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Institute of Condensed Matter and Nanosciences

Molecular Chemistry, Materials and Catalysis

Methodologies Towards the Total Synthesis of Polycavernoside A

Dissertation submitted for the Degree of Doctor in Sciences

by

Nshimyumuremyi Jean-Boris

Members of the Jury

Prof. Yann Garcia (President, Université catholique de Louvain)

Prof. Louis Barriault (University of Ottawa)

Prof. Raphaël Robiette (Université catholique de Louvain)

Prof. Johan Winne (Universiteit Gent)

Prof. István Markó † (Université catholique de Louvain, Supervisor)

Prof. Alexandre Drouin (Bishop's University, Supervisor)

Prof. Sophie Hermans (Université catholique de Louvain, Supervisor)

Prof. Michael Singleton (Université catholique de Louvain, Supervisor)

"Behind the clouds the sky is always blue."

Norwegian proverb

"…le Polycavernoside devrait être fini d'ici 2 mois..."

István E. Markó

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This section will be written in French.

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List of abbreviations

9-BBN	9-Borabicyclo[3.3.1]nonane
Ac	Acetyl
BAIB	Bis(acetoxy)iodobenzene
B-Br-9-BBN	9-Bromo-9-borabicyclo[3.3.1]nonane
BINAP	(2,2′-bis(diphenylphosphino)-1,1′-binaphthyl)
Bn	Benzyl
BOM	Benzylmethylether
CSA	Camphor sulfonic acid
DBAD	Di-*tert*-butylazadicarboxylate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarboxydiimide
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DET	Diethyl tartrate
DIBAL-H	Diisobutylaluminum hydride
DMAP	Dimethylaminopyridine
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethylsulfoxide
dppf	1,1′-Bis(diphenylphosphino)ferrocene
FAB	Fast Atom Bombardment
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HPLC	High Performance Liquid Chromatography
Im	Imidazole
IMSC	Intramolecular Sakurai cyclisation
IPC	Isopinocamphenyl
IR	InfraRed
ISMS	Intramolecular silyl modified sakurai reaction
LDA	Lithium diisopropyl amide
LDBB	Lithium 4,4'-di-*tert*-butylbiphenylide
***m*CPBA**	*meta*-Chloroperbenzoic acid
Me	Methyl
Ms	Methanesulfonyl
MS	Molecular sieves
NBS	N-Bromosuccinimide
NMI	N-methylimidazole
NMO	N-Methylmorpholine N-oxide
NMR	Nuclear Magnetic Resonance
Phen	1,10-Phenanthroline
Piv	Pivaloyl
PMB	*para*-Methoxybenzyl
PPTS	Pyridinium *para*-toluenesulfonate

Py	Pyridine
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDPS	*tert*-Butyldiphenylsilyl
TBHP	*tert*-Butyl hydroperoxide
TBS	*tert*-Butyldimethylsilyl
***t*Bu**	*tert*-Butyl
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
TIPP	2,4,6-triisopropylphenyl
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium perruthenate
Ts	*para*-Toluenesulfonyl
UV	UltraViolet

Summary

Polycavernoside A is a secondary metabolite first isolated from the red algae *Polycavernosa tsudai* in 1991. This macrocyclic lactone was found to be responsible for severe food intoxication, often leading to death. However, due to its scarcity, its biological properties are yet poorly understood. Our group has been interested in the total synthesis of this natural compound for a few years, leading to the development of several methodologies.

The **Chapter I** focuses on Polycavernoside A. The isolation of the natural from the marine algae, the structure of its analogues and the biological activity are described. Then, the different total syntheses reported in the literature are presented and this is followed by the previous results from our group leading to the objectives of this thesis.

In **Chapter II**, the results of our investigation of the synthesis of the Northern are presented. The disconnection of the butyrolactone is described followed by our approaches using first allylation reactions and then an asymmetric aldol reaction to prepare the target compound.

In **Chapter III**, the investigation of the synthesis of the Southern fragment is described. The ene-ISMS sequence, a combination of methodologies developed in the group, is used to prepare the scaffold of this key sub-unit. Additional transformations including a diastereoselective Luche reduction led to a model of this tetrahydropyran.

The **Chapter IV** focuses on the development of a methodology to couple the Northern and Southern fragments of Polycavernoside A. The methodology for this coupling relies on the Horner-Wadsworth-Emmons reaction. This approach proved to be successful using models for each of the fragments but failed to provide the desired coupling product. The causes of this failure are then investigated, leading to the development of a new methodology presented in the following chapter.

In **Chapter V**, the development of a new methodology requires in parallel the preparation of the Northern fragment through a different approach. This new sequence relies on the use of chiral enolates to control the asymmetry present in this fragment. Then, the use of a new class of phosphonate is investigated as they represent promising scaffolds for the union of the Northern and Southern fragments.

Chapter VI summarises the work presented in this thesis followed by the perspectives of the project.

The experiments carried out in the thesis and the characterisations of the different compounds are reported in **Chapter VII**.

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Chapter I

Introduction

I.1 Isolation, characterisation and biological evaluation

I.1.1 Isolation and characterisation

In April 1991, Dr. Robert L. Haddock and Olivia T. Cruz from the Department of Public Health of the Island of Guam, reported an outbreak of food poisoning in the journal The Lancet[1].

"*-Sir, We report preliminary information on a common-source outbreak of foodborne intoxication associated with seaweed. Over a 24 h period five people presented with vomiting, diarrhoea, stomach cramps, respiratory distress, muscle spasms, and numbness of the extremities and were admitted to hospital with a provisional diagnosis of ciguatera fish poisoning. […] Three of those admitted to hospital died about 31, 72, and 120 hours after ingesting amounts of seaweed described by family members as equivalent to half to one cereal bowl."*

While the symptoms presented by the patients were comparable to the ones usually observed in patients suffering from food poisoning by known marine toxins, preliminary studies showed that in this case, the intoxication was induced by an unknown compound. At that time, the Department of Public Health confiscated the remains of *Polycavernosa tsudai*[2] (also called *Gracilaria edulis*), the seaweed suspected to be at the origin of this onset and sent it to the group of Pr. Mari Yotsu-Yamashita from Tohuku University in Japan (Figure 1). Out of 13 people that suffered from the intoxication, three of them died. About a decade later, another intoxication occurred involving 36 people among which 8 perished after ingestion of *Polycavernosa tsudai* and *Acanthophora spicifera* seaweed[3].

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[1] R. Haddock, O. T. Cruz, *Lancet*, **1991**, *338*, *8760*, 195–196.
[2] Pictures extracted from Boldsystem database under the reference "*Gracilaria edulis"* and from the Department of Botany of the University of Hawaii at Manoa under the reference "*Acanthophora spicifera*".
[3] M. Yotsu-Yamashita, T. Yasumoto, S. Yamada, F. F. a Bajarias, M. a. Formeloza, M. L. Romero, Y. Fukuyo, *Chem. Res. Toxicol.*, **2004**, *17*, 1265–1271.

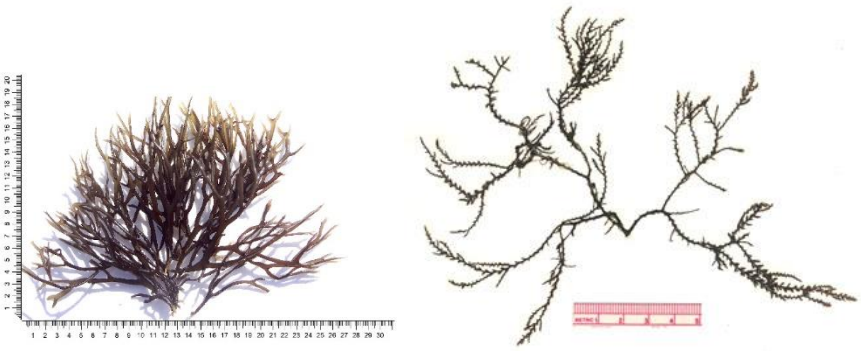


Figure 1 - Polycavernosa tsudai (left) and Acanthophora spicifera (right)

After extraction and purification by HPLC, the research group was able to isolate two new compounds, Polycavernoside A (400 µg) and Polycavernoside B (200 µg). However, due to the limited amount of material, only the structure of Polycavernoside A could be determined[4]. This was achieved using different NMR techniques, UV, IR and mass spectrometry. Thorough interpretation of the data revealed a macrolactone bearing a glycosidic appendage and a (*E*,*E*,*E*) triene moiety (Figure 2).

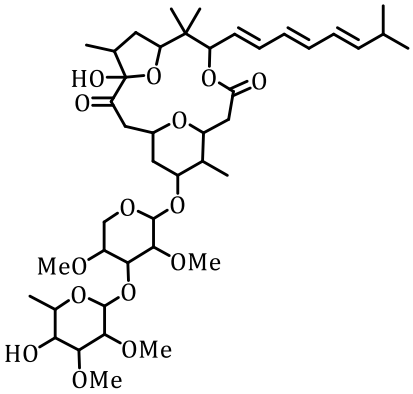


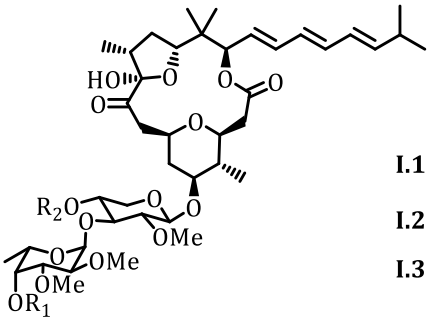
Figure 2 - Structure of Polycavernoside A

While these investigations allowed the determination of the architecture of this new natural compound, its relative and absolute configuration had yet to be established.

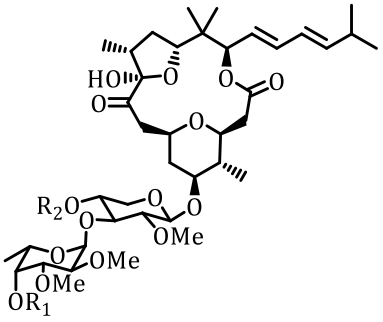
[4] M. Yotsu-Yamashita, R. L. Haddock, T. Yasumoto, *J. Am. Chem. Soc.*, **1993**, *115*, *3*, 1147–1148.

I.1.2 Analogues and related compounds

Since the first article reporting the isolation and characterization of Polycavernoside A **I.1**, numerous papers have been published reporting isolation of analogues of this natural compound[5]. In fact, after the 1991 outbreak, other events were reported in 1992, 1995, 2007 and more recently in 2015. The structures of the different analogues are reported in Figure 3. While these reports revealed the skeleton of these compounds, the stereochemistry was only assigned years later relying on the work of Murai[6] and Paquette[7].



		R_1	R_2
I.1	Polycavernoside A	H	Me
I.2	Polycavernoside A2	H	H
I.3	Polycavernoside A3	Me	Me

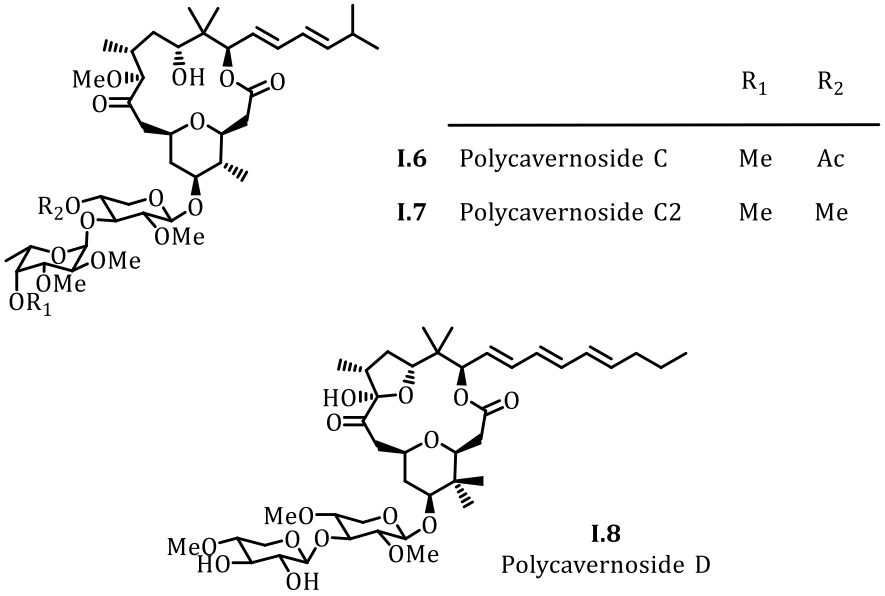


		R_1	R_2
I.4	Polycavernoside B	Me	Ac
I.5	Polycavernoside B2	Me	H

[5] M. Yotsu-yamashita, T. Seki, V. J. Paul, **1995**, *36*, *31*, 5563–5566; M. Yotsu-Yamashita, K. Abe, T. Seki, K. Fujiwara, T. Yasumoto, *Tetrahedron Lett.*, **2007**, *48*, 2255–2259; G. Navarro, S. Cummings, J. Lee, N. Moss, E. Glukhov, F. A. Valeriote, L. Gerwick, W. H. Gerwick, *Environ. Sci. Technol. Lett.*, **2015**, *2*, *7*, 166–170.

[6] K. Fujiwara, S. Amano, A. Murai, *Chem. Lett.*, **1995**, *24*, *3*, 191–192; K. Fujiwara, S. Amano, A. Murai, *Chem. Lett.*, **1995**, 855–856.

[7] L. A. Paquette, D. Pissarnitski, L. Barriault, *J. Org. Chem.*, **1998**, *63*, *1*, 7389–7398.



		R_1	R_2
I.6	Polycavernoside C	Me	Ac
I.7	Polycavernoside C2	Me	Me

I.8
Polycavernoside D

Figure 3 - Members of the Polycavernoside family

Concerning the members of the A, B and C family which were all isolated from *Polycavernosa tsudai*, it can be noticed that the core architecture of the disaccharide, composed of a fucose and a xylose, is maintained. The polyenic moiety varies from two to three (*E*)-conjugated olefins and ends with an isopropyl group.

Compared to the other analogues, the Polycavernoside C family lacks the tetrahydrofuran ring. This characteristic can lead to a less rigid structure and a different three-dimensional arrangement.

Meanwhile, Polycavernoside D **I.8**, which was isolated more recently from a cyanobacteria culture, bears a different glycosidic appendage composed of two xylose units and a polyenic tail substituted with a n-propyl group. The isolation and characterization of this new analogue brought more evidence regarding the origin of all the members of this family. Indeed, as it has been the case for other marine toxins, it was suspected that these secondary metabolites are produced by smaller microorganisms that can invade the marine species[8].

[8] T. Yasumoto, *Chem. Rec.*, **2001**, *1*, *3*, 228–242; T. Higa, M. Kuniyoshi, *Toxin Rev.*, **2000**, *19*, *2*, 119–137; D. Z. Wang, *Mar. Drugs*, **2008**, *6*, 349–371.

I.1.3 Biological evaluation

In a joint effort from the groups of Pr. Yotsu-Yamashita, Pr. Akio Murai from Hokkaido University and Pr. Leo A. Paquette from Ohio State University, biological studies were carried out using Polycavernoside A **I.1**, Polycavernoside B **I.4** and different synthetic analogues[9].

6 analogues of Polycavernoside A were prepared through derivatization of different synthetic intermediates. The modifications were inserted at the polyenic tail and at the glycosidic linkage, leading to the compounds depicted in Figure 4.

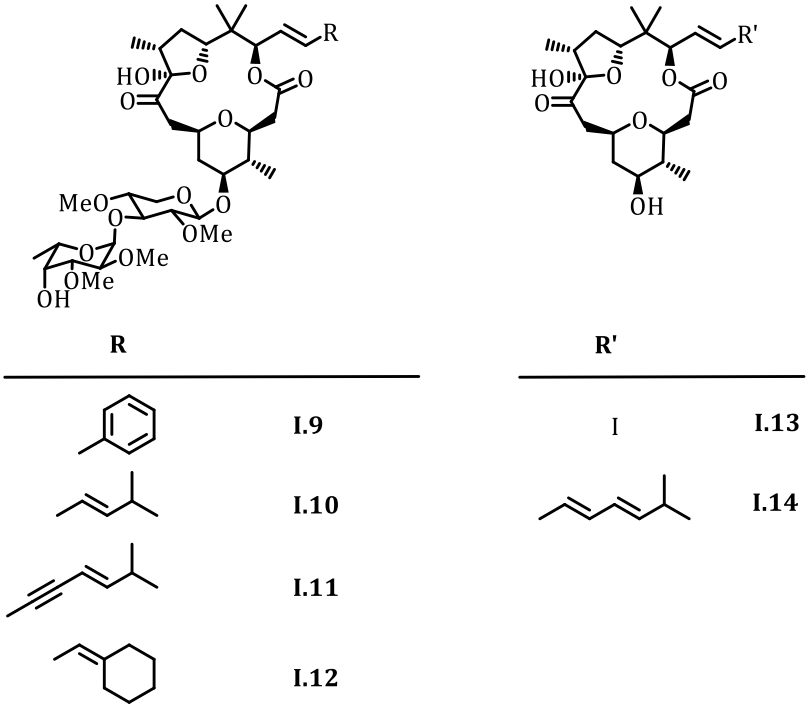


Figure 4 - Structure of Polycavernoside A synthetic analogues

Bioassays in mice showed symptoms similar to those observed in humans after the event in Guam. This study also allowed the determination of the LD_{99} of the different compounds in rats and gave some insights regarding the structure activity relationship.

[9] L. Barriault, S. L. Boulet, K. Fujiwara, A. Murai, L. A. Paquette, M. Yotsu-Yamashita, *Bioorg. Med. Chem. Lett.*, **1999**, *9*, *14*, 2069–2072.

Compound	*Lethal dose (mg/kg)*	*Symptoms*
Polycavernoside A (I.1)	0.2-04	gradual progressive onset of severe scratching of face and body, spasms, paralysis, severe eye damage, and death.
Polycavernoside B (I.4)	0.2-0.4	same as for Polycavernoside A
I.9	>13	no adverse symptoms seen.
I.10	1.5-3.1	same as for Polycavernoside A; paralysis 30 min after injection
I.11	0.38-0.77	same as for Polycavernoside A
I.12	>13	no adverse symptoms seen.
I.13	>13	no adverse symptoms seen
I.14	1.5-3.1	no scratching or eye damage, but frenetic jumping, severe spasms, and ultimately paralysis; if death did not occur within 30 min, total recovery was noted.

From these observations, several conclusions were drawn:

- The bioactive form is probably the aglycone, while the glycosidic unit seems to be important for transportation and absorption as well as biostability.
- The presence of the disaccharide delays the release rate of the active compound leading to a longer exposure of the active toxin.
- The difference of toxicity observed between the Polycavernoside and its analogue **I.14** is apparently due to the different substitution of the hydroxyl group.
- Merging the sugar appended to Polycavernoside B with the aglycone of Polycavernoside A should lead to the most active compound.

It is noteworthy that the biological assays on mice were carried out by intraperitoneal administration while in the case of humans, poisoning occurred by oral ingestion. It was proposed that the acidity of the stomach should increase the rate of hydrolysis of Polycavernoside A therefore leading to a higher bioavailability of the aglycone, hence a higher toxicity.

Another study was carried out by the group of Pr. Luis Botana on the effect of a Polycavernoside analogue **I.11** on human neuroblastoma cells[10]. Since they did not have access to the natural product, this analogue was chosen because its biological activity was similar to the natural product. Based on the observed symptoms in humans and mice, they hypothesised that the toxin had a neurological action, leading them to choose neuroblastoma cells as the target of their experiments. Moreover, because of the secretory activity induced by the

[10] E. Cagide, C. Louzao, I. Ares, M. Vieytes, M. Yotsu-Yamashita, L. Paquette, T. Yasumoto, L. Botana, *Cell. Physiol. Biochem.*, **2007**, *19*, 185–194.

toxin, their study focused on the measurement of intracellular [Ca^{2+}] since these phenomena are usually related.

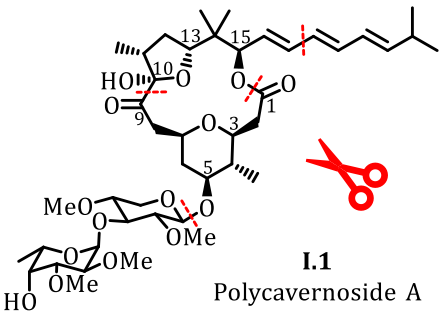
After their study, they concluded that:

- Polycavernoside A analogue **I.11** leads to an increase of the intracellular potential.
- An increase of the [Ca^{2+}] is observed in the cytosol.
- The increase of calcium cation is not related to the influence of the toxin on cholinergic receptors that can act as Ca^{2+} ion channel.
- The penetration of calcium is not related to an effect on voltage-gated ion channels.
- The mechanism of increase of calcium concentration in the cytosol induced by Polycavernoside A analogue **I.11** is still unknown.

The study reported by this group gave access to some of the toxin's properties, however, further investigations should be performed to gain a better understanding of the mode of action.

I.2 Total synthesis of Polycavernoside A

Since its discovery, Polycavernoside A **I.1** has been a target for numerous organic chemistry research groups as its structure represents an interesting challenge. Moreover, its preparation should allow a better understanding of its mechanism of action. In this section, the work of different groups will be presented, highlighting for each of them specific features in the synthetic strategies. However, one aspect seems to remain constant and that is the disconnection strategy used. Common to all these approaches are the disconnection of the polyenic chain and the disaccharide due to their sensitivity and their size respectively (Figure 5). After that, the disconnection generally occurs at the ester bond and at the C_9-C_{10} bond.



I.1
Polycavernoside A

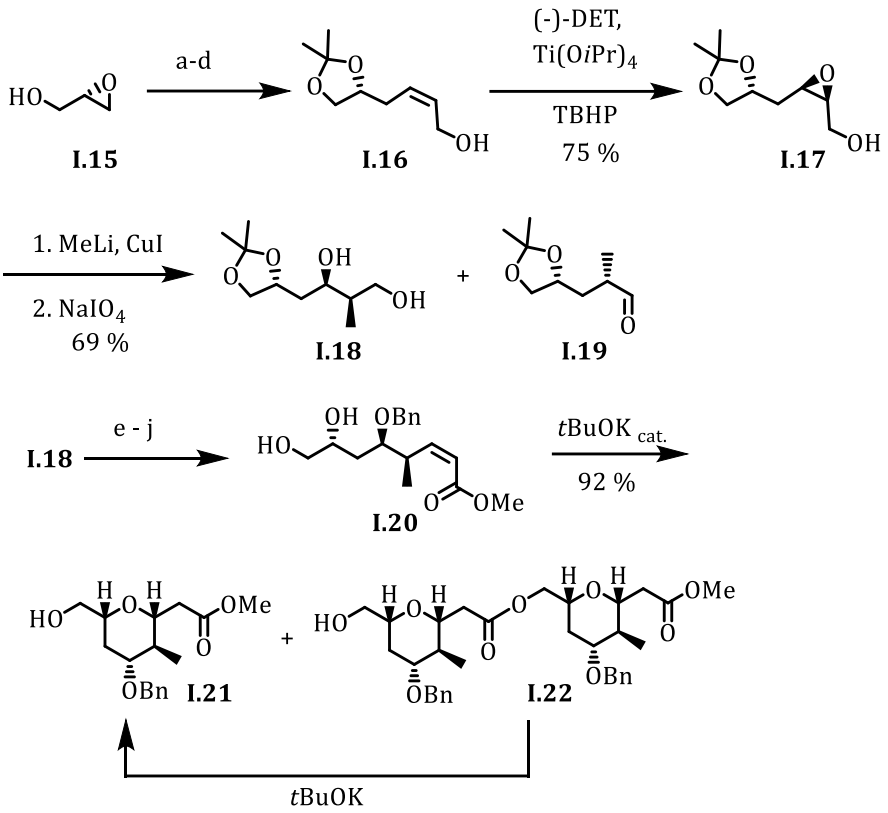
Figure 5 - General disconnection of Polycavernoside A

For the sake of clarity, the top part of the aglycone containing the furan ring will be referred as "Northern fragment" while the tetrahydropyran will be coined as the "Southern fragment". In this chapter, the preparation of the disaccharide that was reported independently by Murai and Paquette will be omitted and we will focus on the description of the different syntheses of the aglycone. These will be organised chronologically starting from the synthesis developed by Akio Murai.

I.2.1 Total synthesis by Murai (1995-2000)[6,11]

The group of Murai was the first to report their efforts in the total synthesis of Polycavernoside A. The preparation of the Southern fragment started with either (*R*)-glycidol **I.15** or (*S*)-glycidol since the stereochemistry of the natural product had not been established yet (Scheme 1). After a four step sequence, allylic alcohol **I.16** could undergo the Sharpless asymmetric epoxidation. The subsequent opening of the epoxide using a methyl cuprate did not allow a completely regioselective reaction. Therefore, the treatment of the mixture of 1,3- and 1,2-diols with sodium periodate lead to the selective oxidative cleavage of the latter. The 1,3-diol **I.18** could then be isolated and used in the following steps. A Horner-Wadsworth-Emmons reaction furnished a separable mixture of Michael acceptor in a 5:1 ratio in favour of the *Z*-olefin. The treatment of this compound in acidic media led to the formation of diol **I.20** that ultimately underwent an intramolecular cyclisation. The desired tetrahydropyran **I.21** was isolated alongside with ester **I.22** arising from a dimerization. This product was smoothly converted into the tetrahydropyran **I.21** using potassium *tert*-butoxide in methanol.

[11] N. Hayashi, T. Mine, K. Fujiwara, A. Murai, *Chem. Lett.*, **1994**, *23*, *11*, 2143–2146; K. Fujiwara, S. Amano, T. Oka, A. Murai, *Chem. Lett.*, **1994**, *23*, *11*, 2147–2150; K. Fujiwara, A. Murai, M. Yotsu-Yamashita, T. Yasumoto, *Tetrahedron Lett.*, **1998**, *120*, *29*, 10770–10771; K. Fujiwara, A. Murai, M. Yotsu-Yamashita, T. Yasumoto, *J. Am. Chem. Soc.*, **1998**, *120*, *13*, 10770–10771.

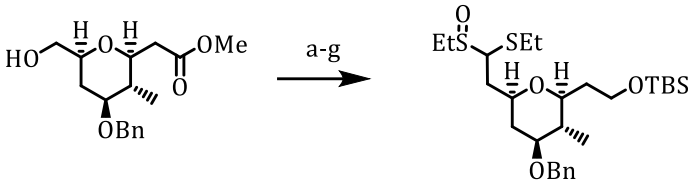


a) TBSCl, Im, 96 %; b) $HCCCH_2OTHP$, BuLi, $BF_3.Et_2O$; c) TsOH, H_2O; d) Dimethoxypropane, TsOH, 71 % over 3 steps; d) H_2, Lindlar cat., quinoline, 91 %; e) TBSCl, DMAP, NEt_3, 91 %; f) *t*BuOK, BnBr, TBAI, 95 %; g) TBAF, 79 %; h) $(COCl)_2$, DMSO, NEt_3; i) $(MeO)_2POCH_2CO_2Me$, KH, 18-crown-6, 93 % over two steps (*E*:*Z* : 5:1); j) TsOH, 92 %;

*Scheme 1 - Synthesis of the Southern fragment **I.21***

The coupling of the disaccharide and the unprotected alcohol derived from **I.21** through the formation of the glycosidic bond allowed the determination of the relative stereochemistry present in Polycavernoside A.

The Southern fragment **I.23** was then prepared for the coupling with the Northern fragment in 7 steps requiring a homologation step (Scheme 2).

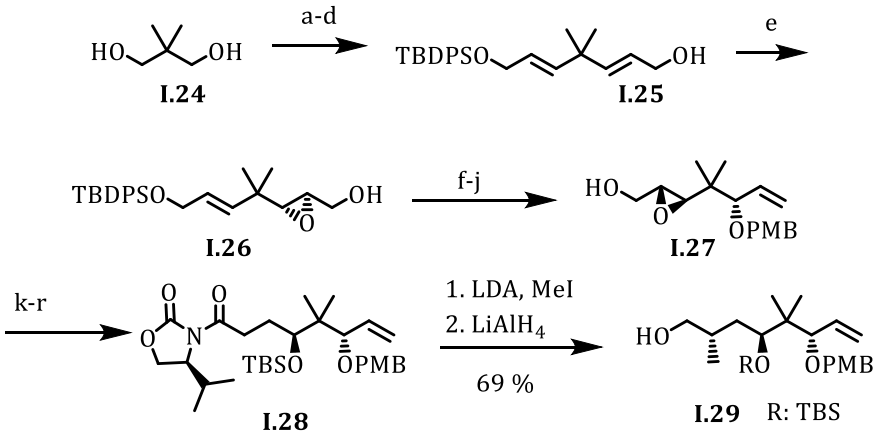


I.21 **I.23**

a) $(COCl)_2$, DMSO, NEt_3; b)$Ph_3PCHOCH_3$, 90% over 2 steps; c) TFA, 92 %; d) TMSSEt, ZnI_2; e) $LiAlH_4$; f) TBSCl, Im, 99 % over 3 steps; g) *m*CPBA, 93 %.

*Scheme 2 - Synthesis of **I.23***

Along the lines of the previous work, Murai's group also reported the preparation of the Northern fragment starting from neopentyl glycol **I.21** (Scheme 3). Therefore, the three asymmetric centres were introduced using the Sharpless asymmetric epoxidation of allylic alcohols twice and the Evans oxazolidinone enolates.

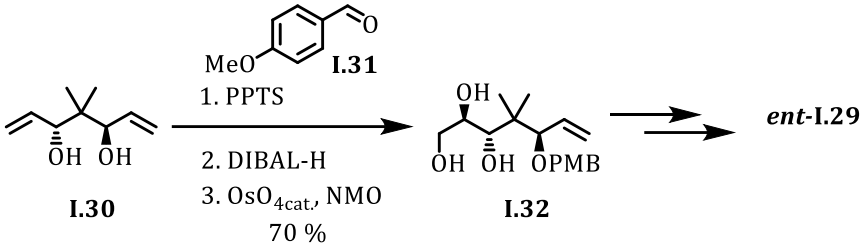


I.24 **I.25** **I.26** **I.27** **I.28** **I.29** R: TBS

a) $(COCl)_2$, DMSO, NEt_3; b) Ph_3PCHCO_2Me, 56 % over 2 steps; c) DIBAL-H, 84%; d) TBDPSCl, Im, 57 %; e) (-)DET, $Ti(OiPr)_4$, TBHP, 100 %; f) I_2, PPh_3, Im; g) Zn, NH_4Cl, 94 % over 2 steps; h) PMBCl, NaH, TBAI; i) TBAF, 69 % over 2 steps; j) (-)-DET, $Ti(OiPr)_4$, TBHP, 100 %; k) Red-Al, 100 %; l) TsCl, NEt_3, DMAP, 98 %; m) TBSOTf, 2,6-Luditine; n) KCN, 92 %; o) DIBAL-H, 96 %; p) $NaClO_2$, NaH_2PO_4; q) PivCl, NEt_3; r) N-lithio-(4*S*)-4-isopropyl-2-oxazolidinone, 100%.

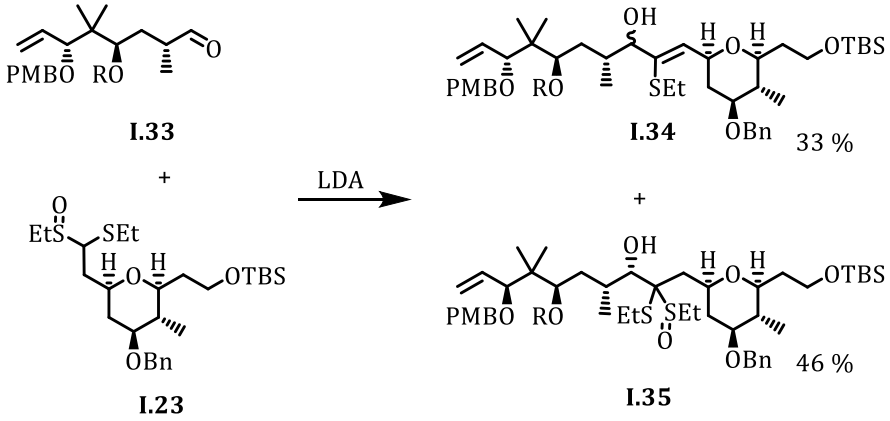
*Scheme 3 - Synthesis of alcohol **I.29***

They also described an optimized sequence that allowed the preparation of the enantiomer of **I.29** (Scheme 4). This approach involved a desymmetrisation of the diol **I.30** which was prepared from the same starting material as before and using a similar procedure for the formation of the allylic alcohol.



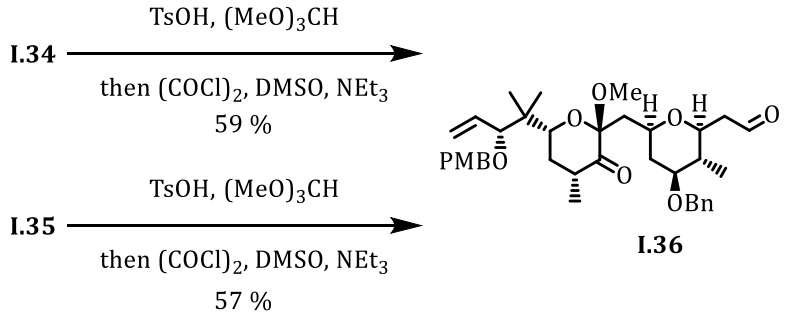
*Scheme 4 - Synthesis of **I.32***

With the proper fragments **I.23** and **I.33** in hands, they could move to their assembly. Deprotonation of the mixed thioacetal **I.23** with LDA followed by the addition of the aldehyde **I.33** led to the formation of alcohol **I.35** as well as vinyl sulphide **I.34** (Scheme 5).



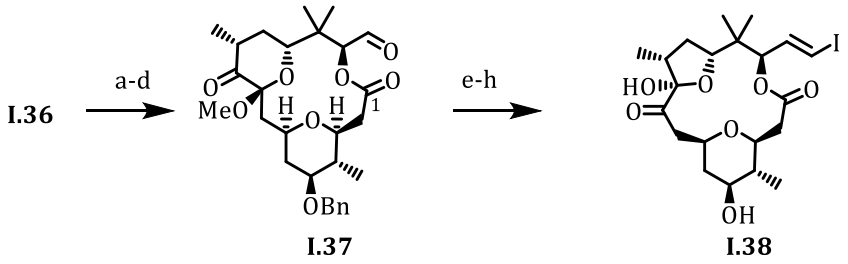
*Scheme 5 - Coupling of aldehyde **I.33** with **I.23***

Fortunately, the treatment of each of those intermediates with *para*-toluenesulfonic acid and trimethylorthoformate led to the formation of a single compound present as a mixture of two diastereoisomers which, upon Swern conditions, led to the formation of the ketone **I.36** (Scheme 6).



*Scheme 6 - Synthesis of ketone **I.36***

The next steps of the synthesis allowed the formation of the macrolactone and set the stage for the insertion of the polyenic tail. Therefore, the PMB ether in **I.36** was cleaved and Pinnick conditions led to the formation of the acid at C_1. Yamaguchi lactonisation afforded the cyclisation adduct which after treatment with osmium tetraoxide led to the intermediate **I.37** (Scheme 7).

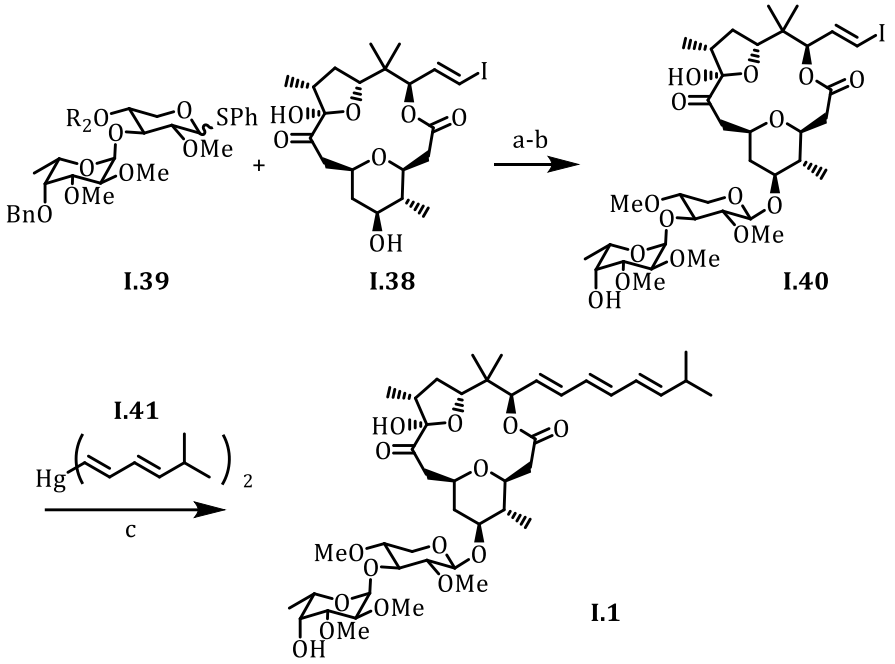


a) DDQ, 92 %; b) $NaClO_2$, NaH_2PO_4, 100 %; c) 2,4,6-trichlorobenzoyl chloride, NEt_3, DMAP, 75 %; d) OsO_4, NMO, then $NaIO_4$, 75 %; e) H_2, Pd/C; f) TBSOTf, 2,6-Luditine, 95 % over two steps; g) $CrCl_2$, CHI_3, 80%; h) TFA, H_2O, 95 %.

*Scheme 7 - Synthesis of vinyl iodide **I.38***

Additional modifications of **I.37** involved the transformation of the aldehyde into a vinyl iodide and the deprotection of the secondary alcohol of the tetrahydropyran. At this step, it is noteworthy that treatment of the 6-membered cyclic acetal in aqueous acidic conditions led to the formation of the 5-membered ring lactol as a single diastereoisomer. It means that the furan is the thermodynamic product and that the stereochemistry of the anomeric carbon is dictated by thermodynamic factors.

From **I.38**, only a few steps were required to finish the total synthesis. The appendage of the disaccharide was performed using NBS while subsequent treatment with DDQ furnished the free alcohol (Scheme 8).



a) NBS, 50 %; b) DDQ, 70 %; c) $Pd(PPh_3)_4$, 75 %

Scheme 8 - Last steps of Murai synthesis of Polycavernoside A

The last step of the synthesis was the connection of the polyenic tail which was performed using a palladium cross-coupling reaction leading to Polycavernoside A **I.1**. Comparison of the NMR, UV, IR and FABMS analysis with the authentic sample confirmed that the compounds were identical. Analysis by circular dichroism revealed the same pattern as the one observed with the natural sample confirming the absolute stereochemistry of Polycavernoside A.

With this, Murai's group had achieved the first total synthesis of Polycavernoside A. Through their work, the relative and absolute configuration of the compound was confirmed and the sample they made allowed for the first studies of its biological activity.

I.2.2 Total synthesis by Paquette's group (1995-2000)[7,12]

On the other side of the Pacific Ocean, Leo Paquette and his co-workers were also investigating the synthesis of the lethal macrolactone. Paquette's group had planned the following disconnections with their assembly using the strategies presented in Figure 6.

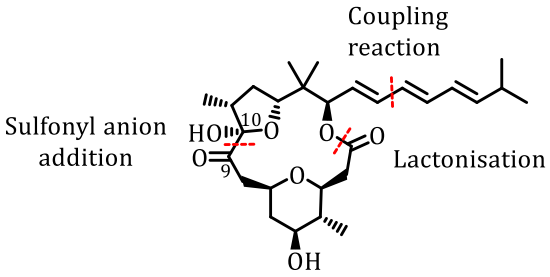
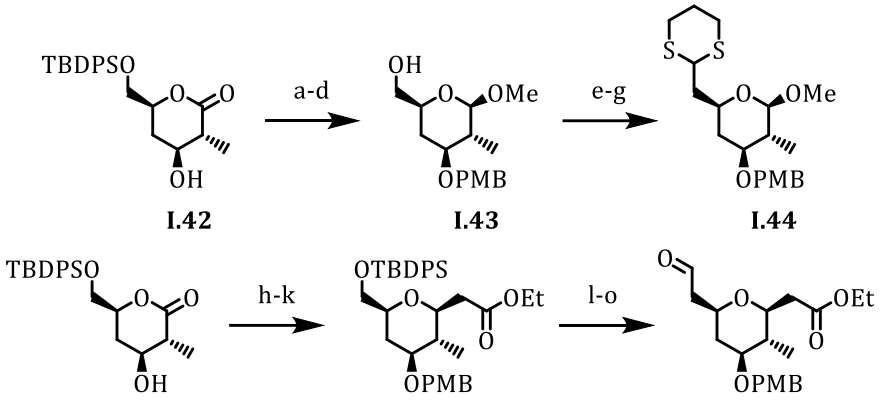


Figure 6 - Disconnection of Polycavernoside A aglycone by Paquette

Looking at the formation of the C_9-C_{10} bond by sulfonyl anion addition, they decided to prepare fragments in ways that would allow either the dithiane nucleophilic anion to be connected to the Northern fragment or the Southern fragment.

The synthesis of the tetrahydropyrans **I.44** and **I.46** started with lactone **I.42** which was previously described in 10 steps starting from L-malic acid.

[12] J. N. Johnston, L. A. Paquette, *Tetrahedron Lett.*, **1995**, *36*, *25*, 4341–4344; L. A. Paquette, L. Barriault, D. Pissarnitski, *J. Am. Chem. Soc.*, **1999**, *121*, 4542–4543; L. A. Paquette, L. Barriault, D. Pissarnitski, J. N. Johnston, *J. Am. Chem. Soc.*, **2000**, *122*, *4*, 619–631.



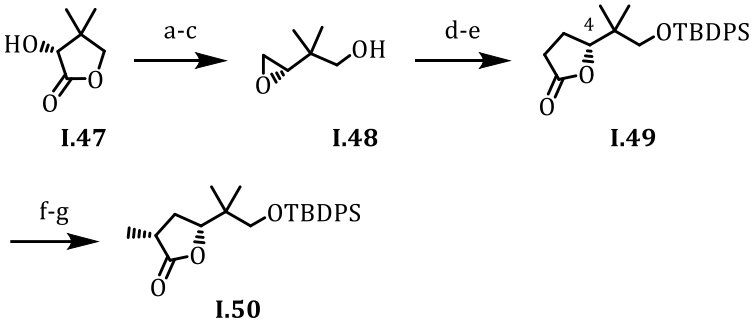
a) PMBOC(=NH)CCl_3, TfOH, 77 %; b) DIBAL-H; c) Ag_2O, CH_3I, 62 % over 2 steps; d) TBAF, 97 %; e) MsCl, NEt_3, 95 %; f) TBAI, 95 %, g) 1,3-dithiane, *n*BuLi, *t*BuOK, 72 %; h) TMSCl, HMDS; i) $CH_2C(OLi)OEt$; j) Et_3SiH, $SnCl_4$, 59 % over 3 steps; k) PMBOC(=NH)CCl_3, TfOH, 59 % over 3 steps; l) TBAF, 95 %; m) DMP, 71 %; n) $Ph_3P{=}CHOCH_3$; o) 1M HCl, 49 % over 2 steps.

*Scheme 9 - Synthesis of the Southern fragments **I.44** and **I.46***

On one side, a four step sequence involving reduction of the lactone using DIBAL-H afforded hemiacetal **I.43** that underwent a homologation through addition of the 1,3-dithiane anion onto the corresponding iodide (Scheme 9). After protection of the secondary alcohol in **I.42**, the lactone was treated with the lithiated ethyl propionate and the corresponding hemiacetal was reduced with triethylsilane in the presence of tin tetrachloride. A protection of the secondary alcohol as a PMB ether in acidic condition afforded **I.45**. The subsequent deprotection of the silyl ether followed by an oxidation using Dess-Martin periodinane and a Wittig olefination led to the corresponding enol ether which after hydrolysis afforded aldehyde **I.46**.

Regarding the synthesis of the Northern fragment, the sequence started with (*R*)-pantolactone **I.47** (Scheme 10). Through a procedure described by Lavallée[13], epoxide **I.48** could be obtained and was protected as a TBDPS ether. Then, addition of the acetic acid bis-anion allowed the opening of the epoxide and an aqueous acidic workup allowed the cyclisation into the butyrolactone **I.49**.

[13] P. Lavallée, R. Ruel, L. Grenier, M. Bissonnette, *Tetrahedron Lett.*, **1986**, *27*, *6*, 679–682.



I.47 **I.48** **I.49** **I.50**

a) TsCl, DMAP, Py, 95 %; b) DIBAL-H, 80 %; c) K_2CO_3, 90 %; d) TBDPSCl, Im, 95 %; e) $CH_2C(OLi)OLi$ then H_3O^+, 72 %; f) LiHMDS, CH_3I, 81 %; g) LDA, NH_4Cl, 81 %.

*Scheme 10 - Synthesis of lactone **I.50***

The deprotonation of **I.49** using LiHMDS led to the formation of an enolate which when treated with methyl iodide led to the alkylation product with complete diastereocontrol. The stereochemistry of the newly formed asymmetric centre could then be inverted using the same strategy with a work up using ammonium chloride. In these two last steps, the diastereocontrol of the reaction is explained by a more accessible face in the enolate due to the bulkiness of the group appended at the C_4 of the butyrolactone (Figure 7).

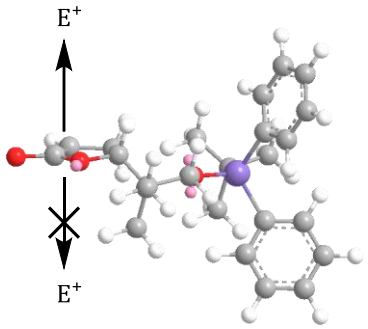
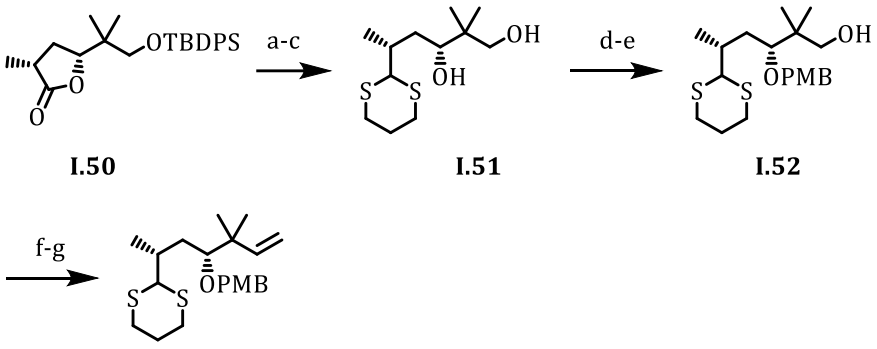


*Figure 7 - Model for the diastereocontrol in the alkylation of **I.49** enolate*

Lactone **I.50** could then be transformed into the coupling precursor **I.53** (Scheme 11).



I.50 **I.51** **I.52**

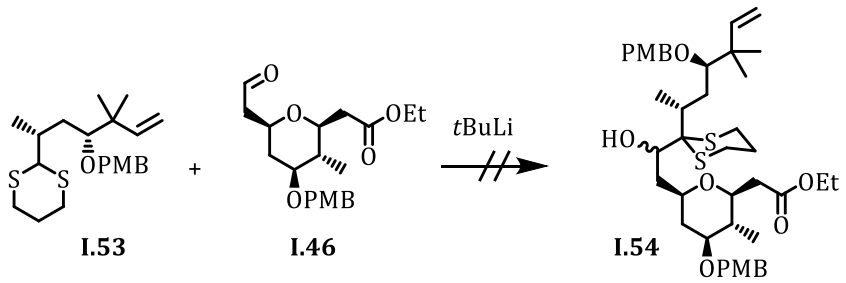
I.53

a) DIBAL-H, 99 %; b) $HS(CH_2)_3SH$, $TiCl_4$, 93 %; c) TBAF, 94 %; d) *p*-$CH_3OC_6H_4CHO$, CSA, 89 %; e) DIBAL-H, 73 %; f) $(COCl)_2$, DMSO, NEt_3, 86 %; g) $Ph_3P{=}CH_2$, 94 %.

*Scheme 11 - Synthesis of dithiane **I.53***

This was done starting with the reduction of the lactone **I.50** to the aldehyde which was then transformed into the corresponding dithiane **I.51**. A series of protection and deprotection steps allowed selective protection of the hindered alcohol as a PMB ether. The primary alcohol was oxidised following the Swern protocol. The corresponding aldehyde could then be transformed into alkene **I.53** with the help of phosphonium ylide in good yields.

With the intermediates **I.44**, **I.46**, **I.50** and **I.53** in hand, the stage was set for their assembly. They started with the approach using the Southern fragment **I.46** as the electrophile (Scheme 12).

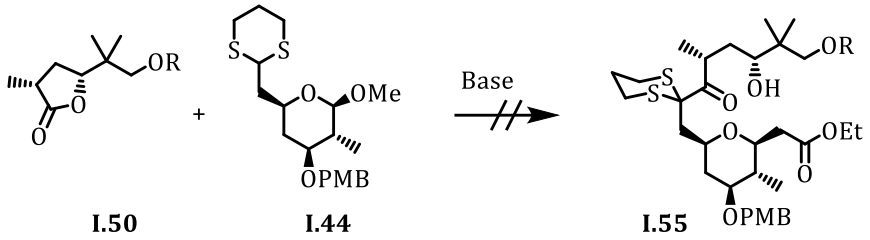


I.53 **I.46** **I.54**

*Scheme 12 - Attempts to the coupling using **I.53** and **I.46***

However, despite several tries, this approach failed to give the desired product **I.54**. The starting dithiane **I.53** was recovered at the end of the reaction and in some cases, degradation of the aldehyde **I.46** was observed. Deprotonation of the thioacetal followed by quench with deuterated water showed that the anion was formed in the reaction media but did not undergo the addition onto the aldehyde **I.41**.

Moving to the other approach proved to be inefficient as well (Scheme 13).



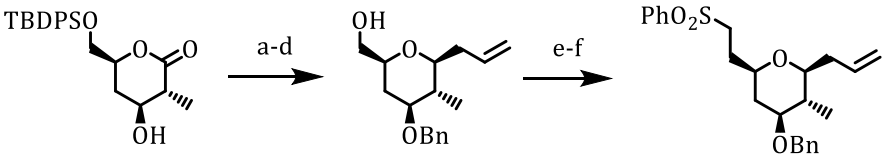
I.50 **I.44** **I.55**

R: TBDPS R: TBDPS

*Scheme 13 - Attempts to the preparation of **I.55***

In this case, they postulated that the absence of reactivity could arise from the highly oxygenated species that could prevent efficient deprotonation. In these conditions, they observed epimerisation of the lactone as well.

At this stage, they had to rethink their coupling strategy and opted for the addition of a sulfone anion onto an aldehyde. The Southern subunit was prepared using a strategy similar to the one previously used. This was done in a straightforward 6 step sequence starting from the same precursor **I.42** (Scheme 14).



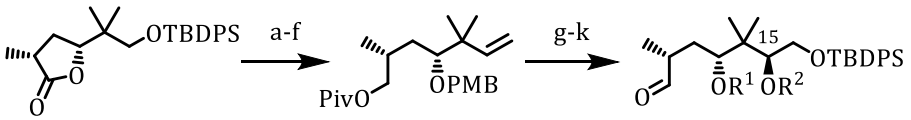
I.42 **I.56** **I.57**

a) CH_2=$CHCH_2MgBr$; b) Et_3SiH, $SnCl_4$, 71 %; c) NaH, BnBr, NaI, 87 %; d) TBAF, 98 %; e) Ph_3P, I_2, 94 %; j) $LiCH_2SO_2Ph$, 69 %.

*Scheme 14 - Synthesis of sulfone **I.57***

Addition of allyl Grignard to **I.42** followed by reduction of the hemiacetal with triethylsilane led to the corresponding tetrahydropyran which after a protection-deprotection sequence afforded primary alcohol **I.56**. This intermediate could then be transformed in two steps into the homologated sulfone **I.57** in good yields.

The elaboration of the aldehyde on the Northern fragment was achieved starting from the known lactone **I.50.** Reduction of the lactone functional group using lithium borohydride followed by protection of the primary and secondary alcohol led after further transformation to olefin **I.58** (Scheme 15). This substrate was subjected to the Sharpless asymmetric dihydroxylation to establish the chiral centre at C_{15} of the natural product. Protection of the diol and cleavage of the ester followed by oxidation with TPAP led to the coupling partner **I.59**.

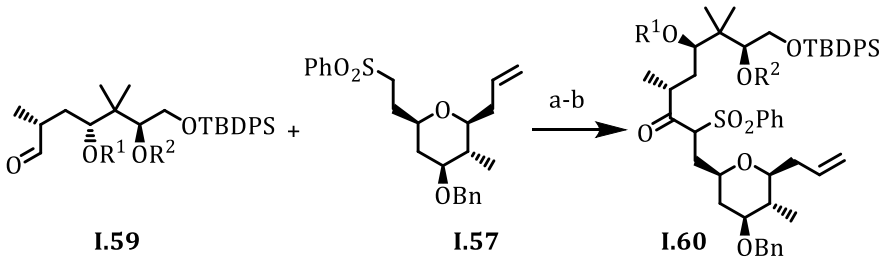


I.50 **I.58** **I.59**

a) $LiBH_4$, 93 %; b) PivCl, Py, 96 %; c) *p*-$CH_3OC_6H_4CH_2OC(=NH)CCl_3$, TfOH, 81 %; d) TBAF, 94 %; e) $(COCl)_2$, DMSO, NEt_3, 99 %; f) $Ph_3P=CH_2$, 89 %; g) OsO_4, $(DHQ)_2PYR$, $K_3Fe(CN)_6$, K_2CO_3, 99 %; h) TBDPSCl, Im; i) TESCl; Im, DMAP, 82 % over 2 steps; j) DIBAL-H, 79 %; k) TPAP, NMO, 89 %.

*Scheme 15 - Synthesis of aldehyde **I.59***

This time, the coupling reaction lead to the formation of the corresponding alcohol which was directly oxidised to the ketosulfone using Dess-Martin reagent (Scheme 16).



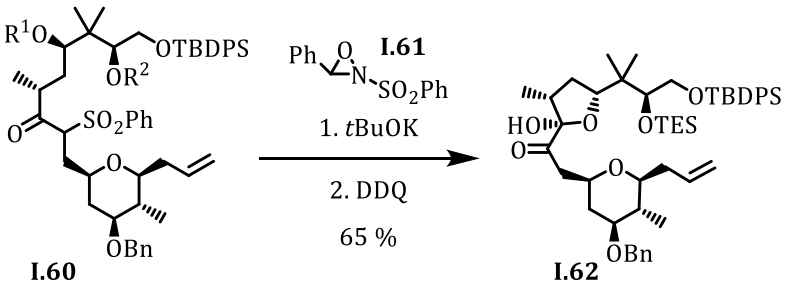
I.59 **I.57** **I.60**

R^1 : PMB, R^2 : TES R^1 : PMB, R^2 : TES

a) *n*BuLi, 76 %; b) Dess-Martin periodinane, 99 %.

*Scheme 16 - Synthesis of ketone **I.60***

From there, the α-ketosulfone **I.60** was transformed into the corresponding diketone. Cleavage of the PMB ether allowed the cyclization exclusively into the 5-membered ring lactol **I.62** in good yield (Scheme 17).



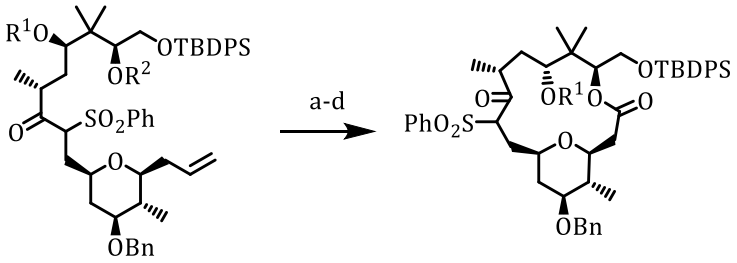
I.60 **I.62**

R^1 : PMB, R^2 : TES

*Scheme 17 - Synthesis of hemiacetal **I.62***

However, subsequent cleavage of the triethylsilyl ether protecting group did not give the desired product. The attempts to transform the lactol into the

corresponding methyl ketal failed as well, so they had to take a few steps back to continue the synthesis.



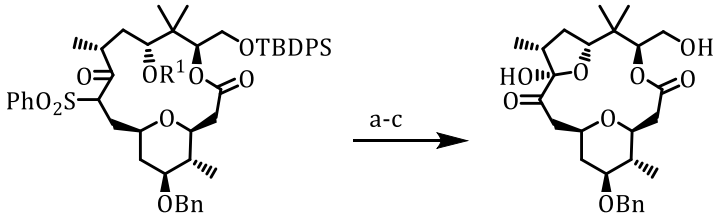
I.60
R^1 : PMB, R^2 : TES

I.63
R^1 : PMB

a) TsOH, 97 %; b) OsO_4, NMO, $NaIO_4$, 85 %; c) $NaClO_2$, NaH_2PO_4, 2-methylbutene, 88 %; d) 2,4,6-$Cl_3C_6H_2COCl$, NEt_3, DMAP, 82 %

*Scheme 18 - Synthesis of macrolactone **I.63***

The silyl ether was successfully removed from intermediate **I.60** (Scheme 18). Then, oxidative cleavage of the alkene produced the corresponding aldehyde which was oxidised to the acid using Pinnick's oxidation conditions. Treatment of this seco acid using the Yamaguchi procedure afforded the macrolactone **I.63** in an excellent yield of 82 %.



I.63
R^1 : PMB

I.64
R^1 : PMB

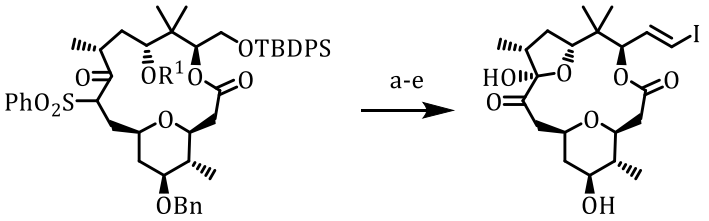
a) *t*BuOK, **I.61**, 70 %; b) DDQ, 63 %; c) HF.Pyr, 56 %

*Scheme 19 - Synthesis of hemiacetal **I.64***

From there, the previously used conditions for the formation of the diketone efficiently provided the desired product which could be transformed into the 5-membered ring lactol exclusively upon treatment with DDQ (Scheme 19). With this intermediate, the core structure of the aglycone was fully assembled.

To introduce the polyenic tail, cleavage of the remaining silyl ether using HF.Pyridine complex was successfully achieved. However, their numerous attempts to transform this primary alcohol **I.64** into the corresponding aldehyde failed. Once again, it seems that an early formation of the lactol forbids further

transformations to occur. With that observation, they decided that the formation of the lactol should be delayed as much as possible.



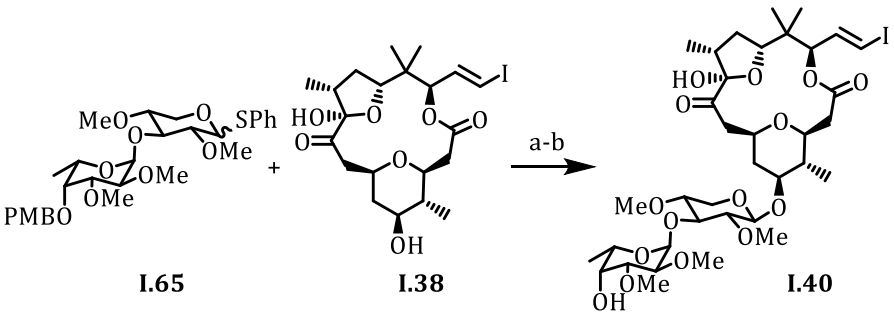
I.63
R^1 : PMB

I.38

a) HF.Py, 64 %; b) Dess-Martin periodinane, 90 %; c) $CrCl_2$, CHI_3, 77 %; d) *t*BuOK, **I.61**; e) DDQ, 73 % avec 2 steps.

*Scheme 20 - Synthesis of intermediate **I.38***

This was done starting from intermediate **I.63** (Scheme 20). The protected primary alcohol was transformed into the corresponding homologated vinyl iodide in 3 steps setting the stage for a cross coupling reaction. The oxidation of the α-ketosulfone was achieved using the same conditions as before giving lactol **I.38**.

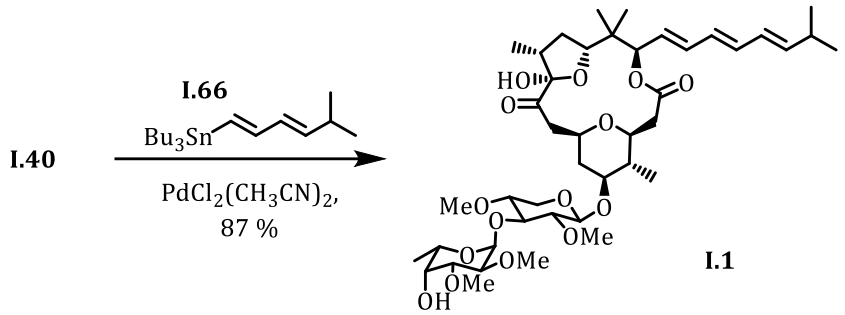


I.65 **I.38** **I.40**

a) NBS, 49 %; b) DDQ, 76 %

*Scheme 21 - Synthesis of **I.40***

The formation of the glycosidic bond could be performed either with the disaccharide protected by a silyl ether as well as the *p*-methoxybenzyl ether **I.65**. However, only the latter underwent a successful removal of the protecting group affording **I.40** (Scheme 21).



*Scheme 22 - Synthesis of Polycavernoside A **I.1***

With intermediate **I.40** in hand, the total synthesis of the natural product was achieved through a Stille coupling using the (*E,E*)-vinyl stannane **I.66** with an excellent yield of 87 % for the last step (Scheme 22).

Almost at the same time as Murai, Paquette had achieved the total synthesis of Polycavernoside A despite having encountered several synthetic issues. His work seems to reveal that the formation of the 5-membered ring lactol at an early stage of the synthesis can lead to a series of unreactive species or degradation and should be elaborated as late as possible in the synthesis.

I.2.3 Total synthesis by White (2001-2005)[14]

The disconnection strategy used by the group of James D. White from Oregon State University was identical to the two previous synthesis. The fragments were planned to be assembled using a Nozaki-Hiyami-Kishi reaction, a Yamaguchi macrolactonisation and a Stille coupling for the polyene (Figure 8).

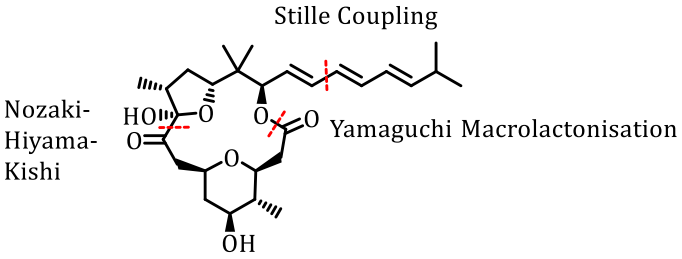
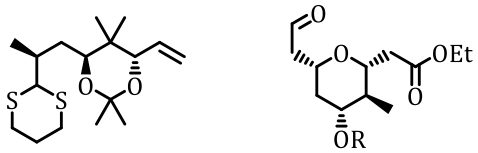


Figure 8 - Disconnection strategy of White

White's group started their work on this topic around the same time as Murai and Paquette. In their first endeavour, they were not aware of the absolute stereochemistry of Polycavernoside A. To overcome this situation, they used strategies that allowed access to both antipodes through the same synthetic pathway.

In their first approach, they planned linking the Northern and Southern fragments using a 1,3-dithiane **I.67** and an aldehyde **I.68** (Figure 9).

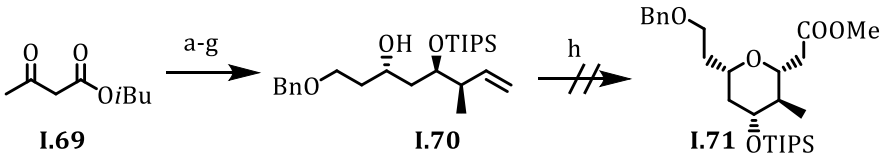


I.67 **I.68**

Figure 9 - Structure of White Northern and Southern fragments

They wanted to form the tetrahydropyran ring of **I.68** through a 6-exo cyclisation of an alcohol onto a double bond under palladium catalysis in the presence of carbon monoxide and methanol. Therefore, they prepared alcohol **I.70** in a 7 step sequence in which the asymmetry was controlled by the reduction of β-ketoester **I.69** using Noyori's catalyst and an asymmetric crotylation using Brown's conditions. However, intermediate **I.70** failed to give the cyclisation product (Scheme 23).

[14] J. D. White, P. R. Blakemore, C. C. Browder, J. Hong, C. M. Lincoln, P. a. Nagornyy, L. a. Robarge, D. J. Wardrop, *J. Am. Chem. Soc.*, **2001**, *123*, *5*, 8593–8595; P. R. Blakemore, C. C. Browder, J. Hong, C. M. Lincoln, P. A. Nagornyy, L. A. Robarge, D. J. Wardrop, J. D. White, *J. Org. Chem.*, **2005**, *70*, *14*, 5449–5460.



a) NaH, *n*BuLi then BOMCl, 56 %; b) H_2, $RuCl_4$[(*S*)-BINAP].NEt_3, 95 %; c) TBSOTF, 2,6-Lutidine, 100 %; d) DIBAL-H, 100 %; e) *cis*-2-butene, *n*BuLi, *t*BuOK, (-)-$(Ipc)_2$BOMe, 47 %; f) TIPSOTf, 2,6-Lutidine, 87 %; g) PPTS, 63 %; h) $Pd(OAc)_2$, CO, MeOH.

*Scheme 23 - Attempts to prepare **I.71** from alcohol **I.70***

They hypothesised that it was due to an important steric hindrance in the transition state of the palladium complex since the silyl ether and the methyl group both lie in the equatorial position as represented in Figure 10.

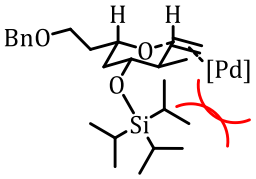
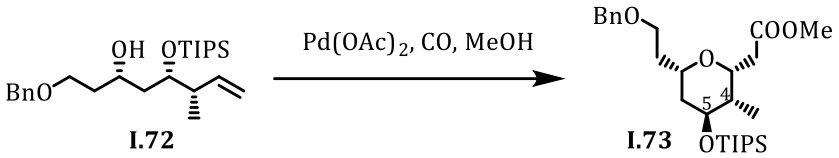


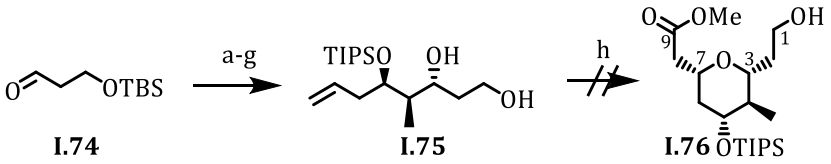
*Figure 10 - Model proposed for the cyclisation of **I.70***

An inversion of these centres led to the tetrahydropyran **I.68**. However, this intermediate did not have the correct stereochemistry at C_4 and C_5 (Scheme 24).



*Scheme 24 - Cyclisation of alcohol **I.72***

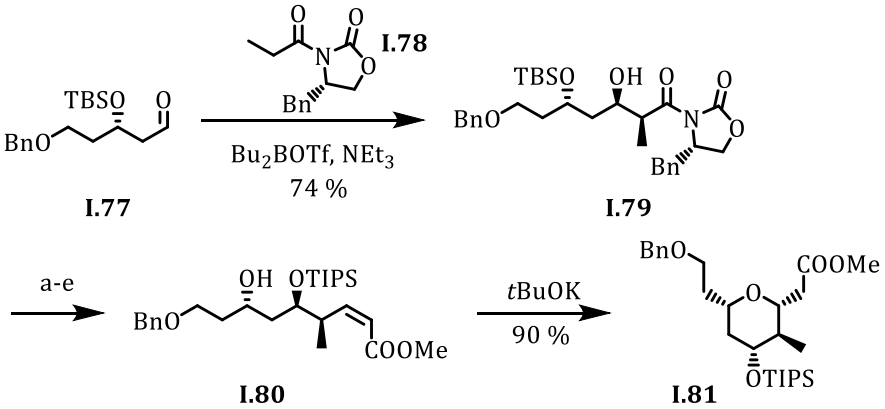
This result led them to a new approach using the same reaction. The required intermediate was prepared in 6 steps starting from aldehyde **I.74** (Scheme 25).



a) *trans*-2-butene, *t*BuOK, *n*BuLi, (-)-$(Ipc)_2BOMe$, $BF_3.Et_2O$, 70 %, dr 12:1, 88 % *ee*; b) PhCOCl, Py, 87 %; c) O_3 then Me_2S, 75 %; d) AllylMgBr, (+)-$(Ipc)_2BOMe$, 93 %; e) TIPSOTf, 2.6-Lutidine, 90 %; f) DIBAL-H, 92 %; g) HF.Py, 91 %; h) $PdCl_2$, CuCl, CO, MeOH.

*Scheme 25 - Attempts to prepare tetrahydropyran **I.76***

Once again, the cyclization they had planned failed. At this point, the Pd-mediated cyclization was abandoned and they moved to a more classical approach similar to the one used by Murai's group.

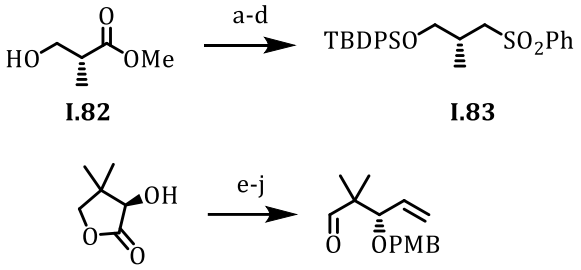


a) MeOHNMe.HCl, $AlMe_3$, 74 %; b) TIPSOTf, 2,6-Lutidine, 94 %; c) DIBAL-H, 96 %; d) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, KHMDS, 18-crown-6, 94 %; e) PPTS, 86 %

*Scheme 26 - Synthesis of tetrahydropyran **I.81***

Starting from aldehyde **I.77** prepared previously, Evans aldol chemistry allowed them to install two chiral centres (Scheme 26). Then, derivatization of this intermediate and olefination using Still-Gennari conditions led to the (*Z*)-Michael acceptor **I.80**. Treatment of this intermediate with potassium *tert*-butoxide led smoothly to the desired tetrahydropyran **I.81**. Deprotection of the benzyl ether followed by oxidation to the aldehyde allowed the isolation of a crystalline compound possessing the right the stereochemistry.

For the elaboration of the Northern fragment, they had chosen (*R*)-pantolactone **I.47** and (*R*)-Roche's ester **I.82** as chiral pool. A 4 step sequence allowed the preparation of sulfone **I.83** while 6 steps were required to reach aldehyde **I.84** (Scheme 27).



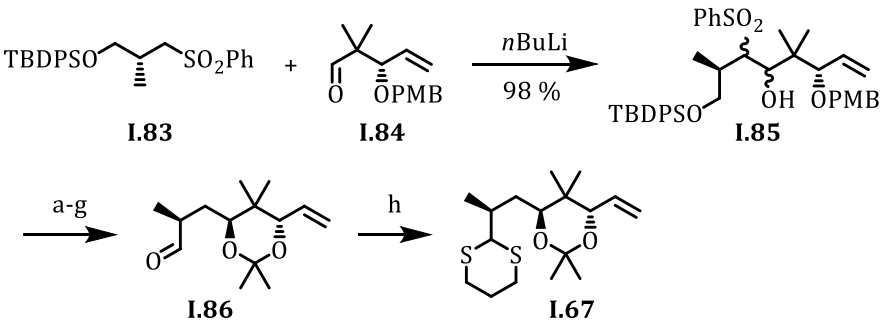
I.82 **I.83**

I.47 **I.84**

a) TBDPSCl, Im; b) $Ca(BH_4)_2$, 92 % over 2 steps; c) PhSSPh, Bu_3P, 90 %; d) Oxone, 82 %; e) $LiAlH_4$, 97 %; f) *p*-$MeOC_6H_4CH(OMe)_2$, $OPCl_3$, 78 %; g) $(COCl)_2$, DMSO, NEt_3, 89 %; h) Ph_3PCH_3Br, *n*BuLi, 89 %; i) DIBAL-H, 97 %; j) $(COCl)_2$, DMSO, NEt_3, 98 %.

*Scheme 27 - Synthesis of sulfone **I.83** and aldehyde **I.84***

From there, the two subunits were assembled through the addition of the sulfone anion to the aldehyde in a non-diastereoselective process affording **I.85** (Scheme 28)**.** The secondary alcohol could be oxidized to the ketone using Dess-Martin reagent and the reduction of the sulfone was carried out using samarium iodide. Subsequent reduction of the ketone proved to be selective with the help of the proximal alcohol acting as a directing group. Protection of the diol and derivatization of the primary alcohol led to aldehyde **I.86** and then dithiane **I.67**.



I.83 **I.84** **I.85**

I.86 **I.67**

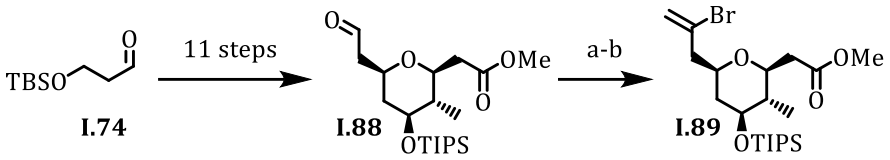
a) Dess-Martin periodinane, 96 %; b) SmI_2, 93 %; c) DDQ, 99 %; d) $Me_4NBH(OAc)_3$, 66 %; e) $Me_2C(OMe)_2$, PPTS, 91 %; f) TBAF, 99 %; g) $(COCl)_2$, DMSO, NEt_3, 75 %; h) $Me_3SiS(CH_2)_3SSiMe_3$, ZnI_2, 40 %.

*Scheme 28 - Synthesis of dithiane **I.67***

However, their attempts to link an aldehyde derived from **I.81** and dithiane **I.67** failed. They proposed that this lack of reactivity was due to the formation of an exceptionally stable 6-membered ring chelate between the lithium and the ketal oxygen atom. This observation can be linked to the problems observed by Paquette.

Around the same time, Murai's work in asserting the absolute stereochemistry of the natural macrolide came out and revealed that they were working towards the wrong enantiomer. The group had no choice but to prepare the antipode of their fragment and modify the strategy used for the coupling reaction.

For the Southern fragment, aldehyde **I.88,** the antipode of aldehyde **I.63,** was prepared in an analogous manner in 11 steps and was transformed into the corresponding vinyl bromide in two steps (Scheme 29).

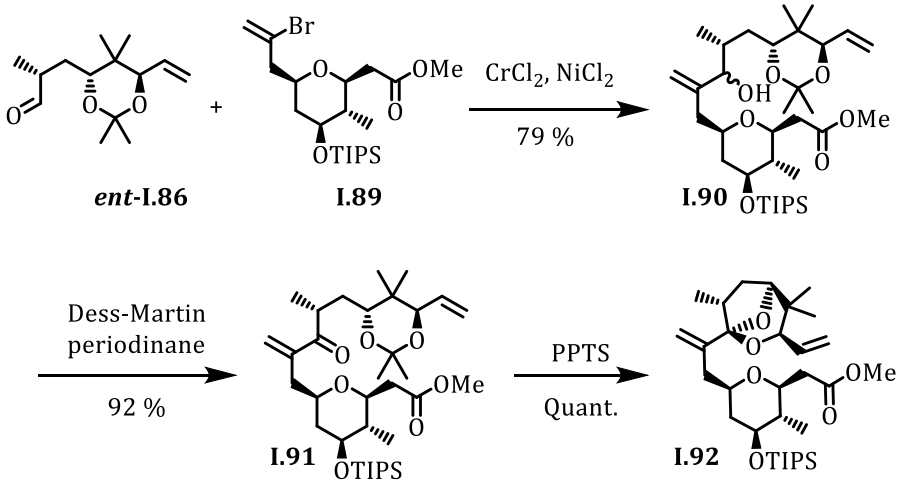


a) $CH_3COC(N_2)P(O)(OMe)_2$, K_2CO_3, 84 %; b) B-Br-9-BBN, 77%.

*Scheme 29 - Synthesis of vinyl bromide **I.89***

The Northern fragment was prepared following the exact same reaction sequence starting from (*S*)-pantolactone.

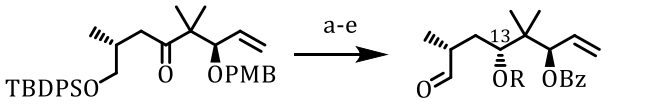
This time, the Nozaki-Hiyama-Kishi coupling they had planned led to the formation of the coupling product with an excellent yield of 79 % affording alcohol **I.90** as a mixture of epimers (Scheme 30). Oxidation using Dess-Martin conditions led to the corresponding enone **I.91**. However, their attempt to form the 5-membered ring ketal by unravelling the 1,3-diol led to the formation of a tricyclic ketal **I.92** that proved to be rather unreactive.



*Scheme 30 - Coupling of aldehyde **ent-I.86** with vinyl bromide **I.84***

This result led them to change the protecting group and aldehyde **I.94** was therefore synthesized (Scheme 31). Since a free alcohol could not be used as

directing group, they switched to an Evans-Tischenko reaction to control de stereochemistry at C_{13}.

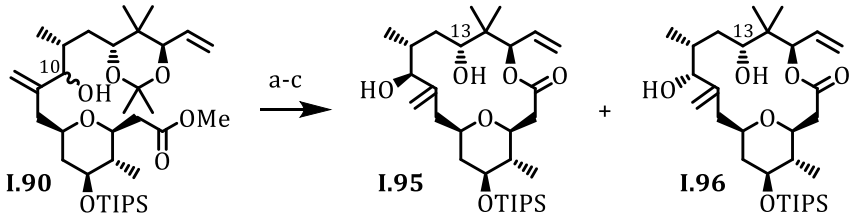


I.93 **I.94** R : PMB

a) DDQ, 99 %; b) PhCHO, SmI_2 cat., 60 %; c) $Cl_3C(=NH)OPMB$, CSA, 51 %; d) TBAF, 89 %; e) $(COCl)_2$, DMSO, NEt_3, 94 %.

*Scheme 31 - Synthesis of aldehyde **I.94***

Unfortunately, aldehyde **I.94** revealed to be a bad candidate for the Nozaki-Hiyama-Kishi reaction. Indeed, due to the excess of chromium (II) used in the reaction, reduction of the benzoate was observed as a side reaction. They envisioned other strategies involving replacement of the benzoate protecting group by an acetate but those proved to be unfruitful as well since migration of the protecting group never allowed to get to the aldehyde. Their last resort led to a strategy where no protecting group was used, leaving a macrolactonisation step for which the reaction could occur with either one of three hydroxyl groups. Computational studies were carried out based on the proposed mechanism of the Yamaguchi coupling and came to the conclusion that the formation of the 16-membered ring lactone should be the lowest in energy for whichever epimer of the C_{10} hydroxy group. Separation of the diastereoisomer of **I.90** followed by deprotection and hydrolysis of the ester afforded intermediates which upon treatment under Yamaguchi conditions afforded the desired 16-membered lactone **I.95** and **I.96** (Scheme 32).

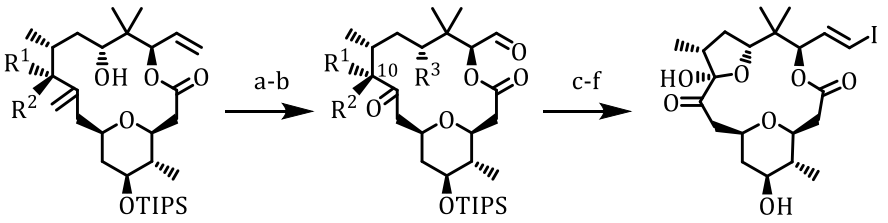


I.90 OTIPS **I.95** OTIPS **I.96** OTIPS

a) Separation; b) PPTS; c) NaOH; c) 2,4,6-$Cl_3C_6H_2COCl$, DMAP, 75 % from **(*10S*)-I.90** and 46 % from **(*10R*)-I.90**.

*Scheme 32 - Synthesis of macrolactone **I.95** and **I.96***

At this point, it proved to be of upmost importance to protect the C_{13} hydroxy group before conducting further modification on the scaffold. This was achieved by treatment of diol **I.95** and **I.96** with triethylsilyl triflate followed by the ozonolysis of the diene to the ketoaldehyde **I.93** and **I.94** (Scheme 33)**.** These intermediates were converted into the corresponding vinyl iodides using iodoform and chromium dichloride. Cleavage of the triethylsilyl ether at C_{10}, oxidation with Dess-Martin reagent and treatment in acidic media led to the isolation of the core unit of Polycavernoside A.



I.95 R^1= H, R^2= OH
I.96 R^1= OH, R^2= H
I.97 R^1= H, R^2= OTES, R^3= OTES
I.98 R^1= OTES, R^2= H, R^3= OTES
I.38

a) TESOTf, 2,6-Lutidine; b) O_3 then PPh_3; c) CHI_3, $CrCl_2$,; d) PPTS, 51 % from **I.95** and 27 % from **I.96** over 4 steps; e) Dess-Martin periodinane; f) HF.Pyr, 88 % over 2 steps.

*Scheme 33 - Synthesis of **I.38** by White*

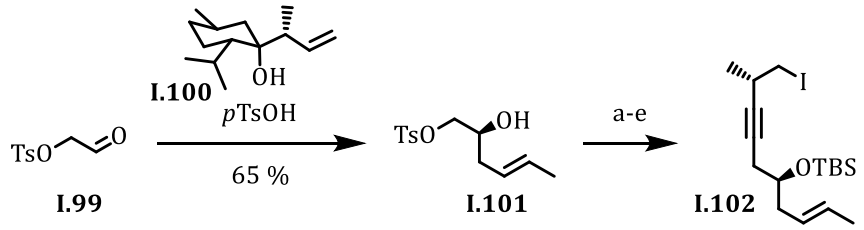
From intermediate **I.38**, they were able to reach the natural product using the exact same conditions as the one described by Paquette's group in three steps involving glycosidation, deprotection of the benzyl ether of the glycoside and a Palladium cross-coupling following Stille conditions.

After having encountered several dead ends along their journey, White and co-workers were able to complete the total synthesis of Polycavernoside A. The elaboration used a Nozaki-Hiyama-Kishi coupling to form the C_9-C_{10} bond and the macrolactonisation, which could have led to the formation of 3 possible products, revealed to be completely selective for the desired product.

I.2.4 Total synthesis by Lee (2010)[15]

In a short JACS Communication published in 2010, the group of Eun Lee from the Seoul National University described the total synthesis of Polycavernoside A. In their strategy, the macrocycle is generated by a Prins-type reaction involving a homoallylic alcohol and a synthetic equivalent of an aldehyde.

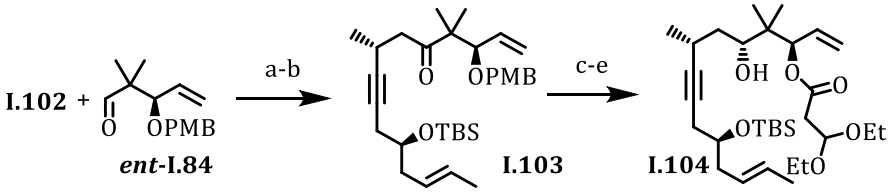
Their synthesis started with aldehyde **I.99** which was transformed into homoallylic alcohol **I.101** using the asymmetric allyl transfer methodology developed by the group of Nokami[16] with exclusive formation of the (*E*)-double bond (Scheme 34).



a) NaH, (*R*)-TBDPSOCH$_2$CHCH$_3$CCH, *n*BuLi, BF_3.Et_2O, 89 %; b) HCl; c) TsCl; d) TBSOTf; e) NaI, 80 % over 4 steps.

*Scheme 34 - Preparation of alkyne **I.102***

Treatment of **I.101** with sodium hydride lead to the formation of the corresponding epoxide which upon treatment with an acetylene anion in the presence of boron trifluoride led to the formation of a primary iodide in the form of **I.102**.



a) *t*BuLi; b) DMP; c) DDQ; d) $Me_4NBH(OAc)_3$; e) $(EtO)_2CHCH_2COOH$, DCC, DMAP, 53 % over 5 steps.

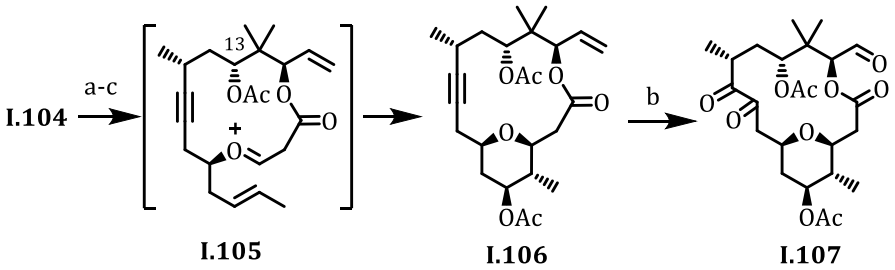
*Scheme 35 - Synthesis of acetal **I.104***

Lithium-halogen exchange on **I.102** using *tert*-butyllithium followed by addition of aldehyde ***ent*-I.84**, previously described by White, led to the corresponding alcohol as a 1.1:1 mixture of diastereoisomers that were subsequently oxidised into the corresponding ketone **I.103** using Dess-Martin's reagent (Scheme 35). Cleavage of the PMB ether upon addition of DDQ followed by a reduction using

[15] S. K. Woo, E. Lee, *J. Am. Chem. Soc.*, **2010**, *132*, 4564–4565.

[16] J. Nokami, M. Ohga, H. Nakamoto, T. Matsubara, I. Hussain, K. Kataoka, *J. Am. Chem. Soc.*, **2001**, *123*, *37*, 9168–9169.

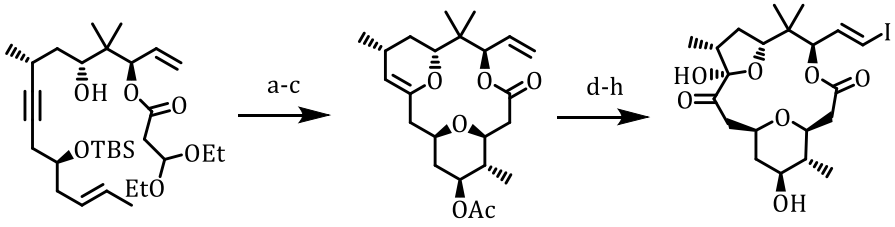
tetramethylammonium triacetoxyborohydride allowed the formation of the secondary alcohol with a selectivity of 6:1 in favour of the desired diastereoisomer. The use of Steglich's condition in the presence of a propionic acid derivative lead to the formation of **I.104**, the precursor required for the planned macrocyclisation.



a) Ac_2O, DMAP; b) HF.Pyr, 90 % over 2 steps; c) TESOTf, TMSOAc, AcOH, 85 %; d) O_3, PPh_3, 79 %.

*Scheme 36 - Synthesis of macrolactone **I.107***

The protection of the C_{13} hydroxy group and the cleavage of the TBS protecting group were carried out, followed by treatment in the conditions developed for the Prins macrocyclisation (Scheme 36). The desired tetrahydropyran was formed with an excellent yield of 85 % in a 6:1 mixture of diastereoisomer. The minor product of the transformation was the tetrahydropyran bearing the acetate group in an axial configuration. The formation of macrolactone **I.106** is proposed to occur through the formation of the oxonium **I.105**. This reaction intermediate can be trapped by the proximal alkene. The generated carbocation can then be quenched by the solvent which is acetic acid or by trimethylsilyl acetate. Compound **I.106** was then treated with ozone leading to the formation of diketoaldehyde **I.107** in good yield. However, the use of Takai's conditions to form the vinyl iodide required for the insertion of the polyenic tail led to the formation of a complex mixture that could not be used to continue the synthesis. Their rationalisation of this result was interference of the diketone in **I.107**. Since selective protection of the diketone seemed impractical and selective deprotection of one acetate versus the other proved troublesome, they decided to take a few steps back.



I.104 **I.108** **I.38**

a) HF.Pyr, 81 %; b) TESOTf, TMSOAc, AcOH, 69 %; c) $PtCl_2$, CO, K_2CO_3, 4A MS; d) DMDO, PPTS, MeOH; e) TPAP, NMO, 4A MS, 72 % over 3 steps; f) O_3, PPh_3; g) $CrCl_2$, CHI_3; h) K_2CO_3, 54 % over 3 steps.

*Scheme 37 - Synthesis of intermediate **I.38** by Eun Lee's group*

From an intermediate **I.104**, removal of the silyl protecting group followed, by treatment under the Prins conditions led to the formation of the desired tetrahydropyran in a 5.5:1 ratio in favour of the desired diastereoisomer (Scheme 37). From there, subsequent reaction with a platinum (II) salt lead to the formation of dihydropyran **I.108**. Epoxidation of the electron rich olefin using DMDO and oxidation with TPAP and NMO afforded the corresponding α-ketoacetal. This intermediate underwent cleanly the two steps required for the formation of the vinyl iodide, and treatment with potassium carbonate set the stage for the glycosidation reaction to come. They were delighted to see that prolonged exposure to Takai's conditions led to the formation of the furan hemiacetal. The intermediate **I.38**, identical to the ones prepared by Paquette and White independently led them to the natural product using the same conditions.

The group of Eun Lee developed a new way to access Polycavernoside A. This approach is straightforward. Even if their strategy is more linear, they were able to be competitive in terms of steps and yield compared to the work of other groups. The challenging Prins cyclisation proved to be reliable for the elaboration of the macrolactone with excellent yields.

I.2.5 Total synthesis by Makoto Sasaki (2012-2017)[17]

The group of Makoto Sasaki from the Tohoku University in Japan was as well interested in the total synthesis of Polycavernoside A. Their first report on the subject was published in Organic Letters in 2012 but they also reported in 2017 an improved synthesis of the Northern fragment as well as the total synthesis of Polycavernoside B. We will herein describe their synthesis of the intermediate **I.38**, identical to the one prepared by other groups previously.

Their strategy was to unite the two key fragments using a Suzuki-Miyaura coupling and a macrolactonisation reaction (Figure 11).

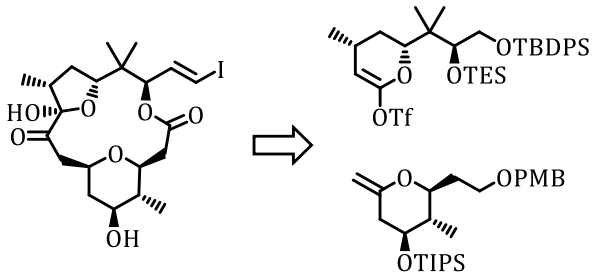
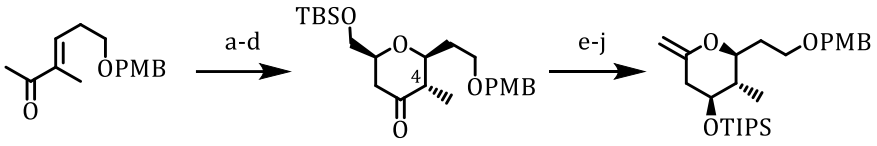


Figure 11 - Sasaki's disconnection of Polycavernoside A aglycone

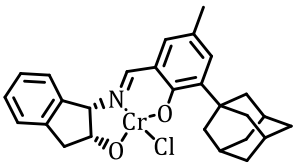
Their synthesis of the southern subunit started with ketone **I.109** that can be prepared readily from 1,3-propanediol (Scheme 38). Formation of the corresponding silyl enol ether led to an electron rich diene. This intermediate was subjected to a hetero Diels-Alder reaction in the presence of an aldehyde derived from ethylene glycol and Jacobsen's tridentate chromium catalyst allowing the formation of the cyclic ether. Hydrolysis of the enol ether led to a mixture of diastereoisomers at C_4 in a 6:1 ratio which could be easily converted into the desired compound using DBU. With ketone **I.110** in hand, Luche reduction smoothly led to the insertion of the last asymmetric centre of the tetrahydropyran. Protection of the newly formed alcohol, cleavage of the TBS ether followed by Ramirez reaction afforded the corresponding primary iodide that could then be transformed into the key unit **I.111** using potassium *tert*-butoxide. This last step concluded an elegant and efficient synthesis of their Southern fragment.

[17] Y. Kasai, T. Ito, M. Sasaki, *Org. Lett.*, **2012**, *14*, *12*, 3186–3189; K. Iwasaki, S. Sasaki, Y. Kasai, Y. Kawashima, S. Sasaki, T. Ito, M. Yotsu-Yamashita, M. Sasaki, *J. Org. Chem.*, **2017**, *82*, *24*, 13204–13219.



I.109 **I.110** **I.111**

a) NEt_3, TMSOTF; b) $TBSOCH_2CHO$, Jacobsen catalyst (**I.112**), 4A MS; c) K_2CO_3; d) DBU, 60 % over 4 steps; e) $NaBH_4$, $CeCl_3$. $7H_2O$, 94 %; f) TIPSOTf, 2.6-Lutidine, quantitative; g) CSA, 95 %; h) I_2, PPh_3, Im, 91 %; j) *t*BuOK

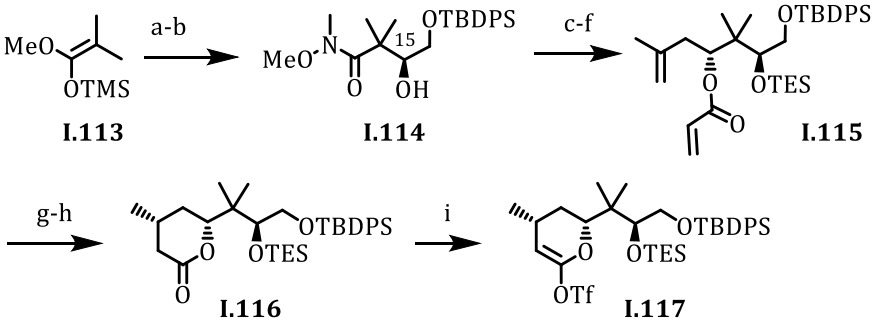


I.112
Jacobsen catalyst

*Scheme 38 - Synthesis of tetrahydropyran **I.111***

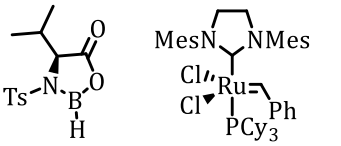
In their first paper, Sasaki reported a 14 steps sequence of the C_9-C_{16} fragment starting from (*R*)-citronellal. Later, they developed a shorter sequence for this key compound that will be described here.

This optimised procedure started from ketene acetal **I.113** that underwent an enantioselective aldol reaction with an aldehyde prepared from ethylene glycol in the presence of N-tosylated valine and borane-THF complex (Scheme 39). In this process, the species **I.118** is generated and acts as a Lewis acid catalyst for the aldol reaction. The ester could then be transformed into the corresponding Weinreb **I.114** amide using classical conditions.



I.113 **I.114** **I.115** **I.116** **I.117**

a) N-Ts-L-Valine, BH_3.THF, $TDBPSOCH_2CHO$, 65 %; b) MeNH(OMe).HCl, *n*BuLi, 79 %; c) MethallylMgCl, 82 %; d) TESCl, Im, 95 %; e) DIBAL-H, *n*BuLi, 62 %; f) Acryloyl chloride, *i*Pr_2NEt, 91 %; g) Grubb's II catalyst (**I.119**) , quantitative; h) H_2, Pd/C, 98 %; i) KHMDS, $PhNTf_2$.

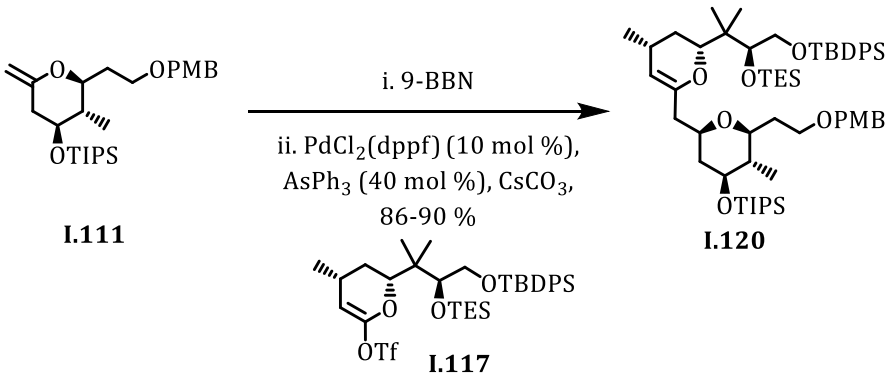


I.118 **I.119**

Grubb's II catalyst

*Scheme 39 - Synthesis of dihydropyran **I.117***

Addition of methallyl Grignard onto intermediate **I.114** proceeded smoothly. While their attempts to use the hydroxy group at C_{15} as a directing group for the reduction of the ketone failed, they were delighted to see that once this alcohol was protected as a TES ether, the reduction proceeded nicely using a mixture of DIBAL-H and *n*BuLi leading to the desired 1,3-*anti*-diol in a 7:1 ratio. Addition of acryloyl chloride led to compound **I.111** which under the action of the second-generation Grubb's catalyst **I.119** led to the formation of cyclic Michael acceptor. Reduction by hydrogenation proceeded with good diastereoselectivity (7:1) affording lactone **I.116**. The desired coupling partner **I.117** could then be prepared by treatment with KHMDS and Collins reagent.

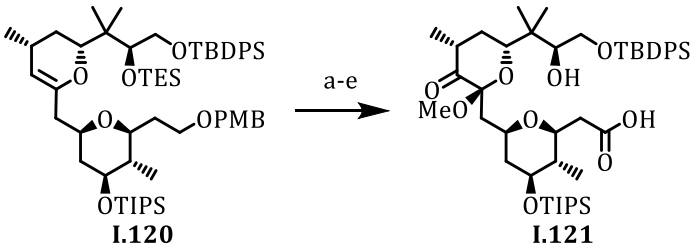


I.111 **I.120** **I.117**

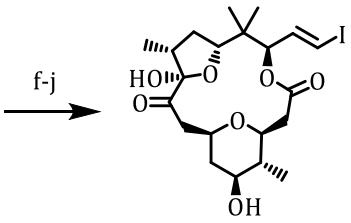
*Scheme 40 - Synthesis of enol ether **I.120***

With vinyl triflate **I.117** and enol ether **I.111** in hands, they could attempt their union using the planned Suzuki-Miyaura cross coupling. Although their previous

attempts with an enol phosphate and the borane generated by reaction of **I.111** with 9-BBN only led to low yield, the use of a more reactive partner in the form of **I.117** gave them promising results (Scheme 40). Optimisation of the conditions led to an excellent yield of 86-90 %. The sensitive enol ether **I.120** was used directly and treated with *m*-chloroperbenzoic acid in the presence of methanol leading to a mixture of diastereoisomers (2.4:1 ratio) (Scheme 41). Nevertheless, their subsequent oxidation led to a single compound in the form of α-ketoacetal **I.121**.



I.120 **I.121**



I.38

a) *m*CPBA, $NaHCO_3$, 82 %; b) TPAP, NMO, 4A MS, 89 %; c) CSA; d) DDQ, 84 % over 2 steps; e) TEMPO, BAIB, H_2O, 97 %; f) DCC, PPTS, Pyr, 89 %; g) HF.Pyr, 85 %; h) DMP, $NaHCO_3$, 88 %; i) CHI_3, $CrCl_2$, 81 %; j) TFA, H_2O, 98 %.

*Scheme 41 - Synthesis of macrolactone **I.38** by Sasaki*

From there, seco acid **I.121** could be transformed into the lactone using the conditions developed by Keck's group. At this point, access to intermediate **I.38** common to the previous total synthesis proceeded smoothly in 4 steps. With this intermediate, the total synthesis was achieved using the same steps as described before.

The group of Makoto Sasaki performed the total synthesis of Polycavernoside A and Polycavernoside B. An asymmetric Diels-Alder reaction allowed a straightforward access to their Southern fragment while an asymmetric aldol reaction, an olefin metathesis and a selective hydrogenation led to the Northern fragment. Their coupling strategy based on a Suzuki-Miyaura cross coupling proved to be well suited for the union of their two keys fragments leading to the natural product in an efficient manner.

I.2.6 Formal synthesis by Fürstner (2013)[18]

The group of Alois Fürstner from the Max-Planck-Institut für Kohlenforschung in Mulheim also brought their contribution to the story of Polycavernoside A. They described a formal synthesis of the natural product where they intercepted intermediate **I.108** described by Lee. Their purpose throughout this work was to test the robustness of different catalytic reactions and asymmetric synthesis methodologies towards more advanced and complex intermediates. Their disconnection in this approach was through the cleavage of the C_9-C_{10} bond and the lactone bond leading to the synthons depicted in Figure 12.

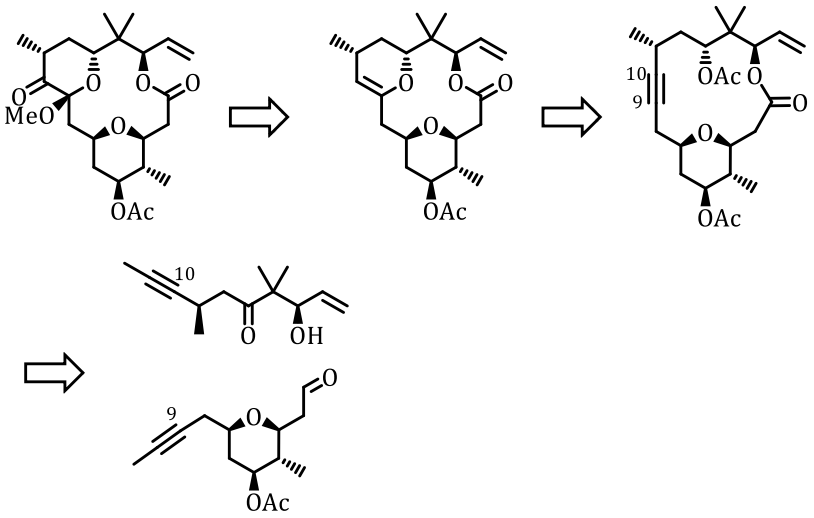
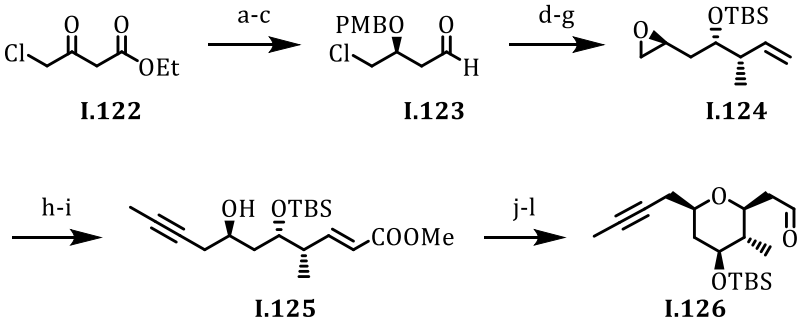


Figure 12 - Disconnection of Polycavernoside A aglycone by Fürstner

The synthesis of the tetrahydropyran fragment started with β-ketoester **I.122** that underwent a Noyori hydrogenation followed by protection of the newly formed secondary alcohol (Scheme 42). Reduction of the ester to the aldehyde **I.123** was carried out using DIBAL-H in toluene which was followed by an asymmetric allylation using (*Z*)-crotyl reagent **I.128** leading to the corresponding homoallylic alcohol with excellent enantiomeric excess. The subsequent protection of the free alcohol and removal of the PMB ether allowed after treatment with potassium hydroxide the isolation of terminal epoxide **I.124**.

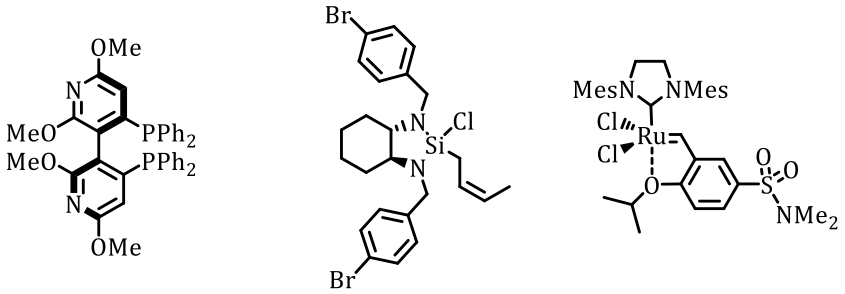
[18] L. Brewitz, J. Llaveria, A. Yada, A. Fürstner, *Chem. - A Eur. J.*, **2013**, *19*, *14*, 4532–4537.



I.122 **I.123** **I.124**

I.125 **I.126**

a) $[RuCl_2((R)\text{-P-Phos})](DMF)_n$, H_2 (35 bar), 94 %, 96 % *ee*; b) $PMBOC(NH)CCl_3$, $Cu(OTf)_2$, 82 %; c) DIBAL-H, 88 %; d) **I.128**, $Sc(OTf)_3$, 78 %; e) TBSCl, Im, DMAP, 85 %; f) DDQ, 99 %; g) KOH, 94 %; h) Methyl acrylate, **I.129,** 75 %; i) *n*BuLi, HCCH, $BF_3.Et_2O$, 89 %; j) *t*BuOK, 58 %; k) DBU, LiCl, 84 %; l) DIBAL-H, 86 %.



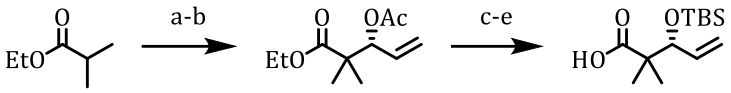
I.127
(*R*)-P-Phos

I.128 **I.129**

Scheme 42 - Synthesis of Fürstner Southern fragment

Olefin metathesis with methyl acrylate using catalyst **I.129** led to the corresponding Michael acceptor bearing an (*E*)-double bond**.** Opening of the epoxide with propyne anion in the presence of boron trifluoride gave secondary alcohol **I.125**. While the use of potassium *tert*-butoxide led to the formation of the *trans*-tetrahydropyran, they found that treatment in the presence of lithium chloride and DBU at high temperature furnished the desired *cis*-isomer. The last step of the synthesis of this Southern fragment was the reduction of the ester to the aldehyde which was accomplished using DIBAL-H affording aldehyde **I.126**.

The assembly of the Northern fragment started with ethyl isobutyrate **I.130** which was subjected to an aldol reaction with acrolein (Scheme 43). The aldol intermediate was then used in a kinetic resolution using Novozyme 435 and vinyl acetate producing enantiomerically enriched acetate **I.131**. The acetate was then replaced by a TBS protecting group in three steps with hydrolysis of the ester to the acid during the process.

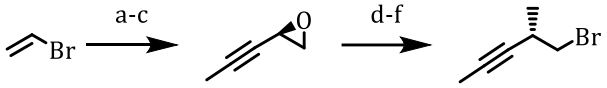


I.130 **I.131** **I.132**

a) LDA, acrolein, 94 %; b) Novozyme 435, vinyl acetate, 33 %, 99 % *ee*; c) NaOH; d) TBSCl, Im; e) K_2CO_3, 67 % over three steps.

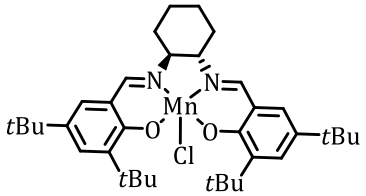
*Scheme 43 - Synthesis of acid **I.132***

Meanwhile, to insert the C_{10}-C_{12} portion, a Sonogashira cross-coupling between vinyl bromide **I.133** and propyne afforded the pent-1-en-3-yne (Scheme 44). This olefin was subjected to both the epoxidation and the kinetic resolution developed by Jacobsen to improve both the yield and the enantiomeric access. This strategy proved efficient since the desired product **I.134** could be isolated with 73 % and more than 99 % *e.e*. Opening of the terminal epoxide with methyl lithium in the presence of boron trifluoride occurred at the internal electrophilic centre with excellent regioselectivity leading to the corresponding alcohol which was then converted into the bromide **I.135** in two steps.

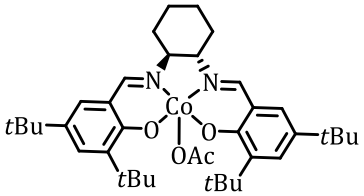


I.133 **I.134** **I.135**

a) Propyne, $[(PPh_3)_2PdCl_2]$, CuI, Et_3N, 81 %; b) **I.136**, NaClO; c) **I.137**, H_2O, 73 % over two steps, 99 % *ee*; d) MeLi, $BF_3.Et_2O$; e) TsCl, Et_3N, DMAP, 71 % over two steps; f) LiBr, 86 %.



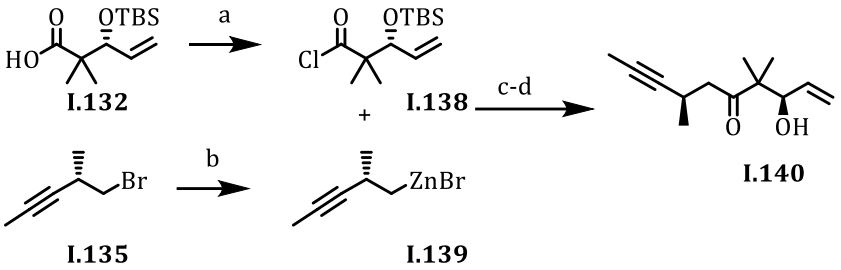
I.136
Jacobsen's asymmetric epoxidation catalyst



I.137
Jacobsen's kinetic resolution catalyst

*Scheme 44 - Synthesis of bromide **I.135***

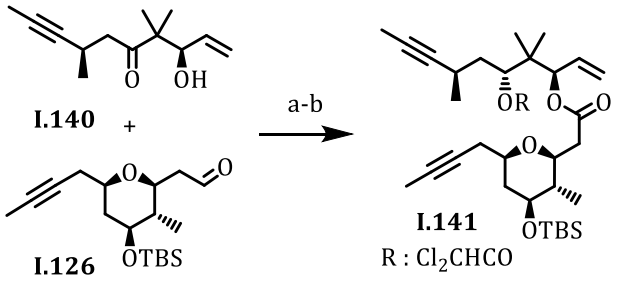
The union of **I.132** with **I.135** required transforming the acid into the corresponding acyl chloride **I.138** and the bromide into the corresponding organozinc **I.139** (Scheme 45). Their assembly proceeded smoothly in the presence of a copper complex and allowed the isolation of alcohol **I.140** in good yield.



a) $(COCl)_2$, quantitative; b) Zn; c) CuCN.2LiCl; d) TFA, 67 % over two steps.

*Scheme 45 - Synthesis of alkyne **I.140***

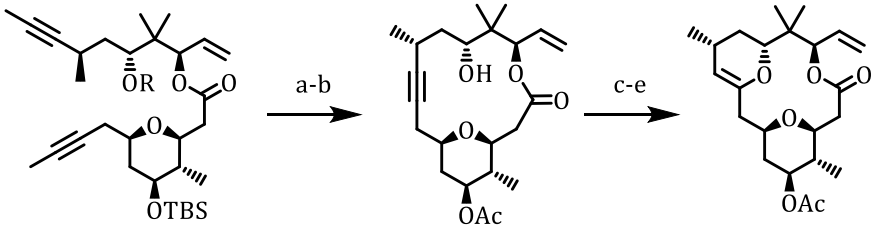
From there, the two fragments were ready to be assembled through the planned Evans-Tishchenko coupling. In the classical reaction conditions (35 mol % SmI_2 in THF at -10°C), they observed the formation of a side product in an equal amount as the starting material, arising from a retroaldol reaction of **I.140** followed by the addition onto the Southern fragment (Scheme 46). This was overcome by lowering the temperature but required an increase of the samarium catalyst loading to ensure sufficient conversion into the desired product **I.141**.



a) SmI_2 (50 mol %), - 50 °C, 68 %; b) $(Cl_2CHCO)_2O$, Pyr, 94 %.

*Scheme 46 - Preparation of ester **I.141***

The formation of the C_9-C_{10} bond was efficiently achieved using alkyne metathesis with catalyst **I.143** (Scheme 47). Subsequent hydrolysis led to the isolation of macrolactone **I.142**.

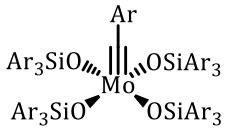


I.141
R : Cl_2CHCO

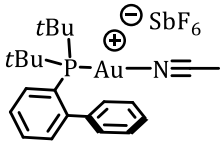
I.142

I.108

a) **I.143**, 5A MS, 91 %; b) K_2CO_3, MeOH, 80 %; c) TFA, 76 %; d) Ac_2O, Pyr, 97 %; e) **I.144**, 4A MS, 84 %.



I.143 Ar : *p*$MeOC_6H_4$



I.144

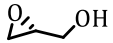
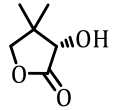
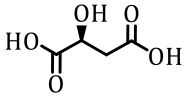
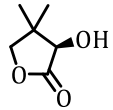
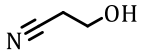
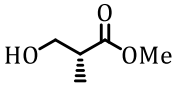
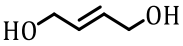
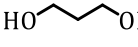
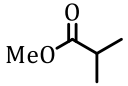
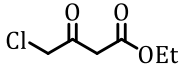
*Scheme 47 - Synthesis of intermediate **I.108***

The treatment of this intermediate **I.142** with $[PtCl_2(C_2H_4)]_2$ to perform the cyclization into the enol ether led to degradation since the reaction product underwent directly hydrolysis followed by a [3,3] -sigmatropic rearrangement at the allylic alcohol. Fortunately, this side reaction was not observed when gold catalyst **I.136** was used, affording intermediate **I.104** identical to the one prepared by Sasaki.

Fürstner and his co-workers described an alternative approach to Polycavernoside A. Through their work a variety of synthetic methodologies proved to be efficient and reliable in the preparation of challenging scaffolds. Moreover, the Evans-Tishchenko reaction and the alkyne metathesis efficiently delivered the macrolactone core of the natural product.

I.2.7 Comparison of the reported total synthesis

The total synthesis that are shown in this section present interesting similarities and will allow a comparison of the synthetic approach and their efficiency. They all share a common synthetic intermediate which is the aglycone **I.38** and the last synthetic steps are glycosidation followed by a palladium cross-coupling to introduce the polyene moiety. For this last step, everyone used vinyl stannane species except Murai who used vinyl mercury species. In the following table, it was chosen to describe the number of steps from readily and commercially available compounds rather than advanced synthetic intermediates to the common intermediate **I.38**.

	Total number of steps	**Longest linear sequence**	**Overall yield**	**Northern fragment**	**Southern fragment**	**From coupling to I.38**
Murai	52 steps	31 steps	2.6 %	21 steps, 7.7 % 	21 steps, 11.1 % 	10 steps, 23.2 %
Paquette	46 steps	28 steps	1.7 %	18 steps, 10.5 % 	16 steps, 12.0 % 	12 steps, 14.4 %
White	36 steps	22 steps	4.2 %	14 steps, 18.1 % 	14 steps, 9.2 % 	8 steps, 23.1 %
Lee	29 steps	22 steps	6.3 %	22 steps, 6.3 % 		
Sasaki	34 steps	22 steps	7.2 %	11 steps, 18.2 % 	11 steps, 39.2 % 	11 steps, 31.4 %
Fürstner (formal synthesis)	39 steps	21 steps	1.5 %	7 steps, 35.59 % 	11 steps, 20.2 % 	14 steps, 7.6 %

The synthesis described by Murai and Paquette have the highest number of steps and were achieved with low yield. This trend is generally observed for the first total synthesis of complex natural products. The initial approach planned by Paquette highlighted the difficulty to couple the Northern and Southern fragments. White encountered similar issues and also had to modify his coupling approach.

The most recent syntheses reported by Lee, Sasaki and Fürstner are more efficient as their longest linear sequences are around 20 steps. They relied on challenging transformations to carry out the coupling between the Northern and Southern fragments and successfully reached their goal. Their efforts highlighted the importance of developing new methodologies that allows efficient transformations on complex substrates. Even though the Lee synthesis did not rely on a convergent approach, it is the shortest in terms of total number of steps and showed that Prins reactions can be used for an intramolecular macrocyclisation.

Other groups have reported the synthesis of Polycavernoside A fragments. The group of Christine Willis reported the preparation of the Southern fragment using a Prins-type cyclisation[19]. More recently the group of Sudhakar Kadari reported the synthesis of the Northern fragment which was achieved using an olefin metathesis[20]. Our group has also been interested in this natural product and our achievements towards its synthesis will be presented in the next section.

[19] C. S. Barry, N. Bushby, J. R. Harding, C. L. Willis, *Org. Lett.*, **2005**, *7*, *13*, 2683–2686.
[20] S. Kadari, H. Yerrabelly, T. Gogula, Y. G. Erukala, J. R. Yerrabelly, P. K. Begari, *J. Heterocycl. Chem.*, **2018**, *55*, *8*, 1986–1990.

I.3 Our journey towards the total synthesis of Polycavernoside A

Several PhD students and post-doctoral researchers of our group have worked on this project. In this section, their work will be briefly mentioned, and it should lead to the state of the project at the beginning of this thesis. This section will be organised by fragments.

The disconnection adopted by the group of Pr. István Markó is different from the one used in the work of the other groups (Figure 13).

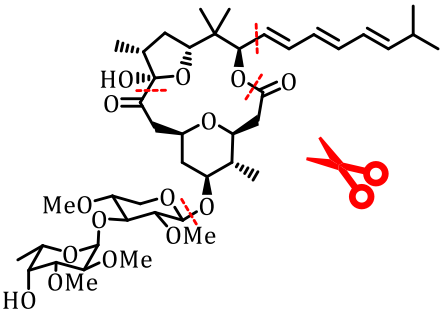


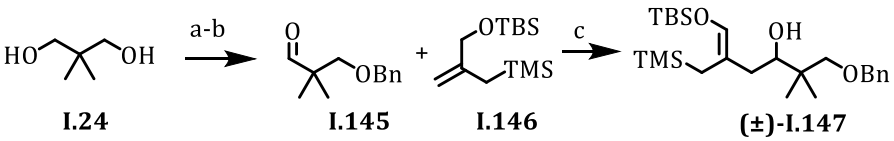
Figure 13 - Polycavernoside A disconnection by the Markó group

Our work focuses on the synthesis of the aglycone since efficient preparation of the disaccharide unit was already reported. The major difference between the disconnection established by the Markó group and the others lies at the connection of the core unit with the polyene fragment. Our group had developed an efficient methodology for the elaboration of conjugated polyenes which made Polycavernoside A an excellent target.

I.3.1 Synthesis of the Northern fragment[21,22]

First as a master student then as PhD student, Dr. Raphaël Dumeunier worked on the synthesis of the Northern fragment of Polycavernoside A. Two methodologies were developed, the first based on the ene reactions used in the group and the second using a Sakurai-Hosomi reaction.

In the first case, aldehyde **I.145** was prepared starting from diol **I.24** (Scheme 48). Then, an ene reaction with allylsilane **I.146** using an aluminium based Lewis acid lead to the silyl enol ether **I.147** in good yield.

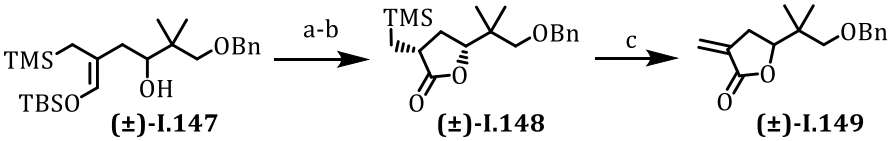


I.24 **I.145** **I.146** **(±)-I.147**

a) KOH, BnCl, 91 %; b) CuCl, Phen, *t*BuOK, DBAD, DMAP, O_2, 97 %; c) Et_2AlCl, 50 %.

*Scheme 48 - Synthesis of homoallylic alcohol **I.147***

From this substrate bearing the skeleton of the Northern fragment, two pathways were developed to reach α-methylene-γ-butyrolactone **I.149.**



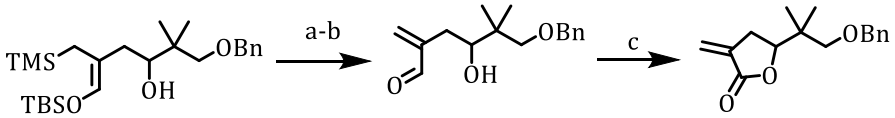
(±)-I.147 **(±)-I.148** **(±)-I.149**

a) TBAF; b) TPAP, NMO, 4A MS, 99 % over two steps; c) LDA then TMSCl then NBS then TBAF, 74 %.

*Scheme 49 - First route to lactone **I.149***

The first pathway goes through intermediate **I.148** which is coming from **I.147** (Scheme 49). Formation of the α-bromolactone and elimination by desilylation leads to lactone **I.149.** On the other hand, enal **I.150** was generated from **I.147** and subsequent oxidation with manganese dioxide in the presence of potassium cyanide led to the desired lactone **I.149** (Scheme 50).

[21] R. Dumeunier, I. E. Markó, *Tetrahedron Lett.*, **2000**, *41*, 10219–10222 ; R. Dumeunier, *PhD Thesis*, **2004**, UCL; R. Dumeunier, *Master Thesis*, **1999**, UCL;
[22] A. Drouin, *Post-doctoral Report*, **2012**, UCL.

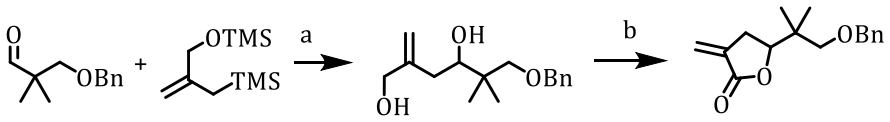


(±)-I.147 **(±)-I.150** **(±)-I.149**

a) NBS; b) TBAF, 86 % over two steps; c) KCN, MnO_2, 77 %.

*Scheme 50 - Second route to lactone **I.149***

For the Sakurai based methodology, the lactone **I.149** could be prepared in only two steps with good yield going through diol **I.152** (Scheme 51).

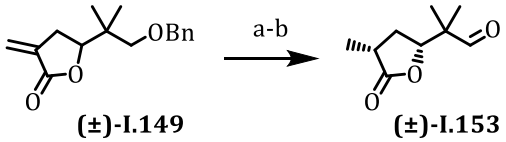


I.145 **I.151** **(±)-I.152** **(±)-I.149**

a) $TiCl_4$, TBAF, 78 %; b) MnO_2, KCN, 65 %.

*Scheme 51 - Preparation of lactone **I.149** by Sakurai reaction*

With lactone **I.149** in hand, two steps, involving a diastereoselective hydrogenation, are required to reach the Northern fragment **I.153** (Scheme 52).

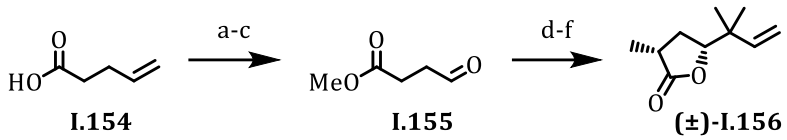


(±)-I.149 **(±)-I.153**

a) H_2, Pd/C, 95 %, >98 % d.e.; b) PCC, 99 %.

*Scheme 52 - Synthesis of the Northern fragment **I.153***

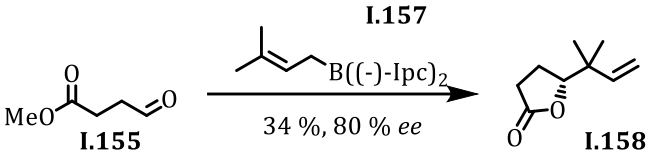
Upon his arrival in the Markó group as a post-doctoral researcher, Pr. Alexandre Drouin worked on the development of a new approach followed by an asymmetric version of the Northern fragment. The synthesis started with acid **I.154** (Scheme 53). Aldehyde **I.155** could be generated in two steps which in the presence of a prenylating reagent based on an organoindium species led to the allylation and cyclisation product. Treatment with LiHMDS followed by addition of methyl iodide generated the *trans*-adduct that could be epimerized to the *cis*-adduct **I.156** in basic conditions



a) $(COCl)_2$; b) MeOH; c) O_3 then Me_2S, 43 % over 3 steps; d) Prenyl bromide, In, 76 %; e) LiHMDS then MeI, 81 %; f) LDA then NH_4Cl, 88 %.

*Scheme 53 - Synthesis of lactone **I.156***

The asymmetric version was achieved with a Brown allylation starting from α-pinene. However, this transformation occurred with low yield due to a difficult purification (Scheme 54).

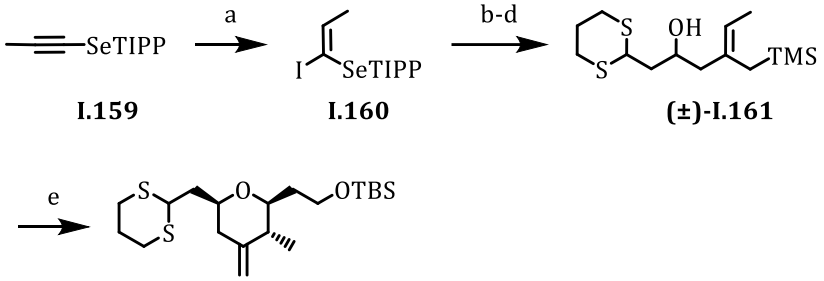


*Scheme 54 - Enantioselective synthesis of lactone **I.158***

I.3.2 Synthesis of the Southern fragment[23,24,22]

Two synthetic pathways have been developed in the group for the elaboration of the tetrahydropyran. The first was described by Carlos Pérez-Balado by combination of two methodologies, the regioselective elaboration of olefins through selenium chemistry and the Intra Molecular Sakuria Cyclization (IMSC).

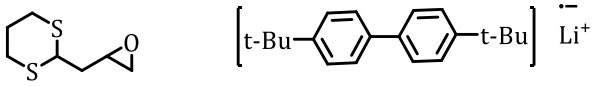
This approach was based on the observation that selenoalkynes like **I.59** underwent clean regioselective hydroalumination reaction leading to substrate **I.160** (Scheme 55). These 1-iodo-1-selenoalkenes were efficient intermediates for the elaboration of stereodefined olefins.



I.159 **I.160** **(±)-I.161**

(±)-I.162

a) DIBAL-H, I_2, 92 %; b) *n*BuLi, **I.163**, $BF_3.Et_2O$, 100 %; c) MeMgBr, LDBB, MeI, I_2, 81 %; d) $TMSCH_2MgCl$, $Pd(PPh_3)_4$, 68 %; e) $TBSO(CH_2)_2CHO$, $BF_3.Et_2O$, 91 %.



I.163 **I.164** LDBB

*Scheme 55 - Synthesis of the Southern fragment **I.162** using selenolalkyne*

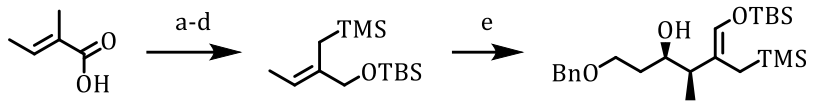
By treatment with *n*BuLi followed by addition of an epoxide **I.163** afforded the alkylation at the halogen position. Subsequent treatment by transformation of the selenide into the iodide followed by a Kumada cross coupling reaction led to trisubstituted olefin **I.161** as a single product. In the IMSC conditions, homoallylic alcohol **I.161** afforded tetrahydropyran **I.162** that embodies the core of the Southern fragment of polycavernoside A.

The other approach to this fragment developed by Dr. Freddi Philippart and Pr. Alexandre Drouin also involved the IMSC reaction. In this case, the homoallylic

[23] C. Pérez-Balado, I. E. Markó, *Tetrahedron Lett.*, **2005**, *46*, *29*, 4887–4890; C. Pérez-Balado, I. E. Markó, *Tetrahedron*, **2006**, *62*, 2331–2349; C. Perez-Balado, *PhD Thesis*, **2002**, UCL.

[24] F. Philippart, *PhD Thesis*, **2012**, UCL.

alcohol required for this reaction originated from an ene reaction as previously described (Scheme 56).

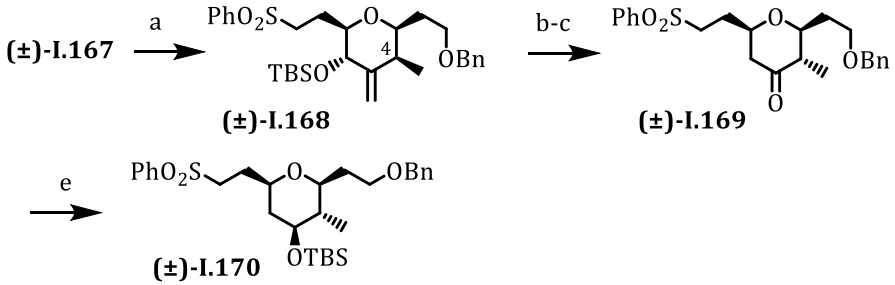


I.165 **I.166** **(±)-I.167**

a) $LiAlH_4$, 47-94 %; b) *n*BuLi, TMEDA, TMSCl, 52 %; c) H_2SO_4; d) TBSCl, Im, 71 % over two steps; e) $BnO(CH_2)_2CHO$, Et_2AlCl, 63 %.

*Scheme 56 - Synthesis of homoallylic alcohol **I.167***

In the IMSC conditions, the homoallylic alcohol **I.167** led to the formation of the desired tetrahydropyran **I.168** (Scheme 57). From this reaction, the methyl group at C_4 was in an axial position due to the stereochemistry of the homoallylic alcohol **I.167** which is opposite to the one in the natural product. However, this could be reversed after ozonolysis of the double bond in **I.168** and treatment with an excess of zinc in acetic acid. During this process, the methyl group can be epimerized to its thermodynamically stable equatorial position and the TBS ether is cleaved leading to intermediate **I.169**. Reduction in Luche's conditions and protection of the alcohol were performed in a single process affording the Southern fragment in the form of **I.170.**



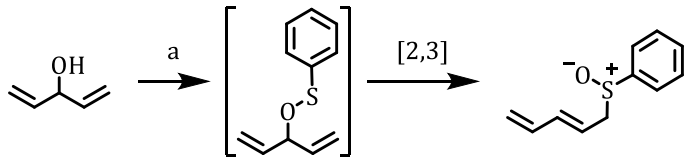
(±)-I.168 **(±)-I.169** **(±)-I.170**

a) $BF_3.Et_2O$, $PhSO_2(CH_2)_2CHO$, 68 %; b) O_3 then Me_2S, 65 %; c) Zn, AcOH, 35 %; d) $NaBH_4$, $CeCl_3$ then TBSCl, NEt_3, 63 %.

*Scheme 57 - Synthesis of Southern fragment **I.170***

I.3.3 Synthesis of the polyene fragment[25,26,21]

Dr. Raphaël Dumeunier also described the synthesis of the polyene fragment. The retrosynthetic idea was to build the triene chain using a double Evans-Mislow rearrangement. The synthesis started from divinylcarbinol **I.171** that was treated with freshly prepared phenylthiochloride (Scheme 58). The intermediate **I.172** cannot be isolated since it directly undergoes a [2,3]-sigmatropic rearrangement leading to terminal sulfoxide **I.173**.



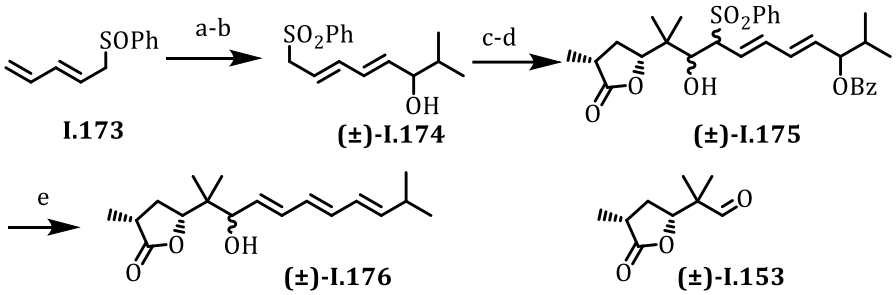
I.171 **I.172** **I.173**

a) *n*BuLi then PhSCl, 74 %.

*Scheme 58 - Synthesis of diene **I.173***

Compound **I.173** proved to be a key intermediate in the construction of several polyene moieties elaborated in our group. In the case of Polycavernoside A, this was done by deprotonation followed by addition of isobutyraldehyde (Scheme 59). With alcohol **I.166** in hand, the use ammonium molybdate tetrahydrate in combination with hydrogen peroxide allowed selective oxidation of the sulfoxide to the sulfone preventing further allylic rearrangements. The deprotonation in the α-position of the sulfone followed by addition of the aldehyde **I.153** led to a diol which upon treatment with benzoyl chloride and triethylamine selectively afforded **I.175**. In the presence of an excess of samarium iodide and HMPA, a conjugated elimination process though the π-system can occur and triene **I.176** can be isolated in excellent yields.

[25] P. Jourdain, F. Philippart, R. Dumeunier, I. E. Markó, *Tetrahedron Lett.*, **2009**, *50*, *26*, 3366–3370.
[26] P. Jourdain, *PhD Thesis*, **2010**, UCL.

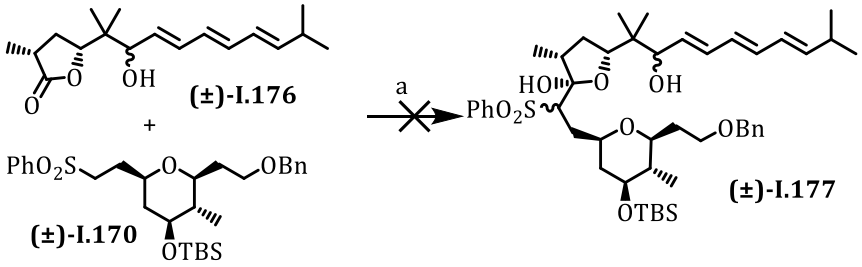


a) *n*BuLi, isobutyraldehyde, 93 %; b) H_2O_2, $(NH_4)_6Mo_7O_{24}.4H_2O$, 82 %; c) *n*BuLi, **I.153**, 94 %; d) BzBr, NEt_3, DMAP, 89 %; e) SmI_2, HMPA, 94 %, d.r. 1:1.

Scheme 59 - Coupling of the Northern and polyene fragments

I.3.4 Coupling of the Northern and Southern fragments[24,22]

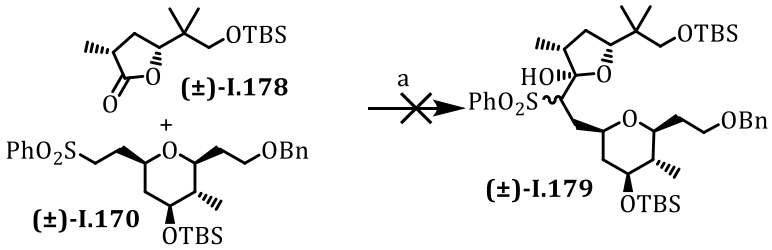
After the preparation of the Southern fragment, Dr. Philippart tackled its assembly with the Northern subunit (Scheme 60). This was intended through the addition of the sulfone anion of the tetrahydropyran **I.170** to the electrophilic lactone **I.176**.



a) *n*BuLi or LDA (2 eq.)

*Scheme 60 - Couplings attempts with sulfone **I.170** and lactone **I.176***

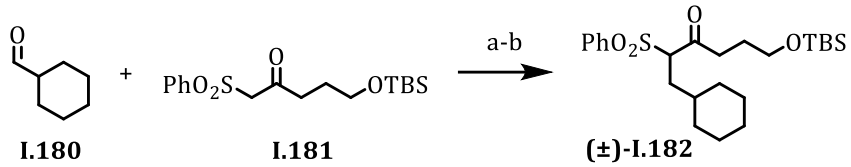
However, in his attempts, degradation of the polyene was observed as the proton signal of the triene chain were nowhere to be found in the crude NMR. They therefore decided to move to the Northern fragment **I.171** and in this case, while no degradation was observed, the coupling product **I.173** could not be observed, and the starting materials were recovered (Scheme 61).



a) *n*BuLi or LDA (1 eq.)

*Scheme 61 - Couplings attempts of sulfone **I.170** with lactone **I.171***

Given this outcome, Pr. Drouin developed a new methodology relying on β-ketosulfones with compounds **I.180** and .**I.181** used as model substrates for the Southern and Northern fragments respectively (Scheme 62). In these conditions, an initial Knoevenagel condensation followed by a 1,4-reduction of the enone intermediate led to the coupling product **I.182**.

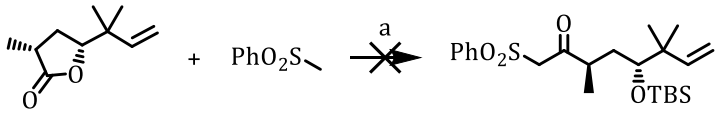


I.180 **I.181** **(±)-I.182**

a) AcOH, Piperidine, 4A MS, 48 %; b) iMesCuDBM, $Me(EtO)_2SiH$, *t*BuOK, 60 %.

*Scheme 62 - Coupling methodology based on β-ketosulfone **I.181***

However, the preparation of a β-ketosulfone **I.184** from the Northern fragment **I.156** could not be achieved (Scheme 63).



(±)-I.156 **I.183** **(±)-I.184**

a) *n*BuLi then TBSCl or i. *n*BuLi; ii. TBSCl.

*Scheme 63 - Attempts to the synthesis of **I.184***

I.4 Objectives

At the beginning of this thesis, we had to review the disconnection strategy based on the results obtained by Dr. Phillipart and Pr. Drouin. While the disconnection at the glycoside, the lactone and the polyene bonds will remain the same, the union between the Northern and the Southern fragments had to be rethought. Therefore, it was decided to move it from C_9-C_{10} to C_8-C_9 (Figure 14).

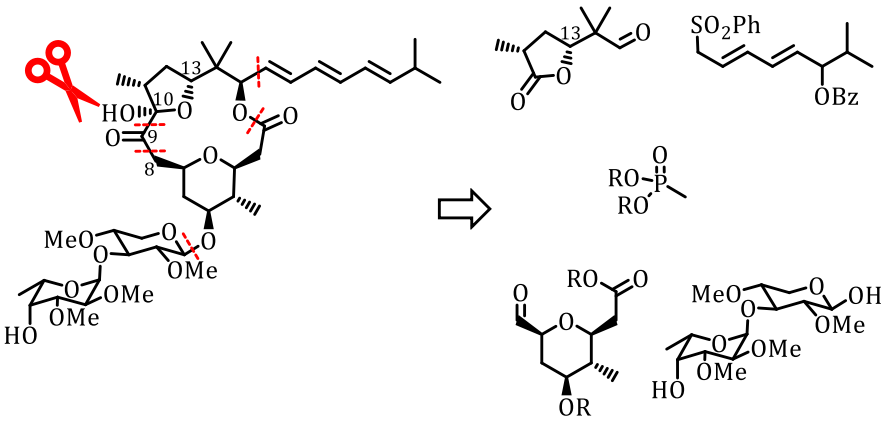


Figure 14 - New disconnection of Polycavernoside A

To minimize modifications of the fragment structures, a linker will be used allowing to keep the core of the Northern fragment. Nonetheless, we would also aim for the preparation of the natural product as a single enantiomer.

As the synthesis of the glycoside had been previously described by Murai[6] and Paquette[12] in an elegant and straightforward manner, we would concentrate our efforts on the aglycone.

The methodology for the construction of the polyene fragment developed in the laboratory was deemed to be original and efficient enough that it did not need to be modified. In addition, its coupling with the butyrolactone proceeded smoothly which encouraged us to keep it as it was.

For the Northern fragment, we needed to modify our approach since the previous methodologies failed to give the desired lactone as a single enantiomer or lacked efficiency in their preparation. Knowledgeable from the previous work, we knew that control of the C_{13} hydroxy group would allow a control of all the chiral information present in the fragment.

The synthesis of the Southern fragment had to be modified as well. One carbon had to be excised from its previous form and we had to prepare it as a single enantiomer. Also, both previous approaches revealed to be long with some low yielding steps that needed to be changed if possible.

The modification of the disconnection led to the introduction of a one carbon atom retron that would serve as a linker between the γ-butyrolactone and the tetrahydropyran. This linker should be able to act as a double nucleophile given the electrophilic nature of both fragments. This strategy should also allow us to modulate the order in which those fragments would be connected. Our choice was for a methyl phosphonate as the Horner-Wadswörth-Emmons olefination is a reaction that allows the desired transformation to be carried out and is well documented.

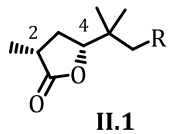
With these guidelines in mind, the following chapters will describe our investigations during this thesis and the results that came out of it.

Chapter II

Synthesis of the Northern fragment

II.1 Introduction to the synthesis of butyrolactones

From our disconnection outlined in the Introduction, the Northern fragment of Polycavernoside A is a 2,4-substituted butyrolactone **II.1** (Figure 15). The butyrolactone scaffold can be found in numerous natural compounds and synthetic molecules and this structural motif is important for a variety of biological processes and applications[27].



II.1

Northern fragment of
Polycavernoside A

Figure 15 - Structure of the Northern fragment

As a consequence, butyrolactones have drawn the attention of the scientific community for developing ways to access them with efficiency. While simple butyrolactone can be prepared easily on industrial scale, for example starting from maleic anhydride[28], more complex structures require the use of different methodologies. Synthetic methods allowing the construction of these scaffolds have been reported and examples can be found in a series of reviews[29].

As an example, Myers reported the synthesis of γ-butyrolactones using the alkylation of epoxides by chiral enolates[30]. In their work, pseudoephedrine derivatives were chosen as chiral inductors and interestingly, the facial selectivity of the addition of the electrophile was shown to be reversed depending on whether an alkyl halide was used instead of an epoxide as represented in Figure 16. Similar observations were made by Askin with prolinol derivatives[31].

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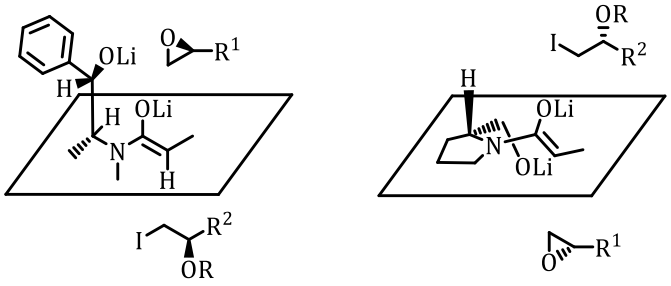
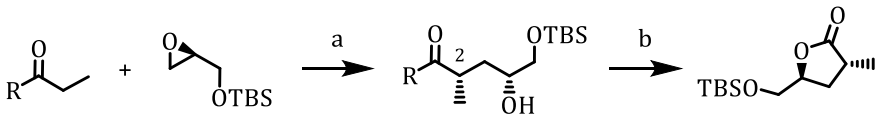
[27] S. S. Canan Koch, A. R. Chamberlin, *Stud. Nat. Prod. Chem.*, **1995**, *16*, 687–725; H. M. R. Hoffmann, J. Rabe, *Angew. Chemie Int. Ed. English*, **1985**, *24*, *2*, 94–110.
[28] R. G. L. Castiglioni, A. S. A. Carlo Fumagalli, US Patent 6,297,389, **2001**.
[29] B. Mao, M. Fañanás-Mastral, B. L. Feringa, *Chem. Rev.*, **2017**, *117*, *15*, 10502–10566; K. J. R. Murauski, A. A. Jaworski, K. A. Scheidt, *Chem. Soc. Rev.*, **2018**, *47*, *5*, 1773–1782.
[30] A. G. Myers, L. McKinstry, *J. Org. Chem.*, **1996**, *61*, *7*, 2428–2440.
[31] D. Askin, R. P. Volante, K. M. Ryan, R. A. Reamer, I. Shinkai, *Tetrahedron Lett.*, **1988**, *29*, *34*, 4245–4248.



Myers **Askin**

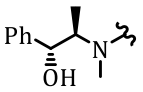
Figure 16 - Model for the alkylation of alkyl halides and epoxides by chiral enolates

It is believed that in the case of alkyl halide, the facial selectivity is dictated by steric factors with the electrophile approaching from the less hindered face while using epoxides, the coordination of the lithium alkoxide to the oxygen of the epoxide directs the approach. It is noteworthy that, in Myers conditions, epoxides revealed to be excellent electrophilic partners for the reaction while the corresponding iodide reacted poorly. As they started with enantiopure epoxides like **II.3**, the chiral group on the enolate allowed the control of the C_2-stereocenter leading to a single diastereoisomer. However, due to the inherent stereochemistry embodied in both partners, match and mis-match effects could be observed (Scheme 64). By treating the intermediate **II.4** in the presence of an acid catalyst, butyrolactones **II.5** could be obtained.



II.2 **II.3** **II.4** **II.5**

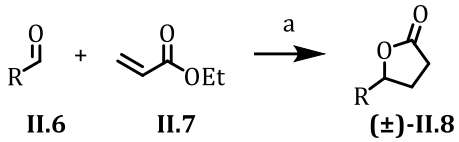
a) LDA (2,1 eq.), LiCl (6eq.), THF, -78°C - RT, 84 %, 96 % *de*; b) H_2SO_4, dioxane, 95 °C, 90 %.

R : 

Scheme 64 - Myers's synthesis of butyrolactones

Another approach for the assembly of butyrolactone has been developed by the group of Fukuzawa[32]. The cyclic ester **II.8** is obtained from acrylate derivative **II.7** and an aldehyde or ketone in the presence of samarium diiodide (Scheme 65).

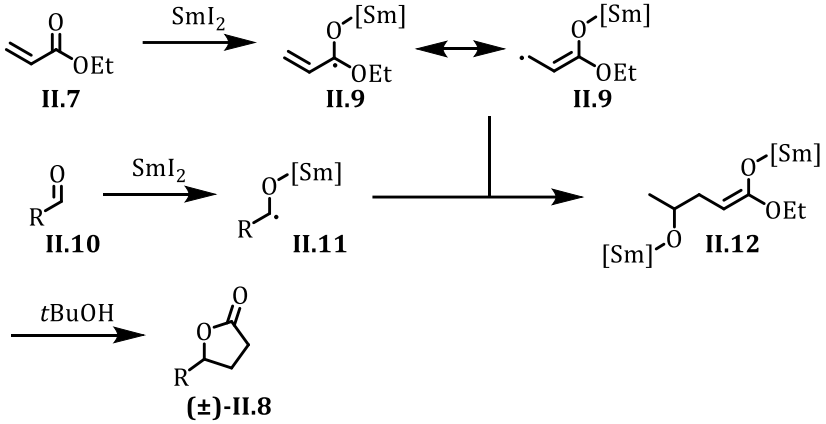
[32] S. Fukuzawa, A. Nakanishi, T. Fujinami, S. Sakai, *J. Chem. Soc. Chem. Commun.*, **1986**, *8*, 624; S. Fukuzawa, A. Nakanishi, T. Fujinami, S. Sakai, *J. Chem. Soc., Perkin Trans. 1*, **1988**, *7*, 1669–1675.



a) SmI_2 (2 eq.), *t*BuOH (1 eq.), THF.

*Scheme 65 - Synthesis of lactone **II.8***

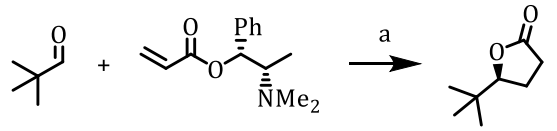
For this transformation, they proposed a mechanism involving the combination of two radical species generated by the reaction of each partner with the samarium iodide acting as a single electron donor, as it has been proposed in their literature (Scheme 66)[33]. However, other mechanisms could be proposed for this transformation since the recombination of two radical species seems unlikely.



*Scheme 66 - Mechanism proposed for the synthesis of **II.8***

Fukuzawa's group extended the methodology to an asymmetric version. It was achieved by appending a chiral auxiliary[34] onto the acrylate derivative. Among the chiral auxiliaries screened, the best enantioselectivities were obtained using acrylic ester derived from *N*-methylephedrine **II.14** (Scheme 67).

[33] A. Krief, A.-M. Laval, *Chem. Rev.*, **2002**, *99*, *3*, 745–778.
[34] S. Fukuzawa, K. Seki, M. Tatsuzawa, K. Mutoh, *J. Am. Chem. Soc.*, **1997**, *119*, *6*, 1482–1483.

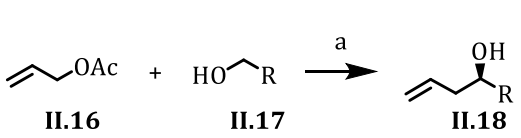


II.13 **II.14** **II.15**

a) SmI_2 (2 eq.), *t*BuOH (1 eq.), THF, 57 %, 94 % *ee*.

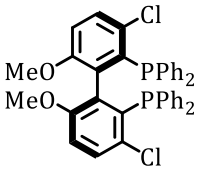
*Scheme 67 - Fukazawa asymmetric synthesis of **II.15***

The group of Michael Krische has worked on iridium catalysed transfer hydrogenative coupling of allyl acetates represented in Scheme 68[35]. Their work allowed the development of efficient asymmetric allylation of aldehydes starting from alcohol **II.17** using chiral phosphine ligands like **II.19** bound to the iridium catalyst.



II.16 **II.17** **II.18**

a) $[Ir(cod)Cl]_2$, (*R*)-Cl,MeO-BIPHEP, Cs_2CO_3, *m*-NO_2BzOH, THF, 100 °C



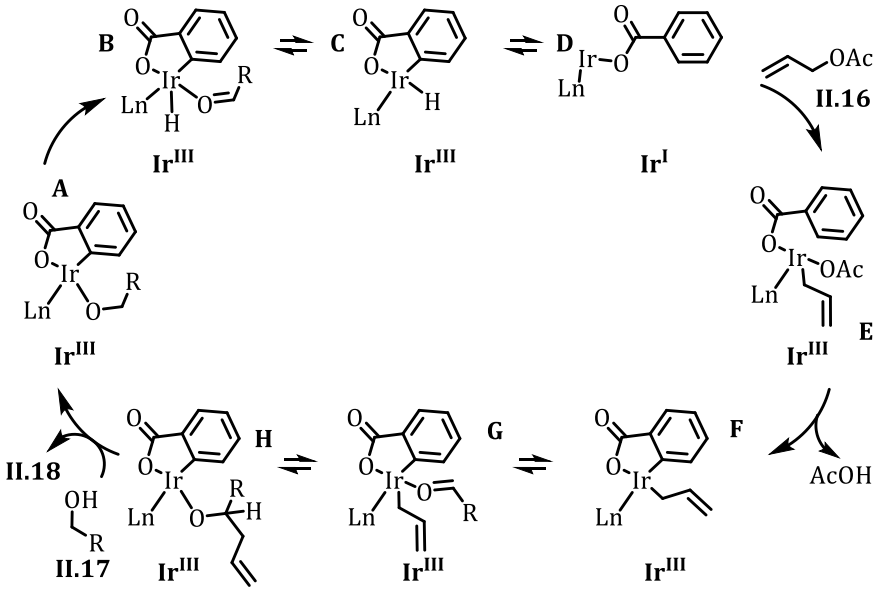
II.19

(R)-Cl,MeO-BIPHEP

Scheme 68 - Krische's asymmetric allylation methodology

In their system, the proposed mechanism involves the redox couple Ir(III)/Ir(I) for the catalytic cycle.

[35] I. S. Kim, M.-Y. Ngai, M. J. Krische, *J. Am. Chem. Soc.*, **2008**, *130*, *44*, 14891–14899.

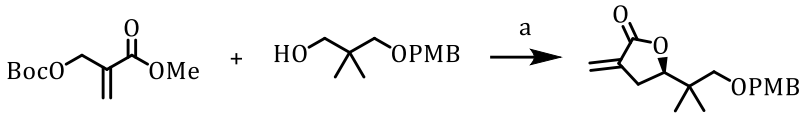


Scheme 69 - Mechanism for the Krische iridium-catalysed allylation

Starting from intermediate **A** (Scheme 69), the Ir(III) complex oxidizes the alcohol **II.17** to the corresponding aldehyde to generate the iridium-hydride complex **B**. Through the release of the aldehyde, **C** can be formed and is in equilibrium with **D**. By reaction of allyl acetate **II.16** with the Ir(I) complex, through an oxidative addition, the intermediate **E** can be formed and by releasing acetic acid, the C-Ir bond in **F** is reformed. This species can coordinate the aldehyde (**G**) and transfer its allyl moiety to generate the homoallylic alcohol leading to **H**. By ligand exchange involving the product **II.18** and starting alcohol **II.17**, the catalytic cycle can restart.

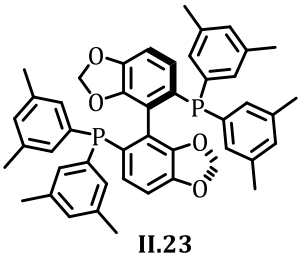
By expanding their methodologies, they found that by using protected Baylis-Hillman adducts like **II.20**, butyrolactones **II.22** could be accessed in an efficient and straightforward manner (Scheme 70)[36]. As it was shown previously[21], the Michael acceptor **II.22** can be easily transformed into the unsaturated lactone with excellent diastereoselectivity.

[36] T. P. Montgomery, A. Hassan, B. Y. Park, M. J. Krische, *J. Am. Chem. Soc.*, **2012**, *134*, *27*, 11100–11103.



II.20 **II.21** **II.22**

a) Ir((*R*)-DM-SEGPHOS), Cs_2CO_3, THF-CH_3CN 1:1, 80 °C, 72 h, 90 %, 92 % *ee*



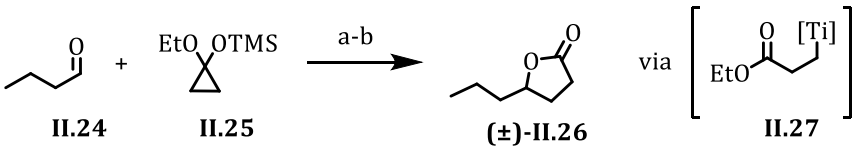
II.23

(*R*)-DM-SEGPHOS

*Scheme 70 - Synthesis of butyrolactone **II.22** by Krische's group*

In the same report, they also demonstrated that these transformations can be carried out using directly the aldehyde but required the addition of isopropanol as a hydride source.

The group of Isao Kuwajima worked on the synthesis of butyrolactone using cyclopropane ketal **II.26** as the starting material (Scheme 71)[37]. These scaffolds proved to be excellent precursors of homoenolates **II.27** allowing the direct formation of butyrolactones by addition of aldehydes or ketones.



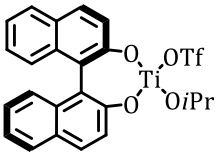
II.24 **II.25** **(±)-II.26** **II.27**

a) $TiCl_4$, DCM, -78°C - RT; b) TsOH, C_6H_6, reflux, 77 % over two steps.

*Scheme 71 - Synthesis of lactone **II.26** using cyclopropaneketal **II.25***

The group of James Gleason developed later an asymmetric version of this transformation by incorporating 10 mol% of the chiral Lewis acid **II.29** (Figure 17)[38]. However, up to now, the enantiomeric excesses observed for this transformation do not exceed 72 % *e.e*.

[37] E. Nakamura, I. Kuwajima, *J. Am. Chem. Soc.*, **1977**, *99*, *22*, 7360–7362.
[38] E. O. Martins, J. L. Gleason, *Org. Lett.*, **1999**, *1*, *10*, 1643–1645; E. D. Burke, N. K. Lim, J. L. Gleason, *Synlett*, **2003**, *3*, 0390–0392.



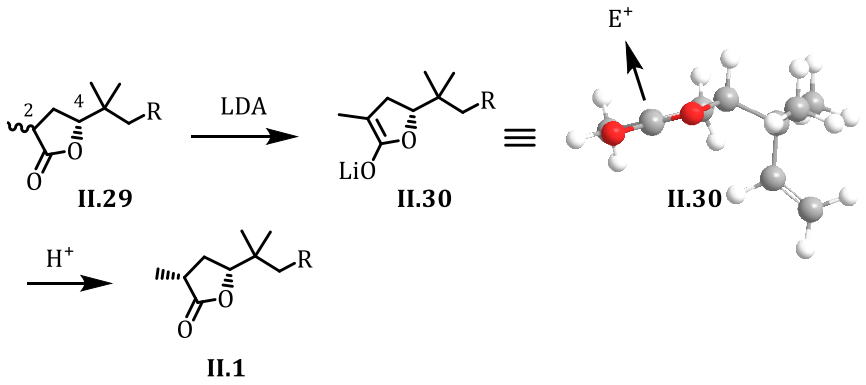
II.28

Figure 17 - Gleason catalyst

II.2 Synthesis of the Northern fragment

II.2.1 First retrosynthetic analysis

Our retrosynthetic analysis of the Northern fragment was based on observations reported earlier by Paquette[12] and by the previous work in the group. Two chiral centres are embodied in its architecture, and the stereochemistry of one can be used to direct the relative arrangement of the other as long as the butyrolactone is formed. By treatment of butyrolactone **II.29** with a base, enolate intermediate **II.30** is formed as shown in Scheme 72.



II.29 **II.30** **II.30** **II.1**

Scheme 72 - Strategy for the diastereocontrol of C_2

Looking at the model[39] of **II.30**, one of the faces of the enolate is more hindered than the other due to the presence of the lateral chain at the C_4, leading to the addition of the electrophile on one face preferentially. The addition of a proton will lead to the butyrolactone were the group appended at C_2 and C_4 are in a *cis* relationship. Therefore, once the asymmetric centre of the C_{13} of the natural product is fixed, it should be possible to control the one at C_{11}. We envisioned that the chiral centre at C_{13} could arise from an allylation reaction and this led us to two possible disconnections shown in Figure 18.

[39] Model of **II.30** obtained from Cambridgesoft Chem 3D using molecular mechanics (MM2) calculations.

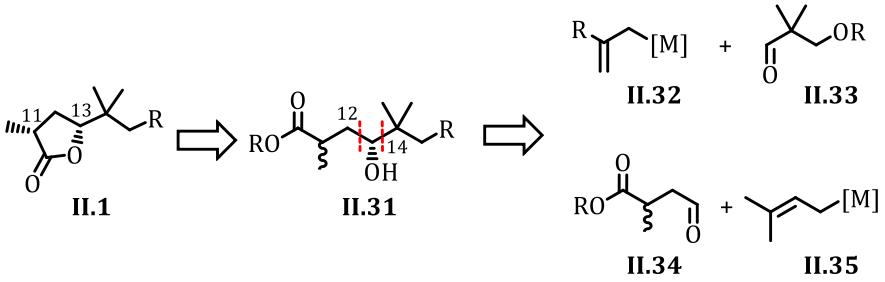


*Figure 18 - Disconnection of lactone **II.1***

Allylation reactions are powerful tools in the elaboration of organic molecules as they usually allow the formation of alcohols or amines and, as an allylic moiety is inserted, it allows post-functionalisation using the double bond or the allylic hydrogens[40]. As enantioselective or diastereoselective versions of these transformations have been developed, they could represent a suitable strategy towards the assembly of the Northern fragment of Polycavernoside A. We decided to investigate two approaches involving either the formation of the C_{12}-C_{13} or the C_{13}-C_{14} bonds using an allylation reaction leading to the two strategies represented in Figure 18. The first would require the synthesis of aldehyde **II.33** and an allylating agent like **II.32** and the second would rely on the synthesis of aldehyde **II.34** and prenylating agent **II.35**.

[40] M. Yus, J. C. González-Gómez, F. Foubelo, *Chem. Rev.*, **2011**, *111*, *12*, 7774–7854; M. Yus, J. C. González-Gómez, F. Foubelo, *Chem. Rev.*, **2013**, *113*, *7*, 5595–5698.

II.2.2 Synthesis of the Northern fragment by methallylation

II.2.2.1 Racemic synthesis

Our first approach would use the addition of the allylic species **II.33** to aldehyde **II.33** to form the C_{12}-C_{13} bond (Figure 19). While the product of this reaction **II.37** would possess the carbon skeleton of the target, additional transformations of the allylic moiety would be required to reach the target **II.38**.

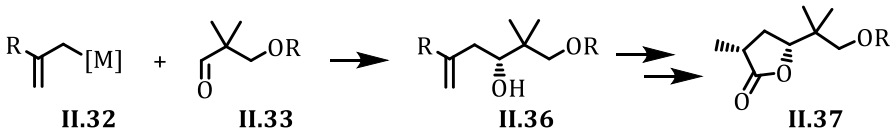
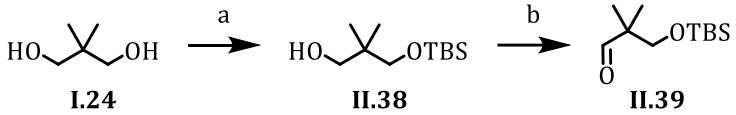


*Figure 19 - Synthetic plan for the elaboration of lactone **II.37***

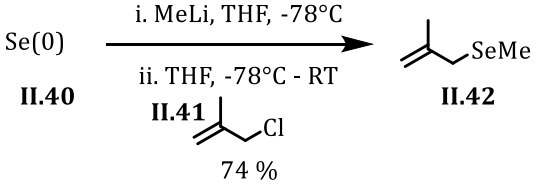
The synthesis started from cheap and readily available alcohol **I.24**. Treatment in the presence of TBSCl and imidazole led to the formation of the protected alcohol **II.38** in quantitative yield (Scheme 73). This intermediate was then oxidised using Swern conditions to yield the corresponding aldehyde **II.39.**



a) TBSCl, Im, DCM, 0°C - RT, quantitative; b) $(COCl)_2$, DMSO, NEt_3, DCM, -78°C - RT, 73 %.

*Scheme 73 - Synthesis of aldehyde **II.39***

The allylation partner was chosen in the form of the methallyl unit. A series of methallylating agents have been described in the literature but our choice was focused on the selenium-based reagent **II.42** developed in the group in collaboration with Pr. Alain Krief[41]. The preparation of the allylating agent was achieved in one step from methallyl chloride **II.41** and elemental selenium **II.40** (Scheme 74).

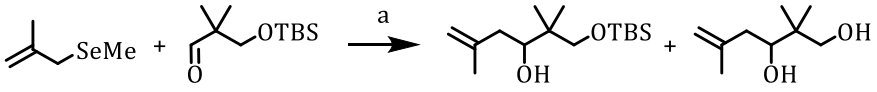


*Scheme 74 - Synthesis of selenide **II.42***

With reagent **II.42** in hand, we could move to the allylation reaction. With the conditions previously used in the group, homoallylic alcohol **II.43** could be

[41] T. Jacques, *PhD Thesis*, **2006**, UCL; S. Dochain, *PhD Thesis*, **2015**, UCL.

isolated in yields ranging from 27 to 40 % (Scheme 75). In addition to the desired product, diol **II.44** could be isolated in yields up to 54 %. This undesired product **II.44** comes from the cleavage of the protecting group in **II.43**.



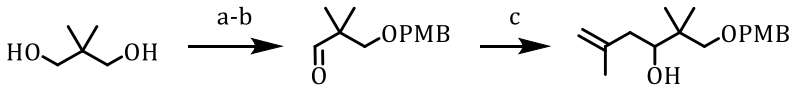
II.42 **II.39** **(±)-II.43** **(±)-II.44**

a) *n*BuLi, Ti(O*i*Pr)$_4$, THF, -78°C - RT, 27-40 % in **(±)-II.43**, up to 54 % in **(±)-II.44.**

*Scheme 75 - Methallylation of aldehyde **II.39** with selenide **II.42***

This result led us to change the protecting group and we opted for a PMB ether since those have been known to be less sensitive to the reaction conditions used throughout the process[42].

Aldehyde **II.45** was therefore prepared in two steps. The monoprotection of the diol was successfully carried out using 5 equivalents of diol **I.24** and one of para-methoxybenzyl alcohol in the presence of a catalytic amount of acid, based on the procedure reported by Chavan (Scheme 76)[43]. From experimental observations, it was found that once the conversion of the benzylic alcohol is achieved, cooling down the reaction mixture allowed the crystallisation of the excess of diol. A simple filtration delivers the pure product. This procedure allowed us to scale up easily this step while avoiding tedious purification. The subsequent oxidation could then be performed using the copper-catalysed aerobic oxidation developed by our group leading to aldehyde **II.45** in almost quantitative yield[44]. Aldehyde **II.45** was then subjected to the selenium-mediated allylation reaction conditions and afforded the desired homoallylic alcohol in an excellent yield of 91 %.



I.24 **II.45** **(±)-II.46**

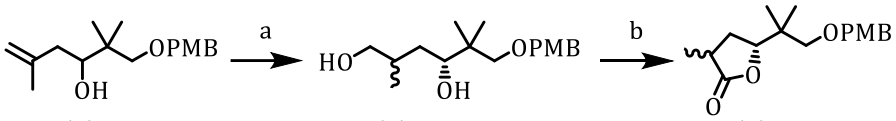
a) *p*MeOC$_6$H$_4$CH$_2$OH, PTSA, DCM, reflux, quantitative; b) CuCl, Phen, K_2CO_3, NMI, O_2, C_6F_6, reflux, 92 %; c) **II.42**, *n*BuLi, Ti(O*i*Pr)$_4$, THF, -78°C - RT, 91 %.

*Scheme 76 - Synthesis of homoallylic alcohol **II.46***

With the desired carbon skeleton in place, hydroboration of **II.46** followed by an oxidative work-up allowed the formation of diol **II.47** (Scheme 77). From the

[42] P. G. M. Wuts (ed.), *Greene's Protective Groups in Organic Synthesis*, (John Wiley & Sons, **2014**).
[43] S. P. Chavan, K. R. Harale, *Tetrahedron Lett.*, **2012**, *53*, *35*, 4683–4686.
[44] I. E. Markó, A. Gautier, R. Dumeunier, K. Doda, F. Philippart, S. M. Brown, C. J. Urch, *Angew. Chemie - Int. Ed.*, **2004**, *43*, *12*, 1588–1591.

NMR spectra of the crude, two diastereoisomers in a 1:3 ratio could be observed but were not easily separable by column chromatography. We suspect that since the alcohol in **II.46** is not protected, it can react with BH_3 and the formed alkoxyborane can then act as the olefin reducing agent in an intramolecular fashion. Since a large excess of borane tetrahydrofuran complex is used for this reaction, we could envision to lower the stoichiometry used for the reaction to determine if improved diastereoselectivity could be achieved. However, it was decided to move further in the synthesis. Upon treatment of diol **II.47** with TEMPO as catalyst and BAIB as stoichiometric oxidant, lactone **II.48** could be isolated successfully.

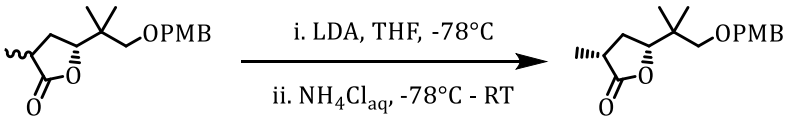


(±)-II.46 **(±)-II.47** **(±)-II.48**

a) BH_3.THF (3 eq.), THF, 0°C then $NaBO_3.4H_2O$, H_2O, 92 %; b) TEMPO, BAIB, DCM, 0°C - RT, 85 %.

*Scheme 77 - Synthesis of lactone **II.48***

Based on the observations mentioned in Scheme 72, lactone **II.48** was treated with LDA followed by quenching the reaction at -78 °C with a saturated solution of NH_4Cl and this afforded the desired product **II.49** as a single diastereoisomer in excellent yield (Scheme 78).

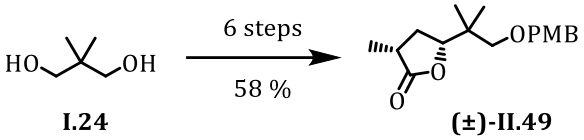


(±)-II.48 **(±)-II.49**

*Scheme 78 - Synthesis of lactone **II.49***

Comparison of the NMR spectra of the lactone **II.49** with the 1:3 mixture of diastereoisomers of **II.48** revealed that the major compound in the mixture of **II.48** is the compound **II.49**. This means that the diastereocontrol of the hydroboration is in favour of the stereochemistry observed in the final target **II.49**.

With this, the racemic synthesis of the Northern fragment **II.49** was achieved in 6 steps starting from 2,2-dimethyl-1,3-propanediol **I.24** with an overall yield of 58 % (Scheme 79). This sequence could be shortened by one step if the diastereoselectivity of the hydroboration reaction could be improved.

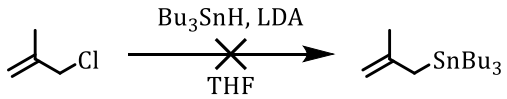


I.24 **(±)-II.49**

*Scheme 79 - Synthesis of the Northern fragment **II.49***

II.2.2.2 Enantioselective synthesis

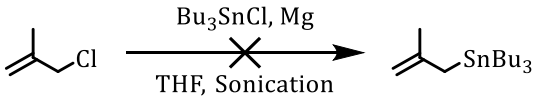
To achieve an enantioselective synthesis of our fragment, we envisioned the Keck's catalytic asymmetric allylation, a method that has proven to be reliable and efficient for these transformations[45]. In this system, a BINOL-titanium complex is involved and the chiral environment surrounding the metallic centre transfers the chiral information to the desired product. A few advantages of this system are the ready availability of the chiral reagents as well as their use in catalytic amount. The preparation of the methallyl transfer reagent **II.50** was first attempted using a procedure that was used in the group for the preparation of the crotyl tributyl stannane[46] starting from methallyl chloride **II.41** (Scheme 80).



II.41 -78 °C - RT **II.50**

*Scheme 80 - Attempts to the preparation of stannane **II.50***

However, in these conditions, the reaction failed to give the desired product **II.50**. The conditions developed by Maruyama[47] using sonication were tried as well but did not allow the formation of the desired product either (Scheme 81).



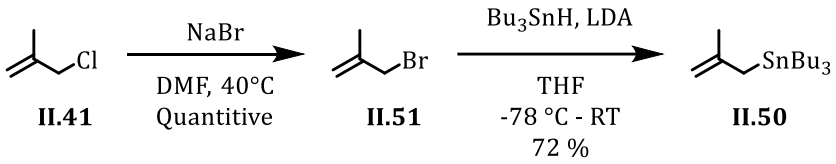
II.41 **II.50**

*Scheme 81 - Attempts to the preparation of stannane **II.50** using Maruyama's conditions*

Based on the hypothesis that the failure of the first attempt can be explained by the lack of reactivity of the methallyl chloride **II.41**, we transformed the latter into the corresponding bromide **II.54**. With this new electrophile, the formation

[45] G. E. Keck, K. H. Tarbet, L. S. Geraci, *J. Am. Chem. Soc.*, **1993**, *115*, *18*, 8467–8468; G. E. Keck, L. S. Geraci, *Tetrahedron Lett.*, **1993**, *34*, *49*, 7827–7828; G. E. Keck, D. Krishnamurthy, M. C. Grier, *J. Org. Chem.*, **1993**, *58*, *24*, 6543–6544.
[46] J.-B. Nshimyumuremyi, *Master Thesis*, **2014**, UCL.
[47] Y. Naruta, Y. Nishigaichi, K. Maruyama, *Chem. Lett.*, **1986**, *15*, *11*, 1857–1860.

of the methallyl tributyl stannane **II.53** proceeded smoothly in good yield (Scheme 82).

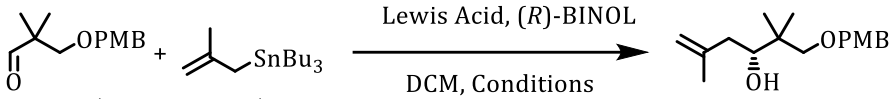


II.41 **II.51** **II.50**

*Scheme 82 - Synthesis of stannane **II.50***

Moving to the asymmetric allylation, a series of conditions have been described by the group of Keck varying the catalyst preparation, the Lewis-acid to chiral ligand ratio, the temperature and the addition of additives. A variant of the Keck procedure reported by the group of Keiji Maruoka[48] was also investigated (Table 1).

*Table 1 - Keck allylation of aldehyde **II.45***

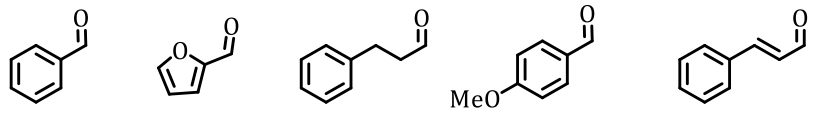


II.45 **II.50** **II.46**

Method	L.A. (eq.)	BINOL eq.	Additives	Temperature, time	Yield
Keck	$Ti(OiPr)_4$ (0.1)	0.2		RT then 0°C, 48h	No conversion
Keck	$Ti(OiPr)_4$ (0.1)	0.1	4 A MS	RT then -20°C, 60h	No conversion
Maruoka	$TiCl_4$ (0.05) $Ti(OiPr)_4$ (0.15)	0.2	Ag_2O	0°C then -15°C	No conversion

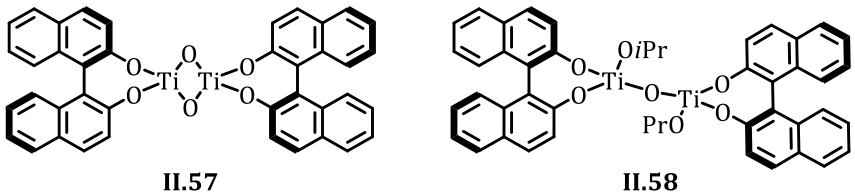
As shown above, no conditions allowed the formation of the desired product **II.46**. Given the outcome of these previous experiments, a control experiment was carried out using a substrate previously used by Keck's group. The use of dihydrocinnamaldehyde **II.54** in Keck's conditions led to the corresponding homoallylic alcohol. In their report on methallylation, Keck and co-workers reported the successful allylation of the aldehydes depicted in Figure 20, and from the literature, it is proposed that the catalyst in Keck's conditions is titanium complex **II.57** while the one generated in Maruoka's conditions is **II.58** (Figure 21).

[48] H. Hanawa, D. Uraguchi, S. Konishi, T. Hashimoto, K. Maruoka, *Chem. - A Eur. J.*, **2003**, *9*, *18*, 4405–4413; S. Konishi, H. Hanawa, K. Maruoka, *Tetrahedron: Asymmetry*, **2003**, *14*, *12*, 1603–1605.



II.52 **II.53** **II.54** **II.55** **II.56**

Figure 20 - Aldehydes reported for the Keck's asymmetric allylation



II.57
Keck

II.58
Maruoka

Figure 21 - Proposed catalyst for the Keck's and Maruoka's asymmetric allylation

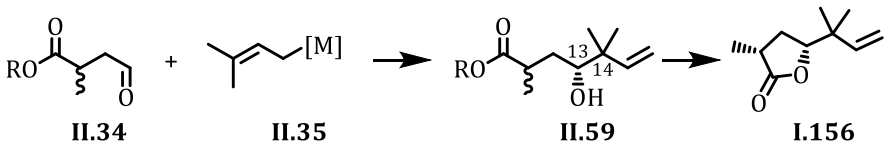
From the scope of the asymmetric allylation and compared to our case, we think that the *gem*-dimethyl substitution at the alpha position of aldehyde **II.45** might lead to a steric environment that does not allow aldehyde **II.45** to get close to the titanium Lewis acid **II.57** or **II.58**.

Even though other alternatives like the Brown asymmetric allylation or its selenium derived version developed in our group (*vide infra*) could be worth trying, we decided to turn our attention to the other disconnection strategy we were working on in parallel.

II.2.3 Synthesis of the Northern fragment by prenylation

II.2.3.1 Racemic synthesis

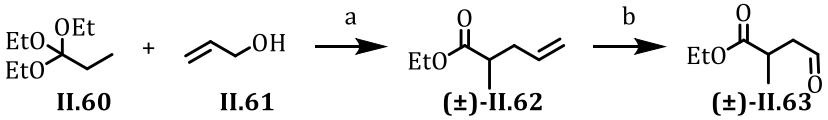
In this second approach represented in Figure 22, the allylation reaction would occur using a prenylating reagent **II.35** leading to the formation of the C_{13}-C_{14} bond in **II.59** and allowing the insertion of the *gem*-dimethyl moiety. With an appropriate aldehyde **II.34**, access to the target butyrolactone **I.156** would be straightforward.



II.34 **II.35** **II.59** **I.156**

*Figure 22 - Synthetic strategy for lactone **I.156***

With this goal in mind, the preparation of the aldehyde started with alcohol **II.66** as allylic substrate for a Claisen-Johnson rearrangement with triethylorthopropionate **II.65** (Scheme 83)[49].



II.60 **II.61** **(±)-II.62** **(±)-II.63**

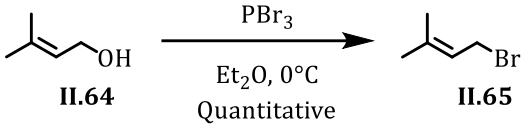
a) Propionic acid, reflux; b) i. O_3, DCM, -78°C ii. NEt_3 , DCM, -78°C - RT, 70 % over two steps.

*Scheme 83 - Synthesis of aldehyde **II.63***

^{1}H NMR monitoring of the reaction showed that a complete conversion of the intermediate mixed orthoester could not be achieved but the yield in **II.62** was deemed good enough to pursue. The crude of the reaction was then subjected to ozonolysis and after treatment with triethylamine as reducing agent, the desired aldehyde **II.63** could be isolated in 70 % over the two steps. The low price and readily availability of both starting materials allowed this reaction to be easily carried out on large scale (>10 g).

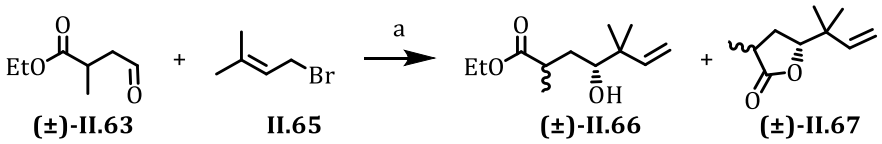
For the next step, we investigated the use of Barbier type conditions[50]. Since the prenylating agent **II.65** was rather unstable and expensive, it was prepared from the corresponding alcohol **II.64** by treatment with phosphorous tribromide (Scheme 84).

[49] W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T.-T. Li, D. J. Faulkner, M. R. Petersen, *J. Am. Chem. Soc.*, **1970**, *92*, *3*, 741–743.
[50] S. R. Wilson, M. E. Guazzaroni, *J. Org. Chem.*, **1989**, *54*, *13*, 3087–3091.



*Scheme 84 - Preparation of prenyl bromide **II.65***

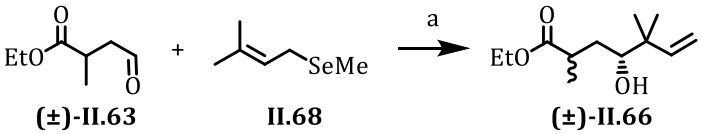
Treatment of aldehyde **II.63** and freshly prepared bromide **II.65** in the presence of freshly activated zinc powder led to the formation of homoallylic alcohol **II.66** in good yield, as a 1:1 mixture of diastereoisomer (Scheme 85). In addition, minor amounts of lactone **II.67** could also be observed as a mixture of diastereoisomers.



a) Zn powder, NH_4Cl, THF, 0°C - RT, 89 %

*Scheme 85 - Prenylation of aldehyde **II.63** in Barbier's conditions*

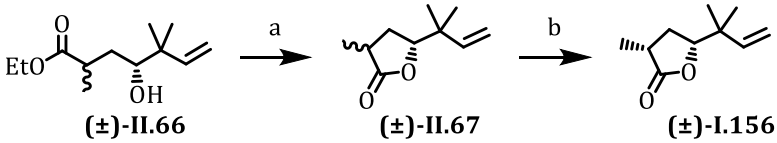
Aldehyde **II.63** could as well be treated with the prenylated selenide **II.68** in the previously described conditions which led to the formation of the same homoallylic alcohol in good yields (Scheme 86).



a) *n*BuLi, $Ti(OiPr)_4$, THF, -78°C - RT, 88 %.

*Scheme 86 - Prenylation of aldehyde **II.63** with prenyl selenide **II.68***

While homoallylic alcohol **II.66** could be isolated from the crude of the Barbier's conditions, it seemed more interesting to carry out the next step on the crude material (Scheme 87).

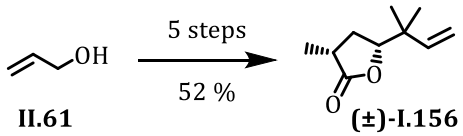


a) PTSA.H_2O, Toluene, reflux, 89 % over two steps; b) i. LDA ii. NH_4Cl, 94 %, d.r. > 95:5.

*Scheme 87 - Synthesis of lactone **I.156***

The treatment of the **II.66** in the presence of a catalytic amount of acid allowed the cyclisation into the butyrolactone **II.67** in 89 % yield. Purification after this step afforded butyrolactone **II.67** as 1:1 mixture of diastereoisomers. With this

intermediate in hand, the generation of the corresponding enolate by treatment with LDA followed by addition of NH_4Cl allowed the formation of the Northern fragment **I.156** as a single diastereoisomer. This step concluded our new methodology for the preparation of the Northern fragment which was achieved in 5 steps with 52 % overall yield starting from allyl alcohol **II.61** (Scheme 88).



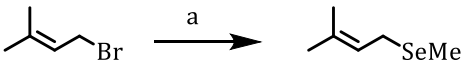
II.61 **(±)-I.156**

*Scheme 88 - Synthesis of the Northern fragment **I.156***

II.2.3.2 Enantioselective synthesis

While the above approach furnished the racemic Northern fragment, an enantioselective route was needed for the natural product. For this, we looked at performing an asymmetric prenylation reaction. A series of example have been reported in the literature, they proved inefficient in terms of enantioselectivities when it comes to their application aliphatic aldehydes. To our knowledge, the most efficient examples are the Brown[51] and the Krische[52] allylation but both require the use of 1,1-dimethylallene, a reagent that is expensive and difficult to prepare.

Based on the chemistry developed in the group[41], we thought that the selenium based allylation could become an alternative for the preparation of Brown's reagent **II.69**. Using prenyl bromide **II.65** as electrophilic partner, selenide **II.68** could be prepared in one step in good yield (Scheme 89).



II.65 **II.68**

a) Se(0), MeLi, THF, 0°C - RT, 73 %.

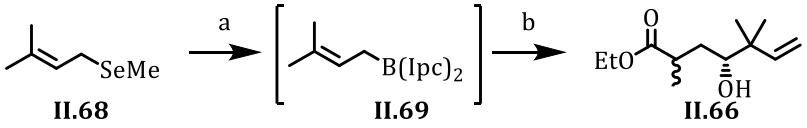
*Scheme 89 - Preparation of prenyl selenide **II.68***

The Brown's prenylating reagent was prepared *in situ* from **II.68** and then, combined with aldehyde **II.63** allowing the formation of enantioenriched homoallylic alcohol **II.66** (Scheme 90).

---

[51] P. K. Jadhav, K. S. Bhat, P. T. Perumal, H. C. Brown, *J. Org. Chem.*, **1986**, *51*, *4*, 432–439.

[52] S. B. Han, I. S. Kim, H. Han, M. J. Krische, *J. Am. Chem. Soc.*, **2009**, *131*, *20*, 6916–6917.

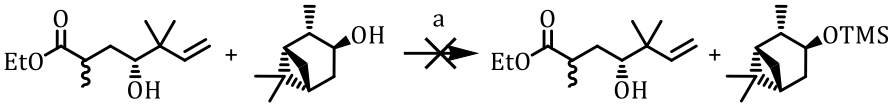


II.68 **II.69** **II.66**

a) *n*BuLi, (+)-DIP-Cl, THF, -78°C - 0°C; b) **II.63**, THF, -78°C - RT.

*Scheme 90 - Brown's asymmetric prenylation of aldehyde **II.63** from selenide **II.68***

From the crude reaction mixture, the allylation product **II.66** can be observed with complete conversion of the aldehyde **II.68**. Along with the desired alcohol **II.66**, 2 equivalents of alcohol **II.77** are formed by oxidation of the chiral auxiliary which proved impossible to separate from the desired product by column chromatography. As we knew that the alcohol in **II.76** is quite unreactive for steric reasons, we planned to facilitate the separation by protecting the secondary alcohol in **II.77** (Scheme 91).



II.66 **II.70** **II.66** **II.71**

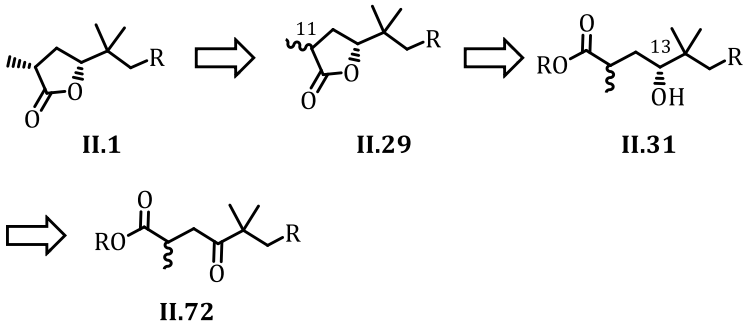
a) TMSCl, NEt_3, DMAP, 0°C - RT

*Scheme 91 - Attempts to the selective protection of alcohol **II.70***

However, we were disappointed to observe that alcohol **II.70** proved as well to be unreactive to these reaction conditions.

II.2.4 Second retrosynthetic analysis

As our previous attempts to prepare an enantiopure Northern fragment using allylation reactions failed, we had to find alternative approaches to this task. However, we still wanted to use a strategy involving a lactone intermediate as it proved useful for the control of the stereocentre at C_{11} and was required for our strategy. As the control of the C_{13} hydroxy group in **II.31** was the key for the elaboration of the target **II.1**, we looked at efficient ways to define that stereocentre (Figure 23).



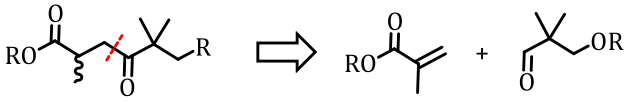
II.1 **II.29** **II.31**

II.72

*Figure 23 - New disconnection for lactone **II.1***

We proposed that the chiral centre in **II.31** could be obtained from the asymmetric reduction of ketone **II.72**. Different methodologies to carry out such transformation have been reported in the literature with some being highly selective for certain types of ketones[53].

Ketone **II.72** bears a 1,4-dicarbonyl scaffold so we thought that an interesting approach could be the coupling of an acrylic acid **II.73** derivative and aldehyde **II.33** that we prepared previously (Figure 24).



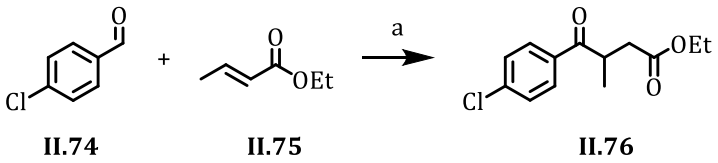
II.72 **II.73** **II.33**

*Figure 24 - Disconnection for **II.72***

The basis of our first approach was to use the Stetter reaction[54]. This transformation is known to give a straightforward access to 1,4-dicarbonyl

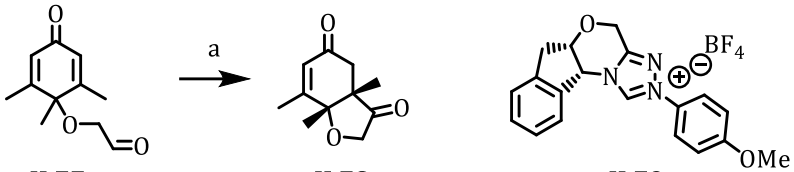
[53] P. G. Andersson, I. J. Munslow, *Modern Reduction Methods*, Wiley, **2008**.
[54] H. Stetter, M. Schreckenberg, *Angew. Chemie Int. Ed. English*, **1973**, *12*, *1*, 81–81; H. Stetter, *Angew. Chemie Int. Ed. English*, **1976**, *15*, *11*, 639–647.

architectures and some enantioselective versions have been described as depicted in Scheme 92[55].



II.74 **II.75** **II.76**

a) NaCN, DMF, 56 %.

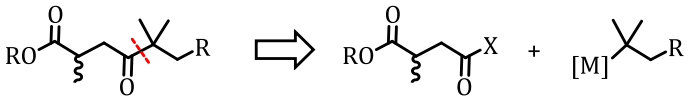


II.77 **II.78** **II.79**

a) **II.79**, KHMDS, 64 %, 99 % *e.e.*, >95 % d.r.

Scheme 92 - Examples of Stetter reaction

On the other hand, we also envisioned that **II.72** could be obtained by the addition of retron **II.81** to a synthetic equivalent of **II.80** (Figure 25).



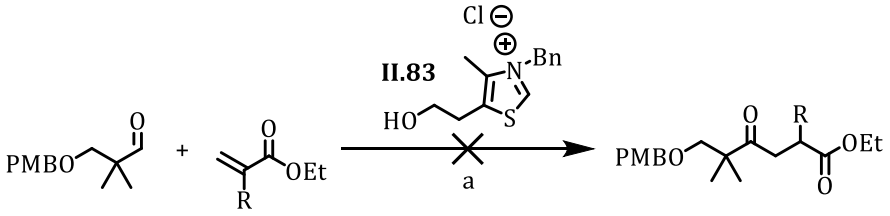
II.72 **II.80** **II.81**

*Figure 25 - Second disconnection for **II.72***

[55] M. Gravel, J. M. Holmes, in , *Compr. Org. Synth. II*, *4*, (Elsevier, **2014**), 1384–1406.

II.2.5 Synthesis of the Northern fragment by asymmetric reduction

We started our investigation by the application of the Stetter reaction to build the ketone **II.72**. However, in our hands, the reaction of aldehyde **II.45** with acrylate **II.7** or **II.82** in the presence of thiazolium salt **II.83** as a catalyst did not lead to any observable trace of the desired ketone **II.84** or **II.85** (Scheme 93). Both acrylate **II.7** and methacrylate **II.82** were used as substrates and even in refluxing dioxane, we could not observe any formation of the ketone.



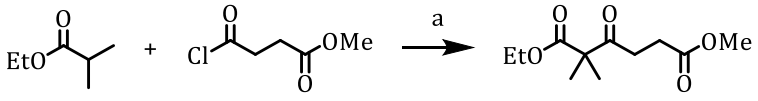
II.45 **II.7** R = H; **II.82** R = Me → **II.84** R = H; **(±)-II.85** R = Me

a) NEt_3, MeOH, reflux or NEt_3, dioxane, reflux.

*Scheme 93 - Synthesis of **II.84** and **II.85** by Stetter reaction*

Looking at the scope of the Stetter reaction, we think that a possible explanation for this result might be a combination of poor reactivity of the aldehyde **II.45** due to unfavourable steric and electronic features, as well as the screen of a single catalyst. As we could only recover the starting material from these reactions, we decided to investigate other methods for the formation of the ketone.

From the disconnection proposed in Figure 25, ketone **II.72** could be obtained by the addition of a synthetic equivalent of **II.81** to an acyl derivative like **II.80**. We decided to carry out the transformation using commercially available acyl chloride **II.86**. The synthetic equivalent we thought of for **II.81** was an enolate as this could be easily generated by the deprotonation of ester **I.130** (Scheme 94).

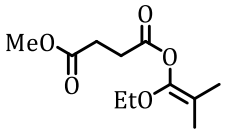


I.130 **II.86** **II.87**

a) LDA, THF, RT then -78°C - RT, 88 %.

*Scheme 94 - Synthesis of ketone **II.87***

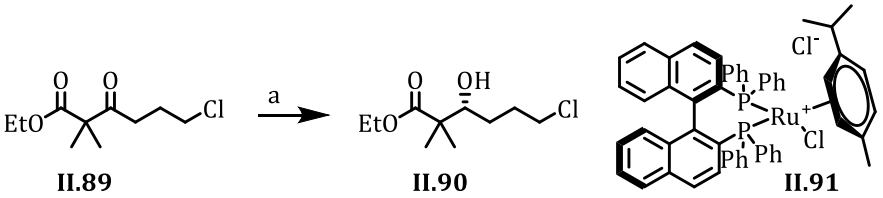
From this reaction, ketone **II.87** could be obtained in excellent yield. We also observed that a control of the reaction temperature before the addition of acyl chloride **II.86** was important since side product **II.88** arising from an O-alkylation could be formed when the reaction is carried out at 0 °C (Figure 26).



II.88

*Figure 26 - Side product of the alkylation of acyl chloride **II.86***

As ketone **II.87** bears a β-ketoester framework, we thought that the Noyori hydrogenation could be suited for this transformation. Moreover, this reaction has been carried out on similar substrates like compound **II.89** using ruthenium catalyst **II.91**[56] as represented in Scheme 95



II.89 **II.90** **II.91**

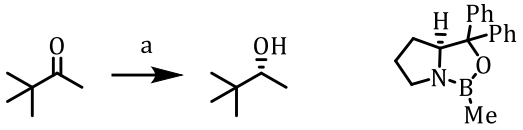
a) **II.91**, H_2, 93 %.

*Scheme 95 - Reduction of ketone **II.89** using Noyori asymmetric reduction*

However, since we were working on other approaches to carry out the asymmetric reduction of ketone **II.87**, we did not have the opportunity to carry out this transformation.

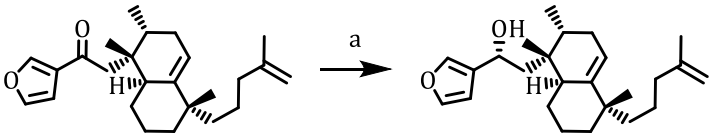
Another alternative for the asymmetric reduction was proposed by the Corey-Bakshi-Shibata (CBS) reduction[57]. The reaction has been used extensively to carry out the reduction of ketone and this is achieved using a readily available catalyst and borane as hydride source. The method has been used efficiently by numerous research groups and allows access to a significant number of chiral alcohols with excellent enantiomeric excess from simple or more complex ketones[58] (Scheme 96).

[56] F. T. Boyle, R. Narquizian, C. Smith, P. Raubo, K. Muir, L. J. Farrugia, P. Kocienski, *J. Chem. Soc. Perkin Trans. 1*, **2002**, *15*, 2357–2384.
[57] E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.*, **1987**, *109*, *18*, 5551–5553.
[58] E. J. Corey, C. J. Helal, *Angew. Chem. Int. Ed. Engl.*, **1998**, *37*, 1986–2012.



II.92 **II.93** **II.94**

a) **II.94**, BH_3.THF, 94 % *e.e.*

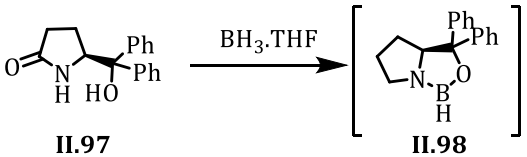


II.95 **II.96**

a) **II.94**, $BH_3.Me_2S$, Tol, 91 %, d.r. > 10:1.

Scheme 96 - Examples of CBS reduction

The selectivity can be explained by the discrimination between the two faces of the carbonyl. It is believed to occur based on steric factors making ketone **II.87** a good substrate for the transformation due to the presence of the quaternary centre in alpha position of the ketone. Therefore, using the conditions described by Kawanami[59], lactame **II.97** was treated in the presence of borane-tetrahydrofuran complex followed by the addition of ketone **II.87**. In these reaction conditions, the asymmetric reduction should happen as intermediate **II.98** is generated *in situ* (Scheme 97).

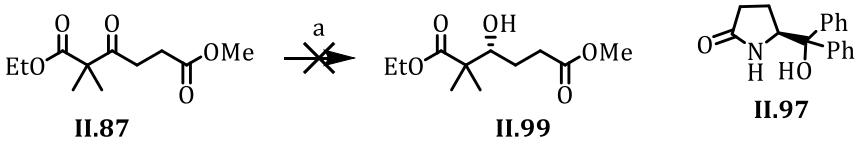


II.97 **II.98**

Scheme 97 - Generation of the CBS reduction catalyst

We were disappointed to observe no reduction product in these conditions (Scheme 98).

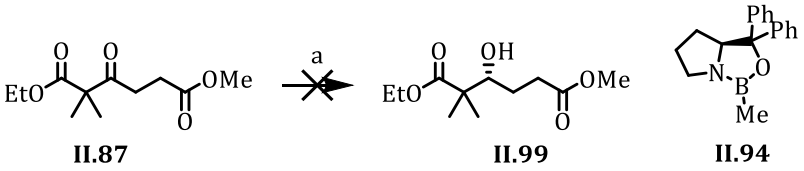
[59] Y. Kawanami, S. Murao, T. Ohga, N. Kobayashi, *Tetrahedron*, **2003**, *59*, *42*, 8411–8414.



a) **II.97**, BH_3.THF, THF, RT then 0°C.

*Scheme 98 - Reduction of ketone **II.87** using Kawanami's methology*

We decided therefore to use the commercial oxazaborolidinone **II.94** but unfortunately, we failed to obtain any reduction product as shown below (Scheme 99).



a) **II.94**, BH_3.THF, THF, RT then 0°C.

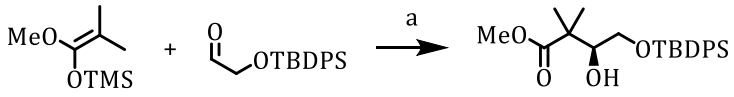
*Scheme 99 - Reduction of ketone **II.87** using Corey's catalyst*

We also carried out these transformations with borane-dimethylsulfide complex as reducing agent but could not observed any desired product either. Looking at other examples in the literature, we noticed that the presence of heteroatoms seems to limit greatly the scope of the CBS reduction[60]. With the hypothesis that the reaction is inhibited by the coordination of the borane to these heteroatoms, we carried out the experiment using a large excess of borane-tetrahydrofuran complex but failed once again to observe any reduction product. Another possibility to explain the failure of the CBS reduction might be the formation of a strong chelate due to the vicinity of the terminal ethyl ester that would forbid the catalyst release. These observations led us to abandon the asymmetric hydrogenation and to look for other transformations to install the desired asymmetric alcohol.

[60] G. J. Quallich, T. M. Woodall, *Tetrahedron Lett.*, **1993**, *34*, *5*, 785–788.

II.2.6 Third retrosynthetic analysis

Looking back at the previous total synthesis of Polycavernoside A, we noticed that Sasaki had used the aldol conditions developed by Kiyooka to install the C_{15} chiral centre[17,61] (Scheme 100).

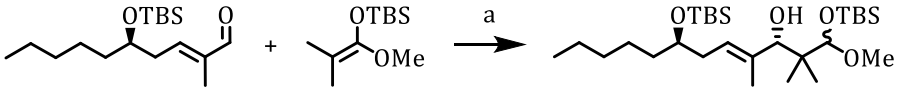


I.113 **II.100** **II.101**

a) Ts-Valine, BH_3.THF, DCM, -78°C, 65 %.

*Scheme 100 - Synthesis of alcohol **II.101** by Sasaki*

We therefore thought that the methodology developed by the group of Kiyooka could be suitable for the assembly of the C_{13} chiral centre of our target. We also noticed that the use of TBS substituted ketene acetal like **VI.40** instead of **VI.36** led to the formation of the mixed ketal **VI.41** instead of the β-hydroxy ester[62] as represented in Scheme 101.

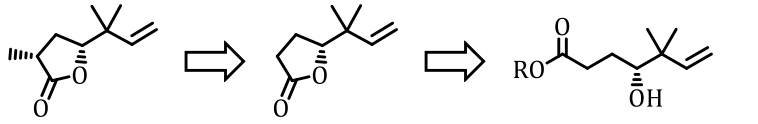


II.102 **II.103** **II.104**

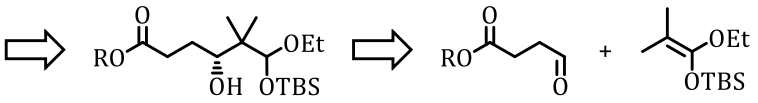
a) Ts-Valine, BH_3.THF, DCM, -78°C, 70 %.

*Scheme 101 - Kiyooka aldol reaction with TBS ketene acetal **II.103***

With the plan to use this method for the installation of the chiral alcohol, we established the disconnection depicted in Figure 27.



I.156 **I.158** **II.105**



II.106 **II.107** **II.103**

*Figure 27 - New disconnection for the synthesis of **II.156***

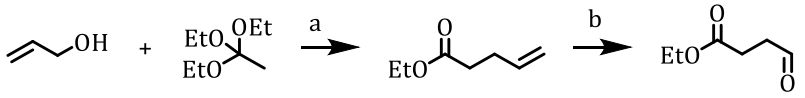
Our target **I.156** could be obtained from the methylation of lactone **I.158** as previously demonstrated by Alexandre Drouin[22]. This lactone **I.158** could arise

[61] S. Kiyooka, Y. Kaneko, M. Komura, H. Matsuo, M. Nakano, *J. Org. Chem.*, **1991**, *56*, *7*, 2276–2278.
[62] S. Kiyooka, M. a. Hena, *J. Org. Chem.*, **1999**, *64*, *15*, 5511–5523.

from the cyclisation of alcohol **II.105** that would as well come from the functionalisation of the acetal in **II.106**. This compound could arise from the use of the Kiyooka aldol reaction between aldehyde **II.107** and ketene acetal **II.103**. Concerning the aldehyde architecture, **II.107** was preferred to **II.63** in order to avoid any match/mismatch effect during the asymmetric aldol reaction. Since **II.63** already bears a chiral centre, this could have an influence of the asymmetric induction of the aldol reaction.

II.2.7 Synthesis of the Northern fragment by asymmetric aldol reaction

The preparation of aldehyde **II.107** was carried out using an approach similar to the one previously used but triethylorthoacetate **II.108** was used instead of triethylorthopropionate. The Claisen-Johnson rearrangement afforded olefin **II.109** in good yield. The treatment of this adduct with ozone followed by a work-up using triethylamine led to the formation of aldehyde **II.110** in excellent yield (Scheme 102).

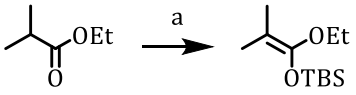


II.61 **II.108** **II.109** **II.110**

a) Propionic acid, reflux, 83 %; b) i) O_3, DCM, -78°C ii) NEt_3, -78°C - RT, 92 %.

*Scheme 102 - Synthesis of aldehyde **II.110***

The preparation of ketene acetal **II.103** was carried out according to the procedure used by Mikami and led to the isolation of the desired product in good yield[63] (Scheme 103).

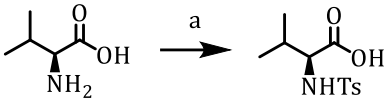


I.130 **II.103**

a) LDA, THF, HMPA, -78°C then TBSCl, -78°C - RT, 73 %.

*Scheme 103 - Synthesis of acetal **II.103***

The preparation of the tosyl valine **II.112** was carried out in one step starting from the commercialy available amino acid (Scheme 104).



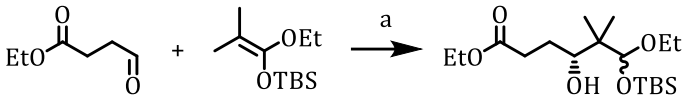
II.111 **II.112**

a) TsCl, Na_2CO_3, H_2O, 0°C - RT, 72 %.

*Scheme 104 - Synthesis of tosyl valine **II.112***

With all partners for the reaction available, the Kiyooka aldol reaction could be set up and afforded the desired acetal **II.113** (Scheme 105).

[63] K. Mikami, S. Matsumoto, A. Ishida, S. Takamuku, T. Suenobu, S. Fukuzumi, *J. Am. Chem. Soc.*, **1995**, *117*, *45*, 11134–11141.

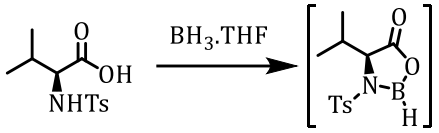


II.110 **II.103** **II.113**

a) Ts-Valine, BH_3.THF, DCM, -78°C, 84 %.

*Scheme 105 - Kiyooka aldol reaction with aldehyde **II.110***

During this reaction, the borane tetrahydrofuran complex reacts with the tosyl valine **II.112** leading to the formation of the oxazaborolidinone **I.118** (Scheme 106). This intermediate first acts as a Lewis acid and coordinates the aldehyde and will later act as a hydride source leading to the formation of the mixed acetal.

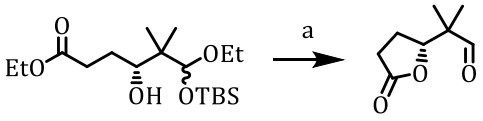


II.112 **I.118**

Scheme 106 - Generation of Kiyooka ctalyst

We could notice by ^{1}H NMR that a mixture of diastereoisomers present as two separate singlets can be observed for the acetal hydrogens. The same observation was made by Kiyooka. Moreover, a partial hydrolysis of the acetal can be observed and is suspected to arise from residual water in the deuterated solvent. This observation led us to confirm that the mixed acetal should be transformed into a more stable form before going further in the synthesis. It is noteworthy that particular attention should be given to the preparation of the tosyl valine **II.112**. Since this reagent is prepared in water, we noticed that if the solid was not carefully dried, an erosion of the yield of the aldol reaction could be observed.

The acetal function of **II.113** could be hydrolysed in the presence of a catalytic amount of an acid and water (Scheme 107).



II.113 **II.114**

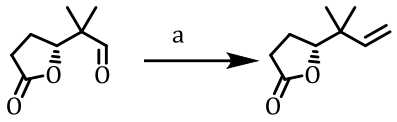
a) PTSA, H_2O, DCM, reflux, 92 %, 84 % *e.e.*

*Scheme 107 - Hydrolysis of acetal **II.113***

This was achieved using PTSA as the acid. Running the reaction in refluxing dichloromethane allowed the cyclization to occur at the same time affording aldehyde **II.114** in good yield. The enantiomeric excess was measured using

chiral gas chromatography by comparison with the racemic mixture and was determined to be of 84 % *e.e*.

Moving further in the synthesis, the treatment of the aldehyde **II.114** with a Wittig salt afforded olefin **I.158** (Scheme 108).

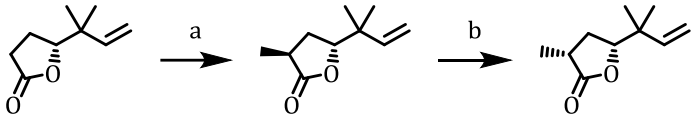


II.117 **I.158**

a) Ph_3PCH_3I, *n*BuLi, THF, 0°C - RT, 64 %.

*Scheme 108 - Wittig olefination of aldehyde **II.114***

The treatment of lactone **I.158** by LDA followed by the addition of methyl iodide led to the formation of lactone **II.118** as a single diastereoisomer as observed by Alexandre Drouin (Scheme 109). Under the conditions used previously, the epimerisation of the chiral centre located at the α-position of the carbonyl of **II.118** successfully led to lactone **I.156** as a single diastereoisomer.



I.158 **II.118** **I.156**

a) LDA, THF, -78°C then MeI, -78°C - RT, 85 %; b) LDA, THF, -78°C then NH_4Cl, -78°C - RT, 92 %, d.r. > 95:5.

*Scheme 109 - Synthesis of the Northern fragment **I.156***

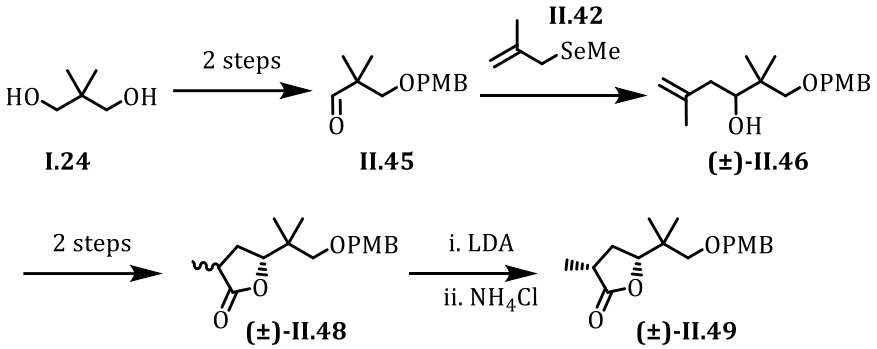
This step concluded the preparation of the Northern fragment of polycavernoside A **I.156** in an enantioenriched fashion. With this new synthetic pathway, the desired lactone was prepared in 7 steps starting from allyl alcohol in an overall yield of 46 % relying on the Kiyooka aldol reaction to induce the asymmetry.

II.3 Conclusions and perspectives

II.3.1 Conclusions

From the work presented in this chapter, two methodologies were developed relying on allylation reaction and allowed the racemic synthesis of the Northern fragment of Polycavernoside A.

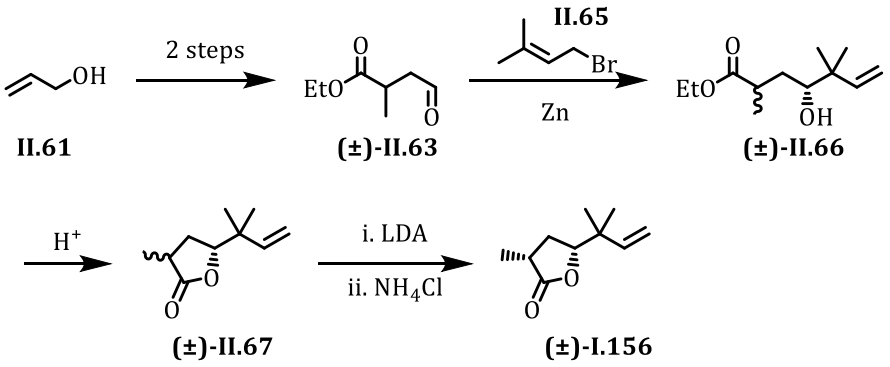
The first route started from diol **I.24** that was transformed into aldehyde **II.45**. Then methallylation under conditions developed in our group afforded homoallylic alcohol **II.46** (Scheme 110)



*Scheme 110 - Synthesis of lactone **II.49***

This intermediate was transformed into the lactone **II.48** in two steps. The treatment of the lactone **II.48** with LDA followed by a selective protonation of the enolate intermediate afforded the desired lactone **II.49** as a single diastereoisomer.

The second approach started from alcohol **II.61** that could be transformed in two steps into aldehyde **II.63** (Scheme 111).



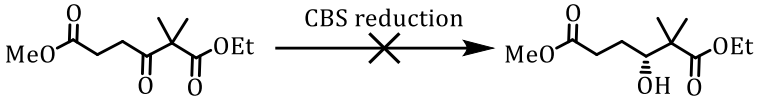
*Scheme 111 - Synthesis of lactone **I.156***

The prenylation of this aldehyde led to the formation of homoallylic alcohol **II.66** that could be cyclised into lactone **II.67**. Deprotonation of this lactone followed

by a subsequent reprotonation afforded lactone **I.156** as a single diastereoisomer.

Our attempts to carry out these transformations in an enantioselective fashion did not provide the desired results. The aldehyde **II.45** proved to be unreactive in the Keck asymmetric allylation conditions and we were unable to purify homoallylic alcohol **II.66** obtained from the selenium based Brown asymmetric prenylation reaction. Therefore, we decided to move to new approaches to carry out the asymmetric transformation.

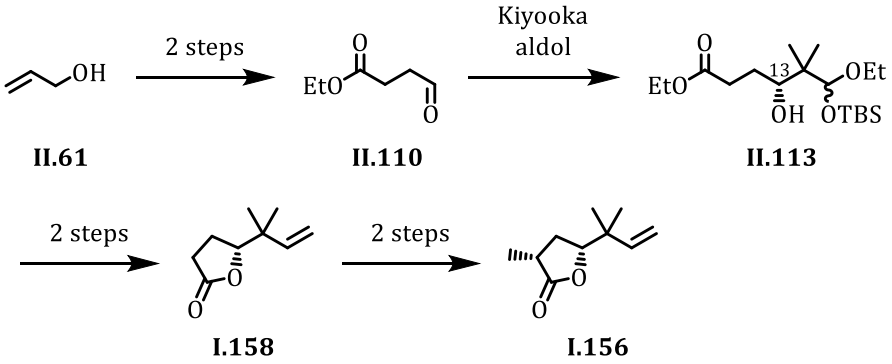
Our strategy relying on the asymmetric reduction of ketone **VI.23** using the CBS catalyst did not provide the desired result (Scheme 112).



II.87 **II.99**

*Scheme 112 - Reduction of ketone **II.87** using Corey-Bakshi-Shibata reduction*

However, Kiyooka asymmetric aldol reaction proved to be suited for the installation of the C_{13} chiral centre (Scheme 113). The aldehyde **II.110** could be obtained starting from allyl alcohol **II.61** and using the Claisen-Johnson rearrangement. With this substrate, the asymmetric transformation successfully afforded the alcohol **II.113**.



II.61 **II.110** **II.113**

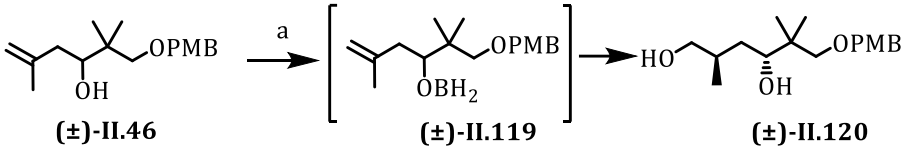
I.158 **I.156**

Scheme 113 - Synthesis of the Northern fragment of Polycavernoside A

Then acetal **II.113** could be converted into lactone **I.158** in two steps. From this intermediate, 2 steps were required to reach the Northern fragment **I.156** as a single diastereoisomer.

II.3.2 Perspectives

Even though the methodologies based on allylation reactions did not allow to access enantioenriched Northern fragments, some transformations led to interesting resulting and further investigations might prove beneficial. The hydroboration of alcohol **II.46** was carried out with borane tetrahydrofuran complex and some diastereoselectivity was observed (Scheme 114). This selectivity is suspected to arise from the formation of alkoxyborane **II.119** an intermediate that might undergo the hydroboration in an intramolecular fashion.



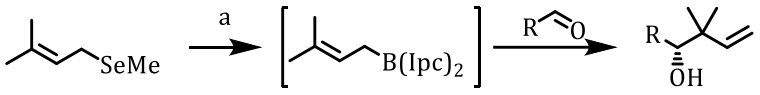
(±)-II.46 **(±)-II.119** **(±)-II.120**

a) BH_3.THF

*Scheme 114 - Diastereoselective hydroboration of **II.46***

Using a 1:1 ratio of borane/ homoallylic alcohol might lead to a completely diastereoselective reaction that would increase the efficiency of the process.

Our second approach to an enantioenriched Northern fragment relied on the use of selenide **II.68** to generate in situ Brown's asymmetric allylating reagent **II.69** (Scheme 115). Even though we could not benefit from this transformation for the elaboration of our target, this new method for the preparation of Brown prenylating reagent followed by the allylation of aldehydes could find interesting applications. The preparation of prenyl selenide **II.68** is straightforward and avoids the use of 1,1-dimethylallene.



II.68 **II.69** **II.121**

a) *n*BuLi, (+)-DIP-Cl.

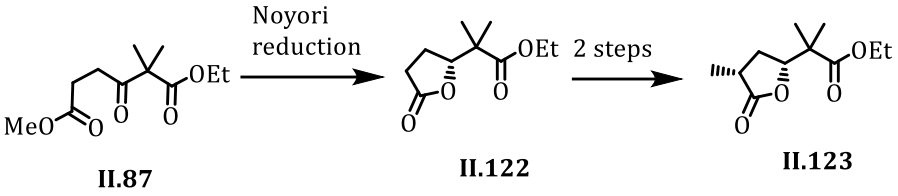
*Scheme 115 - Asymmetric allylation of aldehydes with selenide **II.68***

In addition, the prenylation allows the insertion of a *gem*-dimethyl group which is a feature present in numerous natural products and is of interest in the design of potent molecules[64].

Regarding the asymmetric preparation of the Northern fragment, the Kiyooka aldol reaction requires the use of a stoichiometric amount of reagents as opposed to other transformations. While the CBS reduction did not allow us to access the Northern fragment, an approach using a catalytic asymmetric reduction reaction

[64] T. T. Talele, *J. Med. Chem.*, **2018**, *61*, *6*, 2166–2210.

might be more straightforward. Since only one step is required for the preparation of ketone **II.87**, the use of the Noyori reduction should yield the lactone **II.123** in an efficient manner (Scheme 116).



II.87 **II.122** **II.123**

Scheme 116 - Synthesis of the Northern fragment by Noyori's reduction

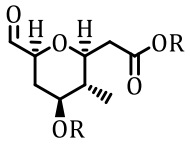
Chapter III

Synthesis of the Southern fragment

III.1 Synthesis of THPs in the Markó group

III.1.1 Development of the ene-IMSC/ISMS sequence

The Southern fragment of Polycavernoside A is a substituted 2,6-*cis*-tetrahydropyran (THP) **III.1** (Figure 28). These structures are present in numerous natural products and, therefore, scientists have developed multiple methodologies to access these scaffolds[65].



III.1

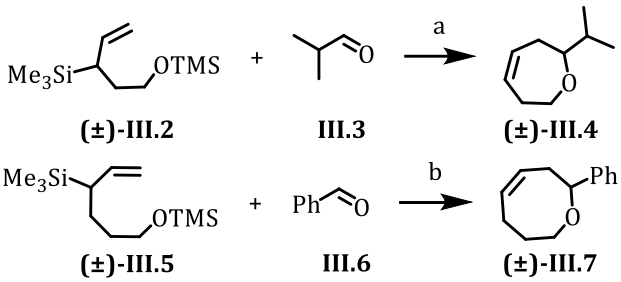
Southern fragment
of Polycavernoside A

Figure 28 - Structure of the Southern fragment

In the introduction, a few examples of these methodologies were presented as they were used in the previous total synthesis. Our lab has been interested in the preparation of tetrahydropyrans for a long time and it started with the work of Mekhalfia in 1991[66] based on the chemistry developed earlier by Miginiac[67] and shown in Scheme 117. Miginiac and co-workers reported the synthesis of 7- and 8-membered ring ethers **III.4** and **III.7** from allylsilane **III.2** and **III.5**. While they thought that the corresponding 6-membered rings could be accessed using their method, they were unable to prepare the homoallylic alcohol required for the transformation.

---

[65] J. Cossy, M. Rings, *Synthesis of Saturated Oxygenated Heterocycles I*, (Springer, **2014**); C. Olier, M. Kaafarani, S. Gastaldi, M. P. Bertrand, *Tetrahedron*, **2010**, *66*, *896*, 413–445.
[66] A. Mekhalfia, I. E. Markó, H. Adams, *Tetrahedron Lett.*, **1991**, *32*, *36*, 4783–4786.
[67] B. Guyot, J. Pornet, L. Miginiac, *J. Organomet. Chem.*, **1989**, *373*, *3*, 279–288.



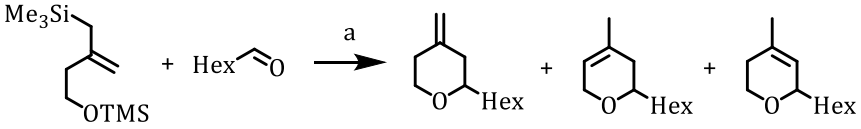
(±)-III.2 **III.3** **(±)-III.4**

(±)-III.5 **III.6** **(±)-III.7**

a) $BF_3.Et_2O$, 84 %; b) $BF_3.Et_2O$, 77 %.

Scheme 117 - Miginiac synthesis of cyclic ethers

A few years later, using a procedure described by Barry Trost[68] for its preparation, the Markó group reported the use of silyl ether **III.8** in the conditions developed by Miginiac. This chemistry allowed the preparation of *exo*-methylene tetrahydropyrans like **III.10** by condensation of silyl ethers with aldehydes, ketone or orthoesters that was coined as Intramolecular Silyl Modified Sakurai or ISMS reaction (Scheme 118).



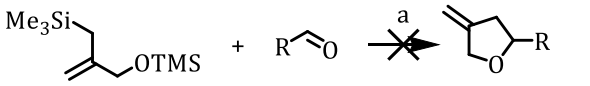
III.8 **III.9** **(±)-III.10** **(±)-III.11** **(±)-III.12**

16:3:2

a) TMSOTf, 88 %.

Scheme 118 - Intramolecular Silyl Modified Sakurai reaction (ISMS)

Our group was interested in the synthesis of several cyclic ethers and therefore attempted the formation of tetrahydrofurans using allylic alcohol **III.13** in the same conditions but failed to isolate the desired product **III.15** (Scheme 119).



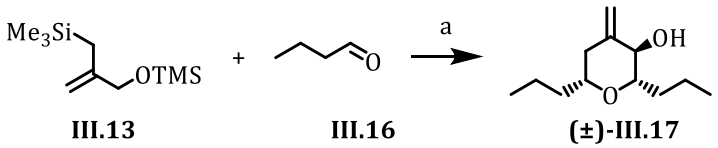
III.13 **III.14** **(±)-III.15**

a) TMSOTf.

*Scheme 119 - Application of the ISMS conditions to allylsilane **III.13***

[68] B. M. Trost, D. M. T. Chan, T. N. Nanninga, *Org. Synth.*, **1984**, *62*, 58.

However, when BF_3 was used as Lewis acid, they were able to isolate from the reaction mixture compound **III.17** that was present as a single diastereoisomer (Scheme 120)[69].

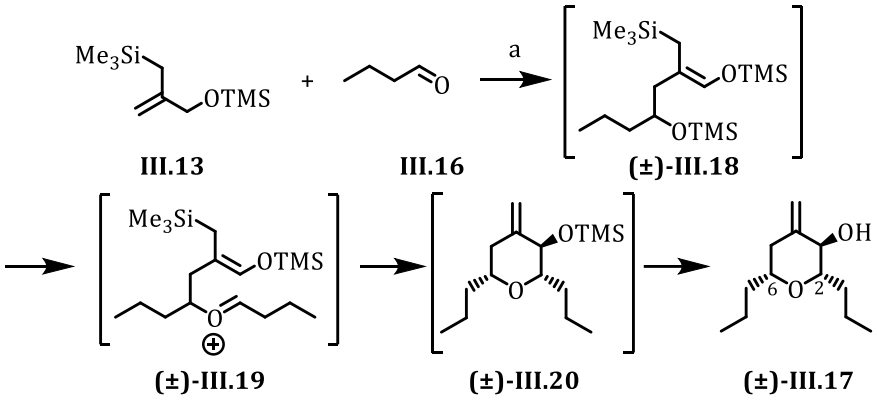


III.13 **III.16** **(±)-III.17**

a) $BF_3.Et_2O$, 43 %.

*Scheme 120 - Formation of tetrahydropyran **III.17***

The formation of tetrahydropyran **III.17** was explained by an initial formation of a homoallylic alcohol **III.18** by reaction between aldehyde **III.16** and allylsilane **III.13** through an ene reaction catalysed by the Lewis acid (Scheme 121). Then, this intermediate is involved in a cyclisation reaction with another equivalent of aldehyde **III.16** in a similar manner as described above while this time being catalysed by BF_3 producing tetrahydropyran **III.20**. In the reaction conditions, the silyl protecting group in **III.20** is cleaved leading to the isolation of compound **III.17**.



III.13 **III.16** **(±)-III.18**

(±)-III.19 **(±)-III.20** **(±)-III.17**

a) $BF_3.Et_2O$.

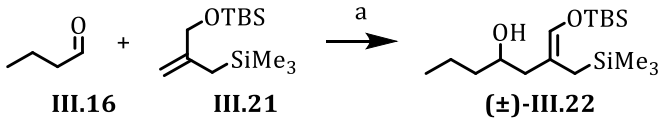
*Scheme 121 - Mechanism for the formation of **III.17***

From this result, it became obvious that if the reaction could be stopped at the formation of **III.18**, this methodology could present as an efficient way to prepare substituted THPs bearing different side chains at the 2 and 6-position with a *cis*-configuration and as a single diastereoisomer.

With this goal in mind, our group worked on the optimisation of the reactions and developed a method that successfully generated these interesting scaffolds. The ene reaction could be performed using aluminium based Lewis acids, most

[69] I. E. Markó, D. J. Bayston, *Tetrahedron Lett.*, **1993**, *34*, *41*, 6595–6598.

often with Et_2AlCl, as the alcohol **III.22** does not undergo the Hosomi-Sakurai reaction under these conditions as shown in Scheme 122.

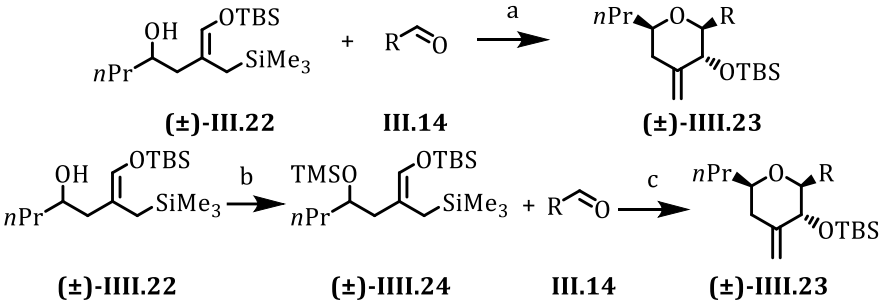


III.16 **III.21** **(±)-III.22**

a) Et_2AlCl, 49 %.

*Scheme 122 - Development of the ene reaction with **III.21***

Having established an efficient way to access intermediates like **III.22**, they were able to carry out the cyclisation reaction using two similar routes (Scheme 123). The first involved using the alcohol **III.22** in combination with a carbonyl partner and BF_3 as Lewis acid (IntraMolecular Sakurai Cyclisation or IMSC reaction). The second route started with the transformation of the alcohol **III.22** into the corresponding silyl ether **III.24** and then the cyclisation could be performed using TMSOTf as Lewis acid in catalytic amount (ISMS reaction). These two strategies allowed the preparation of tetrahydropyran **III.23** in an efficient and straightforward manner.



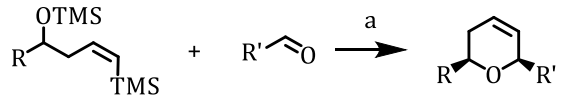
(±)-III.22 **III.14** **(±)-IIII.23**

(±)-IIII.22 **(±)-IIII.24** **III.14** **(±)-IIII.23**

a) BF_3, Et_2O; b) TMSCl, NEt_3; c) TMSOTf.

*Scheme 123 - Synthesis of **III.23** by IMSC and ISMS*

Using vinylsilane **III.25** instead of allylsilane, the methodologies proved equally efficient for the elaboration of dihydropyrans like **III.27** (Scheme 124)[70].



(±)-III.25 **III.26** **(±)-III.27**

a) TMSOTf, 60-89 %.

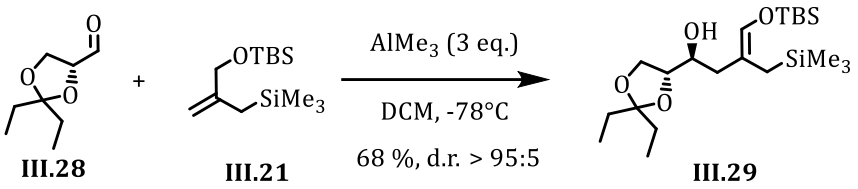
*Scheme 124 - ISMS reaction using vinylsilane **III.25***

[70] I. E. Markó, D. J. Bayston, *Tetrahedron*, **1994**, *50*, *24*, 7141–7156.

These methods proved useful in the preparation of natural products or fragments[71].

The major limitation of the method was the elaboration of enantioselective tetrahydropyrans via the ene-IMSC sequence. At the time, the attempts to develop an enantioselective ene reaction either using chiral Lewis acids or chiral aldehydes in a diastereoselective manner met with failure[21,72].

In 2014, Pol Karier and Thomas Xhurdebise developed a diastereospecific version of the ene reaction (Scheme 125)[73].



Scheme 125 - Diastereoselective ene reaction

This result was of high value for the group as excellent diastereocontrol could be achieved by using only the combination of aldehyde **III.28** with allylsilane **III.21** with trimethyl aluminium as the Lewis acid. During the course of their investigation, they observed that changing either the Lewis acid (using other aluminium-based Lewis acids or BF_3) or the aldehyde (alpha or beta alkoxy aldehydes) led to a dramatic erosion of the diastereoselectivity of the reaction.

From homoallylic alcohol **III.29**, they were able to extend the ISMS and IMSC methodologies to the elaboration of enantioenriched tetrahydropyrans towards the construction of complex organic molecules. Fortunately, the nature of the aldehyde was valuable as the deprotection of the acetonide revealed a 1,2-diol, a versatile function for late stage modifications. From THP **III.30**, protected polyol **III.31** could be prepared as intermediate in the synthesis of Amphidinol 3 (Figure 29). The intermediate **III.32** served in the elaboration of the tetrahydrofuran fragment of Amphidinolide K **III.33**[74] while THP **III.34** was used in the elaboration of ladder polyethers **III.35** towards the synthesis of Brevetoxin B.

[71] I. E. Markó, D. J. Bayston, *Synthesis* , **1996**, *02*, 297–304.
[72] B. Leroy, *PhD Thesis*, **2001**, UCL.
[73] P. Karier, *PhD Thesis*, **2016**, UCL; T. Xhurdebise, *PhD Thesis*, **2017**, UCL.
[74] J. Savary, *PhD Thesis*, **in progress**, UCL.

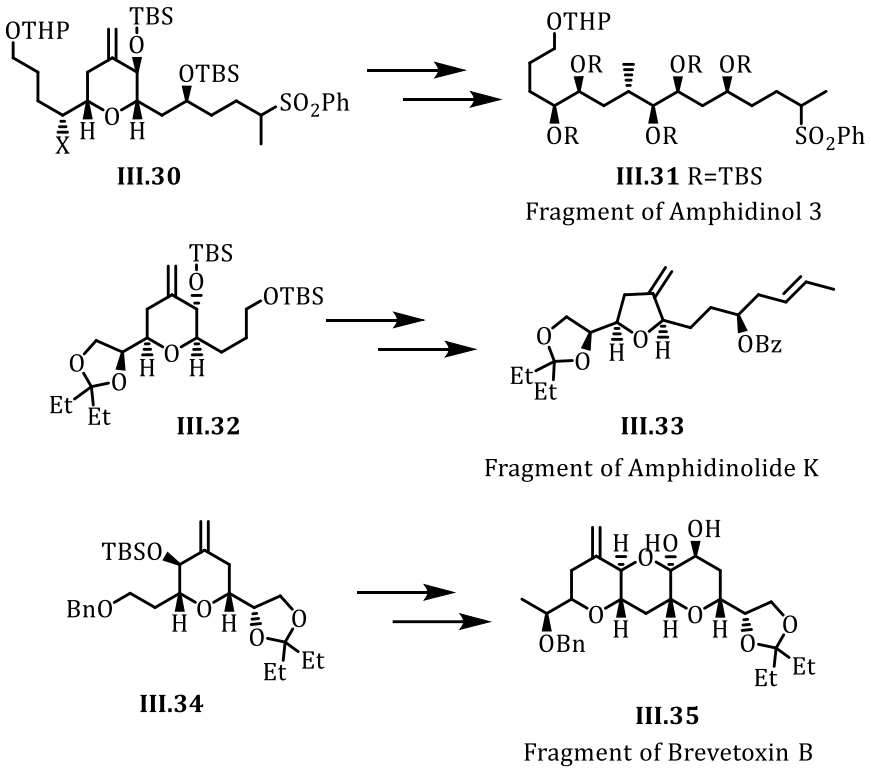


Figure 29 - ISMS and IMSC reaction towards the synthesis of natural products

III.1.2 Previous synthesis of the Southern fragment in the Markó group[75]

In the work reported previously by the Markó group[23], the synthesis of the Southern fragment of Polycavernoside A was achieved through the formation of a tetrahydropyran via the IMSC reaction. The disconnection that the group relied on involved an aldehyde and a homoallylic alcohol, the latter arising either from the selenoalkyne methodology or the ene reaction developed in the group (Figure 30).

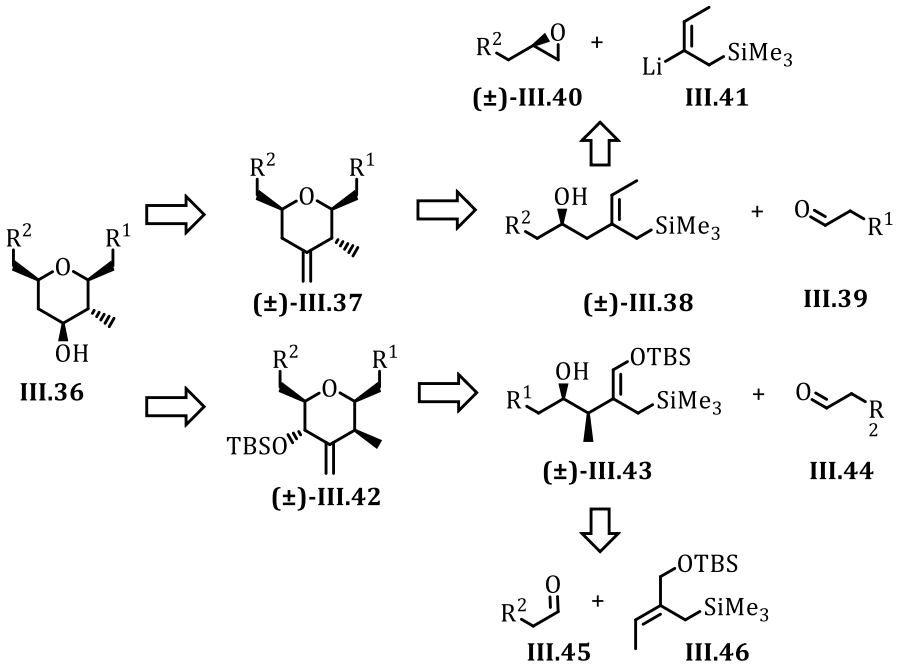
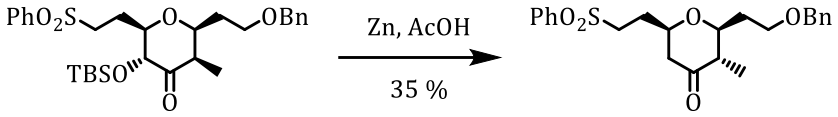


Figure 30 - Previous disconnections of the Southern fragment

However, the methods developed previously were deemed too long or could not allow access to enantiopure material.

While homoallylic alcohols **III.43** was used previously for the elaboration of the Southern fragment of Polycavernoside A[24], the presence of the TBS ether on **III.47** was problematic. As it was shown by Freddi Philippart and Alexandre Drouin, the cleavage of this function occurred with low yield (Scheme 126).

[75] A detailed description of the synthesis is reported in the Introduction chapter.



(±)-III.47 **(±)-I.169**

Scheme 126 - Synthesis of THP ***I.169***

Looking at the promising results obtained for the diastereoselective ene reaction, we decided to investigate its use for the synthesis of the Southern fragment of Polycavernoside A.

III.2 Towards the synthesis of the Southern fragment

III.2.1 Disconnection

From the previous results of the group, we established the disconnection strategy proposed in Figure 31.

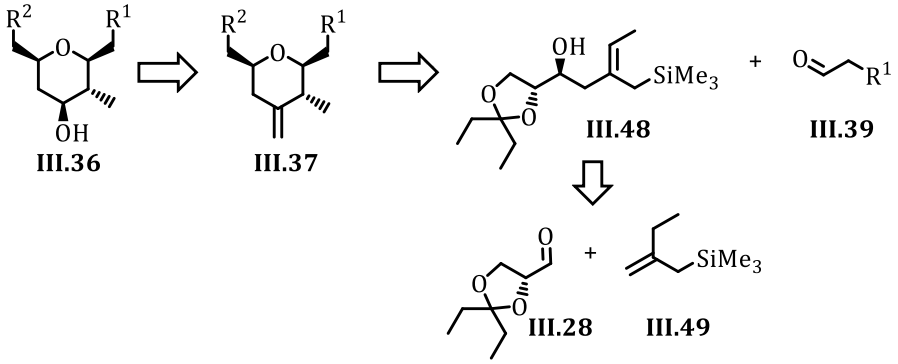


*Figure 31 - Disconnection of **III.38***

The tetrahydropyran **III.36** could arise from the ISMS or IMSC adduct **III.37** which in turn should be accessible by the reaction between an aldehyde **III.39** and a homoallylic alcohol **III.48**. The latter could be prepared starting from aldehyde **III.28** and allylsilane **III.49**. As allylsilane **III.49** could be a suitable partner for the synthesis of the Southern sub-unit, we realised that other similar allylsilanes could lead to the elaboration of new THPs. For example, the tetrahydropyran of Polycavernoside D[5] **III.50** could be assembled from allylsilane **III.52**, while compound **III.53** could arise from methallylsilane **III.55** (Figure 32). Their preparation would also allow to investigate the scope of the reaction.

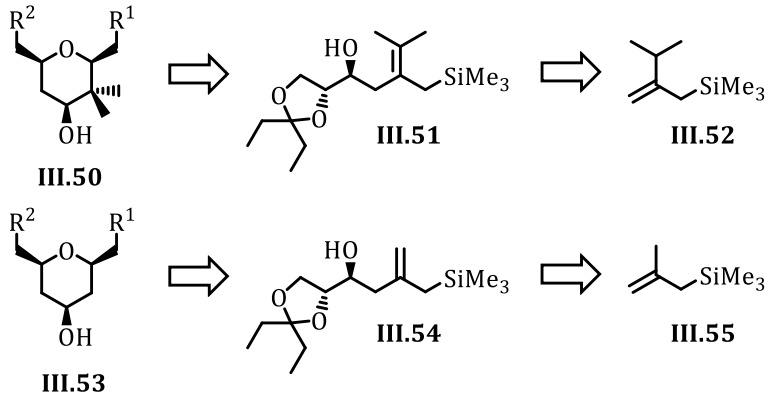
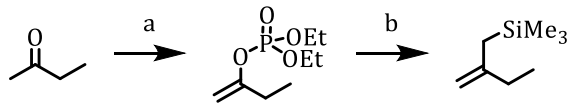


*Figure 32 - Disconnection of **III.50** and **III.53***

III.2.2 Results and discussion

Our investigation started with the preparation of the allylsilane **III.49**. We adapted a procedure described by Baker[76] for the synthesis of a similar compound using 2-butanone **III.56** (Scheme 127).

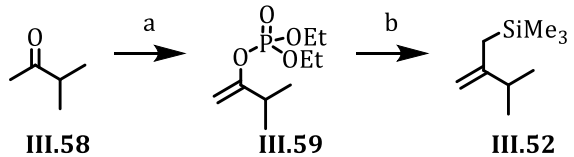


III.56 **III.57** **III.49**

a) i. LDA, THF, -78°C ii. $Cl(O)P(OEt)_2$, -78°C - RT, 91 %; b) $TMSCH_2Cl$, Mg, THF, reflux, then **III.57**, $Ni(acac)_2$, THF, 0°C - RT, 90 %.

*Scheme 127 - Synthesis of allylsilane **III.49***

The use of LDA at low temperature for the deprotonation allowed the selective formation of the kinetic enolate which was trapped by forming the corresponding vinyl phosphonate **III.57**. This substrate proved to be suitable for a nickel (II) catalysed Kumada cross-coupling leading to the isolation of allylsilane **III.49**. While the reaction time was longer compared to the use of vinyl bromide for the preparation of **III.21**, an overnight reaction versus two to three hours reaction time, the vinyl phosphonate proved to be as efficient in terms of yield for the preparation of the allylsilane. Using the same strategy with 3-methyl-2-butanone **III.62**, allylsilane **III.56** could be prepared in good yields (Scheme 128).



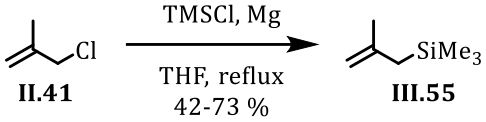
III.58 **III.59** **III.52**

a) i. LDA, THF, -78°C ii. $Cl(O)P(OEt)_2$, -78°C - RT, 73 %; b) $TMSCH_2Cl$, Mg, THF, reflux, then **III.59**, $Ni(acac)_2$, THF, 0°C - RT, 61 %.

*Scheme 128 - Synthesis of allylsilane **III.52***

Methallyltrimethylsilane **III.55** was prepared by the addition of the Grignard of methallyl chloride **II.41** to trimethylsilyl chloride. This method was efficient in terms of number of steps and availability of the starting materials but could be troublesome as the yields were not reproducible (Scheme *129*).

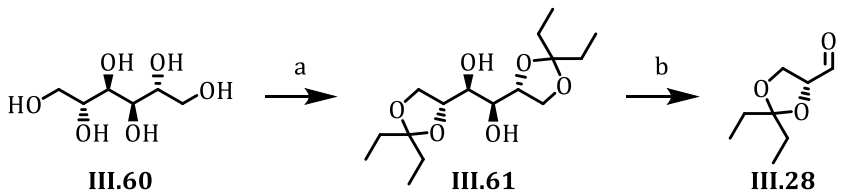
[76] W. R. Baker, J. K. Pratt, *Tetrahedron*, **1993**, *49*, *39*, 8739–8756.



Scheme 129 - synthesis of allylsilane III.55

We suspect that this issue arises from Wurtz type side reactions that kill the active species and also the volatile character of the product **III.55**.

Regarding the synthesis of aldehyde **III.28**, it started from D-mannitol **III.60**, a cheap a readily available hexose. Treatment with 3,3-dimethoxypentane using acid catalysis led to the selective formation of diol **III.61** in good yields (Scheme 130)[77].



a) $Et_2C(OMe)_2$, CSA, DMF, 40°C, 85 %; b) $Pb(OAc)_4$, DCM, 0°C - RT, 40-64 %.

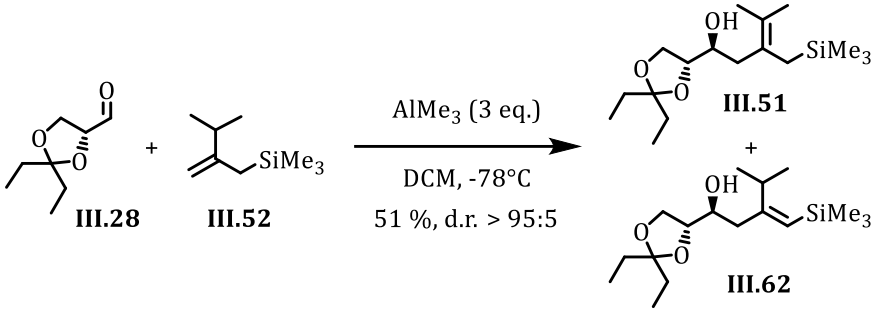
*Scheme 130 - Synthesis of aldehyde **III.28***

While colleagues in the group had previously used sodium periodate for the following oxidative cleavage, lead tetraacetate revealed to be a better option for this transformation. In these conditions, the yield in aldehyde **III.28** was similar or better (40-64 % instead of 42 %), the reaction time shorter (two hours instead of overnight) and the purification easier as well. This observation seemed rather important as aldehyde **III.28** is sensitive and degrades within 24 hours even when kept in the freezer under argon.

With allylsilanes **III.49**, **III.52** and **III.55** and aldehyde **III.28** in hands, the proposed ene reaction could be carried out. As it had been shown that the combination of trimethyl aluminium as Lewis acid with aldehyde **III.28** were the only combination allowing the process to be completely diastereoselective , we did not screen other Lewis acids or aldehydes.

Our first attempt was carried out with allylsilane **III.52** and we were delighted to see the formation of homoallylic alcohol **III.51** but also the formation of vinylsilane **III.62** in a ratio around 1.5:1 respectively (Scheme 131). Each of them was formed as a single diastereoisomer. These two compounds could not be separated using silica gel column chromatography.

[77] C. R. Schmid, D. A. Bradley, *Synthesis* , **1992**, *06*, 587–590.

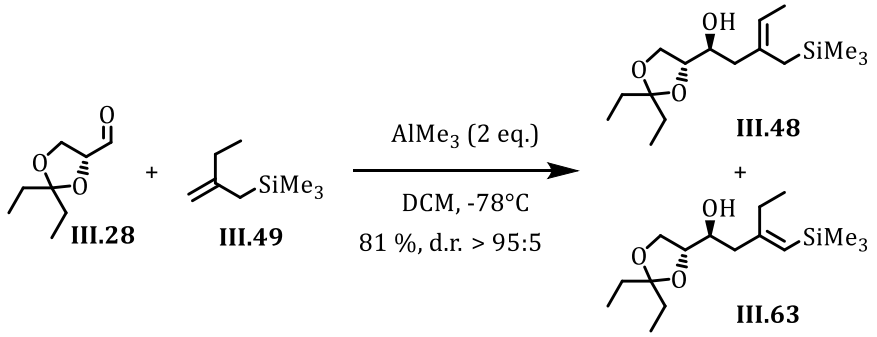


*Scheme 131 - Ene reaction with allylsilane **III.52***

Our hypothesis is that this product **III.62** comes from an ene reaction that involves the allylic protons located at the foot of the silicon atom. From the ^{1}H NMR of the crude, it looks like this product is also formed as a single diastereoisomer. We screened solvents and temperature trying to increase the selectivity but failed to obtain any improvement. In some cases, incomplete conversion could be observed. The following observations were made:

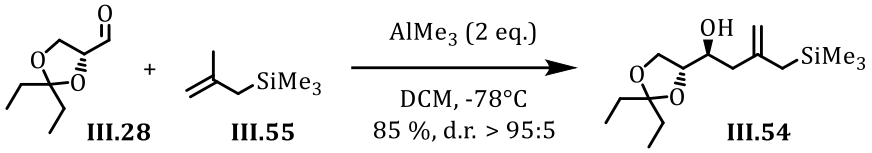
- In each case, the reaction leads to the formation of **III.51** and **III.62**, each being formed as a single diastereoisomer.
- The reaction can be carried out in dichloromethane, pentane or toluene.
- The reaction does not occur in the absence of the Lewis acid.
- Two equivalents of Lewis acid are sufficient with this class of allylsilane for the reaction to occur as opposed to allylsilane **III.21** were 3 equivalents are required.

Carrying out the ene reaction with allylsilane **III.49** led to the observation of a mixture of homoallylic alcohol **III.47** and **III.63** in a 4:1 ratio (Scheme 132).



*Scheme 132 - Ene reaction with allylsilane **III.49***

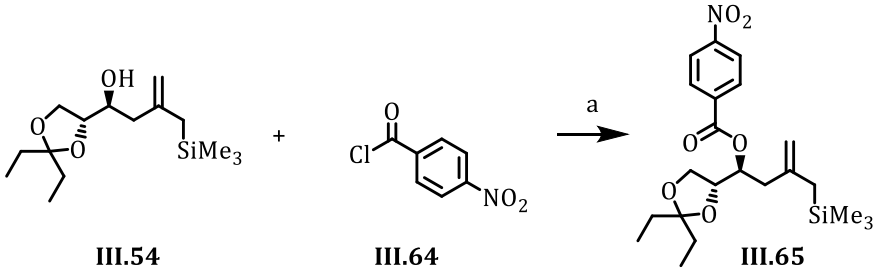
Finally, we investigated allylsilane **III.55** and were delighted to observe the formation of a single product in the form of alcohol **III.54** (Scheme 133).



III.28 **III.55** **III.54**

*Scheme 133 - Ene reaction with allylsilane **III.55***

The diastereoselectivity proposed for the homoallylic alcohols **III.51**, **III.62**, **III.48**, **III.63** and **III.54** are based on the hypothesis that the reaction selectivity is dictated by the Felkin-Ahn model. This stereochemistry was proven for alcohol **III.29** by previous work in the group (Scheme 125). In order to confirm the stereochemistry, homoallylic alcohol **III.54** was treated with acyl chloride **III.64** (Scheme 134).



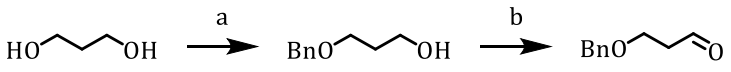
III.54 **III.64** **III.65**

a) DMAP, NEt_3, DCM, 0°C - RT, 84 %.

*Scheme 134 - Synthesis of ester **III.65***

Benzyl ester **III.65** could be isolated in good yield as a solid but did not allow to obtain crystals suited for X-ray diffraction.

With homoallylic alcohol **III.54** in hand, we prepared an aldehyde partner for the subsequent IMSC reaction. Given the structure of the Southern fragment of Polycavernoside A, the partner had to allow access to a three carbon skeleton. Propanediol **III.66** was chosen as precursor and aldehyde **III.68** was therefore prepared from it in two steps (Scheme 135). Monoprotection of diol **III.66** was performed in the presence of benzyl bromide and sodium hydride as a base.



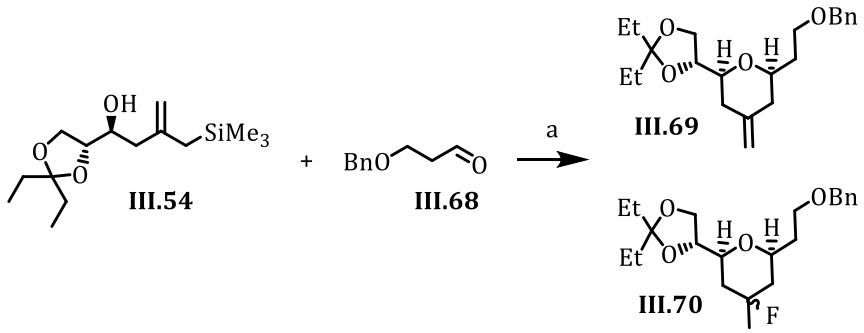
III.66 **III.67** **III.68**

a) NaH, BnBr, THF, RT, 55%; b) $(COCl)_2$, DMSO, NEt_3, DCM, -78°C - RT, 84 %.

*Scheme 135 - Synthesis of aldehyde **III.68***

While the oxidation of the alcohol **III.67** to the aldehyde **III.68** using the Marko's aerobic oxidation conditions[44] failed to give the desired product, the transformation was carried out efficiently using Swern conditions. We think that the failure in the first case arose from the decomposition of the aldehyde into acrolein and benzyl alcohol in refluxing hexafluorobenzene.

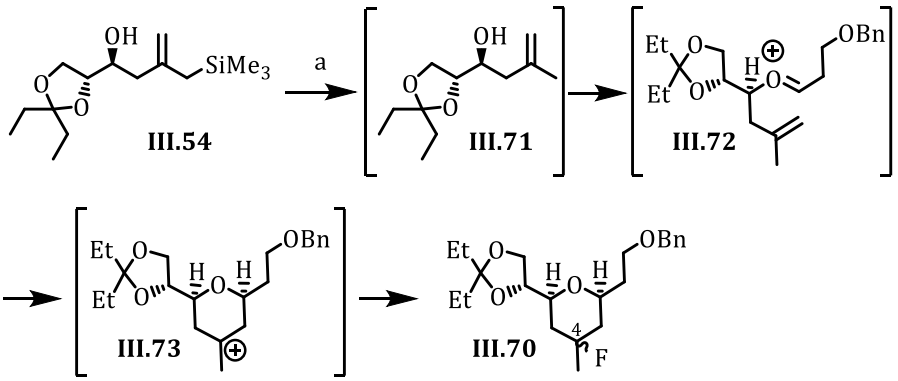
Moving to the IMSC cyclisation, the transformation was carried out using $BF_3.Et_2O$ as the Lewis acid. These conditions proved to be suited for the formation of tetrahydropyran **III.69**. However, compound **III.70** was isolated as well (Scheme 136). From the crude NMR, the ratio between **III.69** and **III.70** was determined to be 1 to 1.5.



a) $BF_3.Et_2O$, DCM, -78°C - -35°C, yield not determined.

*Scheme 136 - IMSC reaction with allylsilane **III.54***

We think that compound **III.70** arises from a Prins-type cyclisation involving homoallylic alcohol **III.71** that in turn comes from a desilylation of the homoallylic alcohol **III.54** in the presence of some hydrofluoric acid in the Lewis acid (Scheme 137).



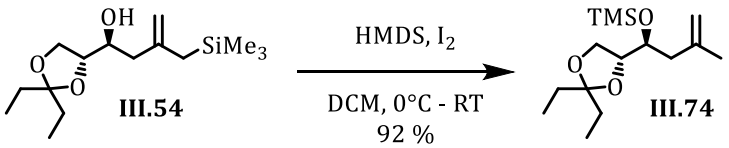
a) $BF_3.Et_2O$, DCM, -78°C - -35°C.

*Scheme 137 - Proposed mechanism for the formation of **III.70***

In this case, the condensation of the aldehyde **III.68** with **III.71** lead to the formation of **III.72**. The intermediate carbocation **III.72** can be trapped by the olefin with the formation of **III.73.** Afterwards, nucleophilic fluoride present in the reaction media can add into the 4-position leading to fluorinated THP **III.70**. The proposed structure for compound **III.70** is in agreement with data from mass spectrometry. However, the stereochemistry of the C_4 of the tetrahydropyran could not be determined. The proposed mechanism seems

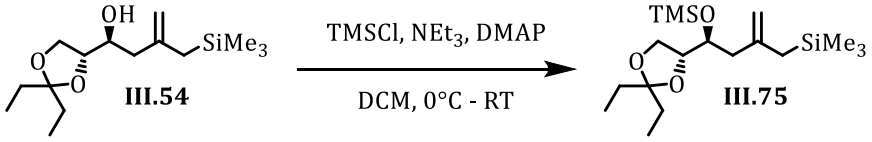
plausible as the preparation of fluorinated tetrahydropyrans like **III.70** using BF_3 as Lewis acid and fluoride source has already been reported[78].

To overcome the formation of side product **III.70**, we turned our attention to the ISMS reaction as alternative. This reaction required a preliminary functionalisation of the secondary alcohol in **III.54** into a silyl ether. This was first attempted using hexamethyldisilazane (HMDS) and iodine[79]. However, while the reaction was carried out in a matter of minutes and the crude mixture was clean, desilylation of the allylsilane was observed during the process (Scheme 138).



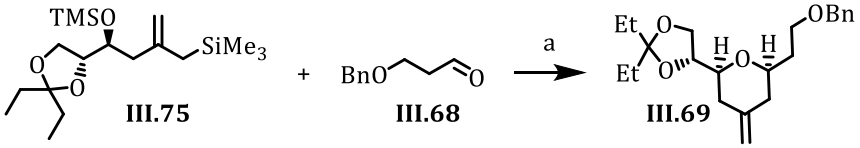
*Scheme 138 - Attempts to the protection of alcohol **III.54***

We therefore moved to more classical conditions for the desired transformation. In the presence of trimethylsilyl chloride, triethylamine and DMAP, silyl ether **III.75** was obtained (Scheme 139). As trimethylsilyl ethers like **III.75** are known to be sensitive to silica gel chromatography, no further purification was performed, and the crude mixture was used for the next step.



*Scheme 139 - Silylation of alcohol **III.54***

Under the ISMS conditions, we were delighted to see the formation of tetrahydropyran **III.75** as represented in Scheme 140.



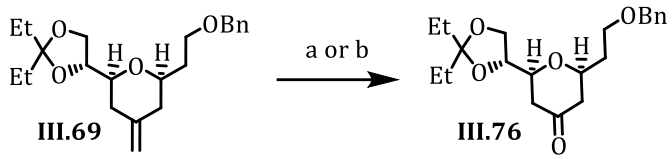
a) TMSOTf, DCM, -78°C, 54 % over two steps.

*Scheme 140 - ISMS reaction with silyl ether **III.75***

With the compound **III.69** at our disposal, an ozonolysis allowed the oxidation of the exocyclic double bond into the ketone **III.82**. While the transformation could be carried out using triphenylphosphine as reducing agent, it was found

[78] E. H. Al-Mutairi, S. R. Crosby, J. Darzi, R. A. Hughes, T. J. Simpson, R. W. Smith, C. L. Willis, J. R. Harding, C. D. King, *Chem. Commun.*, **2001**, *9*, 835–836.
[79] B. Karimi, B. Golshani, *J. Org. Chem.*, **2000**, *65*, *21*, 7228–7230.

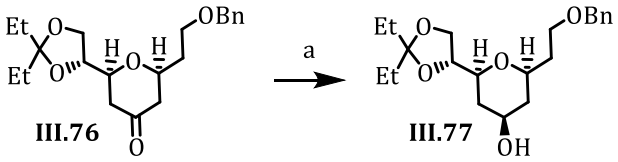
that the use of triethylamine allowed a cleaner reaction with a better yield (Scheme 141).



a) O_3, DCM, -78°C then PPh_3, -78°C - RT, 66 %; b) O_3, DCM, -78°C then NEt_3, -78°C - RT, 90 %.

*Scheme 141 - Ozonolysis of olefin **III.69***

The functionalisation of ketone **III.76** continued with the reduction to the corresponding alcohol **III.77**. This was done using Luche conditions in a mixture of methanol and THF (Scheme 142). The use of dry solvents and dried cerium (III) chloride proved to be important to observe excellent diastereoselectivity.



*Scheme 142 - Reduction of ketone **III.76** under Luche conditions*

In this reaction, the diastereoselectivity of the process is explained by the delivery of the hydride by the more accessible bottom face of the ketone **III.76** as represented in Figure 33.

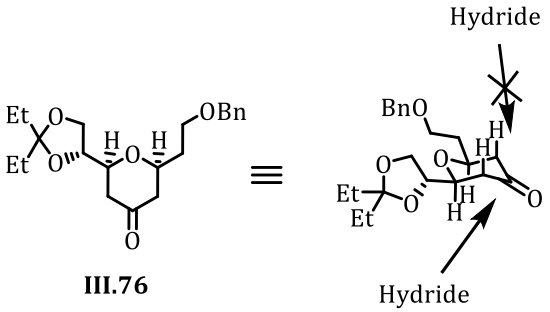
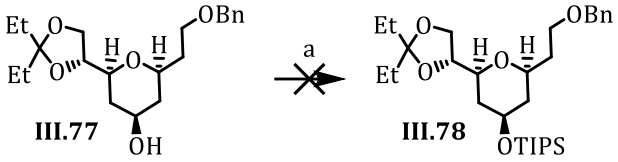


*Figure 33 - Model for the diastereoselective reduction of ketone **III.76***

The protection of the free alcohol in **III.77** was attempted using a robust silyl ether in the form of a TIPS group. The use of TIPSCl and imidazole in DMF did not allow to carry out this transformation (Scheme 143).

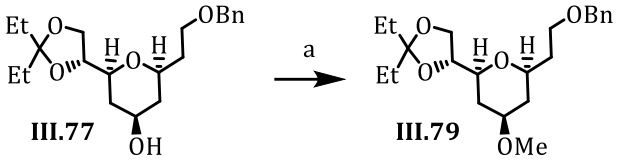


III.77 **III.78**

a) TIPSCl, Im, DMF, RT or 50°C.

*Scheme 143 - Attempts to the protection of **III.77***

Even though stronger reagents could have been used, we decided to move to a smaller yet robust protecting group. We decided to protect the secondary alcohol in **III.77** as a methyl ether using methyl iodide in the presence of potassium *tert*-butoxide (Scheme 144).

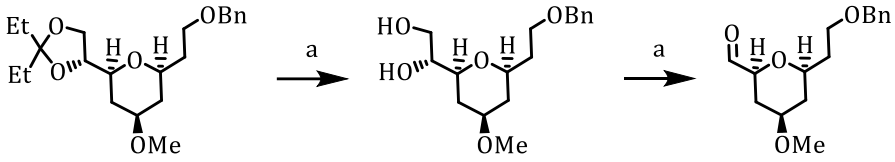


III.77 **III.79**

a) *t*BuOK, THF, 0°C then MeI, 0 °C - RT, 77 %.

*Scheme 144 - Protection of alcohol **III.77***

With **III.79** in hand, a few steps were required to reach the aldehyde needed for the coupling with the Northern fragment. The cleavage of the acetonide was done in aqueous acidic condition leading to diol **III.80** as shown in Scheme 145.



III.79 **III.80** **III.81**

a) PTSA, H_2O, MeOH, 0 °C - RT, 79 %; b) $NaIO_4$, CH_3CN, H_2O, 62 %.

*Scheme 145 - Synthesis of aldehyde **III.81***

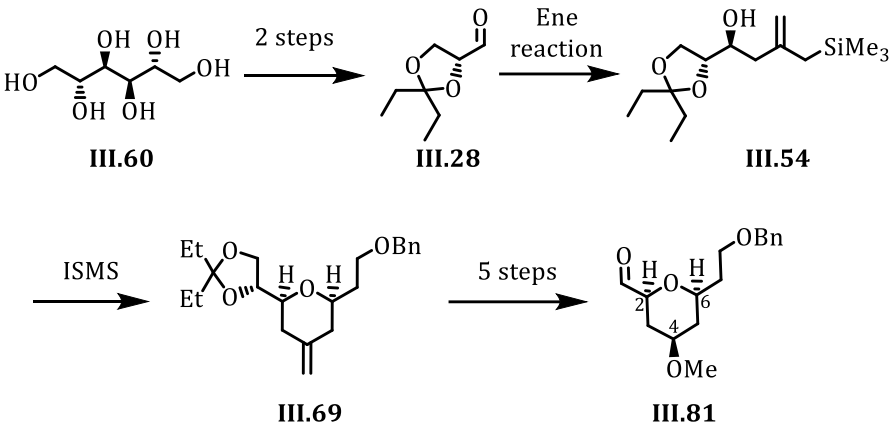
The oxidative cleavage of the diol in **III.80** could then be performed using sodium periodate leading to aldehyde **III.81** in good yield.

This concluded the synthesis of aldehyde **III.81** as a model of the Southern fragment of Polycavernoside A.

III.3 Conclusions and perspectives

III.3.1 Conclusions

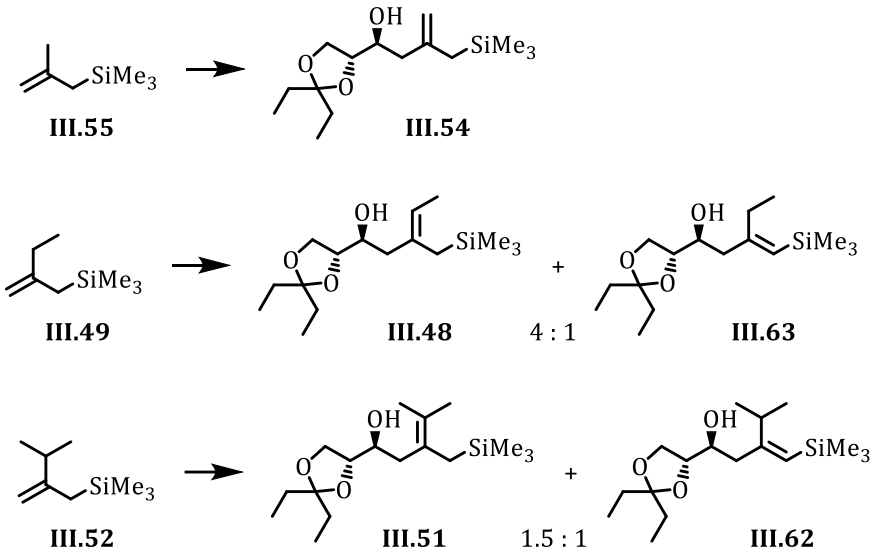
The work presented in this chapter allowed the preparation of tetrahydropyran **III.87** as a model for the Southern fragment of Polycavernoside A. This was achieved in 10 steps with an overall yield of 7 % starting from D-mannitol (Scheme 146). This approach relied on the use of a diastereoselective ene reaction with aldehyde **III.28** followed by the ISMS cyclisation leading to THP **III.69**. Modifications of intermediate **III.69** allowed to reach aldehyde **III.81** in 5 steps.



*Scheme 146 - Synthesis of the Southern fragment model **III.81***

Among the 3 asymmetric centres embodied in THP **III.81**, the first centre was installed by the diastereoselective ene reaction. The ISMS reaction allowed the control of the chiral centre at the 6-position of the tetrahydropyran. Finally, a diastereoselective Luche reduction dictated the stereochemistry observed at the 4-position.

The scope of the ene reaction was extended to a new class of allylsilane (Scheme 147). Even though a diastereoselective reaction could be observed, the formation of side products in the form of vinylsilanes **III.62** and **III.63** was noticed as well.

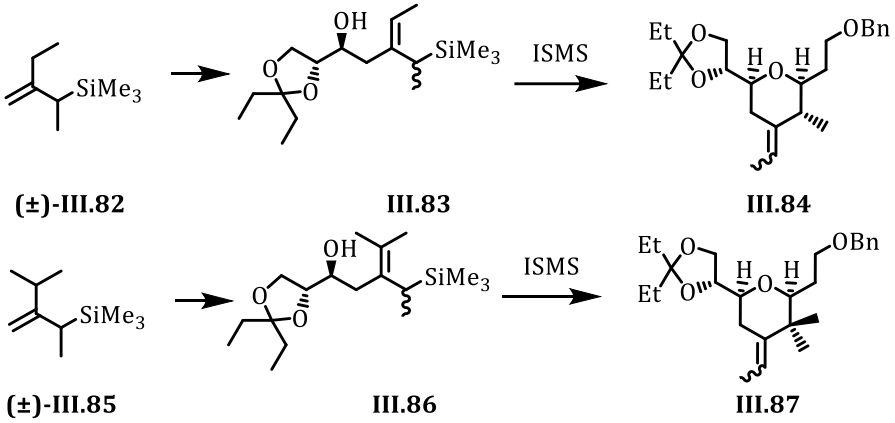


Scheme 147 - Ene reaction with new class of allylsilanes

These results are promising as these substrates should give access to different tetrahydropyrans found in natural products but additional studies are required to gain a better understanding of the reaction and to increase the selectivity of the reaction.

III.3.2 Perspectives

Looking at the different ratios observed in the ene reaction represented in Scheme 147, it seems that the reaction selectivity is under steric control. The synthesis of allylsilanes **III.82** and **III.85** might provide a solution in increasing the regioselectivity of the reaction (Scheme 148). If our hypothesis is correct, these compounds should lead to the preferential formation of homoallylic alcohols **III.83** and **III.86** and eventually, through the ISMS reaction, lead to the formation of THP **III.84** and **III.87**.

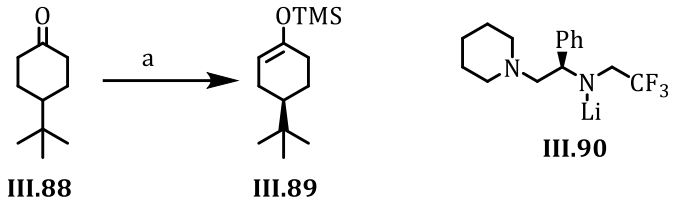


*Scheme 148 - Ene-ISMS sequence with allylsilane **III.82** and **III.85***

The methyl group connected to the exocyclic double bond of THP **III.84** and **III.87** should not be an issue since this olefin undergoes an ozonolysis reaction. However, the presence of a new chiral centre in allylsilane **III.82** and **III.85** might lead to a match/mismatched effect that could influence the diastereoselectivity of the ene reaction.

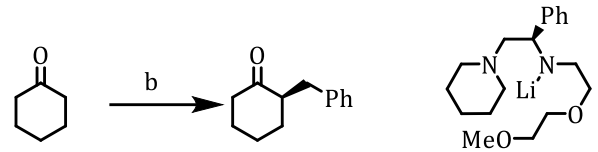
Another solution to the insertion of the additional chiral centre of the Southern fragment could arise from the use of chiral bases. This perspective is based on the work reported independently by the groups of Kenji Koga[80] and Nigel Simpkins (Scheme 149)[81]. Using chiral bases, symmetric ketones like **III.88** can be selectively deprotonated to generate silyl enol ether **III.89** that can be functionalised leading to enantioenriched products[82].

[80] M. Murakata, M. Nakajima, K. Koga, *J. Chem. Soc., Chem. Commun.*, **1990**, *2580*, 1657–1658.
[81] R. P. C. Cousins, N. S. Simpkins, *Tetrahedron Lett.*, **1989**, *30*, *51*, 7241–7244.
[82] N. S. Simpkins, M. D. Weller, in , *Top. Stereochem.*, *26*, *Stereochemical Aspects of Organolithium Compounds*, **2010**, 1–52; A. Harrison-Marchand, J. Maddaluno, in , *Lithium Compd. Org. Synth.*, **2014**, 297–328; N. S. Simpkins, M. D. Weller, *Org. React.*, **2013**, *79*, *1*, 317–635.



III.88 **III.89** **III.90**

a) **III.96**, TMSCl, HMPA, THF, -100 °C, 88 %, 93 % *ee*.

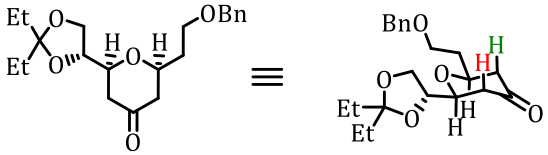


III.91 **III.92** **III.93**

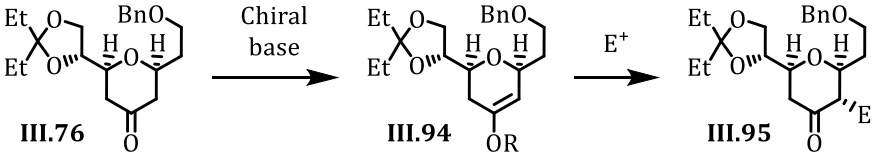
b) **III.99**, LiBr, BnBr, Toluene, -78 °C - 40°C, 63 %, 92 % *ee*.

Scheme 149 - Application of chiral bases to symmetric ketones

In the case of ketone **III.76**, the idea could be interesting as being already chiral, the use of either a non-chiral or a chiral base could allow the differentiation of the two acidic protons (Scheme 150).



III.76 **III.76**

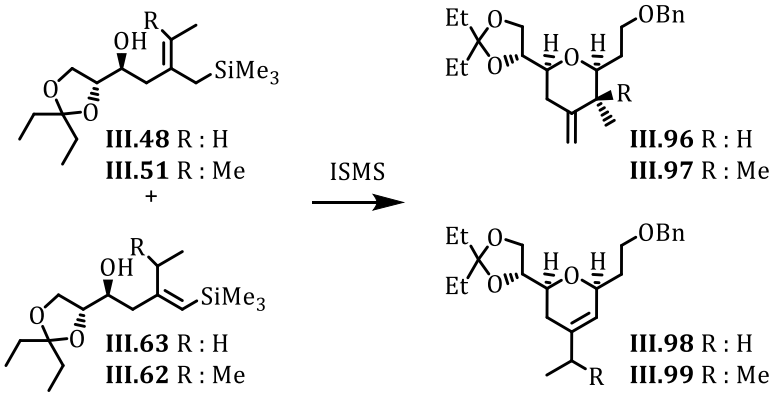


III.76 **III.94** **III.95**

*Scheme 150 - Selective alkylation of ketone **III.76***

The selective deprotonation of ketone **III.76** should lead to enol ether **III.94** which in the presence of an electrophile should lead to the formation of the tetrasubsituted THP **III.95**.

If the selective preparation of homoallylic alcohol **III.83** and **III.86** or the selective deprotonation of ketone **III.76** do not afford the desired outcome, the use of the mixture of homoallylic alcohol **III.48/III.63** or **III.51/III.62** in the ISMS conditions could allow the synthesis of the desired tetrahydropyrans **III.96** or **III.97** along with the dihydropyran **III.98** and **III.99** (Scheme 151).



Scheme 151 - ISMS reaction with homoallylic alcohol mixtures

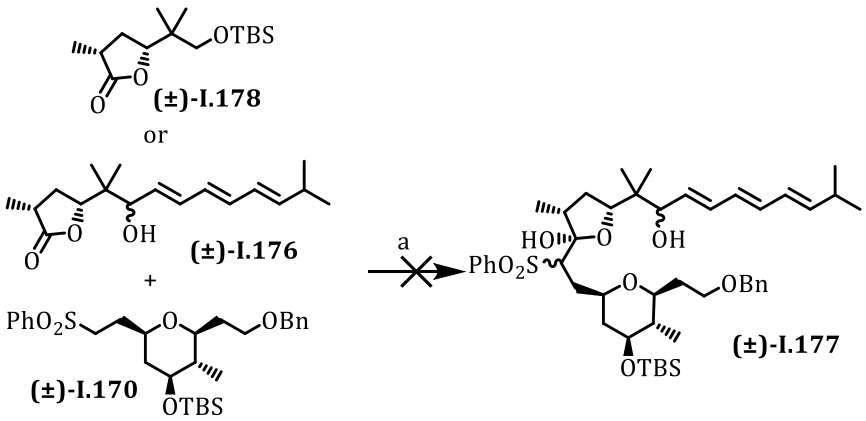
If the separation of the tetrahydropyrans **III.96** and **III.97** from the dihydropyrans **III.98** and **III.99** respectively reveal to be troublesome, the subsequent ozonolysis should lead to compounds easily separable.

Chapter IV

Development of the coupling methodology

IV.1 Previous results from the Markó group

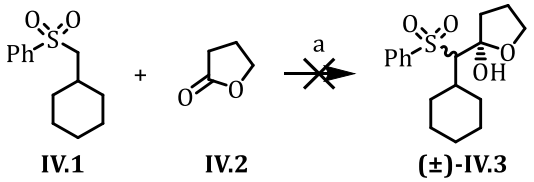
During his thesis, Freddi Philippart worked on the union of the Northern and Southern fragments of Polycavernoside A employing synthons **I.176** and **I.170**. However, the nucleophilic addition of the sulfone anion onto either lactones **I.176** or **I.178** did not allow the formation of the desired lactol **I.177** (Scheme 152)[24].



a) *n*BuLi or LDA (1 eq. or 2 eq.).

Scheme 152 - Coupling attempts by Freddi Philippart

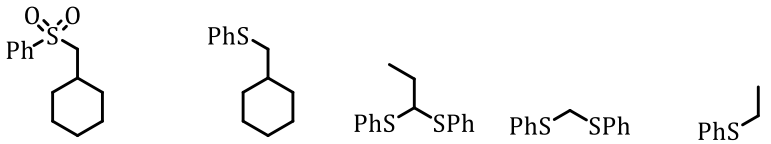
During his postdoctoral research[22], Alexandre Drouin investigated conditions that would allow the coupling using different sulfur based reagents. First, he studied the addition of sulfone **IV.1** onto lactone **IV.2** but failed to isolate sulfone **IV.3** as depicted in Scheme 153.



a) *n*BuLi, THF.

*Scheme 153 - Nucleophilic addition of sulfone anion of **IV.1** to butyrolactone **IV.2***

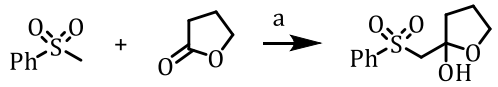
Other lithium or potassium-based nucleophiles were screened but failed to give the addition product or achieved it poorly. These results are summarised in Figure 34.



	IV.1	**IV.4**	**IV.5**	**IV.16**	**IV.17**
Base	*n*BuLi or KHMDS	*n*BuLi	*n*BuLi or KHMDS	*n*BuLi	*n*BuLi
Yield	SM recovered	Degradation	SM recovered	20 %	Degradation

*Figure 34 - Addition of nucleophiles to lactone **IV.2***

The best result of this investigation came from phenyl methyl sulfone **IV.12** that gave a good yield of 78 % for the addition product **IV.13** (Scheme 154).



IV.8 **IV.2** **(±)-IV.9**

a) *n*BuLi, THF, 78 %.

*Scheme 154 - Synthesis of **IV.9***

It seems from this result that the addition of the lactone is sensitive to steric hindrance. This observation led the group to review the coupling as a connection between C_8 and C_9 rather than the previously proposed C_9-C_{10} as shown in Figure 35.

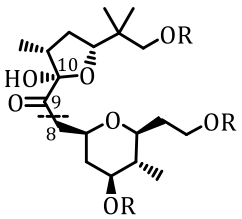
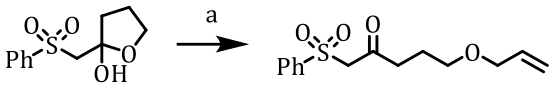


Figure 35 - New disconnection for the Northern-Southern fragments coupling

In order to confirm this new disconnection, linking sulfone **IV.9** with the Southern part had to be investigated. The α-alkylation of the masked β-ketosulfone did not occur with a series of electrophiles but from one experiment, compound **IV.10** could be isolated (Scheme 155).

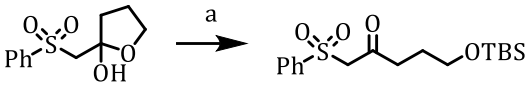


(±)-IV.9 **IV.10**

a) KHMDS, THF, -78°C then allyl bromide.

*Scheme 155 - Synthesis of **IV.10***

This result showed that as compound **IV.10** could be formed**,** the O-alkylation was a competitive reaction to the alkylation of the enolate. This problem could however be overcome by protecting the latent hydroxy group and unveiling a compound that could undergo the α-alkylation more readily. Acetal **IV.9** was easily transformed into *β*-ketosulfone **I.181** in excellent yield (Scheme 156).

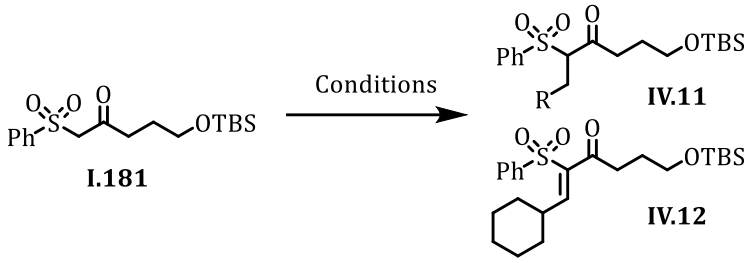


(±)-IV.9 **I.181**

a) TBSCl, Im, DCM, 96 %.

*Scheme 156 - Protection of sulfone **IV.9***

With this substrate, the addition onto some electrophiles could be looked at (Figure 36).



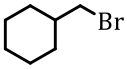
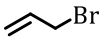
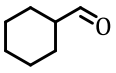
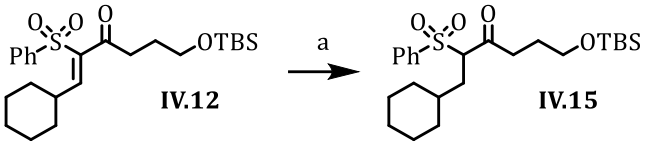
Electrophile	Conditions	Yield
 **IV.13**	LDA then E^+	SM recovered
	LiHMDS then E^+	SM recovered
	LDA, TMEDA then E^+	SM recovered
	Cs_2CO_3 then E^+	SM recovered
 **IV.14**	LDA then E^+	SM recovered
	LiHMDS then E^+	SM recovered
	Cs_2CO_3 then E^+	42 %, **IV. 11** R : vinyl
 **I.180**	AcOH, Piperidine	SM recovered
	MS	35 % of **IV.12**
	AcOH, Piperidine	SM recovered
	AcOH, Piperidine, MS	48 % of **IV.12**

*Figure 36 - Reactivity of sulfone **I.181** with different electrophiles*

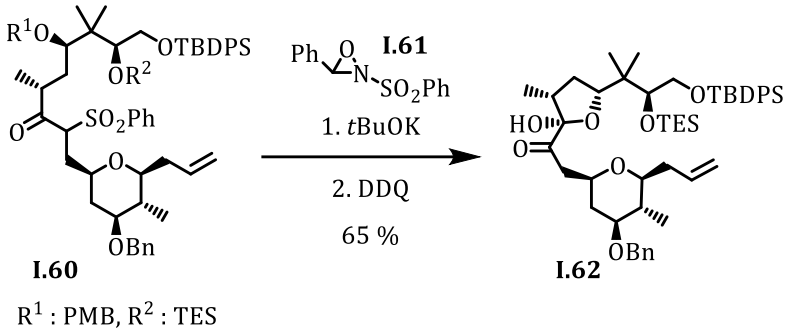
From the scope of the reaction, the Knoevenagel condensation with aldehyde **I.180** seemed to be the most promising while the addition to a series of alkyl halides failed in most cases.

The subsequent functionalisation of **IV.12** was carried out using a copper-catalysed 1,4-reduction of the enone, leading to intermediate **IV.15** (Scheme 157). This *β*-ketosulfone bears a resemblance with **I,60**, a synthetic intermediate described by Paquette[12] during their work and that proved to be suitable for the transformation into the corresponding masked diketone **I.62** proving that the synthesis of β-ketosulfones similar to **IV.15** and their coupling with an aldehyde partner should allow the connection of the Northern and Southern fragments (Scheme 158).



a) IMesCuDBM, $Me(EtO)_2SiH$, *t*BuOK, THF, 60 %

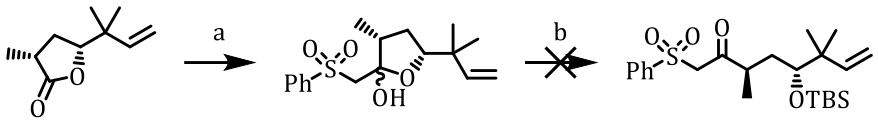
*Scheme 157 - Reduction of sulfone **IV.12***



R^1 : PMB, R^2 : TES

*Scheme 158 - Synthesis of **I.62** by Paquette*

Once the synthesis of the Northern fragment achieved, the addition of phenyl methyl sulfone anion to the lactone **I.156** was carried out and led to the isolation of lactol **IV.16**. However, no conditions allowed formation of the β-ketosulfone **I.184** required for the Knoevenagel condensation (Scheme 159).



(±)-I.156 **(±)-IV.16** **(±)-I.184**

a) *n*BuLi, 57 %. b) TBSCl, Im or TBSOTf, 2,6-Lutidine.

*Scheme 159 - Attempts to the synthesis of **I.184***

This result led us to review the strategy that was proposed for the coupling of the Northern and Southern fragments.

IV.2 Development of the coupling methodology

IV.2.1 Disconnection

At the beginning of this thesis, we decided to look at alternatives to the sulfone based pathway. In the approach depicted in Figure 37, the compound **IV.17** is in equilibrium with diketone **IV.18** that can arise from enone **IV.19**.

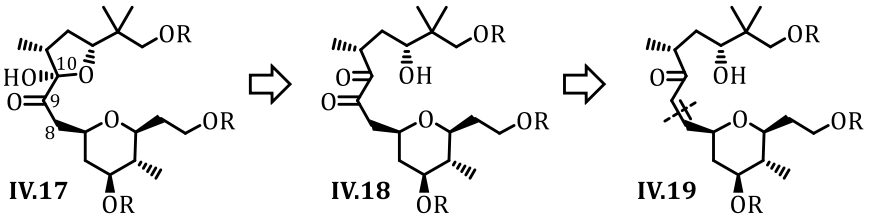


*Figure 37 - Disconnection of fragment **IV.17***

Going further in this disconnection, we proposed that retron **IV.19** would in turn come from a Horner-Wadsworth-Emmons olefination (HWE) between *β*-ketophosphonate **IV.20** and aldehyde **IV.21**. The structure of **IV.20** was interesting as it could be disconnected into methyl phosphonate **IV.22** and lactone **II.37**, our retron for the Northern fragment shown in Figure 38.

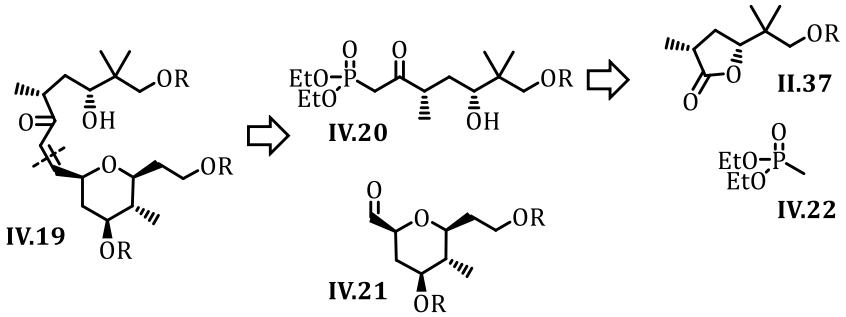


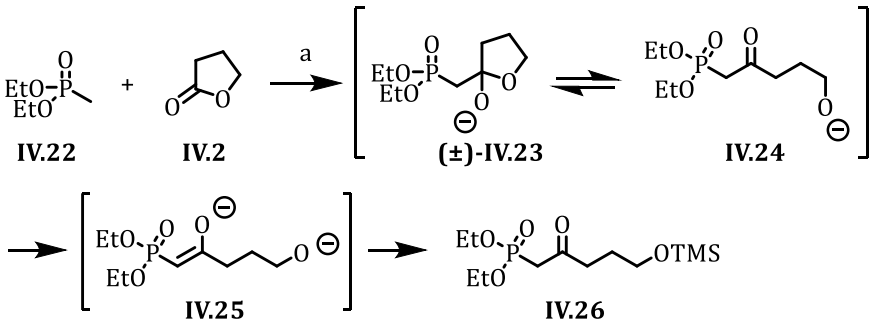
*Figure 38 - Disconnection of **IV.19***

Compared to the previous method using the Knoevenagel condensation of β-ketosulfone, the HWE reaction had also the advantages that in appropriate conditions, once the intermediate *β*-hydroxyphosphonate is formed, the elimination allowing the formation of the olefin could occur in the same step.

To design the HWE based methodology, we based our approach on two literature articles, the first by Reinhard W. Hoffmann[83] and the second by Hans-Josef Altenbach[84] both published in 1985. In the first paper, the reaction of the anion of diethyl methylphosphonate **IV.22** with lactone **IV.2** is described. Product

[83] K. Ditrich, R. W. Hoffmann, *Tetrahedron Lett.*, **1985**, *26*, *51*, 6325–6328.
[84] H.-J. Altenbach, W. Holzapfel, G. Smerat, S. H. Finkler, *Tetrahedron Lett.*, **1985**, *26*, *51*, 6329–6332.

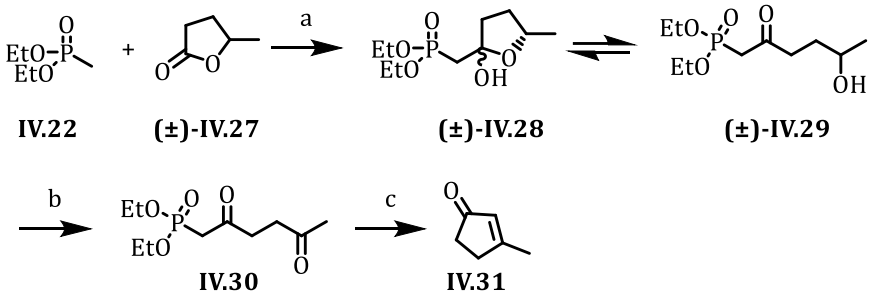
IV.26 is obtained by trapping the corresponding keto-alcohol with trimethylsilyl chloride (Scheme 160).



a) i. *n*BuLi (1 eq.), THF, -78°C; ii. **IV.2** ; iii. *n*BuLi or LDA (1 eq.); iv. TMSCl (2 eq.), 86 %.

Scheme 160 - Synthesis of IV.26 by Hoffmann

In the second article, once the addition of the phosphonate anion of **IV.22** to lactone **IV.27** is achieved, an oxidation of the alcohol **IV.29** is carried out. Then, an intramolecular HWE olefination is performed leading to enone **IV.31** (Scheme 161).



a) *n*BuLi (2 eq.), 77 %; b) $(COCl)_2$, DMSO, NEt_3, 48 %; c) NaH, 59 %.

*Scheme 161 - Synthesis of **IV.31** by intramolecular HWE olefination*

By combining those two approaches, we designed the following plan for the coupling between the Northern and Southern fragments **II.37** and **IV.21** (Figure 39).

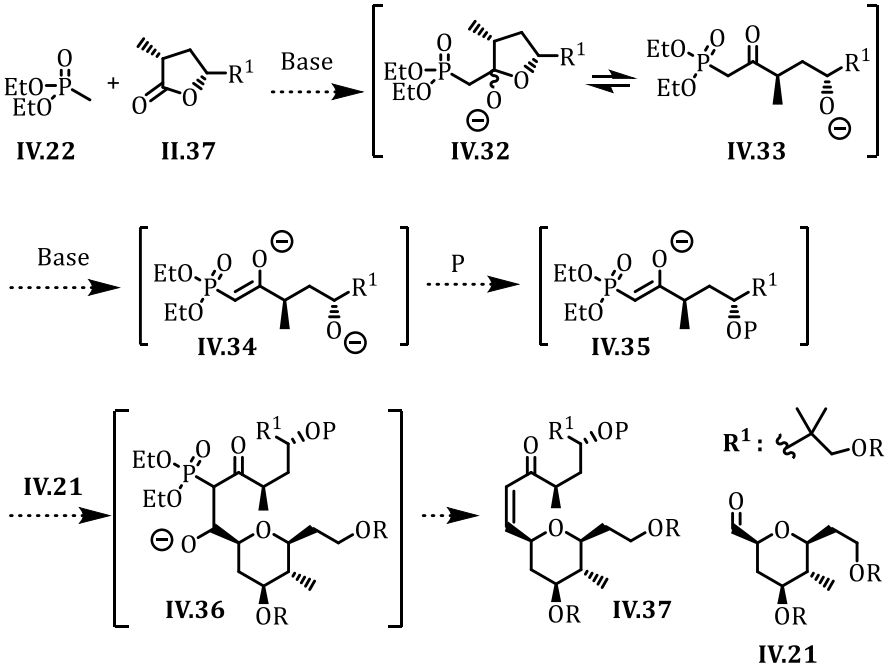


Figure 39 - Synthetic strategy for the Northern-Southern fragment coupling

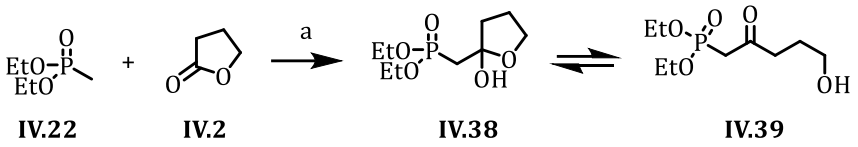
The synthesis would start by the addition of the diethyl methylphosphonate anion to the Northern fragment **II.37** leading to lactol anion **IV.32** which is in equilibrium with β-ketophosphonate **IV.33**. Then, addition of a second equivalent of base would generate the bis anionic species **IV.34** which would undergo the protection of the hydroxy group to prevent possible side reactions at that function. Then, by addition of the Southern fragment **IV.21**, the HWE olefination could be carried out leading by formation of the β-hydroxyphosphonate **IV.36** that should lead to enone **IV.37** as coupling product.

As multiple intermediates are proposed in this mechanism, the isolation of these species will be useful in the optimisation of the coupling.

IV.2.2 Results and discussion

We started our investigation using γ-butyrolactone **IV.2**, diethyl methylphosphonate **IV.22** and hexanal **IV.42** as model substrates.

The first reaction was done as described by Hoffmann and led to the formation of lactol **IV.52** in good yields as shown in Scheme 162.

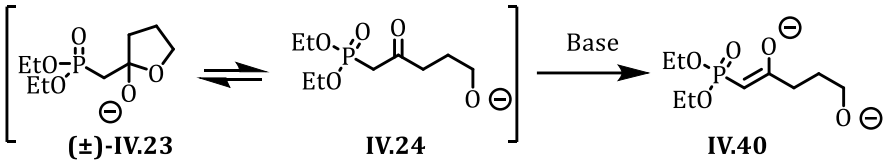


IV.22 **IV.2** **IV.38** **IV.39**

a) *n*BuLi (2 eq.), THF, -78°C - RT, 84 % or **IV.22** (2 eq.), *n*BuLi (2 eq.), THF, -78°C - RT, 78 %.

*Scheme 162 - Synthesis of **IV.38***

Two reactions conditions can be used for this reaction by using either 2 equivalents of phosphonate **IV.34** and two equivalents of base for one equivalent of lactone **IV.2** or by using one equivalent of phosphonate and two equivalents of base for one equivalent of lactone.



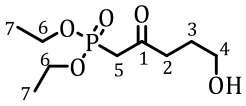
(±)-IV.23 **IV.24** **IV.40**

Base : *n*BuLi or $(EtO)_2P(O)CH_2Li$

*Scheme 163 - Formation of bis-anionic species **IV.40***

The options are possible because the nucleophilic phosphonate anion can also act as a base and deprotonate intermediate **IV.24** leading to the formation of the bis-anionic species **IV.40** (Scheme 163). The second equivalent of base allows the regeneration of the nucleophile. This can also account for the observation that if the addition of the phosphonate anion to the lactone leading to **IV.23** is a reversible process, once the second deprotonation occurs, the equilibrium should be shifted towards the formation of **IV.40** as this last step should be irreversible given the base used. However, upon reprotonation of **IV.40**, the formation of ketone **IV.39** and hemiacetal **IV.38** can be restored and this can be observed by NMR.

From the ^{1}H and ^{13}C NMR experiments, it can be seen that both lactol **IV.38** and β-ketophosphonate **IV.39** are in equilibrium (Figure 40).



IV.39

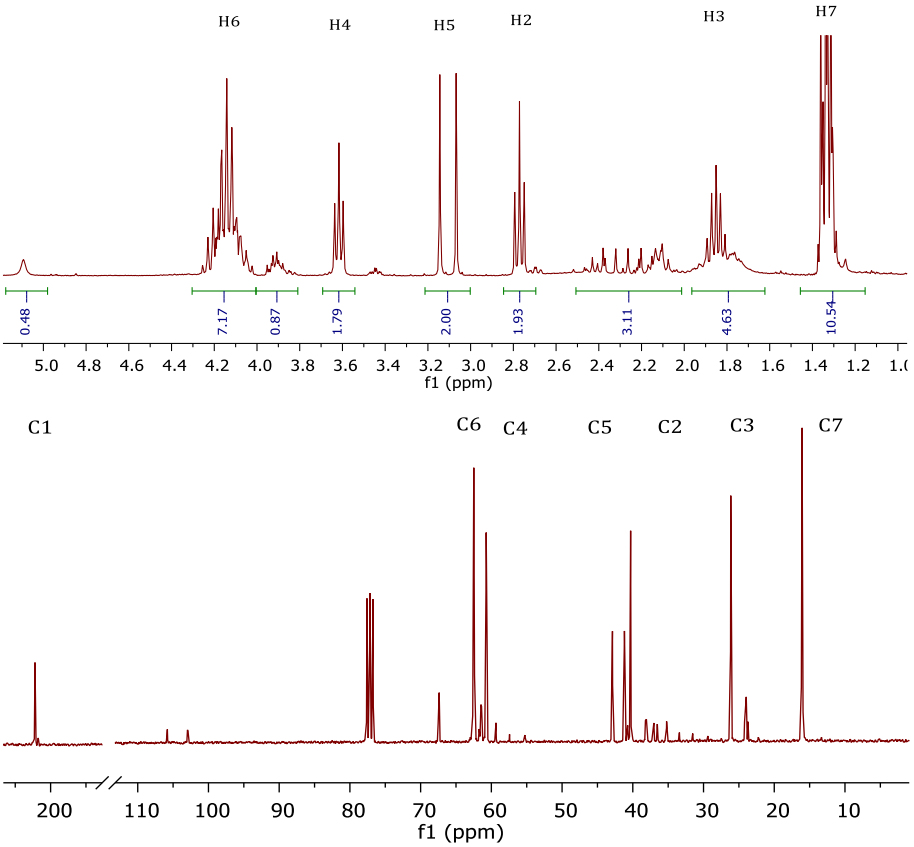
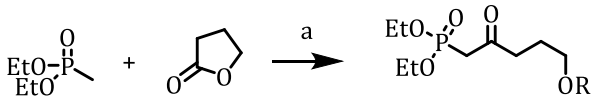


*Figure 40 - ^{1}H (300 MHz) and ^{13}C (75 Hz) NMR spectra of lactol **IV.38** in equilibrium with **IV.39** in $CDCl_3$*

In our sample, the ketone **IV.39** is the major species compared to the lactol **IV.38**. Looking at the ^{1}H NMR spectrum, a doublet located at 3.1 ppm has been assigned to the two hydrogens atoms located between the carbonyl and the phosphorous atom of **IV.39**. By comparison with the integrations of the other signals, it can be said that the ketone is the major species, while the lactol is present in smaller proportions. This observation is supported by the ^{13}C NMR spectrum where an intense signal located at 202 ppm corresponding to the ketone is observed. Less intense signals located at 105 and 102 ppm and corresponding to hemiacetal **IV.38** can also be observed. The observation of two signals might be explained by the presence of the two conformers of the 5-membered ring hemiacetal **IV.38** where the hydroxyl group can be located either in pseudo-axial or pseudo-

equatorial position. Since no solvent effect study was carried out, we cannot certify that the ratio stays the same in other conditions.

Following the designed strategy, we then moved on to the protection of the hydroxy group. The addition of trimethylsilyl chloride or *tert*-butyl dimethylsilyl chloride after the previous sequence allowed isolation of the protected alcohols **IV.26** and **IV.41** (Scheme 164).



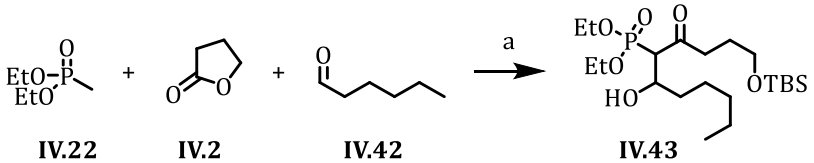
IV.22 **IV.2** **IV.26 R: TMS**
IV.41 R: TBS

a) *n*BuLi (2 eq.), THF, -78°C - RT, then TMSCl or TBSCl, not determined for **IV.26,** 72 % for **IV.41**.

*Scheme 164 - Synthesis of **IV.26** and **IV.41***

However, our attempts to purify **IV.26** by column chromatography led to the cleavage of the protecting group. We decided therefore to continue the sequence using the TBS protecting group in the form of **IV.41**.

With intermediate **IV.41**, the next step was the Horner-Wadsworth-Emmons olefination. We performed the reaction in the same conditions and added hexanal **IV.56** to the reaction mixture (Scheme 165).

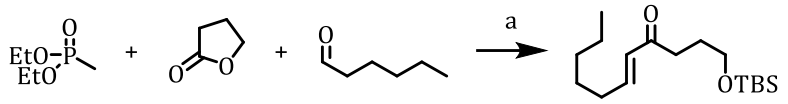


IV.22 **IV.2** **IV.42** **IV.43**

a) *n*BuLi (2 eq.), THF, -78°C - RT, then TBSCl then hexanal, 0°C - RT, yield not determined.

*Scheme 165 - Synthesis of **IV.43***

By stirring the reaction at room temperature, only the β-hydroxyphosphonate **IV.43** could be isolated. The reaction required to be heated under refluxing conditions in order to observe the elimination product **IV.44** in a yield of 28 % (Scheme 166).



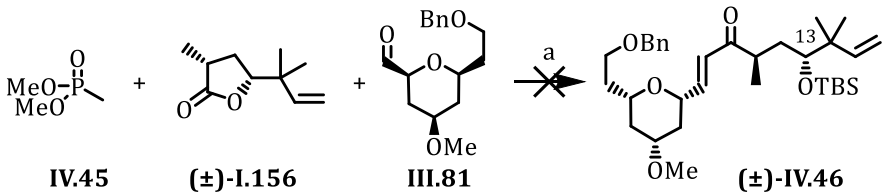
IV.22 **IV.2** **IV.42** **IV.44**

a) *n*BuLi (2 eq.), THF, -78°C - RT, then TBSCl then hexanal, 0°C - reflux, 28 %.

*Scheme 166 - Synthesis of **IV.44***

The coupling constant between the two vinylic protons of **IV.44** is 15.9 Hz suggesting that the geometry of the double bond is *E* as it is usually the selectivity observed for the HWE olefination. While the yield for the whole process could be optimised, we had designed an experimental procedure that should allow us to unite the Northern and Southern fragments.

With these results, we could then move to the union of the Northern fragment in the form of **I.156** and the Southern fragment model **III.81**. To our disappointment, using the conditions developed previously, the desired coupled product **IV.62** could not be observed (Scheme 167).

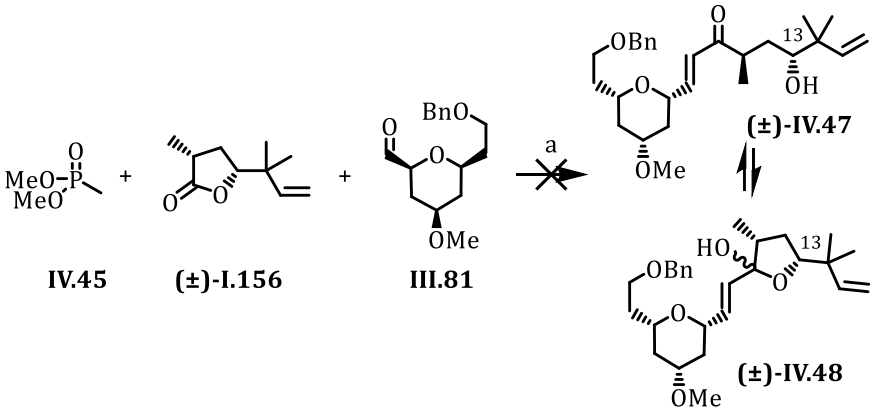


IV.45 **(±)-I.156** **III.81** **(±)-IV.46**

a) *n*BuLi (2 eq.), THF, -78°C - RT, then TBSCl then **III.81**, 0°C - reflux.

*Scheme 167 - Attempts to the synthesis of **IV.46***

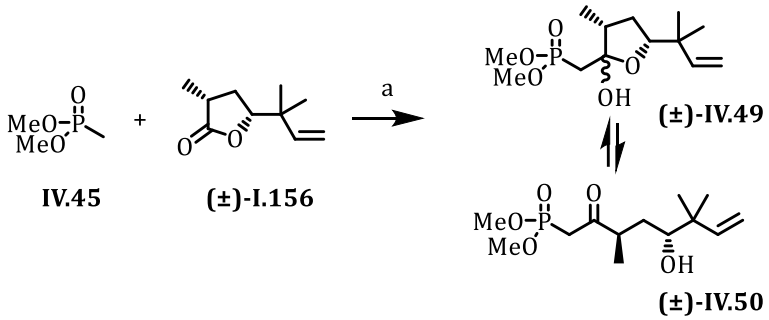
As we knew from previous experiment, the protection of the C_{13} hydroxy group is challenging. Since the addition of the enol phosphonate onto the aldehyde could happen even without protecting the alcohol, the reaction was carried out without the addition of *tert*-butylsilyl chloride. However, even in these conditions, the desired product **IV.47** or **IV.48** could not be observed (Scheme 168).



a) *n*BuLi (2 eq.), THF, -78°C - RT, then **IV.61**, 0°C - reflux.

*Scheme 168 - Attempts at the synthesis of **IV.47** or **IV.48***

At this point, we decided to isolate the proposed intermediates of the reaction sequence in order to understand the origins of the failure. We therefore carried out the addition of phosphonate anion onto the lactone **I.156** and it proceeded smoothly leading to the desired product in good yield (Scheme 169).



a) *n*BuLi (2eq.), THF, -78°C - RT, 88 %.

*Scheme 169 - Addition of **IV.45** anion to the Northern fragment **I.156***

Here again, the ^{1}H NMR suggests that there is an equilibrium between the ketone **IV.50** and the lactol **IV.49** (Figure 41).

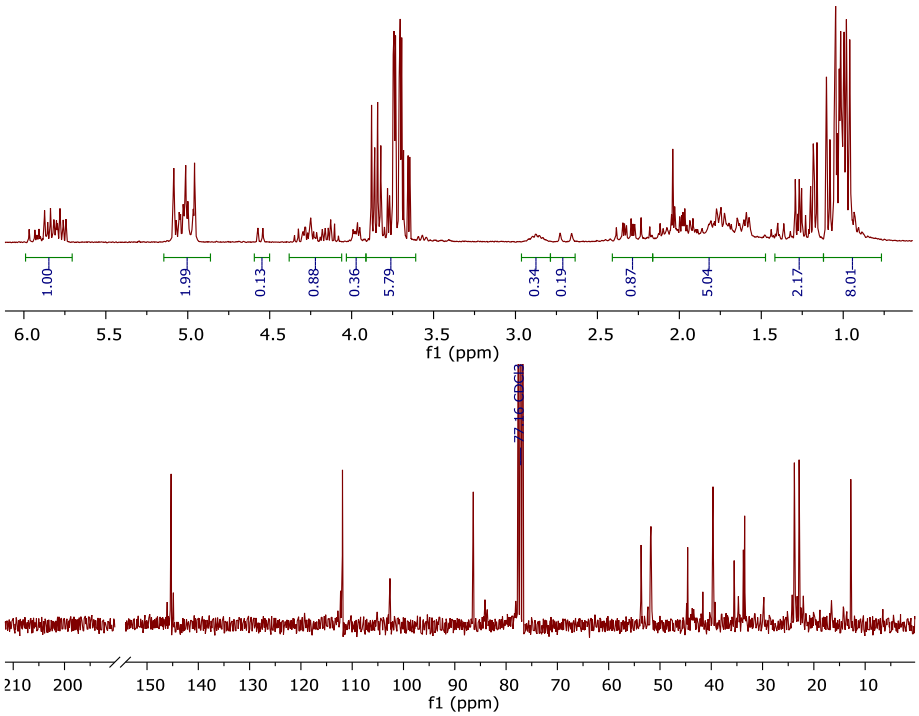


*Figure 41 - ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra of **IV.49** and **IV.50** in $CDCl_3$*

In this case, looking at Figure 42 showing the comparison of this spectra with the ^{1}H NMR spectra of **IV.38** and **IV.39,** there appears to be very little signals in the region between 2.5 and 3.25 ppm, suggesting, that the ketone is present in minute amounts and therefore that the lactol form should be the major species. This is in agreement with the lack of signals around 200 ppm in the ^{13}C NMR spectrum and the presence of a sharp signal around 103 ppm corresponding to a hemiacetal as shown in Figure 41.

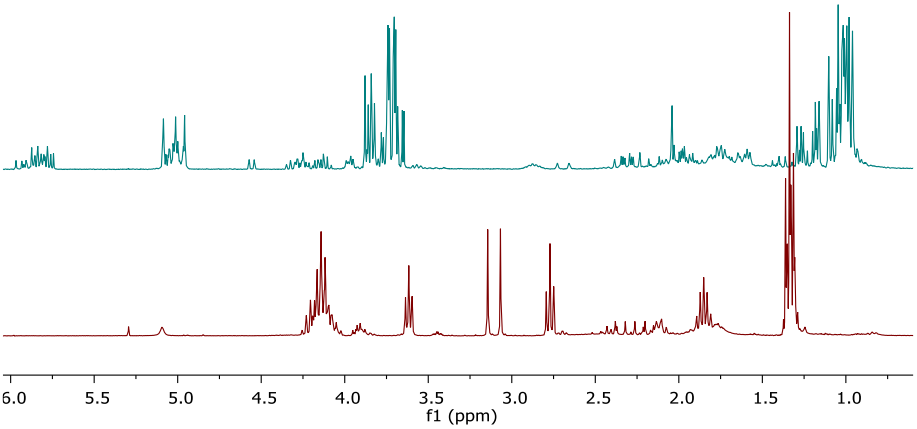


*Figure 42 - Comparison of ^{1}H (300 MHz) NMR spectra of **IV.49/IV.50** (top) and **IV.38/IV.39** (bottom) in $CDCl_3$*

Given the aspect of the spectrum in deuterated chloroform (Figure 40) and the difficulty in assigning the different signals, we decided to screen a series of NMR solvents and see if one would allow a better characterization of the compound. The cleanest spectrum was obtained in DMSO-d_6 and in this solvent, the lactol form **IV.49** appears as the major species (Figure 43).

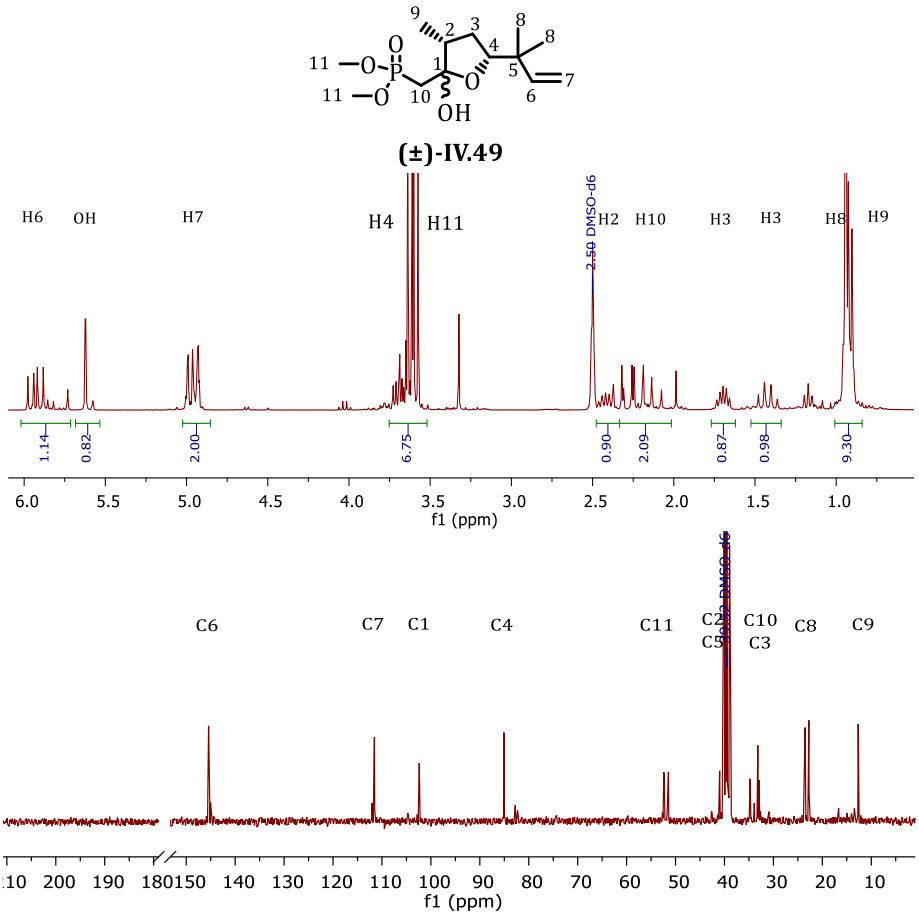


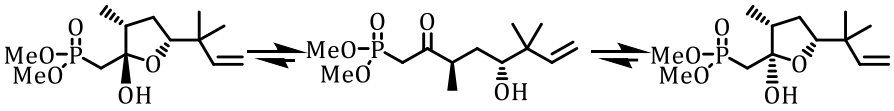
*Figure 43 - ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra of **IV.49/IV.50** in DMSO-d_6*

From these data, the following conclusions can be drawn:

- Under these reaction conditions, the addition product between phosphonate **IV.45** and the lactone **I.156** can occur.
- In this case, the ketone **IV.50** seems to be a minor component of the species that are present. This might be the consequence of a Thorpe-Ingold effect[85] that favours the formation of the hemiacetal **IV.49**.
- There appears to be a major diastereoisomer of **IV.49**.
- We cannot prove if the observation of one major diastereoisomer of **IV.49** comes from a diastereoselective addition reaction or if the observation of one major diastereoisomers comes from the equilibrium between the lactol **IV.49** and the ketone **IV.50**, with one of the lactols

[85] R. M. Beesley, C. K. Ingold, J. F. Thorpe, *J. Chem. Soc., Trans.*, **1915**, *107*, 1080–1106.

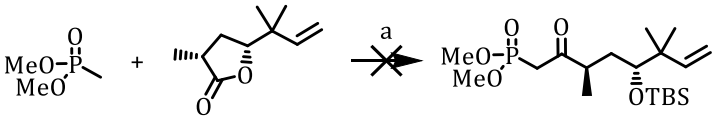
being the most stable form (Figure 44). A stabilisation involving hydrogen bonding and/or the anomeric effect as well as steric factors might favour one diastereoisomer over the other, but we could not propose an experiment that would allow us to find the answer to that question quickly.



(±)-IV.49 **(±)-IV.50** **(±)-IV.49bis**

*Figure 44 - Equilibrium between ketone **IV.50** and lactols **IV.49** and **IV.49bis***

The next step in the methodology development was the double deprotonation of the intermediate phosphonate **IV.49/IV.50** followed by protection of the alcohol. This was done by addition of *tert*-butyldimethylsilyl chloride or the corresponding triflate after addition of the two equivalents of base. However, in neither case could we isolate the ketone **IV.51** (Scheme 170).

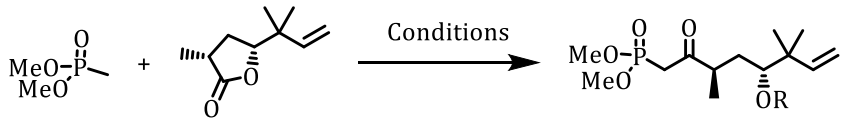


IV.45 **(±)-I.156** **(±)-IV.51**

a) *n*BuLi (2 eq.), THF, -78°C - RT then TBSCl or TBSOTf.

*Scheme 170 - Failure of the synthesis of **IV.51***

We investigated the protection of the hydroxyl group in other conditions starting from lactone **I.156** and phosphonate **IV.45** but no desired product could be isolated. Only lactol **IV.49** could be obtained from the reaction mixture (Figure 45).



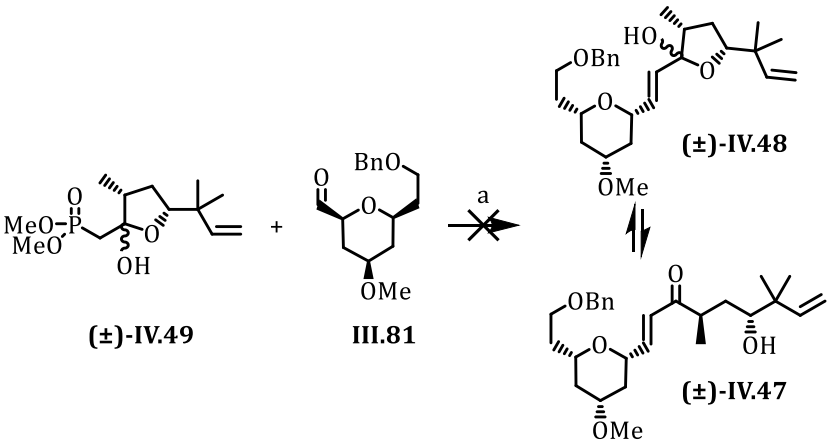
IV.45 **(±)-I.156** **(±)-IV.52**

Conditions	Yield
*n*BuLi then **(±)-I.156** then *n*BuLi then TMSCl	**IV.49**
*n*BuLi then **(±)-I.156** then *n*BuLi then AcCl	**IV.49**

*Figure 45 - Attempts to the synthesis of **IV.52***

At that point, we decided to test if the protection step was required, or if it was possible to directly react with the phosphoenolate. We therefore took lactol

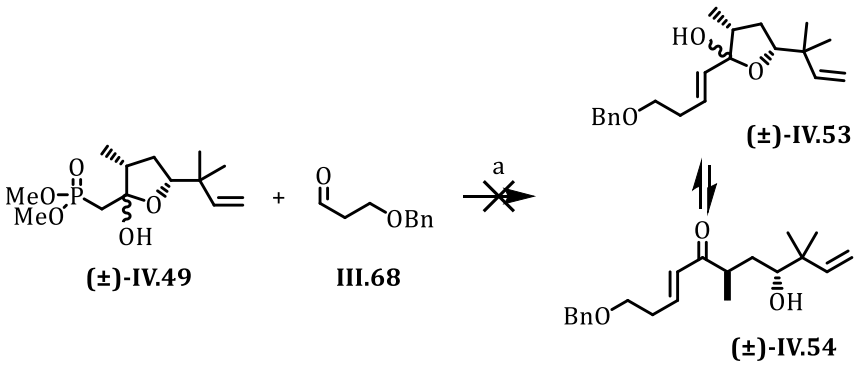
IV.49 which was treated by two equivalents *n*BuLi and followed by the addition of aldehyde **III.81** (Scheme 171). In these conditions, while the TLC showed the consumption of the aldehyde, we could not see any formation of the β-hydroxyphosphonate or the compounds **IV.47** or **IV.48** arising from a HWE olefination.



a) *n*BuLi (2 eq.), THF, -78°C - RT, then **III.81**, 0°C - reflux.

*Scheme 171 - Coupling of **IV.49** with **III.81***

From the crude product of the reaction, we could recover part of compound **IV49**. We hypothesized that the lack of reactivity might arise from aldehyde **III.81** which led us to replace this compound by aldehyde **III.68** but even with this substrate, no product could be observed and the starting material **IV.49** could be recovered (Scheme 172).



a) *n*BuLi (2 eq.), THF, -78°C - RT, then **III.68**, 0°C - reflux.

*Scheme 172 - Coupling of **IV.49** with **III.68***

This result led us to believe that the lactol **IV.49** lacked the desired reactivity. Based on the observations from NMR data and results we gathered, we thought that maybe the lithiated lactol **IV.72** might be unreactive towards a second deprotonation and prevent the formation of the bis-anion that is required for the

Horner-Wadsworth-Emmons reaction to occur. If the intermediate **IV.72** is too stable, then the formation of **IV.73** might be disfavoured leading to the inability to form the bis-anionic species **IV.74** as suggested in Figure 46.

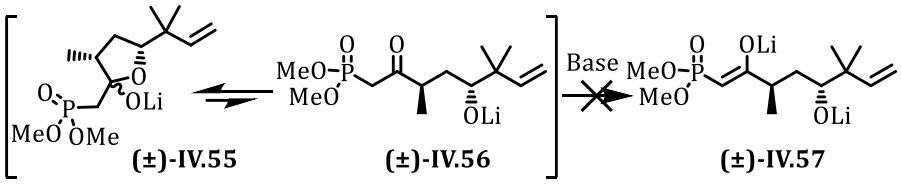
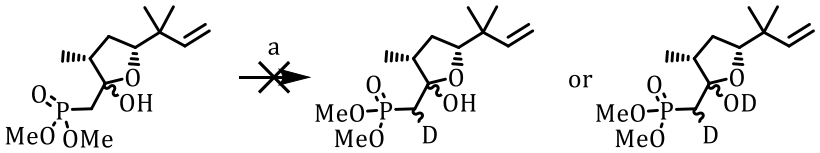


*Figure 46 - Failure of the deprotonation of **IV.56***

We decided to screen other counter cations hoping to lead to the formation of the bis-anion. Deprotonation with potassium *tert*-butoxide or its combination with 18-crown-6 ether were attempted as this base has been used for the HWE olefination but no trace of addition product could be observed.

To confirm our hypothesis involving the non-formation of the bis anionic species, lactol **IV.49** was treated with 2 equivalents of each of the bases screened previously (*n*BuLi, *t*BuOK and *t*BuOK/18-crown-6) followed by a work-up with deuterated water. In each of these cases, deuterium incorporation at the α-position of the phosphonate could not be observed either by ^{1}H NMR or mass spectrometry (Scheme 173).



a) *n*BuLi or *t*BuOK or *t*BuOK/18-crown-6 then D_2O.

*Scheme 173 - Deuterium labelling of **IV.49***

We believe that once the first anion is formed, the lactolate **IV.55** is stabilized by additional interactions due to the chelation of the cation by the oxygen atoms of the phosphonate. Other sources of stabilisation might arise from the anomeric effect and Thorpe-Ingold effect that increase the stability of the cyclic form. The proposed hypothesis is reinforced by the observation that lithiated β-hydroxyphosphonate **IV.63** are stable species since they require higher temperatures and extended reaction time to undergo elimination in the HWE conditions, and that same scaffold is present in lactolate **IV.55** (Figure 47).

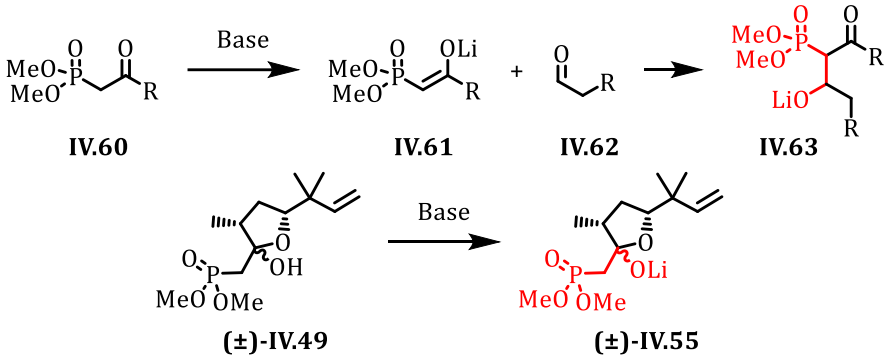
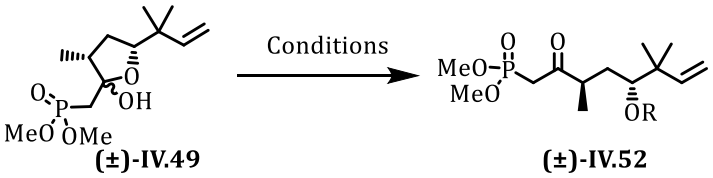


Figure 47 - Formation of lithiated β-hydroxyphosphonate

As lactol **IV.49** proved to be unfit to carry out the coupling with the model of the Southern fragment of Polycavernoside A, we decided to look at possible solutions to this problem. As we suggested, the problem arises from the stability of the lactol **IV.49** and more precisely from its anion **IV.55**. We decided to inhibit the formation of the lactol anion. Therefore, it was treated in a series of conditions that should allow the protection of the alcohol without formation of the anion but all our attempts failed (Figure 48).



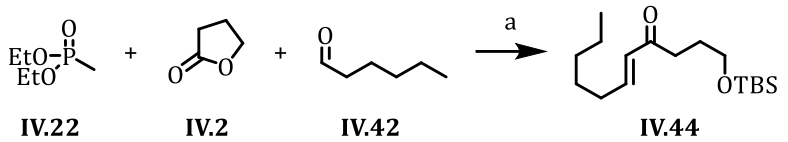
Conditions	Yield
HMDS, I_2, DCM, RT	SM recovered
*t*BuOK, TMSCl, DMF	SM recovered
TMSCl, NaI, CH_3CN	SM recovered

*Figure 48 - Attempts to the protection of **IV.49***

With these results, we decided to move to a strategy that would either allow the protection of the alcohol before the lactol formation or a strategy where the alcohol could be inserted latter. This new strategy would require a revision of the synthesis of the Northern fragment as the use of a lactone was essential for the control of the chiral centre located at C_{11} in the natural product. As a consequence, we were required to develop a new disconnection for the Northern fragment that will be presented in the next chapter.

IV.3 Conclusions and perspectives

In order to connect the Northern and Southern fragment of Polycavernoside A, we developed a coupling methodology based on the Horner-Wadsworth-Emmons reaction. Starting from lactone **IV.2** and aldehyde **IV.42** as models for the fragments, diethyl methylphosphonate **IV.22** could be used as a linker and the developed methodology allowed the formation of enone **IV.44** (Scheme 174).

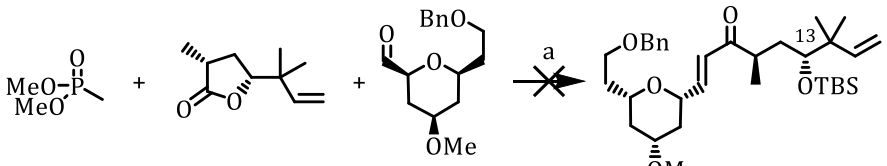


IV.22 **IV.2** **IV.42** **IV.44**

a) *n*BuLi then TBSCl then hexanal, 28 %.

Scheme 174 - Coupling methodology

However, when the lactone **I.156** and aldehyde **III.81** were used as substrate, the desired coupling product could not be isolated (Scheme 175).

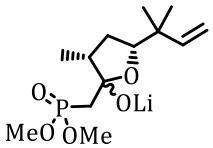


IV.45 **(±)-I.156** **III.81** **(±)-IV.46**

a) *n*BuLi then TBSCl then **III.81.**

*Scheme 175 - Coupling of **I.156** with **III.81***

Investigations of the reasons of this failure led us to the conclusions that the lactol lithiated anion **IV.55**, an intermediate in the proposed mechanism, was too stable and could not undergo a ring opening required for the coupling to proceed (Figure 49). The use of a potassium based base did not allow observation of the double deprotonation of **IV.45**. However, a sodium base like sodium hydride might provide a solution to this problem.



(±)-IV.55

*Figure 49 - Suspected unreactive intermediate **IV.55***

Given the results obtained in this chapter, the strategy that was initially planned to carry out the coupling had to be reviewed. This new strategy should avoid the formation of the lactol intermediate and will be presented in the next chapter.

Chapter V

New approach for the coupling methodology

V.1 Development of a new coupling methodology

V.1.1 Disconnection

In the previous chapter, we observed that the coupling methodology based on the Horner-Wadsworth-Emmons reaction (HWE) did not allow the assembly of our Northern and Southern fragments of Polycavernoside A (Figure 50).

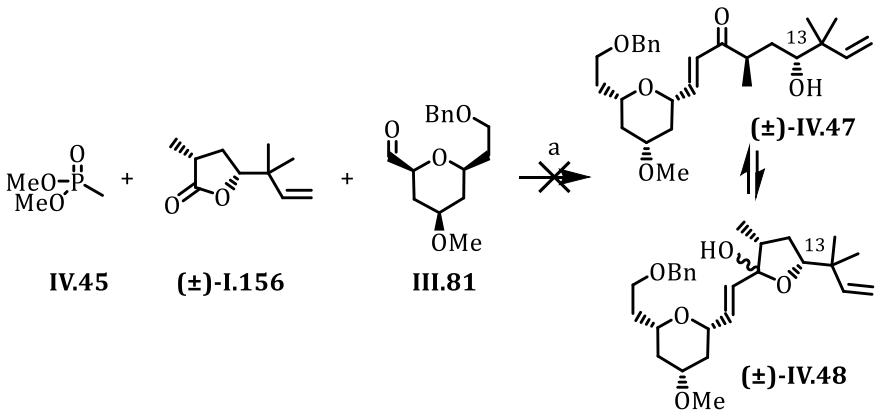


*Figure 50 - Coupling between **IV.45**, **I.156** and **III.81***

Our attempts at using intermediate **IV.49** for the same purpose failed and we proposed that the high stability of **IV.49** could explain the lack of reactivity (Figure 51). Our new strategy was therefore to aim for species where the formation of the lactol could to be avoided.

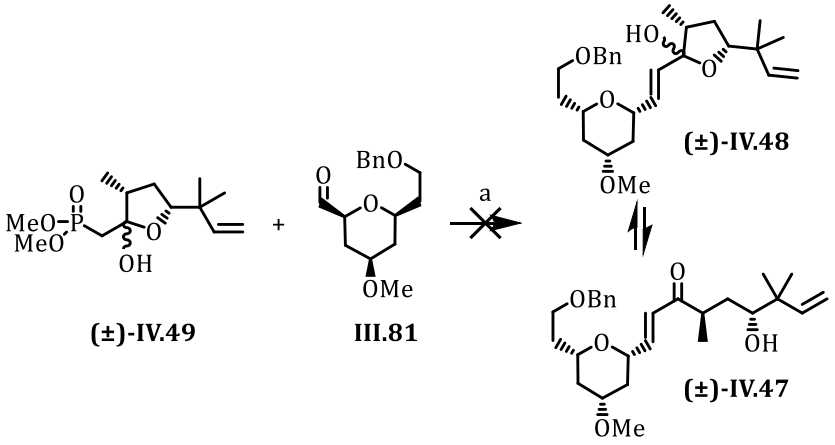
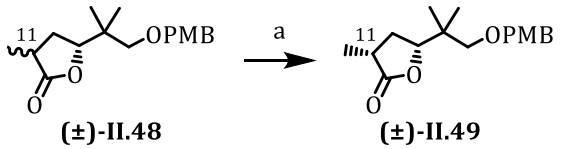


*Figure 51 - Coupling with lactol **IV.49***

For this reason, we had to review our approach for the synthesis of the Northern fragment since in our initial plan, the formation of a lactone was essential for the control of the C_{11} chiral centre (Scheme 176).



a) LDA, THF, -78°C then NH_4Cl, -78°C-RT, 90 %, d.r. > 95:5.

Scheme 176 - Control of the C_{11} stereocentre

Looking at the disconnection proposed in Figure 52, we had to find a suitable way to prepare synthon **V.2.**

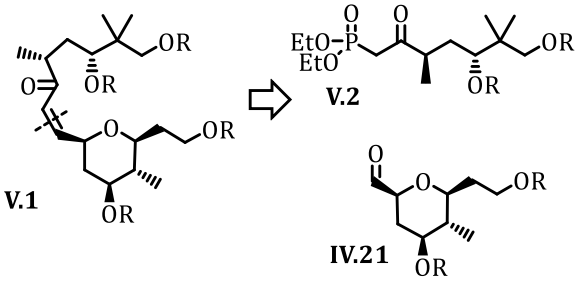


*Figure 52 - Disconnection of enone **V.1***

β-Ketophosphonate **V.2** could arise from the addition of the anion of **IV.45** to a carboxylic acid derivative like **V.3** (Figure 53). With the derivative **V.4** being similar to the compounds used in our initial approach, we thought that a prenylation reaction between **II.35** and aldehyde **V.5** could be proposed as a retrosynthetic strategy.

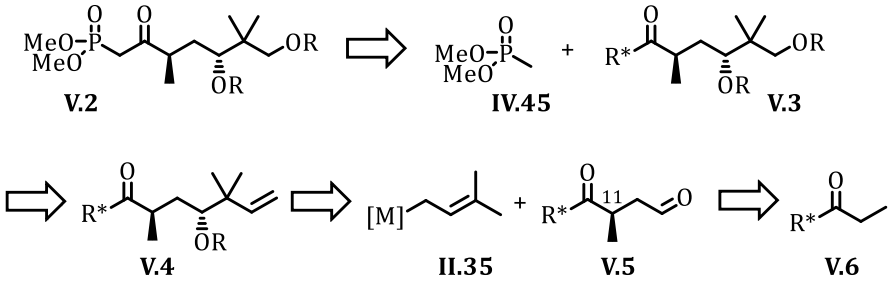
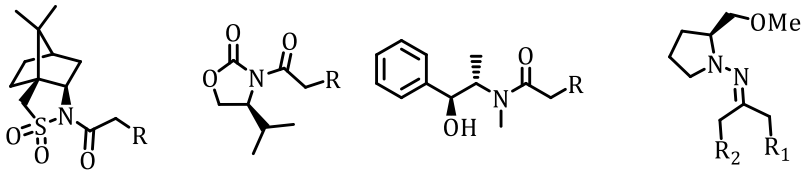


*Figure 53 - Disconnection of ketophosphonate **V.2***

Since the asymmetric centre in **V.5** is located at the alpha position of a carbonyl, the use of chiral enolates derived from **V.6** seemed suited for this purpose. With this new plan in mind, we could move to the synthesis.

V.1.2 Results and discussion

Numerous chiral auxiliaries have been described for the enantioselective α-alkylation of enolates[86]. Among the most famous, Oppolzer, Evans, Myers or Enders have developed the chiral auxiliaries depicted in Figure 54 that allow these transformations to be carried out efficiently.

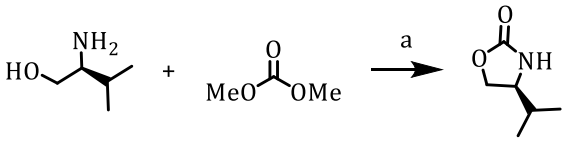


V.7 **V.8** **V.9** **V.10**

Oppolzer **Evans** **Myers** **Enders**

Figure 54 - Chiral auxiliaries for asymmetric alkylation of enolates

Our choice went for the Evans chiral auxiliary **V.8** since they are cheap and readily available[87]. Starting from valinol **V.11** the corresponding oxazolidinone **V.13** was prepared in moderate yield by treatment in the presence of dimethylcarbonate **V.12** (Scheme 177).



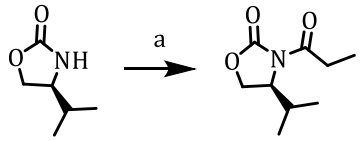
V.11 **V.12** **V.13**

a) K_2CO_3, reflux, 52 %.

*Scheme 177 - Synthesis of oxazolidinone **V.13***

The corresponding propionyl derivative **V.14** was obtained after the treatment in the presence of anhydrous lithium chloride, propionyl anhydride and triethylamine using a procedure described by researchers from Merck[88] (Scheme 178).

[86] E. J. Corey, L. Kürti, *Enantioselective Chemical Synthesis*, Elsevier, **2010**.
[87] D. A. Evans, M. D. Ennis, D. J. Mathre, *J. Am. Chem. Soc.*, **1982**, *104*, *6*, 1737–1739.
[88] G. Ho, D. J. Mathre, *J. Org. Chem.*, **1995**, *60*, *7*, 2271–2273.

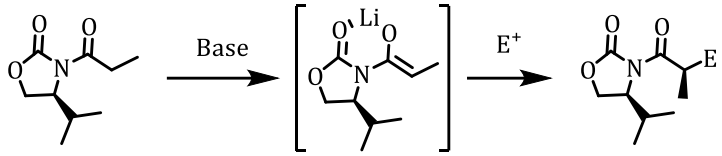


V.13 **V.14**

a) Propionic anhydride, LiCl, NEt_3, THF, -20°C - RT, 92 %.

*Scheme 178 - Synthesis of **V.14***

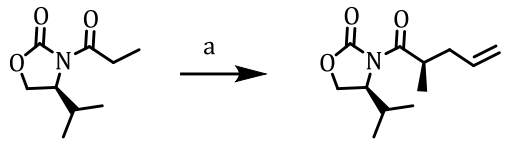
With the chiral auxiliary **V.14** in hand, we could move to the asymmetric alkylation of the enolate. In this process, once the deprotonation of **V.14** occurs, the addition of the electrophile to **V.15** is controlled by the chiral auxiliary and the formation of one diastereoisomers **V.16** should be favoured (Figure 55).



V.14 **V.15** **V.16**

Figure 55 - Enantioselective alkylation of chiral oxazolidinone enolates

Compound **V.14** was treated with LDA to generate the *Z*-enolate and followed by the addition of an excess of allyl bromide (Scheme 179). After purification, the oxazolidinone **V.17** could be isolated in good yield as a single diastereoisomer.

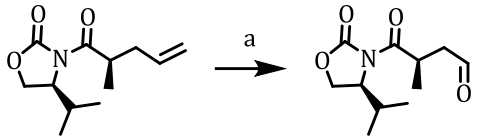


V.14 **V.17**

a) LDA, THF, -78°C then allyl bromide (3 eq.), -78°C - RT, 85 %, d.r. >95:5.

*Scheme 179 - Synthesis of oxazolidinone **V.17***

The next step of the synthesis was the transformation into the corresponding aldehyde and this was achieved by an ozonolysis of **V.17** followed by the addition of triethylamine as reducing agent (Scheme 180).

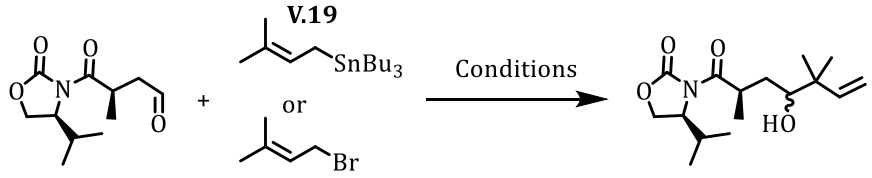


V.17 **V.18**

a) O_3, DCM, -78°C then NEt_3, -78°C - RT, yield not determined.

*Scheme 180 - Ozonolysis of olefin **V.17***

With aldehyde **V.18**, we could move to the allylation step. Looking in the literature for precedents, we were surprised to find very few reports for similar aldehydes and to our knowledge, its use in allylation reactions was not described. Therefore, we wondered if the chiral information that is already present in **V.18** could be used to induce some diastereoselectivity in the allylation reaction. Moreover, looking at the function embodied in the architecture of **V.29**, we wondered if the choice of Lewis acid could play a role in tuning the selectivity of the allylation reaction. We screened a series of conditions used in prenylation reactions leading to the results reported in Figure 56.



V.18 **II.65** **V.20**

Entry	Conditions	Results
1	**V.19**, $TiCl_4$ (1 eq.), DCM, -78°C	Formation of **I.156** and **II.118**, d.r. : 1 : 1.5
2	**V.19**, $TiCl_4$ (2 eq.), DCM, -78°C	Formation of **I.156** and **II.118**, d.r. : 1 : 1.5
3	**V.19**, $BF_3.Et_2O$, DCM, -78°C	**V.20**, d.r. : 1 : 4
4	**II.65**, Zn, $Cp_2TiCl_{2\ cat.}$, THF, RT	Formation of **I.156** and **II.118**, d.r. : 1 : 1
5	**II.65**, Zn, NH_4Cl/THF, 0°C - RT	**V.20**, d.r. : 1 : 1

*Figure 56 - Screening of the allylation conditions of **V.18***

As it can be seen from this study, in some conditions, the formation of the lactone **I.156** and **II.118** occurs due to a cyclization of the desired product (Figure 57).

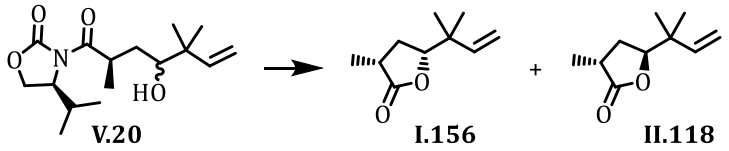


*Figure 57 - Formation of lactone **I.156** and **II.118** from **V.20***

The conditions used in entries **1**, **2** and **4** led to the formation of the lactone we wanted to avoid. We think that in this case, the coordination of the titanium cation to the 1,3-dicarbonyl moiety of the oxazolidinone increases the electrophilicity and favours the cyclization reaction. Entry **3** and **5** furnished the compound we were aiming for and moreover some level of diastereoselectivity was obtained from entry **3**. Using the conditions of entry **3** and by stirring the reaction over an extended period, we could promote the cyclisation, and this allowed us to determine the diastereoselectivity by comparison with the ^{1}H NMR spectra of **I.156** that we had prepared previously. It came out that the selectivity was in favour of the undesired diastereoisomer. The use of zincate in entry **5** lead to a 1:1 ratio of the diastereoisomers of alcohol **V.20** without the formation of the lactones **I.156** and **II.118**. In this case, the 50:50 ratio could be explained by a non-diastereoselective allylation reaction. In aqueous ammonium chloride, we suppose that the Lewis base sites that usually allows the formation of one transition state and therefore selectivity are occupied by other species.

From the allylation reactions that we carried out, we could not find suitable conditions leading to promising results. In addition, in some cases, the formation of the lactones **I.156** and **II.118**, compounds that we were trying to avoid, was observed. Given these results, we decided to modify our methodology.

Our new strategy implied that the target **V.9** should arise from the functionalisation of the terminal double bond in **V.21**. The latter would originate from the HWE coupling between β-ketophosphonate **V.22** and aldehyde **IV.21** as suggested in Figure 58**.** While this approach would be less convergent, it should prevent the side reaction that we described above.

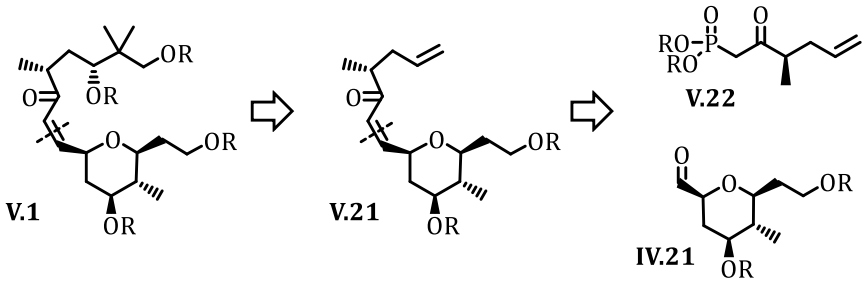
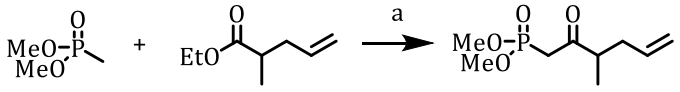


*Figure 58 - New disconnection for **V.1***

The ester **II.62** that we add previously prepared, was chosen as starting point for this new strategy. Treated in the presence of methyl phosphonate **IV.45** and a

base, the ester **II.62** could be transformed in the β-ketophosphonate **V.23** in excellent yield, as shown in Scheme 181.

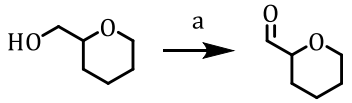


IV.45 **(±)-II.62** **(±)-V.23**

a) *n*BuLi, THF, -78°C - RT, 91 %.

*Scheme 181 - Synthesis of β-ketophosphonate **V.23***

In order to test our coupling methodology, we decided to use aldehyde **V.40** as a model since it prevents wasting material from the Southern fragment while maintaining a structure with a similar reactivity. Starting from commercially available alcohol **V.39**, the oxidation to the aldehyde **V.50** could be carried out using Swern conditions or Dess-Martin reagent (Scheme 182). Our attempt to carry out this transformation using Anelli's conditions[89] failed.



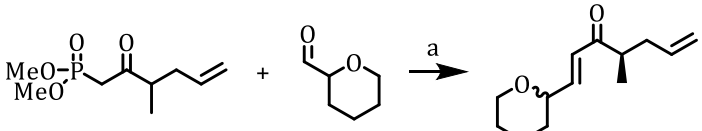
(±)-V.24 **(±)-V.25**

a) $(COCl)_2$, DMSO, NEt_3, DCM, -78°C - RT, 54 % or DMP, DCM, 0°C - RT, 63 %.

*Scheme 182 - Oxidation of alcohol **V.24***

The unexpectedly low yield for this reaction was attributed to the sensitivity of aldehyde **V.25**. Therefore, when required, the aldehyde was preferentially prepared freshly before use or kept in the freezer.

With both partners in hand, the transformation that we had planned could be carried out in classical conditions for the HWE olefination and the coupling product **V.26** could be isolated (Scheme 183).



(±)-V.23 **(±)-V.25** **(±)-V.26**

a) NaH, THF, 0°C then -78°C - RT, 58 % conversion of **V.23**, E/Z >95:5.

*Scheme 183 - Horner-Wadsorth-Emmons olefination with aldehyde **V.25***

From the NMR spectrum of the crude product, a 58% conversion of β—ketophosphonate **V.23** into enone **V.26** was observed while aldehyde **V.25** was

[89] P. Lucio Anelli, C. Biffi, F. Montanari, S. Quici, *J. Org. Chem.*, **1987**, *52*, *12*, 2559–2562.

completely consumed. We think that this is due to the degradation of the aldehyde during the reaction.

With the enone architecture **V.26** in place, we decided to look at the functionalisation that would be required to reach an advanced intermediate like **V.27** (Figure 59).

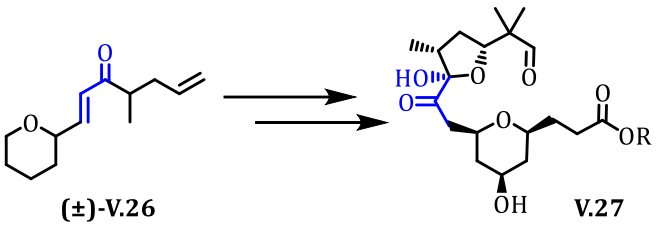
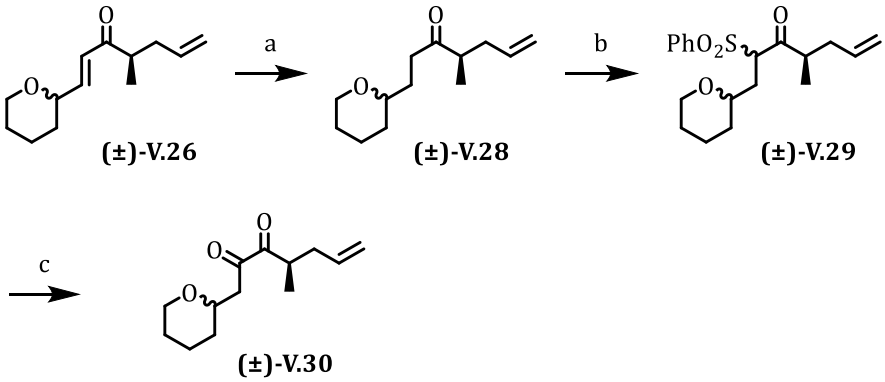


*Figure 59 - Functionalisation of enone **V.27***

Looking at the structure of target **V.27**, we can see that the functionalisation of the enone of **V.26** is the next step. One possibility to carry out this transformation could be using an approach similar to the one used by Paquette[12] that involves going through sulfone **V.29** (Figure 60)**.**



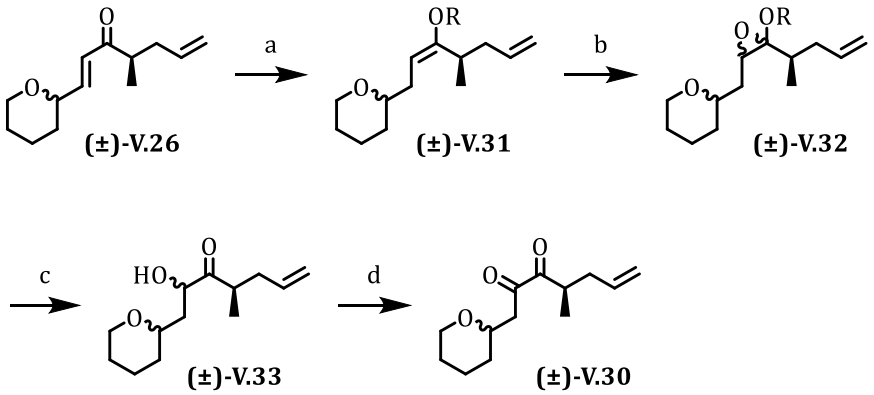
a) 1,4-Reduction of the enone; b) Sulfonylation; c) Oxidation.

*Figure 60 - First synthetic plan towards **V.30***

This approach would require the 1,4-reduction of the enone **V.26** using for example a cupper-based hydride source[90]. Then, the ketone **V.26** would be transformed into sulfone **V.29**, a transformation that might require several steps. The oxidation to the diketone **V.30** would occur using the same conditions as Paquette's group.

We also thought it could be possible to access the diketone though a sequence involving a Rubottom oxidation as shown in Figure 61.

[90] C. Deutsch, N. Krause, B. H. Lipshutz, *Chem. Rev.*, **2008**, *108*, *8*, 2916–2927.



a) Michael-addition to the enone; b) Epoxydation of the enol ether; c) Hydrolysis of the acetal; d) Oxidation of the alcohol.

*Figure 61 - Second synthetic plan towards **V.30***

Starting from the same enone **V.26**, the 1,4-addition of a hydride source followed by the O-alkylation of the enolate should lead to enol ether **V.31.** A subsequent oxidation using Rubottom's conditions should lead to epoxide **V.32** and then α-hydroxyketone **V.33** that could then be oxidised to diketone **V.30**.

These two approaches seemed long in term of the number of steps and looking at the nature of the steps, they involved many oxidation and reduction steps. It came to us that the transformation would be straightforward if we could obtain an intermediate like **V.34** since a simple hydrolysis of the enol ether could lead to the corresponding diketone **V.30** in one step as shown in Figure 62.

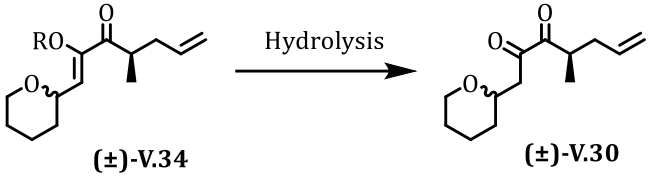


*Figure 62 - Hydrolysis of enol ether **V.34***

In terms of disconnection, the enol ether **V.34** should be accessible using alkoxymethyl phosphonates like **V.35** that could be obtained from ester **II.62** and phosphonate **V.36** (Figure 63). Moreover, the synthesis of enol ethers using alkoxyphosphonate has been described in the literature[91].

[91] Y. Vo-Quang, D. Carniato, L. Vo-Quang, F. Le Goffic, *J. Chem. Soc. Chem. Commun.*, **1983**, *24*, 1505.

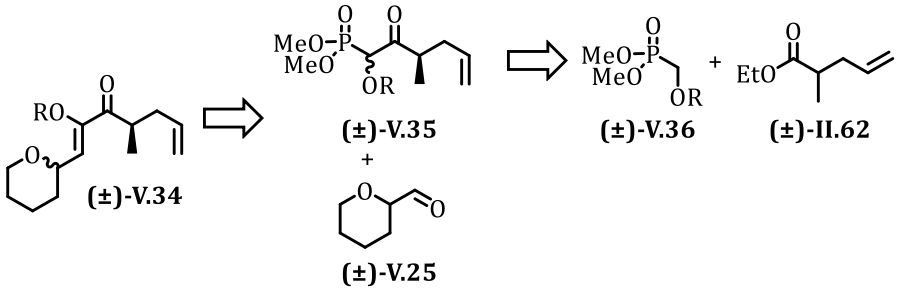
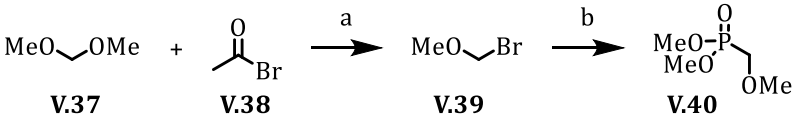


*Figure 63 - Disconnection of enol ether **V.34***

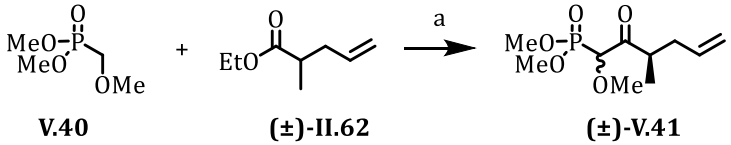
This new strategy started with the synthesis of phosphonate **V.40** which was achieved using an Arbuzov reaction between methoxymethyl bromide **V.39** and trimethylphosphite. As **V.39** is known for its toxicity, it was prepared *in situ* from the reaction between dimethoxymethane **V.37** and acetyl bromide **V.38** as depicted in Scheme 184.



a) neat, RT; b) $P(OMe)_3$, autoreflux, 71 %.

*Scheme 184 - Synthesis of alkoxymethylphosphonate **V.40***

Then, the addition of the phosphonate **V.40** to ester **II.62** was achieved using LDA as a base as described by Lee[92] leading to β-ketophosphonate **V.41** (Scheme 185).

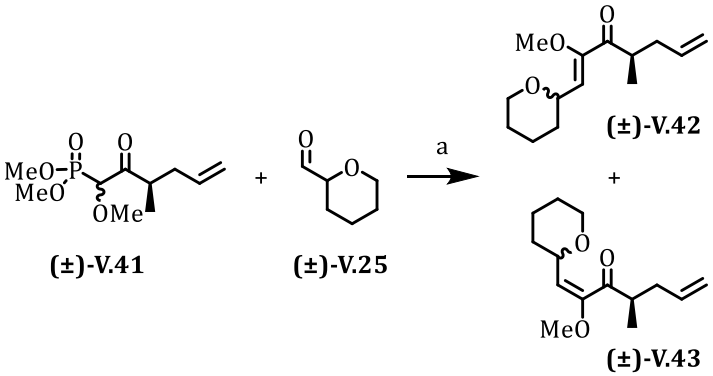


a) LDA, THF, 0°C, 84 %.

*Scheme 185 - Synthesis of **V.41***

The treatment of intermediate **V.41** with sodium hydride followed by the addition of aldehyde **V.25** led to the formation of the HWE product as a mixture of *E* and Z isomers **V.42** and **V.43** (Scheme 186).

[92] S.-M. Son, H.-K. Lee, *J. Org. Chem.*, **2014**, *79*, *6*, 2666–2681.

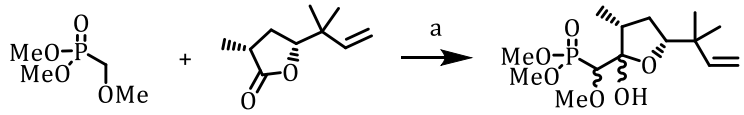


a) NaH, THF, 0°C then -78°C- RT, 55 %.

*Scheme 186 - Synthesis of enol ether **V.42** and **V.43***

From NMR spectra of the crude product, we could see that the conversion of the *β*-ketophosphonate **V.41** was incomplete while no more of the aldehyde **V.25** was present leading us to think that the aldehyde decomposed under the reaction conditions. The ratio between those two isomers was determined to be 2.4 : 1 by ^{1}H NMR but we could not determine the major isomer. However, this was not a major concern as the hydrolysis of the enol ether would remove the isomerism. The isolation of **V.42** and **V.43** led us to believe that the use of the alkoxymethylphosphonate could represent a valuable tool for the elaboration of the coupling reaction.

At the beginning of this chapter, we had decided to review our strategy for the Northern fragment synthesis since the intermediate **IV.49** did not allow us to carry out the coupling with the Southern fragment **III.81** as shown in Figure 50 and Figure 51. However, with the new classes of reagent represented by **V.40**, we wanted to see if they could be used in our initial strategy. To do so, we started with the addition of anion of **V.40** to the lactone **I.156** (Scheme 187).



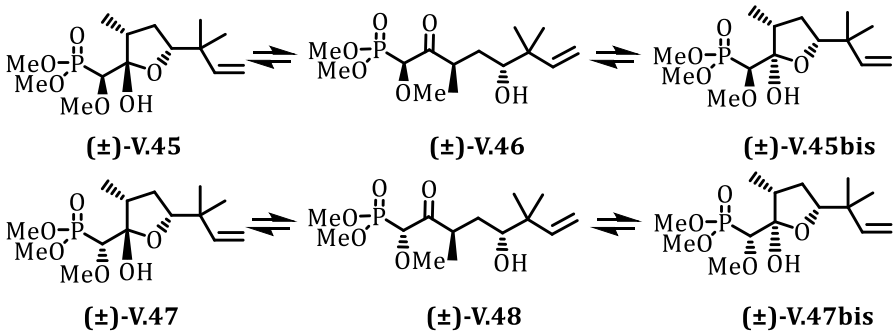
V.40 **(±)-I.156** **(±)-V.44**

a) LDA, THF, 0°C, 87 %.

*Scheme 187 - Addition of phosphonate **V.40** to lactone **I.156***

This transformation occurred with low yield (25 %) and we recovered the majority of the lactone **I.156**. We hypothesized that the low yield of this reaction was due to the instability of the anion of **V.40**. To overcome this issue, we decided to carry out the transformation using a large excess of phosphonate **V.40** and base and found that in these conditions lactol **V.44** could be obtained in an excellent yield of 87 %.

Through this reaction, two new chiral centres are formed meaning that 4 possible products could be obtained. In addition, as the product can exist either as lactol or ketone, two additional structures can be proposed leading to a total of 6 possible products for this reaction represented in Figure 64.



(±)-V.45 **(±)-V.46** **(±)-V.45bis**

(±)-V.47 **(±)-V.48** **(±)-V.47bis**

*Figure 64 - Possible structures for **V.44***

It was possible to rule out the formation of ketone **V.46** and **V.48** as no signals around 200 ppm are visible in the ^{13}C NMR spectrum. This pattern is similar to the one observed for compound **IV.49** where the equilibrium was strongly shifted towards the cyclic form (Figure 65).

(±)-IV.49 **(±)-IV.50**

*Figure 65 - Equilibrium between **IV.49** and **IV.50***

From the TLC of the crude reaction, two spots were observed. We were able to separate them partially leading to a clean NMR spectra for the first while the NMR of the second showed a mixture of the second compound along with the first.

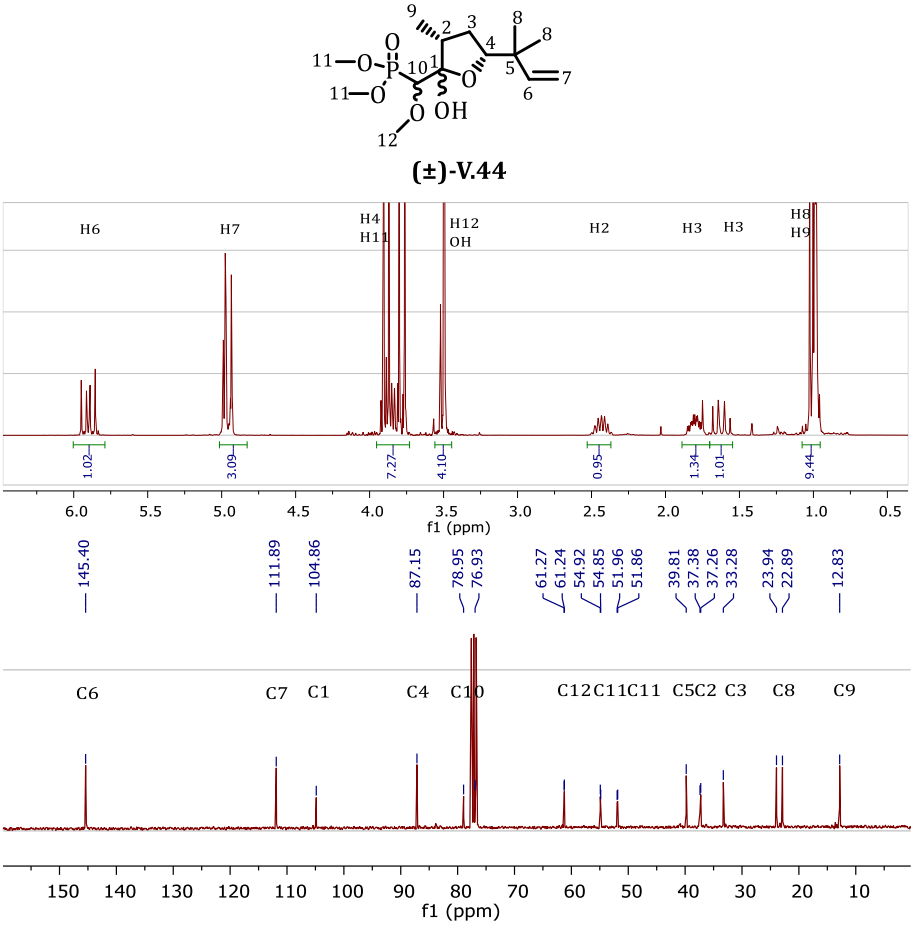


*Figure 66 - ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra of one fraction of **V.44** in $CDCl_3$*

The NMR data in Figure 66 suggests that in this fraction, a single diastereoisomers is present. Considering the equilibrium between **V.45** and its diastereoisomers **V.45bis** (or **V.47** and **V.47bis**) (Figure 64), the observation of a single compound might suggest one diastereoisomer to be more thermodynamically stable than the other, explaining what is observed in the ^{1}H NMR spectra. This thermodynamic stability could originate from different contributions including a stabilisation at the anomeric carbon, H-bonding between the hydroxyl group of the lactol and H-bond acceptors on the phosphonate moiety, minimisation of repulsion, Thorpe-Ingold effect and dipole-dipole interactions. In our opinion, the two compounds that are observed are the diastereoisomers arising from the stereochemistry of the carbon bearing the methoxy group while the anomeric carbon is under thermodynamic control. NOESY experiments of the two different products would maybe allow to confirm our hypothesis. However, since during the next steps, the formation of **V.66** that

is required for the synthesis leads to the loss of both chiral centres, the stereochemistry in these two centres should have a limited influence (Figure 67).

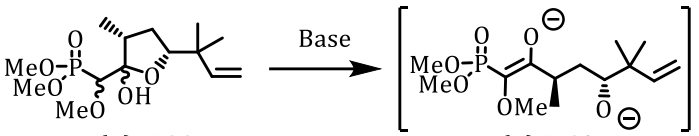
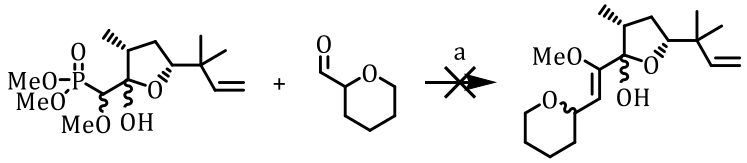


*Figure 67 - Deprotonation of **V.44** with a base*

We then treated lactol **V.44** with aldehyde **V.25** in the presence of sodium hydride. We could not observe by ^{1}H NMR the formation of olefin **V.50** (Scheme 188).



a) NaH, THF, RT then -78°C - RT.

*Scheme 188 - Attempts to the synthesis of **V.50***

From the monitoring of the reaction by TLC, we could see the formation of a new compound. However, in the ^{1}H NMR of the crude product, we could not detect any vinylic proton signals other than the ones corresponding to the terminal olefin. One possible explanation might be the hydrolysis of the enol ether **V.50** into the corresponding diketone followed by hemiacetal formation during the work-up leading to the compounds **V.51** or **V.52** (Figure 68). However, the analysis by mass spectrometry did not fit the proposed structure.

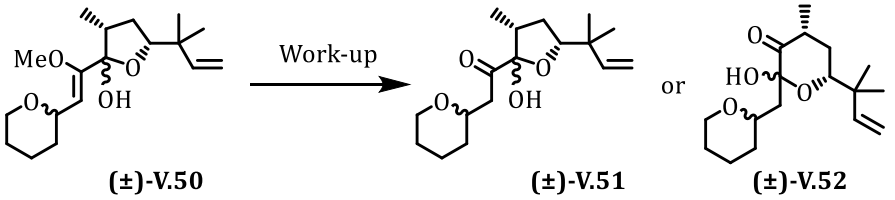
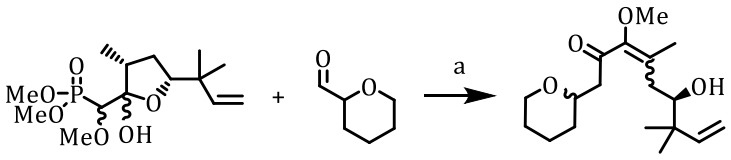


*Figure 68 - Possible hydrolysis products of **V.50***

After investigation, we were able to identify the structure of the product of the reaction. It is enone **V.53** and this structure is in agreement with all of our spectroscopic data (Scheme 189).

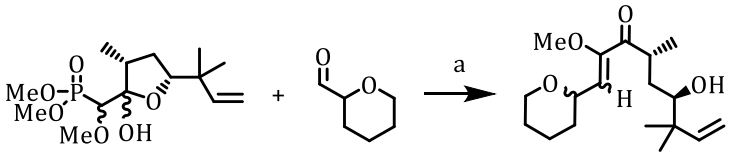


(±)-V.44 **(±)-V.25** **(±)-V.53**

a) NaH, THF, RT then -78°C - RT, yield not determined.

*Scheme 189 - Synthesis of **V.53***

The observation of the enone **V.53** was unexpected. Given its structure, we hypothesized that this compound comes from the rearrangement of a coupling product between **V.44** and **V.25**. Therefore, we decided to reduce the reaction time and the temperature. In these conditions, we could observe in the 1H NMR of the crude reaction signals that could correspond to the enone **V.54** (Scheme 190)**.**



(±)-V.44 **(±)-V.25** **(±)-V.54**

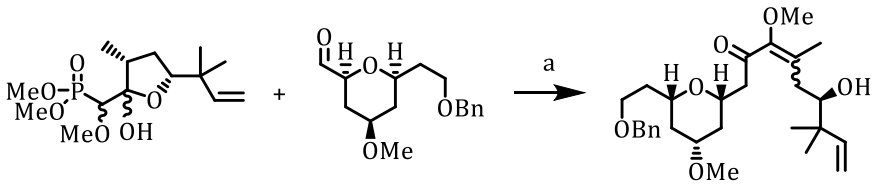
a) NaH, THF, RT then -78°C - 0 °C.

*Scheme 190 - Synthesis of **V.54***

Our attempts to purify compound **V.54** by silica gel column chromatography did not allow isolation of the enone. One possible explanation might be side reactions of this sensitive enol ether to acidic conditions as well as possible transformation into the enone **V.53**.

By comparing the reactivity observed for lactol **V.44** with the inability of lactol **IV.49** to undergo the desired HWE reaction, we hypothesised that this could be explained by two factors. First, the change in counter cation, from lithium in the case of **IV.49** to sodium for **V.44**, might have influenced the reactivity of the anion. While lithium has a smaller ionic radius, the larger sodium cation might not fit as well as the lithium cation. The second explanation might arise from the methoxy group at the α-position of the phosphonate. This additional steric and electronic contribution could displace the equilibrium towards the ketone form once the first deprotonation has occurred leading after the second deprotonation to the formation of **V.49**.

The coupling between the Northern fragment **V.44** and the Southern fragment **III.81** was carried out before the optimisation of the reaction conditions and from the reaction mixture, enone **V.55** could be isolated (Scheme 191).



(±)-V.44 **III.81** **(±)-V.55**

a) NaH, THF, RT then -78°C - RT, yield not determined.

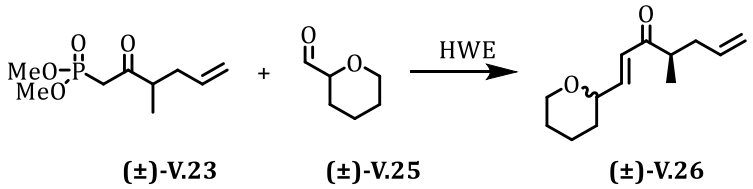
*Scheme 191 - Synthesis of enol ether **V.55***

However, due to a lack of material, this reaction could not be carried out under the optimised conditions. This result suggests that the desired enol ether could be formed from the reaction between lactol **V.44** and aldehyde **III.81** allowing the coupling of the two fragments. The formation of the intermediate **V.55** towards the assembly of the aglycone of Polycavernoside A was however encouraging. Further optimisation of the process is required to establish this method as an efficient approach to the coupling of the Northern and Southern fragments.

V.2 Conclusions and perspectives

V.2.1 Conclusions

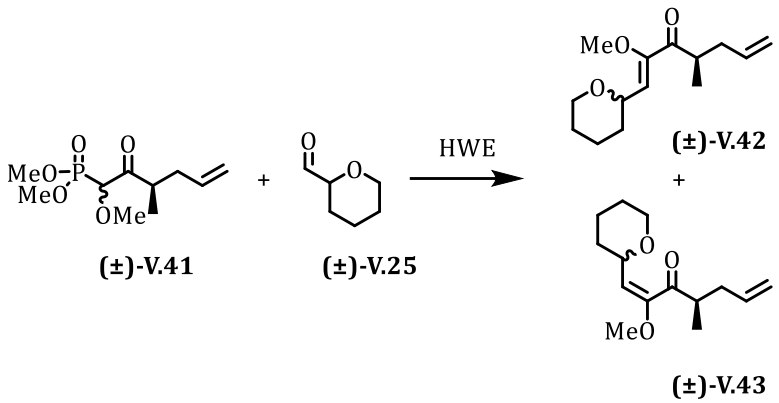
The work presented in this chapter allowed us to successfully couple the Northern fragment and Southern fragment model. This was achieved starting from establishing conditions that allowed us to connect the β-ketophosphonate **V.23** with aldehyde **V.25** leading to enone **V.26** (Figure 69).



(±)-V.23 **(±)-V.25** **(±)-V.26**

*Figure 69 -Synthesis of enone **V.26***

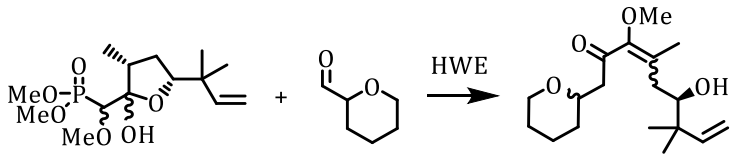
This reaction led us to investigate whether the synthesis of the enol ether through this architecture could allow direct access to the diketone scaffold. This new strategy, which relied on α-alkoxyphosphonate like **V.41**, proved efficient as well since the desired enol ether could be obtained as a mixture of *E* and *Z* isomers **V.42** and **V.43** (Figure 70).



(±)-V.41 **(±)-V.25** **(±)-V.42** **(±)-V.43**

*Figure 70 - Synthesis of enol ether **V.42** and **V.43***

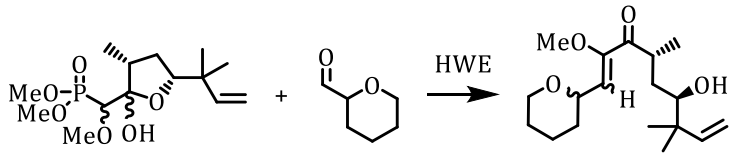
The interesting reactivity observed for the new phosphonate led us to return to our initial strategy and we observed that the coupling of the phosphonate **V.44** with the model aldehyde **V.25** occurred in these reaction conditions and led to the formation of enone **V.53** (Figure 71).



(±)-V.44 **(±)-V.25** **(±)-V.53**

*Figure 71 - Formation of enone **V.53***

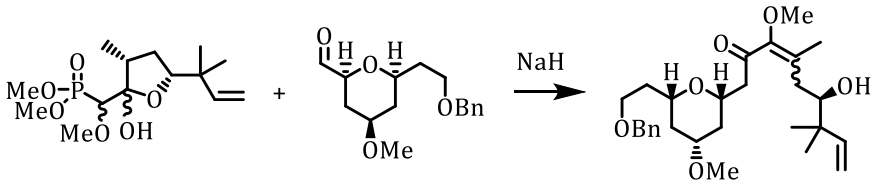
The formation of the enone **V.53** could be prevented by lowering the reaction time and temperature and NMR analysis suggested that the desired enone **V.54** could be formed as a mixture of isomers (Figure 72). However, this product proved to be difficult to purify.



(±)-V.44 **(±)-V.25** **(±)-V.54**

*Figure 72- Coupling of aldehyde **V.25** with phosphonate **V.44***

Carrying out the reaction using aldehyde **III.81** as a model for the Southern fragment led to the formation of enone **V.55** which suggests that under the appropriate conditions, the desired enol ether could be obtained (Figure 73).

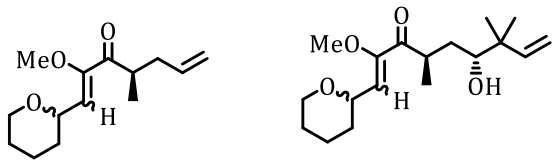


(±)-V.44 **III.81** **(±)-V.55**

*Figure 73 - Formation of enone **V.55** from aldehyde **III.81***

V.2.2 Perspectives

From the work presented in this chapter, enones **V.42/V.43** and **V.54** could be prepared from the new approach using α-alkoxy-β-ketophosphonate with an aldehyde (Figure 74).

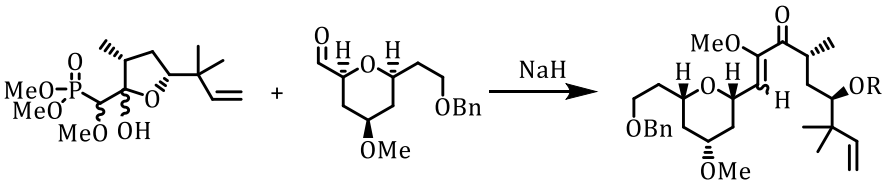


(±)-V.42 and (±)-V.43 **(±)-V.54**

Figure 74 - Enones obtained by the coupling methodology

However, the purification of **V.54** by silica gel column could not be efficiently carried out. In terms of structure, the major difference between both structures arises from the presence of a free hydroxy group in **V.54**. Therefore, a subsequent protection of this hydroxy group before or after the coupling could lead to less sensitive intermediate that could facilitate the synthesis and purification of the coupling product.

An optimisation of the coupling reaction conditions will also be required. This will allow to find suitable conditions to perform the coupling between the Southern fragment model **III.81** and the lactol **V.44** leading to the enone **V.56** (Figure 75).

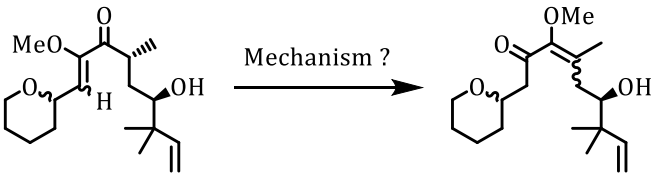


(±)-V.44 **III.81** **(±)-V.56**

*Figure 75 - Synthesis of enone **V.56***

The success of this task will be important as, if the intermediate **V.56** proved to be unstable, the order of the coupling between the different fragments need to be modified.

During the course of our investigation, we observed the unexpected formation of the enone **V.53**. An interesting feature to this product is the suspected migration of a methyl group. This process could occur through an intermolecular or intramolecular process. The study of this mechanism could be interesting and would also allow the study of the features that are required for this migration to occur (Figure 76).



(±)-V.54 **(±)-V.53**

*Figure 76 - Study of the mechanism of formation of **V.53***

Chapter VI

Conclusions and perspectives

VI.1 Conclusions

The work presented in this thesis was centred on the total synthesis of Polycavernoside A **I.1**, a secondary metabolite isolated from the marine algae *Polycavernosa tsudai*. For this purpose, the natural compound was disconnected into 4 fragments and our work focused on the preparation of the Northern fragment **I.153** and Southern fragment **III.1** and their assembly through the development of a coupling methodology (Figure 77).

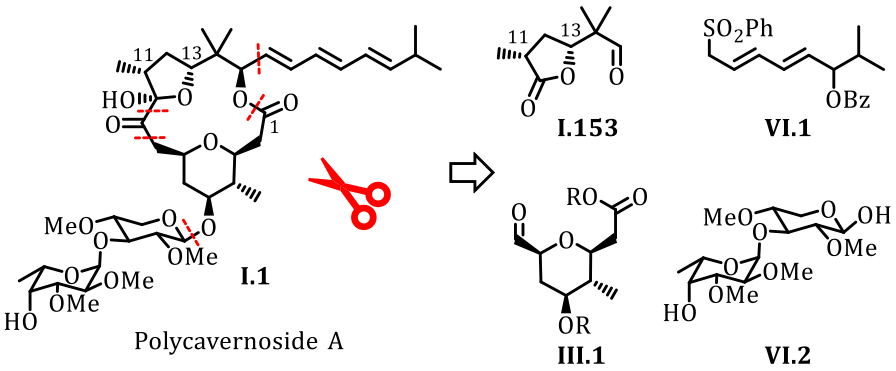


Figure 77 - Disconnection of Polycavernoside A

VI.1.1 Synthesis of the Northern fragment

Our strategy for the synthesis of the Northern fragment relied on the observation that the chirality at C_{11} could be controlled by the chiral centre located at C_{13} (Figure 72). Therefore, we developed two synthetic routes that successfully afforded the Northern fragment in the form of lactones **II.49** and **I.156**.

The first route started from propane-1,3-diol **I.24**. In this approach, a methallylation of aldehyde **II.45** afforded homoallylic alcohol **II.46** which could be transformed into lactone **II.49** in 3 steps (Figure 78).

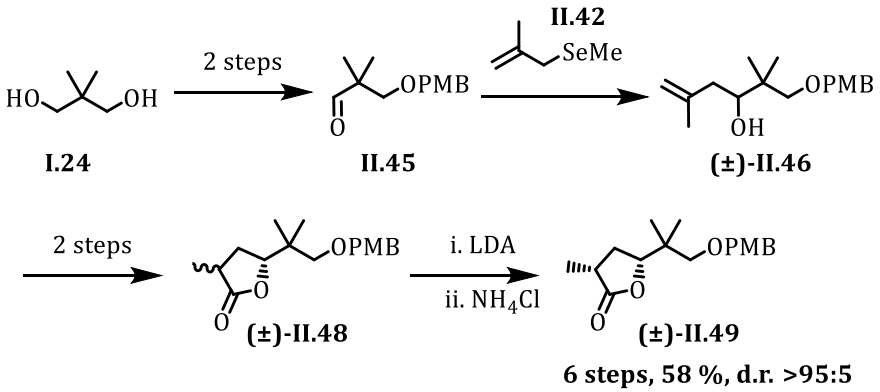


Figure 78 – Racemic synthesis of the Northern fragment II.49

The second route started with a Claisen-Johnson rearrangement with allylic alcohol **II.61** and through the allylation of aldehyde **II.63** afforded the alcohol **II.66** (Figure 79). This intermediate could be transformed into the Northern fragment **I.156** in 2 steps.

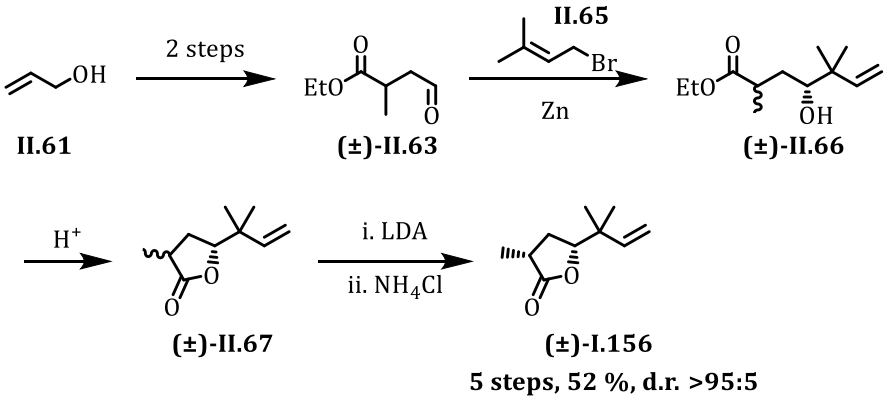
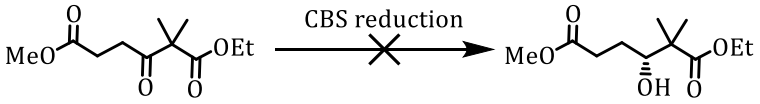


*Figure 79 – Racemic synthesis of the Northern fragment **I.156***

These two methods allowed to reach the synthesis of the Northern fragment but unfortunately, our attempts to prepare these key fragments in an enantioenriched manner using these strategies failed. The Keck asymmetric methallylation and the selenium based asymmetric prenylation did not afford the desired products.

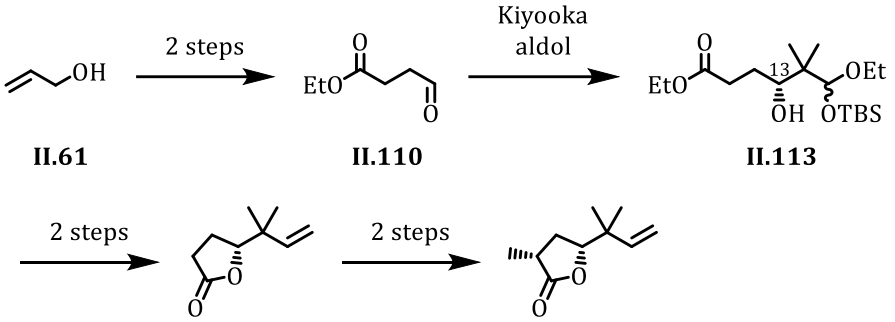
To overcome this issue, we decided to rely on an asymmetric reduction of ketone **II.87** but were not able to find suitable conditions for this transformation (Figure 80).



II.87 **II.99**

*Figure 80 - Attempts to the asymmetric reduction of **II.87***

At last, the chiral centre at C_{13} could be controlled using Kiyooka's asymmetric aldol reaction with aldehyde **II.110** (Figure 81). With mixed ketal **II.113**, the synthesis of the Northern fragment **I.156** could be achieved in 4 steps.



II.61 **II.110** **II.113**

I.158 **I.156**

7 steps, 48 %, d.r. >95:5
84 % *e.e.*

*Figure 81 - Enantioselective synthesis of lactone **I.156***

VI.1.2 Synthesis of the Southern fragment

For the assembly of the tetrahydropyran **III.1**, we relied on methodologies developed previously in the group which are the diastereoselective ene reaction and the ISMS and IMSC reactions. We started from commercially available hexose **III.30** that was transformed into aldehyde **III.28** in two steps (Figure 82). The application of this novel substrate under the ene reaction conditions led to homoallylic alcohol **III.54**. Using the ISMS conditions, tetrahydropyran **III.69** could be formed.

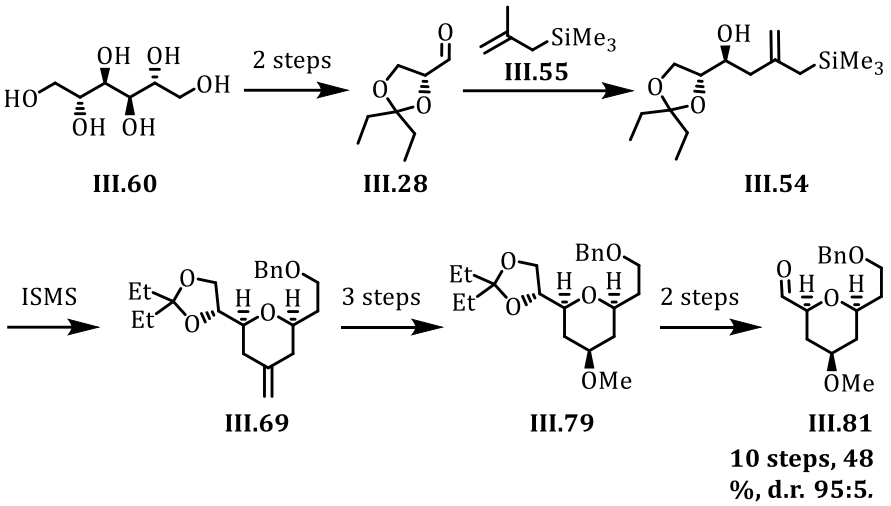


Figure 82 - Synthesis of tetrahydropyran III.81 using the ene-ISMS sequence

The functionalisation of the exocyclic double bond of **III.69** led to protected alcohol **III.79** in 3 steps and this intermediate was further modified to reach aldehyde **III.81** as model of the Southern fragment of Polycavernoside A.

VI.1.3 Coupling of the Northern and Southern fragments

Our methodology for the coupling of the Northern and Southern fragments of Polycavernoside A was based on the Horner-Wadsworth-Emmons reaction. The fragments of our disconnection were designed with the plan to use the C_9 as linker for these two fragments. We developed a coupling methodology using methyl phosphonate **IV.22** as linker together with lactone **IV.2** and aldehyde **IV.42** as models for the Northern and Southern fragments respectively. This methodology allowed the isolation of the coupling product **IV.44** (Figure 83).

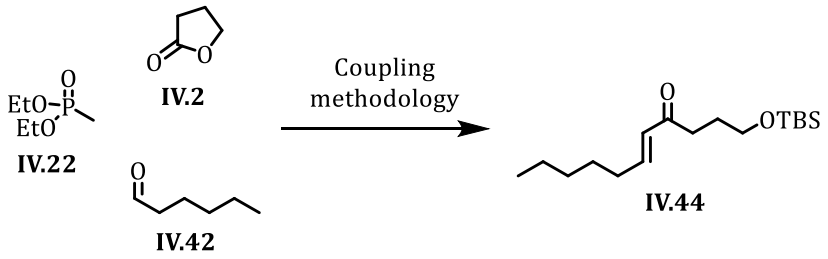


Figure 83 - Development of the coupling methodology

However, when fragments **I.156** and **III.81** were used, we could not observe the formation of any coupling product **IV.46** or equivalents and we proposed that this failure was due to the formation of intermediate **IV.55** that was too stable to react with aldehyde **III.81** (Figure 84).

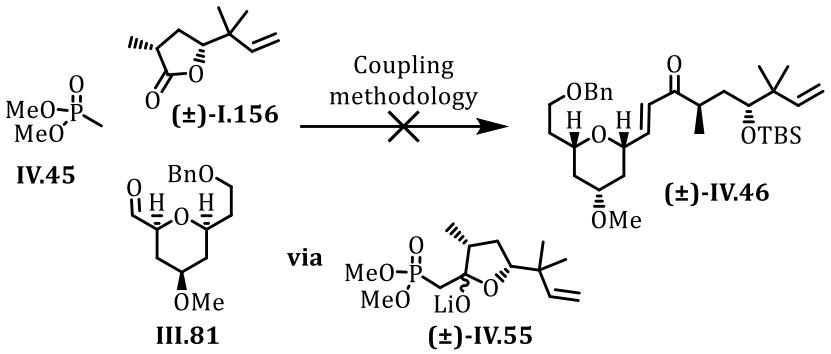


Figure 84 - Attempts to the coupling of Northern and Southern fragments

We therefore developed a strategy that would not involve the formation of intermediate **IV.55** and using phosphonate **V.23** and **V.41**, we were able to connect the Northern fragment with the model aldehyde **V.25** by the formation of olefin **V.26** and enol ether **V.42** and **V.43** (Figure 85). The formation of product **V.42** and **V.43** was interesting as the hydrolysis of the enol ether would generate an intermediate where the oxidation state would be identical to the one found in the natural product.

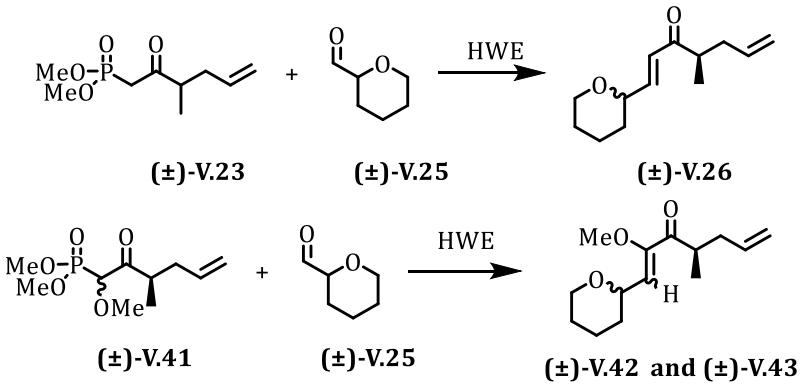
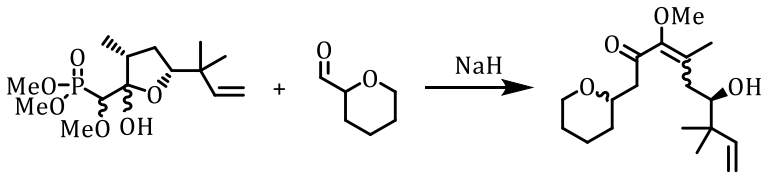


Figure 85 - Coupling reactions based on the HWE olefination

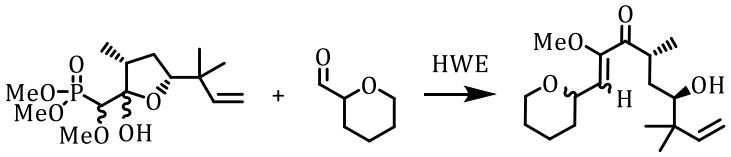
The use of α-alkoxyphosphonate like **V.41** encouraged us to go back to our initial strategy and we observed that intermediate **V.44** reacted with aldehyde **V.25** leading to the formation of enone **V.53** (Figure 86).



(±)-V.44 **(±)-V.25** **(±)-V.53**

*Figure 86 - Formation of enone **V.53***

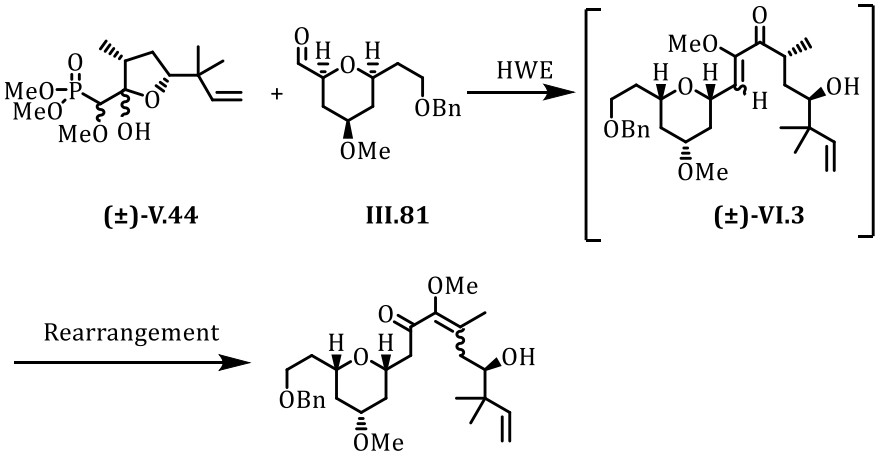
While the formation of enone **V.53** was unexpected, we found that after the modification of the reaction conditions, we could observe from the ^{1}H NMR of the crude reaction signals that could correspond to the enone **V.54** (Figure 87). However, we could not find suitable conditions to carry out its purification.



(±)-V.44 **(±)-V.25** **(±)-V.54**

*Figure 87 - Formation of the coupling product **V.54***

Using the initial conditions that were developed to carry out the coupling between the Northern and Southern fragments, we could isolate the enone **V.55** that we suggest arises from a rearrangement of the desired enol ether **VI.3** (Figure 88).



(±)-V.44 **III.81** **(±)-VI.3**

(±)-V.55

*Figure 88 - Formation of enone **V.55***

VI.2 Perspectives

VI.2.1 Synthesis of the Southern fragment

From the results obtained at the end of this thesis, some synthetic efforts should be dedicated to the synthesis of the Southern fragment. The method we have developed allowed us to efficiently reach the compound **III.81**. This is encouraging as it shows that the ene-ISMS sequence could allow access to tetrahydropyran **VI.5** (Figure 89). The synthesis of homoallylic alcohol **III.48** using the ene reaction should be optimised and upon treatment in the ISMS conditions should lead to tetrahydropyran **VI.4** and later to the Southern fragment **VI.5**.

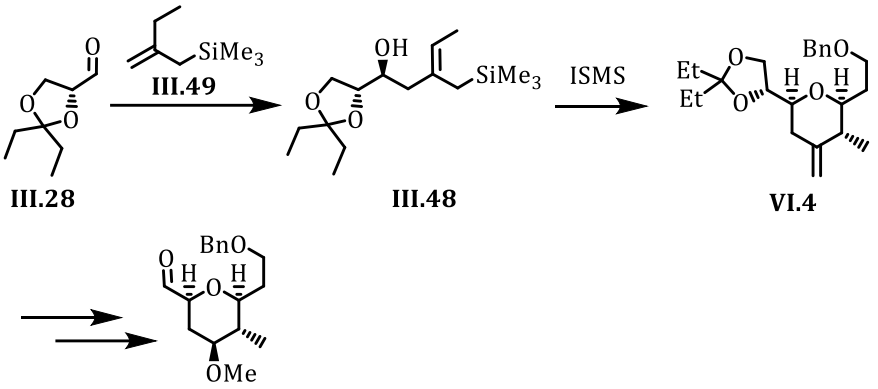


Figure 89 - Synthesis of Southern fragment using the ene-ISMS sequence

VI.2.2 Towards the synthesis of Polycavernoside A aglycone

With an efficient synthesis of the Southern fragment **VI.5**, the study of its coupling with lactol **V.44** should be carried out in order to prepare enone **VI.3** (Figure 90).

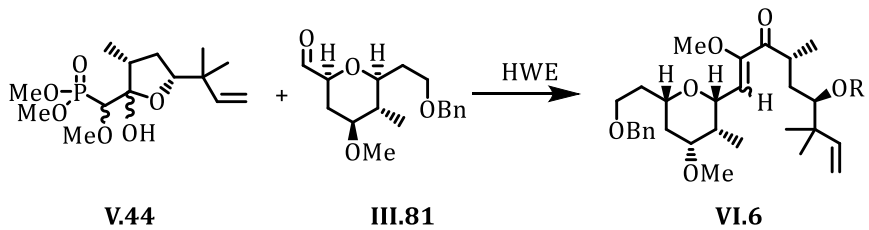
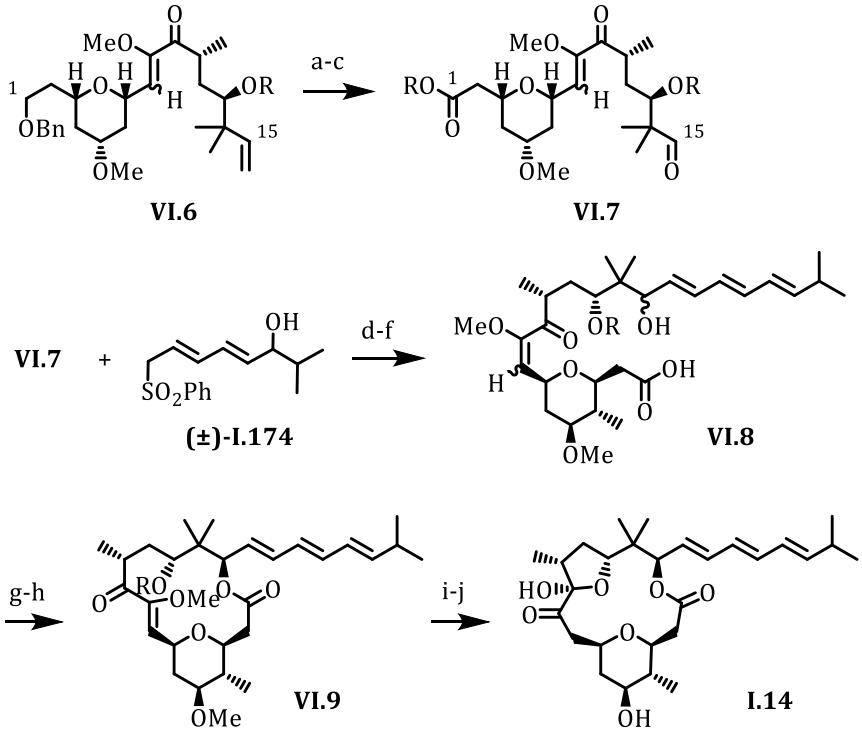


*Figure 90 - Preparation of enone **VI.3***

This intermediate will be crucial as the study of its stability will determine the order of the fragment assembly. If the enone **VI.6** is stable enough, the connection of the polyene fragment could then be carried out

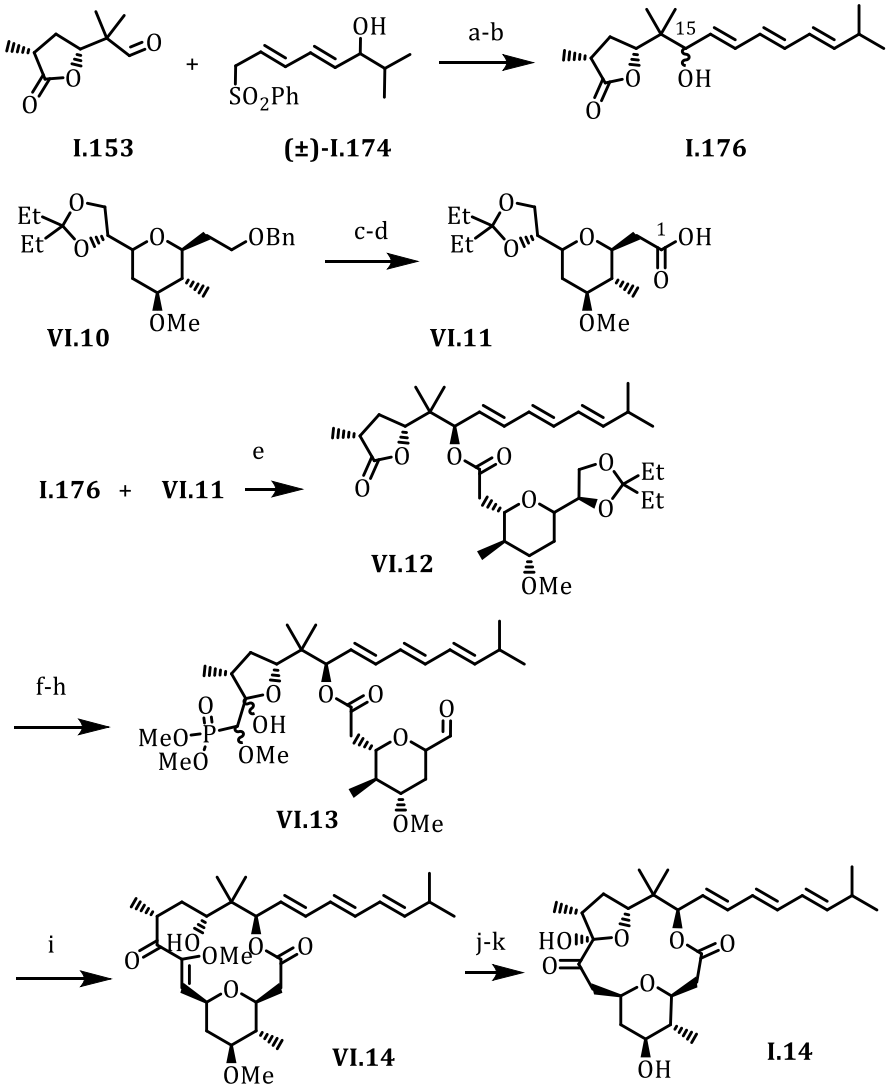


a) DDQ; b) Pinnick oxidation; c) OsO_4, $NaIO_4$; d) *n*BuLi then BzCl; e) SmI_2; f) Saponification; g) Separation of the diastereoisomers h) Mitsunobu or Yamaguchi lactonization; i) Acidic hydrolysis; j) Deprotection.

Figure 91 - Preparation of Polycavernoside A aglycone

The functionalisation of C_1 and C_{15} would lead to intermediate **VI.7**, a precursor to the coupling with the polyene fragment **I.174** (Figure 91). Using the conditions developed previously in our group, the allylic alcohol **VI.8** should be obtained as a mixture of diastereoisomers. The separation of these isomers followed by the either Yamaguchi or Mitsunobu lactonisation should afford macrolactone **VI.9**. Subsequent hydrolysis of the enol ether in **VI.9** and deprotection of the alcohol at C_{13} should afford Polycavernoside A aglycone **I.14**.

If the enone **VI.6** obtained from the coupling is too sensitive, the coupling between the different fragments should be carried out starting with the formation of the ester bond between the C_1 and C_{15}. The polyene fragment **I.174** would therefore be connected the Northern fragment **I.153** as reported previously in our group leading to alcohol **I.176** (Figure 92).



a) *n*BuLi then BzCl; b) SmI_2; c) DDQ; d) Pinnick oxidation; e) Separation of diastereosiomers then Yamaguchi or Mitsunobu lactonisation; f) $(MeO)_2P(O)CH_2OMe$, LDA; g) TsOH; h) $NaIO_4$; i) NaH; j) Acidic hydrolysis; k) BBr_3.

Figure 92 - Alternative approach to Polycavernoside A aglycone

The cleavage of the benzyl protecting group in **VI.10** followed by the oxidation of the alcohol to the corresponding acid should afford compound **VI.11**. This intermediate would then be coupled with the alcohol **I.176** using either Mitsunobu or Yamaguchi lactonisation, depending on the diastereoisomer of **I.176.** Then the insertion of the phosphonate onto the lactone of **VI.12** followed by unveiling the aldehyde of the Southern fragment should give intermediate

VI.13. Under the coupling conditions, the formation of the enol ether **VI.14** should occur and deliver the aglycone of Polycavernoside A **I.14** after hydrolysis and deprotection of the methyl ether.

Chapter VII

Experimental section

VII.1 Instrumentation and chemicals

All reactions were carried out under an atmosphere of dry argon in flame dried glassware. Dry solvents were obtained by standard procedures according to D. D. Perrin and D.R. Perrin, Purification of Laboratory Chemicals.

All products obtained from Sigma-Aldrich, Acros, Fluka Chemical Company, Fluorochem or TCI are used without further purification unless otherwise stated.

Analytical thin layer chromatography (TLC) were performed using 250 μm Silica Gel (Merck GF-UV_{254}). Visualisation was performed by UV lamp and KMnO4 or vanillin staining.

Flash column chromatography was performed using 230-400 Mesh Silica Gel 60 from Merck.

Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded using Brucker Avance II (300 MHz) spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) downfield relative to tetramethylsilane (TMS, 0.00 ppm) or CDCl3 (7.26 ppm) unless stated otherwise. Coupling constants (J) are reported in Hertz (Hz). Multiplicities are reported using the following abbreviations: s: singlet; d: doublet; t: triplet; q: quartet; m: multiplet.

Carbon nuclear magnetic resonance (^{13}C-NMR) spectra were recorded using Brucker Avance II spectrometers at 75 MHz. Chemical shifts are reported using $CDCl_3$ as the internal standard. If necessary, the complete assignment of the different systems is supported by COSY, HMQC and HMBC experiments.

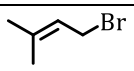
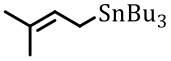
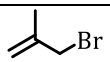
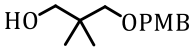
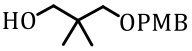
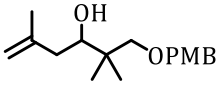
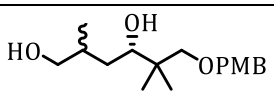
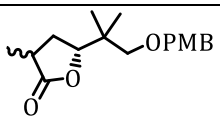
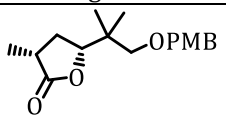
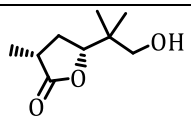
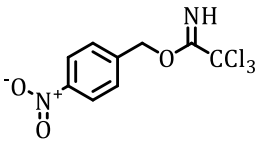
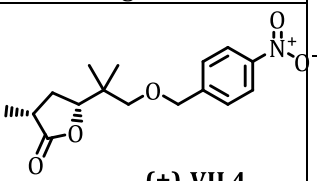
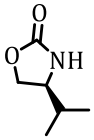
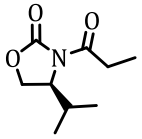
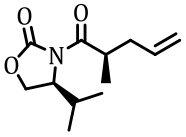
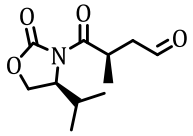
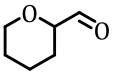
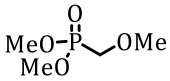
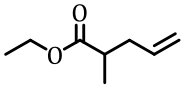
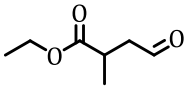
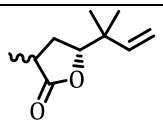
High resolution mass spectra were recorded by Raoul Rozenberg using VARIAN MATT-44, FINNIGAN MAT-TSQ 7000 and THERMOFISCHER ORBITRAP spectrometers.

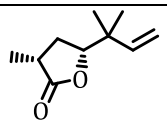
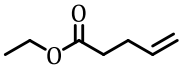
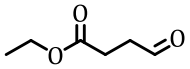
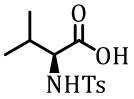
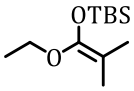
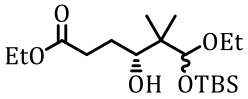
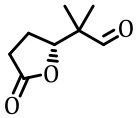
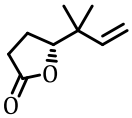
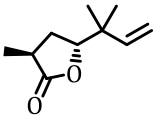
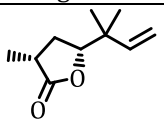
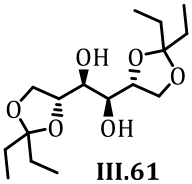
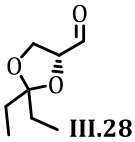
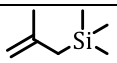
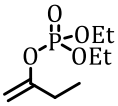
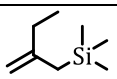
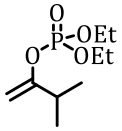
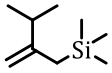
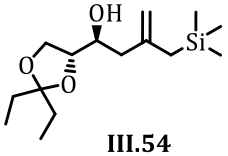
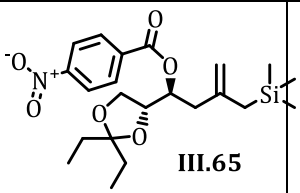
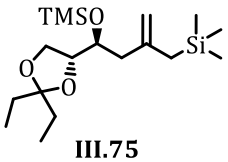
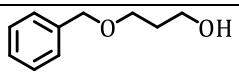
Infrared spectra were recorded by transmittance on a PerkinElmer SpectrumTwo FT-IR spectrometer and reported in wavenumber (cm−1). The samples were analysed as thin films deposited on a ZnSe ATR crystal by solvent evaporation. Signal intensities are denoted as: s = strong; m = medium; w = weak and b = broad.

All analyses are performed at U.C.L.-Louvain-la-Neuve.

VII.2 Experimental procedures

VII.2.1 List of compounds

 **II.65** Page 205	 **V.19** Page 206	 **II.51** Page 207
 **VII.1** Page 208	 **II.45** Page 209	 **(±)-II.46** Page 210
 **(±)-II.47** Page 211	 **(±)-II.48** Page 213	 **(±)-II.49** Page 214
 **VII.2** Page 215	 **VII.3** Page 216	 **(±)-VII.4** Page 217
 **V.13** Page 218	 **V.14** Page 219	 **V.17** Page 220
 **V.18** Page 221	 **V.25** Page 222	 **V.40** Page 223
 **(±)-II.62** Page 224	 **(±)-II.63** Page 225	 **(±)-II.67** Page 226

 **(±)-I.156** Page 227	 **II.109** Page 228	 **II.110** Page 229
 **II.112** Page 230	 **II.103** Page 231	 **II.113** Page 232
 **II.114** Page 233	 **I.158** Page 234	 **II.118** Page 235
 **I.156** Page 236	 **III.61** Page 237	 **III.28** Page 238
 **III.55** Page 239	 **III.57** Page 240	 **III.49** Page 241
 **III.59** Page 242	 **III.52** Page 243	 **III.54** Page 244
 **III.65** Page 245	 **III.75** Page 247	 **III.67** Page 248

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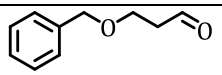
<td> 
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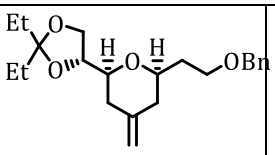
<td> 
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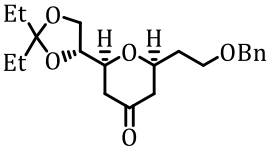
<td> 
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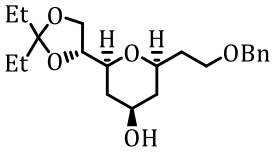
<td> 
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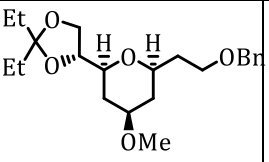
<td> 
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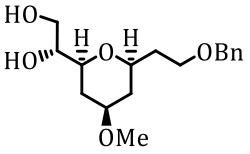
<td> 
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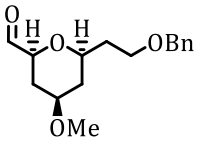
<td> 
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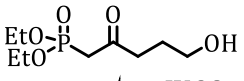
<td> 
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 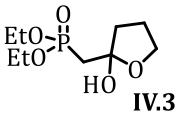
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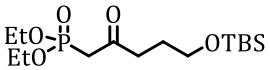
<td> 
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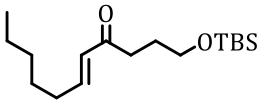
<td> 
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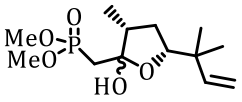
<td> 
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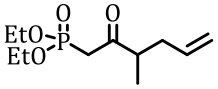
<td> 
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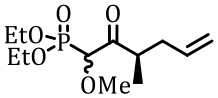
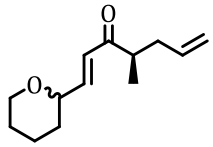
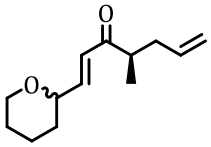
<td> 
(±)-V.41
Page 261</td>
<td> 
(±)-V.26
Page 262</td>
<td> 
(±)-V.42 and (±)-V.43
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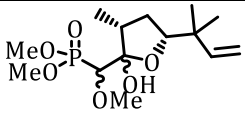
<td> 
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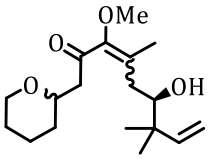
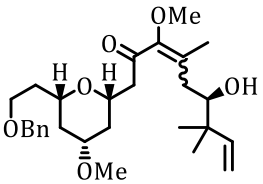
<td> 
(±)-V.53
Page 271</td>
<td> 
(±)-V.55
Page 279</td>
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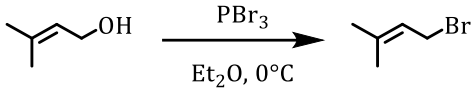
</table>

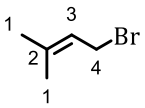
VII.2.2 Experimental descriptions

1-bromo-3-methylbut-2-ene **II.65**



Prenyl alcohol (1eq., 40 mL, 400 mmol) was dissolved in Et_2O (800 mL) and the solution was cooled down to 0°C with an ice bath. PBr_3 (0.5 eq., 30mL, 200 mmol) was then added and the reaction mixture was stirred for 30 minutes. The reaction was then cautiously quenched with saturated NaCl (300 mL). The solvents were separated and the aqueous phase was washed with Et_2O (300 mL). The combined organic layers were dried with Na_2SO_4 and the solvent were removed under reduced pressure affording 56 g (yield: 93 %) of prenyl bromide as a colourless oil which was used without further purification.

Analysis:



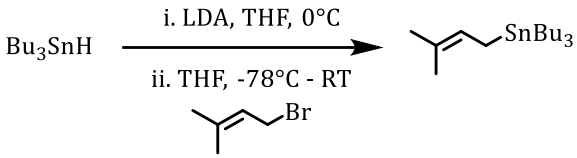
Chemical Formula: C_5H_9Br
Molecular Weight: 149,03

^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.52 (dddt, *J* = 8.5, 7.1, 2.9, 1.5 Hz, 1H, H3), 4.01 (d, *J* = 8.4 Hz, 2H, H4), 1.79 – 1.76 (m, 3H, H1), 1.73 (d, *J* = 1.4 Hz, 3H, H1).

Experimental data were in agreement with the literature[93].

[93]V. J. Davisson, A. B. Woodside, T. R. Neal, K. E. Stremler, M. Muehlbacher, C. D. Poulter, *J. Org. Chem.*, **1986**, *51* , 4768–4779.

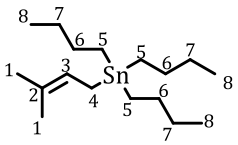
tributyl(3-methylbut-2-en-1-yl)stannane **V.19**



IPr_2NH (1.1 eq., 6.08 mL, 43.86 mmol) was added dropwise to a solution of *n*BuLi (1.1 eq., 17.54 mL, 2.5M in hexane, 43.86 mmol). The freshly prepared LDA was then diluted in THF (200 mL) and cooled to 0°C with an ice bath. Tributyltinstannane (1 eq., 11.65 g, 39.88 mmol) then added dropwise and the reaction was stirred for 5 minutes at 0°C. The ice bath was afterwards replace by a dry ice/acetone bath and the reaction was cooled to -78°C. Prenyl bromide (1 eq., 5.94 g, 39.88 mmol) was then added and the reaction was stirred for one hour during which the reaction was left to warm to room temperature. The reaction mixture was then quenched with NH_4Cl and diluted with Et_2O. The phases were separated and the aqueous phase was washed once with Et_2O. The organic phases were combined and dried over Na_2SO_4. The solvent were removed under reduced pressure. The prenyl tributyl stannane was purified by silica gel chromatography using petroleum ether as eluant affording the desired product in 74% yield as a colourless oil.

Analysis:

CAS : 104108-29-4



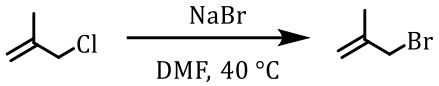
Chemical Formula: $C_{17}H_{36}Sn$
Molecular Weight: 359,19

^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.39 – 5.22 (m, 1H), 1.77 – 1.43 (m, 8H), 1.37 – 1.17 (m, 18H), 1.00 – 0.76 (m, 9H).

Experimental data were in agreement with the literature[94].

[94] I. Suzuki, K. Kiyokawa, M. Yasuda, A. Baba, *Org. Lett.*, **2013**, *15* , 1728–1731.

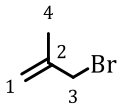
3-bromo-2-methylprop-1-ene **II.51**



A solution of methallyl chloride (1eq., 9.78 mL, 100 mmol) and sodium bromide (1 eq., 10.28 g, 100 mmol) in DMF (17 mL) was heated at 40°C. The reaction was monitored by ^{1}H NMR until complete conversion of the methallyl chloride. The precipitate was then filtered, and the reaction mixture was diluted with Et_2O, washed twice with 10% $CuSO_4$ and with water. The organic phase was dried over Na_2SO_4 and the solvent were removed under reduced pressure. The corresponding bromide was obtained in quantitative yield as a colourless oil without further purification.

Analysis:

CAS : 1458-98-6



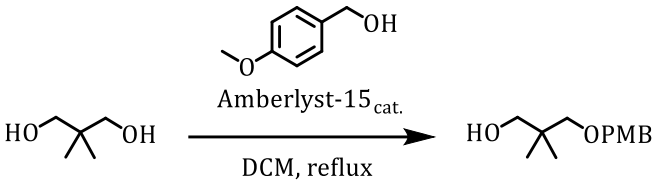
Chemical Formula: C_4H_7Br
Molecular Weight: 135,00

^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.12 (dq, *J* = 1.6, 0.9 Hz, 1H, H1), 4.95 (p, *J* = 1.5 Hz, 1H, H1), 3.95 (d, *J* = 0.8 Hz, 2H, H3), 1.88 (dd, *J* = 1.5, 0.9 Hz, 3H, H4).

Experimental data were in agreement with the literature[95].

[95] U.-P. Apfel, C. R. Kowol, F. Kloss, H. Görls, B. K. Keppler, W. Weigand, *J. Organomet. Chem*, **2011**, 1084-1088.

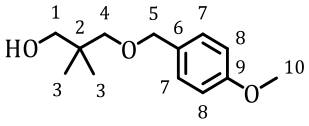
3-((4-methoxybenzyl)oxy)-2,2-dimethylpropan-1-ol **VII.1**



2.2-dimethyl-1.3-propanediol (4 eq., 83.31 g, 800 mmol), anisyl alcohol (1 eq., 24.82 mL, 200 mmol) and Amberlyst-15 (2g) were dissolved in DCM (1000 mL). The solution was heated to reflux and the conversion was monitored by ^{1}H NMR. After complete conversion of the anisyl alcohol which took about 48 hours, the reaction was cooled down to 0°C leading to the precipitation of the excess of 2.2-dimethyl-1.3-propanediol. The reaction was filtered and the solid was washed with a small amount of cold DCM. The organic phase was then washed twice with water and dried over Na_2SO_4. The solvent were then removed under reduced pressure leading to the desired protected alcohol in 92 % yield as a colourless oil.

Analysis:

CAS : 446264-36-4



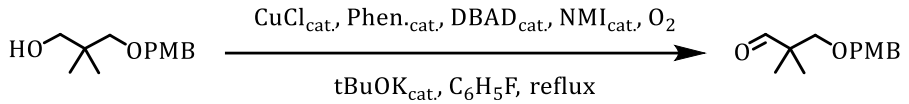
Chemical Formula: $C_{13}H_{20}O_3$
Molecular Weight: 224,30

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.26 – 7.22 (m, 2H, H7), 6.91 – 6.85 (m, 2H, H8), 4.44 (s, 2H, H5), 3.81 (s, 3H, H10), 3.44 (s, 2H, H1), 3.29 (s, 2H, H4), 2.54 (s, 1H, OH), 0.92 (s, 6H, H3).

Experimental data were in agreement with the literature[96].

[96]P. Lu, A. Mailyan, Z. Gu, D. M. Guptill, H. Wang, H. M. L. Davies, A. Zakarian, *J. Am. Chem. Soc.*, **2014**, *136* , 17738–17749.

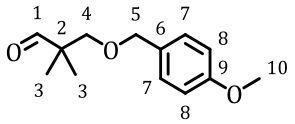
3-((4-methoxybenzyl)oxy)-2,2-dimethylpropanal **II.45**



Phenanthroline (0.05 eq., 200 mg, 1.11 mmol) was dissolved in C_6H_5F (220 mL). CuCl (0.05 eq., 109 mg, 1.11 mmol) was added and the solution was stirred for 5 minutes. Alcohol (1 eq., 5 g, 22.30 mmol) was then added followed by *t*BuOK (0.05 eq., 124 mg, 1.11 mmol) and the reaction was stirred for 10 minutes. N-methylimidazole (0.07 eq., 0.124 mL, 1.56 mmol) and DBAD (0.05eq., 255 mg, 1.11 mmol) were then added. O_2 was then bubbled in the solution using a balloon and the reaction mixture was heated to reflux. After complete conversion by TLC, the solution was cooled to room temperature and celigel was added (5g). The mixture was then filtered and the precipitate was washed with Et_2O. The solvents were then removed in vacuo. The aldehyde was obtained as a colourless oil in quantitative yield and used without further purification.

Analysis:

CAS: 92156-87-1



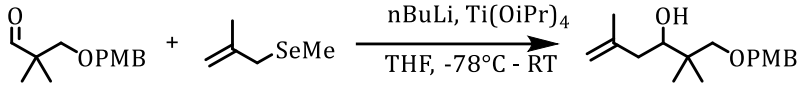
Chemical Formula: $C_{13}H_{18}O_3$
Molecular Weight: 222,28

^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.55 (s, 1H, H1), 7.26 – 7.19 (m, 2H, H7), 6.93 – 6.84 (m, 2H, H8), 4.44 (s, 2H, H5), 3.81 (s, 3H, H10), 3.42 (s, 2H, H4), 1.08 (s, 6H, H3).

Experimental data were in agreement with the literature[97].

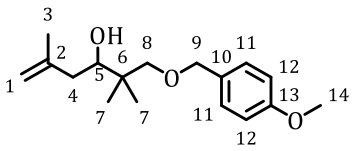
[97] I. Paterson, M. E. Di Francesco, T. Kühn, *Org. Lett.*, **2003**, *5* (4), 599–602.

1-((4-methoxybenzyl)oxy)-2,2,5-trimethylhex-5-en-3-ol **II.46**



Methallyl methyl selenide (1.2 eq., 805.1 mg, 5.4 mmol) was dissolved in THF (30 mL) and the solution was cooled down to -78°C with a dry ice/acetone bath. *n*BuLi (1.2 eq., 2.35 mL, 2.3M in hexane, 5.4 mmol) was added dropwise leading to a dark yellow solution. Titanium isopropoxide (1.3 eq., 1.726 mL, 5.85 mmol) was added at once and the solution was stirred for 5 minutes. Aldehyde (1 eq., 1 g, 4.50 mmol) was added dropwise and the solution was left to warm to room temperature and stirred for one hour. The reaction mixture was diluted with Et_2O and quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted twice with ether and the combined organic layers were washed with saturated $NaHCO_3$ and dried over Na_2SO_4 and the solvent were removed under reduced pressure. Purification on silica gel chromatography using ethyl acetate/petroleum ether 1/20 to 1/10 as eluent afforded 1.151g of homoallylic alcohol in 91% yield as a yellowish oil.

Analysis:



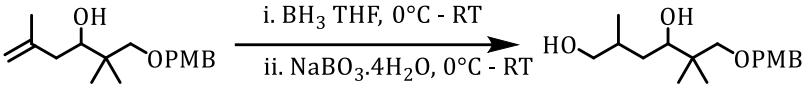
Chemical Formula: $C_{17}H_{26}O_3$
Molecular Weight: 278,39

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 – 7.20 (m, 2H, H11), 6.87 (d, *J* = 8.4 Hz, 2H, H12), 4.85 (s, 1H, H1), 4.79 (s, 1H, H1), 4.45 (s, 2H, H9), 3.80 (s, 3H, H14), 3.62 (dd, *J* = 10.6, 2.3 Hz, 1H, H5), 3.35 (d, *J* = 8.8 Hz, 1H, H8), 3.26 (d, *J* = 8.8 Hz, 1H, H8), 2.17 (d, *J* = 13.3 Hz, 1H, H4), 2.04 (dd, *J* = 9.3, 4.4 Hz, 1H, H4), 1.77 (s, 1H, H3), 0.92 (s, 3H, H7), 0.91 (s, 3H, H7). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.29 (C13), 143.97 (C2), 130.35 (C10), 129.27 (C11), 113.89 (C12), 112.77 (C1), 79.03 (C8), 75.04 (C5), 73.31 (C9), 55.41 (C14), 40.46 (C4), 38.46 (C6), 22.61 (C7), 22.49 (C3), 19.89 (C7).

IR (ν) : 3497 (b), 2954 (b), 1514 (s), 1248 (s), 1089 (s), 1036 (m).

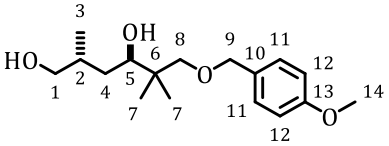
HRMS (ESI): Calculated for $C_{17}H_{27}O_3$ 279.19547; Found 279.19555.

1-((4-methoxybenzyl)oxy)-2,2,5-trimethylhex-5-en-3-ol **II.47**



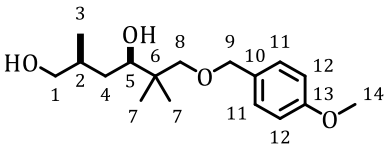
A solution of homoallylic alcohol (1 eq., 200 mg, 0.718 mmol) in THF (8 mL) was cooled to 0°C with an ice bath. BH_3 (3.5 eq., 2.51 mL, 1M in THF, 2.51 mmol) was added dropwise and the reaction was warmed to room temperature and the conversion was checked by TLC. Once complete conversion of the starting alkene was observed, the reaction mixture was cooled to 0°C and $NaBO_3.4H_2O$ (10 eq., 1.104 g, 7.18 mmol) and water (2 mL) was added portionwise and cautiously and the reaction was left to stir at room temperature overnight. The reaction was diluted with ether and the aqueous phase was extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4 and the solvents were removed under reduced pressure. Purification of the diol was performed using silica gel chromatography with EtOAc/PE 1/4 to 1/2 as eluent affording 120 mg of the diol (yield : 56%). Diol is present as a separable mixture of diastereoisomers in a 3.5:1 trans/cis ratio.

Analysis:



Chemical Formula: $C_{17}H_{28}O_4$
Molecular Weight: 296,41

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.7 Hz, 2H, H11), 6.88 (d, *J* = 8.7 Hz, 2H, H12), 4.47 (d, *J* = 11.7 Hz, 1H, H9), 4.41 (d, *J* = 11.6 Hz, 1H, H9), 3.81 (s, 3H, H14), 3.62 (dd, *J* = 7.0, 5.3 Hz, 1H, H5), 3.57 – 3.49 (m, 2H, H1), 3.35 (d, *J* = 8.9 Hz, 1H, H8), 3.29 (d, *J* = 8.9 Hz, 1H, H8), 2.09 – 1.88 (m, 1H, H2), 1.50 – 1.40 (m, 2H, H4), 0.94 (d, *J* = 7.0 Hz, 3H, H3), 0.90 (s, 3H, H7), 0.86 (s, 3H, H7). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.46 513), 129.77 (C10), 129.41 (C11), 114.01 (C12), 80.18 (C8), 75.61 (C5), 73.48 (C9), 67.35 (C1), 55.43 (C14), 38.22 (C6), 35.64 (C4), 32.75 (C2), 23.06 (C7), 19.46 (C7), 17.10 (C3).



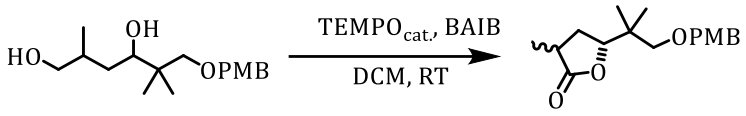
Chemical Formula: $C_{17}H_{28}O_4$
Molecular Weight: 296,41

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.6 Hz, 2H, H11), 6.88 (d, *J* = 8.6 Hz, 2H, H12), 4.47 (d, *J* = 11.6 Hz, 1H, H9), 4.41 (d, *J* = 11.7 Hz, 1H, H9), 3.81 (s, 3H, H14),

3.61 – 3.50 (m, 2H, H5 and H1), 3.44 – 3.26 (m, 3H, H1 and H8), 1.88 – 1.73 (m, 1H, H2), 1.45 (ddd, *J* = 14.2, 5.2, 1.5 Hz, 1H, H4), 1.28 (ddd, *J* = 14.2, 10.2, 7.8 Hz, 1H, H4), 0.94 – 0.83 (m, 9H, H7 and H3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.49 (C13), 129.69 (C10), 129.43 (C11), 114.03 (C12), 80.06 (C8), 78.77 (C5), 73.47 (C9), 69.20 (C1), 55.43 (C14), 38.27 (C6), 37.84 (C2), 35.47 (C4), 23.28 (C7), 19.57 (C7), 18.62 (C3).

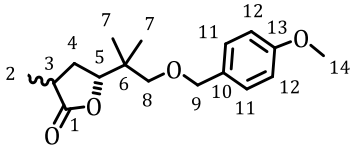
HRMS (ESI): Calculated for $C_{17}H_{27}O_4$ 295.19039; Found 295.19026. Calculated for $C_{17}H_{28}O_4Na$ 319.18798; Found 319.18795.

5-(1-((4-methoxybenzyl)oxy)-2-methylpropan-2-yl)-3-methyldihydrofuran-2(3H)-one **II.48**



Diol (1 eq., 1 g, 3.6 mmol) was dissolved in DCM (40 mL) at room temperature. TEMPO (0.3 eq., 168 mg, 1.08 mmol) and then BAIB (3 eq., 2.55 g, 7.92 mmol) were added and the reaction was stirred until complete conversion of the diol was observed on TLC. The reaction was then quenched with a saturated solution of NH_4Cl. The layers were separated and the aqueous phase was extracted twice with DCM. The combined organic layers were dried over Na_2SO_4 and the solvents were removed under reduced pressure. The lactone was obtained after purification using silica gel chromatography using AcOEt/PE 1:10 to 1/5 in 92 % yield as a colourless oil containing a mixture of diastereoisomers.

Analysis:

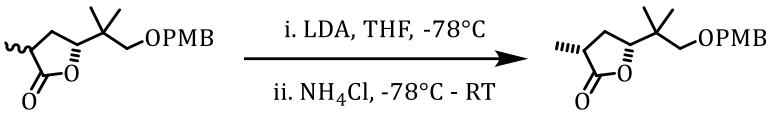


Chemical Formula: $C_{17}H_{24}O_4$
Molecular Weight: 292,38

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.32 – 7.17 (m, 2H, H11), 6.88 (d, *J* = 8.6 Hz, 2H, H12), 4.58 – 4.47 (m, 1H, H5), 4.47 – 4.36 (m, 2H, H9), 3.81 (m, 3H, H14), 3.31 (dd, *J* = 9.0, 5.0 Hz, 1H, H8), 3.21 (dd, *J* = 9.0, 3.5 Hz, 1H, H8), 2.74 – 2.56 (m, 1H, H3), 2.36 – 2.18 (m, 1H, H4), 1.91 – 1.54 (m, 1H, H4), 1.27 (m, 3H, H2), 1.03 – 0.85 (m, 6H, H7).^{13}C NMR (75 MHz, $CDCl_3$) δ 180.69 (C1), 159.25 (C13), 130.66(C10), 129.21 (C11), 113.87 (C12), 82.28 (C5 major), 82.02 (C5 minor), 73.17(C9), 55.41 (C14), 38.34(C6), 37.52 (C6), 36.18 (C3), 35.07 (C3), 31.99 (C4), 30.48 (C4), 20.51 (C7), 20.21 (C7), 19.86 (C7), 16.82 (C2), 15.09(C2).

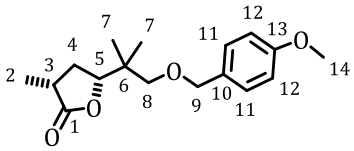
HRMS (ESI): Calculated for $C_{17}H_{24}O_4Na$ 315.15668; Found 315.15662.

5-(1-((4-methoxybenzyl)oxy)-2-methylpropan-2-yl)-3-methyldihydrofuran-2(3H)-one **II.49**



A solution of LDA was prepared by addition of iPr_2NH (1.3 eq., 0.600 mL, 4.33 mmol) to *n*BuLi (1.2 eq., 1.70 mL, 2.3M in hexane, 4.00 mmol) at room temperature followed by addition of THF (10 mL) and cooled down to -78°C with an acetone/dry ice bath. Lactone (1eq., 975 mg, 3.33 mmol) was diluted in THF (5 mL) and added dropwise to the LDA solution. The reaction was stirred for 30 minutes. A saturated solution of NH_4Cl was then added and the reaction temperature was left to rise to room temperature after removal of the acetone/dry ice bath. The reaction was then extracted three time with Et_2O. The combined organic layers were dried over Na_2SO_4 and the solvents were removed under reduced pressure. The lactone was purified via silica gel chromatography using AcOEt/PE 1:10 to 1:5 affording the lactone in 90% yield as a colourless oil.

Analysis:



Chemical Formula: $C_{17}H_{24}O_4$
Molecular Weight: 292,38

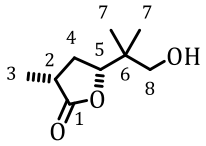
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.25 – 7.19 (m, 2H, H11), 6.93 – 6.83 (m, 2H, H12), 4.50 – 4.34 (m, 3H, H9 and H5), 3.81 (s, 3H, H14), 3.31 (d, *J* = 9.0 Hz, 1H, H8), 3.20 (d, *J* = 9.0 Hz, 1H, H8), 2.65 (ddq, *J* = 12.2, 8.5, 7.1 Hz, 1H, H3), 2.31 – 2.15 (m, 1H, H4), 1.67 (td, *J* = 12.3, 11.1 Hz, 1H, H4), 1.25 (dd, *J* = 7.1, 1.3 Hz, 3H, H2), 0.94 (s, 3H, H7), 0.90 (s, 3H, H7). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.81 (C1), 159.23 (C13), 130.65 (C10), 129.18 (C11), 113.85 (C12), 82.00 (C5), 76.27 (C8), 73.15 (C9), 55.40 (C14), 37.50 (C6), 36.16 (C3), 31.97 (C4), 20.20 (C7), 19.84 (C7), 15.08 (C2).

HRMS (ESI): Calculated for $C_{17}H_{24}O_4Na$ 315.15668; Found 315.15662.

(3R,5R)-5-(1-hydroxy-2-methylpropan-2-yl)-3-methyldihydrofuran-2(3H)-one **VII.2**

Lactone (1eq., 600 mg, 2 mmol) was diluted in DCM (10 mL) and H_2O (10 mL) in water. DDQ (1.2 eq., 544 mg, 2.4 mmol) was then added at once under vigorous stirring. The reaction was stirred for 20 minutes at room temperature and the conversion was monitored by TLC. After complete conversion of the lactone, the reaction mixture was diluted with DCM (100 mL) and filtered over a pad of celite. The celite pad was then washed twice with a saturated solution of $NaHCO_3$ (50 mL). The layers were separated and the aqueous layer was extracted twice with DCM (50 mL). The combined organic layers were dried over Na_2SO_4 and the solvent were removed under reduced pressure. The crude reaction was purified by silica gel chromatography using EtOAc/PE 1/2 to 1/1 as eluant affording 300 mg of alcohol as a colourless oil with a yield of 87%.

Analysis:

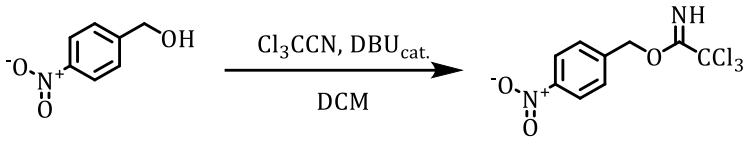


Chemical Formula: $C_9H_{16}O_3$
Molecular Weight: 172,22

^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.36 (dd, *J* = 11.1, 5.5 Hz, 1H, H5), 3.55 (d, *J* = 10.8 Hz, 1H, H8), 3.45 (d, *J* = 10.8, 1H, H8), 2.68 (ddq, *J* = 12.2, 8.6, 7.0 Hz, 1H, H2), 2.31 (ddd, *J* = 12.5, 8.6, 5.6 Hz, 1H, H4), 1.79 – 1.64 (m, 1H, H4), 1.28 (d, *J* = 7.0 Hz, 3H, H3), 0.92 (s, 3H, H7), 0.90 (s, 3H, H3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.53 (C1), 82.29 (C5), 69.80 (C8), 38.00 (C6), 35.97 (C2), 32.05 (C4), 20.02 (C7), 18.61 (C7), 15.07 (C3).

HRMS (ESI): Calculated for $C_9H_{17}O_3$: 173.11722; Found 173.11733.

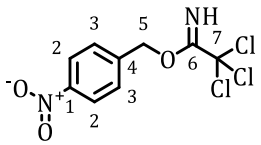
4-nitrobenzyl 2,2,2-trichloroacetimidate **VII.3**



para-Nitrobenzyl alcohol (1 eq., 3 g, 19.5 mmol) was dissolved in DCM (65 mL). DBU (0.1 eq., 2 mmol, 0.30 mL) was added and the solution was cooled down to 0°C with an ice bath. Trichloroacetonitrile ‘2 eq., 3.92 mL, 39.4 mmol) was added and the reaction was left to warm to room temperature and stirred for 18 hours. The conversion was monitored was TLC. Once complete conversion was achieved, the solvents were removed under reduced pressure. The compound was purified by silica gel chromatography using EtOAc/PE 1/8 to 1/6 as eluent affording 5.1g of the desired product as a white solid with a yield of 85%.

Analysis:

CAS: 163193-79-1



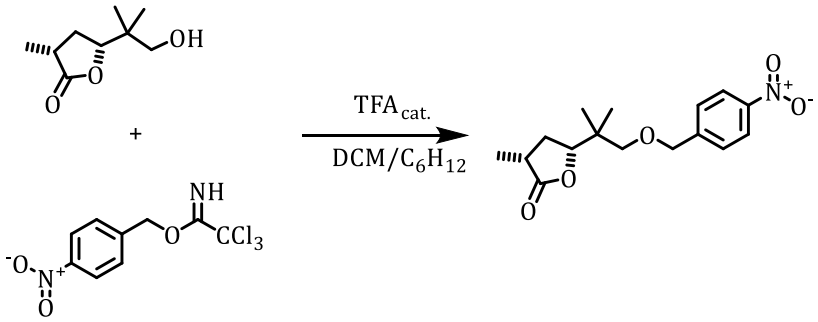
Chemical Formula: $C_9H_7Cl_3N_2O_3$
Molecular Weight: 297,52

^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.49 (s, 1H, NH), 8.35 – 8.10 (d, 2H, H2), 7.66 – 7.49 (d, 2H, H3), 5.44 (s, 2H, H5).

Experimental data are in agreement with the literature[98].

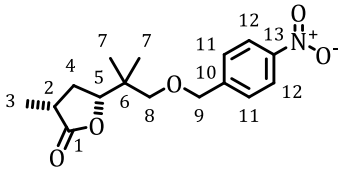
[98] A. A. Adhikari, L. Radal, J. D. Chisholm, *Synlett*, **2017**, 28(17), 2335-2339.

3-methyl-5-(2-methyl-1-((4-nitrobenzyl)oxy)propan-2-yl)dihydrofuran-2(3H)-one **VII.4**



Alcohol (1 eq., 100 mg, 0.58 mmol) and 4-nitrobenzyl 2,2,2-trichloroacetimidate (1.5 eq., 258 mg, 0.57 mmol) were dissolved in a mixture of DCM (0.5 mL) and cyclohexane (1 mL) at room temperature. One drop of triflic acid was then added and the reaction was monitored by TLC. A white precipitate formed during the course of the reaction. Once complete conversion was achieved, the reaction was evaporated to dryness. The crude material was purified by silica gel chromatography using EtOAc/PE 1/20 to 1/6 as eluent affording the protected alcohol as a white solid. The alcohol was recrystallised from a mixture of Et_2O/hexane (1:1) by slow evaporation of the solvent.

Analysis:

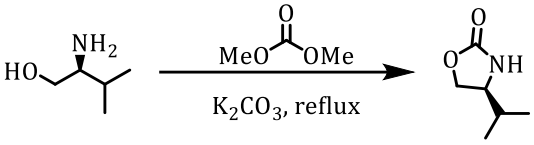


Chemical Formula: $C_{16}H_{21}NO_5$
Molecular Weight: 307,35

^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.21 (d, *J* = 8.8 Hz, 2H, H12), 7.50 – 7.42 (m, 2H, H11), 4.60 (m, 2H, H9), 4.43 (dd, *J* = 11.1, 5.6 Hz, 1H, H5), 3.44 (d, *J* = 8.8 Hz, 1H, H8), 3.30 (d, *J* = 8.9 Hz, 1H, H8), 2.84 – 2.61 (m, 1H, H2), 2.29 (ddd, *J* = 12.4, 8.6, 5.7 Hz, 1H, H4), 1.82 – 1.64 (m, 1H, H4), 1.27 (d, *J* = 7.1 Hz, 3H, H3), 0.97 (s, 3H, H7), 0.96 (s, 3H, H7).

HRMS (APCI): Calculated for C16H22O5N 308.14925; Found 308.14914.

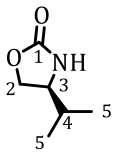
(S)-4-isopropyloxazolidin-2-one **V.13**



A mixture of L-valinol (1 eq., 25 g, 242 mmol), dimethylcarbonate (1.1 eq., 22.62 mL, 266 mmol) and K_2CO_3 (0.1 eq., 3.4 g, 24.2 mmol) was heated at 90 °C in a distillation apparatus with an oil bath. The reaction was stirred until no more MeOH could be collected by distillation. The conversion of the reaction was checked by ^{1}H NMR. The reaction mixture was cooled at room temperature and diluted with ether. The suspension of potassium carbonate was removed by filtration and the solvents were removed under reduced pressure. The oxazolidinone was purified by recrystallisation in ether affording 18.37 g of the product in 52 % yield.

Analysis:

CAS: 17016-83-0



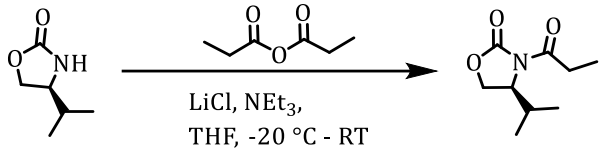
Chemical Formula: $C_6H_{11}NO_2$
Molecular Weight: 129,16

1H NMR (300 MHz, Chloroform-d) δ 4.42 (t, J = 8.7 Hz, 1H, H2), 4.07 (dd, J = 8.7, 6.3 Hz, 1H, H2), 3.59 (dt, J = 8.6, 6.7 Hz, 1H, H3), 3.44 (s, 1H, NH), 1.70 (m, 1H, H4), 0.94 (d, J = 6.7 Hz, 3H, H5), 0.87 (d, J = 6.8 Hz, 3H, H5).

Experimental data are in agreement with the literature[99]

[99]B. Su, F. Chen, Q. Wang, *J. Org. Chem.*, **2013**, *78* (6), 2775–2779.

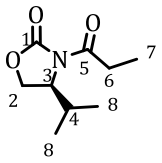
(S)-4-isopropyl-3-propionyloxazolidin-2-one **V.14**



Oxazolidinone (1 eq., 12.9 g, 100 mmol), LiCl (1.1 eq., 4.66 g, 110 mmol) and NEt_3 (1.3 eq., 18.25 mL, 130 mmol) were dissolved in THF (500 mL) and cooled down to -20°C with a dry ice/acetone bath. Propionic anhydride (1.2 eq., 15.13 mL, 120 mmol) was added dropwise. The cooling bath was then removed, and the reaction was left to stir at room temperature for 4 hours. The conversion of the oxazolidinone was checked by TLC. The solvents were then removed under reduced pressure and the reaction was diluted with EtOAc (600 mL) and quenched with 0.2M HCl (300 mL). The layers were separated and the organic layer was washed with brine (250 mL), saturated $NaHCO_3$ (250 mL) then brine (250 mL). The organic phase was dried over Na_2SO_4 and the solvent were removed under reduced pressure. The pure product was obtained after high vacuum distillation (P: $1*10^{-4}$ mbar, T: 78 °C) as a colourless oil in 92 % yield.

Analysis:

CAS: 77877-19-1



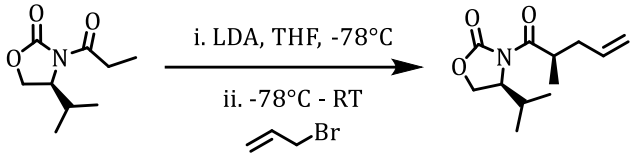
Chemical Formula: $C_9H_{15}NO_3$
Molecular Weight: 185,22

^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.43 (m, 1H, H2), 4.32 – 4.15 (m, 2H, H2 and H3), 3.09 – 2.80 (m, 2H, H6), 2.37 (m, 1H, H4), 1.16 (t, *J* = 7.4 Hz, 3H, H7), 0.91 (d, *J* = 7.0 Hz, 3H, H8), 0.87 (d, *J* = 6.9 Hz, 3H, H8).

Experimental data were in agreement with the literature[100].

[100]D. A. Evans, R. L. Dow, T. L. Shih, J. M. Takacs, R. Zahler, *J. Am. Chem. Soc.*, **1990**, *112* (13), 5290–5313.

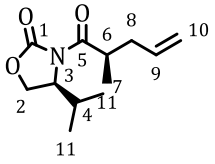
(S)-4-isopropyl-3-((R)-2-methylpent-4-enoyl)oxazolidin-2-one **V.17**



A solution of LDA was prepared by addition of iPr_2NH (1.3 eq., 16.7 mL, 120 mmol) to *n*BuLi (1.2 eq., 47.13 mL, 2.5M in hexane, 110.7 mmol) at room temperature followed by addition of THF (250 mL) and cooled down to -78°C with an acetone/dry ice bath. Oxazolidinone (1 eq., 17.1 g, 92.3 mmol) in THF (30 mL) was added dropwise at -78°C and the reaction was stirred for 30 minutes at -78°C. Allyl bromide (3 eq., 23.39 mL, 276.9 mmol) was then added and the reaction mixture was stirred for 4 hours at 0°C. The reaction mixture was diluted with DCM (500 mL) and quenched with NH_4Cl (500 mL). The layers were separated and the aqueous layer was washed three times with DCM (300 mL). The combined organic layers were dried over Na_2SO_4 and the solvents were removed in vacuo. The desired product was obtained after purification by silica gel chromatography using EtOAc/PE 1:20to 1:6 as a yellowish oil in 85% yield.

Analysis:

CAS: 79563-29-4



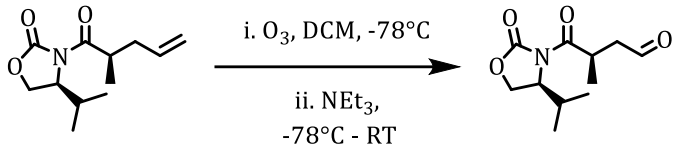
Chemical Formula: $C_{12}H_{19}NO_3$
Molecular Weight: 225,29

^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.79 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1H, H9), 5.13 – 4.94 (m, 2H, H10), 4.45 (dt, *J* = 8.1, 3.5 Hz, 1H, H3), 4.32 – 4.14 (m, 2H), 3.88 (h, *J* = 6.8 Hz, 1H), 2.50 (dtt, *J* = 13.7, 6.8, 1.4 Hz, 1H), 2.31 (ddq, *J* = 10.8, 7.0, 3.5 Hz, 1H), 2.26 – 2.12 (m, 1H,), 1.14 (dd, *J* = 6.8, 0.5 Hz, 3H, H7), 0.90 (d, *J* = 7.1 Hz, 3H, H11), 0.86 (d, *J* = 6.9 Hz, 3H, H11).

Experimental data were in agreement with the literature[101].

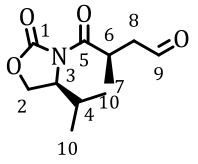
[101] E. J. Trybulski, J. Zhang, R. H. Kramss, R. M. Mangano, *J. Med. Chem.*, **1993**, *36* (23), 3533–3541.

(R)-4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)-3-methyl-4-oxobutanal
V.18



A solution of olefin (1 eq., 1 g, 4.43 mmol) in DCM (50 mL) was cooled to -78°C with an acetone/dry ice bath. Ozone was bubbled through the solution until a blue coloration appeared in the solution. Oxygen was then bubbled through the solution to remove the excess of ozone. NEt_3 (3 eq., 1.8 mL, 13.31 mmol) was then added at once and the dry ice/acetone bath was removed. The reaction mixture was stirred overnight. The solvents were evaporated under reduced pressure. The crude mixture was dissolved in DCM (50 mL) and washed twice with 1M HCl (30 mL) and then a saturated solution of NH_4Cl, dried over Na_2SO_4. The solvents were then removed under reduced pressure. The crude was purified by silica gel chromatography using EtOAc/PE 1:4 as eluent and affording aldehyde as a colourless oil (yield not determined).

Analysis

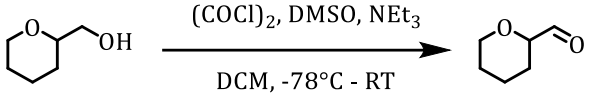


Chemical Formula: $C_{11}H_{17}NO_4$
Molecular Weight: 227,26

^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.72 (s, 1H, H9), 4.42 (dt, *J* = 8.2, 3.4 Hz, 1H, H2), 4.31 – 4.15 (m, 2H, H2, H3 and H6), 3.08 (dd, *J* = 18.5, 9.4 Hz, 1H, H8), 2.60 – 2.50 (m, 1H, H8), 2.34 (ddp, *J* = 10.7, 7.0, 3.7 Hz, 1H, H4), 1.18 (d, *J* = 7.0 Hz, 3H, H7), 0.96 (d, *J* = 6.9 Hz, 3H, H10), 0.90 (d, *J* = 7.1 Hz, 3H, H10). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 200.04 (C9), 175.91 (C5), 153.72 (C1), 63.26 (C2), 58.71 (C3), 47.92 (C6), 32.45 (C8), 28.19 (C4), 18.07 (C10), 17.08 (C10), 14.53 (C7).

HRMS (ESI): Calculated for $C_{11}H_{18}O_4N$ 228.12303; Found 228.12305

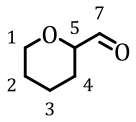
tetrahydro-2H-pyran-2-carbaldehyde **V.25**



DMSO (2 eq., 5.02 mL, 70.73 mmol) in solution in DCM (20 mL) was added dropwise to a solution of oxalyl chloride (1.3 eq., 3.94 mL, 45.97 mmol) in DCM (100 mL) cooled down at -78°C with an acetone/dry ice bath. The solution was stirred for 10 minutes before adding a solution of tetrahydropyran-2-methanol (1 eq., 4 mL, 35.36 mmol) in DCM (20 mL). The reaction mixture was stirred for 10 minutes after which triethylamine (5 eq., 24.7 mL, 176.8 mmol) was added. The reaction was stirred at -78°C for an additional hour and then left to warm to room temperature for 2 hours. The reaction was quenched by addition of a saturated solution of NH_4Cl (150 mL). The layers were separated and the aqueous layer was washed twice with 150 mL of DCM. The combined organic layers were washed three times with 1M HCl (150 mL) then $NaHCO_3$ (150 mL). The solvents were dried over Na_2SO_4 and removed under reduced pressure. Purification of aldehyde was carried out using silica gel chromatography with EtOAc/PE 1/10 to 1/5 as mobile phase. 2.22 g of aldehyde were isolated as a yellow oil with a yield of 55 %.

Analysis:

CAS: 19611-45-1



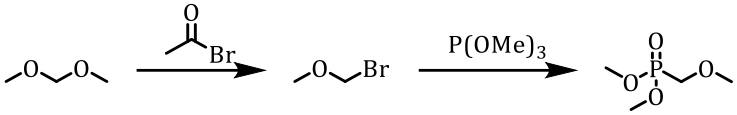
Chemical Formula: $C_6H_{10}O_2$
Molecular Weight: 114,14

^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.62 (d, *J* = 0.7 Hz, 1H), 4.18 – 3.98 (m, 1H, H1), 3.82 (dd, *J* = 10.8, 2.7 Hz, 2H, H5), 3.61 – 3.43 (m, 1H, H1), 1.99 – 1.80 (m, 2H, H4), 1.71 – 1.36 (m, 4H, H2 and H3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.05 (C7), 81.64 (C5), 68.32 (C1), 26.35 (C4), 25.65 (C2 or C3), 22.71 (C3 or C2).

Experimental data were in agreement with the literature[102].

[102] J. M. Bobbitt, A. L. Bartelson, W. F. Bailey, T. A. Hamlin, C. B. Kelly, *J. Org. Chem.*, **2014**, *79* (3), 1055–1067.

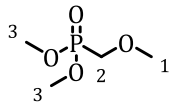
dimethyl (methoxymethyl)phosphonate **V.40**



Dimethoxymethane (1.3 eq., 23.0 mL, 260 mmol) was added to a three-neck round bottom flask equipped with a reflux condenser and an addition funnel. Acetyl bromide (1.2 eq., 18.4 mL, 240 mmol) was then carefully added dropwise using the addition funnel leading to reflux of the dimethoxymethane. After the complete addition of the acetyl bromide, the reaction was left to cool down to room temperature. Trimethylphosphite (1 eq., 23 mL, 200 mmol) was then carefully added using the addition funnel leading to reflux of the reaction mixture. After the complete addition of the trimethylphosphite, the reaction was left to cool to room temperature. The volatiles were then removed under reduced pressure. Methoxymethyl dimethylphosphonate was then purified by distillation (P: water pump T: 107-110°C) affording 21 g of a colourless oil (yield: 71 %).

Analysis:

CAS: 42029-30-1



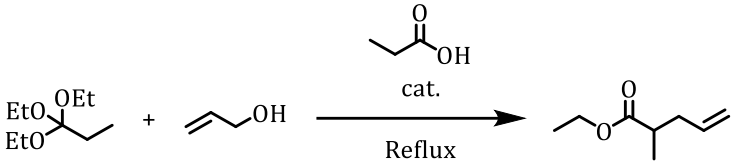
Chemical Formula: $C_4H_{11}O_4P$
Molecular Weight: 154,10

^{1}H NMR (300 MHz, Chloroform-*d*) δ 3.88 – 3.68 (m, 8H, H3 and H2), 3.46 (s, 3H, H1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 67.21 (C2), 64.99 (C1), 61.63 (C3), 61.45 (C3).

Experimental data were in agreement with the literature[103].

[103] S.-M. Son, H.-K. Lee, *J. Org. Chem.* **2014**, 79, 2666−2681.

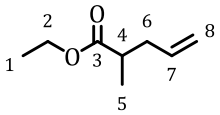
ethyl 2-methylpent-4-enoate **II.62**



To a two-neck round bottom flask equipped with a distillation apparatus, allyl alcohol (1 eq., 5.83 mL, 85.84 mmol), triethyl orthopropionate (1.1 eq., 19 mL, 94.43 mmol) and propionic acid (0.1 eq., 0.63 mL, 8.58 mmol) were mixed and the flask was heated with an oil bath (130 °C). The distillation of ethanol was monitored and the conversion of the reaction was monitored by ^{1}H NMR. After complete conversion of the allyl alcohol, the volatiles were removed under reduced pressure affording 11.13 g of the desired product as a yellowish oil (91% yield). The ester was used in the next step without further purification.

Analysis:

CAS: 53399-81-8



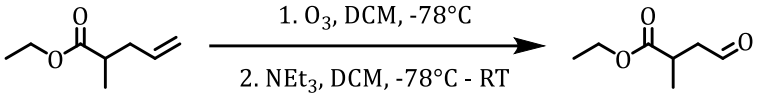
Chemical Formula: $C_8H_{14}O_2$
Molecular Weight: 142,20

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 – 5.57 (m, 1H, H7), 5.03 – 4.83 (m, 2H, H8), 4.06 (q, *J* = 7.1 Hz, 2H, H2), 2.53 – 2.40 (m, 1H, H4), 2.40 – 2.29 (m, 1H, H6), 2.18 – 2.02 (m, 1H, H6), 1.18 (t, *J* = 7.1 Hz, 3H, H1), 1.08 (d, *J* = 6.9 Hz, 3H, H5).

Experimental data were in agreement with the literature[104].

C. U. Grünanger, B. Breit,.*Angew. Chem. – Int. Ed.*, **2010**, 967-970.

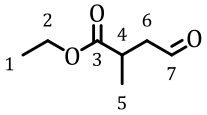
ethyl 2-methyl-4-oxobutanoate **II.63**



A solution of olefin (1 eq., 11.13 g, 78.27 mmol) in DCM (500 mL) was cooled to -78°C with an acetone/dry ice bath. Ozone was bubbled through the solution until a blue coloration appeared in the solution. Oxygen was then bubbled through the solution to remove the excess of ozone. NEt_3 (3 eq., 32.5 mL, 234.8 mmol) was then added at once and the dry ice/acetone bath was removed. The reaction mixture was stirred overnight. The solvents were evaporated under reduced pressure. The crude mixture was dissolved in DCM (400 mL) and washed twice with 1M HCl (200 mL) and then a saturated solution of NH_4Cl, dried over Na_2SO_4. The solvents were then removed under reduced pressure. The crude was purified by distillation (P: 3-5 mbar T: 45-50°C) affording aldehyde (6.35 g, 60% yield) as a colourless oil.

Analysis:

CAS : 39484-57-6



Chemical Formula: $C_7H_{12}O_3$
Molecular Weight: 144,17

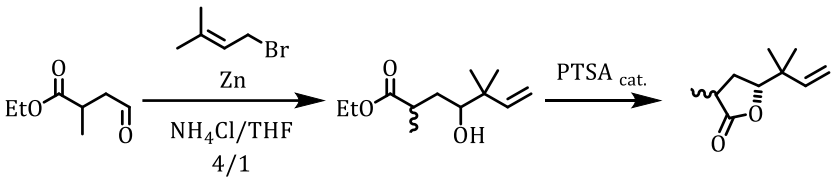
^1H NMR (300 MHz, $CDCl_3$) δ 9.76 (s, 1H, H7), 4.13 (q, *J* = 7.1 Hz, 2H, H2), 3.00 – 2.80 (m, 2H, H4 and H6), 2.51 (dd, *J* = 17.3, 5.0 Hz, 1H, H6), 1.32 – 1.08 (m, 6H, H1 and H5).

IR (ν) : 2980 - 2939 (b), 1778 (s), 1731 (s), 1178 (s), 1027 (m).

Experimental data were in agreement with the literature[105].

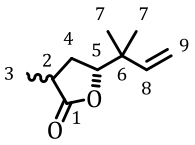
[105] S. N. Kessler, H. A. Wegner, *Org. Lett.*, **2012**, *14* (13), 3268–3271.

(5R)-3-methyl-5-(2-methylbut-3-en-2-yl)dihydrofuran-2(3H)-one
II.67



Prenyl bromide (1.2 eq., 7.87 g, 52.7 mmol) was added to a solution of aldehyde (1 eq., 6.34 g, 43.9 mmol) in THF (10 mL) and saturated NH_4Cl (40 mL). Zn dust (1.2 eq., 3.45 g, 52.7 mmol) was then added portionwise over 20 minutes and the reaction was monitored by TLC. After complete conversion of the aldehyde, the reaction mixture was diluted with Et_2O and NH_4Cl and the phase were separated. The aqueous layer was extracted twice with ether. The combined organic layers were then dried over Na_2SO_4 and the solvents were removed in vacuo. ^1H NMR of the crude reaction showed the presence a mixture of homoallylic alcohol and the lactone. The crude reaction was then diluted in toluene (80 mL) and PTSA (0.1 eq., 817 mg, 4.3 mmol) and the reaction was stirred overnight. The reaction was monitored by ^1H NMR until complete conversion to the lactone. The solvent was then removed under reduced pressure. The crude reaction was purified by silica gel chromatography using EtOAc /PE 1/20 to 1/10 as eluent affording 4.1 g of the lactone as a colourless oil in 55% yield over two steps.

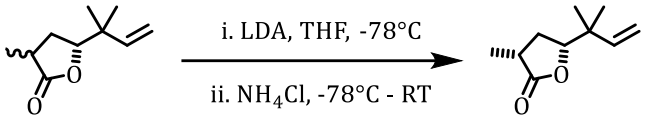
Analysis:



Chemical Formula: $C_{10}H_{16}O_2$
Molecular Weight: 168,24

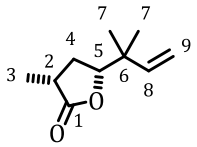
^1H NMR (300 MHz, Chloroform-*d*) δ 5.81 (m, 1H, H8), 5.17 – 5.01 (m, 2H, H9), 4.27 (dd, *J* = 8.1, 6.0 Hz, 1H, H5a), 4.18 – 4.07 (m, 1H, H5b), 2.72 – 2.57 (m, 1H, H2), 2.31 – 2.16 (m, 2H, H4), 1.81 (ddd, *J* = 13.2, 8.1, 6.4 Hz, 1H, H4b), 1.67 – 1.50 (m, 1H, H4a), 1.30 – 1.21 (m, 3H, H3), 1.11 – 1.03 (m, 6H, H7). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.54 (C1), 142.25 (C8b), 142.10 (C8a), 114.70 (C9a), 114.38 (C9b), 84.80 (C5a), 84.76 (C5b), 40.55 (C6a), 39.63 (C6b), 35.92 (C2b), 34.83 (C2a), 32.45 (C4b), 31.07 (C4a), 23.37 (C7b), 22.93 (C7a), 22.90 (C7a), 22.44 (C7b), 16.79 (C3a), 15.10 (C3b).

(5R)-3-methyl-5-(2-methylbut-3-en-2-yl)dihydrofuran-2(3H)-one
I.156



A solution of LDA was prepared by addition of iPr_2NH (1.3 eq., 4.4 mL, 31.69 mmol) to *n*BuLi (1.2 eq., 11.7 mL, 2.5M in hexane, 29.25 mmol) at room temperature followed by addition of THF (50 mL) and cooled down to -78°C with an acetone/dry ice bath. Lactone (1eq., 4.1 g, 24.38 mmol) was diluted in THF (10 mL) and added dropwise to the LDA solution. The reaction was stirred for 30 minutes. A saturated solution of NH_4Cl was then added and the reaction temperature was left to rise to room temperature after removal of the acetone/dry ice bath. The reaction was then extracted three times with Et_2O. The combined organic layers were dried over Na_2SO_4 and the solvents were removed under reduced pressure. The lactone was purified via silica gel chromatography using EtOAc/PE 1:15 to 1:10 affording 3.2 g of lactone in 78% yield as a colourless oil.

Analysis:



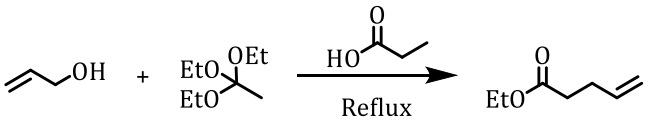
Chemical Formula: $C_{10}H_{16}O_2$
Molecular Weight: 168,24

^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.91 – 5.69 (m, 1H, H8), 5.17 – 4.98 (m, 2H, H9), 4.13 (dd, *J* = 10.7, 5.7 Hz, 1H, H5), 2.78 – 2.54 (m, 1H, H2), 2.27 (ddd, *J* = 12.6, 8.8, 5.7 Hz, 1H, H4), 1.58 (dd, *J* = 24.6, 10.8 Hz, 1H, H4), 1.25 (d, *J* = 7.0 Hz, 3H, H3), 1.11 (s, 3H, H7), 1.06 (s, 3H, H3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.66 (C1), 142.24 (C8), 114.37 (C9), 84.75 (C5), 39.63 (C6), 35.92 (C2), 32.45 (C4), 23.37 (C7), 22.44 (C7), 15.10 (C3).

IR (ν) : 2973 – 2936 (m), 1771 (s), 1735 (m), 1167 (s), 993 (m).

HRMS (ESI): Calculated for $C_{10}H_{17}O_2$ 169.12231; Found 169.12240.

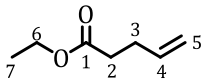
ethyl pent-4-enoate **II.109**



To a two-neck round bottom flask equipped with a distillation apparatus, allyl alcohol (1 eq., 6.83 mL, 100 mmol), triethyl orthoacetate (1.2 eq., 21.9 mL, 120 mmol) and propionic acid (0.1 eq., 0.75 mL, 10 mmol) were mixed and the flask was heated with heating mantle. The distillation of ethanol was monitored and the conversion of the reaction was monitored by ^{1}H NMR. After complete conversion of the allyl alcohol, the volatiles were removed under reduced pressure. The ester was used in the next step without further purification.

Analysis

CAS : 1968-40-7



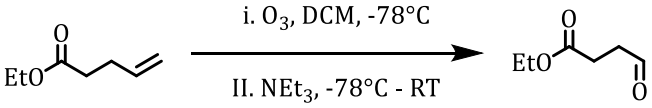
Chemical Formula: $C_7H_{12}O_2$
Molecular Weight: 128,17

1H NMR (300 MHz, Chloroform-d) δ 5.83 – 5.66 (m, 1H, H4), 5.06 – 4.86 (m, 2H, H5), 4.07 (q, J = 7.1 Hz, 2H, H6), 2.45 – 2.25 (m, 4H, H2 and H3), 1.25 – 1.08 (m, 3H, H7).

Experimental data were in agreement with the literature [106]

[106] Y.-L. Lai, J.-M. Huang, *Org. Lett.*, **2017**, *19* (8), 2022–2025.

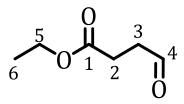
ethyl 4-oxobutanoate **II.110**



A solution of olefin (1 eq., 12.4 g, 100 mmol) in DCM (600 mL) was cooled to -78°C with an acetone/dry ice bath. Ozone was bubbled through the solution until a blue coloration appeared in the solution. Oxygen was then bubbled through the solution to remove the excess of ozone. NEt_3 (3 eq., 42 mL, 300 mmol) was then added at once and the dry ice/acetone bath was removed. The reaction mixture was stirred overnight. The reaction mixture quenched with 1M HCl (200 mL) and the phases were separated. The organic phase was washed twice with 1M HCl (200 mL) and then a saturated solution of NH_4Cl, dried over Na_2SO_4. The solvents were then removed under reduced pressure. The crude was purified by distillation (P: 1.2 mbar T: 39 °C) affording aldehyde (9.1 g, 70 % yield after 2 steps) as a colourless oil.

Analysis

CAS = 10138-10-0



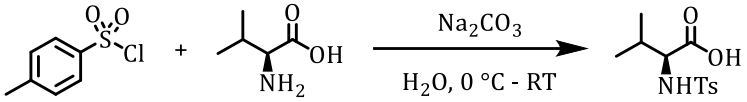
Chemical Formula: $C_6H_{10}O_3$
Molecular Weight: 130,14

^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.81 (s, 1H, H4), 4.14 (q, *J* = 7.1 Hz, 2H, H5), 2.79 (t, *J* = 6.6 Hz, 2H, H3), 2.61 (t, *J* = 6.7 Hz, 2H, H2), 1.25 (t, *J* = 7.1 Hz, 3H).

Experimental data were in agreement with the literature [107]

[107] H. Huang, C. Yu, Y. Zhang, Y. Zhang, P. S. Mariano, W. Wang, *J. Am. Chem. Soc.*, **2017**, *139* (29), 9799–9802.

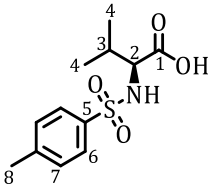
tosyl-L-valine **II.112**



Na_2CO_3 (1.5 eq., 15.89 g, 150 mmol) was dissolved in water (200 mL) and L-Valine (1.5 eq., 17.57 g, 150 mmol) was added to the mixture. Once the L-Valine dissolution was complete, the reaction mixture was cooled at 0°C with an ice bath. Tosyl chloride (1 eq., 19.06 g, 100 mmol) was added in portions over 1 hour. The ice bath was then removed and the reaction mixture was left to stir overnight. The reaction was then carefully quenched with 1M HCl until pH paper indicated pH ~2 leading to the formation of a white precipitate. The reaction mixture was cooled with an ice bath and filtered. The white solid was washed with a buffer pH~2. The white solid was first dried using a freeze drying system and then stored in a KOH/P_2O_5 desiccator. 19.5 g of the desired product could be isolated in 72% yield.

Analysis

CAS : 17360-25-7



Chemical Formula: $C_{12}H_{17}NO_4S$
Molecular Weight: 271,33

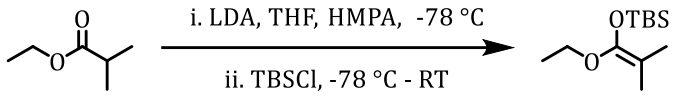
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.74 (d, *J* = 8.4 Hz, 2H, H6), 7.35 – 7.25 (m, 2H, H7), 5.03 (d, *J* = 9.7 Hz, 1H, NH), 3.83 (dd, *J* = 9.8, 4.6 Hz, 1H, H2), 2.43 (s, 3H, H8), 2.20 – 2.04 (m, 1H, H3), 0.99 (d, *J* = 6.8 Hz, 3H, H4), 0.89 (d, *J* = 6.9 Hz, 3H, H4).

Experimental data were in agreement with the literature [108]

[108] S. Balcells, M. B. Haughey, J. C. L. Walker, L. Josa-Culleré, C. Towers, T. J. Donohoe, *Org. Lett.*, **2018**, *20* (12), 3583–3586.

tert-butyl((1-ethoxy-2-methylprop-1-en-1-yl)oxy)dimethylsilane

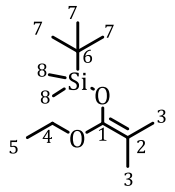
II.103



A solution of LDA was prepared by addition of iPr_2NH (1.1 eq., 7.8 mL, 56.25 mmol) to *n*BuLi (1.1 eq., 11.7 mL, 2.5M in hexane, 56.25 mmol) at room temperature followed by addition of THF (125 mL) and HMPA (30 mL). The reaction mixture was then cooled at -78°C with an acetone/dry ice bath. Ethyl isobutyrate (1 eq., 6.9 mL, 51 mmol) was then added and the reaction was stirred at -78 °C for 30 minutes. A solution of TBSCl (1 eq., 7.8 g, 51 mmol) in THF (25 mL) was then added. The dry ice bath was removed and the reaction was left to warm to room temperature and stirred for one hour. The reaction was diluted with Et_2O then quenched with water and the layers were separated. The aqueous layer was extracted twice with Et_2O. The combined organic layers were washed with a saturated solution of NaCl, dried over Na_2SO_4. The volatiles were evaporated under reduced pressure. The crude mixture was purified by distillation affording 7.4 g of the acetal as a yellowish oil in a yield of 64 %.

Analysis

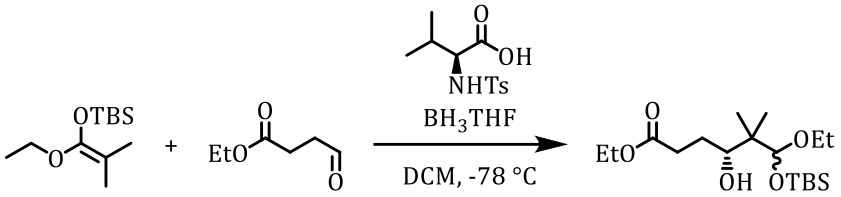
CAS: 133270-76-5



Chemical Formula: $C_{12}H_{26}O_2Si$
Molecular Weight: 230,42

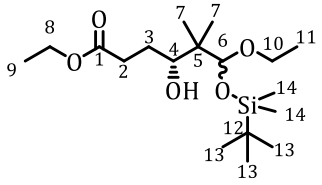
^{1}H NMR (300 MHz, Chloroform-*d*) δ 3.77 (q, *J* = 7.1 Hz, 2H, H4), 1.58 (s, 3H, H3), 1.54 (s, 3H, H3), 1.23 (t, *J* = 7.1 Hz, 3H, H5), 0.95 (s, 9H, H7), 0.14 (s, 6H, H8).

ethyl (4R)-6-((tert-butyldimethylsilyl)oxy)-6-ethoxy-4-hydroxy-5,5-dimethylhexanoate **II.113**



A solution of tosyl-L-Valine (1.2 eq., 2.86 g, 9.63 mmol) in DCM (40 mL) was cooled at 0 °C before adding BH_3.THF (1.2 eq., 9.63 mL, 1M in THF, 9.63 mmol) dropwise. The reaction mixture was stirred 30 minutes at 0 °C, then 30 minutes at room temperature and then cooled at -78 °C. A solution of aldehyde (1 eq., 1.045 g, 8.02 mmol) in DCM (10 mL)) was added and the reaction mixture was stirred for 5 minutes. A solution of silyl ether (1.2 eq., 2.22 g, 9.63 mmol) in DCM (5 mL) was added dropwise and the reaction mixture was stirred for 3 hours at -78 °C. The conversion of the aldehyde was checked by TLC before pouring the reaction mixture in a solution of saturated $NaHCO_3$. Et_2O was added to the mixture and the layers were separated. The aqueous layer was extracted twice with Et_2O. The combined organic layers were dried over Na_2SO_4 and the solvents were removed under reduced pressure. The alcohol present as a yellow oil was used without further purification.

Analysis



Chemical Formula: $C_{18}H_{38}O_5Si$
Molecular Weight: 362,58

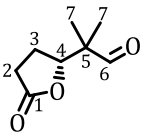
^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.51 (s, 1H, H6), 4.13 (q, *J* = 7.1 Hz, 2H, H8), 3.87 – 3.61 (m, 2H, H4 and H10), 3.39 (dq, *J* = 8.9, 7.0 Hz, 1H, H10), 2.61 (ddd, *J* = 16.1, 9.0, 5.7 Hz, 1H, H2), 2.39 (ddd, *J* = 16.0, 8.7, 6.8 Hz, 1H, H2), 1.87 – 1.73 (m, 1H, H3), 1.58 (m, 1H, H3), 1.26 (t, *J* = 7.1 Hz, 3H, H9), 1.20 (t, *J* = 7.0 Hz, 3H, H11), 0.92 (m, 15H, H13 and H7), 0.14 (s, 3H, H14), 0.10 (s, 3H, H14).

HRMS (ESI): Calculated for $C_{18}H_{38}O_5NaSi$ 385.23807; Found 385.23807.

(R)-2-methyl-2-(5-oxotetrahydrofuran-2-yl)propanal **II.114**

Alcohol (1 eq., 3.4 g, 9.37 mmol) was dissolved in DCM (50 mL). PTSA (0.1 eq., 180 mg, 0.93 mmol) and H_2O (10 mL) were added and the reaction mixture was heated to reflux with an oil bath. The conversion of the starting material was monitored by TLC. Upon completion, the reaction was cooled to room temperature and diluted with DCM. The reaction was quenched with a saturated solution of $NaHCO_3$ and the layers were separated. The aqueous layer was extracted twice with DCM. The combined organic layers were washed with brine and dried with Na_2SO_4. The solvents were removed under reduced pressure. The crude mixture was purified by silica gel chromatography using EtOAc/PE 1:6 to 1:2 as eluent. Aldehyde could be isolated as a colourless oil with a yield of 90 %.

Analysis



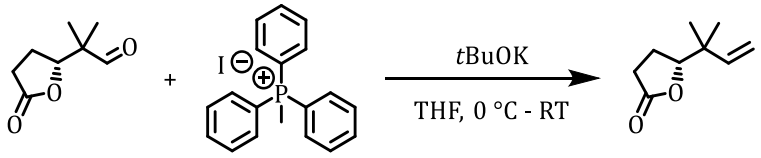
Chemical Formula: $C_8H_{12}O_3$
Molecular Weight: 156,18

^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.56 (s, 1H, H6), 4.60 (dd, *J* = 8.9, 7.0 Hz, 1H, H4), 2.61 – 2.52 (m, 2H, H2), 2.34 – 2.20 (m, 1H, H3), 2.11 – 1.90 (m, 1H, H3), 1.16 (s, 3H, H7), 1.14 (s, 3H, H7). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 203.48 (C6), 176.53 (C1), 83.04 (C4), 49.15 (C5), 28.66 (C2), 23.25 (C3), 18.06 (C7), 17.42 (C7).

IR (ν) : 2981 – 2939 (b), 1767 (s), 1165 (s), 1005 (m).

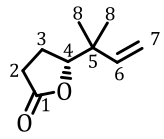
HRMS (ESI): Calculated for $C_8H_{12}O_3Na$ 179.06787; Found 179.06790.

(R)-5-(2-methylbut-3-en-2-yl)dihydrofuran-2(3H)-one **I.158**



Potassium *tert*-butoxide (1.2 eq., 688 mg, 6.14 mmol) was added to a suspension of methyl triphenyl phosphonium iodide (1.2 eq., 2.48 g, 6.14 mmol) in THF (45 mL) at 0 °C and the yellow solution was stirred for 30 minutes. A solution of aldehyde (1 eq., 800 mg, 5.12 mmol)) in THF (5 mL) was then added dropwise. The reaction was left to warm to room temperature and the reaction was monitored by TLC. Upon complete conversion, the reaction was diluted with petroleum ether. The precipitate was filtered and washed with cold petroleum ether. The filtrate was then diluted with ether and quenched with a saturated solution of NH_4Cl. The layers were separated and the aqueous layer was extracted with ether. The organic layers were combined, washed with brine and dried over Na_2SO_4. The solvents were removed under reduced pressure. Olefin was purified by silica gel chromatography using EtOAc/PE 1:10 to 1:4 as eluent affording the alkene as a colourless oil in 64% yield.

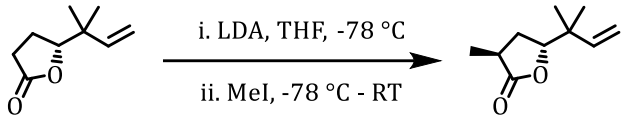
Analysis



Chemical Formula: $C_9H_{14}O_2$
Molecular Weight: 154,21

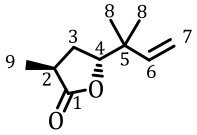
^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.80 (dd, *J* = 17.4, 10.9 Hz, 1H, H6), 5.22 – 5.03 (m, 2H, H7), 4.26 (dd, *J* = 8.3, 7.1 Hz, 1H, H4), 2.57 – 2.45 (m, 2H, H2), 2.19 – 1.84 (m, 2H, H3), 1.10 (s, 3H, H8), 1.06 (s, 3H, H8).

(3S,5R)-3-methyl-5-(2-methylbut-3-en-2-yl)dihydrofuran-2(3H)-one
II.118



A solution of LDA was prepared by addition of iPr_2NH (1.2 eq., 0.168 mL, 1.2 mmol) to *n*BuLi (1.1 eq., 0.44 mL, 2.5M in hexane, 1.1 mmol) at room temperature followed by addition of THF (8 mL) and cooled down to -78°C with an acetone/dry ice bath. Lactone (1eq., 156 mg, 1 mmol) was diluted in THF (2 mL) and added dropwise to the LDA solution. The reaction was stirred for 30 minutes. Methyl iodide (1.5 eq., 0.093 mL, 1.5 mmol) was then added and the reaction temperature was left to rise to room temperature after removal of the acetone/dry ice bath. The reaction was stirred for one hour before being quenched by addition of saturated solution of NH_4Cl. The layers were separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were dried over Na_2SO_4 and the solvents were removed under reduced pressure. The lactone was purified via silica gel chromatography using AcOEt/PE 1:15 to 1:10 affording 143 mg of lactone in 85% yield as a colourless oil.

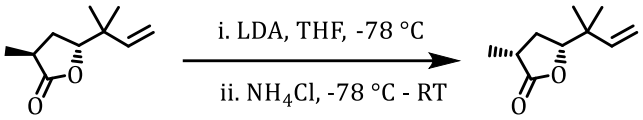
Analysis



Chemical Formula: $C_{10}H_{16}O_2$
Molecular Weight: 168,24

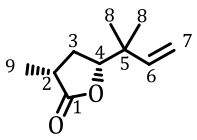
^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.79 (dd, *J* = 17.4, 11.0 Hz, 1H, H6), 5.20 – 5.02 (m, 2H, H7), 4.26 (dd, *J* = 8.1, 6.0 Hz, 1H, H4), 2.72 – 2.57 (m, 1H, H2), 2.22 (ddd, *J* = 13.2, 9.7, 6.0 Hz, 1H, H3), 1.90 – 1.75 (m, 1H, H3), 1.27 (d, *J* = 7.4 Hz, 3H, H9), 1.09 (s, 3H, H8), 1.05 (s, 3H, H8).

(3R,5R)-3-methyl-5-(2-methylbut-3-en-2-yl)dihydrofuran-2(3H)-one
I.156



A solution of LDA was prepared by addition of iPr_2NH (1.2 eq., 0.168 mL, 1.2 mmol) to *n*BuLi (1.1 eq., 0.44 mL, 2.5M in hexane, 1.1 mmol) at room temperature followed by addition of THF (8 mL) and cooled down to -78°C with an acetone/dry ice bath. Lactone (1eq., 156 mg, 1 mmol) was diluted in THF (2mL) and added dropwise to the LDA solution. The reaction was stirred for 30 minutes. A saturated solution of NH_4Cl was then added and the reaction temperature was left to rise to room temperature after removal of the acetone/dry ice bath. The reaction was then extracted three times with Et_2O. The combined organic layers were dried over Na_2SO_4 and the solvents were removed under reduced pressure. The lactone was purified via silica gel chromatography using EtOAc/PE 1:15 to 1:10 affording 154 mg of lactone in 92 % yield as a colourless oil.

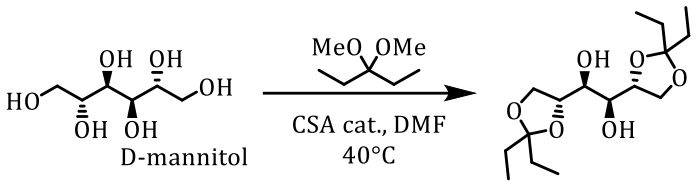
Analysis



Chemical Formula: $C_{10}H_{16}O_2$
Molecular Weight: 168,24

Experimental data were in agreement with samples prepared previously.

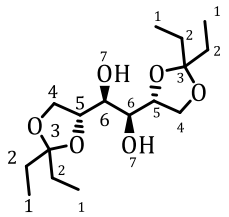
{1S,2S)-1,2-bis((R)-2,2-diethyl-1,3-dioxolan-4-yl)ethane-1,2-diol **III.61**



D-mannitol (1 eq., 11.84 g, 65 mmol) and 3,3-dimethoxypentane (2.1 eq., 20 mL, 136 mmol) were dissolved in DMF (60 mL) at room temperature. CSA (0.1 eq., 1.5 g, 6.5 mmol) was then added and the solution was stirred at 40°C for 6 hours. The reaction was then quenched with triethylamine and diluted in 200 mL of ethyl acetate. The organic phase was washed three times with 75 mL of 10% $CuSO_4$, twice with 75 mL of water and dried over Na_2SO_4. The organic solvents were removed under reduced pressure affording a white solid, sometimes sticky due to the remaining ethyl acetate. The crude was used for the next step without further purification.

Analysis:

CAS: 120157-59-7

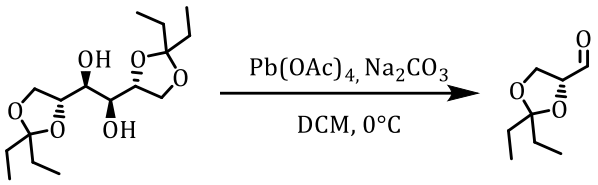


Chemical Formula: $C_{16}H_{30}O_6$
Molecular Weight: 318,41

^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.25 – 4.06 (m, 4H, H4), 3.91 (td, *J* = 6.0, 1.7 Hz, 2H, H5), 3.77 (t, *J* = 6.0 Hz, 2H, H5), 2.58 (d, *J* = 6.5 Hz, 2H, H7), 1.75 – 1.53 (m, 8H, H2), 0.89 (td, *J* = 7.5, 2.5 Hz, 12H, H1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 113.46(C3), 76.58(C5), 71.78(C6), 67.49(C4), 29.71(C2), 29.05(C2), 8.40(C1), 8.22(C1).

Experimental data in agreement with the literature[77].

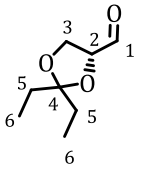
(R)-2,2-diethyl-1,3-dioxolane-4-carbaldehyde **III.28**



Procedure:

Diol (1 eq., 6 g, 18.84 mmol) was dissolved in DCM (75 mL) at room temperature. Na_2CO_3 (10 eq., 19.96 g, 188.4 mmol) was then added and the reaction mixture was cooled at 0°C with an ice bath. $Pb(OAc)_4$ (1.1 eq., 9.18 g, 20.72 mmol) was added portionwise under vigorous stirring and the reaction was stirred at 0°C. The reaction was monitored by TLC (EtOAc/PE : 1/1) until complete conversion of the diol. A mixture of celite and Na_2SO_4 (3/1) was added to the reaction flask and stirring was continued for 15 minutes. The reaction mixture was diluted with DCM, filtrated over a pad of celite/Na_2SO_4 (3/1) and the pad was washed two times with DCM. The organic solvents were evaporated under reduced pressure affording a yellowish oil. The purification was performed by distillation in vacuo (70-90°C – $1.0*10^{-1}$ Torr) affording 3.8 g of aldehyde in 63 % yield as a colourless oil. The aldehyde was prepared just before use since it degrades over time.

Analysis:



Chemical Formula: $C_8H_{14}O_3$
Molecular Weight: 158,20

^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.73 (d, *J* = 2.0 Hz, 1H, H1), 4.38 (ddd, *J* = 7.4, 5.4, 2.0 Hz, 1H, H2), 4.17 (dd, *J* = 8.6, 7.5 Hz, 1H, H3), 4.05 (dd, *J* = 8.6, 5.4 Hz, 1H, H3), 1.90 – 1.57 (m, 4H, H5), 1.07 – 0.80 (m, 6H, H6).

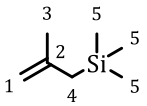
Experimental data in agreement with the literature[77].

trimethyl(2-methylallyl)silane **III.55**

A three-necked flask was equipped with a reflux condenser and an addition funnel. Activated magnesium turnings (416.25 mmol, 1.5 eq., 10.11 g), TMSCl (416.25 mmol, 1.5 eq., 52.82 mL) and THF (80mL) were added and the solution was heated to reflux. Methallyl chloride (277 mmol, 1 eq., 27.16 mL) was then added over six hours and the reflux was maintained overnight. Afterwards, THF was distilled from the reaction mixture at atmospheric pressure. Pentane (400 mL) was then added and the reaction mixture was cooled with an ice bath and slowly quenched with water (200 mL). The organic and aqueous layers were then separated and the aqueous layer was extracted twice with pentane (2*200 mL). The combined organic layers were dried over Na_2SO_4 and the organic solvents were distilled. The crude mixture containing some remaining THF was purified by distillation using a vigreux column affording methallyl trimethylsilane as a colourless oil (25.2 g, 199 mmol) in 72% yield.

Analysis

CAS: 18292-38-1



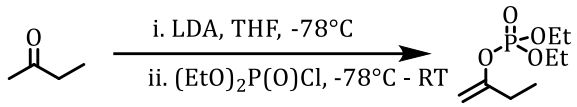
Chemical Formula: $C_7H_{16}Si$
Molecular Weight: 128,29

^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.59 (dd, *J* = 2.5, 1.4 Hz, 1H), 4.47 (dq, *J* = 1.6, 0.8 Hz, 1H), 1.72 (dd, *J* = 1.3, 0.8 Hz, 3H), 1.54 (d, *J* = 1.0 Hz, 2H), 0.04 (s, 9H).

Experimental data in agreement with the literature[109].

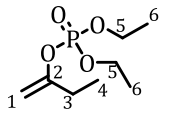
[109]K. Ishihara, M. Mouri, Q. Gao, T. Maruyama, K. Furuta, H. Yamamoto, *J. Am. Chem. Soc.*, **1993**, *115* (24), 11490–11495.

but-1-en-2-yl diethyl phosphate **III.57**



iPr_2NH (1.1 eq., 7.75 mL, 55 mmol) was added to a stirred solution of *n*BuLi (1 eq., 20 mL, 2.5M in hexane, 50 mmol) at room temperature (Note: a large stirring bar should be used since the LDA in viscous). 80 mL of THF were added and the LDA solution was cooled at -78°C with a dry ice acetone bath. 2-butanone (1 eq., 4.47 mL, 50 mmol) was then added dropwise and the solution was stirred for 30 minutes. In another three necked flask, diethyl chlorophosphate (1.2 eq., 8.67 mL, 60 mmol) was diluted in THF (80 mL) and cooled to -78°C with a dry ice/acetone bath. The solution of enolate was then cannulated to the diethyl chlorophosphate solution. The reaction mixture was warmed to room temperature and stirred for one hour. The reaction was then quenched with a saturated solution of NH_4Cl. The reaction was diluted with ether and the layers were separated. The aqueous layer was extracted twice with ether and the combined organic layers were washed with saturated $NaHCO_3$, dried over Na_2SO_4 and the solvents were removed under reduced pressure. 8.33 g of the desired product was obtained as a colourless oil after purification by distillation under vacuum (bp : 64-67°C P:2 mbar) in 80% yield.

Analysis:

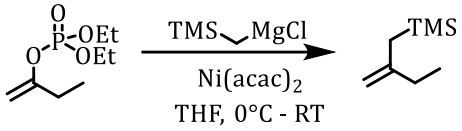


Chemical Formula: $C_8H_{17}O_4P$
Molecular Weight: 208,19

^1H NMR (300 MHz, Chloroform-*d*) δ 4.81 (t, *J* = 2.1 Hz, 1H, H1), 4.51 (tt, *J* = 2.2, 1.2 Hz, 1H, H1), 4.17 (dq, *J* = 8.2, 7.1 Hz, 4H, H5), 2.23 (qt, *J* = 7.4, 0.7 Hz, 2H, H3), 1.36 (tdd, *J* = 7.1, 2.7, 1.0 Hz, 6H, H6), 1.09 (t, *J* = 7.4 Hz, 3H, H4). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 157.47 (C2), 95.90 (d, *J* = 4.1 Hz, C1), 64.34 (d, *J* = 6.0 Hz, C5), 27.75 (d, *J* = 5.5 Hz, C3), 16.22 (d, *J* = 6.8 Hz, C6), 11.18 (C4).

HRMS (ESI): Calculated for $C_8H_{18}O_4P$ 209.09372; Found 209.09373.

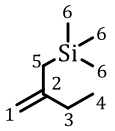
trimethyl(2-methylenebutyl)silane **III.49**



In a two necked flask equipped with a reflux condenser, Mg turnings (3 eq., 700 mg, 28.8 mmol) (washed with 1M HCl then *i*PrOH then Et_2O and dried) were suspended in THF (10 mL) with a small amount of iodine. Chloromethyl trimethylsilane (1.5 eq., 2.09 mL, 14.4 mmol) was added to the solution and the reaction was heated with a heat gun until the brown coloration of the solution faded. The reaction was stirred for 30 minutes and heated again to achieve complete conversion of the Grignard reagent formation. In a two necked flask, vinyl phosphonate (1 eq., 2 g, 9.6 mmol) and $Ni(acac)_2$ (0.05 eq., 123.3 mg, 0.48 mmol) were dissolved in THF (10 mL) and cooled to 0°C with an ice bath. The solution of Grignard reagent was added to this solution and the ice bath was removed. The reaction was stirred overnight and monitored by TLC until complete conversion of the vinyl phosphonate. The reaction mixture was poured into a saturated solution of NH_4Cl and Et_2O. The layers were separated and the aqueous layer was extracted twice with ether. The solvent was removed by distillation at atmospheric pressure. The crude mixture was purified by silica gel column chromatography using pentane as eluent. 1.8 g of allylsilane (colourless oil) could be isolated with a yield of 90 %.

Analysis

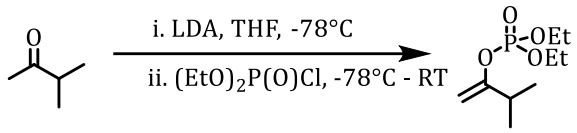
CAS : 156479-01-5



Chemical Formula: $C_8H_{18}Si$
Molecular Weight: 142,32

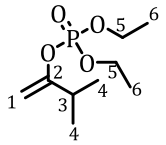
^1H NMR (300 MHz, Chloroform-*d*) δ 4.60 (dt, *J* = 2.2, 1.5 Hz, 1H, H1), 4.51 (dp, *J* = 2.0, 1.0 Hz, 1H, H1), 1.98 (qt, *J* = 7.4, 1.3 Hz, 2H, H5), 1.55 (s, 2H, H5), 1.03 (t, *J* = 7.4 Hz, 3H, H4), 0.02 (s, 9H, H6). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 149.57 (C2), 105.63 (C1), 31.08 (C5), 27.21 (C3), 12.52 (C4), -1.17 (C6).

diethyl (3-methylbut-1-en-2-yl) phosphate **III.59**



iPr_2NH (1.1 eq., 7.75 mL, 55 mmol) was added to a stirred solution of *n*BuLi (1 eq., 20 mL, 2.5M in hexane, 50 mmol) at room temperature (Note: a large stirring bar should be used since the LDA in viscous). 80 mL of THF were added and the LDA solution was cooled at -78°C with a dry ice acetone bath. 3-methyl-2-butanone (1 eq., 5.34 mL, 50 mmol) was then added dropwise and the solution was stirred for 30 minutes. In another three necked flask, diethyl chlorophosphate (1.2 eq., 8.67 mL, 60 mmol) was diluted in THF (80 mL) and cooled to -78°C with a dry ice/acetone bath. The solution of enolate was then cannulated to the diethyl chlorophosphate solution. The reaction mixture was warmed to room temperature and stirred for one hour. The reaction was then quenched with a saturated solution of NH_4Cl. The reaction was diluted with ether and the layers were separated. The aqueous layer was extracted twice with ether and the combined organic layers were washed with saturated $NaHCO_3$, dried over Na_2SO_4 and the solvents were removed under reduced pressure. 8.17 g of the desired product was obtained as a colourless oil after purification by distillation under vacuum (bp : 72°C P:2 mbar) in 73 % yield.

Analysis:

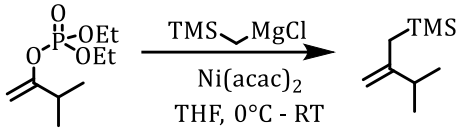


Chemical Formula: $C_9H_{19}O_4P$
Molecular Weight: 222,22

^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.80 (ddd, *J* = 2.8, 1.8, 1.1 Hz, 1H, H1), 4.48 (ddt, *J* = 2.6, 1.5, 0.8 Hz, 1H, H1), 4.16 (m, 4H, H5), 2.40 (p, *J* = 6.8 Hz, 1H, H3), 1.35 (m, 6H, H6), 1.09 (m, 6H, H4). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 160.99 (d, *J* = 9.3 Hz, C2), 94.12 (d, *J* = 3.4 Hz, C1), 64.32 (d, *J* = 6.1 Hz, C5), 33.33 (d, *J* = 6.3 Hz, C3), 20.23 (C6), 16.23 (d, *J* = 6.7 Hz, C4).

HRMS (ESI): Calculated for $C_9H_{20}O_4P$ 223.10937; Found 223.10941.

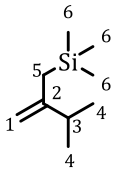
trimethyl(3-methyl-2-methylenebutyl)silane **III.52**



In a two necked flask equipped with a reflux condenser, Mg turnings (3 eq., 2.7 g, 110 mmol) (washed with 1M HCl then *i*PrOH then Et_2O and dried) were suspended in THF (80 mL) with a small amount of iodine. Chloromethyl trimethylsilane (1.5 eq., 7.69 mL, 55.14 mmol) was added to the solution and the reaction was heated with a heat gun until the brown coloration of the solution faded. The reaction was stirred for 30 minutes and heated again to achieve complete conversion of the Grignard reagent formation. In a two necked flask, vinyl phosphonate (1 eq., 8.17 g, 36.76 mmol) and $Ni(acac)_2$ (0.05 eq., 472 mg, 1.83 mmol) were dissolved in THF (80 mL) and cooled to 0°C with an ice bath. The solution of Grignard reagent was added to this solution and the ice bath was removed. The reaction was stirred overnight and monitored by TLC until complete conversion of the vinyl phosphonate. The reaction mixture was poured into a saturated solution of NH_4Cl and Et_2O. The layers were separated and the aqueous layer was extracted twice with ether. The solvent was removed by distillation at atmospheric pressure. The crude mixture was purified by silica gel column chromatography using pentane as eluent. 3.44 g of allylsilane (colourless oil) could be isolated with a yield of 61 %.

Analysis:

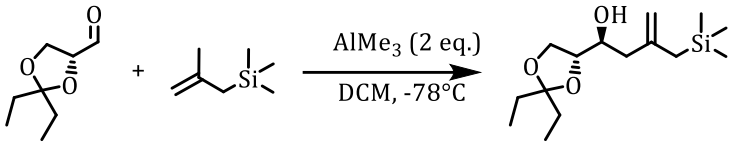
CAS : 102261-99-4



Chemical Formula: $C_9H_{20}Si$
Molecular Weight: 156,34

^1H NMR (300 MHz, Chloroform-*d*) δ 4.59 (dt, *J* = 2.1, 1.5 Hz, 1H, H1), 4.50 (dq, *J* = 2.0, 1.0 Hz, 1H), H1, 1.97 (qt, *J* = 7.4, 1.2 Hz, 2H, H5), 1.54 (d, *J* = 1.0 Hz, H), 1.02 (t, *J* = 7.4 Hz, 3H), 0.01 (s, 9H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 149.57 (C2), 105.63 (C1), 31.08 (C5), 27.21 (C3), 12.52 (C4), -1.17 (C6).

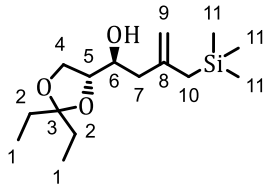
(S)-1-((R)-2,2-diethyl-1,3-dioxolan-4-yl)-3-((trimethylsilyl)methyl)but-3-en-1-ol **III.54**



Procedure:

To a solution of aldehyde (1 eq., 2 g, 12.6 mmol) and methallyl trimethylsilane (1.2 eq., 1.93 g, 15.12 mmol) in dichloromethane (120 mL) at -78°C (dry ice/acetone) was added dropwise a solution of $AlMe_3$ (2 eq., 12.6 mL, 2.0 M in toluene, 25.2 mmol)). The reaction was stirred at -78°C and monitored by TLC until complete conversion of the aldehyde. The reaction was then quenched at -78°C by slow addition of a saturated solution of Rochelle's salt. The dry ice/acetone bath was then removed and the reaction was stirred overnight. The organic and aqueous layers were separated and the aqueous layer was extracted twice with dichloromethane. The combined organic layers were dried over Na_2SO_4 and the organic solvents were removed under reduced pressure. The desired product was obtained after silica gel chromatography using EtOAc/PE 1:20 to 1:10. The desired product was isolated as a yellow oil in 85 % yield.

Analysis:

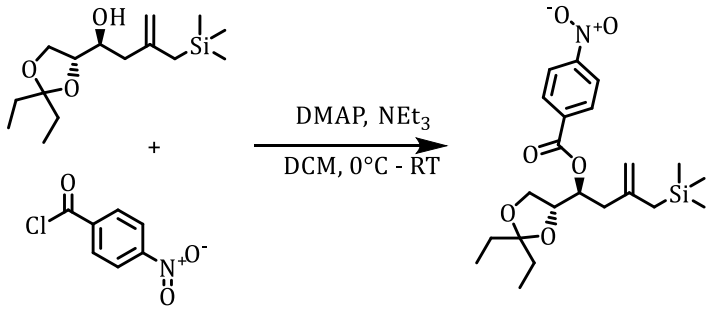


Chemical Formula: $C_{15}H_{30}O_3Si$
Molecular Weight: 286,49

^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.70 (ddt, *J* = 6.5, 2.0, 1.0 Hz, 2H, H9), 4.10 – 4.00 (m, 1H, H4), 3.98 – 3.88 (m, 2H, H4 and H5), 3.81 (dddd, *J* = 9.3, 5.6, 3.7, 2.0 Hz, 1H, H6), 2.35 – 2.25 (m, 1H, H7), 2.10 – 1.99 (m, 1H, H7), 1.76 – 1.48 (m, 6H, H10 and H2), 0.96 – 0.80 (m, 6H, H1), 0.04 (s, 9H, H11). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.99 (C8), 113.07 (C3), 110.80 (C9), 78.62 (C5), 69.40 (C6), 66.39 (C4), 42.55 (C7), 29.68 (C2), 29.15 (C2), 26.65 (C10), 8.41 (C1), 8.18 (C1), -1.23 (C11).

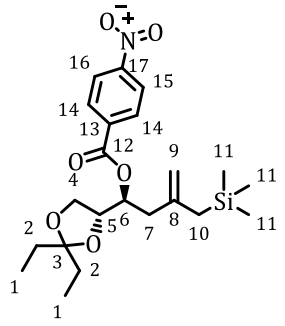
HRMS (ESI): Calculated for $C_{15}H_{30}O_3SiNa$ 309.18564; Found 309.18574.

(S)-1-((R)-2,2-diethyl-1,3-dioxolan-4-yl)-3-((trimethylsilyl)methyl)but-3-en-1-yl 4-nitrobenzoate **III.65**



Alcohol (1 eq., 300 mg, 1.04 mmol), NEt_3 (2 eq., 0.291 mL, 2.04 mmol), para-nitrobenzoyl chloride (1.5 eq., 289 mg, 1.56 mmol) were dissolved in DCM at 0°C. DMAP (0.2 eq., 25 mg, 0.208 mmol) was then added and the ice bath was removed. The reaction was stirred at room temperature and the conversion was monitored by TLC. The reaction was diluted with DCM and quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted with DCM and the combined organic phase was washed with a saturated solution of $NaHCO_3$ and dried over Na_2SO_4. The solvent was removed under reduced pressure. The crude reaction was purified through silica gel chromatography using EtOAc/PE 1/40 to 1:30 as eluent. The protected alcohol was isolated in 84% yield (386 mg) as a white amorphous solid.

Analysis:



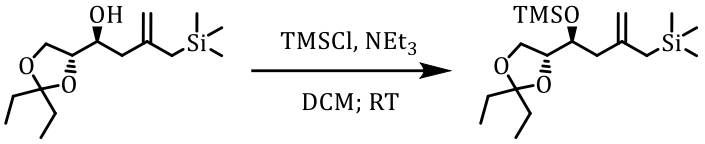
Chemical Formula: $C_{22}H_{33}NO_6Si$
Molecular Weight: 435,59

^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.32 – 8.26 (m, 2H, H15), 8.22 – 8.15 (m, 2H, H14), 5.53 (ddd, *J* = 7.8, 5.6, 4.9 Hz, 1H, H6), 4.64 (dt, *J* = 2.1, 1.1 Hz, 1H, H9), 4.56 (dt, *J* = 2.0, 1.0 Hz, 1H, H9), 4.28 (td, *J* = 6.8, 4.9 Hz, 1H, H5), 4.10 (dd, *J* = 8.1, 6.6 Hz, 1H, H4), 3.92 (dd, *J* = 8.1, 7.0 Hz, 1H, H4), 2.42 – 2.29 (m, 2H, H7), 1.76 – 1.47 (m, 6H, H10 and H2), 0.88 (t, *J* = 7.5 Hz, 3H, H1), 0.79 (t, *J* = 7.5 Hz, 3H, H1), 0.02 (s, 9H, H11). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.05(C12), 150.70 (C16), 142.37 (C8),

135.74 (C13), 130.88 (C14), 123.68 (C15), 113.69 (C3), 111.23 (C9), 76.84 (C5), 73.06 (C6), 66.05 (C4), 40.14 (C7), 29.57(C2), 28.92 (C2), 26.53 (C10), 8.32 (C1), 8.10 (C1), -1.27 (C11).

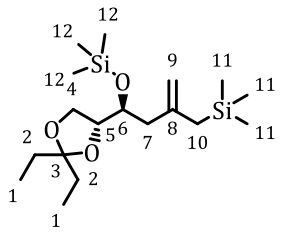
HRMS (ESI): Calculated for $C_{22}H_{33}NO_6SiNa$ 458.19694; Found 458.19693.

((S)-4-((R)-2,2-diethyl-1,3-dioxolan-4-yl)-2-methylene-4-((trimethylsilyl)oxy)butyl)trimethylsilane **III.75**



NEt_3 was added to a solution of alcohol (1 eq., 6.7 g, 23.9 mmol) and TMSCl (1.1 eq., 3.37 mL, 26.26 mmol) in DCM (62 mL). The solution was stirred at room temperature until TLC of the crude reaction showed complete conversion of the alcohol. The reaction was then diluted with DCM and quenched with saturated solution of NH_4Cl. The organic layer was separated, washed with $NaHCO_3$ and dried over Na_2SO4. The solvents were then evaporated under reduced pressure. The crude reaction was used without further purification.

Analysis:

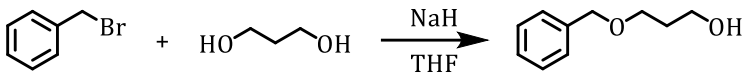


Chemical Formula: $C_{18}H_{38}O_3Si_2$
Molecular Weight: 358,67

^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.66 (dt, *J* = 2.1, 1.0 Hz, 1H, H9), 4.60 (dt, *J* = 2.1, 1.0 Hz, 1H, H9), 4.05 – 3.90 (m, 2H, H4 and H5), 3.90 – 3.82 (m, 1H, H6), 3.81 – 3.74 (m, 1H, H4), 2.34 – 2.17 (m, 1H, H7), 2.07 (ddd, *J* = 13.7, 7.4, 0.8 Hz, 1H, H4), 1.72 – 1.51 (m, 6H, H2 and H10), 0.89 (m, 6H, H1), 0.10 (s, 9H, H12), 0.02 (s, 9H, H11). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.57 (C8), 113.09 (C3)), 110.85 (C9), 78.84 (C5), 72.18 (C6), 66.87 (C4), 43.84 (C7), 29.94 (C2), 29.26 (C2), 27.21 (C10), 8.37 (C1), 0.75 (C11), -1.23 (C12).

HRMS (ESI): Calculated for $C_{18}H_{38}O_3NaSi_2$ 381.22517; Found 381.22519.

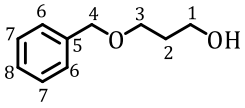
3-(benzyloxy)propan-1-ol **III.67**



Propan-1,3-diol (5 eq., 36.13 mL, 500 mmol) was added dropwise to a suspension of NaH (5 eq., 19.26 g, 60% in mineral oil, 500 mmol) in THF (200 mL) cooled at 0 °C with an ice bath. The reaction was stirred until the hydrogen formation ceased. Benzyl bromide (1 eq., 11.87 mL, 100 mmol) was then added dropwise and the reaction was stirred overnight at room temperature. The reaction was diluted with Et_2O and quenched with a saturated solution of NH_4Cl. The layers were separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were over Na_2SO_4 and the solvent was removed under reduced pressure. The purification was carried out by silica gel column chromatography affording 10.98 g of alcohol as a yellowish oil (yield: 66 %).

Analysis

CAS : 4799-68-2



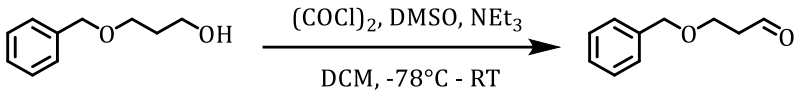
Chemical Formula: $C_{10}H_{14}O_2$
Molecular Weight: 166,22

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.39 – 7.27 (m, 5H, H6, H7 and H8), 4.53 (s, 2H, H4), 3.85 – 3.74 (m, 2H, H3), 3.67 (t, *J* = 5.8 Hz, 2H, H1), 1.87 (p, *J* = 5.7 Hz, 2H, H2).

Experimental data in agreement with the literature[110].

[110] E. Brun, V. Bellosta, J. Cossy, *J. Org. Chem.*, **2015**, *80* (17), 8668–8676.

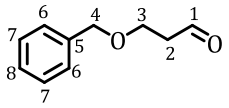
3-(benzyloxy)propanal **III.68**



A solution of DMSO (2 eq., 10.81 mL, 158.4 mmol) in DCM (25 mL) was added dropwise to a solution of oxalyl chloride (1.3 eq., 8.71 mL, 101.6 mmol) in DCM (250 mL) cooled at -78°C with a dry ice/acetone bath. After 15 minutes, a solution of alcohol (1 eq., 13 g, 78.2 mmol) in DCM (25 mL) was added to the reaction mixture. The reaction mixture was then stirred for 30 minutes before adding NEt_3 (5 eq., 54.79 mL, 391 mmol) at once with strong agitation. The reaction was then stirred at -78°C for one hour before removing the dry ice/acetone bath. The reaction mixture was stirred for another hour once it had reached room temperature. The reaction was quenched with NH_4Cl and the aqueous phase was extracted with DCM. The organic layer was then washed twice with an aqueous solution of HCl 1M then water. The organic layer was dried over Na_2SO_4 and the volatiles were removed under reduced pressure. The crude mixture was purified through silica gel chromatography using EtOAc/PE 1:15 to 1/8. The desired aldehyde was isolated in 84% yield as a yellow oil.

Analysis:

CAS : 19790-60-4

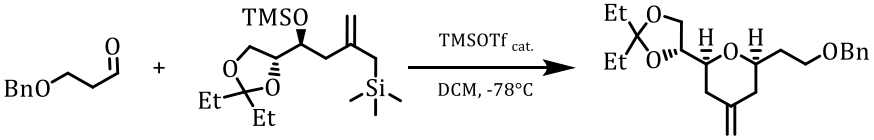


Chemical Formula: $C_{10}H_{12}O_2$
Molecular Weight: 164,20

^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.80 (t, *J* = 1.8 Hz, 1H, H1), 7.46 – 7.22 (m, 5H, H6, H7 and H8), 4.54 (s, 2H, H4), 3.82 (t, *J* = 6.1 Hz, 2H, H3), 2.70 (td, *J* = 6.1, 1.8 Hz, 2H, H2).

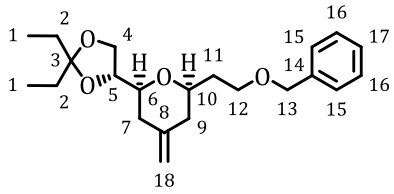
Experimental data in agreement with the literature[110].

{2R,6S)-2-(2-(benzyloxy)ethyl)-6-((R)-2,2-diethyl-1,3-dioxolan-4-yl)-4-methylenetetrahydro-2H-pyran **III.69**



A solution of the crude silyl ether (1 eq., 23.9 mmol) and aldehyde (1 eq., 3.92 g, 23.9 mmol) in DCM was cooled to -78°C. TMSOTf (0.2 eq., 0.87 mL, 4.78 mmol) was then added to the mixture and the reaction was stirred at -78°C until the TLC showed complete conversion of the silyl ether. The reaction was then quenched by addition of a few drops of pyridine then warmed to room temperature. The reaction mixture was diluted with DCM and a saturated solution of $NaHCO_3$ was added. The aqueous phase was extracted twice with DCM. The combined organic layers were then dried over Na_2SO_4 and the solvent was evaporated under reduce pressure. The crude reaction was purified by silica gel chromatography using EtOAc/PE 1:40 to 1/20 as eluent. The desired tetrahydropyran was isolated in 40% yield after two steps (3.3 g) as a colourless oil.

Analysis:



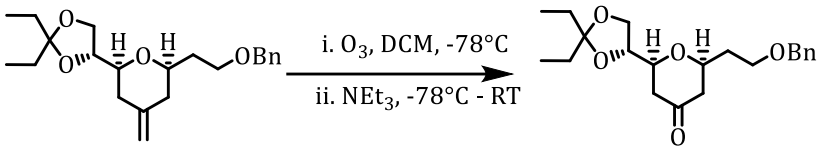
Chemical Formula: $C_{22}H_{32}O_4$
Molecular Weight: 360,49

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.42 – 7.27 (m, 5H, H15, H16 and H17), 4.78 (d, *J* = 1.8 Hz, 1H, H18), 4.74 (d, *J* = 1.8 Hz, 1H, H18), 4.56 – 4.44 (m, 2H, H13), 4.05 (dd, *J* = 8.0, 6.4 Hz, 1H, H4), 3.99 – 3.89 (m, 1H, H5), 3.76 (dd, *J* = 8.0, 6.3 Hz, 1H, H4), 3.64 – 3.51 (m, 2H, H12), 3.51 – 3.40 (m, 1H, H10), 3.21 (ddd, *J* = 11.2, 7.2, 2.4 Hz, 1H, H6), 2.52 – 2.42 (m, 1H, H7), 2.27 – 2.15 (m, 1H, H9), 1.97 (m, 2H, H7 and H9), 1.84 – 1.73 (m, 2H, H11), 1.72 – 1.56 (m, 4H, H2), 0.95 – 0.80 (m, 6H, H1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.82 (C8), 138.59 (C14), 128.51 (C16), 127.80 (C15), 127.73 (C17), 113.36 (C3), 109.34 (C18), 79.57 (C6), 78.52 (C5), 75.67 (C10), 73.16 (C13), 67.98 (C4), 66.65 (C12), 41.04 (C9), 37.83 (C7), 36.45 (C11), 29.82 (C2), 29.39 (C2), 8.37 (C1), 8.19 (C1).

IR (ν) : 2939 – 2883 (b), 1083 (s).

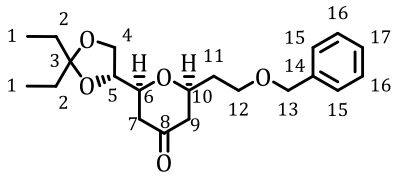
HRMS (ESI): Calculated for $C_{22}H_{33}O_4$ 361.23734; Found 361.23739.

(2S,6S)-2-(2-(benzyloxy)ethyl)-6-((R)-2,2-diethyl-1,3-dioxolan-4-yl)tetrahydro-4H-pyran-4-one **III.76**



A solution of tetrahydropyran (1 eq., 3.7 g, 10.26 mmol) in DCM (100 mL) was cooled down at -78°C using a dry ice/acetone bath. Then, O_3 was bubbled through the solution until the reaction solution turned blue/purple. O_2 was then bubbled through the reaction mixture until the solution became colourless. NEt_3 (3 eq., 4.4 mL, 30.78 mmol) was then added and the reaction was stirred overnight. The solvents were then evaporated under reduce pressure. The crude mixture was purified through column chromatography using EtOAc/PE 1/20 to 1/6 as eluent leading to ketone (3.3 g) in 88% yield as a yellow oil.

Analysis:



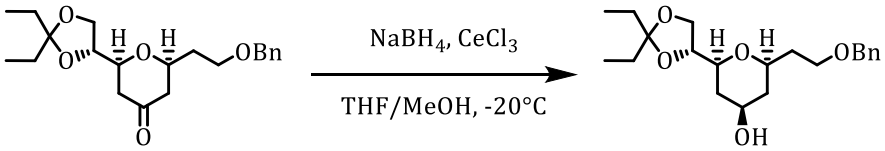
Chemical Formula: $C_{21}H_{30}O_5$
Molecular Weight: 362,47

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.39 – 7.27 (m, 5H, H15, H16 and H17), 4.55 – 4.42 (m, 2H, H13), 4.10 – 3.99 (m, 2H, H4 and H5), 3.87 – 3.71 (m, 2H, H5 and H10), 3.66 – 3.41 (m, 3H, H12 and H6), 2.59 (dt, *J* = 14.6, 2.4 Hz, 1H, H7), 2.45 – 2.21 (m, 3H, H7 and H9), 2.01 – 1.75 (m, 2H, H11), 1.67 – 1.52 (m, 4H, H2), 0.88 (t, *J* = 7.5 Hz, 6H, H1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.14 (C8), 138.32 (C14), 128.57 (C16), 127.84 (C15 and C17), 113.84 (C3), 78.06 (C5), 77.96 (C6), 74.45 (C10), 73.24 (C13), 67.53 (C4), 66.01 (C12), 47.99 (C9), 44.55 (C7), 36.49 (C11), 29.69 (C2), 29.04 (C2), 8.36 (C1), 8.19 (C1).

IR (ν) : 2973 (b), 1722 (s), 1274 (m), 1083 (s).

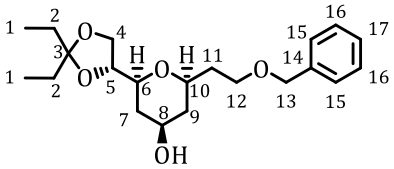
HRMS (ESI): Calculated for $C_{21}H_{31}O_5$ 363.21660; Found 363.21658.

(2S,4R,6S)-2-(2-(benzyloxy)ethyl)-6-((R)-2,2-diethyl-1,3-dioxolan-4-yl)tetrahydro-2H-pyran-4-ol **III.77**



Ketone (1 eq., 1.7 g, 4.69 mmol) and $CeCl_3$ (1 eq., 1.15 g, 4.69 mmol) were dissolved in a mixture of THF (45 mL) and MeOH (15 mL). The solution was cooled to -20°C. $NaBH_4$ (1.5 eq., 265 mg, 7.02 mmol) was then added slowly to the reaction mixture and the solution was stirred at -20°C. The reaction was monitored by TLC until completion. The reaction was then quenched with a saturated solution of NH_4Cl and diluted with ether. The layers were separated, and the aqueous layer was extracted twice with DCM. The combined organic layers were dried of Na_2SO_4 and the solvents were evaporated under reduced pressure. The crude mixture was purified by silica gel column chromatography using AcOEt/PE 1:4 to 1:1. The desired alcohol was isolated in 87 % yield (1.5 g) as a colourless oil.

Analysis:



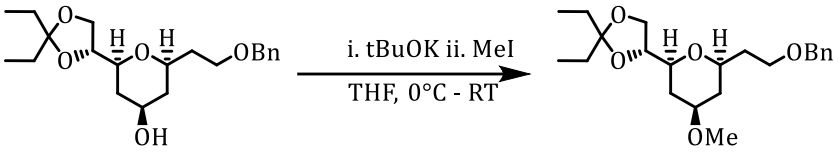
Chemical Formula: $C_{21}H_{32}O_5$
Molecular Weight: 364,48

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.39 – 7.26 (m, 5H, H15, H16 and H17), 4.56 – 4.41 (m, 2H, H13), 4.04 (dd, *J* = 8.0, 6.3 Hz, 1H, H4), 3.92 (dt, *J* = 7.2, 6.2 Hz, 1H, H5), 3.88 – 3.74 (m, 2H, H8 and H4), 3.63 – 3.46 (m, 3H, H12 and H10), 3.24 (ddd, *J* = 11.3, 7.1, 2.0 Hz, 1H, H6), 2.20 (ddt, *J* = 12.3, 4.4, 2.0 Hz, 1H, H7), 1.94 (ddt, *J* = 12.3, 4.3, 1.9 Hz, 1H, H9), 1.85 – 1.73 (m, 2H, H11), 1.70 – 1.52 (m, 4H, H2), 1.29 – 1.09 (m, 2H, H7 and H9), 0.90 (t, *J* = 7.5 Hz, 3H, H1), 0.88 (t, *J* = 7.5 Hz, 3H, H1).
^{13}C NMR (75 MHz, $CDCl_3$) δ 129.70 (C14), 128.53 (C16), 127.83 (C15), 127.77 (C17), 113.35 (C3), 78.14 (C5), 76.84 (C6), 73.20 (C13), 72.84 (C10), 68.05 (C8), 67.83 (C4), 66.58 (C12), 41.40 (C9), 38.28 (C7), 36.24 (C11), 29.81 (C2), 29.27 (C2), 8.38 (C1), 8.22 (C1).

IR (ν) : 3420 (b), 2971 – 2881 (b), 1721 (m), 1274 (m), 1204, 1083 (s), 1038 (m).

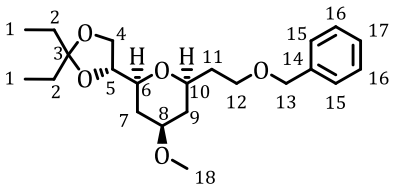
HRMS (ESI): Calculated for $C_{21}H_{31}O_5$ 365.23225; Found 365.23241.

(2S,4R,6S)-2-(2-(benzyloxy)ethyl)-6-((R)-2,2-diethyl-1,3-dioxolan-4-yl)-4-methoxytetrahydro-2H-pyran **III.79**



Alcohol (1 eq., 2.1 g, 5.48 mmol) was dissolved in THF (20 mL) and the solution was cooled to 0°C. *t*BuOK (3 eq., 1.84 g, 16.46 mmol) was then added and the reaction mixture was stirred at that temperature for 30 minutes. MeI (4 eq., 1.35 mL, 21.94 mmol) was added dropwise and the ice bath was removed. The reaction was stirred at room temperature until TLC showed complete conversion. The reaction was then quenched with NH_4Cl and diluted with Et_2O. The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were dried over Na_2SO_4 and the solvents were removed under reduced pressure. The product was used without further purification.

Analysis:



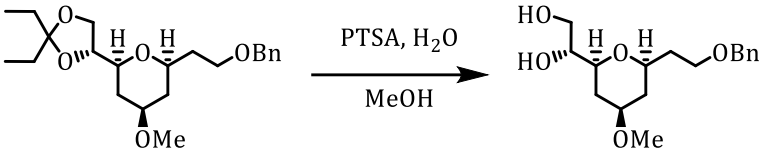
Chemical Formula: $C_{22}H_{34}O_5$
Molecular Weight: 378,51

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.39 – 7.27 (m, 5H, H15, H16 and H17), 4.56 – 4.41 (m, 2H, H13), 4.04 (dd, *J* = 8.0, 6.3 Hz, 1H, H4), 3.97 – 3.86 (m, 1H, H5), 3.77 (dd, *J* = 8.0, 6.2 Hz, 1H, H4), 3.61 – 3.45 (m, 3H, H12 and H10), 3.42 – 3.29 (m, 4H, H8 and H18), 3.23 (ddd, *J* = 11.4, 7.2, 2.0 Hz, 1H, H6), 2.28 (ddd, *J* = 10.4, 4.6, 2.3 Hz, 1H, H7), 2.04 – 1.93 (m, 1H, H9), 1.78 (m, 2H, H11), 1.68 – 1.53 (m, 4H, H2), 1.23 – 1.03 (m, 3H, H7 and H9), 0.90 (t, *J* = 7.5 Hz, 3H, H1), 0.88 (t, *J* = 7.5 Hz, 3H, H1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.95 (C14), 128.54 (C16), 127.82 (C15), 127.76 (C17), 113.37 (C3), 78.26 (C5), 76.99 (C6), 76.42 (C8), 73.19 (C13), 72.91 (C10), 67.88 (C4), 66.60 (C12), 55.54 (C18), 38.15 (C9), 36.36 (C11), 34.78 (C7), 29.83 (C2), 29.33 (C2), 8.37 (C1), 8.22(C1).

IR (ν) : 2932 – 2881 (b), 1459 (w), 1364 (w), 1085 (s).

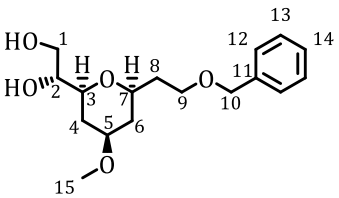
HRMS (ESI): Calculated for $C_{22}H_{35}O_5$ 379.247.90; Found 379.24788.

(R)-1-((2S,4R,6S)-6-(2-(benzyloxy)ethyl)-4-methoxytetrahydro-2H-pyran-2-yl)ethane-1,2-diol **III.80**



Acetonide (1 eq., 1.4 g, 3.69 mmol) was dissolved in MeOH (35 mL) and water (10 mL). PTSA (0.1 eq., 61 mg, 0.36 mmol)) was then added and the solution was stirred at room temperature until complete consumption of the starting material could be observed by TLC. The reaction was then diluted with DCM and quenched with $NaHCO_3$. The aqueous layer was extracted twice with DCM and the combined organic layers were dried with Na_2SO_4. The volatiles were removed under reduced pressure. Diol was purified by silica gel column chromatography using EtOAc/PE 1:1 as eluent and 962 mg were isolated as a colourless oil (yield: 84 %).

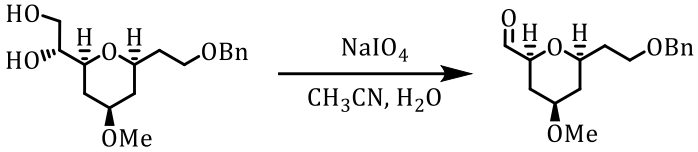
Analysis



Chemical Formula: $C_{17}H_{26}O_5$
Molecular Weight: 310,39

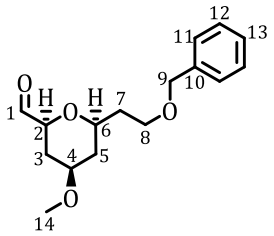
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.38 – 7.28 (m, 5H, H12, H13 and H15), 4.50 (d, *J* = 2.9 Hz, 2H, H10), 3.86 – 3.41 (m, 9H, H1, H2, H3, H5, H7 and H9), 3.36 (s, 3H, H15), 2.27 – 1.96 (m, 4H, H4 and H6), 1.87 – 1.73 (m, 2H, H8).

(2S,4R,6S)-6-(2-(benzyloxy)ethyl)-4-methoxytetrahydro-2H-pyran-2-carbaldehyde **III.81**



Diol (1 eq., 1 g, 3.22 mmol) was dissolved in a mixture of acetonitrile (30 mL) and water (6 mL) at room temperature. Sodium periodate (1.5 eq., 1.03 g, 4.83 mmol) was added and the reaction conversion was monitored by TLC. After complete consumption of the starting material, the reaction was diluted with DCM and quenched with a saturated solution of $Na_2S_2O_3$. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine and dried with Na_2SO_4. The solvents were evaporated under reduced pressure. Purification was carried out by silica gel column chromatography using EtOAc/PE 1:4 to 1:2 allowing the isolation of 550 mg of aldehyde as a colourless oil (yield: 62 %).

Analysis:

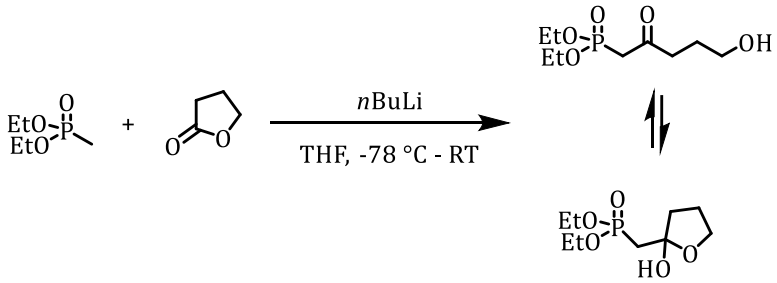


Chemical Formula: $C_{16}H_{22}O_4$
Molecular Weight: 278,35

^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.60 (d, *J* = 0.7 Hz, 1H, H1), 7.36 – 7.27 (m, 5H, H11 H12 and H13), 4.57 – 4.45 (m, 2H, H9), 3.79 – 3.71 (m, 1H), 3.71 – 3.53 (m, 4H), 3.47 – 3.38 (m, 1H), 3.36 (s, *J* = 1.8 Hz, 4H), 2.26 (ddt, *J* = 12.4, 4.5, 2.3 Hz, 1H), 2.09 – 1.98 (m, 3H), 1.98 – 1.75 (m, 3H), 1.29 – 1.08 (m, 5H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 201.35 (C1), 138.52 (C10), 128.51 (C12), 127.84 (C11), 127.77 (C13), 80.00 (C2), 77.36 (C4), 76.13 (C6), 73.12 (C9), 66.20 (C8), 55.66 (C14), 37.81 (C3), 36.17 (C5), 32.25 (C7).

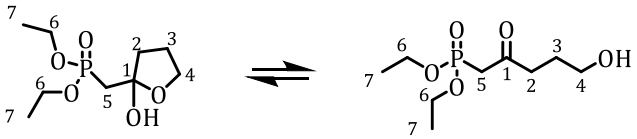
HRMS (ESI): Calculated for $C_{16}H_{23}O$ 279.15909; Found 279.15902.

diethyl ((2-hydroxytetrahydrofuran-2-yl)methyl)phosphonate **IV.38** and diethyl (5-hydroxy-2-oxopentyl)phosphonate **IV.39**



nBuLi (2 eq., 2 mL, 2 M in hexane, 4 mmol) was added to a THF (10 mL) solution of methyl diethylphosphonate (2 eq., 0.584 mL, 4 mmol) cooled at -78 °C with a dry ice/acetone bath. The reaction mixture was stirred for 30 minutes at -78 °C before adding a solution of butyrolactone (1 eq., 0.156 mL, 2 mmol) in THF (1 mL). The dry ice/acetone bath was then removed and the reaction was left to warm to room temperature and stirred while monitoring the conversion of the lactone by TLC. Upon complete conversion, the reaction was quenched with a saturated solution of NH_4Cl and diluted with ether. The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvents were removed under reduced pressure. The purification was carried out by silica gel column chromatography using EtOAc/PE 1:4 to 1:1 as eluent. 370 mg of the desired product was obtained in a yield of 78 %.

Analysis:



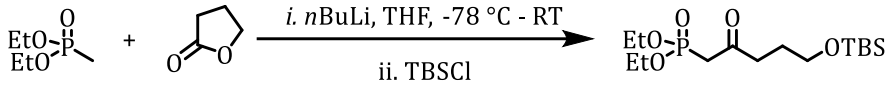
Chemical Formula: $C_9H_{19}O_5P$
Molecular Weight: 238,22

Chemical Formula: $C_9H_{19}O_5P$
Molecular Weight: 238,22

The compound is present as a mixture of ketone and lactol. The data given below are extracted from the NMR of the mixture and correspond to the major product.

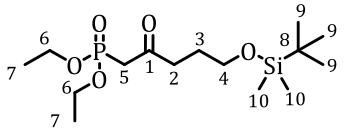
^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.26 – 4.04 (m, 4H, H6), 3.62 (t, *J* = 5.9 Hz, 2H, H4), 3.11 (d, *J* = 22.9 Hz, 2H, H5), 2.77 (t, *J* = 6.6 Hz, 2H, H2), 1.85 (m, 2H, H3), 1.33 (m, 6H, H7). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 202.17 (d, *J* = 6.0 Hz, C1), 62.57 (C6), 62.48 (C6), 60.72 (C4), 42.03 (d, *J* = 127.6 Hz, C5), 40.31 (C2), 26.15 (C3), 16.07 (C7), 15.98 (C7).

diethyl (5-((tert-butyldimethylsilyl)oxy)-2-oxopentyl)phosphonate **IV.41**



nBuLi (2 eq., 2 mL, 2 M in hexane, 4 mmol) was added to a THF (10 mL) solution of methyl diethylphosphonate (2 eq., 0.584 mL, 4 mmol) cooled at -78 °C with a dry ice/acetone bath. The reaction mixture was stirred for 30 minutes at -78 °C before adding a solution of butyrolactone (1 eq., 0.156 mL, 2 mmol) in THF (1 mL). The dry ice/acetone bath was then removed and the reaction was left to warm to room temperature and stirred while monitoring the conversion of the lactone by TLC. Upon complete conversion, a solution of TBSCl (1 eq., 301.4 mg, 2 mmol) in THF was added dropwise and the mixture was stirred overnight. The reaction was quenched with a saturated solution of NH_4Cl and diluted with ether. The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvents were removed under reduced pressure. The purification was carried out by silica gel column chromatography using EtOAc/PE 1:2 to 1:1 as eluent. 410 mg of phosphonate could be isolated with a yield of 55 % as a colourless oil.

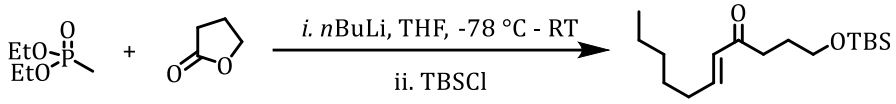
Analysis:



Chemical Formula: $C_{15}H_{33}O_5PSi$
Molecular Weight: 352,48

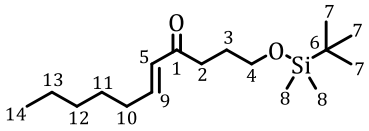
^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.23 – 4.02 (m, 4H, H6), 3.61 (t, *J* = 6.1 Hz, 2H, H4), 3.10 (d, *J* = 22.7 Hz, 2H, H5), 2.69 (t, *J* = 7.2 Hz, 2H, H2), 1.79 (p, *J* = 6.6 Hz, 2H, H3), 1.41 – 1.26 (m, 6H, H7), 0.87 (s, 19H, H9), 0.03 (s, 6H, H10).

(E)-1-((tert-butyldimethylsilyl)oxy)undec-5-en-4-one **IV.44**



nBuLi (2 eq., 2 mL, 2 M in hexane, 4 mmol) was added to a THF (10 mL) solution of methyl diethylphosphonate (2 eq., 0.584 mL, 4 mmol) cooled at -78 °C with a dry ice/acetone bath. The reaction mixture was stirred for 30 minutes at -78 °C before adding a solution of butyrolactone (1 eq., 0.156 mL, 2 mmol) in THF (1 mL). The dry ice/acetone bath was then removed and the reaction was left to warm to room temperature and stirred while monitoring the conversion of the lactone by TLC. Upon complete conversion, a solution of TBSCl (1 eq., 301.4 mg, 2 mmol) in THF was added dropwise and the mixture was stirred overnight. A solution of hexanal (1 eq., 0.24 mL, 2 mmol) in THF (1 mL) was then added and the reaction was heated to reflux for one hour. The reaction was quenched with a saturated solution of NH_4Cl and diluted with ether. The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvents were removed under reduced pressure. The purification was carried out by silica gel column chromatography using EtOAc/PE 1:60 to 1:1 as eluent. 158 mg of enone were isolated with a yield of 28 % as a colourless oil.

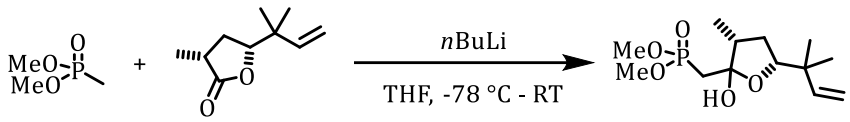
Analysis:



Chemical Formula: $C_{17}H_{34}O_2Si$
Molecular Weight: 298,54

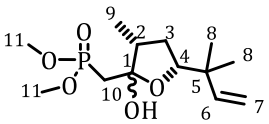
^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.80 (dt, *J* = 15.8, 6.9 Hz, 1H, H9), 6.05 (dt, *J* = 15.9, 1.4 Hz, 1H, H5), 3.59 (t, *J* = 6.1 Hz, 2H, H4), 2.58 (t, *J* = 7.3 Hz, 2H, H2), 2.25 – 2.05 (m, 2H, H10), 1.78 (p, *J* = 7.1, 6.6 Hz, 2H, H3), 1.51–1.26 (m, 6H, H12, H11 and H13), 0.85 (m, 9H , H7 and H14), -0.00 (s, 6H, H8). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.47(C1), 147.34(C9), 130.44(C5), 62.22(C4), 36.20(C2), 32.45(C10), 31.40 (C3), 27.85(C13 or C12), 27.31(C11), 25.95(C7), 22.47(C12 or C13), 18.32 (C6), 13.98(C14), -5.33(C8).

dimethyl (((3R,5R)-2-hydroxy-3-methyl-5-(2-methylbut-3-en-2-yl)tetrahydrofuran-2-yl)methyl)phosphonate **IV.49**



nBuLi (2 eq., 0.803 mL, 2.48 M in hexane, 2 mmol) was added to a THF (5 mL) solution of methyl dimethylphosphonate (2 eq., 0.213 mL, 2 mmol) cooled at -78 °C with a dry ice/acetone bath. The reaction mixture was stirred for one hour at -78 °C before adding a solution of lactone (1 eq., 168.24 mg, 1 mmol) in THF (1 mL). The dry ice/acetone bath was then removed and the reaction was left to warm to room temperature and stirred while monitoring the conversion of the lactone by TLC. Upon complete conversion, the reaction was quenched with a saturated solution of NH_4Cl and diluted with ether. The phases were separated and the aqueous phase was extracted twice with ether. The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvents were removed under reduced pressure. The purification was carried out by silica gel column chromatography using EtOAc/PE 1:4 to 1:1 as eluent allowing the isolation of 255 mg of lactol as a colourless oil.

Analysis:

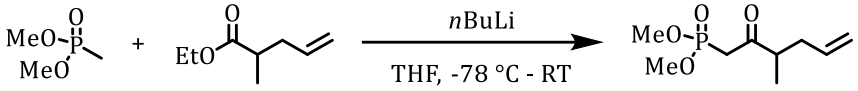


Chemical Formula: $C_{13}H_{25}O_5P$
Molecular Weight: 292,31

The compound is present as a mixture of ketone and lactol. The data given below are extracted from the NMR of the mixture and correspond to the major product.

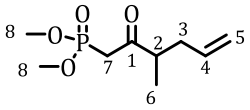
^{1}H NMR (300 MHz, DMSO-d_6) δ 5.93 (dd, *J* = 17.6, 10.9 Hz, 1H, H6), 5.62 (s, 1H, OH), 5.06 – 4.90 (m, 2H, H7), 3.78 – 3.55 (m, 7H, H4 and H11), 2.48 – 2.38 (m, 1H, H2), 2.38 – 2.05 (m, 2H, H10), 1.70 (dt, *J* = 11.8, 5.9 Hz, 1H, H3), 1.42 (q, *J* = 11.4 Hz, 1H, H3), 0.99 – 0.82 (m, 9H, H8 and H9). ^{13}C NMR (75 MHz, DMSO-d_6) δ 145.43 (C6), 111.54 (C7), 102.37 (C1), 85.08 (C4), 52.35 (d, *J* = 6.1 Hz, C11), 51.49 (d, *J* = 6.2 Hz, C11), 40.99 (C2), 39.77 (C5), 33.86 (d, *J* = 135.4 Hz, C10), 33.19(C3), 23.52 (C8), 22.76 (C8), 12.67 (C9).

dimethyl (3-methyl-2-oxohex-5-en-1-yl)phosphonate **V.23**



*n*BuLi (2 eq., 8.79 mL, 2.5 M in hexane, 14.07 mmol) was added to a THF (35 mL) solution of methyl dimethylphosphonate (2 eq., 1.524 mL, 14.07 mmol) cooled at -78 °C with a dry ice/acetone bath. The reaction mixture was stirred for one hour at -78 °C before adding a solution of ester (1 eq., 1g, 7.03 mmol) in THF (5 mL). The dry ice/acetone bath was then removed and the reaction was left to warm to room temperature and stirred while monitoring the conversion of the lactone by TLC. Upon complete conversion, the reaction was quenched with a saturated solution of NH_4Cl and diluted with ether. The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvents were removed under reduced pressure. The purification was carried out by silica gel column chromatography using EtOAc/PE 1:4 to 1:1 as eluent affording 1.4 g of ketone as a colourless oil in 91 % yield.

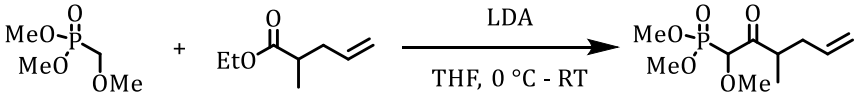
Analysis



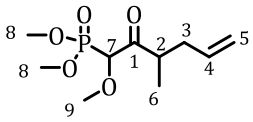
Chemical Formula: $C_9H_{17}O_4P$
Molecular Weight: 220,20

^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.71 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1H, H4), 5.10 – 4.98 (m, 2H, H5), 3.80 – 3.79 (m, 3H, H8), 3.77 – 3.75 (m, 3H, H8), 3.12 (d, *J* = 22.5 Hz, 2H, H7), 2.82 (p, *J* = 6.9 Hz, 1H, H2), 2.41 (dtd, *J* = 13.0, 6.6, 1.3 Hz, 1H, H3), 2.17 – 2.05 (m, 1H, H3), 1.10 (d, *J* = 7.0 Hz, 3H, H6).

dimethyl (1-methoxy-3-methyl-2-oxohex-5-en-1-yl)phosphonate **V.41**



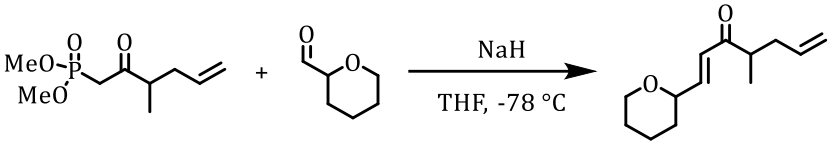
A solution of LDA was prepared by the addition of iPr_2NH (1 eq., 0.350 mL, 2.53 mmol) to *n*BuLi (1 eq., 1.13 mL, 2.13 M in hexane, 2.53 mmol) at room temperature followed by the addition of THF (8 mL). This LDA solution was added dropwise to a solution of methoxymethyl dimethylphosphonate (1 eq., 389 mg, 2.53 mmol) and ester (1 eq., 360 mg, 2.53 mmol) cooled at 0 °C with an ice bath. The reaction was left to warm to room temperature and the consumption of the ester was monitored by TLC. Upon complete consumption, the reaction was diluted with Et_2O and quenched with a saturated solution of NH_4Cl. The layers were separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were dried over Na_2SO_4 and the solvents were removed under reduced pressure. The ketone was purified by silica gel column chromatography using EtOAc/PE 1:2 to 2:1 as eluent. 538 mg of the desired product were isolated in 85 % yield as a yellowish oil.



Chemical Formula: $C_{10}H_{19}O_5P$
Molecular Weight: 250,23

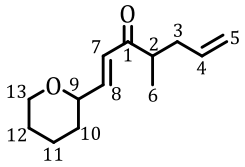
^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.77 – 5.55 (m, 1H), 5.12 – 4.88 (m, 2H), 4.28 (d, *J* = 20.4 Hz, 1H, H7a), 4.24 (d, *J* = 19.9 Hz, 1H, H7b), 3.80 (d, *J* = 1.4 Hz, 3H, H8a), 3.77 (d, *J* = 1.4 Hz, 3H, H8b), 3.76 – 3.75 (m, 3H, H8a), 3.73 – 3.72 (m, 3H, H8b), 3.43 (s, 3H, H9a), 3.41 (s, 3H, H9b), 3.06 (h, *J* = 6.9 Hz, 1H, H2), 2.43 – 2.26 (m, 1H, H3), 2.05 (dq, *J* = 14.4, 7.2 Hz, 1H, H3), 1.05 (d, *J* = 7.1 Hz, 3H, H6a), 1.04 (d, *J* = 6.7 Hz, 1H, H6b).

(E)-4-methyl-1-(tetrahydro-2H-pyran-2-yl)hepta-1,6-dien-3-one **V.26**



A solution of phosphonate (1 eq., 220 mg, 1 mmol) in THF (2 mL) was added dropwise to a suspension of NaH (1 eq., 40 mg, 60 % in mineral oil, 1 mmol) in THF (6 mL) at room temperature. The reaction was stirred until the formation of hydrogen ceased. The reaction mixture was then stirred at -78 °C before adding a solution of aldehyde (1 eq., 114 mg, 1 mmol) in THF (2 mL). The reaction was stirred at -78 °C until the complete conversion of aldehyde was observed by TLC. The reaction was then quenched with a saturated solution of NH_4Cl and diluted with Et_2O. The phases were separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were dried over Na_2SO_4 and the solvents were removed under reduced pressure. The crude was purified by silica gel column chromatography using EtOAC/PE 1:40 to 1:10 as eluant. Enone could be isolated as a colourless oil with 58 % conversion.

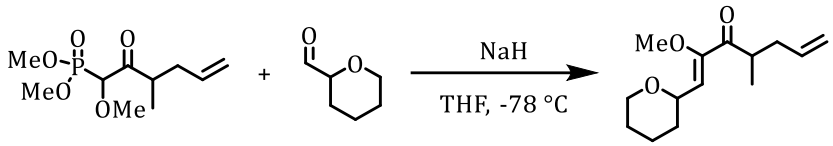
Analysis:



Chemical Formula: $C_{13}H_{20}O_2$
Molecular Weight: 208,30

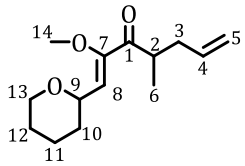
^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.79 (dd, *J* = 15.8, 4.1 Hz, 1H, H8), 6.37 (dd, *J* = 15.8, 1.8 Hz, 1H, H7), 5.83 – 5.61 (m, 1H, H4), 5.12 – 4.90 (m, 2H, H5), 4.09 – 3.91 (m, 2H, H9 and H13), 3.50 (td, *J* = 11.3, 2.8 Hz, 1H, H13), 2.79 (h, *J* = 7.0 Hz, 1H, H2), 2.50 – 2.35 (m, 1H, H3), 2.09 (dt, *J* = 14.4, 7.4 Hz, 1H, H3), 1.88 (dt, *J* = 8.8, 2.5 Hz, 1H, H11), 1.81 – 1.67 (m, 1H, H10), 1.58 (m, 3H, H11 and H12), 1.44 – 1.22 (m, 1H, H10), 1.10 (d, *J* = 6.9 Hz, 3H, H6). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 203.22 (C1), 146.30 (C8), 135.90 (C4), 126.09 (C7), 116.79 (C5), 76.57 (C9), 68.54 (C13), 44.39 (C2), 37.13 (C3), 31.67 (C10), 25.80 (C12), 23.61 (C11), 16.19 (C6).

2-methoxy-4-methyl-1-(tetrahydro-2H-pyran-2-yl)hepta-1,6-dien-3-one **V.42** and **V.43**



A solution of phosphonate (1.3 eq., 100 mg, 0.39 mmol) in THF (1 mL) was added dropwise to a suspension of NaH (1.2 eq., 15 mg, 60 % in mineral oil, 0.368 mmol) in THF (3 mL) at room temperature. The reaction was stirred until the formation of hydrogen ceased. The reaction mixture was then stirred at -78 °C before adding a solution of aldehyde (1 eq., 35 mg, 0.307 mmol) in THF (1 mL). The reaction was stirred at -78 °C until the complete conversion of aldehyde was observed by TLC. The reaction was then quenched with a saturated solution of NH_4Cl and diluted with Et_2O. The layers were separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were dried over Na_2SO_4 and the solvents were removed under reduced pressure. The crude was purified by silica gel column chromatography using EtOAc/PE 1:40 to 1:10 as eluent. 40 mg of enone could be isolated in 55 % yield as a colourless oil.

Analysis



Chemical Formula: $C_{14}H_{22}O_3$
Molecular Weight: 238,33

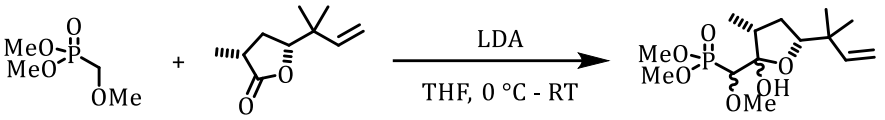
Major isomer: (E) based on comparison with literature and minor isomer: (Z) based on comparison with literature[111].

^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.97 (d, *J* = 7.4 Hz, 1H, H8(Z)), 5.66 (m, 1H), 5.03 – 4.85 (m, 3H, H5 and H8(E)), 4.46 – 4.35 (m, 1H, H9(E)), 4.29 (ddd, *J* = 10.0, 7.4, 2.3 Hz, 1H, H9(Z)), 3.91 (td, *J* = 11.4, 2.8 Hz, 6H, H13), 3.58 (s, 3H, H14 (Z)), 3.52 (s, 3H, H14(E)), 3.43 (ddt, *J* = 15.9, 8.1, 3.9 Hz, 1H, H13), 3.20 – 3.10 (m, 1H,H2), 3.09 – 2.97 (m, 1H, H2), 2.43 – 2.24 (m, 1H, H3), 2.11 – 1.88 (m, 1H, H3), 1.84 – 1.19 (m, 6H, H10, H11 and H12), 1.05 – 0.95 (m, 3H, H6).

HRMS (ESI): Calculated for $C_{14}H_{23}O_3$: 239.16417. Found 239.16414.

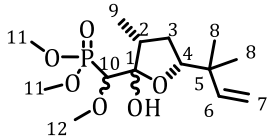
[111] V. Faivre, C. Lila, A. Saroli, A. Doutheau, *Tetrahedron*, **1989**, *45*, 7765-7782.

dimethyl (((3R,5R)-2-hydroxy-3-methyl-5-(2-methylbut-3-en-2-yl)tetrahydrofuran-2-yl)(methoxy)methyl)phosphonate **V.44**



A solution of LDA was prepared by the addition of iPr_2NH (4.4 eq., 1.83 mL, 13.07 mmol) to *n*BuLi (4.2 eq., 5 mL, 2.5 M in hexane, 12.48 mmol) at room temperature followed by the addition of THF (25 mL). This LDA solution was added dropwise to a solution of methoxymethyl dimethylphosphonate (4.2 eq., 1.923 g, 12.48 mmol) and lactone (1 eq., 500 mg, 2.97 mmol) cooled at 0 °C with an ice bath. The reaction was left to warm to room temperature and the consumption of the lactone was monitored by TLC. Upon complete consumption, the reaction was diluted with Et_2O and quenched with a saturated solution of NH_4Cl. The layers were separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were dried over Na_2SO_4 and the solvents were removed under reduced pressure. Lactol could be purified by silica gel column chromatography using EtOAc/PE 1:2 to 2:1 as eluent. 840 mg of the desired product could be isolated in 87 % yield as a yellowish oil.

Analysis:

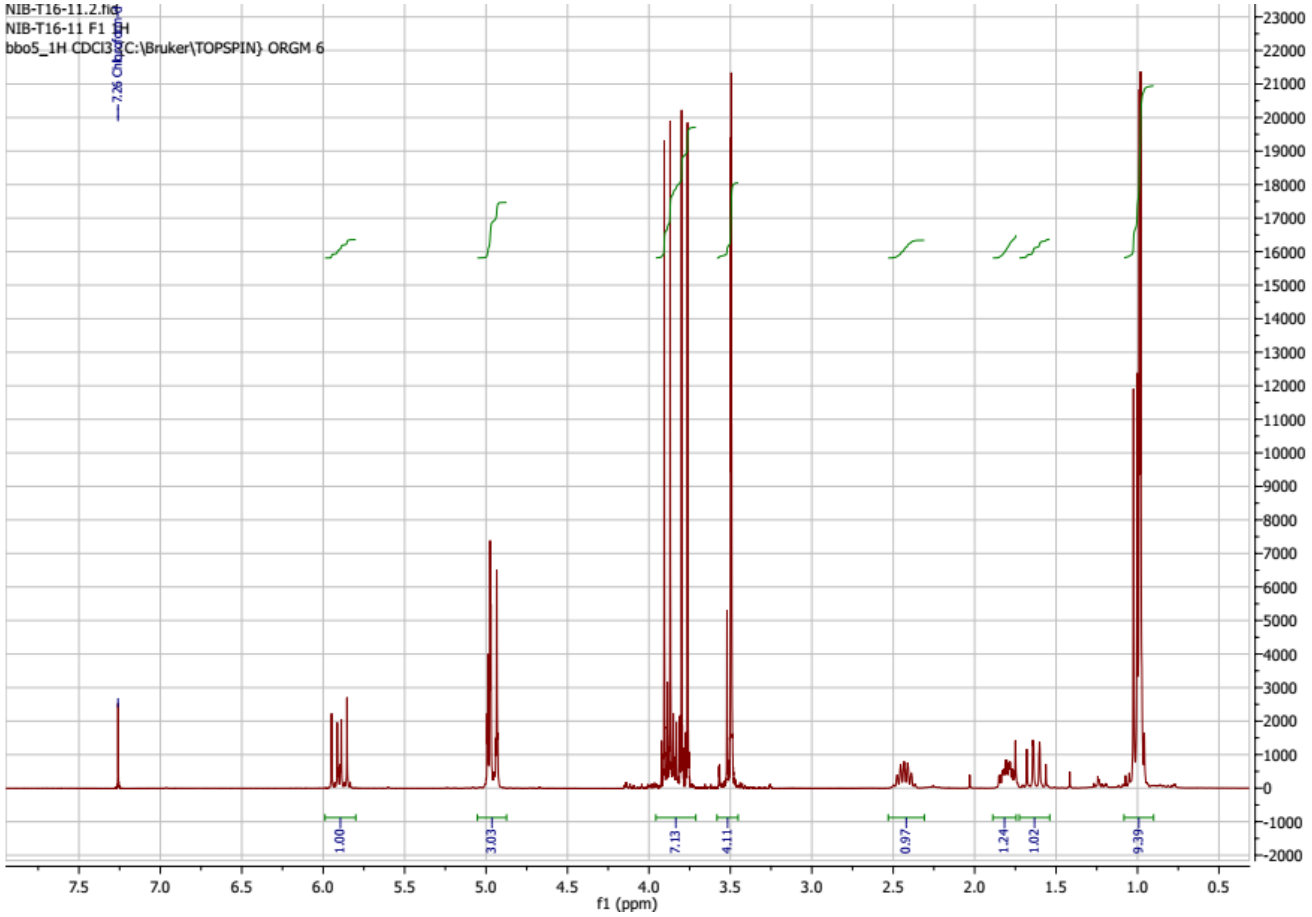


Chemical Formula: $C_{14}H_{27}O_6P$
Molecular Weight: 322,34

^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.91 (dd, *J* = 17.9, 10.4 Hz, 1H, H6), 5.06 – 4.86 (m, 3H, H7 and OH), 3.97 – 3.74 (m, 7H, H11 and H4), 3.55 – 3.42 (m, 4H, H10 and H12), 2.43 (dq, *J* = 13.0, 6.5 Hz, 1H, H2), 1.88 – 1.74 (m, 2H, H3), 1.71 – 1.54 (m, 2H, H3), 1.07 – 0.93 (m, 9H, H8 and H9). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 145.39 (C6), 111.89 (C7), 104.85 (C1), 87.15 (C4), 77.94 (d, *J* = 152.6 Hz, C10), 61.26 (C12), 54.92(C11), 51.91 (C11), 39.81 (C5), 37.33 (C2), 33.29 (C3), 23.95 (C8), 22.90 (C8), 12.84 (C9).

IR (ν) : 2962 (b), 1228 (m), 1184 (m), 1143 (m), 1100 (m), 1033 (s).

HRMS (ESI) Calculated for $C_{14}H_{26}O_6P$: 321.14615 Found 321.14654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bbo5_1H CDCl3 C:\Bruker\TOPSPIN} ORGM 6
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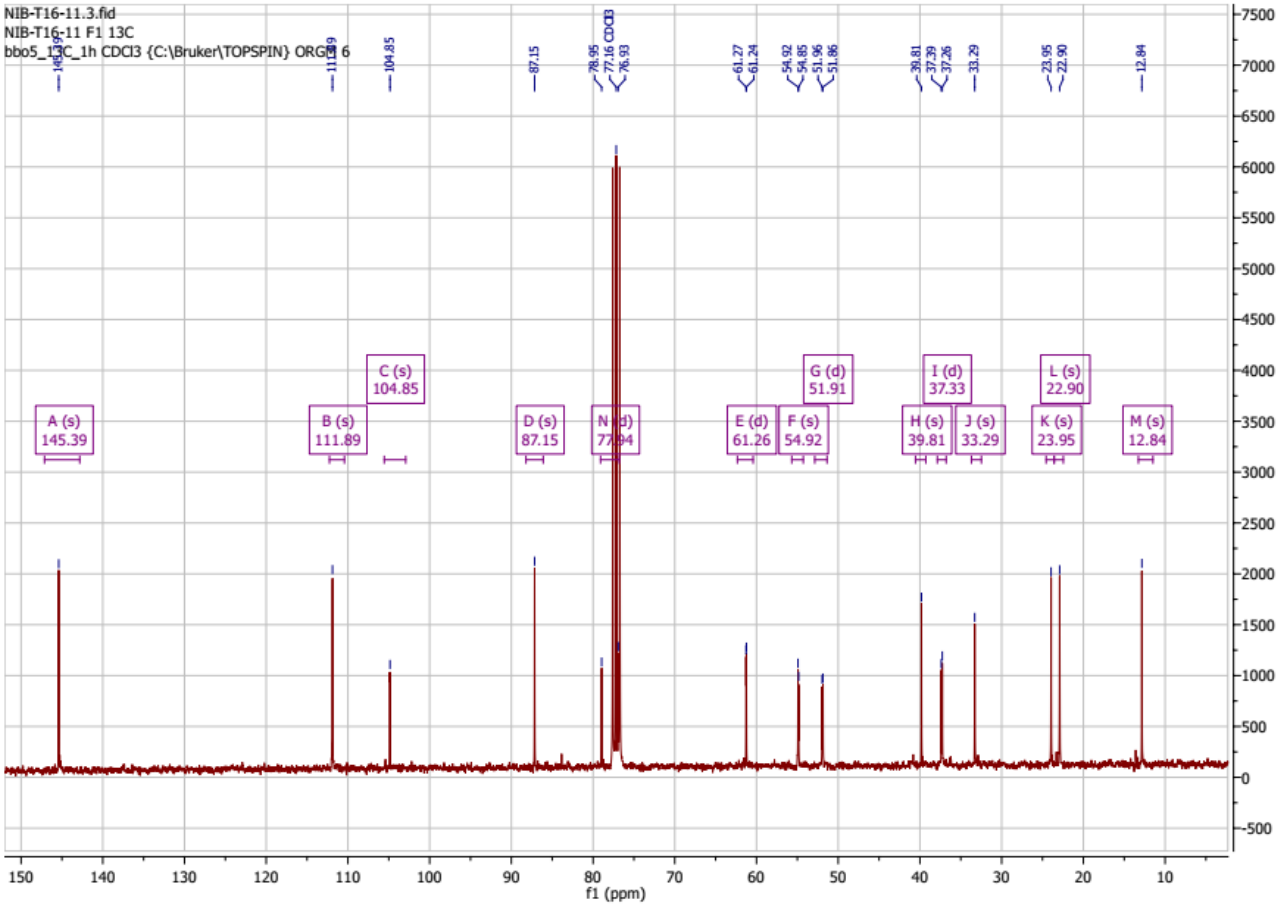
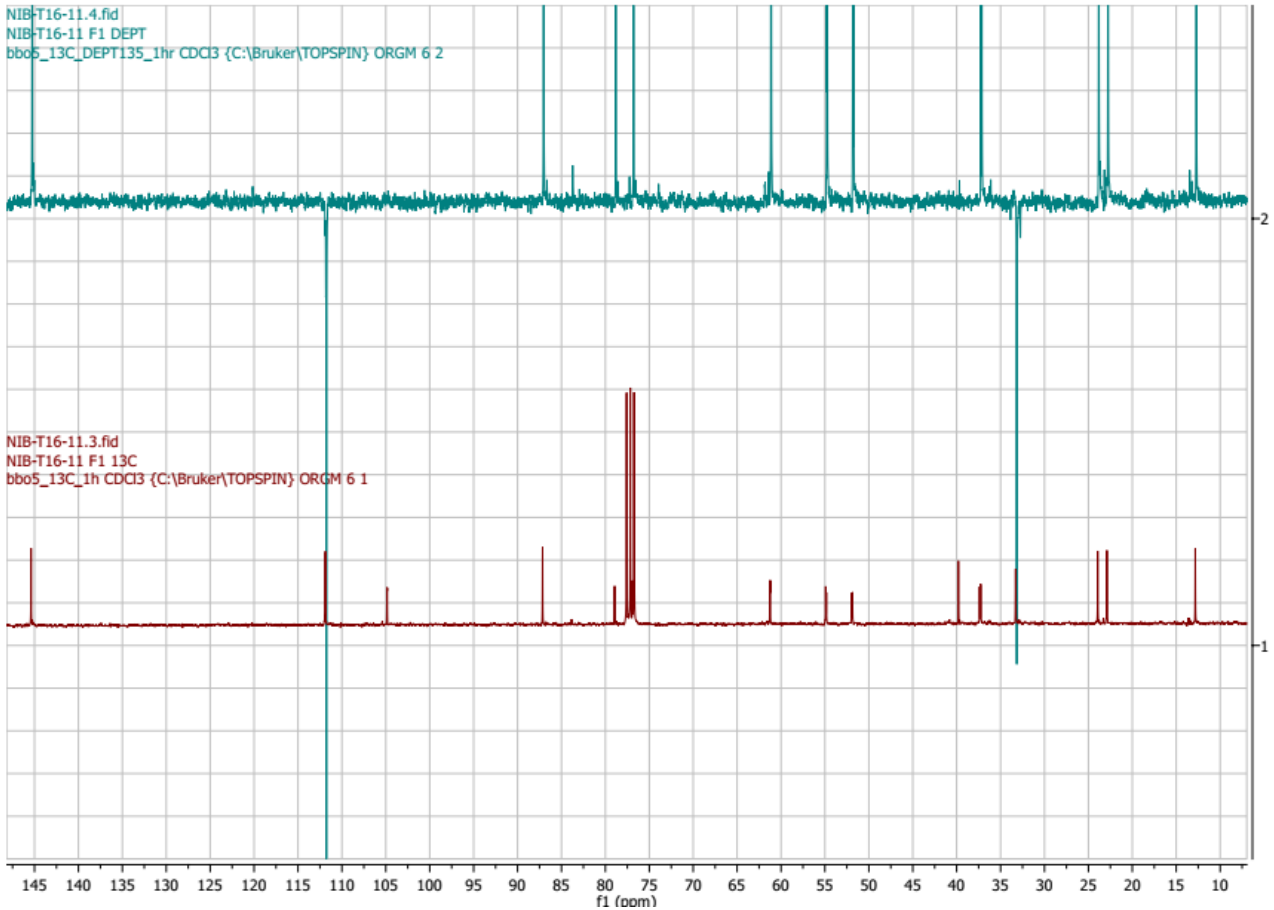
1.00
3.03
7.13
4.11
0.97
1.24
1.02
9.39
f1 (ppm)


NIB-T16-11.3.fid
NIB-T16-11 F1 13C
bbo5_13C_1h CDCl3 {C:\Bruker\TOPSPIN} ORGANIC 6
145.39
111.89
104.85
87.15
78.95
77.16 CDCl3
76.93
61.27
61.24
54.92
54.85
51.96
51.86
39.81
37.39
37.26
33.29
23.95
22.90
12.84
A (s) 145.39
B (s) 111.89
C (s) 104.85
D (s) 87.15
E (d) 61.26
F (s) 54.92
G (d) 51.91
H (s) 39.81
I (d) 37.33
J (s) 33.29
K (s) 23.95
L (s) 22.90
M (s) 12.84
f1 (ppm)


NIB-T16-11.4.fid
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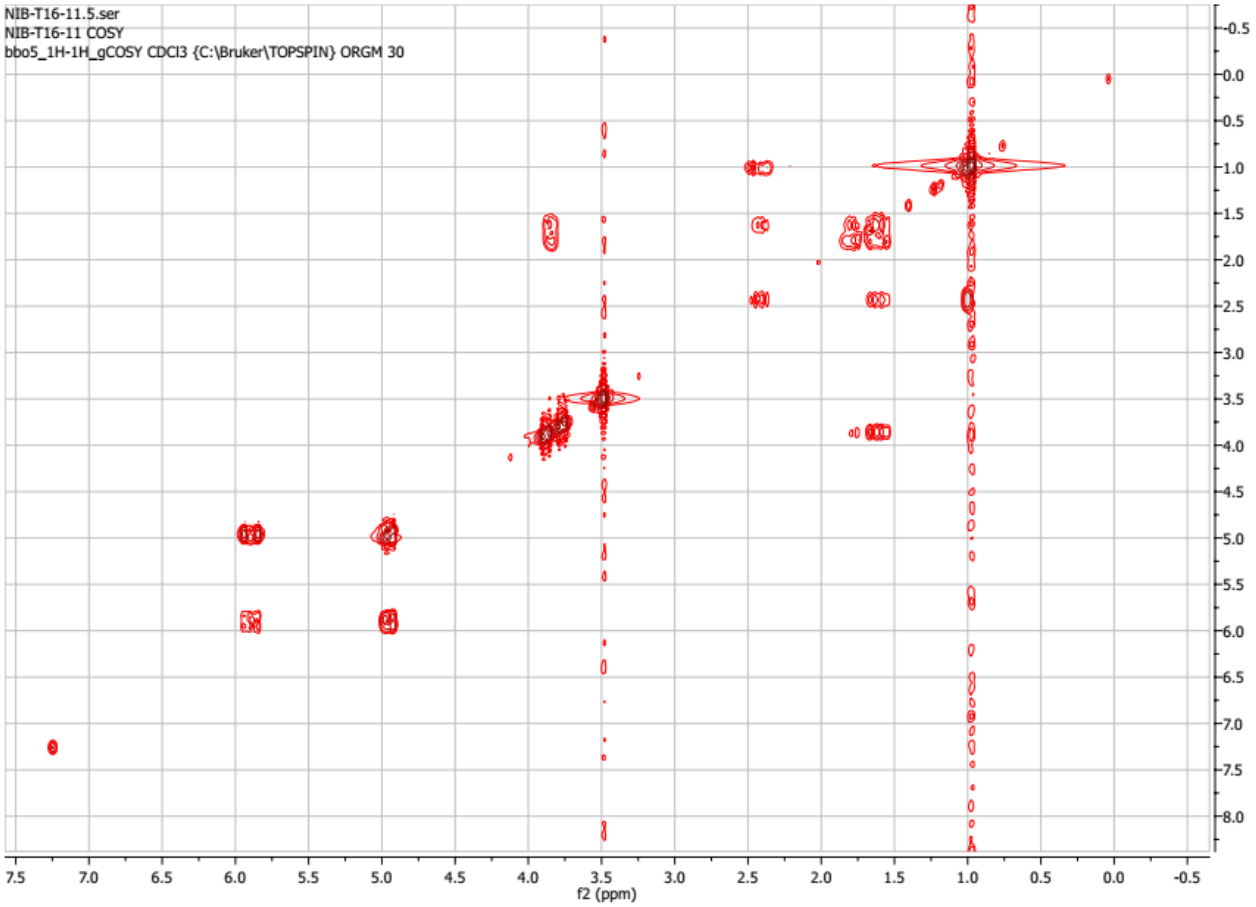
bbo5_13C_DEPT135_1hr CDCl3 {C:\Bruker\TOPSPIN} ORGM 6 2
NIB-T16-11.3.fid
NIB-T16-11 F1 13C
bbo5_13C_1h CDCl3 {C:\Bruker\TOPSPIN} ORGM 6 1
2
1
145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10
f1 (ppm)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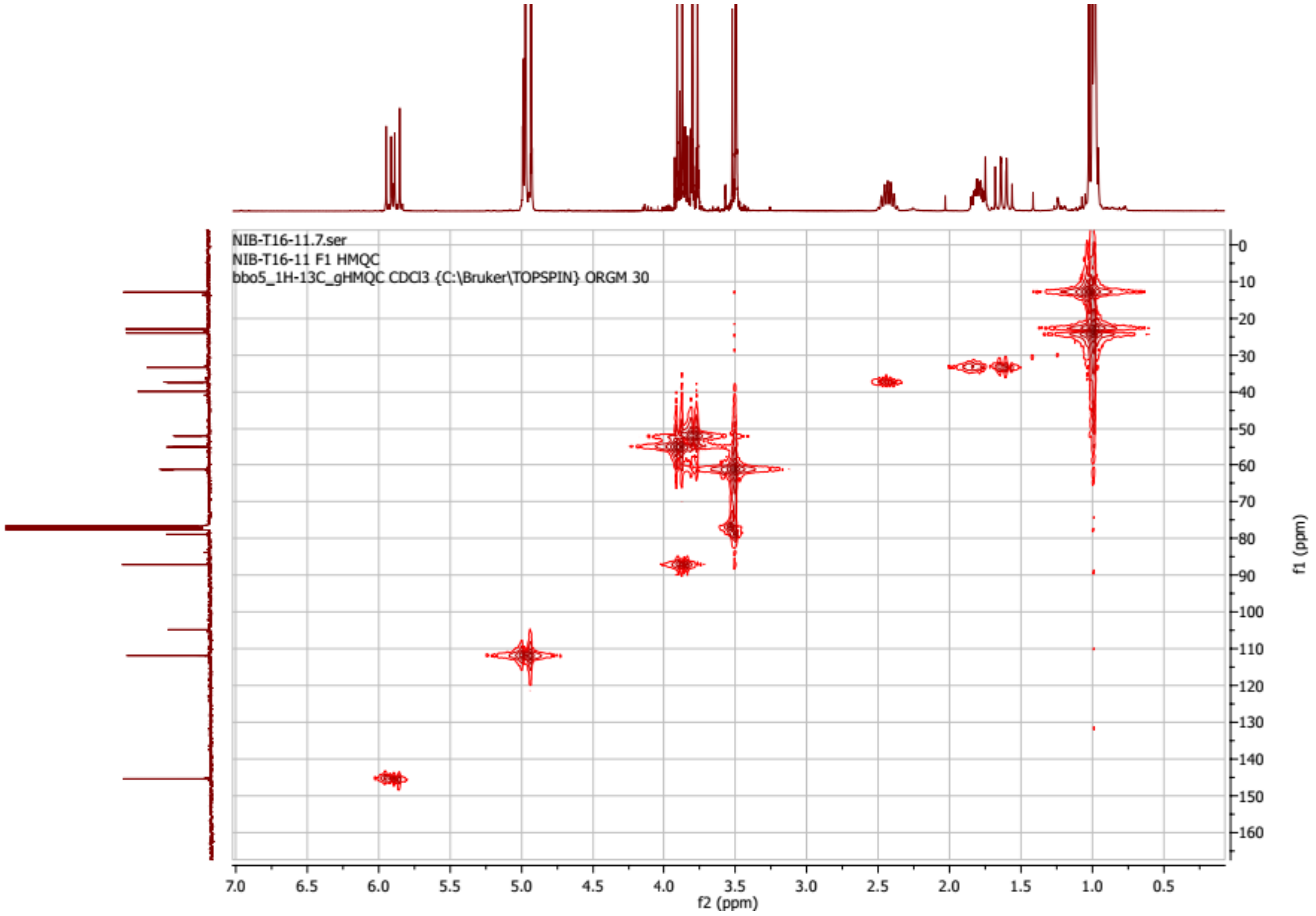
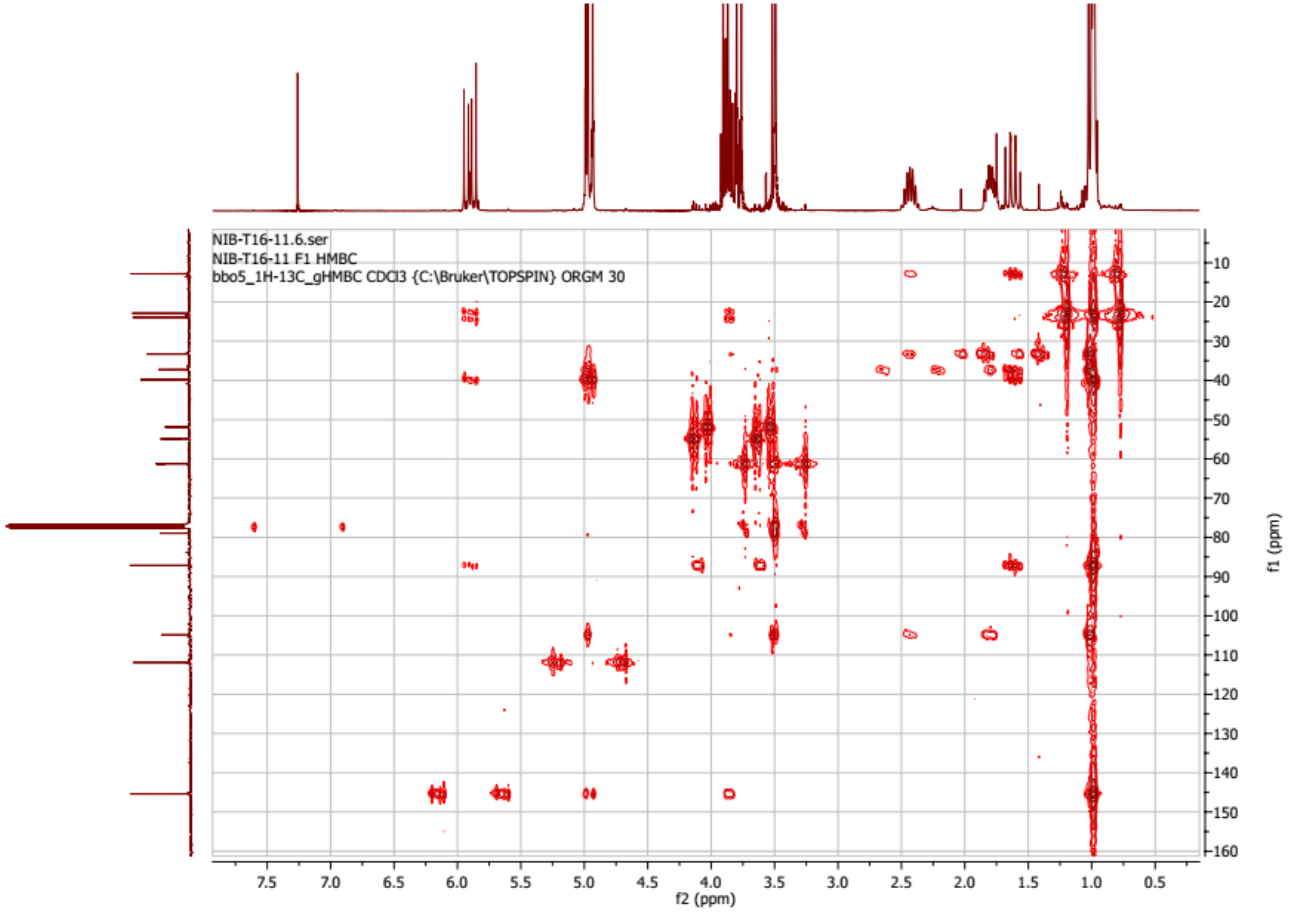
bbo5_1H-1H_gCOSY CDCl3 {C:\Bruker\TOPSPIN} ORGM 30
f2 (ppm)


NIB-T16-11.7.ser
NIB-T16-11 F1 HMQC
bbo5_1H-13C_gHMQC CDCl3 {C:\Bruker\TOPSPIN} ORGM 30
f2 (ppm)
f1 (ppm)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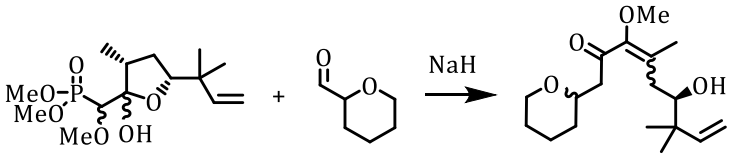
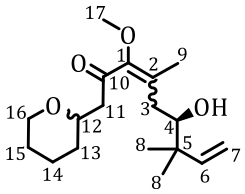
NIB-T16-11 F1 HMBC
bbo5_1H-13C_gHMBC CDCl3 {C:\Bruker\TOPSPIN} ORGM 30
f2 (ppm)
f1 (ppm)

(6R)-6-hydroxy-3-methoxy-4,7,7-trimethyl-1-(tetrahydro-2H-pyran-2-yl)nona-3,8-dien-2-one **V.53**



NaH (2.3 eq., 44 mg, 2.3 mmol) was added to a solution of phosphonate (1.2 eq., 312 mg, 1.2 mmol)) in THF (8mL) cooled at 0 °C with an ice bath. The reaction was stirred at that temperature until no more hydrogen bubbles were observed. The reaction was then cooled at -78 °C using dry ice/acetone bath before adding a solution of aldehyde (1 eq., 92 mg, 1 mmol) in THF (2 mL). The reaction mixture was then stirred for 30 minutes at -78 °C and warmed to room temperature by removing the dry ice/acetone bath. The reaction mixture was stirred for an additional hour before being diluter with Et_2O and quenched with a saturated solution of NH_4Cl. The phases were separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4 and the solvents were removed under reduced pressure. The purification was performed by silica gel column chromatography using EtOAC/PE 1:20 to 1:4 affording the desired product as a colourless oil.

Analysis



Chemical Formula: $C_{18}H_{30}O_4$
Molecular Weight: 310,43

The compound is present as a mixture of diastereoisomers.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.88 – 5.73 (m, 1H, H6), 5.06 (dd, *J* = 2.2, 0.7 Hz, 1H, H7), 5.01 (ddd, *J* = 5.7, 2.2, 1.4 Hz, 1H, H7), 4.25 (ddd, *J* = 10.6, 9.3, 3.0 Hz, 1H, H4), 3.99 – 3.90 (m, 1H, H16), 3.85 (dddd, *J* = 10.6, 7.2, 6.1, 2.0 Hz, 1H, H12), 3.56 – 3.38 (m, 4H, H16 and H17), 2.87 (ddd, *J* = 17.0, 6.8, 1.3 Hz, 1H, H11), 2.71 – 2.46 (m, 3H, H11 and H3), 1.98 (t, *J* = 1.8, 1.0 Hz, 3H, H9), 1.88 – 1.76 (m, 1H, H15), 1.69 – 1.61 (m, 1H, H14), 1.52 – 1.19 (m, 6H, H13, H14 and H15), 1.04 (s, 3H, H8), 1.00 (s, 3H, H8). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 193.91 (C10), 193.73 (C10), 147.34 (C1), 143.30 (C6), 122.81 (C2), 122.70 (C2), 113.29 (C7), 85.75 (C4), 73.56 (C12), 73.25 (C12), 68.71 (C16), 51.03 (C17), 47.41 (C11), 47.30 (C18), 40.95 (C5), 38.99 (C3), 32.04 (C13), 26.03 (C15), 23.55 (C14), 22.80 (C8), 22.74 (C8), 22.67 (C8), 22.60(C8), 12.95 (C9), 12.91 (C9).

HRMS (ESI) Calculated for $C_{18}H_{30}O_4Na$: 333.20363 Found 333.20353.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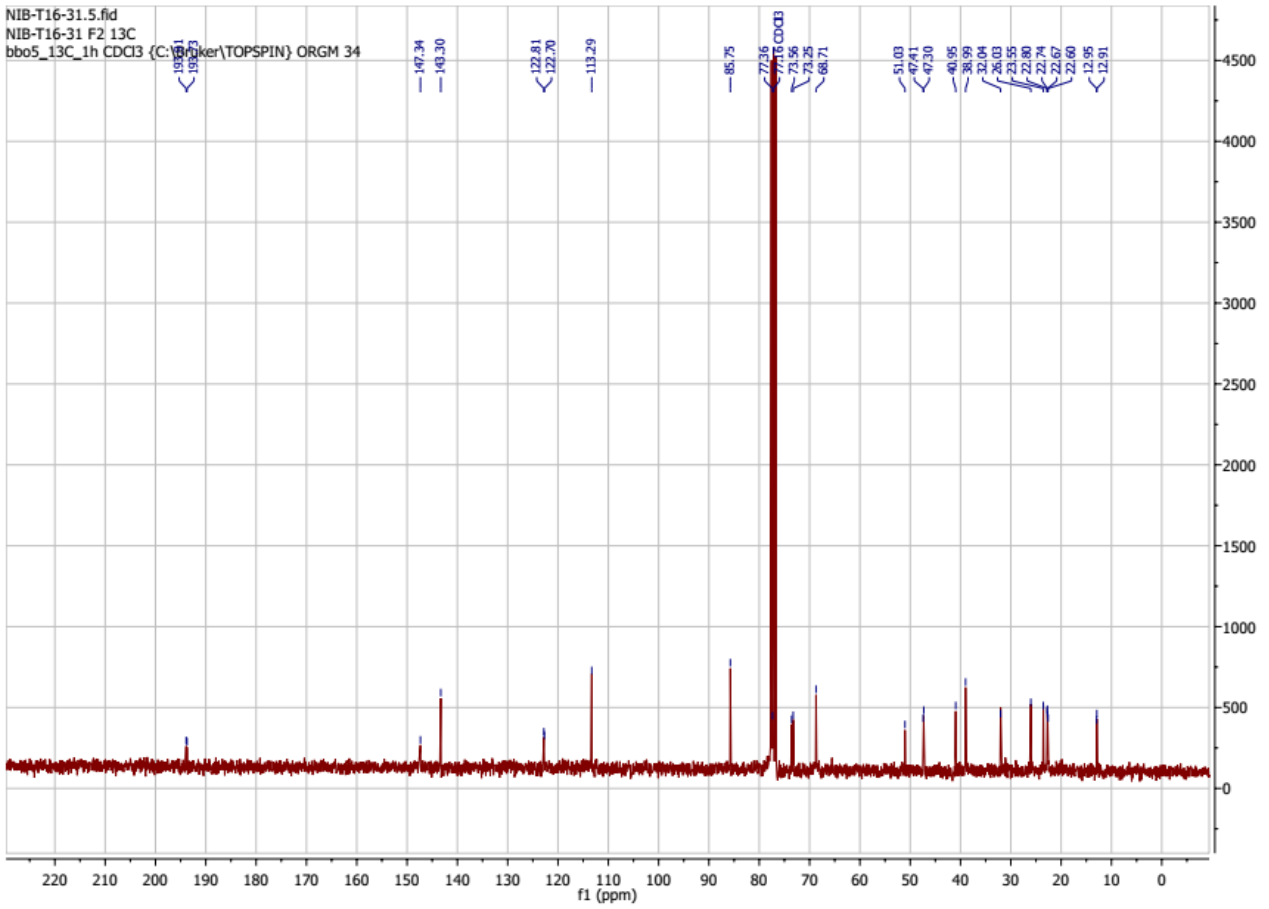
f1 (ppm)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147.34
143.30
122.81
122.70
113.29
85.75
77.36
77.16 CDCl3
73.56
73.25
68.71
51.03
47.41
47.30
40.95
38.99
32.04
26.03
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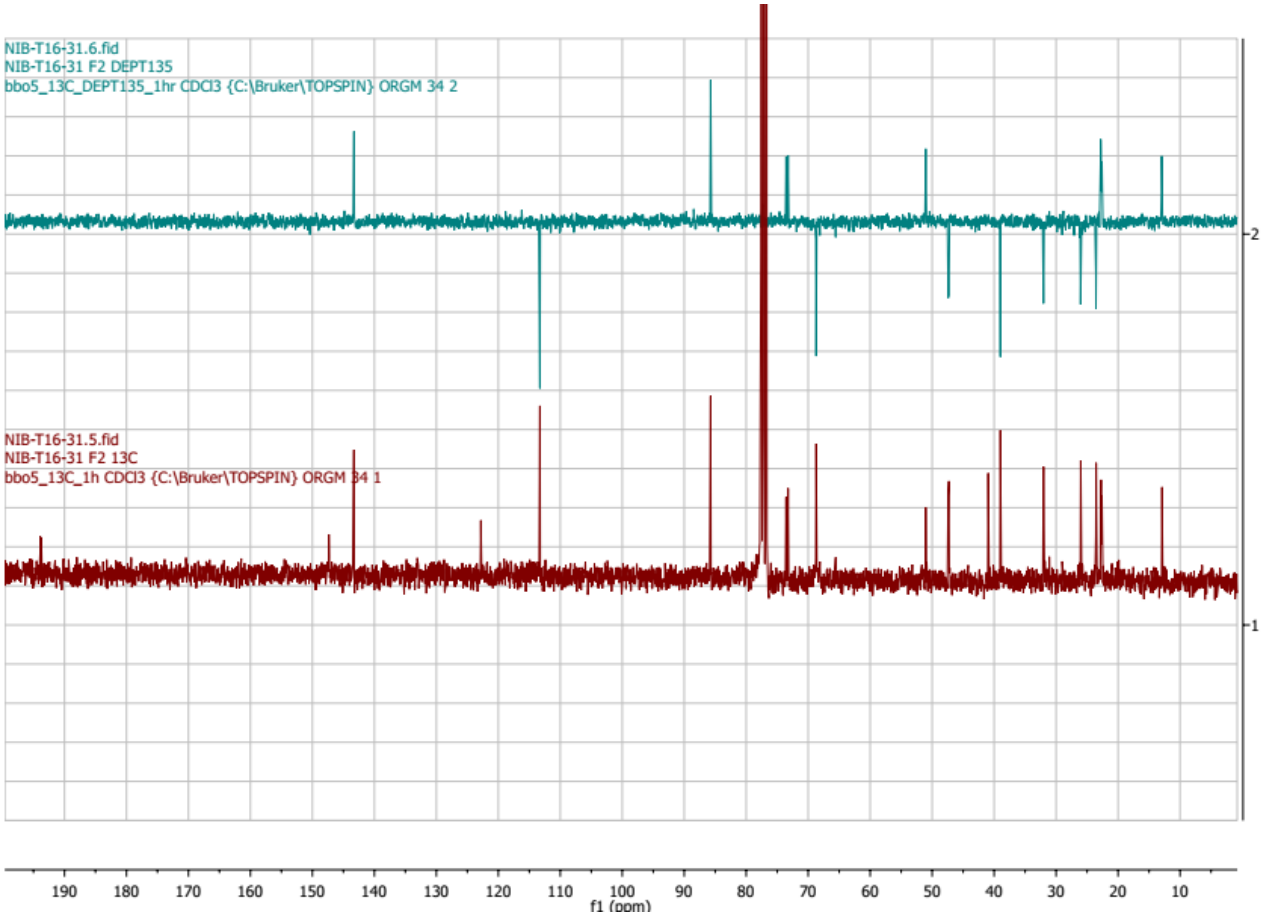
22.07
22.60
12.95
12.91
f1 (ppm)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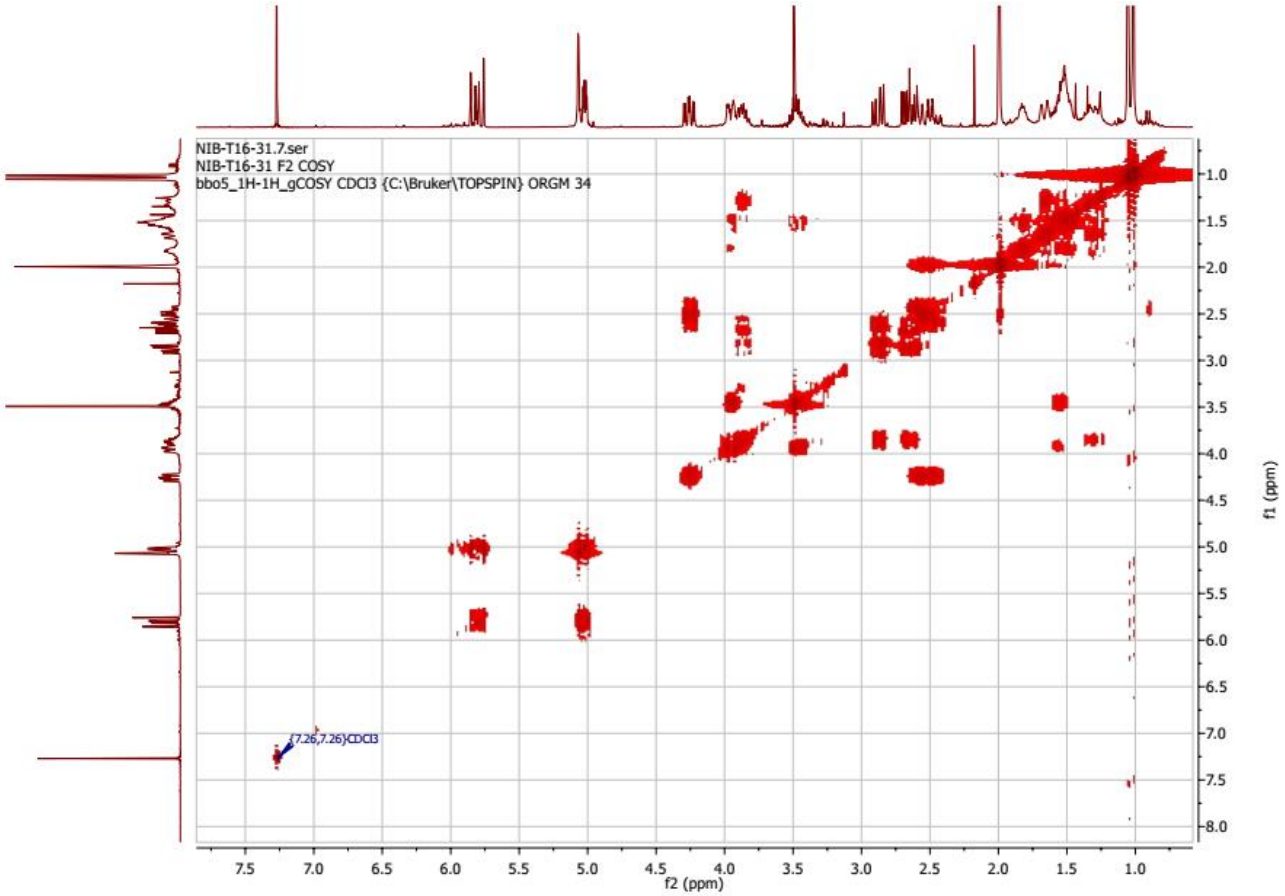
NIB-T16-31.5.fid
NIB-T16-31 F2 13C
bbo5_13C_1h CDCl3 {C:\Bruker\TOPSPIN} ORGM 34 1
2
1
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


NIB-T16-31.7.ser
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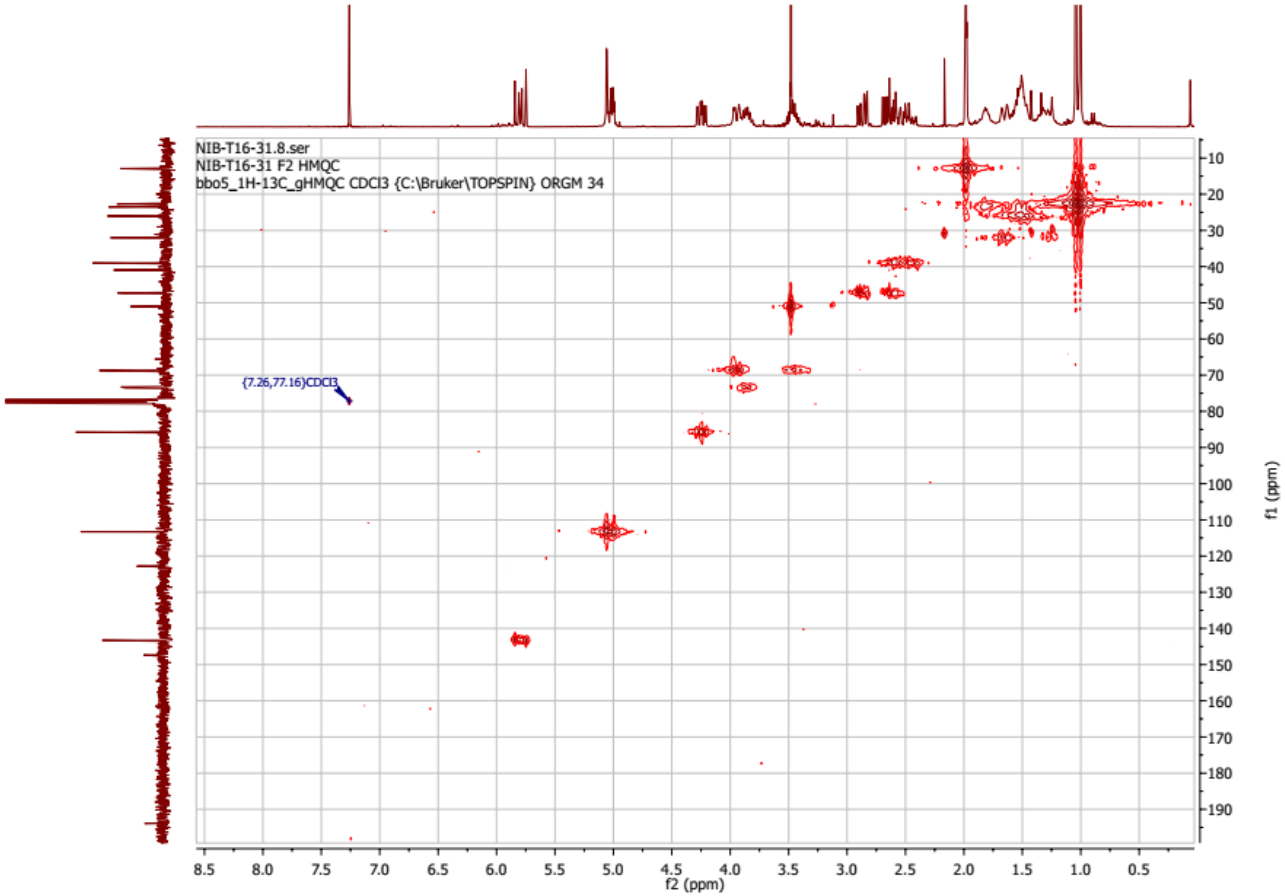
f2 (ppm)
f1 (ppm)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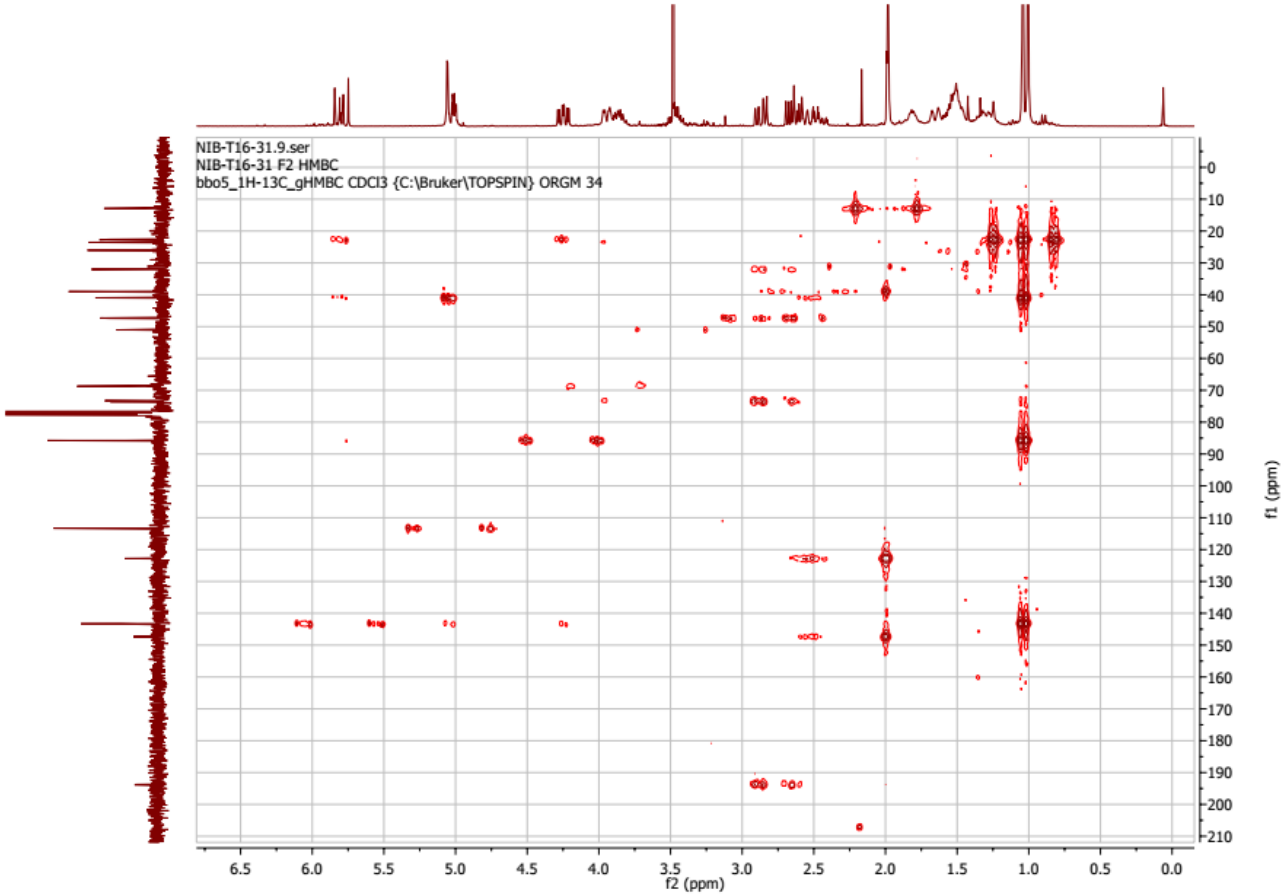
{7.26,77.16}CDCl3
f2 (ppm)
f1 (ppm)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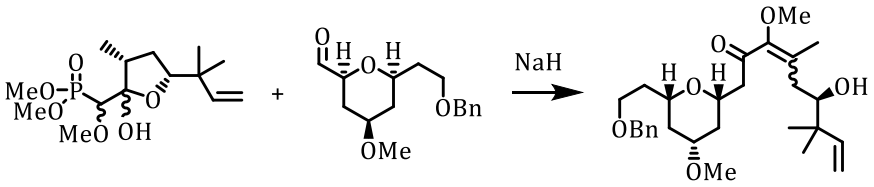
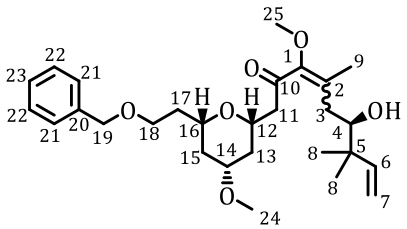
bbo5_1H-13C_gHMBC CDCl3 {C:\Bruker\TOPSPIN} ORGM 34
f2 (ppm)
f1 (ppm)

(R)-1-((2S,4R,6S)-6-(2-(benzyloxy)ethyl)-4-methoxytetrahydro-2H-pyran-2-yl)-6-hydroxy-3-methoxy-4,7,7-trimethylnona-3,8-dien-2-one **V.55**



NaH (2.3 eq., 19 mg, 0.82 mmol) was added to a solution of phosphonate 1.2 eq., 138 mg, 0.43 mmol) in THF (4 mL) cooled at 0 °C with an ice bath. The reaction was stirred at that temperature until no more hydrogen bubbles were observed. The reaction was then cooled at -78 °C using dry ice/acetone bath before adding a solution of aldehyde (1 eq., 100 mg, 0.35 mmol) in THF (1 mL). The reaction mixture was then stirred for 30 minutes at -78 °C and warmed to room temperature by removing the dry ice/acetone bath. The reaction mixture was stirred for an additional hour before being diluter with Et_2O and quenched with a saturated solution of NH_4Cl. The phases were separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4 and the solvents were removed under reduced pressure. The purification was performed by silica gel column chromatography using EtOAc/PE 1:10 to 1:2 affording the desired product as a colourless oil.

Analysis



Chemical Formula: $C_{28}H_{42}O_6$
Molecular Weight: 474,64

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.35 – 7.20 (m, 5H, H21, H22 and H23), 5.82 – 5.62 (m, 1H, H6), 5.02 – 4.87 (m, 2H, H7), 4.41 (s, 2H, H19), 4.27 – 4.09 (m, 1H, H4), 3.90 – 3.65 (m, 1H, H12), 3.56 –3.22 (m, 10H, H25, H24, H18, H16and H14), 2.85 (dd, *J* = 16.9, 6.1 Hz, 1H, H11), 2.64 (dd, *J* = 16.9, 6.8 Hz, 1H, H11), 2.58 – 2.31 (m, 2H, H3), 2.00 – 1.84 (m, 4H, H9 and H13), 1.86 – 1.41 (m, 5H, H13, H15 and H17), 1.08 – 0.86 (m, 6H, H8).

HRMS (ESI) Calculated for $C_{28}H_{42}O_6Na$: 497.28736 Found 497.28753.