile mixed allylsilane/allylselenide **3.284**[86] was transmetallated and added to the cyclohexanone derivative **3.285**. The crude alcohol **3.286** thus obtained was directly treated with 3 equivalents of $BF_3.OEt_2$. This Lewis-acid triggered the cationic cascade depicted in Scheme 3.76. Following ejection of the tertiary alcohol, intramolecular capture of the putative carbocation **3.287** by the allylsilane moiety initially provided decalin **3.288**. This compound is likely to be unstable in the acidic medium and double

[85] Sebastien Brahy, *Application des α-oxocétène dithiocétales à de nouvelles annélations*, Mémoire, Institut Paul Lambin, 2005

[86] For further applications of this and other allylselenides, see: (a) Krief, A.; Dumont, W.; Markó, I. E.; Murphy, F.; Vanherck, J.-C.; Duval, R.; Ollevier, T.; Abel, U. *Synlett* **1998**, 1219-1222; (b) Driesschaert, B.; Leroy, B. *Synlett* **2006**, 2148

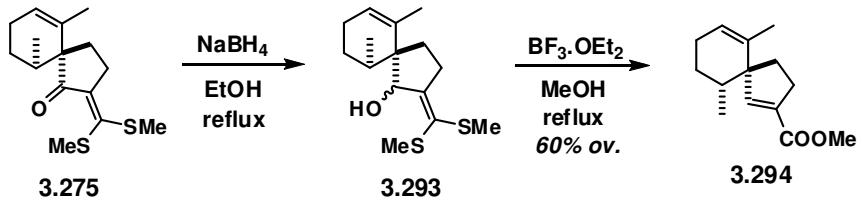
bond migration, combined with methanethiol elimination are presumably driven by the formation of a stable, aromatic product **3.289**.

This preliminary result points towards the feasibility of preparation of *m*,*m'*-disubstituted aromatics from α-oxoketene dithioketals, with full regiocontrol being insured by the silyl-directed capture of the carbocation **3.287**.



Scheme 3.76

Returning to the total synthesis, we recognised that the intermolecular capture by an alcohol nucleophile might provide a useful product for further manipulation. In the event, the ketone function in **3.275** was chemoselectively reduced, using $NaBH_4$ in refluxing ethanol. The crude mixture of diastereoisomeric allylic alcohols **3.293** (ratio not determined) was directly subjected to the action of boron trifluoride etherate, in refluxing methanol, during 15 hours.[83] Gratifyingly, the α,β-unsaturated ester **3.294** could be isolated in 60% overall yield.



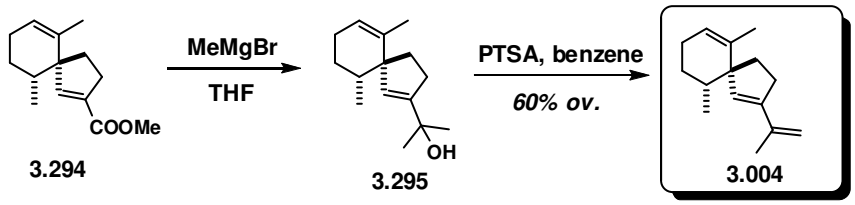
Scheme 3.77

This three-step sequence successfully accomplishes an impressive formal 1,2-transposition of functionality (1,3-carbonyl transposition) within the 5-membered ring whilst providing access to an intermediate already described by Yamada (Cf. Section 3.2.3).[47] Once again, this synthetic strategy for installation of C_2-functionality is, to the best of our knowledge, unique in the context of the Spirovetivanes.[87]

Indeed, the key-intermediate **3.294** has already been transformed into (±)-α-Vetispirene **3.004**. Accordingly (Scheme 3.78), treatment of unsaturated ester **3.294** with excess Grignard reagent in THF, for 2 hours, followed directly by dehydration in the presence of catalytic amounts of *p*-toluenesulphonic acid in dry benzene, smoothly provided (±)-α-Vetispirene **3.004** in an overall yield of 60% (Scheme 9). It should be noted that, contrary to our expectations and to Yamada's claim,[47] the tertiary allylic

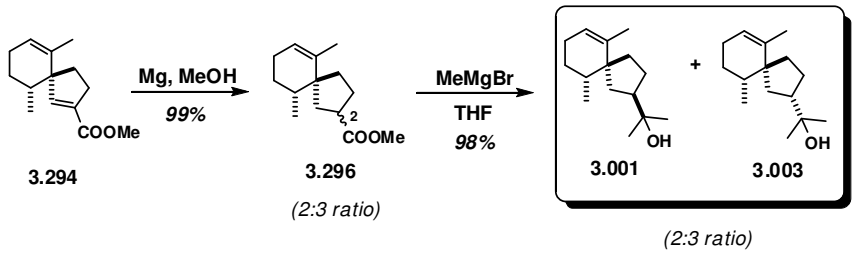
[87] In his formal synthesis of β-vetivone (not discussed herein), William Reusch *et al.* performed a net 1,2-carbonyl transposition through reduction, mesylate formation/ elimination and hydroboration/oxydation. Our sequence is not only shorther, but effects a **1,3**-carbonyl transposition, placing the functionality at the precise location required for further elaboration to the natural products. Cf. Subrahamanian, K. P.; Reusch, W. *Tetrahedron Lett.* **1978**, 3789

alcohol **3.295** could not be dehydrated by simple stirring with SiO_2 in dichloromethane, and should therefore survive chromatographic purification. (±)-α-Vetispirene is a colorless, volatile oil with a faint rosy odor.



Scheme 3.78

Furthermore, the key-intermediate **3.294** should also serve as an advanced precursor towards (±)-Agarospirol **3.001** and (±)-Hinesol **3.003**, requiring only the chemoselective reduction of the conjugated double bond, followed by Grignard addition onto the ester functionality, to provide the natural products.



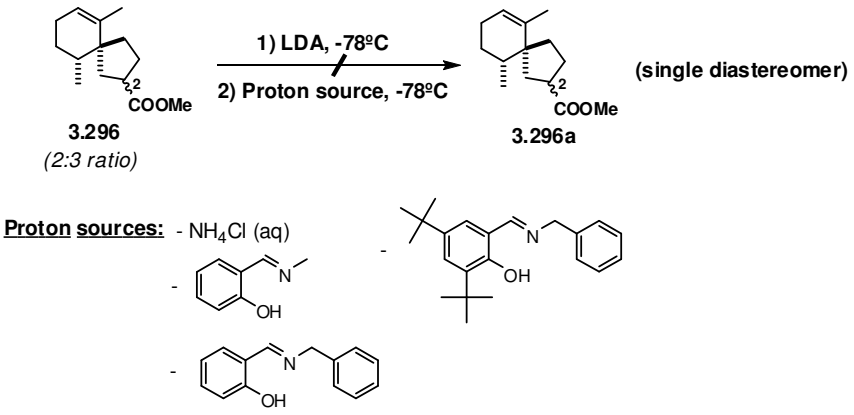
Scheme 3.79

Hence (Scheme 3.79), reacting compound **3.294** with magnesium in methanol produced the saturated ester **3.296** as an inseparable 2:3 mixture of

C_2-epimers, in quantitative yield.[88] Finally, addition of methyl magnesium bromide to this mixture of stereoisomers provided (±)-Agarospirol **3.001** and (±)-Hinesol **3.003** in 98% yield (2:3 ratio).

Attempts at epimerising the C_2-stereocentre of **3.296** by kinetic quench of the ester enolate, under diverse conditions, did not meet with success (Scheme 3.80). Whilst this approach is not exhausted, we believe that the obtention of two diastereoisomers is as much of a nuisance as it is a blessing: a nearly 1:1 ratio of two epimeric natural products is obtained in one single, final synthetic operation. Furthermore, this result is in agreement with most of the previously reported syntheses, involving either a nitrile, a ketone or an ester as the precursor to the isopropylol side-chain. It would thus seem that the 3 : 2 ratio, in favor the epimer leading to Hinesol, is probably the thermodynamic situation for most of the enolisable functions located at C_2.

[88] (a) Hudlicky, T.; Sinai-Singde, G.; Natchus, M.G *Tetrahedron Lett.* **1987**, *28*, 5287; (b) Gabriels, S.; Van Haver, D.; Vandewalle, M.; De Clercq, P.; Viterbo, D. *Eur. J. Org. Chem.* **1999**, 1803



Scheme 3.80

3.7. CAN-catalysed selective deprotections in the presence of enol triflates

The use of protecting groups has long become a generalised, inevitable practice in the field of organic synthesis.[89] Accordingly, a wide variety of reagents and procedures have been devised to efficiently accomplish this task and new methods continue to emerge regularly.[90] This is hardly surprising since, more often than not, the success of a total synthesis depends critically upon the compatibility and selective unraveling of a skillfully designed array of protecting groups.

[89] For beautiful illustrations of the skillful use of protecting groups in synthesis, see: (a) Nicolaou, K.C.; Sorensen, E.J. *Classics in Total Synthesis;* VCH: Weinhem, 1996; (b) Nicolaou, K.C.; Snyder, S.A. *Classics in Total Synthesis II*; VCH: Weinheim, 2003

[90] (a) Kocienski, P.J. *Protecting Groups*; Georg Thieme: New York, 1994; (b) Greene, T.W.; Wuts, P.G.M. *Protecting Groups in Organic Chemistry*; Wiley: New York, 1991

During the above-described total synthesis of spirovetivane sesquiterpenes, we have encountered such a situation (Cf. Section 3.6.3). The crucial, Fe(III)-catalysed coupling of **3.222** was serendipitously shown to proceed smoothly only in the absence of the dioxolanyl ketal protecting group (Scheme 3.71). Thus, the success of our strategy heavily relied upon the chemoselective unmasking of the ketone function in the presence of the labile enol triflate moiety. In the event, our laboratory's previously reported cerium(IV) ammonium nitrate (CAN)-catalysed protocol[91] served this task admirably, delivering the requisite keto-enol triflate **3.268** in quantitative yield. In stark contrast, using conventional acidic conditions, rapid hydrolysis of the enol triflate function took place.

This procedure has a number of advantages, among which are the exceptionally mild conditions employed, the simplicity of the experimental procedure and the high levels of chemoselectivity displayed in the unraveling of ketals, acetals and THP ethers. The genesis and development of this methodology, as well as its growing application in the context of total synthesis, have been reviewed by us elsewhere.[92]

We were intrigued by the exquisite levels of chemoselectivity displayed by the CAN-catalysed protocol in such a stringent scenario and therefore decided to investigate the scope of this hitherto unreported transformation. The prominent role played by enol triflates in synthesis,

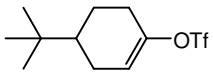
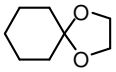
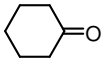
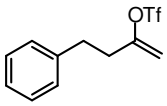
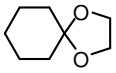
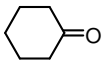
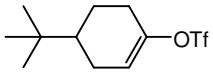
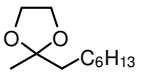
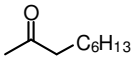
[91] Cf ref. 80. For similar uses of CAN, see: (c) Barone, G.; Bedini, E.; Iadonisi, A.; Manzo, E.; Parrilli, M. *Synlett* **2002**, 1645; (d) Manzo, E.; Barone, G.; Bedini, E.; Iadonisi, A.; Mangoni, L.; Parrilli, M *Tetrahedron* **2002**, *58*, 129

[92] Maulide, N.; Vanherck, J.-C.; Gautier, A.; Markó, I.E. *Acc.Chem.Res.* **2007**, *40*, 381

particularly in metal-mediated coupling processes, further instigated us to study this reaction.[93]

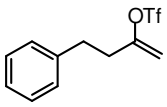
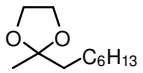
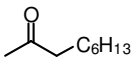
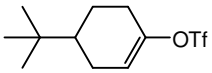
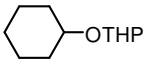
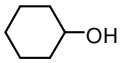
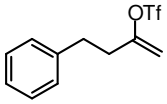
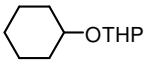
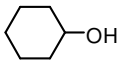
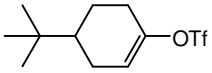
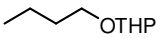
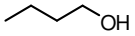
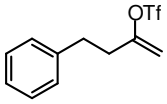
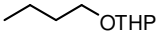
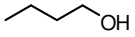
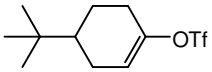
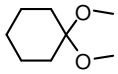
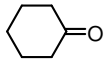
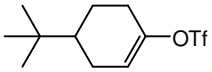
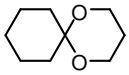
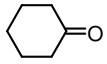
At the onset, the two model enol triflates **3.300** and **3.301**[94] were selected as representative substrates. They were subjected to our CAN-catalysed protocol, under typical competitive conditions (1:1 ratio), in the presence of suitably protected partners. The results of these experiments are collected in Table 3.2.

Table 3.2 [a,b]

Entry	Enol triflate	Protected substrate	Deprotected product
1	 **3.300**	 **3.302**	 **3.302a**
2	 **3.301**	 **3.302**	 **3.302a**
3	 **3.300**	 **3.303**	 **3.303a**

[93] For a general review on enol triflates, see: (a) Ritter, K. *Synlett* **1993**, *8*, 735. For reviews highlighting the uses of vinyl triflates in metal-mediated coupling reactions see, e.g.: (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945 and Ref. 71b

[94] Readily prepared by deprotonation of the corresponding ketones with NaHMDS in THF, followed by capture with $PhNTf_2$.

4	 **3.301**	 **3.303**	 **3.303a**	
5	 **3.300**	 **3.304**	 **3.304a**	
6	 **3.301**	 **3.304**	 **3.304a**	
7	 **3.300**	 **3.305**	 **3.305a**	
8	 **3.301**	 **3.305**	 **3.305a**	
9	 **3.300**	 **3.306**	 **3.302a**	
10	 **3.300**	 **3.307**	 **3.302a**	

a – Reaction conditions: 3 mol% CAN, MeCN/borate buffer [pH=8] (1/1)

b - In all cases, selectivity was >95% as judged by analysis of crude NMR spectra and subsequent isolation.

As can be seen from Table 3.2, dioxolanyl ketals derived from both cyclic and acylic ketones **3.302** and **3.303** were smoothly unravelled under

mild conditions (room temperature to 40ºC, 1 to 2 hours) and in a completely chemoselective manner (Entries 1 to 4). No hydrolysis of the enol triflates, which could be easily recovered after the reaction in quantitative yields, was observed.

The same levels of selectivity were ascertained when the more demanding THP ethers **3.304** and **3.305** were employed as the protected substrates.[95] In these cases (Entries 5 to 8), after 2 to 3 hours at 60ºC, complete deprotection occured without any noticeable decomposition of the enol triflates. Furthermore, a 1,3-dioxane **3.307** and the more labile dimethylketal **3.306** were also chemoselectively excised under these conditions (entries 9 and 10). Finally, it is noteworthy that the vinyl triflate **3.300** could be submitted to the deprotection conditions for up to 12 hours without any sign of competitive hydrolysis of the enol triflate function.

It thus transpires that this unique catalytic deprotection procedure is fully compatible even with the sensitive triflate moiety, thereby highlighting its synthetic usefulness.

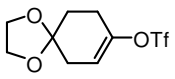
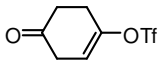
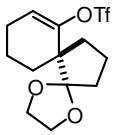
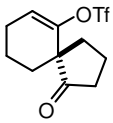
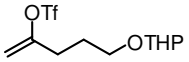
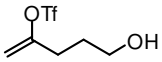
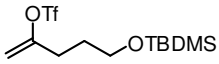
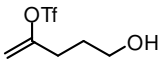
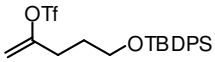
Encouraged by these results, we then assessed the chemoselective deprotection of bifunctional substrates, embodying both the protecting group and the enol triflate functionality.

Some selected examples are displayed in Table 3.3. As can be seen, this protocol offers the exciting possibility of efficiently and selectively constructing mono-enol diketones such as **3.268** and **3.309a** (entries 1 and 2). Furthermore, the system responds well to an important increase in steric

[95] For the deprotection of THF and THP ethers by CAN, see: Markó, I.E.; Ates, A.; Augustyns, B.; Gautier, A.; Quesnel, Y.; Turet, L.; Wiaux, M. *Tetrahedron Lett.* **1999**, *40*, 5613-5616

hindrance, as evidenced by the slightly higher temperature required to cleave the ketal function of **3.310** (entry 2).

Table 3.3

Entry[a]	Substrate	Product	Temperature, time	Yield (%)[b]
1	 **3.309**	 **3.309a**	40ºC, 2h	90
2	 **3.310**	 **3.311**	60ºC, 2h	94
3	 **3.312**	 **3.312a**	60ºC, 3h	76[c]
4	 **3.313**	 **3.312a**	60ºC, 3h	80[c]
5	 **3.314**	---	60ºC, 3h	NR[d]

[a]- All deprotection reactions were performed using 3mol% CAN in buffered (pH=8) acetonitrile.
[b]- Unless otherwise stated, yields are for pure, isolated products.
[c]- Yield of crude product (see text).
[d]- No reaction.

Interesting results were obtained when substrates **3.312** to **3.314**, containing a protected alcohol, were employed. Whilst both the THP-

protected compound **3.312** and its *t*-butyldimethylsilyl (TBDMS) analogue **3.313** could be converted to the desired alcohol **3.312a**, derivative **3.314**, bearing a *t*-butyldiphenylsilyl (TBDPS) group remained unaltered under our reaction conditions. In contrast to **3.309a** and **3.311**, which could be easily purified by rapid column chromatography, enol triflate **3.312a** proved to be particularly labile and decomposed extensively upon attempted purification.[96]

In summary, we have shown that the enol triflate function is compatible with our CAN-catalysed deprotection conditions. Using this mild procedure, ketals, THP- and TBDMS- ethers could be chemoselectively and efficiently unmasked without affecting the acid-labile enol triflate functionality, an observation that has important bearing for subsequent synthetic ventures.

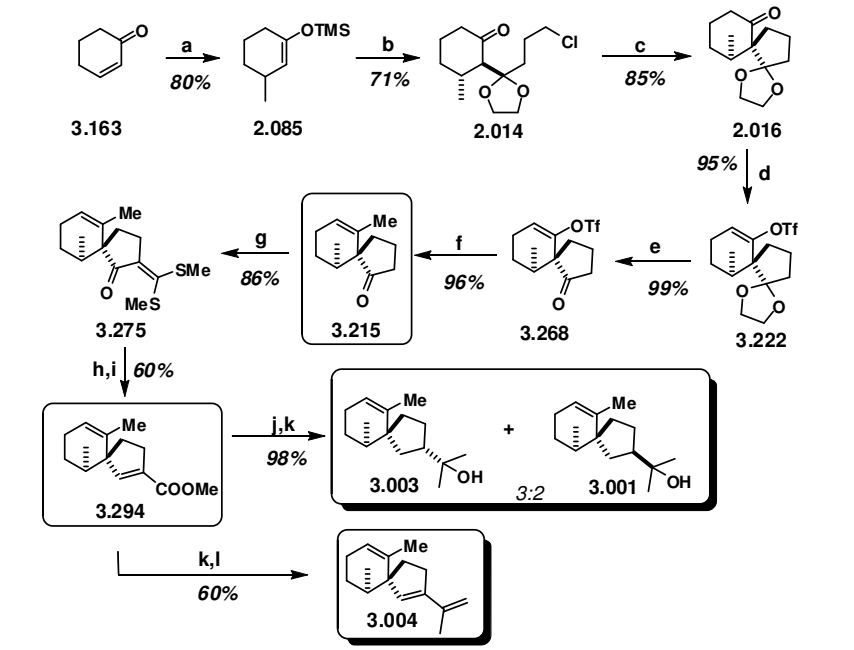
3.8. Conclusions and perspectives

Throughout the latter part of this chapter, we have demonstrated the synthetic usefulness of the methodology previously developed for the preparation of spirocyclic compounds, by applying it to the total synthesis of several members of the spirovetivane sesquiterpenes. Our approach, which is summarised in Scheme 3.81, provides key-intermediate **3.215** in only 5 steps and 54% overall yield. This precursor was subsequently transformed into Agarospirol, Hinesol and α-Vetispirene in 22%, 32% and 34% overall

[96] This type of behaviour has been recently reported: Tanino, K.; Aoyagi, K.; Kirihara, Y.; Ito, Y; Miyashita, M. *Tetrahedron Lett.* **2005**, *46*, 1168-1172.

yields. This translates into 12%, 17% and 18% global yield values, respectively. In addition, since Hinesol **3.003** has been converted into β-Vetivone **3.006** by Kobayashi, our approach can be considered as a formal synthesis of that compound as well.

Our synthesis compares favorably with the previously reported approaches. Furthermore, innovative methodology for the introduction of the spirovetivane characteristic motifs has resulted from this endeavor : a) the first use of an organometallic coupling for the installation of the (elusive) endocyclic double bond, b) a Junjappa rearrangement for the placement of the precursor for the isopropylol side-chain.



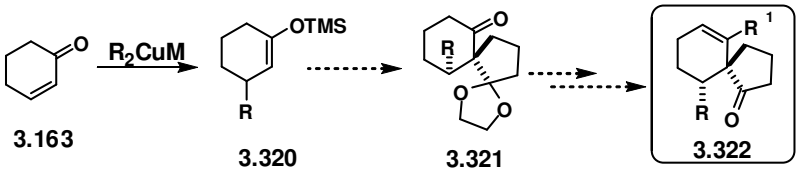
Scheme 3.81

The art of total synthesis often functions as a catalyst and stimulates the development of new reactions and novel broad-scope methodologies. Even though the Spirovetivanes are relatively small molecules, we pleasingly confirm that this was also the case during our studies. Thus, we have developed a new and mild method for the chemoselective deprotection of acetals in the presence of enol triflates, a transformation not possible before. In our synthetic plan, this was a crucial step towards the successful completion of the targets. On the other hand, and with the aid of computational methods, we have uncovered an intriguing behaviour of

secondary « non-classical » carbocations, which not only confers them unusual stability but also appears to enable a number of interesting, direct substitution reactions to be performed on secondary alcohols.

The modular nature of our synthesis also opens the door for the preparation of new analogues. In fact, we were pleasantly surprised to verify that intermediate **3.215** possesses a very pronounced mint-like odor. This compound has, to the best of our knowledge, not been reported in the literature prior to our own studies. One can only speculate about the effect of changing the nature of substituents on the six-membered ring. Since Dr. Jean-Christophe Vanherck's work hinted that the nature of the β-substituent on the silylenol ether does not change the course of the spirocyclisation, a number of compounds **3.322**, bearing different appendages, should be available in diastereomerically (and enantiomerically, *vide infra*) pure fashion. Moreover, since in our synthesis the endocyclic double bond moiety is introduced by a organometallic C-C coupling, substituents other than a methyl group should be readily inserted. This should not be as easy to accomplish through the more commonly employed Grignard/dehydration strategy due to regioselectivity issues.

The effect of such structural modifications on the odoriferous properties of the final compound is *a priori* unpredictable. However, it is surely an interesting area to study which may, eventually, result in commercial exploitation.



R=R1=Me mint-like odor
SOR = structure-odor relationship

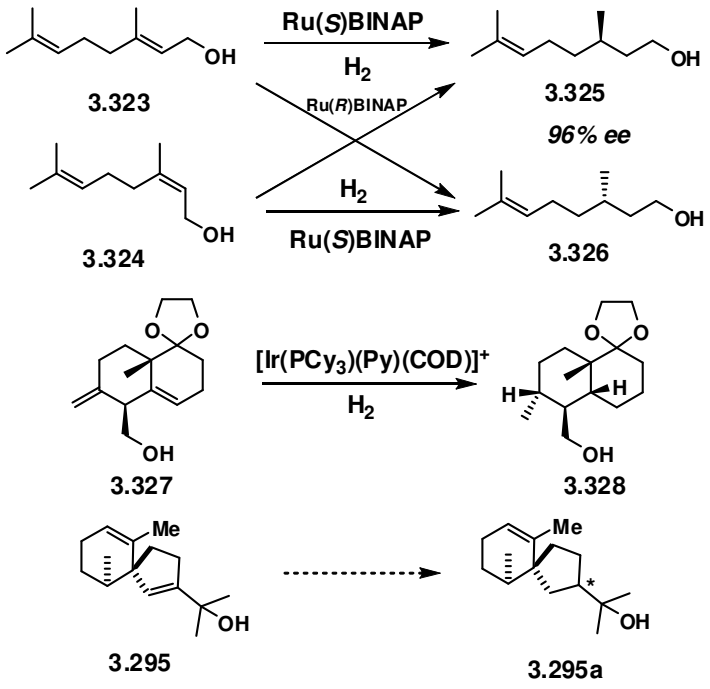
Scheme 3.82

On a more critical note, in our opinion the widespread obtention of Agarospirol and Hinesol as a mixture of epimers somewhat tarnishes the stereocontrol displayed through many of the total syntheses of these compounds. In our case, an intriguing possibility would be the exploitation of allylic alcohol **3.295**, an easily handled compound, as the template for stereochemical control.

The metal-catalysed, selective hydrogenation of allylic alcohols is a mature field in which reagent-control has allowed for impressive levels of diastereo- and enantioselectivity. Noyori's Ru-BINAP procedure and Crabtree's Ir-based catalysts are but some of the most effective systems for this endeavour, as illustrated in Scheme 3.83.[97] Each system works based upon a different concept : while Noyori's reagents convey stereochemical information from the chiral ligand to the substrate, through a *reagent-controlled* interaction, Crabtree's catalyst uses the inherent steric bias of the substrate's docking point to direct the hydrogenation result (*substrate-control*). Although the epimerisation of C_2-esters has proven fruitless and

[97] (a) Takaya, H.; Ohta, T.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Inoue, S.-I.; Kasahara, I.; Noyori, R. *J. Am. Chem. Soc.* **1987**, *109*, 1596; (b) Crabtree, R. *Acc. Chem. Res.* **1979**, *12*, 331. For the example depicted, see: (c) Watson, A.T.; Park, K.; Wiemer, D.F.; Scott, W.J. *J. Org. Chem.* **1995**, *60*, 357

highlighted a lack of stereochemical preference between both C_2-epimers, we do not know at this stage if the allylic alcohol **3.295** has a prefered conformation in solution.

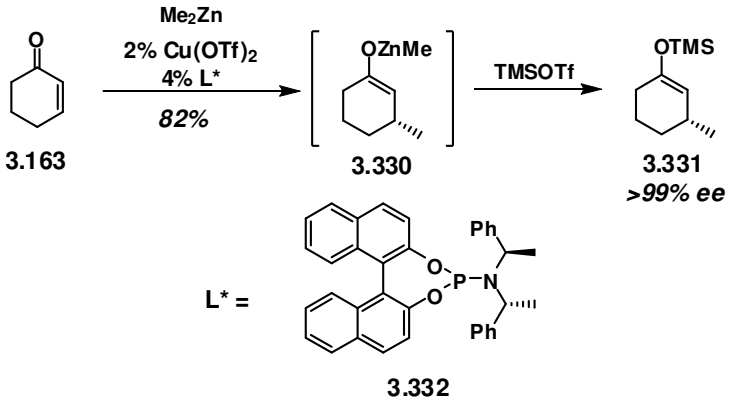


Scheme 3.83

Finally, an enantioselective version of our total syntheses should be readily accessible. Using the elegant cuprate methodology developed by Alexakis at Genève,[98] we should be able to access optically pure silyl enolether **3.331** from cyclohexenone **3.163** (Scheme 3.84). As already

[98] Knopff, O.; Alexakis, A. *Org. Lett.* **2002**, *4(22)*, 3835.

demonstrated, this chiral centre induces diastereoselectivity throughout the synthetic pathway. Thus, it should be straightforward to replay our route, departing from enantiopure **3.331**, thereby allowing the preparation of enantioenriched Agarospirol, Hinesol and α-Vetispirene.



Scheme 3.84

Chapter 4 : Towards the synthesis of GHB-analogues and Perhydrohistrionicotoxin (PHT) – an exercise in diastereocontrol on spirocyclic systems

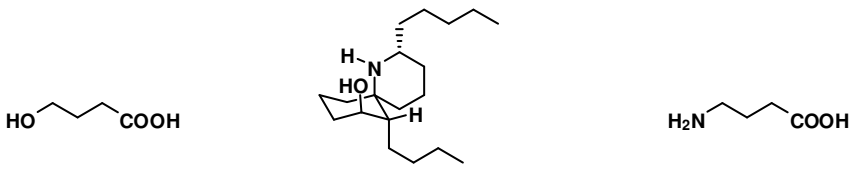
4.1. Introduction

The spiroannelation methodology presented in Chapter 2 provides monoprotected, spirocyclic diketones which are interesting building blocks for further elaboration. Indeed, we have demonstrated their synthetic value through the unified synthesis of the Spirovetivane sesquiterpenes, described in the preceding chapter.

Nonetheless, a number of possibilities remain wide open for the valorisation of such adducts. During our Ph.D., two such possibilities attracted our attention.

While the importance of Natural Products in contemporary Organic Chemistry is undeniable, biologically active man-made compounds are somewhat less appreciated by the practitioner. The present Chapter will introduce and detail synthetic efforts made towards compounds belonging to these two different classes. Initially, an approach to the synthesis of designed analogues of *Gamma*-Hydroxybutyric acid (GHB) **4.001** will be discussed. Later on, our work aimed at the preparation of the classical natural product

Perhydrohistrionicotoxin (PHT) **4.002** will be presented (Scheme 4.1). Though rather different in structural terms, both targets convey similar, highly useful lessons in diastereocontrol on spirocyclic compounds.



GHB **4.001** | *Perhydrohistrionicotoxin (**PHT**)* **4.002** | *GABA* **4.003**

Scheme 4.1

4.2. Towards the synthesis of GHB-analogues

4.2.1. Background and motivation

Gamma-hydroxybutyrate (GHB) **4.001** is a naturally occuring, short-chained fatty acid found in mammalian tissue.[99] It was initially isolated and investigated by Laborit in the 1960's, in an effort to develop a *gamma*-aminobutyric acid (GABA) **4.003** congener which could readily cross the blood brain barrier.[100] Early testing suggested that GHB could produce a dose-dependent sedation and anesthesia in laboratory animals and humans. The action of GHB as a central nervous system depressant was in some ways similar to those of the classical sedatives/hypnotics such as barbiturates and

[99] Bessman, S.P.; Fishbein, W.N. *Fed. Proc.* **1963**, *22*, 334
[100] Laborit, H. *Int. J. Neuropharmacol.* **1964,** *3*, 433

benzodiazepines. While GHB does share some cellular and behavioral effects with these classical sedatives/hypnotics, it is currently considered to represent a unique pharmacological entity, believed to function as a distinct neurotransmitter or neuromodulator.

GHB has a 30-year history of use in medicine, particularly in Europe, and it was also available for many years in the US as a consumer product sold as a dietary supplement. Until the early 1990's, GHB had received only modest attention from medical scientists and little concern from public health officials. Over the past 10 years, however, several developments (mainly in the US) changed this situation. The increased consumer use of GHB has generated concerns about its safety and effectiveness without medical supervision.

Although a detailed analysis of the biological activity, pharmacology, potential for tolerance and dependence, as well as interaction with other drugs, of GHB would be beyond the scope of this dissertation, we shall briefly discuss clinical reports on GHB use (and abuse) to place our synthetic work in perspective.[101]

GHB was initially marketed in the US as a steroid replacement for bodybuilders and weight lifters. Advertised as a "magic supplement" purported to promote muscle growth and decrease body fat, it has been widely used among the body building community although no evidence for its effects has been obtained from scientific studies.[102]

In accord with its reported sedative actions, GHB has also been used as a sleep-inducing agent for insomniacs and persons suffering from sleep disturbances. Importantly, oral doses of 30-50 mg GHB/kg generally induce

[101] For a review, see: Nicholson, K.L.; Balster, R.L. *Drug&Alcohol Dep.* **2001**, *63*, 1
[102] Luby, S. ; Jones, J. ; Zalewski, A. *Am .J. Public Health* **1992**, *82*, 128

sleep, which is virtually indistinguishable from "normal" sleep.[103] In particular, it is currently being developed by Orphan Medical, Inc. as a new drug (Xyrem®) for the treatment of narcolepsy, under the FDA's orphan drug program.

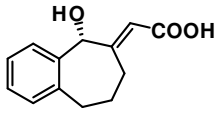
GHB has also been reported to be euphorigenic, producing a pleasurable intoxication state without residual toxic effects (*i.e.*, no "hangover").[104] This has led to significant popularity as one of the new "club drugs", and GHB is sometimes available at "rave parties" and in nightclubs. More dramatically, GHB has been characterised by the media as a "date-rape drug". It is possible that both the ease of its administration and the enhancement of ethanol's behavioral effects by GHB have contributed to its use as a sexual assault-related drug.

The mechanism of action of GHB in the central nervous system remains unclear. There is evidence that GHB binds to a specific GHB receptor (as well as the GABA receptors), although the precise nature of this receptor has not been fully elucidated.[105]

Whereas some inhibitors of GHB have been identified, little information is available on possible ligands with either agonist or antagonist properties at the GHB receptor. To date, the only compound reported to be an antagonist at the GHB receptor sites is NCS-382 **4.004**, a semirigid compound structurally related to GHB (Scheme 4.2).[106]

---

[103] Chin, M.-Y.; Kreutzer, R.A.; Dyer, J.E. *West.J.Med.* **1992**, *156*, 380
[104] Dean, W.; Morgenthaler, J.; Fowkes, S.W. in *GHB: The natural mood enhancer*, Smart Publications, Petaluma, USA, 1998
[105] Crunelli, V.; Emri, Z.; Leresche, N. *Curr.Opin.Pharm.* **2006**, *6*, 44
[106] Castelli, M.P.; Pibiri, F.; Carboni, G.; Piras, A.P. *CNS Drug Rev.* **2004**, *10*, 243



(R)-NCS-382
4.004

Scheme 4.2

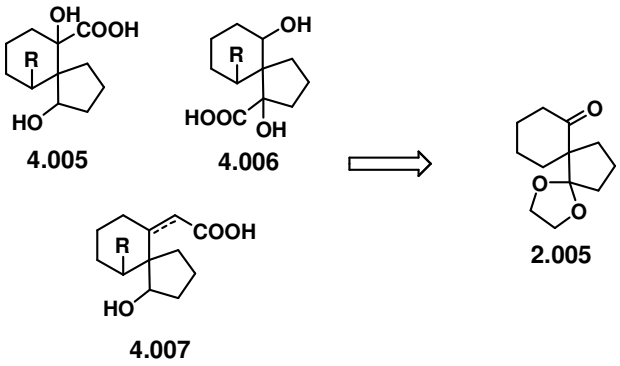
Given the lack of information on the mode of action of GHB and its intriguing array of biological activities, it would be highly desirable to develop structurally diverse analogues of this compound for further study.[107] In particular, the trend for rigidification of the structure (as in NCS-382 **4.004**) appears to be a valid starting point in the design of new analogues.

4.2.2. Strategy

We planned to take advantage of the stereochemically constrained nature of spirocyclic compounds in the design of GHB-analogues. It was hoped that by enforcing a particular conformation between the polar –COOH and –OH substituents, different levels of binding could be observed.

The first designed analogues should be rather simple. Compounds possessing the formulae **4.005-4.007** were selected not only for their structural similarity with GHB but also due to the short synthetic sequences that could be envisaged from readily available spirocycle **2.005**.

[107] The biochemical studies shall be undertaken in collaboration with Dr. Julianna Kardos, Hungarian Academy of Sciences, Budapest, Hungary.



Scheme 4.3

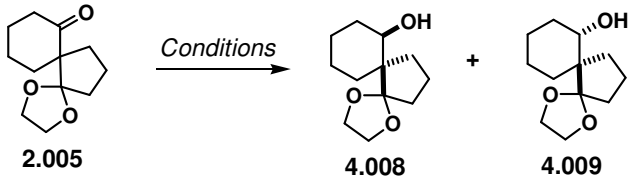
It was anticipated that the monoprotection of the spirocyclic diketone moiety could be used to our advantage in selectively manipulating each of the carbonyl groups. In this way, the carboxylic acid substituent might be appended onto either the 5- or the 6-membered ring. It should be noted that, although stereochemical control is commonly a secondary issue when designing analogues with such structural freedom, we considered this to be an excellent opportunity to test the diastereoselection associated with our spirocyclic ketones.

Armed with this double motivation, we recognised that our work crucially depended upon one factor: the addition of nucleophiles to the ketone carbonyl group(s) of our starting material, spirocyclic ketone **2.005**.

4.2.3. Results and discussion

Our efforts began with the attempted reduction of ketone **2.005**. A part of this work was done in collaboration with Frédéric Toussaint.[108]

Frédéric began by inspecting common reducing agents. The results obtained are summarised in Table 4.1.



2.005 **4.008** **4.009**

Table 4.1

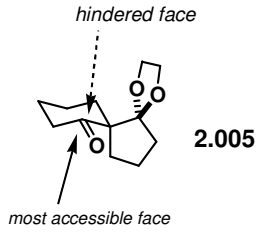
Entry	*Conditions*	*Yield*	*Ratio* ***4.008/4.009***
1	$NaBH_4$, MeOH, rt	80%	60 :40
2	$NaBH_4$, MeOH, -10°C	85%	60 :40
3	$NaBH_4$, $CeCl_3$, MeOH, rt	63%	85 :15
4	DiBAL-H, THF, -78°C	90%	>95 :5

As might be anticipated, diastereoselectivity increases with the bulk of the reducing agent employed. The lack of stereoselection observed with $NaBH_4$ might be useful in increasing the stereodiversity of our analogues. From a synthetic perspective, though, we were pleased to ascertain the

[108] Toussaint, F. *Synthèse de spirocycles potentiellement antagonistes à l'acide γ-hydroxybutyrique*, Institut Meurice/UCL, **2006**

formation of a single diastereoisomer upon reaction with DiBAL-H at low temperature.

This seems to suggest that the dioxolane substituent could be used as a stereodefining element. Indeed, while one might envisage a coordinating character of its oxygen atoms, it appears to function primarily as a bulky substituent which effectively shields one of the faces of the ketone carbonyl (Scheme 4.4). Further examples of this effect punctuate repeatedly our work (Chapters 4-6).



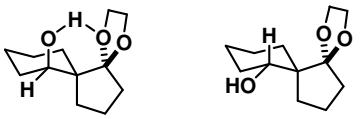
Scheme 4.4

Confirmation of the relative stereochemistry of compound **4.008** could not be achieved through nOe experiments. There are a number of observations, though, that clearly lend support to our stereochemical assignment.

On one hand, there is a significant polarity difference between both diastereomeric alcohols **4.008** and **4.009**. Indeed, we have observed that isomer **4.008** (which becomes the major epimer produced upon reaction with DiBAL-H) is considerably *less polar* than its counterpart **4.009**. Examination of molecular models of these compounds reveals a peculiar feature: in isomer **4.008**, hydrogen-bonding to the dioxolane oxygens is possible given the short contact distance between the hydroxyl- and the ketal substituents

(as depicted in Scheme 4.5). Examples abound in the literature showing that hydrogen-bonding is usually responsible for a reduction in polarity of the alcohols.[109]

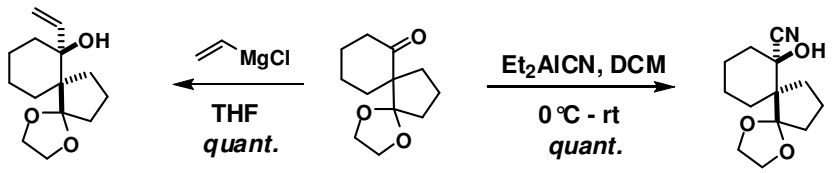
It is a fortunate occurrence that the dioxolane substituent is able to function selectively as either a stereo-blocking element *or* an electron donor through hydrogen-bonding. Further insight supporting our assignment was obtained upon derivatisation of alcohol **4.008** (*vide infra*).



4.008 **4.009**

Scheme 4.5

In analogy to these observations, other nucleophiles added to the carbonyl group of **2.005** with nearly perfect diastereoselectivity, as shown in Scheme 4.6.



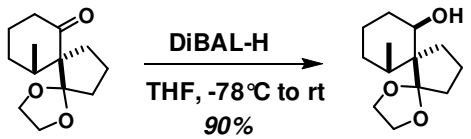
4.010 ***d.r.>14:1*** **2.005** **4.011**

Scheme 4.6

[109] For an example from this laboratory, see : Markó, I.E.; Bailey, M.; Murphy, F.; Declercq, J.-P.; Tinant, B.; Feneau-Dupont, J.; Krief, A.; Dumont, W. *Synlett* **1995**, 123.

As can be seen, nucleophilic entities which can be viewed as precursors to a carboxylic acid functionality, such as a vinyl or a cyanide group, add cleanly to the ketone carbonyl of **2.005** to provide the corresponding tertiary alcohols in good yields and excellent stereoselectivities. In all cases, a single stereoisomer is obtained. Stereochemistry was assigned by analogy to the DiBAL-H reduction product.

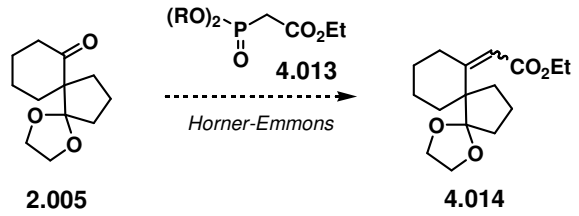
Given the ready availability of substituted spirocyclic ketone **2.016** (used as key building-block in our total synthesis of the Spirovetivanes, Chapter 3), we also investigated its reactivity towards reduction. Similarly to unsubstituted **2.005**, reduction with DiBAL-H provided a single stereoisomeric alcohol in excellent yield (Scheme 4.7).



2.016 **4.012**

Scheme 4.7

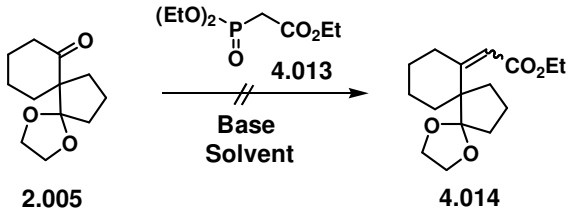
We further extended our studies on the functionalisation of the free carbonyl in **2.005** to homologation reactions. Indeed, it might be interesting to access analogues of GHB in which the carboxyl and the hydroxy-functions are one carbon atom further apart, while still being embedded in a rigid framework. It had been envisaged that a Horner-Emmons reaction on **2.005** would provide homologous ester **4.014**.



2.005 **4.014**

Scheme 4.8

Following a related precedent,[110] we reacted the lithium anion of triethylphosphonoacetate **4.013** (R=Et) with ketone **2.005**. We were disappointed to recover only the unreacted starting material. Attempts at increasing the nucleophilicity of the phosphonate anion by changing the counterion to sodium or potassium led to similar results, as did raising the reaction temperature.



2.005 **4.014**

Base = *t*BuOK, LiHMDS, NaHMDS, KHMDS
Solvent = THF, DME

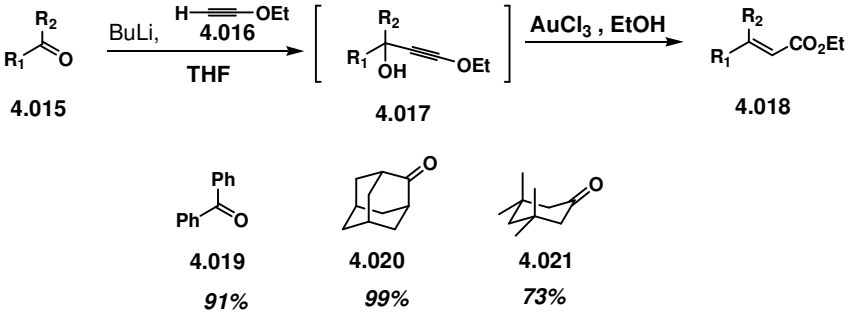
Scheme 4.9

A recent, interesting report in the literature on a "Horner-Emmons-like" homologation of particularly hindered ketones caught our attention.[111]

[110] Robertson, J.; Lam; H. W.; Abazi, S. ; Roseblade, S. ; Lush, R.K. *Tetrahedron* **2000**, *56,* 8959

Indeed, Wittig olefination of, *e.g.*, adamantanone **4.020** is typically a difficult reaction due to severe steric hindrance in the access to the ketone carbonyl group.

In their intriguing communication,[111] Dudley and Engel make use of the classical Meyer-Schuster rearrangement to devise a two-step analog of the Horner-Emmons reaction. As shown in Scheme 4.10, addition of the anion of ethoxyalkyne **4.016** proceeded smoothly. It is generally believed that the non-hindered nature of sp-centered nucleophiles renders them highly effective at attaining even the most inaccessible of electrophilic centers. Also, their reduced basicity prevents undesired proton-transfer processes when enolisable electrophiles are involved.



Scheme 4.10

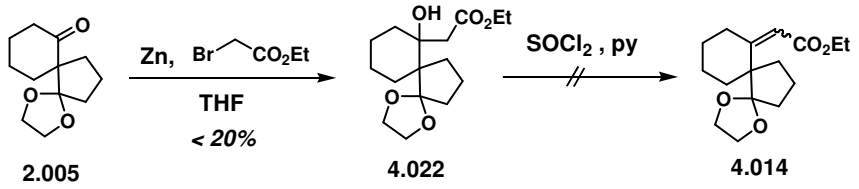
The resulting propargyl alcohols are not isolated. Instead, they are directly engaged in the Meyer-Schuster rearrangement step. Following treatment with a Au^{3+} salt in ethanol, rearrangement to an α,β-unsaturated ester ensues. As exemplified in the Scheme (compounds **4.019-4.021**),

[111] Engel, D.A.; Dudley, G.B. *Org. Lett.* **2006,** *8*, 4027

highly hindered ketones can be olefinated through this procedure in good to excellent yields.

Whereas this might seem an extremely useful reaction, it is not without inconvenients. For instance, the ethoxy alkyne **4.016** is not a stable entity and is marketed only as a temperature-sensitive, 40% solution in hexanes. Unfortunately, and in spite of numerous trials, we were unable to successfully add the anion of **4.016** to spirocyclic ketone **2.005**.

A more classical alternative, the Zn-mediated intermolecular Reformatsky reaction, was also briefly surveyed (Scheme 4.11).[112] While this provided small (<20%) amounts of the desired β-hydroxyester **4.022** as a mixture of diastereomers, attempted dehydration by treatment with $SOCl_2$/py (as usually reported in the literature) led to complex mixtures of products. While puzzling at that time, this result is easily rationalised with the knowledge garnered in the previous chapter. Indeed, we have already witnessed the risks of generating good leaving groups at the position α-to the spirannic center, more so if a dioxolane substituent is present.

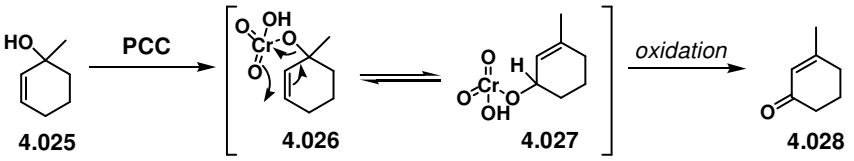


Scheme 4.11

One last strategy envisaged for the generation of the sought unsaturated ester was based upon the known oxidative rearrangement of

[112] For a review, see: Ocampo, R.; Dolbier Jr.; W.R. *Tetrahedron* **2004**, *60*, 9325

allylic tertiary alcohols. Indeed, as shown in Scheme 4.12, Dauben and co-workers found many years ago that treatment of tertiary allylic alcohols with PCC produced an enone issued from skeletal rearrangement.[113] It is surmised that the initially formed chromate ester **4.026**, which is unable to undergo oxidation, experiences a [3,3]-sigmatropic shift to generate the new entity **4.027** which then rapidly oxidises to the observed enone **4.028**.

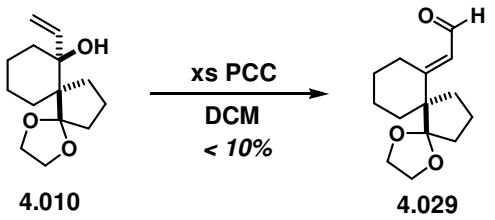


Scheme 4.12

Given the ready availability of such a tertiary allylic alcohol in our case, by virtue of the highly efficient addition of vinylmagnesium chloride, this strategy appeared to be a viable solution to our problem and we envisioned that treatment of **4.010** with PCC might trigger a similar rearrangement.

In the event, exposure of **4.010** to the action of excess PCC in dichloromethane indeed elicited an extremely slow conversion to an unsaturated aldehyde. However, even after addition of further portions of PCC and prolonged reaction times (3-4 days), analysis of the crude mixture revealed only the presence of less than 15% of the desired aldehyde. Increasing the reaction temperature led to the formation of numerous by-products.

[113] Dauben, W.G.; Michno, D.M. *J. Org. Chem.* **1977**, *42*, 682



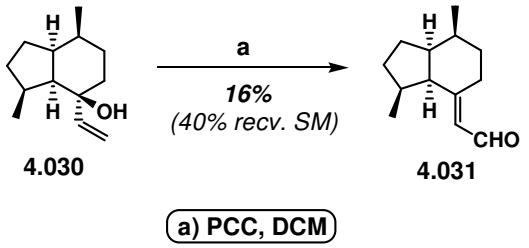
4.010 **4.029**

Scheme 4.13

Closer analysis revealed a fundamental, yet subtle, difference between our allylic alcohol **4.010** and **4.025**. The presence of the double bond in a rigid, constrained cyclic framework such as **4.025** is likely to favor the sigmatropic rearrangement step. The additional mobility of the exocyclic vinyl substituent in **4.010** could raise the activation barrier for the pericyclic reaction by decreasing the probability of attaining the correct conformation. Furthermore, the considerable steric hindrance associated with a tertiary, neopentylic alcohol might hamper the formation of the chromate ester required for the 3,3-shift.

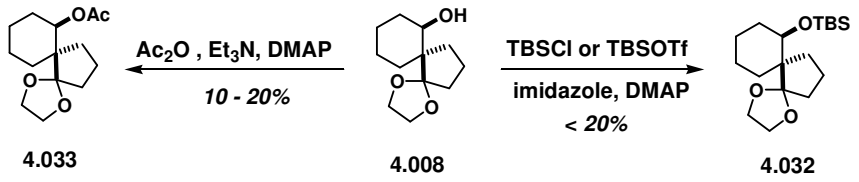
Indeed, we have only found one (modestly) successful example of such a Dauben-rearrangement in the literature.[114] As shown (Scheme 4.14), treatment of the tertiary allylic alcohol **4.030** with PCC elicited a slow reaction, producing only a 16% yield of the desired aldehyde **4.031** along with some recovered starting material.

[114] Tori, M.; Ikawa, M.; Sagawa, T.; Furuta, H.; Sono, M.; Asakawa, Y. *Tetrahedron* **1996**, *52*, 9999



Scheme 4.14

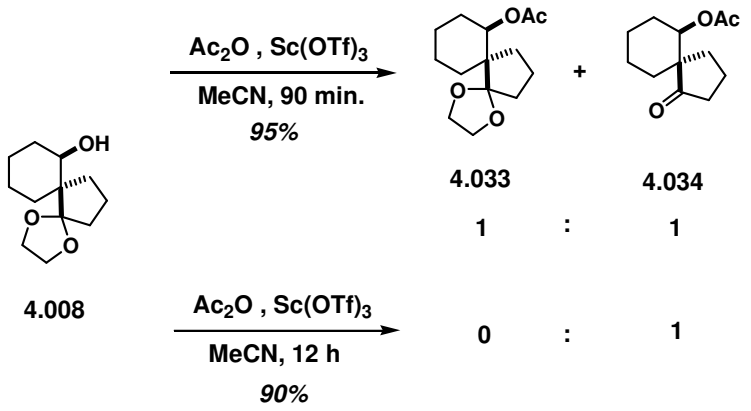
The remainder of our synthetic plan initially featured a protection of the newly formed alcohol before deprotecting and functionalising the five-membered ketone. However, reaction of **4.008** with TBSCl or TBSOTf was very sluggish, with conversion stalling at around 25% even after 3 days. Reasoning that steric constraints might once again be playing against us, we attempted acetylation of **4.008** under typical conditions (Ac_2O, $Sc(OTf)_3$, pyridine, DMAP).



Scheme 4.15

Since this esterification also resulted in a slow conversion, the acetylation of alcohols by catalytic methods was next investigated. The widely employed Yamamoto procedure, which has been studied in some

detail in our laboratory, appeared as an attractive alternative.[115] In this reaction, the alcohol is treated with 10mol% $Sc(OTf)_3$ and 1.1 equivalents of acetic anhydride, in acetonitrile.



Scheme 4.16

In the event, complete conversion of the starting alcohol was observed in less than 2 hours. We were surprised to witness the formation of two products in nearly identical amounts: the protected and deprotected acetates **4.033** and **4.034**. This is most likely a consequence of the use of reagent grade acetonitrile (as indicated in the original procedure), presumably containing trace amounts of water. However, when we deliberately repeated

[115] Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 4413

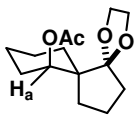
this reaction in a 1:1 water/acetonitrile mixture, no conversion of the starting material was detected.[116]

Complete conversion to a single product, deprotected acetate **4.034**, was simply accomplished by allowing the reaction to proceed overnight. Under these conditions, **4.034** was obtained in 90% yield after a simple aqueous workup.[117]

In accordance with our proposed stereochemical assignment, the acetates **4.033** and **4.034** have spectroscopic properties characteristic of well-defined chair conformers (Scheme 4.17). Thus, the protected analogue **4.033** displays a low-field signal at 4.8 ppm corresponding to proton H_a. This signal is an unresolved doublet of doublet.

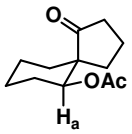
Conversely, in deprotected **4.034,** the signal corresponding to H_a is a well-resolved double doublet with coupling constants of ~9 Hz and ~4 Hz, characteristic of an axially oriented hydrogen atom. Furthermore, as would be expected for an axial hydrogen, its chemical shift is also located at a higher field (5.0 ppm) than in **4.033**. This piece of evidence, combined with the observations described above, without being definitive and unambiguous, nicely accomodates the proposed stereochemical issue for the reduction of ketones **4.033** and **4.034**.

[116] In this case, we presume that the excess water may have hydrolised the catalytic amounts of scandium triflate.
[117] For a more detailed analysis of this unusual tandem acetylation/deprotection reaction, see Chapter 6.



4.033

H_a : unresolved dd at 4,8 ppm
J = 2,3 Hz



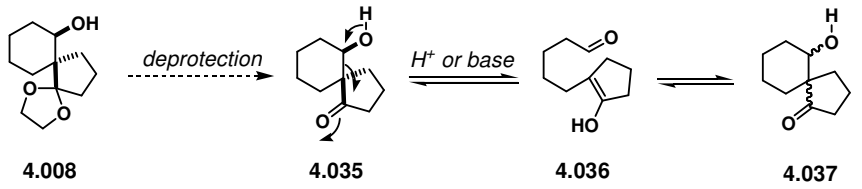
4.034

H_a : well-resolved dd at 5,0 ppm
J_1 = 3,7 Hz
J_2 = 8,8 Hz

Scheme 4.17

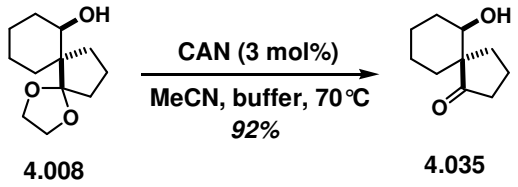
Whilst these deprotective acetylations were being established and understood, studies aimed at the functionalisation of the 5-membered ketone carbonyl, on a compound bearing an unprotected hydroxyl group, were being undertaken.

This was not without concern, though. Indeed, deprotecting a compound such as **4.008** raised important issues. First of all, we were well aware of the danger of manipulating products with the combination of a hydroxyl and a dioxolane functionality given their propensity to generate stabilised carbocations and/or to undergo fragmentation. Secondly, we realised that a ketone such as **4.035** is, indeed, a spirocyclic aldol (β-hydroxyketone). Any trace of acid or base would readily promote retro-aldol ring cleavage (*via* an open structure akin to **4.036**) as shown in Scheme 4.18. Though intramolecular aldol reactions are equilibrating processes, and it might even be possible to drive the equilibrium towards the formation of the spirocycle, we were concerned that scrambling of the stereochemical information initially contained in **4.008** (and **4.035**) would occur. It was therefore of paramount importance to accomplish the deprotection of **4.035** under neutral conditions.



Scheme 4.18

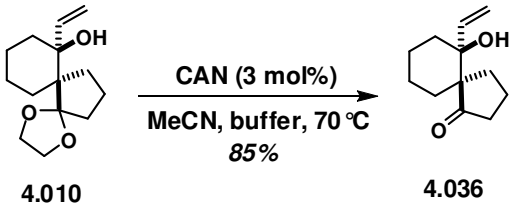
Once again, the CAN-catalysed protocol came to our rescue. Smooth unraveling of the dioxolane in **4.008** took place without any trouble whatsoever. As usual in the CAN-catalysed methodology, the crude product was essentially pure by ^{1}H-NMR analysis. It was important not to submit β-hydroxyketone **4.035** to purification by chromatography on silica gel (even if deactivated by the action of triethylamine), as fragmentation to the corresponding aldehyde readily took place. This cleavage occurred (slowly) upon prolonged storage of **4.035** in untreated $CDCl_3$, containing traces of HCl.



Scheme 4.19

In a similar manner, the tertiary allylic alcohol **4.010** also underwent smooth deprotection upon exposure to catalytic qantitites of CAN, providing **4.036** in 85% yield. The higher level of steric congestion of **4.036** is likely to render it a compound even more sensitive to retro-aldol fragmentation.

Nonetheless, no such fragmentation could be detected upon application of the CAN-mediated deprotection procedure (Scheme 4.20).

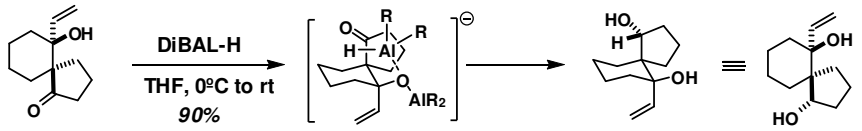


4.010 **4.036**

Scheme 4.20

Our interest in the use of unprotected β-hydroxyketones such as **4.035** or **4.036** arose from consideration that the free, pendant alcohol might direct the addition of incoming nucleophiles onto the ketone carbonyl.

Delightfully, treatment of **4.036** with an excess of DiBAL-H generated diol **4.037** as a single diastereoisomer. As shown in Scheme 4.21, it is quite likely that the free hydroxyl substituent undergoes rapid deprotonation by the first equivalent of organometallic reagent. The ensuing alkoxyde is then ideally placed to direct the nucleophile and thus control the stereochemistry of the resulting adduct.



4.036 **4.037**

Scheme 4.21

It can be hoped that a similar directive effect might occur upon addition of other organometallic reagents. Interestingly, a simple oxidative ozonolysis of **4.037** should deliver a diastereomerically pure GHB-analogue, either as the carboxylic acid or the corresponding methyl ester derivative. Furthermore, through this simple exercise, we have laid down some basic rules that could prove useful in the stereocontrolled functionalisation of spirocycles.

Use of the dioxolane substituent, as a blocking element for facial discrimination during nucleophilic attack, appears to be a viable strategy.[118] Its attempted application as a conformational lock, under the pretext of an approach to the total synthesis of Perhydrohistrionicotoxin, is the subject of the second half of this Chapter.

4.3. A novel approach towards the synthesis of Perhydrohistrionicotoxin

4.3.1. Introduction

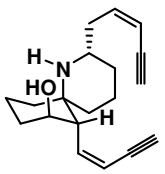
The histrionicotoxins are a family of 16 spirocyclic alkaloids, isolated from the skin extracts of the Columbian "poison arrow" frogs, of the family *Dendrobatidae* (examples are portrayed in Scheme 4.22). The parent compound of the series, Histrionicotoxin **4.045**, was isolated in 1971 by

[118] For further examples, see Chapter 5 and 6.

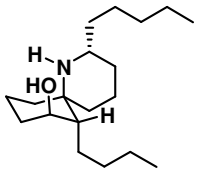
Witkop and co-workers from the neotropical *Dendrobates histrionicus*.[119] The attention given to the synthesis of the histrionicotoxin alkaloids stems from their unique properties as neurotoxins and their scarcity (*ca.* 200 μg per frog). It has been shown that Histrionicotoxin (HT) **4.045** and its non-natural analogue Perhydrohistrionicotoxin (PHT) **4.002** are potent blockers of acetylcholine-mediated ion conductance, thereby interrupting trans-synaptic transmission of neuromuscular impulses.[120] Both compounds are therefore of considerable importance in studying cholinergic receptor mechanisms in the neuromuscular system. From a structural viewpoint, it is interesting to note that the compounds of this family exist as all-axial 1,2,3-trisubstituted cyclohexane conformers (presumably stabilised by internal hydrogen-bonding), as shown.

[119] (a) Witkop, B. *Experientia* **1971**, *27*, 1121; (b) Daly, J.W.; Karle, I.; Meyers, W.; Tokuyama, T.; Waters, J.A.; Witkop, B. *Proc. Natl. Acad. Sci. U.S.A.* **1971,** *68,* 1870; (c) Tokuyama, T.; Venoyama, K.; Brown, G.; Daly, J.W.; Witkop, B. *Helv. Chim. Acta* **1974**, *57*, 2597; (d) Daly, J.W. *J. Nat. Prod.* **1998**, *61*, 162 and references therein.

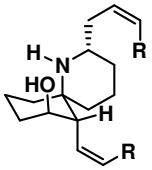
[120] Oliveira, L.; Madison, B.W.; Kapai, H.; Sherby, S.M.; Swanson, K.L.; Edelfraui, M.E.; Albuquerque, E.X. *Eur. J. Pharmacol.* **1987**, *140*, 331



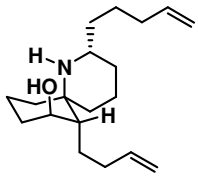
*Histrionicotoxin (**HT**)*
4.045



*Perhydrohistrionicotoxin (**PHT**)*
4.002



R = H *HT235-A* **4.046**
R = -CH=CH$_2$ *HT 287B* **4.047**



*Octahydrohistrionicotoxin (**OHT**)*
4.048

Scheme 4.22

Our interest in this family of natural products arose simultaneously with our entry in the field of fused- and spiro-bicyclic alkaloids, as described later on (Cf. Chapter 6). Recognising the particular challenge associated with the crafting of an azaspiro[5,5]undecane ring system, we viewed this compound as a benchmark for our laboratory's spiroannelation methodology, in analogy with the case of the Spirovetivane sesquiterpenes. Moreover, the nature of the stereochemical features embedded in **4.002** (which we selected as a relevant, preliminary target) predicated that *post*-spiroannelation stereocontrol (as opposed to the *pre*-spiroannelation tactic required in the Spirovetivanes) would be the main strategic element to implement in our design.

The rich chemical history of Histrionicotoxins features many imaginative approaches and a number of successful total syntheses.[121] We shall briefly review some of these endeavours in the following section, thus placing our work in perspective.

4.3.2. Literature survey

In this succint and non-exhaustive review, we will cover some published syntheses of Perhydrohistrionicotoxin (PHT) **4.002**. The syntheses are presented in chronological order and discussion will foccus on key-steps rather than on exhaustive details of every individual step.

4.3.2.1. E.J. Corey: (±)-PHT (1975)

Almost 4 years after the seminal report of Witkop, E.J. Corey reported the first synthesis of (±)-PHT.[122] Corey's elegant approach, highlighted in Scheme 4.23 and Scheme 4.24, would remain a classic among total syntheses of small natural products.

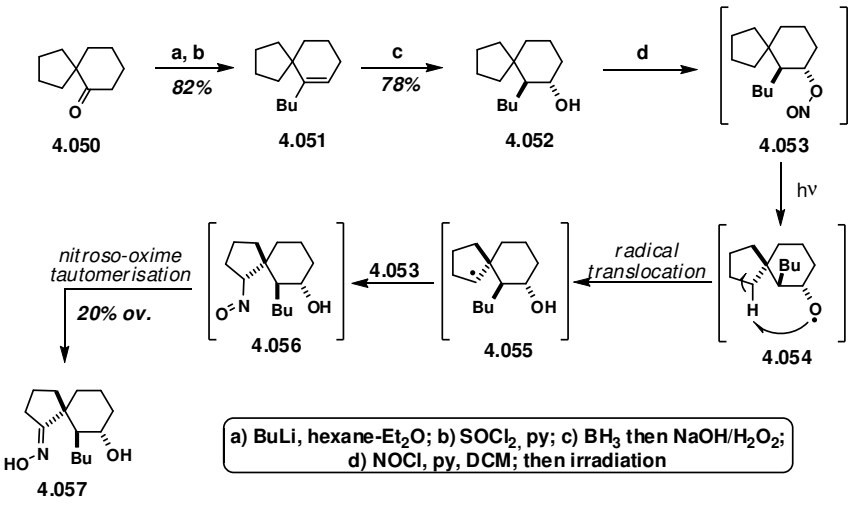
The synthesis begins with spiroketone **4.050**, which is readily olefinated to **4.051** by alkyllithium addition/elimination in good yield. The requisite *trans*-stereochemical relationship between the –OH and the butyl

[121] For early reviews, see: (a) Kotera, M. *Bull. Soc. Chim. Fr.* **1989**, 370; (b) Inubushi, Y.; Ibuka, T. *Heterocycles* **1982**, *17*, 507

[122] Corey, E.J.; Arnett, J.F.; Widiger, G.N. *J. Am. Chem. Soc.* **1975**, *97*, 430

side-chain is then set-up by a hydroboration/oxidation sequence, delivering **4.052** as a single diastereoisomer.

The key-manoeuver of the synthesis then takes place. Conversion of alcohol **4.052** to its nitrite ester **4.053**, directly followed by irradiation, triggers a cascade Barton reaction (remote functionalisation).[123] The mechanistic features of the process are outlined in the Scheme. Homolytic cleavage of the O-NO bond occurs under irradiation. The resulting oxygen-centered radical **4.054** then effects a [1,5]-hydrogen abstraction through the spirocyclic framework, generating the new carbon-centered radical **4.055**. This radical eventually recombines with NO, providing nitrosoalkyl compound **4.056** which undergoes rapid tautomerisation to the corresponding oxime **4.057**.



Scheme 4.23

[123] Barton, D.H.R.; Hesse, R.H.; Pechet, M.M.; Smith, L.C. *J. Chem. Soc., Perkin Trans.I* **1979**, *5*, 1159

Two aspects of this admirable application of the Barton reaction merit further comment. The first is that, since the hydrogen abstraction step is an intramolecular process, effective differentiation of both α-spiro methylene groups of the five-membered ring of **4.054** takes place. This ensures that oxime **4.057** is the only regioisomeric product obtained.

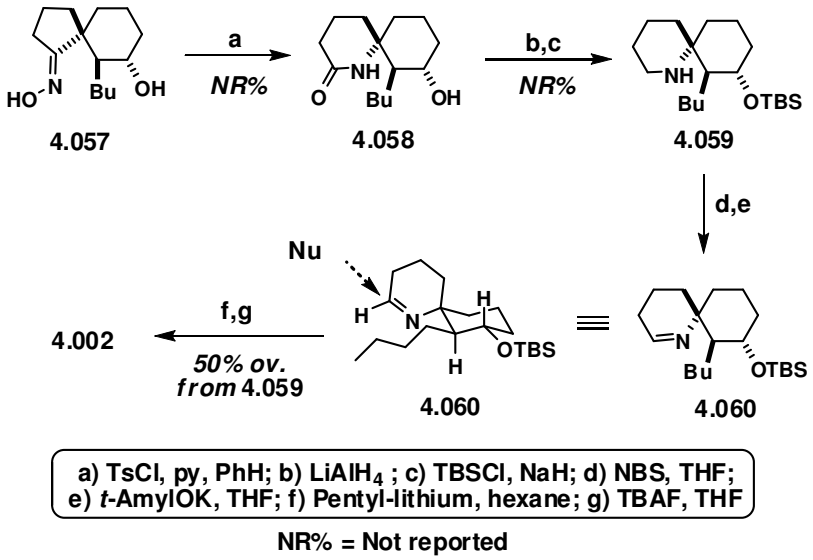
On the other hand, the elegance of this process is undermined by the low overall yield for the transformation (20%). This is probably due to either competitive hydrogen abstraction from the butyl side-chain or fragmentative side-reactions.

The synthesis proceeded from oxime **4.057** by application of the famous Beckmann rearrangement. Treatment of this oxime with tosyl chloride and pyridine gave "as the sole product the lactam **4.058**" (no yield reported). Rather than functionalising the lactam carbonyl, Corey and co-workers chose to completely reduce it to the piperidine with $LiAlH_4$ and protect the free alcohol as its TBS-derivative **4.059** (once again, no yields were reported). It should be noted that the original communication on the protection of alcohols as their silyl ethers by Corey himself had appeared only 3 years prior to this synthesis![124]

Conversion of **4.059** to PHT was accomplished through a four-step sequence, as shown in Scheme 4.24. Oxidation of the piperidine to the imine **4.060** preceded addition of the pentyl side-chain to generate the final stereogenic center of PHT **4.002**. It is at this stage that full perception of Corey's synthetic plan comes to light: the use of a bulky alcohol protecting group indeed blocks the molecule in an all equatorial conformation (as

[124] Corey, E.J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190

shown in Scheme 4.24). Addition of an incoming nucleophile should take place preferentially from the rearside, setting up the desired chiral centre present in the final product. Desilylation then affords PHT **4.002** in 50% overall yield from amine **4.059**.



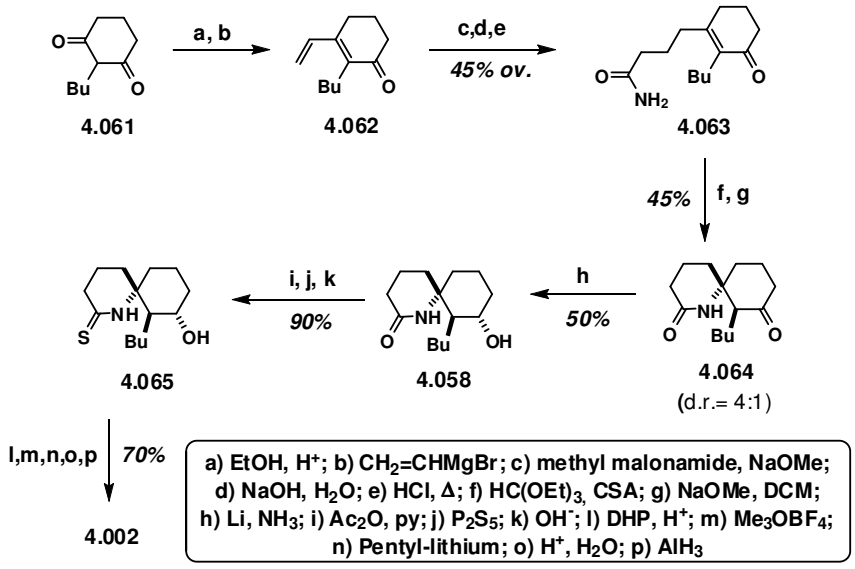
Scheme 4.24

Corey's plan is a masterpiece of its time in the way that it exploits classical reactions to fashion the requisite features of Perhydrohistrionicotoxin. Indeed, subsequent syntheses would target some of Corey's intermediates as interception points for formal synthesis. Unfortunately, the low efficiency of the key Barton-radical rearrangement cascade tarnishes the overall outcome of this approach.

4.3.2.2. Yoshito Kishi: (±)-PHT (1975)

In the same year as Corey's classical synthesis, Kishi and his group at the same University (Harvard) reported a number of approaches to the synthesis of PHT in two back-to-back communications in JOC.[125] The shortest sequence is depicted in Scheme 4.25.

Cyclohexane dione **4.061** is readily converted to vinylcyclohexenone **4.062** in two steps. Conjugate 1,6-addition of methyl malonamide onto **4.062**, followed by hydrolysis and decarboxylation then produces unsaturated amide **4.063**.



Scheme 4.25

[125] (a) Aratani, M.; Dunkerton, L.V.; Fukuyama, T.; Kishi, Y. ; Hakoi, H. ; Sugiura, S.; Inoue, S. *J.Org.Chem.* **1975**, *40*, 2009; (b) Fukuyama, T.; Dunkerton, L.V.; Aratani, M.; Kishi, Y. *J.Org.Chem.* **1975**, *40*, 2011

Formation of the key-spirocyclic framework was achieved through intramolecular conjugate addition under acidic conditions, producing **4.064** as the minor diastereomer. Fortunately, epimerisation afforded **4.064** as the major component of a 4:1 mixture of epimers.

Reduction of **4.064** with Li in ammonia then generated a common intermediate with the Corey synthesis, hydroxyamide **4.058**.

Kishi's endgame was different (and slightly longer) than Corey's route. It featured the conversion of the amide to a thioamide (with temporary protection of the free alcohol as the acetate) **4.065**. Following reprotection of the free alcohol as a THP ether, activation of the amide with Meerwein's reagent preceded nucleophilic attack by pentyl-lithium. Deprotection of the alcohol and reduction of the intermediate imine with alane finally produced PHT **4.002** in 70% yield from thioamide **4.065**.

It is noteworthy that the same sequence starting from the analog of **4.061** substituted with a *4-butenyl*, instead of a butyl side-chain, led to the first synthesis of octahydrohistrionicotoxin **4.048.**

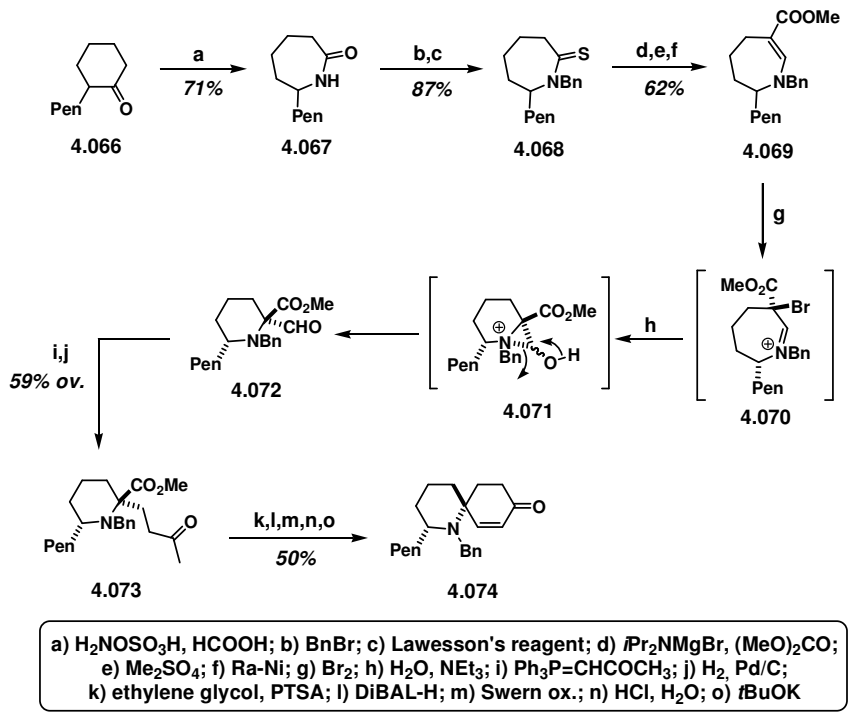
Kishi's pioneering synthesis produced PHT **4.002** in 17 steps and 6% overall yield.

4.3.2.3. Pierre Duhamel: (±)-PHT (1989)

An interesting, rearrangement-based strategy was disclosed by Duhamel *et al.* in France. The Duhamel synthesis hinges upon the ring-contraction of a tetrahydroazepine.[126]

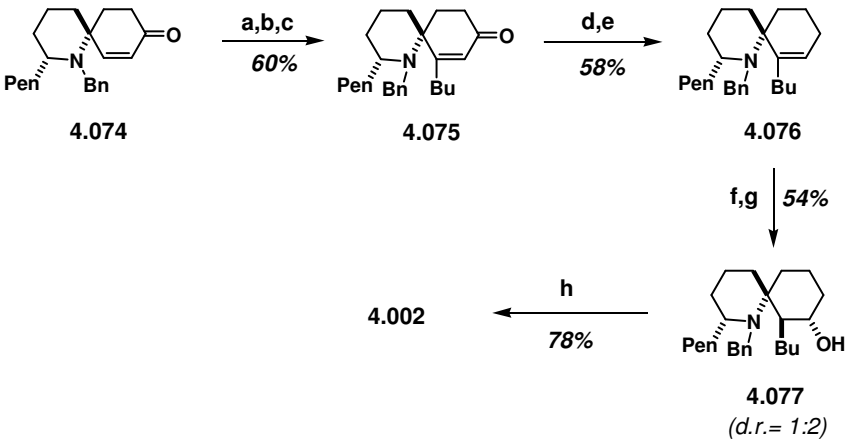
The required precusor for the key contraction step was synthesized as shown in Scheme 4.26. The 2-pentylcyclohexanone **4.066** readily undergoes Beckmann-rearrangement to caprolactam **4.067**. N-protection and conversion to the thiolactam **4.068** are followed by carbomethoxylation and transformation to cyclic enamine **4.069**. This sets the stage for the key-operation of this synthesis.

[126] Duhamel, P.; Kotera, M.; Monteil, T.; Marabout, B. *J. Org. Chem.* **1989**, *54*, 4419



Scheme 4.26

Exposure of **4.069** to the action of bromine, followed by mildly basic quench triggers the series of events depicted in Scheme 4.26. Reaction of the enamine with bromine generates the iminium salt **4.070**, which is captured by water. The tertiary amine thus generated intramolecularly displaces the bromide to form the bicyclic aziridinium salt **4.071**. Fragmentation of the latter in the manner depicted, finally accounts for the formation of aldehyde **4.072** as the single detectable product in the crude mixture. A rather lengthy and trivial elaboration of aldehyde **4.072** *via* the homologated ketone **4.073,** eventually culminates in an aldol ring-closure step generating the requisite spirocyclic piperidine **4.074**.



Scheme 4.27

The endgame in this approach is resumed in Scheme 4.27. Conjugate addition of dibutylcuprate to enone **4.074,** followed by regeneration of the enone function leads to **4.075**. A two-step reduction of the carbonyl group is then followed by a hydroboration/oxidation sequence, required to install the final stereogenic centers present in the natural product. Unfortunately, this step produces mainly the (undesired) diastereomer of **4.077** and proceeds in moderate yield. Debenzylation finally leads to PHT **4.002**.

Duhamel's approach to the construction of the azaspiro[5,5]undecane skeleton employs an elegant and highly efficient ring-contraction strategy. However, the subsequent circuitous sequence required for the elaboration of this adduct into the final product and, particularly, the low level of

stereoselectivity in the crucial hydroboration step are severe drawbacks of this route.

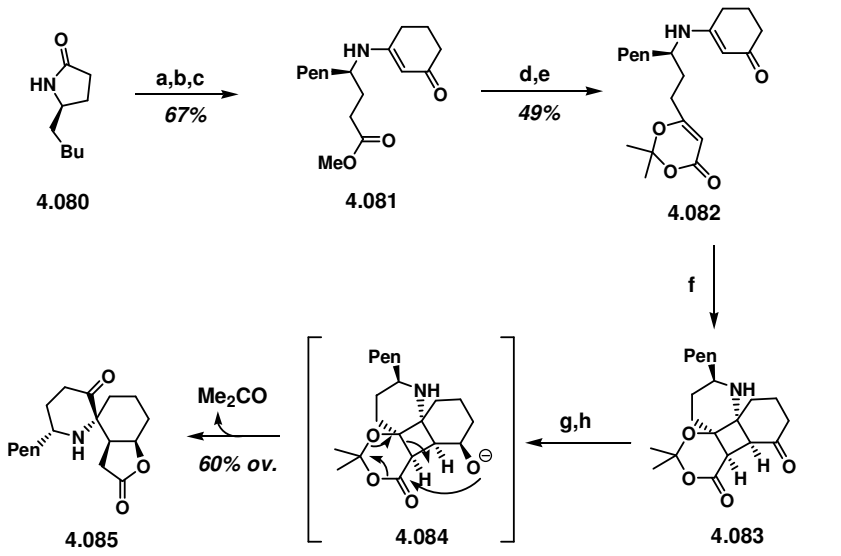
The synthesis described in this paragraph produced PHT **4.002** in 23 steps and 3% global yield.

4.3.2.4. Jeffrey Winkler: (-)-PHT (1989)

In the same year that the Duhamel synthesis was disclosed, Winkler proposed the first enantioselective construction of PHT.[127] His approach featured one of the reactions championed by the Winkler group throughout the years: the intramolecular photocycloaddition of a dioxenone.

The synthesis begins with the optically active glutamate derivative **4.080** (Scheme 4.28). Lactam-opening and condensation with 1,3-cyclohexanedione, followed by esterification, afford enaminoester **4.081** in good yield.

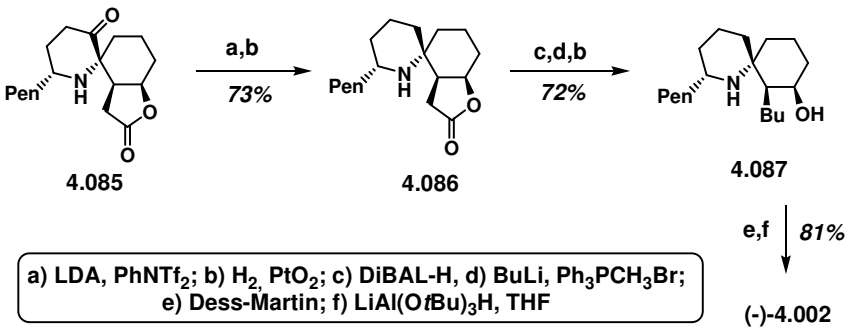
[127] Winkler, J.D.; Hershberger, P.M. *J. Am. Chem. Soc.* **1989**, *111*, 4852



Scheme 4.28

Construction of the dioxenone ring in **4.082** is uneventful and sets the stage for the key photochemical intramolecular [2+2] cycloaddition. Following irradiation, the congested tetracycle **4.083** is obtained and used immediately in for the fragmentation step.

As depicted, stereoselective reduction of the ketone carbonyl of **4.083** to the β-alcohol, followed by treatment with NaH, triggers translactonisation with concomitant loss of acetone and retro-aldol fragmentation, finally providing **4.085** in 60% overall yield from dioxenone **4.082**. In this elegant sequence, the lone stereocenter α- to nitrogen remarkably orchestrates the formation of all the remaining stereoelements of the final product (though one of these centers bears an "incorrect" configuration, *vide infra*).



Scheme 4.29

From **4.085**, a number of steps still remained before the completion of Winkler's synthesis (Scheme 4.29). Removal of the excedentary carbonyl group was achieved through enol triflate formation and exhaustive hydrogenolysis, providing **4.086** in good yield. Reductive lactone ring-opening followed by homologation and further reduction provided *epi*-PHT **4.087**, in which the hydroxyl group is β-oriented. Fortunately, Winkler and co-workers discovered that this could be corrected through oxidation and reduction with $LiAl(OtBu)_3H$, leading stereoselectively to (-)-PHT **4.002** in 81% yield.

Overall, the approach presented in this subsection proceeded in 15 steps and 8% yield from **4.080**. Furthermore, it makes clever use of a remote stereocenter to direct the installation of the subsequent stereogenic elements of the target molecule.

4.3.2.5. Deukjoon Kim: (±)-PHT (2000, Formal)

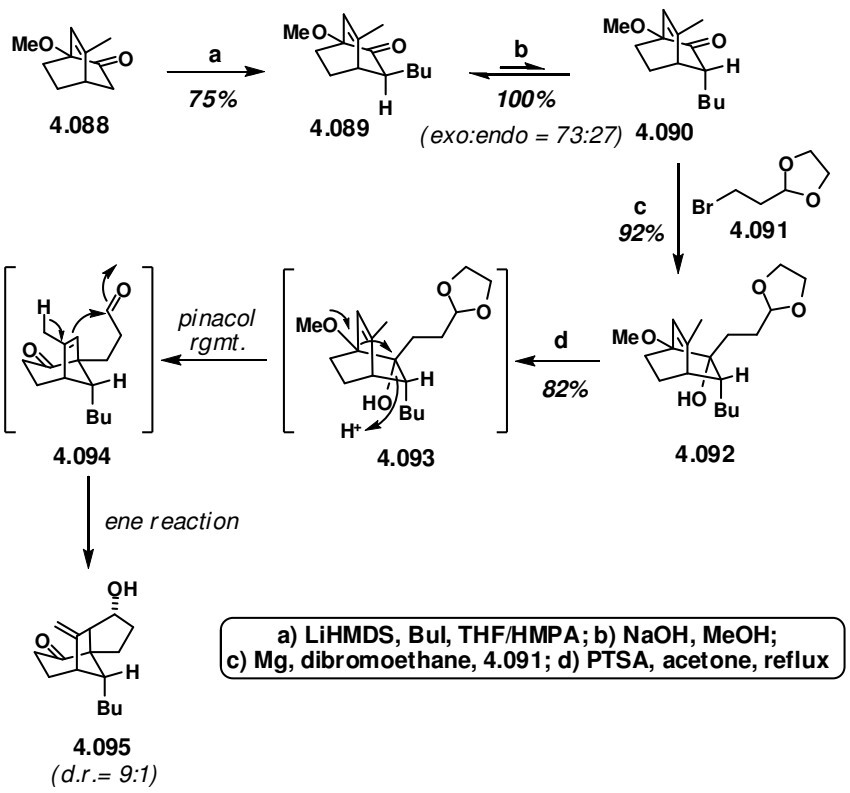
Following the seminal contributions of Corey and Kishi, it is not surprising that a number of synthetic approaches deliberately targeted advanced intermediates of these routes. Although a detailed coverage of all these approaches is beyond the scope of this brief overview, the approach developed by Kim and his group, in Seoul, merits comment for its relevance to our own strategy (*vide infra*).[128] Their synthetic pathway, interesting in its own right, features a number of noteworthy transformations.

As depicted in Scheme 4.30, alkylation of bicyclic ketone **4.088** with butyl iodide delivered the *exo* product **4.089** stereoselectively in 75% yield. Equilibration of this compound produces a mixture of isomers in which the (undesired) *exo*-product is still the main component. However, separation of the desired *endo*-adduct **4.090** and recycling of the *exo*-product allows for the preparation of multigram amounts of **4.090**. As might have been anticipated, Barbier addition of the Grignard reagent derived from **4.091** proceeds stereoselectively, leading to the tertiary alcohol **4.092** in 92% yield. This compound is the required precursor for a projected cascade sequence.

In the event, exposure of alcohol **4.092** to the action of PTSA in refluxing acetone triggered the transformations depicted, leading to tricyclic ketone **4.095** as a mixture of hydroxy-epimers in 82% yield. As shown, this interesting domino reaction features a pinacol-rearrangement with ejection

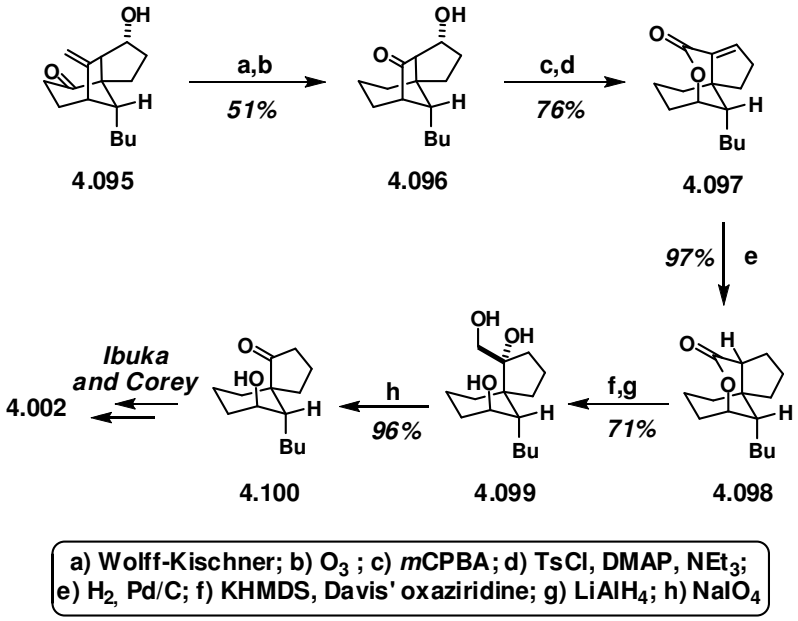
[128] Kim, D.; Shim, P.J.; Lee, J.; Park, C.W.; Hong, S.W.; Kim, S. *J. Org. Chem.* **2000**, *65*, 4864

of water. The *in situ* liberated aldehyde functionality is then ideally placed for a facile intramolecular ene reaction as portrayed in the Scheme.



Scheme 4.30

From the wealth of structural features contained in **4.095**, however, only the butyl side-chain (introduced at the very beginning of the sequence) is present in the target compound. The post-key-step manipulations, required to elaborate **4.095,** are summarised in Scheme 4.31.



Scheme 4.31

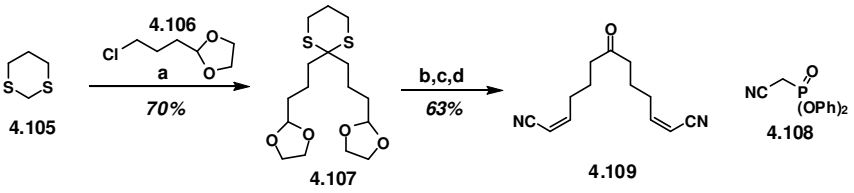
Removal of the carbonyl group of **4.095** was achieved through Wolff-Kischner reduction. Ozonolysis of the double bond then produced a new ketone **4.096**. Regioselective Bayer-Villiger ring-enlargement, followed by dehydration, led to the α,β-unsaturated lactone **4.097**, which was stereoselectively reduced in good yield. The α-oxygenation of the lactone from the rear face, followed by reductive ring-opening in the presence of $LiAlH_4$, generated the triol **4.099**, which was cleaved by the action of periodate, finally revealing ketoalcohol **4.100**. Remarkably, **4.100** already exists in the characteristic 1,2,3-all axial conformation of the Histrionicotoxins. This is presumably a consequence of hydrogen bonding to the ketone carbonyl of **4.100**. Furthermore, **4.100** had been previously

converted to oxime **4.057** (Scheme 4.23) by Ibuka and others.[129] Since **4.057** is an advanced intermediate in Corey's original synthesis, the approach by Kim *et al.* constitutes a formal synthesis of PHT **4.002**.

4.3.2.6. Robert Stockmann: PHT (2004)

We can not conclude this overview of completed syntheses of PHT **4.002** without addressing the elegant approach of Stockmann and co-workers. Relying on a two-directional dipolar cycloaddition, these authors discovered an extremely efficient way to rapidly assemble the requisite structural elements of PHT.[130]

The synthesis of the linear precursor for the key cycloaddition step is outlined in Scheme 4.32.



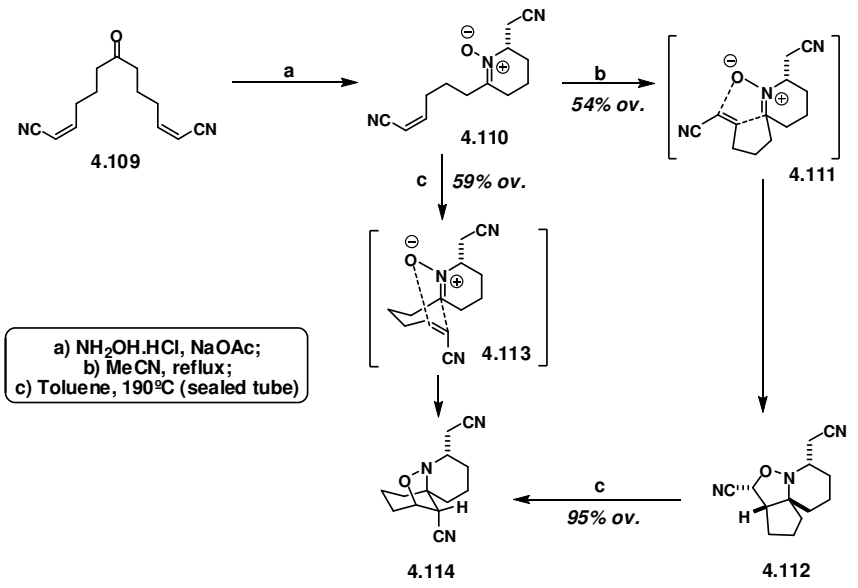
Scheme 4.32

[129] Ibuka, T.; Mitsui, Y.; Hayashi, K.; Minakata, H.; Inubushi, Y. *Tetrahedron Lett.* **1981**, *22*, 4425

[130] Stockmann, R.A.; Sinclair, A.; Arini, L.G.; Szeto, P.; Hughes, D.L. *J. Org. Chem.* **2004**, *69*, 1598

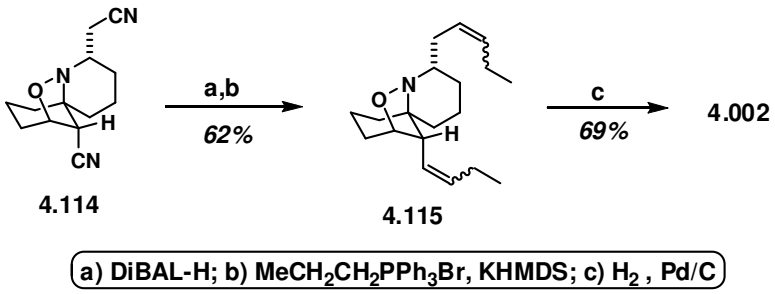
This straightforward sequence begins with the double alkylation of dithiane **4.105** with the chloride **4.106**. Dioxolane deprotection, followed by *Z*-selective (12:1 ratio) olefination with the Ando-like phosphonate **4.108,** affords the double unsaturated nitrile. Unmasking of the dithiane finally provides **4.109** in 44% overall yield from commercially available **4.105**.

The key cycloaddition step is represented in Scheme 4.33. Treatment of ketone **4.109** with hydroxylamine forms a transient oxime which directly adds onto one of the pendant unsaturated nitriles in a Michael fashion, generating nitrone **4.110**. Interestingly, heating the crude nitrone **4.110** in acetonitrile induced an intramolecular [3+2]cycloaddition that gave the kinetic [5,5,6]-tricyclic system **4.112,** through the less hindered transition state represented as **4.111**. Heating adduct **4.112** in toluene at 190ºC gave the desired, thermodynamically favored regioisomer **4.114,** through a presumed retro-[3+2]-cycloaddtion and further cycloaddition *via* transition-state **4.113**. The cycloadduct **4.114** can also be directly accessed from nitrone **4.110** by direct thermolysis in toluene.



Scheme 4.33

From the thermodynamic product **4.114**, the endgame only required three steps (Scheme 4.34). DiBAL-H reduction of the two nitrile functions afforded a dialdehyde which was homologated through a Wittig reaction (8:1 d.r. obtained). Hydrogenolysis of the double bonds, as well as of the N-O linkage, finally provided PHT **4.002**.



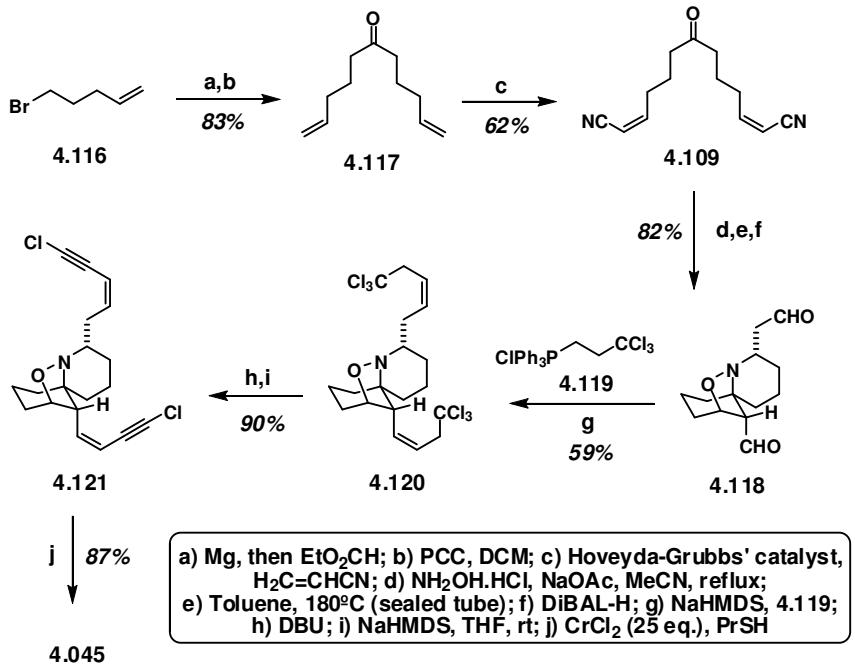
Scheme 4.34

This remarkable synthesis is a beautiful exploitation of symmetry in organic chemistry. Stockmann *et al.* produced PHT in only 9 steps from 1,3-dithiane, with an 11% overall yield.

More recently, Stockmann upgraded this synthetic scheme for the preparation of the unsaturated natural product, HTX **4.045**. His renewed plan featured an improved, three-step access to **4.109** from commercially available substances (Scheme 4.35).[131]

Thus, double addition of the Grignard reagent derived from 5-bromopentene **4.116** to ethylformate, followed by PCC oxidation, led directly to doubly unsaturated ketone **4.117**. The utility of cross-metathesis in supressing a potential ozonolysis-Wittig sequence is put to good use, as it allows the direct homologation of **4.117** to bis-nitrile **4.118** in reasonable yield.

[131] Karatholuvhu, M.S.; Sinclair, A.; Newton, A.F.; alcaraz, M.L.; Stockmann, R.A.; Fuchs, P.L. *J. Am. Chem. Soc.* **2006**, *128*, 12656



Scheme 4.35

Dinitrile **4.109** is then elaborated as before into the dialdehyde **4.118** in 82% overall yield. At this stage, the issue of inserting the unsaturated side-chains comes into play. Stockmann *et al.* based their approach upon previous similar work by Holmes and his group[132]. In this contribution, they used the trichlorophosphonium salt **4.119** for the initial, *Z*-selective Wittig reaction to provide **4.120**. This reaction was particularly problematic and the reported result required extensive optimisation. Double dehydrochlorination of **4.120**, first with DBU and then with NaHMDS, led to bis-chloroalkyne **4.121** in excellent yield.

[132] Williams, G.M.; Roughley, S.D.; Davies, J.E.; Holmes, A.B. *J. Am. Chem. Soc.* **1999**, *121*, 4900

The problem of reducing selectively the N-O bond and the C-Cl linkages, without affecting the rest of the unsaturations in this complex intermediate, was far from trivial. In the event, Stockmann solved this problem by employing a large excess of $CrCl_2$ in the presence of propylsulphide. These conditions finally provided HT **4.045** in 87% yield.

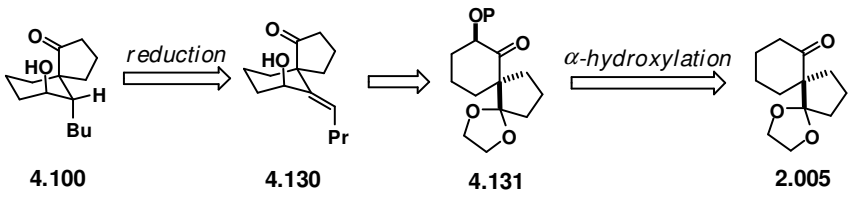
This rounded up Stockmann's work on the Histrionicotoxin family, with an elegant synthesis proceeding in 9 steps and 19% overall yield.

More than 30 years of history lay behind us as we considered an alternative approach to the synthesis of PHT. The challenge posed by the structural features of this compound had been addressed by several researchers, culminating in syntheses as elegant as the Stockmann route. Our own interest in this compound stemmed from the recognition of its inherent similarity with some of our spirocyclic products. The story of our evolving approaches to the synthesis of PHT is laid down in the following subsections.

4.3.3. Strategy

During our work, different approaches towards PHT were envisaged. All of them were guided by structure **4.100**, targeted in the Kim formal synthesis (Cf. Section 4.3.2.5). Initially, we considered the possibility of introducing the hydroxy substituent early in the synthesis, and using it to control the stereochemistry of the butyl side-chain. As shown in Scheme 4.36, hydroxyl-directed reduction of allylic alcohol **4.130** should lead to the stereochemical relationship present in **4.100**. If the alkene could be

fashioned from a ketone carbonyl through Wittig-like processes, our plan should then boil down to a stereocontrolled α-hydroxylation of the readily available spirocycle **2.005**.

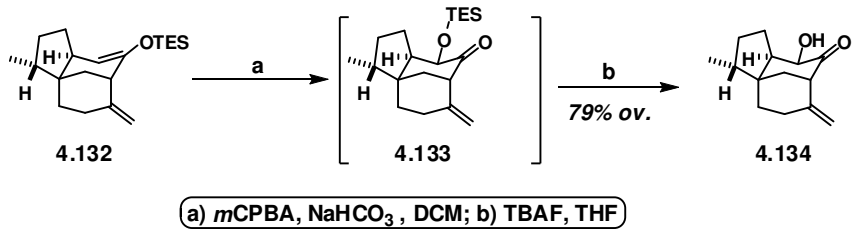


4.100 **4.130** **4.131** **2.005**

Scheme 4.36

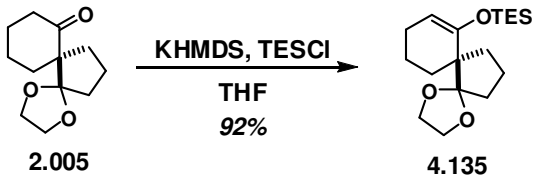
4.3.4. Results and discussion

We began by investigating methods to convert **2.005** to a species such as **4.131**. Arguably, the Rubottom reaction is one of the best methods for the direct introduction of a protected oxygenated function α–to a ketone carbonyl. Although seldom used for the preparation of α-siloxyketones, the Rubottom reaction can lead to the desired product if harsh acidic/basic/fluoride workup conditions are avoided. In particular, if the silyl enolether bears a silicon moiety which is robust enough, good yields of the α-siloxy ketone are usually obtained. For instance, in their synthesis of hispidospermidin, Danishefsky *et al.* achieved the oxygenation of silyl enolether **4.132** through oxidation with *m*CPBA, leading to α-siloxyketone **4.133**. Desilylation with TBAF eventually delivered the desired α-hydroxyketone **4.134**.



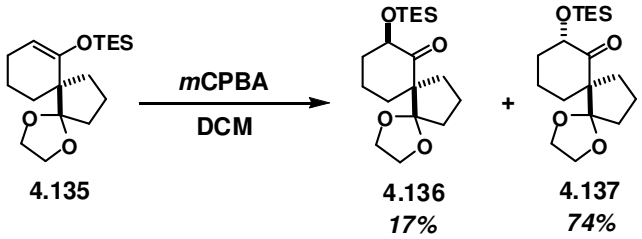
Scheme 4.37

As depicted below (Scheme 4.38), ketone **2.005** was easily converted to its TES-silyl enolether **4.135**, in excellent yield, by treatment with KHMDS and excess TESCl.



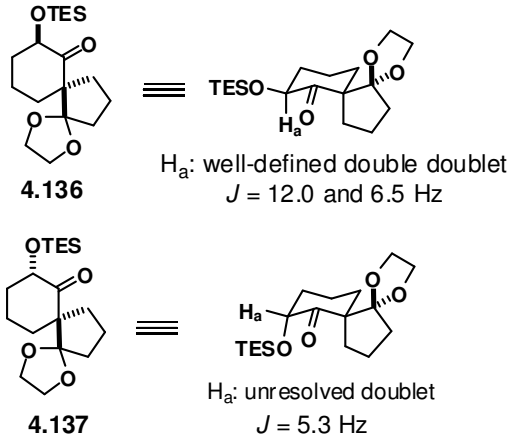
Scheme 4.38

Rubottom oxidation of this compound with *m*CPBA led cleanly to the formation of two new products: the diastereomeric α-silyloxy ketones **4.136** and **4.137**.



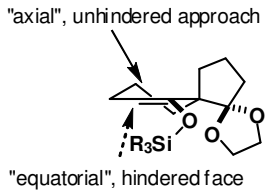
Scheme 4.39

Assignment of the stereochemistry of the α-siloxyketones was readily done through inspection of their ^{1}H-NMR spectra. Particularly revealing is the chemical shift of H_a. As we had previously observed, axially oriented hydrogen atoms have clearly defined features, in terms of multiplicity and pattern of coupling constants. From these analyses, it transpired that the major isomer is **4.137**, accompanied by its epimer **4.136**.



Scheme 4.40

From our previous discussion on GHB-analogues, this is hardly a surprising observation. Indeed, analysis of the structure of silyl enolether **4.135** reveals that the two possible approaches of an incoming electrophile are sterically non-equivalent. The so-called "axial" approach, usually favored on stereoelectronic grounds, also occurs this time from the least-hindered face of the silyl enolether double bond.

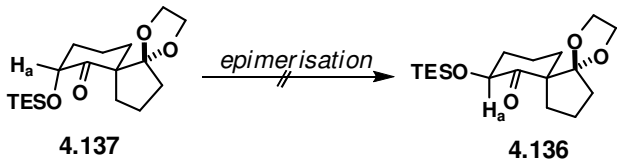


4.138

Scheme 4.41

When Oxone or DMDO were used as the oxidants, **4.137** was the only product detected by analysis of the crude reaction mixtures. This result suggests that the electrophilic character of *m*CPBA is actually responsible for some epoxidation (*ca*. 20%) occuring from the most-hindered face, presumably through hydrogen-bonding to the dioxolane oxygens. Unfortunately, we were unable to reverse the observed tendency for epoxydation *anti*- to the ketal substituent through temperature or solvent changes.

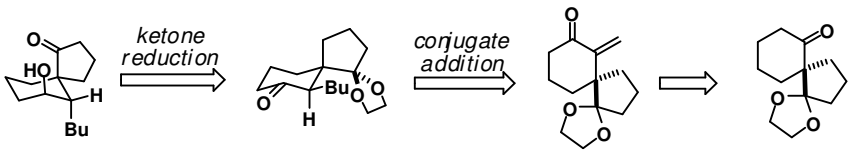
This is not dramatic, since isomer **4.136** is bound to be thermodynamically more stable than its epimer **4.137**. Indeed, all the bulky substituents in **4.136** occupy equatorial positions around the cyclohexane ring. We reasoned that, since the proton H_a is acidic, epimerisation might be possible. Unfortunately, our attempts to bring about such an epimerisation by exposure of **4.137** to either inorganic (NaOH, Na_2CO_3) or organic (DBU) bases, led instead to rapid TES-deprotection and to the formation of a mixture of α-hydroxyketones through the well-known α-ketol reorganisation.



4.137 **4.136**

Scheme 4.42

Our efforts were most likely thwarted by the relatively low stability of TES-ethers in basic media. Although it might be possible to achieve such an epimerisation with an α-silyloxyketone bearing a more robust silyl functionality (such as TBDPS or TIPS), we actually considered an intellectually more stimulating possibility. Instead of trying to fight the pervasive "dioxolane-effect", why not to take advantage of it? This was the motto underlying our revised approach towards the preparation of ketone **4.100** (Scheme 4.43).



4.100 **4.138** **4.139** **2.005**

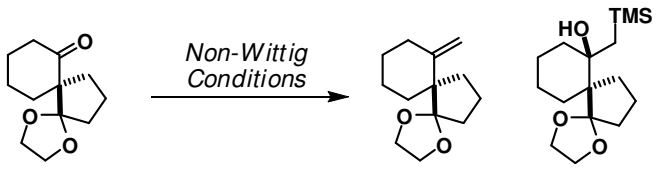
Scheme 4.43

It was thus envisioned that the stereocontrolled ketone reduction of **4.138**, followed by deprotection, might provide the desired product **4.100**. In compound **4.138**, the exploitation of the "dioxolane-effect" is now clear. The preference for equatorial orientation of the dioxolane should ensure that **4.138** is the thermodynamically prefered epimer at the α-ketocarbon.

Removing three carbon atoms from the butyl side-chain leads to enone **4.139**, which might be accessible from building block **2.005**.

For the conversion of **2.005** to carbonyl-transposed enone **4.139**, we considered a sequence involving a methylenation and an allylic oxidation. Since no relevant data on the methylenation of α-spirannic ketones was found in the literature, and since this conversion was deemed to be an important issue, we tested different methods commonly used to effect such a transformation.

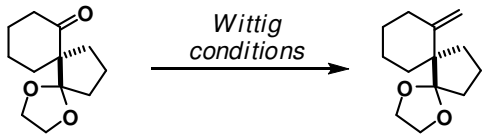
For better visualisation, all non-Wittig reactions are summarised in Table 4.2 whilst Wittig processes follow in Table 4.3.



2.005 **4.140** **4.141**

Table 4.2

Entry	*Reaction type*	*Conditions*	*Result*
1	Peterson	$TMSCH_2Li$, THF	<5% of **4.141**
2		$TMSCH_2MgCl$, THF	20% of **4.141**
3		$TMSCH_2MgCl$, $CeCl_3$, THF	60% of **4.141**
		then NaH, THF	Decomposition (traces of **4.140**)
4	Petasis	Cp_2TiMe_2, THF, reflux	0%
5		Cp_2TiMe_2, toluene, reflux	0%



2.005 **4.140**

Table 4.3

Entry	*Phosphonium salt*	*Conditions*	*Result*
1	Ph_3PMeBr (2 eq)	BuLi, THF	23%
2	Ph_3PMeBr (2 eq)	KHMDS, THF	40%
3	Ph_3PMeBr (2 eq)	KHMDS, THF, reflux	60%
4	Ph_3PMeBr (2 eq)	*t*BuOK, toluene, reflux	80%
5	Ph_3PMeI (2 eq)	*t*BuOK, toluene, reflux	96%
6	Ph_3PMeI (1.3 eq)	*t*BuOK, toluene, reflux	94%

As can be seen from Table 4.2, the Peterson reaction (entries 1-3) was among the first non-Wittig processes investigated.[133] The hindered nature of the carbonyl group in **2.005**, coupled with the lowered nucleophilicity of the anion $TMSCH_2M$ (M=MgBr, Li), contributed to a decreased efficiency of the addition step. Furthermore, when diastereomerically pure β-hydroxysilane **4.141** was treated with NaH in THF, only traces of the desired olefin could be observed along with numerous by-products. Surprisingly, the Petasis reagent left our ketone **2.005** untouched, in spite of numerous attempts (two examples compiled in entries 4-5).

The Wittig reaction[134] was more rewarding in this respect, although subtle factors were at play (Table 4.3). It turned out that the nature of the base and of the counterion employed, as well as of the solvent, were crucial (entries 1-4). The best results were obtained with the *iodide*, Ph_3PMeI, instead of the commercially available bromide Ph_3PMeBr (entries 5-6). It would seem that precipitation of the less soluble KI is an important factor in the success of this reaction. In this manner, the amount of phosphonium salt could be reduced to a slightly suprastoichiometric quantity (1.3 eq) without compromising the efficiency of the reaction. Reproducibly high yields (> 90%) of the particularly fragrant alkene **4.140** could thus be obtained.

Having established a viable route to **4.140**, we then focused on the key allylic oxidation step.

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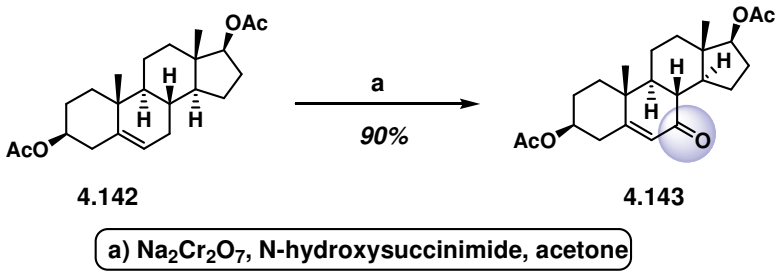
[133] For a recent review, see: van Staden, L.F.; Gravestock, D.; Ager, D.J. *Chem. Soc. Rev.* **2002**, *31*, 195

[134] Maryanoff, B.E.; Reitz, A.B. *Chem. Rev.* **1989**, *89*, 863

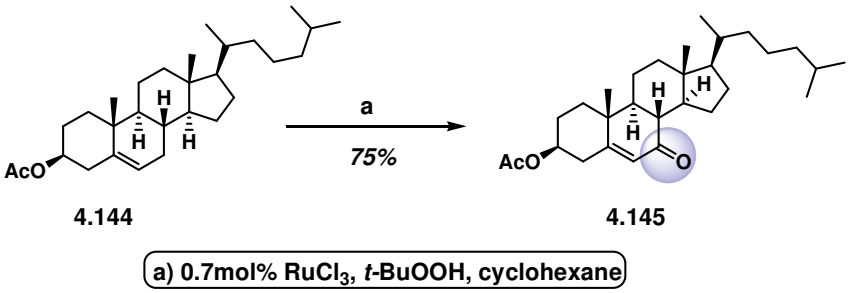
A number of different methodologies have been developed for the allylic oxydation of cycloalkenes. This kind of reactions are extensively used in steroid functionalisation. For instance (Scheme 4.44), the androstene derivative **4.142** can be selectively converted to enone **4.143** by treatment with sodium dichromate and N-hydroxysuccinimide in acetone, in high yield.[135]



Scheme 4.44

Scientists at Merck have reported a similar oxidation proceeding with catalytic amounts of $RuCl_3$, in the presence of *tert*-butylhydroperoxyde (TBHP) as the stoichiometric oxidant.[136]

[135] Zheng, Y.; Li, Y. *J. Org. Chem.* **2003**, *68*, 1603
[136] Miller, R.A.; Li, W.; Humphrey, G.R. *Tetrahedron Lett.* **1996**, 3429

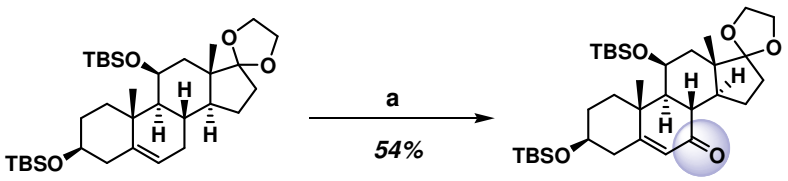


4.144 **4.145**

a) 0.7mol% $RuCl_3$, *t*-BuOOH, cyclohexane

Scheme 4.45

Among the favorite reagents for this transformation is a combination of chromium trioxide and 3,5-dimethylpyrazole. Danishefksy used such a mixture to effect oxidation of **4.146** to **4.147** in his synthesis of a novel steroid with neurotrophic activity (Scheme 4.46).[137]



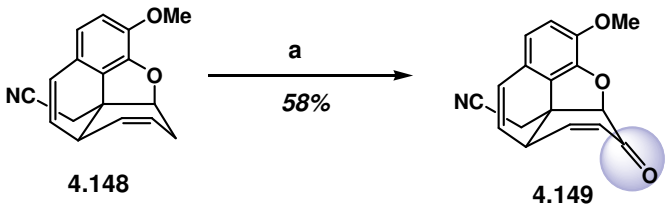
4.146 **4.147**

a) xs. CrO_3, 3,5-dimethylpyrazole, DCM

Scheme 4.46

[137] Hua, Z.; Carcache, D.A.; Tian, Y.; Li, Y.-M.; Danishefsky, S.J. *J. Org. Chem* **2005**, *70*, 9849 and references therein.

Interestingly, when substrates other than steroids are employed, the reagent of choice appears to be SeO_2, pioneered by Sharpless.[138] For example, Trost and Tang combined an allylic oxidation and a Dess-Martin oxidation to install the ketone function in their synthesis of (-)-Morphine and (-)-Codeine (Scheme 4.47).[139]



Scheme 4.47

As depicted, treatment of **4.148** with stoichiometric amounts of SeO_2 in refluxing dioxane afforded a mixture of the allylic alcohol and the corresponding enone. Direct addition of Dess-Martin periodinane to the mixture provided exclusively the enone **4.149** in 58% yield.[140]

With this information in hand, we undertook a study of the conditions required for the allylic oxidation of alkene **4.140**. Our results are summarised in Table 4.4.

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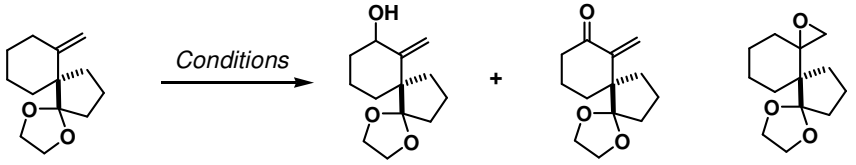
[138] (a) Umbreit, M.A.; Sharpless, K.B. *J. Am. Chem. Soc.* **1977**, *99*, 5526; (b) Arigoni, D.; Vasella, A.; Sharpless, K.B.; Jensen, H.P. *J. Am. Chem. Soc.* **1973**, *95*, 7917

[139] Trost ; B.M.; Tang, W. *J. Am. Chem. Soc.* **2002**, *124*, 14542

[140] For a similar example, cf. Fukuta, Y. ; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am.Chem.Soc.* **2006,** *128,*6312



4.140 **4.155** **4.139** **4.156**

Table 4.4

Entry	*Conditions*	*Result*
1	NOS (4 eq), $Na_2Cr_2O_7$ (1 eq), acetone	**4.140** + traces **4.156**
2	TBHP, $RuCl_3$ (cat), cyclohexane	**4.140**
3	CrO_3, 3,5-dimethylpyrazole	Complex mixture
4	SeO_2, TBHP	**4.140**
5	SeO_2 (2 eq), dioxane, reflux	58% **4.139** + 17% **4.155**
6	As entry 6 + add 1 eq DMP	Complex mixture
7	SeO_2 (4 eq), dioxane, reflux	Complex mixture
8	SeO_2 (2 eq), H_2O (cat), dioxane, reflux	Complex mixture
9	SeO_2 (1 eq), dioxane, reflux	50% **4.140** + mixture containing **4.155**, **4.139**
10	SeO_2 (2 eq), dry THF, reflux + add 20 eq MnO_2	70% **4.139**
11	As entry 10 + add 1,5 eq DMP	75% **4.139**

Legend: NOS = N-hydroxysuccinimide, TBHP = *tert*-butylhydroperoxide, DMP = Dess-Martin periodinane.

Though olefin **4.140** posesses a single methylene group susceptible to allylic oxidation, some efforts were required before the coveted enone **4.139** could be obtained. The only conditions that led to the formation of allylic oxidation products involved the use of selenium dioxide; all other protocols failed (entries 1-4).

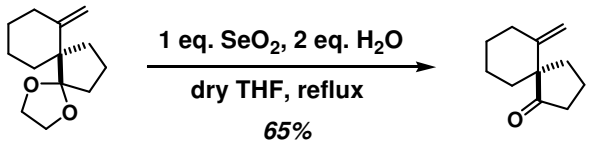
Nonetheless, this reaction also displayed a peculiar behaviour. The direct addition of Dess-Martin periodinane to the reaction mixture led only to mixtures of decomposition products (entry 6). Using more than 2 eq of selenium dioxide afforded numerous side-products, whereas less than that amount provided incomplete conversion of the starting material. Finally, we found that changing the solvent to THF, followed by evaporation, addition of dichloromethane and an excess of manganese dioxide provided good yields of the enone **4.139**. Since the manganse dioxide reactions were somewhat erratic and required a large excess of this inorganic reagent, we settled for Dess-Martin periodinane as the oxidant.

It should be noted that the intermediate alcohol **4.155** was always obtained as a mixture of stereoisomers, with one of them largely predominant. No efforts were made to determine the stereochemistry of this isomer (although a "dioxolane-effect" akin to our previous observations might be at play).

Interestingly, adding water to the reaction mixture contributed to the formation of complex mixtures of products (entry 8), despite the fact that it is commonly accepted that hydration of SeO_2 to seleninic acid precedes the *ene*-like oxidation step.

Furthermore, the reactions in dioxane (reagent-grade dioxane used throughout) displayed a certain degree of variability in terms of yield and reaction profile.

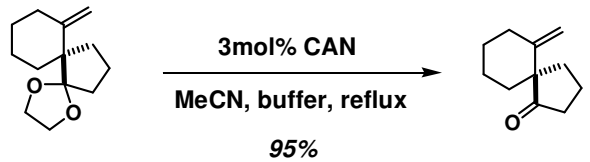
Surprisingly, when the allylic oxidation was performed with 1 eq. of SeO_2, in dry THF containing 2 eq. H_2O, the major product obtained was the deprotected alkene **4.157** (Scheme 4.48).



4.140 **4.157**

Scheme 4.48

The structure of **4.157** was further verified by CAN-catalysed deprotection of **4.140**, which led to the same product (Scheme 4.49).

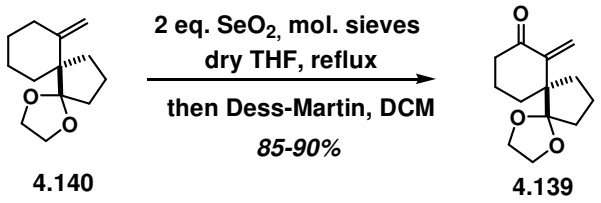


4.140 **4.157**

Scheme 4.49

A plausible explanation could rest upon the formation of seleninic acid in the reaction mixture. Even the mild acidity of this compound could be sufficient to initiate deprotection of the dioxolane in the presence of excess water. The variable amounts of water present in reagent-grade dioxane might be responsible for the erratic behaviour observed in this solvent.

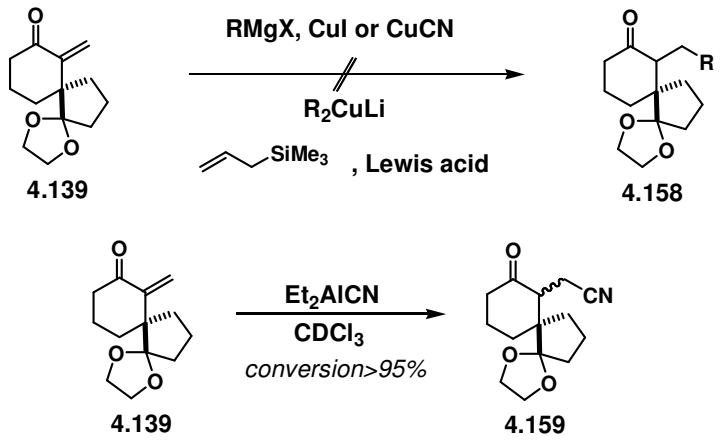
Hence, repeating the allylic oxidation sequence using 4Å molecular sieves and rigorously dried THF, followed by evaporation of the solvent, addition of dichloromethane and of Dess-Martin periodinane, now led to enone **4.139** in consistently high yields (Scheme 4.50).



Scheme 4.50

Having established an efficient reaction sequence for the preparation of enone **4.139**, we then turned our attention to its ability to act as a Michael acceptor.

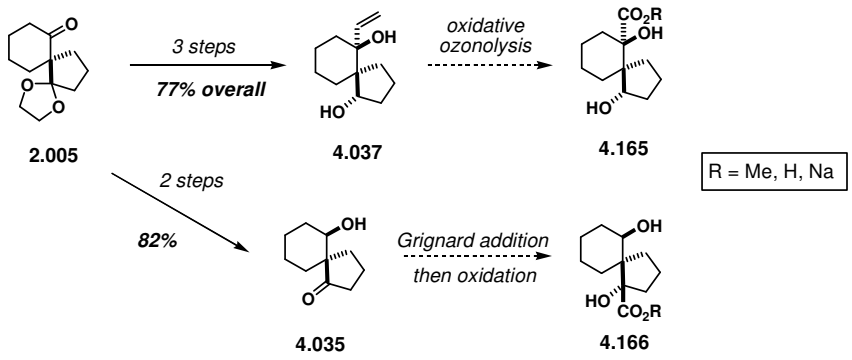
Unfortunately, enone **4.139** eluded all our efforts to add cuprate and cuprate-like reagents, in spite of numerous attempts. Allylation with allyltrimethylsilane in the presence of a variety of Lewis-acids, also failed. In all cases numerous decomposition products were obtained, which may originate from the high sensitivity of enone **4.139**. Indeed, this enone gradually decomposed at room temperature. We believe that bifunctional reagents might hold the solution to this predicament, as a test performed in an NMR-tube with Et_2AlCN indeed led to the rapid formation of what we believe to be the product **4.159**, resulting from the conjugate addition of cyanide.



Scheme 4.51

4.4. Conclusions and perspectives

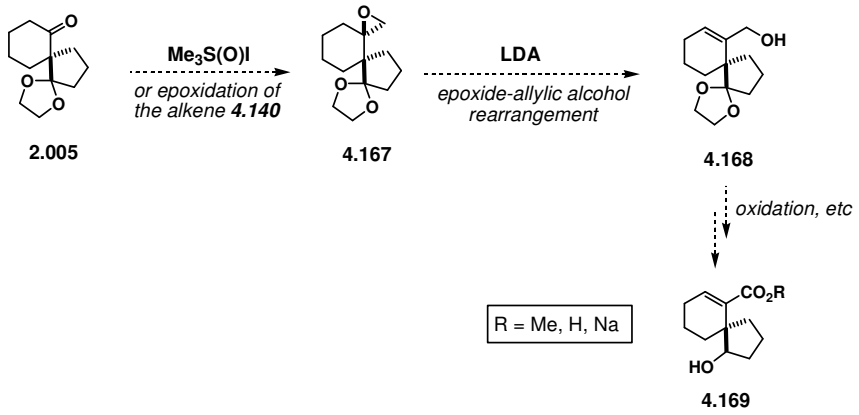
From this little incursion into the chemistry of spirobicycle **2.005**, a number of interesting conclusions can be drawn. First of all, we have gained a better understanding of the factors controlling the stereoselectivity of additions to carbonyl groups at the α-position relative to the spirannic center of our spirocycles. Indeed, we have witnessed what we have (naïvely) coined a "dioxolane-effect", which is essentially a steric blocking of one of the faces of the carbonyl functionality. Making use of this and other simple effects, we have been able to efficiently prepare a precursor for the synthesis of GHB-analogues (**4.037**). It is also conceivable that other, related compounds (such as **4.166**) might be accessed in short order through a similar strategy (Scheme 4.52).



2.005 **4.037** **4.165** **4.035** **4.166**

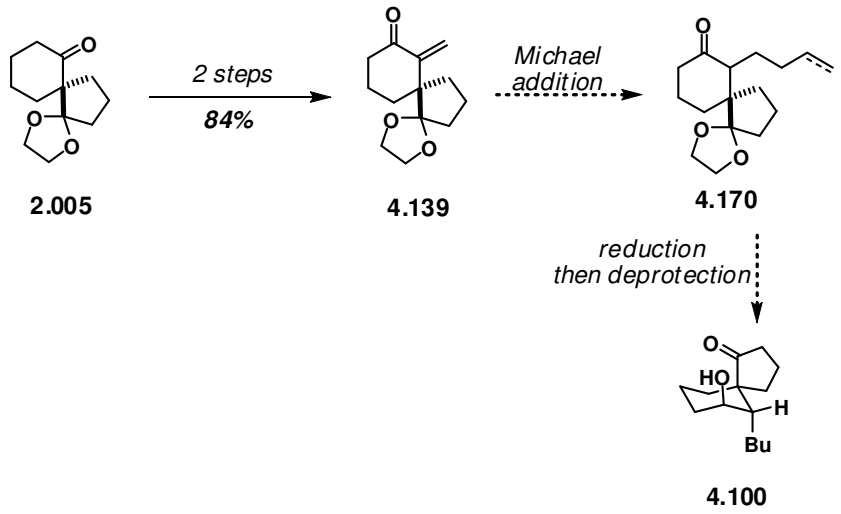
Scheme 4.52

Once these compounds have been prepared, the whole sequence could be reiterated starting from different analogues of **2.005** bearing various ring-sizes and substituents (such as **2.016**, cf. Scheme 4.7). It should also be possible to obtain unsaturated derivatives through a simple application of the epoxide-allylic alcohol rearrangement, as shown in Scheme 4.53.



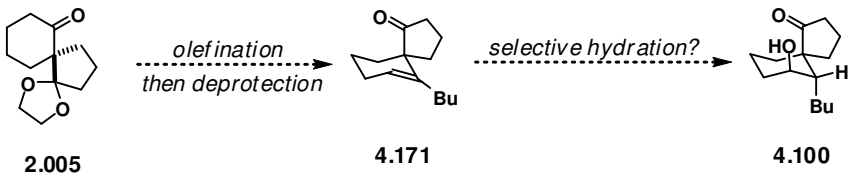
Scheme 4.53

In the latter part of this Chapter, we have described some exploratory work aimed at paving the way towards a synthesis of Perhydrohistrionicotoxin **4.002**. We were able to delineate conditions for the successful Wittig olefination of ketone **2.005** and its subsequent allylic oxidation to enone **4.139**. This compound holds promise as a key building block to access the crucial intermediate **4.100**.



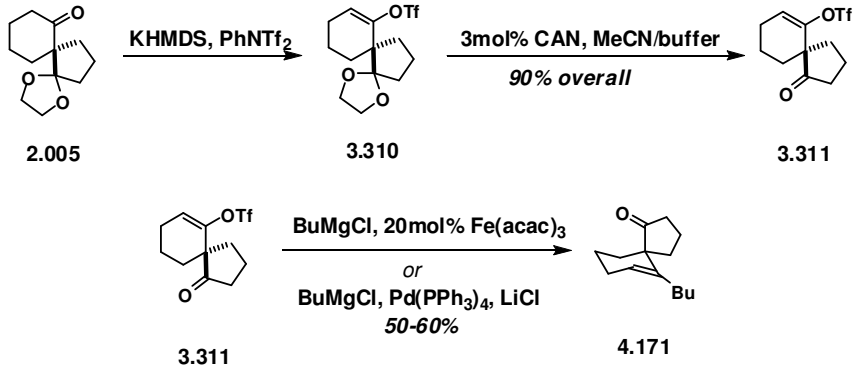
Scheme 4.54

We can also propose other routes to ketone **4.100**. For instance, if the trisubstituted alkene **4.171** could be prepared, it would be interesting to probe the diastereoselectivity of its hydroboration. We might be able to either selective hydrate the double bond or to take advantage of the free carbonyl group to reductively direct the installation of the H-OH groups upon hydration of the double bond (Scheme 4.55).



Scheme 4.55

Some steps in the direction depicted in Scheme 4.55 testify to the viability of preparing compound **4.171**. Indeed, we have (unsurprisingly) confirmed the reluctancy of the protected enol triflate **3.310** to undergo metal-catalysed coupling (Cf. Chapter 3).



2.005 → 3.310 → 3.311

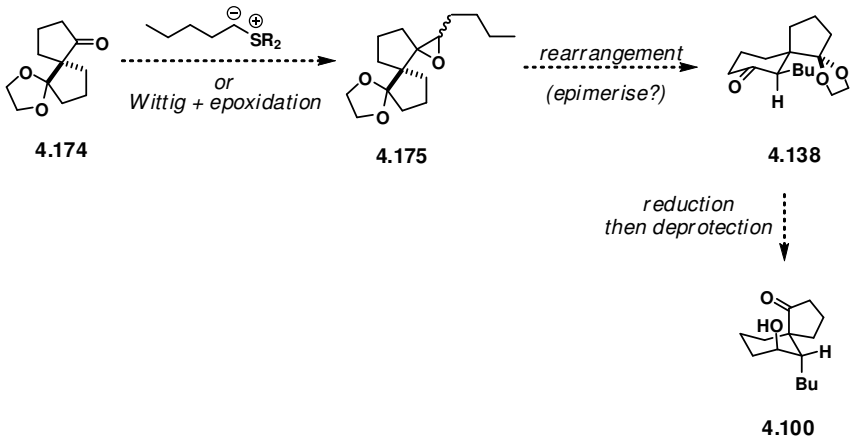
3.311 → 4.171

Scheme 4.56

As we had then found, deprotection of **3.110** to **3.311** proceeded smoothly. Furthermore, coupling of the triflate **3.311** with a butyl donor under either iron- or palladium-mediated catalysis, provided **4.171** in moderate yield. The main side reaction in this largely unoptimised process is the reduction of the triflate **3.311** to a disubstituted alkene, possible by reductive elimination of a β-hydrogen atom from the organometallic alkyl donor.

A final, even more interesting possibility for the synthesis of ketone **4.100** derives from our fondness for ring-enlargement reactions (Scheme 4.57). If the lower homologue **4.174** is employed, Corey-Chaykovsky reaction using a suitable sulphur ylide (or electrophilic epoxidation of the corresponding alkene) should generate epoxide **4.175**. Ring-expansion

through rearrangement of this epoxide (Cf. Chapters 7 and 8) might provide the ketone **4.138**, which should be amenable to epimerisation to place all substituents in equatorial orientation.

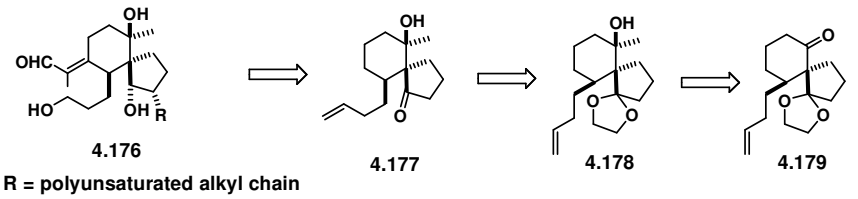


4.174 **4.175** **4.138** **4.100**

Scheme 4.57

The ensemble of simple observations made in this Chapter should prove particularly useful in designing future syntheses of spirocyclic products. Consider, for instance, the generic formula of the Spiroiridals **4.176** depicted in Scheme 4.58.[141] From the information garnered through this Chapter, one may design a reasonably secured approach to prepare advanced intermediates to this product.

[141] Miyake, Y. ; Ito, H. ; Yoshida, T. *Can. J. Chem.* **1997**, *75*, 734



Scheme 4.58

Thus, retrosynthetic disassembly of the polyene side chain (and removal of the enal, which might be inserted from the beginning of the synthesis as a masked entity) defers the synthesis to an intermediate such as **4.177**. At this stage, the information garnered throughout the last three Chapters can be fully exploited. Indeed, alcohol-directed reduction of **4.177** should lead to the correct –OH stereochemistry found in the natural products. Moreover, deprotection of **4.178** should be possible without retro-aldol fragmentation using the CAN-catalysed protocol. It could even be possible to perform a tandem, OH-protection/ketal removal if the Yamamoto acetylation procedure is employed.

From our results, it is quite likely that MeMgX addition to ketone **4.179** will proceed in the desired stereochemical sense to afford **4.178**. As for ketone **4.179**, it is simply the butenyl homologue of **2.016** (Scheme 4.7), which we have employed in the Spirovetivane saga.

Therefore, even though there is still much work to be done in understanding and taming the reactivity of spirocyclic adducts such as **2.005**, the lessons learned from these brief incursions may prove useful in future synthetic endeavours and should pave the way for several years of research in this domain.

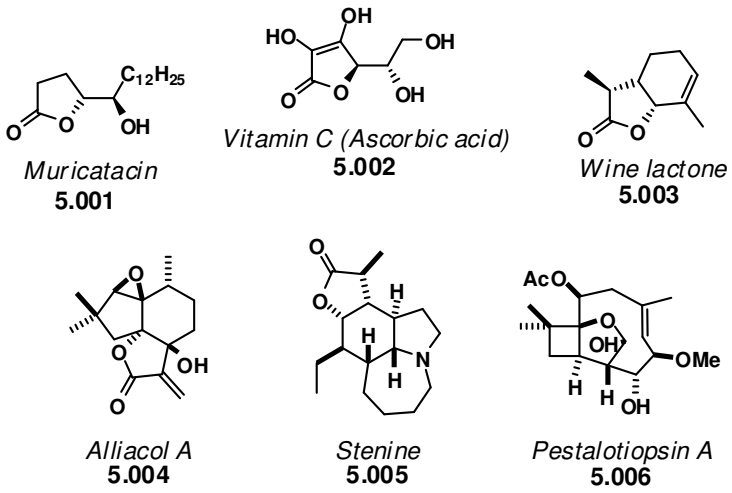
Throughout these initial Chapters, we have presented the evolution of a spiroannelation methodology, as the prelude to discovering novel cyclisation modes of β-ketoketals and improved spirocyclisation conditions (Chapter 2), successful applications to total synthesis (Chapter 3) and target-oriented, preliminary work aimed at understanding the fundamental issues of reactivity and stereodifferentiation of the spirocyclic adducts (Chapter 4). Interestingly, functionalised orthoesters should not react only with simple cyclic silyl enolethers. The results obtained during the condensation of our orthoesters with alternative partners form the subject of the following Chapters.

Chapter 5 : Stereoselective annelations of 2-(trimethylsilyloxy)furan (TMSOF) derivatives

5.1. Introduction

Sesquiterpene lactones with broad structural variety are ubiquitous in Nature. In particular, γ-butyrolactones incorporate a large class of naturally occuring substances.[142] As illustrated in Scheme 5.1, such lactonic products range from mono- (as in Muricatacin **5.001** or the familiar Vitamin C **5.002**) to bi- (as in wine lactone **5.003**) and polycyclic (Cf. the more complex **5.004-5.006**) structures.

[142] See, *e.g.* : Park, H.-J.; Jung, H.-J.; Lee, K.-T.; Choi, J. *Nat. Prod. Sci.* **2006**, *12*, 175 and references therein.

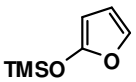


Scheme 5.1

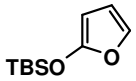
Accordingly, a large number of creative solutions have been disclosed throughout the years to address the synthetic problem of preparing γ-lactones.[143] Among the most effective strategies are those which convey the merging of two fragments, one of them being a masked γ-lactone precursor while the other comprises the external appendages.[144]

[143] For a review, see: Fischer, H.D. ; Fischer, N.H. ; Franck, R.W. ; Olivier, E.J. *Progress in the Chemistry of Organic Natural Products* vol. 38; Springer-Verlag, Vienna, **1979**, p.47

[144] For selected recent examples on the synthesis of lactones, see: (a) Krawczyk, H.; Sliwinski, M.; Wolf, W. M.; Bodalski, R. *Synlett* **2004**, 1995; (b) Paddon-Jones, G. C.; McErlean, C. S. P.; Hayes, P.; Moore, C. J.; Konig, W. A.; Kitching, W. *J. Org. Chem.* **2001**, *66*, 7487; (c) Madhushaw, R. J.; Li, C.-L.; Shen, K.-H.; Hu, C.-C.; Liu, R.-S. *J. Am. Chem. Soc.* **2001**, *123*, 7427; (d) Snider, B. B.; Shi, B.; Quickley, C. A. *Tetrahedron* **2000**, *56*, 10127; (e) Gathergood, N.; Anker Jorgensen, K. *Chem. Commun.* **1999**, *18*, 1869



5.007



5.008

Scheme 5.2

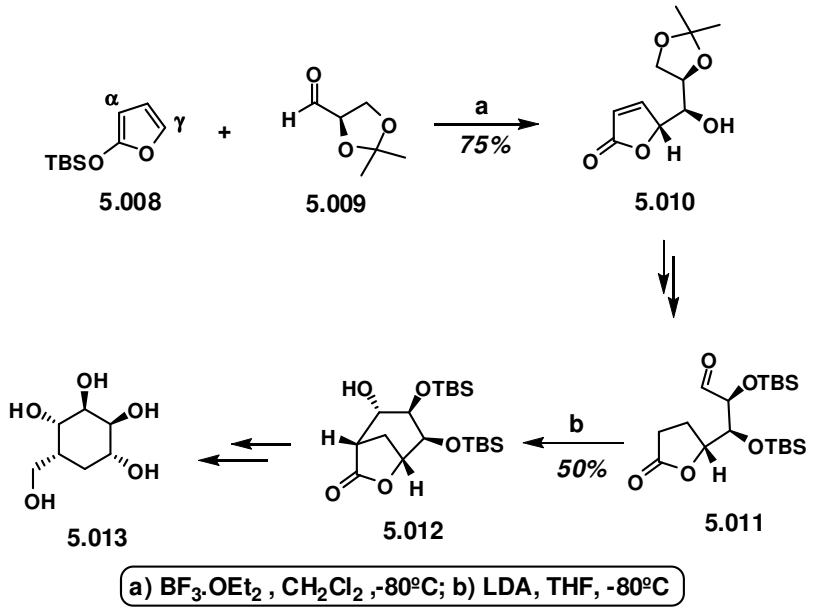
One such strategy involves the use of 2-trimethylsilyloxy furan **5.007** (TMSOF) or 2-*tert*-butyldimethylsilyloxyfuran (TBSOF) as nucleophilic entities onto which suitable electrophilic fragments are then « stitched » in a molecular sense. Although the chemistry of **5.007** and its derivatives has been comprehensively reviewed,[145] we shall illustrate this concept with selected examples from the literature.

The use of **5.007** (and higher silyl analogues) in Mukaiyama aldol reactions for the synthesis of carbasugars was extensively developed by Casiraghi and Rassu.[146] As depicted in Scheme 5.3, TBSOF **5.008** reacts smoothly and diastereoselectively with sugar-derived aldehydes, such as gliceraldehyde acetonide **5.009**, in the presence of BF_3 as the Lewis Acid. As is usually observed with siloxydienes, only the conjugate, γ-addition product **5.010** is observed.[147]

[145] For reviews on the chemistry of trimethylsilyloxyfuran derivatives, see: (a) Casiraghi, G.; Rassu, G. *Synthesis* **1995**, 607; (a) Bur, S.K.; Martin, S.F. *Tetrahedron* **2001**, *57*, 3211

[146] Cf. Casiraghi, G. ; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929

[147] Rassu, G.; Auzzas, L.; Pinna, L.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Org. Lett.* **1999**, *1*, 1213.

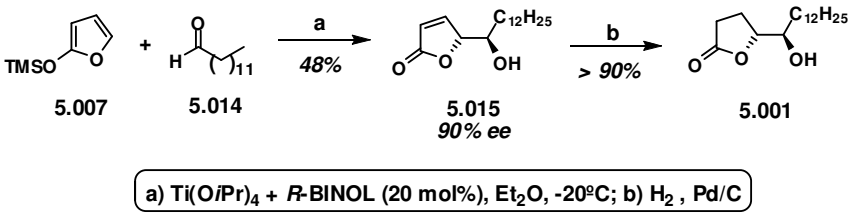


Scheme 5.3

Following subsequent elaboration to the densely functionalised aldehyde **5.011**, treatment by LDA at low temperature effects diastereoselective ring closure to **5.012**. Reductive opening of the lactone moiety finally leads to the pentasubstituted, optically active carbasugar **5.013** with complete stereocontrol.

Figadère's total synthesis of (+)-muricatacin exploited the same principle but employed asymmetric catalysis to introduce absolute chirality (Scheme 5.4).[148]

[148] Szlosek, M.; Franck, X.; Figadere, B.; Cave, A. *J. Org. Chem.* **1998**, *63*, 5169



5.007 5.014 5.015 *90% ee* 5.001

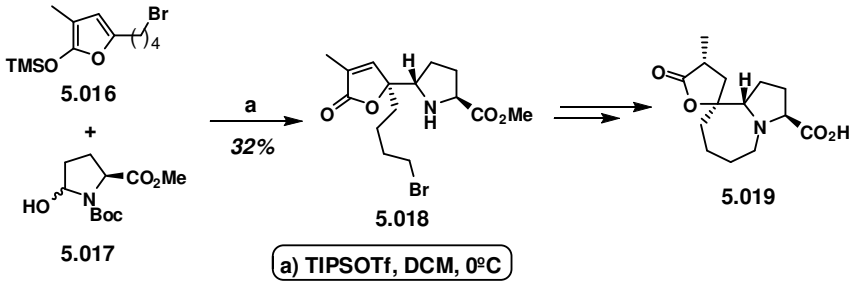
a) Ti(O*i*Pr)$_4$ + *R*-BINOL (20 mol%), Et$_2$O, -20ºC; b) H$_2$, Pd/C

Scheme 5.4

In the event, Ti(IV)-BINOL-catalysed Mukaiyama aldol with aldehyde **5.014** leads to enantioenriched butenolide **5.015**. Hydrogenation of this compound completes this efficient two-step synthesis. Figadère's preparation of muricatacine beautifully illustrates the aforementioned concept of « stitching ».

Other reactive electrophiles, such as acetals and *in situ*-generated iminium cations, can be employed in analogous processes. In an example from the Martin group (Scheme 5.5),[149] a substituted TIPS-siloxyfuran **5.016** adds onto the acyliminium salt derived from **5.017** to provide adduct **5.018**, wherein Boc-deprotection has occured under the strongly acidic conditions employed, in modest yield. The brominated side-arm is then appended to the nitrogen atom forming **5.019**, which embodies the basic skeleton of croomine, another member of the *Stemona* family of alkaloids.

[149] (a) Martin, S. F.; Clark, C. W.; Corbett, J. W. *J. Org. Chem.* **1995**, *60*, 3236; (b) Martin, S. F.; Chen, K. X.; Eary, C. T. *Org.Lett.* **1999**, *1*, 79

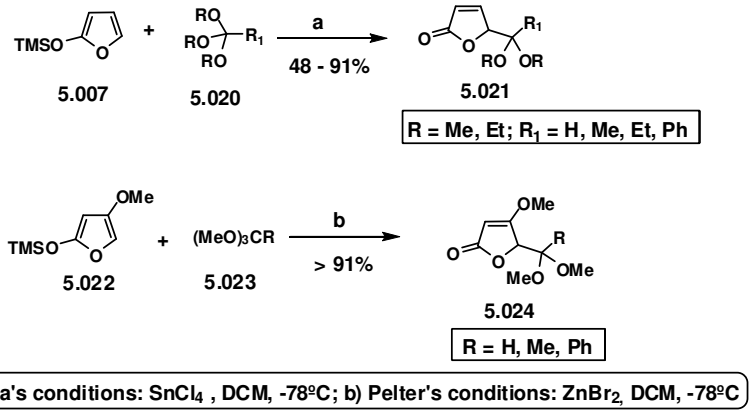


Scheme 5.5

Surprisingly, little attention has been devoted to the reaction of TMSOF and its derivatives with orthoesters. In their seminal work, Asaoka[150] and Pelter[151] demonstrated the feasibility of the condensation between TMSOF derivatives and the simple formate, acetate and benzoate orthoesters **5.020-5.023** (Scheme 5.6). Pelter's conditions, somewhat milder in nature, allowed the isolation of adducts **5.024** in excellent yields.

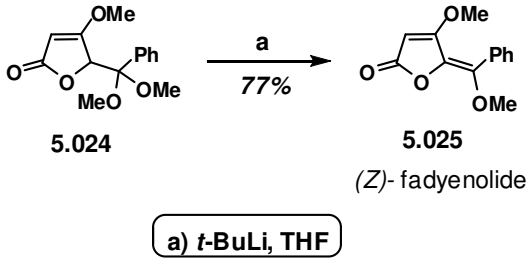
[150] Asaoka, M.; Sugimura, N.; Takei, H. *Bull. Chem. Soc. Jpn* **1979**, *52*, 1953

[151] (a) Pelter, A.; Al-Bayati, R.; Lewis, W. *Tetrahedron Lett.* **1982**, *23*, 353; (b) Pelter, A.; Al-Bayati, R.; Pardasani, P. *Tetrahedron Lett.* **1986**, *27*, 749; (c) Pelter, A.; Al-Bayati, R. I. H.; Ayoub, M. T.; Lewis, W.; Pardasani, P.; Hansel, R. *J. Chem. Soc., Perkin Trans. 1* **1987**, *4*, 717



Scheme 5.6

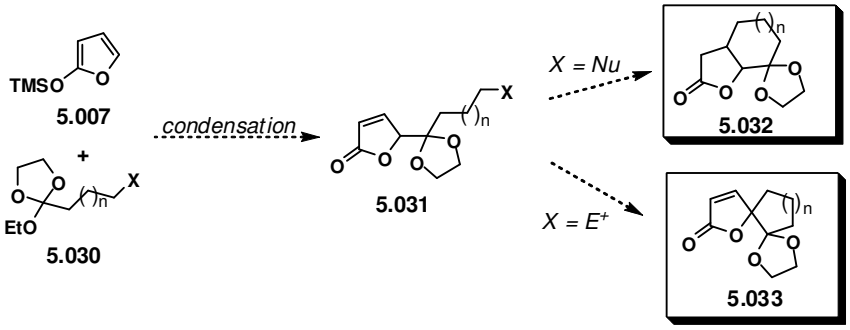
Pelter was interested in the synthesis of polyunsaturated natural products and eventually found that treating condensation adducts **5.024** with *t*-BuLi effected alkoxy-elimination.[151] This allowed him to synthesize *Z*-fadyenolide **5.025** as shown in Scheme 5.7.



Scheme 5.7

5.2. Proposed strategy

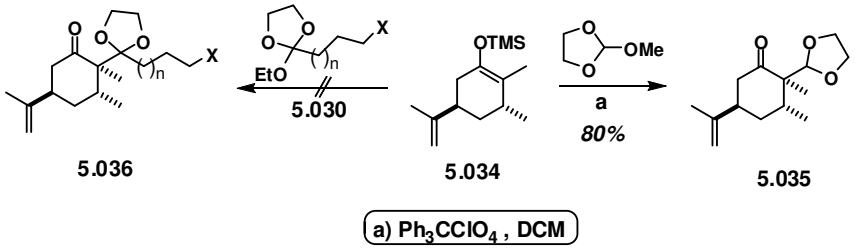
We envisaged the use of TMSOF as a nucleophilic entity onto which we might be able to append our laboratory's functionalised orthoesters. The condensation adducts **5.031** (Scheme 5.8) were anticipated to provide useful functionality for further elaboration. In tune with our previous results, we were intrigued by the possibility of using the halogen terminus (X in Scheme 5.8) both as an electrophile and as a nucleophile. Indeed, butenolide **5.031** should be a competent Michael acceptor. On the other hand, should proton abstraction be possible by treatment with a base, ring closure to a spirocyclic butenolide **5.033** would constitute a very attractive prospect.



Scheme 5.8

Although the results by Asaoka and Pelter provided proof of principle for the reaction between TMSOF and simple orthoesters, there was concern that the more hindered nature of our dioxolane-substituted orthoesters might hamper such a reaction. On the other hand, examples abound where

condensation is possible with orthoformate and orthoacetate but not with **5.030**. For example, the coupling of the thermodynamic silylenolether **5.034** derived from 2-methylcyclohexanone with orthoformate derivatives is well-documented.[152] In contrast, when our functionalised orthoesters **5.030** are employed, no traces of condensation adduct **5.036** could be detected (Scheme 5.9).



Scheme 5.9

Our task therefore began by delineating suitable conditions to prepare condensation products **5.031**, before the reactivity of such interesting adducts might be exploited.

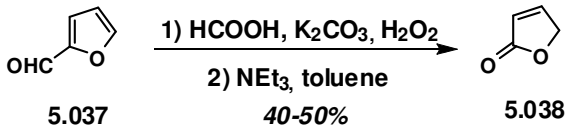
[152] See, *e.g.* Meulemans, T. M.; Stork, G. A.; Jansen, B. J. M.; De Groot, A. *Tetrahedron Lett.* **1998**, *39*, 6565

5.3. Synthesis of TMSOF derivatives and assessment of the condensation reaction

5.3.1. Preparation of TMSOF and derivatives

Although TMSOF **5.007** is commercially available from Aldrich, its large-scale preparation is desirable from an economical point of view.

Thus, Dakin-West oxydation of abundant furfuraldehyde **5.037**, in the presence of H_2O_2 and formic acid, followed by *in situ* isomerisation with triethylamine, produces **5.038** in reproducible 40-50% yields after distillation.[153] Butenolide **5.038** is an unstable substance and, though distillation affords **5.038** as a light yellow oil, it eventually darkens considerably upon storage (even if conserved at low temperature). We have found that both the pale yellow and the brown substances can be used for the subsequent reaction.



5.037 **5.038**

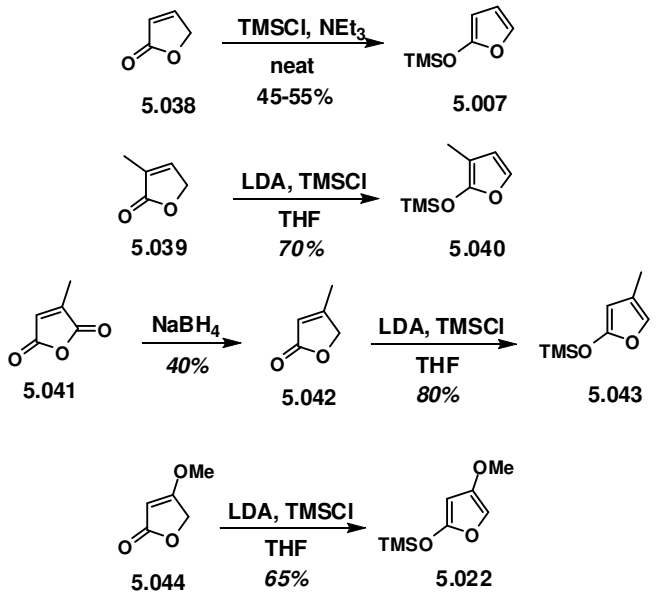
Scheme 5.10

[153] Nässman, H. ; Pensar, K.G. *Synthesis* **1985**, 786

Brimble and others have described that treatment of **5.038** with NEt_3 and trimethylsilyl chloride afforded TMSOF.[154] In our hands, TMSOF and its derivatives were found to be extremely sensitive to moisture and a considerable amount of experimentation and screening was required before we could obtain these compounds in a reproducible manner (Scheme 5.11).

For the unsubstitued **5.007**, we settled for Brimble's procedure : the reaction is performed in the absence of a solvent and proceeds overnight. The product is obtained by direct distillation from the reaction vessel. Although this distillate sometimes contained minor impurities, a second distillation usually affords pure **5.007**. Another alternative consists of stirring the first crude distillate for 30 min. under Ar before filtration and redistillation. Indeed, the major nuisance in this reaction is the copious formation of triethylammonium chloride, which literally turns the reaction mixture into a « cake ». In this manner, yields of 40-55% of TMSOF **5.007** could be obtained.

[154] See : Brimble,M.A.; Brimble,M.T.; Gibson, J.J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 179



Scheme 5.11

Another alternative was a procedure kindly supplied by Prof. Reinhardt Brückner,[155] essentially involving the same reaction but performed in an ether solution. We found no particular advantage in using this procedure.

Three substituted TMSOF derivatives, **5.040, 5.043** and **5.022** were also prepared. The α-methylsubstituted **5.040** was prepared from commercially available butenolide **5.039**. Although the Brimble and Brückner procedures worked well on >5g scale, we did not have a similar access to large amounts of lactone **5.039**. As such, we found it preferable to use a conventional, more laborious LDA/TMSCl/THF protocol.[156] The β-

[155] Professor Reinhardt Brückner, private communication.
[156] Cf. v.d.Ohe, F.; Bruckner, R. *New. J. Chem.* **2000**, *24,* 650

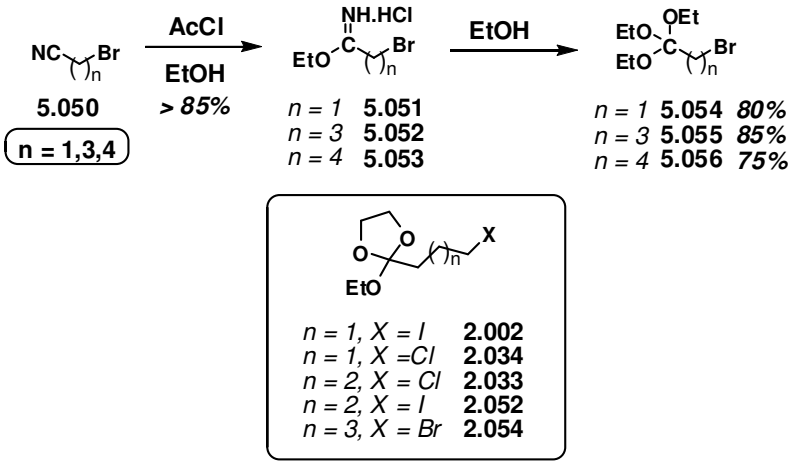
methylsubstituted butenolide **5.042** was prepared by a literature procedure involving mono reduction of inexpensive citraconic anhydride **5.041**.[157]

As for methoxyfuran **5.022**, considerable problems were encountered in its preparation, as it was found to be tremendously sensitive to moisture. Only by performing all operations under an argon atmosphere, with the most rigorous exclusion of moisture, could we obtain pure **5.022** from commercially available methyl tetronate **5.044**.

5.3.2. Preparation of orthoesters

Other than the orthoesters described in Chapters 2 to 4 (**2.002-2.054**, see box inside the Scheme), we also wanted to couple other derivatives with 2-5 carbon tethers to these substituted furans. These annelating agents **5.054-5.056**, including « open » compounds (*i.e.* trialkoxy-orthoesters) were prepared through the conventional Pinner reaction/alcoholysis two-step procedure that we outlined previously (Scheme 5.12).

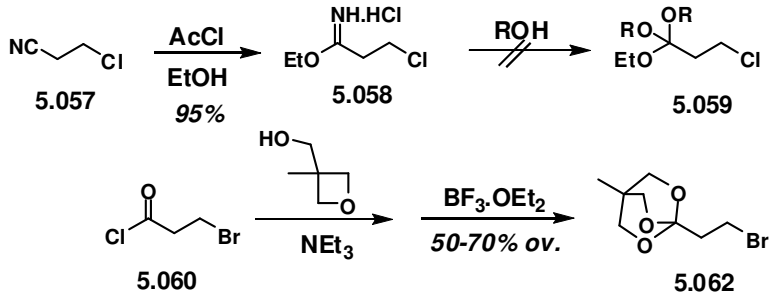
[157] Johnson, A.W.; Gowda, G.; Hassanali, A.; Knox, J.; Monaco, S.; Razavi, Z. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1734



Scheme 5.12

Nevertheless, since the preparation of analogous 3-carbon orthoesters has eluded our efforts so far, we selected the OBO-orthoester **5.062** as an acceptable replacement.[158] This somewhat « desperate » alternative would at the same time enable us to probe OBO-orthoesters as potential condensation partners, something not described yet in the literature.

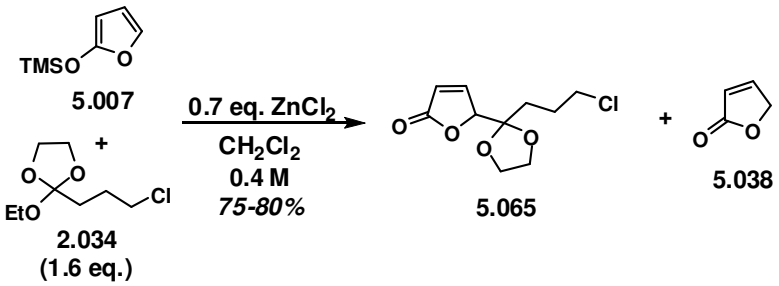
[158] For the original reference on the preparation of OBO orthoesters, cf. : (a) Corey, E.J.; Raju, N. *Tetrahedron Lett.*, **1983**, *24*, 5571. For subsequent modifications of these orthoesters, see : (b) Giner, J.L. *Org. Lett.* **2005**, *7*, 499 and references therein.



Scheme 5.13

5.3.3. Condensation of functionalised orthoesters with TMSOF

Our studies began with the reaction between chlorinated orthoester **2.034** and TMSOF **5.007** (Scheme 5.14). By analogy with Pelter's and our own conditions, we reacted **5.007** with 1,1 equivalents of orthoester **2.034** in the presence of 0,7 equivalents of dried, solid $ZnCl_2$, in dichloromethane solution (0.4M), from -78ºC to rt. Analysis of the crude reaction mixture revealed concomitant formation of **5.065** and butenolide **5.038**. Suspecting that butenolide **5.038** had been formed through hydrolysis of unreacted TMSOF during the workup, we increased the amount of orthoester **2.034** to 1,6 equivalents. This time (Scheme 5.14), we were pleased to isolate **5.065** in 75-85% yields, with minimal amounts of hydrolysis product **5.038**.

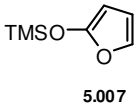
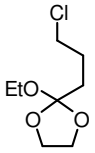
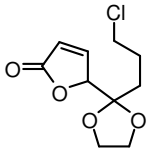
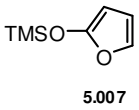
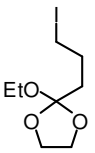
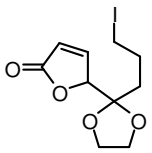
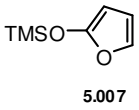
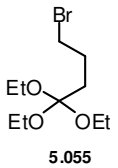
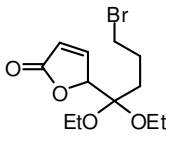
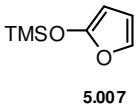
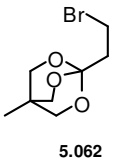
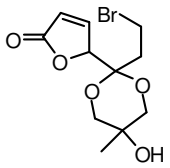
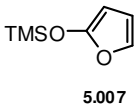
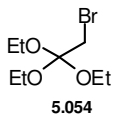
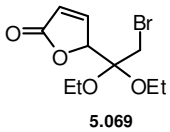


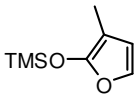
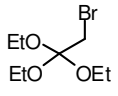
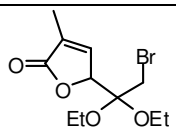
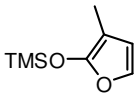
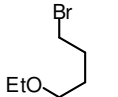
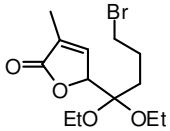
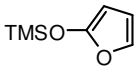
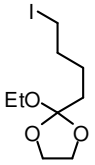
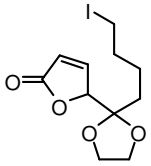
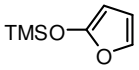
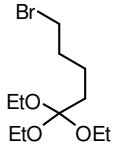
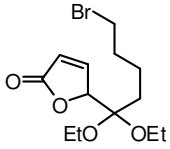
Scheme 5.14

Varying the concentration or the temperature of this reaction, or further increasing the amount of orthoester did not improve the yields. Importantly, although conversion was essentially complete within 1 hour, allowing the reaction to proceed longer did not lead to an erosion of the yield. This observation stands in sharp contrast with previous condensations of orthoester **2.034** with simple cyclic silyl enolethers. In these cases, the reactions proved to be more sluggish (3-4 hours) and extensive decomposition of the products was noticed if proper time control was not exercised.

Having found optimal conditions for this condensation reaction, we then sought to apply them to other orthoesters. Initial results using TMSOF **5.007** and its derivative **5.040** are compiled in Table 5.1.

Table 5.1

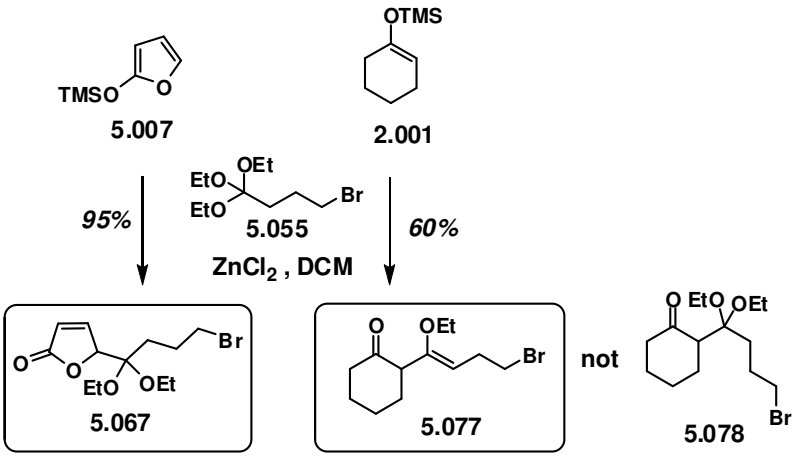
Entry	Furan derivative	Orthoester	Product	Yield[b]
1	 **5.007**	 **2.034**	 **5.065**	75%
2	 **5.007**	 **2.002**	 **5.066**	95%
3	 **5.007**	 **5.055**	 **5.067**	95%
4	 **5.007**	 **5.062**	 **5.068**	61%[c]
5	 **5.007**	 **5.054**	 **5.069**	94%

6	 **5.040**	 **5.054**	 **5.070**	80%
7	 **5.040**	 **5.055**	 **5.071**	86%
8	 **5.007**	 **2.052**	 **5.072**	80%
9	 **5.007**	 **5.062**	 **5.073**	90%

[a]-Unless otherwise stated, all reactions were carried out in the presence of 0.7 eq. $ZnCl_2$ in CH_2Cl_2 with a ***[furan:orthoester]*** ratio of 1:1.5, from –78ºC to r.t. [b] – Yields refer to pure, isolated products.[c] – See text.

As had been hinted by Asaoka and Pelter, « open » orthoesters readily condense with TMSOF and derivatives, affording the desired adducts in excellent isolated yields (entries 3,5,6 and 9). This highlights an additional difference relative to cyclic silyl enolethers. Indeed, upon reaction between **2.001** and **5.055**, the only product obtained was the vinylogous ester

5.077.[159] This product is presumably formed through the intermediacy of adduct **5.078**, which spontaneously eliminates EtOH to form the stable, conjugated product **5.077** (Scheme 5.15). This is clearly not the case with butenolide **5.067**, as attested by the aggressive conditions required by Pelter to effect such an elimination.



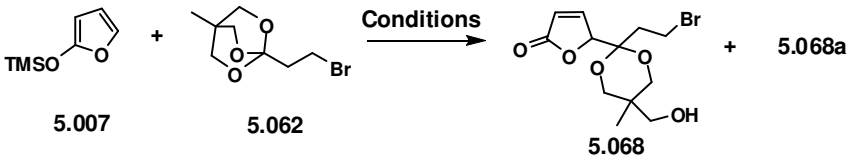
Scheme 5.15

A variety of other adducts could be prepared in similarly good yields. The case of 3-carbon OBO orthoester **5.062** deserves further comment. In fact, no reaction was observed in the presence of $ZnCl_2$ as the Lewis Acid and recourse to TMSOTf was needed. When TMSOF **5.007** and orthoester **5.062** were treated with catalytic amounts of TMSOTf, two different products were detected by TLC analysis and in the crude mixture following workup. While one of these products could be readily assigned by

[159] Ates, A. *Ph.D.Thesis,* UCL, **1999**

spectroscopic analysis to be the desired adduct **5.068**, the determination of the structure of the accompanying compound **5.068a** eluded our efforts. Another interesting observation (Table 5.2) was that the ratio of these products consistenly changed as the amounts of Lewis Acid were increased : the desired compound **5.068** was formed in higher yields as more Lewis Acid was added. Thus, when 3 eq. of TMSOTf were used, the compound assigned as **5.068** could be obtained as the major component in a 47% isolated yield.

Table 5.2



5.007 5.062 5.068

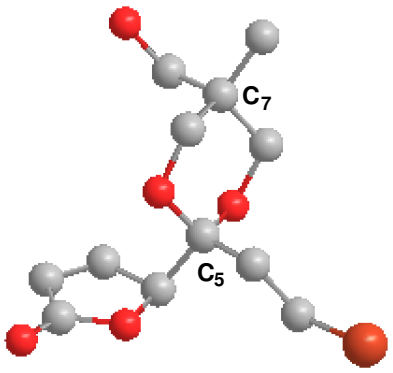
Conditions	Yield of **5.068**[a]	Yield of **5.068a**[a]
0.7 eq. $ZnCl_2$, -78ºC to rt	-	-
0.3 eq. TMSOTf, idem	20%	34%
1 eq. TMSOTf, idem	34%	19%
3 eq. TMSOTf, idem	**47%**	**14%**

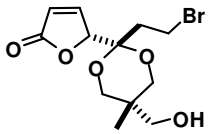
[a]- Yields refer to pure, isolated products

A solution to this conundrum was found when the combined fractions of « unknown » compound **5.068a** were pooled and left standing at room temperature. In time, crystals formed which were found suitable for X-ray analysis (Scheme 5.16). We were baffled to notice that the X-ray structure

actually appeared to correspond to compound **5.068**, specially since the NMR spectra of these crystals were not different from the ones corresponding to the "unknown" **5.068a**!

Careful analysis of the structure of these compounds revealed that, although only one stereogenic centre existed in the molecule, the stereochemical relationship between C_5 and C_7 could lead to two diastereoisomers possessing either the *cis* or the *trans* relative stereochemistry.

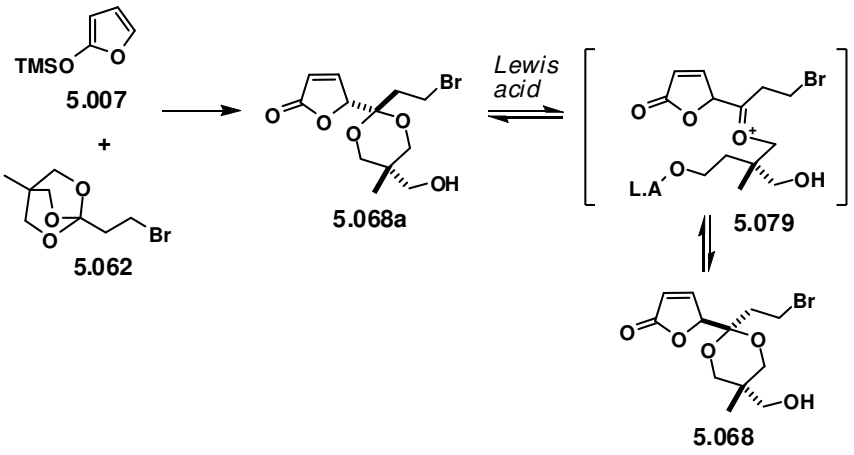




5.068a

Scheme 5.16

The variation in the proportion of these two products according to the reaction conditions can now be easily understood. Indeed, in the presence of an excess of Lewis Acid, a reversible ring-opening of the ketal to generate an oxonium cation **5.079,** followed by re-closure could effect interconversion between diastereomers **5.068a** and **5.068**.



Scheme 5.17

We believe that isomer **5.068a**, obtained as the major component with low amounts of TMSOTf, is the « kinetic » isomer (structure secured by X-ray), whereas **5.068**, formed preferentially under equilibrating conditions, should be the « thermodynamic » adduct. Indeed, subjecting pure compound **5.068a** to catalytic amounts of TMSOTf in dichloromethane solution provided a mixture of **5.068** and isomer **5.068a** as detected by TLC analysis.[160]

It should be noted that TBSOF **5.008**, the higher silyl-analogue of TMSOF **5.007**, can be used instead of TMSOF in all these condensation reactions. However, the results are often inferior (yields are ~20% lower) as TBSOF is obviously less reactive than its trimethylsilyl counterpart. The

[160] Our initial communication of the synthesis of these compounds was done before having the X-ray structure of **5.068a**. Thus, in good faith we have reported a 46% yield for the preparation of compound **5.068**, which is only the major diastereomer. The total yield of the condensation adduct actually amounts to 61%.

advantage is that TBSOF can be stored for longer periods and is much less sensitive to moisture than TMSOF.

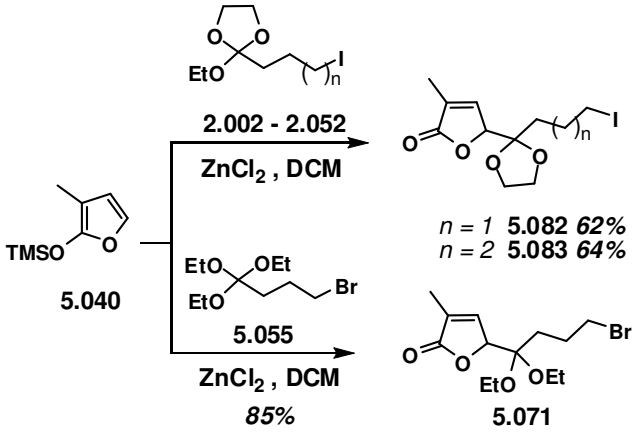
A final comment should be made regarding the relative stability of the condensation adducts. As a matter of fact, compounds possessing « open » ketals such as **5.067** were found to be less stable than their « closed » analogs (such as **5.065**), as observed by their behaviour towards chromatographic purification. Thus, derivatives bearing a diethoxy-ketal should be purified by quick chromatography through silica gel previously deactivated with NEt_3 in order to avoid decomposition, whereas the dioxolanyl-substituted butenolides survive purification using untreated silica gel.

5.3.4. Condensation of functionalised orthoesters with substituted TMSOF derivatives

We also examined in detail the condensation of the substituted TMSOF derivatives, prepared previously, in order to delineate the scope of this reaction.

3-methyl TMSOF **5.040** afforded only a 62% yield of condensed product when reacted with dioxolanyl orthoesters **2.002**-**2.052** under the usual procedure. Since the remainder of the mass balance corresponded to hydrolysed lactone **5.039**, we attempted the reaction with the analogous « open » triethyl orthoester **4.055**. Interestingly, an 85% yield was obtained in this case. This difference in reactivity suggests that steric hindrance, in the

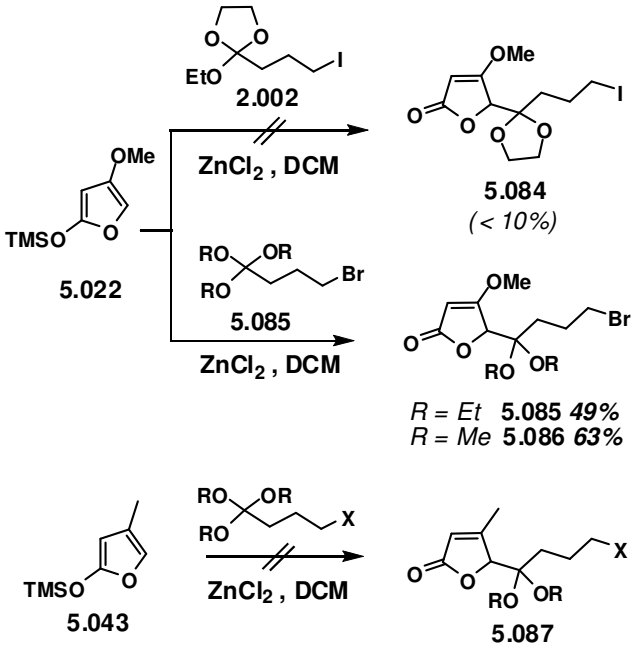
silyl enolether partner, might play an important role in the efficiency of the condensation reaction.



Scheme 5.18

Further support for this assumption came when 4-methoxy TMSOF **5.022** was examined. This silyl enolether afforded only traces (<10%) of the condensed product when reacted with dioxolanyl-orthoester **2.034**. In contrast, the triethoxy-butyrate **5.055** yielded adduct **5.085** in 49% yield and the trimethoxy-analogue raised this value to 63%.

Dramatically, 4-methyl TMSOF **5.043** was essentially unreactive towards these three orthoester derivatives.



Scheme 5.19

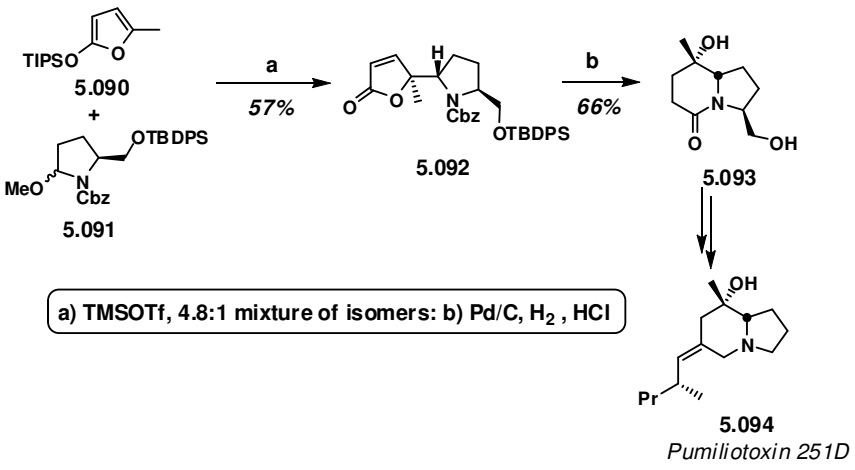
It would thus seem that the condensation reaction is sensitive to both steric and electronic factors, in this order of priority. Thus, even a remote substituent such as a methyl group at the 3-position, considerably reduces the reactivity of TMSOF, causing a drop in yield of *ca.* 25% when the dioxolanyl-orthoester **2.002** is employed. We believe that the hindered nature of the cyclic oxonium intermediate might hamper a proper approach for its condensation due to non-bonded interactions. In contrast, the diethyl- and dimethyl-oxonium intermediates, derived from the triethoxy- and trimethoxy derivatives, possess increased rotational freedom about the C-O axis and might be able to avoid such repulsive interactions. When the

methyl-substituent is shifted closer to the reaction locus, such as in **5.043**, the reactivity towards these orthoesters is nearly shut down.

Electronic effects come to play when 4-methoxy TMSOF **5.022** is considered. Though suffering from similar non-bonded interactions, due to the proximity of the 4-methoxy group and the reaction site, the electronic activation provided by the resonance-donor methoxy moiety appears to counterbalance this antagonistic steric effect. Reactivity is then sufficient to enable the condensation to proceed with the least hindered orthoesters, in reasonable yields.

Interestingly, 4-methyl- and even 5-methyl- substituted TMSOF derivatives have been condensed with other, more reactive electrophiles. In their formal synthesis of Pumiliotoxin 251D **5.094**, Martin and Bur used the reaction between the TIPSOF derivative **5.090** and hemiaminal **5.091** as a key-step (Scheme 5.20).[161] In the presence of TMSOTf as the Lewis acid, the vinylogous-Mannich adduct **5.092** was obtained in 57% yield as a mixture of diastereomers favoring the one depicted. Hydrogenolysis of **5.092** under acidic conditions triggered double-bond reduction, Cbz- and silyl-deprotection and lactone ring-opening to afford indolizidine **5.093** in 66% yield. The (limited) success in this condensation reaction underlines the more electrophilic nature of the acyliminium salt derived from **5.091** when compared to the oxonium intermediates generated from our orthoesters.

[161] Martin, S.F.; Bur, S.K. *Tetrahedron* **1999**, *55*, 8905



Scheme 5.20

5.4. Preparation of bicyclic lactones

5.4.1. Cyclisation results

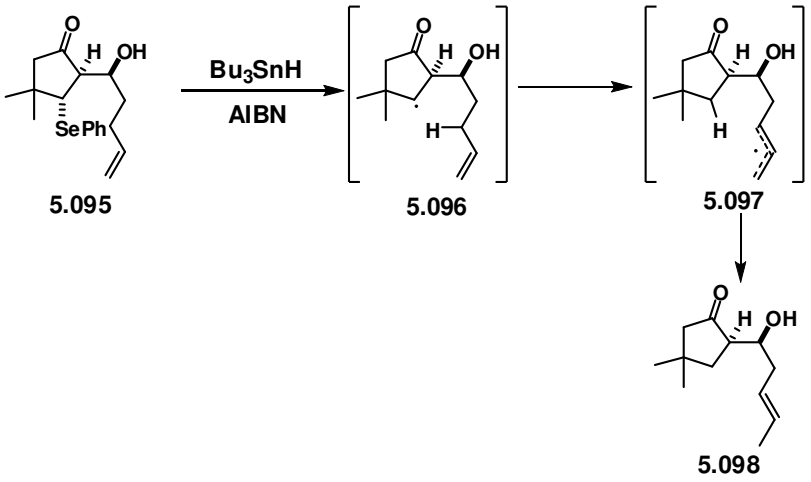
Having a ready access to a number of condensation adducts bearing different ketal moieties and halogenated termini, we then focused upon their elaboration into bicyclic lactones. It appeared to us that an intramolecular radical cyclisation could be one of the best ways to accomplish this task.

Indeed, over the past 20 years, radical-promoted cyclisations have emerged as one of the most powerful ways to construct ring systems.[162] In particular, radical polycyclisation cascades constitute extremely efficient and elegant processes.

There are, however, potential pitfalls that require careful planning in order to achieve success.[162] Whilst 5-*exo* cyclisations are known to be very fast, leading smoothly to cyclopentane derivatives, three- and four-membered rings cannot generally be formed due to the high rate of the ring-opening as compared to the ring-closure process. Furthermore, when 6-*exo* cyclisations are involved, a [1,5]-allylic hydrogen abstraction (proceeding through a 6-membered transition state) can become a seriously competing reaction. For example, as shown in Scheme 5.21, the attempted cyclisation of selenide **5.095** resulted in the exclusive formation of **5.098**, most likely through the intermediacy of the translocated radical **5.097**.[163] It should be noted that in such a case, substrate re-design is often the only solution to promote the desired cyclisation.

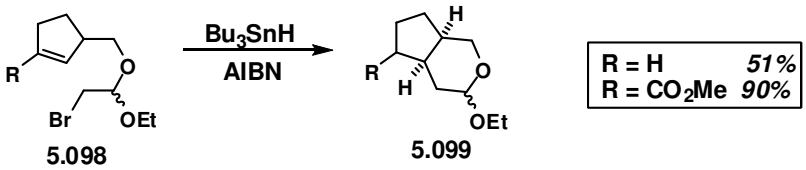
[162] For some reviews on radicals and radical cyclisations, see : (a) Curran, D.P. *Synthesis* **1988**, 417 and 489 ; (b) Majumdar, K. C.; Basu, P. K.; Chattopadhyay, S. K. *Tetrahedron* **2007**, *63*, 793; (c) *Advances in Free Radical Chemistry* Zard, S. Z. Ed., JAI Greenwich, USA, 1999; (d) Rossi, R. A.; Penenory, A. B. *Curr. Org. Synth.* **2006**, *3*, 121 and references therein.

[163] Leonard, W.R.; Livinghouse, T. *Tetrahedron Lett.* **1985**, *26*, 6431



Scheme 5.21

On the other hand, it is known that the presence of electron-withdrawing substituents on the double bond of the acceptor often stabilises the radical formed upon cyclisation. For example, Stork's linchpin procedure for the preparation of bicyclic acetal **5.099** proceeds with a nearly doubled yield when the acceptor **5.098** is an enoate rather than an isolated double bond (Scheme 5.22).[164]

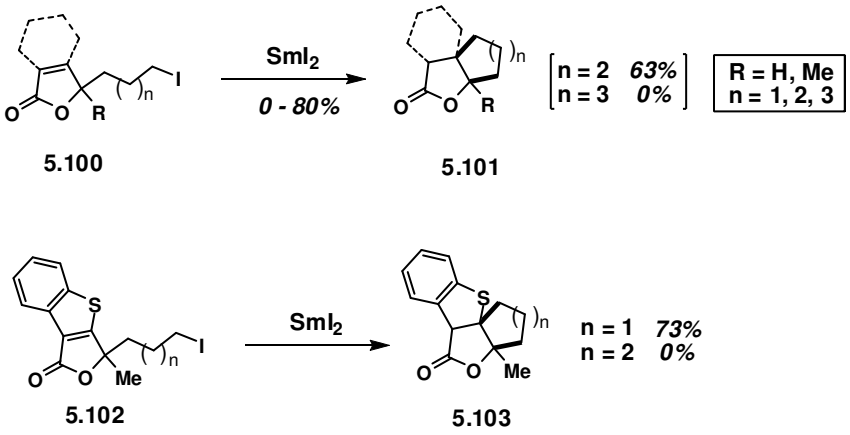


Scheme 5.22

[164] Stork, G. ; Krafft, M.E. ; Biller, S.A. *Tetrahedron Lett.* **1987**, *28*, 1035

Examples of cyclisation onto butenolides have also been reported in the literature. In a comprehensive study, Molander showed that SmI_2-mediated ring-closure of a number of unsaturated lactones was an efficient process.[165]

As depicted in the Scheme, most 5-*exo* cyclisations proceeded in good yields, even when the acceptor double-bond is part of an aromatic system. However, only one example of the closure of a 6-membered ring is reported, and it occurs with a slightly lower yield than the 5-*exo* process. Finally, no 7-*exo* cyclisations could be accomplished using these substrates.



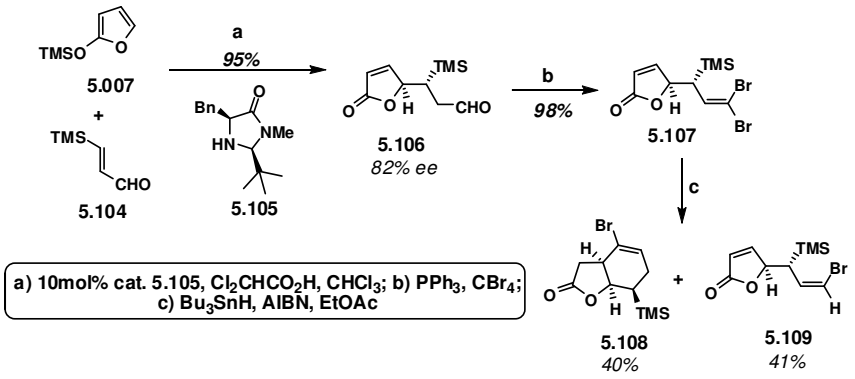
Scheme 5.23

Similar precedents relating the difficulties encountered in the formation of 5,6-fused bicyclic γ-lactones through radical cyclisation come from the recent work of Robichaud.[166] In their formal asymmetric synthesis

[165] (a) Molander, G.A.; St. Jean, D.J. *J. Org. Chem.,* **2002**, *67*, 3861. See also : (b) Wagner, S.H.; Lundt, I.J. *J. Chem. Soc. Perkin Trans. 1*, **2001**, 780

[166] Robichaud, J.; Tremblay, L. *Org. Lett.* **2006**, *8*, 597

of (+)-Compactin (Scheme 5.24), Robichaud and Tremblay prepared butenolide **5.106** by enantioselective Mukaiyama-Michael condensation of TMSOF **5.007** with enal **5.104**. Appel bromination then converted the aldehyde moiety of **5.106** into a vinyl dibromide substituent, setting the stage for the radical cyclisation. In the event, subjection of **5.107** to Bu_3SnH/AIBN under high-dilution conditions resulted only in a 40% yield of cyclised product **5.108**, with concomitant formation of an equal amount of reduced material **5.109**.[167]



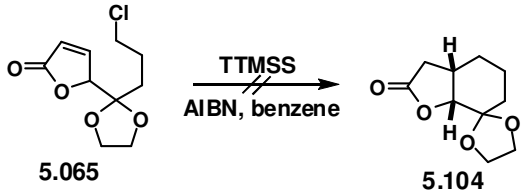
Scheme 5.24

Cognisant of these precedents, we embarked on the cyclisation reaction of chlorinated lactone **5.065**. Due to our previous experience with multi-step radical processes,[168] we elected to use TTMSS [$(Me_3Si)_3$-SiH] as the chain carrier.[169] Its diminished ability to reduce alkyl radicals could

[167] For a similar case, see : Nishida, M.; Hayashi, H.; Yamaura, Y.; Yanaginuma, E.; Yonemitsu, O.; Nishida, A.; Kawahara, N. *Tetrahedron Lett.* **1995**, *36*, 269.
[168] (a) Maulide, N. *Erasmus Report*, UCL/IST, **2003** ; (b) Augustyns, B.; Maulide, N.; Markó, I.E. *Tetrahedron Lett.* **2005**, *46*, 3895
[169] Chatgilialoglu, C. *Acc.Chem.Res.* **1992**, *25*, 188

potentially allow the use of an operationally simple, « mix-and-heat » experimental procedure.

However, treating **5.065** with 1,5 eq. of TTMSS in the presence of a catalytic amount of AIBN, in refluxing benzene, resulted in the recovery of the starting material.

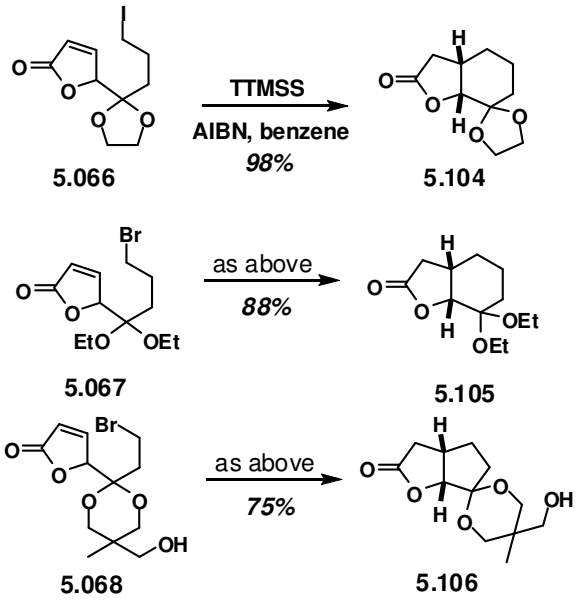


Scheme 5.25

Although there are examples of the reduction of alkyl chlorides by TTMSS, examination of the rate constants available[169] suggests that the rate of reaction between TTMSS-radical and a primary chloride is bound to be several orders of magnitude (>4) lower than the analogous process involving a bromide or an iodide.

Therefore, the iodinated analogue **5.066** was subjected to the same reaction conditions. Delightfully, the formation of lactone **5.104**, as a single diastereomeric substance and in excellent yield, was observed. No trace of reduced product could be detected in the crude reaction mixture.

Extension of this cyclisation to the analog **5.067**, bearing a bromine instead of an iodine, also proceeded in excellent yield. Additionally, the 3-carbon tethered **5.068** cyclised smoothly to afford the cyclopentane annulation product **5.106**.

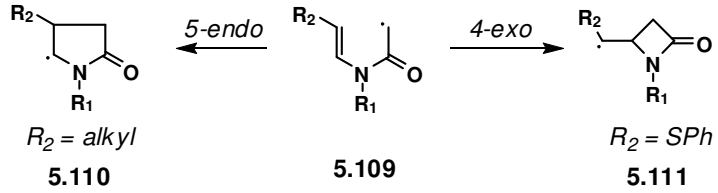


Scheme 5.26

We then turned our attention to the 2-carbon derivative **5.069**. Cyclobutane annulations by radical 4-*exo* trig processes are unusual and generally ineffective, because the reverse ring-opening process is as fast as the cyclisation itself, enabling the competing 5-*endo* cyclisation pathway to predominate.

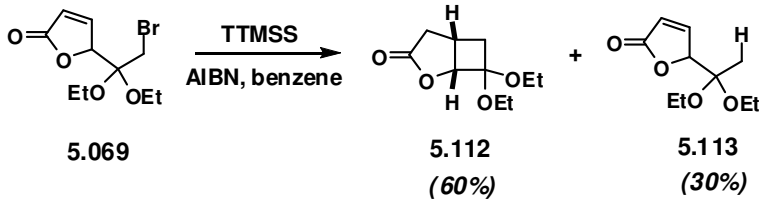
Nevertheless, some examples of cyclobutannelation do exist in the literature. For example (Scheme 5.27), Ishibashi and Ikeda found that, in general, carbamoylmethyl radicals **5.109**, generated from the corresponding α-haloamides, undergo 4-*exo* cyclisation (to **5.111**) preferentially when the

N-vinylic double bond contains a sulphur-substituent. If this substituent is absent, then the 5-*endo* pathway (to **5.110**) becomes the dominant process.[170]



Scheme 5.27

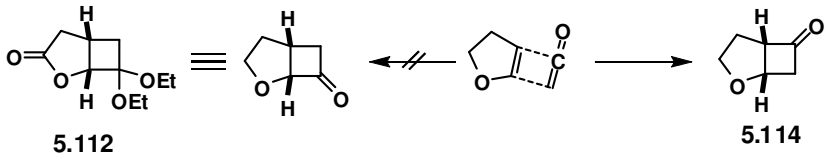
In the event, we were pleased to ascertain that **5.069** indeed underwent cyclisation to form bicyclo[3.2.0]derivative **5.112** in 60% yield. It should be noted that the reduced product **5.113** accounted for the remaining mass balance (Scheme 5.28).



Scheme 5.28

[170] The authors subsequently realised that, among other factors, temperature also exerts control on the cyclisation mode observed in these systems. See : (a) Ishibashi, H.; Kameoka, C.; Iriyama, H.; Kodama, K.; Sato, T.; Ikeda, M. *J. Org. Chem.* **1995**, *60*, 1276 ; (b) Ishibashi, H.; Kameoka, C.; Kodama, K.; Kawanami, H.; Hamada, M.; Ikeda, M. *Tetrahedron* **1997**, *53*, 9611 ; (c) Ishibashi, H.; Higuchi, M.; Ohba, M.; Ikeda, M. *Tetrahedron Lett.* **1998**, *39*, 75.

It is interesting to note that bicyclo[3.2.0]heptane **5.112** is the opposite regioisomer of a putative product **5.114,** resulting from the [2+2] cycloaddition of ketene to a dihydrofuran derivative (Scheme 5.29).



Scheme 5.29

We believe that in our case, two factors contribute decisively for the favorable outcome reported.

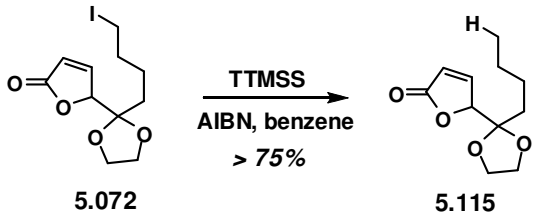
On the one hand, the cyclised radical intermediate benefits from the α-stabilising effect of the lactone carbonyl, which should confer a stability bonus when compared to its primary, acyclic radical precursor.

In addition, all the cyclisations described with our orthoesters are likely to be enhanced by a Thorpe-Ingold effect [171] provided by the dioxolane substituent. Such an effect is predicted to bring the reactive partners closer in space and thus accelerate the cyclisation step.

We have attempted to increase the yield for this unusual 4-*exo* trig cyclisation through the use of high-dilution conditions, syringe pump addition of TTMSS and solvent changes (to toluene or xylenes) to increase the boiling point and, consequently, the reaction temperature. A similar 60% yield was obtained regardless of the conditions employed.

[171] For a review, see : Jung, M.E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735

To complete this preliminary study of cyclisations onto unsubstituted butenolides, we examined the possibility of a 7-*exo* trig ring-closure of compound **5.072** (Scheme 5.30). Unfortunately, all our attempts returned only the reduced product **5.115**. It is conceivable that, as the distance between the dioxolane substituent and the tether-terminus increases, the aforementioned Thorpe-Ingold effect becomes less effective. It should be noted, however, that this is in accordance with Molander's work (*vide supra*).



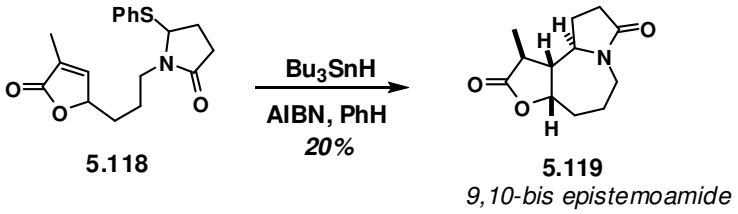
5.072 **5.115**

Scheme 5.30

To the best of our knowledge, there is only a single, isolated report of a 7-*exo* trig cyclisation onto a butenolide double bond. It is the final step in Cossy's synthesis of 9,10-epistemoamide **5.119** (Scheme 5.31).[172] When γ-thiolactam **5.118** was exposed to the action of Bu_3SnH and AIBN in boiling benzene, cyclisation ensued to form tricycle **5.119** in 20% yield, as a single diastereomer. The inclusion of the radical center in a ring system probably limits its conformational freedom, allowing the desired cyclisation to take place.[173]

[172] Bogliotti, N.; Dalko, P.I. ; Cossy, J. *Synlett* **2005**, 349

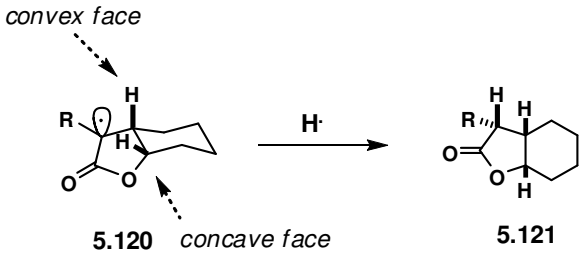
[173] An identical approach to the same compound has been reported by others : see Kim, S.-K.; Schultz, A.G. *J. Org. Chem.* **2004**, *69*, 7734



Scheme 5.31

We then turned our attention to the cyclisation of substituted butenolides such as **5.071**. The presence of a substituent on the double bond was expected to lead to the formation of a third stereogenic center. We were confident, though, that such a center would be formed with good diastereoselectivity. Indeed, as depicted in Scheme 5.32, the intermediate γ-lactone radical **5.120** has a roof-shaped architecture, clearly distinguishing a convex and a concave face. It was therefore anticipated that hydrogen delivery (by the bulky TTMSS reagent) would occur stereoselectively from the most accessible, convex face, affording only the product **5.121**.[174]

[174] Interestingly, this is not the case in Cossy's work reported above. In this event, the authors proposed a different structure for the intermediate radical due to the existence of non-bonded interactions within the tricyclic structure. Cf reference 172.

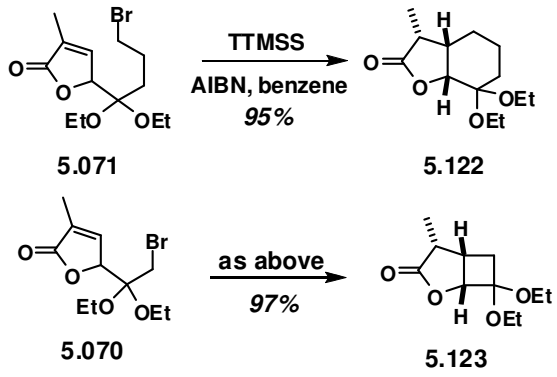


Scheme 5.32

In practice, reaction of **5.071** with TTMSS in hot benzene, led to the desired lactone **5.122** in quantitative yields and as a single diastereoisomer (Scheme 5.33). The stereochemical assignment was confirmed by nOe studies and independent synthesis of the opposite epimer (*vide infra*). It is noteworthy that 3 contiguous stereocenters are formed with complete stereocontrol in this reaction.

Attempted 4-*exo* cyclisation of substituted butenolide **5.070** led to a pleasant surprise (Scheme 5.33). Indeed, cyclised product **5.123** was also obtained as a single diastereomer, but in considerably higher yields than its unsubstituted partner.

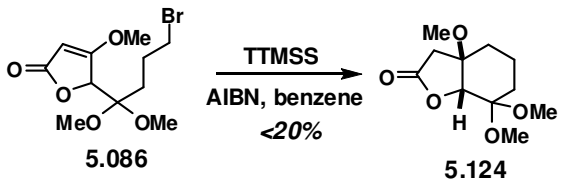
Although a detailed explanation would surely require further studies, we can only assume that the enhanced stability of the intermediate radical is responsible for this observation.



Scheme 5.33

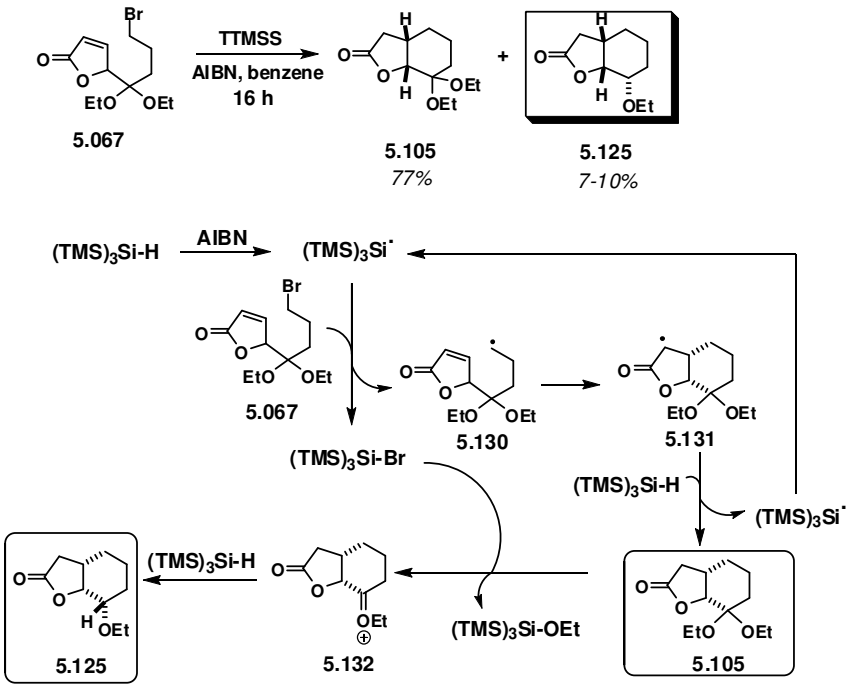
By adding an extra methyl substituent, and thus rendering the intermediate radical tertiary, further stabilisation is imparted to the radical. It is possible that this additional stabilisation of the intermediate radical is enough to raise the 4-*exo* trig cyclisation to a similar level of efficiency as its 5- and 6- membered counterparts.

We have also attempted the cyclisation of tetronate **5.086**, which would generate a quaternary center upon ring-closure. Unfortunately, exposure of **5.086** to the cyclisation conditions resulted in the formation of complex mixtures from which **5.124** could only be isolated in < 20% yields (Scheme 5.34).



Scheme 5.34

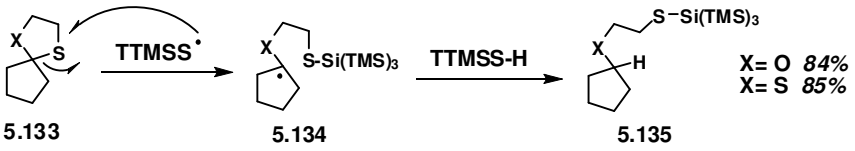
Finally, it should be emphasized that the bicyclic adducts bearing an « open » diethyl- or dimethyl- ketal functionality are also slightly less stable than their dioxolanyl-substituted counterparts. A clear testimony to this fact is the observation that, when the cyclisation of **5.067** was inadvertedly allowed to proceed for 16 hours, the cyclised product (77% yield) was no longer pure but was accompanied by small (<10%) amounts of a new compound, assigned as **5.125** (presumed stereochemistry shown). A plausible mechanism for the formation of this interesting ether **5.125** is displayed in Scheme 5.35.



Scheme 5.35

As the cyclisation reaction proceeds, TTMSS-Br is also formed and accumulates in the reaction mixture. Analogously to the less bulky TMS-Br, this compound should display a certain (though small, due to steric hindrance) degree of Lewis acidity. Since an excess of TTMSS-H is employed (1.5 equivalents), it is conceivable that, under the forcing conditions (refluxing benzene, prolonged reaction time) employed, ionisation of ketal **5.105** occured under the action of TTMSS-Br, generating the oxonium cation **5.132**. This cationic species can then be reduced by the remaining TTMSS-H (a hydride donor analogous to Et_3SiH), exclusively from the convex face, to provide ether **5.125** as a single diastereomer.

It is interesting to note that this process does not seem to be precedented. In fact, TTMSS is known for effecting the radical-mediated cleavage of X,S-ketals **5.133** (X = O, S) through direct addition of the TTMSS-radical to the sulphur atom and formation of an α-heteroatom radical species **5.134** (Scheme 5.36).[175] This species then undergoes reduction to **5.135**. However, the exploitation of the Lewis acidity of by-products generated during radical-promoted processes is (to the best of our knowledge) scarcely documented, particularly in the case of TTMSS.[176]



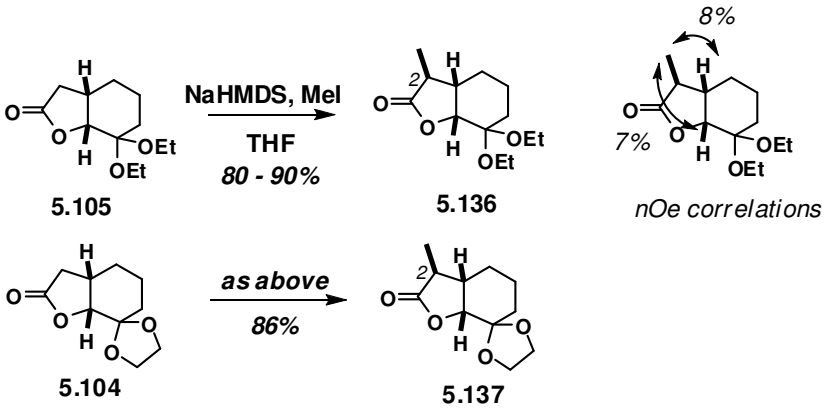
Scheme 5.36

5.4.2. Functionalisation of adducts

The adducts obtained through this novel sequence of condensation/ radical cyclisation contain interesting functionalities in the form of a γ-butyrolactone moiety and a latent, masked carbonyl group. In one of our first functionalisation attempts, compound **5.105** was treated with NaHMDS and excess MeI to provide, in excellent yield, a single monoalkylated lactone

[175] See: (a) Arya, P.; Samson, C.; Lesage, M.; Griller, D. *J. Org. Chem.* **1990**, *55*, 6248; (b) Arya, P.; Lesage, M.; Wayner, D.D.M. *Tetrahedron Lett.* **1991**, *32*, 2853.
[176] For an interesting example, in the case of Bu_3SnH, cf : Markó, I.E.; Warriner, S.L.; Augustyns, B. *Org. Lett.* **2000**, *2*, 3123

5.136. Interestingly, this compound displayed different spectroscopic properties than the previously obtained, isomeric adduct **5.122**. NOESY studies clearly demonstrated the *cis*-orientation of the methyl substituent and the ring junction hydrogens in **5.136**, allowing us to establish the relative stereochemistry of compounds **5.136** and **5.122**.



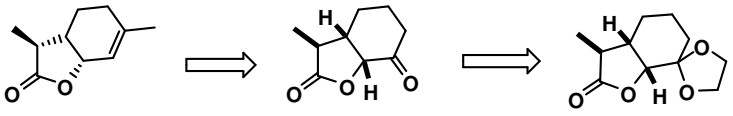
Scheme 5.37

Once again, the roof-shaped framework of the bicyclic lactone **5.105** is responsible for this exquisite stereoselectivity (Cf. Scheme 5.32). In this case, methyl-delivery occurs from the more accessible, convex face of the enolate, leading to the opposite epimer at C_2 of compound **5.122**. The possibility of obtaining, at will, either diastereomer is a clear asset of our methodology.

In an analogous fashion, dioxolane-protected lactone **5.104** was alkylated under similar conditions and an identical result was obtained.

At this stage, the resemblance between adducts **5.136-5.137** and wine lactone **5.003** (Cf. Scheme 5.1) became obvious and we decided to undertake studies aimed at its synthesis.

Wine lactone **5.003** is an important fragrance found in a number of foodstuffs from wine (hence its name) to oranges. Intriguingly, only 3 total syntheses of this substance have been reported to date.



Wine lactone
5.003

5.140

5.137

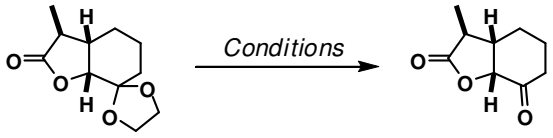
Scheme 5.38

As shown in Scheme 5.38, our synthetic plan was rather simple and consisted in taking advantage of the ketal protection to stereoselectively alkylate lactone **5.104**, then unravel the ketone carbonyl and employ it to install the final methyl substituent and the requisite double bond.

Since stereoselective alkylation had already been achieved (*vide supra*), we focused our efforts on deprotection of the dioxolane moiety of **5.137**.

Although this would seem a trivial task, our efforts were thwarted in achieving clean ketal deprotection. As shown in Table 5.3, the CAN-catalysed procedure, upon which we have abundantly relied (Cf. Chapters 2, 3 and 4), was of little use in this case. Even after 48 hours at reflux, only 20% of the deprotected product **5.140** could be isolated. Other procedures and reagents, including PPTS/acetone and I_2 / MeOH resulted in recovered

starting material. More forcing conditions, such as our laboratory's initial stoichiometric-CAN conditions or concentrated HCl in ethereal solvents, resulted in extensive decomposition. This was wholly unexpected since a number of other ketals, formed through our orthoester-based annelations, have been successfully deprotected in high yield. Nonetheless, we eventually recognised that the presence of an oxygen atom (heteroatom) at the α-position of the ketal to be deprotected, has a significantly negative influence on the success of such reactions (Cf. Section 5.5 for further discussion).



5.137 **5.140**

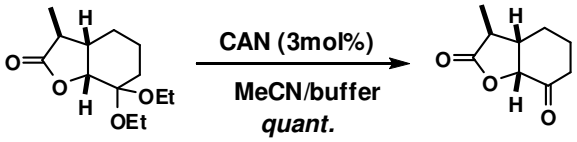
Table 5.3

Entry	Conditions	Yield of **5.140**
1	CAN (3 mol%), MeCN/buffer	20% after 48h (50% SM recovered)
2	CAN (2.5eq), MeCN	<10% and degradation
3	I_2 (cat.), acetone	No reaction
4	PPTS, acetone, water	No reaction
5	3M HCl, THF	Degradation

Disappointed by this setback, we reconsidered the nature of the ketal protecting group and turned our attention to the « open » congener of **5.137**. Indeed, the diethylketal moiety had already proved labile on two occasions :

after the condensation stage (more sensitive to chromatography) and during the cyclisation step (unexpected propensity to ketal mono-reduction). It was therefore reasonable to assume that its deprotection would be easier than that of the cyclic ketal.

Pleasingly, subjection of **5.136** to our CAN-catalysed protocol resulted in clean and quantitative formation of ketolactone **5.140**, confirming our assumptions (Scheme 5.39).



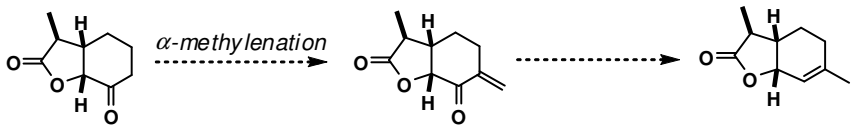
5.136 **5.140**

Scheme 5.39

Having at last established a viable pathway for the preparation of **5.140**, we then turned our attention to possible endgame sequences.

One attractive possibility is illustrated in Scheme 5.40. We had anticipated that, should an α-methylene group be installed, hydrazone reduction would occur in a 1,4-fashion to directly provide Wine lactone **5.003**. One of the most straightforward manners of introducing an α-methylene group is through addition of the stable iminium salt **5.142**, Eschenmoser's salt, followed by elimination.

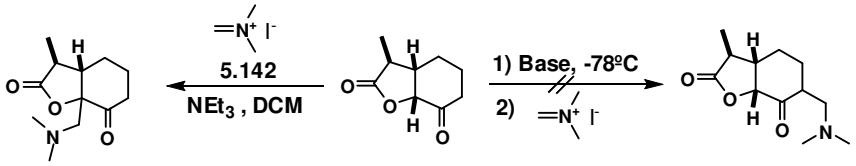
In the event, treatment of **5.141** with triethylamine and Eschenmoser's salt in DCM at room temperature resulted in methylenediamino-incorporation at the ring-junction as judged by analysis of the NMR spectra of the crude product (Scheme 5.41).



5.140 5.141 5.003

Scheme 5.40

We then attempted to generate the kinetic enolate of **5.140** through exposure to stronger bases. Unfortunately, whenever **5.140** was treated with either LDA, NaHMDS, KHMDS or Ph_3CLi followed by addition of Eschenmoser's salt **5.142** only multiple, unidentifiable products or unreacted starting materials could be recovered.



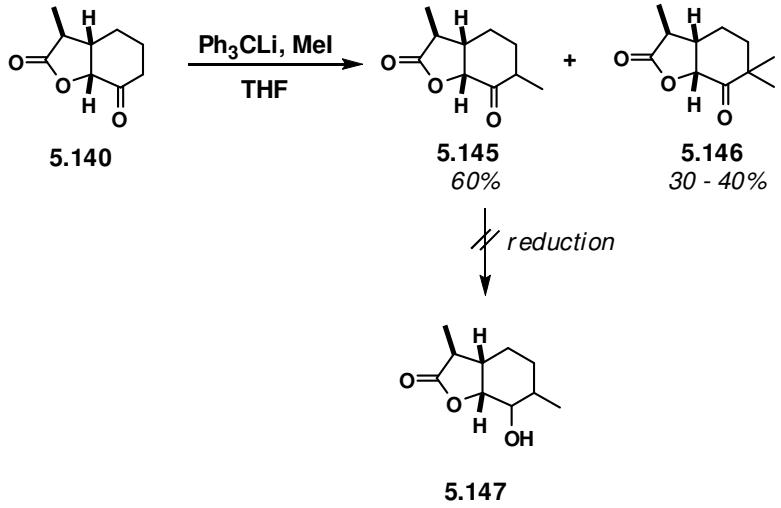
5.143 5.140 5.144

Scheme 5.41

Surmising that iminium salt **5.142** might not be the most suitable partner for alkylations of **5.140**, we elected a slight change in strategy. In the event that methylation of ketone **5.140** would be possible at its least substituted position, a chemoselective carbonyl reduction followed by elimination of water would lead to Wine lactone.

After extensive investigations, we found that monomethylation of **5.140** was only possible with Ph_3CLi as the base. Even under optimised conditions, compound **5.145** was always contamined with its dialkylated

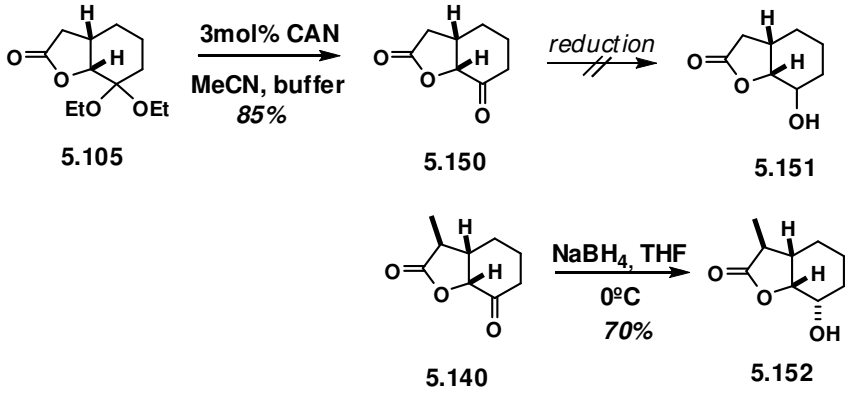
congener **5.146**. Unfortunately, chemoselective reduction of the ketone carbonyl in **5.145** through the action of (*inter alia*) $NaBH_4$ or $Li(OtBu)_3AlH$ resulted in recovered starting material. The use of more forcing conditions led to the degradation of this compound (Scheme 5.42).



Scheme 5.42

Puzzled by this ensemble of observations, we returned to a simpler model (Scheme 5.43). The cyclisation product **5.105** was deprotected smoothly, using the CAN-catalysed procedure to provide the unsubstituted ketolactone **5.150**. All our attempts to chemoselectively reduce the ketone carbonyl through recourse to low temperatures and/or mild reducing agents proved fruitless, as competitive lactone reduction always took place. In sharp contrast, when the alkylated lactone **5.140** was subjected to the action of $NaBH_4$ in THF (and not in EtOH), chemoselective ketone reduction ensued,

providing alcohol **5.152** in good yield (stereochemistry confirmed through NOESY studies on its *p*-bromobenzoate derivative).

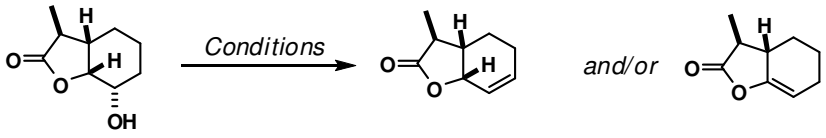


Scheme 5.43

It would seem that, in our system, the reactivity of the ketone- and the lactone-carbonyl groups is rather similar. Our results, nonetheless, seem to suggest that differentiation is possible through steric hindrance. Therefore, whenever the γ-lactone position is substituted at the α-position, selective reduction of the ketone carbonyl can be achieved under controled conditions. However, when both carbonyl groups are flanked by similar α-alkyl groups, nucleophilic addition to either of the carbonyl moieties becomes sluggish and non-selective.

In parallel with our fruitless attempts to selectively alkylate compound **5.140**, we tested the elimination of alcohol **5.152** to generate alkene **5.153** (Table 5.4). The use of a range of conditions failed to provide the desired product. For example, $SOCl_2$/Py returned mainly the substituted chloride,

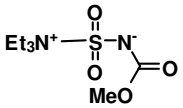
CuCl/DCC provided only decomposition products and, while xanthate formation was possible, its thermal elimination yielded complex mixtures. Soon, we had to recognise the need for a selective *syn*-elimination to take place. Only through such a process, would we be able to reach the coveted alkene selectively, since the alternative enol lactone product **5.154** would be a trisubstituted, hence potencially more stable, olefin.



5.152 **5.153** **5.154**

Table 5.4

Entry	Conditions	Result
1	$SOCl_2$, py	Mostly chloride
2	CuCl/DCC, PhH	Degradation
3	PTSA, PhH	Degradation
4	Xanthate elimination	Complex mixture
5	Burgess reagent, PhH	60% of **5.153**



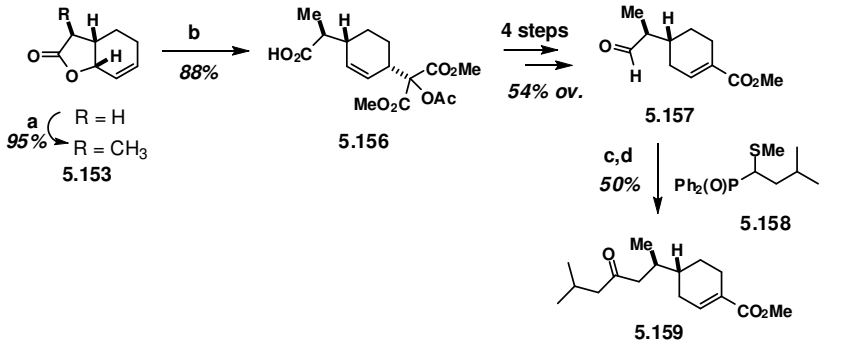
5.155

Scheme 5.44

In the event, subjection of **5.152** to the action of fresh Burgess' reagent, in refluxing benzene, enabled at last the obtention of compound **5.153** in 40-50% overall yield from ketolactone **5.140**. Burgess' salt **5.155** (Scheme 5.44) is known for effecting the selective *syn*-dehydration of secondary and tertiary alcohols.[177]

[177] For the original publications, see: (a) Crabbé, P.; Léon, C. *J. Org. Chem.* **1970**, *35*, 2594; (b) Burgess, E.M.; Penton, H.R.; Taylor, E.A. *J. Org. Chem.* **1973**, *38*, 1973

Unfortunately, this reaction proved to be highly capricious and difficult to reproduce. We presume that the sensitivity of the Burgess' zwitterionic salt **5.155** is at least partly responsible for this fact. Further confirmation of the structure of **5.153** was possible since this lactone is a key-intermediate in Helmchen's 2002 synthesis of Juvabione. As shown in Scheme 5.45, Helmchen used π-allyl Palladium chemistry to effect the nucleophilic ring-opening of **5.153**.[178] Homologation eventually provided Juvabione **5.159**. We have halted our investigations on bicyclolactones at this point.

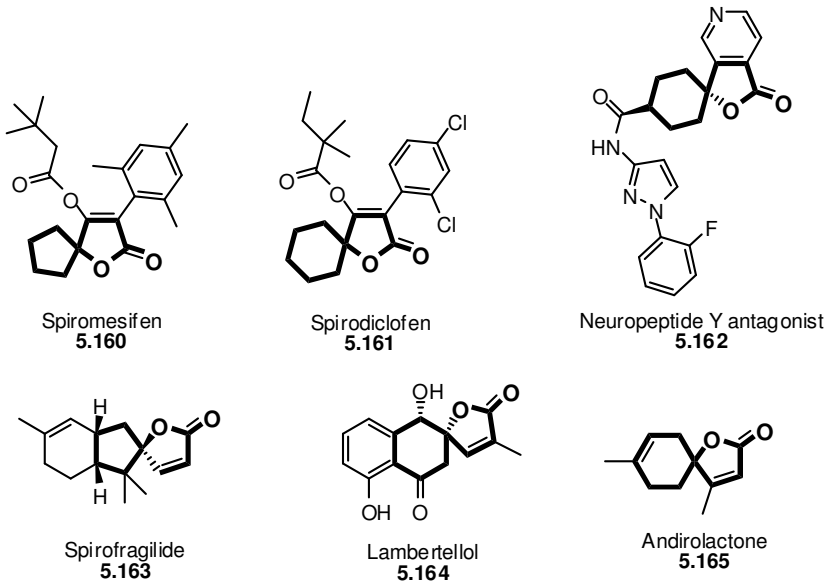


Scheme 5.45

[178] We have used similar π-allyl Palladium chemistry in a wholly different context : see Liao, J.-H.; Maulide, N.; Augustyns, B.; Markó, I.E. *Org.Biomol.Chem.* **2006**, *4*, 1464

5.5. Synthesis of spirocyclic butenolides

As we have highlighted in the very first Chapter, our functionalised orthoesters can be considered either as mixed electrophilic/nucleophilic entitites, or as double electrophiles. Their use as the former has been illustrated in the preceding subsection. As for the latter, it would conceivably lead to the synthesis of spirocyclic butenolide frameworks. These substructures are found in a number of natural and non-natural biologically active substances. Examples are shown in Scheme 5.46.



Scheme 5.46

These representative examples include man-made molecules, such as the remarkably active acaricides and insecticides spirodiclofen **5.161** and spiromesifen **5.160**,[179] the spirocyclic neuropeptide Y antagonist **5.162**,[180] and naturally occuring substances, such as the recently isolated lambertellol A **5.164**.[181]

In contrast to the field of saturated γ-lactones, there are no comprehensive literature reviews on the preparation of spirocyclic butenolides. We shall therefore briefly analyse the different strategies that have been employed for their preparation. Particular emphasis will be given to the bond disconnections employed, as explicited in the following paragraph.

5.5.1. Literature survey

The simplest way to classify the different approaches employed to prepare spirocyclic butenolides is to consider the different bond disconnections that can be used (portrayed in Scheme 5.47). Each type of bond disconnection shall be discussed separately.

Spiroketals and α-methylene spirolactones are not included in this survey. However, approaches to saturated spirolactones will be discussed when deemed relevant. It is obvious that these saturated analogues can be dehydrogenated to spirobutenolides by various methods.

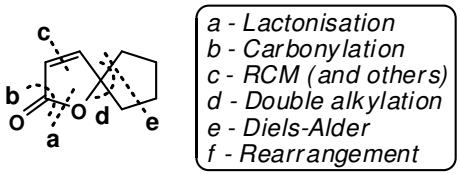
---

[179] Liu, T.-X. *Crop Prot.* **2004**, *23*, 505

[180] Iida, T.; Satoh, H.; Maeda, K.; Yamamoto, Y.; Asakawa, K.-i.; Sawada, N.; Wada, T.; Kadowaki, C.; Itoh, T.; Mase, T.; Weissman, S. A.; Tschaen, D.; Krska, S.; Volante, R. P. *J. Org. Chem.* **2005**, *70*, 9222

[181] Murakami, T.; Morikawa, Y.; Hashimoto, M.; Okuno, T.; Harada, Y. *Org. Lett.* **2004**, *6*, 157

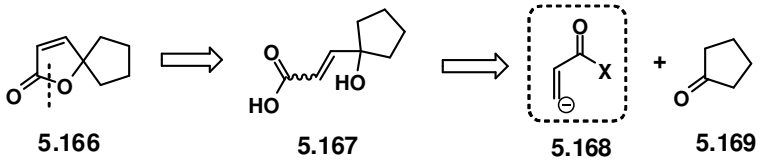
Most of the methodologies presented were actually designed for the preparation of 4,4-disubstituted butenolides, of which spirobutenolides are a particular case. Wherever possible, emphasis shall be given to the general scope of the procedures.



Scheme 5.47

5.5.1.1. Bond disconnection a : Lactonisation

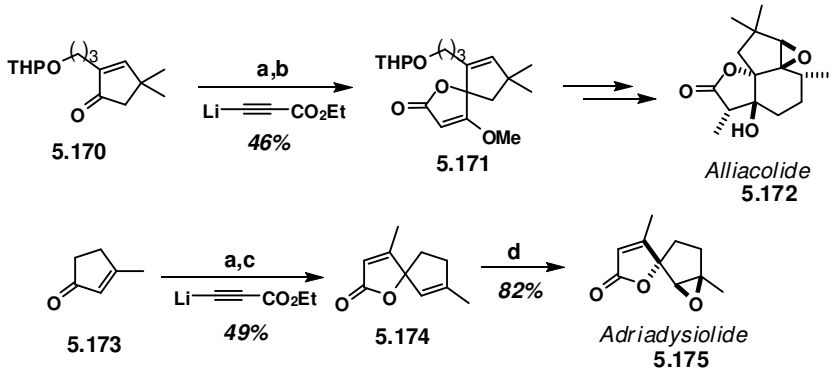
Unsurprisingly, most syntheses of spirocyclic butenolides employ a « lactonisation » retron, involving hydroxyacid **5.167** (or an equivalent) as the key intermediate (Scheme 5.48). The methods used to access this hydroxyacid precursor as well as the nature of the synthons employed are diverse.



5.166 **5.167** **5.168** **5.169**

Scheme 5.48

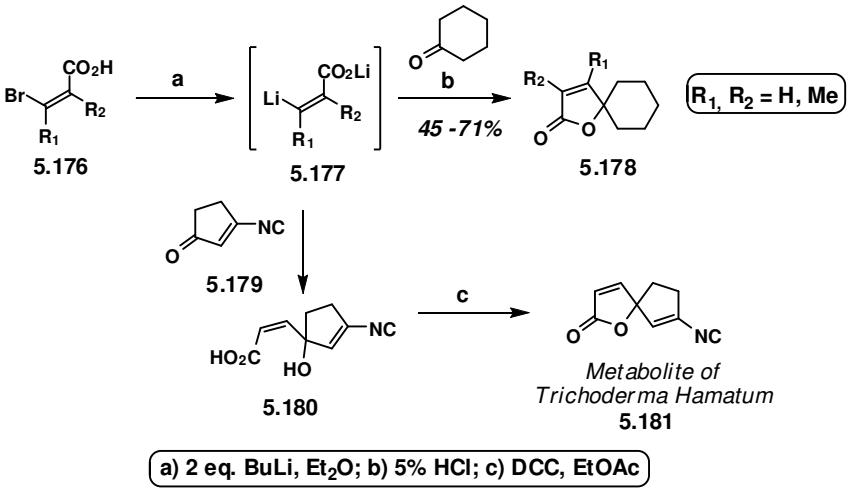
The most widely used strategy comprises the addition of an organometallic equivalent of **5.168** to a ketone **5.169**, followed by acidic treatment. Among such equivalents, propiolate ester anions are the most often employed. For example, in his total synthesis of Alliacolide **5.172**, Pattenden[182] added the lithium salt of ethyl propiolate to ketone **5.170** (Scheme 5.49). When the resulting hydroxy-ynoate was treated with sodium methoxyde in methanol, spirotetronate **5.171** was obtained in 46% yield. In this reaction, a reversible Michael addition of methoxyde ion to the propiolate triple bond is likely to be responsible for the tandem cyclisation. Other nucleophiles can be employed for such a process, such as dimethylcuprate, as shown below[183] (Scheme 5.49).



Scheme 5.49

[182] Ladlow, M.; Pattenden, G. *J.Chem. Soc., Perkin Trans.I* **1988**, 1107
[183] Mancini, I.; Guella, G.; Guerriero, A.; Boldrin, A.; Pietra, F. *Helv. Chim. Acta* **1987**, *10*, 2011

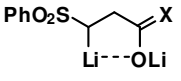
Caine showed that dianion **5.177** was indeed available from (*Z*)-β-bromoacrylic acid **5.176** by treatment with butyllithium at low temperatures.[184] Acidification of the reaction mixture during workup then afforded a one-pot preparation of spirobutenolides **5.178**. As an illustration, Baldwin and co-workers used this approach when preparing an interesting cyclopentenyl isonitrile **5.181** that they had isolated from *Trichoderma hamatum* a couple of years before.[185] In the event, addition of **5.177** to ketone **5.179** provided a *seco*-acid which was cyclised under milder conditions (DCC), affording the spirocyclic butenolide **5.181** (no yields are reported).



Scheme 5.50

[184] Caine, D.; Frobese, S. *Tetrahedron Lett.* **1978**, *52*, 5167

[185] Baldwin, J.E.; Adlington, R.M.; Chondrogianni, J.; Edenborough, M.S.; Keeping, J.W.; Ziegler, C.B. *J. Chem. Soc., Chem. Commun.* **1985**, 816



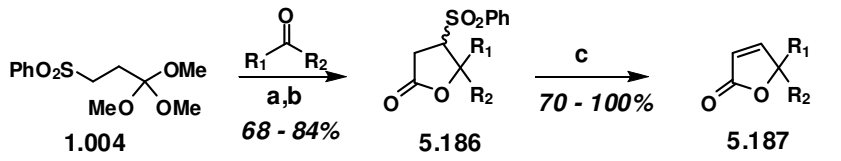
5.182 X = NPh
5.183 X = O

Scheme 5.51

Many other variations on this theme have been reported. For example, Nájera employed 3-lithio-3-tosylpropionate **5.183**,[186] and others have prepared similar β-acylvinyl anion equivalents (Scheme 5.51). Among them, the procedure devised by Ghosez *et al.* deserves a special note, for obvious reasons.

As we have mentioned in the opening Chapter, the Ghosez group pioneered the use of orthoester **1.004** as a 3-carbon linchpin for the cyclopentannelation of enones (Scheme 5.52). In 1987, they disclosed an interesting approach to spirolactones and spirobutenolides using the same underlying principle of a mixed electrophilic-nucleophilic behaviour of **1.004**.[187] Thus, when the anion of orthoester **1.004** was added onto ketones or aldehydes and the resulting ω-hydroxyorthoesters hydrolised, lactonisation occurred spontaneously, leading to **5.186** (mixture of diastereomers). If the phenylsulphonyl group was then eliminated under basic conditions, butenolides **5.187** could be obtained in moderate to good yields.[188] It is a fortunate event that analogous orthoesters can be used in different manners to craft similar motifs (*vide infra*).

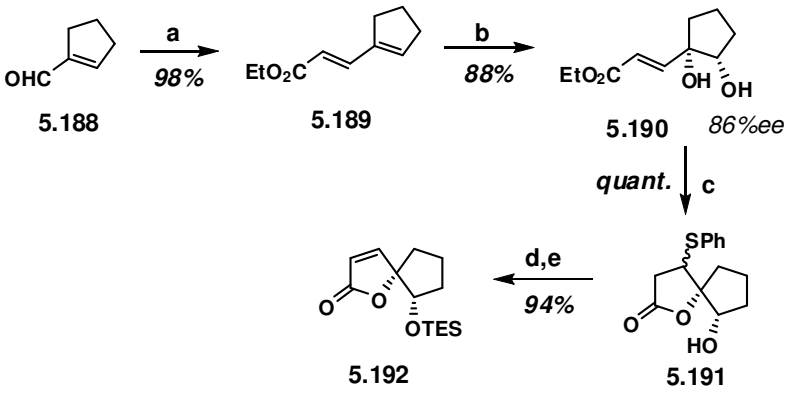
[186] Cf. Bonete, P.; Nájera, C. *J. Org. Chem.* **1984**, *59*, 3202 and references therein.
[187] Carretero, J.C.; De Lombaert, S. ; Ghosez, L. *Tetrahedron Lett.* **1987**, *28*, 2135
[188] The Nájera group later reported an identical scheme using the corresponding acetals instead : Bonete, P.; Nájera, C. *Tetrahedron* **1995**, *51*, 2763.



Scheme 5.52

Yet a slightly different alternative was disclosed by researchers at Syngenta, in Basel (Scheme 5.53).[189] Interested in the synthesis of constrained spironucleoside building blocks (*vide infra*), their strategy consisted in the enantioselective dihydroxylation of dienoate **5.189**, readily available by Horner-Emmons homologation of enal **5.188**. In analogous fashion to the ynoate cyclisations presented above, addition of thiophenolate to compound **5.190** eventually led to the functionalised spirocyclic lactone **5.191** in quantitative yield. Phenylsulphanyl elimination from **5.191** then afforded butenolide **5.192** in very high yield.

[189] Wenderborn, S.; Binot, G.; Nina, M.; Winkler, T. *Synlett* **2002**, 1683

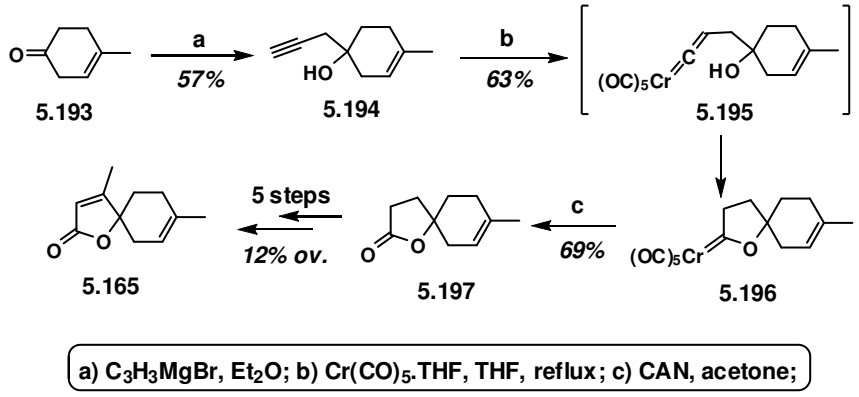


Scheme 5.53

Finally, a different « lactonisation » reaction merits some comment. Peter Quayle and his group at Manchester did considerable amounts of work on acetylene isomerisation reactions.[190] Subsequently, they applied it to the synthesis of Andirolactone **5.165**.

As shown in Scheme 5.54, the key intermediate is homopropargylic alcohol **5.194**, readily available from cyclohexanone derivative **5.193**.[191] Exposure of this compound to the action of stoichiometric (pentacarbonyl)chromium in THF, followed by oxidative decomplexation with CAN, afforded spirolactone **5.197**. In the event, the terminal acetylene moiety isomerised to the chromium vinylidene **5.195,** which was then rapidly captured to form the stable carbene complex **5.196**. Oxidation of this complex then provided the observed lactone product.

[190] Cf. Rahman, S.; Quayle, P.; Ward, E.L.M.; Herbert, J. *Tetrahedron Lett.* **1994**, *35*, 1000.
[191] Quayle, P.; Ward, E.L.M.; Taylor, P. *Tetrahedron Lett.* **1994**, *35*, 8883



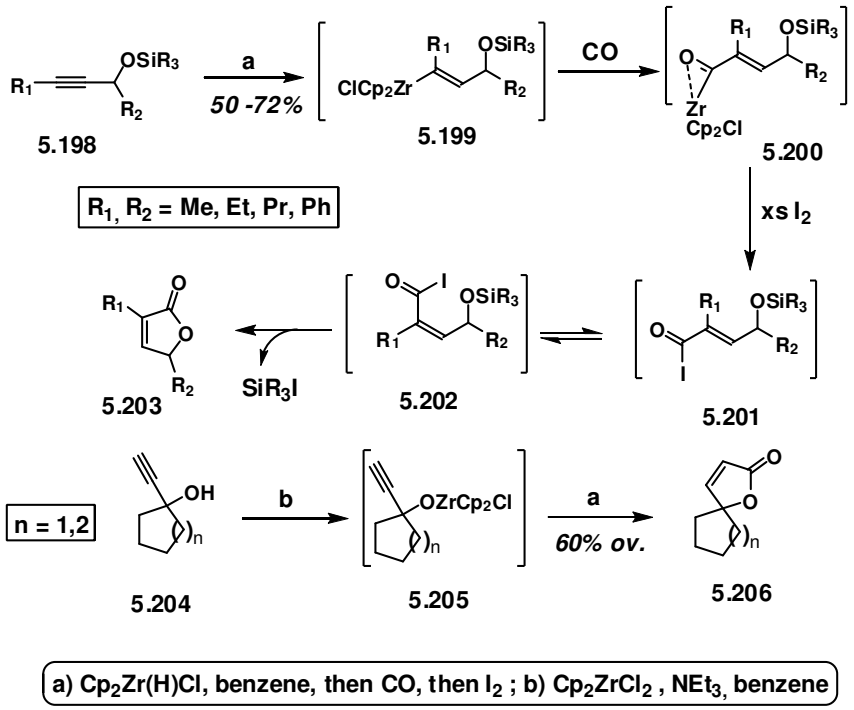
Scheme 5.54

Most of the methodologies described in this section share a common feature: they all begin with the nucleophilic addition of a lithiated species onto a cyclic ketone. The resulting alcohols are then lactonised either *in situ* or through an additional cyclisation step. The low functional-group tolerance of such procedures can be a severe drawback.

5.5.1.2. Bond disconnection b : Carbonylation

To circumvent the use of functionalised propiolate equivalents, some groups have investigated the direct carbonylative cyclisation of propargylic alcohols into butenolides. As early as in 1988, Buchwald disclosed an interesting zirconium-mediated carbonylation (Scheme 5.55).[192]

[192] Buchwald, S.L.; Fang, Q.; King, S.M. *Tetrahedron Lett.* **1988**, *29*, 3445



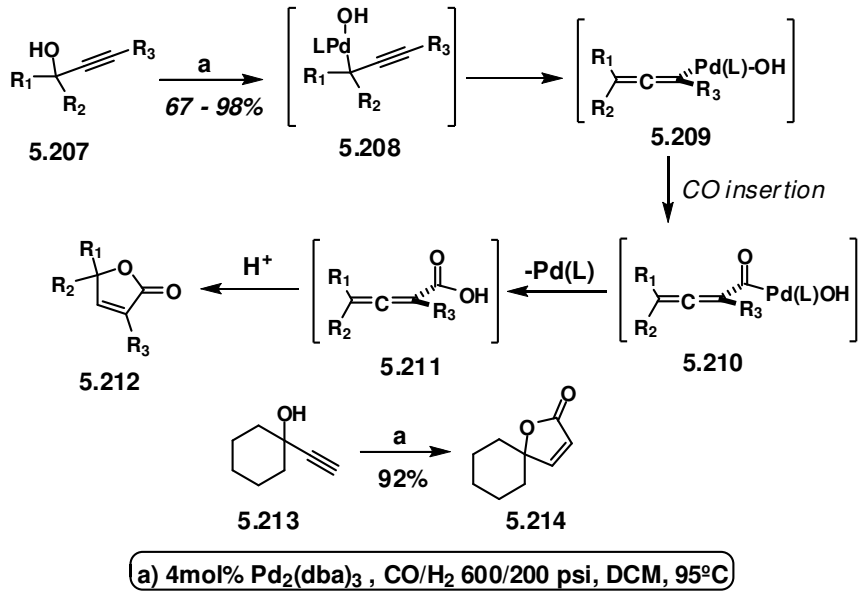
Scheme 5.55

Treatment of propargylic ethers **5.198** with 1.1 eq. of Schwartz reagent $Cp_2Zr(H)Cl$, followed by sequential exposure to CO and I_2, leads to butenolides **5.203** in good overall yields. In this one-pot procedure, regioselective hydrozirconation to **5.199** takes place, followed by carbonylation of the vinyl zirconium adduct. Iodinative dezirconation then provides acyl iodide **5.201**, which is presumed to equilibrate to the *Z*-isomer **5.202** in the presence of excess iodine. The electrophilic nature of acyl iodides being well precedented, intramolecular attack of the silyl ether followed by the loss of R_3Si-I completes this sequence. Interestingly, the

unprotected alcohols **5.204** can also be used. However, the initial generation of a zirconium alkoxyde **5.205** becomes mandatory in these cases.

A more atom-economical carbonylation approach was recently reported by Alper.[193] Propargyl and allyl alcohols **5.207** are reacted with $Pd_2(dba)_3$ in the presence of dppb and under a mixed pressure of CO and hydrogen to provide the requisite butenolides **5.212** in good to excellent yields (Scheme 5.56). Although the mechanistic details of this reaction are not well defined, the Authors propose that oxidative addition of Pd^0 to the propargylic alcohol takes place, ultimately leading to allenyl palladium complex **5.209**. Carbonylation of this intermediate followed by reductive elimination then probably generates allenic acid **5.211**, which is susceptible to rapid cyclisation to a butenolide **5.212** in the presence of traces of acid.

[193] Yu, W.-Y.; Alper, H. *J. Org. Chem.* **1997**, *62*, 5684 and references therein.



Scheme 5.56

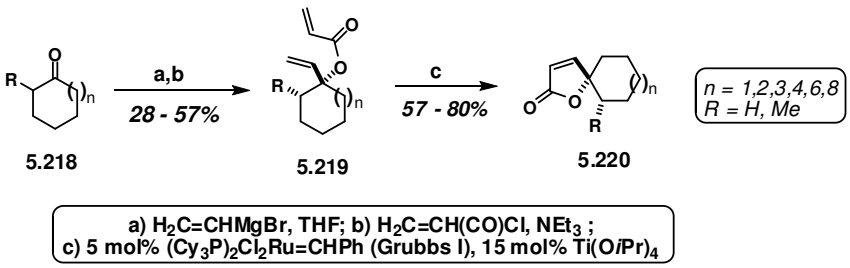
Though conceptually intriguing, these carbonylation approaches are of somewhat limited interest, due to the stoichiometric amounts of metal complexes or the harsh conditions required (high pressures of CO and hydrogen).

5.5.1.3. Bond disconnection c : Ring-closing metathesis and others

Given the prominence of ring-closing metathesis (RCM) as an exceedingly useful tool for the preparation of cyclic scaffolds, it is

unsurprising that a number of groups have investigated such a process in the context of butenolide synthesis.

The broad concept is perhaps best demonstrated through the systematic work of Peter Langer (Scheme 5.57).[194] Stereoselective addition of vinylmagnesium bromide to cyclic ketones **5.218**, followed by esterification with acryloyl chloride, provides the substrates **5.219**. RCM in the presence of Grubbs' first-generation catalyst and a catalytic amount of $Ti(OiPr)_4$ as first demonstrated by Furstner[195], generates the desired spirocyclic butenolides **5.220** in 60-80% yields.

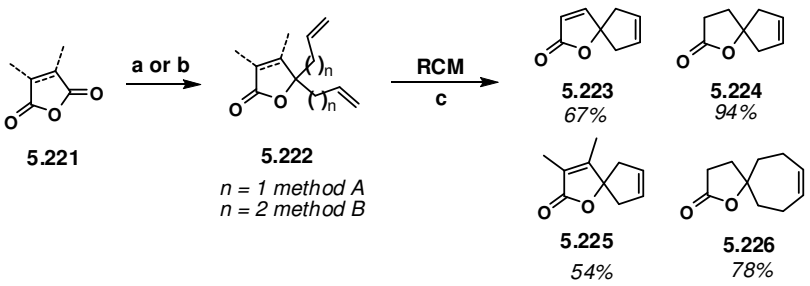


Scheme 5.57

Other cyclisations by RCM (different bond disconnection but same retron) employ a preformed, 4,4-dialkylated butenolide. For example (Scheme 5.58), addition of excess allyltrimethylsilane or 3-butenylmagnesium bromide to cyclic anhydrides affords 4,4-disubstituted lactones **5.222** (yields not provided). RCM of these compounds furnishes the requisite spirolactones or butenolides in good yields (cf. Scheme 5.58 for

[194] Langer, P.; Albrecht, U. *Synlett* **2002**, 1841
[195] Furstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130

examples).[196] Interestingly, in the preparation of all the γ-lactones reported, no Lewis-acidic additives were required in contrast to the results of Langer.[194]



Scheme 5.58

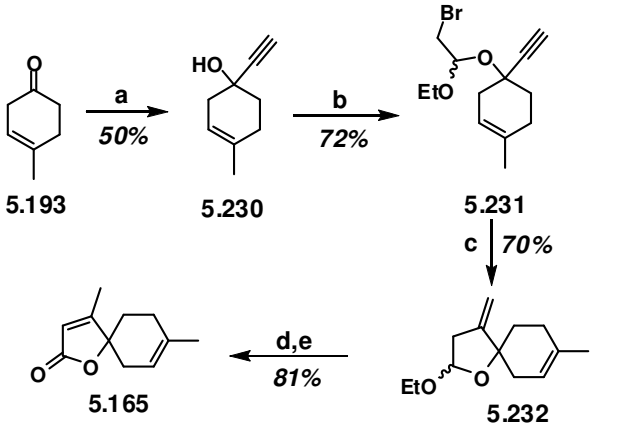
Two other butenolide syntheses employ the same disconnection, albeit not using RCM as the bond-forming process. Both have been applied to the synthesis of Andirolactone **5.165** (Cf. Sections *a* and *e* for other approaches to this natural product).

In 1988, Srikrishna reported the preparation of Andirolactone using the Stork linchpin radical cyclisation as the key-step,[197] as portrayed in Scheme 5.59. The propargylic alcohol **5.230**, prepared by ethynylmagnesium bromide addition onto cyclohexenone **5.193**, was converted to bromoacetal **5.231** in 72% yield. Radical-mediated ring closure of ths compound provided spirohemiacetal **5.232**. Following oxidation with Jones' reagent,

[196] (a) Michaut, M.; Santelli, M.; Parrain, J.-L. *J. Organomet. Chem.* **2000**, *606*, 93 and references therein. For a different access to the substrates, see : (b) Sabitha, G.; Reddy, C.S.; Babu, R.S.; Yadav, J.S. *Synlett* **2001**, 1787

[197] Srikrishna, A.; Sharma, G.V.R. *Tetrahedron Lett.* **1988**, *29*, 6487

the resulting β-methylene-γ-lactone was readily isomerised by treatment with silica gel. This afforded Andirolactone in 81% overall yield from hemiacetal **5.232**.



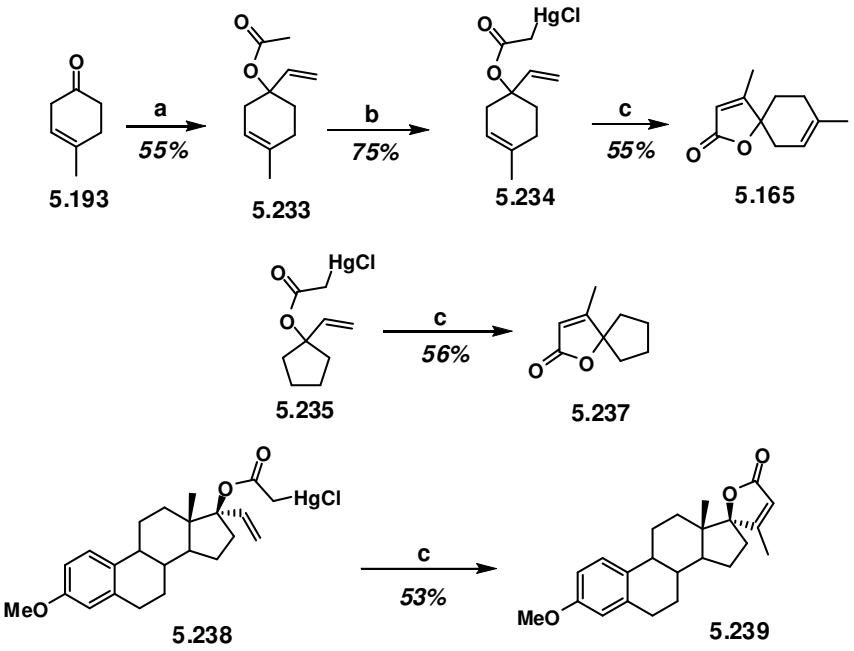
Scheme 5.59

Only 2 years later, Richard Larock and co-workers disclosed a palladium-promoted cyclisation of organomercurials as a route to spirocyclic butenolides.[198] As shown in Scheme 5.60, they also applied this concept to the synthesis of Andirolactone.

Starting from the same ketone as Srikrishna, vinylmagnesium bromide addition, followed by acetylation, afforded **5.233**. After formation of the

[198] Larock, R.C.; Stinn, D.E.; Kuo, M.-Y. *Tetrahedron Lett.* **1990**, *31*, 17

ester enolate with LDA, quenching with $HgCl_2$ provided organomercurial reagent **5.234**. Exposure of this compound to lithium tetrachloropalladate then effected transmetallation-initiated cyclisation to directly afford butenolide **5.165** in 55% yield. As depicted, Larock demonstrated the generality of this concept in the preparation of other spirocyclic butenolides, including cardenolide analogues **5.239**.



Scheme 5.60

The two alternative uses of bond disconnection *c* just described are clearly limited to the preparation of β-substituted butenolides and involve the

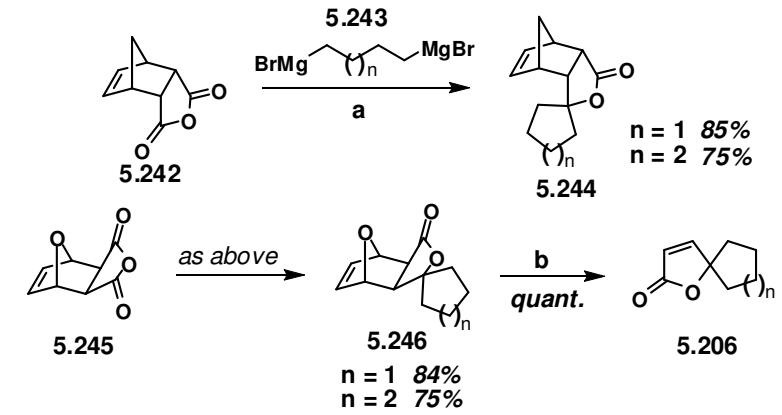
use of toxic reagents in stoichiometric amounts. Nevertheless, each of them provides a ready access to unsaturated butenolides (such as Andirolactone), which might prove rather tricky to prepare using RCM.

5.5.1.4. Bond disconnection d : Double alkylation

An interesting alternative for the construction of spirobutenolides would consist in the direct « stitching » of the carbon-cycle onto a preformed butenolide moiety. To date, little work exists in this domain and all efforts focused on the addition of bis-nucleophiles onto an anhydride or its equivalent (our own work should fit in this subsection, *vide infra*).

More than 20 years ago, Canonne and his co-workers introduced the use of bis-Grignard reagents for the annelation of cyclic anhydrides (Scheme 5.61 for examples),[199] readily assembled by Diels-Alder cycloaddition of maleic anhydride. Upon exposure to either 1,4-bis(bromomagnesio)butane or its higher homologue **5.243**, the corresponding spirolactones **5.244** were obtained in high yields. Thermolysis of these compounds effects a retro-Diels-Alder reaction, affording spirobutenolides **5.206** in quantitative yields. Importantly, such compounds could not be obtained by direct bis-Grignard annelation of maleic anhydride.

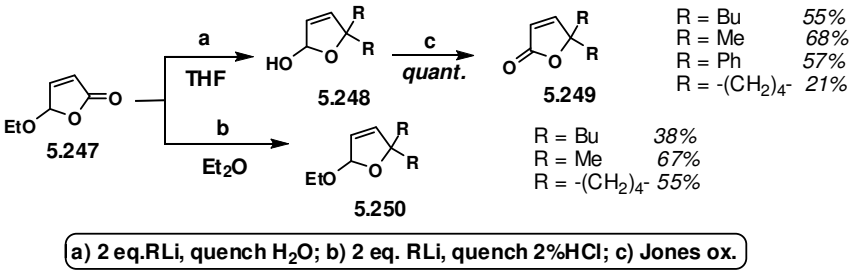
[199] Cannone, P.; Bélanger, D.; Lemay, G. *J. Org. Chem.* **1982**, *47*, 3953 and references therein.



Scheme 5.61

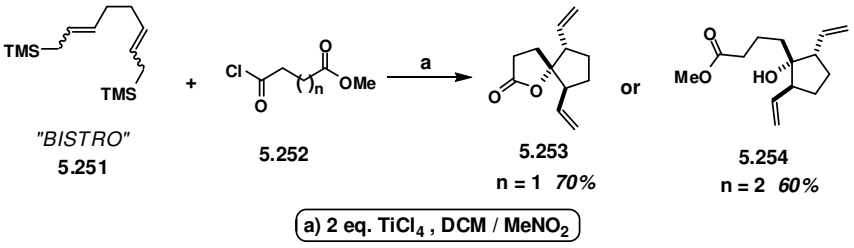
In a similar fashion, it was later demonstrated that the addition of 2 equivalents of an organolithium reagent onto lactone-acetal **5.247** led to 4,4-bisalkylated products.[200] As shown in Scheme 5.62, if 1,4-dilithiobutane was employed in ether, a spirocyclic hemiacetal **5.250** was obtained in 55% yield. Interestingly enough, this reaction provided different results according to the solvent and quenching method employed.

[200] Machado-Araujo, F.W.L.; Gore, J. *Tetrahedron* **1982**, *38,* 2897



Scheme 5.62

A different, intramolecular double alkylation approach was developed by Arlette Tubul and her group in Marseille.[201] They used 1,8-bis(trimethylsilyl)-2,6-octadiene **5.251** (for which they later coined the acronym « BISTRO ») for the double cyclopentannelation of mixed esters/acyl chlorides of succinic and glutaric acid **5.252**. In the event (Scheme 5.63), treatment of BISTRO with these compounds in the presence of 2 eq. titanium tetrachloride effected double allylation to provide divinylspirolactone **5.253** in 70% yield (*seco*-ester **5.254** was obtained in the case of glutaric acid). It is noteworthy that the (*d,l*) isomers were the major products observed.



Scheme 5.63

[201] Tubul, A.; Ouvrard, P.; Santelli, M. *Synthesis* **1991**, 173

5.5.1.5. Bond disconnection e : Diels-Alder reaction

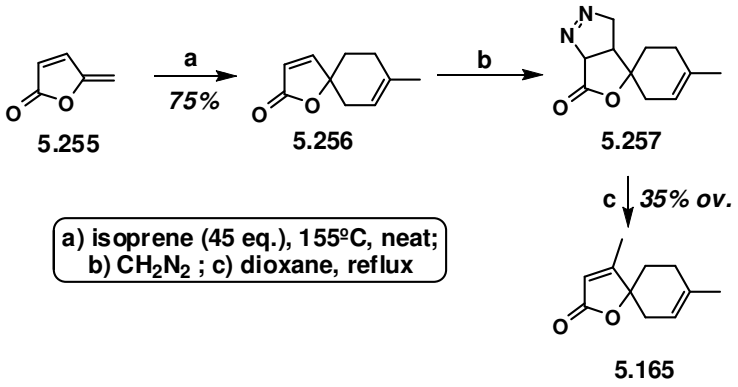
In this subsection we shall consider essentially the work carried out by Ortuño and co-workers in Barcelona. They were the first to recognise that a Diels-Alder cycloaddition of protoanemonin **5.255**, if selective for the *exo*-double bond, would provide a spirocyclic butenolide as the product. The Ortuño group undertook detailed studies, including theoretical calculations, to ascertain which kinds of anemonin derivatives would retain reactivity at the *exo*-double bond.[202] Though a thorough discussion of such work is clearly beyond the scope of this review, it is important to note that once substituents are placed on the enol ether double bond of **5.255**, its Diels-Alder reactivity shifts to the more classical, endocyclic alkene moiety. The broad diene-scope of the method, nonetheless, can be rather useful in certain cases, and this is nicely illustrated by the Ortuño synthesis of Andirolactone **5.165**, the synthetic benchmark of this entire section.[203]

As shown in Scheme 5.64, the thermal cycloaddition of protoanemonin **5.255** with isoprene affords, in a single step, spirobutenolide **5.256** in 75% yield. This reaction can be easily scaled-up. Although a « conventional » synthesis of Andirolactone **5.165** from **5.256** would involve cuprate addition, followed by dehydrogenation of the resulting saturated

[202] For the leading references, see : (a) Alonso, D.; Font, J.; Ortuño, R.M.; d'Angelo, J.; Guingant, A.; Bois, C. *Tetrahedron* **1991**, *47*, 5895; (b) Branchadell, V.; Font, J.; Oliva, A.; Ortí, J.; Ortuño, R.M.; Rafel, S.; Terris, N.; Ventura, M. *Tetrahedron* **1991**, *47*, 8775 ; (c) Alonso, D.; Font, J.; Ortuño, R.M. *J.Org.Chem.* **1991**, *56*, 5567 ; (d) Branchadell, V.; Font, J.; Moglioni, A.G.; Ochoa de Echagijen, C.; Oliva, A.; Ortuño, R.M.; Veciana, J.; Vidal-Gancedo, J. *J. Am. Chem. Soc.* **1997**, *119*, 9992 and references cited.

[203] Planas, M.; Segura, C.; Ventura, M.; Ortuño, R.M. *Synth. Comm.* **1994**, 651

lactone, the Ortuño team devised an elegant pathway to circumvent this. Thus, when **5.256** was treated with an excess of diazomethane, cycloaddition ensued to afford pyrazoline **5.257**, contaminated with several other products. Without purification, this mixture was then heated in dioxane for 50h, affording Andirolactone **5.165** in 30% overall yield. Although such nitrogen-extrusion reactions might tend to provide the corresponding cyclopropanated compound, it is possible that the tension associated with the creation of a fused cyclopropane would render such a process too high in energy.



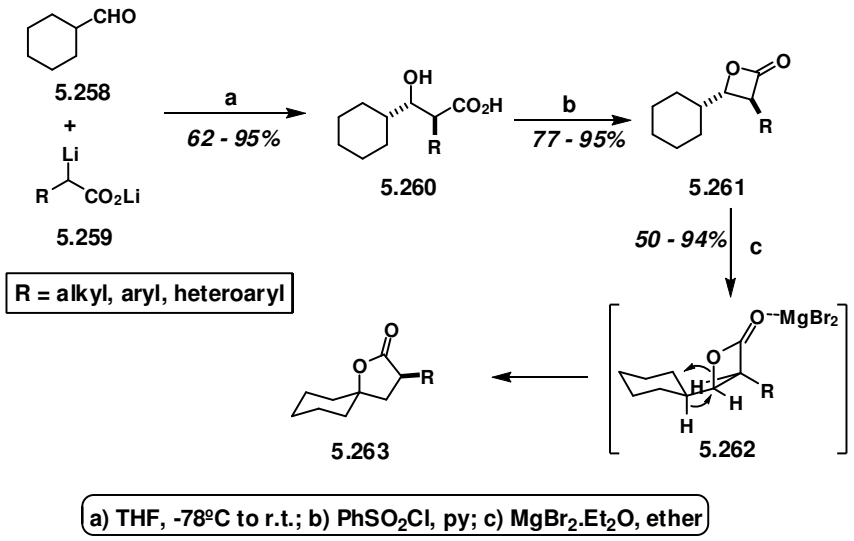
Scheme 5.64

5.5.1.6. Bond disconnection f : Rearrangements

Chemists have always been fond of skeletal reorganisations, and it is only natural that some approaches to spirobutenolides/spirolactones, relying on such rearrangements, have been disclosed. When effective, these are usually aesthetically pleasing synthetic schemes.

One of these studies employs the dyotropic rearrangement of cycloalkyl β-lactones (Scheme 5.65). In a very interesting report,[204] Howard Black *et al.* showed that the dianion of a variety of acetic acid derivatives can be added stereoselectively to cyclohexanecarbaldehyde **5.258**. The resulting *threo*-seco acids **5.260** are readily lactonised by $PhSO_2Cl$ and pyridine, setting the stage for the crucial reorganisation. When the β-lactones **5.261** are treated with $MgBr_2.Et_2O$, a highly stereoselective rearrangement takes place affording the spirocyclic lactones **5.263** in very high yields. As depicted, facile β-lactone opening is expected to take place upon interaction with the Lewis acid. The concerted nature of dyotropic rearrangements ensures that the transfer of stereochemical information (*via* **5.262**) into the products is near complete.

[204] (a) Black, T.H.; DuBay III, W.J.; Tully, P.S. *J. Org. Chem.* **1988**, *53*, 5922. For a review on dyotropic rearrangements, see : (b) Reetz, M. *Adv. Organomet.Chem.* **1977**, 33



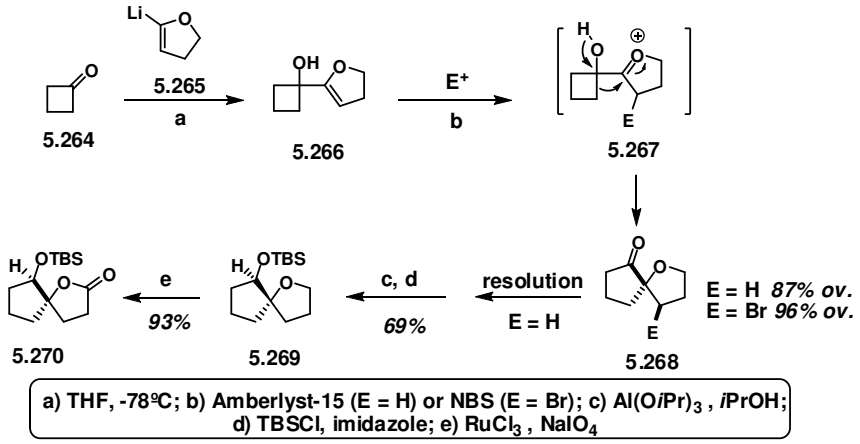
Scheme 5.65

Interestingly (though beyond the scope of the present review), if the corresponding cyclo*pentane* carbaldehyde was used instead, ring expansion to a fused bicyclic lactone occured (not shown) rather than the hydrogen shift depicted above.

As a prelude to his extensive work on the preparation of spiro-constrained DNA-building blocks, Paquette reported the synthesis of such spirannic motifs as depicted in Scheme 5.66.[205] Addition of dihydrofurannyl lithium to cyclobutanone provides carbinol **5.266** in quantitative yield. This unstable compound readily participates in ring-expansion upon treatment with either acid or NBS, leading to spiroethers **5.268**. These compounds can

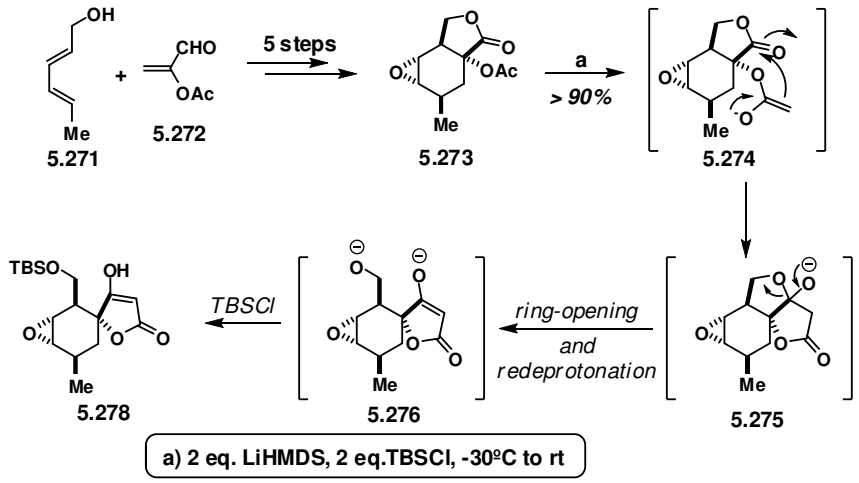
[205] (a) Paquette, L.A.; Owen, D.R.; Bibart, R.T.; Seekamp, C.K.; Kahane, A.L.; Lanter, J.C.; Corral, M.A. *J. Org. Chem.* **2001**, *66*, 2828. For other references by the same author, see : (b) Dong, S.; Paquette, L.A. *J. Org. Chem.* **2006**, *71*, 1647 and work cited therein.

then be elaborated, through conventional reactions, into optically pure (by resolution) spirobutenolides such as **5.270**.



Scheme 5.66

Finally, in their synthesis of the tricyclic spirotetronic core of the Abyssomicins, Georgiadis and his group in Greece employed a very interesting bicycle-spirocycle rearrangement. Thus (Scheme 5.67), treatment of a mixture of bicyclolactone **5.273** (prepared through an expeditious 5-step sequence) and 2 eq. TBSCl with 2 eq. of LiHMDS at low temperature (-30ºC) triggered this interesting transformation. The spirotetronic acid **5.278** was obtained as the major product (>85% yield) following workup. As depicted in Scheme 5.67, deprotonation of the acetate group and Dieckmann ester-exchange presumably occur to provide dianion **5.276**, following redeprotonation by the second equivalent of base. Reaction of this anion with TBSCl then accounts for the observed product (the tetronate is, presumably, also silylated but readily hydrolysed during workup).

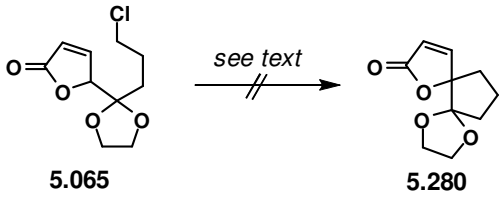


Scheme 5.67

This concludes our screening of the literature. A critical analysis of the methods presented for the synthesis of spirocyclic butenolides or lactones reveals that some of the procedures make use of either harsh conditions or require high amounts of metallic complexes as promoters. Though sometimes elegant, the relatively limited scope of most of the reported methodologies showcases the need for alternative, complementary disconnections, particularly those which can directly produce the spirobutenolide moiety as such. It is one of such conceptually new disconnective approaches that is described in depth throughout the following subsection.

5.5.2. Spiroannelation results

Our initial experiments focused on the chlorinated adduct **5.065**, which was treated with 1.4 equivalents of *t*-BuOK in both wet and dry THF. Unfortunately, only the starting material could be recovered from these reactions. Changing the base to NaHMDS, NaH, KHMDS or LDA afforded similar results. Raising the temperature only led to the decomposition of the starting material, as did the addition of small amounts of NaI (Scheme 5.68).



5.065 **5.280**

Scheme 5.68

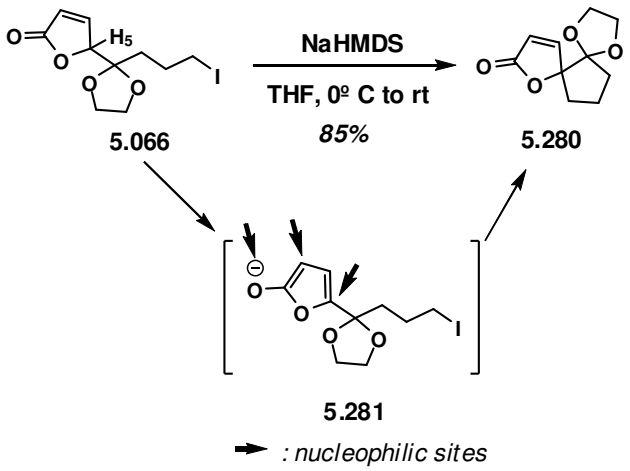
Gratifyingly, changing the nature of the leaving group from chlorine to iodine solved our problem. In the event, when **5.066** was treated with NaHMDS, from -78ºC to rt, in dry THF, smooth formation of a new product was observed.[206]

The identity of this new compound was established as spirobutenolide **5.280** through comparison with products reported in the literature coupled with two essential observations:

(a) the disappearance of the characteristic H_5-signal

(b) the formation of an adduct bearing a new quaternary carbon at 94-95 ppm (APT/DEPT NMR analysis)

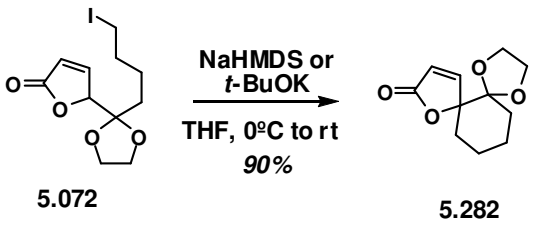
[206] The use of *t*-BuOK afforded a similar result.



Scheme 5.69

This result is all the more interesting as it is an SN_2-driven spirocyclisation of a delocalised furanone enolate **5.281** (Scheme 5.69). Being a delocalised anion, **5.281** could conceivably react at three different positions. Geometric restrictions, however, should favour reaction at C_5 and concomitant formation of a spirannic center.

Furthermore, when compound **5.072**, bearing a 5-carbon tether, was submitted to the spirocyclisation conditions, the formation of a 6-membered ring **5.282** ensued with nearly identical (actually slightly higher) yields.

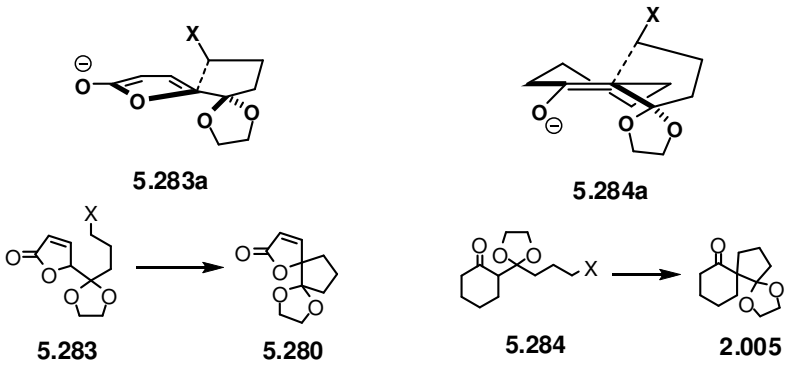


5.072 **5.282**

Scheme 5.70

These observations pinpoint a significant difference in the spirocyclisation-behaviour between TMSOF- and cyclic ketone- derived adducts **5.283** and **5.284** respectively (Scheme 5.71). Not only did cyclisations of **5.284** proceed smoothly with chloride as the leaving group but they displayed significant rate differences in the formation of 5- and 6-membered rings through spirocyclisation. This dichotomy in reactivity might originate from the following factors.

On one hand, the delocalised, aromatic furanolate anion **5.283a** could be expected to exhibit lower nucleophilicity than simpler ketone enolates **5.284a**. The aromatic stabilisation of this intermediate could be responsible for the lack of reactivity of **5.283a** towards chloride as a leaving group. Nevertheless, the anionic moiety of **5.283a** is essentially planar. In this regard, it offers two flat, unencumbered faces to the incoming electrophile. As opposed to this, enolate **5.284a** has a half-chair conformation which always presents at least one CH_2-substituent in close proximity to the cyclisation locus. Therefore, in purely steric grounds the spiroannelation of **5.283** should be easier than that of **5.284**.



Scheme 5.71

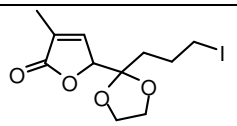
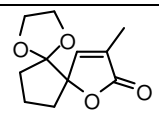
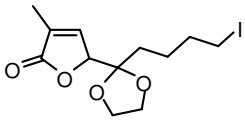
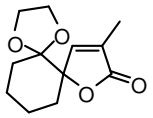
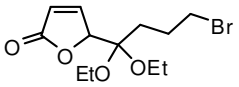
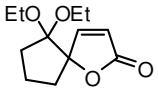
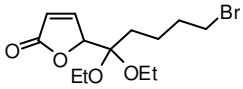
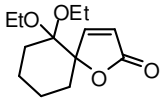
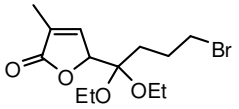
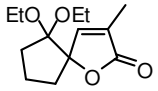
With suitable conditions for the cyclisation in hand, we next tried to delineate the scope of this new methodology. Our results are compiled in Table 5.5.

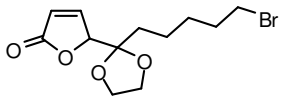
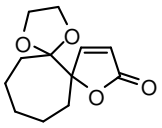
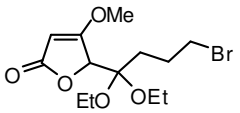
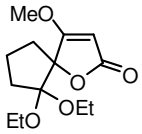
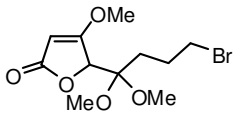
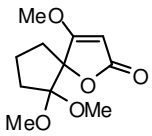
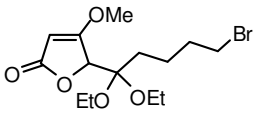
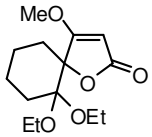
As can be seen, 5- and 6-membered rings can be formed with equal efficiency (entries 1-4). On the other hand, the smooth generation of spirocycles from diethyl- and dimethyl-ketals was a pleasant surprise. This shows that cyclisation in these systems is prefered to elimination of MeOH or EtOH, a process previously described by Pelter (Cf. Section 5.1) in analogous compounds. Attempted 7-membered spiroannelation returned only unreacted starting material, as would be expected (entry 6).

Finally, interesting spirotetronates **5.294-5.297** can be prepared through this methodology (entries 7-9). It should be noted that the spiroannelation of these tetronate derivatives proceeded faster than for their counterparts and afforded pure products after a simple aqueous workup. This is presumably a consequence of the enhanced nucleophilicity of the intermediate furanolate anions **5.283a**, in which a suitably located donor methoxy substituent reinforces the reactivity of the enolate. We had already

benefited from this favorable electronic effect in the condensation of the corresponding 4-methoxy TMSOF derivatives (Cf Section 5.2).

Table 5.5

Entry	Condensation product	Spirobutenolide	Yield (%)[b]
1	 **5.082**	 **5.286**	*63*
2	 **5.083**	 **5.287**	*75*
3	 **5.067**	 **5.288**	*76*
4	 **5.073**	 **5.289**	*70*
5	 **5.290**	 **5.291**	*64*

6	 **5.292**	 **5.293**	NR
7	 **5.085**	 **5.294**	*92*
8	 **5.086**	 **5.295**	*91*
9	 **5.296**	 5.297	*80*

[a] – All reactions were performed in the presence of 1.3 eqs of *t*-BuOK or NaHMDS, in THF, from 0ºC to rt. [b] – All yields refer to pure, isolated products. NR = no reaction.

5.5.3. Functionalisation of adducts

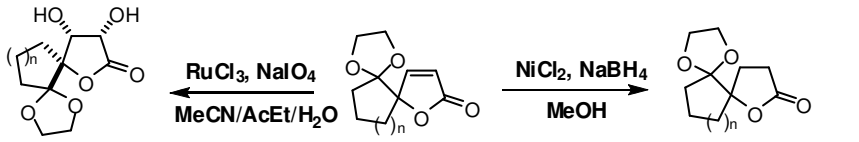
The products obtained *via* the method described above also contain useful appendages for subsequent functionalisation. Bearing in mind the structures of naturally occuring substances presented earlier, we attempted some modifications of the structure of these spiroderivatives. However, no particular target was selected as it appeared wiser to first delineate which

reactions could be successfully implemented, rather than to hastily embark in a total synthesis project without such valuable information at hand.

Given that α,β-unsaturated lactones are known to be good Michael acceptors, we reasoned that conjugate addition to this double bond would be a feasible process. In the event, though, these butenolides proved surprisingly inert towards a large variety of cuprates, higher-order cuprates, malonates, cyanide donors and even acetylide derivatives. We had anticipated that the spirocyclic center adjacent to the β-position might somewhat hamper the reactivity of these lactones but we certainly did not expect such an unfavourable panorama. In fact, as these negative results accumulated, our literature research failed to unearth a successful example of a Michael addition onto a simple spirocyclic butenolide. It would thus seem that, unless additional electron-withdrawing substituents are present at the α-position of these unsaturated lactones, their reactivity towards Michael donors is essentially nil.[207]

Nonetheless, simple though valuable synthetic transformations could be effected on these compounds provided a judicious choice of reaction conditions was made (Scheme 5.72).

[207] For a rare example of the conjugate addition of a silyl nucleophile to such systems, see ref. 189. Binot, G., private communication.



5.302 n = 1 *(88%)*
5.303 n = 2 *(95%)*

5.280 n = 1
5.282 n = 2

5.300 n = 1 *(94%)*
5.301 n = 2 *(97%)*

Scheme 5.72

Saturation of the double bond could be accomplished through the action of *in situ*-generated Nickel boride,[208] affording the saturated lactones **5.300** and **5.302** in quantitative yields.

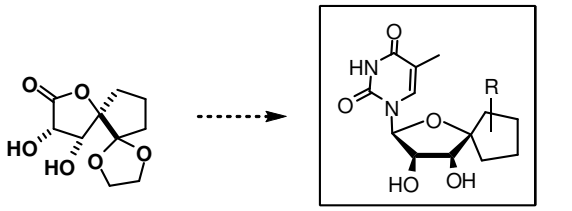
Similarly, the Ru-catalysed « flash » dihydroxylation[209] of compounds **5.280** and **5.282** proved to be quite effective, providing diols **5.302** and **5.303** once again as the sole products following extractive workup. Interestingly, diols **5.302-5.303** were obtained as single diastereomers. The depicted stereochemistry was secured through NOE-correlation between the alkoxy-methine protons and the dioxolane substituent. It would seem that, once more, the dioxolane substituent effectively shields one of the diastereofaces of the butenolide double bond, allowing attack to proceed only from the opposite side. We shall encounter yet further examples of this pervasive "dioxolane-effect" in subsequent chapters.

It should be noted that these diols effectively mimic a considerable portion of spiro-constrained DNA blocks, popularised through the recent work of Paquette. Indeed, Paquette and co-workers have been particularly busy since 2001 synthesizing spiro-analogues of deoxyribonucleotide

[208] (a) Khurana, J. M.; Sharma, P. *Bull. Chem. Soc. Jpn.* **2004**, 549; (b) George, A; Schulte, M.; Reiser, O. *J. Org. Chem.* **2006**, *71*, 2173

[209] (a) Shing, T.K.M.; Tam, E.K.W.; Tai, V.W.-F.; Chung, I.H.F.; Jiang, Q. *Chem. Eur. J.* **1996**, *2*, 50. See also: (b) Paquette, L.A.; Seekamp, C.K.; Kahane, A.L.; Hilmey, D.G.; Galucci, J. *J. Org. Chem.* **2004**, *69*, 7443

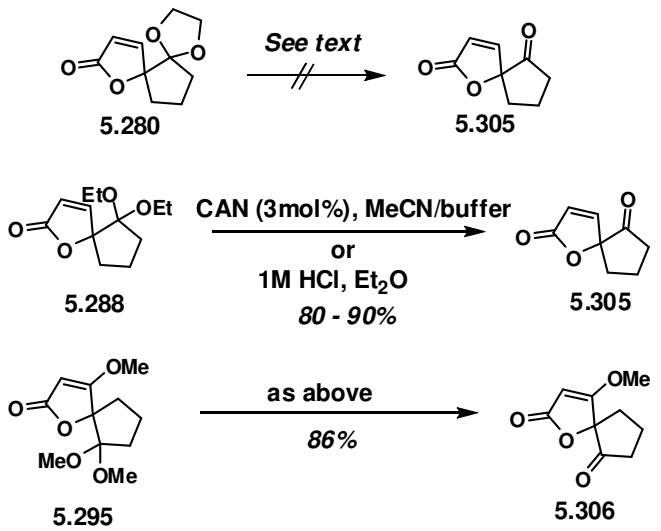
fragments such as **5.304**.[205] The methodology employed, though efficient, comprises lengthy multi-step sequences to access the products. The diastereomerically pure diol **5.302**, on the contrary, is assembled in only 3 steps from TMSOF **5.007** and orthoester **2.034** and is produced with an overall yield of 81%.



5.302 *2'-deoxyspironucleoside* **5.304**

Scheme 5.73

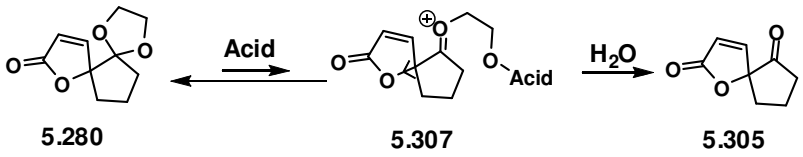
Finally, as would be expected from the precedent established in the bicyclolactone project, dioxolane cleavage from **5.280** proved impossible under conventional protocols. In contrast, the "open" ketals of **5.288** or **5.295** were particularly labile and responded well upon subjection to the CAN-catalysed protocol. For practical reasons, the prefered method of deprotection was exposure to 1M HCl in ether. The ketones thus obtained are rather volatile compounds, as might be anticipated (their reduced analogs have been patented as fruity fragrances).



Scheme 5.74

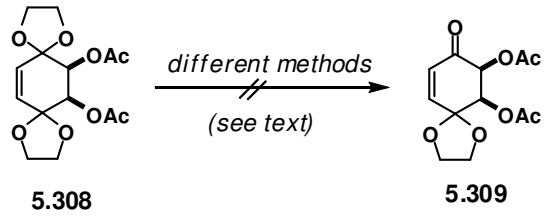
We believe that the effect of an α-acyloxy substituent on the rate of deprotection of a cyclic ketal could be sufficient to slow it down considerably (Scheme 5.75). If one considers the putative oxonium intermediate **5.307**, formed through Lewis- or Bronsted-Acid catalysed ring-opening, the electron-withdrawing effect of an acyloxy substituent at its α-position is likely to be destabilising. If the lifetime of intermediate **5.307** is reduced, then the rate of the overall deprotection process will also drop.[210]

[210] It should be noted, though, that α-acyloxy substituents could also conceivably exert a stabilising effect on intermediates **5.307** through anchimeric assistance of the nucleophilic acyloxy-carbonyl group. However, the geometric impossibility of such an assistance in our compounds renders this effect negligible.



Scheme 5.75

A recent report from a German group appears to lend further credence to our proposal.[211] These researchers encountered considerable difficulties in the deprotection of simple bis-ketals **5.308**, using *inter alia* the CAN-catalysed procedure (Scheme 5.76).



Scheme 5.76

5.6. Conclusions and perspectives

Throughout this chapter, we have presented a sequence of results from which a number of interesting, coherent and useful conclusions can be drawn.

It transpires that TMSOF and its derivatives are particularly competent donors in condensation reactions with our functionalised

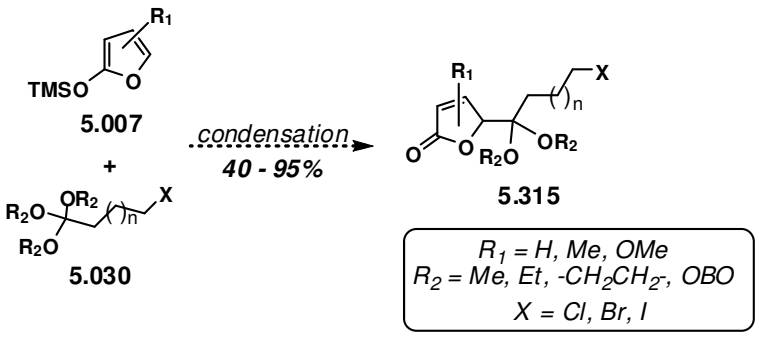
[211] Lang, M.; Ziegler, T. *Eur. J. Org. Chem.* **2007**, 768

orthoesters. We believe that the planar structure of the furan ring, as well as the increased electronic density of TMSOF are responsible for the very high yields (80-99%) observed. In support of this hypothesis, it can be seen that the introduction of substituents, even remote from the reactive site, considerably reduces the effectiveness of this condensation, lowering the isolated yields to values closer to the cycloalkanone series (40-70%).

However, this can be counterbalanced by a judicious choice of the orthoester partner. For the first time, functionalised triethyl- and trimethyl-orthoesters can be successfuly used in condensation reactions, without suffering from the undesired elimination of EtOH or MeOH. Furthermore, in the most difficult cases, these orthoesters led to an increase in yield of up to 25%, in the condensation adducts.

Importantly, we have performed the first intermolecular condensations of OBO orthoesters.[212] This should help in establishing these compounds as viable electrophilic partners rather than mere, inert protective groups.

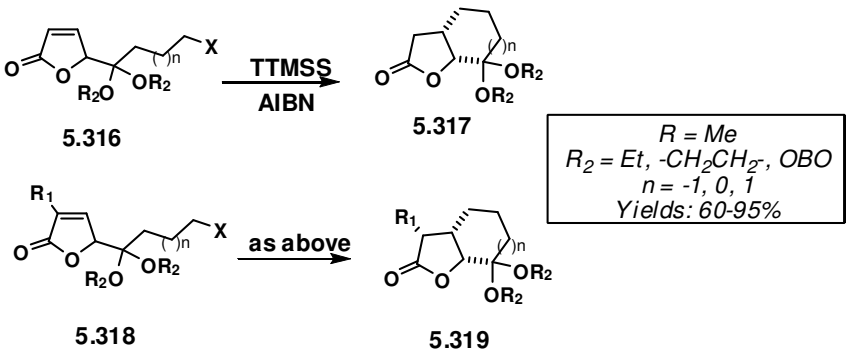
[212] For *intramolecular* condensations of such orthoesters, see: (a) Huang, J.-W.; Chen, C.-D.; Leung, M.-K. *Tetrahedron Lett.* **1999**, *40*, 8647; (b) Andres, J. M.; Munoz, E. M.; Pedrosa, R.; Perez-Encabo, A. *Eur. J. Org. Chem.* **2003**, *17*, 3387; (c) Ding, P.; Ghosez, L. *Tetrahedron* **2002**, *58*, 1565



Scheme 5.77

The condensation products are particularly versatile substructures. They can be converted, at will, into bicyclic lactones or spirocyclic butenolides.

Thus, when these compounds are subjected to the action of TTMSS and AIBN in refluxing benzene, smooth intramolecular radical addition occurs onto the butenolide double bond. This cyclisation is effective for the formation of 4-, 5- and 6-membered rings (Scheme 5.78). Furthermore, whenever substituents are present in the butenolide ring, the process is highly diastereoselective, enabling the generation of three contiguous stereocenters in a single step (Scheme 5.78)!

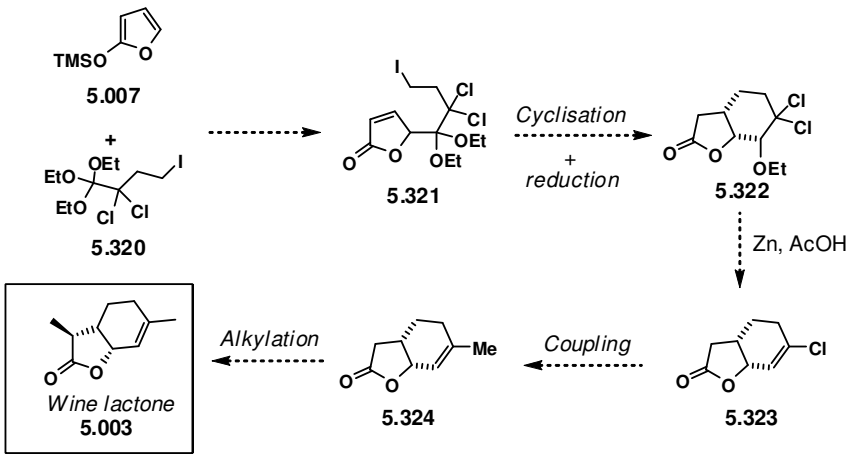


Scheme 5.78

The synthetic possibilities offered by such bicyclolactones are far from being exhausted. A successful synthesis of Wine lactone could be possible through an alternative, intriguing approach (Scheme 5.79).

If di-chlorinated orthoester **5.320** can be synthesized, its condensation with TMSOF should yield butenolide **5.321**. Subjection of this compound to the action of TTMSS should then selectively effect iodine-cleavage, followed by cyclisation, since chlorine abstraction is probably not competitive under these conditions.

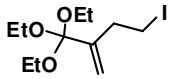
At this stage, mono reduction of ketal **5.322** should be possible either *in situ* (as we had inadvertedly observed before) or by treatment with a Lewis Acid and a hydrogen donor. Mono-ethoxy ether **5.323** would be our pivotal intermediate. Exposure of this compound to the action of a reducing agent would effect de-alkoxylative reduction of chlorine and yield the vinyl chloride **5.324**, a suitable substrate for metal-catalysed introduction of the methyl substituent through cross-coupling. Finally, alkylation of the lactone would complete this short synthesis.



Scheme 5.79

This approach would also take advantage of the unexpected ketal monoreduction that we observed during our studies on radical cyclisation of the condensation products.

Alternatively, the unsaturated orthoester **5.325** as a coupling partner might fullfill the same purpose. A systematic approach to the use of other types of unsaturated orthoesters is outlined in Chapter 8.

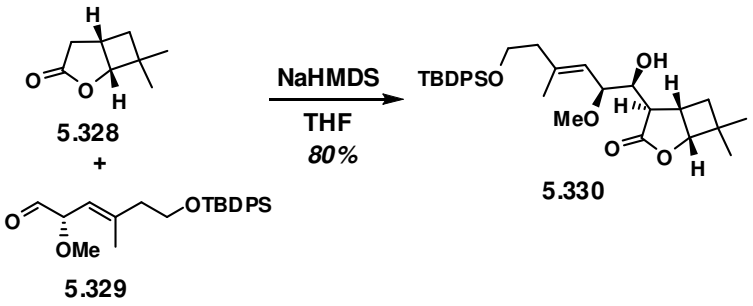


5.325

Scheme 5.80

More interestingly, compound **5.112**, issued from a 4-*exo* trig process, contains the entire functionalised core of Pestalotiopsin A **5.006** (Scheme 5.1). In particular, it is conceivable that a suitably functionalised chain,

protruding from the lactone ring, could be installed stereoselectively through enolate chemistry. In fact, Tadano *et al.* have already prepared optically active **5.328** in a 14-step (!) sequence and showed that reaction of this lactone with optically active aldehyde **5.329** proceeds with good diastereoselectivity to afford compound **5.330** in 80% yield.[213] In our case, a number of different possibilities are available for the introduction of functionality, particularly at the ring-junction.[214] We believe that the synthesis of a variety of simplified analogues of Pestalotiopsin A should be accessible in less than 10 steps (from TMSOF).



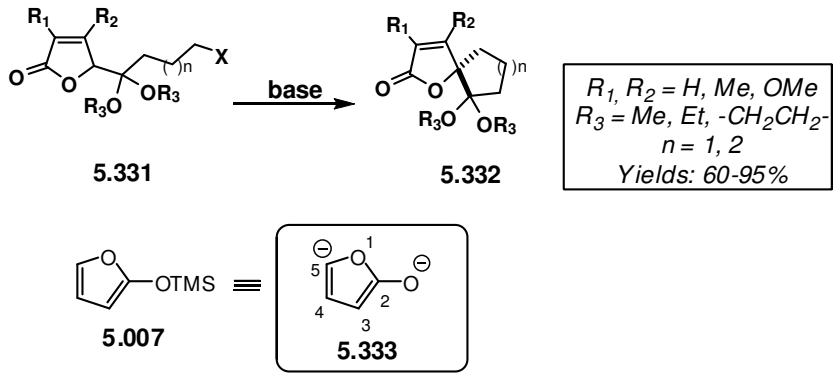
Scheme 5.81

In a complementary manner, if the condensation adducts are treated with base, spiroannelation takes place. The main feature of this reaction is its efficiency. This is specially true in the case of tetronate substrates, which cyclise faster and in higher yields than any other precursors examined so far. No alkoxy-elimination takes place, as might have been anticipated based

[213] Takao, K.-i.; Saegusa, H.; Tsujita, T.; Washizawa, T.; Tadano, K-i. *Tetrahedron Lett* **2005**, *46*, 5815

[214] Such approaches have been presented and discussed in the context of confidential research proposals and will not be detailed here.

upon previous reports from the literature. Conceptually, our two-step approach is quite different from the ones already described earlier and boils down to the use of TMSOF as a dianionic synthon at C_5 (Scheme 5.82).



Scheme 5.82

Close examination of our results highlights the main differences between TMSOF and cycloalkanone-derived silyl enolethers :

(a) TMSOF is definitely the most reactive cyclic silyl enolether examined thus far in our laboratory for the condensation with functionalised orthoesters ;

(b) TMSOF reacts with « open » triethyl- or trimethyl-orthoester derivatives without subsequent elimination of alcohols,

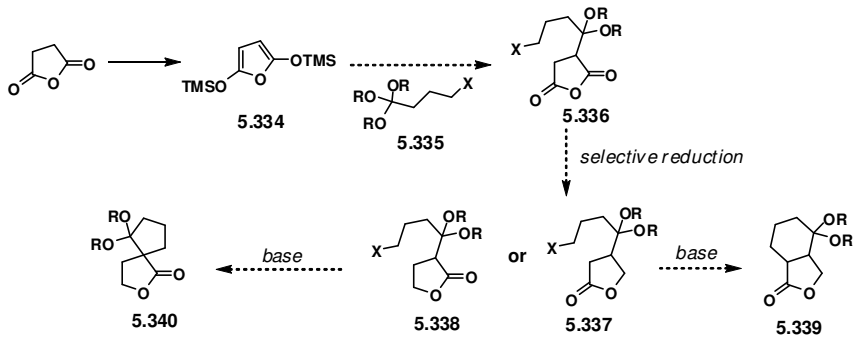
(c) dioxolane substituents adjacent to a lactone oxygen are particularly reluctant to undergo hydrolysis whereas dimethyl- or diethylketals are readily unravelled;

(d) The extreme reactivity of TMSOF even led to the first reported *intermolecular* condensation with an OBO orthoester and thus the synthesis of an adduct bearing a halogenated 3-carbon tether;

(e) Spiroannelations onto TMSOF produce 5- and 6-membered rings with equal efficiency.

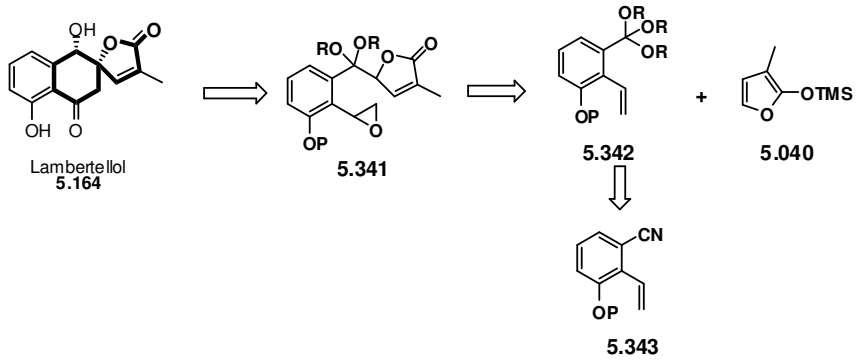
On the other hand, variations of the reactivity could be observed if different analogues of TMSOF were used. As we have seen, the reactivity decreases as alkyl substituents are introduced in the furan ring. It would therefore be interesting to probe the use of the symmetric **5.334** as the nucleophilic partner (Scheme 5.83). We presume that **5.334** would only reluctantly undergo reaction at the 4-position, due to steric crowding. In contrast, it could react quite easily at the 2-position. If this should to be the case, then monosubstituted anhydride **5.336** would be obtained. The difference between both anhydride carbonyls should be large enough to allow selective reduction to take place prior to- or after spirocyclisation (as in the monoreduction of citraconic anhydride, *vide supra*). This could lead *e.g.* to α-spirolactone **5.340** in 3-4 steps from readily available substances.[215] These spirolactones are key subunits of important natural products, such as the Bakkenolides.[216]

[215] We have prepared heteroatom-substituted α-spirolactones akin to **5.340** by a totally different approach: see Chapter 7.
[216] Cf. Demarke, M. *Mémoire de licence* UCL, **1999**.



Scheme 5.83

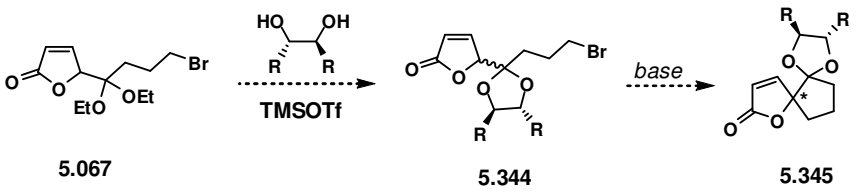
We can also envisage an expeditious synthesis of the Lambertellols using our spiroannelation methodology. As shown in Scheme 5.84, Lambertellol A might conceivably arise from the annelation of 3-methyl-TMSOF **5.040** with the aromatic orthoester **5.342**, which should be readily available from nitrile **5.343.** Condensation, followed by oxidation of the olefinic linkage should deliver **5.341**. At this stage, we plan to create the spirannic centre by a stereocontrolled epoxyde ring-opening. Should this key-step afford the desired product, enantioselective preparation of the epoxyde **5.341** would allow an entry into the optically active series. Our approach should also enable the synthesis of diversely decorated or truncated analogues.



Scheme 5.84

Obviously, all the compounds reported so far are racemic. Although many possible solutions for the introduction of asymmetry are available, the labile nature of the « open » ketals present in the condensation adducts offers the intriguing possibility of testing a simple diastereoinduction strategy (Scheme 5.85). Therefore, if ketal exchange is performed on **5.067** with an optically pure diol (preferably of C_2-symmetry), the epimers **5.344** should be obtained in a 1 :1 ratio. This is inconsequential, since exposure of **5.344** to base should destroy the C_5-stereocenter and generate a spirobutenolide **5.345**. In the case of the worst scenario, a 1 :1 mixture of optically active diastereoisomers would be formed. However, we believe that the enantiofacial discrimination provided by a judiciously chosen ketal substituent could lead to interesting results.[217]

[217] The use of chiral amide bases in the deprotonation of racemic condensation adducts such as **5.066** was tested, alas to no avail (0% ee observed).



5.067 5.344 5.345

Scheme 5.85

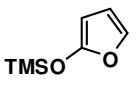
The overall strategy presented in this chapter discloses a novel approach based upon a two-step electrophilic/nucleophilic or electrophilic/electrophilic annelation onto a heteroaromatic nucleophile. As such, it should not be limited to furan derivatives but could be extended to other heteroaromatic cores. It is one such extensions (to the pyrrole analogues), which is documented in the following chapter.

Chapter 6 : From Oxygen to Nitrogen: annelations of 2-(*t*-butyldimethylsilyloxy)-N-Boc-pyrrole (TBSOP) with functionalised orthoesters

6.1. Introduction

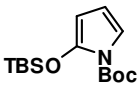
After reading the preceding Chapter, it becomes quite clear that a wealth of new scaffolds have been made available by employing heteroaromatic extended silylenol ethers such as TMSOF **5.007**. Interestingly, the nature of the substituents and their pattern can be easily varied, leading to unique members of these lactone families.

The success encountered with TMSOF naturally prompted us to investigate the analogous nitrogen counterpart. From a literature search, it transpired that the archetype of such compounds was 2-(*t*-butyldimethylsilyloxy)-N-Boc-pyrrole (TBSOP) **6.001**. The differences between TBSOP **6.001** and TMSOF **5.007** are notorious. Not only is there a more robust TBS- substituent on silicon, but there is also an electron-withdrawing protecting group on the nitrogen atom.



TMSOF

5.007



TBSOP

6.001

Scheme 6.1

The challenge and synthetic appeal associated with an incursion in the province of alkaloids further instigated us to examine what may appear at first sight as a trivial change. The results of this endeavour form the subject of the present Chapter.

6.2. Literature survey

As usual, we will briefly analyse the reactivity of **6.001** and its known analogues. For the sake of conciseness, only a few relevant examples will be discussed. Emphasis will be placed upon reactivity features which are characteristic of **6.001** (and thus different from **5.007**).

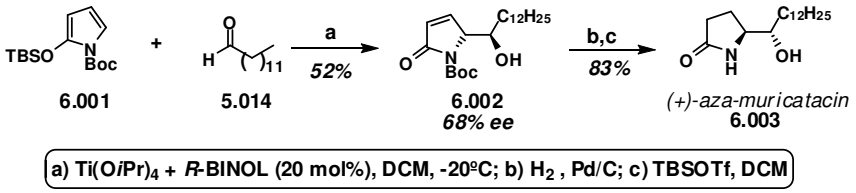
The vinylogous Mukaiyama-aldol reaction is one of the most well-documented reactions of TBSOP **6.001**.[218] Since the pioneering reports of Ricci and Taddei,[219] who actually completed the triad (furan + previously unknown pyrrole and thiophene) of heteroaromatic siloxydienes, a number

[218] For reviews, see: (a) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929; (b) Casiraghi, G.; Rassu, G. *Synthesis* **1995**, 607

[219] (a) Fiorenza, M.; Ricci, A.; Romanelli, M.N.; Taddei, M.; Dembech, P.; Seconi, G. *Heterocycles* **1982**, *19*, 2327; (b) Fiorenza, M.; Reginato, G.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1984**, *49*, 551

of efforts have been devoted to preparing optically enriched compounds through reaction of **6.001** with aldehydes and/or ketones.

Thus, in analogy to his work presented in Chapter 5, Figadère and co-workers[220] also applied the Ti/BINOL catalytic system to the preparation of non-natural aza-muricatacin **6.003**. The stereochemical outcome (68% *ee*), however, was less favorable than in the case of the oxygenated system.



Scheme 6.2

Considerably better results were obtained when chiral-pool derived electrophiles were employed. Among the plethora of work reported by the Casiraghi group,[221] additions to glyceraldehyde acetonide proved to be a key-step in the preparation of aminated carbasugars. As shown in Scheme 6.3, addition of TBSOP to aldehyde **5.009** proceeds with complete diastereoselectivity to afford adduct **6.004** in excellent yield. A number of synthetic manipulations convert **6.004** to **6.005**, which undergoes aldol-like ring closure under Lewis acidic conditions. The bridged bicycle **6.006** is then reductively cleaved to afford the enantiomerically enriched aminated carbasugar **6.007** after some functional group adjustments.

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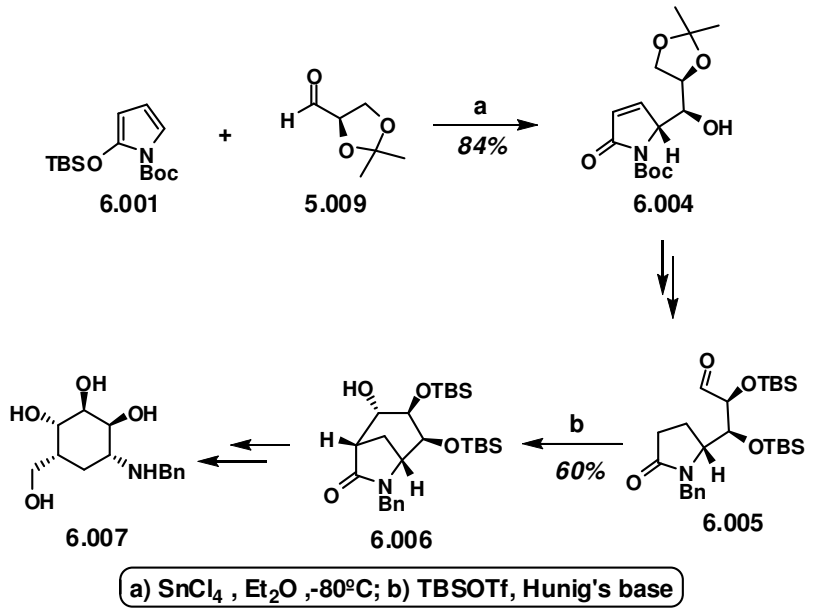
[220] Szlosek, M.; Franck, X.; Figadere, B.; Cave, A. *J. Org. Chem.* **1998**, *63*, 5169

[221] See, *e.g.:* (a) Rassu, G.; Auzzas, L.; Pinna, L.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Org. Lett.* **1999**, *1*, 1213; (b) Rassu, G.; Auzzas, L.; Pinna, L.; Zambrano, V.; Zanardi, F.; Battistine, L.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J.Org. Chem.* **2002**, *67*, 5338



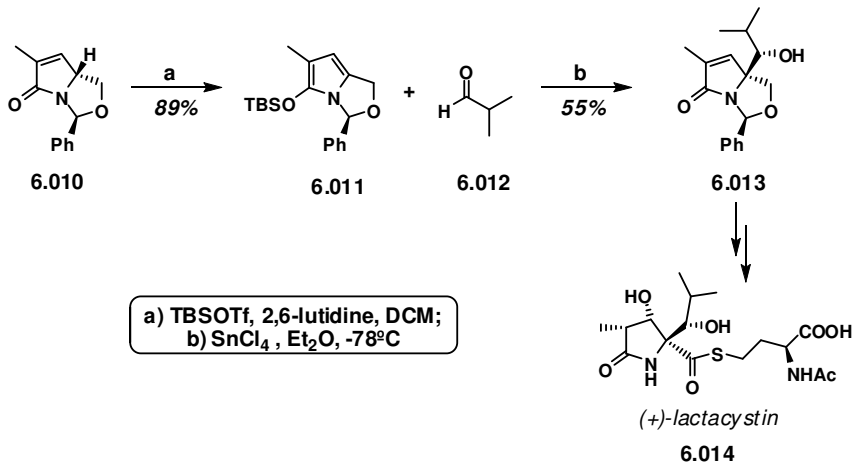
Scheme 6.3

These two examples mimic the chemistry of TMSOF, which also undergoes similar enantio- and distereo-controlled condensation reactions. However, with TBSOP and its derivatives, a third option presents itself: the use of a chiralsiloxydiene. In particular, the nitrogen atom constitutes an ideal site for the placement of chiral appendages for asymmetric induction. A few examples of this type of process exist in the literature.

In his synthesis of (+)-lactacystin **6.014**, Baldwin employed such a strategy.[222] As depicted in Scheme 6.4, use of the glutamate-derived hemiaminal **6.010** allows the formation of a chiral TBSOP-derivative **6.011**.

[222] (a) Uno, H.; Baldwin, J. E.; Russell, A. T. *J. Am. Chem. Soc.* **1994**, *116*, 2139. See also: (b) Uno, H.; Baldwin, J. E.; Churcher, I.; Russell, A. T. *Synlett* **1997**, 390

Interestingly, in the preparation of **6.011**, the original stereogenic center from the glutamate precursor is lost. Lewis-acid mediated vinylogous aldol addition to isobutyraldehyde **6.012** proceeds in moderate yield, but with very high diastereo- and enantioselectivity to afford adduct **6.013**. This compound already contains most of the structural features of the final target **6.014**.



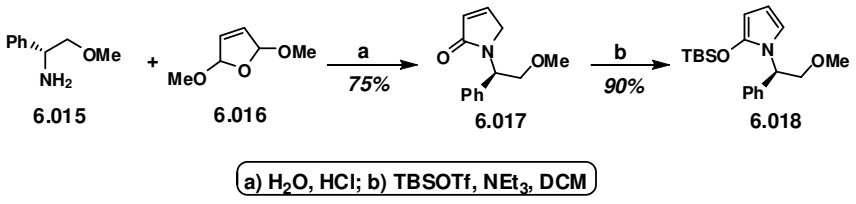
Scheme 6.4

Most of the applications of chiral TBSOP derivatives originate from the laboratory of Jacques Royer.[223] The Royer group found that the condensation of a primary amine with 2,5-dimethoxydihydrofuran led to the formation of an α,β-unsaturated lactam.[224] This reaction is fairly general and can be applied to numerous chiral primary amines. Thus, phenylglycinol-derived amine **6.015** (Scheme 6.5) reacts with dihydrofuran **6.016** in acidic

[223] For a recollective account, see: Baussanne, I.; Dudot, B.; Pérard-Viret, J.; Planas, L.; Royer, J. *ARKIVOC* **2006**, *vii*, 57

[224] Baussanne, I.; Chiaroni, A.; Riche, C.; Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1994**, *35*, 3931.

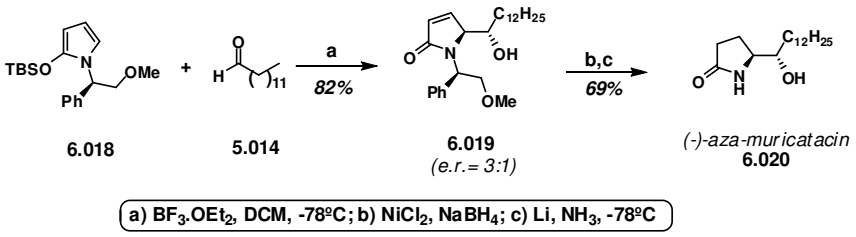
water to provide the lactam **6.017** in good yield. Conversion of this lactam to a chiral non-racemic TBSOP-derivative **6.018** can then be achieved under conventional conditions.



Scheme 6.5

The Royer group has employed this type of chiral silyl dienolether in various aldol-like condensations. Their first example is analogous to the Figadère synthesis of (-)-aza-muricatacin **6.020** and is depicted in Scheme 6.6.

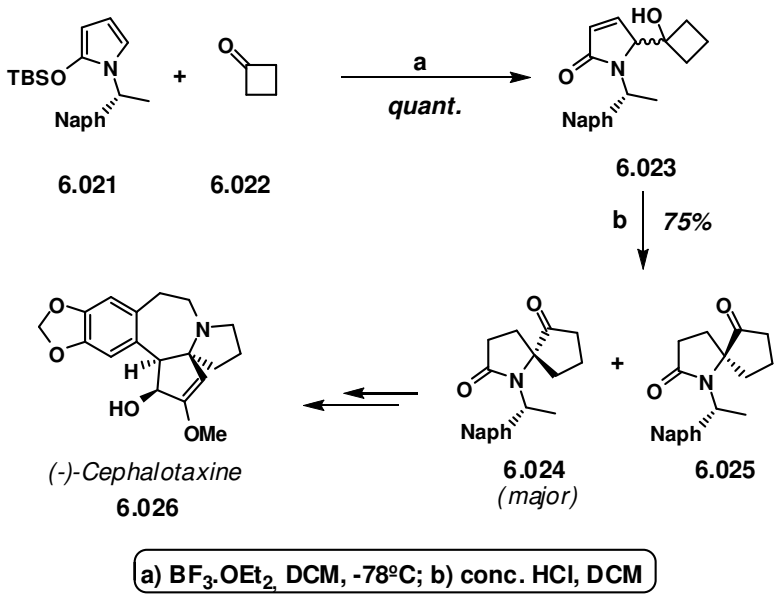
Thus, condensation of chiral TBSOP-derivative **6.018** with aldehyde **5.014** led to adduct **6.019** with excellent *threo* diastereoselection and moderate enantioselection. Reduction of the double bond and cleavage of the chiral auxiliary completed the sequence.



Scheme 6.6

The second type of application the Royer group developed for chiral TBSOP-derivative **6.018** is of a more intriguing nature, particularly in view of our own projected annelations (*vide infra*).

With the aim of preparing enantioenriched spirocyclic lactams for use as building blocks in total synthesis, Royer *et al*. used an interesting ring-expansion process.[225]



Scheme 6.7

As shown in Scheme 6.7, Lewis-acid promoted addition of naphtyl-substituted **6.021** to cyclobutanone **6.022** proceeded in quantitative yield, affording tertiary alcohol **6.023** as a mixture of diastereomers. It was found that treatment this compound with concentrated HCl in dichloromethane

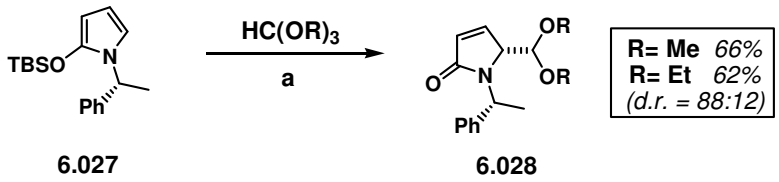
[225] Planas, L. ; Pérard-Viret, J.; Royer, J. *J. Org. Chem.* **2004**, *69,* 3087.

induced a semipinacolic rearrangement, with concomitant ring-expansion and formation of an azaspiro[4.4]nonane. The naphtyl substituted compound provided the best results, with a diastereomeric excess approaching 80%. The major diastereoisomer was eventually used in the total synthesis of (-)-Cephalotaxine **6.026**. It should be noted that this process is limited to the preparation of azaspiro[4.4]nonanes. The synthesis of higher homologues through a similar reaction scheme is thwarted by both the lower reactivity of higher cycloalkanones and their reduced propensity to undergo ring-expansion through semi-pinacolic processes.[226]

Apart from the use of aldehydes and ketones, very little is known about the reactivity of TBSOP derivatives towards other electrophilic species. To the best of our knowledge, the N-Boc compound **6.001** has never been reacted with orthoesters; nonetheless, there is one report on the condensation of derivative **6.027**. Giovanni Poli[227] studied the reactions of this siloxydiene with trimethyl- and triethylorthoformate (Scheme 6.8). He found that, while useful levels of diastereoselection could be obtained, the reaction could not be made catalytic in Lewis Acid and a two-fold amount of the orthoformate partner was required.

[226] For a detailed study on the synthesis of azaspirocycles through semipinacolic rearrangements, see: Dake, G.R.; Fenster, M.D.B.; Fleury, M.; Patrick, B.O. *J. Org. Chem.* **2004**, *69*, 5676

[227] Poli, G. ; Baffoni, S.C.; Giambastiani, G.; Reginato, G. *Tetrahedron* **1998**, *54*, 10403



6.027 **6.028**

a) 1 eq. 6.027, 2 eq. $HC(OR)_3$, 2 eq. $BF_3.OEt_2$, -78°C

Scheme 6.8

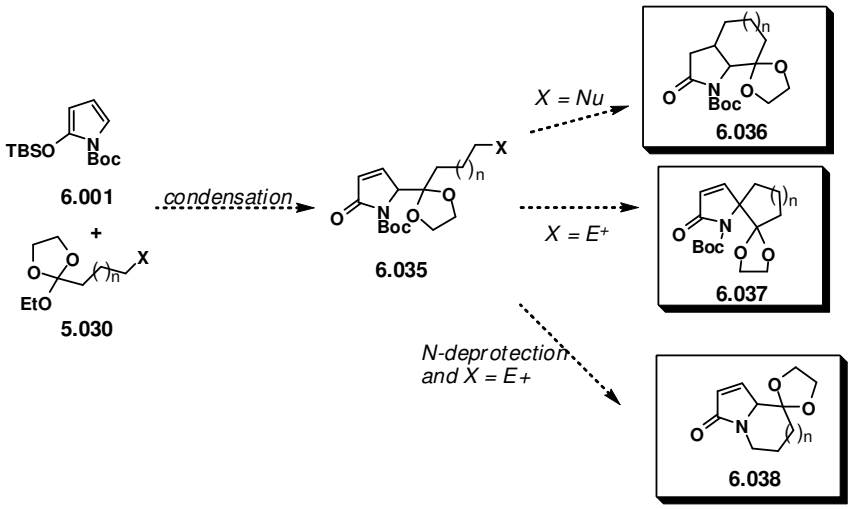
In contrast to the situation encoutered with TMSOF and derivatives, it appears that the panorama with TBSOP consists of largely "uncharted territory" in what concerns the possibilities of reaction with our functionalised orthoesters.

6.3. Strategy

Deriving from the solid background acquired previously (Chapter 5), we envisaged the use of "standard" pyrrole-based siloxydiene TBSOP **6.001** in condensation reactions with our functionalised orthoesters. Although there were concerns that the –Boc substituent might significantly remove electron-density from the silyl enolether moiety, we knew that this group could be modified if required (Scheme 6.9).

In analogy to the case of butenolides, the adducts **6.035** should be amenable to the same modes of reaction. Treatment of compounds **6.035** under radical conditions might provide a similar Michael-like ring-closure to perhydroindoles **6.036**. On the other hand, the acidity of the remaining sp^3-hydrogen in the hetreocyclic core of **6.035** should be at least comparable to

that of the analogous butenolides. Base treatment of **6.035** should, therefore, elicit a similar spiroannelation process leading to compounds such as **6.037**.



Scheme 6.9

However, the most interesting possibility would consist in ring-closure *onto the nitrogen atom* of **6.035**! Indeed, deprotection of the –Boc group should release a potentially nucleophilic nitrogen atom. Although we have not yet employed the halogen terminus of our orthoesters in substitution reactions with heteronucleophiles,[228] this possibility seems more than reasonable. Should this be reduced to practice, yet another type of compounds, fused bicyclic alkaloids **6.038**, might be accessible.

[228] For another example of such a ring-closure, see Chapter 7.

As in the previous Chapter, the synthesis of TBSOP **6.001** by an expeditious and large-scale process will be described. Then, a detailed study of its condensation reactions with orthoesters will be reported.

6.4. Results and discussion

All the results discussed in this Section were obtained in collaboration with Benoît Driesschaert (M.Sc.student), Christophe Eviolitte (B.Sc. student) and Dr. Saiphon Songarsa (Postdoctoral fellow).

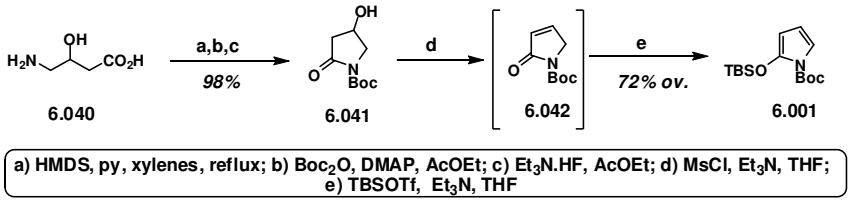
6.4.1. Preparation of TBSOP

The synthesis of TBSOP **6.001** is classically done in analogy to the preparation of TMSOF **5.007**, *via* the oxidation of a pyrrole derivative to a pyrrolidone **6.042** (*vide infra*) followed by subsequent silyl enolether formation.[218b] However, this procedure presents a number of safety and reproducibility issues. Recently, an alternative, multistep route to TBSOP from cheap and readily available compounds has been disclosed which is amenable to pilot plant production (4.5 kg of TBSOP have been made by this method in the Abbot Laboratories).[229]

The procedure is detailed in Scheme 6.10. Therefore, cyclisation of racemic 4-amino-3-hydroxybutyric acid **6.040** promoted by HMDS in

[229] Tian, Z.; Rasmussen, M.; Wittenberger, S.J. *Org. Proc. Res.&Dev.* **2002**, *6*, 416

refluxing xylenes, followed by Boc protection and post-reactional desilylation provides β-hydroxylactam **6.041** in very high yields. Dehydration of **6.041** and silyl enolether formation under standard conditions finally provide TBSOP **6.001** in good yields.



Scheme 6.10

Though at first sight this route might appear as a long and circuitous pathway, it actually holds a number of advantages over previous syntheses of TBSOP **6.001**. For instance, the three initial steps are performed without isolation of any intermediates, and only one solvent exchange is required (from xylenes to ethyl acetate). The compound **6.041** is obtained as a white solid which crystallises directly from the reaction mixture. As might be deduced from the reproducible, excellent yields obtained, all steps in the sequence are quantitative.

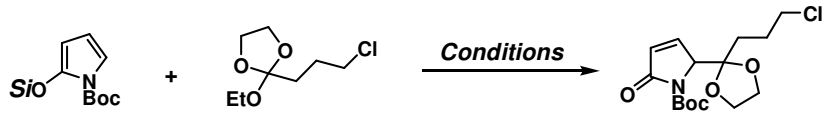
Another interesting aspect is the fact that **6.041** can be stored for indefinite periods of time, in stark contrast to **6.042** which gradually decomposes upon standing. Thus, intermediate **6.041** can be stockpiled until its transformation into **6.001** is required. This simple two-step operation (dehydration and silyl enolether formation) can be conveniently performed in 4-5 hours.

The overall efficiency of the process, coupled with its operational simplicity (which precludes any chromatographic purification and includes a single isolation step) renders it the method of choice for the preparation of TBSOP. Of additional interest to us is the fact that silicon substituents other than –TBS and protective groups other than –Boc could be easily employed in the procedure.

A final note should be made concerning the stability of TBSOP. This compound appears to display a long shelf-life (at low temperature), similar to that of the simple silyl enolethers derived from cyclic ketones which we have used in Chapters 2-4.

6.4.2. Condensation of substituted orthoesters with TBSOP

Having in hands an access to large amounts of TBSOP **6.001**, we then focused on its condensation reactions with our functionalised orthoesters, choosing **2.034** as a model compound. This reaction required an extensive optimisation and differed in many aspects from the analogous process involving TMSOF **5.007**. Some of our results are compiled in Table 6.1.



***Si* = TBS 6.001**
***Si* = TMS 6.043**

2.034

6.044

Table 6.1

Entry	*Pyrrole*	*Pyrrole :**2.034** :L.A.*	*Conditions*	*Yield*
1	**6.001**	1 :1.6 :0.7	$ZnCl_2$, [0.15 M], DCM, rt	16%
2	**6.001**	1 : 3.0 :0.7	$ZnCl_2$, [0.15 M], DCM, rt	20%
3	**6.001**	1 :1.6 :1.6	$ZnCl_2$, [0.3 M], DCM, rt	47%
4	**6.001**	1 : 1.6 :1.6	$ZnCl_2$, [0.6 M], DCM, rt	30%
5	**6.043**	1 :1.6: 0.7	$ZnCl_2$, [0.3 M], DCM, rt	7%
6	**6.001**	1 :1.6: 0.7	$BF_3.OEt_2$, [0.3 M], DCM, rt	12%
7	**6.001**	1 :1.6: 1.4	$ZnCl_2$, [0.3 M], DCM, 0°C	60%
8	**6.001**	1 :1.6 :1.4	$ZnCl_2$, [0.6 M], DCM, 0°C	42%
9	**6.001**	1 :1.6 : 1.4	$ZnCl_2$, [0.3 M], DCM, 0°C	77%[a]

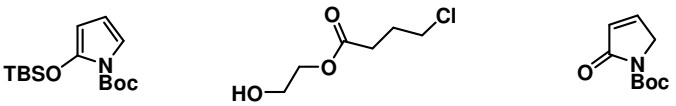
[a] – Modified procedure for the purification of the product: see text. L.A. = Lewis acid.

As can be seen from the Table, the reaction is rather sensitive to the amount of Lewis acid employed. Indeed, suprastoichiometric amounts of

zinc chloride[230] were required for the obtention of useful yields. We presume that this is a consequence of the increased presence of Lewis-basic sites in both the starting materials and the products.

Concentrations higher than 0.3 M proved to be inappropriate. On the other hand, temperature appeared to be a crucial parameter. In order to obtain reproducibly high yields, the reaction must not be allowed to go over 5°C and should not be performed for more than 30 minutes at this same temperature. It is possible that the remaining zinc(II) salts in solution are able to promote a retro-aldol decomposition of the products, and that a thin balance between productive coupling and unproductive destruction may be at hand.

A significant breakthrough was accomplished when the structures of the byproducts of this reaction were fully determined. Indeed, the crude mixture contains, other than the desired **6.044**, three further compounds: unreacted TBSOP **6.001**, orthoester-decomposition product **6.045** and hydrolysis product **6.042**.



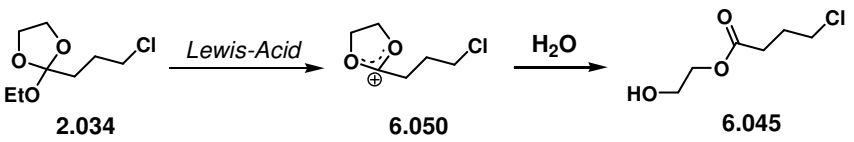
6.001 **6.045** **6.042**

Scheme 6.11

The hydrolysis product **6.045** is a common by-product in our orthoester-based coupling reactions. It is probably formed by the hydrolytic decomposition of the remaining, non-reacted, oxonium **6.050** (either through

[230] Zinc chloride once again proved to be the best Lewis acid for this kind of reaction; other acids tested include TMSOTf, $TiCl_4$, etc.

attack on the central carbon atom and subsequent ring-opening or by direct addition to one of the dioxolane methylene groups).



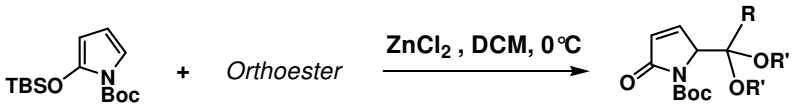
2.034 **6.050** **6.045**

Scheme 6.12

The polarity of these by-products being rather similar to that of the desired product **6.044**, purification through chromatography was fairly complicated. Furthermore, we often recovered variable, non-negligible amounts of Boc-deprotected material following chromatographic purification, suggesting that the product itself was not stable under these conditions.

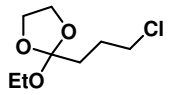
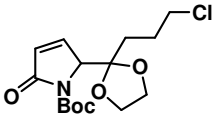
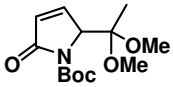
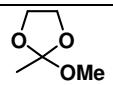
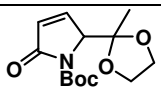
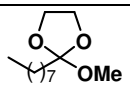
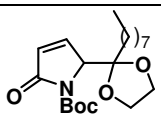
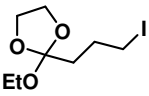
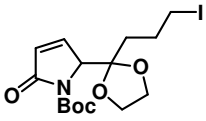
We realised that these by-products might lend themselves to an easier purification technique. It was discovered that dissolving the crude reaction mixture in dichloromethane, followed by adding an equal volume of 2M KOH and gentle stirring overnight (without allowing phase-mixing) effected smooth decomposition of **6.001**, **6.042** and **6.045**. A simple phase separation the next morning delivered analytically pure condensation product **6.044** in high yields (Table 6.1, entry 9)! Under these conditions, the by-products were likely converted into water-soluble compounds, while leaving the condensation adduct **6.044** untouched.

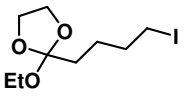
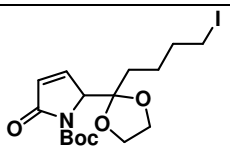
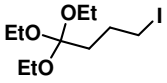
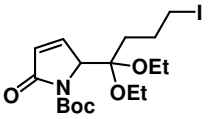
Using this optimised protocol, we were able to successfully couple a number of other orthoesters with TBSOP in moderate to good yields (Table 6.2).



6.001 **6.051**

Table 6.2

Entry	*Orthoester*	*Product*	*Yield*
1	 **2.034**	 **6.044**	77%
2	**$CH_3(OCH_3)_3$** **6.052**	 **6.053**	53%
3	 **6.054**	 **6.055**	55%
4	 **6.056**	 **6.057**	44%
5	 **2.003**	 **6.058**	65%

6	 **2.052**	 **6.059**	61%
7	 **2.002a**	 **6.060**	50%

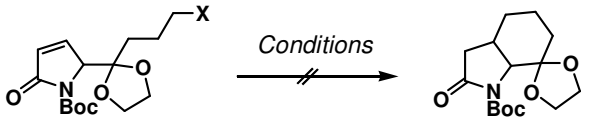
Though these are preliminary, unoptimised results, the condensation of TBSOP **6.001** with functionalised orthoesters appears to be a fairly general process. As these lines are being written, further examples of this reaction with other functionalised orthoesters are underway.

6.4.3. Replicating butenolide reactivity: towards perhydroindoles and azaspirocycles

Having an access to highly functionalised compounds such as **6.044**, **6.058** or **6.059**, our attention turned to the now "obvious" application of these compounds in annelation reactions. In particular, and in analogy with the results discussed in Chapter 5, we considered these molecules as suitable precursors to two types of ring-closing reactions: radical-mediated

cyclisations for the synthesis of perhydroindoles, and base-promoted spiroannelation for the preparation of azaspiranes.

Unfortunately, and despite numerous attempts, we have never been able to effect a radical-mediated cyclisation of either **6.044** or its iodinated counterpart **6.058** to the perhydroindole **6.065**.



X = Cl **6.044**
X = I **6.058**

6.065

Conditions : TTMSS/AIBN, Bu_3SnH/AIBN, SmI_2/THF/HMPA, etc.

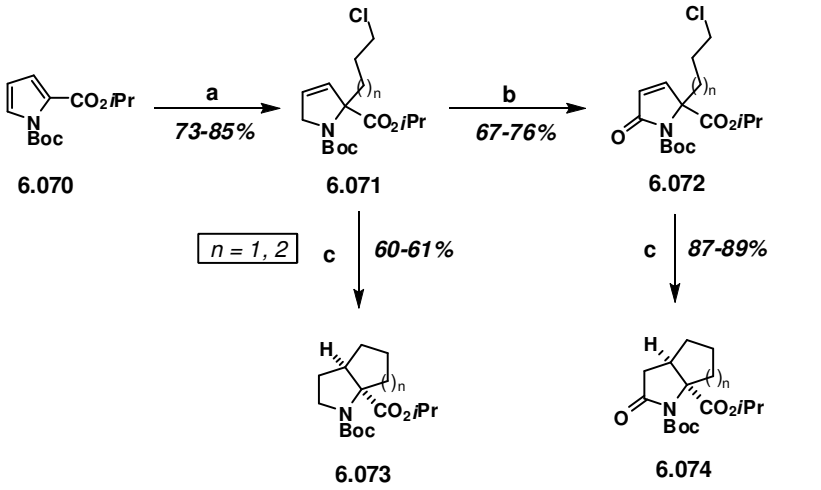
Scheme 6.13

In all cases, only intractable mixtures of products were obtained. Though we have no tangible proofs, it is tempting to speculate that the increased electron-withdrawing ability of the N-Boc substituent, compared to an oxygen atom, might be enough to favor 1,5-hydrogen abstraction over cyclisation in these systems.

Although there is hardly any precedent for similar cyclisations in the construction of perhydroindoles, an intriguing and particularly relevant example was reported by Donohoe and his group.[231] In 2004, these researchers described that the alkylative Birch reduction of electron-deficient N-Boc pyrroles such as **6.070** afforded 2,2-disubstituted pyrrolines **6.071** in

[231] Turner, P.G.; Donohoe, T.J.; Cousing, R.P.C. *Chem. Commun.* **2004**, 1422

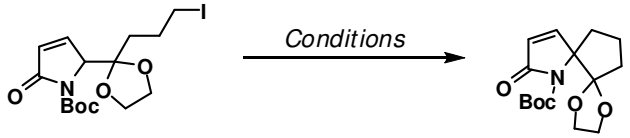
good yields. Oxidation of the latter under conventional conditions then provided lactams **6.072**.



Scheme 6.14

Particularly noteworthy is that the radical cyclisation of precursors **6.071-6.072** proceeded in good yields, with the best results being obtained when the lactams **6.072** were used. This is presumably a consequence of both the increased electrophilicity of the acceptor double bond, and the higher stabilisation provided to the cyclised radical. Remarkably, all compounds reported by Donohoe possess a *quaternary center* at the 5-position, thus avoiding an eventual allylic hydrogen abstraction. From these results, one might deduce that a different strategy shall be required if we are to achieve a synthesis of perhydroindoles through this type of methodology (*vide infra*).

In contrast with the aforementioned lack of success in the radical-mediated cyclisation to perhydroindoles, spirocyclisation was found to proveed smoothly. Benoît Driesschaert and Dr. Saiphon Songarsa both ascertained the efficient spirocyclisation of precursor **6.058,** upon treatment with 1.4 equivalents of *t*BuOK in dry THF. The results of a more detailed study of this reaction are presented in Table 6.3.



6.058 **6.075**

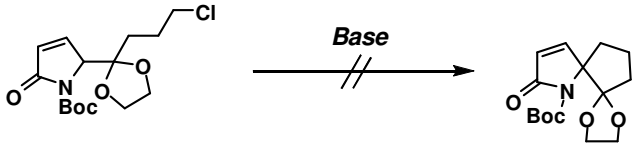
Table 6.3

Entry	*Conditions*	*Result*
1	LDA, THF	**6.058** + degradation
2	NaHMDS, THF	50-60% **6.075**
3	KHMDS, THF	**6.058**
4	DBU, THF or DCM	**6.058**
5	*t*BuOK, THF/H_2O	**6.058**
6	NaH/*t*BuOK, THF	**6.058**
7	*t*BuOK, THF	80% **6.075**

Once more, it would seem that NaHMDS and *t*BuOK are the most competent bases for this spiroannelation. In this case, though, *t*BuOK

presented rather clear advantages over the nitrogen base, as the yields were higher and the reactions cleaner.

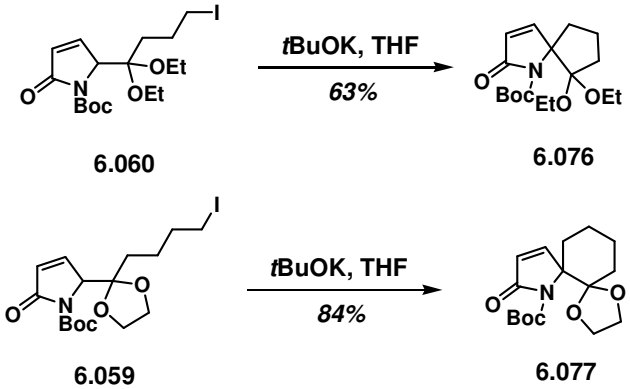
As we had observed in the case of butenolides, the analogous chlorinated product **6.044** was also tested for such a spirocyclisation. Unfortunately, only recovered starting material (or decomposition products under more forcing conditions) was obtained.



6.044 **6.075**

Scheme 6.15

The full scope and limitations of this reaction are currently being thoroughly investigated. In particular, Dr. Songarsa has recently succeeded in the preparation of azaspirocycles **6.076** and **6.077**.

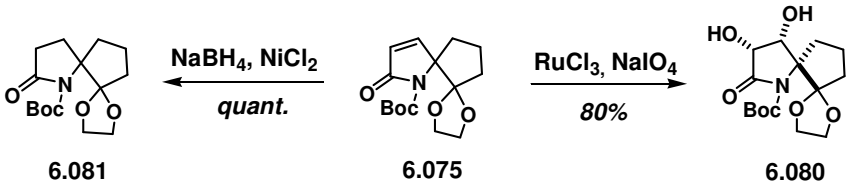


6.060 **6.076**

6.059 **6.077**

Scheme 6.16

Additionally, the azaspirocycle **6.075** lends itself to transformations similar to the ones performed on the analogous spirobutenolide (Scheme 6.17). Thus, saturation of the double bond by the action of nickel boride proceeded uneventfully, whereas dihydroxylation under the "flash"-protocol[232] took place with complete stereocontrol to afford diol **6.080** as a single stereoisomer (stereochemistry assigned by analogy to the butenolide case, cf. Chapter 5).

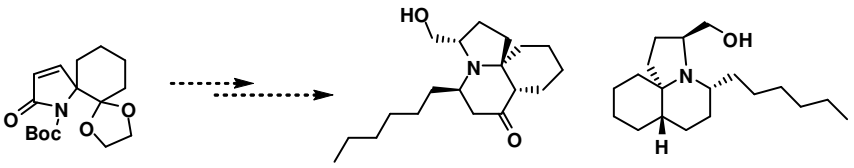


6.081 **6.075** **6.080**

Scheme 6.17

These results are encouraging in that they suggest a similar nucleophilic behaviour for furanolate and pyrrolate anions in intramolecular substitution reactions. Furthermore, they provide an easy access to functionalised azaspiro[4.4]-nonanes or [4.5]-decanes. While we have already shown an attractive synthetic application for spirocycles **6.075** or **6.076** in Royer's synthesis of Cephalotaxine (Scheme 6.7), compound **6.077** would conceptually allow an entry into the Cylindricine and Lepadiformine families (Scheme 6.18).

[232] (a) Shing, T.K.M.; Tam, E.K.W.; Tai, V.W.-F.; Chung, I.H.F.; Jiang, Q. *Chem. Eur. J.* **1996**, *2*, 50



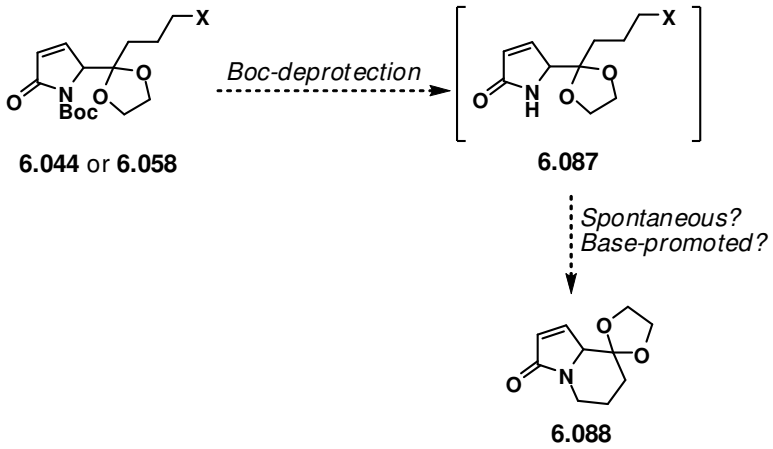
6.077 | *Cylindricine C* **6.082** | *Lepadiformine* **6.083**

Scheme 6.18

6.4.4. Probing the specificities of TBSOP: towards the synthesis of indolizidines

If the previous section provided results which are interesting in their own right, it was undisputedly the possibility to synthesize fused bicyclic alkaloids which most attracted us.

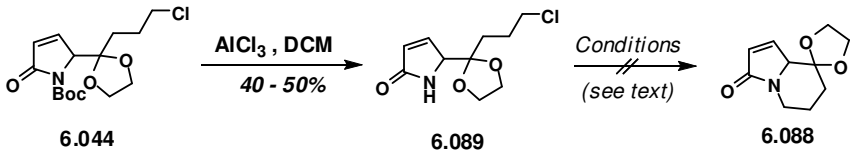
We reasoned that N-Boc deprotection at the stage of the condensation adduct **6.044** (or its iodinated analogue **6.058**) should be enough to either trigger spontaneous indolizidine formation or to provide a compound amenable to base-mediated ring closure (Scheme 6.19).



6.044 or **6.058** **6.087** **6.088**

Scheme 6.19

After considerable efforts, Benoît Driesschaert found that $AlCl_3$ was capable of inducing Boc-deprotection on compound **6.044**,[233] albeit in modest yields. Unfortunately, when the free amino adduct **6.089** was treated with either DBU, K_2CO_3, *t*BuOK, NaH or NaHMDS, only recovered starting material or complex mixtures of products (without any trace of the coveted indolizidinone **6.088**) were obtained.

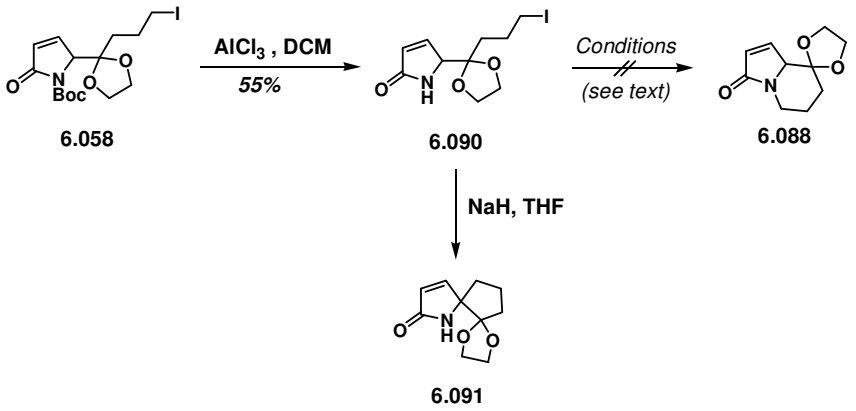


6.044 **6.089** **6.088**

Scheme 6.20

[233] Gheorghe, A. ; Schulte, M. ; Reiser, O. *J. Org. Chem.* **2006**, *71*, 2173

Reasoning that chloride was probably too poor a leaving group for the desired ring-closure to take place, the deprotection reaction was performed on iodide **6.058**. The free lactam **6.090** was obtained in moderate yield.



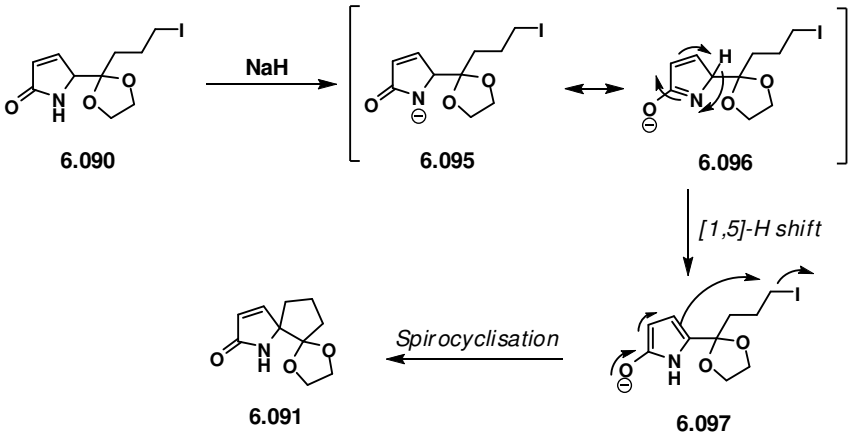
Scheme 6.21

Once again, we were dismayed to obtain only complex mixtures of products in what should conceivably be a simple intramolecular nitrogen alkylation, and this regardless of the nature of the base employed (*t*BuOK, NaHMDS, etc.). When NaH was employed, we were astonished to observe the exclusive formation of azaspirocycle **6.091**, apparently issued from a counter-intuitive C-cyclisation!

Consulting commonly used pKa tables comforted our assumption that the N-H proton in **6.090** should be the most acidic hydrogen.[234] In order to accommodate the surprising result shown in Scheme 6.21, we propose another mechanistic rationale (Scheme 6.22).

[234] Cf Bordwell, F.G. *et al. J. Org. Chem.* **1991**, *56*, 4218. For a comprehensive table, see, *e.g.* http://www.chem.wisc.edu/areas/reich/pkatable.

As illustrated, we believe that N-deprotonation is the first event taking place. As expected, the resulting anion is stabilised by amide resonance and should therefore be less nucleophilic than a saturated pyrrolidide anion. Interestingly, resonance structure **6.096** lends itself to a very favorable [1,5]-hydrogen sigmatropic shift, as shown. Indeed, such a pericyclic reaction would lead to a highly stabilised, *aromatic* pyrrolate anion **6.097**. It is therefore reasonable to assume that the transition **6.096**-**6.097** is extremely favorable from an energetic viewpoint.

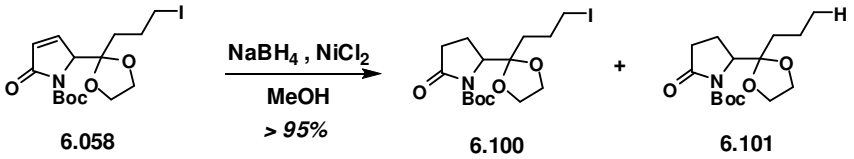


Scheme 6.22

In the event, this shift generates an intermediate which is highly prone to C-spirocyclisation as we had previously witnessed (Cf. Section 6.4.3). Rapid ring-closure to **6.091** is therefore not a surprising outcome.

This undesired (though interesting) observation prompted us to avoid dealing with pro-aromatic anions such as **6.095**-**6.096**. We recognised that removing the conjugated double bond in the condensation adduct **6.058** would be the easiest solution.

Since an efficient protocol for the reduction of conjugated double bonds through the action of nickel boride has already been established for similar compounds, it was therefore logical to employ these conditions on compound **6.058**. In the event, Benoît Driesschaert was disappointed to observe that reduction of the carbon-iodine bond took place competitively, delivering high amounts of the inseparable, fully saturated alkane **6.101**. [235]



6.058 **6.100** **6.101**

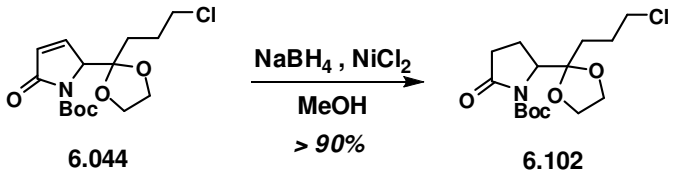
Scheme 6.23

Reducing the amounts of $NaBH_4$ used or performing the reaction at lower temperatures did not prevent formation of this compound. Stopping the reaction at intermediate conversions revealed that **6.101** (probably generated from **6.100**) begins to form almost consecutively to **6.100**. Although it might have been possible to defer separation to a later stage, the considerable amounts of **6.101** obtained deterred us from such an option.

[235] For a related example, see: Back, T.G.; Baron, D. L.; Yang, K. *J. Org. Chem.* **1993**, *58*, 2407

Deciding to sacrifice leaving group ability in favor of stability and eventual survival to reductive conditions, we re-evaluated the potential of the chloride **6.044**.

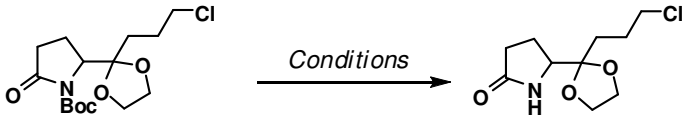
Gratifyingly, when Christophe Eviolitte treated **6.044** with excess $NaBH_4$ in the presence of catalytic amounts of $NiCl_2$ in methanol, smooth C=C reduction was observed without affecting the carbon-chlorine bond, even after long reaction times (Scheme 6.24). The saturated lactam **6.102** was obtained in quantitative yields.



6.044 **6.102**

Scheme 6.24

Having an access to large quantities of **6.102** through this procedure, he then proceeded to evaluate the N-Boc deprotection of saturated lactam **6.102** as a prelude to the ultimate ring-closure. Some of the conditions screened for this deprotection are listed in Table 6.4.



6.102 **6.103**

Table 6.4

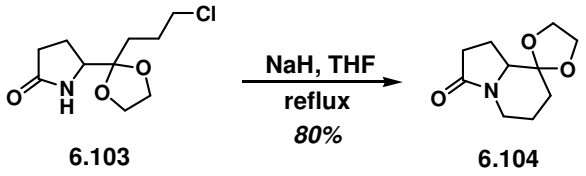
Entry	*Conditions*	*Result*
1	$Yb(OTf)_3$, THF	**6.102**
2	$AlCl_3$, DCM, 0ºC	24% **6.103**
3	TMSCl, NaI, MeCN, rt	47% **6.103** + partial dioxolane cleavage
4	TMSCl, NaI, MeCN, 0ºC	**6.102** + various products
5	TFA, DCM [0.03M]	**6.102**
6	TFA, DCM [0.01M]	63% **6.103**

As can be inferred from the Table, either $AlCl_3$ or TMSI (generated *in situ* from TMSCl and sodium iodide according to the Olah procedure)[236] afforded modest yields of product **6.103**. Whereas the use of $Yb(OTf)_3$ did not induce any appreciable deprotection (*vide infra*), treatment of **6.102** with excess TFA in *dilute* solution, from 0ºC to rt, did elicit a reproducible removal of the Boc-group in yields ranging around 60%. The remainder of the mass balance corresponds to recovered starting material.

Although optimisation of this process is likely to be possible and work in that direction is currently underway, we were eager to test the key

[236] Olah, G.A.; Narang, S.C.; Gupta, B.G.B.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247

cyclisation step. Delightfully, treatment of **6.103** with NaH in refluxing THF for 3 hours, delivered the long sought-after bicycle **6.104** in 80% yield.[237]



6.103 **6.104**

Scheme 6.25

This pleasant result thus established the viability of our approach involving the ring-closure of the pendant chlorinated side-chain onto the nitrogen atom of the condensation adducts.[238]

6.5. Conclusions, perspectives and recent developments

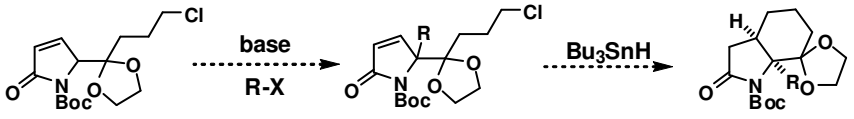
As can be seen, the benefits of this brief incursion into the pyrrole domain are numerous. Not only have we been able to perform the first condensations of pyrrole silyl enolethers with functionalised orthoesters in synthetically useful yields (50-70%), but the corresponding adducts were probed in their ability to undergo ring-closure.

---

[237] For multistep syntheses of indolizidines and pyrrolizidines from TBSOP, see: (a) Casiraghi, G.; Spanu, P.; Rassu, G.; Pinna, L.; Ulgheri, F. *J. Org. Chem.* **1994**, *59*, 2906; (b) Planas, L.; Pérard-Viret, J.; Royer, J.; Selkti, M.; Tomas, A. *Synlett* **2002**, 1629

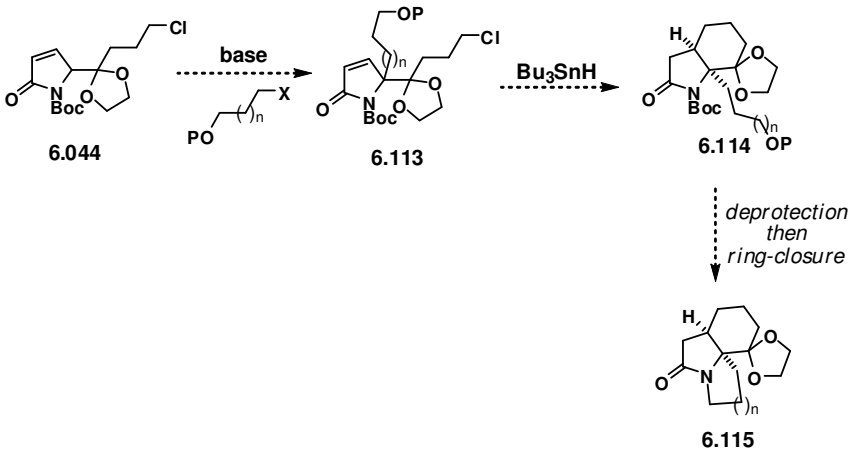
[238] Eviolitte, C. *Mémoire de licence*, UCL, in progress

Concerning the radical-mediated cyclisation to perhydroindoles, we believe that future experiments must address the problem of allylic hydrogen abstraction. One of the best ways to do so, mimicking the Donohoe results discussed above, would be to alkylate this position (Scheme 6.26).



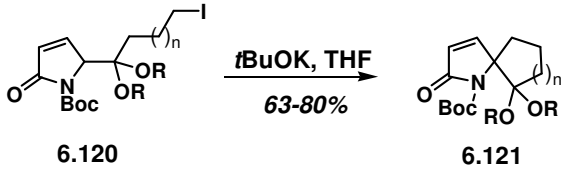
Scheme 6.26

This should be possible since we have demonstrated that chlorinated **6.044** is resistant to spiroannelation under basic conditions. Once diverse alkylated compounds **6.110** are obtained, radical cyclisation using tin-chemistry should provide a number of differently substituted lactams **6.111**. The obvious advantage in comparison to Donohoe's results is that we should not be obliged to have an ester or an electron-withdrawing substituent at the 5-position. One might even envisage placing an R-substituent which might allow for subsequent ring-closure onto nitrogen (Scheme 6.27). This could constitute an alternative access to the tricyclic alkaloids displayed in Scheme 6.18.



Scheme 6.27

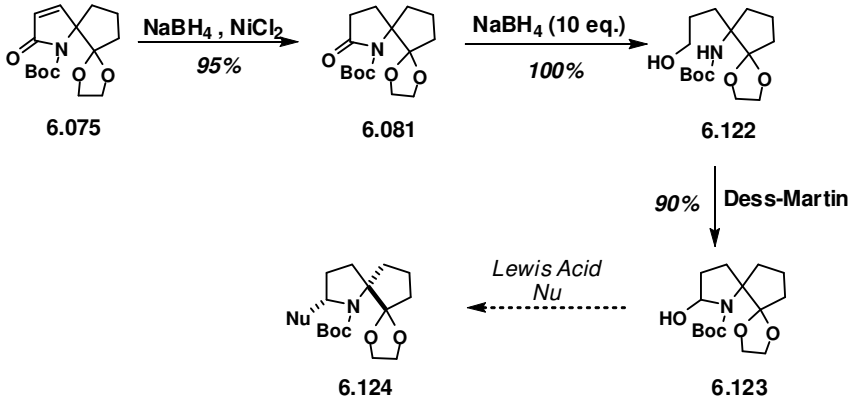
On the other hand, two-step spiroannelation proved to be almost directly analogous to the butenolide case. Upon treatment with *t*BuOK, a number of <u>*iodinated*</u> condensation adducts smoothly underwent cyclisation to provide azaspiranes in good yields. These azaspirocycles could be functionalised through simple transformations.



Scheme 6.28

Use of the "dioxolane-effect" might be possible in functionalising the position α- to nitrogen in spirocycles **6.121**. Indeed, Dr. Saiphon Songarsa

has recently been able to convert **6.075** to hemiaminal **6.123** in short order (Scheme 6.29).

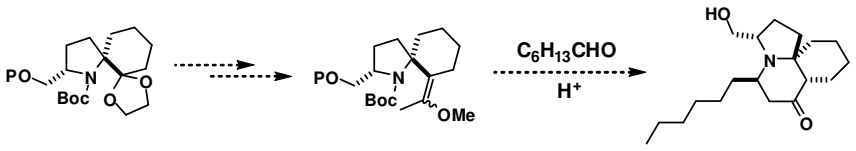


Scheme 6.29

If an acyliminium ion can be generated from hemiaminal **6.123** through the action of a Lewis Acid, then attack by an incoming nucleophile might be directed from the opposite face to the dioxolane substituent, hopefully providing compounds **6.124** as single diastereoisomers. This might allow for the introduction of the characteristic hydroxymethyl-substituent present in the Cylindricines and Lepadiformine (Scheme 6.18).

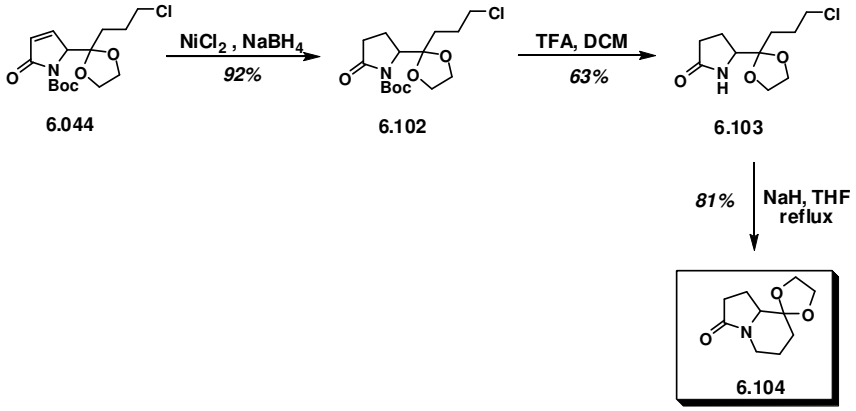
An elegant synthesis of the Cylindricines could then be envisaged as presented below. Homologation of **6.125** (the 6-membered analog of **6.124**) to **6.126** through conventional Wittig chemistry would set the stage for our proposed, biogenetically inspired, key-step. Treatment of **6.126** with heptanal in acidic media, should accomplish a number of operations: Boc- and –OP deprotection, enol ether hydrolysis and Mannich-like condensation to provide the natural product in a single step (note that all the newly created

stereogenic centers are epimerisable under the reaction conditions, presumably favoring the natural product-like configuration).



Scheme 6.30

Last but not least, we were able to demonstrate a third cyclisation mode of condensation adduct **6.044**: the formation of the fused bicycle **6.104** which contains the core of the indolizidine alkaloids. The novel sequence developed by Christophe Eviolitte is summarised in Scheme 6.31.

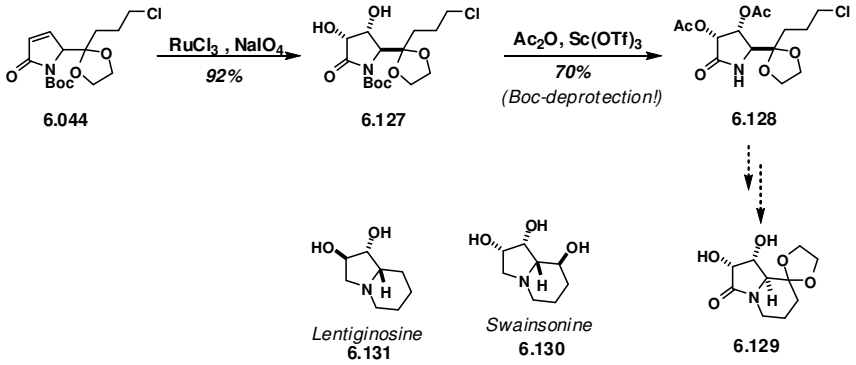


Scheme 6.31

Through this efficient pathway, indolizidinone **6.104** could be prepared in 3 steps from **6.044** (4 steps from TBSOP **6.001**) and 47% overall yield (36% from TBSOP **6.001**).

One concern throughout the sequence is the potential loss of structural diversity that accompanies the crucial double-bond reduction. We believe that this need not be the case. In fact, adduct **6.044** should be amenable to many other, *stereoselective* double-bond transformations benefitting from the ubiquitous "dioxolane-effect".

As a testimony to this fact, Christophe Eviolitte has recently demonstrated that the "flash" dihydroxylation of **6.044** proceeded with complete stereocontrol to provide a single diastereomeric diol **6.127**.



Scheme 6.32

Most interestingly, when he performed the acetylation of this diol, under the Yamamoto procedure[239], an unexpected Boc-deprotection to **6.128** took place. This is reminiscent of the results obtained in Chapter 4, when dioxolane deprotection accompanied alcohol acetylation under these conditions. Although a complete discussion of the factors at play in these reactions is clearly beyond the scope of our dissertation, and would require further mechanistic work, it should be noted that Dr. Raphael Dumeunier made similar observations during his Ph.D. Thesis. Through clever experiments and argumentation, he concluded that TfOH is the true catalyst in such reactions.[240] It is therefore conceivable that catalytic amounts of TfOH, liberated from $Sc(OTf)_3$ through ligand exchange, are responsible for the results obtained. The importance of the metal ion, the presence of Ac_2O and, perhaps, the solvent (MeCN) in this unique Boc-deprotection are underlined by the fact that attempted –Boc deprotection using $Yb(OTf)_3$ in THF (Cf. Table 6.4, entry 1) returned only starting material. Further studies to delineate wether this might be applicable as a novel deprotection methodology for N-Boc lactams (and amines) are underway.

Importantly, the direct obtention of **6.128** obviates the need for a further Boc-removal step and sets the stage for the preparation of a diastereomerically pure, hydroxylated indolizidinone such as **6.129**. This would allow an entry into bioactive polyhydroxylated indolizidine natural products, typified by Swainsonine **6.130** and Lentiginosine **6.131** (Scheme 6.32).

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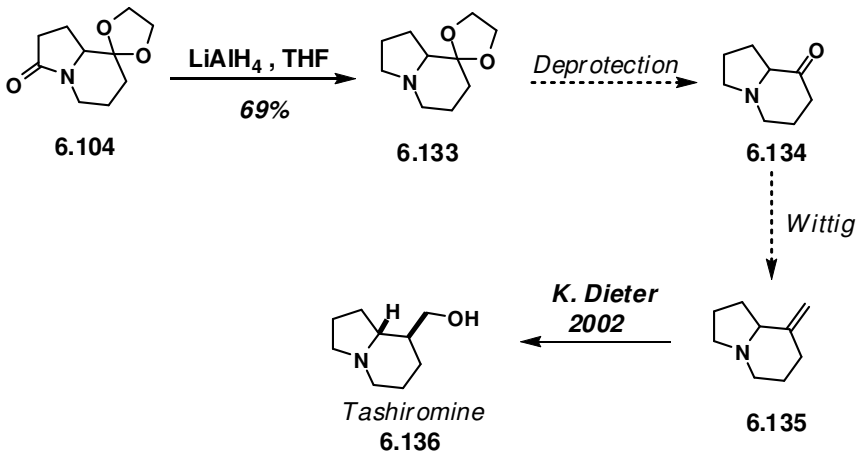
[239] Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc*. **1995**, *117*, 4413. Cf. Chapter 4.

[240] (a) Dumeunier, R.; Markó, I.E. *Tetrahedron Lett.* **2004**, 825 ; (b) Dumeunier, R. *Ph.D.Thesis*, UCL, 2004

Work is also in progress to complete the total synthesis of Tashiromine **6.136**. Christophe Eviolitte has already succeeded in the reduction of the amide functionality in **6.104** to **6.133**, in high yield (Scheme 6.33).



Scheme 6.33

After deprotection of the dioxolane and methylenation, compound **6.135** should be obtained. Dieter and co-workers have converted this compound (yield not reported) into Tashiromine in one synthetic step (hydroboration-oxidation).[241]

Though essentially novel in its nature, the chemistry of TBSOP reported herein is conceptually and operationally simple. The developments

[241] Dieter, R.K.; Watson, R. *Tetrahedron Lett.* **2002**, 7725

currently underway in our laboratory (of which only a few were presented in this final Section) are bound to provide even more surprising and intriguing results, as various classes of alkaloids should eventually fall within our grasp.

Particularly important in the longterm are the numerous possibilities for asymmetric synthesis which are unique to TBSOP. In the opening section of this Chapter, we have witnessed the good levels of asymmetric induction that result from the use of chiral TBSOP derivatives, in particular the ones pioneered by Jacques Royer and his team. The use of such enantiopure siloxydienes shall provide an easy entry into the optically active version of the compounds prepared thus far. Interestingly, benzylated TBSOP derivatives may also offer the added bonus of increased reactivity, since the nitrogen substituent will no longer be a strongly electron-withdrawing moiety (such as the –Boc group).

The following Chapter will deal with the final class of silyl enolethers that we have investigated during the span of our Thesis. It implies a more fundamental structural change, while conveying additional insight into the reactivity of our functionalised orthoesters.

Chapter 7 : Revisiting the chemistry of cyclobutanones – new twists on an old ring

7.1. Introduction

After witnessing the power of orthoesters as annelating agents for simple cyclic- and heteroaromatic silyl enolethers, one may be tempted to believe that no condensation adducts are beyond reach.

In addition to our innate curiosity for unveiling novel reaction manifolds, we have long been intrigued by issues associated with strain in small rings and the fascinating reactivity derived from that strain. Our fondness for rearrangements would eventually lead us to study the chemistry of cyclobutanes, and this final Chapter recollects our findings in that domain. As for the previous Chapters, we will briefly review the most relevant and well-known aspects of the chemistry of cyclobutanones, thus setting the stage for the report and discussion of our own experiments.

7.2. General aspects of the chemistry of cyclobutanones

Although cyclobutanes have been known for more than a century, their use as synthetic intermediates has only flourished during the last 30 years.

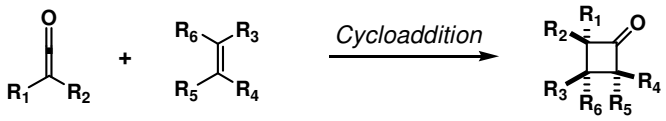
The diversity of reactions they can undergo is the result of the inherent strain associated with the four-membered ring contributing to both angular and torsional effects. Thus, cyclobutanes undergo reactions such as ring opening to acyclic products (23-26 kcal/mol release of energy), ring enlargement to five- or six-membered ring products (20 and 25 kcal/mol, respectively), and ring contraction to cyclopropanes. The latter reaction is energy neutral since cyclopropanes have strain energies comparable to those of cyclobutanes, but it is often exothermic since most of these products or intermediates possess the stabilizing conjugated cyclopropyl carbinyl unit. Cyclobutanones and cyclobutenones are arguably the most readily available derivatives of cyclobutane, and the ones that have been most often studied in the literature.

7.2.1. Synthesis

Since the early report by Kishner on the oxidative decarboxylation of cyclobutane carboxylic acid to cyclobutanone, many different approaches to these derivatives have been described. For the sake of conciseness, only a

few representative examples of methodologies developed for the preparation of cyclobutanones will be addressed in this subsection. A number of excellent, comprehensive reviews on this subject already exist in the literature.[242]

In general, the majority of these methodologies involve a cycloaddition between a ketene **7.001** and an alkene **7.002**.



7.001 **7.002** **7.003**

Scheme 7.1

In this reaction, highly reactive ketenes are generated *in situ* either by the dehydrohalogenation of acid chlorides by a base (generally triethylamine) or by the metal-promoted dehalogenation of α-halogenoacid chlorides. When performed in the presence of an excess of olefin, smooth formation of cyclobutanones ensued.

Importantly, this reaction (exemplified in Scheme 7.2) is usually accompanied by high levels of regio- and stereoselectivity. Since ketenes are electrophilic reagents, they react essentially by interaction of their LUMO, which is centered on the sp-carbon, with the alkene HOMO. This is why cycloadditions of ketenes work best with electron-rich olefins.

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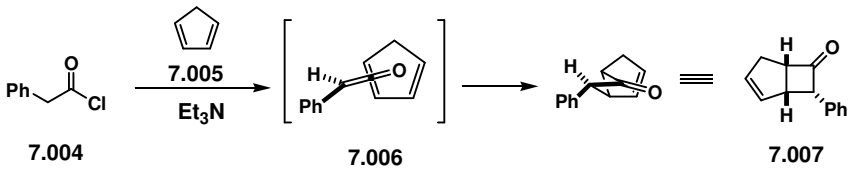
[242] (a) Namyslo, J. C.; Kaufman, D. E. *Chem. Rev.* **2003**, *103*, 1485; (b) Fu, N.-Y.; Chan, S.-H. *The application of cyclobutane derivatives in organic synthesis.* In *The Chemistry of Cyclobutanes*; Rappoport, Z., Liebman, J. F., Eds.; Patai Series: The Chemistry of Functional Groups; J. Wiley: Chichester, **2005**; p 357. (c) Lee-Ruff, E. *Synthesis of cyclobutanes.* In *The Chemistry of Cyclobutanes*; Rappoport, Z., Liebman, J. F., Eds.; Patai Series: The Chemistry of Functional Groups; J. Wiley: Chichester, **2005**; p 281-355



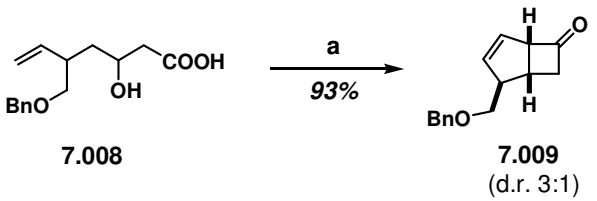
Scheme 7.2

The stereoselectivity originates from the *suprafacial-antarafacial* approach of the two reacting entities (Cf. Scheme 7.2), which is why these reactions are actually symmetry-allowed according to the Woodward-Hoffmann rules. Therefore, *endo*-adducts such as **7.007** are usually formed.

The main limitation of this strategy is the high tendency of ketenes to dimerise, therefore requiring the use of excess amounts of the alkene. This becomes an inconsequential limitation in the case of intramolecular cycloadditions, which readily take place.

For instance, the group of Rosini has employed this type of cycloaddition in their approach to Prostaglandins (Scheme 7.3).[243] As depicted, the hydroxyacid **7.008**, upon exposure to potassium acetate in boiling acetic anhydride, smoothly provides the bicyclo[3.2.0]hexane **7.009** in very high yield. In this reaction, dehydration of the carboxylic acid was accomplished by mixed anhydride formation followed by elimination. Additional elimination of the β-hydroxygroup from **7.008** accounts for the formation of compound **7.009**.

[243] Marotta, E.; Righi, P.; Rosini, G. *Org. Lett.* **2000**, *2*, 4145

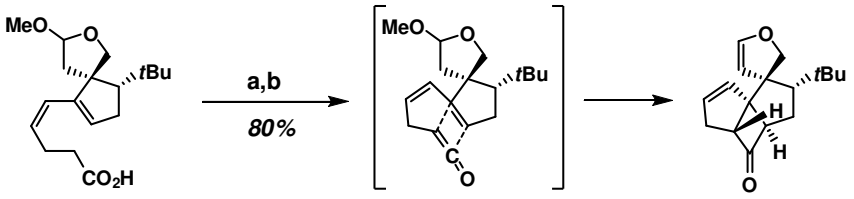


7.008 **7.009** (d.r. 3:1)

a) KOAc, Ac_2O, then reflux

Scheme 7.3

A further, spectacular example of the intramolecular [2+2] ketene-olefin cycloaddition can be found in Corey's landmark total synthesis of Gingkolide B (Scheme 7.4).[244]



7.010 **7.011** **7.012**

a) $(COCl)_2$, benzene; b) Bu_3N, PhMe, reflux

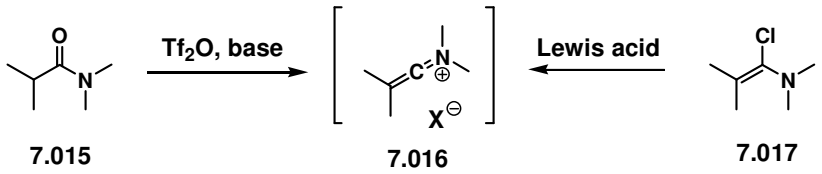
Scheme 7.4

When the acid chloride, derived from the action of oxalyl chloride on carboxylic acid **7.010**, is treated with tributylamine in refluxing toluene, it undergoes smooth conversion to the tetracycle **7.012** *via* ketene **7.011**. Remarkably, this reaction is completely stereoselective and proceeds in a

[244] Corey, E. J.; Kang, M. C.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110*, 649

very good yield. Interestingly enough, these conditions also bring about the elimination of the anomeric methoxy group in **7.010**.

A clever solution to the ketene-dimerisation issue was discovered with the use of keteniminium salts as synthetic equivalents, as pioneered by Léon Ghosez.[245] Keteneiminium intermediates **7.016** can be formed by dehydration of the corresponding amides **7.015** or by Lewis-acid activation of chloroenamines **7.017** (Scheme 7.5).

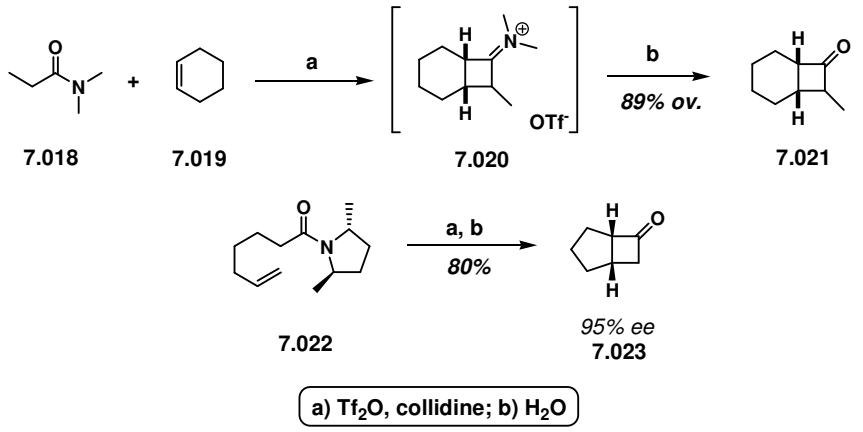


Scheme 7.5

Following hydrolysis of the [2+2] adducts, this method provides the desired cyclobutanones in good yields. Ghosez and his group employed the triflate salts of tertiary amides to prepare numerous examples of cyclobutanones in very good yields.[246] Importantly, cyclobutanones of high enantiomeric purity were obtained by using keteniminium salts derived from chiral amides (Scheme 7.6).

[245] Marchand-Brynaert, J.; Ghosez, L. *J. Am. Chem. Soc.* **1972**, *94*, 2870

[246] (a) Houge, C.; Frisque-Hesbain, A.M.; Mockel, A.; Ghosez, L.; Declercq, J.-P. *J.Am.Chem.Soc.* **1982**, *104*, 2920; (b) Ghosez, L.; Markó, I.; Frisque-Hesbain, A.M.; *Tetrahedron Lett.* **1986**, 5211; (c) Chen, L.; Ghosez, L. *Tetrahedron: Asym.* **1991**, 1181



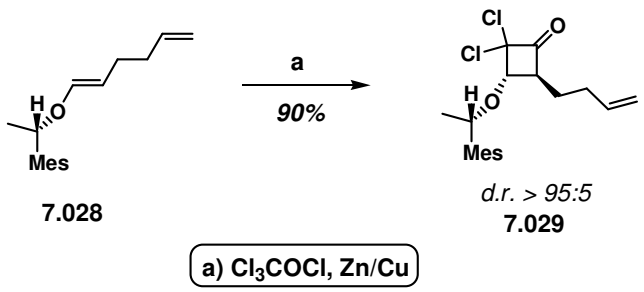
Scheme 7.6

Keteniminium salts are not prone to dimerisation. They readily react with a broad variety of substrates bearing a C-C double or triple bond donors. In some cases, even electron-deficient alkenes can be induced to react with keteniminium salts. Conversely, this methodology for the synthesis of cyclobutanones is not applicable to electron-rich double bonds such as enol ethers and enamines.[247]

The more commonly used ketene equivalent is dichloroketene, readily generated by either of the methods mentioned previously. Due to its high electrophilic nature, dichloroketene is much more reactive than the classical ketenes. Nonetheless, its use often implies a reduction step to remove the superfluous chlorine atoms.

[247] In these cases, no formal [2+2]-cycloaddition takes place due to the enhanced stability of the dipolar intermediate.

The enhanced reactivity of dichloroketene with regard to electron-rich alkenes allowed Andrew Greene and his group in Grenoble to devise a method for the asymmetric synthesis of cyclobutanones by using chiral enolethers such as **7.028**. When reacted with dichloroketene (generated by the zinc/copper-mediated dehalogenation of trichloroacetyl chloride), this enol ether undergoes [2+2] cycloaddition in excellent yield, providing the cyclobutanone **7.029** with complete diastereocontrol. The chemoselectivity of cycloaddition (exclusive reaction at the enol ether portion of diene **7.028**) is also worthy of note.[248]



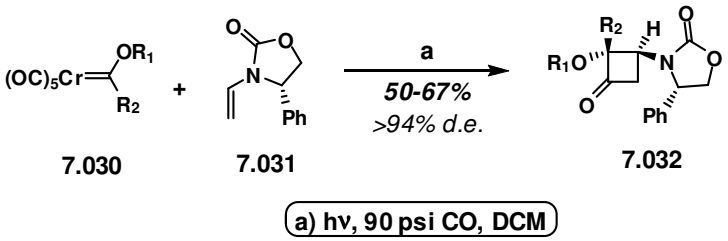
Scheme 7.7

Photochemical [2+2] methods for the production of cyclobutanes abound in the literature, but few can directly deliver cyclobutanones. Due in part to its relevance for the subsequent discussion, the work of Hegedus on this area merits some comments.

As shown in Scheme 7.8, the irradiation of Fischer-type chromium carbene complexes **7.030**, in the presence of enantiopure vinyl oxazolidinones, leads to the optically active, densely functionalised

[248] Pourashraf, M.; Delair, P.; Rasmussen, M. O.; Greene, A. E. *J. Org. Chem.* **2000**, *65*, 6966

cyclobutanones **7.032** with very good diastereocontrol.[249] The Hegedus group has studied this reaction extensively and we will encounter further examples of related work throughout this chapter (*vide infra*).

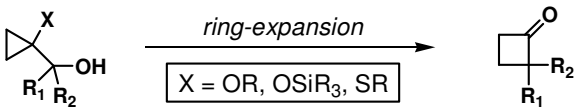


Scheme 7.8

Given the aforementioned thermoneutrality of the transition cyclopropane/cyclobutane, it is not surprising that a number of methodologies for the synthesis of cyclobutanones employ the ring-expansion of cyclopropane starting materials.

For instance, cyclopropylcarbinols possessing an oxygen or sulphur substituent α-to the carbinol function, are prone to pinacol rearrangement to the corresponding, α-substituted cyclobutanones, as depicted in Scheme 7.9.[250]

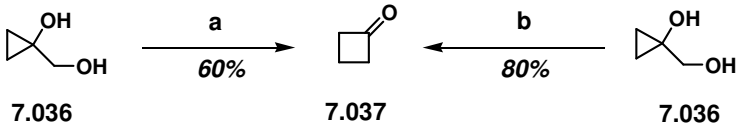
[249] Soderberg, B. C.; Hegedus, L. S.; Sierra, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 4364
[250] Fitjer, L., *Cyclobutanes. Synthesis : By Ring Enlargement*, in *Houben-Weyl (Methods of Organic Chemistry)*, de Meijere, A., Ed.; Thieme Verlag, **1997**, Vol E, 251-316



7.034 **7.035**

Scheme 7.9

This kind of ring-expansion usually takes place in the presence of catalytic amounts of acid, but can also be induced under basic conditions (Scheme 7.10).[251]



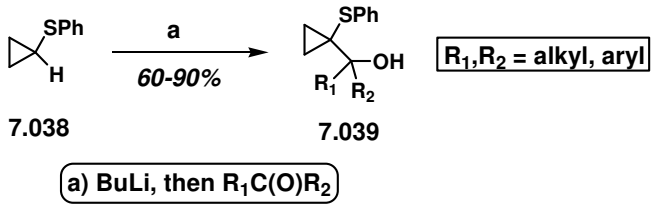
7.036 **7.037** **7.036**

a) $BF_3.OEt_2$, $CHCl_3$; b) TsCl, py, DCM

Scheme 7.10

As for the starting materials for this kind of ring-enlargement, they can be obtained by a multitude of reactions. For example, Trost and co-workers championed the use of cyclopropyl sulphides such as **7.039**.[252]

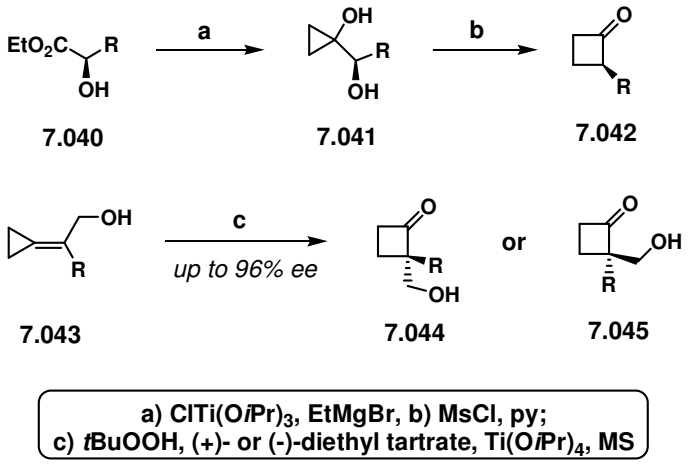
[251] Salaun, J.; Garnier, B.; Conia, J.M. *Tetrahedron* **1974**, *30*, 1413
[252] Trost, B.M.; Keeley, D.E.; Arndt, H.C.; Rigby, J.H.; Bogdanowicz, M.J. *J. Am. Chem. Soc.* **1977**, *99*, 3080



Scheme 7.11

Numerous asymmetric versions of such rearrangements have been developed. Two instances are shown in Scheme 7.12. Cha has exploited the Kulinkovich reaction of readily available, optically active α-hydroxyesters **7.040**.[253] This titanium-mediated reaction effects the conversion of esters into cyclopropanols under conditions compatible with the presence of the hydroxy substituent, thus affording the diols **7.041** in good yields. Their *stereospecific* rearrangement under basic conditions leads to optically active α-substituted cyclobutanones which would otherwise be difficult to access (*vide infra*). The observed selectivity can be rationalised by invoking S_N2-like antiperiplanar bond migration.

[253] Cho, S.Y.; Cha, J.K. *Org. Lett.* **2000**, *2*, 1337



Scheme 7.12

On the other hand, Nemoto has taken advantage of the Sharpless asymmetric epoxidation (SAE) of allylic alcohols and applied it to methylenecyclopropane **7.043**.[254] He found that, under the mild conditions of this reaction, the intermediate oxaspiropentanes directly rearrange to cyclobutanones **7.044/7.045** with high levels of enantioselectivity. Interestingly, either antipode of the enantiomerically pure cyclobutanones can be prepared since both forms of diethyl tartrate are commercially available.

This non-exhaustive promenade already reveals a wealth of chemistry aimed at the preparation of cyclobutanones. In order to further develop our motivations to enter this field, the specific and fascinating reactivity of the thus prepared cyclobutane derivatives (particularly focused on the case of cyclobutanones) will be briefly surveyed.

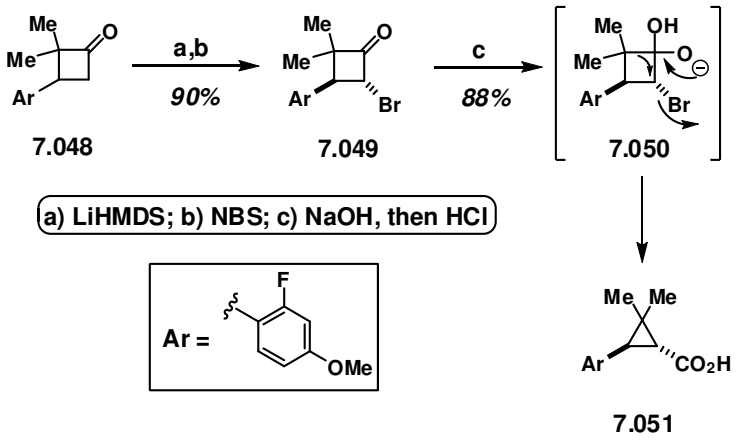
[254] Nemoto, H.; Fukumoto, K. *Synlett* **1997**, 863

7.2.2. Reactivity of cyclobutanones

Here, too, it would be foolish to even attempt to summarise the immense body of work that is documented in the chemical literature.[255] The enhanced reactivity of the cyclobutanone carbonyl (mainly due to ring strain), as compared to higher cycloalkanone homologues, is mainly responsible for this plethora of interesting reactions. We will rather provide a brief overview mentioning the most widely applicable and efficient reactions that cyclobutanones are prone to undergo, with a particular emphasis on both ring-expansion and ring-regression rearrangements.

The latter class generally plays a minor role in the applications of cyclobutanones in organic synthesis, since it is often easier to build up a cyclopropane ring from an acyclic precursor than to contract a larger ring. Nevertheless, mechanistically interesting examples exist. For instance, in 2001, Chen and Ahmand published a facile method for the stereoselective synthesis of cyclopropane carboxylic acids reminiscent of chrysantemic acid by a Favorski-type rearrangement. As shown below, treatment of α-bromocyclobutanone **7.049** with sodium hydroxide effects ring-contractive rearrangement, providing the thermodynamically favored *trans*-2-arylcyclopropane carboxylic acid **7.051** in 88% yield after acidic workup.[256]

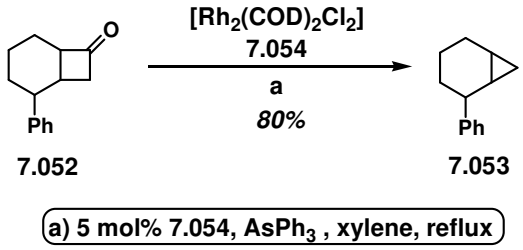
[255] For reviews, see ref. 242a.
[256] Chen, B.C.; Ngu, K.; Guo, P.; Liu, W.; Sundeen, J.E.; Weinstein, D.S.; Atwal, K.S.; Ahmad, S. *Tetrahedron Lett.* **2001**, 6227



Scheme 7.13

Metal-catalysed variants also exist for this interesting ring-contraction. The group of Murakami has reported the decarbonylation of cyclobutanones to cyclopropanes in the presence of a rhodium(I) catalyst.[257] This transformation, which had been achieved previously only under stoichiometric conditions, required the use of 5 mol% of dirhodium complex **7.054** in the presence of $AsPh_3$. Thus, the 2-phenylnorcarane **7.053** is obtained from the fused cyclobutanone **7.052** in 80% yield (the stoichiometric variant gives a quantitative yield).

[257] Murakami, M.; Amii, H.; Shigeto, K.; Ito, Y. *J. Am. Chem. Soc.* **1996**, *118*, 8285

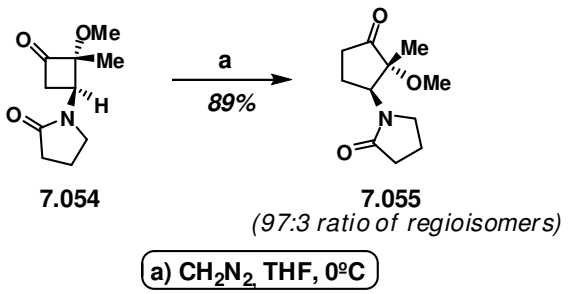


Scheme 7.14

Ring expansions of four-membered ring systems frequently offer efficient and stereocontrolled access to functionalised monocyclic or ring-annelated carbo- and heterocycles. This kind of ring-expansion is particularly important for the formation of five- and six-membered rings, although higher homologues can be formed in particular cases.

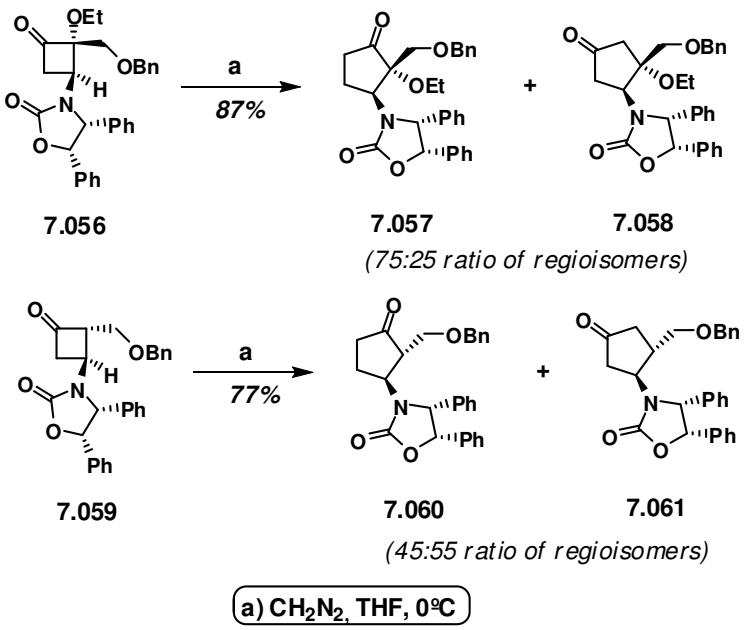
For example, Hegedus applied the regioselective ring-expansion of the cyclobutanone adducts produced by his group's methodology (Cf. Scheme 7.8) with diazomethane.[258] For example, homologation of **7.054** with excess diazomethane in cold THF led to cyclopentanone **7.055** in excellent yield and selectivity (Scheme 7.15).

[258] Reeder, L. M.; Hegedus, L. S. *J. Org. Chem.* **1999**, *64*, 3306



Scheme 7.15

Although the example shown would seem to suggest that diazomethane-mediated ring enlargements of cyclobutanones are selective reactions *per se*, the real picture is quite different. In general, for unsymmetrical cyclobutanones, migration of the less substituted carbon atom usually predominates though many other factors influence the regioselectivity of this reaction and predictions are actually quite difficult.



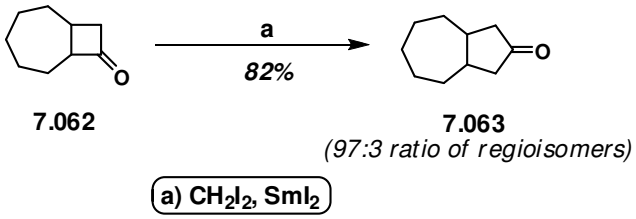
Scheme 7.16

Consider, for instance, the examples from the same group, depicted in Scheme 7.16.[259] Depending on the nature of the α-substituents of the starting cyclobutanone, the selectivity can actually drop significantly (as for **7.056**) or even be reversed (as in the structurally related **7.059**)!

A similar reaction can be induced by using a combination of CH_2I_2 and the reducing agent SmI_2, as developed by Fukuzawa and Tsuchimoto (Scheme 7.17).[260] Interestingly, this reaction (exemplified with the conversion of **7.062** to the perhydroazulenone **7.063**) appears to provide the

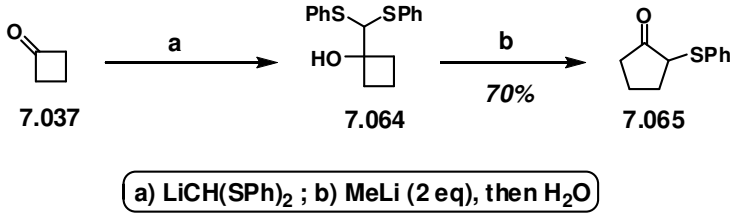
[259] Brown, B.; Hegedus, L. S. *J. Org. Chem.* **2000**, *65*, 1865
[260] Fukuzawa, S.-i.; Tsuchimoto, T. *Tetrahedron Lett* **1995**, *36*, 5937

opposite regioselectivity to the diazoalkane case (compare with Scheme 7.15).



Scheme 7.17

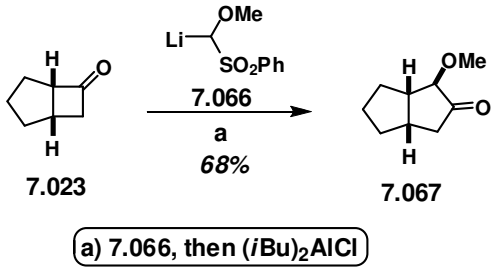
Other carbenoids or carbenoid-like species have been used for similar rearrangements involving two- (or more) step sequences. In connection with his vast work on the chemistry of sulphur, Cohen took advantage of the ready addition of the anion of bisthiophenylmethane onto cyclobutanone **7.037** (Scheme 7.18).[261] Upon two-fold deprotonation, compound **7.064** generates a carbenoid which readily rearranges to the ring-expanded enolate. After protolytic workup, 2-phenylthiocyclopentanone **7.065** is obtained in good yield.



Scheme 7.18

[261] Cohen, T.; Yu, L. C.; Daniewski, W. M. *J. Org. Chem.* **1985**, *50*, 4596

Similarly, Trost developed a simple one-pot procedure for the ring expansion of cyclic ketones with concomitant introduction of an α-methoxy group (Scheme 7.19).[262] The procedure begins with the addition of lithiated methoxymethylphenyl sulfone **7.066**. Subsequently, a cationic rearrangement is triggered by excess diisobutylaluminim chloride. Through such a procedure, the fused cyclobutanone **7.023** affords methoxylated **7.067** regio- and stereoselectively.



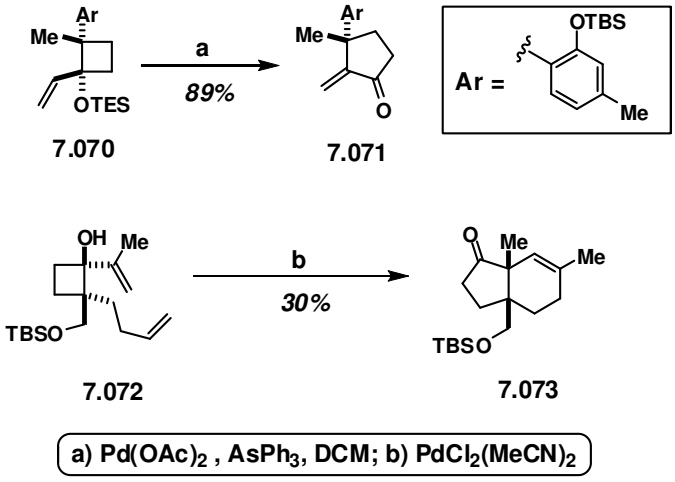
Scheme 7.19

Many other sulfur-derived anionic species related to **7.066** have been employed for similar purposes.

Among metal-mediated processes, palladium (II) complexes are particularly effective in promoting the ring-expansion of vinyl cyclobutanols (readily available by Grignard addition onto the corresponding cyclobutanones) or the corresponding silyl ethers. The group of Fukumoto developed a palladium-promoted ring enlargement of both classes of compounds using palladium acetate in the presence of triphenylarsine.[263] In this reaction, the final products are methylene cyclopentanones. For example

[262] Trost, B. M.; Mikhail, G. K. *J. Am. Chem. Soc.* **1987**, *109*, 4124
[263] Nemoto, H.; Nagamochi, M.; Ishibashi, H.; Fukumoto, K. *J. Org. Chem.* **1994**, *59*, 74

(Scheme 7.20), the silyl ether **7.070** was converted to the α,β-unsaturated cyclopentanone **7.071** in excellent yield. In the same year, Fukumoto disclosed an interesting extension of this reaction in that $PdCl_2(MeCN)_2$ was able to mediate a tandem ring-expansion/Heck-like alkene insertion.[264] The power of such a domino process is testified by the conversion of 1,2-tetrasubstituted vinyl cyclobutanol **7.072** into the functionalised hydrindanone **7.073**, albeit in modest yield.



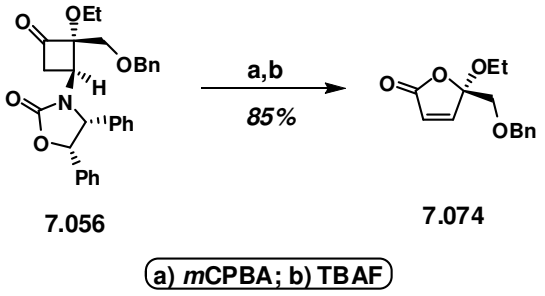
Scheme 7.20

We have previously encountered other examples of ring expansions of cyclobutanones in this document. One might recall Paquette's approach to spirocyclic butenolides as spironucleoside precursors (Chapter 5, Section 5.5.1) or Royer's strategy for preparing enantioenriched azaspiranes in his

[264] Nemoto, H.; Shiraki, M.; Fukumoto, K. *Synlett* **1994**, 599

synthesis of Cephalotaxine (Chapter 6, Section 6.2). Further examples of alkylative ring-expansions will be discussed later in this Chapter.

The wealth of ring-expansion processes to which cyclobutanones readily respond is not limited to the insertion of carbon units. The classical Baeyer-Villiger and Beckmann rearrangements, well-known to selectively insert oxygen- and nitrogen atoms into cyclic substructures, are obviously applicable to the cyclobutanone case. For instance, Hegedus[265] successfully employed the common *m*CPBA-promoted Baeyer-Villiger ring expansion to his cyclobutanone adduct **7.056**, thus preparing 5,5-disubstituted butenolides[266] such as **7.074** in good yields.



7.056 **7.074**

a) *m*CPBA; b) TBAF

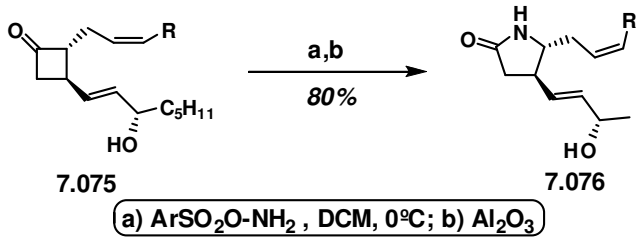
Scheme 7.21

As for the Beckmann rearrangement of cyclobutanones, it is commonly performed with O-arylsulfonylated hydroxylamines (*vide infra*). For example, Andrew Greene prepared a nitrogen-modified prostaglandin

[265] Bueno, A. B.; Hegedus, L. S. *J.Org.Chem.* **1998**, *63*, 684

[266] The chemistry of similar butenolides has been thoroughly discussed in Chapter 5.

analogue **7.076** by an efficient and regioselective Beckmann ring-expansion of cyclobutanone **7.075**.[267]

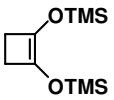


Scheme 7.22

From this brief, superficial expedition onto the chemistry of cyclobutanones, one can only be awed at the amazing body of work developed through the years to address not only their synthesis but also their transformations. Indeed, since each synthetic methodology employed delivers cyclobutanones with particular structural features, their subsequent reactivity is expected to be a function of those structural characteristics.

Our interest in this area was triggered by considerations similar to those invoked for the TMSOF saga (Chapter 5). We were interested in the use of readily available, *preformed* cyclobutane templates onto which it might be possible to attach other functionalised subunits in a convergent manner. We expected that the combination of the synthetic potential of our orthoesters and the exciting reactivity of cyclobutanones would give rise to interesting (and perhaps unexpected) reaction pathways.

[267] Roche, C. ; Delair, P. ; Greene, A.E. *Org. Lett.* **2003**, *5*, 1741



7.080

Scheme 7.23

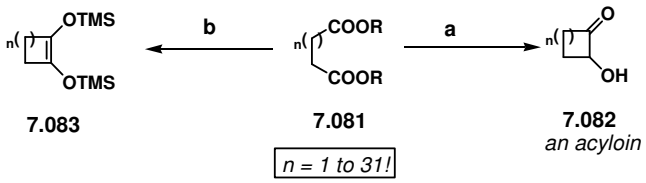
We recognised one such template in the form of 1,2-bis(trimethylsilyloxy)cyclobutene **7.080**, a silylated acyloin (Scheme 7.23). Before laying down our strategy, we will delve into the known relevant chemistry of this compound and its derivatives.

7.3. Literature survey

The classical acyloin condensation, discovered in the 19th century, consists in the reaction of aliphatic esters with molten, highly dispersed sodium in a boiling apolar solvent (Scheme 7.24).[268] The resulting disodium acyloin derivatives are then acidified to liberate the corresponding α-hydroxyketones (acyloins). Of course, diesters **7.081** lead to cyclic acyloins **7.082** and the intramolecular acyloin condensation remains one of the best ways of closing rings of 10 up to 34 (!) members.

A major improvement consisted in the observation that yields were greatly improved in the presence of TMSCl, particularly in the case of smaller rings (4-6 membered).[269] The addition of TMSCl prevents base-catalysed side reactions such as β-elimination and Claisen or Dieckmann condensations. The TMSCl-modification now leads to the formation of 1,2-bis-siloxyalkenes (such as **7.083**) which can be isolated or converted to the acyloins by simple hydrolysis or alcoholysis.

[268] For an early review, see : Finley, K.T. *Chem.Rev.* **1964**, *64*, 573
[269] Ruehlmann, K. *Synthesis* **1971**, 236



a) Na, xylene or toluene, reflux, then H_3O^+; b) Na, TMSCl, xylene or toluene, reflux

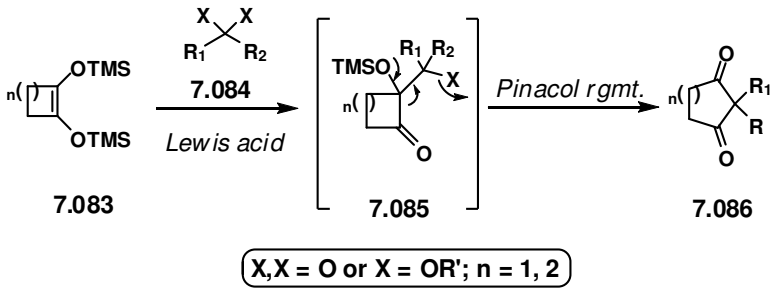
Scheme 7.24

In contrast to its popularity, applications of the acyloin adducts in synthesis have only blossomed in the early 1980's. At that time, Kuwajima discovered that 1,2-bis(trimethylsilyloxy)alkenes could be employed in Mukaiyama aldol reactions and readily afforded ring-expanded products, if the smaller family member **7.080** was employed.[270]

In particular, the Burnell group in Canada has worked relentlessly towards the development of what they termed a "geminal acylation" reaction.[271] The main features of this process are highlighted in Scheme 7.25.

[270] Shimada, J.; Hashimoto, K.; Kim, B. H.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 1759

[271] See : (a) Gao, F.; Burnell, D. J. *J. Org. Chem.* **2006**, *71*, 356; (b) Crane, S. N.; Burnell, D. J. *J. Org. Chem.* **1998**, *63*, 1352; (c) Wu, Y.-J.; Zhu, Y.-Y.; Burnell, D. J. *J. Org. Chem.* **1994**, *59*, 104; (d) Jenkins, T. J.; Burnell, D. J. *J. Org. Chem.* **1994**, *59*, 1485; (e) Wu, Y. J.; Strickland, D. W.; Jenkins, T. J.; Liu, P. Y.; Burnell, D. J. *Can. J. Chem.* **1993**, *71*, 1311 and references therein.



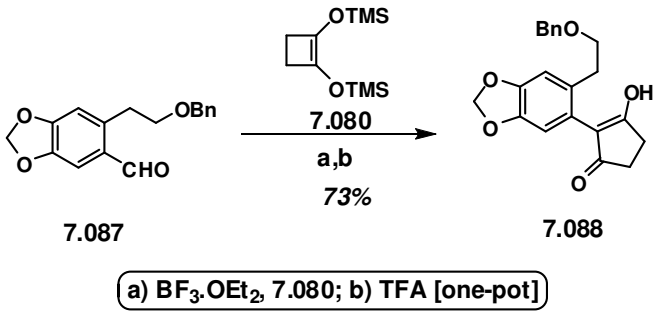
Scheme 7.25

Thus, when cyclobutene **7.083** is reacted with aldehydes, ketones or aldehyde acetals in the presence of excess Lewis acid, Mukaiyama aldol condensation ensues, transiently affording **7.085**. In the highly acidic medium, these intermediate monosilylated diols are not stable and readily undergo pinacol rearrangement to produce cyclopentane-1,3-diones **7.086**. Many improvements and modifications of this process have been developed throughout the years by the Burnell group and by others, but it should be kept in mind that good yields are obtained only when n = 1 (*i.e.*, in the case of cyclobutene **7.080**), most probably due to the high proclivity of cyclobutanes to undergo ring-expansion. Also, aldehydes and their acetals are by far the best electrophiles in this procedure.

Kavash and Mariano demonstrated an excellent example of this procedure in their approach to the E-ring of harringtonine alkaloids (such as Cephalotaxine, Cf. Chapter 6).[272] Thus, the addition of **7.080** to aromatic aldehyde **7.087** was followed by reaction of the *in-situ* generated adducts with of TFA, to induce the pinacol rearrangement. The resulting enolised

[272] Kavash, R. W.; Mariano, P. S. *Tetrahedron Lett.* **1989**, *30*, 4185

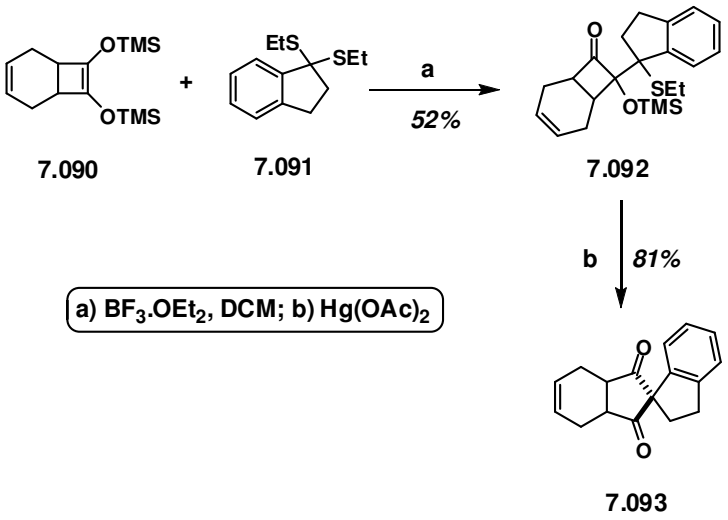
arylcyclopentanedione **7.088** was obtained in 73% yield from aldehyde **7.087**.



Scheme 7.26

Dithioketals are also competent electrophiles for geminal acylations of 1,2-bis-siloxycyclobutenes **7.083**. For instance, Bach reported that condensation of bicyclic silylated acyloin **7.090** with dithioketal **7.091** proceeded to afford the adduct **7.092** in modest yield.[273] Rearrangement of this intermediate was then chemoselectively performed in the presence of a thiophilic mercury(II) salt, providing the spirodiketone **7.093** in good yield. This methodology was applied as the key step in a synthesis of Fredericamycin A by the same group.[274]

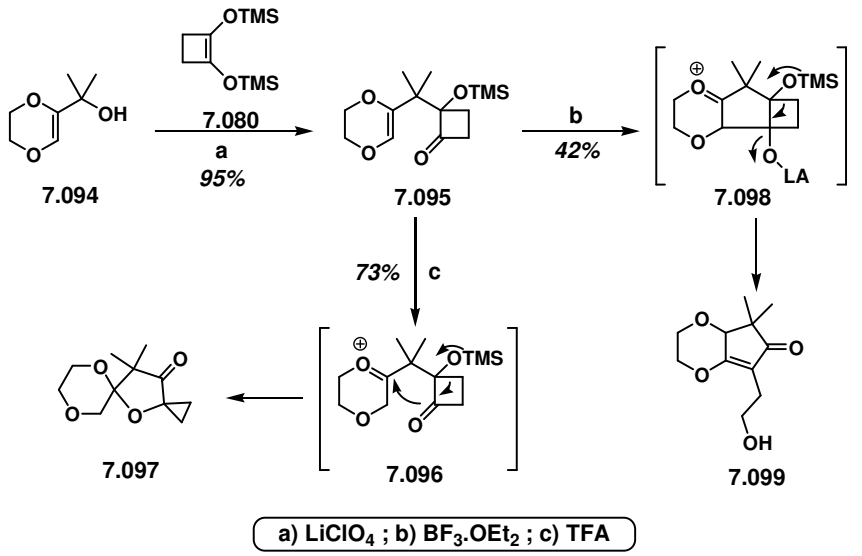
[273] Bach, R. D.; Klix, R. C. *J. Org. Chem.* **1986**, *51*, 749
[274] Wendt, J. A.; Gauvreau, P. J.; Bach, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 9921



Scheme 7.27

On a different note, Issam Hanna, at the Ecole Polytechnique, studied the reactivity of dioxene-derived allylic alcohols towards 1,2-bis(trimethylsilyloxy)cyclobutadiene **7.080**.[275] He found that selective reactions took place and that the corresponding adducts displayed interesting behaviour in acidic conditions (Scheme 7.28).

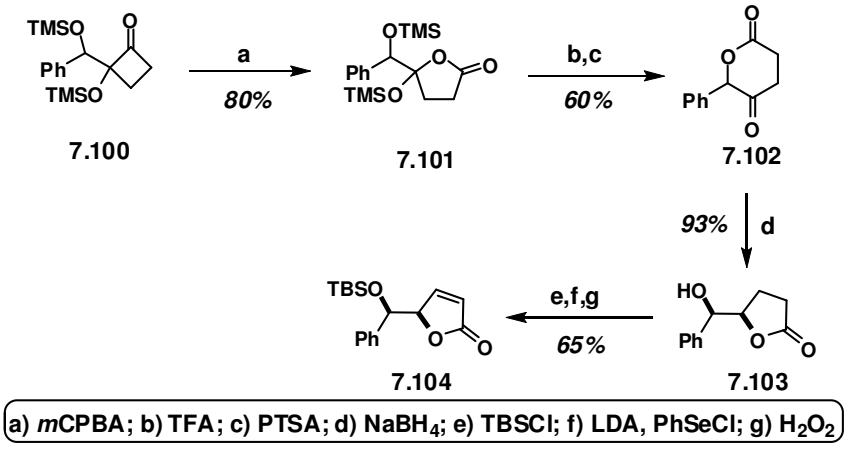
[275] Hanna, I.; Ricard, L. *Tetrahedron Lett.* **1999**, *40*, 863



Scheme 7.28

As shown above, the displacement of the allylic alcohol **7.094** can be easily and smoothly induced by even weak Lewis-acidic salts such as $LiClO_4$. The adduct **7.095**, obtained in excellent yield, can then be rearranged under different acidic conditions through different pathways, as illustrated. When exposed to a strong Lewis acid (such as boron trifluoride), selective carbonyl activation of **7.095** takes place to afford tricyclic compound **7.098**. Ring-contraction as shown, followed by opening of the putative cyclopropyl intermediate, account for the formation of **7.099**. On the other hand, if treated with a strong Brönsted-acid, protonation of the electron-rich dioxene double bond ensues, and the transient oxonium **7.096** is captured by the neighbouring carbonyl oxygen in an intramolecular fashion. Concomitant cyclobutanone ring-regression finally provides the spirocyclopropane **7.097**.

Direct applications of the intermediate Mukaiyama aldol adducts of 1,2-bis(trimethylsiloxy)cyclobutene in processes other than ring-expansions or rearrangements are rather unusual. To the best of our knowledge, an isolated example was reported by Wei-Dong Li in 2002.[276] These researchers highlighted the usefulness and mild nature of MgI_2 for promoting Mukayiama-aldol condensations of various silyl enolethers, including **7.080**, with aromatic aldehydes. The ensuing adduct **7.100** was then converted into butenolide **7.104** (which coincidentally might be seen as the product of a vinylogous aldol reaction of TBSOF with benzaldehyde, Cf. Chapter 5) through the circuitous sequence of operations depicted (Scheme 7.29).



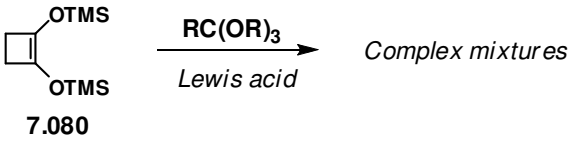
Scheme 7.29

In the event, the bis-silylated diol **7.100** was amenable to a Baeyer-Villiger homologation to functionalised butyrolactone **7.101**. Upon

[276] Li, W.-D. Z.; Zhang, X.-X. *Org. Lett.* **2002**, *4*, 3485

deprotection of the silyl ethers and exposure to PTSA, **7.101** underwent translactonisation to **7.102**; the latter could be regressed back to the γ-butyrolactone stage after reduction by sodium borohydride.

Finally, a comment should be made on the hitherto known reactivity of silylated acyloins towards orthoesters. In a full account of the geminal acylation reaction,[271e] Burnell reports attempted reaction of **7.080** with simple orthoesters. Unfortunately, only complex mixtures of products, including ring-opened materials, could be obtained. This prompted the comment by the authors that "the geminal acylation of orthoesters (…) does not appear to hold synthetic usefulness".



Scheme 7.30

7.4. Strategy

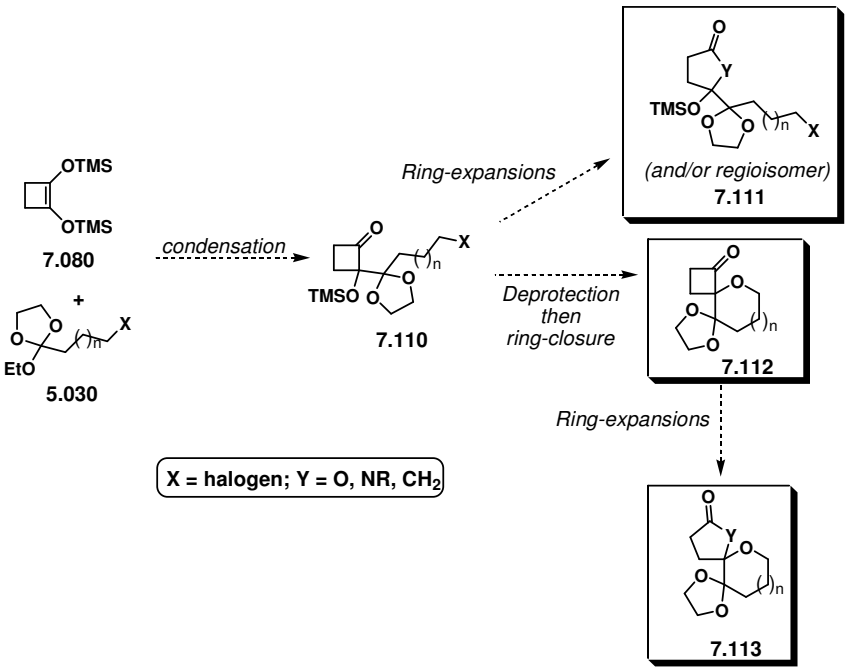
The survey presented above reveals a number of interesting trends. For one, the ready availability of silylated acyloins such as **7.080** and their competence as nucleophilic partners in Mukaiyama-aldol reactions appears to be well-established. Nonetheless, whilst yields can be good in the case of aldehydes and their acetals, ketones and ketals are significantly less effective in such processes. Furthermore, most applications deal with cyclobutenes akin to **7.080**. We presume that this is probably the most reactive silylated

acyloin and that higher homologues might be considerably more inert towards electrophiles (*vide infra*).

Some reasons for concern can also be derived from the overview presented. For instance, the promptness of the condensation adducts from **7.080** to undergo ring-expansion reactions is clearly detrimental to the possibilities of finding further applications for these compounds. Furthermore, the reports of Burnell on the reaction of orthoesters with silylated acyloins made us beware of the potential instability of condensation products derived from **7.080**.

Not all was grim, though. We were confident that our dioxolane-containing orthoesters, originally designed for enhanced stability of the condensation adducts, might give us a good chance of success in this endeavour. Additionally, and in analogy to Wei-Dong Li's results, our previous experience concerning the use of zinc chloride as a mild Lewis-acid further reassured us.

The main axes for our proposed use of **7.080** (and derivatives) as a cyclobutanone template are outlined in Scheme 7.31.



Scheme 7.31

Our plan departs from the premise that condensation products such as **7.110** can be obtained. From these adducts, a number of different options are at our disposal. For instance, direct application of the ring-expansion reactions analysed in the opening sections would lead to **7.111**. On the other hand (and more intriguingly), we hypothesized that, upon desilylation, the tertiary oxygen in **7.110** might be induced to intramolecularly displace the pending halogen to form a spirocyclic ether **7.112**. Our success in the preparation of indolizidines from TBSOP and our orthoesters (Chapter 6) was seen as an encouraging precedent.

Subsequent ring-expansions on **7.112** were seen favorably since the possibilities for regiocontrol in a locked, spirocyclic precursor would probably be quite high. Of course, it might also be possible to reach **7.113** through ring-closure of **7.111** (not shown).

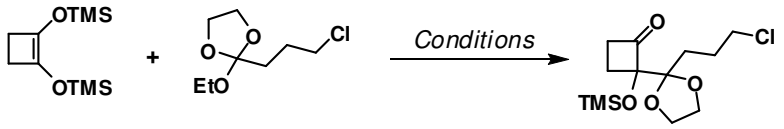
Given the wealth of accumulated knowledge on the typical reactivity and stereodifferentiation of condensation adducts from our orthoesters, we were also interested in studying the additions of nucleophiles to **7.110**. The carbocyclic nature of **7.110** and its analogous structural composition to the first compounds described in this dissertation (Cf. Chapters 2 – 4) further spurred our curiosity in attempting to probe their behaviour in comparison to those.

All these conjectures, of course, necessitated the validation of the initial condensation step. Once more (Cf. Chapter 6), there was no favorable literature precedent in our support. In fact, the Burnell report was clearly discouraging to our plans. It was thus with trepidation that we set to study the condensation reaction between **7.080** and our orthoesters.

7.5. Results and discussion

7.5.1. Condensation of silylated acyloins with functionalised orthoesters

Our initial efforts focused on model compound **7.080** and the 4-carbon chlorine-containing orthoester **2.034**. Some selected results are summarised in Table 7.1.



7.080 **2.034** **7.120**

Table 7.1

Entry	***7.080*** *:****2.034*** *:L.A.*	*Lewis acid*	*Conditions*	*Yield*
1	1 : 1 : 0.7	$ZnCl_2$	[0.2 M], 0ºC-rt, 4h	10%
2	1 : 1.6 : 0.7	$ZnCl_2$	[0.2 M], 0ºC-rt, 4h	30%
3	1 : 1.6 : 0.7	$ZnCl_2$	[0.2 M], rt, 16h	55%
4	1 : 1.6 : 0.7	$ZnCl_2$	[0.4 M], rt, 16h	75%
5	1 : 1.6 : 0.7	$ZnCl_2$	[0.6 M], rt, 16h	61%
6	1 : 1.6 : 0.7	$ZnCl_2$	[0.8 M], rt, 16h	43%
7	1 : 1.6 : 1.0	$BF_3.OEt_2$	[0.4 M], rt, 16h	<5%
8	1 : 1.6 : 1.0	TMSOTf	[0.6 M], rt, 16h	0%

NB: all reactions were run in DCM solution.

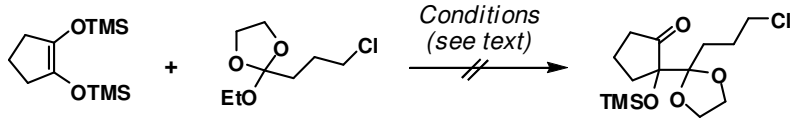
From the onset, we were encouraged to observe the formation of the condensation adduct **7.120**, even if the yields were low when the reaction was left for the usual lengths of time employed previously (Cf. Chapter 2). It was then realised that longer reaction times were actually beneficial to this coupling. This is in contrast with reactions of simple cyclic silyl enolethers with orthoesters such as **2.034**. Indeed, in those cases, the mixtures should be quenched after 4-5 hours reaction time to avoid decomposition of the remaining starting materials and the products.

Conversely, in these instances we have often detected the presence of unreacted **7.080** in the crude mixtures, indicating that this silyl enolether is more stable towards hydrolysis than the simple cyclic silyl enolethers that we have employed previously.

Pleasingly, after a fine-tuning of the reaction time, the concentration and the proportions of the reactants involved, we were able to reproducibly obtain yields between 70 and 80% of adduct **7.120**. Importantly, only low conversions or complex mixtures were obtained when other Lewis acids were employed (entries 7-8).

The significance of these results goes far beyond the simple attainment of yet another condensation reaction with our functionalised orthoesters. On one hand, to the best of our knowledge, it is the first example of the successful merging of an orthoester with a silylated acyloin *without further rearrangement*. We believe that the mild conditions of the procedure and the more robust nature of our orthoesters are responsible for this observation. On the other hand, it constitutes the first example of the creation of a quaternary center through condensation between a functionalised orthoester and a silyl enolether.

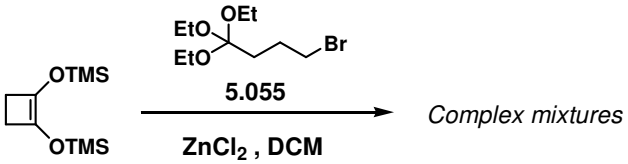
As a testimony to the exceptional character of this observation, the corresponding cyclopentene homologue **7.121** has thus far eluded all our efforts to form adduct **7.122** (Scheme 7.32). As often occurs in resilient reactions of orthoester **2.034**, under the mild conditions aforementioned ($ZnCl_2$, DCM, rt), little conversion to products occurs and under more forcing conditions (stronger Lewis acids, higher temperature) complex mixtures of decomposed materials are obtained.



7.121 **2.034** **7.122**

Scheme 7.32

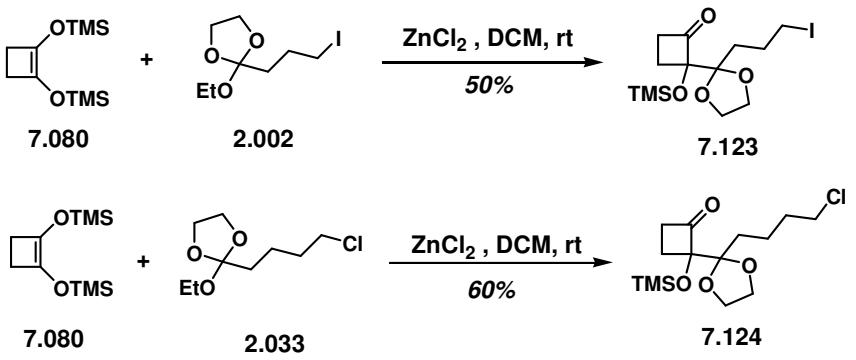
Further experiments with cyclobutene **7.080** enabled a clearer definition of its reactivity. As expected based on the Burnell precedent, reaction with an "open" orthoester such as **5.055** led only to degradation products, even if the zinc-chloride procedure was employed (Scheme 7.33).



7.080

Scheme 7.33

In contrast, **7.080** reacted smoothly with orthoester derivatives **2.002** and **2.033**, affording the corresponding β-ketoketals **7.123** and **7.124** in moderate to good yields (Scheme 7.34).



Scheme 7.34

These results allow us to qualitatively position silyl enolether **7.080** at the last place on an empiric reactivity scale of the different silyl enolethers employed throughout this dissertation. Indeed, **7.080** appears to be less reactive than TMSOF (the runaway "champion" on such a scale), TBSOP and the simple cyclic silyl enolethers previously investigated by our laboratory. This probably stems from the fact that, upon condensation, a quaternary center is created (as evoked previously), which might severely counter the obvious increase in double-bond electron density. Indeed, the two oxygen substituents are likely to significantly enhance the reactivity of **7.080** on purely electronic grounds.

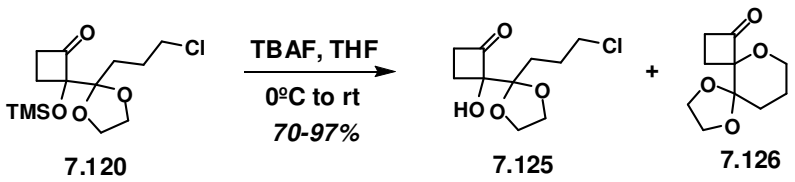
As the corolary to these assumptions, we believe that the main reason underlying the fact that **7.080** reacts at all is the considerable release in ring-strain associated with the transition cyclobutene (**7.080**) – cyclobutanone

(**7.120**). Once this driving force is lost, as for **7.121**, reactivity drops to near zero. Further comparative (and quantitative) considerations on the reactivity of all the silyl enolethers employed during our work shall be done in the closing Chapter of this manuscript.

7.5.2. Ring-closure studies

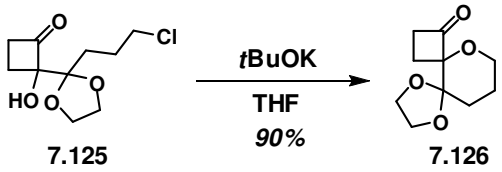
The β-ketoketal **7.120** has an interesting concatenation of functional groups. In its framework are installed a cyclobutanone (whose exceptional reactivity we have already addressed), a silylated alcohol, a dioxolane ketal and a halide moiety. In connection with our proposed strategy, we intended to effect a desilylative ring-closure to a cyclic ether.

Deprotection of silyl ethers is commonly achieved with TBAF as a fluoride source. When we treated **7.120** with 1.1 to 3 equivalents of TBAF, the major product obtained was always the alcohol **7.125**. Nevertheless, in some instances small amounts of the coveted ether **7.126** were also detected and isolated. Unfortunately, as the amounts of TBAF were raised further, a number of unidentified polar by-products appeared, signaling the existence of unproductive reaction pathways (*e.g.*, the semipinacolic ring-contraction of **7.120** to a cyclopropanol derivative).



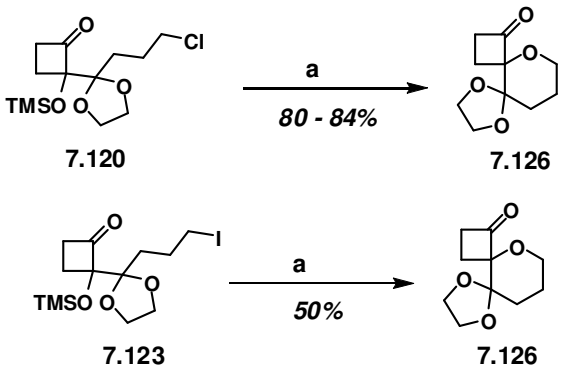
Scheme 7.35

We then studied the ring-closure of isolated alcohol **7.125**. It was found that *t*BuOK, in dry THF, was the reagent of choice for effecting the proposed ring closure (Scheme 7.36). Other bases, such as NaH, NaHMDS, KHMDS or K_2CO_3 provided worse results.



Scheme 7.36

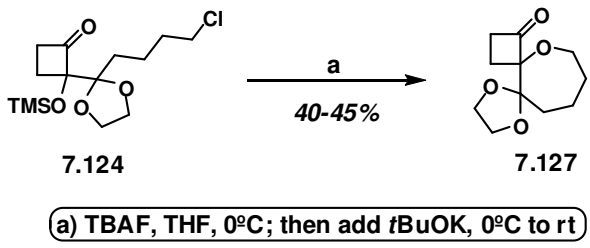
Since the deprotection step and the subsequent cyclisation were performed in the same solvent, we wondered whether the whole sequence could be done in a single vessel. Gratifyingly, this "one-pot" deprotection/cyclisation was indeed possible and the overall yields for the transformation of **7.120** into **7.126** averaged 80%. Interestingly enough, when the same sequence was applied to the iodine-containing derivative **7.123,** lower yields of spirocyclic ether **7.126** were obtained (Scheme 7.37).



Scheme 7.37

This observation is reminiscent of the results of Dr. Jean-Christophe Vanherck on the spiroannelation of simple, cyclic silyl enolethers (Cf. Chapter 2). Indeed, in specific cases Dr. Vanherck noticed that the iodinated β-ketoketals actually provide lower yields of the spiroannelated product than their chlorinated counterparts. It is possible that, under these strongly basic conditions (stoichiometric amounts of *t*BuOK and/or KOH), elimination of HI might take place to form some olefinic by-products (*vide infra*). For this reason, we continued our investigations using the chlorinated adducts.

Remarkably, the 5-carbon tether on **7.124** could also be induced to cyclise to a spiro-oxepane **7.127**, albeit in lower yield. This represents a rare example of the ring-closure of an oxepane ring through a direct S_N2-reaction. It is noteworthy that this two-step sequence provides an average yield of 40% for oxepane **7.127** (Scheme 7.38).



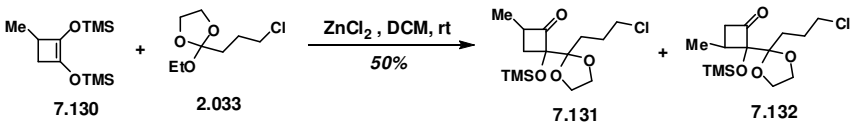
7.124 7.127

a) TBAF, THF, 0ºC; then add *t*BuOK, 0ºC to rt

Scheme 7.38

It is important to mention that, for the sake of simplicity, the whole sequence from 1,2-bis(trimethylsilyloxy)cyclobutene **7.080** and the functionalised orthoesters **2.033** or **2.034** until the spirocyclic ethers **7.126** and **7.127** can be performed without the isolation of any intermediates. When this is the case, the overall yields correlate well (with deviations of *ca.* 10-15%) with the yields for each individual step.

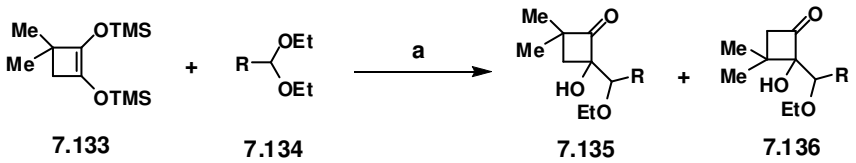
Yearning to broaden the scope of this reaction, we sought to use substituted analogues of **7.080**. The methyl-substituted **7.130**, readily prepared by acyloin condensation of the corresponding succinate diester, was probed. Surprisingly, we obtained a nearly inseparable mixture of products in moderate yield, which at first we thought to be the diastereoisomers of **7.131**. Further transformations of this mixture and analysis of the products showed that we had actually obtained two *regioisomeric* condensation adducts, **7.131** and **7.132**!



7.130 2.033 7.131 7.132

Scheme 7.39

This unexpected result is in fact precedented in the literature. In his most recent publication on the geminal acylation using aldehyde acetals, Burnell reports obtaining mixtures of regioisomers upon reaction of *gem*-dimethylated acyloin **7.133** (Scheme 7.40).[277]



7.133 7.134 7.135 7.136

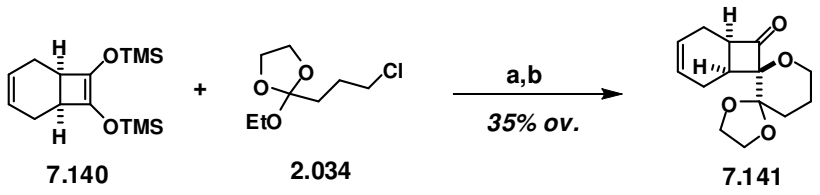
a) $BF_3.OEt_2$, DCM

Scheme 7.40

We believe (in agreement with the authors' considerations) that the formation of the least-favored isomers **7.132** and **7.136** occurs from the initially generated, kinetically prefered **7.131/7.135** through retro-aldol/aldol reaction. Indeed, we have previously observed, in specific cases, that the products of condensation of silyl enolethers with our orthoesters are prone to retro-aldol cleavage (Cf. Chapter 6). These disappointing results and the inability to preparatively separate the regioisomeric products led us to turn our attention to *symmetrical* silylated acyloins, such as **7.140**.

[277] Cf reference 271a.

In the event, condensation of **7.140** with orthoester **2.034** occurred uneventfully. For convenience and to maximise the yield, we found it better to defer purification to a later stage. Interestingly, we discovered that, upon treatment of the crude condensation mixture with TBAF in cold THF, a new compound was formed which proved to be the spirocyclic ether **7.141** (Scheme 7.41)!

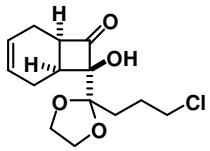


7.140 **2.034** **7.141**

a) $ZnCl_2$, DCM; b) TBAF, THF, 0ºC to rt

Scheme 7.41

Interestingly, **7.141** was formed as a single diastereoisomer possessing the configuration shown in the Scheme. This relative arrangement (supported by nOe studies) is consistent with an approach of the incoming orthoester from the less-shielded *exo*-face, thus irreversibly fixing the stereochemistry of the newly formed quaternary center as shown. Of further interest is the facile cyclisation of the intermediately formed β-ketoketal **7.142**, without recourse to the basic conditions of our one-pot protocol.



7.142

Scheme 7.42

7.5.3. Having fun with cyclobutanones: ring-expansions and regressions for all tastes

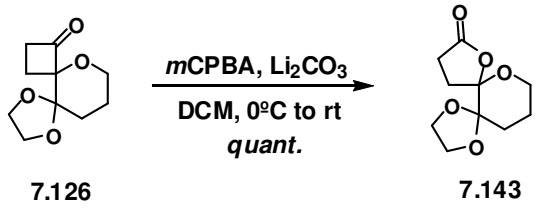
With an access to a number of condensation adducts and their ring-closure products in hand, we then considered the second stage of our plan, namely the possibility to exploit the rich chemistry of cyclobutanones (especially concerning ring-expansions, regressions and/or rearrangements).

Our first efforts concentrated on the Baeyer-Villiger oxidation. In this classical reaction, of which we have already witnessed the power (Scheme 7.21), migrating aptitudes are directly related to the ability to stabilise an incipient cationic center.[278] In the case of our spiroethers, we had some concerns that the combined electron-withdrawing effect of the dioxolane and the spiroether oxygen might contribute to (at least partially) reverse the regioselectivity.

As matters transpired, our concerns were unfounded. Treatment of **7.126** with *m*CPBA in the presence of Li_2CO_3, smoothly afforded the spirolactone **7.143** in quantitative yield (Scheme 7.43). The completely selective migration of the most substituted center was unambiguously

[278] Renz, M.; Meunier, B. *Eur. J. Org. Chem.* **1999**, 737

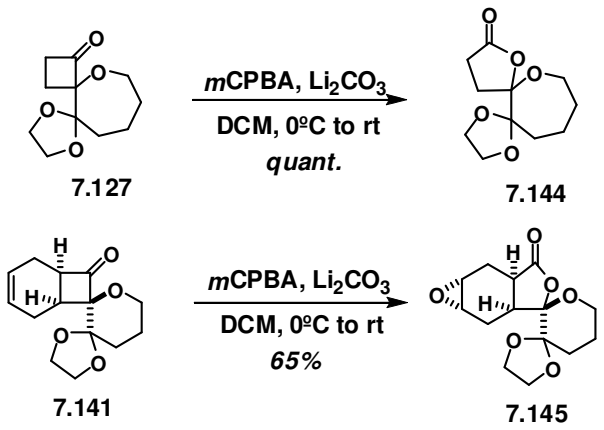
confirmed by both spectroscopic analysis and subsequent synthesis of the other regioisomer (*vide infra*).



7.126 **7.143**

Scheme 7.43

Excited at the possibility of obtaining spiroketal-lactones such as **7.143** through this highly effective reaction, we then attempted its replication on the other spiroethers. Pleasingly, the oxepane **7.127** readily participated in this ring-expansion process to afford the corresponding spiroketal-lactone **7.144** in similar yield (Scheme 7.44). Application of this protocol to the fused bicyclic **7.141** led to ring-expansion, accompanied by double-bond epoxydation, to provide **7.145** with complete diastereocontrol. Remarkably, compound **7.145**, bearing a total of 5 non-contiguous stereocenters, is produced with complete diastereocontrol in only three steps from simple, achiral substances (Scheme 7.44).

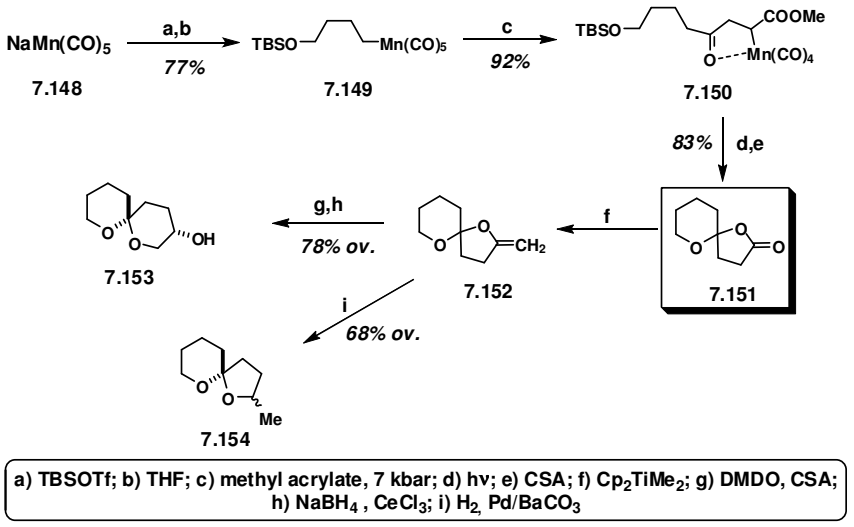


Scheme 7.44

It should be noted that the *m*CPBA protocol provided the best results. Attempts at inducing a similar ring-expansive rearrangement with magnesium monoperphtalate (MMPP) or hydrogen peroxyde/sodium hydroxide led to either recovered starting material or very low conversions.

The resemblance of the compounds thus obtained and spiroketals is striking. In particular, Philip DeShong has employed a similar spirolactone (**7.151**) in the preparation of a number of naturally occuring pheromones.[279] As depicted in Scheme 7.45, the method employed by DeShong was completely different from our orthoester-based procedure.

[279] DeShong, P.; Rybczynski, P. J. *J. Org. Chem.* **1991**, *56*, 3207



Scheme 7.45

The sequence depicted above takes advantage of the well-known and elegant (though stoichiometric in nature) chemistry of pentacarbonylmanganese alkyl complexes. Thus, ring opening of THF by the *in situ* generated [TBS-$Mn(CO)_5$] complex leads to the unstable alkyl manganese **7.149** in good yield. When such complexes are treated with electrophiles, they readily undergo tandem CO-insertion/carbometallation. In this case, the action of methyl acrylate under high pressure leads to the manganacycle **7.150** in good yield. Photodemetallation of **7.150**, followed by treatment with acid, leads to formation of the spirolactone **7.151** through TBS-deprotection and domino cyclisation.

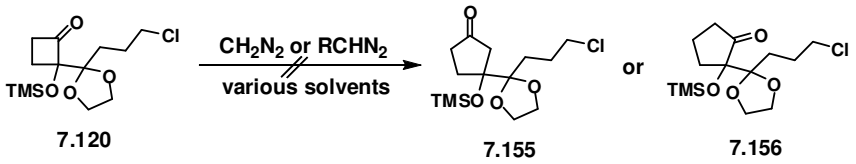
The spirolactone **7.151** was actually a key-intermediate to access different spiroketal pheromones. Methylenation of the lactone carbonyl was achieved with the Petasis reagent, and the ensuing vinyl ether **7.152** can be reduced to **7.154**, a pheromone of the common wasp (naturally occuring as a

mixture of diastereomers). On the other hand, epoxidation and skeletal reorganisation in acidic conditions leads to a ketone, which upon reduction furnishes **7.153**, one of the main pheromones found in *Dacus oleae*, the fruit fly.

One might envisage intercepting the synthetic route of DeShong by simple reductive removal of the dioxolane substituent in **7.143** (cf. the final section of this chapter). Nevertheless, the benefit of the added functionalities of **7.143** ensure that more rewarding applications of these spirolactones might be within reach.

The following goal was the examination of carbon-insertions on either the condensation products or their derived spiroethers. Given the much more subtle factors at play, as demonstrated previously by Hegedus for the diazomethane insertion (Scheme 7.15 and Scheme 7.16), we expected a particular reactivity in the case of our compounds.

At first, we concentrated on the β-ketoketal **7.120**, for a series of reasons. First, we didn't know whether this compound might display a different regioselectivity in comparison to its spirocyclic analogue **7.126**. Second, the possible ring-expanded products **7.155** and **7.156** are interesting in their own right. **7.155** might be dehydrated to an enone onto which many interesting reactions should be possible. Conversely, **7.156** would indeed be the product of direct condensation between **7.121** and orthoester **2.034**, a reaction which, as mentioned previously, has thus far eluded our efforts.

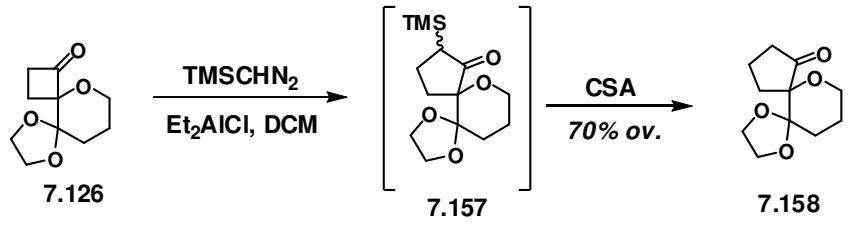


7.120 7.155 7.156

Scheme 7.46

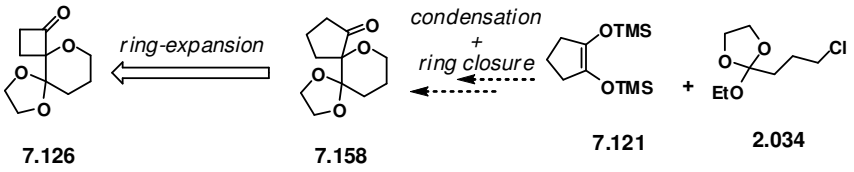
Unfortunately, treatment of **7.120** with diazomethane and other diazoalkanes, in different solvents, in the presence or absence of Lewis acids, never led to the coveted cyclopentanones **7.155** or **7.156** (Scheme 7.46). Instead, we were surprised to observe the rapid desilylation of **7.120** to is corresponding alcohol **7.125** and, in some cases, to the spirocyclic ether **7.126**.

Disappointed with these initial setbacks, and although one might hypothesize that the introduction of different alkoxy residues on **7.120** (conceptually viable on a substance such as **7.125**) could allow the desired ring-expansions to take place, we elected to maintain our direct approach and decided to study the one-carbon enlargement of **7.126**. After many unsuccessful experimentations with diazomethane, we were finally rewarded by the use of a protocol involving reaction of **7.126** with trimethylsilyl-diazomethane, followed by hydrolysis of the ensuing α-silylketones (Scheme 7.47).



Scheme 7.47

As shown in Scheme 7.47, this procedure allowed finally the one-carbon expansion of our cyclobutanone **7.126**. Importantly, the only regioisomer detected was compound **7.158**, thus reinforcing the general tenet that dictates preferential migration of the less-substituted carbon atom upon ring-expansion. We presume that the higher stability and thus longer lifetime of $TMSCHN_2$ when compared to diazomethane, may be at the origin of this positive result. Finally, one can readily ascertain that compound **7.158** is the product which would have originated from 1,2-bis(trimethylsilyl)cyclopentene **7.121** (Scheme 7.48) by sequential condensation and cyclisation.

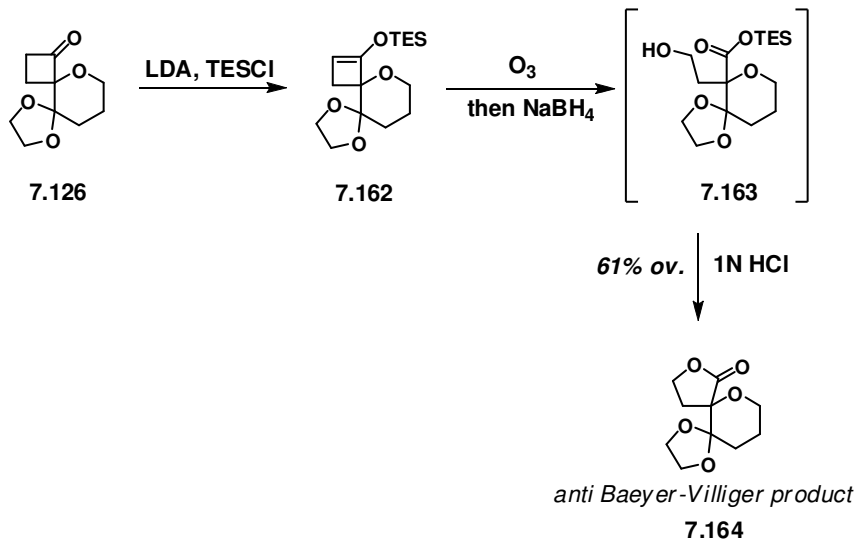


Scheme 7.48

At this stage, selective carbon- and oxygen-insertions had been realised onto ketone **7.126**. We were intrigued, however, by the possibility of

effecting the same ring-enlargement reactions but with *opposite* regioselectivity.

The direct, one-step "anti-Baeyer-Villiger" expansion of a ketone is hitherto an unknown reaction. However, the same result can be accomplished through a simple, multi-step procedure.[280] As shown in the Scheme below, this sequence begins with the formation of the silyl enolether of ketone **7.126**. It should be noted that the TMS-analogue of **7.162** was extremely labile (as reported for other TMS-silyl enolethers of cyclobutanones), in contrast to higher homologues.



Scheme 7.49

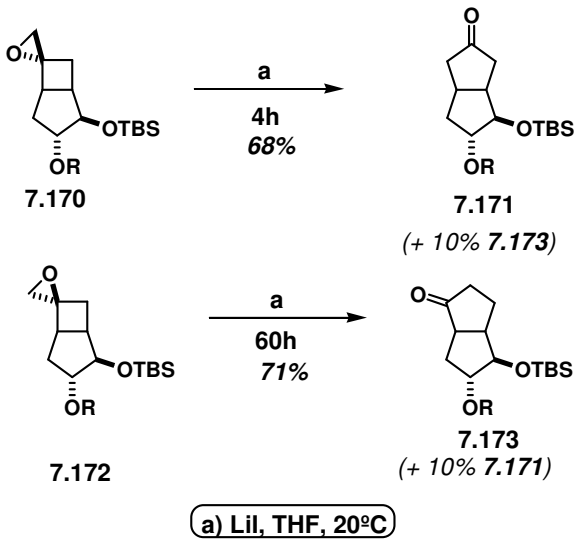
Ozonolysis of this silyl enolether, followed by $NaBH_4$-mediated reductive workup of the ozonide, transiently afforded the mixed alcohol/silyl

[280] Nemoto, H.; Tanabe, T.; Fukumoto, K. *J. Org. Chem.* **1995**, *60*, 6785

ester **7.163**. Acidification of the reaction mixture with 1N HCl finally liberated the γ-hydroxycarboxylic acid, which spontaneously cyclised to the observed butyrolactone **7.164**. This procedure can be performed without isolating any of the intermediates and the "anti-Baeyer-Villiger" lactone **7.164** was obtained in a good yield of 60%, taking into account the number of operations involved.

As for effecting a reverse-diazo methylene insertion into **7.126**, we turned our attention to the Lewis-acid rearrangement of spiroepoxides into cycloalkanones, reported as early as 1982 by Krief and co-workers.[281] However, Hart and Comte seemed to suggest that the outcome of this reaction might depend upon the stereochemistry of the starting spiroepoxide.[282] In their 1985 communication, they reported that the α-epoxide **7.170** rearranged smoothly to ketone **7.171** when treated with lithium iodide in THF at room temperature. Conversely, the β-epoxide **7.172** slowly rearranged under the same conditions to produce mainly the regioisomeric ketone **7.173**. These spiroepoxides can be readily prepared from the corresponding cyclobutanones *via* the Corey-Chaykovsky reaction.[283]

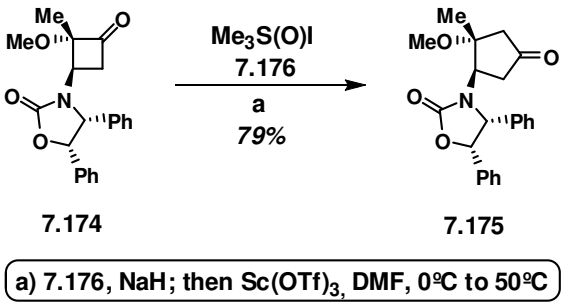
[281] Halazy, S.; Krief, A. *J. Chem. Soc., Chem. Commun.* **1982**, 1200
[282] Hart, T. W.; Comte, M.-T. *Tetrahedron Lett.* **1985**, *26*, 2713
[283] Corey, E.J. ; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353



Scheme 7.50

More recently, Hegedus developed a one-pot procedure for spiroepoxide formation and rearrangement.[284] Thus, addition of the sulfoxonium ylide, prepared by deprotonation of **7.176**, to cyclobutanone **7.174** provides the corresponding spiroepoxide. Rearrangement of this *in situ*-generated epoxide with the aid of scandium triflate as the Lewis acid, finally affords the cyclopentanone **7.175** in excellent yield.

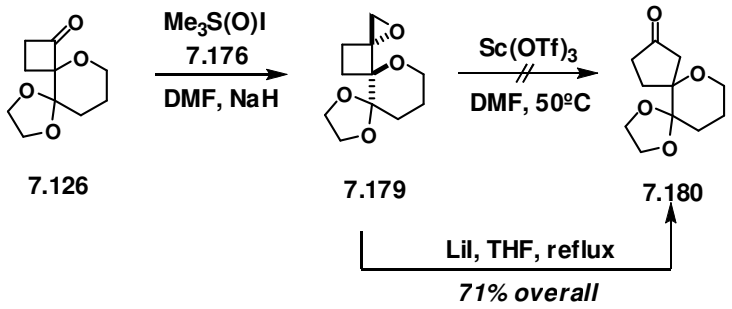
[284] Brown, B.; Hegedus, L. S. *J. Org. Chem.* **2000**, *65*, 1865



Scheme 7.51

This procedure has many remarkable features. On the one hand, it delivers products which are regioisomeric to the conventional diazomethane protocol. On the other hand, the compound **7.175** is a β-alkoxyketone. The fact that no elimination takes place further testifies of the mild conditions involved.

We then proceeded to apply these conditions to our cyclobutanone **7.126** (Scheme 7.52). In agreement with Hegedus' results, spiroepoxide formation took place smoothly upon treatment with trimethylsulfoxonium ylide. However, no rearrangement occurred when $Sc(OTf)_3$ was added to the reaction mixture, and only a single diastereomeric spiroepoxide, presumed to be **7.179**, was recovered. When this epoxide was dissolved in THF and lithium iodide added, a slow rearrangement ensued which could be driven to completion by heating the mixture to reflux.



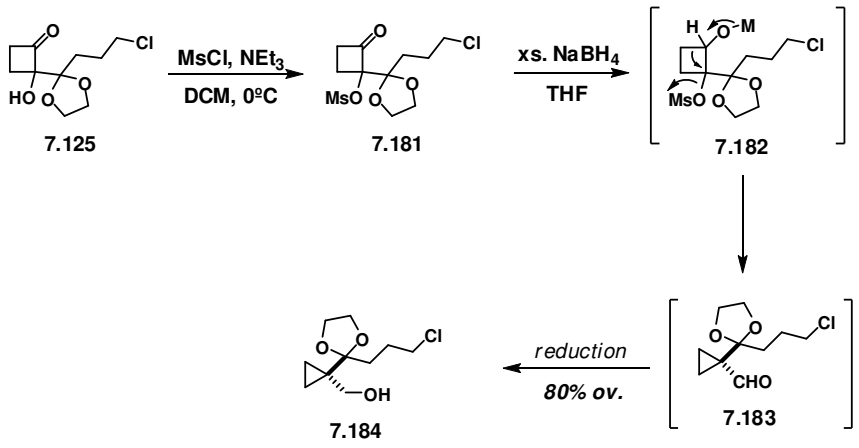
Scheme 7.52

We find this reaction to be intriguing. Indeed, Hegedus proposes the transient formation of an iodohydrin, by Lewis acid-assisted opening of the epoxide – hence the addition of scandium triflate, although Li^+ appears to be sufficiently acidic in selected cases to trigger a similar process. In Hegedus' case, though, it is the residual NaI formed during deprotonation of **7.176** which acts as the source of iodide. Subsequent rearrangement of this epoxide should then provide the final products.

What is particularly interesting is the complete control of regiochemistry in the migration, and its opposite nature to the diazoalkane case. We believe that stereoelectronic factors might be at play, for instance, in the case of the α- and β-epoxides of Hart and Comte. If one considers the *in situ* formation of iodohydrins as intermediates, then the observed regiochemical outcome might be the result of preferential antiperiplanar migration to effect S_N2-like backside displacement. In the substrates of Hegedus and our own, however, the nature of the oxygenated substituents that decorate the cyclobutane ring could be less innocent than it seems (*vide infra*).

Throughout the literature survey proposed at the beginning of this Chapter, we have seen a number of ring-enlargement reactions and an example of Favorskii-like regression to a cyclopropane. We wondered wether such a regression would be possible in our adducts, and the potential of alcohol **7.125** for this endeavour was tested (Scheme 7.53). As we have already seen, compound **7.120** can be deprotected to the alcohol **7.125** and cyclised in one-pot. Importantly though, the intermediate alcohol **7.125** can be isolated in good yields if desired.

As a demonstration of synthetic usefulness, we verified that treatment of this tertiary alcohol with mesyl chloride and triethylamine in cold dichloromethane cleanly delivered the corresponding mesylate **7.181** as shown by TLC and crude NMR analysis (Scheme 7.53).



Scheme 7.53

Solvent exchange for THF and addition of excess sodium borohydride triggered a cascade sequence, as depicted (Scheme 7.53). Following rapid

reduction of the ketone carbonyl, the resulting complex alkoxide **7.182** presumably underwent contractive rearrangement to aldehyde **7.183**. Given the presence of excess borohydride in the medium, this aldehyde was finally reduced to afford cyclopropylmethanol **7.184** in excellent yield. One might easily envisage using other nucleophiles to trigger similar ring-contractions, leading to different oxidation states and substituents in the cyclopropyl ring. The relevance of cyclopropanes in synthesis is, of course, a well-established reality.[285]

7.5.4. Further functionalisation of adducts

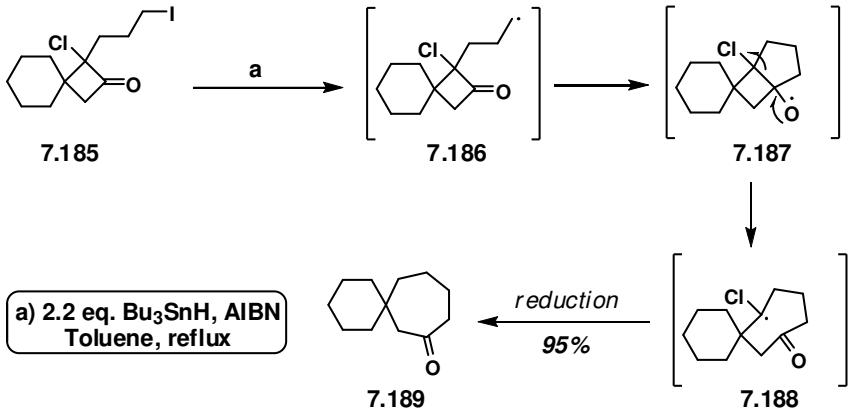
In this Section, we will briefly cover the reactivity of adducts such as **7.120**, mostly their response to incoming nucleophiles.

In connection with the rearrangements described in the previous subsection, Dowd has reported a free-radical ring-expansion reaction of ω-iodocyclobutanones to provide a variety of ring-expanded systems.[286] For example, the α-chlorospirocyclobutanone **7.185** responded to treatment with tributyltin hydride by undergoing the series of reactions shown in Scheme 7.54.

Initial scission of the carbon-iodine bond precedes attack onto the cyclobutanone carbonyl group. Fragmentation of the ensuing oxygen-centered radical **7.187** leads to the ring-enlarged radical **7.188**. Reduction of

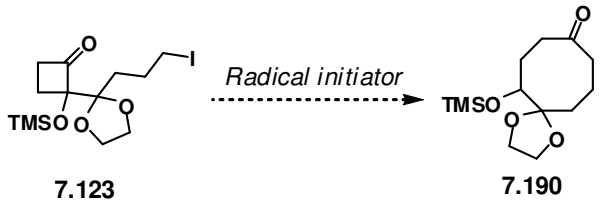
[285] For a review on the synthesis of cyclopropanes, see: Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977
[286] Zhang, W.; Dowd, P. *Tetrahedron Lett.* **1992**, *33*, 3285

this radical and further reduction of the carbon-chlorine bond, finally provides **7.189**.



Scheme 7.54

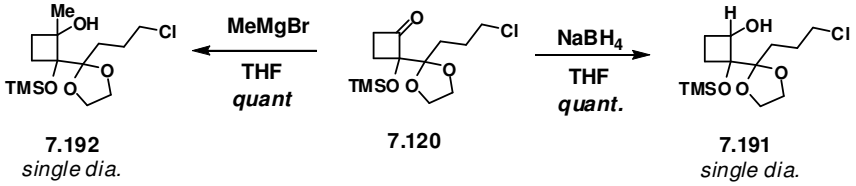
Given the proliferation of examples similar to the one shown above, we wondered if a similar reaction might take place on our iodinated adduct **7.123** (Scheme 7.55). Unfortunately, upon exposure to different radical initiators, including not only Bu_3SnH but also the previously employed TTMSS, only complex mixtures of products could be obtained.



Scheme 7.55

Although further studies would be required, we believe that the system chosen might not be ideally suited for such a reaction. For instance, the tether length connecting the putative initial radical and the ketone carbonyl is one unit longer than the wide majority of successful examples mentioned in the literature. Furthermore, the eventual sensitivity of the siloxy substituent to the reaction conditions shouldn't be underestimated. Finally, the sequence bicycle formation/fragmentation might still be achieved in two discrete steps, by using the methodology described in the work of Dr. Ali Ates and Dr. Corinne DeDobbeleer.[287]

Returning to chlorinated adduct **7.120**, we briefly examined its response to the addition of nucleophiles. Interestingly, both $NaBH_4$ and MeMgBr reacted smoothly with **7.120**, affording adducts **7.191** and **7.192** as *single stereoisomers*.



7.192
single dia.

7.120

7.191
single dia.

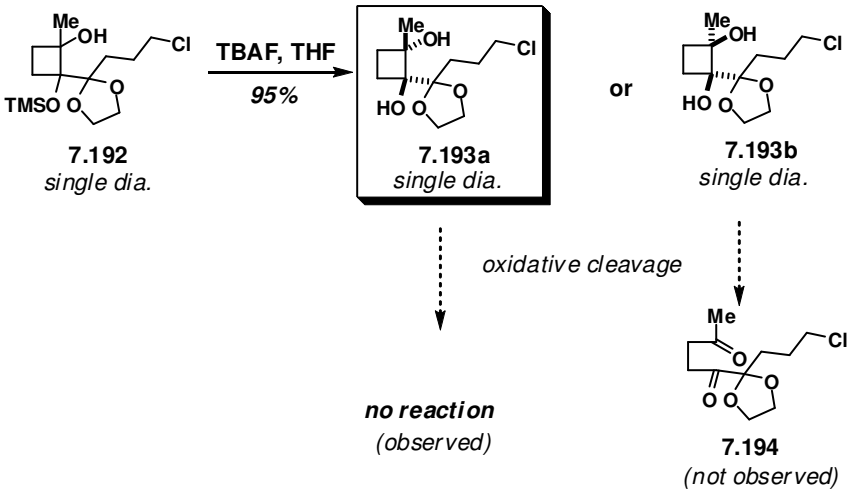
Scheme 7.56

The excellent diastereoselectivity observed in these reactions is absolutely remarkable, since these are two of the smallest nucleophiles one can add to a carbonyl group! We further confirmed that no silyl migration

[287] (a) Ates, A. *Ph.D. Thesis,* UCL, **1999**; (b) DeDobbeleer, C. *Ph.D. Thesis*, UCL, **2005**

had taken place: the OH- hydrogen resonates as a doublet in **7.191** (thus confirming its coupling with the newly added hydrogen), and a weak interaction could be detected between the OH- proton of **7.192** and the methyl substituent's hydrogens in the COSY-spectrum.

As for the stereochemical assignment, it is not surprising that we anticipated a return of the "dioxolane-effect" that punctuates nearly every Chapter of this document. Although nOe studies were not conclusive, we sought chemical evidence for an eventual "anti-dioxolane-effect". Deprotection of the silyl ether in **7.192** was readily accomplished with TBAF. The diol **7.193**, once again, was a diastereomerically pure substance.

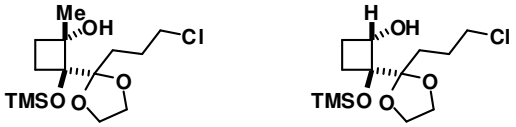


Scheme 7.57

We reasoned that a means to distinguish between both possible configurations **7.193a** and **7.193b** could reside in the intrinsic propensity of *syn*-diols such as **7.193b**, particularly when embedded into rigid cyclic

frameworks, to undergo cleavage when exposed to an oxidant such as $NaIO_4$. This would generate an achiral diketone **7.194**. Of course, the product arising from a presumed "dioxolane-effect", diol **7.193a**, should remain inert to the action of such a reagent.

In the event, neither $NaIO_4$ nor the combined action of $NaIO_4/H_5IO_6$ did affect the diol obtained by desilylation of **7.192**, and we quantitatively recovered the starting material in these attempts. This result, though not unambiguous, greatly accomodates our assumption that the compound obtained was indeed **7.193a**. Furthermore, the fact that this is in strict agreement with the pervasive "dioxolane-effect" lends further credit to the stereochemistry proposed. We thus believe that the alcohols obtained by nucleophilic attack bear the stereochemistries depicted in Scheme 7.58.



7.192 **7.191**

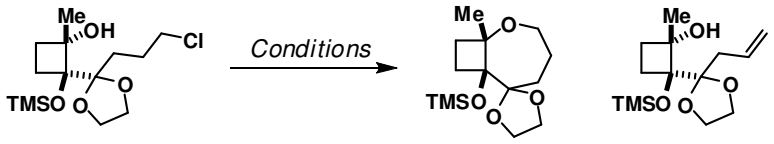
Scheme 7.58

Although molecular modeling studies (using the Chem3D software package) tend to suggest that the dioxolane substituent might hinder one of the faces of the ketone carbonyl of **7.120**, a more skeptical analysis reveals that this cannot *per se* explain the exquisite diastereoselectivity of addition of $NaBH_4$. The reader might recall that this same reducing agent was almost unable to discriminate between both carbonyl faces in a rigid, spirocylic compound such as **2.005** (Cf. Chapter 4). Recourse to DiBALH was necessary to achieve complete stereoselection. Indeed, in such a stringent

context, the stereoselectivity would normally be expected to be higher than in a conformationally mobile compound such as **7.120**. Furthermore, the enhanced kinetic reactivity of the cyclobutanone carbonyl and the relatively high temperature at which the reaction is conducted (0ºC to room temperature) would likely contribute to worsen the stereochemical outcome even further.

Although additional studies would surely be required, it is possible that the adjacent –OTMS substituent might direct the approach of the incoming nucleophiles by chelation. Though chelated reductions of α- or β-hydroxy- and alkoxy-ketones are usually performed with reagents other than $NaBH_4$, a synergistic weak chelation and "dioxolane-effect" would be enough to explain the observed stereochemical preference.

We then wondered if a ring-closure to a bicyclic oxepane would be possible starting from compound **7.192** (Table 7.2).



7.192 **7.195** **7.196**

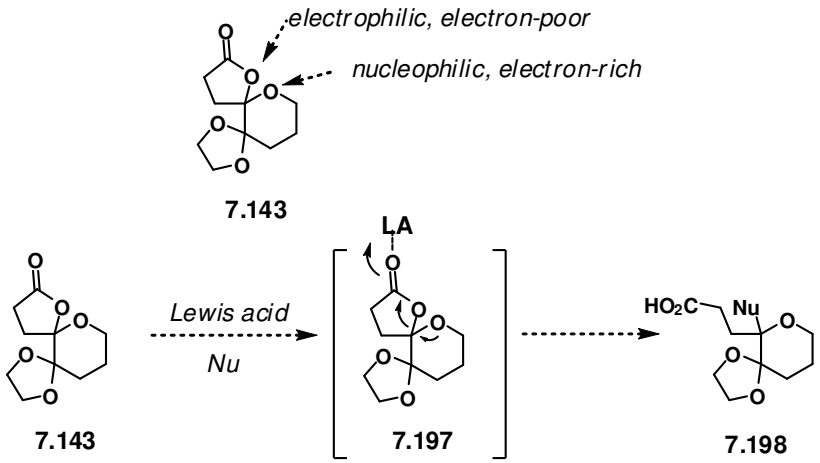
Table 7.2

Entry	*Conditions*	*Result*
1	*t*BuOK (1 eq), THF	60% **7.192** + 28% **7.196**
2	*t*BuOK (3 eq), THF	84% **7.196** + 5% **7.195**
3	*t*BuOK (5 eq), THF	47% **7.196** + 20% **7.195**
4	NaHMDS (1 eq), THF	**7.192**
5	LiHMDS (1 eq), THF	**7.192**
6	NaH (1.5 eq), THF	**7.192** + Degradation

Interestingly, the treatment of **7.192** with *t*BuOK mainly elicited elimination of HCl to generate olefin **7.196**. In the best case (entry 3), the oxepane **7.195** could be formed in 20% yield but significant decomposition took place (note that the mass balance is considerably below 75%). It is noteworthy that the simple fact that the cyclic ether **7.195** was formed at all further supports our stereochemical assignment, which places the –OH group *syn* to the ω-chlorinated tether.

On the other hand, if 3 eq. *t*BuOK were employed, reproducible formation of the alkene **7.196** was observed in good yields (entry 2). This alkene, though an undesired product, could prove useful for subsequent annelating processes.

Finally, we investigated further the reactivity of the Baeyer-Villiger lactones, obtained in three steps from 1,2-bis(trimethylsilyloxy)cyclobutene **7.080**. These spiroketal-lactones, typified by **7.143**, actually contain two very different oxygens in their spiroketal framework (Scheme 7.59).



Scheme 7.59

If the tetrahydropyran oxygen is electron-rich, the oxygen of the lactone moiety is obviously "electron-poor" (in a relative sense) due to delocalisation of its electrons in the carbonyl function. In fact, it might be anticipated that a Lewis acid would preferentially interact with the lactone carbonyl, which could be the best compromise between steric accessibility and Lewis basicity. Such an interaction would then conceivably trigger spiroketal opening, and capture of the incipient oxonium by an incoming nucleophile could lead to **7.198**.

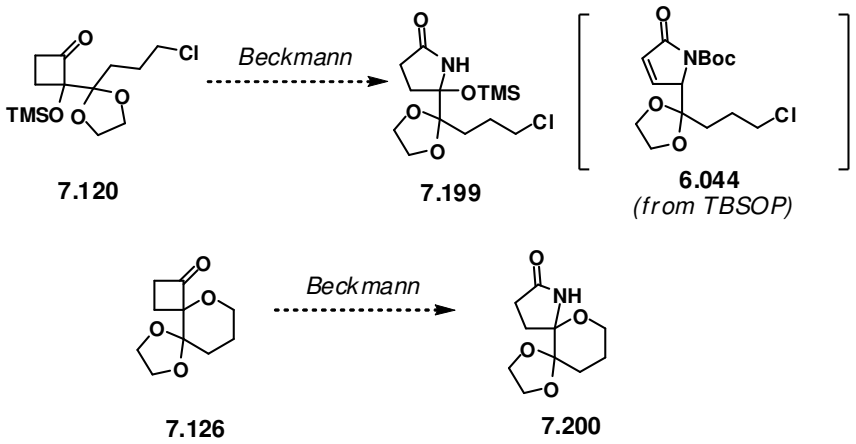
In the event, we were frustrated in all our attempts to effect such a reaction. Different Lewis Acids, from BF_3 to $TiCl_4$ or $ZnCl_2$ were assayed in

model reactions with allyltrimethyl silane or allyltributyl tin as the nucleophiles. Starting materials were recovered in most of the occasions.

Having tested nearly all the representative rearrangements and ring-expansions of cyclobutanones on our substrates, one might wonder what might be left to try at this stage. The following subsection shows that "behind the smallest of doors may lay the biggest of palaces".

7.5.5. The Beckmann rearrangement

Our personal appreciation for nitrogen-containing substructures made an evaluation of the Beckmann rearrangement mandatory. As we had previously seen, the propensity of cyclobutanones to undergo Beckmann ring-expansion to γ-lactams meant that we could actually intercept the results of the TBSOP project departing from completely different starting materials (Scheme 7.60).



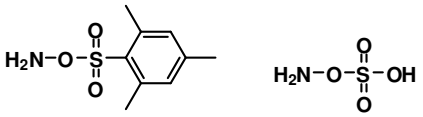
Scheme 7.60

Although the Beckmann rearrangement is not controlled by the same parameters as its Baeyer-Villiger counterpart, migration of the most substituted center usually occurs. In fact, the decisive factor is the geometry of the intermediate oxime. Since migration of the *anti*-substituent usually predominates and since steric factors tend to dictate the oxime geometry, the results are usually identical to the Baeyer-Villiger situation (a case of being right for the wrong reasons!).[288]

Thus, direct nitrogen insertion onto **7.120** should lead to α-siloxylactam **7.199**. This lactam is reminiscent of the TBSOP condensation product **6.044**. On the other hand, if the nitrogen insertion step would be performed on the ring-closed **7.126**, spiroaminal **7.200** might be produced. Since spiroaminals are interesting and exotic features of only a few natural products, we hoped that this could be an interesting access route for these subunits.

[288] Donaruma, L.G. ; Heldt, W.Z. *Org. React.* **1960**, *11*, 1

The Beckmann rearrangement classically involves two discrete steps; formation of an oxime and its rearrangement to the desired products. Almost 30 years ago, however, Tamura reported the use of specific O-substituted hydroxylamine derivatives, such as mesitylenesulfonylhydroxylamine **7.201** (MSH, Scheme 7.61).[289] These hydroxylamines are "second-generation" versions of hydroxylamine-O-sulfonic acid **7.202**. Indeed, such reagents, bearing suitable leaving groups at the oxygen atom, are able to mediate oxime formation and *in situ* dehydration with concomitant rearrangement, thus obviating the need for two steps.



MSH
7.201

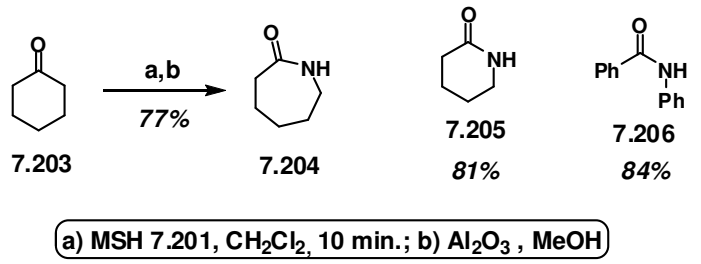
7.202

Scheme 7.61

We have already seen reagent **7.201** in action (Scheme 7.22), in Greene's synthesis of modified prostaglandin analogues.

Other ketones can also be conveniently converted to the corresponding amides or lactams using this reagent in good yields (Scheme 7.62).[289] Following brief reaction with MSH **7.201** in cold dichloromethane, the intermediate oxime is directly rearranged by adding basic alumina. Filtration (and/or usual post-reaction treatment) usually delivers the products in good purity and high yields.

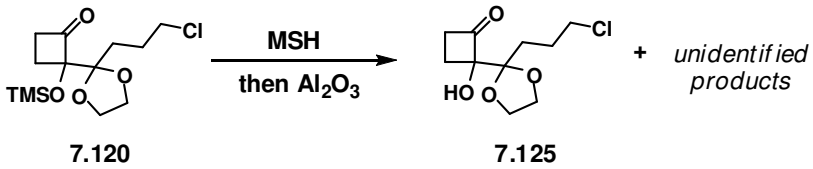
[289] Tamura, Y. ; Minamikawa, J. ; Ikeda, M. *Synthesis* **1977**, 1



Scheme 7.62

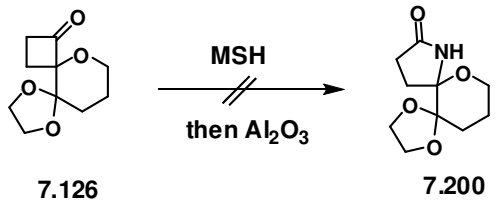
Given the efficiency of MSH, we thus decided to test it on our cyclobutanone adducts.

Preparation of this reagent (not available commercially) was uneventful, following Tamura's procedure.[289] When we treated **7.120** with MSH, followed by filtration through an alumina pad, we observed the rapid consumption of the starting cyclobutanone, but mainly to form O-desilylated product **7.125** and small amounts of unidentified compounds (Scheme 7.63). It seems that once again, the sensitivity of the –OTMS substituent precluded the successful attack of the hydroxylamine derivative on the cyclobutanone carbonyl, as we had already witnessed in the attempted diazoalkane ring-expansions.



Scheme 7.63

We then turned our attention to the ring-closed analogue **7.126**. In spite of numerous trials under different conditions, we always recovered mostly the starting spirocycle **7.126** upon exposure to Tamura's conditions.

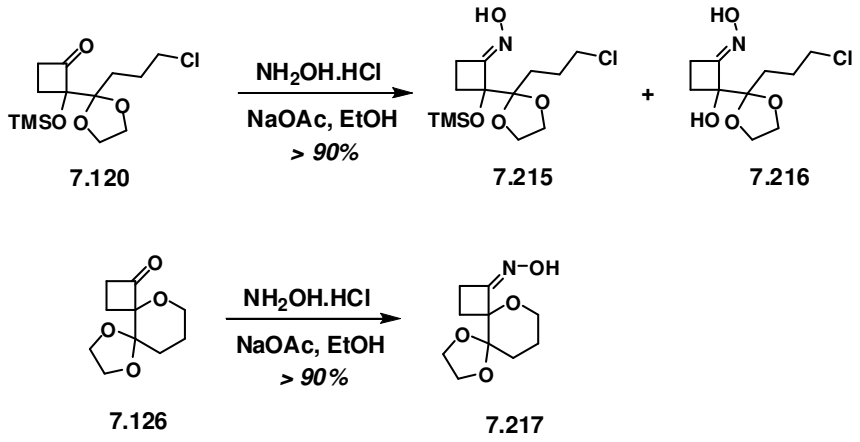


7.126 **7.200**

Scheme 7.64

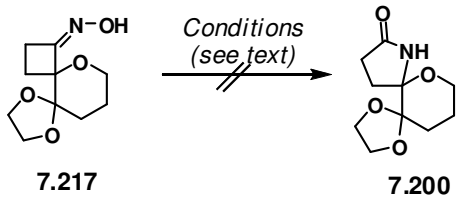
Disappointed at these initial results, we reasoned that in **7.126** the carbonyl center is probably too hindered. Indeed, and in spite of its high nucleophilicity, MSH **7.201** is quite hindered and would presumably experience severe non-bonded interactions upon approaching **7.126**. We were therefore probably facing a case where the classical two-step Beckmann protocol would be the best option after all!

Oxime formation in cycloalkanones is usually best done with the hydrochloride salt of hydroxylamine, in a polar solvent containing excess sodium acetate. When these conditions were applied to **7.120**, complete consumption of the starting material ensued but once again desilylation took place, as observed previously (Scheme 7.65). We therefore returned to the closed analogue **7.126**. In this case, conversion to a single compound could be ascertained, whose crude spectroscopic data were consistent with the formation of oxime **7.217**.



Scheme 7.65

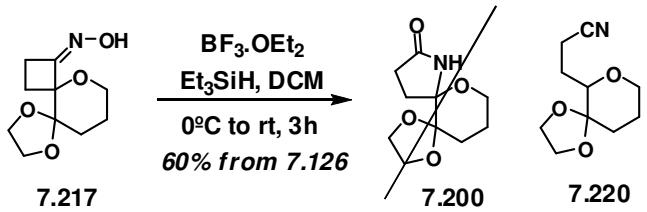
Rearrangement of such ketoximes is usually effected under acidic conditions or by converting the oxime hydroxyl substituent to a suitable leaving group. In the case of cyclobutanones, it would be expected that mild conditions might suffice given the propensity of the cyclobutane ring to undergo ring-expansion. Unfortunately, all our attempts to rearrange oxime **7.217** under such conditions, including the use of Lewis and Brönsted acids or treatment with MsCl/pyridine or TsCl/Pyridine, led only to the formation of complex mixtures of products.



Scheme 7.66

Surprised at these results, we reasoned that the formation of numerous products could be the result of the *in situ* generation of unstable and highly reactive electron-deficient intermediates.

We therefore repeated the reaction using Lewis-acid activation ($BF_3.OEt_2$) but in the presence of triethylsilane as a soft hydride donor. The reaction was conducted in cold dichloromethane and slowly warmed to room temperature after addition of all the reagents. Unexpectedly, the smooth formation of a single new product could be verified, which was not the coveted spiroaminal **7.200**. After extensive spectroscopic investigation, we assigned the structure **7.220** to this new compound.



7.217 **7.200** **7.220**

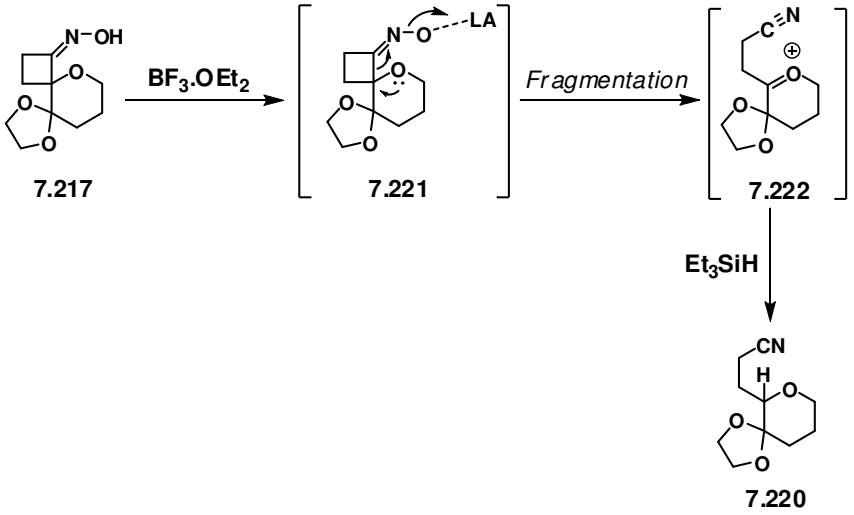
Scheme 7.67

Decisive in our assignment of this compound was the sharp infrared absorption at around 2250 cm^{-1}, which is characteristic of a nitrile functionality, along with a ^{13}C-NMR resonance near 120 ppm. Given our laboratory's longterm experience with tetrahydropyrans, comparison with related compounds was possible and a confident determination of structure could therefore be done.

The formation of this compound can be rationalised (Scheme 7.68) by assuming that departure of the oxime hydroxyl from **7.221**, promoted by interaction with the Lewis Acid, is assisted by the neighbouring oxygen and

leads, not to the ring-expansion product, but to the formation of an oxonium cation **7.222** (Scheme 7.68).

The reduction of this cation by excess triethylsilane, present in the medium, eventually accounts for the formation of **7.220**.



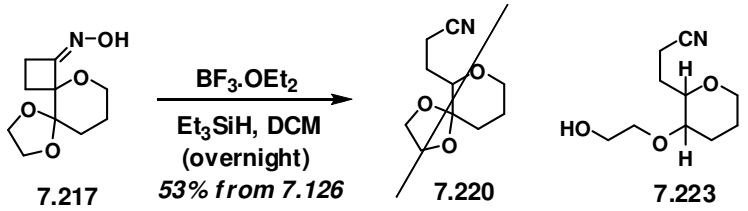
Scheme 7.68

One can now better understand the reasons for our previous failures. Indeed, oxonium **7.222** was presumably generated in the majority of the experiments done previously (Scheme 7.66), through a similar mechanism. However, in the absence of suitable nucleophiles, oxonium ions such as **7.222** are prone to a number of unproductive side-reactions. Although the internal position is blocked by the dioxolane substituent, proton loss to form an unstable exocyclic enolether can take place. On the other hand, should **7.222** be quenched by adventitious water (or survive until the workup), it

would afford a hemiketal which is bound to exist in equilibrium with the open-chain form, considerably complicating the panorama.

Conversely, in the presence of a nucleophile, such oxonium cations are readily trapped to afford neutral species, which are otherwise stable in the reaction mixture.

The word "otherwise" should be stressed in this context. Indeed, in a subsequent experiment in which the reaction discussed above was inadvertedly allowed to proceed overnight, a new compound of considerably higher polarity became the single component of the reaction mixture. After purification, we were surprised to observe the formation of **7.223**.



Scheme 7.69

It should not be forgotten that the conditions employed are also suitable for the reduction of other oxonium ions that can eventually form in solution. It would seem that, if given the chance to proceed for longer times, the remaining Lewis acids in solution will subsequently attack the dioxolane ketal causing its ring-opening. Reduction by Et_3SiH then affords the product **7.223**.

Nevertheless, this is clearly a much slower process than the Beckmann-like fragmentation mentioned before. Indeed, TLC analysis and

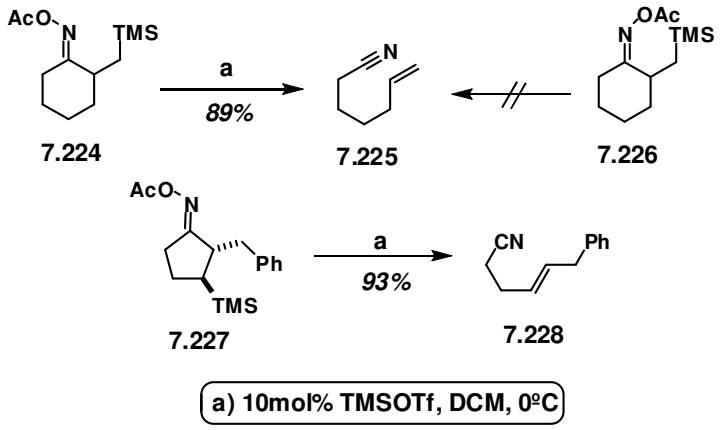
control experiments reveal that formation of **7.220** is the fastest event in solution. Compound **7.220** then slowly converts to **7.223** if left under these conditions for extended periods of time.

Returning to the serendipitously discovered Beckmann fragmentation of oxime **7.217**, it is instructive to make a digression at this stage. In fact, it is well-known that oximes derived from aldehydes do not undergo Beckmann rearrangement but rather dehydrate to form the corresponding nitriles in what is called the "abnormal Beckmann rearrangement".[290] However, examples of "Beckmann fragmentations" are known, though scarce in the literature. Scattered examples of fragmentations of oximes α-substituted with heteroatoms are described, but little synthetic exploitation of this process has been reported thus far.

Among the published data on this subject, the work of Nishiyama and Fleming is worth mentioning. In 1988, Nishiyama disclosed the silicon-directed fragmentation of cyclic oxime acetates, depicted in Scheme 7.70.[291]

As shown, the (*E*)-β-silyl oxime acetate **7.224** readily undergoes regioselective fragmentation with loss of the TMS group, leading to ω-cyanoalkene **7.225** in excellent yield. In the case of stereodefined oxime acetates such as **7.227**, there is an excellent correlation between alkene geometry of the final product and the configuration of the starting oxime acetate, showing that the process is likely to be of concerted nature.

[290] Conley, R.T. ; Ghosh, S. *Mechanisms of Molecular Migrations*, **1971**, 197-308
[291] Nishiyama, H. ; Sakuta, K. ; Osaka, N.; Arai, H.; Matsumoto, M.; Itoh, K. *Tetrahedron* **1988**, *44*, 2413



Scheme 7.70

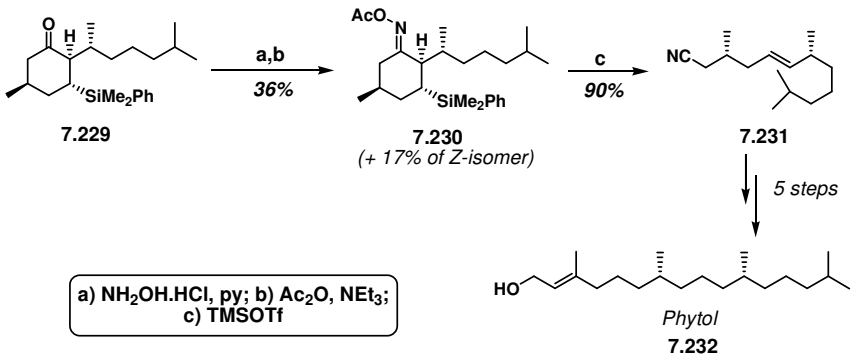
Interestingly though, the (*Z*)-isomeric oximes fail to react under these conditions (cf. **7.226**). This confirms even further the stringent requirement for *anti* alignment between the oxime departing hydroxyl group and the migrating substituent, even in the case of formation of a β-silicon-stabilised carbocation.

Nevertheless, the applicability of this method in the preparation of internal olefins with excellent control of stereochemistry led Fleming, one of the leading specialists in silicon chemistry of the last century, to use this reaction in his total synthesis of phytol **7.232** (Scheme 7.71).[292]

Thus, the enantiopure ketone **7.229** was converted in two steps to the oxime acetate **7.230**. Rearrangement of this oxime, under conditions analogous to Nishiyama, afforded in excellent yield the stereodefined nitrile **7.231**. It should be noted that 17% of the oxime (*Z*)-isomer was isolated alongside **7.230** and that Fleming reports that this isomer "did not undergo

[292] Fleming, I. ; Maiti, P. ; Ramarao, C. *Org.&Biomol.Chem.* **2003**, *1*, 3989

the fragmentation reaction". The nitrile **7.231** was uneventfully elaborated to phytol **7.232** in 5 steps.

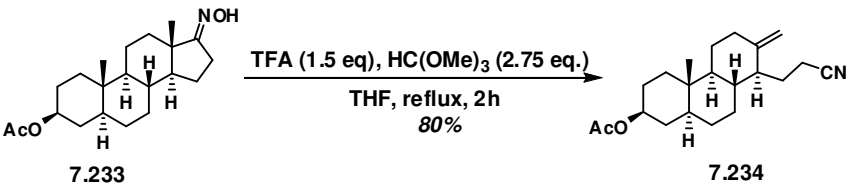


Scheme 7.71

Directed Beckmann fragmentations are also possible through the formation of unsubstituted carbon-centered cations, though regiochemistry is naturally more difficult to control in these cases. Even when the regiochemistry of the fragmentation can be secured, the elimination from the ensuing carbocation often follows the known tenets for E_1-processes, giving mixtures of olefins.

Hu has recently reported the extensive optimisation of such a situation in the field of steroidal oximes (Scheme 7.72).[293]

[293] Wang, C.; Jiang, X.; Shi, H.; Lu, J.; Hu, Y.; Hu, H. *J. Org. Chem.* **2003**, *68*, 4579

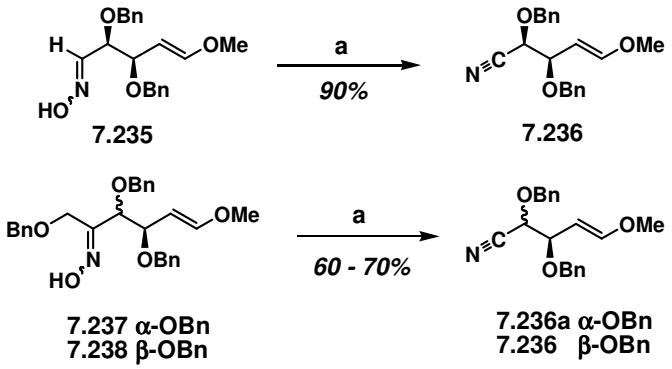


Scheme 7.72

After considerable optimisation, Hu found conditions suitable for the rearrangement of **7.233** and related steroidal ketoximes as shown. In this case, the driving force is obviously the formation of a stable, tertiary carbocation which finally undergoes elimination to form mainly the exocyclic olefin. The harsh conditions required are probably a consequence of the lesser stability of the cationic intermediate when compared to heteroatom stabilisation. Nonetheless, it is worth noting that only one alkene regioisomer (the least substituted olefin) is formed.

An Italian group has studied the Beckmann fragmentation of linear oximes derived from glycals.[294] They found that exposure of α-benzyloxy aldoximes such as **7.235** to dehydrating conditions susceptible to induce Beckmann fragmentation always led to the abnormal rearrangement and to the formation of nitrile **7.236**. In contrast, when ketoximes **7.237** and **7.238** were treated under the same conditions, fragmentation ensued, eventually leading to **7.236** or **7.236a** through expulsion of $[PhCH_2O{=}CH_2]^+$ as the assisting group.

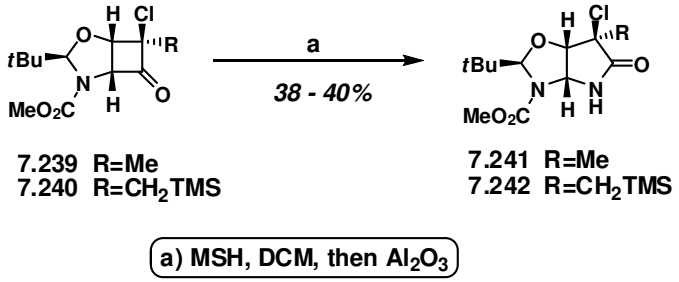
[294] Passacantilli, P.; Centore, C.; Ciliberti, E.; Piancatelli, G.; Leonelli, F. *Eur. J. Org. Chem.* **2004**, 5083



Scheme 7.73

Interestingly, in a recent report, Ghosez and Marchand-Brynaert reported the successful Beckmann rearrangement of an α-heteroatom substituted cyclobutanone.[295] In the event, when cyclobutanones **7.239** and **7.240** were exposed to Tamura's reagent, formation of the highly functionalised ring-expanded products **7.241** and **7.242** took place, albeit in modest yield. This raises interesting questions as to what the electronic requirements for fragmentation might be. One might argue that the carbamate nitrogen in **7.239/7.240** is not sufficiently electron-donating to trigger the fragmentation (for further mechanistic discussions on this, *vide infra*).

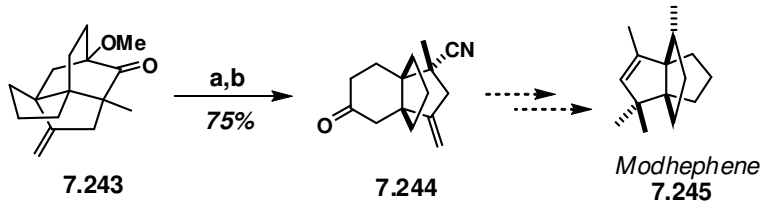
[295] Ghosez, L.; Yang, G.; Cagnon, J. R.; Le Bideau, F.; Marchand-Brynaert, J. *Tetrahedron* **2004**, *60*, 7591



Scheme 7.74

An elegant application of this rearrangement issued from the laboratory of Subba Rao, in India.[296] In his approach to the synthesis of Modhephene **7.245**, Subba Rao prepared the congested ketone **7.243** through a short sequence. When the oxime derived from **7.243** was treated with triflic anhydride as the dehydrating agent, a smooth methoxy-assisted Beckmann fragmentation took place, generating the propellane **7.244** in very good yield. Presumably, release of tension in compound **7.243** is the driving force underlying this particularly efficient reaction. Albeit no details are given, one may assume that the intermediate oxonium ion is either dealkylated *in situ* or eliminates to an enol ether which is hydrolised upon workup.

[296] Laxmisha, M.S.; Subba Rao, G.S.R. *Tetrahedron Lett.* **2000**, *41*, 3759

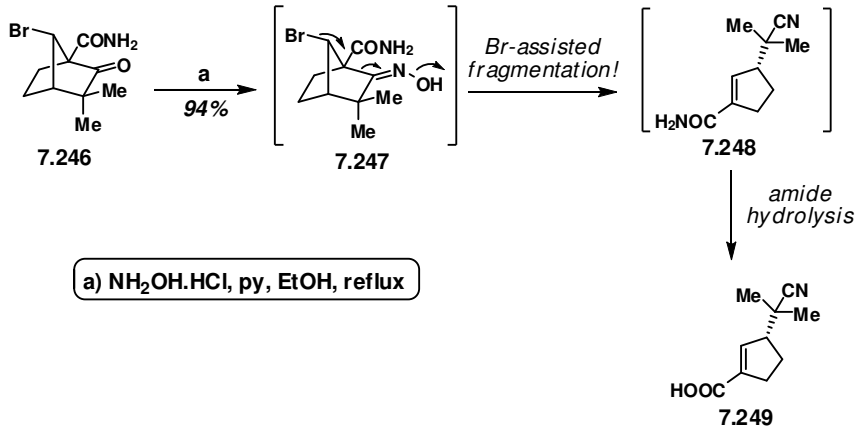


Scheme 7.75

One final, slightly "exotic" example was recently reported by a Spanish group.[297] They prepared the optically pure norbornenone **7.246** and intended to study the regiochemical issue of its Beckmann fragmentation. Indeed, Beckman fragmentations of similar compounds often display little selectivity, with mixtures of alkene regioisomers being commonly observed.

In the event, they were surprised to obtain the optically pure cyclopentene carboxylic acid **7.249** in 94% yield upon treatment of **7.246** with hydroxylamine in boiling ethanol (Scheme 7.76).

[297] Martinez, A.G.; Vilar, E.T.; Fraile, A.G.; Cerero, S.M.; Maroto, B.L. *Eur. J. Org. Chem.* **2002**, 781

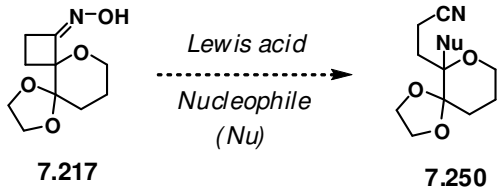


Scheme 7.76

This puzzling result can only be rationalised by assuming a sequence of events similar to that depicted in Scheme 7.76. Subsequently to the formation of oxime **7.247**, an unprecedented bromine-assisted fragmentation of the norbornene skeleton presumably leads to **7.248**. Amide hydrolysis then completes the sequence. This elimination of bromine is probably assisted by the addition of a nucleophile present in solution (*e.g.* by pyridine). Similar reactions are known on α-haloketones.

From this brief digression into the literature, it is apparent that the Beckmann fragmentation of oximes or oxime derivatives is a sparsely developed reaction. In particular, its use is almost always aimed at the formation of ω-alkenenitriles.[298] We were intrigued by a different possibility (Scheme 7.77).

[298] For examples of radical-mediated fragmentations of oximes and derivatives, see: (a) Zard, S. Z. *Synlett* **1996**, 1148; (b) Boivin, J.; Fouquet, E.; Zard, S. Z. *J. Am. Chem. Soc.* **1991**, *113*,



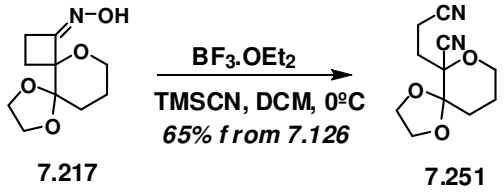
7.217 **7.250**

Scheme 7.77

Given that triethylsilane had successfully intercepted the oxonium cation resulting from the fragmentation of **7.217**, we hypothesized that, in principle, any competent, external nucleophile might be able to perform a similar operation. *In fine*, this would empower us with the possibility to prepare variously substituted tetrahydropyrans **7.250** simply by varying the external nucleophile employed. We were particularly interested by heteroatom-containing nucleophiles but also by carbon-centered nucleophilic entities that would allow C-C bond formation upon capture by the intermediate cation. In this manner, tetrasubstituted tetrahydropyrans **7.250** would be within our reach.

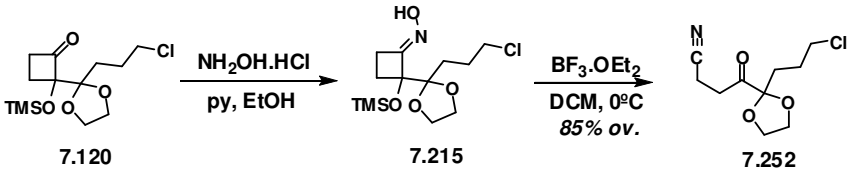
Initial efforts were aimed at the introduction of cyanide, through the action of TMSCN. Although TMSCN is only weakly Lewis acidic, we reasoned that the addition of 1 eq. of boron trifluoride etherate would accelerate the reaction. In the event (Scheme 7.78), we were pleased to observe the smooth formation of **7.251** under these conditions in 65% overall yield (since the oxime **7.217** is always used crude).

1055. For palladium-promoted processes, see : (c) Nishimura, T.; Nishiguchi, Y.; Maeda, Y.; Uemura, S. *J. Org. Chem.* **2004**, *69*, 5342



Scheme 7.78

The Beckmann rearrangement of the monocyclic precursor **7.120** was next investigated (Scheme 7.79). After some optimisation, we found that if pyridine was used in the oxime-forming reaction, no desilylation of **7.120** took place. In this manner, the oxime **7.215** could be obtained in essentially pure form. The crude material was employed as such in the subsequent transformation. Adding boron trifluoride etherate to a solution of **7.215** in cold dichloromethane rapidly elicited formation of a new product, the acyclic ketonitrile **7.252**. After a simple aqueous workup, this compound was obtained in excellent yield (Scheme 7.79).

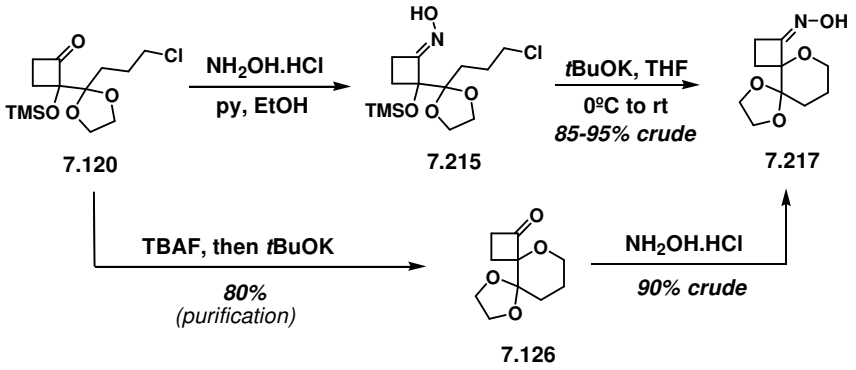


Scheme 7.79

In our case, as in the Modhephene approach by Subba Rao, the fragmentation is triggered by a simple alkoxy substituent, namely a silylether. Desilylation, *e.g.* by fluoride (from BF_3), rapidly leads to **7.252** without formation of long-lived carbocationic intermediates.

Reassured and encouraged by these results, we could now confidently return to the spirocyclic ether case. One additional observation, though, proved very useful from an experimental point of view. As we have previously mentioned, the preparation of **7.126** from the adduct **7.120** is realised through a two-step, one-pot reaction including desilylation and spirocyclisation. Oxime formation then completes the synthesis of **7.217**, the precursor for our projected fragmentation/trapping experiments (Scheme 7.80).

In the event, we discovered that when crude oxime **7.215** is treated with *t*BuOK in THF, a smooth cyclisation to **7.217** takes place. A simple aqueous workup (for the removal of any residual salts from the oxime formation step) provides essentially analytically pure oxime **7.217** (Scheme 7.80)!



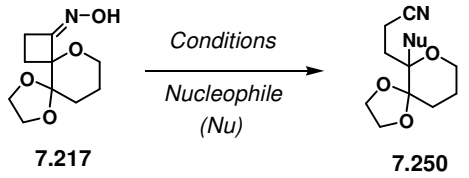
Scheme 7.80

This protocol actually provides an operationally simpler (2 discrete steps, no chromatographic purification) and more efficient (85-95% overall

crude yield) route to the spiroketoxime **7.217** from the readily available condensation product **7.120**. Mechanistic considerations are deferred to the latter part of this Chapter.

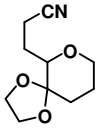
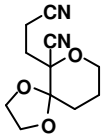
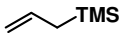
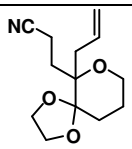
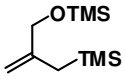
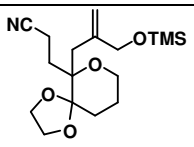
With a simple protocol for the rapid preparation of large amounts of **7.217** in hands, we next proceeded to generalise the scope of the Beckmann fragmentation/nucleophilic capture reaction. Our results are summarised in Table 7.3.

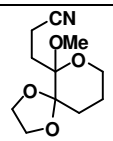
As can be seen, this reaction enables the creation of C-C bonds by the use of allylating reagents such as allyltrimethylsilane **7.254** or even the functionalised allylsilane reagent **7.256**. Importantly, if the fragmentation is performed under solvolytic conditions (CSA, MeOH, entry 5), the hemiacetal **7.258** is formed. This last entry also corresponds to the fastest and highest-yielding process: upon dissolving **7.217** in methanol and adding a small amount of camphorsulphonic acid, complete conversion to pure **7.258** takes place in less than 60 minutes.



7.217 **7.250**

Table 7.3

Entry	*Nucleophile*	*Conditions*	*Product*	*Yield*[a]
1	Et_3SiH	3 eq. Nu, 1 eq. $BF_3.Et_2O$, DCM, 0ºC to rt	 **7.220**	60%
2	TMSCN	as above	 **7.251**	65%
3	 **7.254**	as above	 **7.255**	50%
4	 **7.256**	as above	 **7.257**	47%

5	MeOH	cat. CSA, MeOH	 **7.258**	70%

[a]- All yields refer for pure, isolated compounds and are *overall* for the three-step conversion **7.120** →**7.215** →**7.217** →Products.

Although the yields reported are moderate, it should be kept in mind that these values refer to the overall sequence from the condensation product **7.120**, since no chromatographic purification of intermediates was required. It thus transpires that this is an efficient and expeditious method for the preparation of functionalised tetrahydropyrans. Furthermore, it constitutes, to the best of our knowledge, the first comprehensive study and synthetic exploitation of the Beckmann fragmentation reaction.

Throughout this Section, we have repeatedly aluded to the mechanistic intricacies of the Beckmann rearrangement, and the mention *vide infra* was often used. In the following, final subsection, we devote our attention to an understanding of the factors at play in this reaction and, eventually, dare to make some predictions on thus far untested hypotheses.

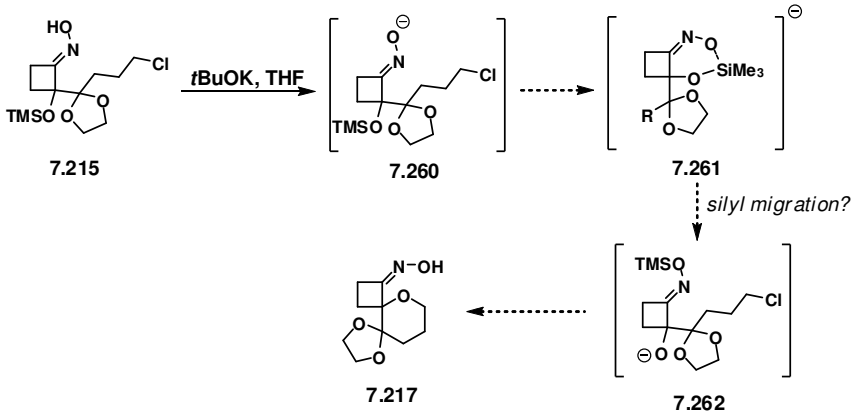
7.5.6. Mechanistic analysis of the Beckmann fragmentation

After analysing the literature precedent and our own results on the Beckmann fragmentations, a number of questions arose. What is the true nature of this fragmentation: a concerted process or a stepwise reaction that begins as the classical Beckmann rearrangement? Is the oxime geometry important? If so, why don't we observe any complications from this factor (in contrast to the results of Fleming and Nishiyama)? Is this reaction feasible simply because the ring being cleaved is a four-membered one? Could we predict the influence of additional substituents on the cyclobutanone ring?, only to list a few. We were also particularly interested in obtaining some qualitative answers to the synthetically useful (though not less puzzling) cyclisation of oxime **7.215** to spiroether **7.217** (Scheme 7.80).

Given the relative success experienced during the research reported in Chapters 2 and 3, it was decided once more to call upon the aid of quantum chemical calculations. As before, this work was done with the kind collaboration of Dr. Luís Veiros of the Instituto Superior Técnico at Lisbon, Portugal. All DFT calculations were performed at the PBE1PBE/6-31G level.

Prior to the actual investigations of the Beckmann fragmentation *per se*, we formulated two hypotheses for the conversion of **7.215** to spiroether

7.217. The first one postulates a direct attack of *t*BuOK or of adventitious KOH (from the eventual presence of traces of water) onto the silyl ether moiety, thus liberating the anion **7.262**, required to account for the observed cyclisation. The most intriguing one is depicted in Scheme 7.81.



Scheme 7.81

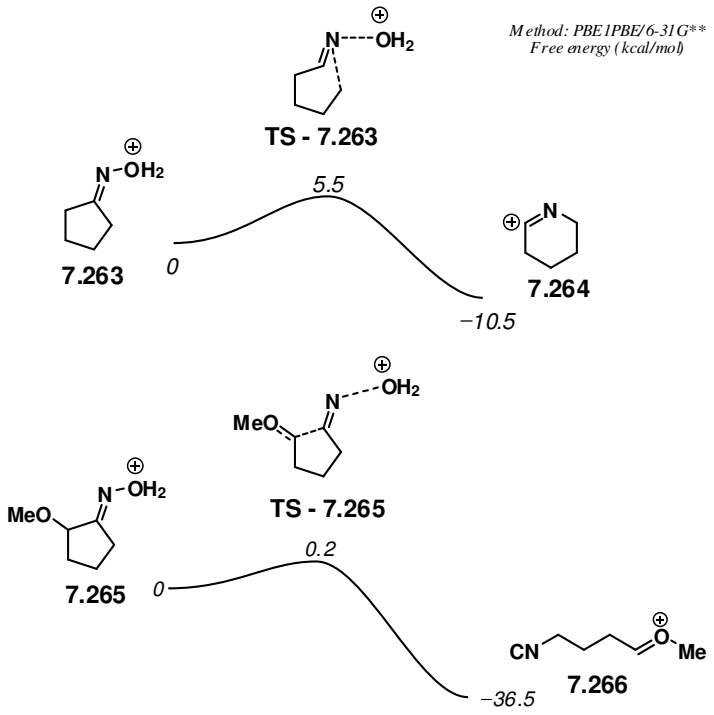
Given the potentially short distance between the initially formed oxime anion **7.260** and the –OTMS moiety, the formation of a 6-membered cyclic silicate complex **7.261** (either as a true intermediate or a transition state) could trigger silyl migration with generation of the requisite anion **7.262** (please note that the represented oxime geometries of all the intermediates, except **7.261**, are arbitrary).

The easiest way to discard the latter option computationally is to calculate the relative energies of the anions **7.260** and **7.262**. If there is a significant energy barrier between these two compounds, interconversion is less likely to occur.

In the event, Dr. Veiros found a 8 kcal/mol difference between anions **7.260** and **7.262**, with the former being the most stable. This suggests that a direct desilylation of **7.215** by nucleophilic entities in the reaction mixture was taking place, in analogy to similar TMSO- deprotections reported by Duhamel *et al*..[299]

Dr. Veiros then proceeded to perform calculations that might address the Beckmann fragmentation. In order to obtain some preliminary insight, he modelled two typical substrates that might be expected to undergo the classical rearrangement and the fragmentation, respectively (Scheme 7.82).

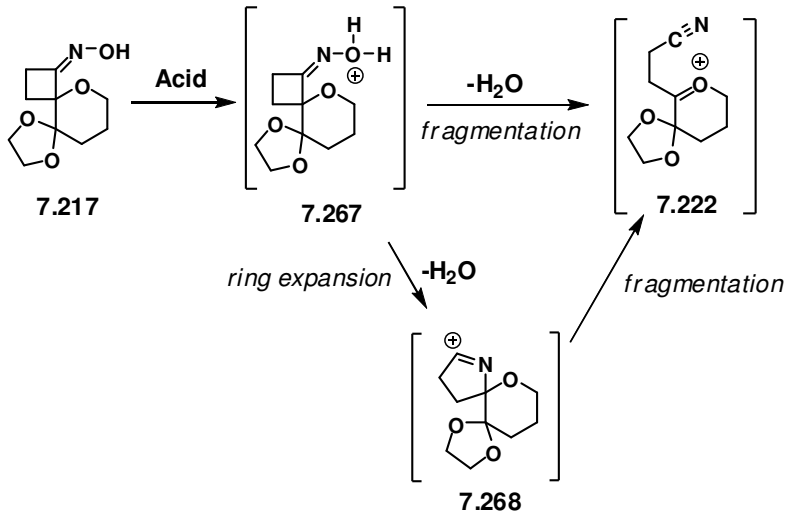
[299] For an example, see: Duhamel, P.; Hennequin, L.; Poirier, N.; Poirier, J. M. *Tetrahedron Lett.* **1985**, *26*, 6201



Scheme 7.82

As expected, the protonated cyclopentanone oxime **7.263** is found to produce only the expected Beckmann rearrangement adduct, the ring-expanded carbocation **7.264**. Conversely, the protonated α-methoxycyclopentanone oxime **7.265** leads smoothly to the Beckmann fragmentation product, the nitrile **7.266**. These calculations strongly suggest that these reactions could be fairly general, rather than a consequence of a particular feature of our (or other) substrates. We could now move on to analyse the compounds prepared during our studies.

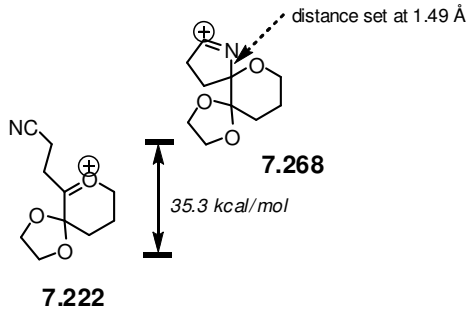
Our first conjectures were on the very nature of the reaction. Indeed, one might envisage at least two pathways for this process, as shown below (Scheme 7.83).



Scheme 7.83

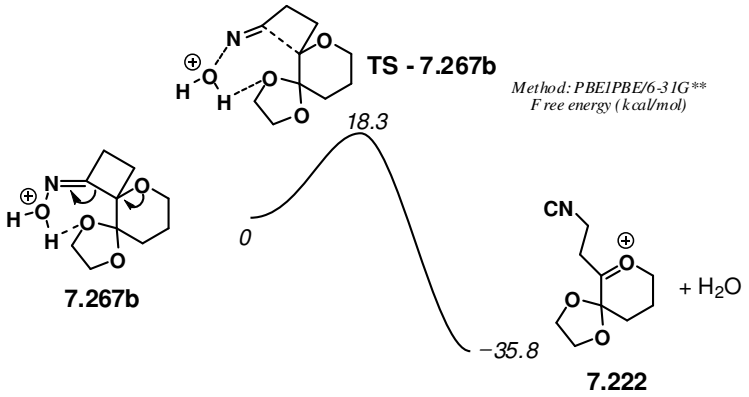
The initially protonated oxime **7.267** could fragment in a fully concerted manner, to the oxonium cation **7.222**. Alternatively, a Beckmann-like ring-expansion might occur, providing the "usual" intermediate **7.268**. Due to the presence of the β-oxygen, this intermediate might then collapse to the oxonium **7.222**. As fundamental as this question can be, its synthetic implications could be profound. For instance, if **7.268** is a true intermediate in this process, then it might be amenable to intramolecular trapping by a tethered nucleophile. Access to spiroaminal-like structures could therefore still be possible from an experimental point of view.

Dr. Veiros simply optimised the structures for both carbocationic entities. The results are rather clear (Scheme 7.84). Indeed, the removal of water from **7.267** leads directly to **7.222**, *without any activation energy barrier*. Intermediate **7.268** has to be arbitrarily modelled, with the new C-N bond-distance set at a specific value, for its energy to be calculated (otherwise it spontaneously collapses to **7.222**). The energy difference between the two cations strongly suggests that departure of water is accompanied by fragmentation rather than ring-enlargement.



Scheme 7.84

Dr. Veiros therefore computed the reaction **7.267-7.222** in more detail. Interestingly enough, the direct conversion **7.267**-**7.222** has no activation barrier, as mentioned, provided that the oxime geometry is (*E*). If the oxime geometry is (*Z*), then calculations provide an optimised structure **7.267b** in which there is a stabilisation by hydrogen bonding to one of the dioxolane oxygens. With this additional stabilisation, an activation barrier appears (Scheme 7.85).



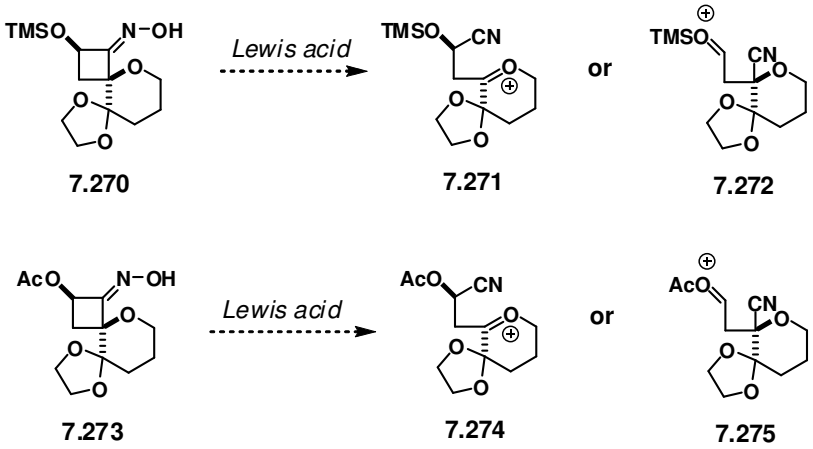
Scheme 7.85

The calculated scenario depicted above, has direct experimental correspondence only with the CSA/MeOH solvolytic reaction, which was actually the fastest process among those studied. In all other reactions, departure of the oxime hydroxyl was assisted by complexation to BF_3, which probably precludes the intermediacy of **7.267b**. The higher reaction rate observed in MeOH could be a consequence of either the higher polarity of the reaction medium and/or the breaking of such intramolecular hydrogen bondings by the solvent. Interestingly, these results appear to indicate that the oxime geometry could be an important factor. It is commonly assumed that under the acidic conditions usually employed for the Beckmann rearrangement, E-Z isomerisation takes place.[300]

Work in this area is still in progress. At the time of writing, though, we already hold some insight into a particularly puzzling matter. As

[300] Fleming, I.; Woodward, R. B. *J.Chem.Soc., Perkin Trans. I* **1973**, *16*, 1653

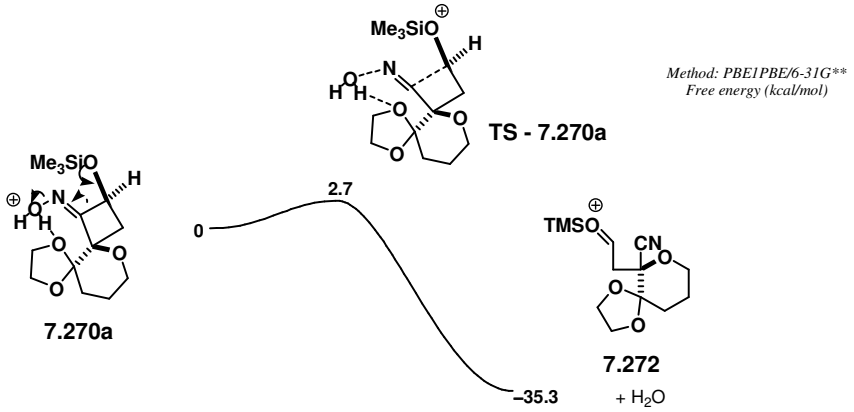
mentioned above, we wondered whether an additional oxygenated substituent on the cyclobutanone α-position would affect, disrupt or completely detour the course of the rearrangement. In particular, we considered two possible substrates **7.270** and **7.273** as candidates, bearing in mind the ease of their synthesis (Scheme 7.86).



Scheme 7.86

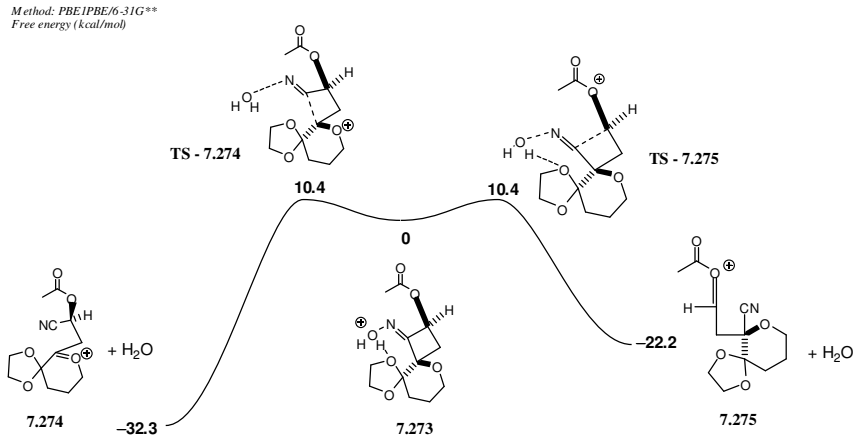
Indeed, these compounds provide an interesting test for the Beckmann fragmentation reaction. Examination of α-siloxy **7.270** and α-acetoxy **7.273** substituted oximes raises the exciting question of whether the pyran oxygen will decide of the main pathway for the fragmentation pathway (with generation of a more strained cyclic oxonium **7.271/7.274**) or if the newly added oxygenated substituent will be able to compete with or even override this effect.

Of course, in this case the hydrogen bonding issue becomes more complex since donation from the α-oxygenated moiety is a further possibility. Preliminary results from Dr. Veiros appear to suggest that in silylated **7.270**, the isomer which is hydrogen bonded to the dioxolane, *i.e.* **7.270a**, is the most stable one. More importantly, fragmentation assisted by the α-siloxy substituent is the only detected pathway, even for the other oxime isomer (Scheme 7.87).



Scheme 7.87

In the case of the acetoxy substituent, and rather counter-intuitively, preliminary calculations indicate that acetoxy-assisted fragmentation is possible and is likely to be competitive with the pyran-assisted process (similar activation barrier)! However, the considerable difference in stability between both oxonium cations might lead to some kind of thermodynamic preference (Scheme 7.88).



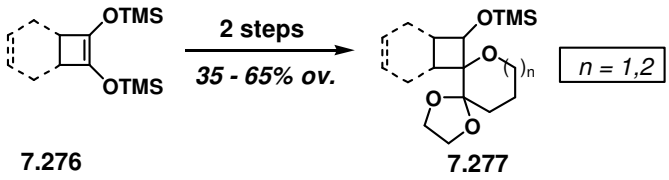
Scheme 7.88

Altogether, these first calculations provide a useful background for further experiment design. One is tempted to speculate that a multitude of different electron donating substituents might be able to reverse the observed fragmentation pathway. These and other calculations could eventually help to draw a clearer picture of the Beckmann fragmentation reaction.

7.6. Conclusions and perspectives

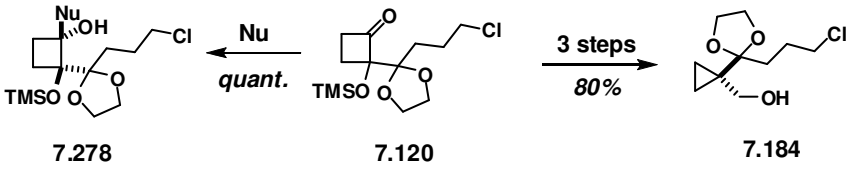
Throughout this final Chapter, we have accompanied the consequences of yet another change in the silyl enolether coupling partner. Indeed, and in contrast to the heteroaromatic series, silylated acyloins are much more limited as donor partners in reactions with our orthoesters.

Nevertheless, we were still able to capitalise on the reaction of 1,2-bis(trimethylsilyloxy)cyclobutene **7.080** and derivatives to prepare a number of condensation adducts. These adducts could then be elaborated through a novel one-pot deprotection/cyclisation, providing cyclobutanone-containing spiroethers **7.277** in moderate to good yields (Scheme 7.89).



Scheme 7.89

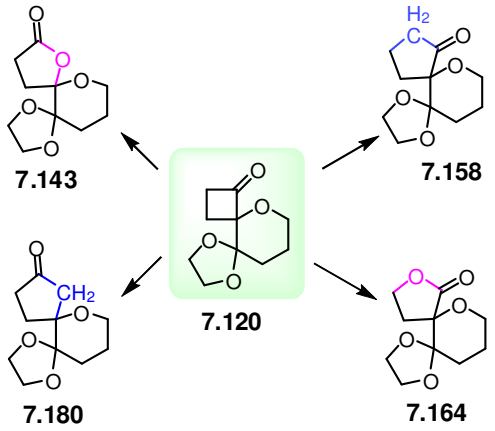
Intermediates such as **7.120** also possess considerable synthetic usefulness. We have ascertained the possibility of effecting interesting ring-contraction reactions on a derivative of this compound. Further, the return of the "dioxolane-effect" enabled (perhaps not entirely on its own) the stereoselective addition of even the smallest of nucleophiles (Scheme 7.90).



Scheme 7.90

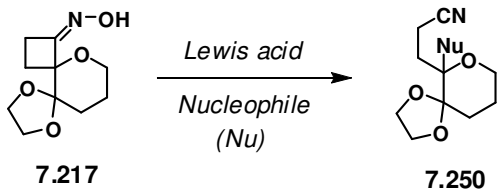
The spiroether **7.126** was then taken as a model for the study of ring-expansion reactions. In this field, considerable success was achieved in that

all conceivable methylene- and oxygen- insertions could be realised with full selectivity and in good yields. This is a rather unique situation which opens new vistas in the future synthetic applications of these regiocontroled ring expansions.



Scheme 7.91

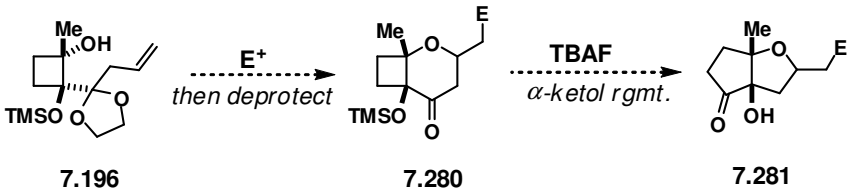
Finally, serendipity led us to the unveiling of an interesting reaction of **7.120**: the Beckmann fragmentation. Using this transformation, we were able to prepare a variety of substituted tetrahydropyrans **7.250** in good yields (Scheme 7.92).



Scheme 7.92

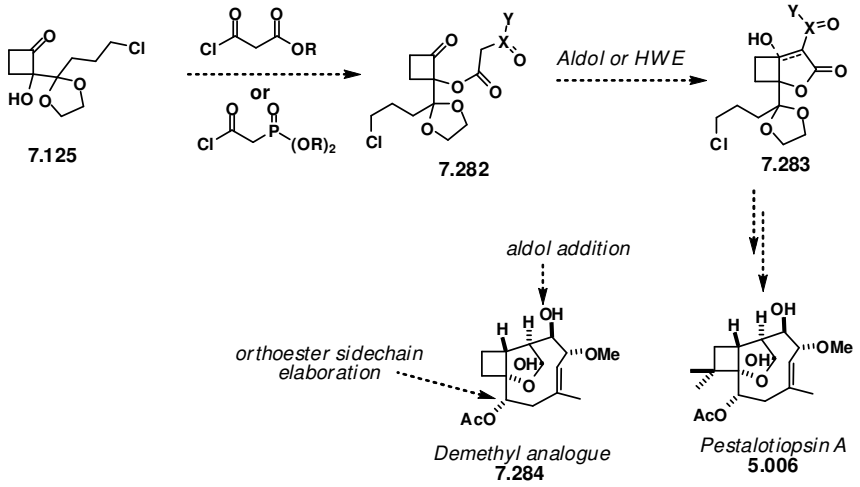
As can be seen, this area of research, initially foreseen as rather limited in scope, actually lends itself to numerous synthetic applications. Some interesting perspectives are described below.

For instance, we believe that the alkene product **7.196**, unadvertedly obtained during our attempts to cyclise the corresponding chloroalcohol, could be exploited (Scheme 7.93). Cyclisation in the presence of a π-electrophile (*e.g.* NBS) should lead to bicycle **7.280** after deprotection of the dioxolane. This compound should be amenable to ring-reorganisation through the α-ketol rearrangement, providing the more stable bicyclo[3.3.0]octane **7.281**. Needless to say, ozonolysis of **7.196** would lead, *via* a similar ring closure to the corresponding lactol.



Scheme 7.93

We are also intrigued by the simplicity of access to cyclobutanes that this methodology affords, and our fascination by the natural product Pestalotiopsin A **5.006** (Cf. Chapter 5) compels us to envisage yet another possible route for the core of this substance (Scheme 7.94).



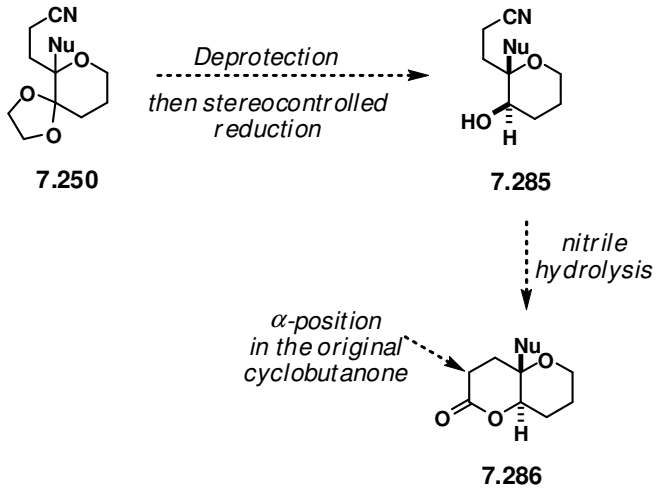
Scheme 7.94

As shown, should the alcohol **7.125** respond well to esterification with either monomalonyl chloride or the acid chloride of diethyl phosphonoacetate, the intermediate **7.282** is quite likely to undergo intramolecular aldol or HWE reaction onto the reactive cyclobutanone carbonyl. This reaction should deliver either the alcohol or the conjugated alkene **7.283**, which actually contains in place most of the required elements for subsequent elaboration into Pestalotiopsin A (except for the *gem*-dimethyl substituent). The thus obtained compound would therefore be highly suited for elaboration into a desmethyl analogue **7.284**. One can then

envisage to start the sequence with compounds akin to **7.125** but bearing even simpler orthoester side chains. It is a testimony to the high versatility of our functionalised orthoesters that the same family of compounds allows the design of two completely different approaches for the preparation of the same natural product (Cf. Chapter 5)!

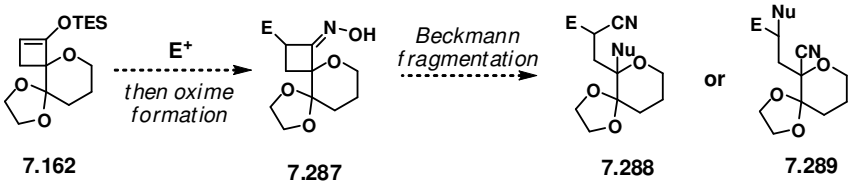
We cannot conclude this brief proposal section without mentioning possible applications of the Beckmann fragmentation products. The reader will surely have noticed the potential elaboration to ladder polyether subunits (Scheme 7.95). Indeed, the compounds **7.250** can be deprotected and reduced in a stereoselective manner to **7.285**, then nitrile hydrolysis (or reduction) should trigger spontaneous cyclisation to **7.286** (or the corresponding lactol). **7.286** is, of course, the smallest constituent of a polyether chain.

Further elaboration of **7.286** would require the presence of suitable oxygenated functionality at the position indicated by the arrow. This can be traced to the original α-position at the starting spirocyclobutanone **7.126**. It now becomes apparent why we had an interest in the outcome of the Beckmann fragmentation in the presence of such α-oxygenated functionality: should the acetoxy group indeed allow for the "usual" fragmentation pathway to take place, functionality would already be installed for subsequent elaboration.



Scheme 7.95

It is therefore left to experimental design to verify the results foreseen by the theoretical calculations. It would be interesting to probe the influence of other heteroatom-based substituents at the α-position of cyclobutanone oxime **7.217**. The synthesis of these compounds could be straightforward, starting from the silyl enolether **7.162** which we have already used for the "anti-Baeyer-Villiger" expansion (Scheme 7.96).



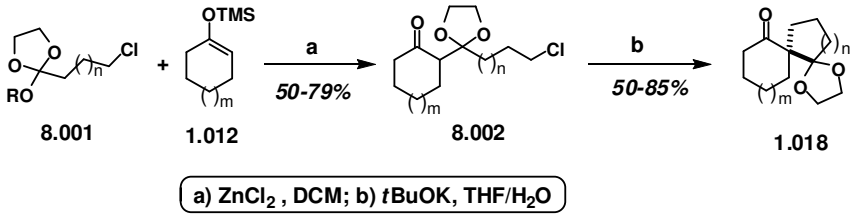
Scheme 7.96

Throughout the past six Chapters, we have described in detail our logical progression, starting from the firm ground which was the work precedented in our laboratory, striving for improvements and subsequent applications to total synthesis. This was the prelude to a leap into a completely different dimension of the use of orthoesters, from heteroaromatic siloxydienes to the challenging silylated acyloins. In all these cases, moderate levels of success were achieved, but limitations and pitfalls awaited at every corner. The lessons learned were diverse and instructive, and empower us with a personal view on the future developments in this area. It is such a critical, predictive and rational analysis that will be laid down in the concluding Chapter of this manuscript.

Chapter 8 : Conclusions and Perspectives

During our Ph.D., we have worked towards the fullfilment of the general goals expressed in the opening Chapter of this manuscript. As might be recalled, this work hinged upon the original spiroannelation methodology previously developed in our laboratory.

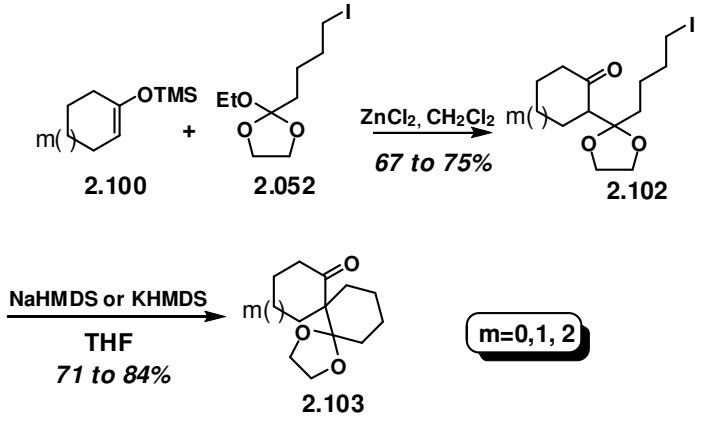
This procedure implies the Lewis-Acid mediated condensation of functionalised ω-chloro orthoesters **8.001** with simple, cyclic silyl enolethers such as **1.012**. The ensuing β-ketoketals **8.002** can then be efficiently cyclised by treatment with *t*BuOK in wet THF (Scheme 8.1).



Scheme 8.1

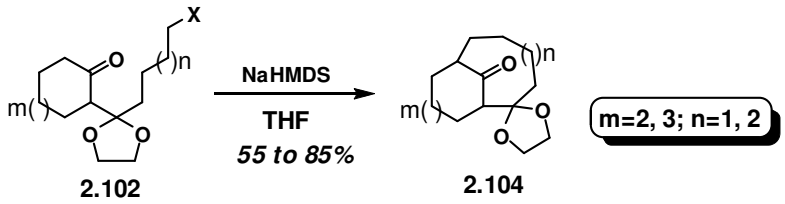
Our initial efforts were aimed at broadening the scope of this method and improving on its weak points. For instance, we recognised that, whilst the closure of 5-membered rings (**1.018**, n = 1) proceeded efficiently under these conditions, the analogous 6-membered cycles (**1.018**, n = 2) could only be formed in moderate yields.

Fortunately, we have found that by changing the nature of the leaving group to iodine and by modifying the spiroannelation conditions, high yields could be attained in the cyclohexannelation of β-ketoketals **2.102** (Scheme 8.2). This modification is general in scope and nicely complements the original procedure.



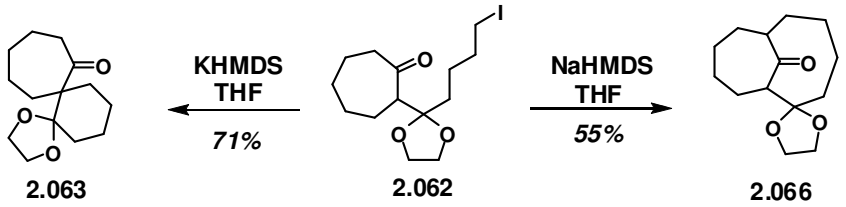
Scheme 8.2

During these investigations, we have also serendipitously discovered a new cyclisation mode of medium-ring ketals (such as **2.102**, m = 2). All evidences point towards the formation of bridged bicycles **2.104** *via* a novel transannular cyclisation. This unprecedented reaction was briefly examined and it appears to hold some generality for medium-sized ring ketones and orthoester tethers equal to- or larger than 5 carbons (Scheme 8.3).



Scheme 8.3

This intriguing reaction is exquisitely dependent upon the nature of the metal counterion of the base employed (Scheme 8.4). For instance, β-ketoketal **2.062** can be cyclised *at will* into either spirocycle **2.062** or bridged bicycle **2.066**, simply by modulating the reaction conditions. This kind of versatility of our condensation adducts would be fully expressed later on.

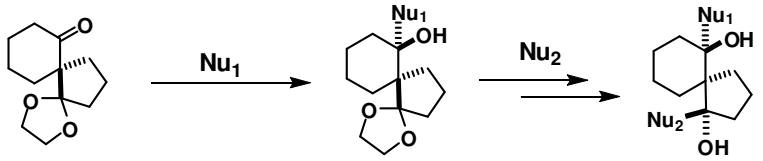


Scheme 8.4

No synthetic methodology has fully proven its worth until it is applied in the total synthesis of naturally occuring substances. We believe that, once the basic rules of reactivity of the intermediate adducts are established and understood, such successful applications are more likely to flourish.

Under the pretext of approaching the synthesis of GHB-analogues and of Perhydrohistrionicotoxin, we have unearthed some of those basic tenets. It was found that the addition of nucleophiles to spirocycles such as **2.005**

proceeds under substrate-control and occurs *anti* to the dioxolane substituent (Scheme 8.5). Preliminary results hint at the possibility that the thus formed –OH substituent might be used to direct the stereocontrolled functionalisation of the five-membered ring. In this manner, highly functionalised, diastereopure diols **8.005** could be prepared in short order (Scheme 8.5).



2.005 **8.004** **8.005**

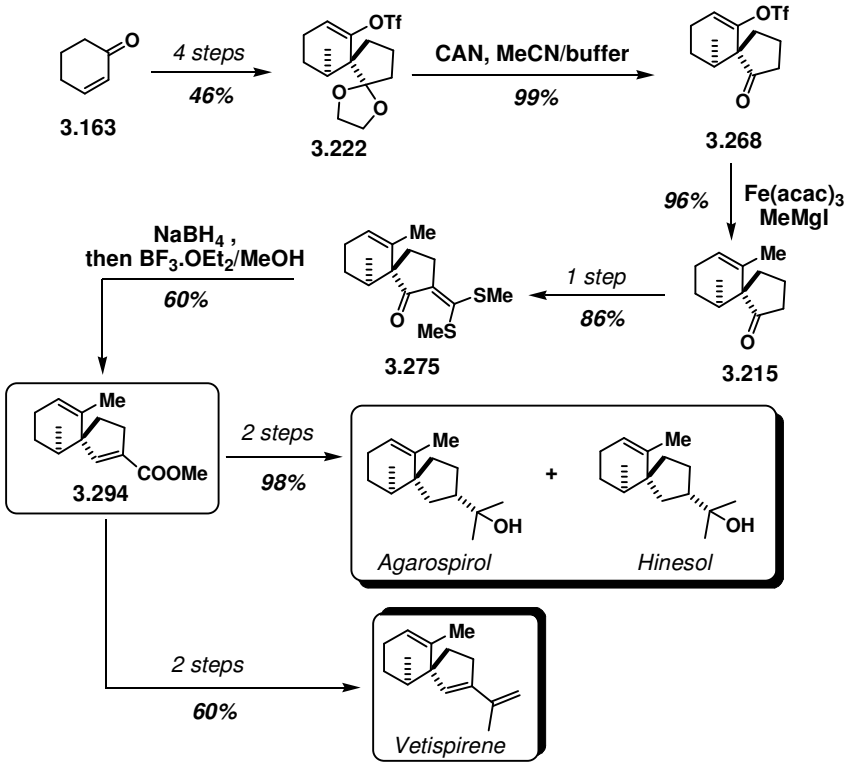
Scheme 8.5

We also had the opportunity to apply the spiroannelation procedure as one of the key-steps in our completed total synthesis of the Spirovetivanes. The milestones of this synthesis are highlighted in Scheme 8.6. They include the CAN-catalysed ketal deprotection in the presence an enol triflate, a Fe^{III}-catalysed Grignard coupling and an efficient rearrangement of an α-oxoketene dithioketal **3.275**.

As depicted, a common intermediate (the α,β-unsaturated ester **3.294**) is used to generate all three natural products. The numerous pitfalls encountered in this work denote (if necessary) the capricious nature of small molecules and the unpredictability of total synthesis.

Importantly, this synthetic endeavour has set new boundaries on the Spirovetivane domain. The characteristic motifs of the natural products were installed using completely different methodology than employed in the

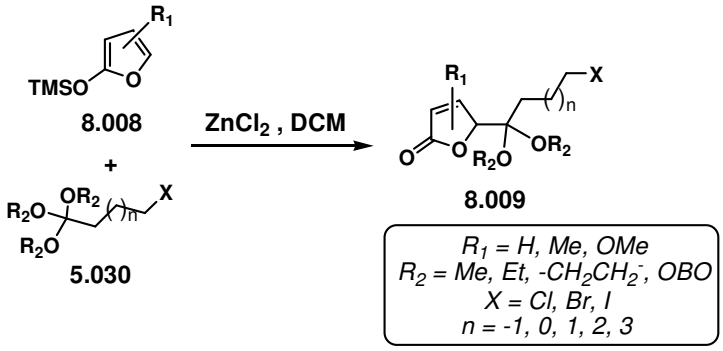
preceding syntheses, showing that this 40 year-old field of research is far from being scientifically exhausted.



Scheme 8.6

Having further developed and applied the spiroannelation procedure which triggered our Ph.D., we then looked in other directions. We chose to do so by changing the nature of the silyl enolether partner.

This journey began with the inspection of TMSOF and derivatives **8.008**. This heteroaromatic silyl *dienolether* proved to be an excellent starting point. Indeed, it reacts efficiently, not only with our dioxolanyl-orthoesters, but also with the more classical trialkyl derivatives.



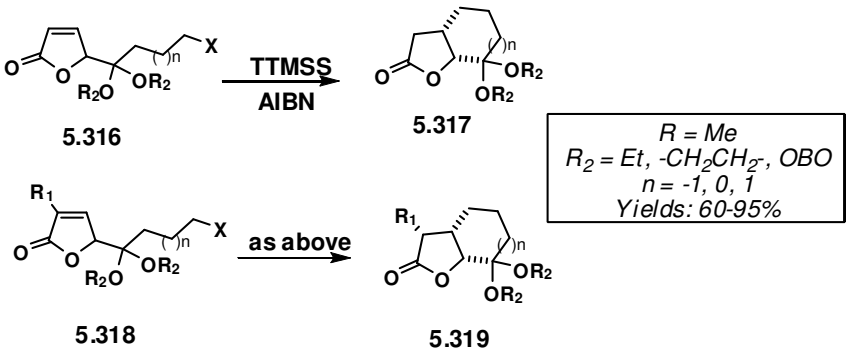
Scheme 8.7

This observation greatly expands the scope of our methodology. Indeed, condensation of simple, cyclic silyl enolethers to provide ketal-containing products was limited to the dioxolanyl-orthoesters specifically designed and developed in our laboratory. In contrast, TMSOF and derivatives made no distinction between the different classes of orthoesters studied and even enabled the first *intermolecular* condensations of Corey's OBO- derivatives.

Through the use of TMSOF, we further recognised the differential steric demands of cyclic and acyclic orthoesters. As matters transpired, it was found that the introduction of alkyl substituents (R_1) onto **8.008** significantly reduced the reactivity of the furan moiety, apparently due to steric hindrance. Nevertheless, this could be countered by changing to

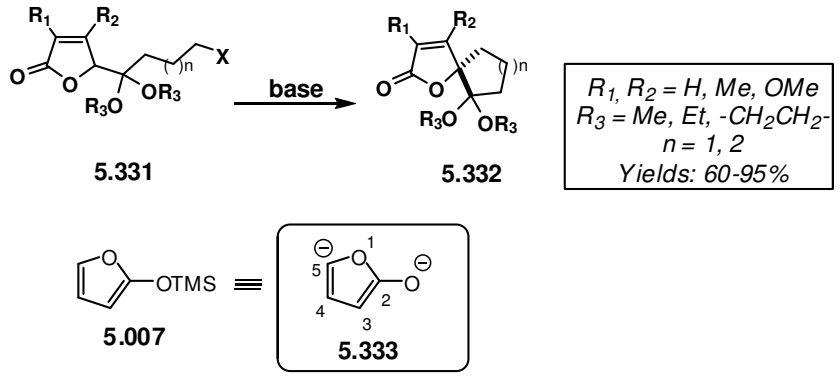
triethyl- and trimethyl-orthoesters (**5.030**, R_2 = Me and Et) which enabled synthetically useful yields of the adducts to be obtained.

TMSOF was to reveal yet other differences and similarities relative to simple cyclic silyl enolethers. Its condensation adducts underwent *stereocontroled* radical-mediated cyclisation to bicyclic lactones (Scheme 8.8).



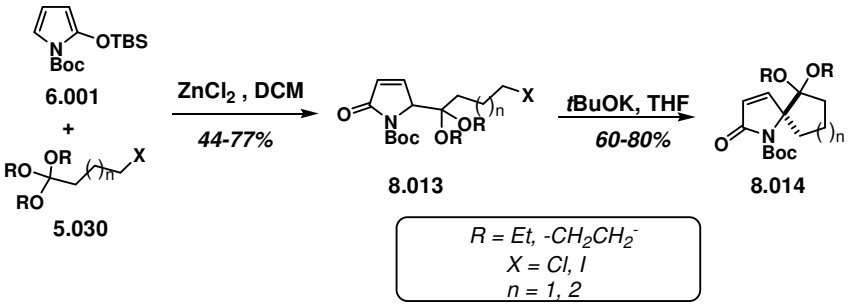
Scheme 8.8

Moreover, they lend themselves to a spiroannelation procedure, affording interesting spirobutenolide substructures (Scheme 8.9). In a nutshell, TMSOF can be regarded as a furan dianionic synthon, as shown below.



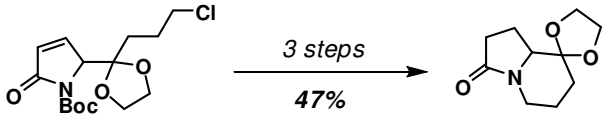
Scheme 8.9

Furthermore, recent preliminary work indicates that some of the basic principles of reactivity discovered during the study of TMSOF can be applied to its nitrogen analogue, TBSOP **6.001**. As depicted below (Scheme 8.10), TBSOP can be condensed with functionalised orthoesters in moderate to good yields, and the corresponding iodinated adducts **8.013** (X = I) are prone to undergo spiroannelation. This sequence efficiently delivers azaspirocycles **8.014**, which are synthetically useful building blocks.



Scheme 8.10

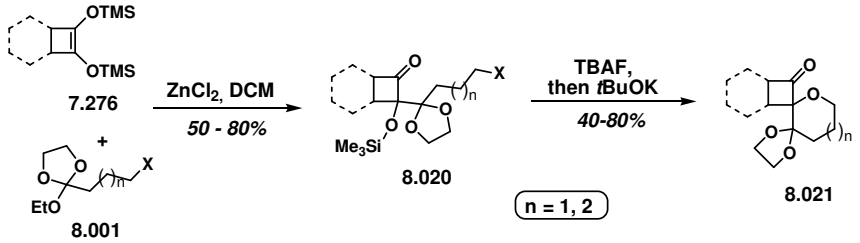
Additionally, a different cyclisation mode is available in the case of TBSOP-derived adducts **8.013** (Scheme 8.11). In particular, it was shown that a functionalised indolizidine **6.014** could be readily accessed from the condensation adduct **6.044** in 3 steps and 47% overall yield.



6.044 **6.104**

Scheme 8.11

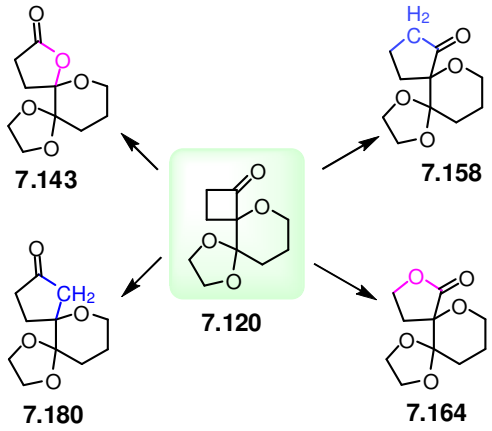
Finally, the chemistry of cyclobutanones was revisited and silylated acyloins were investigated as the nucleophilic reaction partners.



Scheme 8.12

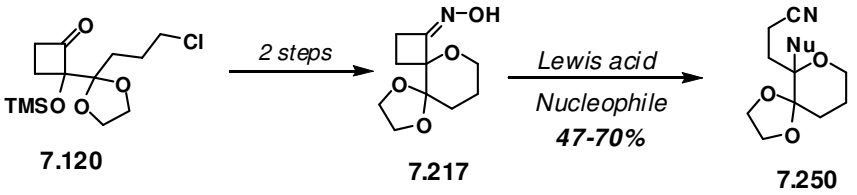
As portrayed in the Scheme, 1,2-bistrimethylsilyloxy cyclobutenes **7.276** can be united to our functionalised dioxolanyl orthoesters to afford the Mukaiyama-like products **8.020**. An interesting one-pot deprotection-cyclisation sequence then converts these adducts into spiroethers **8.021**.

Subsequently, the reactivity of representative compound **7.120** towards ring-expansion processes was investigated. Among a number of useful and selective reactions examined, the ones shown in Scheme 8.13 deserve a special comment, as they represent all the possible methylene- and oxygen-insertions into the carbonyl function of **7.120**.



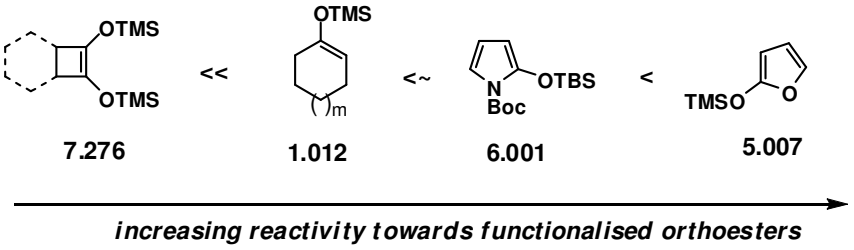
Scheme 8.13

During the study of these ring-expansions, serendipity made its appearance once again. We have discovered and developed a new Beckmann-fragmentation methodology that delivers functionalised tetrahydropyran derivatives **7.250** in 3 steps and good overall yields from **7.120**.



Scheme 8.14

On a more global perspective, our work led to the establishment of an empirical "reactivity-scale" for the different silyl enolethers investigated. This ordering is, of course, valid only for the functionalised orthoesters employed in this work (Scheme 8.15).

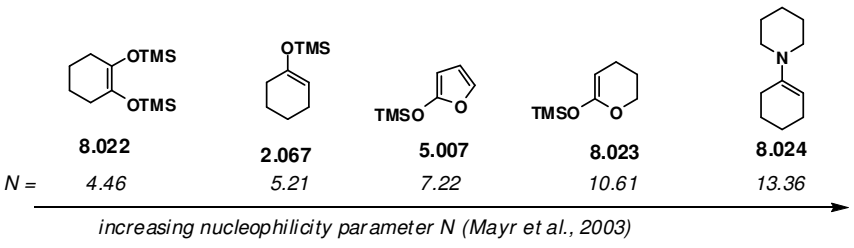


Scheme 8.15

From this scale, it transpires that the silylated acyloins used in the last part of our work are clearly the least reactive partners and that they lead to the lowest yields. Interestingly, TBSOP **6.001** appears to be only slightly more reactive than the simple cyclic silyl enolethers used previously in our laboratory. Undisputedly, TMSOF **5.007** provides the highest yields of condensation products and occupies the top of this scale, although we have witnessed the dramatic effect exerted by alkyl substituents on its reactivity.

While elaborating this essentially qualitative picture, we stumbled upon the impressive body of work developed by Herbert Mayr and his group in Munich.[301] They have determined and developed relative nucleophilicity scales (the so-called "*N*-parameter" or *N*-value) for a series of compounds, including π-nucleophiles in general, and silyl enolethers in particular. It was therefore extremely interesting to compare our qualitative evaluation with a more rigorous, physico-chemical approach.

This scale, based upon measurements of the rate of reaction between different π-nucleophiles and a variety of stabilised benzylic carbocations, is logarithmic in nature, exactly like the pKa scale..



Scheme 8.16

As shown in Scheme 8.16, the only silylated acyloin examined by Mayr (**8.022**) is kinetically less reactive than the cyclohexanone-derived silyl enolether **2.067**. On the other hand, TMSOF **5.007** is at least 2 orders of magnitude more reactive than any of the preceding compounds. Mayr's accurate measurements thus seem to corroborate our empirical observations.

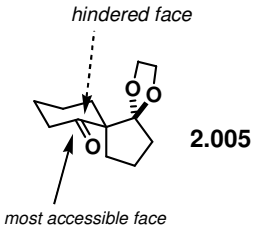
However, TMSOF is largely offset in this scale by the very high reactivity of the cyclic ketene acetal **8.023** or the enamine **8.024**. It would

[301] For an account, see: Mayr, H.; Kempf, B.; Ofial, A.R. *Acc. Chem. Res.* **2003**, *36*, 66

therefore be interesting to examine the behaviour of such π-nucleophiles towards our functionalised orthoesters.

Throughout this work, the seemingly unrelated series of compounds examined in each Chapter actually arose a number of interesting common questions and highlighted similar features shared by nearly all the condensation and annelation products prepared.

For instance, we have repeatedly witnessed what was coined as the "dioxolane-effect": the dioxolane substituent, present on one of the cycles in many of the annelation products, enabled an effective facial discrimination. Indeed, it appears to direct the addition of nucleophiles on the most accessible face of the electrophile present in the other ring, as exemplified below for spirocycle **2.005**. Moreover, it locks the conformation of the other ring system and leads to kinetic products which are difficult to access otherwise.

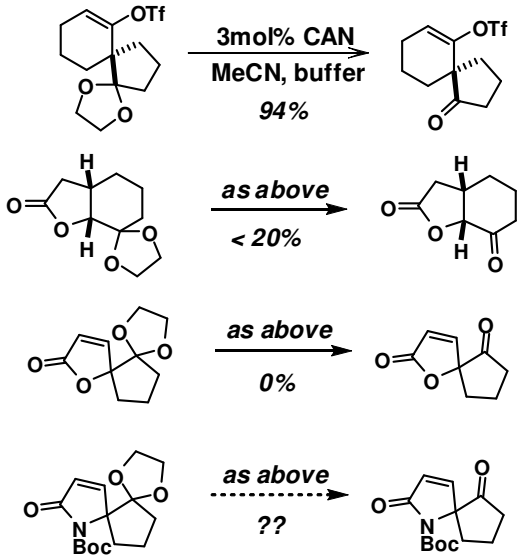


2.005

Scheme 8.17

Furthermore, the very efficient CAN-catalysed procedure, previously developed in our laboratory, was pushed to its limits during this work. If, on the one hand, we have discovered that its mild character allows the deprotection of ketals and acetals in the presence of enol triflates (Chapter

3), we have also observed its failure in the removal of α-heteroatom substituted cyclic ketals (Chapter 5). In this regard, it will be very interesting to probe the efficiency of the CAN-catalysed methodology in the case of the TBSOP (and cyclobutanone) adducts (Scheme 8.18).



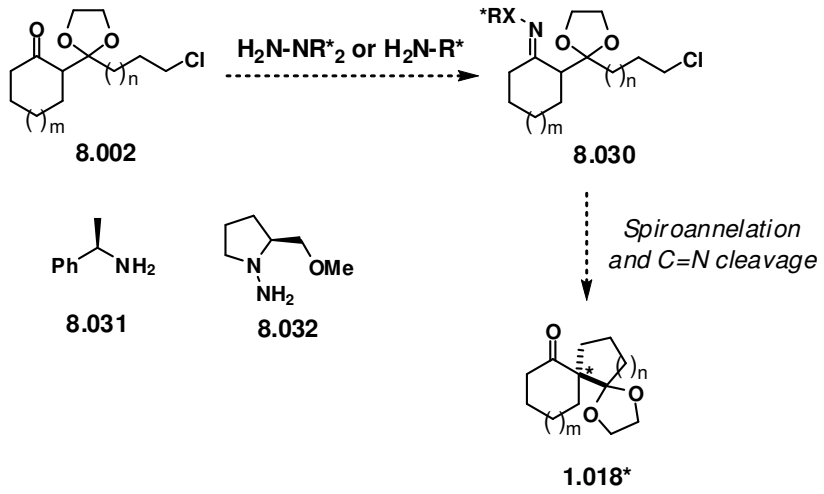
Scheme 8.18

Similar observations concerned the use of scandium triflate as a catalyst for the acetylation of alcohols by acetic anhydride. Under several occasions (Chapters 4 and 6), unforeseen deprotections were observed. A detailed discussion of these results was provided in Chapter 6.

All the products prepared during our work are racemic. Although a logical approach to the introduction of absolute chirality might consist in the use of optically active orthoesters, on which the dioxolanyl substituent bears

a C_2-symmetric chiral auxiliary (as already described in the literature for some cases[302]), this approach does not appear to be very general[303] and would clearly require a large screening of chiral auxiliaries. We believe that each class of silyl enolether presents different opportunities for the introduction of asymmetry. We have already presented three such possibilities in Chapter 3, Chapter 5 and Chapter 6.

Additionally, the condensation adducts **1.012** could be converted into the chiral imines/hydrazones **8.030** under standard conditions.



Scheme 8.19

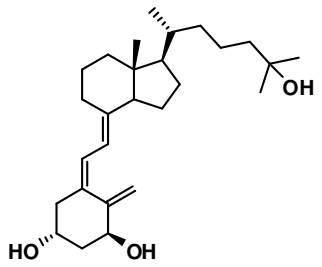
If these adducts **8.030** can be spiroannelated, chiral non-racemic spirocycles **1.018*** would be obtained after cleavage of the C=N bond. Given

[302] Longobardo, L.; Mobbili, G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *Tetrahedron* **1992**, *48*, 1299

[303] Cf. preliminary results in Vanherck, J.C. *Ph.D. Thesis*, **2004**, UCL

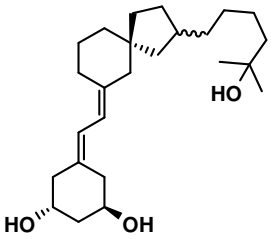
the known selectivity in the alkylation reactions of the hydrazones derived from **8.032**, as extensively described by Enders,[304] it might be anticipated that the quaternary center in **1.018*** would be formed with good stereocontrol.

The obtention of enantioenriched spirocycles is a very important endeavour. Throughout the past years, researchers have sought the introduction of the spiro-moiety as a conformational lock in biologically active substances. Recently, Pierre DeClercq and co-workers at Gent have reported the synthesis of Vitamin-D analogues **8.034** bearing a spirocyclic motif (Scheme 8.20).[305]



1α,25-dihydroxyvitamin D_3 (Calcitriol)

8.033



Spirocyclic analogue

8.034

Scheme 8.20

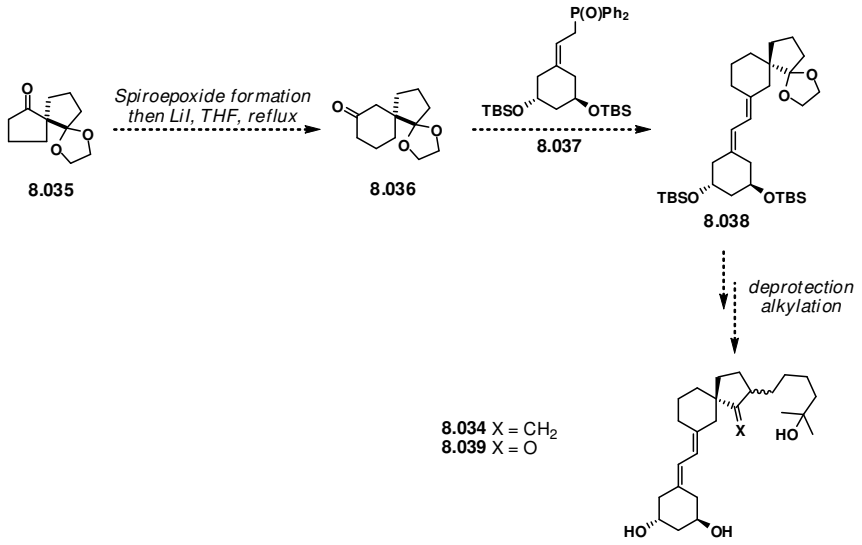
The synthesis of these analogues, however, was cumbersome and more than 13 steps were required for the elaboration of the spirocyclic core,

[304] Job, A. ; Janeck, C. ; Bettray, W. ; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253

[305] Schepens, W.; Van Haven, D.; Vandewalle, M.; Bouillon, R.; Verstuyf, A. ; De Clercq, J.P. *Org. Lett.* **2006**, *8*, 4247

which was finally coupled with the lower-portion of the molecule through a Wittig-Horner reaction.

We believe that such compounds could be easily accessed using our spiroannelation methodology. The spiroepoxide ring-expansion of **8.035** should provide the homologated, carbonyl-*transposed* ketone **8.036**. This compound could be directly coupled with the phosphine oxide **8.037** to provide the complete cyclic core of the Vitamin-D analogue, **8.038** in only 3 steps!

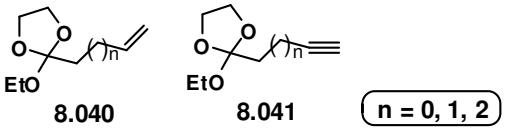


Scheme 8.21

The convergency of this approach (as opposed to the late-stage Wittig-Horner coupling in De Clercq's synthesis), the short number of steps required for the construction of the spirocyclic core and the possibility to evaluate different alkyl tethers through alkylation of **8.038** with various

electrophiles, are major assets of our proposed pathway. This synthetic approach is merely an example from the wealth of possible applications of enantioenriched versions of our spirocycles, including the synthesis of spirannic ligands for asymmetric catalysis.[303]

We also believe that some of the future developments in this area will involve the preparation and use of "second-generation" orthoesters, bearing different functionalities. The alkenes **8.040** and alkynes **8.041** are well-suited candidates. Preliminary work indicates the viability of the synthesis of such compounds through the conventional Pinner-alcoholysis procedure and even by novel electrochemical methods[306].

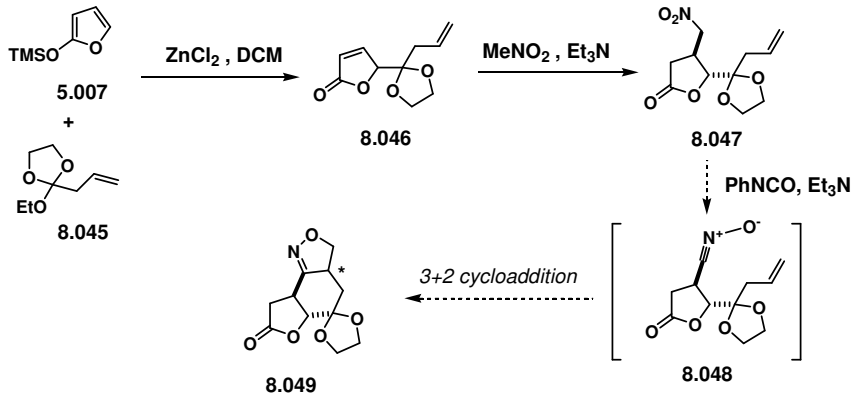


Scheme 8.22

The apparent inoccuous change of a halogen for an unsaturation should actually prove quite useful, as well as providing completely different reactivity patterns. For instance, preliminary results indicate that zinc chloride is much less efficient in promoting condensations of **8.040** and analogues, due to the propensity of zinc(II) salts to complexate double bonds. Among the many possibilities of application (and due to space limitations), we will only refer to two intriguing situations arising in the case of TMSOF **5.007**.

[306] Lebreux, F. *Ph.D. Thesis*, UCL, in progress

For instance (Scheme 8.23), we have already prepared the condensation adduct **8.046** in moderate yield using zinc chloride. Its conjugate attack by nitromethane provided the substituted lactone **8.047** exclusively as the *trans*-isomer, providing yet another example of the "dioxolane-effect"!

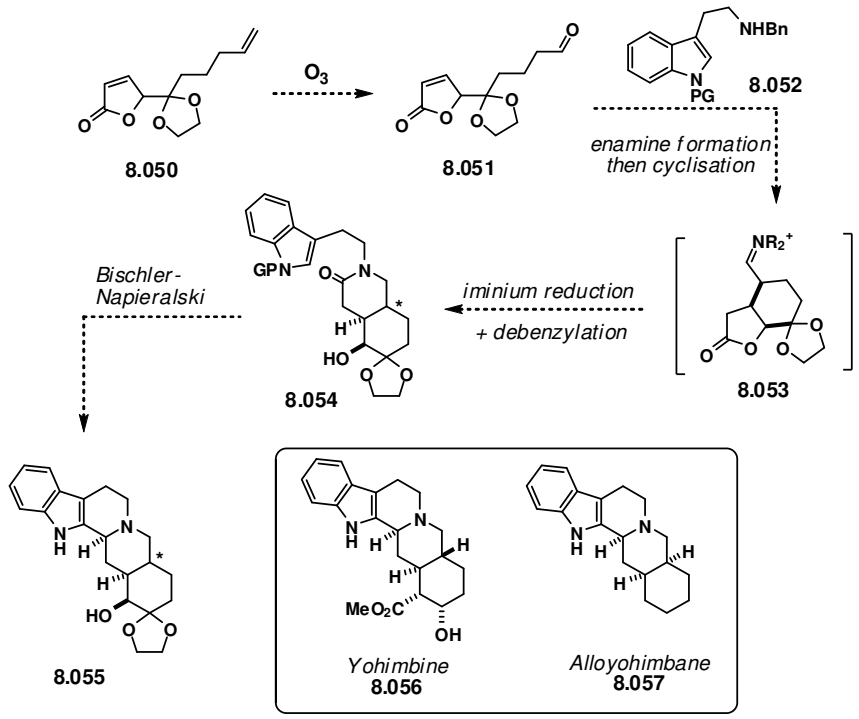


Scheme 8.23

If this nitrolactone is treated with a dehydrating agent such as PhNCO, the sequence of events depicted above might take place. Formation of the intermediate nitrile oxide **8.048** could be followed by an intramolecular [3+2]-cycloaddition onto the tethered double bond, affording the tricyclic oxazoline **8.049**. Interestingly, compound **8.049** is a highly functionalised, *trans*-fused analogue of the bicyclic lactones prepared in the TMSOF project. Moreover, the oxazoline moiety can be readily elaborated into further useful appendages.

Derivatives such as **8.046** (with longer or shorter tethers and bearing an alkyne terminus instead of the alkene) can also be used in other cyclisation processes, in particular Palladium-, Zinc- or Gold-promoted spiroannelations. The Kolbe decarboxylative-cyclisation of the derived carboxylic acids (after ozonolysis and oxidation) is currently being investigated in collaboration with Fréderic Lebreux and promising results have already been obtained.[306]

A completely different application of these adducts might lay in the exploitation of aldehyde **8.051**, as shown in Scheme 8.24.



Scheme 8.24

This aldehyde, available by ozonolysis of the alkene **8.050**, should undergo enamine formation when treated with a secondary amine such as the protected N-benzyltryptamine **8.052**. The enamine thus generated might then cyclise onto the pendant butenolide double bond, affording the iminium salt **8.053**. Reduction of this iminium salt (to the amine) followed by debenzylation might trigger a spontaneous transamidation. In such a process, the liberated amine moiety would intramolecularly add onto the γ-lactone ring and form the more stable 6-membered lactam **8.054**. This compound should then be amenable to classical Bischler-Napieralski cyclisation onto the indole ring, leading to tetracycle **8.055** in only 4-5 steps from condensation adduct **8.050**!

Such tetracycles actually embody most of the structural elements of the famous natural product Yohimbine **8.056** and its congeners.[307] In analogy with our previous results, we believe that kinetic formation of the *cis* ring-junction **8.053** might take place upon cyclisation. However, it is not sure wether the additional center formed (marked with an * in the Scheme) will be α- or β-oriented. In any case, it should be noted that Yohimbine and the Yohimbanes in general are not the only diastereomers found in nature. Indeed, besides the related family of Alloyohimbanes (such as the parent compound **8.057**), which are epimeric at the ring-junction, Reserpine, which also possesses a *trans* ring-junction, might be reached using this approach. Therefore, the orientation of the center marked with * is a key-step that will have to be controlled since it will determine which family of alkaloids shall become accessible through application of this methodology.

[307] Dorfman, L.; Furlenmeier, A.; Huebner, C.F.; Lucas, R.; MacPhillamy, H.B.; Mueller, J.M.; Schlitter, E.; Schwyzer, R.; St. André, A.F. *Helv Chim. Acta* **1954**, *37*, 59

From this brief recollection of perspectives, it is clear not only that the "orthoester adventure" on which we embarked at the beginning (Cf Chapter 1) still has a long road ahead, but also that possibilities for further development are rapidly expanding. If one may now confidently state that "imagination is the limit", it should be kept in mind that advances in both novel methodology and total synthesis, using functionalised orthoesters, will surely go hand-in-hand with additional pieces of evidence on the more fundamental questions of reactivity, stereocontrol and chemoselectivity. And, as it occurred for us, success, failure and serendipitous discovery are probably just lurking through each step of the way.

Chapter 9 : Experimental Section

Routine nuclear magnetic resonance (NMR) spectra were recorded on a VARIAN GEMINI-200 VXR-200 (^{1}H: 200 MHz and ^{13}C: 50 MHz), a BRUKER AC-250 (^{1}H: 250 MHz and ^{13}C: 62.5 MHz), a VARIAN GEMINI-2000 (^{1}H: 300 MHz and ^{13}C: 75 MHz) and a BRUKER AC-300 Avance II (^{1}H: 300 MHz and ^{13}C: 75 MHz). High field spectra were recorded on a BRUKER AM-500 (^{1}H: 500 MHz and ^{13}C: 125 MHz). ^{1}H chemical shifts (δH) are reported in ppm downfield from internal tetramethylsilane or calibrated from $CHCl_3$. ^{13}C NMR spectra were recorded using $CDCl_3$ as the internal standard. Detailed NMR assignments were done through analysis of 2D (COSY, HMQC) spectra.

Low-resolution mass spectra were recorded using VARIAN MATT-44 and FINNIGAN MAT-TSQ 70 spectrometers.

Infrared (IR) spectra were recorded as KBr disks or thin films, on a PERKIN ELMER 681 spectrometer and a SHIMADZU FTIR-8400S spectrometer and recorded in cm^{-1}.

Elemental analyses were carried out at the University of Stuttgart, Germany.

X-ray analyses were performed in the laboratory of Prof. Bernard Tinant and Prof. J. P. Declercq (UCL).

Thin-layer chromatographies (TLC) were performed on TLC aluminium sheets coated with Silica gel 60 F_{254} (Merck). The plates were visualised using ultra-violet light (256 nm) and developed using $KMnO_4$

and/or vanillin stain, which were prepared according to the following procedures:

Potassium permanganate: This stain was prepared by dissolving 3 g of $KMnO_4$ and 20 g of K_2CO_3 in 5 mL of 5% NaOH and 300 mL of water.

Vanillin: This stain was prepared by dissolving 2 g of vanillin in 100 mL of EtOH containing 1 mL of concentrated H_2SO_4.

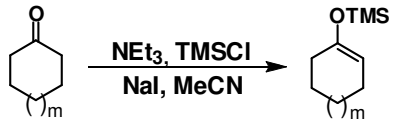
Flash chromatography was performed using Merck Silica Gel 60 (230-400 mesh) under pressure with the stated solvents.

All solvents were routinely distilled prior to use. Dry solvents were obtained by standard procedures according to D.D.Perrin and D.R.Perrin, *Purification of Laboratory Chemicals*. All commercially available compounds (Acros, Aldrich, Fluka and Lancaster) were used as received unless otherwise stated. All reactions were carried out under an atmosphere of argon in flame-dried apparatus with magnetic stirring, unless otherwise indicated.

9.1. Synthesis of silyl enolethers

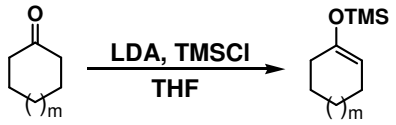
9.1.1. General procedures

Method A: DuBoudin procedure



To a round-bottomed flask containing the cyclic ketone (1 mmol, 1 eq.) and trimethylsilyl chloride (1.2 mmol, 1.2 eq.) in MeCN (1 mL, 1M) is added triethylamine (1.2 mmol, 1.2 eq.). Then, 1.2 mmol of sodium iodide in MeCN (1.2 mL, 1M) are added dropwise. After 14 hours stirring at room temperature, 1.5 mL water are added to the solution. The organic layer is extracted with 3 x 1.2 mL of pentane and dried ($MgSO_4$). The solvents are removed by evaporation under reduced pressure. The product thus obtained is further purified by distillation under reduced pressure.

Method B: Kinetic procedure



Diisopropylamine (0.18 mmol, 1.25 eq.) is introduced to a round-bottomed flask and cooled to 0°C. BuLi (0.16 mol, 1.1 eq.) is then added dropwise with stirring. Adeq.uate generation of LDA is indicated by the formation of a slightly yellowish gel. To this gel is then added THF (360 mL, 0.45M) and the resulting solution is cooled to -78°C. Then, 0.15 mol of the cyclic ketone (1 eq.) are added dropwise to the LDA solution. After 1h stirring at the same temperature, 0.24 mol of trimethylsilyl chloride (1.6 eq.) are slowly added. The temperature is allowed to rise up to 0°C over 2 hours,

at which point 200 mL water are added. The organic layer is extracted with 3 x 200 mL of pentane and dried ($MgSO_4$). The solvents are removed by evaporation under reduced pressure. The product thus obtained is further purified by distillation under reduced pressure.

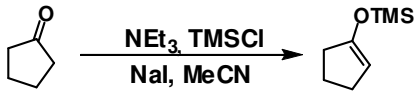
Modified Method B: for TMSOF derivatives

Same procedure as Method B until the addition of trimethylsilyl chloride, *inclusive*. The temperature is allowed to rise up to 0°C over 2 hours, at which point the volatiles are removed under high vaccuum (oil pump). 50 mL Pentane are added to the residue, which is then rapidly filtered over celite, under a blanket of Ar. After rinsing with 2 x 25 mL pentane, removal of the solvents under reduced pressure and distillation affords the corresponding products.

Note: Due to their instability, ^{13}C spectra could not be acquired for some of these known silyl enolethers. They are best characterised by their condensation adducts with our functionalised orthoesters.

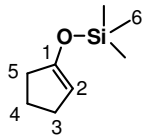
9.1.2. Synthesis of simple cyclic silyl enolethers (Chapters 2, 3 and 4)

(Cyclopent-1-enyloxy)trimethylsilane 2.032



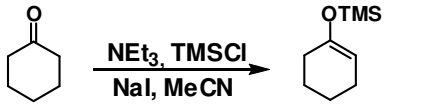
$C_8H_{16}OSi$
MW: 156.30
CAS: 19980-43-9

Method A: Starting from 8 g of cyclopentanone. After workup, 13 g (88%) of the product silyl enolether are obtained without further purification.



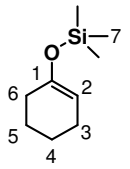
^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 0.21 (s, 9H, H-6), 1.85 (m, 2H, H-4), 2.25 (m, 4H, H-5 and H-3), 4.63 (t, 1H, *J* = 2.5 Hz, H-2).
^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 0.1 (C-6), 21.3 (C-4), 28.6 (C-3), 33.5 (C-5), 102.1 (C-2), 154.9 (C-1).
IR (film, cm^{-1}): 2958 (C-H), 1646 (C=C), 1343, 1253.

(Cyclohex-1-enyloxy)trimethylsilane 2.001



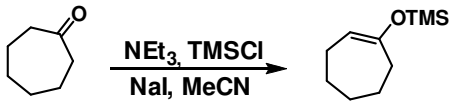
$C_9H_{18}OSi$
MW: 170.30
CAS: 6651-36-1

Method A: Starting from 9.8 g of cyclopentanone. After workup, 13.5 g (80%) of the product silyl enolether are obtained without further purification.



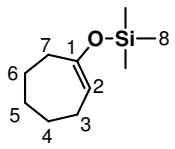
^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 0.17 (s, 9H, H-7), 1.47-1.68 (m, 4H, H-4 and H-5), 1.95 (m, 4H, H-3 and H-6), 4.86 (m, 1H, H-2).
^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 0.3 (C-7), 22.3, 23.2, 23.8 (C-3, C-4 and C-5), 29.9 (C-6), 104.2 (C-2), 150.2 (C-1).
IR (film, cm^{-1}): 2931 (C-H), 1670 (C=C), 1252, 1191.

(Cyclohept-1-enyloxy)trimethylsilane 2.067



$C_{10}H_{20}OSi$
MW: 184.35
CAS: 22081-48-7

Method A: Starting from 10.6 g of cycloheptanone. After workup, 13 g (70%) of the product silyl enolether are obtained without further purification.

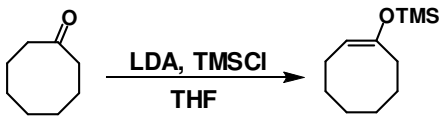


^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 0.15 (s, 9H, H-8), 1.45-1.75 (m, 6H, H-4, H-5 and H-6), 1.93-2.01 (m, 2H, H-3), 2.18-2.23 (m, 2H, H-7), 5.00 (t, 1H, J = 6.5 Hz, H-2).

^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 0.2 (C-8), 25.2, 25.3, 27.8, 31.5 (C-3, C-4, C-5 and C-6), 35.5 (C-7), 108.7 (C-2), 156.0 (C-1).

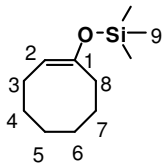
IR (film, cm^{-1}): 2922 (C-H), 1661 (C=C), 1446, 1251.

(Cyclooct-1-enyloxy)trimethylsilane 2.070



$C_{11}H_{22}OSi$
M.W.: 198,38
CAS: 50338-42-6

Method B: Starting from 10.0 g of cyclooctanone. After workup and distillation, 13.2 g (85%) of the product silyl enolether are obtained (bp: 92ºC/15 mm Hg).

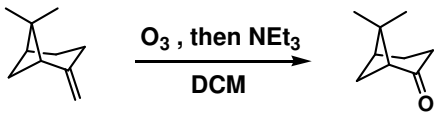


^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 0.18 (s, 9H, H-9), 1.45-1.60 (m, 8H, H-4, H-5, H-6 and H-7), 1.97-2.04 (m, 2H, H-3), 2.15-2.19 (m, 2H, H-8), 5.00 (t, 1H, *J* = 8.3 Hz, H-2).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 0.4 (C-9), 25.5, 26.3, 26.4, 27.8, 30.9, 31.0 (C-3, C-4, C-5, C-6, C-7 and C-8), 105.4 (C-2), 153.0 (C-1).

IR (film, cm^{-1}): 2918 (C-H), 1653 (C=C), 1442, 1191.

Nopinone (6,6-dimethylbicyclo[3.1.1]heptan-2-one) 2.079



$C_9H_{14}O$
M.W.: 138,21
CAS: 38651-65-9

In a 500 mL three-necked round-bottomed flask, are introduced 11.6 mL (10.0 g, 0.073 mol, 1 eq.) of β-pinene **2.078** and 250 mL of dichloromethane. The mixture is cooled to -78ºC and a flow of ozone (10

L/hour of oxygen) is passed through the solution for 6 hours at the same temperature. The solution is purged with Ar and allowed to warm to 0ºC. Then, 20.0 mL (15.0 g, 0.146 mol, 2 eq.) of triethylamine are carefully added and the mixture is allowed to reach room temperature overnight (12 h). 250 mL water are added and the organic layer is separated. The aqueous layer is extracted with 2 x 200 mL dichloromethane. The combined organic extracts are washed seq.uentially with water (200 mL) and brine (200 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue is dissolved in a minimum of diethyl ether and filtered through a plug of silica gel. After eluting with 100 mL diethyl ether, 9.8 g (98%) of the product ketone are obtained.

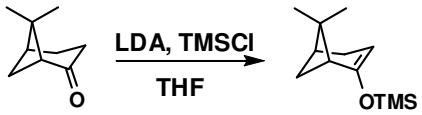
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 0.79 (s, 3H, H-8), 1.27 (s, 3H, H-8'), 1.51 (d, 1H, *J* = 9.5 Hz, H-3), 1.83-2.02 (m, 2H, H-5), 2.17-2.30 (m, 3H, H-4 and H-6), 2.32-2.48 (m, 2H, H-2 and H-3').

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 21.3 (C-5), 22.0 (C-8), 25.1 (C-8'), 25.8 (C-3), 32.7 (C-6), 40.3 (C-4), 41.2 (C-7), 57.8 (C-2), 214.8 (C-1).

IR (film, cm^{-1}): 2935 (C-H), 1704 (C=O), 1446.

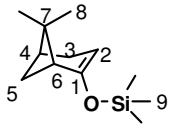
MS (CI+ev): *m/z* (%): 139 (25) $[M+H]^{+\cdot}$, 121 (5), 95 (20), 83 (45), 69 (60), 55 (50).

Nopinone silyl enolether ((6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yloxy)trimethylsilane) 2.087



$C_{12}H_{22}OSi$
M.W.: 210,14
CAS: 72453-33-9

Method B: Starting from 10.0 g of nopinone. After workup and distillation, 14.0g (90%) of the product silyl enolether are obtained (bp: 83-85ºC/8 mm Hg).



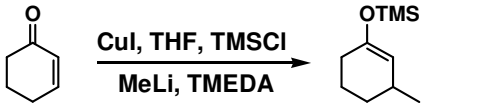
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 0.18 (s, 9H, H-9), 0.92 (s, 3H, H-8), 1.28 (apparent s, 4H, H-8' and H-5), 2.00 (dt, 1H, H-6, *J* = 5.5, 2.1 Hz), 2.05-2.09 (m, 1H, H-4), 2.14-2.19 (td, 2H, *J* = 11.0, 3.0 Hz, H-3), 2.36-2.42 (m, 1H, H-5), 4.54 (br s, 1H, H-2).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 0.4 (C-9), 21.2 (C-8), 26.0 (C-8), 27.9 (C-3), 31.3 (C-5), 38.5 (C-7), 40.7 (C-4), 48.0 (C-6), 96.3 (C-2), 158.7 (C-1).

IR (film, cm^{-1}): 2970 (C-H), 1622 (C=C), 900, 854.

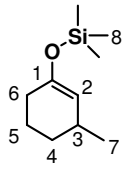
MS (APCI+ev): *m/z* (%): 211 (15) $[M+H]^{+\cdot}$, 155 (100), 121 (50), 93 (50).

Trimethyl(3-methyl-cyclohex-1-enyloxy)silane 2.085



$C_{10}H_{20}OSi$
M.W.: 184,35
CAS: 55373-58-5

In a 500 mL round-bottomed flask, 200 mL of THF are added to 21 g of CuI (0.11 mol, 1.1 eq.) and 50 mL TMEDA (0.33 mol, 3.3 eq.), at room temperature. The resulting mixture is stirred for 30 minutes to ensure complete dissolving of the copper salts. The green solution is then cooled to -78°C and 62 mL of MeLi (1.6 M, 0.1 mol, 1 eq.) are added dropwise over an hour. The solution turns from green to yellow. Still at -78°C, 33 mL of TMSCl (0.26 mol, 2.6 eq.) are slowly added, directly followed by 10 mL of cyclohexenone (0.1 mol, 1 eq.) dissolved in 100 mL of THF. After 2 hours stirring at -78°C, 400 mL of cold pentane are poured into the solution. The organic layer is successively washed with 2 x 250 mL cold HCl (0.1N), 3 x 250 mL of a cold saturated solution of $NaHCO_3$ and finally by 250 mL of water. The organic extract is dried ($MgSO_4$) and the solvents are removed by evaporation under reduced pressure. The silyl enolether is purified by flash chromatography (silica, PE/AcOEt 4:1, Rf = 0.9), affording 15.7 g (85%) of **2.085** as a colorless oil.



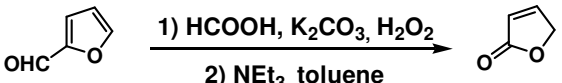
^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 0.17 (s, 9H, H-8), 0.92 (d, 3H, *J* = 8.1 Hz, H-7), 1.51-1.77 (m, 4H, H-4 and H-5), 1.92-2.00 (m, 2H, H-6), 2.23 (m, 1H, H-3), 4.74 (br s, 1H, H-2).

^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 0.3 (C-8), 21.8 (C-5), 22.5 (C-7), 29.5 (C-3), 29.9 (C-4), 31.2 (C-6), 111.1 (C-2), 150.1 (C-1).

IR (film, cm^{-1}): 2958 and 2931 (C-H), 1662 (C=C), 1252, 1191, 951.

9.1.3. Synthesis of TMSOF-derivatives (Chapter 5)

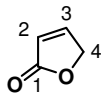
Furan-2(5H)-one 5.038



$C_4H_4O_2$
Mol. Wt.: 84,07
CAS: 497-23-4

A 1L-two necked round-bottomed flask, eq.uipped with a reflux condenser and a dropping funnel, is charged seq.uentially with 96 g of furfuraldehyde (1 mol, 1 eq.), 500 mL CH_2Cl_2, 92 g formic acid (2 mol, 2

eq.), 100 g Na_2SO_4 and 35 g K_2CO_3. The resulting mixture is vigorously stirred and 75 mL of 30% H_2O_2 are added in one portion. Stirring is continued for 30-45 minutes, after which time the mixture begins to gently reflux. Then 125 mL of 30% H_2O_2 are added dropwise over 3 hours. The mixture is allowed to cool down to room temperature, with stirring, overnight. After phase separation, the aqueous layer was extracted with 100 mL of dichloromethane and the combined organic extracts are concentrated under reduced pressure. 200 mL Toluene are then added followed by 2g of NEt_3 and the dark mixture is allowed to stand for 1 hour. After evaporation of the solvents under reduced pressure, distillation typically afforded 35.0 g (40%) of **5.038** as a yellow oil (bp 89-91°C/15 mm Hg).

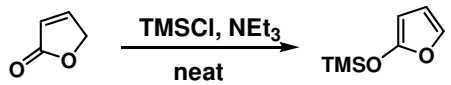


^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 4.91 (dd, 2H, *J* = 2.0, 1.5 Hz, H-4), 6.17 (ddd, 1H, *J* = 5.5, 2.0, 1.5 Hz, H-2), 7.59 (ddd, 1H, *J* = 5.5, 2.0, 1.5 Hz, H-3).

^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 72.1 (C-4), 121.5 (C-2), 152.8 (C-3), 173.6 (C-1).

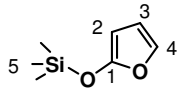
IR (neat, cm^{-1}): 3098, 2936, 1773 and 1741 (C=O), 1600, 1448, 1348, 1159, 1094.

2-(trimethylsilyloxy)-furan 5.007



$C_7H_{12}O_2Si$
Mol. Wt.: 156,25
CAS: 61550-02-5

To a 100 mL two-necked round-bottomed flask are added 12.0 g of furanone **5.038** (0.142 mol, 1 eq.) and 21.6 mL triethylamine (0.155 mol, 1.1 eq.). The mixture is cooled to 0°C and 18.8 mL of TMSCl (0.149 mol, 1 eq.) are added dropwise. A colorless precipitate forms instantly and the reaction mixture is stirred for 12 h. Direct fractional distillation of the mixture under reduced pressure afforded a crude product containing a small amount of a colorless precipitate. This crude material is stirred for 30 minutes under Ar at room temperature whereby more colorless precipitate formed. Rapid filtration and redistillation afforded pure silyl enolether (11.0 g, 49%) as a colorless liquid (bp 41-42°C/15 mm Hg).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 0.30 (s, 9H, H-5), 5.10 (dd, 1H, *J* = 3.0, 1.0 Hz, H-2), 6.21 (dd, 1H, *J* = 3.0, 2.0 Hz, H-3), 6.82 (dd, 1H, *J* = 2.0, 1.0 Hz, H-4).

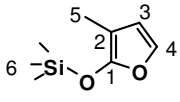
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): -0.3 (C-5), 83.2 (C-3), 111.0 (C-2), 132.4 (C-4), 156.7 (C-1).

IR (neat, cm^{-1}): 3134, 2964, 2903, 1780, 1618, 1383, 1256, 1148.

3-methyl-2-(trimethylsilyloxy)furan 5.040

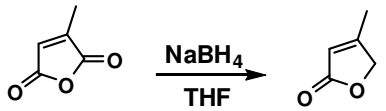
$C_8H_{14}O_2Si$
Mol. Wt.: 170,28
CAS: 61550-03-6

Modified method B: Starting from 5.0 g of 3-methylfuran-2-one **5.039**. After workup and distillation, 6.0 g (70%) of the product silyl enolether are obtained (bp 75-80°C/20 mbar).



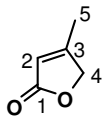
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 0.24 (s, 9H, H-6), 1.79 (s, 3H, H-5), 6.07 (d, 1H, *J* = 2.1 Hz, H-3), 6.72 (d, 1H, *J* = 1.8 Hz, H-4).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 0.2 (C-6), 8.5 (C-5), 92.3 (C-2), 113.4 (C-3), 131.3 (C-4), 156.8 (C-1).

4-methyl-furan-2-one 5.042



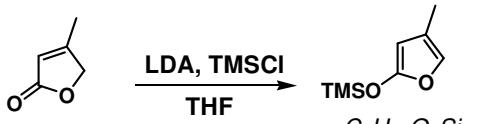
$C_5H_6O_2$
M.W.: 98,10
CAS: 6124-79-4

In a 500 mL round-bottomed flask are introduced 6.8 g (0.178 mol, 1 eq.) of sodium borohydride and 80 mL of THF. The mixture is cooled to 0ºC. Then, 20 g of citraconic anhydride (0.178 mol, 1 eq.) in 100 mL THF are added dropwise over 10 minutes and the mixture is stirred at 0ºC for 45 minutes, warmed to room temperature and then stirred for a further 45 minutes. The solution is recooled to 0ºC and 80 mL of 6M HCl are added slowly with stirring, after which slow warming to room temperature is effected. After removal of volatiles under reduced pressure, 150 mL water are added to the residue, which is extracted with 2 x 100 mL diethyl ether (thus removing minor by-products). The aqueous layer is then extracted with 3 x 100 mL ethyl acetate. The pooled ethyl acetate extracts are dried ($MgSO_4$) and the solvents are removed under reduced pressure. Distillation finally affords 6.0 g (40%) of the product (bp 60-64ºC/3.5 mm Hg).



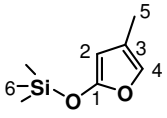
^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 2.11 (s, 3H, H-5), 4.72 (s, 2H, H-4), 5.84 (s, 1H, H-2).

4-methyl-2-(trimethylsilyloxy)furan 5.043



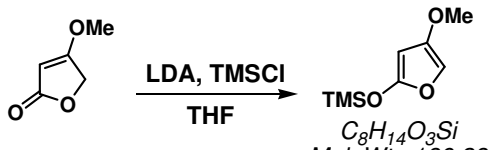
$C_8H_{14}O_2Si$
Mol. Wt.: 170,28
CAS: 61550-04-7

Modified method B: Starting from 6.9 g of 4-methylfuran-2-one **5.042**. After workup and distillation, 9.5 g (80%) of the product silyl enolether are obtained (bp 47-50°C/15 mm Hg).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 0.30 (s, 9H, H-6), 1.90 (s, 3H, H-5), 4.97 (s, 1H, H-2), 6.42 (s, 1H, H-4).

4-methoxy-2-(trimethylsilyloxy)furan 5.022

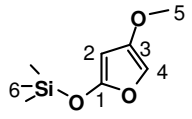


$C_8H_{14}O_3Si$
Mol. Wt.: 186,28
CAS: 82204-15-7

Modified method B: Starting from 5.0 g of 4-methoxyfuran-2-one **5.044** and performing all technical operations under Ar and all solvent exchanges at the high-vacuum oil pump.

Alternatively, deprotonation can be done with BuLi. In a 500 mL round-bottomed flask, 30.1 mL of BuLi (1.6M solution, 50 mmol, 1 eq.) are dissolved in 200 mL THF and cooled to -78°C. A solution of 5.7 g (50 mmol, 1 eq.) 4-methoxyfuran-2-one **5.044** in 100 mL THF is precooled and added *via cannula* to the BuLi solution, over 5 minutes. Then, a solution of 10.8 mL (85 mmol, 1.7 eq.) of trimethylsilyl chloride in 10 mL THF is cooled and added *via cannula* into the above mixture, at -78°C. Workup is done as previously, excluding moisture as much as possible.

After workup and distillation, 5.3 g (65%) of the product silyl enolether are obtained (bp 80-85°C/15 mm Hg).

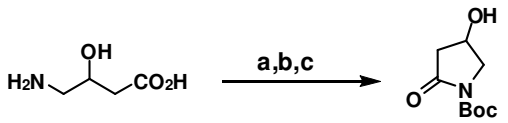


^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 0.10 (s, 9H, H-6), 3.31 (s, 3H, H-5), 4.72 (d, 1H, *J* = 2.0 Hz, H-2), 6.19 (d, 1H, *J* = 1.9 Hz, H-4).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 0.3 (C-6), 57.2 (C-5), 79.4 (C-2), 113.0 (C-4), 151.2 (C-3), 155.4 (C-1).

9.1.4. Synthesis of TBSOP (Chapter 6)

tert-butyl 4-hydroxy-2-oxopyrrolidine-1-carboxylate 6.041

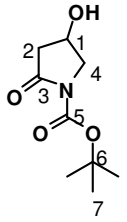


$C_9H_{15}NO_4$
M.W.: 201,22
CAS: 409341-03-3

a) HMDS, py, xylene, reflux; b) Boc_2O, DMAP, AcOEt; c) NEt_3.HF, AcOEt

In a three-necked, 250 mL round-bottomed flask with reflux condenser are introduced 10.0 g (83.9 mmol, 1 eq.) of (±)-4-amino-3-hydroxybutyric acid and 100 mL of xylene. Then, 50 mL (618.2 mmol, 7.4 eq.) of pyridine and 28,6 mL (135.6 mmol, 1.6 eq.) of HMDS are added. The ensuing mixture is heated at reflux for 14 hours. After evaporation of the solvents under reduced pressure, the residue is dissolved in 20 mL of ethyl acetate. The solution is cooled to 0ºC and 500 mg (4.1 mmol, 0.05 eq.) of DMAP and 21.5 g (98.5 mmol, 1.2 eq.) of di-*tert*-butyl dicarbonate in 21 mL of ethyl acetate are added dropwise. The mixture is stirred for 30 minutes at 0ºC and for 17 hours at room temperature.

At this stage, 5.9 ml (36.6 mmol, 0.4 eq.) of NEt_3.HF are slowly added and stirring is continued for 1 hour, after which 163 mL of heptane are added dropwise *via* a dropping funnel and the mixture is stirred for 2.5 hours at 0ºC. The product is collected by filtration and washed with 75 mL of heptane. The resulting grey solid is dried under vacuum for 2 hours and placed in a desiccator for 12 h, affording 15.8 g (94%) of **6.041** as a white solid.



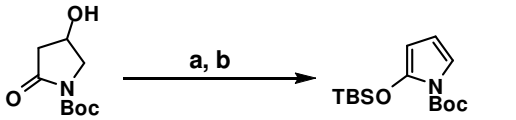
^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.52 (s, 9H, H-7), 2.48-2.56 (br d, 1H, *J* = 17.7 Hz, H-2), 2.78 (dd, 1H, *J* = 17.7, 6.2 Hz, H-2'), 3.74-3.80 (br d, 1H, *J* = 12.0 Hz, H-1), 4.44-4.52 (m, 2H, H-4).

^{13}C-NMR (62.5 MHz, $CDCl_3$) δ (ppm): 28.2 (C-7), 42.9 (C-4), 55.4 (C-2), 63.4 (C-1), 83.4 (C-6), 150.2 (C-5), 172.5 (C-3).

IR (film, cm^{-1}): 3452 (O-H), 2981 (C-H), 2935 (C-H), 1776 (C=O), 1716 (C=O), 1369, 1304, 1151.

MS (CI+ev): *m/z* (%) 202 (5) $[M+H]^+$, 146 (100), 128 (12), 110 (15), 57 (13).

2-(*tert*-butyldimethylsilyloxy)-1-*tert*butoxycarbonylpyrrole 6.001



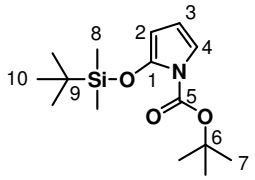
$C_{15}H_{27}NO_3Si$
M.W.: 297,47
CAS: 141293-28-9

a) MsCl, NEt_3, THF; b) TBSOTf, NEt_3, THF

In a 250 mL round-bottomed flask, 3.2 g (15.9 mmol, 1 eq.) of the lactam **6.041** are added to 35 mL THF. To this solution are added 6.1 mL (21.9 mmol, 1.4 eq.) of triethylamine and the mixture is cooled to 0°C. Then, 1.5 mL (20.2 mmol, 1.3 eq.) of methanesulfonyl chloride are introduced dropwise, after which stirring is continued for 30 minutes at 0°C and 2 hours at room temperature. At this point, 40 mL of ethyl acetate are added and stirring is continued for another 30 minutes. The mixture is filtered and the filtrate is washed with 2 x 20 mL of brine. The aqueous layer is further extracted with 50 mL AcOEt. The combined organic fractions are dried ($MgSO_4$) and evaporated under reduced pressure.

Subseq.uently, the residue is dissolved in 37 mL dichloromethane. 3.3 g of celite, 30 mL of heptane and 6.2 mL (44.5 mmol, 2.8 eq.) of triethylamine are seq.uentially introduced, before cooling to 0°C. Then, 4.1 mL (17.8 mmol, 1.1 eq.) of TBSOTf are added dropwise, after which stirring is continued at 0°C for a further 1 hour. 1 mL of MeOH is added and the mixture is kept under stirring at 0°C for 20 minutes. After evaporation of the solvents under reduced pressure, the resulting solid is washed with 100 mL heptane. The filtrate is collected and evaporated under reduced pressure, furnishing 4.5 g (94%) of the silyl enolether **6.001**. If req.uired, rapid

filtration of this product through a small pad of silica gel, eluting with heptane, affords pure silyl enolether.



^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 0.23 (s, 6H, H-8), 0.99 (s, 9H, H-10), 1.57 (s, 9H, H-7), 5.23 (dd, 1H, *J* = 3.5, 2.0 Hz, H-2), 6.90 (t, 1H, *J* = 3.6 Hz, H-3), 6.70 (dd, 1H, *J* = 4.0, 2.0 Hz, H-4).

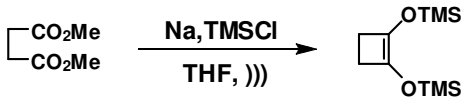
^{13}C-NMR (62.5 MHz, $CDCl_3$) δ (ppm): -2.9 (C-8), 18.5 (C-9), 25.9 (C-10), 28.2 (C-7), 82.3 (C-6), 92.6 (C-2), 108.2 (C-3), 113.2 (C-4), 143.7 (C-1), 148.4 (C-5).

IR (film, cm^{-1}): 2932 (C-H), 2858 (C-H), 1751 (C=O), 1585, 1369, 1514, 1323, 1134.

MS (APCI+ev): *m/z* (%) 298 (23) $[M+H]^+$, 242 (100), 238 (37), 182 (7).

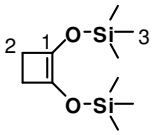
9.1.5. Synthesis of silylated acyloins (Chapter 7)

1,2-bis(trimethylsilyloy)cyclobutene 7.080



$C_{10}H_{22}O_2Si_2$
M.W.: 230,45
CAS: 17082-61-0

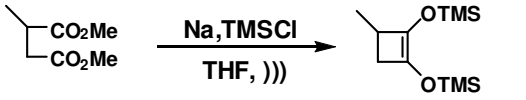
In a two-necked 500 mL round-bottomed flask eq.uipped with a reflux condenser, sodium (14 g, 0.63 mol, 4.2 eq.) is added to toluene (200 ml) and refluxed for 0.5 hours, during which time molten sodium forms. The flask is then carefully removed from the heating source and shaken vigorously, upon which the formation of numerous small particles of metallic sodium is instantly observed. The mixture is allowed to cool to room temperature, toluene is decanted and exchanged with 200 mL THF. The resulting suspension is cooled to 0°C in an ultrasound bath and a solution of trimethylsilyl chloride (80 ml, 0.63 mol, 4.2 eq.) and dimethyl succinate (22 g, 0.15 mol, 1 eq.) in THF (40 ml) is then added dropwise with stirring over a period of 1.5 hours. Stirring is continued for a further 2 hours, after which dry diethyl ether (200 ml) is added and the mixture is allowed to stand at 4°C overnight. The resulting precipitate is filtered off and the filtrate is concentrated in vacuo. Fractional distillation of the residue affords 20 g (60%) of the product (bp: 73°C/12 mm Hg).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 0.09 (s,18H, H-3), 2.15 (s, 4H, H-2).

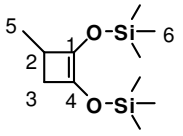
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): -0.4 (C-3), 25.4 (C-2), 119.4 (C-1).

3-methyl-1,2-bis(trimethylsilyloxy)cyclobutene 7.130



$C_{11}H_{24}O_2Si_2$
M.W.: 244,45
CAS: 36332-35-1

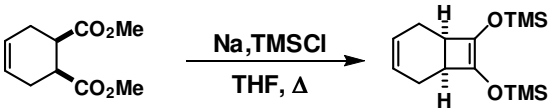
In a two-necked 250 mL round-bottomed flask eq.uipped with a reflux condenser, sodium (7 g, 0.31 mol, 4.2 eq.) is added to toluene (100 ml) and refluxed for 0.5 hours, during which time molten sodium forms. The flask is then carefully removed from the heating source and shaken vigorously, upon which the formation of numerous small particles of metallic sodium is instantly observed. The mixture is allowed to cool to room temperature, toluene is decanted and exchanged with 100 mL THF. The resulting suspension is cooled to 0°C in an ultrasound bath and a solution of trimethylsilyl chloride (40 ml, 0.31 mol, 4.2 eq.) and 3-methyldimethyl succinate (11 g, 0.07 mol, 1 eq.) in THF (20 ml) is then added dropwise with stirring over a period of 1.5 hours. Stirring is continued for a further 2 hours, after which dry diethyl ether (100 ml) is added and the mixture is allowed to stand at 4°C overnight. The resulting precipitate is filtered off and the filtrate is concentrated in vacuo. Fractional distillation of the residue affords 8.4 g (50%) of the product (bp: 74-75°C/15 mm Hg).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 0.22 (s, 9H, H-6), 0.23 (s, 9H, H-6'), 1.12 (d, 3H, *J* = 6.5 Hz, H-5), 1.67 (dd, 1H, *J* = 9.5 Hz, 1.8 Hz, H-3), 2.20-2.40 (m, 1H, H-3'), 2.35-2.47 (m, 1H, H-2).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 0.32 (C-6), 0.35 (C-6'), 17.8 (C-5), 33.2 (C-2), 35.4 (C-3), 131.3 (C-4), 135.2 (C-1).

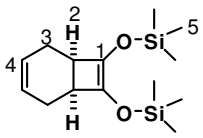
cis-7,8-bis(trimethylsilyloxy)bicyclo[4.2.0]octa-3,7-diene 7.140



$C_{14}H_{26}O_2Si_2$
M.W.: 282,53
CAS: 18014-24-9

In a two-necked 250 mL round-bottomed flask eq.uipped with a reflux condenser, sodium (3.5 g, 0.15 mol, 4.2 eq.) is added to toluene (50 ml) and refluxed for 0.5 hours, during which time molten sodium forms. The flask is then carefully removed from the heating source and shaken vigorously, upon which the formation of numerous small particles of metallic sodium is instantly observed. To the resulting suspension is added dropwise a solution of trimethylsilyl chloride (20 ml, 0.15 mol, 4.2 eq.) and the diester (7.5 g,

0.03 mol, 1 eq.) in THF (10 ml) and the mixture is refluxed. Stirring is continued for a further 2 hours, after which the solvents are evaporated under reduced pressure. The residue is dissolved in dry diethyl ether and the resulting precipitate is filtered off. After concentration under reduced pressure, fractional distillation of the residue affords 3.4 g (42%) of the product.

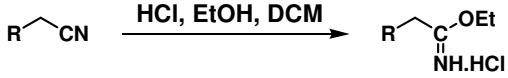


^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 0.18 (s, 18H, H-5), 2.10 (m, 4H, H-3), 3.00 (m, 2H, H-2), 5.56 (m, 2H, H-4).

9.2. Synthesis of orthoesters

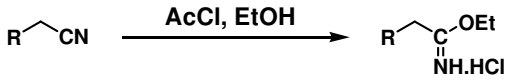
9.2.1. General procedures

Method A : Synthesis of imidate salts from nitriles using gaseous HCl



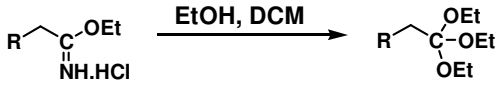
In a 2L three-necked round-bottomed flask, 0.6 mol of the nitrile (1 eq.) are added to 50 mL ethanol (0.85 mol, 1.45 eq.) dissolved in 1L of dichloromethane. The solution is cooled between -40°C and -30°C before being saturated in gaseous HCl. After reaching saturation, the temperature is gradually raised to 8°C, whilst allowing excess HCl to leave *via* a trap containing a 2M KOH solution. The flask is then closed under Ar and the solution is stirred for 6 days at 8°C. After this period, the solvents are evaporated under reduced pressure, leading to the obtention of a white solid. In order to eliminate excess HCl, the solid is thoroughly washed with diethyl ether (1 L) and dried under high-vaccuum (0.3 mbar) for 12 hours.

Method B : Synthesis of imidate salts from nitriles using in-situ generated HCl



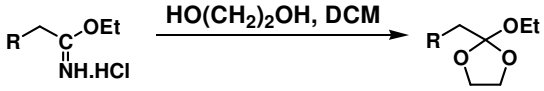
In a 150 mL round-bottomed flask, 55.4 mmol (1 eq.) of the nitrile are dissolved in 39.2 mL (0.66 mol, 12 eq.) of ethanol. The resulting solution is cooled to 0°C and 31.6 mL (0.44 mol, 8 eq.) of acetyl chloride are added dropwise (strongly exothermic reaction). The mixture is stirred at room temperature for 12 hours, after which the solvents are removed under reduced pressure. The thus obtained solid is thoroughly washed with diethyl ether (150 mL) and dried under high-vaccuum (0.3 mbar) for 12 hours.

Method C : Synthesis of acyclic orthoesters from imidate salts



In a 250 mL round-bottomed flask, 14.5 mL of ethanol (0.25 mol, 10 eq.) are added to 25 mmol of imidate (1 eq.) in 100 mL of dichloromethane. The suspension is stirred for 4 days at room temperature, after which the solvents are evaporated under reduced pressure. The residue is diluted with 75 mL of diethyl ether and the precipitate is removed by filtration. The filtrate is stirred over a biphasic system with an aqueous solution of KOH (2M) for 2 hours at room temperature, taking care not to mix the phases. After phase separation, the aqueous layer is extracted with 2 x 50 mL of dichloromethane. The combined organic extracts are dried ($MgSO_4$) and concentrated under reduced pressure. The product thus obtained is used without further purification.

Method D : Synthesis of cyclic (dioxolane) orthoesters from imidate salts

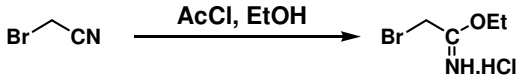


In a 3 L round-bottomed flask, 31.1 g of ethylene glycol (0.50 mol, 0.85 eq.) are added to 0.59 mol of imidate (1 eq.) in 2 L of dichloromethane. The suspension is stirred for 6 days at room temperature, after which the solvents are evaporated under reduced pressure. The residue is diluted with 800 mL of diethyl ether and the precipitate is removed by filtration. The

filtrate is concentrated under reduced pressure and the residue dissolved in 250 mL dichloromethane. This solution is then stirred over a biphasic system with an aqueous solution of KOH (2M) for 12 hours at room temperature, taking care not to mix the phases. After phase separation, the aqueous layer is extracted with 2 x 50 mL of dichloromethane. The combined organic extracts are dried ($MgSO_4$) and concentrated under reduced pressure. The product thus obtained is used without further purification.

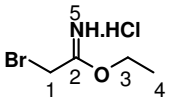
9.2.2. Preparation of imidates

Ethyl 2-bromo-acetimidate 5.051



$C_4H_9BrClNO$
M.W.: 202,48

Method B: Starting from 10.0 g of 2-bromoacetonitrile. After workup, 14.6 g (87%) of the product imidate are obtained.

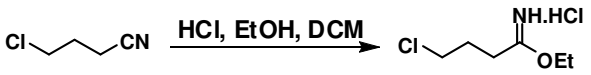


^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.56 (t, 3H, *J* = 7.0 Hz, H-4), 4.21 (s, 2H, H-1), 4.76 (q, 2H, *J* = 7.0 Hz, H-3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 13.5 (C-4), 32.1 (C-1), 72.4 (C-3), 173.2 (C-2).

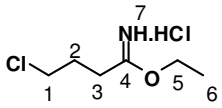
IR (film, cm^{-1}): 3406 (N-H), 2986 (C-H), 1690 (C=N), 1412.

Ethyl 4-chloro-butyrimidate 2.051



$C_6H_{13}Cl_2NO$
M.W.: 186,08
CAS: 89224-42-0

Method A: Starting from 61.0 g of 4-chlorobutyronitrile. After workup, 105.2 g (96%) of the product imidate are obtained.

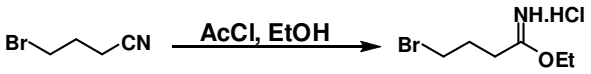


^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 1.51 (t, 3H, *J* = 7.0 Hz, H-6), 2.22-2.29 (m, 2H, H-2), 2.95 (t, 2H, *J* = 7.5 Hz, H-3), 3.64 (t, 2H, *J* = 6.0 Hz, H-1), 4.67 (q, 2H, *J* = 7.0 Hz, H-5), 11.59 (br s, 1H, H-7), 12.45 (br s, 1H, H-7').

^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 13.4 (C-6), 28.2, 30.3 (C-2 and C-3), 43.1 (C-1), 70.9 (C-5), 178.3 (C-4).

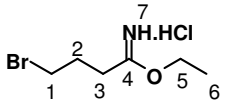
IR (film, cm^{-1}): 2609 (C-H), 1651 (C=N), 1437, 1129, 1092.

Ethyl 4-bromo-butyrimidate 5.052



$C_6H_{13}BrClNO$
M.W.: 230,53
CAS: 36743-67-6

Method B: Starting from 8.2 g of 4-bromobutyronitrile. After workup, 11.6 g (91%) of the product imidate are obtained.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.51 (t, 3H, *J* = 7.1 Hz, H-6), 2.25-2.40 (m, 2H, H-2), 2.93 (t, 2H, *J* = 7.5 Hz, H-3), 3.47 (t, 2H, *J* = 6.3 Hz, H-1), 4.67 (q, 2H, *J* = 6.9 Hz, H-5), 11.62 (br s, 1H, H-7).

^{13}C-NMR (62.5 MHz, $CDCl_3$) δ (ppm): 13.8 (C-6), 28.6, 31.3, 32.1 (C-1, C-2 and C-3), 71.3 (C-5), 178.4 (C-4).

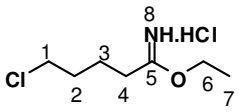
IR (film, cm^{-1}): 2856, 1652 (C=N), 1446, 1265, 1097.

MS (APCI+ev): *m/z* (%): 196 (100) [*M for ^{81}Br-Cl*]$^{+\cdot}$, 194 (98) [*M for ^{79}Br-Cl*]$^+$, 168 (20), 166 (17).

Ethyl 5-chloro-pentanimidate 2.052

$C_7H_{15}Cl_2NO$
M.W.: 200,11
CAS: 89569-57-3

Method A: Starting from 25.0 g of 4-chloropentanenitrile. After workup, 41.7 g (98%) of the product imidate are obtained.



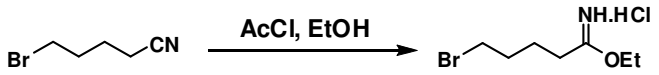
^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 1.51 (t, 3H, *J* = 7.0 Hz, H-7), 1.87-1.94 (m, 4H, H-2 and H-3), 2.80 (t, 2H, *J* = 7.0 Hz, H-4), 3.58 (t, 2H, *J* = 5.7 Hz, H-1), 4.66 (q, 2H, *J* = 7.0 Hz, H-6), 11.60 (br s, 1H, H-8), 12.50 (br s, 1H, H-8').

^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 15.5 (C-7), 22.1, 31.3, 32.2 (C-2, C-3 and C-4), 43.8 (C-1), 70.7 (C-6), 178.7 (C-5).

IR (film, cm^{-1}): 3396 (N-H), 2958 (C-H), 1654 (C=N), 1390, 1095.

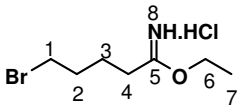
MS (FAB): *m/z* (%): 166 (100), 164 (79) $[M\text{-}Cl]^+$, 138 (25), 136 (17), 91 (7).

Ethyl 5-bromo-pentanimidate 5.053



$C_7H_{15}BrClNO$
M.W.: 244,56
CAS: 85691-63-0

Method A: Starting from 12.5 g of 4-bromopentanenitrile. After workup, 20.8 g (97%) of the product imidate are obtained.

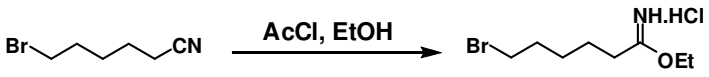


^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.50 (t, 3H, *J* = 7.0 Hz, H-7), 1.84-1.99 (m, 4H, H-2 and H-3), 2.80 (t, 2H, *J* = 7.0 Hz, H-4), 3.44 (t, 2H, *J* = 6.1 Hz, H-1), 4.67 (q, 2H, *J* = 7.0 Hz, H-6), 11.40 (br s, 1H, H-8), 12.36 (br s, 1H, H-8').

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 15.5 (C-7), 22.4, 31.1, 31.9, 32.1 (C-1, C-2, C-3 and C-4), 71.0 (C-6), 178.2 (C-5).

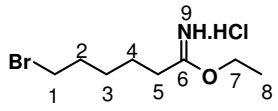
IR (film, cm^{-1}): 3390 (N-H), 2960 (C-H), 1651 (C=N), 1410, 1093.

Ethyl 5-bromo-hexanimidate



$C_8H_{17}BrClNO$
M.W.: 258,58
CAS: 94115-35-2

Method A: Starting from 10.0 g of 6-bromohexanenitrile. After workup, 12.2 g (83%) of the product imidate are obtained.



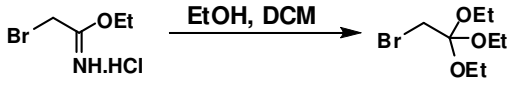
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.50 (t, 3H, *J* = 7.0 Hz, H-8), 1.95-2.05 (m, 6H, H-2, H-3 and H-4), 2.77 (t, 2H, *J* = 7.1 Hz, H-5), 3.52 (t, 2H, *J* = 6.4 Hz, H-1), 4.70 (q, 2H, *J* = 7.0 Hz, H-7), 11.50 (br s, 1H, H-9), 12.16 (br s, 1H, H-9').

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 13.7 (C-8), 22.9, 31.2, 31.4, 32.2, 32.3 (C-1, C-2, C-3, C-4 and C-5), 71.0 (C-7), 178.8 (C-6).

IR (film, cm^{-1}): 3390 (N-H), 2982 (C-H), 1650 (C=N), 1410, 1093.

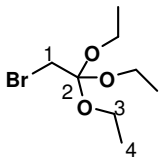
9.2.3. Preparation of orthoesters

2-bromo-1,1,1-triethoxyethane 5.054



$C_8H_{17}BrO_3$
M.W.: 241,12
CAS: 40070-39-1

Method C: Starting from 5.0 g of 2-bromoacetimidate. After workup, 6.0 g (86%) of the product orthoester are obtained.

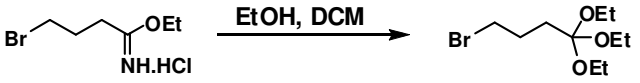


^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.17 (t, 9H, *J* = 7.5 Hz, H-4), 3.49-3.56 (m, 8H, H-1 and H-3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 15.0 (C-4), 30.1 (C-1), 57.7 (C-3), 112.4 (C-2).

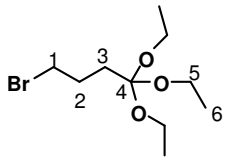
IR (film, cm^{-1}): 2960 (C-H), 2932 (C-H), 1440, 1201, 1048.

4-bromo-1,1,1-triethoxybutane 5.055



$C_{10}H_{21}BrO_3$
M.W.: 269,18
CAS: 98897-63-3

Method C: Starting from 14.5 g of 4-bromobutyrimidate. After workup, 15.2 g (90%) of the product orthoester are obtained.

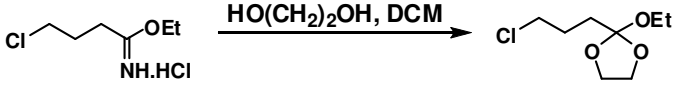


^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.15 (t, 9H, *J* = 7.0 Hz, H-6), 1.80-1.91 (m, 4H, H-2 and H-3), 3.40-3.64 (m, 8H, H-1 and H-5).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 15.0 (C-6), 26.6, 29.6, 30.1 (C-1, C-2 and C-3), 57.0 (C-5), 114.4 (C-4).

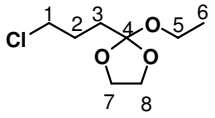
IR (film, cm^{-1}): 2978 (C-H), 1446, 1220, 1113, 1048.

2-(3-chloropropyl)-2-ethoxy-[1,3]dioxolane 2.034



$C_8H_{15}ClO_3$
M.W.: 194,66
CAS: 335645-38-0

Method D: Starting from 110 g of 4-chlorobutyrimidate. After workup, 101 g (88%) of the product orthoester are obtained.



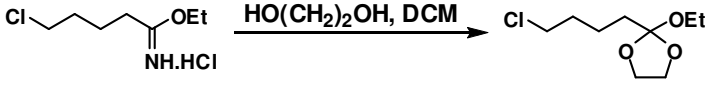
^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 1.17 (t, 3H, *J* = 7.1 Hz, H-6), 1.92-1.97 (m, 4H, H-2 and H-3), 3.54-3.64 (m, 4H, H-1 and H-5), 3.95-3.98 (m, 2H, H-7 or H-8), 4.07-4.10 (m, 2H, H-7 or H-8).

^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 15.2 (C-6), 27.2, 32.7 (C-2 and C-3), 44.9 (C-1), 57.4 (C-5), 64.9 (C-7 and C-8), 122.3 (C-4).

IR (film, cm^{-1}): 2974 (C-H), 1478, 1106, 951.

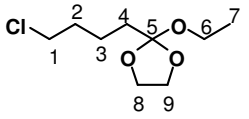
MS (EI+ev): *m/z* (%): 195 (15) $[M+H]^{+\cdot}$, 151 (40), 149 (100), 117 (30), 89 (17).

2-(4-chlorobutyl)-2-ethoxy-[1,3]dioxolane 2.033



$C_9H_{17}ClO_3$
M.W.: 208,68
CAS: 335645-39-1

Method D: Starting from 110 g of 4-chloropentanimidate. After workup, 101 g (88%) of the product orthoester are obtained.



^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 1.18 (t, 3H, *J* = 7.0 Hz, H-7), 1.58-1.66 (m, 2H, H-3), 1.75-1.88 (m, 4H, H-2 and H-4), 3.50-3.62 (m, 4H, H-1 and H-6), 3.94-4.15 (m, 4H, H-8 and H-9).

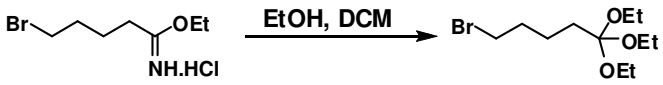
^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 15.2 (C-7), 21.3, 32.3, 34.6 (C-2, C-3 and C-4), 44.8 (C-1), 57.4 (C-6), 65.0 (C-8 and C-9), 122.5 (C-4).

IR (film, cm^{-1}): 2961 (C-H), 1540, 1446, 1219, 1061.

MS (EI+ev): *m/z* (%): 209 (4) $[M+H]^{+\cdot}$, 173 (3), 165 (47), 163 (100), 117 (37), 91 (21), 89 (47).

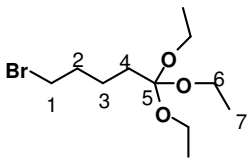
HRMS (CI): Calculated for $C_9H_{18}ClO_3$: 209.9444. Found: 209.9408.

5-bromo-1,1,1-triethoxypentane 5.056



$C_{11}H_{23}BrO_3$
M.W.: 283,20
CAS: 85691-40-3

Method C: Starting from 10.0 g of 5-bromopentanimidate. After workup, 9.3 g (80%) of the product orthoester are obtained.

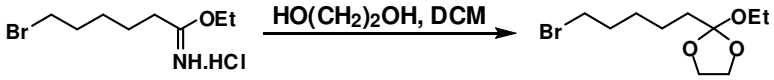


^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.15 (t, 9H, *J* = 7.0 Hz, H-7), 1.58-1.65 (m, 2H, H-3), 1.75-1.88 (m, 4H, H-2 and H-4), 3.45-3.64 (m, 8H, H-1 and H-6).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 14.9 (C-7), 21.3, 26.6, 29.6, 30.1 (C-1, C-2, C-3 and C-4), 54.7 (C-6), 115.0 (C-5).

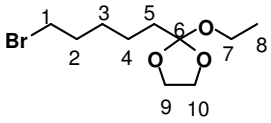
IR (film, cm^{-1}): 2968 (C-H), 1436, 1120, 1048.

2-(5-bromopentyl)-2-ethoxy-[1,3]dioxolane 2.054



$C_{10}H_{19}BrO_3$
M.W.: 267,16

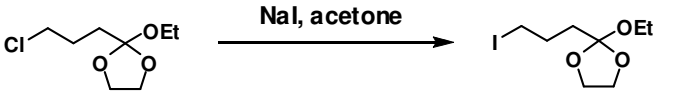
Method D: Starting from 12.0 g of 6-bromohexanimidate. After workup, 10.9 g (88%) of the product orthoester are obtained.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.18 (t, 3H, *J* = 7.0 Hz, H-8), 1.45-1.88 (m, 8H, H-2, H-3, H-4 and H-5), 3.50-3.66 (m, 4H, H-1 and H-7), 3.94-4.12 (m, 4H, H-9 and H-10).

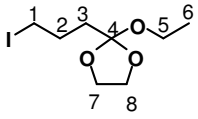
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 15.1 (C-8), 21.3, 32.3, 33.1, 33.9, 34.6 (C-1, C-2, C-3, C-4 and C-5), 57.4 (C-7), 65.0 (C-9 and C-10), 122.5 (C-6).
IR (film, cm^{-1}): 2961 (C-H), 1540, 1446, 1219, 1061.
MS (EI+ev): *m/z* (%): in progress.

2-(3-iodopropyl)-2-ethoxy-[1,3]dioxolane 2.002



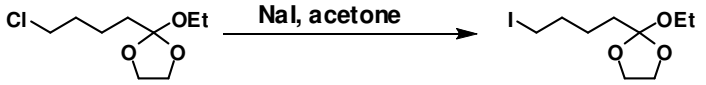
$C_8H_{15}IO_3$
M.W.: 286,11
CAS: 198895-90-8

In a 1L round-bottomed flask eq.uipped with a reflux condenser, 45 g of sodium iodide (0.30 mol, 1.7 eq.) are added to a solution of chlorinated orthoester (34 g, 0.18 mol, 1 eq.) in 400 mL of acetone. After 15 hours of stirring at reflux, the solvent is evaporated under reduced pressure. The residue is dissolved in 400 mL of diethyl ether and filtered over a celite plug. The filtrate is washed with 2 x 200 mL of a saturated aqueous solution of sodium thiosulfate. The organic layer is dried ($MgSO_4$) and concentrated under reduced pressure. 39.6 g (77%) of the iodinated orthoester are obtained.



^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 1.17 (t, 3H, *J* = 7.1 Hz, H-6), 1.89-2.00 (m, 4H, H-2 and H-3), 3.24 (t, 2H, *J* = 5.6 Hz, H-1), 3.56 (q, 2H, *J* = 7.1 Hz, H-5), 3.96-4.02 (m, 2H, H-7 or H-8), 4.04-4.11 (m, 2H, H-7 or H-8).
^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 6.7 (C-1), 15.1 (C-6), 28.0, 36.1 (C-2 and C-3), 57.2 (C-5), 64.0 (C-7 and C-8), 121.9 (C-4).
IR (film, cm^{-1}): 2981 (C-H), 1383, 1225, 1175.
MS (EI+ev): *m/z* (%): 287 (11) $[M+H]^{+\cdot}$, 241 (100), 197 (15), 159 (4).

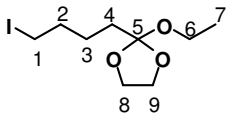
2-(4-iodobutyl)-2-ethoxy-[1,3]dioxolane 2.052



$C_9H_{17}IO_3$
M.W.: 300,13
CAS: 909546-39-0

In a 100 mL round-bottomed flask eq.uipped with a reflux condenser, 4.5 g of sodium iodide (0.03 mol, 3.0 eq.) are added to a solution of chlorinated orthoester (2.1 g, 0.01 mol, 1.0 eq.) in 40 mL of acetone. After 15 hours of stirring at reflux, the solvent is evaporated under reduced pressure. The residue is dissolved in 40 mL of diethyl ether and filtered over a celite plug. The filtrate is washed with 2 x 20 mL of a saturated aqueous solution of sodium thiosulfate. The organic layer is dried ($MgSO_4$) and concentrated under reduced pressure. 2.3 g (77%) of the iodinated orthoester

are obtained, which still contains 10-20% of the chlorinated starting material.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.09 (t, 3H, *J* = 7.0 Hz, H-7), 1.53-1.76 (m, 6H, H-2, H-3 and H-4), 3.07-3.13 (m, 2H, H-1), 3.41-3.38 (m, 2H, H-6), 3.88-4.05 (m, 4H, H-8 and H-9).

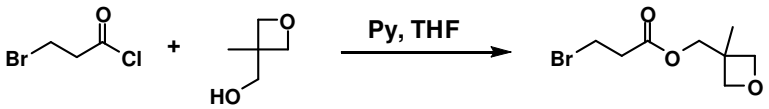
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 6.6 (C-1), 15.0 (C-7), 24.5, 32.3, 34.0 (C-2, C-3 and C-4), 57.1 (C-6), 60.9 (C-8 and C-9), 122.2 (C-5).

IR (film, cm^{-1}): 2981 (C-H), 1440, 1207, 1058.

MS (EI+ev): *m/z* (%): 301 (35) $[M+H]^{+\cdot}$, 257 (20), 211 (22), 101 (100).

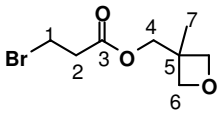
HRMS (ESI): Calculated for $C_9H_{17}O_3INa$ (M+Na): 323.0120. Found: 323.0109.

(3-methyloxetan-3-yl)methyl 3-bromopropanoate



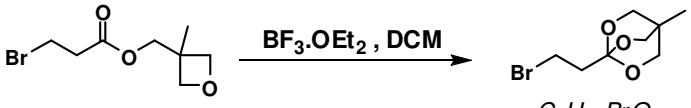
$C_9H_{15}BrO_2$
M.W.: 235,12
CAS: 135940-10-2

In a 250 mL round-bottomed flask are introduced 3.6 g of 3-methyl-3-hydroxymethyloxetane (35.3 mmol, 1 eq.), pyridine (3.0 mL, 35.3 mmol, 1 eq.) and 70 mL of THF. The mixture is cooled to 0ºC. Then, a solution of 6.2 g of 3-bromopropionyl chloride (35.5 mmol, 1 eq.) in 50 mL THF is added dropwise. The mixture is stirred at the same temperature for 1 hour prior to dilution with 100 mL of water and extraction with 3 x 100 mL dichloromethane. The combined organic extracts are dried ($MgSO_4$) and concentrated under reduced pressure affording 5.92 g (71%) of the product, which is very sensitive to chromatography. It is used in the subseq.uent reaction without further purification.



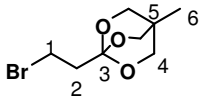
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.37 (s, 3H, H-7), 2.93-3.03 (m, 2H, H-2), 3.55-3.66 (m, 2H, H-1), 4.22 (s, 2H, H-4), 4.41-4.44 (m, 2H, H-6), 4.51-4.56 (m, 2H, H-6').

1-(2-bromoethyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane 5.062



$C_8H_{13}BrO_3$
M.W.: 237,09
CAS: 135956-78-4

In a 50 mL round-bottomed flask, the oxetane ester (3.0g, 12.65 mmol, 1 eq.) is dissolved in 15 mL dichloromethane and cooled to 0ºC. 0.37 mL of boron trifluoride etherate (3.16 mmol, 0.25 eq.) are added dropwise at the same temperature and stirring is continued for 3.5 hours at 0ºC. The mixture is then quenched with triethylamine (1.93 mL, 13.9mmol, 1.1 eq.), after which 15 mL of diethyl ether are added and stirring is continued for 20 minutes. The ensuing precipitate is filtered off and the filtrate is concentrated under reduced pressure to afford crude orthoester. Purification by short-path column chromatography (PE, NEt_3) gives 2.3 g (76%) of the orthoester as a pale yellow solid.

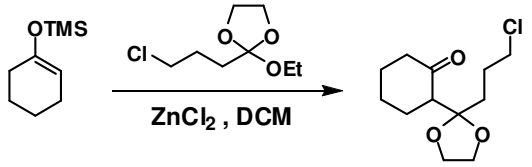


^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 0.82 (s, 3H, H-6), 2.23-2.29 (m, 2H, H-2), 3.40-3.45 (m, 2H, H-1), 3.89 (s, 6H, H-4).
^{13}C-NMR (62.5 MHz, $CDCl_3$) δ (ppm): 14.4 (C-6), 26.0, 30.2 (C-1 and C-2), 41.1 (C-5), 72.9 (C-4), 118.8 (C-3).

9.3. Condensations with simple cyclic silyl enolethers (Chapters 2, 3 and 4)

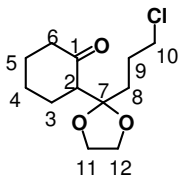
Condensations with 4-carbon chlorinated orthoester

2-[2-(3-chloropropyl)-[1,3]dioxolan-2-yl]cyclohexanone



$C_{12}H_{19}ClO_3$
M.W.: 246,73

In a 100 mL round-bottomed flask, 1.2 g of zinc chloride (8.2 mmol, 0.7 eq.) are added to 2.5 g of orthoester (12.9 mmol, 1.1 eq.) and 2.0 g of cyclohexanone silyl enolether (11.7 mmol, 1 eq.) dissolved in 30 mL of dichloromethane. After 4 hours stirring at room temperature, 20 mL of an aqueous saturated bicarbonate solution are added to quench the reaction. After phase separation, the aqueous layer is extracted with 2 x 30 mL dichloromethane. The combined organic fractions are dried ($MgSO_4$) and the solvents are removed under reduced pressure. Purification of the residue by flash chromatography (silica, PE/AcOEt 7:3) affords 2.25 g (78 %) of the product (Rf = 0.33).



^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 1.64-2.28 (m, 10H, H-3, H-4, H-5, H-8 and H-9), 2.30-2.50 (m, 2H, H-6), 2.68-2.78 (m, 1H, H-2), 3.55 (td, 2H, *J* = 5.8, 2.2 Hz, H-10), 3.99 (br s, 4H, H-11 and H-12).

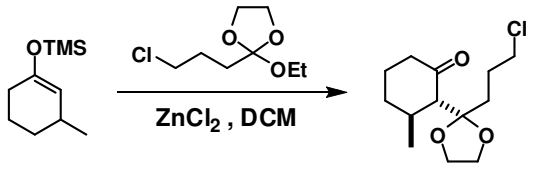
^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 24.4 (C-3), 26.7, 27.7, 28.6 (C-4, C-5 and C-9), 32.9 (C-8), 42.9 (C-6), 45.0 (C-10), 56.7 (C-2), 65.2, 65.4 (C-11 and C-12), 110.5 (C-7), 209.9 (C-1).

IR (film, cm^{-1}): 2942 (C-H), 1715 (C=O), 1448, 1314, 1052.

MS (CI+ev): *m/z* (%): 245 (3) $[M+H]^{+}$, 211 (24), 170 (24), 151 (32).

Elemental analysis: Calculated for $C_{12}H_{19}ClO_3$: C: 58.42%, H: 7.76%. Found: C: 58.18%, H: 7.89%.

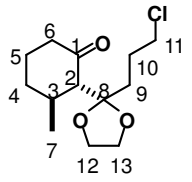
2-[2-(3-chloropropyl)-[1,3]dioxolan-2-yl]-3-methylcyclohexanone 2.014



$C_{13}H_{21}ClO_3$
M.W.: 260,76

In a 250 mL round-bottomed flask, 2.6 g of zinc chloride (19 mmol, 0.7 eq.) are added to 5.8 g of orthoester (30 mmol, 1.1 eq.) and 5 g of 3-methylcyclohexanone silyl enolether (27 mmol, 1 eq.) dissolved in 100 mL of dichloromethane. After 8 hours stirring at room temperature, 100 mL of an aqueous saturated bicarbonate solution are added to quench the reaction. After phase separation, the aqueous layer is extracted with 2 x 100 mL dichloromethane. The combined organic fractions are dried ($MgSO_4$) and the

solvents are removed under reduced pressure. Purification of the residue by flash chromatography (silica, PE/AcOEt 7:3) affords 5.0 g (71 %) of the product (Rf = 0.57).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.00 (d, 3H, *J* = 7.1 Hz, H-7), 1.73-2.10 (m, 7H, H-3, H-4, H-5 and H-10), 2.28-2.39 (m, 3H, H-6 and H-9), 2.46 (d, 1H, *J* = 2.8 Hz, H-2), 2.57 (ddd, 1H, *J* = 13.5, 9.5, 7.6 Hz, H-6'), 3.47-3-60 (m, 2H, H-11), 3.98 (br s, 4H, H-12 and H-13).

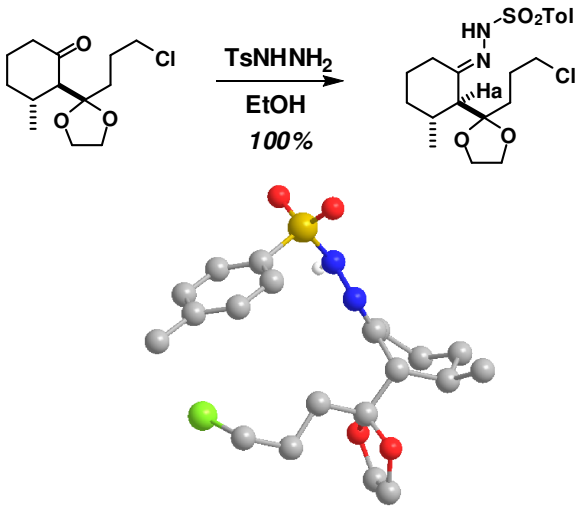
^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 20.9 (C-7), 22.7 (C-5), 26.9 and 29.2 (C-4 and C-10), 32.2 (C-3), 33.9 (C-9), 41.4 (C-6), 45.0 (C-11), 62.8 (C-2), 64.8, 65.0 (C-12 and C-13), 110.9 (C-8), 212.3 (C-1).

IR (film, cm^{-1}): 2957, 2928 and 2874 (C-H), 1702 (C=O), 1446, 1230, 1047.

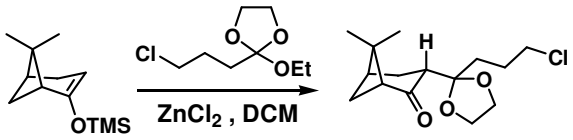
MS (CI+ev): *m/z* (%): 261 (10) $[M+H]^{+\cdot}$, 225 (12), 151 (14), 149 (36), 113 (92), 106 (36), 104 (100).

Elemental analysis: Calculated for $C_{13}H_{21}ClO_3$: C: 59.88%, H: 8.12%. Found: C: 59.45%, H: 8.33%.

X-ray analysis: tosylhydrazone derivative



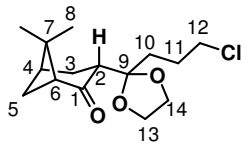
2-[2-(3-chloropropyl)-[1,3]dioxolan-2-yl]nopinone 2.088



$C_{15}H_{23}ClO_3$
M.W.: 286,79

In a 10 mL round-bottomed flask, 192 mg of zinc chloride (1.4 mmol, 0.7 eq.) are added to 0.54 g of orthoester (1.4 mmol, 1.4 eq.) and 0.42 g of nopinone silyl enolether (1 mmol, 1 eq.) dissolved in 4 mL of dichloromethane. After 4 hours stirring at room temperature, 5 mL of an aqueous saturated bicarbonate solution are added to quench the reaction. After phase separation, the aqueous layer is extracted with 2 x 8 mL

dichloromethane. The combined organic fractions are dried ($MgSO_4$) and the solvents are removed under reduced pressure. Purification of the residue by flash chromatography (silica, PE/AcOEt 5:1) affords 0.24 g (46 %) of the product (Rf = 0.24).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 0.82 (s, 3H, H-8), 1.29 (s, 3H, H-8'), 1.78-2.04 (m, 7H, H-3, H-5, H-10 and H-11), 2.12-2.17 (m, 1H, H-4), 2.35-2.43 (m, 1H, H-5'), 2.48-2.53 (m, 1H, H-6), 2.79 (dd, 1H, *J* = 10.1, 5.3 Hz, H-2), 3.48-3.61 (m, 2H, H-12), 3.96-4.00 (m, 4H, H-13 and H-14).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 22.0 (C-8), 24.0, 24.6, 27.8 (C-3, C-11 and C-5), 25.9 (C-8'), 33.7 (C-10), 40.2 (C-4), 41.4 (C-7), 45.2 (C-12), 49.1 (C-6), 58.8 (C-2), 65.0, 65.4 (C-13 and C-14), 112.1 (C-9), 211.4 (C-1).

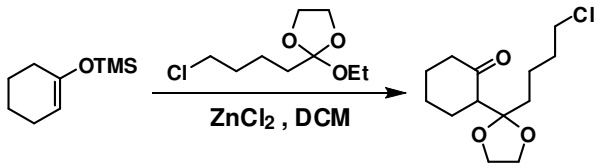
IR (film, cm^{-1}): 2981 (C-H), 1705 (C=O), 1430.

MS (APCI+ev): *m/z* (%): 287 (15) $[M+H]^{+\cdot}$, 269 (10), 243 (95), 225 (25), 197 (100), 187 (20).

Elemental analysis: Calculated for $C_{15}H_{23}ClO_3$: C: 62.88%, H: 8.11%. Found: C: 62.82%, H: 8.08%.

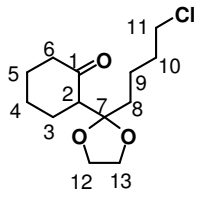
Condensations with 5-carbon chlorinated orthoester

2-[2-(4-chlorobutyl)-[1,3]dioxolan-2-yl]cyclohexanone 2.040



$C_{13}H_{21}ClO_3$
M.W.: 260,76

In a 20 mL round-bottomed flask, 194 mg of zinc chloride (2.8 mmol, 0.7 eq.) are added to 1.08 g of orthoester (5.3 mmol, 1.3 eq.) and 0.68 g of cyclohexanone silyl enolether (4.0 mmol, 1 eq.) dissolved in 10 mL of dichloromethane. After 5 hours stirring at room temperature, 10 mL of an aqueous saturated bicarbonate solution are added to quench the reaction. After phase separation, the aqueous layer is extracted with 2 x 15 mL dichloromethane. The combined organic fractions are dried ($MgSO_4$) and the solvents are removed under reduced pressure. Purification of the residue by flash chromatography (silica, PE/AcOEt 4:1) affords 0.67 g (65 %) of the product (Rf = 0.32).



^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 1.39-2.49 (m, 14H, H-3, H-4, H-5, H-6, H-8, H-9 and H-10), 2.67-2.75 (m, 1H, H-2), 3.53 (t, 2H, *J* = 6.5 Hz, H-11), 3.89-3.95 (m, 4H, H-12 and H-13).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 20.8 (C-9), 24.5 (C-3), 27.9 (C-4), 28.7 (C-5), 32.7 (C-10), 35.0 (C-8), 43.1 (C-6), 44.9 (C-11), 56.8 (C-2), 65.3, 65.4 (C-12 and C-13), 110.9 (C-7), 210.4 (C-1).

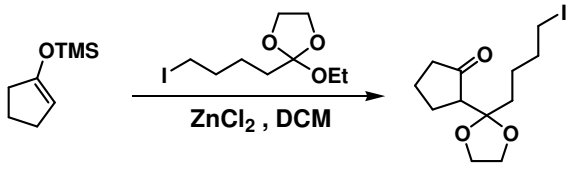
IR (film, cm^{-1}): 2941 and 2872 (C-H), 1716 (C=O), 1449, 1221, 1123.

MS (CI+ev): *m/z* (%): 261 (2) $[M+H]^{+\cdot}$, 225 (5), 169 (26), 165 (38), 163 (100), 127 (30).

Elemental analysis: Calculated for $C_{13}H_{21}ClO_3$: C: 59.88%, H: 8.12%. Found: C: 59.42%, H: 8.15%.

<u>Condensations with 5-carbon iodinated orthoester</u>

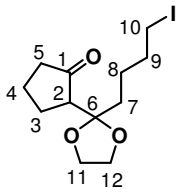
2-[2-(4-iodobutyl)-[1,3]dioxolan-2-yl]cyclopentanone 2.061



$C_{12}H_{19}IO_3$
M.W.: 338,18

In a 10 mL round-bottomed flask, 110 mg of zinc chloride (0.8 mmol, 0.7 eq.) are added to 0.45 g of orthoester (1.5 mmol, 1.3 eq.) and 0.18 g of cyclopentanone silyl enolether (1.15 mmol, 1 eq.) dissolved in 3 mL of dichloromethane. After 5 hours stirring at room temperature, 3 mL of an

aqueous saturated bicarbonate solution are added to quench the reaction. After phase separation, the aqueous layer is extracted with 2 x 8 mL dichloromethane. The combined organic fractions are dried ($MgSO_4$) and the solvents are removed under reduced pressure. Purification of the residue by flash chromatography (silica, PE/AcOEt 4:1) affords 0.26 g (67 %) of the product (Rf = 0.33), contaminated with 10-20% of the chlorinated analog.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.41-1.46 (m, 2H, H-8), 1.60-2.01 (m, 7H, H-3, H-4, H-7 and H-9), 2.13-2.19 (m, 3H, H-5 and H-3'), 2.48 (t, 1H, *J* = 8.9 Hz, H-2), 3.14 (t, 2H, *J* = 7.0 Hz, H-10), 3.89-4.00 (m, 4H, H-11 and H-12).

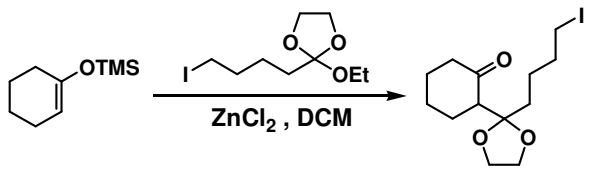
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 6.9 (C-10), 20.1, 24.7, 25.6 (C-3, C-4 and C-8), 33.3, 34.9 (C-7 and C-9), 39.7 (C-5), 53.6 (C-2), 65.3, 65.5 (C-11 and C-12), 111.4 (C-6), 216.9 (C-1).

IR (film, cm^{-1}): 2981 (C-H), 1705 (C=O), 1430.

MS (APCI+ev): *m/z* (%): 339 (5) $[M+H]^{+\cdot}$, 321 (20), 295 (100), 255 (10), 211 (5).

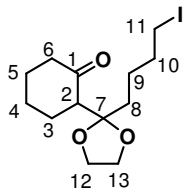
HRMS (ESI): Calculated for $C_{12}H_{19}O_3INa$ (M+Na): 361.0277. Found: 361.0269.

2-[2-(4-iodobutyl)-[1,3]dioxolan-2-yl]cyclohexanone 2.060



$C_{13}H_{21}IO_3$
M.W.: 352,21

In a 25 mL round-bottomed flask, 187 mg of zinc chloride (1.4 mmol, 0.7 eq.) are added to 0.59 g of orthoester (2.0 mmol, 1.0 eq.) and 0.40 g of cyclohexanone silyl enolether (2.4 mmol, 1.2 eq.) dissolved in 6 mL of dichloromethane. After 5 hours stirring at room temperature, 10 mL of an aqueous saturated bicarbonate solution are added to quench the reaction. After phase separation, the aqueous layer is extracted with 2 x 10 mL dichloromethane. The combined organic fractions are dried ($MgSO_4$) and the solvents are removed under reduced pressure. Purification of the residue by flash chromatography (silica, PE/AcOEt 3:1) affords 0.58 g (70 %) of the product (Rf = 0.3).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.41-1.46 (m, 2H, H-8), 1.54-1.95 (m, 11H, H-3, H-4, H-5, H-8, H-9 and H-10), 2.07-2.13 (m, 1H, H-3'), 2.20-2.40 (m, 2H, H-6), 2.64 (dd, 1H, *J* = 10.3, 5.2 Hz, H-2), 3.12 (t, 2H, *J* = 7.0 Hz, H-11), 3.86-3.94 (m, 4H, H-12 and H-13).

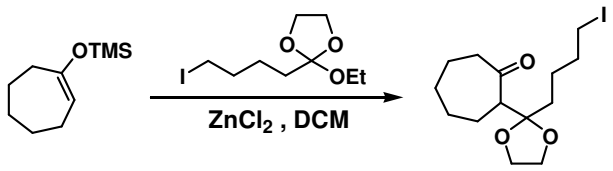
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 7.0 (C-11), 24.4, 24.6, 28.0, 28.8 (C-3, C-4, C-5 and C-9), 33.5, 34.5 (C-8 and C-10), 43.1 (C-6), 56.8 (C-2), 65.3, 65.4 (C-12 and C-13), 110.8 (C-7), 210.4 (C-1).

IR (film, cm^{-1}): 2937 and 2866 (C-H), 1709 (C=O), 1448, 1365, 1313.

MS (APCI+ev): *m/z* (%): 353 (10) $[M+H]^{+\cdot}$, 309 (5), 255 (100), 163 (10), 99 (15).

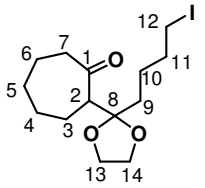
HRMS (ESI): Calculated for $C_{13}H_{21}O_3INa$ (M+Na): 375.0433. Found: 375.0431.

2-[2-(4-iodobutyl)-[1,3]dioxolan-2-yl]cycloheptanone 2.062



$C_{14}H_{23}IO_3$
M.W.: 366,24

In a 25 mL round-bottomed flask, 286 mg of zinc chloride (2.1 mmol, 0.7 eq.) are added to 1.0 g of orthoester (3.3 mmol, 1.1 eq.) and 0.55 g of cycloheptanone silyl enolether (3.0 mmol, 1 eq.) dissolved in 7.5 mL of dichloromethane. After 5 hours stirring at room temperature, 10 mL of an aqueous saturated bicarbonate solution are added to quench the reaction. After phase separation, the aqueous layer is extracted with 2 x 10 mL dichloromethane. The combined organic fractions are dried ($MgSO_4$) and the solvents are removed under reduced pressure. Purification of the residue by flash chromatography (silica, PE/AcOEt 4:1) affords 0.83 g (75 %) of the product (Rf = 0.34), contaminated with 10-20% of the chlorinated analog.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.10-2.05 (m, 14H, H-3, H-4, H-5, H-6, H-9, H-10 and H-11), 2.36-2.43 (m, 1H, H-7), 2.68-2.83 (m, 2H, H-2 and H-7'), 3.16 (t, 2H, *J* = 6.9 Hz, H-12), 3.97 (br s, 4H, H-13 and H-14).

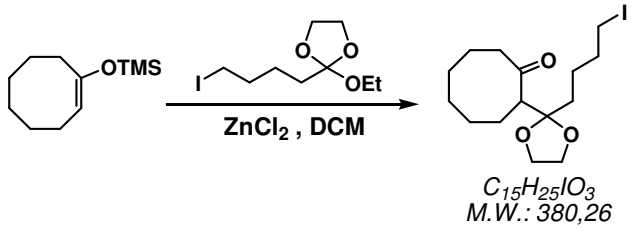
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 6.7 (C-12), 20.8 (C-10), 25.3 (C-6), 26.1, 27.4, 30.0 (C-3, C-4 and C-5), 32.6 (C-11), 35.5 (C-9), 43.0 (C-7), 59.6 (C-2), 65.2, 65.6 (C-13 and C-14), 214.2 (C-1) .

IR (film, cm^{-1}): 2923 and 2852 (C-H), 1699 (C=O), 1456, 1340, 1180, 1045.

MS (CI+ev): *m/z* (%): 365 (100) $[M\text{-}H]^{+\cdot}$, 321 (7), 211 (20), 183 (10), 155 (5), 137 (12).

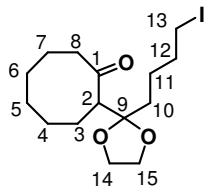
HRMS (ESI): Calculated for $C_{14}H_{23}O_3INa$ (M+Na): 389.0590. Found: 389.0594.

2-[2-(4-iodobutyl)-[1,3]dioxolan-2-yl]cyclooctanone 2.071



$C_{15}H_{25}IO_3$
M.W.: 380,26

In a 10 mL round-bottomed flask, 87 mg of zinc chloride (0.64 mmol, 0.7 eq.) are added to 0.3 g of orthoester (1.0 mmol, 1.1 eq.) and 0.18 g of cyclooctanone silyl enolether (0.91 mmol, 1 eq.) dissolved in 2.5 mL of dichloromethane. After 4 hours stirring at room temperature, 4 mL of an aqueous saturated bicarbonate solution are added to quench the reaction. After phase separation, the aqueous layer is extracted with 2 x 7 mL dichloromethane. The combined organic fractions are dried ($MgSO_4$) and the solvents are removed under reduced pressure. Purification of the residue by flash chromatography (silica, PE/AcOEt 4:1) affords 0.22 g (73 %) of the product (Rf = 0.32), contaminated with 10-20% of the chlorinated analog.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.30-1.87 (m, 16H, H-3, H-4, H-5, H-6, H-7, H-10, H-11 and H-12), 2.25-2.33 (m, 1H, H-8), 2.60 (dt, 1H, *J* = 16.1, 4.7 Hz, H-8'), 2.90 (dd, 1H, *J* = 10.3, 4.7 Hz, H-2), 3.17 (t, 2H, *J* = 7.0 Hz, H-13), 3.95-3.98 (m, 4H, H-14 and H-15).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 7.1 (C-13), 24.2, 24.8, 26.2, 26.4, 26.7, 27.1 (C-3, C-4, C-5, C-6, C-7 and C-11), 33.5, 34.7 (C-10 and C-12), 42.8 (C-8), 58.2 (C-2), 65.4, 65.6 (C-14 and C-15), 111.6 (C-9), 217.4 (C-1).

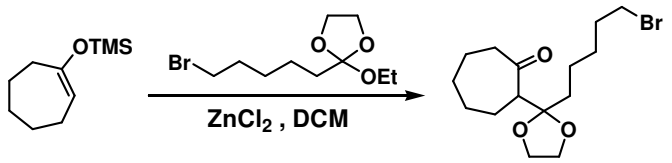
IR (film, cm^{-1}): 2923 and 2852 (C-H), 1695 (C=O), 1466, 1337, 1030.

MS (APCI+ev): *m/z* (%): 381 (5) $[M+H]^{+\cdot}$, 363 (15), 337 (100), 255 (25).

HRMS (ESI): Calculated for $C_{15}H_{25}O_3INa$ (M+Na): 403.0746. Found: 403.0755.

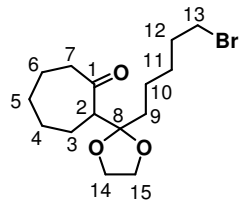
Condensations with 6-carbon brominated orthoester

2-[2-(5-bromopentyl)-[1,3]dioxolan-2-yl]cycloheptanone 2.068



$C_{15}H_{25}BrO_3$
M.W.: 333,26

In a 10 mL round-bottomed flask, 143 mg of zinc chloride (1.05 mmol, 0.7 eq.) are added to 0.44 g of orthoester (1.65 mmol, 1.1 eq.) and 0.28 g of cyclooctanone silyl enolether (1.5 mmol, 1 eq.) dissolved in 3.5 mL of dichloromethane. After 4 hours stirring at room temperature, 4 mL of an aqueous saturated bicarbonate solution are added to quench the reaction. After phase separation, the aqueous layer is extracted with 2 x 7 mL dichloromethane. The combined organic fractions are dried ($MgSO_4$) and the solvents are removed under reduced pressure. Purification of the residue by flash chromatography (silica, PE/AcOEt 4:1) affords 0.29 g (59 %) of the product (Rf = 0.41).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.24-1.70 (m, 10H, H-3, H-5, H-6, H-10, and H-11), 1.82-2.01 (m, 6H, H-4, H-9, H-12), 2.35 (t, 1H, *J* = 7.5 Hz,

H-7), 2.76 (m, 2H, H-2 and H-7'), 3.41 (m, 2H, H-13), 3.94 (br s, 4H, H-14 and H-15).

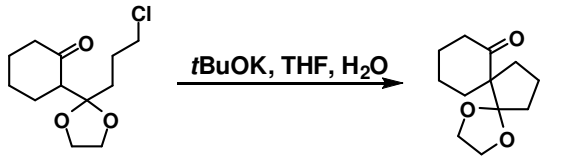
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 22.6, 25.4, 26.2, 27.4, 28.2, 30.1, 32.7, 33.8 (C-3, C-4, C-5, C-6, C-9, C-10, C-11 and C-12), 36.0 (C-13), 43.1 (C-7), 59.6 (C-2), 65.2, 65.6 (C-14 and C-15), 111.6 (C-8), 214.3 (C-1).

IR (film, cm^{-1}): 2923 and 2852 (C-H), 1695 (C=O), 1466, 1337.

MS (APCI+ev): *m/z* (%): 334 (3) $[M+H]^{+\cdot}$, 222 (100), 183 (30), 141 (40).

9.4. All-carbon spirocycles (Chapters 2, 3 and 4)

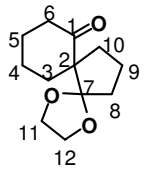
1,4-dioxa-dispiro[4.0.5.3]tetradecan-7-one 2.005



$C_{12}H_{18}O_3$
M.W.: 210,27

In a 10 mL round-bottomed flask, 100 mg of potassium *tert*-butoxide (0.9 mmol, 1.5 eq.) are added to 0.20 g of β-ketoketal (0.6 mmol, 1 eq.) dissolved in 6 mL of THF containing 11 mg of water (0.6 mmol, 1 eq.). The reaction mixture becomes an orange suspension. After 30 minutes stirring at room temperature, TLC-analysis shows the reaction to be complete. If incomplete conversion is observed, heating the mixture to reflux can drive the reaction to completion. At this point, 4 mL of an aqueous saturated

bicarbonate solution are added to quench the reaction. After phase separation, the aqueous layer is extracted with 3 x 15 mL diethylether. The combined organic fractions are dried ($MgSO_4$) and the solvents are removed under reduced pressure. Purification of the residue by flash chromatography (silica, PE/AcOEt 7:3) affords 0.12 g (95 %) of the product (Rf = 0.64).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.21-2.03 (m, 10H, H-3, H-4, H-8, H-9 and H-10), 2.18-2.63 (m, 4H, H-5 and H-6), 3.86-3.92 (m, 1H, H-11 or H-12), 4.03-4.06 (m, 3H, H-11 or H-12).

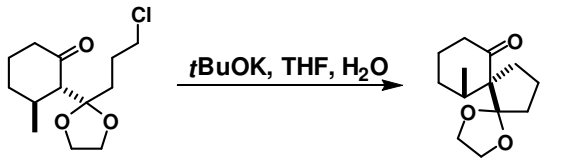
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 18.8 (C-9), 22.2 (C-4), 26.9 (C-5), 33.8, 34.5 (C-3 and C-10), 34.6 (C-8), 41.4 (C-6), 59.4 (C-2), 64.2, 64.4 (C-11 and C-12), 118.0 (C-7), 212.5 (C-1).

IR (film, cm^{-1}): 2942 and 2886 (C-H), 1700 (C=O), 1463, 1312.

MS (EI+ev): *m/z* (%): 210 (16) $[M]^{+\cdot}$, 122 (6), 112 (12), 99 (100).

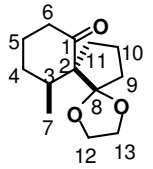
Elemental analysis: Calculated for $C_{12}H_{18}O_3$: C: 68.55%, H: 8.63%. Found: C: 68.29%, H: 8.53%.

11-methyl-1,4-dioxa-dispiro[4.0.5.3]tetradecan-7-one 2.086



$C_{13}H_{20}O_3$
M.W.: 224,30

In a 250 mL round-bottomed flask, 2.05 g of potassium *tert*-butoxide (18 mmol, 1.4 eq.) are added to 3.40 g of β-ketoketal (13 mmol, 1 eq.) dissolved in 75 mL of THF containing 0.2 mL of water (13 mmol, 1 eq.). The reaction mixture becomes an orange suspension. After 30 minutes stirring at room temperature, TLC-analysis shows the reaction to be complete. At this point, 50 mL of an aqueous saturated bicarbonate solution are added to quench the reaction. After phase separation, the aqueous layer is extracted with 3 x 60 mL diethylether. The combined organic fractions are dried ($MgSO_4$) and the solvents are removed under reduced pressure. Purification of the residue by flash chromatography (silica, PE/AcOEt 9:1) affords 2.4 g (85 %) of the product (Rf = 0.32).



^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 1.17 (d, 3H, *J* = 6.8 Hz, H-7), 1.43-2.09 (m, 10H, H-4, H-5, H-9, H-10 and H-11), 2.39-2.46 (m, 2H, H-3 and H-6), 2.62-2.68 (m, 1H, H-6'), 3.80-3.88 (m, 1H, H-12 or H-13), 3.91-4.06 (m, 3H, H-12 and H-13).

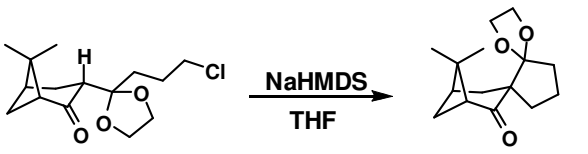
^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 17.5 (C-7), 20.2 (C-10), 26.1 (C-5), 30.4 (C-11), 31.0 (C-4), 36.8 (C-9), 40.7 (C-6), 42.4 (C-3), 62.7 (C-2), 63.0, 64.2 (C-12 and C-13), 119.2 (C-8), 211.0 (C-1).

IR (film, cm^{-1}): 2962 (C-H), 1739 and 1712 (C=O), 1470, 1459, 1318, 1307, 1145, 1069.

MS (CI+ev): *m/z* (%): 225 (100) $[M+H]^{+\cdot}$, 224 (10) $[M]^{+\cdot}$, 112 (20), 99 (20).

Elemental analysis: Calculated for $C_{13}H_{20}O_3$: C: 69.61%, H: 8.99%. Found: C: 69.69%, H: 9.21%.

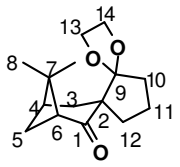
6,6-dimethylbispiro[bicyclo[3.1.1]heptane-3,1'-cyclopentane-2',2''(1'' ,3''-dioxolan)]-2-one 2.089



$C_{15}H_{22}O_3$
M.W.: 250,33

In a 25 mL round-bottomed flask, 0.37 mL of NaHMDS (2M solution in THF, 0.74 mmol, 1.3 eq.) are added to 0.16 g of β-ketoketal (0.56 mmol, 1 eq.) dissolved in 10 mL of THF at 0ºC. The reaction mixture becomes a light orange solution. After 12 hours stirring at room temperature, TLC-analysis shows the reaction to be complete. At this point, 10 mL of an aqueous saturated NH_4Cl solution are added to quench the reaction. After phase separation, the aqueous layer is extracted with 3 x 10 mL diethylether.

The combined organic fractions are dried ($MgSO_4$) and the solvents are removed under reduced pressure. Purification of the residue by flash chromatography (silica, PE/Et_2O 2:1) affords 0.13 g (90 %) of the product (Rf = 0.3).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 0.94 (s, 3H, H-8), 1.30 (s, 3H, H-8'), 1.66-1.95 (m, 6H, H-3', H-5', H-9, H-10', H-11 and H-12'), 2.09-2.24 (m, 3H, H-3, H-4 and H-10), 2.34-2.43 (m, 2H, H-5 and H-12), 2.55 (t, 1H, *J* = 5.4 Hz, H-6), 3.92-3.99 (m, 4H, H-13 and H-14).

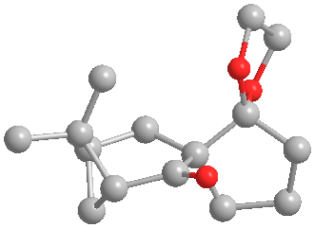
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 19.6 (C-11), 20.1 (C-8), 26.1 (C-5), 26.9 (C-8'), 32.3 (C-3), 34.5 (C-12), 40.1 (C-4), 42.0 (C-10), 44.1 (C-7), 56.2 (C-2), 57.7 (C-6), 63.4, 65.5 (C-13 and C-14), 119.8 (C-9), 214.2 (C-1).

IR (film, cm^{-1}): 2962 (C-H), 1712 (C=O), 1433, 1190.

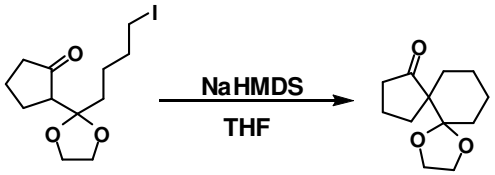
MS (APCI+ev): *m/z* (%): 251 (100) $[M+H]^{+\cdot}$, 233 (20), 207 (20), 189 (30), 163 (20), 147 (20), 89 (10).

Elemental analysis: Calculated for $C_{15}H_{22}O_3$: C: 71.97%, H: 8.86%. Found: C: 71.69%, H: 9.01%.

X-ray analysis

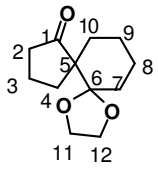


1,4-dioxa-dispiro[4.0.4.4]tetradecan-7-one 2.041



$C_{12}H_{18}O_3$
M.W.: 210,27

In a 25 mL round-bottomed flask, 0.38 mL of NaHMDS (2M solution in THF, 0.76 mmol, 1.3 eq.) are added to 0.2 g of β-ketoketal (0.6 mmol, 1 eq.) dissolved in 6 mL of THF at 0ºC. The reaction mixture becomes a light orange solution. After 3 hours stirring at room temperature, TLC-analysis shows the reaction to be complete. At this point, 10 mL of an aqueous saturated NH_4Cl solution are added to quench the reaction. After phase separation, the aqueous layer is extracted with 3 x 10 mL diethylether. The combined organic fractions are dried ($MgSO_4$) and the solvents are removed under reduced pressure. Purification of the residue by flash chromatography (silica, PE/AcOEt 4:1) affords 0.11 g (80 %) of the product.



^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 1.35-2.06 (m, 12H, H-3, H-4, H-7, H-8, H-9 and H-10), 2.24-2.32 (m, 2H, H-2), 3.90-3.95 (m, 4H, H-11 and H-12).

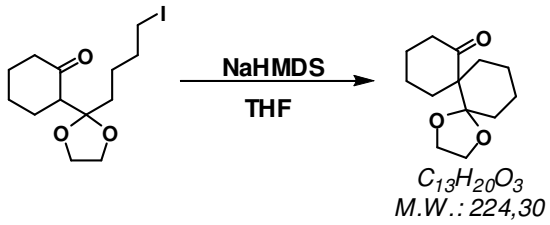
^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 18.4 (C-4), 20.4, 23.1 (C-8 and C-9), 31.2 (C-7), 32.3, 32.7 (C-3 and C-10), 39.7 (C-5), 55.3 (C-2), 64.6, 65.0 (C-11 and C-12), 110.9 (C-6), 218.7 (C-1).

IR (film, cm^{-1}): 2961 (C-H), 1732 (C=O), 1446, 1349, 1291, 1276.

MS (EI+ev): *m/z* (%): 211 (8) $[M+H]^+$, 210 (37) $[M]^+$, 166 (7), 99 (100).

Elemental analysis: Calculated for $C_{12}H_{18}O_3$: C: 68.55%, H: 8.63%. Found: C: 68.20%, H: 8.63%.

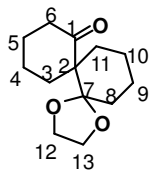
1,4-dioxa-dispiro[4.0.5.4]pentadecan-7-one 2.035



$C_{13}H_{20}O_3$
M.W.: 224,30

In a 10 mL round-bottomed flask, 0.18 mL of NaHMDS (2M solution in THF, 0.36 mmol, 1.3 eq.) are added dropwise to 100 mg of β-ketoketal

(0.28 mmol, 1 eq.) dissolved in 3 mL of THF at 0ºC. The reaction mixture gradually becomes a light orange suspension. The mixture is allowed to reach room temperature overnight. At this point, 5 mL of an aqueous saturated NH_4Cl solution are added to quench the reaction. After phase separation, the aqueous layer is extracted with 3 x 10 mL ethyl acetate. The combined organic fractions are dried ($MgSO_4$) and the solvents are removed under reduced pressure. Purification of the residue by flash chromatography (silica, PE/AcOEt 6:1) affords 53 mg (84 %) of the product (Rf = 0.32).



^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 1.15-2.47 (m, 16H, H-3, H-4, H-5, H-6, H-8, H-9, H-10 and H-11), 3.82-3.98 (m, 4H, H-12 and H-13).

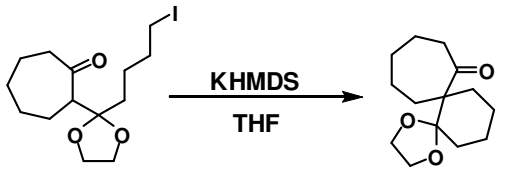
^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 20.4, 20.9, 23.0 (C-4, C-9 and C-10), 26.9 (C-5), 31.5, 32.6, 33.1 (C-3, C-8 and C-11), 40.2 (C-6), 56.6 (C-2), 63.9, 64.7 (C-12 and C-13), 110.7 (C-7), 212.6 (C-1).

IR (film, cm^{-1}): 2931 and 2866 (C-H), 1706 (C=O), 1448, 1348, 1233, 1183.

MS (EI+ev): *m/z* (%): 225 (12) $[M+H]^{+\cdot}$, 224 (45) $[M]^{+\cdot}$, 180 (17), 99 (100).

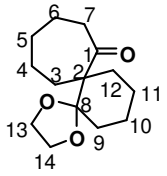
Elemental analysis: Calculated for $C_{13}H_{20}O_3$: C: 69.61%, H: 8.99%. Found: C: 69.52%, H: 9.10%.

1,4-dioxa-dispiro[4.0.6.4]hexadecan-7-one 2.063



$C_{14}H_{22}O_3$
M.W.: 238,32

In a 10 mL round-bottomed flask, 0.71 mL of KHMDS (0.5M solution in toluene, 0.36 mmol, 1.3 eq.) are added dropwise to 100 mg of β-ketoketal (0.28 mmol, 1 eq.) dissolved in 3 mL of THF at 0ºC. The reaction mixture gradually becomes a yellow suspension. After stirring for 2 hours, 5 mL of an aqueous saturated NH_4Cl solution are added to quench the reaction. After phase separation, the aqueous layer is extracted with 3 x 10 mL ethyl acetate. The combined organic fractions are dried ($MgSO_4$) and the solvents are removed under reduced pressure. Purification of the residue by flash chromatography (silica, PE/AcOEt 6:1) affords 45 mg (71 %) of the product (Rf = 0.32).



^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 1.02-2.18 (m, 16H, H-3, H-4, H-5, H-6, H-9, H-10, H-11 and H-12), 2.38 (t, 1H, *J* = 7.6 Hz, H-7), 3.02 (td, 1H, *J* = 11.2, 2.7 Hz, H-7'), 3.80-3.95 (m, 4H, H-13 and H-14).

^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 20.8, 22.8, 24.0 (C-4, C-10 and C-11), 27.8, 29.0 (C-5 and C-6), 29.6, 30.8, 31.6 (C-3, C-9 and C-12), 42.8 (C-7), 58.1 (C-2), 64.1, 64.6 (C-13 and C-14), 111.5 (C-8), 215.6 (C-1).

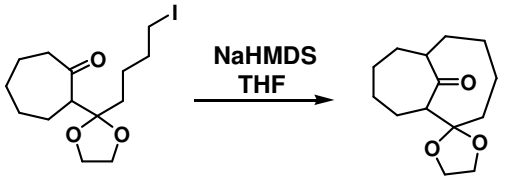
IR (film, cm^{-1}): 2948 and 2855 (C-H), 1698 (C=O), 1450, 1351, 1178, 1085.

MS (EI+ev): *m/z* (%): 239 (8) $[M+H]^{+\cdot}$, 238 (28) $[M]^{+\cdot}$, 194 (18), 193 (37), 99 (100).

Elemental analysis: Calculated for $C_{14}H_{22}O_3$: C: 70.56%, H: 9.30%. Found: C: 70.43%, H: 9.29%.

9.5. Transannular cyclisations (Chapter 2)

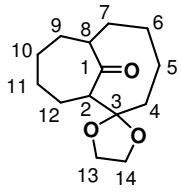
2-dioxolanyl-bicyclo[5.4.1]dodecan-12-one 2.066



$C_{14}H_{22}O_3$
M.W.: 238,32

In a 25 mL round-bottomed flask are introduced 0.35 g (1 mmol, 1 eq.) of the iodinated β-ketoketal and 10 mL of THF. The solution is cooled to 0°C and 0.6 mL (2M solution in THF, 1.2 mmol, 1.3 eq.) of NaHMDS are added dropwise. The yellow mixture is gradually allowed to reach room temperature overnight. After stirring for 12 hours, 10 mL of a saturated

NH_4Cl solution are added. After phase separation, the aqueous layer is extracted with 3 x 10 mL of diethyl ether and the combined organic fractions are dried ($MgSO_4$). Removal of the solvents under reduced pressure yields a residue, which is purified by flash chromatography (silica, PE/AcOEt 2:1) to afford 0.13 g (55%) of the product bridged ketone (Rf = 0.25).



^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 1.20-2.05 (m, 15H, H-4, H-5, H-6, H-7, H-9, H-10, H-11 and H-12), 2.13 (apparent q, 1H, *J* = 9.2 Hz, H-11'), 2.41 (m, 1H, H-8), 3.32 (dd, 1H, *J* = 19.1, 4.8 Hz, H-2), 3.80-4.06 (m, 4H, H-13 and H-14).

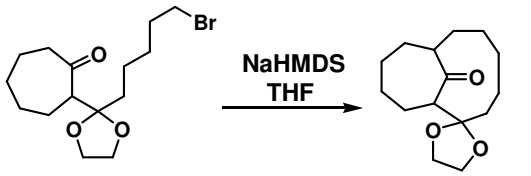
^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 24.1, 24.2, 24.7, 27.3, 28.7, 31.7, 36.4 (C-4, C-5, C-6, C-7, C-9, C-10, C-12), 37.7 (C-11), 51.8 (C-2), 53.5 (C-8), 63.6, 66.6 (C-13 and C-14), 110.7 (C-3), 216.7 (C-1).

IR (film, cm^{-1}): 2923 and 2852 (C-H), 1695 (C=O), 1466, 1337, 1030.

MS (APCI+ev): *m/z* (%): 239 (100) $[M+H]^{+\cdot}$, 221 (40), 149 (10).

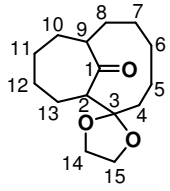
HRMS (ESI): Calculated for $C_{14}H_{22}O_3Na$ (M+Na): 261.1467. Found: 261.1469.

2-dioxolanyl-bicyclo[6.4.1]tridecan-13-one 2.069



$C_{15}H_{24}O_3$
M.W.: 252,35

In a 25 mL round-bottomed flask are introduced 50 mg (0.16 mmol, 1 eq.) of the brominated β-ketoketal and 3 mL of THF. The solution is cooled to 0°C and 0.1 mL (2M solution in THF, 0.2 mmol, 1.3 eq.) of NaHMDS are added dropwise. The yellow mixture is gradually allowed to reach room temperature overnight. After stirring for 12 hours, 4 mL of a saturated NH_4Cl solution are added. After phase separation, the aqueous layer is extracted with 3 x 5 mL of diethyl ether and the combined organic fractions are dried ($MgSO_4$). Removal of the solvents under reduced pressure yields a residue, which is purified by flash chromatography (silica, PE/AcOEt 4:1) to afford 28 mg (75%) of the product bridged ketone (Rf = 0.16).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.11-2.09 (m, 18H, H-4, H-5, H-6, H-7, H-8, H-10, H-11, H-12 and H-13), 2.35-2.47 (m, 1H, H-9), 3.60 (dd, 1H, *J* = 11.3, 2.1 Hz, H-2), 3.82-4.12 (m, 4H, H-14 and H-15).

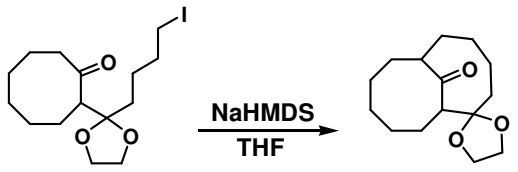
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 17.2, 19.4, 25.6, 26.8, 27.0, 28.6, 29.9, 30.0, 30.9 (C-4, C-5, C-6, C-7, C-8, C-10, C-11, C-12, C-13), 51.1 (C-2), 56.4 (C-9), 63.6, 66.4 (C-14 and C-15), 111.5 (C-3), 216.8 (C-1).

IR (film, cm^{-1}): 2913 (C-H), 1694 (C=O), 1337, 1130.

MS (APCI+ev): *m/z* (%): 253 (100) $[M+H]^{+\cdot}$, 209 (7), 163 (10).

HRMS (ESI): Calculated for $C_{15}H_{24}O_3Na$ (M+Na): 275.1623. Found: 275.1617.

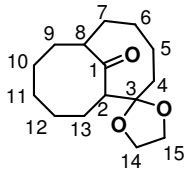
2-dioxolanyl-bicyclo[5.5.1]tridecan-13-one 2.072



$C_{15}H_{24}O_3$
M.W.: 252,35

In a 10 mL round-bottomed flask are introduced 50 mg (0.13 mmol, 1 eq.) of the iodinated β-ketoketal and 3 mL of THF. The solution is cooled to 0°C and 0.1 mL (2M solution in THF, 0.2 mmol, 1.3 eq.) of NaHMDS are added dropwise. The yellow mixture is gradually allowed to reach room temperature overnight. After stirring for 12 hours, 4 mL of a saturated NH_4Cl solution are added. After phase separation, the aqueous layer is extracted with 3 x 5 mL of diethyl ether and the combined organic fractions are dried ($MgSO_4$). Removal of the solvents under reduced pressure yields a

residue, which is purified by flash chromatography (silica, PE/AcOEt 4:1) to afford 27 mg (75%) of the product bridged ketone (Rf = 0.30).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.21-1.91 (m, 18H, H-4, H-5, H-6, H-7, H-9, H-10, H-11, H-12 and H-13), 2.31-2.40 (m, 1H, H-8), 3.34-3.45 (m, 1H, H-2), 3.84-4.01 (m, 4H, H-14 and H-15).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 22.0, 24.5, 25.2, 25.5, 28.6, 29.7, 31.2, 32.4, 35.2 (C-4, C-5, C-6, C-7, C-9, C-10, C-11, C-12, C-13), 51.5 (C-2), 54.6 (C-8), 64.2, 66.0 (C-14 and C-15), 111.0 (C-3), 220.6 (C-1).

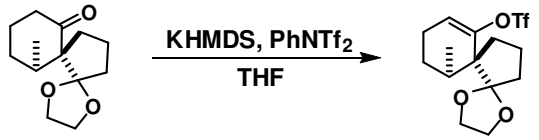
IR (film, cm^{-1}): 2913 (C-H), 1690 (C=O), 1438, 1332, 1048.

MS (APCI+ev): *m/z* (%): 253 (100) $[M+H]^{+\cdot}$, 235 (25), 209 (5), 191 (25), 173 (80), 163 (35), 131 (20).

HRMS (ESI): Calculated for $C_{15}H_{24}O_3Na$ (M+Na): 275.1623. Found: 275.1619.

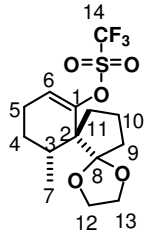
9.6. Total synthesis of the Spirovetivanes (Chapter 3)

11-methyl-1,4-dioxadispiro[4.0.5.3]tetradec-7-en-7-yltrifluoro-methanesulfonate 3.222



$C_{14}H_{19}F_3O_5S$
M.W.: 356,36

In a 100 mL round-bottomed flask, 0.24 g of the spirocyclic ketone (1.1 mmol, 1 eq.) are dissolved in 20 mL of THF and cooled to -78ºC. To this solution are added dropwise 4 mL of KHMDS (0.5M solution in toluene, 2 mmol, 1.9 eq.), upon which the reaction mixture becomes slightly yellow. After 10 minutes stirring at -78ºC, 0.69 g of $PhNTf_2$ (1.9 mmol, 1.8 eq.) dissolved in 10 mL of THF are added dropwise over 10 minutes. The mixture turns to orange and is stirred for 4 hours, gradually rising to room temperature. At this point, 20 mL of an aqueous saturated NH_4Cl solution are added to quench the reaction. After phase separation, the aqueous layer is extracted with 2 x 20 mL diethylether. The combined organic fractions are dried ($MgSO_4$) and the solvents are removed under reduced pressure. Purification of the residue by flash chromatography (silica, PE/AcOEt 9:1) affords 0.37 g (95 %) of the product (Rf = 0.65).



^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 1.17 (d, 3H, *J* = 6.7 Hz, H-7), 1.42-1.98 (m, 8H, H-4, H-9, H-10 and H-11), 2.02-2.24 (m, 3H, H-3 and H-5), 3.79-3.98 (m, 4H, H-12 and H-13), 5.68 (t, 1H, *J* = 3.9 Hz, H-6).

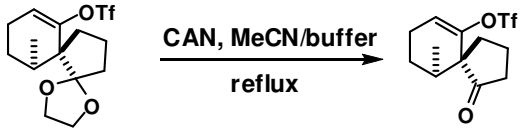
^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 16.7 (C-7), 21.5, 23.2, 26.1 (C-5, C-10 and C-11), 34.8, 38.3 (C-4 and C-9), 39.8 (C-3), 53.0 (C-2), 63.9, 64.7 (C-12 and C-13), 115.2 (C-14), 117.4 (C-8), 119.4 (C-6), 152.8 (C-1).

IR (film, cm^{-1}): 2966 and 2884 (C-H), 1677 (C=C), 1412, 1243, 1038.

MS (APCI+ev): *m/z* (%): 357 (40) $[M+H]^{+\cdot}$, 207 (18), 163 (100), 149 (10), 145 (45).

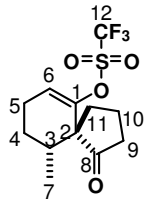
HRMS (EI): Calculated for $C_{14}H_{19}F_3O_5S$: 356.9050. Found: 356.9012.

10-methyl-1-oxospiro[4.5]dec-6-en-6-yl trifluoromethanesulfonate 3.268



$C_{12}H_{15}F_3O_4S$
M.W.: 312,31

In a 250 mL round-bottomed flask eq.uipped with a reflux condenser, 1.5 g of enol triflate (4.2 mmol, 1 eq.) are dissolved in 40 mL of acetonitrile and 40 mL of borate buffer (pH=8). To this solution are added 70 mg of CAN (0.13 mmol, 0.03 eq.), upon which the reaction mixture turns to yellow. The mixture is heated to reflux. After 2-3 hours stirring at reflux, TLC-analysis shows complete conversion. In case of remaining starting material, additional 3 mol% amounts of CAN can be added to drive the reaction forth. At this point, 50 mL of water are added to quench the reaction. The mixture is extracted with 3 x 75 mL dichloromethane. The combined organic fractions are dried ($MgSO_4$) and the solvents are removed under reduced pressure. Purification of the residue by flash chromatography (silica, PE/Et_2O 1:1) affords 1.25 g (96 %) of the product (Rf = 0.50).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 0.93 (d, 3H, *J* = 6.6 Hz, H-7), 1.73-2.40 (m, 11H, H-3, H-4, H-5, H-9, H-10, H-11), 5.93 (td, 1H, *J* = 4.2, 1.2 Hz, H-6).

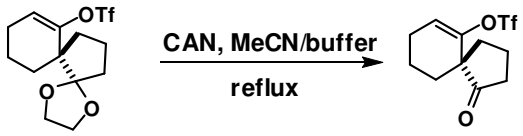
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 16.2 (C-7), 19.5, 22.4, 25.6, 32.9 (C-4, C-5, C-10 and C-11), 37.7 (C-3), 39.3 (C-9), 55.5 (C-2), 116.0 (C-12), 119.5 (C-6), 149.0 (C-1), 216.9 (C-8).

IR (film, cm^{-1}): 2985 (C-H), 1741 (C=O), 1419, 1255.

MS (CI+ev): *m/z* (%): 313 (5) $[M+H]^+$, 163 (30), 145 (100), 130 (10).

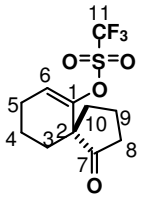
HRMS (CI): Calculated for $C_{12}H_{16}F_3O_4S$ [*M+1*]: 313.0721. Found: 313.0712.

1-oxospiro[4.5]dec-6-en-6-yl trifluoromethanesulfonate 3.311



$C_{11}H_{13}F_3O_4S$
M.W.: 298,28

In a 250 mL round-bottomed flask eq.uipped with a reflux condenser, 0.8 g of enol triflate (2.0 mmol, 1 eq.) are dissolved in 20 mL of acetonitrile and 20 mL of borate buffer (pH=8). To this solution are added 35 mg of CAN (0.06 mmol, 0.03 eq.), upon which the reaction mixture turns to yellow. The mixture is heated to reflux. After 2-3 hours stirring at reflux, TLC-analysis shows complete conversion. In case of remaining starting material, additional 3 mol% amounts of CAN can be added to drive the reaction forth. At this point, 40 mL of water are added to quench the reaction. The mixture is extracted with 3 x 50 mL dichloromethane. The combined organic fractions are dried ($MgSO_4$) and the solvents are removed under reduced pressure. Purification of the residue by flash chromatography (silica, PE/Et_2O 1:1) affords 0.55 g (93 %) of the product (Rf = 0.51).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.45-2.10 (m, 8H, H-3, H-5, H-9, H-10), 2.20-2.44 (m, 4H, H-8 and H-4), 5.93 (t, 1H, *J* = 3.9 Hz, H-6).

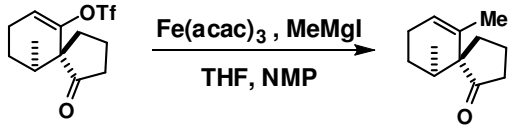
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 17.8, 18.9, 24.1, 32.0, 33.4 (C-3, C-4, C-5, C-9 and C-10), 37.8 (C-8), 53.2 (C-2), 106.3 (C-11), 120.8 (C-6), 148.1 (C-1), 216.7 (C-7).

IR (film, cm^{-1}): 3054 and 2987 (C-H), 2306, 1743 (C=O), 1420, 1265, 1216, 1141.

MS (CI+ev): *m/z* (%): 298 (10) $[M]^+$, 225 (100), 174 (60), 155 (10), 91 (20).

HRMS (ESI): Calculated for $C_{11}H_{14}F_3O_4S$ [*M+1*]: 299.0565. Found: 299.0558.

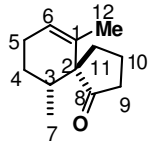
6,10-dimethylspiro[4.5]dec-6-en-1-one 3.215



$C_{12}H_{18}O$
M.W.: 178,27

In a 25 mL round-bottomed flask, $Fe(acac)_3$ (136 mg, 0.38 mmol, 0.2 eq.) is added to a solution of 600 mg of enol triflate (1.92 mmol, 1 eq.) in

a mixture of THF (25 mL) and NMP (17.5 mL). The resulting red solution is then cooled to –15ºC and 1.92 mL of methylmagnesium iodide (3M solution in diethylether, 5.76 mmol, 3 eq.) are added dropwise. The resulting greenish suspension is stirred for 20 minutes at the same temperature, then water is added to quench the reaction. The aqueous layer is extracted with 3 x 40 mL ether and the combined organic fractions are washed with a 10% aqueous NaOH solution to remove most of the acac ligand. The organic layer is dried ($MgSO_4$) and evaporated under reduced pressure. The crude residue is then purified by flash chromatography (silica, PE/Et_2O 10:1) to yield the coupled product (330 mg, 96%). This compound has a distinct, pleasant mint-like aroma.



^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 1.08 (d, 3H, *J* = 6.8 Hz, H-7), 1.74-2.58 (m, 14H, H-3, H-4, H-5, H-9, H-10, H-11 and H-12), 5.78 (br s, 1H, H-6).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 16.1 (C-7), 19.4 (C-10), 20.2 (C-12), 22.7, 26.2 (C-5 and C-11), 34.7 (C-4), 35.0 (C-3), 39.5 (C-9), 56.6 (C-2), 125.5 (C-6), 133.2 (C-1), 221.6 (C-8).

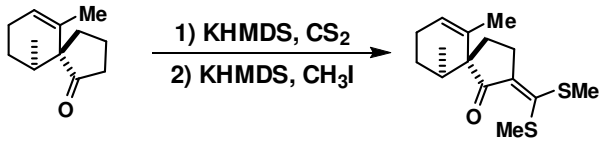
IR (film, cm^{-1}): 2967 (C-H), 1715 (C=O), 1452, 1332.

MS (CI+ev): *m/z* (%):179 (100) $[M+H]^+$, 178 (55) $[M]^+$, 161 (70), 135 (25).

HRMS (CI): Calculated for $C_{12}H_{18}O$: 178.13576. Found: 178.13577.

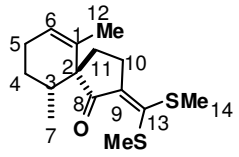
2-(bis(methylthio)methylene)-6,10-dimethylspiro[4.5]dec-6-en-1-one

3.275



$C_{15}H_{22}OS_2$
M.W.: 282,46

In a 25 mL round-bottomed flask, 4 mL of THF are added to 100 mg (0.56 mmol, 1 eq.) of the enone. The resulting solution is then cooled to –78ºC and 1.24 mL of KHMDS (0.5M solution in toluene, 0.62 mmol, 1.1 eq.) are added dropwise. The resulting yellow solution is stirred for 25 minutes at the same temperature, after which 0.051 mL (8.42 mmol, 1.5 eq.) of CS_2 are added at once. The mixture, which instantly turns bright orange, is allowed to gradually reach 0ºC during 1 hour, before cooling back to -78ºC. Another 1.24 mL of KHMDS (0.5M solution in toluene, 0.62 mmol, 1.1 eq.) are added dropwise and the red mixture is stirred for 20 minutes at this temperature. Then, methyl iodide (0.1 mL, 1.7 mmol, 3 eq.) is added and the mixture is allowed to gradually reach room temperature overnight. After 14 hours stirring, the yellow suspension is quenched by addition of 4 mL of a saturated aqueous NH_4Cl solution. The aqueous layer is extracted with 3 x 10 mL ether and the combined organic fractions are dried ($MgSO_4$) and evaporated under reduced pressure. The crude residue is then purified by flash chromatography (silica, PE/Et_2O 5:1) to yield 136 mg (86%) of the ketene dithioketal (Rf = 0.3).



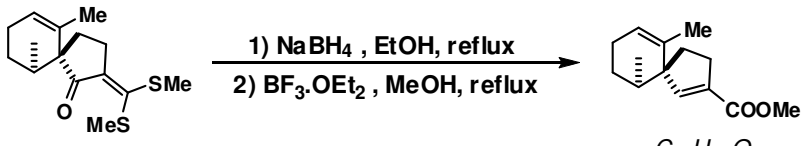
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 0.83 (d, 3H, *J* = 6.6 Hz, H-7), 1.55 (br s, 3H, H-12), 1.60-2.18 (m, 7H, H-3, H-4, H-5, H-11), 2.44 (s, 6H, H-14), 2.74-2.79 (m, 2H, H-10), 5.57 (br s, 1H, H-6).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 16.0 (C-7), 17.6, 18.9, 20.2 (C-12 and C-14), 22.6, 26.4, 30.2, 31.2 (C-4, C-5, C-10, C-11), 35.0 (C-3), 59.3 (C-2), 125.2 (C-6), 133.9 (C-1), 135.7 (C-9), 149.8 (C-13), 203.6 (C-8).

MS (CI+ev): *m/z* (%):283 (75) $[M+H]^+$, 282 (100) $[M]^+$, 267 (25), 219 (15), 143 (10).

HRMS (CI): Calculated for $C_{15}H_{23}OS_2$ *[M+1]*$^+$: 283.1190. Found: 283.1189.

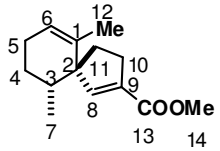
Methyl 6,10-dimethylspiro[4.5]deca-1,6-diene-2-carboxylate 3.294



$C_{14}H_{20}O_2$
M.W.: 220,31
CAS: 52528-52-6

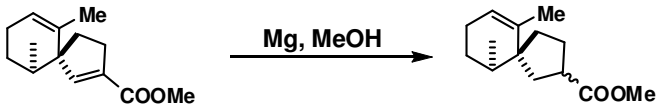
In a 10 mL round-bottomed flask eq.uipped with a reflux condenser, 4 mL of abs. EtOH are added to 100 mg (0.36 mmol, 1 eq.) of the ketene dithioketal. To the resulting solution are then added at once 68 mg (1.8 mmol, 5 eq.) of sodium borohydride, upon which foaming is observed. The mixture is heated at reflux for 4 hours, at which time TLC analysis indicates complete consumption of the starting ketone with formation of two new products (alcohol diastereomers). The reaction mixture is poured into ice and extracted with 3 x 20 mL of dichloromethane. The combined organic fractions are washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to yield a residue.

The residue is taken in 6 mL of MeOH. To this solution, 0.17 mL (1.44 mmol, 4 eq.) of $BF_3.OEt_2$ are added, which causes the mixture to turn pink. The solution is heated to reflux for 16 hours, after which the dark grey solution is poured into ice and extracted with 3 x 20 mL dichloromethane. The combined organic fractions are washed with 30 mL of an aqueous saturated bicarbonate solution, dried ($MgSO_4$) and concentrated under reduced pressure to yield a residue The crude residue is then purified by flash chromatography (silica, PE/Et_2O 10:1) to yield 52 mg (66% overall for the two steps) of the α,β-unsaturated ester (Rf = 0.51 in PE/Et_2O 5:1).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 0.85 (d, 3H, *J* = 6.6 Hz, H-7), 1.53 (br s, 3H, H-12), 1.23-2.01 (m, 7H, H-3, H-4, H-5, H-11), 2.59 (m, 2H, H-10), 3.72 (s, 3H, H-14), 5.41 (br s, 1H, H-6), 6.53 (t, 1H, *J* = 2.1 Hz, H-8).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 16.5 (C-7), 20.0 (C-12), 23.7, 27.9, 29.8, 31.4 (C-4, C-5, C-10, C-11), 34.1 (C-2), 37.5 (C-3), 51.5 (C-14), 122.8 (C-6), 135.3 (C-1), 136.4 (C-9), 148.4 (C-8), 165.8 (C-13).
MS (CI+ev): *m/z* (%): 221 (100) $[M+H]^+$, 178 (20), 139 (15), 119 (5).
HRMS (CI): Calculated for $C_{14}H_{21}O_2$ $[M+1]^+$: 221.1541. Found: 221.1539.

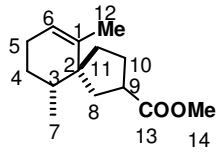
Methyl 6,10-dimethylspiro[4.5]dec-6-ene-2-carboxylate 3.296



$C_{14}H_{22}O_2$
M.W.: 222,32
CAS: 121840-74-2

In a 25-mL round-bottomed flask are introduced 50 mg (0.22 mmol, 1 eq.) of the unsaturated ester and 4 mL of MeOH. To this solution are added 50 mg (2.2 mmol, 10 eq.) of magnesium powder at once. Stirring is continued for 4 hours, at which point TLC-analysis shows complete conversion of the UV-active starting material to a new, UV-inactive compound. The reaction is quenched by addition of 4 mL of a 2M HCl solution followed by 4 mL of water. The organic layer is extracted with 3 x 15 mL of diethyl ether. The combined organic fractions are dried ($MgSO_4$) and concentrated under reduced pressure. The residue thus obtained is pure

enough for subseq.uent transformations. For analytical purposes, a small sample can be purified by flash chromatography (silica, PE/Et_2O 20:1, Rf = 0.34). The ester thus obtained in quantitative yield (52 mg, 100%) is an inseparable 3:2 mixture of epimers.



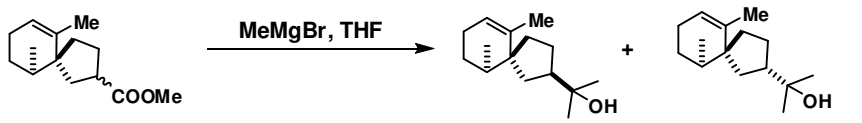
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 0.85-0.90 (m, 3H, H-7), 1.23-2.23 (m, 14H, H-3, H-4, H-5, H-8, H-10, H-11, H-12), 2.62-2-81 (m, 2H, H-9 and H-8' or H-5'), 3.65 (br s, 3H, H-14), 5.24 (br s, 1H, H-6 for minor epimer), 5.32 (br s, 1H, H-6 for major epimer).

^{13}C-NMR of major epimer (75 MHz, $CDCl_3$) δ (ppm): 16.5 (C-7), 20.0 (C-12), 23.7, 27.9, 28.5, 29.8, 31.4 (C-4, C-5, C-8, C-10, C-11), 37.5 (C-3), 43.1 (C-2), 44.3 (C-9), 51.4 (C-14), 122.8 (C-6), 137.3 (C-1), 174.3 (C-13).

MS (CI+ev): *m/z* (%): 223 (80) $[M+H]^+$, 163 (90), 131 (25), 107 (55), 93 (75), 81 (100).

HRMS (CI): Calculated for $C_{14}H_{23}O_2$ $[M+1]^+$: 223.1698. Found: 223.1703.

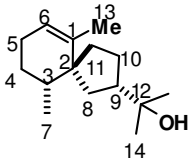
2-(6,10-dimethylspiro[4.5]dec-6-en-2-yl)propan-2-ol [Agarospirol 3.001 and Hinesol 3.003]



$C_{15}H_{26}O$
M.W.: 222,37
CAS: 1460-73-7
Agarospirol

$C_{15}H_{26}O$
M.W.: 222,37
CAS: 23811-08-7
Hinesol

In a 10-mL round-bottomed flask are introduced 40 mg (0.18 mmol, 1 eq.) of the saturated esters and 4 mL of THF. The resulting solution is cooled to 0ºC, and 0.24 mL of MeMgBr (3M solution in ether, 0.72 mmol, 4 eq.) are added dropwise. Stirring is continued for 3 hours, as the mixture is gradually allowed to reach room temperature. The reaction is quenched by addition of 4 mL of water. The organic layer is extracted with 3 x 15 mL of diethyl ether. The combined organic fractions are dried ($MgSO_4$) and concentrated under reduced pressure. The residue thus obtained (39 mg, 100%) is pure by ^{1}H-NMR analysis. For analytical purposes, a sample is purified by flash chromatography (silica, PE/Et_2O 5:1, Rf = 0.18), affording Agarospirol and Hinesol in a 2:3 ratio .



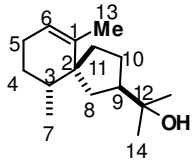
Hinesol

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 0.92 (d, 3H, *J* = 6.8 Hz, H-7), 1.20 (s, 6H, H-14), 1.25-1.79 (m, 12H, H-3, H-4, H-8, H-10, H-11, H-13), 1.90-2.00 (m, 3H, H-5 and H-9), 5.31 (br s, 1H, H-6).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 16.2 (C-7), 19.9 (C-13), 27.7, 27.9 (C-14 and C-14'), 24.2, 28.0, 28.4, 33.3, 35.7, 36.6 (C-3, C-4, C-5, C-8, C-10, C-11), 48.7 (C-2), 51.3 (C-9), 72.0 (C-12), 121.7 (C-6), 140.0 (C-1).

IR (neat, cm^{-1}): 3400 (br), 1659.

MS (CI+ev): *m/z* (%): 223 (3) $[M+H]^{+\cdot}$, 222 (7) $[M]^{+\cdot}$, 205 (100), 161 (20), 149 (10), 123 (10).



Agarospirol

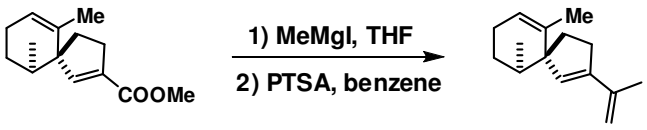
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 0.91 (d, 3H, *J* = 6.8 Hz, H-7), 1.21 (s, 6H, H-14), 1.17-1.81 (m, 12H, H-3, H-4, H-8, H-10, H-11, H-13), 1.85-2.00 (m, 3H, H-5 and H-9), 5.28 (br s, 1H, H-6).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 15.3 (C-7), 20.5 (C-13), 27.2, 27.6 (C-14 and C-14'), 22.5, 28.4, 29.7, 35.6, 38.7, 39.2 (C-3, C-4, C-5, C-8, C-10, C-11), 48.4 (C-2), 53.2 (C-9), 71.9 (C-12), 120.7 (C-6), 140.0 (C-1).

IR (neat, cm^{-1}): 3400 (br), 1659.

MS (CI+ev): *m/z* (%): 223 (3) $[M+H]^{+\cdot}$, 222 (7) $[M]^{+\cdot}$, 205 (100), 161 (20), 149 (10), 123 (10).

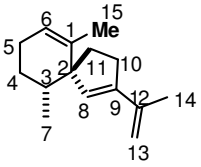
6,10-dimethyl-2-(prop-1-en-2-yl)spiro[4.5]deca-1,6-diene [α-Vetispirene 3.004]



$C_{15}H_{22}$
M.W.: 202,34
CAS: 51196-11-3
α-Vetispirene

In a 25-mL round-bottomed flask are introduced 40 mg (0.18 mmol, 1 eq.) of the unsaturated ester and 3 mL of THF. The resulting solution is cooled to 0ºC, and 0.24 mL of MeMgBr (3M solution in ether, 0.72 mmol, 4 eq.) are added dropwise. Stirring is continued for 3 hours, as the milky-white mixture is gradually allowed to reach room temperature. The reaction is quenched by addition of 4 mL of water. The organic layer is extracted with 3 x 15 mL of diethyl ether. The combined organic fractions are dried ($MgSO_4$) and concentrated under reduced pressure, affording a residue.

To a 25-mL round-bottomed flask containing 7 mg of PTSA (0.036 mmol, 0.2 eq.) in 2 mL benzene at 0ºC is added a solution of the aforementioned residue in 3 mL of benzene, at once. The resulting solution is allowed to gradually reach room temperature over 5 hours. At this time, 5 mL water are added to quench the reaction. The aqueous layer is extracted using 3 x 20 mL diethyl ether. The combined organic fractions are washed seq.uentially with 10 mL of a saturated aqueous bicarbonate solution, 10 mL of water and 10 mL of brine. The organic layer is dried ($MgSO_4$) and carefully concentrated under reduced pressure (volatile product). Purification of the residue by flash chromatography (silica, PE/Et_2O 20:1), affording 22 mg (60%) of the volatile natural product (Rf = 0.90, PE/Et_2O 5:1).



α-Vetispirene

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 0.86 (d, 3H, *J* = 6.8 Hz, H-7), 1.38-2.09 (m, 7H, H-3, H-4, H-5, H-11), 1.56 (d, 3H, *J* = 1.5 Hz, H-15), 1.94 (s, 3H, H-14), 2.46-2.60 (m, 2H, H-10), 4.88 (br s, 1H, H-13), 4.91 (br s, 1H, H-13'), 5.39 (br s, 1H, H-6 or H-8), 5.51 (br s, 1H, H-6 or H-8).

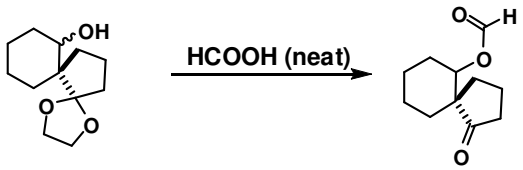
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 16.5 (C-7), 19.9 (C-15), 20.7 (C-14), 23.8, 28.2, 32.3, 34.4 (C-4, C-5, C-10 and C-11), 37.8 (C-3), 57.3 (C-2), 112.3 (C-13), 121.7, 132.7 (C-6 and C-8), 138.7, 140.3, 143.8 (C-1, C-9 and C-12).

IR (film, cm^{-1}): 3087 (C-H), 1630, 1597, 1375, 1200, 1076, 881.

MS (CI+ev): *m/z* (%): 203 (15) $[M+H]^{+\cdot}$, 202 (15) $[M]^{+\cdot}$, 160 (100), 145 (10), 121 (10).

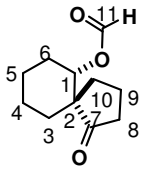
HRMS (CI): Calculated for $C_{15}H_{23}$ *[M+1]*: 203.1799. Found: 203.1794.

1-oxospiro[4.5]decan-6-yl formate 3.255



$C_{11}H_{16}O_3$
M.W.: 196,24

In a 10-mL round-bottomed flask are introduced 50 mg (0.24 mmol, 1 eq.) of the spirocyclic alcohol (mixture of epimers) and 2 mL of formic acid. The yellow solution is stirred for 14 hours, at which point TLC-analysis shows complete conversion of the starting material. The reaction is quenched by addition of 4 mL of water. The organic layer is extracted with 3 x 7 mL of dichloromethane. The combined organic fractions are washed with a saturated aqueous sodium bicarbonate solution, dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica, PE/Et_2O 4:1, Rf = 0.21) affords 37 mg (80%) of the major diastereoisomeric formate ester.



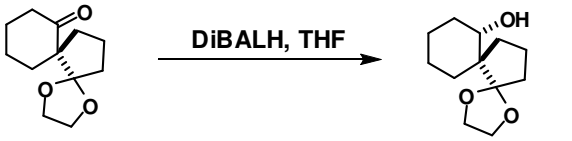
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.37-1.43 (m, 2H, H-4), 1.61-1.95 (m, 8H, H-3, H-5, H-6, H-9 and H-10), 2.04-2.11 (m, 2H, H-6' and H-10'), 2.31 (t, 2H, *J* = 7.4 Hz, H-8), 4.94 (d, 1H, *J* = 9.2, 3.6 Hz, H-1), 8.04 (d, 1H, *J* = 0.8 Hz, H-11).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 18.6 (C-9), 20.6 (C-4), 22.8 (C-5), 26.9 (C-3), 31.4 (C-10), 35.3 (C-6), 39.2 (C-8), 50.2 (C-2), 74.6 (C-1), 160.6 (C-11), 219.2 (C-7).

MS (CI+ev): *m/z* (%): 197 (2) $[M+H]^+$, 151 (100), 141 (25), 83 (35).

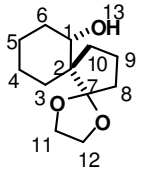
9.7. Towards GHB-analogues and PHT (Chapter 4)

1,4-dioxa-dispiro[4.0.5.3]tetradecan-7-ol 4.008



$C_{12}H_{20}O_3$
M.W.: 212,29

In a 10 mL round-bottomed flask, 0.10 g of the spirocyclic ketone (0.48 mmol, 1 eq.) are dissolved in 2.5 mL of THF and cooled to -78ºC. To this solution are added dropwise 0.95 mL of DiBALH (1M solution in toluene, 0.96 mmol, 2 eq.). After 3 hours stirring at -78ºC, 5 mL of an aqueous solution of sodium and potassium tartrate tetrahydrate (Rochelle's salt) are added to quench the reaction and vigorous stirring is maintained for 30 minutes at room temperature. After phase separation, the aqueous layer is extracted with 3 x 5 mL of diethylether. The combined organic fractions are dried ($MgSO_4$) and the solvents are removed under reduced pressure. The crude residue (100 mg, 98%) is pure by ^{1}H-NMR analysis. Purification of the residue for analytical purposes is done by flash chromatography (silica, PE/AcOEt 9:1, Rf = 0.22).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.26-1.44 (m, 4H, H-9 and H-10), 1.44-1.82 (m, 10H, H-3, H-4, H-5, H-6 and H-8), 3.62 (br s, 1H, H-13), 3.91-4.00 (m, 5H, H-1, H-11 and H-12).

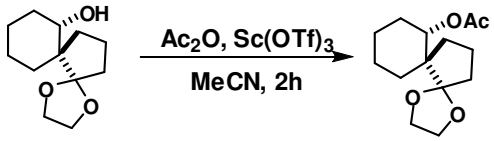
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 18.0 (C-9), 19.5, 22.0 (C-4 and C-5), 25.4, 29.3 (C-3 and C-10), 31.5 (C-8), 32.7 (C-6), 48.3 (C-2), 63.9, 64.3 (C-11 and C-12), 70.7 (C-1), 120.0 (C-7).

IR (film, cm^{-1}): 3510 (br, OH), 2933, 2891 and 2862 (C-H).

MS (CI+ev): *m/z* (%): 213 (3) $[M+H]^{+\cdot}$, 195 (100), 99 (85).

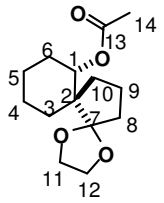
HRMS (ESI): Calculated for $C_{12}H_{20}O_3Na$ (M+Na): 235.1310. Found: 235.1311.

1,4-dioxa-dispiro[4.0.5.3]tetradecan-7-ol acetate 4.033



$C_{14}H_{22}O_4$
M.W.: 254,32

In a 10 mL round-bottomed flask, 50 mg of the spirocyclic alcohol (0.24 mmol, 1 eq.) are dissolved in 1 mL of MeCN. To this solution are seq.uentially added 0.07 mL of acetic anhydride (0.706 mmol, 3 eq.) and 2 mg (2 mol%) of $Sc(OTf)_3$. The reaction mixture instantly turns bright yellow. After 2 hours stirring, 5 mL of an aqueous saturated sodium bicarbonate solution are added to quench the reaction. After phase separation, the aqueous layer is extracted with 3 x 5 mL of diethylether. The combined organic fractions are dried ($MgSO_4$) and the solvents are removed under reduced pressure. Purification of the residue by flash chromatography (silica, PE/AcOEt 9:1) affords 27 mg (45%) of the protected acetate, accompanied by an eq.uimolar amount of its unprotected counterpart.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.24-1.68 (m, 10H, H-3, H-4, H-8, H-9 and H-10), 1.69-1.87 (m, 4H, H-5 and H-6), 2.04 (s, 3H, H-14), 3.75-3.91 (m, 4H, H-11 and H-12), 4.80 (apparent d, 1H, J = 2.3 Hz, H-1).

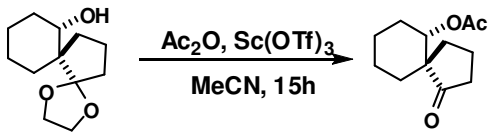
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 18.2 (C-9), 20.0, 21.1 (C-4 and C-5), 21.5 (C-14), 26.6, 27.6 (C-3 and C-10), 31.9 (C-8), 34.4 (C-6), 47.7 (C-2), 64.0, 64.3 (C-11 and C-12), 72.8 (C-1), 118.8 (C-7), 170.2 (C-13).

IR (film, cm^{-1}): 2937, 2925 (C-H), 1731 (C=O).

MS (CI+ev): *m/z* (%): 255 (3) $[M+H]^{+\cdot}$, 195 (75), 151 (35), 99 (100).

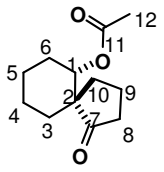
HRMS (ESI): Calculated for $C_{14}H_{23}O_4$ *[M+1]*: 255.1596. Found: 255.1602.

1-oxospiro[4.5]decan-6-yl acetate 4.034



$C_{12}H_{18}O_3$
M.W.: 210,27

In a 10 mL round-bottomed flask, 50 mg of the spirocyclic alcohol (0.24 mmol, 1 eq.) are dissolved in 1 mL of MeCN. To this solution are seq.uentially added 0.07 mL of acetic anhydride (0.706 mmol, 3 eq.) and 2 mg (2 mol%) of $Sc(OTf)_3$. The reaction mixture instantly turns bright yellow. After 15 hours stirring, 5 mL of an aqueous saturated sodium bicarbonate solution are added to quench the reaction. After phase separation, the aqueous layer is extracted with 3 x 5 mL of diethylether. The combined organic fractions are dried ($MgSO_4$) and the solvents are removed under reduced pressure. Purification of the residue by flash chromatography (silica, PE/AcOEt 9:1) affords 48 mg (95%) of the deprotected acetate.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.14-1.48 (m, 4H, H-9 and H-10), 1.58-2.34 (m, 10H, H-3, H-4, H-5, H-6 and H-8), 2.30 (s, 3H, H-12), 5.04 (dd, 1H, *J* = 8.8, 3.6 Hz, H-1).

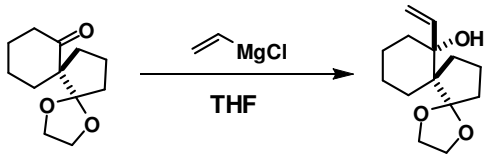
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 21.1 (C-9), 21.6, 23.1 (C-4 and C-5), 27.3 (C-12), 30.1, 32.1 (C-3 and C-10), 35.9 (C-8), 39.7 (C-6), 50.8 (C-2), 74.9 (C-1), 171.1 (C-11), 219.7 (C-7).

IR (film, cm^{-1}): 2935, 2916 and 2856 (C-H), 1739 (ketone C=O), 1731 (ester C=O).

MS (CI+ev): *m/z* (%): 211 (8) $[M+H]^{+\cdot}$, 151 (21).

HRMS (ESI): Calculated for $C_{12}H_{18}O_3Na$ (M+Na): 233.1154. Found: 233.1158.

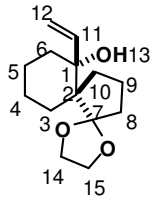
7-vinyl-1,4-dioxa-dispiro[4.0.5.3]tetradecan-7-ol 4.010



$C_{14}H_{22}O_3$
M.W.: 238,32

In a 10 mL round-bottomed flask, 80 mg of the spirocyclic ketone (0.38 mmol, 1 eq.) are dissolved in 2 mL of THF and cooled to 0ºC. To this solution are added 0.70 mL of vinylmagnesium chloride (*ca.* 1.7M solution in THF, 1.14 mmol, 3 eq.). The reaction mixture is allowed to gradually reach room temperature, as it turns to a yellow limpid solution. After 1 hour

stirring, 5 mL of an aqueous saturated NH_4Cl solution are added to quench the reaction. After phase separation, the aqueous layer is extracted with 3 x 5 mL of diethylether. The combined organic fractions are dried ($MgSO_4$) and the solvents are removed under reduced pressure. The crude residue (88 mg, 98%), which is pure by ^{1}H-NMR analysis, indicates a diastereomer ratio >15:1. Purification of the residue for analytical purposes is done by flash chromatography (silica, PE/AcOEt 9:1, Rf = 0.65 with PE/AcOEt 1:1).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.45-1.66 (m, 15H, H-3, H-4, H-5, H-6, H-8, H-9 and H-10), 2.30-2.36 (m, 1H, H-3'), 3.78-3.90 (m, 5H, H-13, H-14 and H-15), 5.01 (dd, 1H, *J* = 10.8, 2.3 Hz, H-12), 5.33 (dd, 1H, *J* = 17.1, 2.3 Hz, H-12' *trans* to H-11), 6.64 (dd, 1H, *J* = 17.0, 10.8 Hz, H-11).

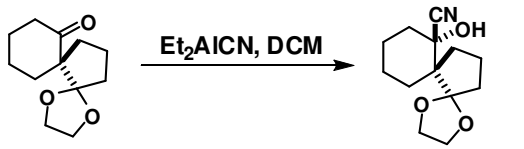
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 18.9 (C-9), 21.1, 22.6 (C-4 and C-5), 27.6 (C-3), 30.5 (C-10), 34.1 (C-8), 38.9 (C-6), 52.9 (C-2), 63.3, 63.9 (C-14 and C-15), 74.9 (C-1), 110.8 (C-7), 121.7 (C-12), 143.6 (C-11).

IR (film, cm^{-1}): 3950 (br, OH), 2937 (C-H), 1430.

MS (APCI+ev): *m/z* (%): 239 (2) $[M+H]^{+\cdot}$, 221 (100), 159 (15), 99 (25).

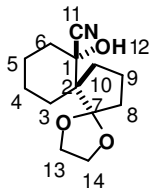
HRMS (ESI): Calculated for $C_{14}H_{22}O_3Na$ (M+Na): 261.1467. Found: 261.1462.

7-cyano-1,4-dioxa-dispiro[4.0.5.3]tetradecan-7-ol 4.011



$C_{13}H_{19}NO_3$
M.W.: 237,29

In a 10 mL round-bottomed flask, 100 mg of the spirocyclic ketone (0.48 mmol, 1 eq.) are dissolved in 4 mL of dichloromethane and cooled to 0ºC. To this solution are added 0.60 mL of diethylaluminum cyanide (1M solution in toluene, 0.6 mmol, 1.2 eq.). The reaction mixture turns to a deep orange solution and is allowed to gradually reach room temperature. After stirring for 45 minutes, 5 mL of an aqueous solution of sodium and potassium tartrate tetrahydrate (Rochelle's salt) are added to quench the reaction and vigorous stirring is maintained for 30 minutes at room temperature. After phase separation, the aqueous layer is extracted with 3 x 5 mL of dichloromethane. The combined organic fractions are dried ($MgSO_4$) and the solvents are removed under reduced pressure. The crude residue (108 mg, 94%) is pure by ^{1}H-NMR analysis, indicating a diastereomer ratio >95:5. Purification of the residue for analytical purposes is done by flash chromatography (silica, PE/AcOEt 9:1, Rf = 0.65 with PE/AcOEt 4:1).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.49-1.91 (m, 12H, H-3, H-4, H-5, H-6, H-8, H-9 and H-10), 1.99-2.12 (m, 2H, H-3' and H-6'), 3.93-3.98 (m, 2H, H-13 or H-14), 4.20-4.25 (m, 2H, H-13 or H-14), 4.92 (s, 1H, H-12).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 19.9 (C-9), 20.4, 22.6 (C-4 and C-5), 27.7 (C-3), 31.4 (C-10), 34.8 (C-8), 35.3 (C-6), 52.9 (C-2), 64.1, 64.4 (C-13 and C-14), 71.2 (C-1), 120.3 (C-7), 121.7 (C-11).

IR (film, cm^{-1}): 3950 (br, OH), 2937 (C-H), 2251 (C≡N), 1430.

MS (APCI+ev): *m/z* (%): 238 (3) $[M+H]^{+\cdot}$, 220 (5), 211 (95), 193 (50), 164 (20), 149 (20), 121 (100), 99 (7).

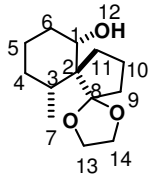
HRMS (ESI): Calculated for $C_{13}H_{19}NO_3Na$ (M+Na): 260.1263. Found: 260.1261.

11-methyl-1,4-dioxa-dispiro[4.0.5.3]tetradecan-7-ol 4.012

$C_{13}H_{22}O_3$
M.W.: 226,31

In a 50 mL round-bottomed flask, 0.50 g of the spirocyclic ketone (2.4 mmol, 1 eq.) are dissolved in 10 mL of THF and cooled to -78ºC. To this solution are added dropwise 3.97 mL of DiBALH (20% solution in toluene, 4.8 mmol, 2 eq.). After 3 hours stirring at -78ºC, 15 mL of an aqueous solution of sodium and potassium tartrate tetrahydrate (Rochelle's salt) are

added to quench the reaction and vigorous stirring is maintained for 30 minutes at room temperature. After phase separation, the aqueous layer is extracted with 3 x 20 mL of diethylether. The combined organic fractions are dried ($MgSO_4$) and the solvents are removed under reduced pressure. The crude residue (488 mg, 90%) is pure by ^{1}H-NMR analysis. Purification of the residue for analytical purposes is done by flash chromatography (silica, PE/AcOEt 9:1).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.13 (d, 3H, *J* = 7.1Hz, H-7), 1.23-1.32 (m, 1H, H-5), 1.47-1.82 (m, 11H, H-3, H-4, H-5', H-6, H-9, H-10 and H-11), 1.92-1.98 (m, 1H, H-9'), 3.68 (br s, 1H, H-1), 3.85-4.03 (m, 4H, H-13 and H-14), 4.22 (d, 1H, *J* = 3.6 Hz, H-12).

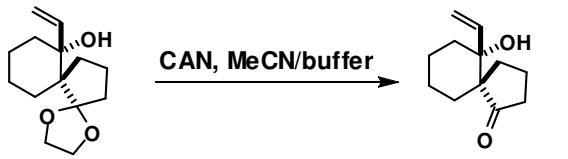
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 16.8 (C-7), 18.2, 19.0 (C-5 and C-10), 30.2, 30.6 (C-4 and C-11), 34.7, 35.1 (C-6 and C-9), 36.5 (C-3), 50.7 (C-2), 62.7, 63.4 (C-13 and C-14), 74.5 (C-1), 121.1 (C-8).

IR (film, cm^{-1}): 3500 (br, OH), 2923 (C-H), 1420.

MS (CI+ev): *m/z* (%): 227 (20) $[M+H]^{+\cdot}$, 209 (100), 165 (20), 147 (30), 121 (25), 99 (80).

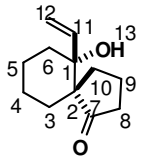
HRMS (EI): Calculated for $C_{13}H_{22}O_3$ $[M^{+\cdot}]$: 226.1569. Found: 226.1570.

6-hydroxy-6-vinylspiro[4.5]decan-1-one 4.036



$C_{12}H_{18}O_2$
M.W.: 194,27

In a 10 mL round-bottomed flask, 75 mg of the spirocyclic ketone (0.32 mmol, 1 eq.) are dissolved in 1 mL of MeCN and 1 mL of borate buffer (pH = 8). To this solution are added 1 mg of CAN (9.4 μmol, 0.03 eq.). After 12 hours stirring at room temperature, 4 mL of water are added to quench the reaction. After phase separation, the aqueous layer is extracted with 3 x 5 mL of dichloromethane. The combined organic fractions are dried ($MgSO_4$) and the solvents are removed under reduced pressure. The crude residue (50 mg, 82%) is pure by ^{1}H-NMR analysis. Purification of the residue for analytical purposes is done by flash chromatography (silica, PE/AcOEt 4:1, Rf = 0.31).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.34-1.66 (m, 8H, H-3, H-4, H-5, H-6 and H-10), 1.77-1.84 (m, 2H, H-9), 2.02-2.24 (m, 2H, H-8 and H-10'), 2.27-2.38 (m, 2H, H-6' and H-8'), 5.09 (dd, 1H, *J* = 10.8, 1.4 Hz, H-12), 5.25 (dd,

1H, *J* = 17.2, 1.5 Hz, H-12' *trans* to H-11), 5.81 (dd, 1H, *J* = 17.3, 10.8 Hz, H-11).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 18.1 (C-9), 20.4, 20.8 (C-4 and C-5), 29.6 (C-3), 33.1 (C-10), 34.7 (C-6), 39.6 (C-8), 54.6 (C-2), 74.7 (C-1), 113.6 (C-12), 142.7 (C-11).

IR (film, cm^{-1}): 3930 (br, OH), 2934 (C-H), 1710 (C=O).

MS (APCI+ev): *m/z* (%): 195 (5) $[M+H]^{+\cdot}$, 177 (100), 159 (20), 149 (35), 135 (10).

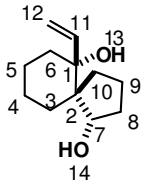
HRMS (ESI): Calculated for $C_{12}H_{18}O_2Na$ (M+Na): 217.1204. Found: 217.1206.

6-vinylspiro[4.5]decane-1,6-diol 4.037

$C_{12}H_{20}O_2$
M.W.: 196,29

In a 10 mL round-bottomed flask, 37 mg of the spirocyclic ketoalcohol (0.19 mmol, 1 eq.) are dissolved in 3 mL of THF and cooled to -78ºC. To this solution are added dropwise 0.39 mL of DiBALH (20% solution in toluene, 0.48 mmol, 2.5 eq.). The mixture is allowed to gradually reach room temperature over 3 hours, at which point 5 mL of an aqueous solution of sodium and potassium tartrate tetrahydrate (Rochelle's salt) are added to quench the reaction and vigorous stirring is maintained for 30

minutes at room temperature. After phase separation, the aqueous layer is extracted with 3 x 5 mL of diethyl ether. The combined organic fractions are dried ($MgSO_4$) and the solvents are removed under reduced pressure. The crude residue is purified by flash chromatography (silica, PE/AcOEt 4:1, Rf = 0.20), affording 35 mg (95%) of the diol.



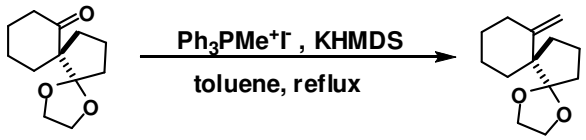
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.32-1.69 (m, 11H, H-3, H-4, H-5, H-6, H-8, H-9 and H-10), 1.78-1.90 (m, 2H, H-4' and H-8'), 2.17-2.26 (m, 1H, H-10'), 2.54 (d, 1H, *J* = 2.9 Hz, H-14), 3.74 (s, 1H, H-13), 3.87 (br s, 1H, H-7), 5.19 (dd, 1H, *J* = 10.8, 1.9 Hz, H-12), 5.51 (dd, 1H, *J* = 17.1, 1.9 Hz, H-12' *trans* to H-11), 6.62 (dd, 1H, *J* = 17.1, 10.8 Hz, H-11).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 21.0, 21.3, 22.7 (C-4, C-5 and C-9), 26.0 (C-10), 31.7 (C-3), 33.5 (C-8), 38.0 (C-6), 53.9 (C-2), 75.7 (C-1), 82.5 (C-7), 113.3 (C-12), 142 (C-11).

IR (film, cm^{-1}): 3921 (br, OH), 2934 (C-H), 1660, 1442.

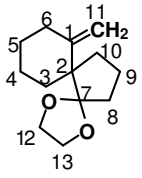
MS (CI+ev): *m/z* (%): 179 (100) $[M\text{-}H_2O]^{+\cdot}$, 161 (25), 135 (10), 119 (15), 95 (10), 81 (70), 43 (10).

7- methylene-1,4-dioxa-dispiro[4.0.5.3]tetradecane 4.140



$C_{13}H_{20}O_2$
M.W.: 208,30

In a 25 mL round-bottomed flask, 7.1 mL of KHMDS (0.5M solution in toluene, 3.6 mmol, 1.5 eq.) are added to 1.5 g of triphenylphosphonium iodide (3.6 mmol, 1.5 eq.). The reaction mixture becomes a bright yellow suspension. After 30 minutes stirring at room temperature, 0.5 g of the spiroketone (2.4 mmol, 1 eq.) dissolved in 3 mL of toluene are added dropwise. The resulting orange suspension is heated to reflux. After 1 hour stirring at reflux, 7 mL of diethylether are added, followed by 7 mL of brine. After phase separation, the aqueous layer is extracted with 3 x 15 mL diethylether. The combined organic fractions are dried ($MgSO_4$) and the solvents are removed under reduced pressure. Purification of the residue by flash chromatography (silica, PE/AcOEt 20:1) affords 0.5 g (98 %) of the product (Rf = 0.50 in PE/AcOEt 9:1).



^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 1.25-1.33 (m, 1H, H-5), 1.34-1.43 (m, 3H, H-5' and H-9), 1.60-1.78 (m, 5H, H-4, H-8 and H-10), 1.89-1.95 (m, 2H, H-3), 2.03-2.08 (m, 1H, H-8'), 2.18-2.23 (m, 1H, H-6), 2.38-2.44 (m,

1H, H-6'), 3.88-3.96 (m, 4H, H-12 and H-13), 4.82 (s, 1H, H-11), 4.87 (s, 1H, H-11').

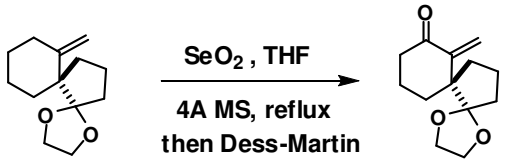
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 17.7 (C-9), 23.2 (C-4), 28.5 (C-5), 33.4, 34.1, 34.9, 35.5 (C-3, C-6, C-8 and C-10), 52.0 (C-2), 63.9, 64.4 (C-12 and C-13), 108.7 (C-11), 118.2 (C-7), 152.0 (C-1).

IR (film, cm^{-1}): 2934 and 2883 (C-H), 1634 (C=C), 1436, 1212, 1119.

MS (EI+ev): *m/z* (%): 209 (25) $[M+H]^{+\cdot}$, 165 (5), 147 (55), 99 (100).

HRMS (EI): Calculated for $C_{13}H_{20}O_2$ $[M^{+\cdot}]$: 208.1463. Found: 208.1458.

7- methylene-1,4-dioxa-dispiro[4.0.5.3]tetradecan-8-one 4.139

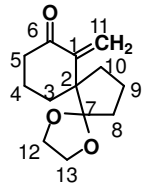


$C_{13}H_{18}O_3$
M.W.: 222,28

In a 10-mL round-bottomed flask, 100 mg (0.48 mmol, 1 eq.) of the alkene are dissolved in 4 mL of THF containing 4Å molecular sieves. To this mixture are added 54 mg of selenium dioxide (0.48 mmol, 1 eq.) and the resulting suspension is heated at reflux. After 1 hour stirring at reflux, a further 54 mg of selenium dioxide (0.48 mmol, 1 eq.) are added and the mixture is stirred overnight. After 14 hours stirring, TLC-analysis shows complete consumption of the starting olefin. At this stage, 5 mL of an aqueous saturated solution of $NaHCO_3$ are added to quench the reaction. The

mixture is filtered over a Celite pad and, after phase separation, the aqueous layer is extracted with 3 x 10 mL of diethyl ether. The combined organic fractions are washed with 2 x 5 mL of saturated $NaHCO_3$, dried ($MgSO_4$) and concentrated under reduced pressure to yield a residue.

The aforementioned residue is dissolved in 3 mL of dichloromethane and cooled to 0ºC. To this solution, 300 mg of Dess-Martin periodinane (0.72 mmol, 1 eq.) are added and the resulting suspension is allowed to gradually reach room temperature during 2 hours. Then, 5 mL of a 10% $Na_2S_2O_3$ solution are added to quench the reaction. The mixture is extracted with 3 x 10 mL of dichloromethane. The combined organic fractions are washed with 2 x 5 mL of saturated $NaHCO_3$, dried ($MgSO_4$) and concentrated under reduced pressure to yield a residue. Purification by flash chromatography (silica, PE/AcOEt 4:1) affords 48 mg (90%) of the enone. This enone slowly decomposes at room temperature or in slightly acidic solution and is best used directly in subseq.uent operations.

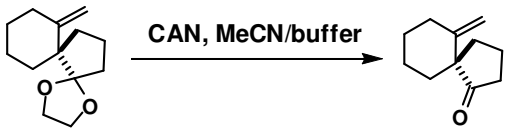


^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.69-1.86 (m, 7H, H-3, H-8, H-9 and H-10), 2.02-2.15 (m, 3H, H-4 and H-8'), 2.26-2.37 (m, 1H, H-5), 2.53 (dddd, 1H, *J* = 6.7, 5.7, 4.3, 1.7 Hz, H-5'), 3.82-3.95 (m, 4H, H-12 and H-13), 5.29 (d, 1H, *J* = 1.2 Hz, H-11), 5.85 (d, 1H, *J* = 1.2Hz, H-11').

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 17.8 (C-9), 20.2 (C-10), 31.8, 32.6, 34.9 (C-3, C-4 and C-8), 40.3 (C-5), 52.5 (C-2), 64.4, 64.5 (C-12 and C-13), 108.7 (C-7), 119.0 (C-11), 204.4 (C-6).

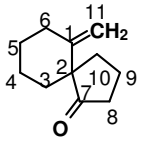
MS (APCI+ev): *m/z* (%): 223 (15) $[M+H]^{+\cdot}$, 203 (5), 179 (10), 161 (70), 133 (10), 99 (100).

6-methylenespiro[4.5]decan-1-one 4.157



$C_{11}H_{16}O$
M.W.: 164,24
CAS: 35653-42-0

In a 10-mL round-bottomed flask, 125 mg of the alkene (0.6 mmol, 1 eq.) are dissolved in 2 mL of acetonitrile and 2 mL of borate buffer (pH=8). To this solution are added 10 mg of CAN (0.02 mmol, 0.03 eq.), upon which the reaction mixture turns to yellow. The mixture is heated at 50ºC. After 1-2 hours stirring at this temperature, TLC-analysis shows complete conversion. In case of remaining starting material, additional 3 mol% amounts of CAN can be added to drive the reaction forth. At this point, 10 mL of water are added to quench the reaction. The mixture is extracted with 3 x 8 mL dichloromethane. The combined organic fractions are dried ($MgSO_4$) and the solvents are removed under reduced pressure. The crude residue is >95% pure by ^{1}H-NMR analysis.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.37-1.55 (m, 3H, H-3, H-4 and H-5), 1.65-1.93 (m, 6H, H-3', H-4', H-5', H-9 and H-10), 2.18-2.38 (m, 5H, H-6, H-8 and H-10'), 4.44 (s, 1H, H-11), 4.78 (s, 1H, H-11').

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 18.8 (C-9), 22.4 (C-4), 27.8 (C-5), 3.2 (C-6), 34.8, 35.5 (C-3 and C-10), 38.5 (C-8), 56.0 (C-2), 108.2 (C-11), 148.9 (C-1), 221.2 (C-7).

9.8. Stereoselective annelations of TMSOF derivatives (Chapter 5)

9.8.1. General procedures

Method A: Condensations with TMSOF-derivatives

In a 25-mL round-bottomed flask, 116 mg of zinc chloride (0.85 mmol, 0.7 eq.) are suspended in 5 mL of dichloromethane and cooled to 0ºC. To this mixture are added dropwise 377 mg of the orthoester (1.94 mmol, 1.6 eq.) and stirring is continued at the same temperature for 5 minutes. Then, 0.2 mL (1.21 mmol, 1 eq.) of the trimethylsilyloxyfuran are added

dropwise. The mixture is allowed to gradually reach room temperature over 3 hours with stirring. At this point, TLC-analysis indicates complete conversion to a single product. Then, 5 mL of a saturated aqueous sodium bicarbonate solution are added to quench the reaction. After phase separation, the aqueous layer is extracted with 3 x 10 mL of dichloromethane. The combined organic fractions are dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by recrystallisation or column chromatography affords the coupling product.

Method B: Reduction of spirocyclic butenolides

In a 10-mL round-bottomed flask, 0.5 mmol of spirobutenolide (1 eq.) are dissolved in 5 mL of methanol. The resulting solution is cooled to 0ºC and treated with $NiCl_2.6H_2O$ (0.7 mmol, 0.7 eq.). The mixture is stirred at the same temperature for 15 min before adding $NaBH_4$ (1 mmol, 1 eq.). The reaction is gradually allowed to reach room temperature. Once TLC-analysis indicates complete conversion, the reaction is quenched by addition of 5 mL of a saturated solution of NH_4Cl. The aqueous phase is extracted with 3 x 15 mL of diethyl ether. The combined organic fractions are dried ($MgSO_4$) and concentrated under reduced pressure to afford the reduced lactones in analytically pure form without the need for any further purification.

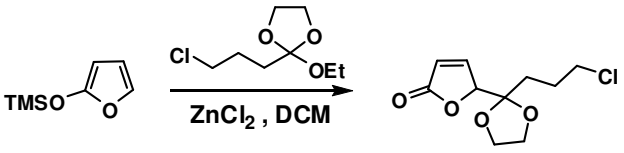
Method C: "Flash"-dihydroxylation of spirocyclic butenolides

To a vigorously stirred solution of the spirocyclic butenolide (0.2 mmol, 1 eq.) in CH_3CN/AcOEt (1 mL each) at 0º C is added a preformed

solution of $RuCl_3.3H_2O$ (0.014 mmol, 0.07 eq.) and $NaIO_4$ (0.3 mmol, 1.5 eq.) in distilled water (1 mL). The mixture was stirred for precisely 90 seconds after which a 3 mL of saturated solution of $Na_2S_2O_3$ are added. The aqueous layer is extracted with 3 x 5 mL of AcOEt. The combined organic fractions are dried ($MgSO_4$) and concentrated under reduced pressure to afford the dihydroxylated lactones in analytically pure form without the need for any further purification.

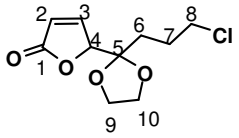
9.8.2. Condensations with TMSOF derivatives

5-(2-(3-chloropropyl)-1,3-dioxolan-2-yl)furan-2(5H)-one 5.065



$C_{10}H_{13}ClO_4$
M.W.: 232,66

Method A : Starting from 0.2 mL (1.21 mmol) of trimethylsilyloxyfuran. After crystallisation from PE/Et_2O 10:1 or flash chromatography (silica, PE/AcOEt 2:1), 210 mg (75%) of the condensation product are obtained.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.77-1.89 (m, 4H, H-6 and H-7), 3.47-3.53 (m, 2H, H-8), 3.96-4.11 (m, 4H, H-9 and H-10), 4.97 (t, 1H, *J* = 1.8 Hz, H-4), 6.15 (dd, 1H, *J* = 5.7, 1.8 Hz, H.2), 7.39 (apparent d, 1H, *J* = 6.6 Hz, H-3).

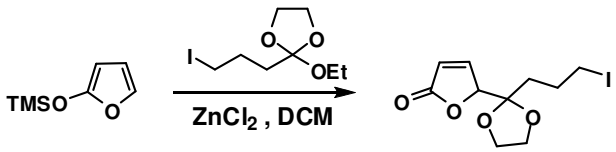
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 25.7 (C-7), 32.1 (C-6), 44.8 (C-8), 66.3, 66.4 (C-9 and C-10), 85.6 (C-4), 108.7 (C-5), 123.1 (C-2), 152.0 (C-3), 172.5 (C-1).

IR (film, cm^{-1}): 2975 (C-H), 2362, 1759 (C=O), 1732 (C=O), 1596, 1443, 1375.

MS (APCI+ev): *m/z* (%): 233 (5) $[M+H]^{+\cdot}$, 217 (10), 149 (100), 105 (15).

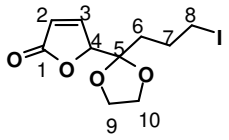
HRMS (ESI): Calculated for $C_{10}H_{13}O_4NaCl$ [*M+Na*]: 255.0400. Found: 255.0394.

5-(2-(3-iodopropyl)-1,3-dioxolan-2-yl)furan-2(5H)-one 5.066



$C_{10}H_{13}IO_4$
M.W.: 324,11

Method A : Starting from 0.2 mL (1.21 mmol) of trimethylsilyloxyfuran. After crystallisation from PE/Et_2O 15:1 or flash chromatography (silica, PE/AcOEt 2:1), 380 mg (97%) of the condensation product are obtained.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.76-1.97 (m, 4H, H-6 and H-7), 3.14-3.20 (m, 2H, H-8), 4.00 (br s, 4H, H-9 and H-10), 4.98 (br s, 1H, H-4), 6.20 (dd, 1H, *J* = 5.7, 1.8 Hz, H-2), 7.39 (dd, 1H, *J* = 5.7, 1.8 Hz, H-3).

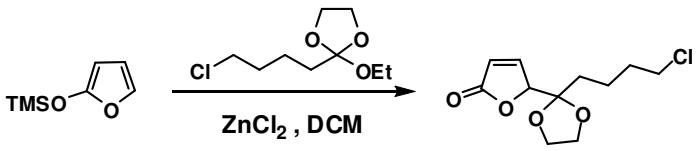
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 6.2 (C-8), 26.7 (C-7), 35.8 (C-6), 66.4 (C-9 and C-10), 85.7 (C-4), 108.6 (C-5), 123.3 (C-2), 151.8 (C-3).

IR (film, cm^{-1}): 2956 and 2921 (C-H), 2358, 1784 (C=O), 1751 (C=O), 1658, 1467, 1371, 1157, 1083.

MS (APCI+ev): *m/z* (%): 325 (15) $[M+H]^{+\cdot}$, 280 (100), 197 (5), 153 (7).

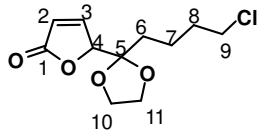
HRMS (CI): Calculated for $C_{10}H_{14}O_4I$ [*M+1*]: 324.9936. Found: 324.9932.

5-(2-(4-chlorobutyl)-1,3-dioxolan-2-yl)furan-2(5H)-one



$C_{11}H_{15}ClO_4$
M.W.: 246,69

Method A : Starting from 0.1 mL (0.60 mmol) of trimethylsilyloxyfuran. After crystallisation from PE/Et_2O 10:1 or flash chromatography (silica, PE/AcOEt 2:1, Rf = 0.35), 62 mg (89%) of the condensation product are obtained.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.52-1.83 (m, 6H, H-6, H-7 and H-8), 3.54 (t, 2H, *J* = 6.6 Hz, H-9), 4.04 (s, 4H, H-10 and H-11), 5.01 (br s, 1H, H-4), 6.20 (dd, 1H, *J* = 5.7, 1.8 Hz, H-2), 7.41 (dd, 1H, *J* = 5.7, 1.8 Hz, H-3).

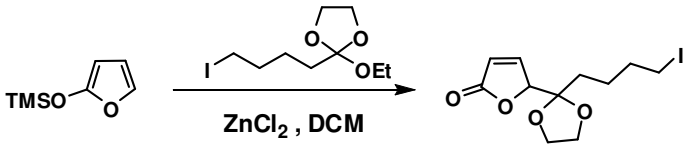
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 19.9 (C-7), 32.4, 34.2 (C-6 and C-8), 44.8 (C-9), 66.4 (C-10 and C-11), 85.7 (C-4), 109.0 (C-5), 123.1 (C-2), 152.0 (C-3), 172.5 (C-1).

IR (film, cm^{-1}): 2965 (C-H), 2352, 1780 (C=O), 1750 (C=O), 1658, 1443.

MS (APCI+ev): *m/z* (%): 247 (21) $[M+H]^{+\cdot}$, 203 (5), 163 (100).

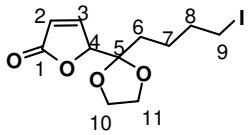
Elemental analysis: Calculated for $C_{11}H_{15}O_4Cl$: C: 53.54%; H: 6.13%. Found: C: 53.54%; H: 6.16%.

5-(2-(4-iodobutyl)-1,3-dioxolan-2-yl)furan-2(5H)-one 5.072



$C_{11}H_{15}IO_4$
M.W.: 338,14

Method A : Starting from 1 mL (6.0 mmol) of trimethylsilyloxyfuran. After flash chromatography (silica, PE/AcOEt 2:1, Rf = 0.36), 1.75 g (86%) of the condensation product are obtained.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.51-1.86 (m, 6H, H-6, H-7 and H-8), 3.18 (t, 2H, *J* = 6.9 Hz, H-9), 4.04 (s, 4H, H-10 and H-11), 5.02 (br s, 1H, H-4), 6.20 (dd, 1H, *J* = 5.7, 1.8 Hz, H-2), 7.41 (d, 1H, *J* = 5.7 Hz, H-3).

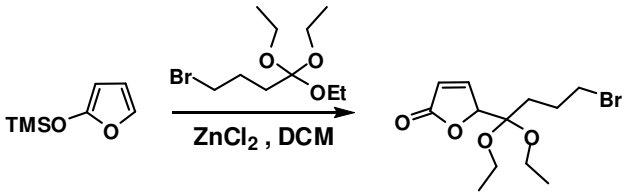
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 6.6 (C-9), 23.5 (C-7), 33.2, 33.9 (C-6 and C-8), 66.4 (C-10 and C-11), 85.7 (C-4), 109.0 (C-5), 123.2 (C-2), 152.0 (C-3), 172.5 (C-1).

IR (film, cm^{-1}): 2962 and 2925 (C-H), 2353, 1781 (C=O), 1748 (C=O), 1650.

MS (APCI+ev): *m/z* (%): 339 (10) $[M+H]^{+\cdot}$, 295 (5), 282 (10), 255 (100), 99 (15).

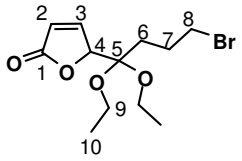
HRMS (ESI): Calculated for $C_{11}H_{15}O_4INa$ [*M+Na*]: 360.9913. Found: 360.9920.

5-(4-bromo-1,1-diethoxybutyl)furan-2(5H)-one 5.067



$C_{12}H_{19}BrO_4$
M.W.: 307,18

Method A : Starting from 0.4 mL (2.4 mmol) of trimethylsilyloxyfuran. After flash chromatography (silica, PE/AcOEt 2:1, Rf = 0.60), 750 mg (97%) of the condensation product are obtained.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.11-1.24 (m, 6H, H-10), 1.66-1.92 (m, 4 H, H-6 and H-7), 3.22-3.61 (m, 6H, H-8 and H-9), 5.08 (br s, 1H, H-4), 6.126 (dd, 1H, *J* = 5.7, 2.1 Hz, H-2), 7.54 (dd, 1H, *J* = 5.7, 1.8 Hz, H-3).

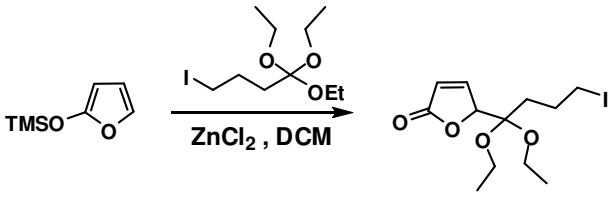
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 15.1, 15.5 (C-10 and C-10'), 21.1 (C-7), 27.2 (C-6), 33.9 (C-8), 56.7, 56.8 (C-9 and C-9'), 84.0 (C-4), 100.8 (C-5), 122.0 (C-2), 154.5 (C-3), 172.7 (C-1).

IR (film, cm^{-1}): 2975 (C-H), 2362, 1759 and 1732 (C=O), 1596, 1443, 1375.

MS (APCI+ev): *m/z* (%): 262 (100) $[M\text{-}OEt]^{+\cdot}$, 233 (50), 227 (25), 181 (20), 153 (20), 111 (15).

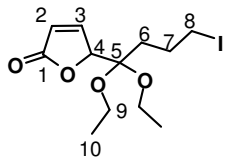
HRMS (ES): Calculated for $C_{12}H_{19}O_4NaBr$ (M+Na): 329.0364. Found: 329.0363.

5-(4-iodo-1,1-diethoxybutyl)furan-2(5H)-one



$C_{12}H_{19}IO_4$
M.W.: 354,18

Method A : Starting from 0.4 mL (2.4 mmol) of trimethylsilyloxyfuran. After flash chromatography (silica, PE/AcOEt 2:1), 756 mg (89%) of the condensation product are obtained.



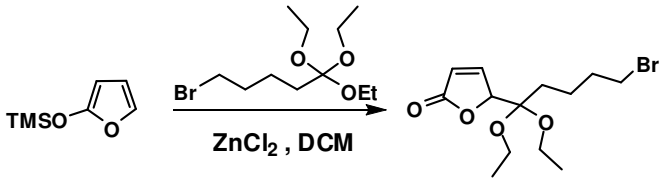
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.11-1.23 (m, 6H, H-10), 1.66-1.92 (m, 4H, H-6 and H-7), 3.10-3.17 (m, 2H, H-8), 3.35-3.61 (m, 4H, H-9), 5.08 (br s, 1H, H-4), 6.10 (dd, 1H, *J* = 5.7, 2.1 Hz, H-2), 7.55 (dd, 1H, *J* = 5.7, 2.0 Hz, H-3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 6.9 (C-8), 15.1, 15.5 (C-10 and C-10'), 21.1 (C-7), 27.2 (C-6), 56.8, 57.2 (C-9 and C-9'), 84.1 (C-4), 100.8 (C-5), 122.1 (C-2), 154.4 (C-3), 172.9 (C-1).

IR (film, cm^{-1}): 2975 (C-H), 2362, 1758 (br, C=O), 1596, 1440.

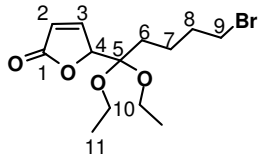
MS (CI+ev): *m/z* (%): 355 (100) $[M+H]^{+\cdot}$, 309 (30), 281 (7), 182 (10).

5-(5-bromo-1,1-diethoxypentyl)furan-2(5H)-one 5.073



$C_{13}H_{21}BrO_4$
M.W.: 321,21

Method A : Starting from 0.4 mL (2.4 mmol) of trimethylsilyloxyfuran. After flash chromatography (silica, PE/AcOEt 2:1, Rf = 0.57), 692 mg (90%) of the condensation product are obtained.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.11-1.26 (m, 6H, H-11), 1.40-1.48 (m, 2H, H-7), 1.60-1.80 (m, 4H, H-6 and H-8), 3.35 (t, 2H, *J* = 6.6 Hz, H-9), 3.46-3.59 (m, 4H, H-10), 5.10 (apparent t, 1H, *J* = 1.9 Hz, H-4), 6.12 (dd, 1H, *J* = 5.8, 2.1 Hz, H-2), 7.58 (dd, 1H, *J* = 5.7, 1.8 Hz, H-3).

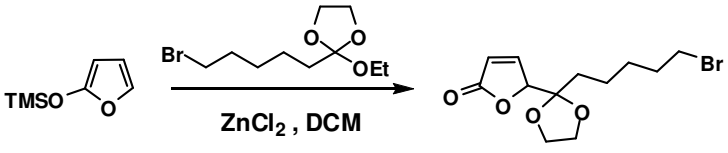
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 15.1, 15.4 (C-11 and C-11'), 22.2 (C-7), 32.3, 32.8, 33.2 (C-6, C-8 and C-9), 56.7, 57.4 (C-10 and C-10'), 83.9 (C-4), 101.2 (C-5), 121.7 (C-2), 154.9 (C-3), 172.6 (C-1).

IR (film, cm^{-1}): 2974 (C-H), 1755 (br, C=O), 1664, 1597, 1444, 1390, 1307.

MS (APCI+ev): *m/z* (%): 277 (100) $[M\text{-}OEt]^{+}$, 247 (65), 203 (40), 167 (15), 111 (30).

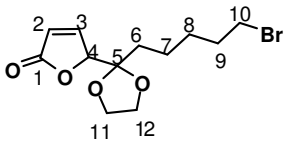
HRMS (ESI): Calculated for $C_{13}H_{21}O_4NaBr$ [*M+Na*]: 343.0521. Found: 343.0516.

5-(2-(5-bromopentyl)-1,3-dioxolan-2-yl)furan-2(5H)-one 5.292



$C_{12}H_{17}BrO_4$
M.W.: 305,16

Method A : Starting from 0.2 mL (1.2 mmol) of trimethylsilyloxyfuran. After flash chromatography (silica, PE/AcOEt 2:1, Rf = 0.36), 0.3 g (82%) of the condensation product are obtained.



^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 1.40-1.61 (m, 4H, H-7 and H-8), 1.77-1.89 (m, 2H, H-9), 1.92-1.95 (m, 2H, H-6), 3.40 (t, 2H, *J* = 6.9 Hz, H-10), 3.97-4.01 (m, 4H, H-11 and H-12), 5.02 (br s, 1H, H-4), 6.21 (dd, 1H, *J* = 5.8, 1.8 Hz, H-2), 7.41 (dd, 1H, *J* = 5.7, 1.6 Hz, H-3).

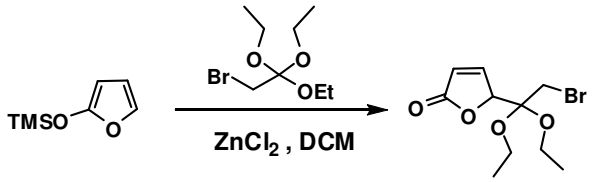
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 21.5 (C-7), 28.0 (C-8), 32.5, 33.6, 34.8 (C-6, C-9 and C-10), 66.4 (C-11 and C-12), 85.8 (C-4), 109.1 (C-5), 123.2 (C-2), 152.2 (C-3), 172.7 (C-1).

IR (film, cm^{-1}): 2960 and 2920 (C-H), 2347, 1780 (C=O), 1749 (C=O), 1443.

MS (APCI+ev): *m/z* (%): 307 (10) [*M+H for* ^{81}Br]$^{+\cdot}$, 305 (10) [*M+H for* ^{79}Br]$^{+\cdot}$, 239 (15), 223 (100), 177 (40), 141 (15).

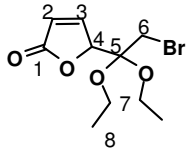
HRMS (CI): Calculated for $C_{12}H_{18}O_4Br$ [*M+1*]: 305.0388. Found: 305.0382.

5-(2-bromo-1,1-diethoxyethyl)furan-2(5H)-one 5.069



$C_{10}H_{15}BrO_4$
M.W.: 279,13

Method A : Starting from 0.2 mL (1.2 mmol) of trimethylsilyloxyfuran. After flash chromatography (silica, PE/AcOEt 1:1, Rf = 0.70), 340 mg (100%) of the condensation product are obtained.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.11-1.26 (m, 6H, H-8), 3.41-3.68 (m, 6H, H-6 and H-7), 5.10 (br s, 1H, H-4), 6.06-6.11 (m, 1H, H-2), 7.65-7.69 (m, 1H, H-3).

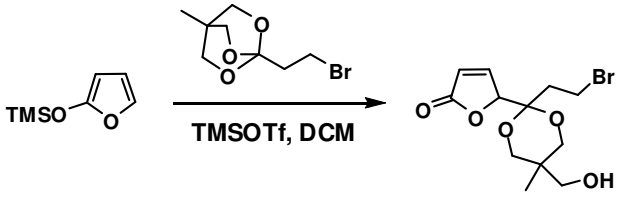
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 15.0, 15.2 (C-8 and C-8'), 30.4 (C-6), 57.5, 58.0 (C-7 and C-7'), 82.3 (C-4), 100.3 (C-5), 121.4 (C-2), 154.5 (C-3), 172.5 (C-1).

IR (film, cm^{-1}): 2974 (C-H), 1755 (br, C=O), 1664, 1597, 1444, 1390, 1307.

MS (APCI+ev): *m/z* (%): 281 (20) [*M+H for* ^{81}*Br*]$^{+\cdot}$, 233 (70), 194 (70), 94 (100).

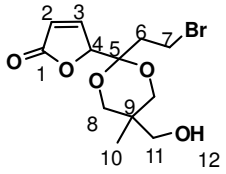
HRMS (CI): Calculated for $C_8H_{10}O_3Br$ [*M+1*]: 232.9813. Found: 232.9822.

5-(2-(2-bromoethyl)-5-(hydroxymethyl)-5-methyl-1,3-dioxan-2-yl)furan-2(5H)-one 5.068



$C_{12}H_{17}BrO_5$
M.W.: 321,16

In a 25-mL round-bottomed flask, 190 mg of the OBO-orthoester (0.8 mmol, 1.3 eq.) are dissolved in 4 mL dichloromethane and cooled to -78ºC. To this solution are added 0.1 mL of trimethylsilyloxyfuran (0.6 mmol, 1 eq.). The resulting mixture is then treated with 0.22 mL of trimethylsilyltrifluoromethanesulfonate (TMSOTf, 1.2 mmol, 2 eq.) dropwise. The mixture is allowed to gradually reach room temperature with continued stirring. After 2 hours, 5 mL of a saturated aqueous sodium bicarbonate solution are added. After phase separation, the aqueous layer is extracted with 3 x 5 mL of dichloromethane. The combined organic fractions are dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by column chromatography (silica, PE/AcOEt 1:2, Rf = 0.33) affords 90 mg (47%) of the major, thermodynamic isomer and 14% of the minor isomer.



Major isomer :

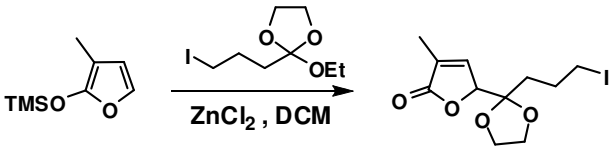
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 0.95 (s, 3H, H-10), 1.67 (br s, 1H, H-12), 2.11-2.38 (m, 2H, H-6), 3.43-3.49 (m, 2H, H-7), 3.59 (s, 2H, H-11), 3.64-3.91 (m, 4H, H-8), 5.50 (t, 1H, *J* = 1.8 Hz, H-4), 6.23 (dd, 1H, *J* = 5.7, 3 Hz, H-2), 7.72 (dd, 1H, *J* = 5.8, 2.1 Hz , H-3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 18.2 (C-10), 25.8 (C-7), 34.6 (C-6), 35.4 (C-9), 65.5, 66.5, 66.8 (C-8, C-8' and C-11), 80.6 (C-4), 98.2 (C-5), 122.3 (C-2), 152.9 (C-3), 172.3 (C-1).

MS (APCI+ev): *m/z* (%): 322 (10) $[M+H]^{+\cdot}$, 305 (15), 241 (20), 221 (100).

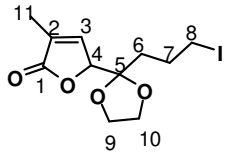
HRMS (ESI): Calculated for $C_{12}H_{17}O_5BrNa$ [*M+Na*]: 343.0157. Found: 343.0149.

5-(2-(3-iodopropyl)-1,3-dioxolan-2-yl)-3-methylfuran-2(5H)-one 5.082



$C_{11}H_{15}IO_4$
M.W.: 338,14

Method A : Starting from 0.17 g (1.0 mmol) of 3-methyltrimethylsilyloxyfuran. After purification by flash chromatography (silica, PE/AcOEt 4:1), 210 mg (62%) of the condensation product are obtained (Rf = 0.30 in PE/AcOEt 2:1).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.73-1.95 (m, 4H, H-6 and H-7), 1.91 (s, 3H, H-11), 3.13-3.19 (m, 2H, H-8), 3.93-4.01 (m, 4H, H-9 and H-10), 4.82 (m, 1H, H-4), 6.97 (m, 1H, H-3).

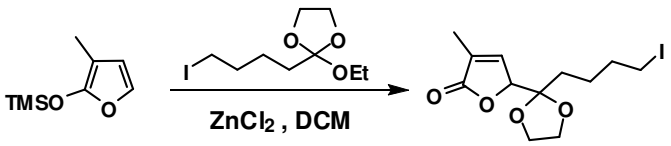
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 6.2 (C-8), 10.9 (C-11), 26.8 (C-7), 35.8 (C-6), 66.4, 66.5 (C-9 and C-10), 83.6 (C-4), 108.7 (C-5), 131.8 (C-2), 144.1 (C-3), 173.6 (C-1).

IR (film, cm^{-1}): 2956 and 2921 (C-H), 1751 (sh, C=O), 1659, 1451.

MS (APCI+ev): *m/z* (%): 339 (5) $[M+H]^{+\cdot}$, 282 (15), 241 (100), 211 (15), 197 (15), 86 (17).

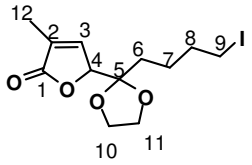
HRMS (ESI): Calculated for $C_{11}H_{15}O_4INa$ [*M+Na*]: 360.9913. Found: 360.9922.

5-(2-(4-iodobutyl)-1,3-dioxolan-2-yl)-3-methylfuran-2(5H)-one 5.083



$C_{12}H_{17}IO_4$
M.W.: 352,17

Method A : Starting from 0.13 g (0.78 mmol) of 3-methyltrimethylsilyloxyfuran. After purification by flash chromatography (silica, PE/AcOEt 3:1, Rf = 0.25), 200 mg (80%) of the condensation product are obtained.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.48-1.55 (m, 2H, H-7), 1.64-1.71 (m, 2H, H-8), 1.76-1.83 (m, 2H, H-6), 1.93 (s, 3H, H-12), 3.16 (t, 2H, *J* = 6.8 Hz, H-9), 4.02 (s, 4H, H-10 and H-11), 4.85 (br s, 1H, H-4), 6.97 (br s, 1H, H-3).

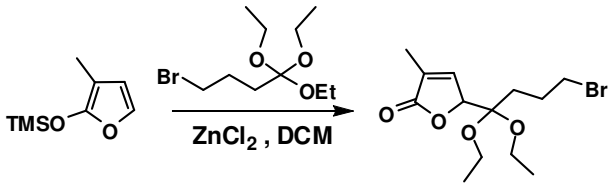
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 6.5 (C-9), 10.8 (C-12), 23.4 (C-7), 33.2, 33.8 (C-6 and C-8), 66.3, 66.4 (C-10 and C-11), 83.5 (C-4), 109.1 (C-5), 131.7 (C-2), 144.3 (C-3), 173.8 (C-1).

IR (film, cm^{-1}): 2921 and 2852 (C-H), 1755 (C=O), 1659, 1631, 1456.

MS (APCI+ev): *m/z* (%): 353 (3) $[M+H]^{+\cdot}$, 309 (5), 255 (100), 163 (80), 121 (80), 99 (10).

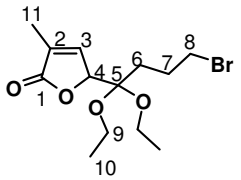
HRMS (CI): Calculated for $C_{12}H_{18}O_4I$ [*M+1*]: 353.0249. Found: 353.0257.

5-(4-bromo-1,1-diethoxybutyl)-3-methylfuran-2(5H)-one 5.071



$C_{13}H_{21}BrO_4$
M.W.: 321,21

Method A : Starting from 0.34 g (2.0 mmol) of 3-methyltrimethylsilyloxyfuran. After purification by flash chromatography (silica, PE/AcOEt 2:1, Rf = 0.65), 540 mg (85%) of the condensation product are obtained.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.09-1.24 (m, 6H, H-10), 1.60-1.85 (m, 4H, H-6 and H-7), 1.89 (s, 3H, H-11), 3.28-3.33 (m, 2H, H-8), 3.40-3.59 (m, 4H, H-9), 4.82 (d, 1H, *J* = 0.9 Hz, H-4), 7.09 (d, 1H, *J* = 1.4 Hz, H-3).

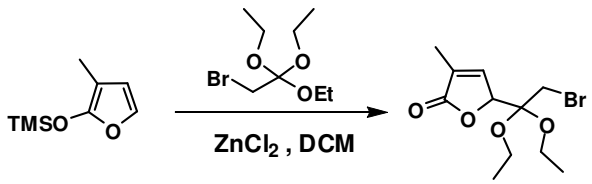
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 10.8 (C-11), 15.2, 15.3 (C-10 and C-10'), 27.2 (C-7), 31.9 (C-8), 34.1 (C-6), 56.7, 57.2 (C-9 and C-9'), 81.8 (C-4), 101.9 (C-5), 130.5 (C-2), 146.7 (C-3), 173.9 (C-1).

IR (film, cm^{-1}): 2950 and 2920 (C-H), 1755 (sh, C=O), 1447.

MS (CI+ev): *m/z* (%): 277 (35) $[M+OEt]^{+\cdot}$, 223 (42), 167 (100), 151 (20).

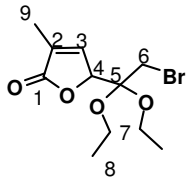
HRMS (ESI): Calculated for $C_{13}H_{21}O_4BrNa$ [*M+Na*]: 343.0521. Found: 343.0532.

5-(2-bromo-1,1-diethoxyethyl)-3-methylfuran-2(5H)-one 5.070



$C_{11}H_{17}BrO_4$
M.W.: 293,15

Method A : Starting from 0.17 mg (1.0 mmol) of 3-methyltrimethylsilyloxyfuran. After flash chromatography (silica, PE/AcOEt 2:1, Rf = 0.57), 180 mg (80%) of the condensation product are obtained.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.17 (t, 3H, *J* = 6.9 Hz, H-8), 1.24 (t, 3H, *J* = 6.6 Hz, H-8'), 1.93 (s, 3H, H-9), 3.47-3.67 (m, 6H, H-6 and H-7), 5.12 (br s, 1H, H-4), 7.24 (br s, 1H, H-3).

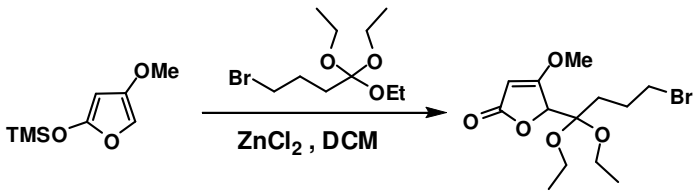
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 11.2 (C-9), 15.5, 15.7 (C-8 and C-8'), 30.7 (C-6), 58.5, 58.8 (C-7 and C-7'), 80.5 (C-4), 100.8 (C-5), 130.2 (C-2), 147.1 (C-3), 174.2 (C-1).

IR (film, cm^{-1}): 2974 (C-H), 1750 (sh, C=O), 1597, 1444, 1391, 1305.

MS (CI+ev): *m/z* (%): 293 (5) $[M]^{+\cdot}$, 247 (10), 219 (11), 195 (55), 167 (60), 139 (100), 121 (19), 111 (12).

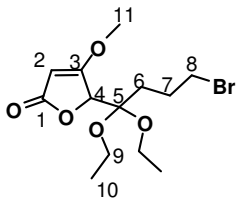
HRMS (ESI): Calculated for $C_{11}H_{17}O_4BrNa$ [*M+Na*]: 315.0208. Found: 315.0217.

5-(4-bromo-1,1-diethoxybutyl)-4-methoxyfuran-2(5H)-one 5.085



$C_{13}H_{21}BrO_5$
M.W.: 337,21

Method A : Starting from 93 mg (0.5 mmol) of 4-methoxy-2-trimethylsilyloxyfuran. After purification by flash chromatography (silica, PE/AcOEt 6:1, Rf = 0.20), 30 mg (49%) of the condensation product are obtained.



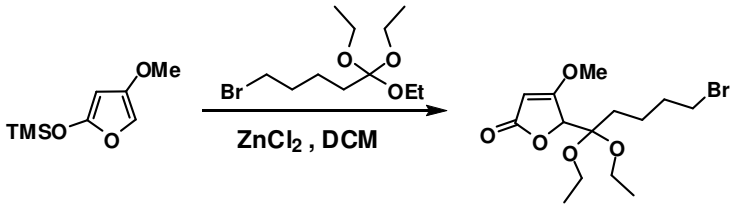
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.12 (t, 6H, *J* = 7.0 Hz, H-10), 1.77-1.92 (m, 4H, H-6 and H-7), 3.34-3.38 (m, 2H, H-8), 3.53-3.61 (m, 4H, H-9), 3.88 (s, 3H, H-11), 4.87 (br s, 1H, H-4), 5.12 (br s, 1H, H-2).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 15.2, 15.4 (C-10 and C-10'), 26.9 (C-7), 31.9 (C-8), 34.2 (C-6), 56.8, 57.2 (C-9 and C-9'), 59.7 (C-11), 80.0 (C-2), 90.3 (C-4), 100.4 (C-5), 171.9 (C-1), 180.5 (C-3).

IR (film, cm^{-1}): 2975 and 2890 (C-H), 1755 (br, C=O), 1622, 1450, 1360, 1237.

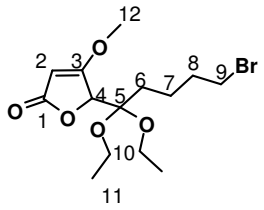
MS (CI+ev): *m/z* (%): 337 (27) $[M]^{+\cdot}$, 291 (15), 263 (20), 223 (100).

5-(5-bromo-1,1-diethoxypentyl)-4-methoxyfuran-2(5H)-one 5.296



$C_{14}H_{23}BrO_5$
M.W.: 351,23

Method A : Starting from 186 mg (1 mmol) of 4-methoxy-2-trimethylsilyloxyfuran. After purification by flash chromatography (silica, PE/AcOEt 6:1, Rf = 0.20), 185 mg (52%) of the condensation product are obtained.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.15 (t, 6H, *J* = 7.0 Hz, H-11), 1.45 (q, 2H, *J* = 7.7 Hz, H-7), 1.62-1.78 (m, 4H, H-6 and H-8), 3.35 (t, 2H, *J* = 6.6 Hz, H-9), 3.45-3.59 (m, 4H, H-10), 3.86 (s, 3H, H-12), 4.87 (br s, 1H, H-4), 5.09 (br s, 1H, H-2).

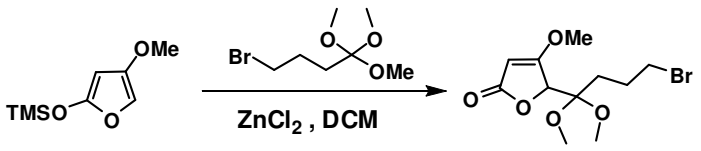
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 15.1, 15.2 (C-11 and C-11'), 26.9 (C-7), 31.9, 32.3 (C-8 and C-9), 34.2 (C-6), 56.8, 56.9 (C-10 and C-10'), 59.9 (C-12), 80.3 (C-2), 91.3 (C-4), 100.8 (C-5), 172.2 (C-1), 181.5 (C-3).

IR (film, cm^{-1}): 2974, 2931 and 2894 (C-H), 1755 (br, C=O), 1620, 1456, 1359, 1244, 1157.

MS (CI+ev): *m/z* (%): 291 (100) $[M\text{-}OEt+H]^{+\cdot}$, 256 (40), 227 (45), 128 (55), 102 (45).

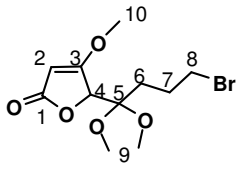
HRMS (ESI): Calculated for $C_{14}H_{23}O_5BrNa$ [*M+Na*]: 373.0627. Found: 373.0630.

5-(4-bromo-1,1-dimethoxybutyl)-4-methoxyfuran-2(5H)-one 5.086



$C_{11}H_{17}BrO_5$
M.W.: 309,15

Method A : Starting from 93 mg (0.5 mmol) of 4-methoxy-2-trimethylsilyloxyfuran. After purification by flash chromatography (silica, PE/AcOEt 6:1, Rf = 0.20), 100 mg (65%) of the condensation product are obtained.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.72-1.89 (m, 4H, H-6 and H-7), 3.30 (s, 3H, H-9), 3.31 (s, 3H, H-9'), 3.35 (t, 2H, *J* = 6.3 Hz, H-8), 3.90 (s, 3H, H-10), 4.88 (br s, 1H, H-4), 5.13 (br s, 1H, H-2).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 26.6 (C-7), 30.9 (C-8), 33.9 (C-6), 49.1, 49.4 (C-9 and C-9'), 59.8 (C-10), 79.2 (C-2), 90.5 (C-4), 100.8 (C-5), 171.6 (C-1), 180.2 (C-3).

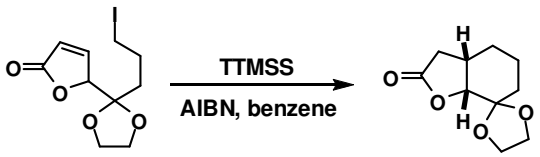
IR (film, cm^{-1}): 2945 and 2837 (C-H), 1757 (br, C=O), 1629, 1456, 1359, 1244.

MS (CI+ev): *m/z* (%): 279 (95) $[M\text{-}OMe+H]^{+\cdot}$, 229 (20), 197 (22), 165 (11), 153 (7), 122 (8).

HRMS (ESI): Calculated for $C_{11}H_{17}O_5BrNa$ [*M+Na*]: 331.0157. Found: 331.0150.

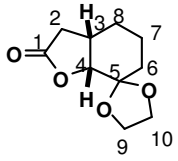
9.8.3. Synthesis of bicyclic lactones by radical cyclisation

Hexahydro-2H-spiro[benzofuran-7,2'-[1,3]dioxolan]-2-one 5.104



$C_{10}H_{14}O_4$
M.W.: 198,22

In a 100-mL round-bottomed flask eq.uipped with a reflux condenser, 150 mg of the iodinated butenolide (0.46 mmol, 1 eq.) are dissolved in 40 mL of benzene. To this mixture, 11 mg of AIBN (0.07mmol, 0.15 eq.) are added followed by 0.19 mL of TTMSS (0.6 mmol, 1.3 eq.). The resulting mixture is heated to reflux for 3 hours. At this point, the solvent is evaporated under reduced pressure and the crude residue is directly purified by flash chromatography (silica, PE/Et_2O 5:1 then 0:1). The bicyclic lactone is obtained in 97% yield (110 mg).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.40-1.77 (m, 6H, H-6, H-7 and H-8), 2.28 (dd, 1H, *J* = 17.1, 8.7 Hz, H-2), 2.53 (dd, 1H, *J* = 16.4, 10.8 Hz, H-2'), 2.74-2.80 (m, 1H, H-3), 3.88-4.09 (m, 4H, H-9 and H-10), 4.30 (d, 1H, *J* = 7.8 Hz, H-4).

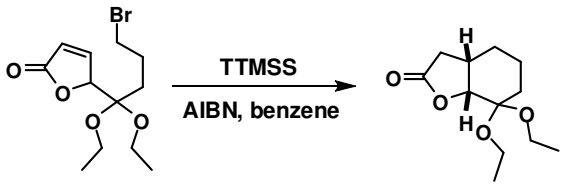
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 18.3 (C-7), 24.7 (C-8), 32.4, 32.9 (C-2 and C-6), 36.0 (C-3), 65.2, 66.3 (C-9 and C-10), 81.7 (C-4), 107.5 (C-5), 177.2 (C-1).

IR (film, cm^{-1}): 2970 and 2930 (C-H), 1782 (C=O), 1629.

MS (CI+ev): *m/z* (%): 199 (100) $[M+H]^{+\cdot}$, 139 (21), 109 (10), 95 (25), 81 (17), 67 (19).

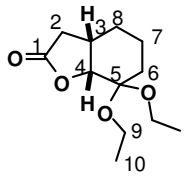
Elemental analysis: Calculated for $C_{10}H_{14}O_4$: C: 60.59%; H: 7.12%. Found: C: 60.86%; H: 7.26%.

7,7-diethoxyhexahydrobenzofuran-2(3H)-one 5.105



$C_{12}H_{20}O_4$
M.W.: 228,28

In a 250-mL round-bottomed flask eq.uipped with a reflux condenser, 1.3 g of the brominated butenolide (4.23 mmol, 1 eq.) are dissolved in 170 mL of benzene. To this mixture, 90 mg of AIBN (0.55mmol, 0.15 eq.) are added followed by 1.7 mL of TTMSS (5.5 mmol, 1.4 eq.). The resulting mixture is heated to reflux for 6 hours. At this point, the solvent is evaporated under reduced pressure and the crude residue is directly purified by flash chromatography (silica, PE/AcOEt 6:1 then 2:1, Rf = 0.60 in PE/AcOEt 2:1). The bicyclic lactone is obtained in 87% yield (839 mg).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.17-1.23 (m, 6H, H-10), 1.40-1.82 (m, 6H, H-6, H-7 and H-8), 2.28-2.34 (m, 1H, H-2), 2.52-2.60 (m, 2H, H-2' and H-3), 3.60-3.45 (m, 4H, H-9), 4.36 (d, 1H, *J* = 3.9 Hz, H-4).

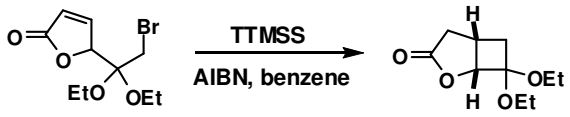
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 15.1, 15.3 (C-10 and C-10'), 19.2 (C-7), 26.6 (C-8), 28.5 (C-6), 34.9 (C-2), 36.8 (C-3), 55.4, 55.5 (C-9 and C-9'), 79.8 (C-4), 98.0 (C-5), 176.7 (C-1).

IR (film, cm^{-1}): 2972 and 2927 (C-H), 2854, 1786 (C=O), 1662.

MS (APCI+ev): *m/z* (%): 183 (100) $[M\text{-}OEt]^{+}$, 169 (25), 155 (35), 137 (15), 123 (15), 109 (20), 95 (30), 81 (12).

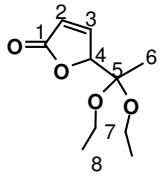
Elemental analysis: Calculated for $C_{12}H_{20}O_4$: C: 63.18%; H: 8.84%. Found: C: 62.74%; H: 8.86%.

7,7-diethoxy-2-oxabicyclo[3.2.0]heptan-3-one 5.112



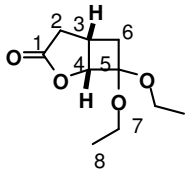
$C_{10}H_{16}O_4$
M.W.: 200,23

In a 50-mL round-bottomed flask eq.uipped with a reflux condenser, 100 mg of the brominated butenolide (0.36 mmol, 1 eq.) are dissolved in 14 mL of benzene. To this mixture, 9 mg of AIBN (0.05 mmol, 0.15 eq.) are added followed by 0.17 mL of TTMSS (0.55 mmol, 1.5 eq.). The resulting mixture is heated to reflux for 18 hours. At this point, the solvent is evaporated under reduced pressure and the crude residue is directly purified by flash chromatography (silica, PE/AcOEt 6:1, Rf = 0.50). The bicyclic lactone is obtained in 60% yield (40 mg), accompanied by 20 mg of the reduced product.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.11-1.26 (m, 6H, H-8), 1.53 (s, 3H, H-6), 3.41-3.68 (m, 4H, H-7), 5.20 (br s, 1H, H-4), 6.11 (d, 1H, *J* = 5.8 Hz, H-2), 7.60 (dd, 1H, *J* = 5.7, 1.3 Hz, H-3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 15.0, 15.2 (C-8 and C-8'), 21.1 (C-6), 57.5, 58.1 (C-7 and C-7'), 84.3 (C-4), 99.6 (C-5), 122.4 (C-2), 154.9 (C-3), 171.7 (C-1).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.17-1.29 (m, 6H, H-8), 1.96 (dd, 1H, *J* = 13.5, 4.8 Hz, H-6), 2.48-2.57 (m, 2H, H-6' and H-2), 2.75-2.95 (m, 2H, H-2' and H-3), 3.48-3.65 (m, 4H, H-7), 4.89 (d, 1H, *J* = 7.8 Hz, H-4).

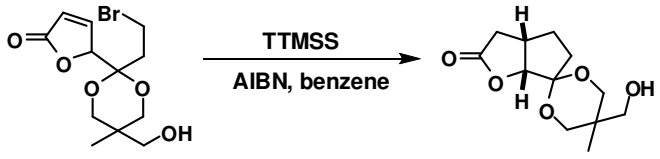
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 15.0, 15.1 (C-8 and C-8'), 25.9 (C-3), 34.5 (C-2), 37.0 (C-6), 57.2, 58.5 (C-8 and C-8'), 82.5 (C-4), 101.4 (C-5), 178.1 (C-1).

IR (film, cm^{-1}): 2972 and 2926 (C-H), 2854, 1783 (C=O), 1659.

MS (APCI+ev): *m/z* (%): 201 (16) $[M+H]^{+\cdot}$, 183 (5), 173 (10), 155 (100), 141 (10), 127 (40), 109 (7).

HRMS (ESI): Calculated for $C_{10}H_{16}O_4Na$ [*M+Na*]: 223.0946. Found: 223.0954.

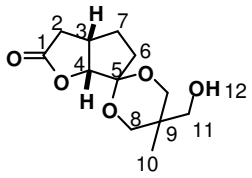
5'-(hydroxymethyl)-5'-methyltetrahydrospiro[cyclopenta[b]furan-6,2'-[1,3]dioxan]-2(6aH)-one 5.106



$C_{12}H_{18}O_5$
M.W.: 242,27

In a 50-mL round-bottomed flask eq.uipped with a reflux condenser, 0.18 g of the brominated butenolide (0.56 mmol, 1 eq.) are dissolved in 22 mL of benzene. To this mixture, 14 mg of AIBN (0.08 mmol, 0.15 eq.) are added followed by 0.26 mL of TTMSS (0.84 mmol, 1.5 eq.). The resulting mixture is heated to reflux for 13 hours. At this point, the solvent is

evaporated under reduced pressure and the crude residue is directly purified by flash chromatography (silica, PE/AcOEt 1:2, Rf = 0.68). The bicyclic lactone is obtained in 75% yield (100 mg).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 0.80 (s, 3H, H-10), 1.42-1.45 (m, 1H, H-7), 1.71 (br s, 1H, H-12), 1.83-2.01 (m, 3H, H-6 and H-7'), 2.28 (dd, 1H, *J* = 18.7, 4.4 Hz, H-2), 2.79 (dd, 1H, *J* = 18.0, 10.5 Hz, H-2'), 2.95-3.04 (m, 1H, H-3), 3.56-3.78 (m, 6H, H-8 and H-11), 4.90 (d, 1H, *J* = 6.6 Hz , H-4).

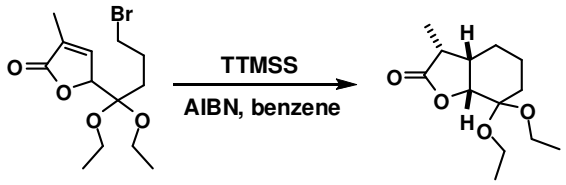
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 17.4 (C-10), 27.9 (C-7), 34.3 (C-6), 34.8 (C-9), 35.4, 36.1 (C-2 and C-3), 65.4 (C-11), 67.4, 68.5 (C-8 and C-8'), 80.7 (C-4), 106.0 (C-5), 176.9 (C-1).

IR (film, cm^{-1}): 3900 (br, OH), 2965 (C-H), 1785 (C=O), 1443.

MS (APCI+ev): *m/z* (%): 243 (100) $[M+H]^{+\cdot}$, 225 (40), 180 (15), 159 (25), 155 (40).

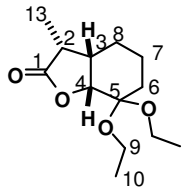
Elemental analysis: Calculated for $C_{12}H_{18}O_5$: C: 59.49%; H: 7.49%. Found: C: 58.95%; H: 7.55%.

7,7-diethoxy-3-methylhexahydrobenzofuran-2(3H)-one 5.122



$C_{13}H_{22}O_4$
M.W.: 242,31

In a 25-mL round-bottomed flask eq.uipped with a reflux condenser, 100 mg of the brominated butenolide (0.31 mmol, 1 eq.) are dissolved in 12 mL of benzene. To this mixture, 8 mg of AIBN (0.047 mmol, 0.15 eq.) are added followed by 0.15 mL of TTMSS (0.47 mmol, 1.5 eq.). The resulting mixture is heated to reflux for 5 hours. At this point, the solvent is evaporated under reduced pressure and the crude residue is directly purified by flash chromatography (silica, PE/AcOEt 7:1, Rf = 0.50 in PE/AcOEt 2:1). The bicyclic lactone is obtained in 97% yield (73 mg).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.11-1.20 (m, 9 H, H-10, H-10' and H-13), 1.51-1.94 (m, 6H, H-6, H-7 and H-8), 2.42-2.51 (m, 1H, H-2), 2.72 (apparent quintuplet, 1H, *J* = 6.7 Hz, H-3), 3.34-3.60 (m, 4H, H-9), 4.21 (dd, 1H, *J* = 3.8, 1.9 Hz, H-4).

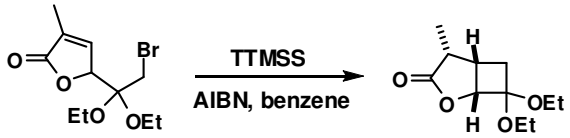
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 12.2 (C-13), 15.1, 15.3 (C-10 and C-10'), 19.2 (C-7), 26.9 (C-8), 29.5 (C-6), 37.4 (C-2), 39.2 (C-3), 57.4, 57.6 (C-9 and C-9'), 80.2 (C-4), 98.7 (C-5), 178.1 (C-1).

IR (film, cm^{-1}): 2972 and 2926 (C-H), 2854, 1784 (C=O), 1662.

MS (APCI+ev): *m/z* (%): 243 (25) $[M+H]^{+\cdot}$, 197 (100), 169 (10), 151(25), 123 (100), 95 (50).

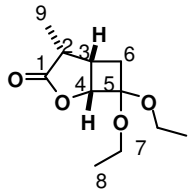
Elemental analysis: Calculated for $C_{13}H_{22}O_4$: C: 64.44%; H: 9.15%. Found: C: 63.99%; H: 9.04%.

7,7-diethoxy-4-methyl-2-oxabicyclo[3.2.0]heptan-3-one 5.123



$C_{11}H_{18}O_4$
M.W.: 214,26

In a 50-mL round-bottomed flask eq.uipped with a reflux condenser, 100 mg of the brominated butenolide (0.36 mmol, 1 eq.) are dissolved in 25 mL of benzene. To this mixture, 9 mg of AIBN (0.05 mmol, 0.15 eq.) are added. Then, 0.17 mL of TTMSS (0.55 mmol, 1.5 eq.) in 5 mL of benzene are added *via* syringe-pump over 8 hours, whilst the mixture is heated to reflux. Once the addition is finished, the solvent is evaporated under reduced pressure and the crude residue is directly purified by flash chromatography (silica, PE/AcOEt 6:1, Rf = 0.50). The bicyclic lactone is obtained in 97% yield (72 mg).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.07-1.28 (m, 9H, H-8, H-8' and H-9), 1.86-2.01 (m, 1H, H-6), 2.13-2.31 (m, 1H, H-6'), 2.65-2.76 (m, 1H, H-3), 2.84-2.96 (m, 1H, H-2), 3.37-3.58 (m, 4H, H-7), 4.71 (dd, 1H, *J* = 6.6, 2.7 Hz, H-4).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 10.5 (C-9), 14.9, 15.2 (C-8 and C-8'), 30.8, 31.0 (C-3 and C-6), 36.2 (C-2), 57.0, 58.2 (C-7 and C-7'), 80.5 (C-4), 100.1 (C-5), 179.8 (C-1).

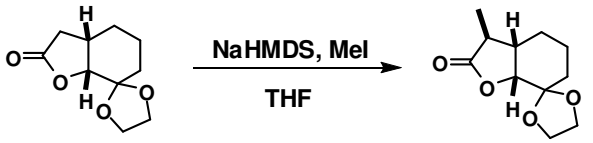
IR (film, cm^{-1}): 2972 and 2926 (C-H), 1781 (C=O), 1659, 1437.

MS (APCI+ev): *m/z* (%): 215 (15) $[M+H]^{+\cdot}$, 191 (8), 169 (35).

HRMS (ESI): Calculated for $C_{11}H_{18}O_4Na$ [*M+Na*]: 237.1103. Found: 237.1108.

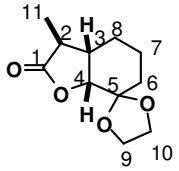
3-methylhexahydro-2H-spiro[benzofuran-7,2'-[1,3]dioxolan]-2-one

5.137



$C_{11}H_{16}O_4$
M.W.: 212,24

In a 25-mL round-bottomed flask, 400 mg of the bicyclic lactone (2.02 mmol, 1 eq.) are dissolved in 10 mL of THF and cooled to -78ºC. Then, 1.3 mL of NaHMDS (2M solution in THF, 2.63 mmol, 1.3 eq.) are added dropwise upon which a bright yellow-orange color develops. The mixture is stirred for 1 hour at this temperature. Then, 0.75 mL of MeI (12.1 mmol, 6 eq.) are added dropwise and the resulting solution is allowed to gradually reach room temperature over 3 hours, at which stage TLC-analysis indicates complete conversion to a new compound. Then, 10 mL of a saturated aqueous NH_4Cl solution are added to quench the reaction. After phase separation, the aqueous layer is extracted with 3 x 15 mL of diethylether. The combined organic fractions are dried ($MgSO_4$) and the solvents are removed under reduced pressure. Purification of the residue by short-path flash chromatography (PE/AcOEt 2:1, Rf = 0.35) affords 435 mg (98%) of the alkylated product.



^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 1.17 (d, 3H, *J* = 6.9 Hz, H-11), 1.43-1.78 (m, 6H, H-6, H-7 and H-8), 2.33-2.42 (m, 1H, H-3), 2.64-2.75 (m, 1H, H-2), 3.87-4.00 (m, 3H, H-9 and H-10), 4.09-4.14 (m, 1H, H-9' or H-10'), 4.34 (d, 1H, *J* = 7.8 Hz, H-4).

^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 14.1 (C-11), 18.0 (C-7), 23.6 (C-8), 33.7 (C-6), 35.5 (C-2), 43.9 (C-3), 65.3, 66.6 (C-9 and C-10), 80.5 (C-4), 107.7 (C-5), 180.2 (C-1).

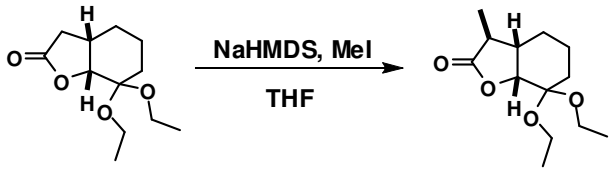
IR (film, cm^{-1}): 2970 and 2930 (C-H), 1785 (C=O), 1635.

MS (APCI+ev): *m/z* (%): 213 (70) $[M+H]^{+\cdot}$, 195 (50), 151 (25), 139 (100), 123 (35), 95 (37).

HRMS (CI): Calculated for $C_{11}H_{17}O_4$ [*M+1*]: 213.1126. Found: 213.1118.

Elemental analysis: Calculated for $C_{11}H_{16}O_4$: C: 62.25%; H: 7.60%. Found: C: 62.02%; H: 7.59%.

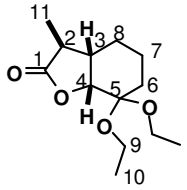
7,7-diethoxy-3-methylhexahydrobenzofuran-2(3H)-one 5.136



$C_{13}H_{22}O_4$
M.W.: 242,31

In a 25-mL round-bottomed flask, 300 mg of the bicyclic lactone (1.32 mmol, 1 eq.) are dissolved in 7 mL of THF and cooled to -78ºC. Then,

0.92 mL of NaHMDS (2M solution in THF, 1.9 mmol, 1.4 eq.) are added dropwise upon which a deep orange color develops. The mixture is stirred for 1 hour at this temperature. Then, 0.49 mL of MeI (7.92 mmol, 6 eq.) are added dropwise and the resulting solution is allowed to gradually reach room temperature over 3 hours, at which stage TLC-analysis indicates complete conversion to a new compound. Then, 10 mL of a saturated aqueous NH_4Cl solution are added to quench the reaction. After phase separation, the aqueous layer is extracted with 3 x 15 mL of diethylether. The combined organic fractions are dried ($MgSO_4$) and the solvents are removed under reduced pressure. Purification of the residue by flash chromatography (PE/AcOEt 2:1, Rf = 0.50) affords 250 mg (75%) of the alkylated product.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.10-1.17 (m, 9H, H-10 and H-11), 1.43-1.78 (m, 5H, H-6, H-7 and H-8), 1.85-1.93 (m, 1H, H-6'), 2.27-2.35 (m, 1H, H-3), 2.50-2.70 (m, 1H, H-2), 3.45-3.68 (m, 4H, H-9), 4.38 (d, 1H, *J* = 6.9 Hz, H-4).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 8.7 (C-11), 15.4, 15.5 (C-10 and C-10'), 20.7 (C-7), 27.3 (C-8), 28.4 (C-6), 37.0 (C-2), 42.9 (C-3), 54.5, 55.6 (C-9 and C-9'), 83.4 (C-4), 99.0 (C-5), 178.4 (C-1).

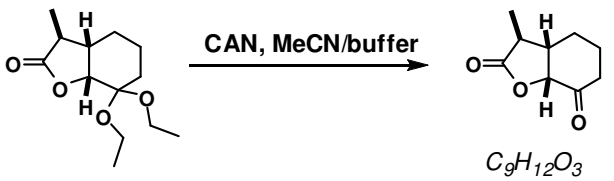
IR (film, cm^{-1}): 2985 (C-H), 1782 (C=O), 1635, 1449.

MS (APCI+ev): *m/z* (%): 197 (30) $[M\text{-}OEt]^{+\cdot}$, 183 (15), 169 (15), 123 (16), 109 (20), 95 (20).

HRMS (ESI): Calculated for $C_{13}H_{22}O_4Na$ [*M+Na*]: 265.1416. Found: 265.1417.

Elemental analysis: Calculated for $C_{13}H_{22}O_4$: C: 64.44%; H: 9.15%. Found: C: 64.38%; H: 8.80%.

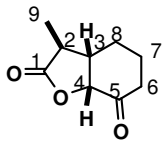
3-methyltetrahydrobenzofuran-2,7(3H,7aH)-dione 5.140



$C_9H_{12}O_3$
M.W.: 168,19

In a 50 mL round-bottomed flask eq.uipped with a reflux condenser, 250 mg of bicyclic lactone (1.0 mmol, 1 eq.) are dissolved in 10 mL of acetonitrile and 10 mL of borate buffer (pH=8). To this solution are added 17 mg of CAN (0.031 mmol, 0.03 eq.), upon which the reaction mixture turns to yellow. The mixture is heated at 50ºC. After 1-2 hours stirring at this temperature, TLC-analysis shows complete conversion. In case of remaining starting material, additional 3 mol% amounts of CAN can be added to drive the reaction forth. At this point, 10 mL of water are added to quench the reaction. The mixture is extracted with 3 x 15 mL dichloromethane. The combined organic fractions are dried ($MgSO_4$) and the solvents are removed under reduced pressure. The crude residue is >95% pure by ^{1}H-NMR

analysis. Purification of the residue for analytical purposes is done by flash chromatography (silica, PE/AcOEt 2:1 then 1:1) affords 163 mg (96 %) of the product (Rf = 0.13).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.21 (d, 3H, *J* = 6.9 Hz, H-9), 1.78-2.25 (m, 4H, H-7 and H-8), 2.40-2.57 (m, 3H, H-2 and H-6), 2.77-2.84 (m, 1H, H-3), 4.84 (d, 1H, *J* = 8.7 Hz, H-4).

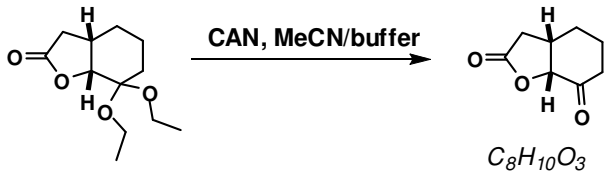
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 13.0 (C-9), 22.5 (C-7), 24.4 (C-8), 35.6 (C-6), 39.9 (C-2), 47.5 (C-3), 80.3 (C-4), 177.2 (C-1), 205.2 (C-5).

IR (film, cm^{-1}): 2985 (C-H), 1782 (C=O), 1706 (C=O), 1635, 1459.

MS (CI+ev): *m/z* (%): 169 (100) $[M+H]^{+\cdot}$, 151 (5), 123 (15), 95 (100), 67 (55), 55 (20).

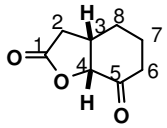
HRMS (CI): Calculated for $C_9H_{13}O_3$ [*M+1*]: 169.0864. Found: 169.0863.

Tetrahydrobenzofuran-2,7(3H,7aH)-dione 5.150



$C_8H_{10}O_3$
M.W.: 154,16

In a 10 mL round-bottomed flask eq.uipped with a reflux condenser, 150 mg of bicyclic lactone (0.66 mmol, 1 eq.) are dissolved in 3 mL of acetonitrile and 3 mL of borate buffer (pH=8). To this solution are added 11 mg of CAN (0.02 mmol, 0.03 eq.), upon which the reaction mixture turns to yellow. The mixture is heated at 50ºC. After 1-2 hours stirring at this temperature, TLC-analysis shows complete conversion. In case of remaining starting material, additional 3 mol% amounts of CAN can be added to drive the reaction forth. At this point, 10 mL of water are added to quench the reaction. The mixture is extracted with 3 x 15 mL dichloromethane. The combined organic fractions are dried ($MgSO_4$) and the solvents are *carefully* removed under reduced pressure. The crude residue is >95% pure by ^{1}H-NMR analysis. Purification of the residue for analytical purposes is done by flash chromatography (silica, PE/AcOEt 2:1 then 1:1) affords 90 mg (90 %) of the volatile product (Rf = 0.20).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.70-2.06 (m, 4H, H-7 and H-8), 2.20 (dd, 1H, *J* = 17.1, 10.5 Hz, H-2), 2.37-2.51 (m, 3H, H-2' and H-6), 3.14-3.24 (m, 1H, H-3), 4.78 (d, 1H, *J* = 7.8 Hz, H-4).

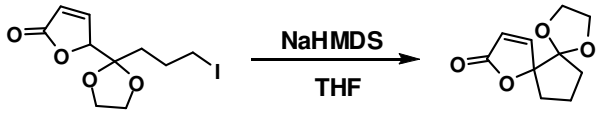
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 22.9 (C-7), 26.2 (C-8), 32.5 (C-6), 39.6, 40.1 (C-2 and C-3), 82.4 (C-4), 175.4 (C-1), 205.6 (C-5).

IR (film, cm^{-1}): 2982 (C-H), 1786 (C=O), 1705 (C=O) , 1645.

MS (APCI+ev): *m/z* (%): 155 (100) $[M+H]^{+\cdot}$, 137 (25), 109 (15).

9.8.4. Synthesis of spirocyclic butenolides

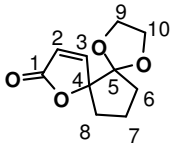
1,4,7-trioxa-dispiro[4.0.4.3]-tridecan-9-en-8-one 5.280



$C_{10}H_{12}O_4$
M.W.: 196,20

In a 25-mL round-bottomed flask 200 mg (0.62 mmol, 1 eq.) of the iodinated butenolide are dissolved in 12 mL of THF and cooled to -78ºC. To this solution are added dropwise 0.4 mL of NaHMDS (2M solution in THF, 0.8 mmol, 1.3 eq.). The bright yellow mixture is allowed to gradually reach room temperature over 2 hours, at which point TLC-analysis shows complete conversion of the starting material (NB: although both starting material and product have similar Rf values, TLC development with Vanillin provides differently coloured stains and allows a correct evaluation of the end-point for this reaction). At this stage, 10 mL of a saturated aqueous solution of NH_4Cl are added to quench the reaction. After phase separation, the aqueous layer is extracted with 3 x 15 mL of ethyl acetate. The combined organic fractions are washed with saturated aqueous NH_4Cl solution and brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue is

filtered through a pad of silica gel, eluting with PE/AcOEt 1:1 (Rf = 0.33) to afford 102 mg (85%) of the spirocyclic butenolide.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.80-1.97 (m, 4H, H-7 and H-8), 2.13-2.25 (m, 2H, H-6), 3.70-3.97 (m, 4H, H-9 and H-10), 6.08 (d, 1H, *J* = 5.7 Hz, H.2), 7.33 (d, 1H, *J* = 5.7 Hz, H-3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 18.3 (C-7), 32.3, 33.6 (C-6 and C-8), 65.1, 66.5 (C-9 and C-10), 95.6 (C-4), 116.9 (C-5), 122.8 (C-2), 154.4 (C-3), 171.9 (C-1).

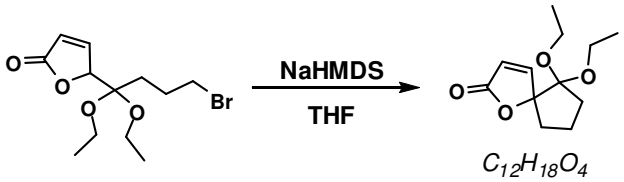
IR (film, cm^{-1}): 3359, 2921 (C-H), 1751 (C=O), 1697, 1391.

MS (APCI+ev): *m/z* (%): 197 (15) $[M+H]^{+\cdot}$, 179 (15), 153 (35), 135 (100), 107 (11), 99 (15).

HRMS (CI): Calculated for $C_{10}H_{13}O_4$ [*M+1*]: 197.0813. Found: 197.0811.

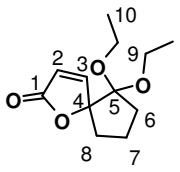
Elemental analysis: Calculated for $C_{10}H_{12}O_4$: C: 61.26%; H: 6.17%. Found: C: 60.82%; H: 6.16%.

6,6-diethoxy-1-oxaspiro[4.4]non-3-en-2-one 5.288



$C_{12}H_{18}O_4$
M.W.: 226,27

In a 100-mL round-bottomed flask 450 mg (1.47 mmol, 1 eq.) of the brominated butenolide are dissolved in 50 mL of THF and cooled to -78ºC. To this solution are added dropwise 0.95 mL of NaHMDS (2M solution in THF, 1.91 mmol, 1.3 eq.). The bright yellow mixture is allowed to gradually reach room temperature over 2 hours, at which point TLC-analysis shows complete conversion of the starting material (NB: although both starting material and product have similar Rf values, TLC development with Vanillin provides differently coloured stains and allows a correct evaluation of the end-point for this reaction). At this stage, 40 mL of a saturated aqueous solution of NH_4Cl are added to quench the reaction. After phase separation, the aqueous layer is extracted with 3 x 35 mL of diethylether. The combined organic fractions are washed with saturated aqueous NH_4Cl solution and brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue is filtered through a pad of silica gel, eluting with PE/AcOEt 1:1 (Rf = 0.33) to afford 250 mg (76%) of the spirocyclic butenolide.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.05 (t, 3H, *J* = 7.8 Hz, H-10), 1.16 (t, 3H, *J* = 7.2 Hz, H-10'), 1.65-1.89 (m, 3H, H-7 and H-8), 2.03-2.11 (m, 2H, H-8' and H-6), 2.21-2.26(m, 1H, H-6'), 3.35-3.51 (m, 4H, H-9), 6.00 (d, 1H, *J* = 6.0 Hz, H-2), 7.58 (d, 1H, *J* = 5.7 Hz, H-3).

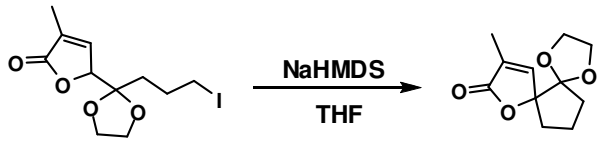
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 15.4, 15.7 (C-10 and C-10'), 18.7 (C-7), 31.1, 34.2 (C-6 and C-8), 57.0, 59.6 (C-9 and C-9'), 96.3 (C-4), 110.4 (C-5), 121.1 (C-2), 157.4 (C-3), 172.2 (C-1).

IR (film, cm^{-1}): 2954, 2911 (C-H), 1750 (C=O), 1677, 1411.

MS (APCI+ev): *m/z* (%): 227 (100) $[M+H]^{+\cdot}$, 209 (5), 181 (15), 153 (20), 135 (15), 107 (7).

HRMS (ESI): Calculated for $C_{12}H_{18}O_4Na$ [*M+Na*]: 249.1103. Found 249.1102.

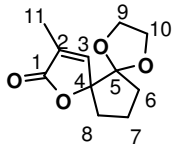
9-methyl-1,4,7-trioxa-dispiro[4.0.4.3]-tridecan-9-en-8-one 5.286



$C_{11}H_{14}O_4$
M.W.: 210,23

In a 25-mL round-bottomed flask 95 mg (0.28 mmol, 1 eq.) of the iodinated butenolide are dissolved in 10 mL of THF and cooled to -78ºC. To this solution are added dropwise 0.18 mL of NaHMDS (2M solution in THF, 0.37 mmol, 1.3 eq.). The bright yellow mixture is allowed to gradually reach room temperature over 3 hours, at which point TLC-analysis shows

complete conversion of the starting material (NB: although both starting material and product have similar Rf values, TLC development with Vanillin provides differently coloured stains and allows a correct evaluation of the end-point for this reaction). At this stage, 10 mL of a saturated aqueous solution of NH_4Cl are added to quench the reaction. After phase separation, the aqueous layer is extracted with 3 x 15 mL of ethyl acetate. The combined organic fractions are washed with saturated aqueous NH_4Cl solution and brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue is filtered through a pad of silica gel, eluting with PE/AcOEt 2:1 (Rf = 0.21) to afford 37 mg (63%) of the spirocyclic butenolide.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.81-1.99 (m, 4H, H-7 and H-8), 1.93 (s, 3H, H-11), 2.14-2.23 (m, 2H, H-6), 3.73-3.77 (m, 1H, H-9 or H-10), 3.82-4.07 (m, 3H, H-9 and H-10), 6.94 (d, 1H, J = 2.1 Hz, H-3).

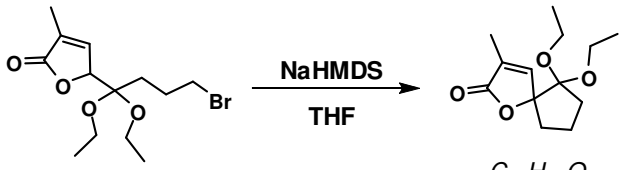
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 10.9 (C-11), 18.2 (C-7), 32.3, 33.5 (C-6 and C-8), 65.1, 66.4 (C-9 and C-10), 93.2 (C-4), 116.7 (C-5), 131.4 (C-2), 146.6 (C-3), 173.0 (C-1).

IR (film, cm^{-1}): 3360, 2919, 2844 (C-H), 1759 (C=O), 1655, 1415.

MS (APCI+ev): *m/z* (%): 211 (100) $[M+H]^{+\cdot}$, 193 (15), 167 (55), 149 (90), 123 (30), 99 (20).

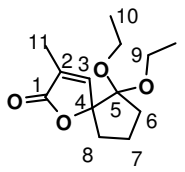
Elemental analysis: Calculated for $C_{11}H_{14}O_4$: C: 62.85%; H: 6.71%. Found: C: 62.38%; H: 6.80%.

6,6-diethoxy-3-methyl-1-oxaspiro[4.4]non-3-en-2-one 5.291



$C_{13}H_{20}O_4$
M.W.: 240,30

In a 25-mL round-bottomed flask 100 mg (0.31 mmol, 1 eq.) of the brominated butenolide are dissolved in 10 mL of THF and cooled to -78ºC. To this solution are added dropwise 0.20 mL of NaHMDS (2M solution in THF, 0.41 mmol, 1.3 eq.). The bright yellow mixture is allowed to gradually reach room temperature over 2 hours, at which point TLC-analysis shows complete conversion of the starting material (NB: although both starting material and product have similar Rf values, TLC development with Vanillin provides differently coloured stains and allows a correct evaluation of the end-point for this reaction). At this stage, 10 mL of a saturated aqueous solution of NH_4Cl are added to quench the reaction. After phase separation, the aqueous layer is extracted with 3 x 15 mL of diethylether. The combined organic fractions dried ($MgSO_4$) and evaporated under reduced pressure. The residue is purified by flash chromatography (silica, PE/AcOEt 4:1, Rf = 0.66 in PE/AcOEt 2:1) to afford 47 mg (63%) of the spirocyclic butenolide.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.08 (t, 3H, *J* = 6.6 Hz, H-10), 1.19 (t, 3H, *J* = 7.2 Hz, H-10'), 1.64-1.94 (m, 3H, H-7 and H-8), 1.91 (s, 3H, H-11), 2.01-2.12 (m, 2H, H-8' and H-6), 2.19-2.27 (m, 1H, H-6'), 3.35-3.55 (m, 4H, H-9), 7.16 (br s, 1H, H-3).

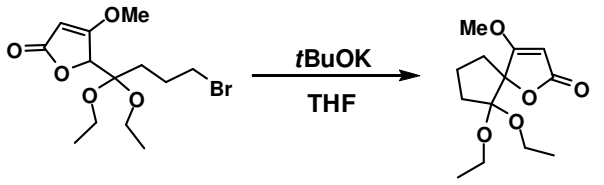
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 10.8 (C-11), 15.4, 15.7 (C-10 and C-10'), 18.5 (C-7), 30.8, 34.1 (C-6 and C-8), 56.9, 59.6 (C-9 and C-9'), 93.9 (C-4), 110.1 (C-5), 129.6 (C-2), 149.4 (C-3), 173.3 (C-1).

IR (film, cm^{-1}): 3200, 2920 (C-H), 1755 (C=O), 1429.

MS (APCI+ev): *m/z* (%): 241 (15) $[M+H]^{+\cdot}$, 195 (90), 177 (25), 149 (100), 121 (5), 79 (15).

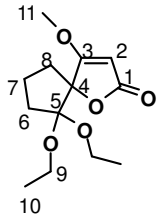
Elemental analysis: Calculated for $C_{13}H_{20}O_4$: C: 64.98%; H: 8.39%. Found: C: 65.06%; H: 8.19%.

6,6-diethoxy-4-methoxy-1-oxaspiro[4.4]non-3-en-2-one 5.294



$C_{13}H_{20}O_5$
M.W.: 256,29

In a 10-mL round-bottomed flask 100 mg (0.30 mmol, 1 eq.) of the brominated butenolide are dissolved in 3 mL of THF and cooled to 0ºC. To this solution are added 44 mg of *t*BuOK (0.40 mmol, 1.3 eq.) at once. The bright yellow mixture is allowed to gradually reach room temperature over 60 minutes, at which point TLC-analysis shows complete conversion of the starting material (NB: although both starting material and product have similar Rf values, TLC development with Vanillin provides differently coloured stains and allows a correct evaluation of the end-point for this reaction). At this stage, 5 mL of a saturated aqueous solution of NH_4Cl are added to quench the reaction. After phase separation, the aqueous layer is extracted with 3 x 10 mL of diethylether. The combined organic fractions dried ($MgSO_4$) and evaporated under reduced pressure. The residue is >95% pure by ^{1}H-NMR analysis, affording 71 mg (92%) of the spirotetronate.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.12 (apparent q, 6H, *J* = 6.8 Hz, H-10), 1.63-1.89 (m, 2H, H-7), 1.95-2.20 (m, 4H, H-6 and H-8), 3.39-3.66 (m, 4H, H-9), 3.86 (s, 3H, H-11), 4.99 (s, 1H, H-2).

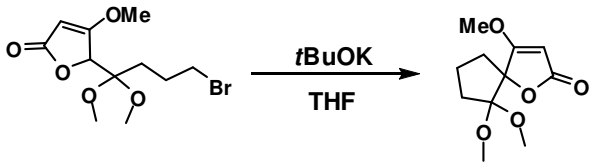
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 15.3, 15.6 (C-10 and C-10'), 17.7 (C-7), 31.9, 32.4 (C-6 and C-8), 57.7, 58.5 (C-9 and C-9'), 59.7 (C-11), 88.9 (C-2), 92.1 (C-4), 108.9 (C-5), 171.7 (C-1), 183.2 (C-3).

IR (film, cm^{-1}): 3050, 2925 (C-H), 1750 (C=O), 1438.

MS (APCI+ev): *m/z* (%): 257 (10) $[M+H]^{+\cdot}$, 211 (50), 179 (25), 165 (100), 133 (10), 105 (5).

HRMS (ESI): Calculated for $C_{13}H_{21}O_5$ [*M+1*]: 257.1389. Found: 257.1401.

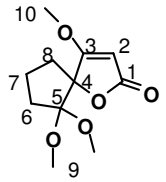
4,6,6-trimethoxy-1-oxaspiro[4.4]non-3-en-2-one 5.295



$C_{11}H_{16}O_5$
M.W.: 228,24

In a 10-mL round-bottomed flask 309 mg (1.0 mmol, 1 eq.) of the brominated butenolide are dissolved in 10 mL of THF and cooled to 0ºC. To this solution are added 145 mg of *t*BuOK (1.30 mmol, 1.3 eq.) at once. The bright yellow mixture is allowed to gradually reach room temperature over

50 minutes, at which point TLC-analysis shows complete conversion of the starting material (NB: although both starting material and product have similar Rf values, TLC development with Vanillin provides differently coloured stains and allows a correct evaluation of the end-point for this reaction). At this stage, 5 mL of a saturated aqueous solution of NH_4Cl are added to quench the reaction. After phase separation, the aqueous layer is extracted with 3 x 10 mL of diethylether. The combined organic fractions dried ($MgSO_4$) and evaporated under reduced pressure. The residue is >95% pure by ^{1}H-NMR analysis, affording 206 mg (91%) of the spirotetronate.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.69-1.86 (m, 2H, H-7), 1.96-2.23 (m, 4H, H-6 and H-8), 3.24 (s, 3H, H-9), 3.32 (s, 3H, H-9'), 3.89 (s, 3H, H-10), 5.03 (s, 1H, H-2).

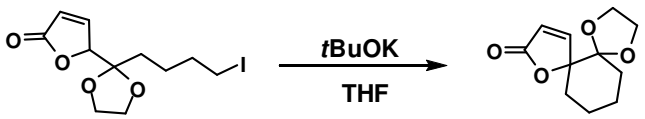
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 17.5 (C-7), 30.9, 32.6 (C-6 and C-8), 49.9, 50.9 (C-9 and C-9'), 59.7 (C-10), 89.0 (C-2), 91.8 (C-4), 109.3 (C-5), 171.5 (C-1), 182.9 (C-3).

IR (film, cm^{-1}): 3116, 2837 (C-H), 1751 (C=O), 1622, 1456, 1440.

MS (APCI+ev): *m/z* (%): 229 (35) $[M+H]^{+\cdot}$, 197 (50), 165 (100), 137 (5).

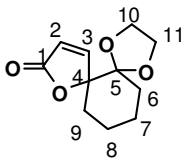
HRMS (ESI): Calculated for $C_{11}H_{17}O_5$ [*M+1*]: 229.1076. Found: 229.1076.

1,4,7-trioxa-dispiro[4.0.4.4]-tetradecan-9-en-8-one 5.282



$C_{11}H_{14}O_4$
M.W.: 210,23

In a 25-mL round-bottomed flask 140 mg (0.42 mmol, 1 eq.) of the iodinated butenolide are dissolved in 8 mL of THF and cooled to 0ºC. To this solution are added 70 mg of *t*BuOK (0.6 mmol, 1.4 eq.). The bright yellow suspension is allowed to gradually reach room temperature over 2 hours, at which point TLC-analysis shows complete conversion of the starting material (NB: although both starting material and product have similar Rf values, TLC development with Vanillin provides differently coloured stains and allows a correct evaluation of the end-point for this reaction). At this stage, 10 mL of a saturated aqueous solution of NH_4Cl are added to quench the reaction. After phase separation, the aqueous layer is extracted with 3 x 15 mL of ethyl acetate. The combined organic fractions are washed with saturated aqueous NH_4Cl solution and brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue is filtered through a pad of silica gel, eluting with PE/AcOEt 1:1 (Rf = 0.33) to afford 79 mg (90%) of the spirocyclic butenolide.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.54-1.90 (m, 8H, H-6, H-7, H-8 and H-9), 3.77-4.01 (m, 4H, H-10 and H-11), 6.08 (d, 1H, *J* = 6.0 Hz, H-2), 7.39 (d, 1H, *J* = 6.0 Hz, H-3).

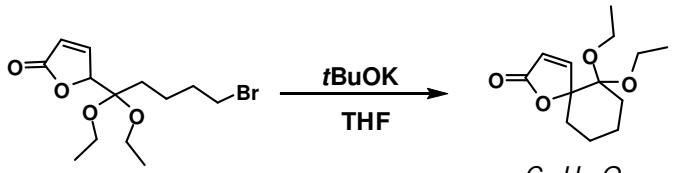
^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 21.5, 22.8 (C-7 and C-8), 33.4, 33.6 (C-6 and C-9), 65.8, 65.9 (C-10 and C-11), 95.6 (C-4), 115.9 (C-5), 122.4 (C-2), 155.7 (C-3), 172.9 (C-1).

IR (film, cm^{-1}): 2967 and 2893 (C-H), 1751 (C=O), 1143, 1103.

MS (APCI+ev): *m/z* (%): 211 (70) $[M+H]^{+\cdot}$, 193 (25), 167 (75), 149 (100), 139 (70), 121 (50), 93 (10).

HRMS (ESI): Calculated for $C_{11}H_{14}O_4Na$ [*M+Na*]: 233.0790. Found: 233.0795.

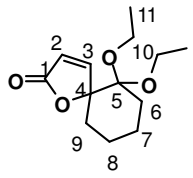
6,6-diethoxy-1-oxaspiro[4.5]dec-3-en-2-one 5.289



$C_{13}H_{20}O_4$
M.W.: 240,30

In a 25-mL round-bottomed flask 160 mg (0.50 mmol, 1 eq.) of the brominated butenolide are dissolved in 10 mL of THF and cooled to 0ºC. To this solution are added 78 mg of *t*BuOK (0.70 mmol, 1.4 eq.). The bright yellow suspension is allowed to gradually reach room temperature over 2 hours, at which point TLC-analysis shows complete conversion of the

starting material (NB: although both starting material and product have similar Rf values, TLC development with Vanillin provides differently coloured stains and allows a correct evaluation of the end-point for this reaction). At this stage, 10 mL of a saturated aqueous solution of NH_4Cl are added to quench the reaction. After phase separation, the aqueous layer is extracted with 3 x 15 mL of ethyl acetate. The combined organic fractions are washed with saturated aqueous NH_4Cl solution and brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue is filtered through a pad of silica gel, eluting with PE/AcOEt 1:1 to afford 84 mg (90%) of the spirocyclic butenolide.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.15-1.22 (m, 6H, H-11), 1.56-1.96 (m, 8H, H-6, H-7, H-8 and H-9), 3.45-3.52 (m, 4H, H-10), 6.04 (d, 1H, *J* = 5.7 Hz, H-2), 7.58 (d, 1H, *J* = 5.7 Hz, H-3).

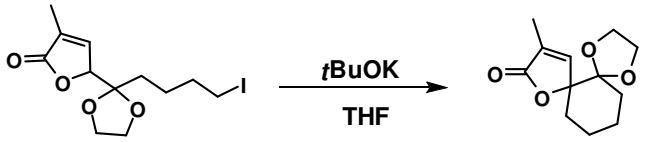
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 15.4, 15.7 (C-10 and C-10'), 18.7, 19.6 (C-7 and C-8), 31.0, 34.1 (C-6 and C-9), 57.0, 57.5 (C-10 and C-10'), 94.4 (C-4), 105.4 (C-5), 120.1 (C-2), 153.4 (C-3), 172.2 (C-1).

IR (film, cm^{-1}): 3359, 2921, 2852 (C-H), 1758 (C=O), 1658, 1631.

MS (CI+ev): *m/z* (%): 241 (55) $[M+H]^+$, 195 (5), 167 (55), 149 (100), 121 (80), 93 (10).

HRMS (CI): Calculated for $C_{13}H_{21}O_4$ [*M+1*]: 241.1439. Found: 241.1445.

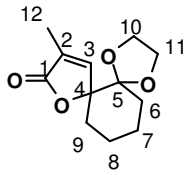
9-methyl-1,4,7-trioxa-dispiro[4.0.4.4]-tetradecan-9-en-8-one 5.287



$C_{12}H_{16}O_4$
M.W.: 224,25

In a 25-mL round-bottomed flask 100 mg (0.28 mmol, 1 eq.) of the iodinated butenolide are dissolved in 4 mL of THF and cooled to 0ºC. To this solution are added 41 mg of *t*BuOK (0.37 mmol, 1.4 eq.). The dark bordeaux suspension is allowed to gradually reach room temperature over 30 minutes, at which point TLC-analysis shows complete conversion of the starting material (NB: although both starting material and product have similar Rf values, TLC development with Vanillin provides differently coloured stains and allows a correct evaluation of the end-point for this reaction). At this stage, 10 mL of a saturated aqueous solution of sodium bicarbonate are added to quench the reaction. After phase separation, the aqueous layer is extracted with 3 x 15 mL of ethyl acetate. The combined organic fractions are washed with saturated aqueous NH_4Cl solution and

brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue is filtered through a pad of silica gel, eluting with PE/AcOEt 3:1 (Rf = 0.33) to afford 44 mg (70%) of the spirocyclic butenolide.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.61-1.89 (m, 8H, H-6, H-7, H-8 and H-9), 1.91 (d, 3H, *J* = 1.5 Hz, H-12), 3.80-3.99 (m, 4H, H-10 and H-11), 7.01 (d, 1H, *J* = 1.5 Hz, H-3).

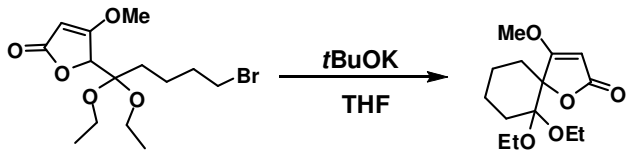
^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 10.6 (C-12), 21.5, 22.8 (C-7 and C-8), 33.5, 33.7 (C-6 and C-9), 65.8, 65.9 (C-10 and C-11), 95.6 (C-4), 116.7 (C-5), 131.4 (C-2), 146.6 (C-3), 173.0 (C-1).

IR (film, cm^{-1}): 3357, 2923 and 2825 (C-H), 1757 (C=O), 1660, 1434, 1321.

MS (APCI+ev): *m/z* (%): 225 (90) $[M+H]^{+\cdot}$, 207 (25), 197 (15), 181 (40), 163 (40), 163 (55), 153 (80), 135 (100), 117 (5), 107 (10).

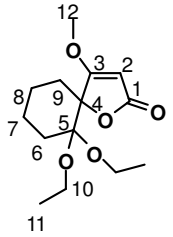
HRMS (ESI): Calculated for $C_{12}H_{17}O_4$ [*M+1*]: 225.1127. Found: 225.1119.

6,6-diethoxy-4-methoxy-1-oxaspiro[4.5]dec-3-en-2-one 5.297



$C_{14}H_{22}O_5$
M.W.: 270,32

In a 10-mL round-bottomed flask 351 mg (1.0 mmol, 1 eq.) of the brominated butenolide are dissolved in 10 mL of THF and cooled to 0ºC. To this solution are added 145 mg of *t*BuOK (1.30 mmol, 1.3 eq.) at once. The bright yellow mixture is allowed to gradually reach room temperature over 35 minutes, at which point TLC-analysis shows complete conversion of the starting material (NB: although both starting material and product have similar Rf values, TLC development with Vanillin provides differently coloured stains and allows a correct evaluation of the end-point for this reaction). At this stage, 5 mL of a saturated aqueous solution of NH_4Cl are added to quench the reaction. After phase separation, the aqueous layer is extracted with 3 x 10 mL of diethylether. The combined organic fractions dried ($MgSO_4$) and evaporated under reduced pressure. The residue is >95% pure by ^{1}H-NMR analysis, affording 235 mg (87%) of the spirotetronate.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.12 (apparent sextuplet, 6H, *J* = 3.7 Hz, H-11), 1.46-1.67 (m, 4H, H-7 and H-8), 1.76-1.84 (m, 1H, H-9), 1.89-2.03 (m, 3H, H-6 and H-9'), 3.40-3.57 (m, 4H, H-10), 3.85 (s, 3H, H-12), 4.99 (s, 1H, H-2).

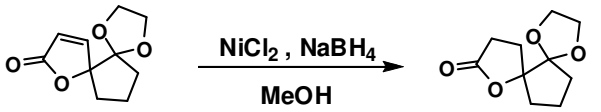
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 15.5, 15.7 (C-11 and C-11'), 20.9, 21.6 (C-7 and C-8), 29.9 (C-9), 33.2 (C-6), 56.9, 58.3 (C-10 and C-10'), 59.7 (C-12), 88.0 (C-2), 89.4 (C-4), 100.9 (C-5), 172.1 (C-1), 185.0 (C-3).

IR (film, cm^{-1}): 3116, 2837 (C-H), 1751 (C=O), 1622, 1456, 1440.

MS (APCI+ev): *m/z* (%): 271 (65) $[M+H]^{+\cdot}$, 225 (10), 197 (100), 179 (60), 151 (25), 137 (15), 113 (10), 91 (10).

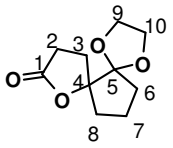
HRMS (ESI): Calculated for $C_{14}H_{23}O_5$ [*M+1*]: 271.1545. Found: 271.1540.

1,4,7-trioxa-dispiro[4.0.4.3]-tridecan-8-one 5.300



$C_{10}H_{14}O_4$
M.W.: 198,22

Method B: Starting from 98 mg (0.5 mmol) of the spirocyclic butenolide. After workup, 99 mg (100%) of pure saturated lactone are obtained.



^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 1.67-1.72 (m, 1H, H-7), 1.81-1.92 (m, 3H, H-7' and H-8), 1.96-2.02 (m, 2H, H-3 and H-6), 2.06-2.11 (m, 1H, H-6'), 2.40 (dtd, *J* = 11.5, 4.0, 3.5 Hz, 1 H, H-3'), 2.48-2.54 (m, 1H, H-2), 2.61-2.68 (m, 1H, H-2'), 3.96-4.05 (m, 4H, H-9 and H-10).

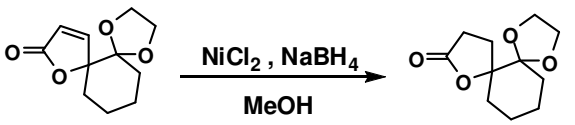
^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 17.2 (C-7), 25.9 (C-3), 29.1 (C-2), 31.7, 33.8 (C-6 and C-8), 65.3, 65.8 (C-9 and C-10), 92.4 (C-4), 115.6 (C-5), 176.8 (C-1).

IR (film, cm^{-1}): 3527, 2954 and 2887 (C-H), 1770 (C=O), 1458, 1332, 1230, 1159.

MS (APCI+ev): *m/z* (%): 199 (15) $[M+H]^{+\cdot}$, 181 (5), 155 (5), 137 (55), 109 (25).

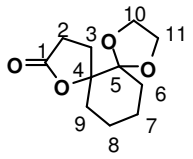
HRMS (ESI): Calculated for $C_{10}H_{15}O_4$ $[M+1]$: 199.0970. Found: 199.0965.

1,4,7-trioxa-dispiro[4.0.4.4]-tetradecan-8-one 5.301



$C_{11}H_{16}O_4$
M.W.: 212,24

Method B: Starting from 105 mg (0.5 mmol) of the spirocyclic butenolide. After workup, 108 mg (100%) of pure saturated lactone are obtained.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.54-1.88 (m, 8H, H-6, H-7, H-8 and H-9), 1.96-2.04 (m, 1H, H-3), 2.34-2.53 (m, 2H, H-3' and H-2), 2.61-2.74 (m, 1H, H-2'), 3.94-4.02 (m, 4H, H-10 and H-11).

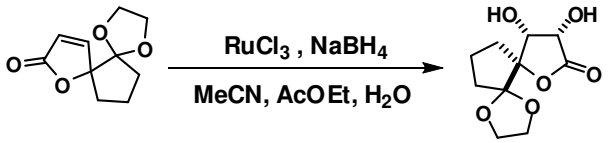
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 21.5 (C-7), 21.5, 22.6 (C-8 and C-9), 28.4, 29.0 (C-6 and C-3), 32.2 (C-2), 65.7 (C-9 and C-10), 88.6 (C-4), 109.8 (C-5), 177.1 (C-1).

IR (film, cm^{-1}): 2950 (C-H), 1771 (C=O), 1460.

MS (APCI+ev): *m/z* (%): 213 (100) $[M+H]^{+\cdot}$, 195 (30), 185 (60), 151 (90), 141 (70), 123 (100), 99 (10).

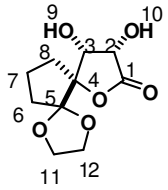
HRMS (ESI): Calculated for $C_{11}H_{17}O_4$ [*M+1*]: 213.1127. Found: 213.1129.

9,10-dihydroxy-1,4,7-trioxa-dispiro[4.0.4.3]-tridecan-8-one 5.302



$C_{10}H_{14}O_6$
M.W.: 230,21

Method C: Starting from 50 mg (0.25 mmol) of the spirocyclic butenolide. After workup, 50 mg (88%) of pure dihydroxylated lactone are obtained.



^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 1.70-1.78 (m, 1H, H-7), 1.85-1.90 (m, 2H, H-7' and H-8), 1.95-1.99 (m, 1H, H-8'), 2.01-2.08 (m, 1H, H-6), 2.25-2.31 (m, 1H, H-6'), 2.68 (br s, 1H, H-9 or H-10), 2.98 (br s, 1H, H-9 or H-10), 3.86-3.98 (m, 4H, H-11 and H-12), 4.45 (d, 1H, *J* = 5.3 Hz, H-3), 4.62 (d, 1H, *J* = 5.2 Hz, H-2).

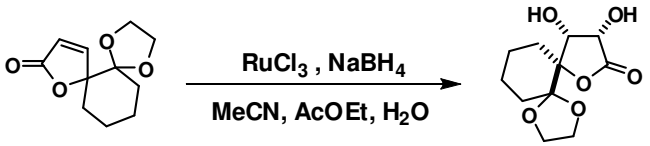
^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 17.6 (C-7), 29.3, 32.9 (C-6 and C-8), 65.5, 65.9 (C-11 and C-12), 69.7 (C-3), 70.3 (C-2), 94.4 (C-4), 115.7 (C-5), 176.0 (C-1).

IR (film, cm^{-1}): 3367 (br, OH), 2924, 1772 (C=O), 1132.

MS (APCI+ev): *m/z* (%): 231 (100) $[M+H]^{+\cdot}$, 213 (10), 169 (15), 149 (5).

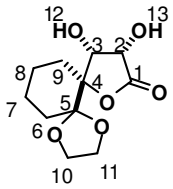
HRMS (ESI): Calculated for $C_{10}H_{15}O_6$ $[M+1]$: 231.0869. Found: 231.0871.

9,10-dihydroxy-1,4,7-trioxa-dispiro[4.0.4.4]-tetradecan-8-one 5.303



$C_{11}H_{16}O_6$
M.W.: 244,24

Method C: Starting from 60 mg (0.28 mmol) of the spirocyclic butenolide. After workup, 62 mg (88%) of pure dihydroxylated lactone are obtained.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.50-1.79 (m, 8H, H-6, H-7, H-8 and H-9), 2.83 (br s, 1H, H-12 or H-13), 3.12 (br s, 1H, H-12 or H-13), 3.98-3.94 (m, 4H, H-10 and H-11), 4.40 (d, 1H, *J* = 5.9 Hz, H-3), 4.80 (d, 1H, *J* = 5.9 Hz, H-2).

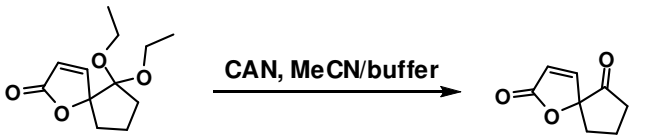
^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 21.1, 22.5 (C-7 and C-8), 29.4, 32.4 (C-6 and C-9), 65.2, 65.4 (C-10 and C-11), 69.0 (C-3), 69.3 (C-2), 90.8 (C-4), 109.1 (C-5), 176.1 (C-1).

IR (film, cm^{-1}): 3354 (br, OH), 2911, 1770 (C=O), 1412.

MS (APCI+ev): *m/z* (%): 245 (100) $[M+H]^{+\cdot}$, 233 (8), 201 (20), 183 (10).

HRMS (ESI): Calculated for $C_{11}H_{17}O_6$ $[M+1]$: 245.1025. Found: 245.1022.

1-oxaspiro[4.4]non-3-ene-2,6-dione 5.305

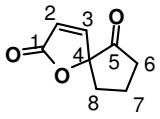


$C_8H_8O_3$
M.W.: 152,15

In a 25 mL round-bottomed flask eq.uipped with a reflux condenser, 190 mg of spirocyclic butenolide (0.84 mmol, 1 eq.) are dissolved in 3 mL of acetonitrile and 3 mL of borate buffer (pH=8). To this solution are added 14 mg of CAN (0.025 mmol, 0.03 eq.), upon which the reaction mixture turns to yellow. The mixture is heated at 45ºC. After 10 hours stirring at this temperature, TLC-analysis shows complete conversion. In case of remaining starting material, additional 3 mol% amounts of CAN can be added to drive the reaction forth. At this point, 5 mL of water are added to quench the reaction. The mixture is extracted with 3 x 10 mL dichloromethane. The combined organic fractions are dried ($MgSO_4$) and the solvents are *carefully* removed under reduced pressure (volatile compound). The crude residue is

>95% pure by ^{1}H-NMR analysis. Purification of the residue for analytical purposes is done by flash chromatography (silica, PE/AcOEt 1:1, Rf = 0.40) affords 130 mg (99 %) of the deprotected spirobutenolide.

Alternatively, 100 mg (0.47 mmol, 1 eq.) of the spirocyclic butenolide are dissolved in 2 mL of THF and cooled to 0ºC. To this solution are added 1 mL of a 1M HCl solution (1 mmol, 2.1 eq.) and stirring is continued for 1 hour at the same temperature. Then 3 mL of an aqueous saturated sodium bicarbonate solution are added to quench to reaction. After phase separation, the aqueous layer is extracted with 3 x 5 mL of diethylether. The combined organic fractions are dried ($MgSO_4$) and the solvents are *carefully* removed under reduced pressure (volatile compound). The crude residue is >95% pure by ^{1}H-NMR analysis and can be purified as above.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 2.00-2.67 (m, 6H, H-6, H-7 and H-8), 6.18 (d, 1H, *J* = 5.7 Hz, H-2), 7.20 (d, 1H, *J* = 5.7 Hz, H-3).

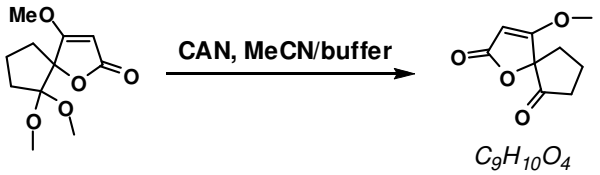
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 18.1 (C-7), 32.8 (C-8), 36.3 (C-6), 91.2 (C-4), 122.0 (C-2), 152.5 (C-3), 171.6 (C-1), 208.3 (C-5).

IR (film, cm^{-1}): 3204, 2965 (C-H), 1755 (C=O), 1735 (C=O), 1635, 1459.

MS (CI+ev): *m/z* (%): 153 (100) $[M+H]^{+\cdot}$, 135 (10), 102 (5).

HRMS (CI): Calculated for $C_8H_9O_3$ [*M+1*]: 153.0551. Found: 153.0553.

4-methoxy-1-oxaspiro[4.4]non-3-ene-2,6-dione 5.306

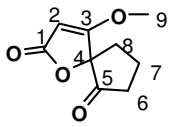


$C_9H_{10}O_4$
M.W.: 182,17

In a 25 mL round-bottomed flask eq.uipped with a reflux condenser, 193 mg of spirocyclic butenolide (0.84 mmol, 1 eq.) are dissolved in 3 mL of acetonitrile and 3 mL of borate buffer (pH=8). To this solution are added 14 mg of CAN (0.025 mmol, 0.03 eq.), upon which the reaction mixture turns to yellow. The mixture is heated at 45ºC. After 10 hours stirring at this temperature, TLC-analysis shows complete conversion. In case of remaining starting material, additional 3 mol% amounts of CAN can be added to drive the reaction forth. At this point, 5 mL of water are added to quench the reaction. The mixture is extracted with 3 x 10 mL dichloromethane. The combined organic fractions are dried ($MgSO_4$) and the solvents are *carefully* removed under reduced pressure (volatile compound). The crude residue is >95% pure by ^{1}H-NMR analysis. Purification of the residue for analytical purposes is done by flash chromatography (silica, PE/AcOEt 1:1) affords 130 mg (99 %) of the deprotected spirobutenolide.

Alternatively, 100 mg (0.44 mmol, 1 eq.) of the spirocyclic butenolide are dissolved in 2 mL of THF and cooled to 0ºC. To this solution

are added 1 mL of a 1M HCl solution (1 mmol, 2.1 eq.) and stirring is continued for 1 hour at the same temperature. Then 3 mL of an aqueous saturated sodium bicarbonate solution are added to quench to reaction. After phase separation, the aqueous layer is extracted with 3 x 5 mL of diethylether. The combined organic fractions are dried ($MgSO_4$) and the solvents are *carefully* removed under reduced pressure (volatile compound). The crude residue is >95% pure by ^{1}H-NMR analysis and can be purified as above.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 2.08-2.19 (m, 2H, H-7), 2.27-2.59 (m, 4H, H-6 and H-8), 3.88 (s, 3H, H-9), 5.16 (s, 1H, H-2).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 18.4 (C-7), 32.0 (C-8), 36.6 (C-6), 59.7 (C-9), 86.1 (C-2), 89.7 (C-4), 171.1 (C-1), 179.9 (C-3), 208.8 (C-5).

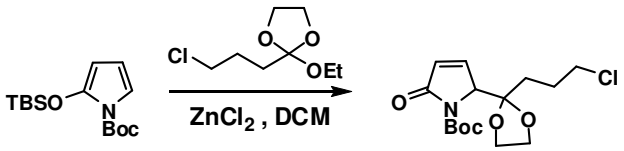
IR (film, cm^{-1}): 2921 and 2852 (C-H), 1768 (br, C=O), 1629, 1352, 1213.

MS (CI+ev): *m/z* (%): 183 (100) $[M+H]^{+\cdot}$, 165 (70), 151 (50), 137 (65), 123 (50), 105 (10).

HRMS (ESI): Calculated for $C_9H_{11}O_4$ $[M+1]$: 183.0657. Found: 183.0659.

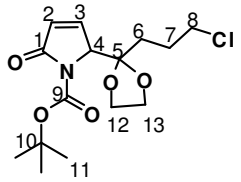
9.9. Sample annelations of TBSOP (Chapter 6)

***tert*-butyl 2-(2-(3-chloropropyl)-1,3-dioxolan-2-yl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate 6.044**



$C_{15}H_{22}ClNO_5$
M.W.: 331,79

In a 25-mL round-bottomed flask, 524 mg of orthoester (2.7 mmol, 1.6 eq.) are dissolved in 1 mL of dichloromethane and cooled to 0ºC. To this solution are added 321 mg of zinc chloride (2.3 mmol, 1.4 eq.), and subseq.uently 500 mg of TBSOP (1.68 mmol, 1 eq.) are introduced dropwise. Stirring is continued for 30 minutes, after which 3 mL of a saturated aqueous solution of $NaHCO_3$ are added. After phase separation, the aqueous layer is extracted with 3 x 5 mL of dichloromethane. The combined organic fractions are dried (Na_2SO_4) and concentrated under reduced pressure. The resulting solid is washed with 20 mL of heptane and then dissolved in 5 mL of dichloromethane. 5 mL of 1M KOH are then added and the biphasic mixture is slowly stirred (without allowing phase mixture) overnight. After 15 hours stirring, phase separation and removal of the organic solvent affords 432 mg (77%) of the condensation product.



^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 1.54 (s, 9H, H-11), 1.60-1.90 (m, 4H, H-6 and H-7), 3.48-3.51 (m, 2H, H-8), 3.91-4.04 (m, 4H, H-12 and H-13), 4.87 (s, 1H, H-4), 6.12 (dd, 1H, *J* = 6.2, 1.7 Hz, H-2), 7.11 (dd, 1H, *J* = 6.2, 2.2 Hz, H-3).

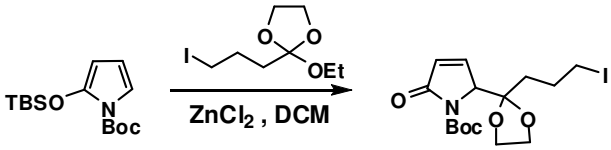
^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 26.0, 31.6 (C-6 and C-7), 28.1 (C-11), 45.0 (C-8), 65.7, 66.2 (C-12 and C-13), 66.3 (C-4), 83.3 (C-10), 110.2 (C-5), 127.7 (C-2), 147.8 (C-3), 149.8 (C-9), 170.0 (C-1).

IR (film, cm^{-1}): 3005, 2987 (C-H), 1774 (sh, C=O), 1731 (C=O), 1275.

MS (ESI+ev): *m/z* (%): 356 (12) [*M+Na for* ^{37}*Cl*]$^{+\cdot}$, 149 (13).

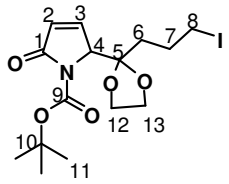
Elemental analysis: Calculated for $C_{15}H_{22}NO_5$: C: 54.30%; H: 6.68%; N: 4.22%. Found: C: 53.60%; H: 6.52%; N: 4.08%.

tert-butyl 2-(2-(3-iodopropyl)-1,3-dioxolan-2-yl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate 6.058



$C_{15}H_{22}INO_5$
M.W.: 423,24

In a 25-mL round-bottomed flask, 769 mg of orthoester (2.7 mmol, 1.6 eq.) are dissolved in 1 mL of dichloromethane and cooled to 0ºC. To this solution are added 321 mg of zinc chloride (2.3 mmol, 1.4 eq.), and subseq.uently 500 mg of TBSOP (1.68 mmol, 1 eq.) are introduced dropwise. Stirring is continued for 30 minutes, after which 3 mL of a saturated aqueous solution of $NaHCO_3$ are added. After phase separation, the aqueous layer is extracted with 3 x 5 mL of dichloromethane. The combined organic fractions are dried (Na_2SO_4) and concentrated under reduced pressure. The resulting solid is washed with 20 mL of heptane and then dissolved in 5 mL of dichloromethane. 5 mL of 1M KOH are then added and the biphasic mixture is slowly stirred (without allowing phase mixture) overnight. After 15 hours stirring, phase separation and removal of the organic solvent affords 512 mg (72%) of the condensation product.



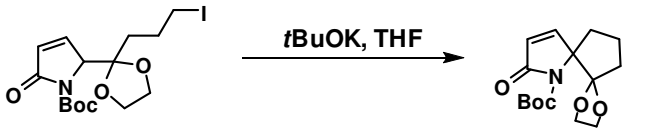
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.49 (s, 9H, H-11), 1.52-2.00 (m, 4H, H-6 and H-7), 3.00-3.20 (m, 2H, H-8), 3.80-4.05 (m, 4H, H-12 and H-13), 4.82 (s, 1H, H-4), 6.08 (dd, 1H, *J* = 6.0, 1.5 Hz, H-2), 7.08 (dd, 1H, *J* = 6.1, 2.2 Hz, H-3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 6.28 (C-8), 26.9, 35.0 (C-6 and C-7), 28.0 (C-11), 65.5, 66.0, 66.1 (C-4, C-12 and C-13), 83.1 (C-10), 109.9 (C-5), 127.5 (C-2), 147.7 (C-3), 149.5 (C-9), 169.8 (C-1).

IR (film, cm^{-1}): 3004, 2987 (C-H), 1774 (sh, C=O), 1731 (C=O), 1275, 1259, 750.

MS (ESI+ev): *m/z* (%): 446 (21) $[M+Na]^{+\cdot}$, 241 (10).

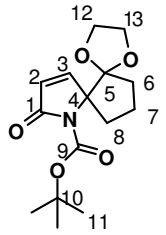
7-*tert*-butyl-7-aza-1,4-dioxadispiro[4.0.4.3]tridecan-9-en-8-one carboxylate 6.075



$C_{15}H_{21}NO_5$
M.W.: 295,33

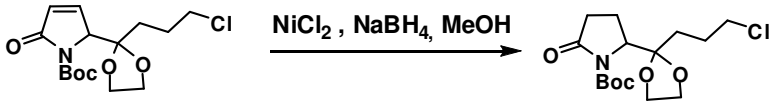
In a 25-mL round-bottomed flask 100 mg (0.24 mmol, 1 eq.) of the iodinated butenolide are dissolved in 3 mL of THF and cooled to 0ºC. To this solution are added 37 mg of *t*BuOK (0.33 mmol, 1.4 eq.) at once. The bright yellow mixture is stirred at the same temperature for 30 minutes, at which point TLC-analysis shows complete conversion of the starting material (NB: although both starting material and product have similar Rf values, TLC development with Vanillin provides differently coloured stains and allows a correct evaluation of the end-point for this reaction). At this stage, 5 mL of a saturated aqueous solution of NH_4Cl are added to quench the reaction. After phase separation, the aqueous layer is extracted with 3 x 10 mL of diethylether. The combined organic fractions are dried (Na_2SO_4)

and evaporated under reduced pressure. The residue is purified by flash chromatography (silica, PE/AcOEt 2:1), affording 60 mg (86%) of the azaspirocycle.



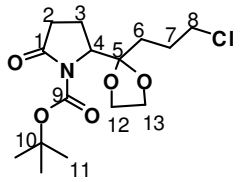
^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 1.56 (s, 9H, H-11), 1.65-2.00 (m, 4H, H-6 and H-7), 2.18-2.26 (m, 1H, H-8), 2.80-2.87 (m, 1H, H-8'), 3.67-3.91 (m, 4H, H-12 and H-13), 5.88 (d, J = 6.0 Hz, H-2), 7.17 (d, J = 6.0 Hz, H-3). ^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 21.1 (C-7), 28.3 (C-11), 32.3, 37.8 (C-6 and C-8), 64.6, 65.8 (C-12 and C-13), 77.9 (C-4), 82.8 (C-10), 117.9 (C-5), 121.6 (C-2), 150.3 (C-9), 153.4 (C-3), 170.3 (C-1).

***tert*-butyl 2-(2-(3-chloropropyl)-1,3-dioxolan-2-yl)-5-oxo-2,5-tetrahydro-1H-pyrrole-1-carboxylate 6.102**



$C_{15}H_{24}ClNO_5$
M.W.: 333,81

Method B (Section 5.8.1) for the reduction of spirobutenolides was employed. Starting from 103 mg of condensation adduct, 95 mg of the saturated lactam (92%) are obtained.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.50 (s, 9H, H-11), 1.60-2.00 (m, 4H, H-6 and H-7), 2.00-2.06 (m, 2H, H-3), 2.35 (dm, 1H, *J* = 8.4 Hz, H-2), 2.45-2.65 (m, 1H, H-2'), 3.48-3.56 (m, 2H, H-8), 3.91-4.04 (m, 4H, H-12 and H-13), 4.37 (d, 1H, *J* = 8.5 Hz, H-4).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 20.2 (C-7), 26.5 (C-6), 27.8 (C-11), 31.9, 32.9 (C-2 and C-3), 44.8 (C-8), 61.2 (C-4), 65.5, 66.0 (C-12 and C-13), 82.4 (C-10), 111.8 (C-5), 149.9 (C-9), 174.9 (C-1).

IR (film, cm^{-1}): 2960 (C-H), 1774 (sh, C=O), 1731 (C=O), 1151.

MS (ESI+ev): *m/z* (%): 358 (34) [*M+Na for* ^{37}Cl]$^{+\cdot}$, 279 (6), 234 (11).

9.10. Annelations of silylated acyloins and chemistry of cyclobutanones (Chapter 7)

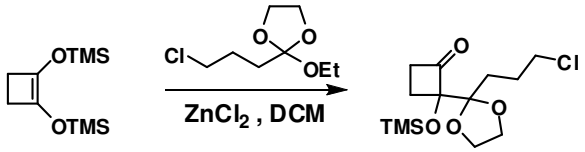
9.10.1. General procedures

Method A: Baeyer-Villiger expansion of spiroethers

To a solution of spiroether (450 mg, 2.3 mmol, 1 eq.) in CH_2Cl_2 (23 mL) are sequentially added in one portion Li_2CO_3 (50 mg, 0.68 mmol, 0.3 eq.) and 70-75% *m*-CPBA (847 mg, 3.45 mmol, 1.5 eq.) and the mixture is stirred at room temperature until TLC indicates complete conversion. At this point, the reaction is quenched by adding 10 mL of a saturated $NaHCO_3$ solution and the aqueous layer is extracted with 3 x 15 mL of CH_2Cl_2. After drying ($MgSO_4$) and removal of the solvent under reduced pressure, short-path flash chromatography of the residue affords the spirolactone in quantitative yield.

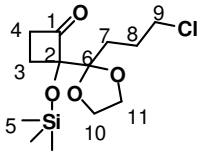
9.10.2. Condensations with silylated acyloins and ring-expansions

2-(2-(3-chloropropyl)-1,3-dioxolan-2-yl)-2-(trimethylsilyloxy) cyclobutanone 7.120



$C_{13}H_{23}ClO_4Si$
M.W.: 306,86

In a 25-mL round-bottomed flask, 1.2 g of orthoester (6 mmol, 1.5 eq.) are dissolved in 10 mL of dichloromethane. To this solution are added seq.uentially 1.0 mL of 1,2-bis-trimethylsilyloxycyclobutene (4 mmol, 1 eq.) and 400 mg of zinc chloride (2.8 mmol, 0.7 eq.) at room temperature. The resulting mixture is stirred for 14 hours at room temperature, at which point 10 mL of an aqueous saturated sodium bicarbonate solution are added. After phase separation, the aqueous layer is extracted by 3 x 10 mL of dichloromethane. The combined organic fractions are dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue can be directly used in the cyclisation step. It can also be purified by flash chromatography (silica, PE/AcOEt 9:1) to afford 0.98 g (80%) of the condensation adduct (Rf = 0.80 in PE/AcOEt 2:1).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 0.13 (s, 9H, H-5), 1.79-1.96 (m, 5H, H-7, H-8 and H-3), 2.35 (dt, 1H, *J* = 11.4, 5.7 Hz, H-3'), 2.65-2.91 (m, 2H, H-4), 3.49-3.53 (m, 2H, H-9), 3.93-4.05 (m, 4H, H-10 and H-11).

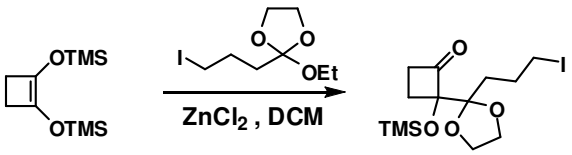
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 1.54 (C-5), 25.6, 26.2 (C-3 and C-8), 31.2 (C-7), 41.5 (C-4), 45.3 (C-9), 66.0, 66.3 (C-10 and C-11), 96.6 (C-2), 111.5 (C-6), 210.4 (C-1).

IR (film, cm^{-1}): 2960, 2898, 2856 (C-H), 1786 (sh, C=O), 1679, 1444, 1389, 1313, 1249, 1170, 1054.

MS (APCI+ev): *m/z* (%): 307 (35) $[M+H]^{+\cdot}$, 291 (15), 263 (25), 245 (65), 217 (100), 175 (70), 145 (10).

HRMS (ESI): Calculated for $C_{13}H_{23}O_4NaSiCl$ [*M+Na*]: 329.0952. Found: 329.0946.

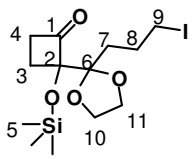
2-(2-(3-iodopropyl)-1,3-dioxolan-2-yl)-2-(trimethylsilyloxy) cyclobutanone 7.123



$C_{13}H_{23}IO_4Si$
M.W.: 398,31

In a 10-mL round-bottomed flask, 0.86 g of iodinated orthoester (3 mmol, 1.5 eq.) are dissolved in 4 mL of dichloromethane. To this solution are added seq.uentially 0.5 mL of 1,2-bis-trimethylsilyloxycyclobutene (2 mmol, 1 eq.) and 200 mg of zinc chloride (1.4 mmol, 0.7 eq.) at room temperature. The resulting mixture is stirred for 14 hours at room temperature, at which point 6 mL of an aqueous saturated sodium bicarbonate solution are added. After phase separation, the aqueous layer is extracted by 3 x 6 mL of dichloromethane. The combined organic fractions are dried ($MgSO_4$) and concentrated under reduced pressure. The crude

residue is purified by flash chromatography (silica, PE/AcOEt 9:1) to afford 0.40 g (51%) of the condensation adduct (Rf = 0.85 in PE/AcOEt 2:1).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 0.14 (s, 9H, H-5), 1.83-1.96 (m, 5H, H-7, H-8 and H-3), 2.35 (dt, 1H, *J* = 11.4, 5.9 Hz, H-3'), 2.65-2.90 (m, 2H, H-4), 3.15-3.27 (m, 2H, H-9), 3.94-4.04 (m, 4H, H-10 and H-11).

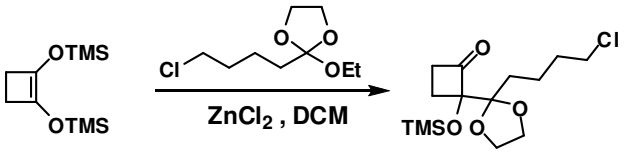
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 1.54 (C-5), 7.10 (C-9), 25.6, 27.2 (C-3 and C-8), 34.6 (C-7), 41.6 (C-4), 66.0, 66.3 (C-10 and C-11), 96.5 (C-2), 111.3 (C-6), 210.3 (C-1).

IR (film, cm^{-1}): 2960, 2898 (C-H), 1786 (sh, C=O), 1645, 1440, 1363.

MS (CI+ev): *m/z* (%): 399 (15) $[M+H]^{+\cdot}$, 267 (45), 237 (10), 155 (10), 73 (100).

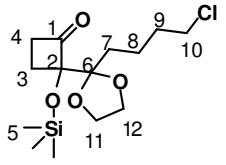
HRMS (ESI): Calculated for $C_{13}H_{23}O_4NaSiI$ [*M+Na*]: 421.0308. Found: 421.0312.

2-(2-(4-chlorobutyl)-1,3-dioxolan-2-yl)-2-(trimethylsilyloxy) cyclobutanone 7.124



$C_{14}H_{25}ClO_4Si$
M.W.: 320,88

In a 10-mL round-bottomed flask, 0.63 g of chlorinated orthoester (3 mmol, 1.5 eq.) are dissolved in 4 mL of dichloromethane. To this solution are added seq.uentially 0.5 mL of 1,2-bis-trimethylsilyloxycyclobutene (2 mmol, 1 eq.) and 200 mg of zinc chloride (1.4 mmol, 0.7 eq.) at room temperature. The resulting mixture is stirred for 14 hours at room temperature, at which point 6 mL of an aqueous saturated sodium bicarbonate solution are added. After phase separation, the aqueous layer is extracted by 3 x 6 mL of dichloromethane. The combined organic fractions are dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue is purified by flash chromatography (silica, PE/AcOEt 9:1) to afford 0.39 g (61%) of the condensation adduct (Rf = 0.90 in PE/AcOEt 2:1).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 0.13 (s, 9H, H-5), 1.41-1.52 (m, 1H, H-8), 1.70-1.82 (m, 6H, H-7, H-8', H-9 and H-3), 2.35 (dt, 1H, *J* = 11.8, 5.7

Hz, H-3'), 2.64-2.90 (m, 2H, H-4), 3.50 (t, 2H, *J* = 6.6 Hz, H-10), 3.96-4.08 (m, 4H, H-11 and H-12).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 1.60 (C-5), 20.1 (C-8), 25.7 (C-3), 32.8, 33.0 (C-7 and C-9), 41.6 (C-4), 45.1 (C-10), 66.2, 66.5 (C-11 and C-12), 96.6 (C-2), 111.8 (C-6), 210.6 (C-1).

IR (film, cm^{-1}): 2957, 2920 (C-H), 1785 (sh, C=O), 1650, 1621, 1460, 1360.

MS (CI+ev): *m/z* (%): 321 (15) $[M]^{+\cdot}$, 219 (5), 189 (20), 159 (5), 113 (10), 73 (90).

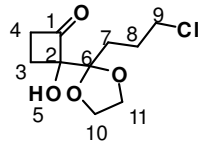
HRMS (ESI): Calculated for $C_{14}H_{25}O_4NaSiCl$ [*M+Na*]: 343.1108. Found: 343.1113.

2-(2-(3-chloropropyl)-1,3-dioxolan-2-yl)-2-hydroxycyclobutanone 7.125

$C_{10}H_{15}ClO_4$
M.W.: 234,68

In a 10 mL round-bottomed flask, 75 mg of the condensation adduct (0.24 mmol, 1 eq.) are dissolved in 1 mL of THF and cooled to 0ºC. To this solution are added dropwise 0.61 mL of TBAF (1M solution in THF, 0.61 mmol, 2.5 eq.). Stirring is continued at the same temperature for 1 hour, at which point TLC-analysis indicated complete consumption of the starting material. At this stage, 2 mL of water are added to quench the reaction. The mixture is extracted with 3 x 5 mL of ethyl acetate. The combined organic

fractions are dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue is filtered through a pad of silica (PE/AcOEt 6:1) to afford 40 mg (70%) of the deprotected alcohol (Rf = 0.25 in PE/AcOEt 2:1).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.80-2.05 (m, 5H, H-7, H-8 and H-3), 2.40 (dt, 1H, *J* = 11.5, 5.8 Hz, H-3'), 2.77-3.01 (m, 2H, H-4), 3.10 (br s, 1H, H-5), 3.49-3.53 (m, 2H, H-9), 3.93-3.97 (m, 3H, H-10 and H-11), 4.00-4.13 (m, 1H, H-10' or H-11').

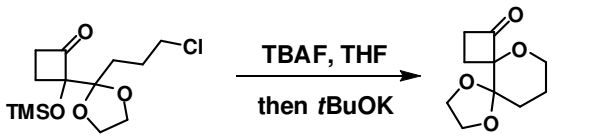
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 23.5, 25.8 (C-3 and C-8), 30.6 (C-7), 42.4 (C-4), 45.1 (C-9), 66.1, 66.8 (C-10 and C-11), 94.6 (C-2), 111.2 (C-6), 210.5 (C-1).

IR (film, cm^{-1}): 3438 (br, OH), 2964, 2929, 2871 (C-H), 1774 (sh, C=O), 1479, 1446, 1313, 1255, 1199.

MS (CI+ev): *m/z* (%): 235 (55) $[M]^{+\cdot}$, 217 (10), 191 (15), 175 (100), 145 (20), 113 (50), 81 (60).

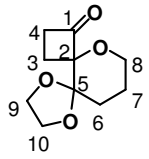
HRMS (ESI): Calculated for $C_{10}H_{15}O_4NaCl$ [*M+Na*]: 257.0557. Found: 257.0562.

1,4,10-trioxa-dispiro[4.0.3.4]decan-7-one 7.126



$C_{10}H_{14}O_4$
M.W.: 198,22

In a 50 mL round-bottomed flask, 500 mg (1.6 mmol, 1 eq.) of the condensation adduct are dissolved in 16 mL of THF and cooled to 0ºC. To this solution are added dropwise 1.8 mL of TBAF (1M solution in THF, 1.8 mmol, 1.1 eq.). After 1 hour stirring, 240 mg of *t*BuOK (2.2 mmol, 1.3 eq.) are added at once and the resulting suspension is stirred from 0ºC to room temperature over 3 hours. 10 mL of a saturated aqueous NH_4Cl solution are added to quench the reaction. The mixture is extracted by 3 x 20 mL of diethyl ether. The combined organic fractions are dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue is purified by flash chromatography (PE/AcOEt 6:1) to afford 260 mg (80%) of the spiroether (Rf = 0.45 in PE/AcOEt 2:1).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.76-2.02 (m, 5H, H-6, H-7 and H-3), 2.29 (apparent q, 1H, *J* = 9.6 Hz, H-3'), 2.85 (t, 2H, *J* = 10.5 Hz, H-4), 3.69 (dm, 1H, *J* = 11.4 Hz, H-8), 4.00 (br s, 5 H, H-8', H-9 and H-10).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 22.1, 24.0 (C-3 and C-7), 30.5 (C-6), 42.1 (C-4), 64.4, 65.2, 65.4 (C-8, C-9 and C-10), 96.3 (C-2), 105.3 (C-5), 208.1 (C-1).

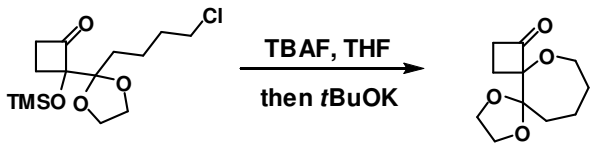
IR (film, cm^{-1}): 3053, 2985 (C-H), 2304, 1784 (C=O), 1421, 1263.

MS (CI+ev): *m/z* (%): 199 (70) $[M+H]^{+\cdot}$, 157 (75), 115 (100), 99 (25), 29 (75).

HRMS (ESI): Calculated for $C_{10}H_{14}O_4Na$ [*M+Na*]: 221.0790. Found: 221.0783.

Elemental analysis: Calculated for $C_{10}H_{14}O_4$: C: 60.59%; H: 7.12%. Found: C: 60.37%; H: 7.16%.

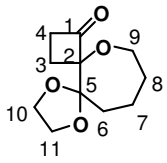
1,4,10-trioxa-dispiro[4.0.3.5]undecan-7-one 7.127



$C_{11}H_{16}O_4$
M.W.: 212,24

In a 10 mL round-bottomed flask, 100 mg (0.31 mmol, 1 eq.) of the condensation adduct are dissolved in 3 mL of THF and cooled to 0ºC. To this solution are added dropwise 0.34 mL of TBAF (1M solution in THF, 0.34 mmol, 1.1 eq.). After 1 hour stirring, 45 mg of *t*BuOK (0.40 mmol, 1.3 eq.) are added at once and the resulting suspension is stirred from 0ºC to room temperature over 3 hours. 3 mL of a saturated aqueous NH_4Cl solution are added to quench the reaction. The mixture is extracted by 3 x 7 mL of

diethyl ether. The combined organic fractions are dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue is purified by flash chromatography (PE/AcOEt 9:1) to afford 30 mg (50%) of the spiroether (Rf = 0.50 in PE/AcOEt 2:1).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.61-1.64 (m, 4H, H-7 and H-8), 1.73-1.95 (m, 3H, H-6 and H-3), 2.29 (dt, 1H, *J* = 11.4, 6.6 Hz, H-3'), 2.79-2.91 (m, 2H, H-4), 3.69 (m, 1H , H-9), 3.94 (br s, 5H, H-9', H-10 and H-11).

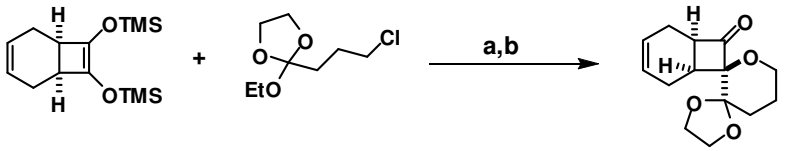
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 20.5, 22.9 (C-7 and C-8), 29.9 (C-3), 34.6 (C-6), 42.5 (C-4), 64.6, 65.1, 66.4 (C-9, C-10 and C-11), 99.3 (C-2), 110.9 (C-5), 207.0 (C-1).

IR (film, cm^{-1}): 3043, 2950 (C-H), 1785 (C=O), 1625, 1410, 1263.

MS (CI+ev): *m/z* (%): 213 (20) $[M+H]^{+\cdot}$, 195 (10), 169 (20), 151 (100), 123 (10), 95 (5).

HRMS (ESI): Calculated for $C_{11}H_{16}O_4Na$ [*M+Na*]: 235.0946. Found: 235.0943.

Spirocyclic ether 7.141

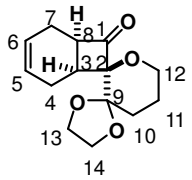


$C_{14}H_{18}O_4$
M.W.: 250,29

a) $ZnCl_2$, DCM; b) TBAF, THF, 0ºC to rt

In a 10-mL round-bottomed flask, 0.30 g of orthoester (1.5 mmol, 1.5 eq.) are dissolved in 3 mL of dichloromethane. To this solution are added seq.uentially 0.28 g of the bicyclic acyloin (1 mmol, 1 eq.) and 96 mg of zinc chloride (0.7 mmol, 0.7 eq.) at room temperature. The resulting mixture is stirred for 14 hours at room temperature, at which point 5 mL of an aqueous saturated sodium bicarbonate solution are added. After phase separation, the aqueous layer is extracted by 3 x 10 mL of dichloromethane. The combined organic fractions are dried ($MgSO_4$) and concentrated under reduced pressure.

The crude residue is dissolved in 7 mL of THF and cooled to 0ºC. To this solution are added 0.77 mL of TBAF (1M solution in THF, 0.77 mmol, 1.1 eq.) and the resulting mixture is allowed to gradually reach room temperature overnight. After 12 hours stirring, 10 mL of a saturated aqueous NH_4Cl solution are added to quench the reaction. The mixture is extracted by 3 x 10 mL of diethyl ether. The combined organic fractions are dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue is purified by flash chromatography (PE/AcOEt 9:1) to afford 87 mg (35%) of the spiroether (Rf = 0.50 in PE/AcOEt 2:1).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.70-1.91 (m, 4H, H-10 and H-11), 2.01-2.21 (m, 2H, H-7 and H-4), 2.38-2.46 (m, 2H, H-7' and H-4'), 2.81 (dtd, 1H, *J* = 10.0, 2.9, 2.7 Hz, H-3), 3.34 (dtd, 1H, *J* = 9.6, 3.1, 2.5 Hz, H-8), 3.74-3.81 (m, 1H, H-12), 4.04-4.18 (m, 5H, H-12', H-13 and H-14), 5.73-5.84 (m, 2H, H-5 and H-6).

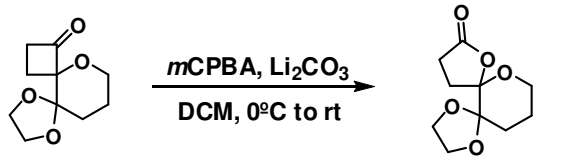
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 19.1, 20.7 (C-4 and C-7), 24.0 (C-11), 30.5 (C-3), 30.7 (C-10), 53.0 (C-8), 65.0, 65.2, 65.3 (C-12, C-13 and C-14), 93.4 (C-2), 105.5 (C-9), 125.9, 127.6 (C-5 and C-6), 213.2 (C-1).

IR (film, cm^{-1}): 3361, 2956, 2921, 2852 (C-H), 1771 (C=O), 1660, 1465, 1166.

MS (APCI+ev): *m/z* (%): 215 (10) $[M+H]^{+\cdot}$, 233 (40), 223 (25), 207 (60), 189 (100), 161 (25), 151 (35), 135 (10), 99 (5).

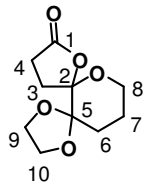
HRMS (ESI): Calculated for $C_{14}H_{18}O_4Na$ [*M+Na*]: 273.1103. Found: 273.1113.

1,4,7,11-tetraoxa-dispiro[4.0.4.4]decan-8-one 7.143



$C_{10}H_{14}O_5$
M.W.: 214,22

Method A: Starting from 450 mg of the spiroether. After workup and filtration over a pad of silica, 455 mg (100%) of the spirolactone are obtained.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.62-1.65 (m, 1H, H-7), 1.76-1.80 (m, 1H, H-7'), 1.91-2.02 (m, 3H, H-6 and H-3), 2.27-2.38 (m, 1H, H-3'), 2.40-2.54 (m, 1H, H-4), 2.60-2.71 (m, 1H, H-4'), 3.70-3.74 (m, 1H, H-8), 3.85-4.09 (m, 5H, H-8', H-9 and H-10).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 23.5 (C-7), 27.7, 28.3, 28.8 (C-3, C-4 and C-6), 62.3, 65.5, 65.6 (C-8, C-9 and C-10), 105.3 (C-2), 108.3 (C-5), 175.4 (C-1).

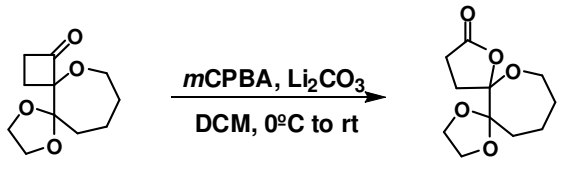
IR (film, cm^{-1}): 3114 (C-H), 2252, 1780 (C=O), 1683, 1647, 1263.

MS (APCI+ev): *m/z* (%): 215 (100) $[M+H]^+$, 197 (15), 187 (100), 143 (20), 73 (55).

HRMS (ESI): Calculated for $C_{10}H_{14}O_5Na$ [*M+Na*]: 237.0739. Found: 237.0739.

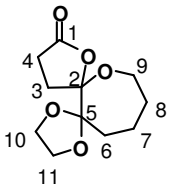
Elemental analysis: Calculated for $C_{10}H_{14}O_5$: C: 56.07%; H: 6.59%. Found: C: 56.30%; H: 6.70%.

1,4,7,11-tetraoxa-dispiro[4.0.5.4]undecan-8-one 7.144



$C_{11}H_{16}O_5$
M.W.: 228,24

Method A: Starting from 50 mg of the spiroether. After workup and filtration over a pad of silica, 52 mg (100%) of the spirolactone are obtained.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.63-2.02 (m, 7H, H-6, H-7, H-8 and H-3), 2.51-2.63 (m, 3H, H-3' and H-4), 3.70.3-81 (m, 2H, H-9 and H-10 or H-11), 3.92-4.08 (m, 3H, H-10 and H-11), 4.12-4.27 (m, 1H, H-9').

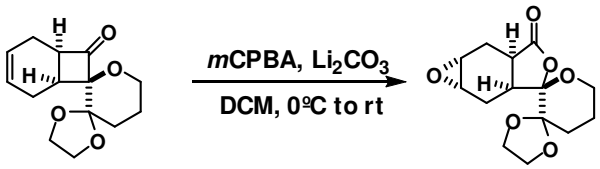
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 20.9 (C-7), 29.1, 29.5, 31.3 (C-4, C-6 and C-8), 33.6 (C-3), 64.5, 65.7, 66.4 (C-9, C-10 and C-11), 110.7 (C-2), 112.0 (C-5), 176.2 (C-1).

IR (film, cm^{-1}): 2985 (C-H), 2242, 1781 (C=O), 1683, 1635, 1263.

MS (APCI+ev): *m/z* (%): 229 (100) $[M+H]^{+\cdot}$, 211 (15), 167 (70), 157 (95), 139 (35), 111 (10), 73 (23).

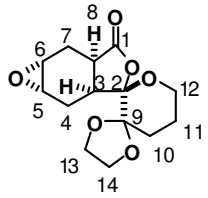
HRMS (ESI): Calculated for $C_{11}H_{16}O_5Na$ [*M+Na*]: 251.0895. Found: 251.0899.

Bicyclic epoxy-spirolactone 7.145



$C_{14}H_{18}O_6$
M.W.: 282,29

Method A: Starting from 45 mg of the spiroether. After workup and filtration over a pad of silica, 30 mg (60%) of the spirolactone are obtained.



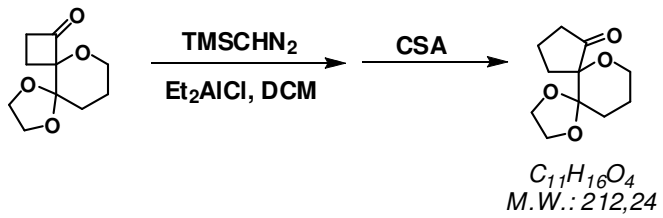
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.62-1.68 (m, 2H, H-11), 1.92-2.18 (m, 4H, H-4, H-7 and H-10), 2.27 (ddd, 1H, *J* = 15.9, 7.6, 1.5 Hz, H-4' or H-7'), 2.45 (ddd, 1H, *J* = 14.8, 7.8, 3.3 Hz, H-4' or H-7'), 2.63-2.72 (m, 1H, H-3), 2.79-2.89 (m, 1H, H-8), 3.17-3.24 (m, 2H, H-5 and H-6), 3.76-3.81 (m, 1H, H-12), 3.89-4.06 (m, 5H, H-12', H-13 and H-14).

^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 20.4 (C-11), 23.3, 23.8 (C-4 and C-7), 29.0 (C-10), 32.2 (C-3), 35.3 (C-8), 50.5, 50.7 (C-5 and C-6), 62.7 (C-12), 65.3, 65.5 (C-13 and C-14), 105.7 (C-2), 108.2 (C-9), 178.0 (C-1).

MS (APCI+ev): *m/z* (%): 282 (100) $[M+H]^{+\cdot}$, 265 (5), 239 (7), 221 (25), 193 (10).

HRMS (ESI): Calculated for $C_{14}H_{19}O_6$ [*M+1*]: 283.1182. Found: 283.1173.

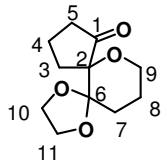
1,4,11-trioxa-dispiro[4.0.4.4]undecan-7-one 7.158



$C_{11}H_{16}O_4$
M.W.: 212,24

In a 10 mL round-bottomed flask are introduced 100 mg (0.5 mmol, 1 eq.) of the spirocyclobutanone and 2.5 mL of DCM. The solution is cooled to 0ºC and 0.6 mL of Et_2AlCl (1M solution in hexanes, 0.6 mmol, 1.2 eq.) are added, followed by 1.5 mL of TMS-diazomethane (2M solution in ether, 3 mmol, 6 eq.). The deep-orange solution is stirred during 4 hours while gradually warming to room temperature. The reaction is quenched by addition of 4 mL of an aqueous saturated $NaHCO_3$ solution. After phase separation, the aqueous layer is extracted with 3 x 10 mL of dichloromethane. The combined organic fractions are dried ($MgSO_4$) and concentrated under pressure to yield a residue.

This residue is dissolved in 2.5 mL of dichloromethane and 120 mg of CSA (0.54 mmol, 1.1 eq.) are added at once, which causes some foaming. The mixture is stirred for 2 hours at room temperature, at which point the solvents are removed under reduced pressure. The residue is purified by flash chromatography to afford 65 mg (65%) of the ring-expanded product.



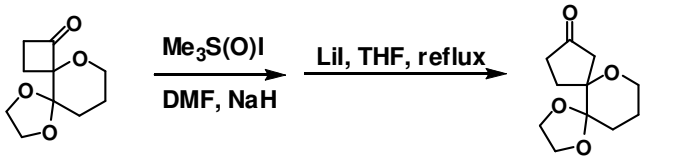
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.76-2.31 (m, 9H, H-3, H-4, H-5, H-7 and H-8), 2.39-2.45 (m, 1H, H-5'), 3.59-3.71 (m, 1H, H-9), 3.77 (dt, 1H, *J* = 11.5, 2.7 Hz, H-9'), 3.91-4.00 (m, 4H, H-10 and H-11).

^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 24.3, 24.4, 26.0 (C-3, C-4 and C-8), 31.2 (C-7), 38.5 (C-5), 61.6 (C-9), 65.0, 65.8 (C-10 and C-11), 86.8 (C-2), 106.9 (C-6), 214.5 (C-1).

IR (film, cm^{-1}): 2985 (C-H), 2242, 1736 (C=O), 1443, 1263.

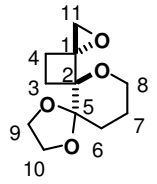
MS (APCI+ev): *m/z* (%): 213 (100) $[M+H]^{+\cdot}$, 195 (10), 183 (20), 151 (30), 123 (25), 113 (30), 99 (15).

1,4,11-trioxa-dispiro[4.0.4.4]undecan-8-one 7.180



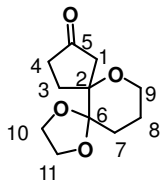
$C_{11}H_{16}O_4$
M.W.: 212,24

In a 25 mL round-bottomed flask, 24 mg of NaH (0.6 mmol, 1.2 eq.) are suspended in 4 mL of DMF. To this suspension are added 143 mg of trimethylsulfoxonium iodide (0.65 mmol, 1.3 eq.), upon which gas evolution is observed. The resulting mixture is stirred for 30 minutes and then cooled to 0ºC. Then, a solution of 110 mg of spirocyclobutanone (0.5 mmol, 1 eq.) dissolved in 1 mL of DMF is added dropwise and stirring is continued at 0ºC during 1 hour, at which point TLC-analysis indicates complete conversion. At this stage, 5 mL of water are added to quench the reaction. The mixture is extracted by 3 x 10 mL of diethylether. The combined organic fractions are dried ($MgSO_4$) and evaporated under reduced pressure, affording the crude spiroepoxide.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.63-1.91 (m, 5H, H-3, H-6 and H-7), 2.02-2.10 (m, 1H, H-3'), 2.16-2.34 (m, 2H, H-4), 2.62 (d, 1H, *J* = 5.5 Hz, H-11), 3.07 (d, 1H, *J* = 5.5 Hz, H-11'), 3.45-3.53 (m, 1H, H-8), 3.63-3.69 (m, 1H, H-8'), 3.91-4.22 (m, 4H, H-9 and H-10).

The crude spiroepoxide is dissolved in 10 mL of THF and 60 mg of lithium iodide (0.48 mmol, 1 eq.) are added. The mixture is heated at reflux for 3 hours. After removal of the solvent, the residue is directly purified by flash chromatography (PE/AcOEt 9:1, Rf = 0.30 in PE/AcOEt 1:1), affording 112 mg (70%) of the rearranged product.

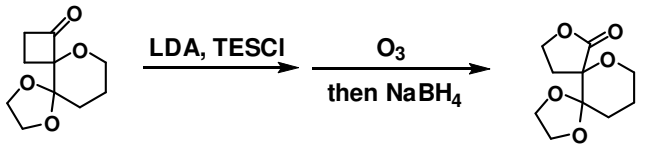


^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.69-1.85 (m, 4H, H-7 and H-8), 2.14-2.45 (m, 4H, H-3 and H-4), 2.49 (d, 2H, *J* = 3.1 Hz, H-1), 3.57-3.65 (m, 1H, H-9), 3.69-3.77 (m, 1H, H-9'), 3.97-4.03 (m, 4H, H-10 and H-11).

^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 24.2 (C-8), 27.6 (C-3), 29.6 (C-7), 36.3 (C-4), 44.7 (C-1), 61.6 (C-9), 65.1, 65.4 (C-10 and C-11), 84.9 (C-2), 107.1 (C-6), 216.5 (C-5).

IR (film, cm^{-1}): 2983 (C-H), 2242, 1730 (C=O), 1615, 1462.

1,4,8,11-tetraoxa-dispiro[4.0.4.4]decan-7-one 7.164

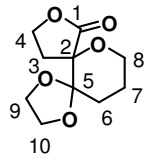


$C_{10}H_{14}O_5$
M.W.: 214,22

In a 25-mL round-bottomed flask, 100 mg of the spirocyclobutanone (0.5 mmol, 1 eq.) are dissolved in 10 mL of THF and cooled to -78ºC. To this solution are added dropwise 0.31 mL of LDA (2M solution in THF, 0.61 mmol, 1.2 eq.) and stirring is continued for 30 minutes at the same temperature. Then, 0.13 mL of TESCl (0.8 mmol, 1.6 eq.) dissolved in 1 mL of THF are added and the mixture is gradually allowed to reach room temperature. After 2 hours stirring, 3 mL of triethylamine are added followed by 5 mL of water. The mixture is extracted by 3 x 10 mL of diethyl ether. The combined organic fractions are dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude silyl enolether.

The residue is then dissolved in 10 mL of MeOH and cooled to -78ºC. A stream of ozone is bubbled through this solution for 15 minutes, at

which point the mixture turns blue. After repeatedly flushing with argon, 160 mg of sodium borohydride (2 mmol, 4 eq.) are added and the mixture is gradually allowed to reach room temperature with continued stirring. After 1 hour stirring, 10 mL of ethyl acetate are added followed by 1 mL of a 1M solution of HCl. Upon completion of the reaction by TLC-analysis, the mixture is extracted by 3 x 7 mL of ethyl acetate. The combined organic fractions are dried ($MgSO_4$) and concentrated. The residue is purified by flash chromatoraphy (silica, PE/AcOEt 1:1, Rf = 0.50), affording 56 mg (60%) of the "anti-Baeyer-Villiger" lactone.



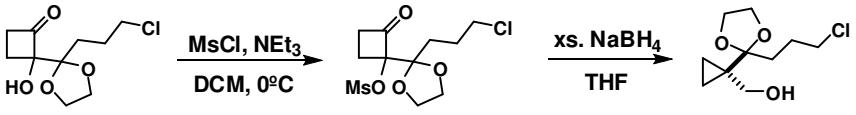
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.83-2.22 (m, 5H, H-3, H-6 and H-7), 2.30-2.40 (m, 1H, H-6'), 2.52 (td, 1H, *J* = 13.6, 8.0 Hz, H-3'), 3.69-3.74 (m, 1H, H-8), 3.97-4.08 (m, 5H, H-8', H-9 and H-10), 4.19-4.36 (m, 2H, H-4).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 23.6 (C-7), 28.5 (C-6), 31.6 (C-3), 63.4, 65.2, 65.3, 65.5 (C-4, C-8, C-9 and C-10), 80.1 (C-2), 105.9 (C-5), 172.8 (C-1).

IR (film, cm^{-1}): 3114, 2987 (C-H), 1780 (C=O), 1645, 1263.

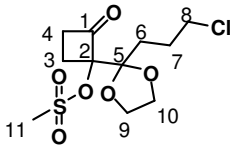
MS (APCI+ev): *m/z* (%): 215 (75) $[M+H]^+$, 187 (100), 169 (30), 143 (7), 113 (10).

(1-(2-(3-chloropropyl)-1,3-dioxolan-2-yl)cyclopropyl)methanol 7.184



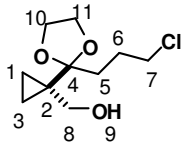
$C_{10}H_{17}ClO_3$
M.W.: 220,69

In a 10 mL round-bottomed flask, 77 mg of spirocyclobutanone (0.33 mmol, 1 eq.) are dissolved in 2 mL of dichloromethane and cooled to 0ºC. To this solution are added seq.uentially 0.9 mL of triethylamine (0.66 mmol, 2 eq.) and 0.04 mL of mesyl chloride (0.5 mmol, 1.5 eq.). The mixture is stirred from 0ºC to room temperature during 1 hour. Addition of 3 mL of a saturated aqueous solution of $NaHCO_3$ to quench the reaction is followed by extraction with 3 x 7 mL of dichloromethane. The combined organic fractions are dried ($MgSO_4$) and evaporated under reduced pressure, affording the crude mesylate.



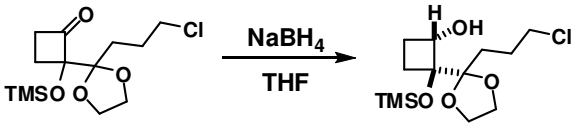
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.82-2.02 (m, 4H, H-6 and H-7), 2.47-2.57 (m, 1H, H-3), 2.61-2.72 (m, 1H, H-3'), 2.81-2.96 (m, 1H, H-4), 3.03-3.16 (m, 1H, H-4'), 3.26 (s, 3H, H-11), 3.54-3.60 (m, 2H, H-8), 3.95-4.20 (m, 4H, H-9 and H-10).

The crude mesylate is dissolved in 3 mL THF and cooled to 0ºC. 66 mg of sodium borohydride (2 mmol, 6 eq.) are then added to this mixture, upon which some foaming occurs. After 1 hour stirring at room temperature, the reaction is quenched by addition of 3 mL of an aqueous saturated NH_4Cl solution. The mixture is extracted by 3 x 10 mL of ethyl acetate. The combined organic fractions are dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue is purified by flash chromatography (PE/AcOEt 9:1) to afford 58 mg (80%) of the cyclopropane (Rf = 0.33 in PE/AcOEt 2:1).



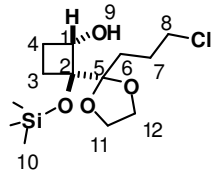
^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 0.42 (dt, 2H, *J* = 3.1, 1.0 Hz, H-1 and H-3), 0.67 (dt, 2H, *J* = 3.1, 1.0 Hz, H-1' and H-3), 1.87-1.91 (m, 2H, H-6), 2.00-2.03 (m, 2H, H-5), 2.87 (t, 1H, *J* = 3.0 Hz, H-9), 3.51 (d, 2H, *J* = 2.9 Hz, H-8), 3.56 (t, 3H, *J* = 4.0 Hz, H-7), 3.93-4.02 (m, 4H, H-10 and H-11).
^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 7.5 (C-1 and C-3), 12.7 (C-2), 26.7 (C-6), 33.7 (C-5), 45.2 (C-7), 65.7 (C-10 and C-11), 68.2 (C-8), 112.0 (C-4).
IR (film, cm^{-1}): 3940 (br, OH), 2240, 1615, 1443, 1263.
MS (APCI+ev): *m/z* (%): 203 (100) $[M\text{-}H_2O]^{+\cdot}$, 172 (50), 149 (25), 123 (10).

2-(2-(3-chloropropyl)-1,3-dioxolan-2-yl)-2-(trimethylsilyloxy) cyclobutanol 7.191



$C_{13}H_{25}ClO_4Si$
M.W.: 308,87

In a 10-mL round-bottomed flask, 100 mg (0.33 mmol, 1 eq.) of the condensation adduct are dissolved in 3 mL of THF and cooled to 0ºC. To the resulting solution are added 26 mg (0.66 mmol, 2 eq.) of sodium borohydride. The reaction mixture is stirred for 16 hours while gradually reaching room temperature. At this stage, 3 mL of an aqueous saturated NH_4Cl solution. The mixture is extracted by 3 x 10 mL of ethyl acetate. The combined organic fractions are dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue is purified by flash chromatography (PE/AcOEt 4:1) to afford 90 mg (90%) of the alcohol (Rf = 0.40).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 0.16 (s, 9H, H-10), 1.46-1.68 (m, 2H, H-3), 1.81-2.00 (m, 6H, H-4, H-6 and H-7), 2.68 (d, 1H, *J* = 11.0 Hz, H-9), 3.53 (t, 2H, *J* = 6.9Hz, H-8), 4.06-4.18 (m, 5H, H-1, H-11 and H-12).

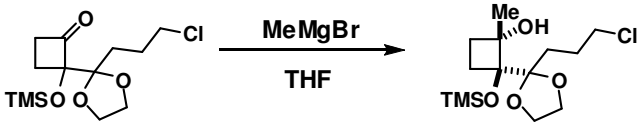
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 1.84 (C-10), 25.4, 25.8, 26.8 (C-3, C-4 and C-7), 33.2 (C-6), 45.4 (C-8), 66.3, 66.6 (C-11 and C-12), 77.4 (C-1), 86.0 (C-2), 113.5 (C-5).

IR (film, cm^{-1}): 3940 (br, OH), 1643, 1447, 1263.

MS (APCI+ev): *m/z* (%): 309 (10) $[M+H]^{+\cdot}$, 291 (10), 247 (15), 219 (65), 201 (20), 175 (100), 157 (15).

Elemental analysis: Calculated for $C_{13}H_{25}O_5ClSi$: C: 50.55%; H: 8.16%. Found: C: 50.61%; H: 8.63%.

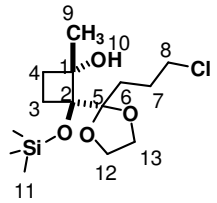
2-(2-(3-chloropropyl)-1,3-dioxolan-2-yl)-1-methyl-2-(trimethylsilyloxy) cyclobutanol 7.192



$C_{14}H_{27}ClO_4Si$
M.W.: 322,90

In a 10-mL round-bottomed flask, 100 mg (0.33 mmol, 1 eq.) of the condensation adduct are dissolved in 3 mL of THF and cooled to 0ºC. To the resulting solution are added 0.33 mL (3M solution in ether, 1.0 mmol, 3 eq.) of methylmagnesium bromide. The reaction mixture is stirred for 1 hour while gradually reaching room temperature. At this stage, 3 mL of an aqueous saturated NH_4Cl solution. The mixture is extracted by 3 x 10 mL of ethyl acetate. The combined organic fractions are dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue is purified by flash

chromatography (PE/AcOEt 4:1) to afford 105 mg (99%) of the alcohol (Rf = 0.63 in PE/AcOEt 1:1).



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 0.13 (s, 9H, H-11), 1.23 (s, 3H, H-9), 1.53-1.68 (m, 2H, H-6 and H-7), 1.79-1.89 (m, 5H, H-3, H-4, H-6' and H-7'), 2.09-2.20 (m, 1H, H-4'), 3.17 (s, 1H, H-10), 3.50 (dt, 2H, *J* = 6.9, 3.8 Hz, H-8), 4.08-4.14 (m, 4H, H-12 and H-13).

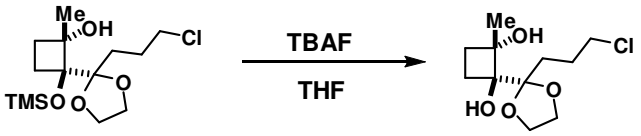
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 1.86 (C-11), 22.6 (C-9), 25.7 (C-7), 26.7 (C-3), 33.0, 33.5 (C-4 and C-6), 45.1 (C-8), 66.4, 66.6 (C-12 and C-13), 78.6 (C-1), 86.7 (C-2), 114.1 (C-5).

IR (film, cm^{-1}): 3940 (br, OH), 1643, 1447, 1263.

MS (APCI+ev): *m/z* (%): 323 (15) $[M+H]^{+\cdot}$, 305 (5), 279 (5), 261 (15), 233 (65), 189 (15), 175 (100), 151 (12), 113 (17).

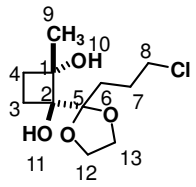
HRMS (ESI): Calculated for $C_{14}H_{27}O_4NaSiCl$ [*M+Na*]: 345.1265. Found: 345.1278.

1-(2-(3-chloropropyl)-1,3-dioxolan-2-yl)-2-methylcyclobutane-1,2-diol 7.193a



$C_{11}H_{19}ClO_4$
M.W.: 250,72

In a 10 mL round-bottomed flask, 42 mg of the tertiary alcohol (0.13 mmol, 1 eq.) are dissolved in 1 mL of THF and cooled to 0ºC. To this solution are added dropwise 0.614 mL of TBAF (1M solution in THF, 0.14 mmol, 1.1 eq.). Stirring is continued at the same temperature for 1 hour, at which point TLC-analysis indicated complete consumption of the starting material. At this stage, the solvent is evaporated under reduced pressure and the residue is filtered through a pad of silica (PE/AcOEt 1:1) to afford 29 mg (95%) of the deprotected alcohol (Rf = 018).



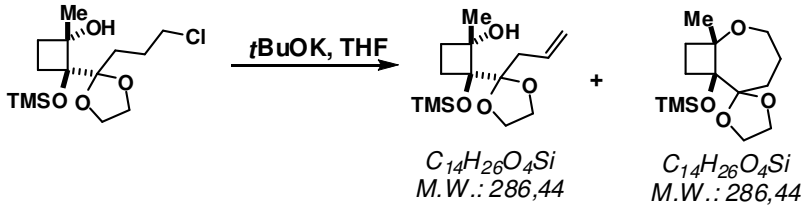
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.31 (s, 3H, H-9), 1.45-2.20 (m, 8H, H-3, H-4, H-6 and H-7), 3.13 (br s, 1H, H-10), 3.52 (t, 2H, *J* = 6.9 Hz, H-8), 4.06-4.17 (m, 4H, H-12 and H-13).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 22.3 (C-9), 26.0 (C-7), 26.7 (C-3), 32.4, 32.8 (C-4 and C-6), 45.2 (C-8), 66.4, 66.8 (C-12 and C-13), 77.8 (C-1), 84.0 (C-2), 113.3 (C-5).

MS (CI+ev): *m/z* (%): 233 (100) $[M\text{-}H_2O]^{+\cdot}$, 215 (20), 189 (60), 175 (100), 153 (65).

Elemental analysis: Calculated for $C_{11}H_{19}O_4Cl$: C: 52.70%; H: 7.64%. Found: C: 52.62%; H: 7.96%.

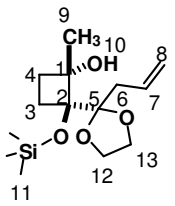
2-(2-allyl-1,3-dioxolan-2-yl)-1-methyl-2-(trimethylsilyloxy)cyclobutanol 7.196



$C_{14}H_{26}O_4Si$
M.W.: 286,44

$C_{14}H_{26}O_4Si$
M.W.: 286,44

In a 10-mL round-bottomed flask, 60 mg (0.18 mmol, 1 eq.) of the tertiary alcohol are dissolved in 2.5 mL of THF and cooled to 0ºC. To this solution are added 62 mg of *t*BuOK (0.56 mmol, 3 eq.). The mixture becomes an orange suspension. Stirring is continued as the suspension is allowed to gradually reach room temperature overnight. After 16 hours stirring, 3 mL of an aqueous saturated NH_4Cl solution are added to quench the reaction. The mixture is extracted by 3 x 10 mL of ethyl acetate. The combined organic fractions are dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue is purified by flash chromatography (PE/AcOEt 9:1) to afford 42 mg (84%) of the alkene (Rf = 0.60 in PE/AcOEt 4:1) and 8 mg (5%) of the cyclic ether (Rf = 0.50 in PE/AcOEt 4:1).

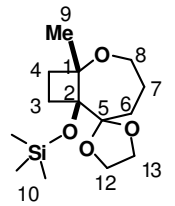


^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 0.14 (s, 9H, H-11), 1.24 (s, 3H, H-9), 1.51-1.70 (m, 2H, H-3 and H-4), 1.82-2.02 (m, 2H, H-3' and H-4'), 2.72 (dq, 2H, *J* = 14.8, 7.2 Hz, H-6), 3.25 (s, 1H, H-10), 4.05-4.14 (m, 4H, H-12 and H-13), 5.03-5.15 (m, 2H, H-8), 5.79-5.93 (m, 1H, H-7).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 1.90 (C-11), 22.7 (C-9), 22.7 (C-3), 33.5 (C-4), 40.4 (C-6), 66.4, 66.6 (C-12 and C-13), 78.5 (C-1), 86.7 (C-2), 113.8 (C-5), 118.0 (C-8), 133.7 (C-7).

IR (film, cm^{-1}): 3940 (br, OH), 1662 (C=C), 1443, 1263.

MS (APCI+ev): *m/z* (%): 287 (15) $[M+H]^{+\cdot}$, 269 (15), 225 (10), 197 (100), 179 (60), 139 (65).

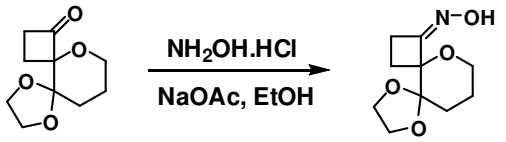


^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 0.11 (s, 9H, H-10), 1.27 (s, 3H, H-9), 1.39-2.02 (m, 7H, H-3, H-4, H-6 and H-7), 2.17 (dt, 1H, *J* = 13.4, 4.4 Hz, H-4'), 3.45 (dt, 1H, *J* = 12.3, 1.3 Hz, H-8), 3.61-3.67 (dm, 1H, H-8'), 3.88-4.00 (m, 2H, H-12 or H-13), 4.06-4.10 (m, 2H, H-12 or H-13).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 1.9 (C-10), 20.3 (C-9), 25.1, 26.1 (C-3 and C-7), 29.9, 31.8 (C-4 and C-6), 63.7, 64.1 (C-12 and C-13), 66.2 (C-8). MS (APCI+ev): *m/z* (%): 287 (20) $[M+H]^{+\cdot}$, 243 (5), 197 (100), 153 (40), 125 (10).

9.10.3. Beckmann fragmentations

1,4,10-trioxa-dispiro[4.0.3.4]decan-7-one oxime 7.217

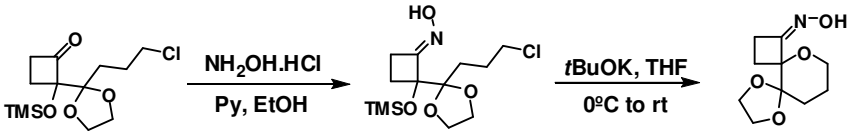


$C_{10}H_{15}NO_4$
M.W.: 213,23

In a 10-mL round-bottomed flask, 70 mg of the spirocyclobutanone (0.35 mmol, 1 eq.) are dissolved in 4 mL of ethanol. To this solution are added seq.uentially 58 mg of sodium acetate (0.71 mmol, 2 eq.) and 29 mg of hydroxylamine hydrochloride (0.42 mmol, 1.1 eq.). The resulting mixture is stirred for 4 hours, at which point TLC-analysis indicates complete conversion of the starting material. To the reaction mixture are added 5 mL of water, followed by 5 mL of ethyl acetate. After phase separation, the aqueous layer is extracted by 3 x 10 mL of ethyl acetate. The combined organic fractions are dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue is >95% pure by ^{1}H-NMR analysis. It can be

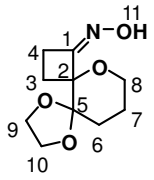
purified by flash chromatography (PE/AcOEt 1:1) to afford 65 mg (87%) of the oxime (Rf = 0.30 in PE/AcOEt 1:1).

Alternative two-step procedure from condensation adduct **7.120**



In a 10-mL round-bottomed flask, 400 mg of the condensation adduct (1.33 mmol, 1 eq.) are dissolved in 8 mL of ethanol. The resulting solution is treated with 0.8 mL of pyridine (8 mmol, 6 eq.) and 280 mg of hydroxylamine hydrochloride (4 mmol, 3 eq.). The mixture is stirred for 6 hours at room temperature, at which point 8 mL of water are added, followed by 10 mL of ethyl acetate. After phase separation, the aqueous layer is extracted by 3 x 15 mL of ethyl acetate. The combined organic fractions are dried ($MgSO_4$) and concentrated under reduced pressure.

This residue is then dissolved in 30 mL of THF and cooled to 0ºC. To the solution are added 164 mg of *t*BuOK (1.46 mmol, 1.1 eq.) and stirring is continued for 1 hour at the same temperature. Then, 15 mL of an aqueous saturated NH_4Cl solution are added. After phase separation, the aqueous layer is extracted by 3 x 20 mL of ethyl acetate. The combined organic fractions are dried ($MgSO_4$) and concentrated under reduced pressure. The crude waxy solid is >90% pure by ^{1}H-NMR analysis and may be used as such for the Beckmann fragmentation reactions. It can also be purified as mentioned above.



^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 1.74-1.93 (m, 4H, H-6 and H-7), 1.95-2.01 (m, 1H, H-3), 2.26-2.32 (dt, 1H, *J* = 6.8, 3.5 Hz, H-3'), 2.59-2.66 (m, 1H, H-4), 2.83-2.89 (m, 1H, H-4'), 3.67-3.71 (m, 1H, H-8), 3.90-3.95 (m, 1H, H-8'), 4.00-4.08 (m, 4H, H-9 and H-10), 6.99 (br s, 1H, H-11).

^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 24.0, 24.9, 25.4 (C-3, C-6, C-7), 29.9 (C-4), 63.7 (C-8), 65.5, 65.6 (C-9 and C-10), 87.3 (C-2), 106.3 (C-5), 160.3 (C-1).

IR (film, cm^{-1}): 3369 (br, OH), 2958 (C-H), 2360, 1685 (C=N), 1465, 1436, 1172, 1120.

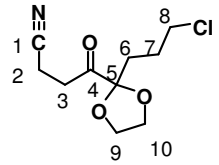
MS (CI+ev): *m/z* (%): 214 (45) $[M+H]^{+\cdot}$, 196 (100), 152 (15), 124 (25).

4-(2-(3-chloropropyl)-1,3-dioxolan-2-yl)-4-oxobutanenitrile 7.252

(crude)

$C_{10}H_{14}ClNO_3$
M.W.: 231,68

A solution of crude oxime (0.66 mmol theoretical, 1 eq.) in 6.5 mL of dichloromethane is cooled to 0ºC. To this vessel are added dropwise 0.16 mL of boron trifluoride etherate (1.22 mmol, 2 eq.) and the resulting mixture is placed at room temperature and stirred for 30 minutes. The reaction is quenched by addition of 3 mL of an aqueous saturated $NaHCO_3$ solution. After phase separation, the aqueous layer is extracted by 3 x 10 mL of dichloromethane. The combined organic fractions are dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue is purified by column chromatography (silica, PE/AcOEt 1:1) to afford 120 mg (80%) of the fragmentated product.

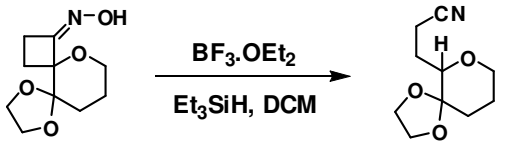


^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.81-1.97 (m, 4H, H-6 and H-7), 2.59 (t, 2H, *J* = 7.2 Hz, H-2), 2.96 (t, 2H, *J* = 7.1 Hz, H-3), 3.56 (t, 2H, *J* = 6.2 Hz, H-8), 3.97-4.07 (m, 4H, H-9 and H-10).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 11.4 (C-2), 25.9 (C-7), 31.1 (C-6), 32.8 (C-3), 44.7 (C-8), 65.9 (C-9 and C-10), 108.7 (C-5), 118.8 (C-1), 203.9 (C-4).

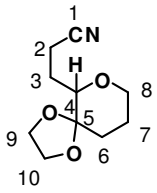
MS (APCI+ev): *m/z* (%): 232 (100) $[M+H]^{+\cdot}$, 214 (20), 204 (50), 188 (50), 175 (45), 151 (45).

3-(1,4,7-trioxaspiro[4.5]decan-6-yl)propanenitrile 7.250



$C_{10}H_{15}NO_3$
M.W.: 197,23

In a 10-mL round-bottomed flask, 70 mg of the crude oxime (0.32 mmol theoretical, 1 eq.) are dissolved in 3 mL of dichloromethane and cooled to 0ºC. Then, 0.1 mL of triethylsilane (0.64 mmol, 2 eq.) are added followed by 0.05 mL of boron trifluoride etherate (0.30 mmol, 1 eq.). The mixture is allowed to gradually reach room temperature and stirred for 30 minutes. At this point, 2 mL of an aqueous saturated $NaHCO_3$ solution are added to quench the reaction. After phase separation, the aqueous layer is extracted by 3 x 5 mL of dichloromethane. The combined organic fractions are dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue is purified by column chromatography (silica, PE/AcOEt 1:1, Rf = 0.35 in PE/AcOEt 1:2) to afford 37 mg (60%) of the tetrahydropyran.



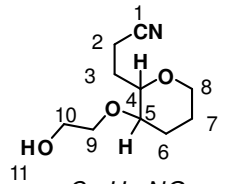
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.62-1.69 (m, 2H, H-6), 1.78-1.99 (m, 4H, H-3 and H-7), 2.37-2.57 (m, 2H, H-2), 3.38-3.46 (m, 2H, H-4 and H-8), 3.87-4.05 (m, 5H, H-8', H-9 and H-10).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 13.5 (C-2), 24.0, 24.6 (C-3 and C-7), 33.1 (C-6), 65.0, 65.3 (C-9 and C-10), 67.7 (C-8), 79.8 (C-4), 105.6 (C-5), 119.8 (C-1).

IR (film, cm^{-1}): 2929, 2854 (C-H), 2247 (C≡N), 1650, 1461, 1442, 1114.

MS (APCI+ev): *m/z* (%): 198 (100) $[M+H]^{+\cdot}$, 180 (45), 154 (35).

NB: If the reaction is allowed to proceed for too long, a new compound gradually forms, which is identified as the over-reduced product **7.223**.

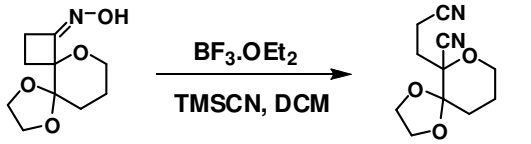


$C_{10}H_{17}NO_3$
M.W: 199,25

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.24-1.40 (m, 1H, H-6), 1.59-1.77 (m, 3H, H-3 and H-7), 1.92 (br s, 1 H, H-11), 2.19-2.30 (m, 2H, H-3' and H-6'), 2.38-2.57 (m, 2H, H-2), 3.02 (dddd, 1H, *J* = 9.4, 7.1, 1.5 Hz, H-5), 3.16 (dt, 1H, *J* = 9.2, 2.8 Hz, H-4), 3.33 (dt, 1H, *J* = 11.4, 3.0 Hz, H-8), 3.43-3.49 (m, 1H, H-9), 3.70-3.73 (m, 3H, H-9' and H-10), 3.86-3.91 (m, 1H, H-8').

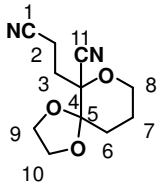
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 13.2 (C-2), 25.1 (C-7), 28.2, 29.1 (C-3 and C-6), 62.1 (C-10), 67.7 (C-8), 69.7 (C-9), 77.7 (C-5), 78.6 (C-4), 119.9 (C-1).

6-(2-cyanoethyl)-1,4,7-trioxaspiro[4.5]decane-6-carbonitrile 7.251



$C_{11}H_{14}N_2O_3$
M.W.: 222,24

In a 10-mL round-bottomed flask, 50 mg of the crude oxime (0.21 mmol theoretical, 1 eq.) are dissolved in 2 mL of dichloromethane and cooled to 0ºC. Then, 0.09 mL of trimethylsilyl cyanide (0.65 mmol, 3 eq.) are added followed by 0.04 mL of boron trifluoride etherate (0.2 mmol, 1 eq.). The mixture is allowed to gradually reach room temperature and stirred for 60 minutes. At this point, 2 mL of an aqueous saturated $NaHCO_3$ solution are added to quench the reaction. After phase separation, the aqueous layer is extracted by 3 x 5 mL of dichloromethane. The combined organic fractions are dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue is purified by column chromatography (silica, PE/AcOEt 1:1, Rf = 0.40) to afford 25 mg (58%) of the tetrahydropyran.



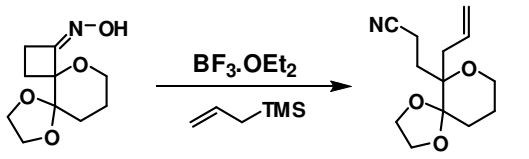
^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 1.71-1.74 (m, 1H, H-7), 1.87-2.04 (m, 3H, H-6 and H-7'), 2.12-2.18 (m, 1H, H-3), 2.24-2.30 (m, 1H, H-3'), 2.52-2.59 (m, 1H, H-2), 2.63-2.70 (m, 1H, H-2'), 3.79 (dt, 1H, *J* = 12.0, 2.5 Hz, H-8), 3.95-3.99 (m, 1H, H-8'), 4.03-4.09 (m, 4H, H-9 and H-10).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 12.1 (C-2), 23.1 (C-7), 28.4, 30.7 (C-3 and C-6), 65.3, 65.6, 66.1 (C-8, C-9 and C-10), 79.3 (C-4), 104.9 (C-5), 116.8, 118.9 (C-1 and C-11).

IR (film, cm^{-1}): 2962, 2933, 2869 (C-H), 2250 (C≡N), 1770, 1444, 1199, 1155.

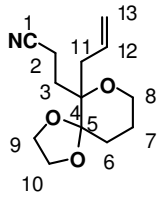
MS (APCI+ev): *m/z* (%): 223 (90) $[M+H]^{+\cdot}$, 205 (35), 196 (65), 161 (70).

3-(6-allyl-1,4,7-trioxaspiro[4.5]decan-6-yl)propanenitrile 7.255



$C_{13}H_{19}NO_3$
M.W.: 237,29

In a 10-mL round-bottomed flask, 50 mg of the crude oxime (0.24 mmol theoretical, 1 eq.) are dissolved in 4 mL of dichloromethane and cooled to 0ºC. Then, 0.30 mL of allyltrimethylsilane (1.80 mmol, 8 eq.) are added followed by 0.04 mL of boron trifluoride etherate (0.2 mmol, 1 eq.). The mixture is allowed to gradually reach room temperature and stirred for 2 hours. At this point, 4 mL of an aqueous saturated $NaHCO_3$ solution are added to quench the reaction. After phase separation, the aqueous layer is extracted by 3 x 10 mL of dichloromethane. The combined organic fractions are dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue is purified by column chromatography (silica, PE/AcOEt 1:1, Rf = 0.55) to afford 24 mg (50%) of the tetrahydropyran.



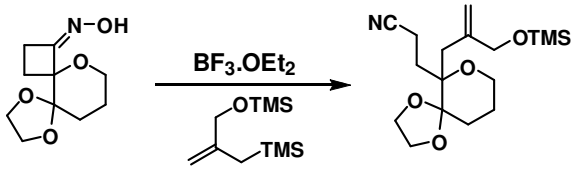
^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 1.71-1.83 (m, 4H, H-6 and H-7), 2.00-2.06 (m, 2H, H-3), 2.34-2.60 (m, 4H, H-2 and H-11), 3.63-3.67 (m, 2H, H-8), 3.94-4.00 (m, 4H, H-9 and H-10), 5.08-5.14 (m, 2H, H-13), 5.76-5.90 (m, 1H, H-12).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 11.6 (C-2), 24.0 (C-7), 27.9, 28.4 (C-3 and C-6), 36.1 (C-11), 60.7 (C-8), 64.5, 64.7 (C-9 and C-10), 78.0 (C-4), 108.7 (C-5), 118.0 (C-13), 120.9 (C-1), 133.3 (C-12).

IR (film, cm^{-1}): 2958, 2920 (C-H), 2248 (C≡N), 1603, 1436, 1263.

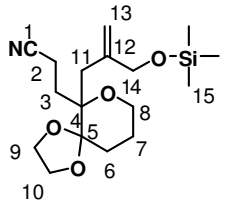
MS (APCI+ev): *m/z* (%): 238 (40) $[M+H]^{+\cdot}$, 220 (20), 194 (60), 176 (100), 166 (15).

3-(6-(2-((trimethylsilyloxy)methyl)allyl)-1,4,7-trioxaspiro[4.5]decan-6-yl)propanenitrile 7.257



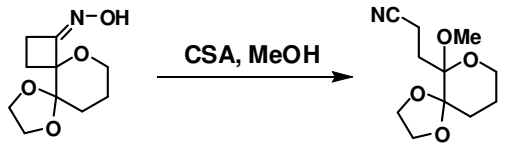
$C_{17}H_{29}NO_4Si$
M.W.: 339,50

In a 10-mL round-bottomed flask, 50 mg of the crude oxime (0.24 mmol theoretical, 1 eq.) are dissolved in 4 mL of dichloromethane and cooled to 0ºC. Then, 87 mg of the functionalised allylsilane (0.40 mmol, 2 eq.) are added followed by 0.04 mL of boron trifluoride etherate (0.2 mmol, 1 eq.). The mixture is allowed to gradually reach room temperature and stirred for 2 hours. At this point, 4 mL of an aqueous saturated $NaHCO_3$ solution are added to quench the reaction. After phase separation, the aqueous layer is extracted by 3 x 10 mL of dichloromethane. The combined organic fractions are dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue is purified by column chromatography (silica, PE/AcOEt 1:1, Rf = 0.30) to afford 26 mg (40%) of the tetrahydropyran.



^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 0.03 (s, 9H, H-15), 1.76-2.20 (m, 6H, H-3, H-6 and H-7), 2.29-2.46 (m, 2H, H-11), 2.59 (t, 1H, *J* = 7.2 Hz, H-2), 2.97 (t, 1H, *J* = 7.1 Hz, H-2'), 3.49-3.58 (m, 2H, H-8), 3.96-4.08 (m, 4H, H-9 and H-10), 4.13 (br s, 2H, H-14), 4.98 (s, 1H, H-13), 5.13 (s, 1H, H-13').
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): -0.23 (C.15), 11.4 (C-2), 25.9 (C-7), 31.1, 32.8 (C-3 and C-6), 37.6 (C-11), 60.7 (C-8), 65.9, 66.5 (C-9, C-10 and C-14), 86.2 (C-4), 113.6 (C-5), 118.0 (C-13).
IR (film, cm^{-1}): 2976, 2915 (C-H), 2250 (C≡N), 1476, 1445, 1150.
MS (CI+ev): *m/z* (%): 339 (40) $[M]^{+\cdot}$, 282 (100), 268 (40), 206 (45).

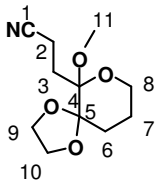
3-(6-methoxy-1,4,7-trioxaspiro[4.5]decan-6-yl)propanenitrile 7.258



$C_{11}H_{17}NO_4$
M.W.: 227,26

In a 10-mL round-bottomed flask, 40 mg of the crude oxime (0.20 mmol theoretical, 1 eq.) are dissolved in 2 mL of methanol. Then, 53 mg of

camphorsulphonic acid are added (0.23 mmol, 1.1 eq.). This solution is stirred for 1 hour. At this point, 2 mL of water are added to quench the reaction. The mixture is extracted by 3 x 10 mL of ethyl acetate. The combined organic fractions are dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue is >95% pure by NMR-analysis. It can be purified by column chromatography (silica, PE/AcOEt 1:1, Rf = 0.40) to afford 26 mg (70%) of the tetrahydropyran.



^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.55-1.71 (m, 2H, H-6 and H-7), 1.86-2.04 (m, 3H, H-6', H-7' and H-3), 2.12-2.23 (m, 1H, H-3'), 2.54 (t, 2H, *J* = 7.8 Hz, H-2), 3.29 (s, 3H, H-11), 3.58-3.64 (m, 2H, H-8), 4.02 (s, 4H, H-9 and H-10).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 12.5 (C-2), 23.5 (C-7), 26.0 (C-3), 27.8 (C-6), 48.2 (C-11), 60.8 (C-8), 64.6, 65.9 (C-9 and C-10), 99.6 (C-4), 107.5 (C-5).

IR (film, cm^{-1}): 2956, 2889, 2852 (C-H), 2360, 2245 (C≡N), 1731, 1461, 1442, 1135.

MS (APCI+ev): *m/z* (%): 228 (100) $[M+H]^{+\cdot}$, 196 (10), 184 (25), 156 (35).