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En route towards novel Jerangolid analogues

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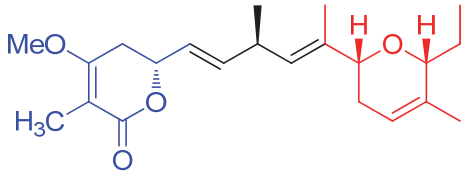
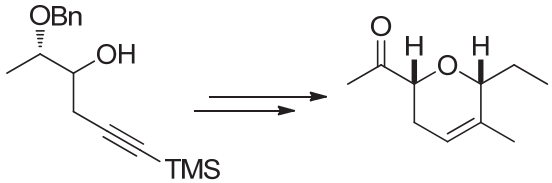
ABSTRACT

The continuous growth of fungal infections, coupled with the increased resistance of many microorganisms towards antifungal compounds, is an alarming health problem and the discovery of new antifungal agents has become a particularly important area of research. Jerangolid D is a potential antifungal agent of major interest. Recently, the first total synthesis of this natural product has been reported by our group.

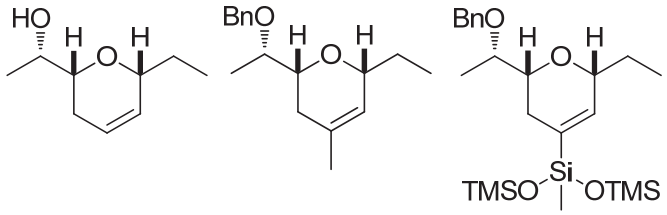


Its structure can be divided into three subunits: a substituted dihydropyran, an unsaturated lactone and a skipped 1,4-diene middle fragment. Our purpose is to operate a series of chemical modifications on these three subunits in order to create a set of new compounds, similar to Jerangolid D, but possessing hopefully enhanced stability, increased activity and lower toxicity.

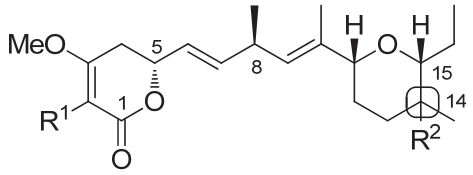
Initially, we shall describe our efforts towards the synthesis of the substituted dihydropyran. In order to do so, two methodologies have been developed, based upon previous work in our laboratory. The second one gave the best results and enabled access to the desired dihydropyran in 6 operations using an intramolecular silyl modified Sakurai cyclisation (ISMS) as the key step.



The same pathway was used to construct new dihydropyrans by modifying the C-C triple bond.



With the natural DHP in hand, different modifications were applied to the double bond in order to reach the right-hand fragment of jerangolid B, E and H in which the stereochemistry at C14 was still unknown.



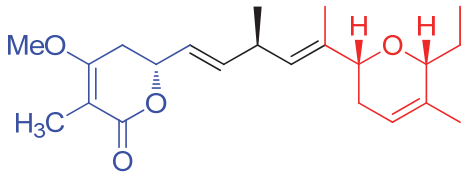
Jerangolid B, $R^1=CH_3$, $R^2=OH$
Jerangolid E, $R^1=CH_3$, $R^2=H$
Jerangolid H, $R^1=CH_2OH$, $R^2=H$

Subsequently, we will describe our efforts towards the preparation of the left-hand lactone of jerangolid D as well as a set of new analogues.

Finally, we will present some preliminary investigations on the synthesis of new analogues of the central part of these natural products.

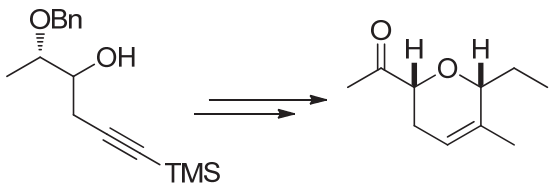
RÉSUMÉ

L'augmentation continuelle des infections fongiques, de paire avec l'augmentation de la résistance des microorganismes vis-à-vis des antifongiques, est un problème de santé alarmant et la découverte de nouveaux composés antifongiques est devenue un domaine de recherche particulièrement important. Le jérangolide D est un composé dont l'activité antifongique potentielle est d'intérêt majeur. Récemment, la première synthèse totale de ce produit naturel a été décrite par notre groupe.

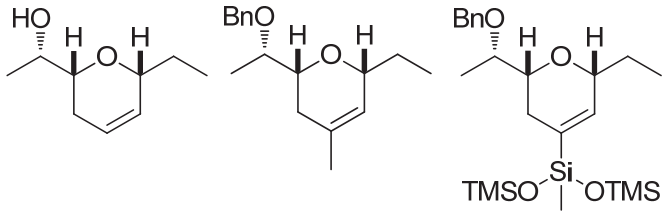


Sa structure peut être divisée en 3 sous-unités : un dihydropyrane substitué, une lactone insaturée et un fragment central bioléfinique. Notre but est d'opérer une série de modifications chimiques sur ces trois fragments pour créer un set de nouveaux composés, similaires au jérangolide D, mais possédant éventuellement une stabilité accrue, une meilleure activité et une toxicité plus faible.

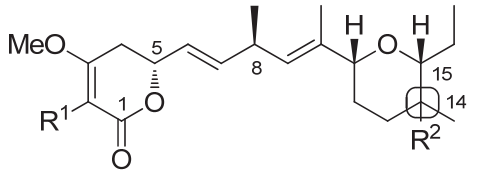
Dans un premier temps, nous allons décrire les efforts déployés pour la synthèse du dihydropyrane substitué. Pour ce faire, deux méthodologies, basées sur des travaux antérieurs du laboratoire, ont été développées. La seconde a donné les meilleurs résultats et nous a permis d'accéder au dihydropyrane désiré en six opérations, avec comme étape-clé une cyclisation ISMS.



Le même schéma réactionnel a été utilisé pour construire des nouveaux dihydropyranes en fonctionnalisant la triple liaison carbone-carbone.



Une fois le DHP naturel obtenu, différentes modifications ont été apportées à la double liaison afin d'accéder à la partie droite des jérangolides B, E et H, dans lesquels la stéréochimie du carbone 14 était encore inconnue.



Jerangolid B, $R^1=CH_3$, $R^2=OH$
Jerangolid E, $R^1=CH_3$, $R^2=H$
Jerangolid H, $R^1=CH_2OH$, $R^2=H$

D'autre part, nous décrirons ensuite nos efforts dirigés vers la synthèse de la lactone du jérangolide D ainsi que de nouveaux analogues de cette sous-unité.

Finalement, la synthèse de nouveaux analogues de la partie centrale des jérangolides et leurs tentatives d'union aux autres fragments seront présentées.

ABREVIATIONS

Å	:	Angström
AcOEt	:	Ethyl acetate
AcOH	:	Acetic acid
AmB	:	Amphotericin B
AmdeB	:	Amphoteronolide B
Aq.	:	Aqueous
Ar	:	Aryl
Bn	:	Benzyl
n-Bu	:	Butyl
t-Bu	:	*Tert*-butyl
Bz	:	Benzoate
CBS	:	Corey-Bakshi-Shibata reagent
cm	:	Centimeter
Cp	:	Cyclopentadienyl
CSA	:	Camphorsulfonic acid
Cy	:	cyclohexyl
CYP	:	Cytochrome P450
DCM	:	Dichloromethane
DCC	:	Dicyclohexyl carbodiimide
DDQ	:	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHP	:	Dihydropyran
DIAD	:	Diisopropyl azodicarboxylate
DIBAL-H	:	Diisobutylaluminium hydride

DMAP : 4-dimethylamino pyridine

DMF : *N,N*-dimethylformamide

DMP : Dess-Martin periodane

DMSO : Dimethylsulfoxide

DNA : Deoxyribonucleic acid

d.e. : Diastereomeric excess

e.e. : Enantiomeric excess

EF2 : Elongation Factor 2

Eq. : Equivalent

Et : Ethyl

5-FC : 5-fluorocytosine

FDA : Food and Drugs Administration

FdUMP : 5-fluorodeoxyuridine monophosphate

FUTP : 5-fluorouridine triphosphate

5-FU : 5-fluorouracil

GC : Gas chromatography

GC-I : Grubbs catalyst-I

h : Hour

HIV : Human Immunodeficiency Virus

HMPA : Hexamethylphosphoramide

HRMS : High resolution mass spectroscopy

HOG : High Osmolarity Glycerol

Hz : Hertz

IFIs : Invasive Fungal Infections

i-Pr	:	Isopropyl
IR	:	Infra-red
LA	:	Lewis Acid
Me	:	Methyl
MeOH	:	Methanol
MS	:	Mass Spectrometry
mmol	:	Millimole
N	:	Normal
n-BuLi	:	*n*-butyllithium
n.d.	:	Non determined
NMR	:	Nuclear Magnetic Resonance
o.n.	:	overnight
PCC	:	Pyridinium chlorochromate
PDC	:	Pyridinium dichromate
PE	:	Petroleum Ether
Ph	:	Phenyl
PMB	:	p-methoxy benzyl
PPTS	:	Pyridinium p-toluenesulfonate
n-Pr	:	*n*-Propyl
ppm	:	Part par million
RCM	:	Ring-closing metathesis
RNA	:	Ribonucleic acid
r.t.	:	Room temperature
TBAF	:	Tetrabutylammonium fluoride

TBS : Tert-butyl dimethyl silyl

TBDPS : Tert-butyl diphenyl silyl

Tf : CF_3SO_2

TfOH : Triflic acid

TFA : Trifluoroacetatic acid

THF : Tetrahydrofuran

TLC : Thin layer chromatography

TMS : Trimethylsilyl

TMEDA : Tetramethylethylenediamine

Tol. : Toluene

"If you keep on believing,

The dreams that you wish will come true."

Cinderella

"Things dont always work out the first time,

But keep trying."

Donald Duck

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GENERAL INTRODUCTION

I. Fungal Infections

In recent years, there has been an increase of fungal infections all around the world. These infections pose a continuous and serious threat to human health[1]. In humans, fungal diseases can be classified into (1) allergic reactions to fungal proteins, (2) toxic reactions to toxins present in some fungi, (3) infections also called mycoses. The latest are by far the most serious, hard to diagnose and eventually treat, as they exist in various forms. Healthy individuals can develop superficial, cutaneous, subcutaneous, and in some instances, systemic infections that cause a wide range of conditions from athletes foot and nail infections to severe life-threatening diseases such as histoplasmosis[2]. Many fungal infections are caused by opportunistic pathogens that may be endogenous (*Candida* infections) or caught from the environment (*Cryptococcus, Aspergillus* infections)[3].

Immuno-compromised individuals are susceptible to a large number of opportunistic systemic mycoses, resulting from the inability of the host immune system to fight off attacks from normally benign fungal pathogens[2]. These infections, commonly called invasive fungal infections (IFIs), have increased steadily due to the rise of immunocompromised patients and those

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[1] F. M. Garibotto, A. D. Garro, M. F. Masman, A. M. Rodríguez, P. G. M. Luiten, M. Raimondi, S. A. Zacchino, C. Somlai, B. Penke, R. D. Enriz, *Bioorg. Med. Chem.* **2010**, *18*, 158-167.

[2] D. Barrett, *Biochim. Biophys. Acta - Molecular Basis of Disease* **2002**, *1587*, 224-233.

[3] a. M. K. Kathiravan, A. B. Salake, A. S. Chothe, P. B. Dudhe, R. P. Watode, M. S. Mukta, S. Gadhwe, *Bioorg. Med. Chem.* **2012**, *20*, 5678-5698 b. T. Lorand, B. Kocsis, *Mini Rev. Med. Chem.* **2007**, *7*, 900-911.

with critical illnesses[4]. The reasons are numerous: the emergence of aggressive cancer chemotherapy, highly efficient immunosuppressants for organ transplantation, widespread use of powerful broad spectrum antibacterial agents and the explosion of HIV infection cases have all contributed to the increase of life-threatening fungal diseases[2].

Most IFIs are caused by *Candida* and *Aspergillus fumigatus*. Clinically, candidiasis[5] and aspergillosis[6] account for 80% to 90% of systemic fungal infections in immunocompromised patients[3]. However, the number of previously uncommon or new pathogens, many of which are resistant to antifungal agents is increasing; these include non-*fumigatus Aspergillus* spp, Zygomycetes, *Scedosporium* and *Fusarium*[4].

Although the panel of antifungal drugs has expanded, currently available antifungal agents for effective treatments of these emerging infections are in short supply, thereby contributing to a high mortality rate. Moreover, the increasing antifungal resistance is particularly problematic as initial diagnosis of systemic fungal infection can be delayed and there are few antifungal drugs available[7]. Thus, the development of new antifungal drugs has been a constant requirement in clinical therapy[3].

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[4] a. S. C. A. Chen, E. G. Playford, T. C. Sorrell, *Current Opinion in Pharmacology* **2010**, *10*, 522-530 b. T. J. Walsh, A. Groll, J. Hiemenz, R. Fleming, E. Roilides, E. Anaissie, *Clin. Microbiol. Infect.* **2004**, *10*, 48-66

[5] M. A. Pfaller, R. N. Jones, S. A. Messer, M. B. Edmond, R. P. Wenzel, *Diagn. Microbiol. Infect. Dis.* **1998**, *31*, 327-332.

[6] W. W. Hope, D. W. Denning, *Clin. Microbiol. Infect.* **2004**, *10*, 2-4.

[7] R. D. Cannon, E. Lamping, A. R. Holmes, K. Niimi, K. Tanabe, M. Niimi, B. C. Monk, *Microbiology* **2007**, *153*, 3211-3217.

II. Commercially available antifungal drugs

During the second half of the 20th century, especially during the last two decades, several classes of antifungal agents have been discovered[8].

There are four main classes of antifungal compounds with different targets in fungi cells[7] (Figure 1). They will be described in this section.

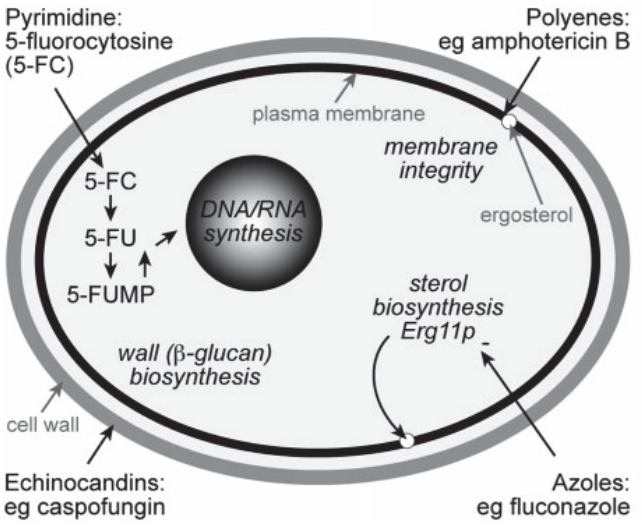


Figure 1 : targets of current antifungal drugs

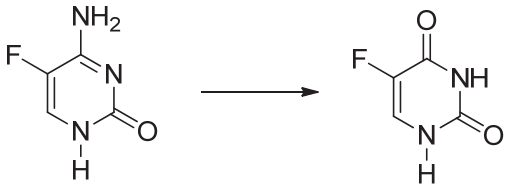
II.1. 5-Fluorocytosine

5-Fluorocytosine **1.001** (5-FC), a fluorinated pyrimidine analogue, is one of the oldest antifungal agents. It was first synthesized in 1957 as a potential anti-tumour agent but failed in this role. Four years later, it was proved to be

[8] V. T. Andriole, *J. Ant. Chemother.* **1999**, *44*, 151-162.

active in treating candidosis in mice and, in 1968, it was used for the first time to treat human candidosis[9].

5-FC itself shows no antifungal activity. It is only after entering the fungal cell that it is converted to 5-fluorouracil **1.002** (5-FU) by cytosine deaminase (scheme 1). After this conversion, two mechanisms for the antifungal activity of 5-FU can be distinguished. The first one involves the conversion of 5-FU to 5-fluorouridine triphosphate (FUTP) which is further incorporated in fungal RNA. It results in the inhibition of protein synthesis by altering the aminoacylation of tRNA. The second mechanism is the transformation of 5-FU to 5-fluorodeoxyuridine monophosphate (FdUMP) which is a potent inhibitor of thymidylate synthetase. This results in the inhibition of fungal DNA synthesis[10]. It is still unclear whether one mechanism is more important than the other for the total antifungal effect of 5-FC.



5-FC **1.001** 5-FU **1.002**

Scheme 1 : conversion of 5-FC to 5-FU in fungal cells

5-Fluorocytosine is available in oral form and as intravenous preparation. Its spectrum is restricted to *Candida* species and *Cryptococcus neoformans*[9].

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[9] a. A. Vermes, H.-J. Guchelaar, J. Dankert, *J. Ant. Chemother.* **2000**, *46*, 171-179 b. R. Herbrecht, Y. Nivoix, C. Fohrer, S. Natarajan-Amé, V. Letscher-Bru, *J. Ant. Chemother.* **2005**, *56*, i39-i48.

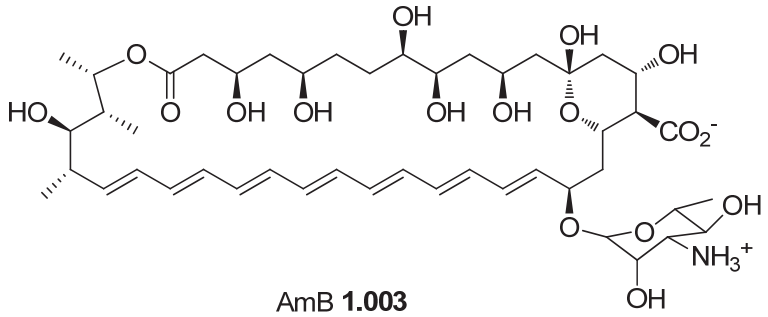
[10] A. R. Waldorf, A. Polak, *Antimicrob. Agents Chemother.* **1983**, *23*, 79-85.

Unfortunately, a significant proportion of *C. albicans* isolates are resistant to 5-FC, thus limiting its utility[7].

II.2. Polyenes

Amphotericin B (AmB) and nystatin are the currently available and employed polyenes, although nystatin has been limited to topical use due to differing safety profiles[11].

AmB **1.003** was first isolated from a soil bacterium *Streptomyces nodosus* obtained from the bed of the Orinoco River in Venezuela in 1955[12].



AmB **1.003**

Figure 2 : structure of amphotericin B

It is a macrocyclic polyene with *in vitro* antifungal activity that covers most of the fungal pathogens involved in human diseases[9]. Moreover, resistance to AmB has remained exceptionally rare despite its extended use worldwide to treat life-threatening IFIs for more than half a century[7].

The usual formulation of AmB is a micellar deoxycholate complex (Fungizone) that has been on the market for over 40 years. Unfortunately, it is highly toxic to patients, often causing decreased renal function, chills, high fever, nausea, phlebitis, anorexia and many other unpleasant side-

[11] G. R. Thompson, J. Cadena, T. F. Patterson, *Clin. chest med.* **2009**, *30*, 203-215.

[12] C. M. McNamara, S. Box, J. M. Crawforth, B. S. Hickman, T. J. Norwood, B. J. Rawlings, *J. Chem. Soc. Perkin Trans. 1* **1998**, 83-88.

effects. Coupled with long therapeutic uses, these negative effects restrict its usefulness to all but the most life-threatening systemic fungal infections[13]. However, to avoid the high nephrotoxicity, several other formulations have been developed such as lipid preparations. This solution has drastically reduced the toxicity of this drug without diminishing its powerful antifungal action[14].

Despite five decades of investigations, the mode of action of AmB remains unclear. In the now widely accepted leading model, AmB kills yeast by self-assembly of several molecules to form barrel-stave-like trans-membrane pores. This channel mode has also been extended to rationalize the lack of resistance to AmB. The number of molecules involved in forming the pores is not known but 4 to 12 units have been proposed[15]. In 2011, the group of Ide proposed a rectification and claims that AmB channel consists of 6 monomeric units[16].

However, in a recent paper, the group of Burke determined that AmB binds directly to membrane-embedded ergosterol (the main sterol found in yeast cell), in a way that requires the mycosamine fragment present in AmB. Indeed, when this fragment was removed to yield a derivative called

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[13] S. Hartsel, J. Bolard, *Trends Pharmacol. Sci.* **1996**, *17*, 445-449.

[14] a. J. P. Barrett, K. A. Vardulaki, C. Conlon, J. Cooke, P. Daza-Ramirez, E. G. V. Evans, P. M. Hawkey, R. Herbrecht, D. I. Marks, J. M. Moraleda, G. R. Park, S. J. Senn, C. Viscoli, *Clin. Ther.* **2003**, *25*, 1295-1320 b. A. Antoniadou, B. Dupont, *J. Med. Mycol.* **2005**, *15*, 230-238

[15] a. R. W. Holz, *Ann. N. Y. Acad. Sci.* **1974**, *235*, 469-479 b. T. E. Andreoli, ibid., 448-468 c. A. A. Volmer, A. M. Szpilman, E. M. Carreira, *Nat. Prod. Rep.* **2010**, *27*, 1329-1349.

[16] M. Hirano, Y. Takeuchi, N. Matsumori, M. Murata, T. Ide, *J. Membrane Biol.* **2011**, *240*, 159-164

amphoteronolide B (AmdeB), which can not bind to ergosterol but can still form pores, no fungal activity was observed (figure 3).

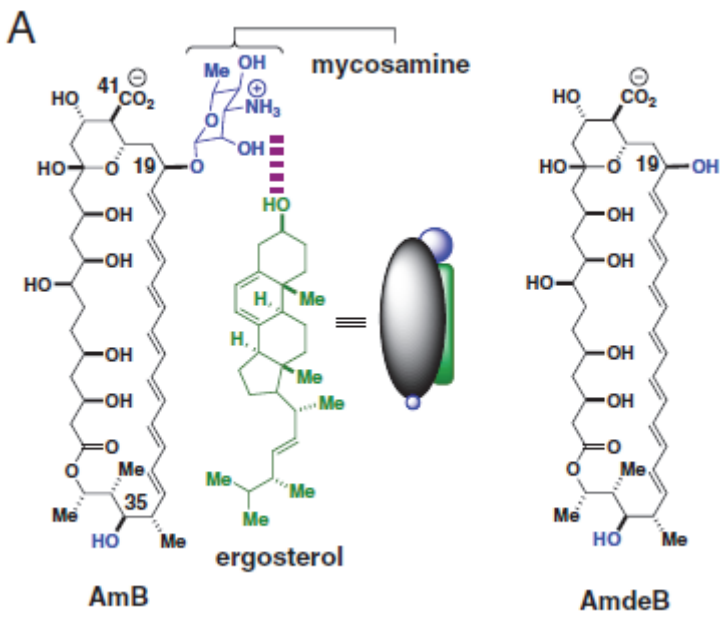


Figure 3 : Structures of AmB and AmdeB

These findings, along with other observations, led them to the conclusion that ergosterol binding alone is the primary mechanism of action of Amb; channel formation represents a second complementary mode of action[17].

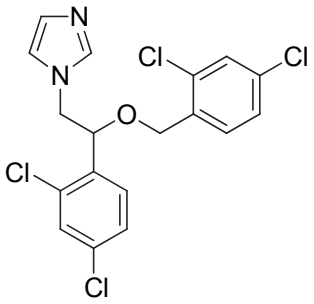
II.3. Azoles

The azoles are a family of synthetic compounds that were discovered in the 1960s. They are the largest class of antifungal agents in clinical use[18]. The

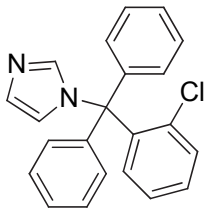
[17] a. K. C. Gray, D. S. Palacios, I. Dailey, M. M. Endo, B. E. Uno, B. C. Wilcock, M. D. Burke, *Proc. Natl. Acad. Sci.* **2012**, *109*, 2234-2239 b. Y. Umegawa, T. Adachi, N. Matsumori, M. Murata, *Bioorg. Med. Chem.* **2012**, *20*, 5699-5704.

family of azoles can be divided into two subclasses: the imidazoles and the triazoles.

Miconazole **1.004**, the very first member of the imidazole family, was discovered in 1969 by Janssen Pharmaceutica when they initiated a research program on imidazole chemistry (figure 4).



Miconazole **1.004**



Clotrimazole **1.005**

Figure 4 : structures of miconazole and clotrimazole

Unfortunately, miconazole shows poor oral bioavailability. However, it is a useful topical drug for the treatment of superficial mycoses[19]. The same year, some researchers at Bayer discovered clotrimazole **1.005** which cannot be given parenterally and showed poor oral absorption, but is used for the treatment of oral and vaginal candidosis and athlete's foot infection[8,20].

Many synthetic explorations and modifications on miconazole at Jansen Pharmaceutica led to the discovery of ketoconazole **1.006** in 1977 as the first orally active broad-spectrum antifungal agent that can be used to treat superficial and deep mycoses[19,21] (figure 5).

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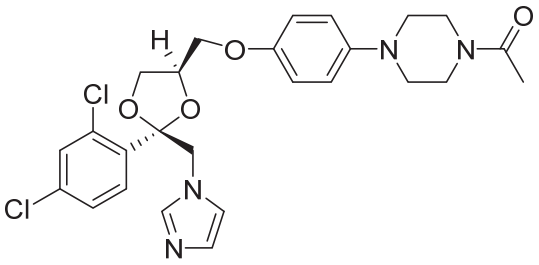
[18] F. C. Odds, A. J. P. Brown, N. A. R. Gow, *Trends Microbiol.* **2003**, *11*, 272-279.

[19] J. Heeres, L. Meerpoel, P. Lewi, *Molecules* **2010**, *15*, 4129-4188

[20] R. A. Fromtling, *Clin. Microbiol. Rev.* **1988**, *1*, 187-217.

[21] J. Heeres, L. J. J. Backx, J. H. Mostmans, J. Van Cutsem, *J. Med. Chem.* **1979**, *22*, 1003-1005.

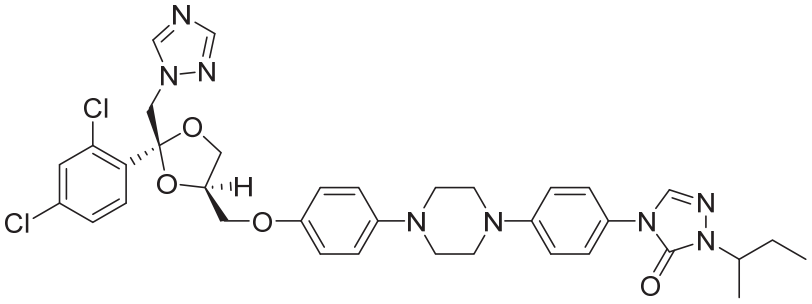


Ketoconazole **1.006**

Figure 5 : structure of ketoconazole

Oral ketoconazole is effective in patients with candidosis, coccidioidomycosis, blastomycosis, histoplasmosis, paracoccidioidomycosis and cutaneous dermatophyte infections. It has nowadays been replaced by newer azoles for the treatment of many of these infections[8].

In 1986, a new antifungal agent with broad-spectrum antifungal activity was discovered at Janssen Pharmaceutica by replacing the imidazole moiety by a triazole and by functionalizing the structure even more. It was named itraconazole **1.007**[22] (figure 6).



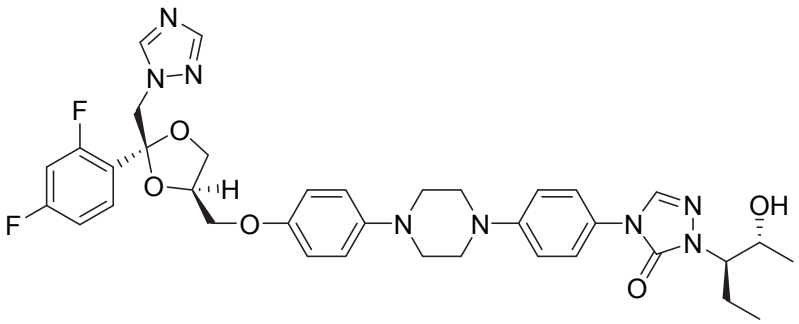
Itraconazole **1.007**

Figure 6 : structure of itraconazole

Further structure modifications of the itraconazole family led to the discovery of posaconazole **1.008** by Schering-Plough (Figure 7). It was

[22] J. Heeres, L. J. J. Backx, J. Van Cutsem, *J. Med. Chem.* **1984**, *27*, 894-900

approved by the FDA in 2006 for the prophylaxis of invasive A*spergillus* and *Candida* infections[23].



Posaconazole **1.008**

Figure 7 : structure of Posaconazole

At the same time as itraconazole was born, another important series of antifungal agents was developed by Pfizer by shifting the benzyl moiety in miconazole from the oxygen to the α-carbon (figure 8) and replacing the imidazole ring by a triazole[19].

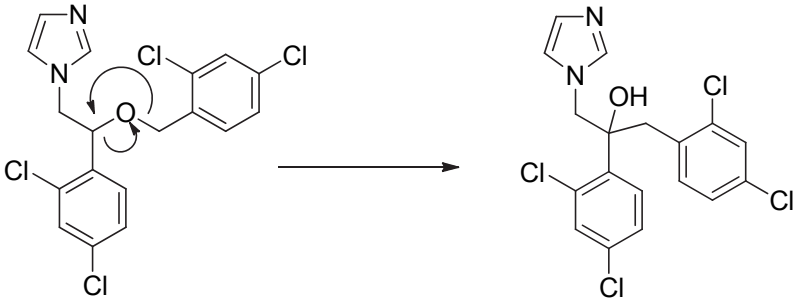
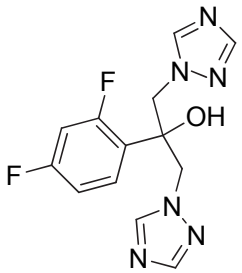


Figure 8

[23] a. C. A. Kauffman, A. N. Malani, C. Easley, P. Kirkpatrick, *Nat. Rev. Drug Discov.* **2007**, *6*, 183-184 b. V. Nagappan, S. Deresinski, *Clin. Infect. Dis.* **2007**, *45*, 1610-1617.

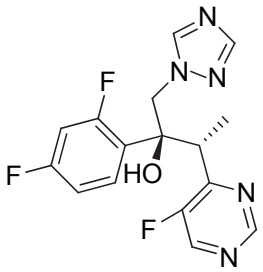
These modifications gave rise to fluconazole **1.009**, which is one of the most frequently prescribed triazoles due to its excellent bioavailability, tolerability and side-effect profile[11,24] (figure 9).



Fluconazole **1.009**

Figure 9 : structure of fluconazole

More recently, further modifications provided voriconazole **1.010** which has been marketed in several countries since 2002 (figure 10). The spectrum of activity of this new triazole covers most pathogenic yeasts[9].



Voriconazole **1.010**

Figure 10 : structure of voriconazole

Concerning their mode of action, the family of azoles blocks the synthesis of ergosterol, an important component of fungal cytoplasmic membranes. They inhibit the 14-α-demethylation of lanosterol into ergosterol in the

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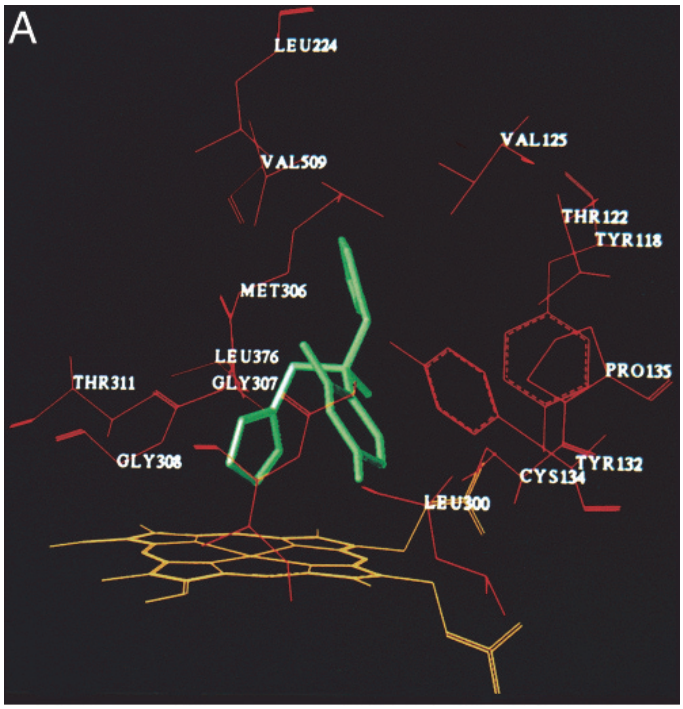
[24] D. J. Sheehan, C. A. Hitchcock, C. M. Sibley, *Clin. Microbiol. Rev.* **1999**, *12*, 40-79.

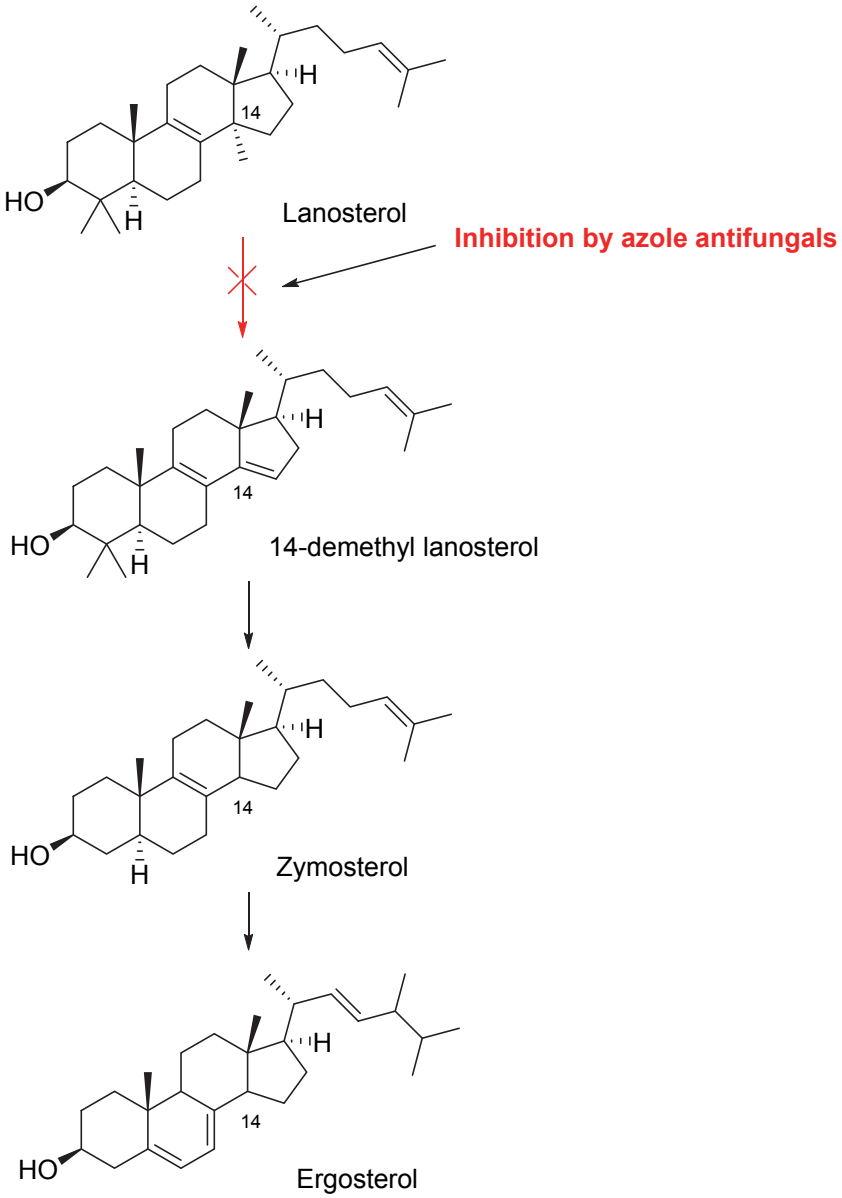
biosynthetic pathway (scheme 2). This mechanism leads to the depletion of ergosterol and the increase of 14-α-methylated sterols thus disturbing the structure, permeability and fluidity of the fungal membrane. The azole antifungals target a cytochrome P450-Erg11P enzyme possessing a monooxygenase activity. This enzyme contains an iron protoporphyrin unit at its active site. The azoles bind to iron *via* a nitrogen atom of the imidazole or triazole ring. The rest of the molecule binds to the apoprotein[18,25]. A stereoview of active site of lanosterol 14α-demethylase (heme iron in yellow) of *Candida albicans* with bound fluconazole (in green) is shown in figure 11[26].



[25] H. V. Bossche, L. Koymans, H. Moereels, *Pharmacol. Ther.* **1995**, *67*, 79-100.

[26] H. Ji, W. Zhang, Y. Zhou, M. Zhang, J. Zhu, Y. Song, J. Lü, J. Zhu, *J. Med. Chem.* **2000**, *43*, 2493-2505.

Figure 11



Scheme 2: Inhibtion of ergosterol synthesis by azole antifungals

As a class, the azoles are safe, have a broad spectrum of activity and can be administered intraveinously or orally. However, their mechanism of action

leads to some drug-drug interactions that need to be taken into account when administered to patients[27].

It should be noted that there is an increasing drug resistance to these drugs. This resistance can occur either by mutations, that modify the target molecule, or by overexpression of membrane efflux pumps that export the antifungals from the cell[18,28].

II.4. Echinocandins

Echinocandins form the newest family of antifungal agents that act by a different pathway[9]. They are fungal secondary metabolites, composed of a cyclic hexapeptide core bearing a lipid side-chain. Random screening in the 1970s led to the discovery of two prototypes with interesting antifungal activities: echinocandin B and aculeacin A. A modified version of echinocandin B, cilofungin, was developed to phase 2 in clinical trials but was abandoned because its formulation was toxic to patients.

In the late 1990s, three synthetically modified echinocandin derivatives entered clinical developments[18]. In 2001, the first of them, caspofungin (Merck), was approved by the FDA, followed by anidulafungin and micafungin[2]. The molecular weight of all three of them is large, and this presumably explains their poor oral absorption. Therefore, they are all for intravenous use only[29].

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[27] P. O. Gubbins, S. Heldenbrand, *Mycoses* **2010**, *53*, 95-113.

[28] M. M. Canuto, F. G. Rodero, *Lancet Infect. Dis.* **2002**, *2*, 550-563.

[29] a. D. Cappelletty, K. Eiselstein-McKitrick, *Pharmacotherapy* **2007**, *27*, 369-388

b. D. W. Denning, *J. Antimicrob. Chemother.* **2002**, *49*, 889-891.

Caspofungin **1.011** is a semi-synthetic water-soluble aminoderivative of pneumochandin B_0 [30](figure 12).

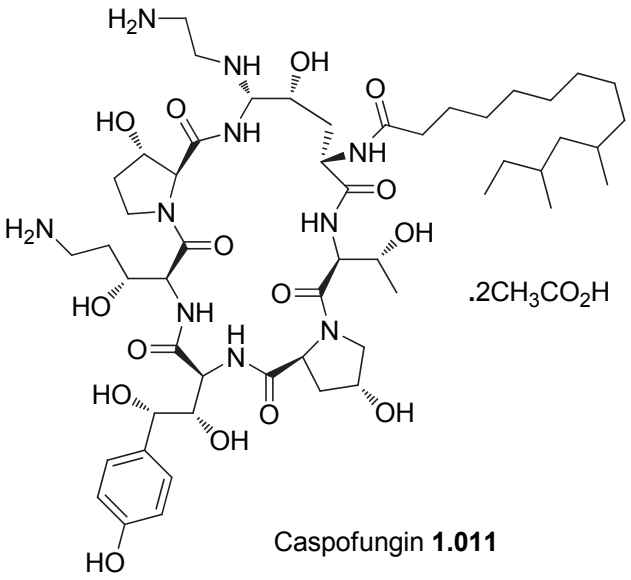

Figure 12 : Structure of caspofungin

Echinocandins possess antifungal activities mainly against *Candida* spp. and *Aspergillus* spp[31]. Their mode of action is different from the other antifungal agents as they block the synthesis of β(1,3)-D-glucan of the fungal cell wall, by a non-competitive inhibition of the enzyme β(1,3)-D-glucan synthase. β(1,3)-D-glucan is a component of the cell wall, giving it its shape and mechanical strength. This inhibition has a double effect: fungistatic, which results from blockade of the cell wall synthesis, reducing fungal growth and fungicidal, which originates from a change in the integrity of the cell wall resulting in the loss of its mechanical strength. The cell is thus unable to resist the intracellular osmotic pressure and lysis occurs[29].

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[30] V. Letscher-Bru, R. Herbrecht, *J. Antimicrob. Chemother.* **2003**, *51*, 513-521.

[31] P.-L. Shao, L.-M. Huang, P.-R. Hsueh, *Int. J. Antimicrob. Agents* **2007**, *30*, 487-495.

Since there is no counterpart of fungal cell walls in mammalian cells, the echinocandins are usually well tolerated with few adverse effects. Furthermore, unlike triazoles, the CYP450-independent metabolism and degradation reduces concern about drug-drug interaction[30].

Clinical resistance is rare, despite case reports of caspofungin resistance in several *Candida* spp[32].

Due to their clinical efficacy and safety, echinocandins are today among the first-line therapies recommended for treatment of candidemia and invasive candidiasis. However, they are expensive[33].

III. Emerging antifungal compounds

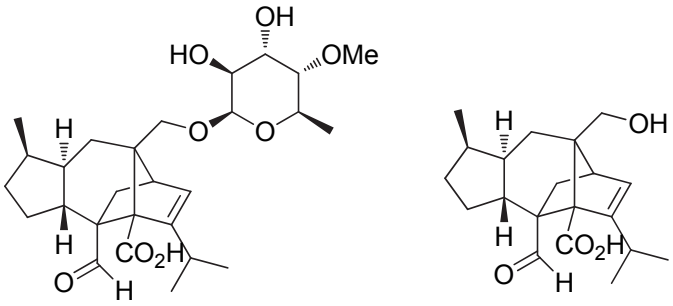
III.1. The sordarins

Sordarin **1.012** is a fungal metabolite isolated in 1969 from the fungus *Sordaria araneosa* by scientists at the Sandoz Co. Its degradation with concentrated HCl releases a diterpenoid aglycone called sordaricin **1.013** (figure 13)[34].

[32] S. A. Chen, M. Slavin, T. Sorrell, *Drugs* **2011**, *71*, 11-41.

[33] C. F. Neoh, M. Slavin, S. C. A. Chen, K. Stewart, D. C. M. Kong, *Int. J. Antimicrob. Agents* **2014**, *43*, 207-214.

[34] H. Liang, *Beilstein J. Org. Chem.* **2008**, *4*, 31.



Sordarin **1.012** Sordaricin **1.013**

Figure 13 : structures of sordarin and sordaricin

These products were shown to have antifungal activities in the 1970s but they generated considerable interest only 2 decades later, when several types of novel sordarins derivatives were developed preclinically by Glaxo-Wellcome and Merck[35].

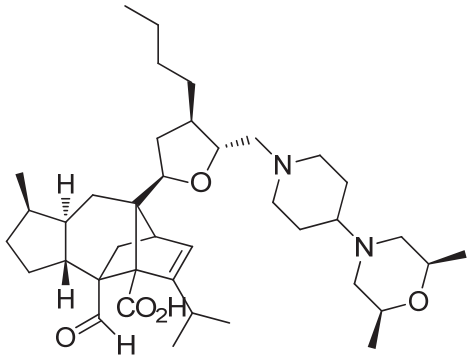
The sordarins are interesting because they inhibit a novel target for antifungal agents: elongation factor 2 (EF2) in protein biosynthesis. This enzyme catalyzes the translocation of the ribosome along the mRNA during elongation of the emerging polypeptide chain. Sordarin inhibits this translocation by stabilizing the EF2/ribosome complex[36].

A number of molecules based on the sordarin pharmacophore were shown to have therapeutic efficacy in various animal models but no obvious candidate for clinical development has emerged yet[3,34]. Recently, Astellas pharma reported a novel sordarin derivative, FR290581 **1.014**, modified at the

[35] L. Ostrosky-Zeichner, A. Casadevall, J. N. Galgiani, F. C. Odds, J. H. Rex, *Nat. Rev. Drug Discov.* **2010**, *9*, 719-727.

[36] G. R. Andersen, P. Nissen, J. Nyborg, *Trends Biochem. Sci.* **2003**, *28*, 434-441.

aglycone part, which shows good *in vivo* activities against *Candida albicans*[37] (figure 14).



FR290581 **1.014**

Figure 14

III.2. Isavuconazole

Isavuconazole **1.015** is a triazole in phase III clinical development for treatment of invasive candidemia and candidiasis (figure 15). It is active *in vitro* and *in vivo* against *Aspergillus* spp. and *Candida* spp.[38].

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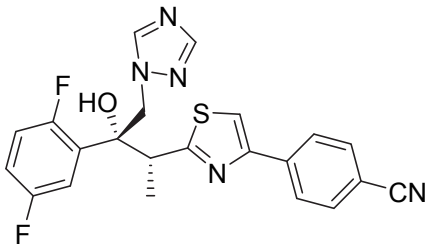
[37] T. Hanadate, M. Tomishima, N. Shiraishi, D. Tanabe, H. Morikawa, D. Barrett, S. Matsumoto, K. Ohtomo, K. Maki, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1465-1468.

[38] a. S. Perkhofer, V. Lechner, C. Lass-Flörl, *Antimicrob. Agents Chemother.* **2009**, *53*, 1645-1647 b. A. C. Pasqualotto, D. W. Denning, *J. Antimicrob. Chemother.* **2008**, *61*, i19-i30.

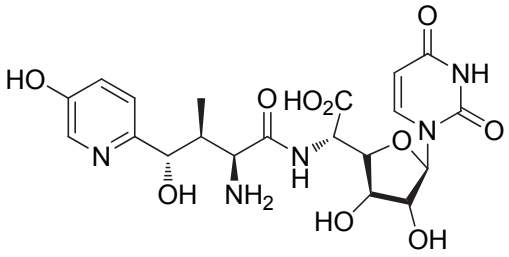


Isavuconazole **1.015**

Figure 15 : structure of isavuconazole

III.3. Nikkomycin Z

Nikkomycin Z **1.016** is a peptide-nucleoside isolated from *Streptomyces tendae* that was initially identified by Bayer Pharmaceutical Company in the 1970s as a potential antifungal agent (figure 16).



Nikkomycin Z **1.016**

Figure 16 : structure of nikkomycin Z

Nikkomycin Z inhibits chitin synthase and thereby interferes with cell wall construction. While chitin is essential for fungi, it is absent in human organisms.

Shaman Pharmaceuticals started the phase I study for the development of nikkomycin Z. However, after they closed down, the trial was acquired by the Valley Fever Center for Excellence at the University of Arizona[34].

Nikkomycin Z is currently under development as a first in class orphan product for treatment of coccidioidomycoses. Phase II of the clinical trials will begin in the near future[39].

Over the last 50 years during which antifungal agents have been discovered, the clinical needs have evolved constantly. Superficial mycoses remain easy to treat with a wide range of over-the-counter antimycotic products. However, whilst the availibilty of the extended-spectrum triazoles and the echinocandins represents remarkable advances in the treatment of IFIs, the mortality rate remains high. Moreover, due to the growth of susceptible populations, limitations of the activity spectrum or tolerability of current antifungals and the development of antifungal resistance, there is a constant need for new solutions with novel antifungal agents[3,30,34].

IV. Ambruticin and Jerangolids

Natural compounds among myxobacterial metabolites often show interesting antifungal bioactivities. Amongst the wide list of these compounds are two families of polyketides with similar structures and related mode of actions: ambruticins and jerangolids[40].

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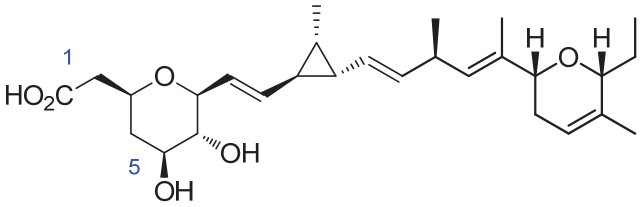
[39] a. D. E. Nix, R. R. Swezey, R. Hector, J. N. Galgiani, *Antimicrob. Agents Chemother.* **2009**, *53*, 2517-2521 b. L. F. Shubitz, H. T. Trinh, R. H. Perrill, C. M. Thompson, N. J. Hanan, J. N. Galgiani, D. E. Nix, *J. Infect. Dis.* **2014**.

[40] K. J. Weissman, R. Muller, *Nat. Prod. Rep.* **2010**, *27*, 1276-1295.

IV.1. Ambruticins

Ambruticin S **1.017** was isolated in the 1970s, in the laboratories of Warner-Lambert, from an isolate of *Polyangium cellulosum* var. *fulvum*[41] (figure 17).



Ambruticin S **1.017**

Figure 17 : structure of ambruticin S

The exact structure was elucidated by systematic degradative studies coupled with spectroscopic analysis. Derivatization of ambruticin afforded a crystalline product on which a single-crystal X-ray diffraction analysis could be performed unambiguously establishing the relative stereochemistry of the natural product[42]. Shortly afterwards, the same group isolated a less polar molecule from the same fermentation broth as ambruticin and determined its structure as being 5-*epi* ambruticin, named ambruticin F[43].

Later, ambruticin variants containing a free or methyl substituted amino group instead of an –OH function were discovered by the group of Reichenbach. They were labeled ambruticin VS[44] (figure 18).

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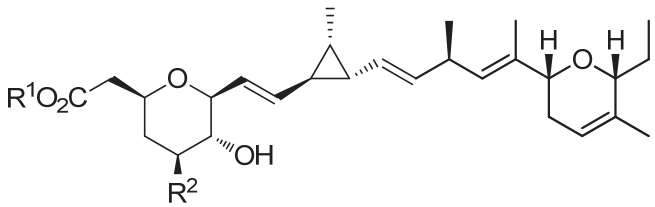
[41] S. M. Ringel, R. C. Greenough, S. Roemer, D. Connor, A. L. Gutt, B. Blair, G. Kanter, S. von, *J. Antibiot.* **1977**, *30*, 371-375.

[42] D. T. Connor, R. C. Greenough, M. Von Strandtmann, *J. Org. Chem.* **1977**, *42*, 3664-3669.

[43] D. T. Connor, M. Von Strandtmann, *J. Org. Chem.* **1978**, *43*, 4606-4607.

[44] G. Höfle, H. Steinmetz, K. Gerth, H. Reichenbach, *Liebigs Ann. Chem.* **1991**, *1991*, 941-945.



Ambruticin VS **1.018**

R^1	R^2	ambruticin
CH_3	$^+NMe_3$	VS-1
H	$^+NHMe_2$	VS-2
H	$^+NOMe_2$	VS-3
H	$^+NH_2Me$	VS-4
H	$^+NH_3$	VS-5

Figure 18 : structures of ambruticin VS

Ambruticins are of interest because of their antifungal effect which is quite impressive.

The antibiotic is highly active *in vitro* against systemic pathogens such as *Histoplasma capsulatum, Coccidioides immitis*, *Blastomyces dermatidis* as well as the dermatophytic filamentous fungi[40]. Moreover, ambruticin compared favorably with amphotericin B and miconazole when tested against the dimorphic pathogens *Histoplasma capsulatum, Coccidioides immitis*, *Blastomyces dermatidis* and against *Aspergillus fumigatus*[45].

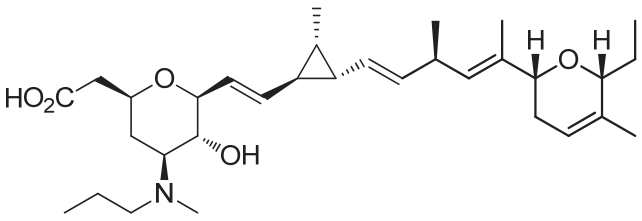
[45] S. Shadomy, D. M. Dixon, A. Espinel-Ingroff, G. E. Wagner, H. P. Yu, H. J. Shadomy, *Antimicrob. Agents Chemother.* **1978**, *14*, 99-104.

Furthermore, it has been disclosed that ambruticin S has a low animal toxicity (LD_{50} > 1000 mg/kg for an oral dose)[46].

Various studies on mice revealed its oral activity for the treatment of histoplasmosis even though the day dose was higher for ambruticin (150 mg/kg) than for amphotericin B (25 mg/kg)[47].

Ambruticin S showed curative effects against murine coccidioidal infection. When mice were infected with lethal doses of *Coccidioides* spp. and treated with ambruticin S from 17 to 56 days, 73% to 100% of them survived and were found to be free of the fungus[48]. More recently, based on these results, two analogs of ambruticin S with greater *in vitro* potency were developed and tested against lethal murine *Coccidioides* infection. Both improved the survival rate of treated mice over that of control mice[49].

In another study, a derivative of ambruticin VS4, designated KOSN-2079 **1.019**, was tested in the mouse model of invasive apergillosis (figure 19).



KOSN-2079 **1.019**

Figure 19 : structure of Ambruticin VS4 analogue

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[46] S. M. Ringel, *Antimicrob. Agents Chemother.* **1978**, *13*, 762-769.

[47] S. Shadomy, C. J. Utz, S. White, *Antimicrob. Agents Chemother.* **1978**, *14*, 95-98.

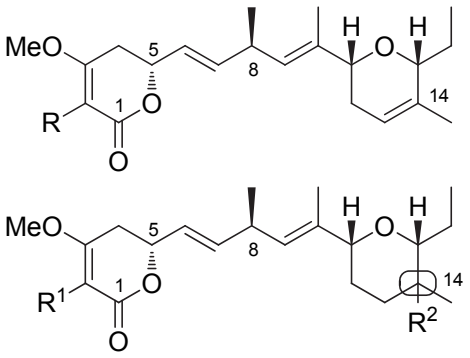
[48] H. B. Levine, S. M. Ringel, J. M. Cobb, *CHEST Journal* **1978**, *73*, 202-206.

[49] L. F. Shubitz, J. N. Galgiani, Z.-Q. Tian, Z. Zhong, P. Timmermans, L. Katz, *Antimicrob. Agents Chemother.* **2006**, *50*, 3467-3469.

It significantly reduced pulmonary fungal burdens and increased survival compared to mice that received the vehicle alone. This study suggests that additional ambruticin analogues should be explored for the treatment of this disease in human[50].

IV.2. Jerangolids

Jerangolids were isolated in 1992 from the myxobacteria *Sorangium cellulosum* So ce 307, which was isolated at the GBF in 1987 from a soil sample collected in Jerusalem. Jerangolids are rare metabolites of *Sorangium cellulosum* strains (4 in 1000). Five compounds from this family are known and their structures are depicted in figure 20.



Jerangolid A, R=CH_2OH
Jerangolid D, R=CH_3

Jerangolid B, R^1=CH_3, R^2=OH
Jerangolid E, R^1=CH_3, R^2=H
Jerangolid H, R^1=CH_2OH, R^2=H

Figure 20 : structures of jerangolids

For jerangolid B, E and H, the stereochemistry at C_{14} is still unknown.

In vitro tests on jerangolid A show that it possesses potent antifungal activity against a wide range of pathogenic fungi such as *Hansenula anomala* and

[50] L. Y. Chiang, D. E. Ejzykowicz, Z. Q. Tian, L. Katz, S. G. Filler, *Antimicrob. Agents Chemother.* **2006**, *50*, 3464-3466.

Mucor hiemalis (MIC 0.7µg/mL), *Debaryomyces hansenii* and *Trisporo terrestre* (0.1-0.4 µg/mL) and *Candida albicans* (4.2 µg/mL)[51].

IV.3. Mode of action

Jerangolids and ambruticins possess a similar mode of action. They are believed to induce the high-osmolarity glycerol (HOG) signaling pathway, resulting in the accumulation of triacylglycerols and free fatty acids. In the absence of high external osmolarity, intracellular accumulation of glycerol causes leakage of cellular content which presumably results in cell death[52].

It was shown recently that ambruticin targets Hik1, a histidine kinase, and that binding of the drug results in an inappropriate cellular response, including intracellular accumulation of glycerol and, ultimately, cell death. Binding of ambruticin would result in the production of dephosphorylated Ssk1 (active form), the phosphate signal is carried downstream to Hog1, resulting in overstimulation of the HOG pathway[53]. The proposed mechanism of the HOG pathway without the effect of a drug in *Candida albicans* is represented in figure 21. The left side shows unstressed conditions while the right side illustrates stressed conditions[54]. The exact mechanism of binding of the drug is still unknown.

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[51] K. Gerth, P. Washausen, G. Hofle, H. Irschik, H. Reichenbach, *J. Antibiot.* **1996**, *49*, 71-75.

[52] P. Knauth, H. Reichenbach, *J. Antibiot.* **2000**, *53*, 1182-1190.

[53] a. L. Vetcher, H. G. Menzella, T. Kudo, T. Motoyama, L. Katz, *Antimicrob. Agents Chemother.* **2007**, *51*, 3734-3736 b. A. Dongo, N. Bataillé-Simoneau, C. Campion, T. Guillemette, B. Hamon, B. Iacomi-Vasilescu, L. Katz, P. Simoneau, *Appl. Environ. Microbiol.* **2009**, *75*, 127-134.

[54] Y. Bahn, *Eukaryotic cell* **2008**, *7*, 2017-2036.

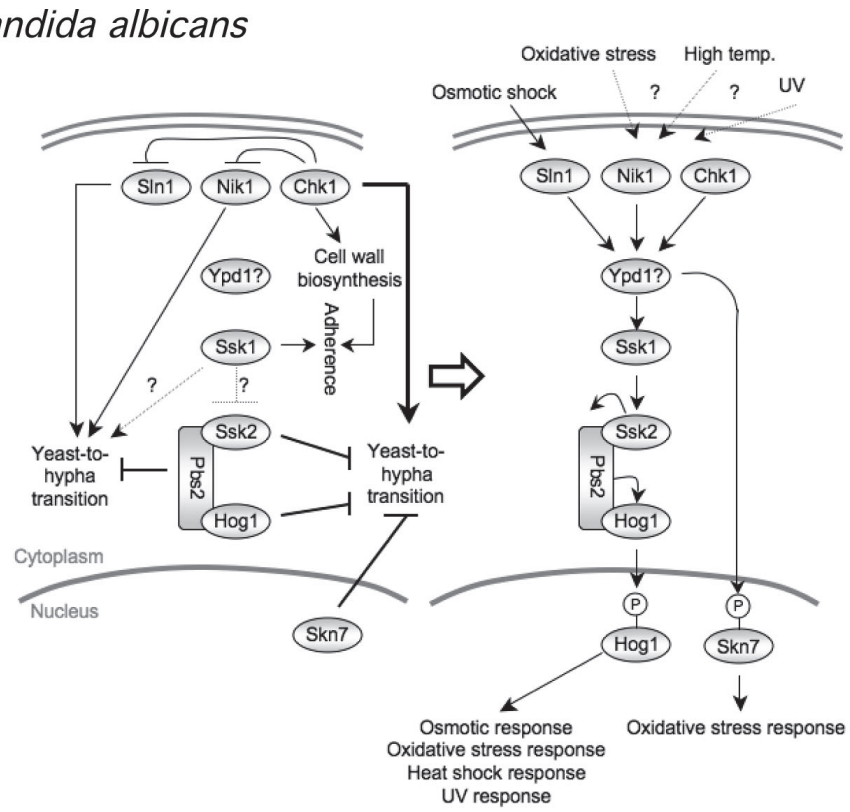
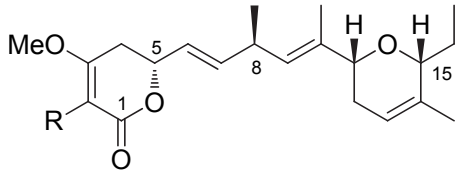


Figure 21

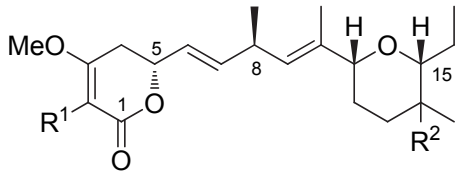
Despite the recently extended armamentarium of antifungal agents to treat the continuously increasing infections with invasive mycoses, there is a constant need for new solutions. Indeed, the increase of immunosuppressed patients as well as the rising resistance of fungi makes the discovery of new antifungal agents an important area of research. In this context, we are interested in the two families of natural products presented above, which have shown interesting potential antifungal activities. In this thesis, we will specifically direct our efforts towards the synthesis of jerangolids and some new analogues.

JERANGOLIDS

As shown in the general introduction, jerangolids are a family of natural products with interesting potential antifungal activities.



Jerangolid A, R=CH_2OH
Jerangolid D, R=CH_3



Jerangolid B, R^1=CH_3, R^2=OH
Jerangolid E, R^1=CH_3, R^2=H
Jerangolid H, R^1=CH_2OH, R^2=H

Figure 1: structures of jerangolids

Despite their promising activity, there have only been two total syntheses and two partial syntheses of jerangolid A and D reported so far. Syntheses of jerangolid A were published by the groups of Donaldson and Hanessian whilst work about jerangolid D was described in our group. These syntheses will be described in this chapter.

I. Syntheses of jerangolid A

I.1. A short synthesis of the dihydropyran

In 2005, the group of Donaldson reported the first enantioselective preparation of the common dihydropyranyl segment **2.001** present in jerangolid A and D as well as in ambruticin S[1].

[1] J. M. Lukesh, W. A. Donaldson, *Tetrahedron Lett.* **2005**, *46*, 5529-5531.

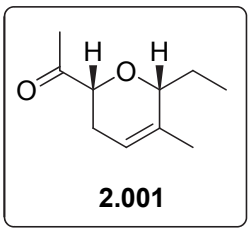
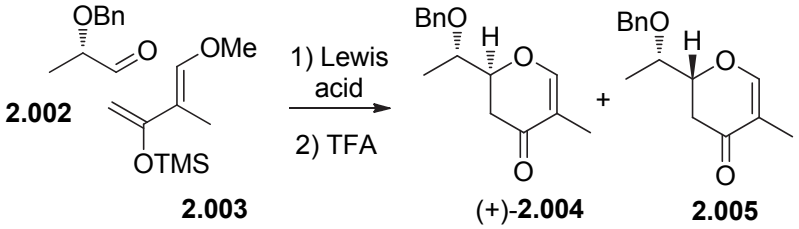


Figure 2 : structure of dihydropyran 2.001

They envisioned the construction of this oxane ring by a Lewis acid catalyzed hetero Diels-Alder reaction followed by a C-glycosidation of the derived pseudoglycal[2].

To this end, reaction of optically pure aldehyde[3] **2.002** with butadiene[4] **2.003**, in the presence of BF_3-etherate, followed by work-up with TFA, gave a mixture of two inseparable diastereomers **2.004** and **2.005** (scheme 1).



$BF_3.OEt_2/CH_2Cl_2$/-78 °C to 23 °C	1:1.6 (71 %)
$MgBr_2$/THF/0 °C to 23 °C	1:0 (86 %)

Scheme 1 : hetero Diels-Alder reaction

---

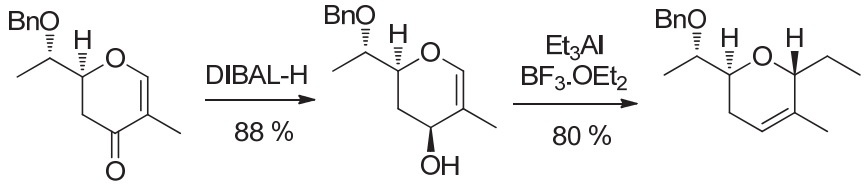
[2] a .S. J. Danishefsky, M. T. Bilodeau, *Angew. Chem. Int. Ed.* **1996**, *35*, 1380-1419 b. J. M. Lukesh, W. A. Donaldson, *Tetrahedron: Asymm.* **2003**, *14*, 757-762.

[3] D. Enders, S. von Berg, B. Jendeleit, *Org. Synth.* **2002**, *78*, 177-188.

[4] S. Danishefsky, C.-F. Yan, R. K. Singh, R. B. Gammill, P. M. McCurry, N. Fritsch, J. Clardy, *J. Am. Chem. Soc.* **1979**, *101*, 7001-7008.

To solve this problem, they switched to $MgBr_2$ as a Lewis acid which allowed them to reach dihydropyranone (+)-**2.004** as a single diastereomer after work-up with TFA.

Reduction of **2.004** with DIBAL-H gave the pseudoglycal (+)-**2.006** as a single diastereomer (scheme 2).



(+)-**2.004** (+)-**2.006** (-)-**2.007**

Scheme 2

Subsequent treatment of pseudoglycal (+)-**2.006** with triethylaluminium in the presence of BF_3-etherate gave a mixture of *trans*- and *cis*-dihydropyrans (8:1 ratio). Purification by silica gel column chromatography separated the isomers and afforded the pure *trans*-isomer (-)-**2.007** in good yield. An axial attack of the weak nucleophile on the cyclic oxonium generated by ionization of **2.006** explains the formation of the major *trans*-product (figure 3).

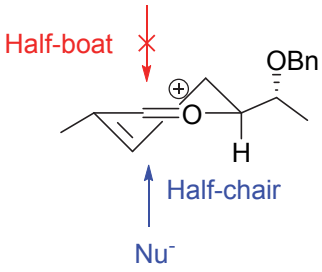
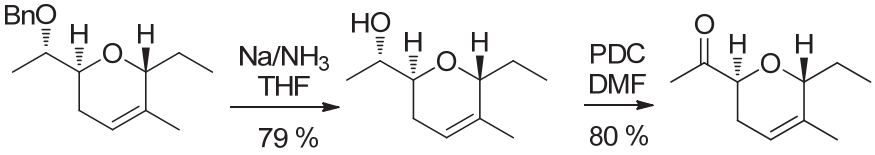


Figure 3

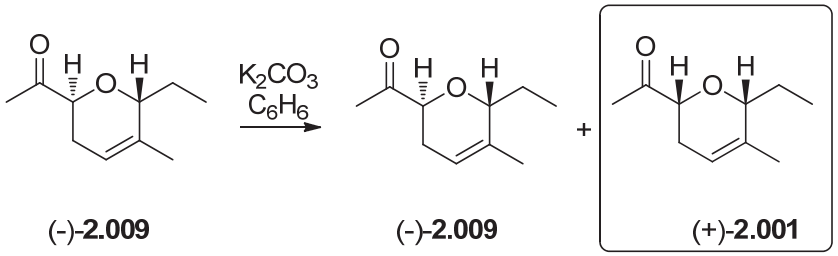
Deprotection of the benzyl-group with sodium in ammonia followed by oxidation of the alcohol to the corresponding ketone gave (-)-**2.009** (scheme 3).



(-)-**2.007** (-)-**2.008** (-)-**2.009**

Scheme 3

Base-catalyzed epimerization of the *trans*-ketone afforded the desired right-hand part of jerangolid A **2.001**, after two equilibration/separation cycles in 83 % combined yield (scheme 4).



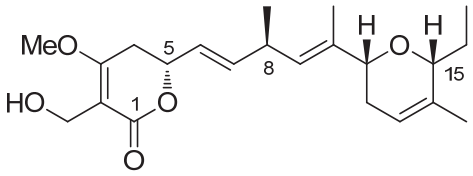
Scheme 4

In summary, the dihydropyranyl segment **2.001** was synthetized in six steps from optically active aldehyde **2.002** in 31.7 % overall yield.

I.2. Total synthesis of jerangolid A

The group of Hanessian reported the first total synthesis of jerangolid A **2.010** in 2010[5].

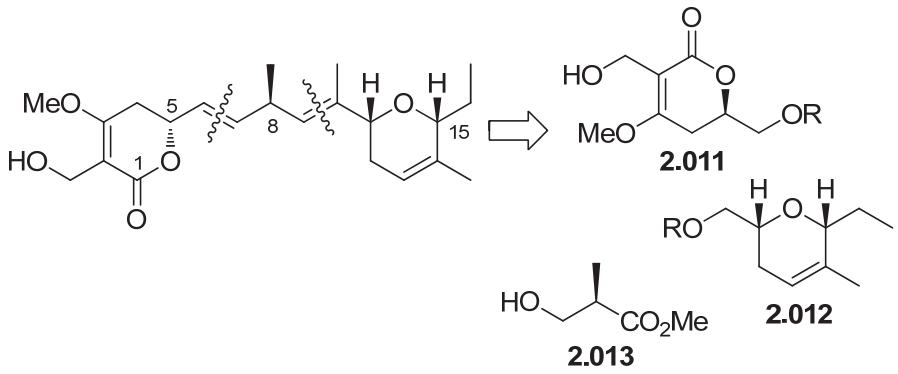
[5] S. Hanessian, T. Focken, R. Oza, *Org. Lett.* **2010**, *12*, 3172-3175.



Jerangolid A **2.010**

Figure 4 : structure of jerangolid A 2.010

They envisioned a late-stage assembly of two ring segments through a phosphonamide anion-based olefination methodology developed in their group[6] and a Julia-Kociensky reaction (scheme 5).



Scheme 5

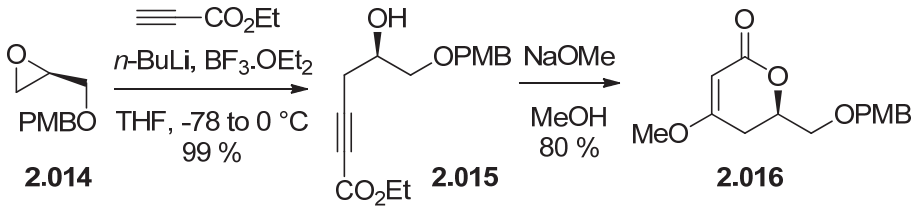
I.2.1. Synthesis of lactone 2.011

They began building the lactone from PMB protected (*R*)-glycidol. Opening of this epoxide **2.014** with the anion derived from ethyl propiolate, in the presence of BF_3-etherate, afforded quantitatively previously known alkyne[7] **2.015**. Further treatment of the latter with NaOMe in MeOH furnished lactone **2.016** in good yield (scheme 6).

---

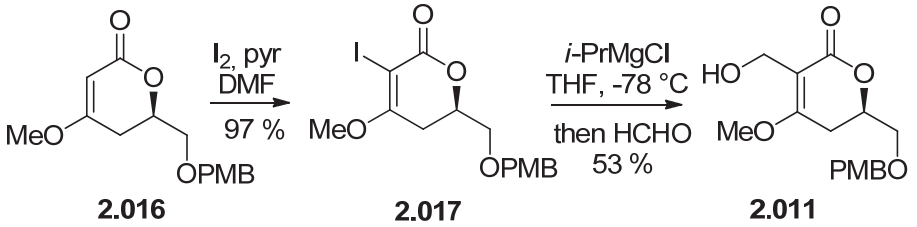
[6] Y. L. Bennani, S. Hanessian, *Chem. Rev.* **1997**, *97*, 3161-3196.

[7] A. Ahmed, E. K. Hoegenauer, V. S. Enev, M. Hanbauer, H. Kaehlig, E. Öhler, J. Mulzer, *J. Org. Chem.* **2003**, *68*, 3026-3042.



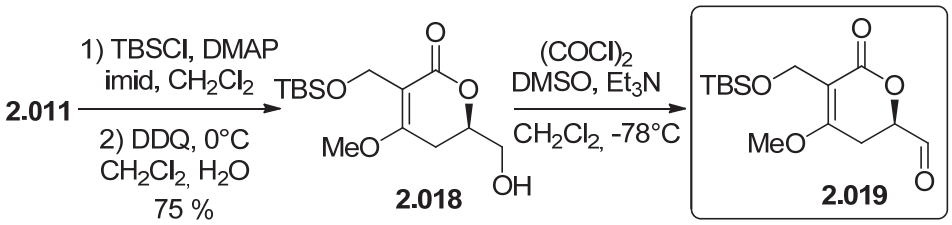
Scheme 6

Two more steps were required to introduce the hydroxymethyl group. In order to do so, lactone **2.016** was iodinated and the resulting adduct **2.017** was then treated with *i*-PrMgCl at -78°C. The resulting organomagnesium species reacted with a solution of formaldehyde to yield hydroxymethyl lactone **2.011** (scheme 7).



Scheme 7

Protection of the alcohol with TBS and removal of PMB with DDQ successfully delivered alcohol **2.018** in 75 % yield. Oxidation to the corresponding aldehyde was tricky due to the unstable nature of the latter. Swern conditions proved to be the best, affording aldehyde **2.019** in sufficient purity for subsequent transformation (scheme 8).

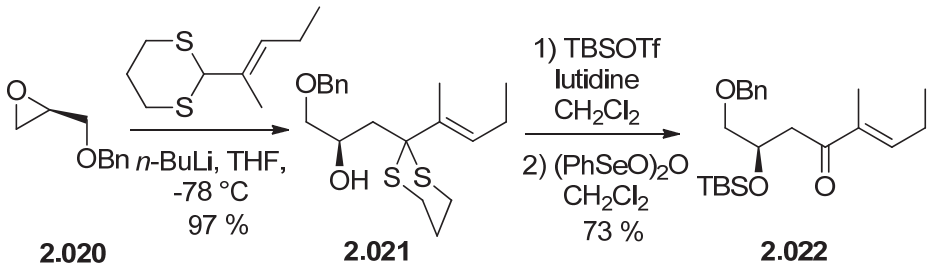


Scheme 8

I.2.2. Synthesis of dihydropyran 2.012

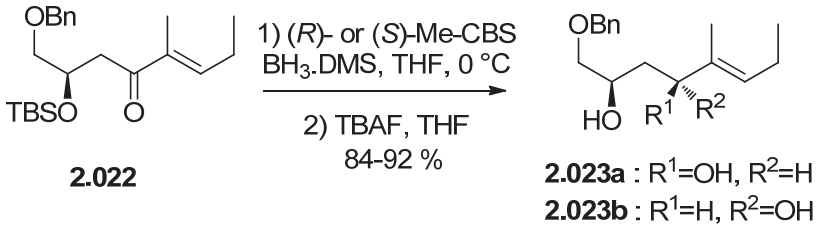
The synthesis of this subunit is based on a palladium-catalyzed cyclization of allylic diols developed by Uenishi and others. Upon treatment with $Pd(CH_3CN)_2Cl_2$, tetrahydro- or dihydro-pyrans are formed *via* a 6-*exo* or 6-*endo-trig* cyclization respectively. The selectivity is controlled by the relative configuration of the diol[8].

The allylic diols are reached by opening of (*R*)-benzylated glycidol with dithiane to yield **2.021** followed by unmasking of the enone system. Protection of the free alcohol was necessary in order for the smooth removal of the dithiane (scheme 9).



Scheme 9

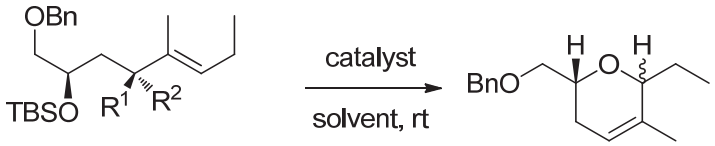
Reduction of enone **2.022** with (*R*)- or (*S*)-Me-CBS and subsequent treatment with TBAF furnished the diastereomerically pure diols **2.023a** and **2.023b** (scheme 10).



Scheme 10

[8] a. J. i. Uenishi, M. Ohmi, *Angew. Chem. Int. Ed.* **2005**, *44*, 2756-2760 b. N. Kawai, S. Mahadeo Hande, J. i. Uenishi, *Tetrahedron* **2007**, *63*, 9049-9056.

The following cyclization was conducted under Uenishi's conditions. Unfortunately, with these particular substrates, treatment of diols **2.023a** and **2.023b** with $Pd(CH_3CN)_2Cl_2$ led to a 1.5:1 ratio of *syn*/*anti* dihydropyrans. After optimizations based on other studies[9], they were able to obtain the desired *syn*-dihydropyran **2.024** using either the cationic complex $Pd(CH_3CN)_2Cl_2$, $BF_3.OEt_2$ or TfOH, starting from either diols (table 1). This observation suggests that the stereochemistry of the allylic alcohol is of no importance in the final outcome of this cyclization process, indicating a cationic mechanism.



2.023a : R^1=OH, R^2=H
2.023b : R^1=H, R^2=OH

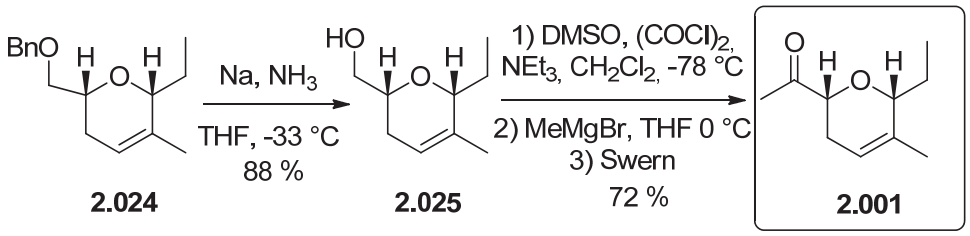
entry	Catalyst (equiv)	solvent	Yield (%)	Syn/anti
1	$Pd(CH_3CN)_2Cl_2$ (1.0)	THF	53	1.5:1
2	$Pd(CH_3CN)_2(BF_4)_2$ (0.05)	CH_2Cl_2	72	25:1
3	BF_3OEt_2 (0.1)	CH_2Cl_2	82	20:1
4	TfOH (0.1)	CH_2Cl_2	81	16:1

Table 1

The end of the sequence proceeds smoothly. The benzyl group was removed under Birch conditions. Swern oxidation, addition of methyl Grignard on the

[9] a. M. Reiter, H. Turner, V. Gouverneur, *Chemistry – A European Journal* **2006**, *12*, 7190-7203bA. Guérinot, A. Serra-Muns, C. Gnamm, C. l. Bensoussan, S. b. Reymond, J. Cossy, *Org. Lett.* **2010**, *12*, 1808-1811.

resulting aldehyde and a second Swern oxidation afforded the desired dihydropyran **2.001** in 72 % yield (scheme 11).



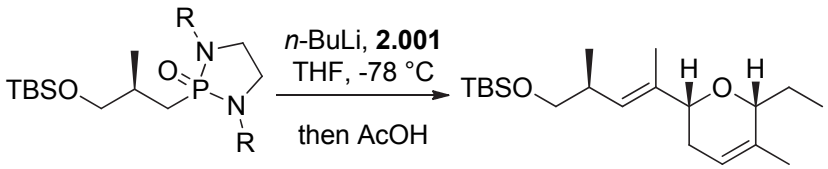
2.024 **2.025** **2.001**

Scheme 11

I.2.3. Completion of the synthesis

The two rings were connected using two olefination methods. The first one employs cyclic phosphonamides[10]. Deprotonation with *n*-BuLi was followed by the addition of ketone **2.001**. After quenching with acetic acid, a separable mixture of *E*/*Z* isomers containing the desired one as the major product was obtained (table 2).

[10] K. J. Koeller, C. D. Spilling, *Tetrahedron Lett.* **1991**, *32*, 6297-6300.



2.026a R=Me
2.026b R=*i*-Pr

2.027

Entry	phosphonamide	Yield[a]	E/Z
1	**2.026a**	57	3:1
2	**2.026a**	62	6:1[b]
3	**2.026b**	20	13:1

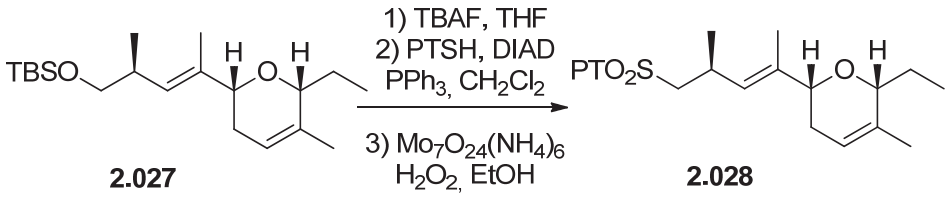
[a] Recovery of ketone **2.027** : 20-60 %.

[b] Addition of AcOH at r.t.

Table 2

As shown in table 2, changing the substituents from methyl to isopropyl led to increased selectivity, though at the expense of the yield.

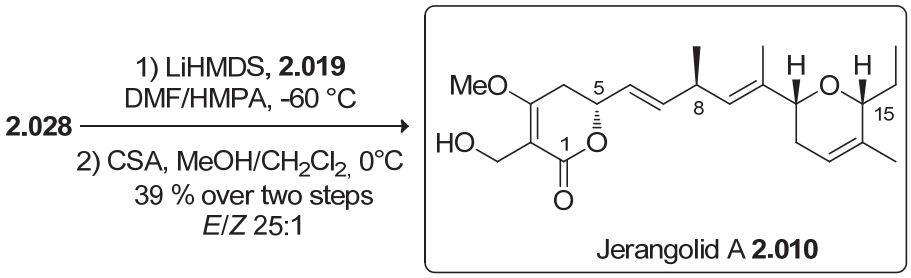
Removal of the TBS with TBAF afforded the corresponding alcohol in 90 % yield, which was then transformed into PT-sulfide under Mitsunobu conditions. Subsequent oxidation afforded compound **2.028** which is ready for coupling with aldehyde **2.019** under Julia-Kociensky conditions (scheme 12).



2.027 **2.028**

Scheme 12

After some optimizations[11], the desired *E*-olefin was obtained almost exclusively in 46 % yield (*E*/*Z* > 25:1). Final removal of the TBS group under mild acidic conditions provided jerangolid A (scheme 13).



Scheme 13

In summary, the first total synthesis of jerangolid A was reported in 16 linear steps and 6 % overall yield from glycidol **2.020**.

II. Jerangolid D

Jerangolid D is very similar to jerangolid A. The only difference between them occurs at C_2 where the CH_2-OH substituent is replaced by a methyl group (figure 5).

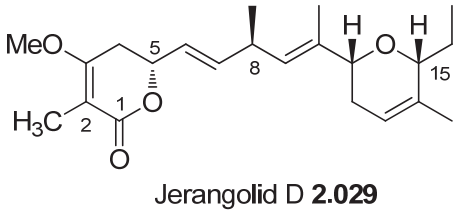


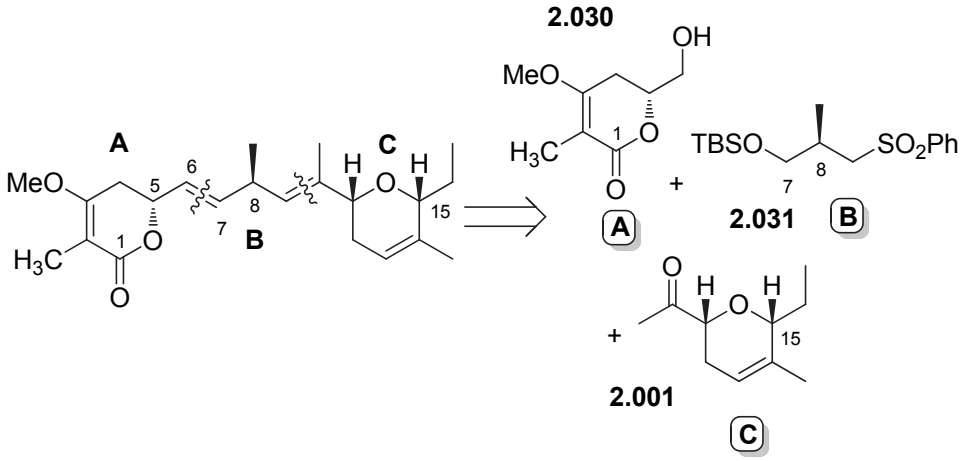
Figure 5 : structure of jerangolid D

II.1. Total synthesis

The first total synthesis of jerangolid D was described by our group in 2007 by Dr J. Pospísil[12]. The molecule was divided into three fragments: lactone

[11] P. Liu, E. N. Jacobsen, *J. Am. Chem. Soc.* **2001**, *123*, 10772-10773.

A, sulfone **B** and dihydropyrane **C** that would ultimately be connected *via* two Julia olefinations (scheme 14).



Scheme 14

II.1.1. Synthesis of lactone 2.030

The synthesis of lactone **2.030** began with (*R*)-benzylated glycidol **2.020** which was opened using Nagata's reagent[13] to access *β*-hydroxynitrile **2.032** in quantitative yield. The latter reacted with methyl 2-bromopropanoate in the presence of activated zinc dust under Blaise conditions[14]. The corresponding *β*-ketoester **2.033** was isolated in good yield. Surprisingly, the free hydroxyl group was tolerated under these conditions[15] (scheme 15).

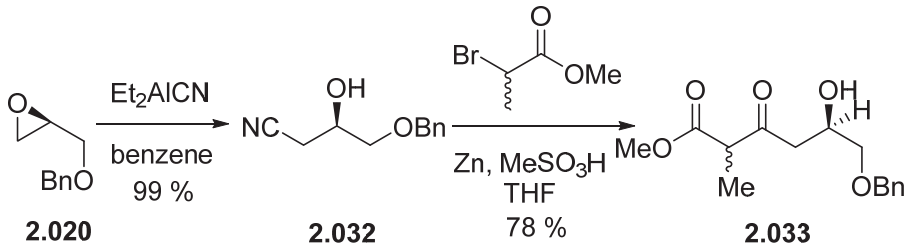
---

[12] J. Pospíšil, I. E. Markó, *J. Am. Chem. Soc.* **2007**, *129*, 3516-3517.

[13] a. F. Benedetti, F. Berti, S. Norbedo, *Tetrahedron Lett.* **1999**, *40*, 1041-1044. b. W. Nagata, M. Yoshioka, T. Okumura, *Tetrahedron Lett.* **1966**, *7*, 847-852.

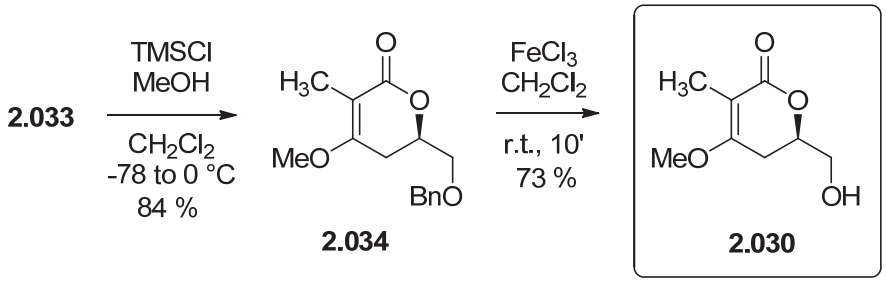
[14] For a review on Blaise reaction: H. S. Prakash Rao, S. Rafi, K. Padmavathy, *Tetrahedron* **2008**, *64*, 8037-8043.

[15] For similar observation : F.-D. Wang, J.-M. Yue, *Synlett* **2005**, *2005*, 2077-2079.



Scheme 15

One-pot cyclisation/enol-ether formation, promoted by TMSCl in MeOH, furnished protected lactone **2.034** in 84 % yield. The benzyl group was removed using $FeCl_3$ to complete the synthesis of the left-hand fragment **2.030** (scheme 16).

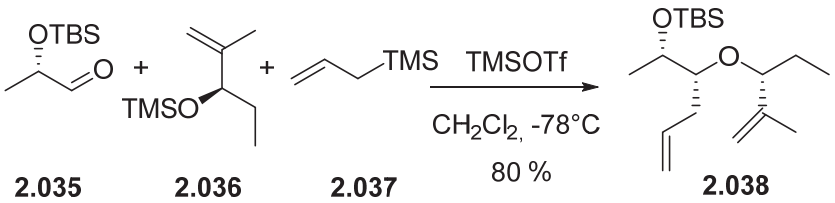


Scheme 16

II.1.2. Synthesis of dihydropyran 2.001

The dihydropyran moiety was assembled using a diastereoselective three-component Sakurai condensation previously developed in our laboratory[16] (scheme 17).

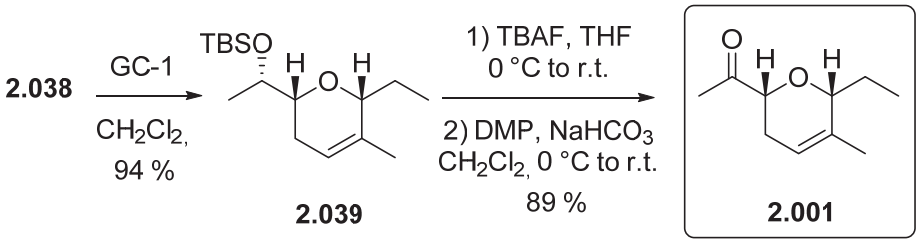
[16] J. Pospíšil, T. Kumamoto, I. E. Markó, *Angew. Chem. Int. Ed.* **2006**, *45*, 3357-3360.



Scheme 17

Aldehyde **2.035**, silyl ether **2.036** and allylsilane **2.037** were mixed together at -78 °C and a catalytic amount of TMSOTf was added. The *syn-syn* adduct **2.038** was obtained as a single diastereomer in 80 % yield.

Ring-closing metathesis with Grubbs-I catalyst provided protected dihydropyran **2.039** in excellent yield. Deprotection of the TBS group with TBAF, followed by oxidation with Dess-Martin periodane, finished the synthesis of the right-hand fragment **2.001** (scheme 18).



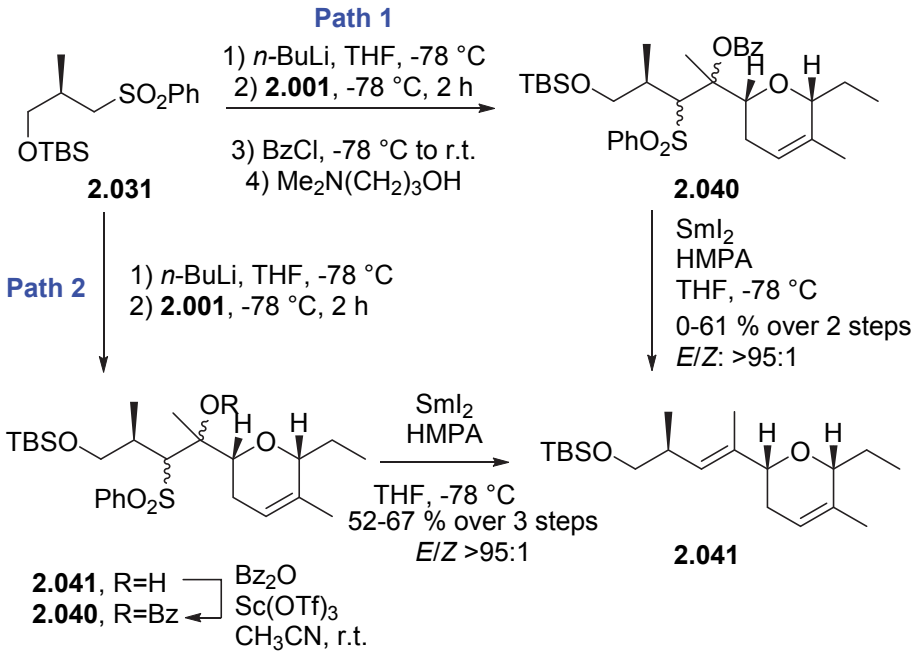
Scheme 18

II.1.3. Completion of the synthesis

A Julia olefination between ketone **2.001** and sulfone **2.031** was selected to form the first olefin. Initially, a one-pot condensation and benzoylation was attempted (path 1). Surprisingly, this procedure proved to be irreproducible and therefore, a two-steps procedure had to be used (path 2)[17]. Reductive

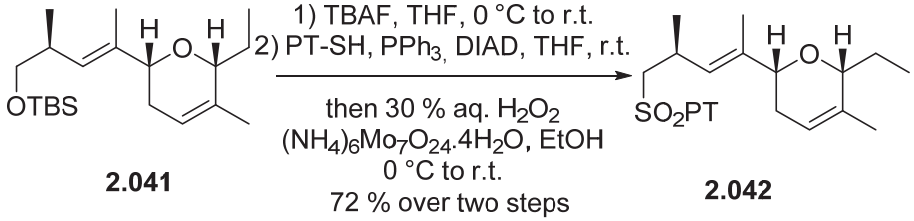
[17] R. Dumeunier, I. E. Markó, *Tetrahedron Lett.* **2004**, *45*, 825-829.

elimination with SmI_2 provided the desired olefin **2.041** with good yield and excellent *E*/*Z* selectivity[18] (scheme 19).



Scheme 19

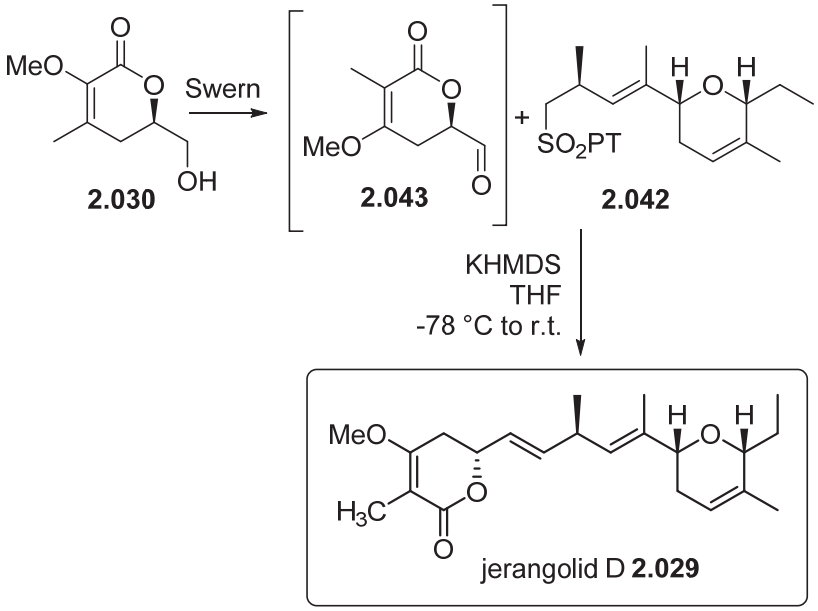
The remaining TBS group was removed with TBAF and the corresponding alcohol was transformed into PT-sulfone **2.042** (scheme 20).



Scheme 20

[18] a. I. E. Markó, F. Murphy, S. Dolan, *Tetrahedron Lett.***1996**, *37*, 2089-2092 b. I. E. Markó, F. Murphy, L. Kumps, A. Ates, R. Touillaux, D. Craig, S. Carballares, S. Dolan, *Tetrahedron* **2001**, *57*, 2609-2619.

In parallel, alcohol **2.030** was oxidized into aldehyde **2.043** which, due to its lack of stability, was directly reacted with sulfone **2.042** under standard Julia-Kociensky olefination conditions. Jerangolid D **2.029** was isolated in 54 % yield and >95:1 *E*/*Z* selectivity (scheme 21).



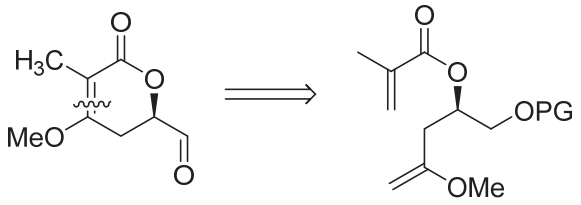
Scheme 21

In summary, the first total synthesis of jerangolid D was accomplished in 22 steps (12 steps in the longest linear sequence) and 6.1 % overall yield starting from epoxide **2.020**, Roche ester and ethyl lactate.

II.2. Synthesis of lactone 2.030

A second strategy for the synthesis of the left-hand lactone of jerangolid D was developed in our group a short time after the publication of the first total

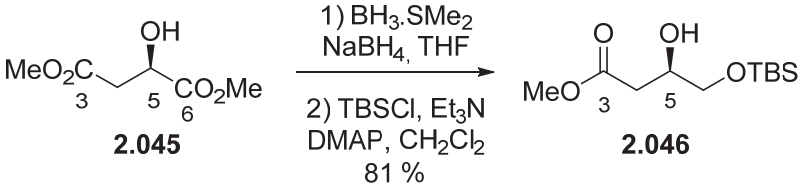
synthesis[19]. This second approach is based upon a retrosynthesis using ring-closing metathesis (RCM) as the key step (scheme 22).



2.043 **2.044**

Scheme 22

The synthesis began with the selective reduction of the C6 ester of dimethyl malate **2.045**. The corresponding primary alcohol was then protected with a TBS group (scheme 23).



2.045 **2.046**

Scheme 23

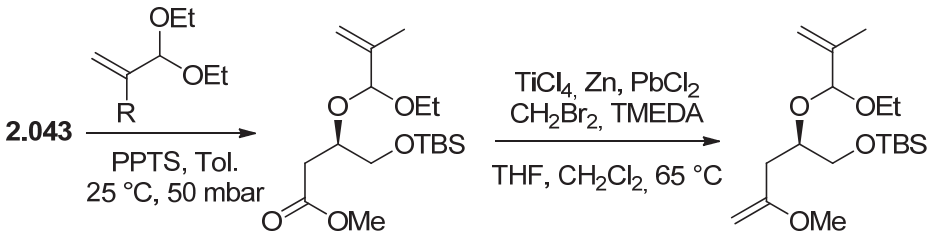
The free alcohol was transformed into acetal **2.044** by PPTS-catalyzed *trans*-acylation of methacrolein diethyl acetal[20]. A subsequent Takai-Utimoto olefination[21] yielded the desired precursor for RCM in 85 % yield (scheme 24).

---

[19] J. Pospíšil, I. E. Markó, *Tetrahedron Lett.* **2008**, *49*, 1523-1526.

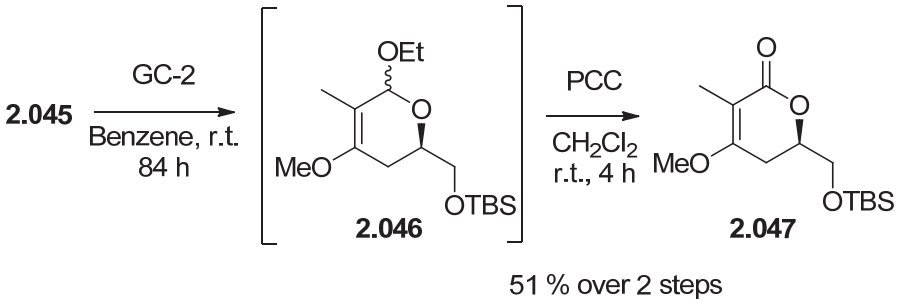
[20] J. A. VanAllan, *Org. Synth.* **1952**, *32*, 5-8

[21] T. Okazoe, K. Takai, K. Oshima, K. Utimoto, *J. Org. Chem.* **1987**, *52*, 4410-4412.



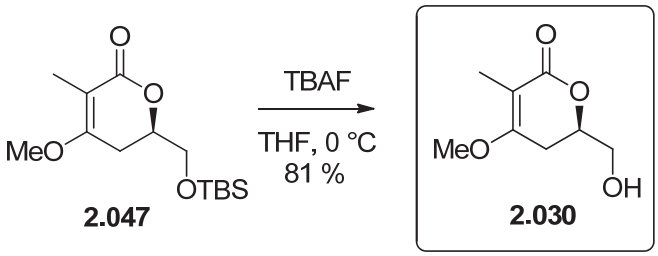
Scheme 24

After numerous optimization studies, the ring was closed using Grubbs-II catalyst (GC-2) (10 mol %) at room temperature with excellent yield. The corresponding acetal was directly oxidized with PCC to afford the protected lactone **2.047** (scheme 25).



Scheme 25

Final removal of the TBS group furnished the left-hand part **2.030** of jerangolid D in 81 % yield (scheme 26).



Scheme 26

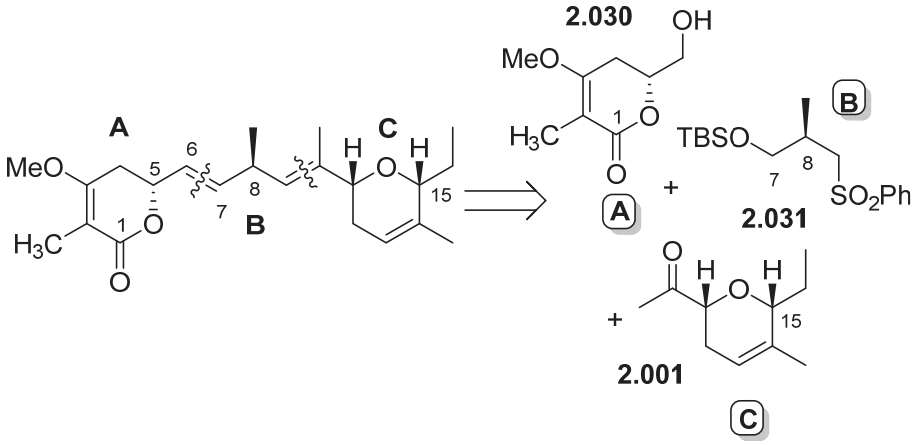
In our project, we are interested in the synthesis of new analogues of jerangolid D. Based upon the synthesis described in our laboratory and detailed above (see II.1), our goal is to operate a series of chemical modifications on the three fragments in order to create a set of new compounds, similar to jerangolid D, but possessing enhanced stability and hopefully, increased activity and lower toxicity.

The high convergence of our total synthesis enables us to modify at will each of these three subunits before connecting them to construct analogues of jerangolid D.

OBJECTIVES

The main goals of this thesis are to synthesize jerangolid D, as a reference sample and to prepare some new analogues, based upon the synthesis described in our laboratory.

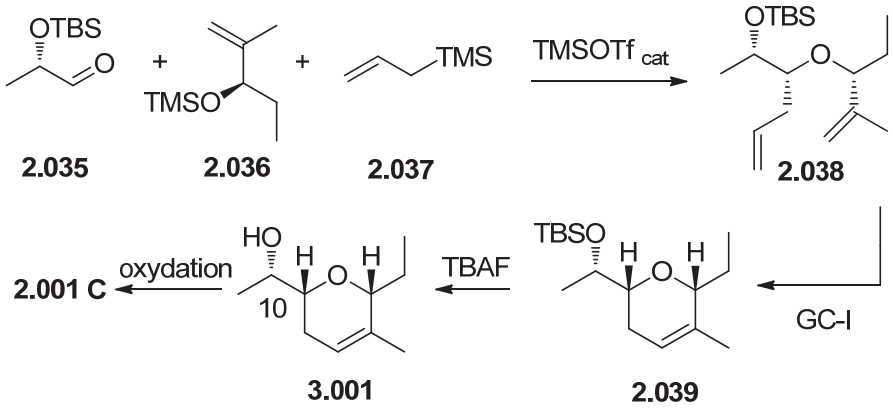
As depicted before, jerangolid D can be divided into three fragments: a lactone **A**, an unsaturated central part **B** and a dihydropyran **C** (scheme 1).



Scheme 1

I. Synthesis of DHP C

Initially, we shall focus our efforts on the synthesis of DHP **2.001**, using the methodology previously developed in the lab (vide supra chapter 2).



Scheme 2

Since this dihydropyran is present in ambruticin, as well as in jerangolids family, different esters of alcohol **3.001** will be prepared. To mimic both families, different vinylic, aromatic and polyenic side-chain esters have been chosen (figure 1).

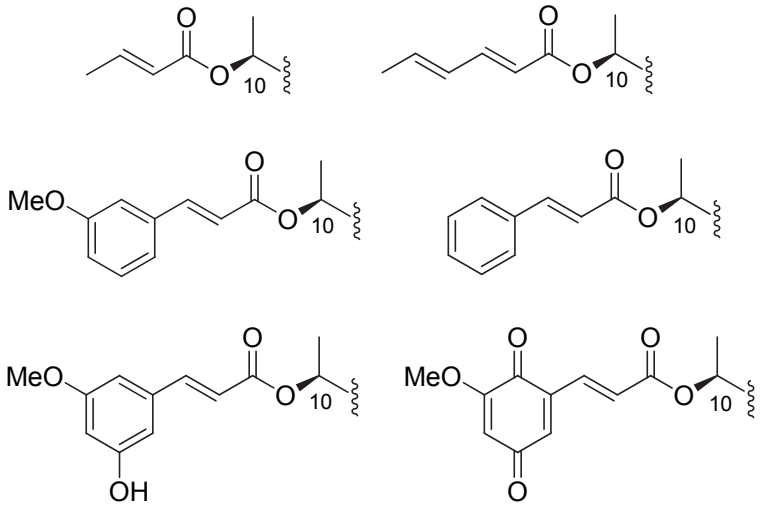
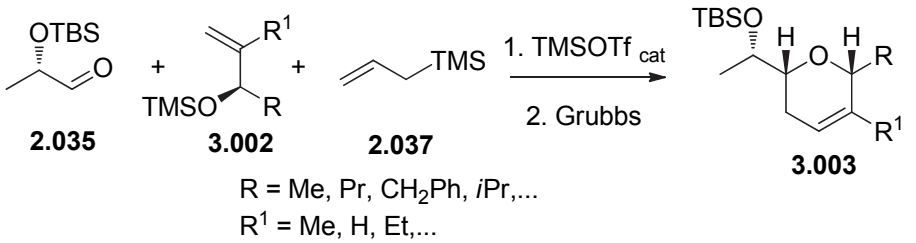


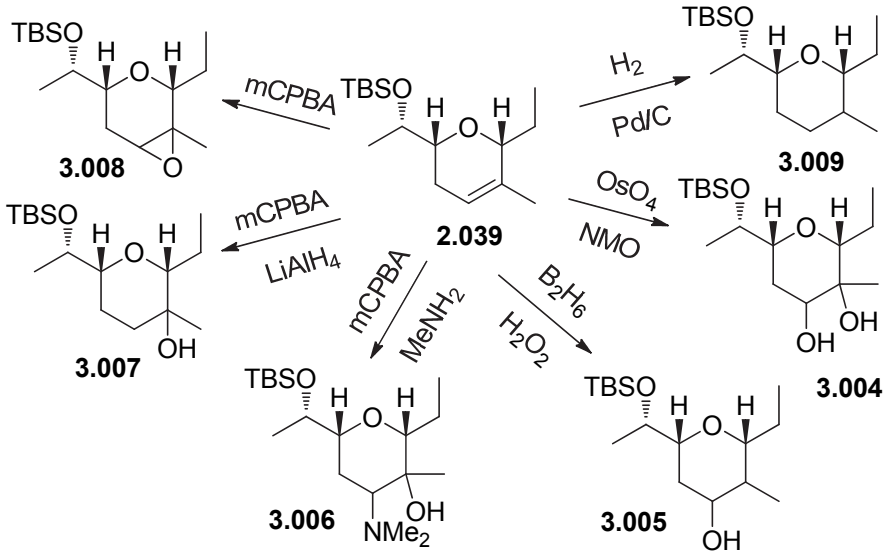
Figure 1

Moreover, it would be interesting to replace the ethyl and the methyl groups on the DHP cycle by other substituents. This should be easily accomplished by changing the substituents on silyl ether **3.002** (scheme 3).



Scheme 3

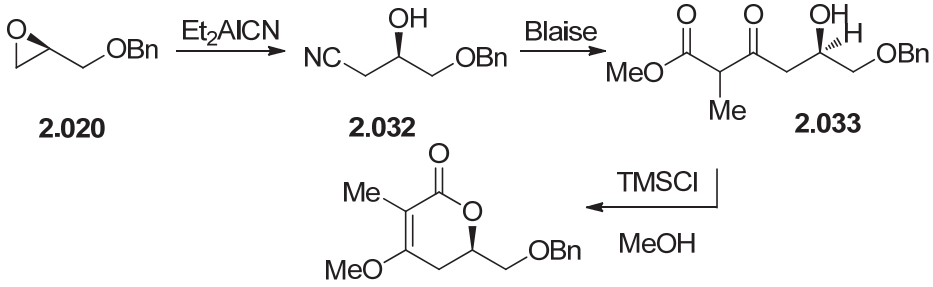
Finally, we would like to work on the modifications of the double bond of cycle **C** in order to determine if these functionalities are of importance for its biological activity. Some of these structures will serve to assemble jerangolid B, E and H and we will try to establish their stereochemistry at C14 which is still unknown (see chapter 1, IV.2) (scheme 4).



Scheme 4

II. Synthesis of lactone A

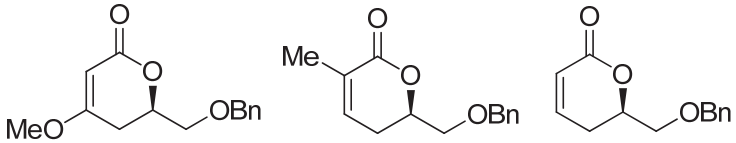
Secondly, we will focus on the synthesis of the left-hand lactone of jerangolid D, once again employing methodologies that have been developed in the group (scheme 5).



2.020 **2.032** **2.033** **2.034**

Scheme 5

The importance of the substituents on the lactone would also be determined. Lactones lacking the methyl group (**3.010**), the methoxy group (**3.011**) or both substituents (**3.012**) will therefore be synthesised (figure 2).



3.010 **3.011** **3.012**

Figure 2

III. Central fragment B

The central fragment could also be modified. We could remove the methyl group, inverse its stereochemistry, or add a second one. It could also be replaced by a 5-membered spiro cycle (figure 3).

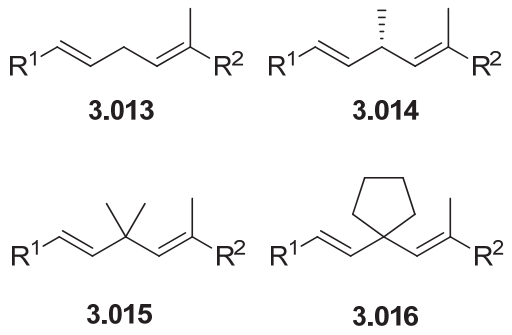


Figure 3

We could also remove one carbon, to form conjugated olefins. Moreover, some studies have demonstrated the importance of the cyclopropane ring present in ambruticin on the antifungal activity displayed by this natural product[1]. An analogue bearing that cyclopropane could be synthetized in our case (figure 4).

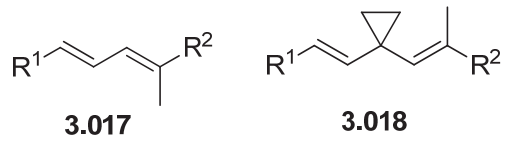


Figure 4

IV. Coupling

At this stage, in order for our approach to be very powerful and versatile, it would be very useful to develop a one-pot methodology to couple the three fragments at once. A selective double Julia olefination has been imagined and is the object of another thesis currently ongoing in our group.

[1] V. Michelet, J.-P. Genet, *Current Org. Chem.* **2005**, *9*, 405-418.

DIHYDROPYRAN SYNTHESIS

In this chapter, we wish to report the results obtained for the synthesis of the dihydropyran moiety **2.001 C** present in jerangolid D. However, before presenting them, we thought it would be interesting to give an overview of the different methodologies employed for the construction of such an heterocycle and illustrate it with selected examples from the literature.

I. Dihyropyrans in the literature

Substituted pyrans are a common structural motif found in a wide range of natural products. The dihydropyran (DHP) skeleton is an especially attractive scaffold present in many natural compounds and the olefin function is a useful platform for further functionalizations. It is often used as a key intermediate in the generation of substituted tetrahydropyrans (THP)[1]. Henceforth, there are many routes described in the literature to construct DHPs. In this chapter, we have selected a few approaches that we seemed interesting to form these particular cycles. It is important to point out that this list is not exhaustive.

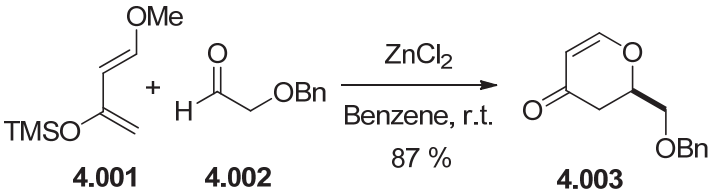
I.1. Hetero Diels-Alder

The formal hetero-Diels-Alder (HDA) reaction between dienes and carbonyl compounds has been an important area of research in asymmetric catalysis. Pioneering work in this field was accomplished by Danishefsky who described Lewis acid catalyzed cyclocondensations of functionalized dienes with unactivated aldehydes in 1982 (scheme 1)[2].

---

[1] A. P. Dobbs, S. Martinović, *Tetrahedron Lett.* **2002**, *43*, 7055-7057

[2] S. Danishefsky, J. F. Kerwin, S. Kobayashi, *J. Am. Chem. Soc.* **1982**, *104*, 358-360



Scheme 1

Since then, there have been many examples in the literature of asymmetric HDA reactions between electron rich dienes and/or electron-deficient dienophiles[3].

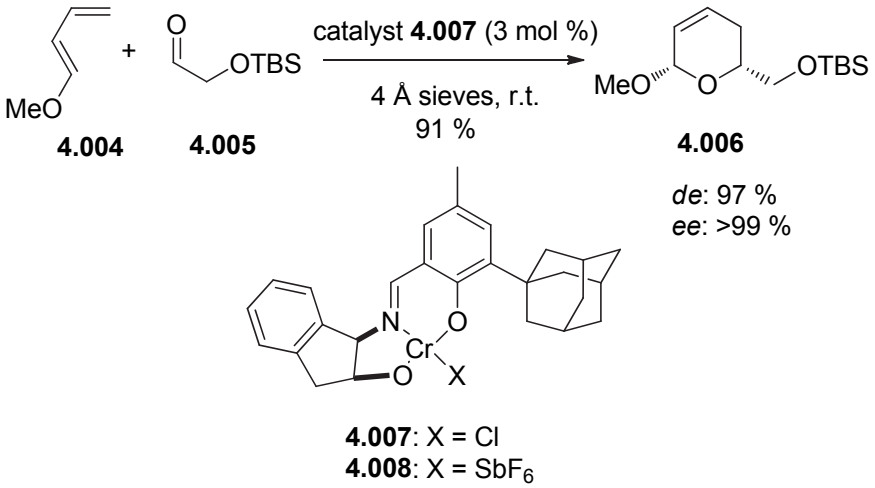
In 1999, the group of Jacobsen developed a new class of asymmetric HDA between less nucleophilic dienes bearing fewer than two oxygens and unactivated carbonyl compounds. These reactions provide a direct route to enantioenriched (2,6)-*syn*-dihydropyrans.

Using a chiral chromium catalyst and depending on the counter-anion, they were able to access the desired dihydropyrans in high yields, diastereoselectivities and enantioselectivities[4] (scheme 2).

---

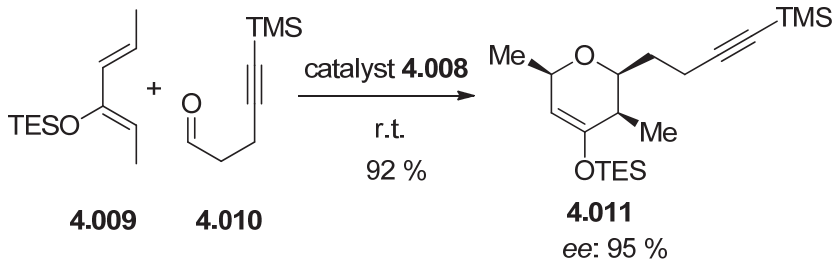
[3] a. M. Bednarski, S. Danishefsky, *J. Am. Chem. Soc.***1983**, *105*, 6968-6969. b. H. Waldmann, *Synthesis* **1994**, 535-551. c. K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2000**, *39*, 3558-3588.

[4] A. G. Dossetter, T. F. Jamison, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **1999**, *38*, 2398-2400.



Scheme 2

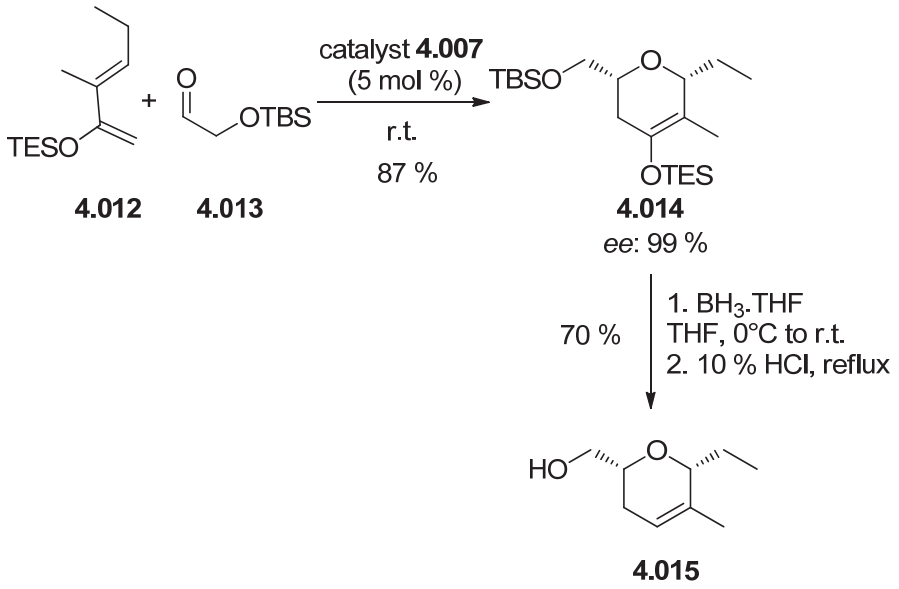
They further used this methodology as a key step in their synthesis of FR901464[5] (scheme 3) and Ambruticin[6] (scheme 4).



Scheme 3

[5] C. F. Thompson, T. F. Jamison, E. N. Jacobsen, *J. Am. Chem. Soc.* **2000**, *122*, 10482-10483.

[6] P. Liu, E. N. Jacobsen, *J. Am. Chem. Soc.* **2001**, *123*, 10772-10773.

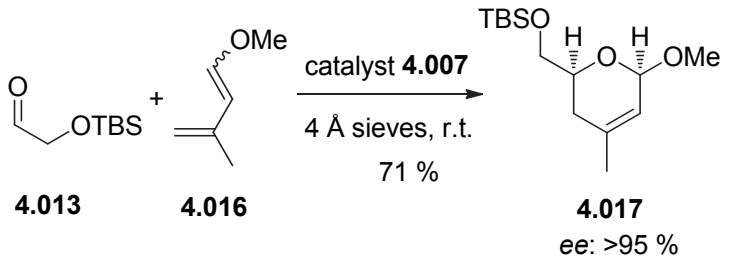


Scheme 4

Removal of the triethylsilyloxy group in **4.014** by hydroboration and acid-catalyzed elimination gave access to the right-hand part of ambruticin **1.017**. This subunit is also present in jerangolid D **2.029**.

Other groups applied this methodology in their synthesis of natural products, such as the group of Paterson in their approach to (-)-Laulimalide[7] (scheme 5).

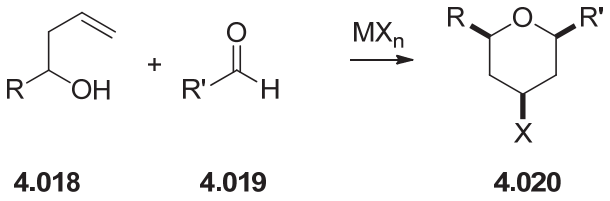
[7] I. Paterson, C. De Savi, M. Tudge, *Org. Lett.* **2001**, *3*, 3149-3152.



Scheme 5

I.2. Prins and Silyl-Prins cyclization

The Prins cyclization provides a powerful access to tetrahydropyran derivatives. In its simplest case, it involves a homoallylic alcohol **4.018**, an aldehyde **4.019** and a Lewis acid (scheme 6). There are many examples in the literature where a Prins cyclization is used for the synthesis of tetrahydropyrans[8].



Scheme 6

In this work, we are more interested in dihydropyrans so we will focus on the variants of the Prins cyclisation that lead to DHP's.

If a vinylsilane, a vinylstannane or an allylsilane is used as a terminating group instead of a simple alkene, the transformation will lead to the formation of dihydropyrans. It has been called "silyl-Prins cyclisation".

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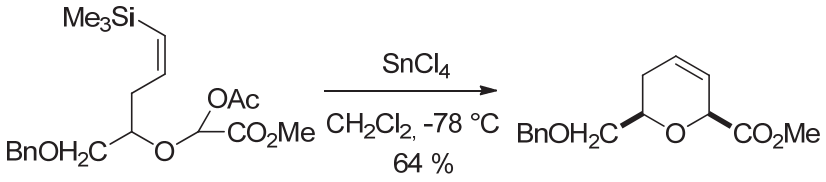
[8] For a recent review, see: C. Olier, M. Kaafarani, S. Gastaldi, M. P. Bertrand, *Tetrahedron* **2010**, *66*, 413-445.

The group of Speckamp reported the cyclization of a vinylsilane onto an oxocarbenium ion in 1997. Depending upon the geometry of the vinylsilane, the *cis/trans* ratio varies. The *Z*-isomer gives the *syn*-dihydropyran with remarkably high diastereoselectivity (scheme 7)[9].

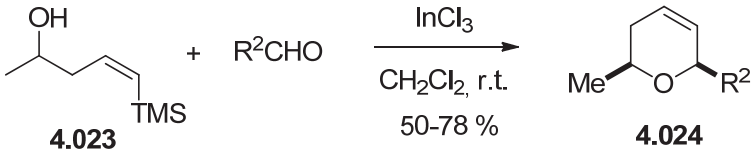


4.021 **4.022**

cis/trans >98:2

Scheme 7

The group of Dobbs has extended this methodology to various aldehydes and epoxides. They have shown that using $InCl_3$ as a Lewis acid allows the formation of dihydropyrans in good yields and excellent diastereoselectivity at room temperature (scheme 8). BF_3-etherate or TMSOTf also lead to high yields but require lower temperatures[10].



4.023 **4.024**

R^2= $PhCH_2$, *n*-C_5H_{11}, Cy, Ph_2Ch, *p*-$NO_2C_6H_4$

Scheme 8

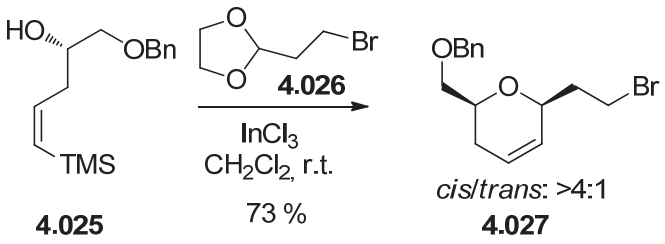
In her synthesis of the spiro moiety of spirolides B and D, Brimble used the silyl-Prins cyclization to form the dihydropyran present in these natural

---

[9] C. Semeyn, R. H. Blaauw, H. Hiemstra, W. N. Speckamp, *J. Org. Chem.* **1997**, *62*, 3426-3427.

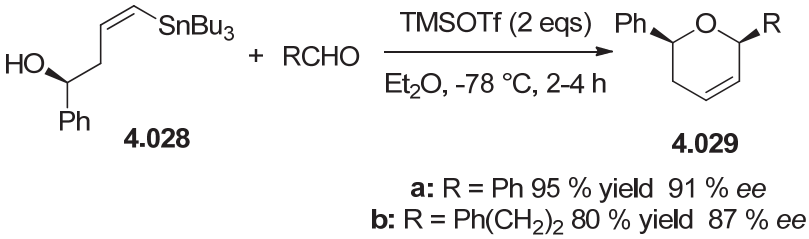
[10] A. P. Dobbs, S. Martinović, *Tetrahedron Lett.* **2002**, *43*, 7055-7057.

products. Alcohol **4.025** reacted with acetal **4.026** to give **4.027** as a mixture of *cis* and *trans* isomers in a ratio exceeding 4:1 (scheme 9)[11].



Scheme 9

It has recently been shown that the use of vinylstannanes instead of vinylsilanes also leads to the formation of *syn*-dihydropyrans in high yields in the presence of TMSOTf. The use of optically pure starting material produced optically pure DHPs without racemization (scheme 10) [12].



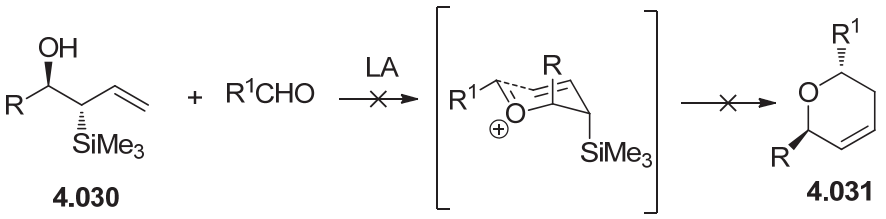
Scheme 10

Allylsilanes have also been used to form dihydropyrans. For example, the group of Roush wanted to synthesise *trans*-DHP by reacting allylsilane **4.030** with different aldehydes (scheme 11).

---

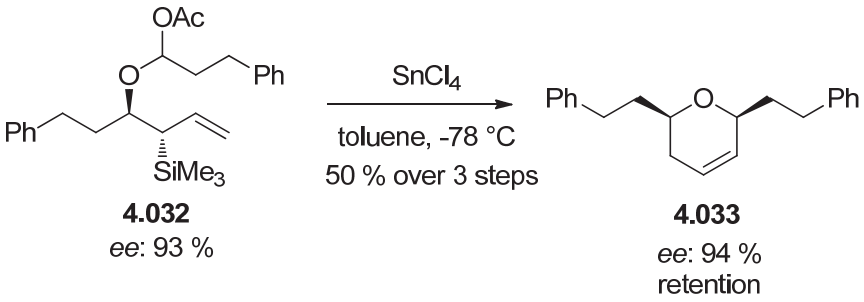
[11] K. Meilert, M. A. Brimble, *Org. Lett.* **2005**, *7*, 3497-3500.

[12] M. Dziedzic, B. Furman, *Tetrahedron Lett.* **2008**, *49*, 678-681



Scheme 11

Despite their predictions based on the stereoelectronic effects of the TMS group, only *cis*-dihydropyrans were isolated (scheme 12). Based on their results, they explain that all of the intramolecular allylation reactions leading to the preferential formation of the 2,6-*cis*-dihydropyrans proceed with high stereochemical fidelity *via* boat-like transition states[13].



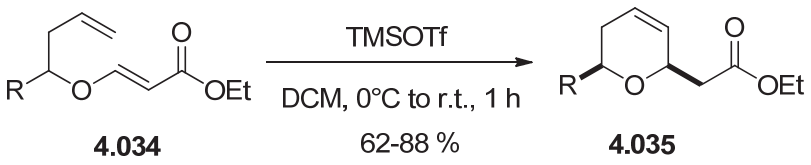
Scheme 12

Most recently, Saikia's group developed a methodology using the Prins cyclisation that doesn't need the presence of a vinyl- or an allyl-silane. The use of acrylyl enol ethers in the presence of TMSOTf in DCM allows the formation of *syn*-dihydropyrans stereo- and regioselectively in good yields[14] (scheme 13).

---

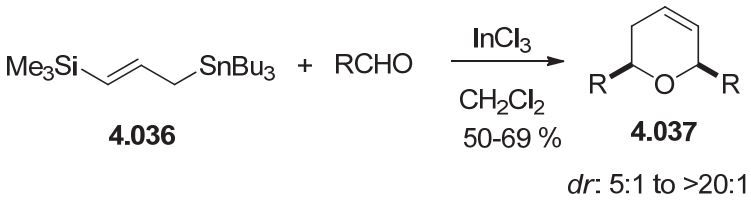
[13] W. R. Roush, G. J. Dilley, *Synlett* **2001**, 955-959.

[14] S. Sultana, K. Indukuri, M. J. Deka, A. K. Saikia, *J. Org. Chem.* **2013**, *78*, 12182-12188.



Scheme 13

Another interesting example comes from the group of Li who developed a tandem allylation-Prins cyclization to form symmetrical *syn*-dihydropyrans (scheme 14). The reaction is promoted by $InCl_3$ and works only with aliphatic aldehydes[15].



Scheme 14

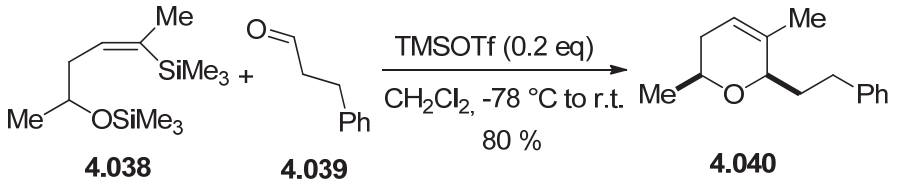
I.3. ISMS

When the alcohol moiety present on the allyl- or vinyl-silane is protected with a silyl group, the reaction is called intramolecular silyl-modified Sakurai cyclisation (ISMS). This reaction was developed in our group in the early 1990s. It enables the formation of *exo*-methylene *cis*-tetrahydropyrans or *syn*-dihydropyrans in good yields and diastereoselectivity.

During his studies towards the total synthesis of ambruticin, D.J. Bayston developed this ISMS condensation of vinyl silanes with aldehydes and

[15] G. S. Viswanathan, J. Yang, C.-J. Li, *Org. Lett.* **1999**, *1*, 993-995.

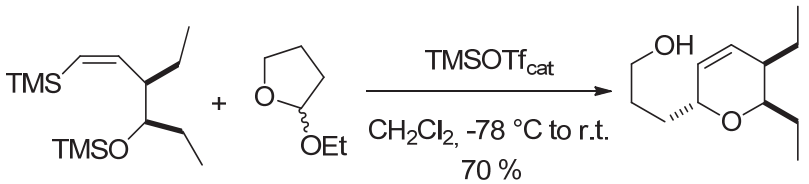
acetals and showed that it can also lead to the formation of dihydropyrans bearing a trisubstituted double bond (scheme 15)[16].



4.038 **4.039** **4.040**

Scheme 15

By placing two substituents on the annelating agent, and depending upon their relative stereochemistry, *trans*-DHP can also be prepared using the same methodology[17].



4.041 **4.042** **4.043**

Scheme 16

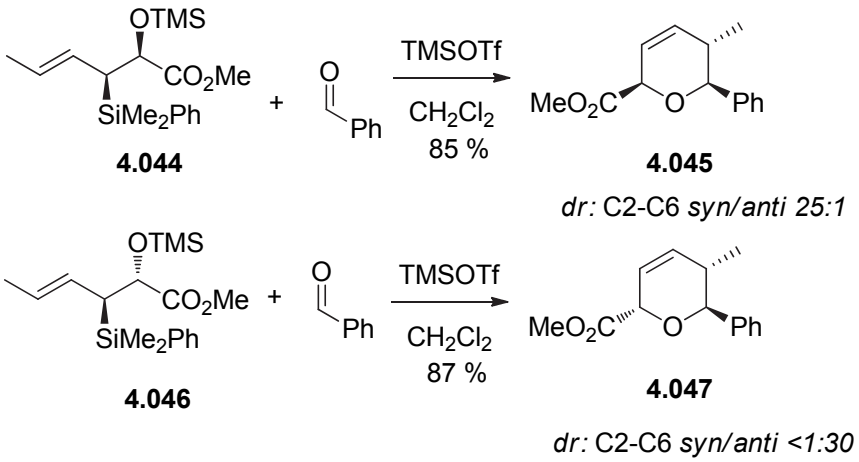
Based on the same principle, the group of Panek used a protected homoallylic alcohol bearing an allylsilane. By varying the stereochemistry, they were able to access the eight possible different stereoisomers of the DHP.

The *syn*-annelating agent **4.044** leads to the *cis-trans* diastereomer **4.045** whilst the *anti*-silane **4.046** gives rise to the *trans-trans* diastereomer **4.047** [18] (scheme 17).

---

[16] I. E. Markó, D. J. Bayston, *Tetrahedron* **1994**, *50*, 7141-7156.

[17] I. E. Markó, A. P. Dobbs, V. Scheirmann, F. Chellé, D. J. Bayston, *Tetrahedron Lett.* **1997**, *38*, 2899-2902.



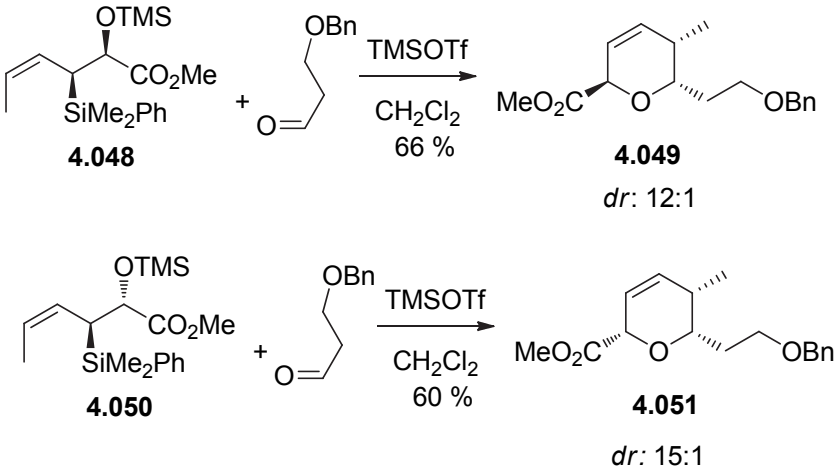
Scheme 17

Finally, more recent studies by the same group showed that the use of (*Z*)-crotylsilanes **4.048** and **4.050** affords the *trans-cis* adduct **4.049** and the all *cis*-derivative **4.051** respectively[19] (scheme 18).

---

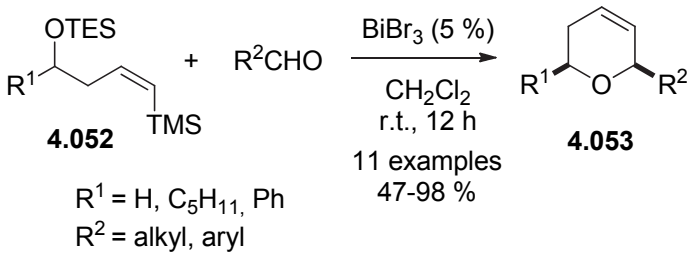
[18] H. Huang, J. S. Panek, *J. Am. Chem. Soc.* **2000**, *122*, 9836-9837.

[19] I. E. Wrona, J. T. Lowe, T. J. Turbyville, T. R. Johnson, J. Beignet, J. A. Beutler, J. S. Panek, *J. Org. Chem.* **2009**, *74*, 1897-1916.



Scheme 18

More recently, the group of Hinkle developed a $BiBr_3$-initiated intermolecular addition followed by ISMS cyclisation with *cis*-diastereoselectivity[20] (scheme 19).



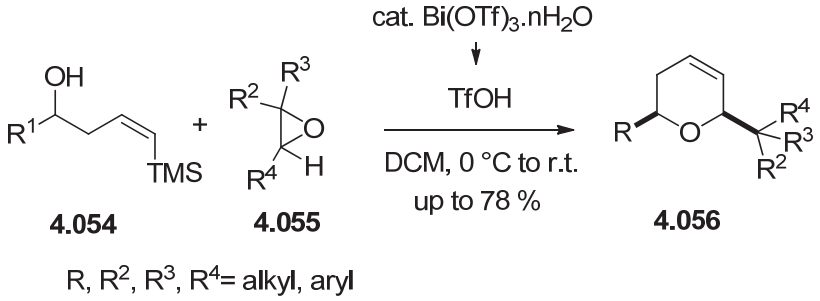
Scheme 19

Further studies showed that when the alcohol is not protected and the reaction is carried out with an epoxide, $BiBr_3$ is not appropriate anymore to facilitate the rearrangement of the epoxide to the corresponding aldehyde, thus no reaction occurs. In contrast, bismuth triflate promoted the reaction to

---

[20] a. Y. Lian, R. J. Hinkle, J. Org. Chem. **2006**, *71*, 7071-7074. b. R. J. Hinkle, Y. Lian, L. C. Speight, H. E. Stevenson, M. M. Sprachman, L. A. Katkish, M. C. Mattern, *Tetrahedron* **2009**, *65*, 6834-6839.

afford the desired dihydropyrans. More detailed studies showed that an initial Lewis acid/base interaction between $Bi(OTf)_3$ and the corresponding substrates generates TfOH *in situ*, which in turn catalyzed the reaction[21] (scheme 20).



Scheme 20

I.4. Olefin ring closing metathesis

Olefin metathesis is a unique carbon skeleton redistribution in which carbon carbon double bonds are rearranged in the presence of metal carbene complexes. Since its discovery, it has been widely used in organic synthesis for the formation of C-C bonds[22]. This transformation has been applied to the synthesis of various dihydropyrans and a few examples are depicted below.

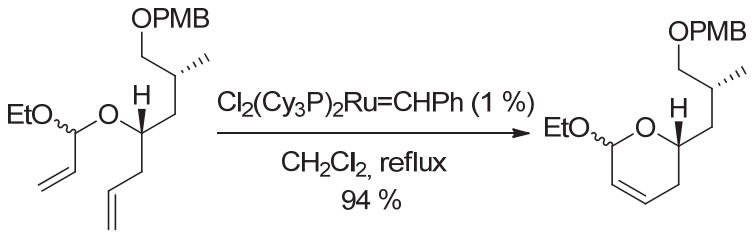
The group of Mulzer used this approach for the formation of the dihydropyran present in Laulimalide. Addition of a minimum amount of

---

[21] R. F. Lambert, R. J. Hinkle, S. E. Ammann, Y. Lian, J. Liu, S. E. Lewis, R. D. Pike, *J. Org. Chem.* **2011**, *76*, 9269-9277.

[22] For a review, see: R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413-4450.

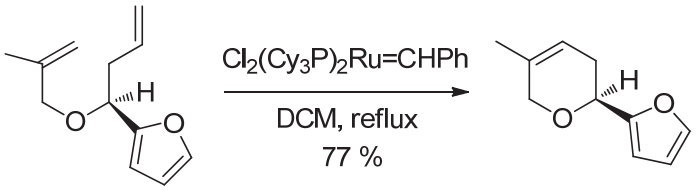
Grubbs I catalyst provided the desired dihydropyran **4.058** in an excellent 94 % yield[23] (scheme 21).



4.057 **4.058**

Scheme 21

The dihydropyran **4.060** was also prepared using Grubbs I catalyst in good yield. This adduct is a key intermediate in the synthesis of the bioactive natural product cacospongionolide B[24] (scheme 22).



4.059 **4.060**

Scheme 22

Ring-closing metathesis has also been used in our laboratory for the synthesis of jerangolid D (see chapter II and III). Repeating this reaction was the starting point of this thesis.

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[23] J. Mulzer, M. Hanbauer, *Tetrahedron Lett.* **2000**, *41*, 33-36.

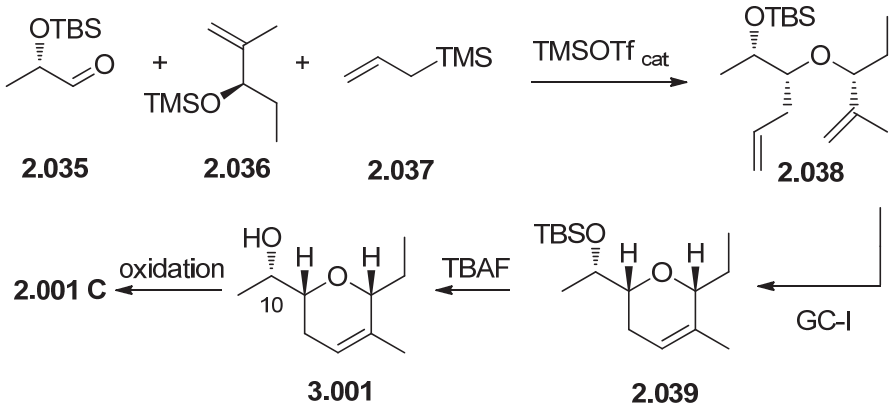
[24] M. de Rosa, A. Solladié-Cavallo, A. Scettri, *Tetrahedron Lett.* **2000**, 41, 1593-1596.

II. Results

As presented in the objectives, we started our work by attempting to reproduce the synthesis that was developed in our laboratory and applying this route to the synthesis of various analogues of DHP **2.025**. In this part, we will first present the synthesis of different substrates, followed by our results for the SMS reaction and the end of the sequence. As we encountered some problems with this approach, we will then discuss the solutions we employed to reach our goal.

II.1. SMS + RCM

As a reminder, the original sequence is described in scheme 23.



Scheme 23

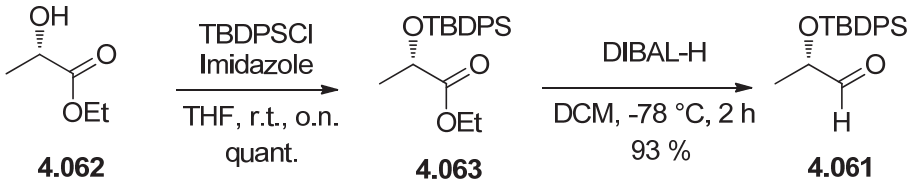
II.1.1. Substrates synthesis

In order to carry out the SMS reaction, aldehyde **2.035** and silyl ether **2.036** had to be synthesised. However, for stability reasons, aldehyde **4.061** bearing a TBDPS protecting group was synthetized and used instead of **2.035** which bears a TBS protecting group. Moreover, silyl ether **2.036** was prepared in its racemic version in order to simplify that synthetic step. Two

other silyl ethers were prepared as well to test them in the reaction and form some new analogues.

II.1.1.1. Synthesis of aldehyde 4.061

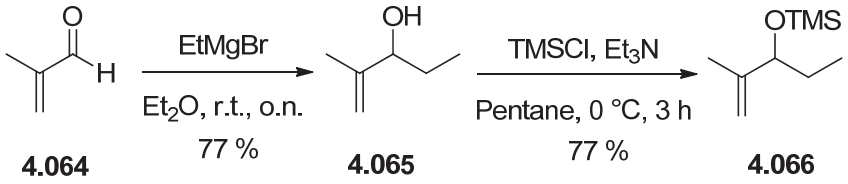
Aldehyde **4.061** can be prepared in two steps starting from commercially available (*S*)-ethyl lactate **4.062** in excellent yields (scheme 24)[25].



Scheme 24

II.1.1.2. Synthesis of racemic silyl ether 2.036

Silyl ether **4.066**, which is the racemic version of **2.036**, was synthesised in two steps by the addition of ethyl Grignard to methacrolein[26] followed by alcohol silylation[27] in very good yields (scheme 25).



Scheme 25

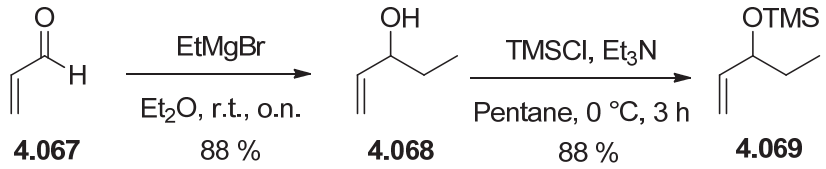
The same conditions were used with acrolein to afford silyl ether **4.069** in excellent yields (scheme 26).

---

[25] a.Y. Takashima, Y. Kaneko, Y. Kobayashi, *Tetrahedron* **2010**, *66*, 197-207. b. Jiri Pospisil, PhD thesis, UCL **2006**.

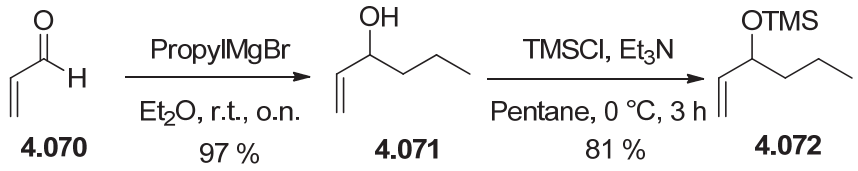
[26] J. Cossy, D. Bauer, V. Bellosta, *Tetrahedron* **2002**, *58*, 5909-5922.

[27] L. Baudrenghien, Master thesis, UCL **2009**.



Scheme 26

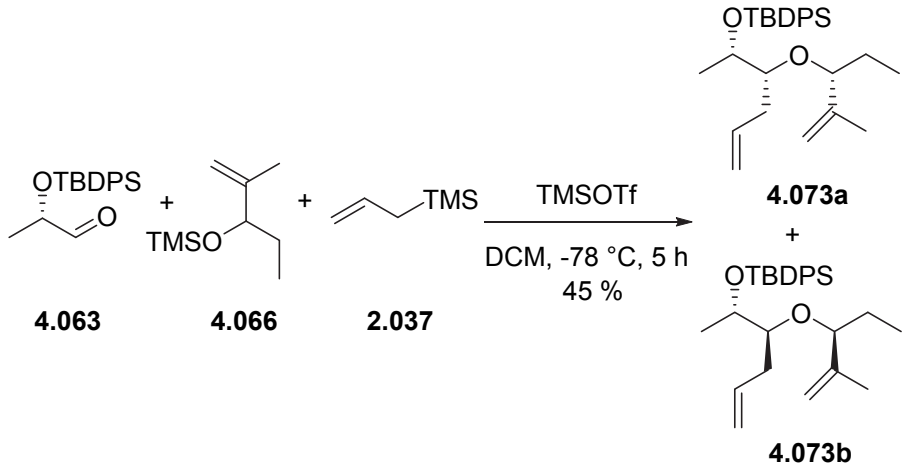
Addition of propyl Grignard to acrolein, followed by silylation using the same conditions as above, delivered silyl ether **4.072** in excellent yields (scheme 27)**.**



Scheme 27

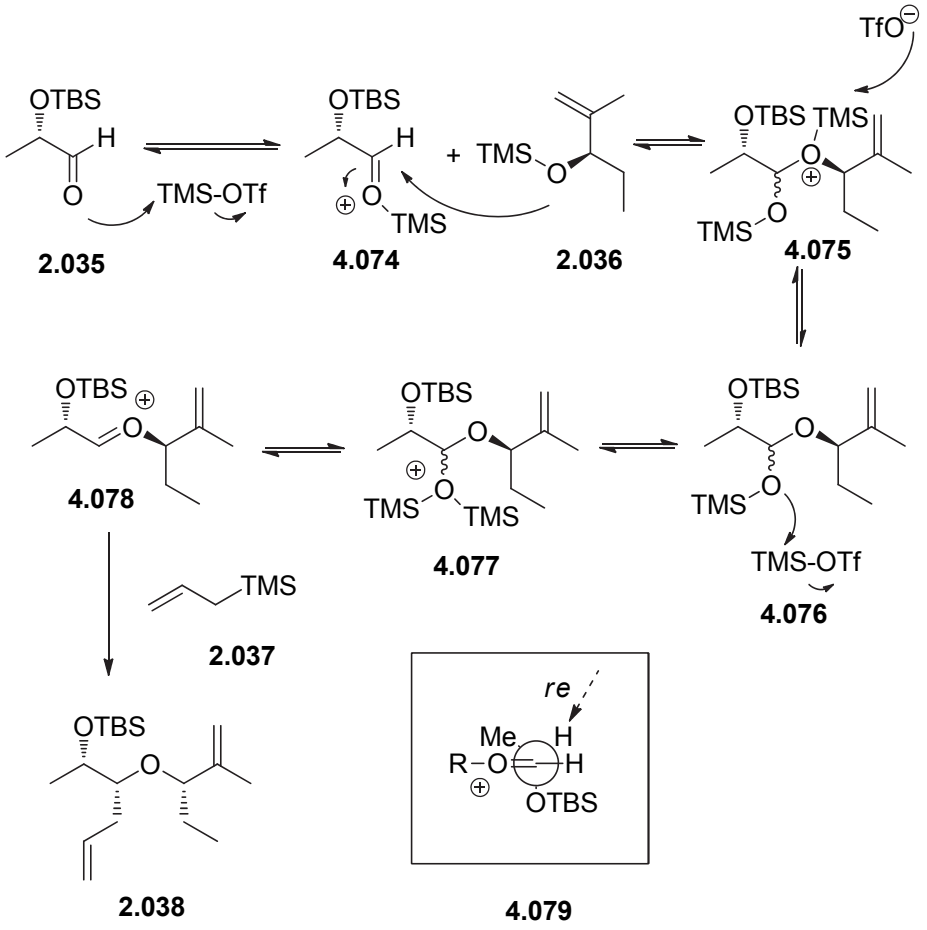
II.1.2. SMS reaction

With the desired substrates in hand, the SMS reaction was carried out using the conditions that were described in our group (scheme 28).



Scheme 28

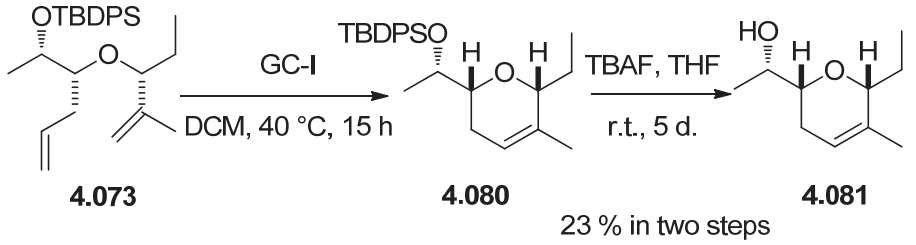
The proposed mechanism for the SMS reaction is described in scheme 29. It is believed that oxonium **4.078** is generated under the reaction conditions. The addition of the allylsilane **2.037** is then believed to proceed according to the Felkin-Anh transition state **4.079**, thus delivering the *syn* adduct.



Scheme 29

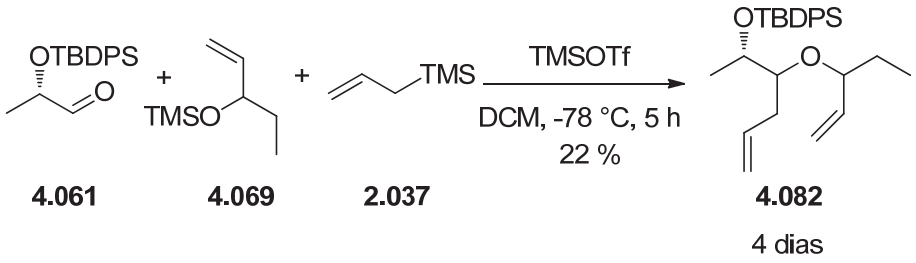
In our case, since the silyl ether **4.066** is racemic, we were expecting to form the two *syn*-diastereomers. Indeed, compounds **4.073a** and **4.073b** were isolated in a 1:1 ratio. However, a much lower yield was afforded.

The mixture of diastereomers **4.073** was next engaged in the rest of the sequence. Ring closing metathesis afforded the corresponding dihydropyran which was directly deprotected. This last step proved to be quite hard, taking five days and proceeding in poor yields (scheme 30).



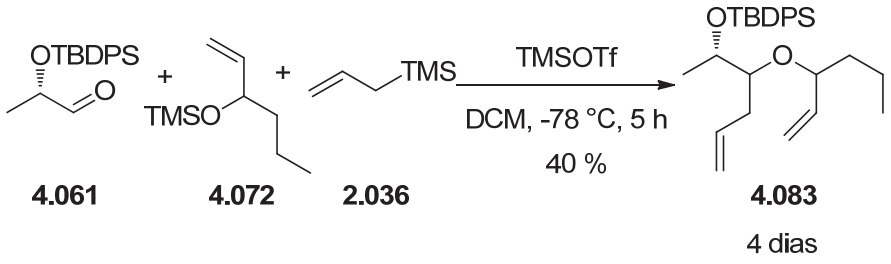
Scheme 30

The reaction was then applied to substrate **4.069** using the same conditions as above (scheme 31).



Scheme 31

We were disappointed to see the formation of 4 diastereomers in only 22 % yield. The same observation was made with substrate **4.072** (scheme 32).



Scheme 32

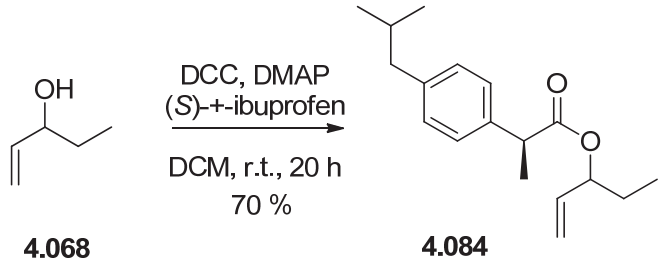
In view of these disappointing preliminary results, we decided to go back and try to access the enantiomerically pure silyl ether in order to reproduce exactly the results described previously in the laboratory. The structure of the silyl ether **4.066** might indeed have a big influence on the disatereoselectivity of the reaction.

II.1.3. Attempts to obtain allylic alcohols enantiomerically pure

II.1.3.1. Esterification

The first option was to esterify the allylic alcohol with an enantiopure acid in order to form two diastereomers, which could be separated by column chromatography and then hydrolysed to furnish the desired enantiomerically pure allylic alcohols. The following reactions were performed using racemic silyl ether **4.068** because it is cheaper to access and would then be transposed to **4.065** when the right conditions were found.

The first attempt was the coupling with ibuprofen. The reaction afforded the corresponding ester in good yield[28] (scheme 33). Unfortunately, the two diastereomers can not be separated on silica gel column chromatography.

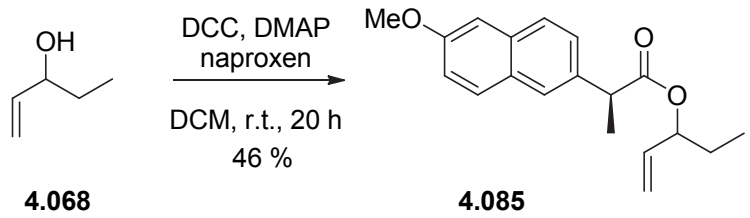


4.068 **4.084**

Scheme 33

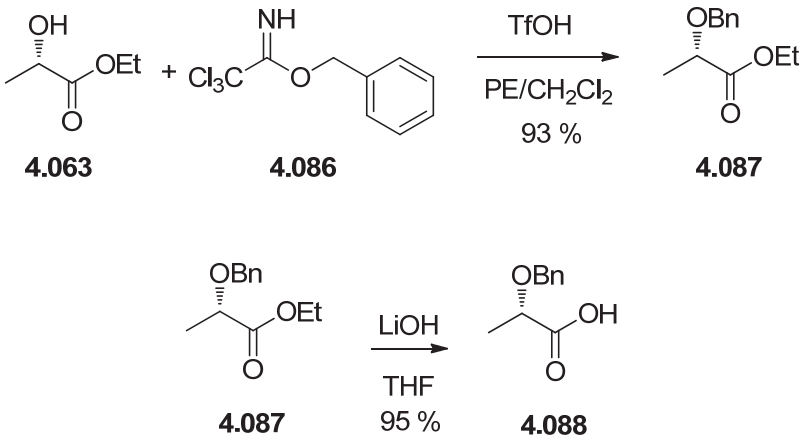
[28] B. Linclau, A. J. Boydell, R. S. Timofte, K. J. Brown, V. Vinader, A. C. Weymouth-Wilson, *Org. Biomol. Chem.* **2009**, *7*, 803-814.

The second partner that was tried was naproxen. This time, the desired ester was isolated in moderate yield. Alas, once again, we were not able to separate the two diastereomers (scheme 34).



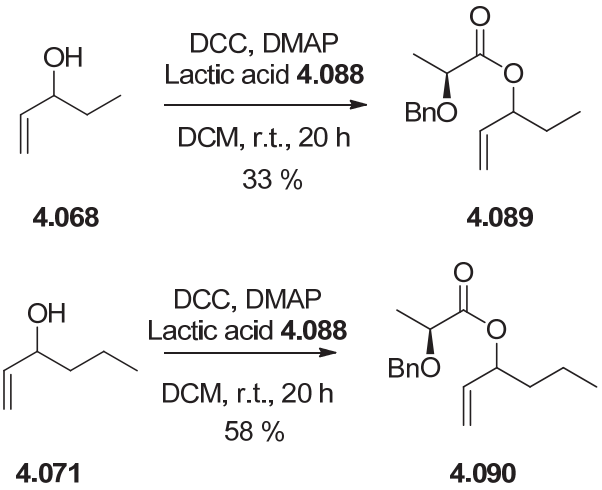
Scheme 34

A final attempt was made using benzylated lactic acid **4.082** which can be synthesized in two steps from (*S*)-ethyl lactate in good yields (scheme 35).



Scheme 35

Two different allylic alcohols were coupled with acid **4.088** in moderate yields but unfortunately, this strategy failed to deliver the separated diastereomers (scheme 36).



Scheme 36

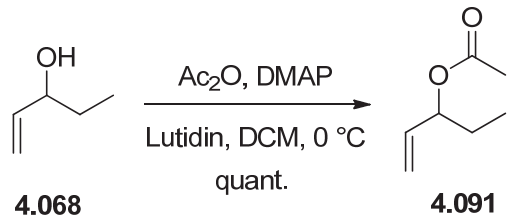
At this point, we realized that to be successful, this approach would require the generation of a large number of esters without ever being sure of finding out the right one. Therefore, we decided to abandon this separation method and turn our attention to a kinetic resolution instead.

II.1.3.2. Kinetic resolution

II.1.3.2.1. Botanochemistry

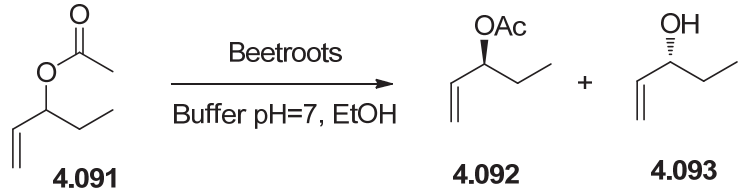
We decided to apply a methodology that was developed in our laboratory and that we nicknamed "botanochemistry". This method employs pieces of vegetables or fruits to perform various asymmetric transformations, such as enantioselective reductions and ester hydrolysis. Among the vegetables tested, beetroots were found to be particularly suited for the kinetic resolution of benzylic alcohols[29]. To test this method, the corresponding acetate was initially formed in quantitative yield (scheme 37).

[29] A. Vandenberghe, PhD thesis, UCL **2012.**



Scheme 37

Acetate **4.085** was then dissolved in EtOH at pH 7 and pieces of beetroots were added (scheme 38). The reaction was stirred at 23 °C and its progress was monitored by chiral gas chromatography.



Scheme 38

To our disappointment, the two peaks corresponding to the acetate substrates decreased at the same rate as the two signals for the corresponding alcohols appeared. Unfortunately, this system turned out to be non selective for our substrate.

II.1.3.2.2. Sharpless resolution

Our last attempt was to use the Sharpless kinetic resolution which is well documented and is particularly efficient for allylic alcohols[25,30]. This precise reaction had been done on a large scale in our laboratory a few years ago. Unfortunately, analysis by chiral gas chromatography showed that the

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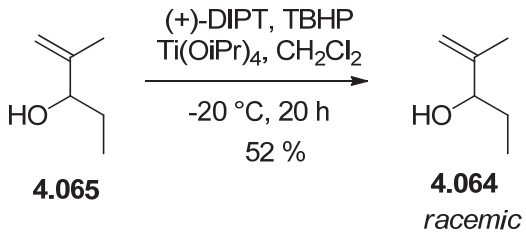
[30] V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, K. B. Sharpless, *J. Am. Chem. Soc.* **1981**, *103*, 6237-6240.

resolution did not proceed and the recovered alcohol was still racemic (scheme 39).



Scheme 39

In fact, it transpired that one of the components of the Sharpless catalytic mixture was ineffective. The kinetic resolution was successfully repeated later on but in the meantime, we had decided to move on and to use the racemic silyl ether again. However, this time we would use the TBS-protected aldehyde as the coupling partner in order to ease the deprotection step which was rather tricky.

II.1.4. SMS with TBS-protected aldehyde

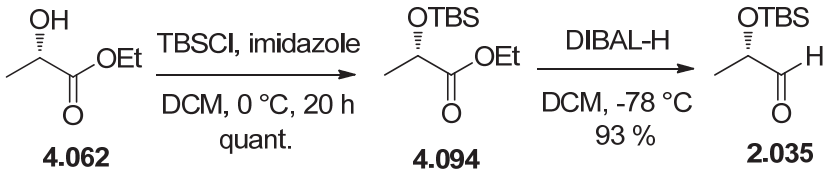
II.1.4.1. Synthesis of aldehyde 2.031

Thus, (*S*)-ethyl lactate **4.055** was protected with a TBS group and the ester function was reduced to the corresponding aldehyde with Dibal-H in excellent yields[3132] (scheme 40).

---

[31] G. D. Joly, E. N. Jacobsen, *Org. Lett.* **2002**, *4*, 1795-1798.

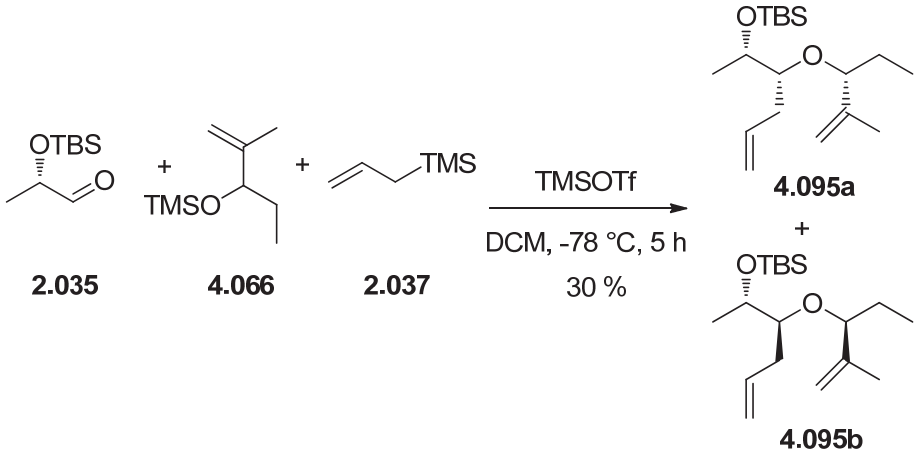
[32] It is important to remove the last traces of acid after the work-up and to prepare the aldehyde immediately before using it in order to avoid any epimerization.



Scheme 40

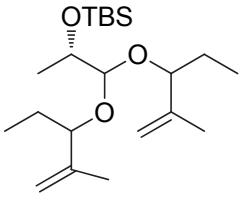
II.1.4.2. SMS

Once again, the reaction was carried out using the same previous conditions (scheme 41).



Scheme 41

We were delighted to find out that, in this case, the two *syn*-diastereomers **4.095a** and **4.095b** were the major ones (ratio *syn*/*anti*: 8:1). Unfortunately, the yield was still quite low. We were also rather surprised to isolate some of the symmetric acetal **4.096**. Its presence can partially explain the moderate yield of the reaction (figure 1).



4.096

Figure 1

At this point, we tried to optimize the reaction conditions in order to increase the yield. Initially, the reaction was followed by chiral gas chromatography during 24 hours. After that time, the allylsilane and the aldehyde were consumed. The diastereomers **4.095** were isolated in 24 % yield and some silyl ether **4.066** was recovered.

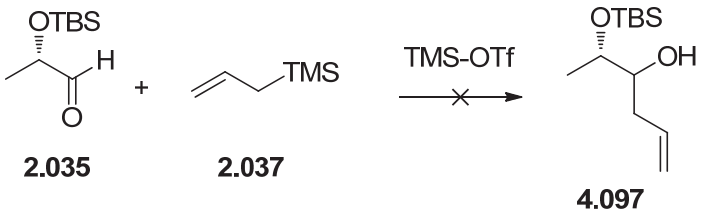
Special distillation of the dichloromethane[33] coupled with enhanced purification of allylsilane **2.037** enabled the yield to increase to 39 %. Once again, acetal **4.096** was isolated in 23 % yield (ratio **4.095a,b/4.096** = 1:0.6). Some silyl ether **4.066** was recovered as well.

Since aldehyde **2.035** is never recovered, we employed an excess of it at the onset of the reaction. Unfortunately, no improvement could be observed and the product was isolated in 27 % yield.

One possible explanation for the low yield of this reaction relies on a competitive reaction that would consume both the aldehyde and the allylsilane. In every reaction they disappear whilst the silyl ether is still present. Indeed, a Sakurai addition of the allylsilane to the aldehyde would be a possibility, but this adduct **4.097** has never been isolated (scheme 42).

---

[33] Special DCM is washed 4 times with concentrated sulfuric acid then with water, dried over calcium chloride and finally distilled from CaH_2.



2.035 **2.037** **4.097**

Scheme 42

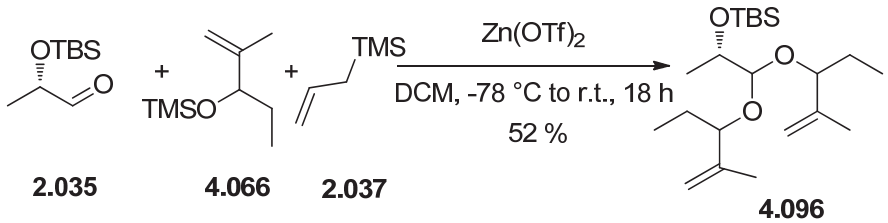
At this stage, we have no rationalization to offer.

We then decided to employ other triflates as Lewis acids. $Bi(OTf)_3$ was first attempted, unfortunately no reaction was observed either at -78 °C or at room temperature (scheme 43).

2.035 **4.066** **2.037** **4.095**

Scheme 43

Suprisingly, when using $Zn(OTf)_2$, aldehyde **2.035** and acetal **4.096** were observed suggesting that this Lewis acid is much milder than TMSOTf (scheme 44). After purification, the acetal **4.096** was isolated in moderate yield.

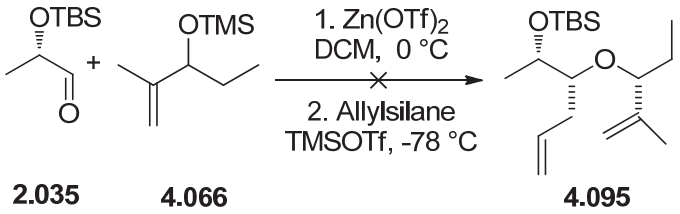


2.035 **4.066** **2.037** **4.096**

Scheme 44

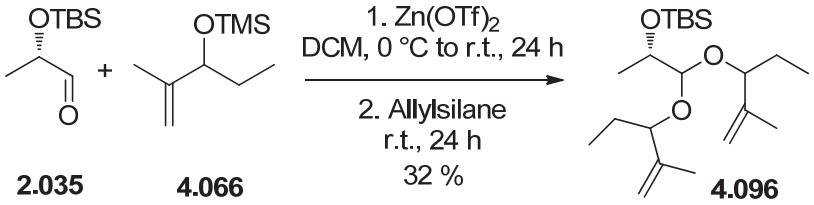
In light of this result, we decided to access the desired adduct **4.095** in two steps, using $Zn(OTf)_2$ to form the acetal and then submit this compound to the action of a stronger Lewis acid in the presence of allyltrimethylsilane.

Our first attempt was to add allylsilane and TMSOTf directly to the reaction mixture, without isolating the acetal. After 48 hours, **4.096** was still the major product (scheme 45). No Sakurai reaction appears to be occuring.



Scheme 45

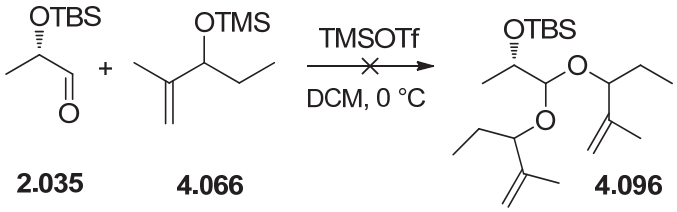
A particularly puzzling observation stems from the attempted preparation of acetal **4.096** by the direct reaction between **2.035** and **4.066** catalyzed by zinc triflate. Indeed, in the absence of allyltrimethylsilane, no acetal **4.096** could be detected. After 24 hours, 1.1 equivalents of allylsilane were added. The acetalisation then proceeded smoothly and after another 24 hours, the condensation stopped since the silyl ether was totally consumed. Acetal **4.096** was then isolated in 32 % yield (scheme 46).



Scheme 46

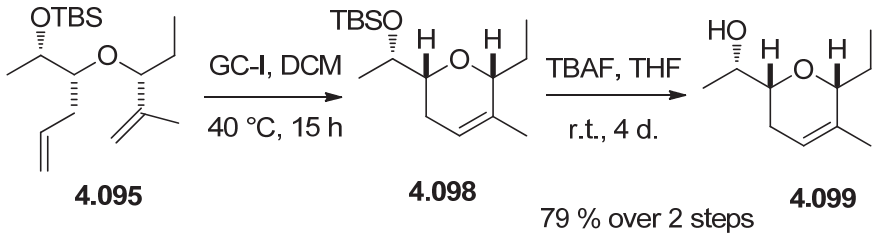
At the moment, we have no plausible explanation to offer that accounts for the requisite presence of the allylsilane in this ketalisation reaction.

Our last attempt was to stir together aldehyde **2.031** and silyl ether **4.066** in the presence of TMSOTf at 0 °C (scheme 47). In this case, the temperature is too high and only degradation of the aldehyde was observed.



Scheme 47

Despite the low yield, we were able to isolate the desired product **4.090** and to continue the sequence. Ring-closing metathesis, followed by TBAF deprotection, yielded dihydropyran **4.075** in 79 % over two steps (scheme 48). At this point, the two diastereomers could easily be separated by silica gel column chromatography.

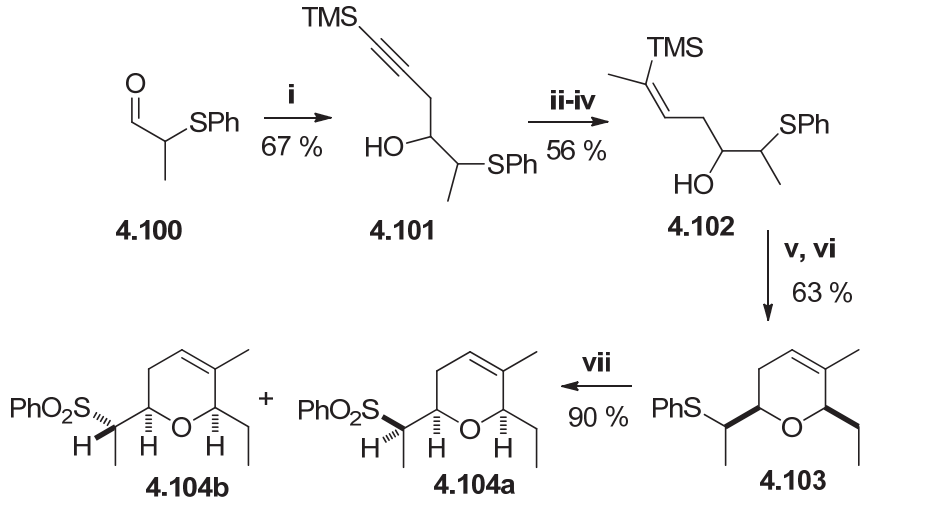


Scheme 48

At this point, in view of the disappointing results obtained with the direct three-components SMS reaction or the acetal formation, and since the optimization and study of this reaction was not the main goal of this thesis, we decided to move on to another approach and synthetize our fragments *via* a different sequence.

II.2. ISMS

The approach we decided to follow is based on another methodology which was developed in our lab in the early 1990s and was introduced previously in this chapter (vide supra I.3). The key step is an ISMS cyclization. In his studies towards the total synthesis of ambruticin, Dr. D. Bayston developed the sequence described in scheme 49 to prepare the fully functionalized right-hand fragment of the natural product[34].



i = $Me_3SiC{\equiv}CCH_3$, tBuLi, CuI, THF, -78°C to 0°C; **ii** = DHP, PPTS, CH_2Cl_2, 20°C; **iii** = Dibal-H, Et_2O, 20°C then I_2; **iv** = MeLi, THF, 20°C then PPTS, EtOH, H_2O, 60°C; **v** = Me_3SiCl, Et_3N, CH_2Cl_2, 20°C; **vi** = CH_3CH_2CHO, Me_3SiOTf_{cat}, CH_2Cl_2, -78°C to 20°C; **vii** = PhSeSePh, H_2O_2, CH_2Cl_2, Et_2O, 20°C

Scheme 49

Based on these results, we decided to use this sequence and replace aldehyde **4.100** by aldehyde **2.035** (scheme 50)**.** After deprotection, the very same DHP **4.099** we are trying to synthesise from the beginning should be obtained.

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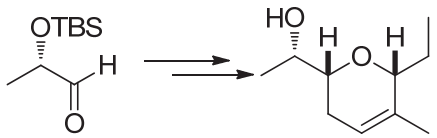
[34] I. E. Markó, D. J. Bayston, *Synthesis* **1996**, 297-304.

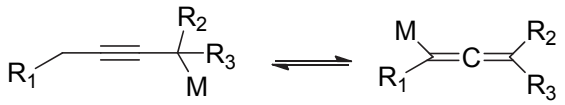


2.035 **4.099**

Scheme 50

II.2.1. Substrates synthesis

Propargylic anion equivalents such as organometallic reagents **4.105** (M=Li or MgX) provide an important route to acetylenic compounds (figure 2).



4.105a **4.105b**

Figure 2

However, their use is limited by the tendency of these ambident nucleophiles to react with electrophiles to produce both allenic and acetylenic products. For example, when reacted with aldehydes or ketones, they afford a mixture of homopropargylic and homoallenic alcohols[35]. Transmetallations with several metals (e.g. Sn[36], Zn[37], Ce[38], Cu[39],...) have been described in the

[35] R. L. Danheiser, D.J. Carini, *J. Org. Chem.* **1980**, *45*, 3927-3929.

[36] J. A. Marshall, J.F. Perkins, M. A. Wolf, *J. Org. Chem.* **1995**, *60*, 5556-5559.

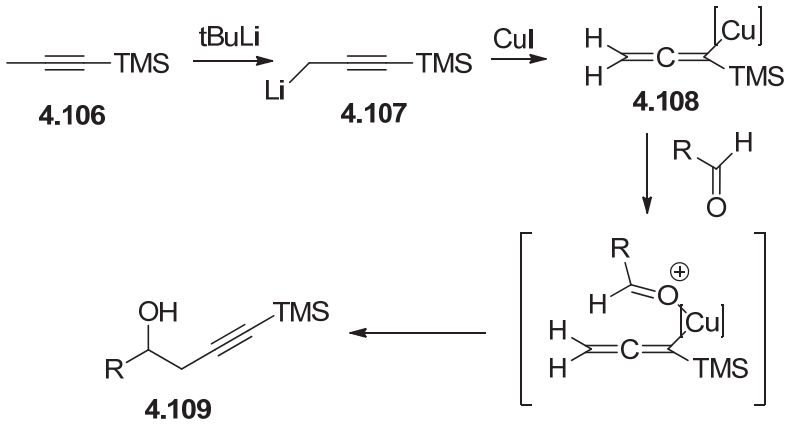
[37] J. A. Marshall, N. D. Adams, *J. Org. Chem.* **1998**, *63*, 3812-3813.

[38] U. Groth, C. Kesenheimer, J. Neidhöfer, *Synlett* **2006**, *12*, 1859-1862.

[39] a. E. Vedejs, W. H. Dent, D. M. Gapinski, C. K. McClure, *J. Am. Chem. Soc.* **1987**, *109*, 5437-5446. b. K. R. Fandrick, D. R. Fandrick, J. T. Reeves, J. Gao, S. Ma, W. Li, H. Lee, N. Grinberg, B. Lu, C. H. Senanayake, *J. Am. Chem. Soc.* **2011**, *133*, 10332-10335.

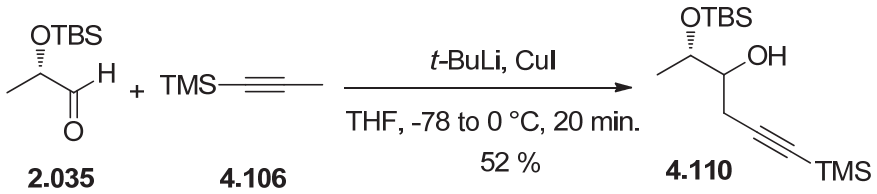
literature to displace the equilibrium and form preferably the homoallenic reagent **4.105b**, thus allowing the selective synthesis of homopropargylic alcohols.

This new sequence starts with the formation of homopropargylic alcohol **4.109**. Deprotonation of trimethyl(prop-1-yn-1-yl)silane **4.096** with *t*butyl lithium, followed by exchange with copper, forms the corresponding allenylcuprate **4.100**. The latter is then added onto the aldehyde to access the desired homopropargylic alcohol **4.101** selectively (scheme 51).



Scheme 51

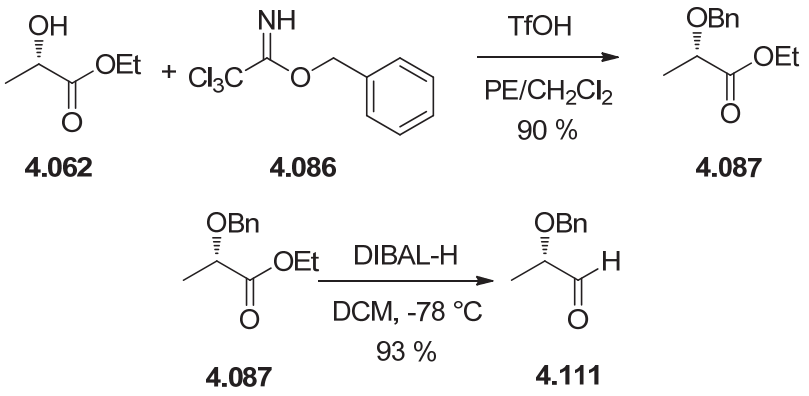
Addition of *in situ* deprotonated **4.106** to aldehyde **2.035** led to the formation of adduct **4.110** in moderate yield (scheme 52).



Scheme 52

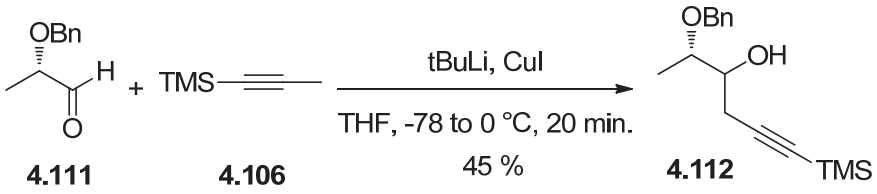
It appears that some of the aldehyde undergoes loss of the silicon protecting group under the reaction conditions. Therefore, we decided to prepare the benzylated aldehyde **4.111** which should not undergo deprotection during

this transformation. It was synthetized in two steps from (*S*)-ethyl lactate in excellent yields[40] (scheme 53).



Scheme 53

Addition of the anion of **4.106**, in the presence of copper iodide, leads to the desired product **4.112** in only 45 % yield as a mixture of two epimers of the newly formed chiral center (ratio = 1:1) (scheme 54).



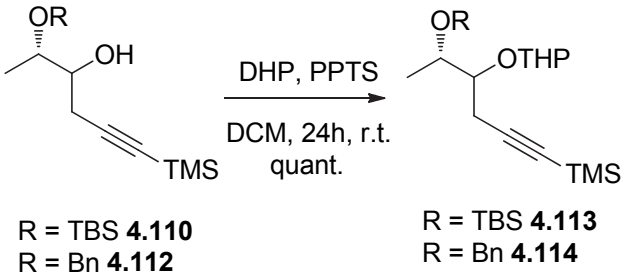
Scheme 54

It transpires that the addition of the allenylcopper reagent to **4.108** is a rather slow process and a longer reaction time is required to reach completion. Thus, the yield of **4.112** could be increased to 74 % by stirring the reaction for 3 hours instead of 20 minutes. A change in the work-up also improved the process.

---

[40] Fujisawa Pharmaceutical Co., Ltd. Patent: US6359145 B1, **2002.** b. D. Enders, S. von Berg, B. Jandeleit, *Org. Synth.* **2002**, *78*, 177.

Protection of the free alcohol with DHP yields **4.113** and **4.114** which are ready for the reduction of the triple bond to the corresponding (*Z*)-double bond (scheme 55).

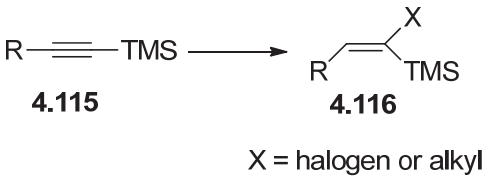


Scheme 55

Different methods to transform an alkyne to the corresponding substituted (Z)-alkene are described in the literature. The major ones are described in the next section.

II.2.2. From alkynes to substituted (Z)-alkenes

The needed transformation at this point is the conversion of alkyne **4.115** into the corresponding substituted (*Z*)-vinylsilane **4.116** (scheme 56).



Scheme 56

The first method that could be used for such a transformation is the hydroboration of the C-C triple bond[41] followed by transmetalation and carbodemetalation or halogenation[42].

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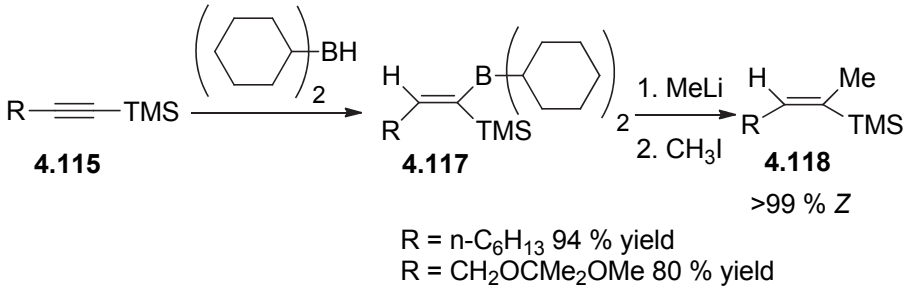
[41] N. G. Bhat, C. P. Aguirre, *Tetrahedron Lett.* **2000**, *41*, 8027-8031.

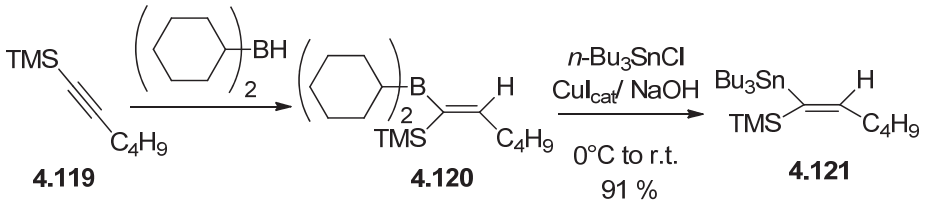
[42] H. C. Brown, T. Hamaoka, N. Ravindran, *J. Am. Chem. Soc.* **1973**, *17*, 5786-5788.

For example, the group of Utimoto described the hydroboration of 1-trimethylsilyl-1-octyne with excess dicyclohexylborane to give vinylborane **4.110** regioselectively. The resulting mixture was treated with methyl lithium followed by methyl iodide to afford vinylsilane **4.118** in excellent yield (scheme 57)[43].



Scheme 57

A more recent example described a copper(I) iodide-catalyzed transfer of 1-(trimethylsilyl)-1-alkenyl group from boron to tin to form compound **4.121** in excellent yield (scheme 58).



Scheme 58

Further functionalization either through iodination or palladium-catalyzed cross-coupling reactions allows the synthesis of trisubstituted vinylsilanes with high stereospecificity and excellent yields (scheme 59)[44].

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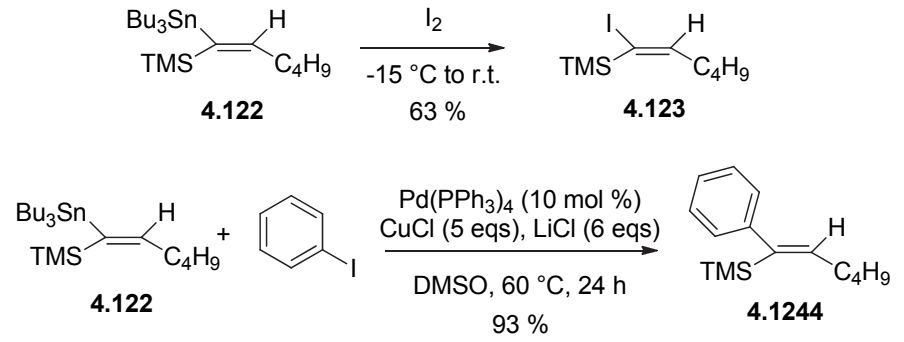
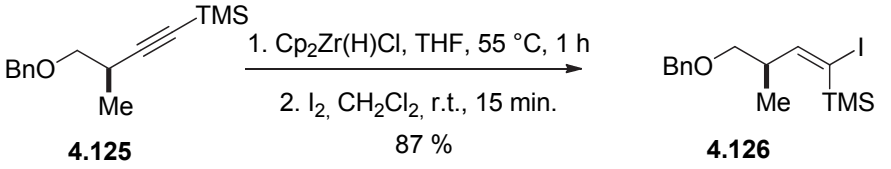
[43] K. Uchida, K. Utimoto, H. Nozaki, *J. Org. Chem.* **1976**, *17*, 2941-2942.

[44] M. Hoshi, K. Shirakawa, K. Takeda, *Synlett* **2001**, *3*, 403-405.



Scheme 59

A second option is to use the hydrozirconation reaction employing Schwartz reagent. When applied to silyl acetylenes, this transformation has been shown to proceed with good levels of regio- and stereoselectivity to give the α-silyl alkenyl zirconium complexes[45]. Iodination of these complexes allows the formation of 1-iodo-(trimethylsilyl)-1-alkenes such as **4.126** in excellent yield which can further be transformed using, for example, palladium(0)-catalyzed cross-coupling reactions (scheme 60)[46].



Scheme 60

Hydroalumination, which has been extensively studied by Eisch and Zweifel[47], is another option. Hydroalumination of (1-alkynyl)silanes with Dibal-H in ether solvents proceeds in a stereo- and regiospecific manner to

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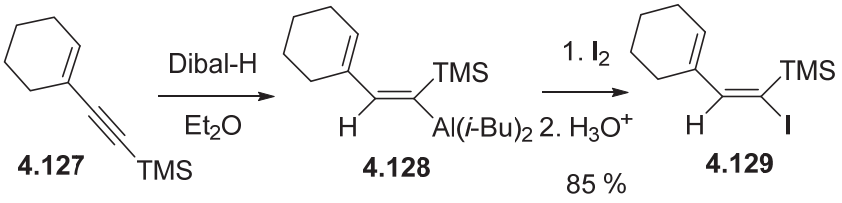
[45] X. H. Zhu, W. X. Zheng, W. X. Huang, *Synth. Commun.* **1998**, *78*, 4165-4170.

[46] A. Arefolov, N. F. Langille, J. S. Panek, *Org. Lett.* **2001**, *21*, 3281-3284.

[47] a. J. J. Eisch, W. C. Kaska, *J. Am. Chem. Soc.* **1966**, *88*, 2213. b. G. Zweifel, C. C. Whitney, *J. Am. Chem. Soc.***1967**, *89*, 2753.

afford ((*Z*)-1-alumino-1-alkenyl)silanes which can then be halogenated or complexated with methyl lithium and subsequently alkylated[48].

For example, alkyne **4.127** reacted with Dibal-H to give aluminosilane **4.128** which was treated *in situ* with iodine to furnish compound **4.129** in excellent yield (scheme 61)[49].



Scheme 61

As planned earlier, we decided to use the hydroalumination reaction of the internal alkyne, followed by an *in situ* methylation, to access the (*Z*)-vinylsilane needed for the ISMS cyclisation. Unfortunately, this simple sequence turned out to be much harder to put in practice.

II.2.3. Hydroalumination

Initially, we followed the experimental procedure described by Dr D. Bayston. Hence, acetal **4.114** was stirred in Et_2O at 0°C and Dibal-H was added. The mixture was then brought to room temperature and after 10 minutes, iodine was added. Ten minutes later, the reaction mixture was quenched and worked-up. Disappointingly, only deprotected starting material **4.112** was recovered (scheme 62).

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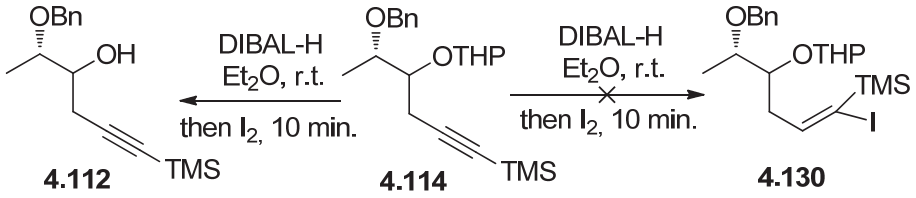
[48] a. J. J. Eisch, G. A. Damasevitz, *J. Org. Chem.* **1976**, *12*, 2214-2215. b. K. Uchida, K. Utimoto, H. Nozaki, *J. Org. Chem.* **1976**, *12*, 2215-2216.

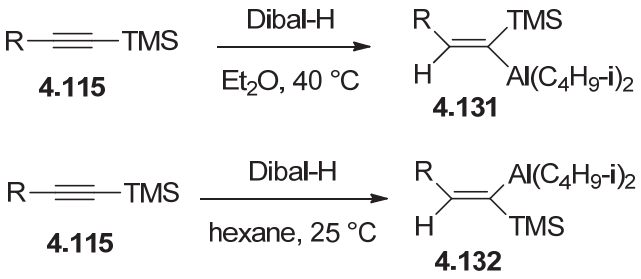
[49] G. Zweifel, W. Lewis, *J. Org. Chem.* **1978**, *14*, 2739-2744.



Scheme 62

Since no addition of Dibal-H took place, we thought that the reaction time must have been far too short and thus decided to leave the hydroalumination to proceed overnight before adding the iodine (table 1, entry 2). Alas, only deprotected starting material was again recovered.

During his seminal contribution to the hydroalumination of alkynes, Zweifel has reported the crucial role played by the solvent. In fact, the stereochemistry depends on the solvent used. Selective *cis* hydroalumination is observed when the reaction is carried out in donar solvents (diethyl ether or tertiary amines). On the other hand, (*E*)-1-alumino-1-silyl-1-alkenes **4.132** are obtained when the reaction medium is a hydrocarbon solvent (scheme 63)[50].

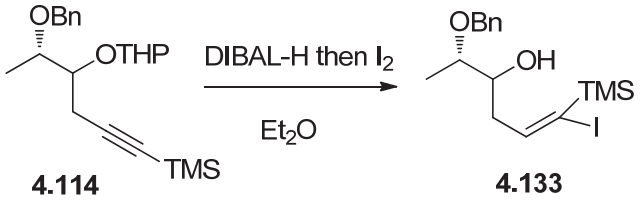


Scheme 63

It has been suggested that hydroalumination reactions are kinetically controlled in a *syn* manner. Donar solvents decrease the rate of hydroalumination but they stabilize the initial *syn* configuration. In the case

[50] G. Zweifel, J. Miller, *Org. React.* **1984**, *32*, 375.

of non-polar solvents, the *anti* adduct results from subsequent isomerization to the more stable configuration through a second addition of Dibal-H[51]. Therefore, we envisioned that the solvent in which Dibal-H was in solution might play a role in the fate of this reaction. Thus, Dibal-H in toluene was employed for hydroalumination of **4.114**. In this case, a 1:1 ratio of deprotected the desired product **4.133** and the starting material was obtained (table 1, entry 3). Product **4.133** was isolated after purification in 25 % yield. Encouraged by this result, we tried the reaction with Dibal-H in hexane which is one of the solvents usually employed in hydroalumination reactions[52]. Unfortunately, it wasn't fruitful (table 1, entry 4-8).



4.114 **4.133**

Entry	**Dibal-H**	**Eq.**	**Time before adding I_2**	**Results**
1	1M in Et_2O	2	10 min.	Deprotected Starting Material
2	1M in Et_2O	2	o.n.	Deprotected Starting Material
3	1M in Toluene Acros	2	o.n.	Product/SM 1:1 25 % yield

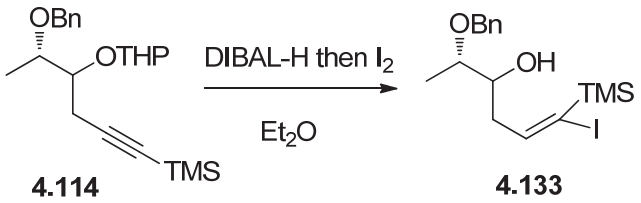
[51] J. J. Eisch, M. W. Foxton, *J. Org. Chem.* **1971**, *23*, 3520-3526.

[52] H. P. On, W. Lewis, G. Zweifel, *Synthesis* **1981**, 999-1001.

4	1M in hexane p.a	2	o.n.	Deprotected Starting Material
5	1M in distilled hexane	2	o.n.	Product 14 % yield
6	1M in hexane Acros	2	o.n.	Deprotected Starting Material
7	1M in hexane Acros	3	o.n.	Small amount product
8	1M in hexane Acros	4	o.n.	Decomposition

Table 1

A survey of the literature indicates that, depending upon the structure of the alkyne substrate, it is necessary to warm the reaction mixture for the hydroalumination to proceed. Therefore, we reacted **4.114** with two equivalents of Dibal-H at 50 °C. Gratifyingly, product **4.133** could be isolated in 28 % yield. Increasing the amount of Dibal-H to three equivalents raised the yield to 40 % (table 2).

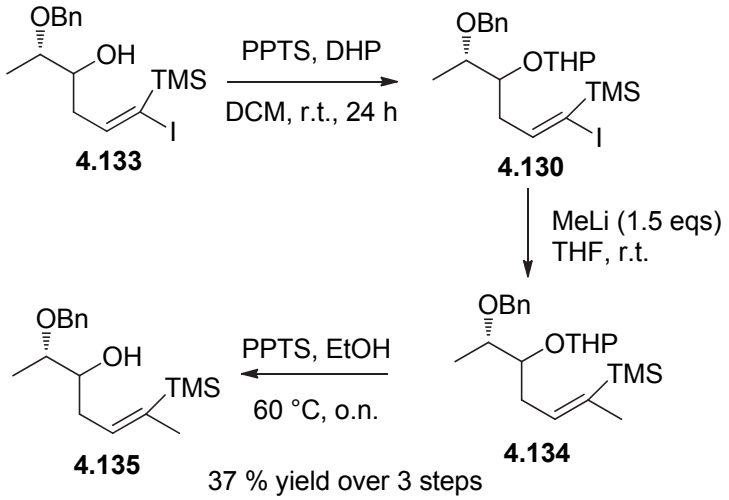


4.114 **4.133**

Dibal-H	**Eq.**	**Time before adding I_2**	**Temperature**	**Yield**
1M in hexane Acros	2	o.n.	50 °C	28 %
1M in hexane Acros	3	o.n.	50 °C	40 %

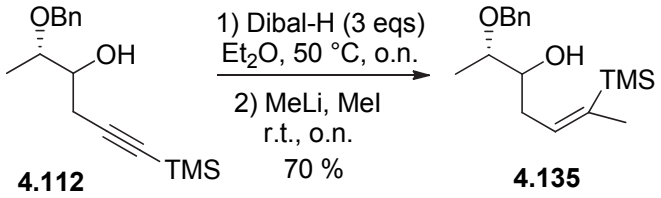
Table 2

Though the yield is rather modest, we had some of the desired vinyliodide in our hands. It was then decided to explore its conversion into the methylated alkene **4.135** before optimizing further the alumination/iodination sequence. For that purpose, product **4.133** was reprotected before being subjected to methylation in the presence of methyl lithium. Final deprotection afforded the thought-after vinylsilane **4.135** in 37 % yield over three steps (scheme 64).



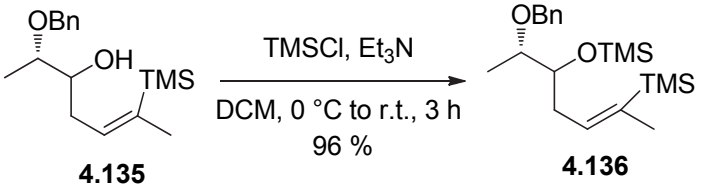
Scheme 64

At this point, we had secured the sequence leading to the desired vinylsilane. Unfortunately, this route is by far too long, possesses too many protection/deprotection steps and overall the yield is rather low. To render such an approach truly competitive and efficient, it became mandatory to attempt the direct, one-pot transformation of **4.112** to the (*Z*)-alkyne **4.135**. In the event, substrate **4.112** was reacted with Dibal-H at 50 °C overnight, after which time MeLi was added, followed by MeI at room temperature. The reaction was stirred for another night to furnish the desired product **4.135** in a pleasing 70 % yield (scheme 65).



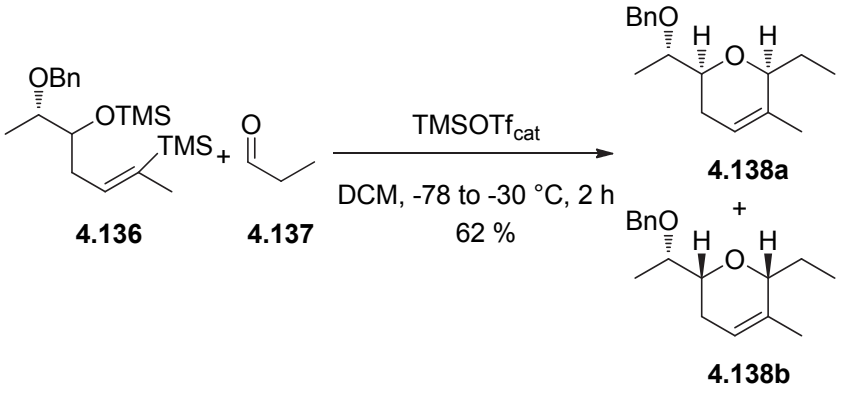
Scheme 65

Protection of the free alcohol with a TMS group was attained in excellent yield and the corresponding product **4.136** was engaged in the next step without any further purification (scheme 66).



Scheme 66

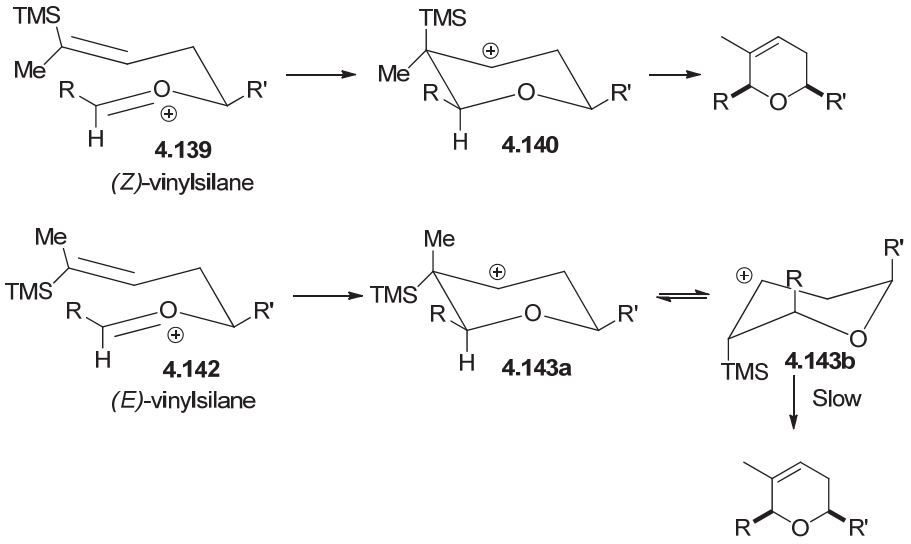
Cyclisation of adduct **4.136** with propionaldehyde, catalyzed by TMSOTf, furnished the desired protected dihydropyran **4.138** in good yield as a mixture of the two *syn*-diastereomers **4.138a** and **4.138b** in a 1:1 ratio (scheme 67).



Scheme 67

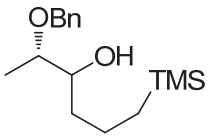
The ISMS cyclisation is believed to take place through a 6-membered ring transition state, as described in scheme 68. The transition state **4.139** in which the R substituent of the aldehyde occupies an equatorial position in order to decrease the 1,3-diaxial repulsion is preferred, thus leading to the formation of *syn*-dihydropyrans. Moreover, the reaction is favoured with a (*Z*)-vinylsilane. In the case of the (*E*)-vinylsilane **4.142**, the carbocation is

not stabilized by the silicon hyperconjugative effect and it can not be eliminated easily. For that to occur, the chair needs to flip; the substituents are then axial disfavouring that transition state.



Scheme 68

In addition to DHPs **4.138 a** and **b**, an aliphatic product was also isolated. Spectroscopic analysis revealed it to possess the over-reduced structure **4.144** probably originating from the hydroalumination step **(**figure 3).



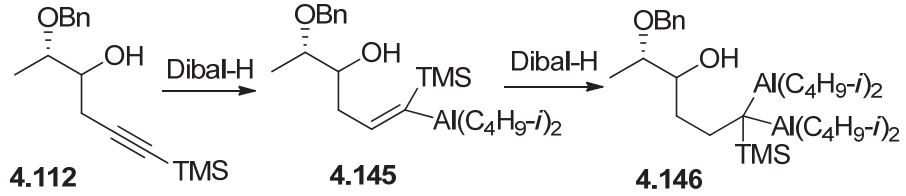
4.144

Figure 3

When looking at the ^{1}H NMR of pure product **4.135** (spectrum 1) and the ^{1}H NMR of the mixture of **4.135** and **4.144** (spectrum 2), it is not that obvious to detect side-product **4.144**, especially because both products are composed of two diastereomers (figure 4). It is only when pure **4.144** (spectrum 3) was isolated after the ISMS step and fully characterized that we realized that this

product had been there all along, in a ratio of 28 % to 44 %, as calculated from the crude ^{1}H NMR.

This side-product **4.144** probably originates from a second addition of Dibal-H to form intermediate **4.133**[50]. This species is probably stable because of the possible coordination between the alcohol and the aluminium therefore leading to the formation of **4.146** after the acidic work-up (scheme 69).



Scheme 69

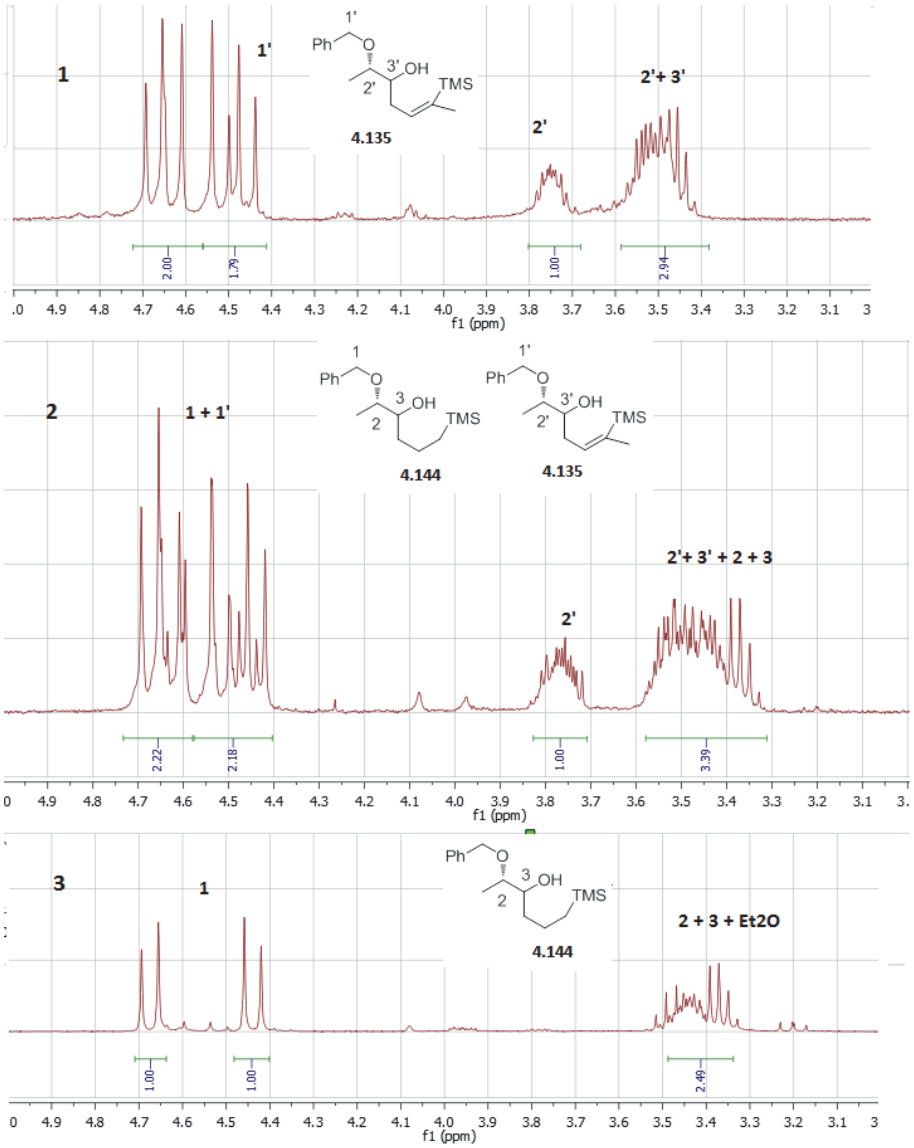
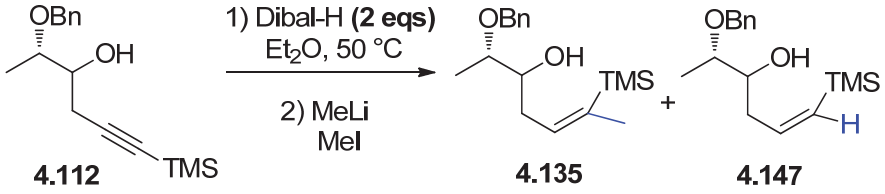


Figure 4

To solve this problem, the number of equivalent of Dibal-H was lowered from three to two. This solution eliminated adduct **4.144** but other troubles started to appear. As a new bottle of Dibal-H was used, the last one being empty, the reaction provided a mixture of protonated and methylated

products, **4.147** and **4.135** respectively, which proved to be really difficult to separate.

We found out that the conversion for the mixture of adducts **4.135** and **4.147** varied between 10 to 23 % with a ratio changing according to the different conditions (table 3). Addition of EtMgCl, to deprotonate the alcohol function of **4.112** increased the conversion but only adduct **4.147** was isolated.



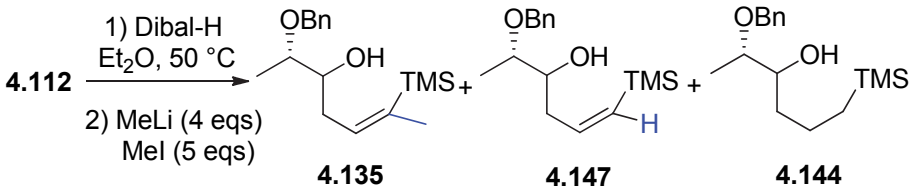
Conditions	4.135 : 4.147	Conversion in mixture
3 days	1 : 1	10 %
10 eqs MeI	0.63 : 1	23 %
3 eqs MeI freshly distilled	1 : 0.42	17 %
Addition -78°C	1 : 0.58	20 %
Addition EtMgCl	0 : 1	54 %

Table 3

When employing 3 equivalents of Dibal-H and using a new bottle of MeLi, we were dismayed to observe that the conversion stayed again at 22 %, with a ratio of 1 : 0.71 in favour of **4.135**. Going back to the original conditions was even worse and we had to conclude that this bottle of Dibal-H had definitely a problem.

We ordered a new bottle of Dibal-H. In this case, using 4 equivalents of MeLi and 5 equivalents of MeI, the conversion was much better, and the two

undesired products **4.144** and **4.147** were almost completely suppressed (table 4). The conditions in entry 4 were used until the bottle was empty.



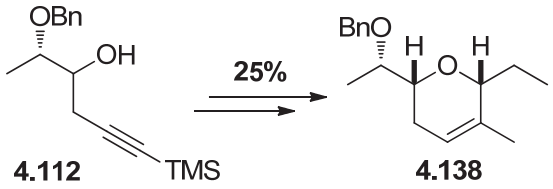
Entry	Conditions	4.135 : 4.147 : 4.144	Conversion in mixture
1	2.8eqs Dibal-H	1 : 0.2	76 %
2	3eqs Dibal-H	1 : 0.05 : 0.5	72 %
3	MeLi/MeI -78°C	1 : 0.1 : 0.45	72 %
4	1 eq THF	1 : 0.1 : 0.39	70 %

Table 4

Unfortunately, when a new bottle was employed again, the reaction stopped working and no conversion was observed.

It thus transpires that this step is not reproducible due to a varying quality of the hydroaluminating agent. What exactly is the problem could not be determined. It is possible that, depending upon the lot of Dibal-H, some impurities are present that inhibit the reaction on our substrate. In any case, attempting to optimize this process has taken a lot of time and energy and, due to its erratic nature, it was decided to find another alternative. Among the various methods known to convert **4.112** to **4.135**, we selected the hydrozirconation.

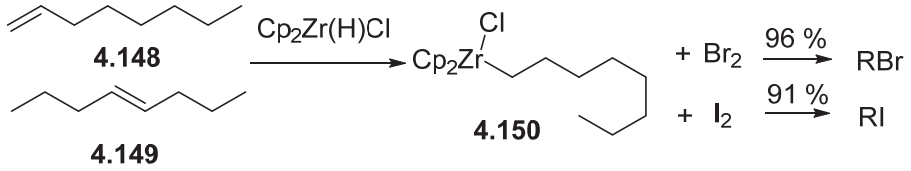
Before the reproductibility issues started, the sequence using Dibal-H afforded the protected DHP **4.138** in 25 % overall yield starting from substrate **4.112** (scheme 70).



Scheme 70

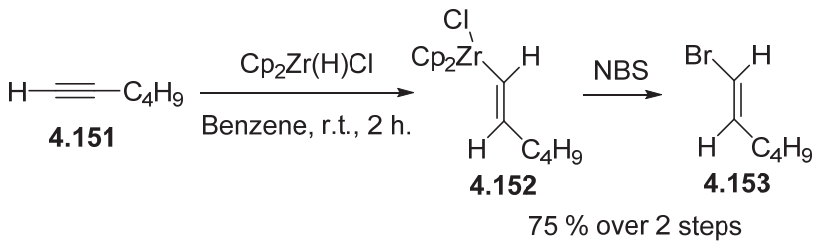
II.2.4. Hydrozirconation

The process of hydrozirconation was developed by Schwartz in the 70s as a highly valued route to functionalized carbon chains[53]. The reagent, $Cp_2Zr(H)Cl$, reacts with alkenes and alkynes at the least hindered position to form the corresponding alkyl- and alkenylzirconium derivatives. Electrophilic halogenation reagents (*e.g.*, Br_2, I_2, NBS or NCS,...) react with alkyl- and alkenylzirconium complexes to yield the corresponding organic halides[54] (scheme 71).



[53] J. Schwartz, J. A. Labinger, *Angew. Chem. Int. Ed.* **1976**, *15*, 333-340.

[54] D. W. Hart, T. F. Blackburn, J. Schwartz, *J. Am. Chem. Soc.* **1975**, *3*, 679-680.



Scheme 71

The reagent, $Cp_2Zr(H)Cl$, is nowadays commercially available but is quite expensive and has a short shelf-life. Two literature procedures for its preparation from inexpensive Cp_2ZrCl_2 were originally available. The first one used $LiAl(OtBu)_3H$ to reduce zirconocene dichloride but suffered from three problems: high cost of the reducing agent; difficulty to isolate the product by filtration; overreduction to Cp_2ZrH_2[55]. The second method employed bis (2-methoxyethoxy)aluminium hydride (RED-Al) but Schwartz reagent prepared in this manner contained 30 % of sodium chloride and little details about the experimental procedure were provided in the paper[56].

Ten years later, the group of Buchwald reported an experimentally simple procedure for the preparation of Schwartz's reagent on large scale which does not need expensive reducing agents. They discovered that the use of filtered solutions of $LiAlH_4$ in ether simplified product isolation and that Cp_2ZrH_2 could be rapidly converted to $Cp_2Zr(H)Cl$ by reaction with methylene chloride (scheme 72) [57].

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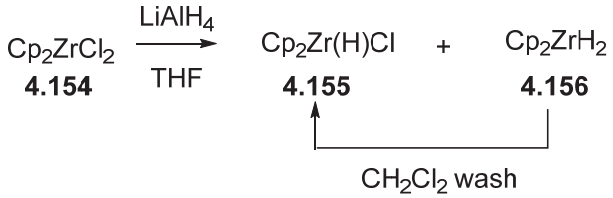
[55] P. C. Wailes, H. Weigold, *J. Organomet. Chem.* **1970**, *24*, 405.

[56] D. B. Carr, J. Schwartz, *J. Am. Chem. Soc.* **1979**, *101*, 3521-3531.

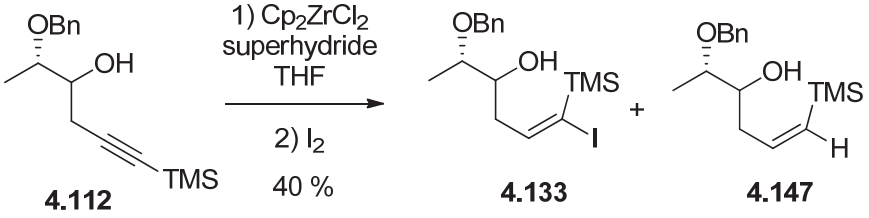
[57] S. L. Buchwald, S. J. LaMaire, R. B. Nielsen, B. T. Watson, S. M. King, *Tetrahedron Lett.* **1987**, *28*, 3895-3898.



Scheme 72

Unfortunately, the issue of stability over time remained an inconveniance. Therefore, methods for the *in situ* generation have also been developed[58]. The group of Lipshutz developed a process using $LiEt_3BH$ (superhydride) as the source of hydride. In this case, the by-product is presumably Et_3B which is a mild Lewis acid, tolerant towards sensitive groups such as THP-protected alcohols[59].

Based upon the latter procedure, substrate **4.112** was added to a solution of *in situ* generated $Cp_2Zr(H)Cl$. After 15 minutes, a solution of iodine was added (scheme 73). A mixture of iodinated and protonated products was isolated in 40 % yield (1:1.3 ratio).



Scheme 73

Based on these observations, we wondered if the capture of the vinylzirconium intermediate was not slower than expected. Hence, we decided to wait for three hours after addition of iodine and to isolate the

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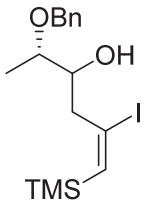
[58] E.-i. Negishi, T. Takahashi, *Synthesis* **1988**, 1-19.

[59] B. H. Lipshutz, R. Keil, E. L. Eiisworth, *Tetrahedron Lett.* **1990**, *31*, 7257-7260.

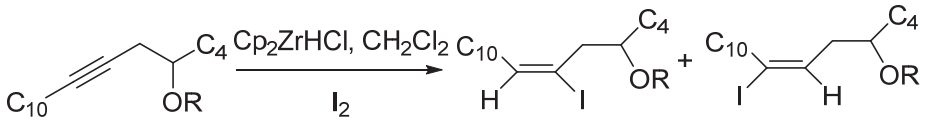
adduct thus produced. After purification, the iodinated product was obtained in 20 % yield. However, after spectroscopic analysis, we realized that this compound was not the expected product **4.133** but its regioisomer **4.157** (figure 5). We then found a report from Liu and Ready in which it is described that homopropargylic alcohols undergo directed hydrozirconation with the zirconium proximal to the directing group[60].



4.157

Figure 5

To better understand this regioselectivity, they compared homopropargylic alcohol **4.158a** to its methyl ether **4.158b** (scheme 74). These experiments showed that converting the free alcohol to a methyl ether substantially diminished the regioselectivity of hydrozirconation.



4.158 **4.159** **4.160**

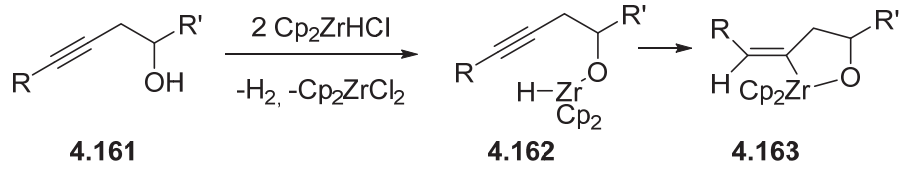
C_{10} = n-$C_{10}H_{21}$ **4.158a :** R = H Ratio **4.159a : 4.160a** = 9 : 1
C_4 = n-C_4H_9 **4.158b** : R = CH_3 Ratio **4.159b : 4.160b** = 1.6 :1

Scheme 74

To explain this regioselectivity, they propose a model involving an intramolecular hydrozirconation with an alkoxy-zirconium hydride, forming a five-membered chelate which is very stable and likely contributes to the

[60] X. Liu, J. M. Ready, *Tetrahedron* **2008**, *64*, 6955-6960.

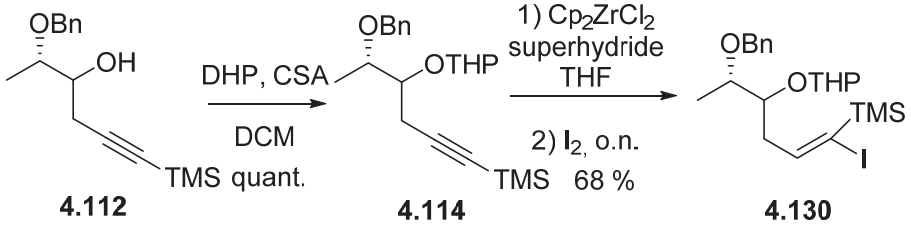
resistance of the oxazirconacycle **4.163** to isomerization to the distal product (scheme 75).



4.161 **4.162** **4.163**

Scheme 75

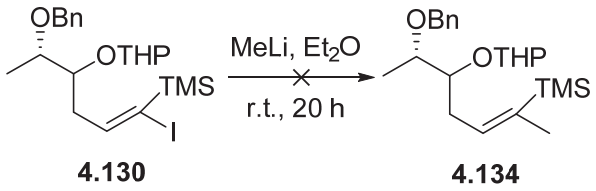
To avoid this regioselectivity problem, we decided to protect the free alcohol with a THP group. To our delight, hydrozirconation, using the conditions described by Panek[61], followed by iodation overnight, allowed us to isolate the desired product **4.130** in 68 % yield (scheme 76).



4.112 **4.114** **4.130**

Scheme 76

The subsequent methylation was attempted as before, by adding methyl lithium to the iodinated adduct **4.130**. Unexpectedly, in this case, no reaction was observed (scheme 77).

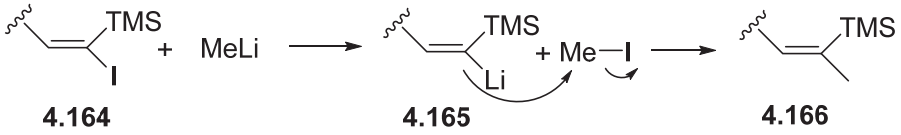


4.130 **4.134**

Scheme 77

[61] A. Arefolov, N. F. Langille, J. S. Panek, *Org. Lett.* **2001**, *3*, 3281-3284.

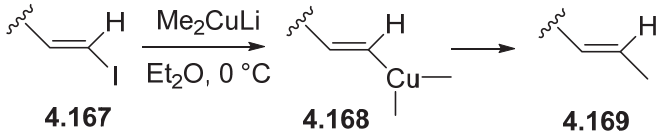
The transformation of vinyl iodides into the corresponding methyl-substituted alkenes has been performed using a variety of reagents. In our case, it is believed that addition of MeLi to **4.164** results in the formation of the vinylic anion **4.165** and of MeI by a transmetallation process. Addition of the anion on MeI then leads to the desired alkene **4.166** (scheme 78).



Scheme 78

It is possible that the presence of numerous oxygen atoms in our substrate may lead to complexation of the vinyllithium species (intermolecular), resulting in a decreased reactivity.

To overcome this limitation, it was decided to employ the corresponding cuprate, which is less prone to such coordination. For example, Corey has shown that treatment of iodide **4.167** by Me_2CuLi resulted in a smooth and high yielding conversion into **4.169** via the intermediate copper derivative (scheme 79)[62].



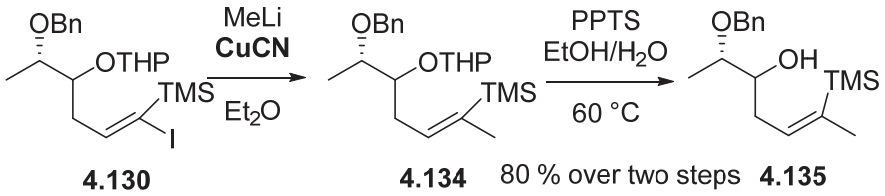
Scheme 79

In the event, addition of CuCN to the reaction mixture proved to be successful to methylate **4.130**[63]. Further deprotection with PPTS afforded pure product **4.135** in 80 % yield over two steps (scheme 80).

---

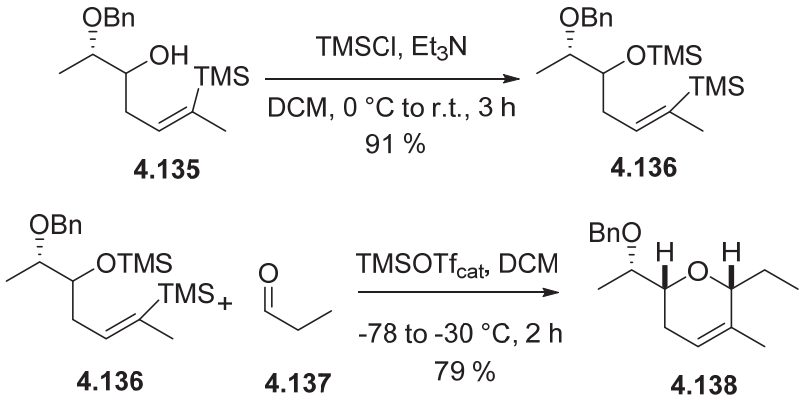
[62] E. J. Corey , G. H. Posner, *J. Am. Chem. Soc.* **1967**, *15*, 3911-3912.

[63] G. L. Simpson, T. P. Heffron, E. Merino, T. F. Jamison, *J. Am. Chem. Soc.* **2006**, *128*, 1056-1057.



Scheme 80

Silylation of the free alcohol followed by ISMS cyclisation afforded the benzylated DHP **4.138** in excellent yields (scheme 81).



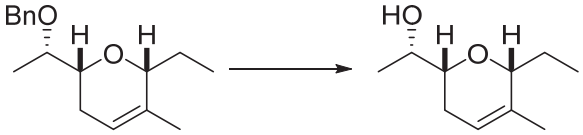
Scheme 81

At this point, we turned our attention to the deprotection of the benzyl group. A first attempt was made using iron trichloride. Unfortunately, these conditions led to the degradation of the starting material (table 5, entry 1). Deprotection with boron trichloride[64] did not take place, and only the starting material was recovered (table 5, entry 2). Lithium in liquid ammonia[65] afforded the desired product in moderate yield (table 5, entry 3).

[64] O.-Y. Jeon, E. M. Carreira, *Org. Lett.* **2010**, *12*, 1772-1775.

[65] A. Merz, S. Anikin, B. Lieser, J. Heinze, H. John, *Chemistry – A European Journal* **2003**, *9*, 449-455.

Gratifyingly, lithium/naphthalenide[66] gave the desired deprotected DHP **4.099** in very good yield (table 5, entry 4).



4.138 **4.099**

Entry	Deprotecting agent	Yield
1	$FeCl_3$	Decomposition
2	BCl_3	Starting Material
3	Li/NH_3	50 %
4	**Li/naphthalene**	**77-83 %**

Table 5

It is noteworthy that, after deprotection, the two diastereomers could finally be separated by silica gel column chromatography. Diastereomer **4.099b** possesses the same stereochemistry as the right-hand fragment of jerangolid D and was extensively described by Dr J. Pospisil in his Ph.D. thesis. Protons 1 and 2 in these molecules have different chemical shifts and multiplicity. After full characterization and comparison with known data, the two disatereomers were attributed as shown in figure 6.

[66] E. Alonso, D. J. Ramón, M. Yus, *Tetrahedron* **1997**, *53*, 14355-14368.

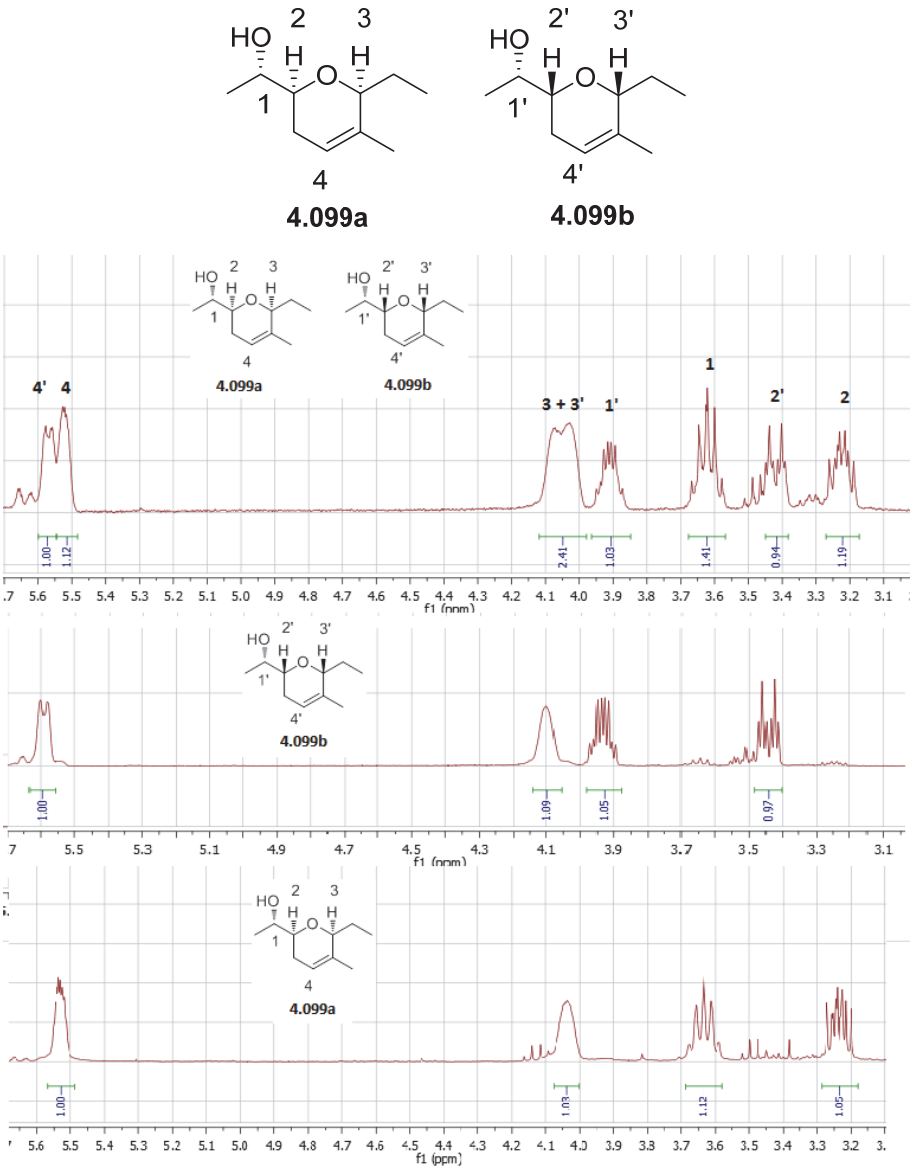
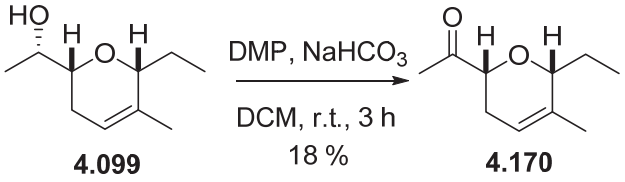


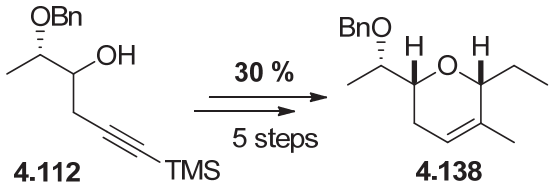
Figure 6

Oxidation of the free alcohol to the corresponding ketone **4.170** was performed on the mixture of diastereomers. This transformation is complete within 3 hours. However, after purification, ketone **4.170** was isolated in only 18 % yield due to the high volatility of this compound (scheme 82).



Scheme 82

Overall, this approach enabled us to obtain the desired protected DHP **4.138** in 30 % overall yield starting from adduct **4.112** in a reproducible manner (scheme 83)!



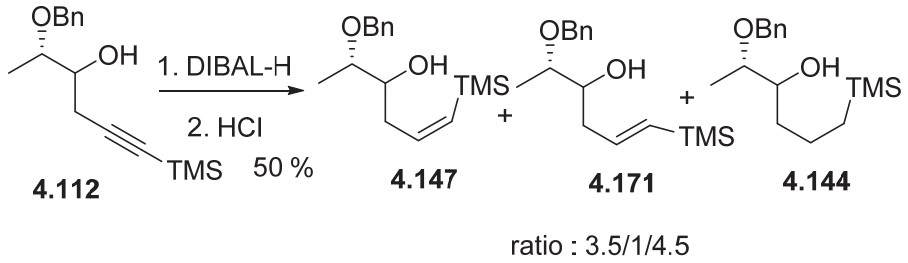
Scheme 83

In conclusion, DHP **4.099** can be synthetized in 10 steps with an overall yield of 20 % starting from commercially available (*S*)-ethyl lactate.

II.3. Sequence with no methyl

In parallel, we also wanted to access dihydropyran lacking the methyl group at the C3 position. In order to prepare them, we modified our current route, though decided to keep the same starting material **4.112.**

Hydroalumination, followed by acidic work-up, was initially attempted. The desired product **4.147** was formed, as well as the (*E)*-isomer **4.171** and the overeduced product **4.144** (scheme 84).

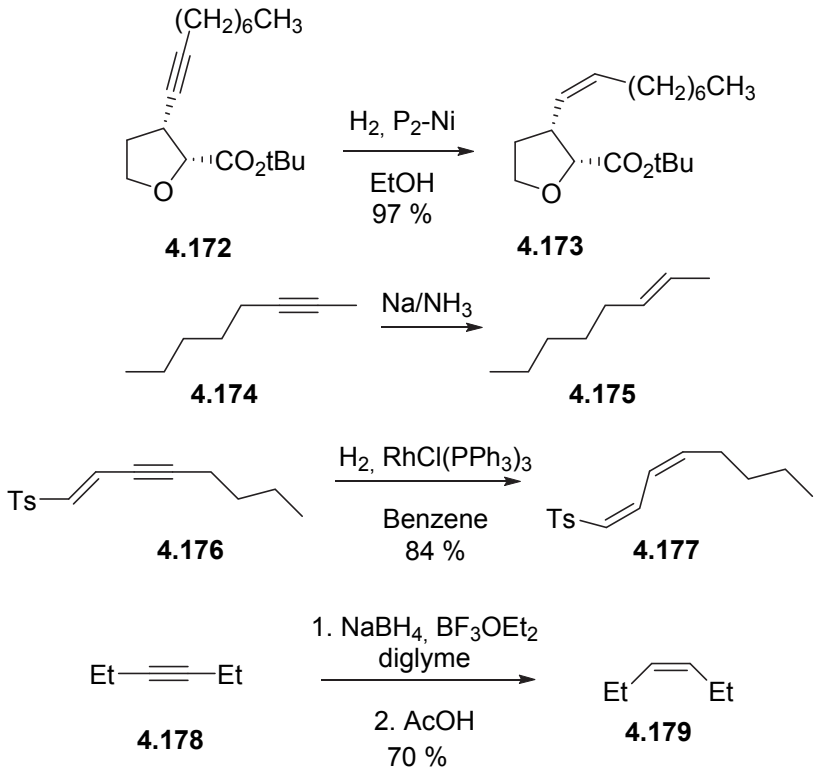


Scheme 84

Since we have encountered previously numerous problems with this reaction, we turned our attention to other known methods for the semi-reduction of alkynes to the corresponding (*Z*)-alkene. The solution that immediately comes to mind for an organic chemist is to use Lindlar's catalyst. This had been tried before in the lab and a mixture of (*E*) and (*Z*) isomers was formed. Many procedures have been reported in the literature for the conversion of an alkyne into a (*E*) or a (*Z*)-alkene. A brief selection is summarized in scheme 85[67].

---

[67] a. J. S. Yadav, S. Chandrasekhar, R. Kache, *Synth. Commun.* **1995**, *25*, 4035-4043. b. E. –i. Negish, D. Choueiry, in *Preparation of Alkenes*, J. M. J. Williams, Ed., Oxford University Press, Oxford, **1996**, 137-155. c. R. S. Paley, A. deDios, A. Estroff, J. A. Lafontaine, C. Montero, D. J. McCulley, M. B. Rubio, M. P. Ventura, H. L. Weers, R. F. delaPradilla, S. Castro, R. Doraod, M. Morente, *J. Org. Chem* **1997**, *62*, 6326-6343. d. J. Howarth, in *Preparation of Alkenes*, J. M. J. Williams, Ed., Oxford University Press, Oxford, **1996**, 117-136.



Scheme 85

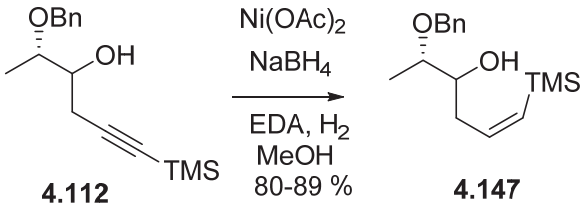
Among these, we selected the P2-nickel catalyst. This catalyst is formed by reducing nickel acetate in the presence of sodium borohydride in MeOH. The active species is then stabilized by ethylene diamine and is used in catalytic amounts with hydrogen to reduce triple bonds to the corresponding (*Z*)-double bonds[68].

This procedure was then applied to our substrate. Surprisingly, in the presence of 5 mol % of catalyst, ~5 % conversion of the starting material was observed. Increasing the amount of P2-Ni resulted in similar rise in the

[68] a. D. F. Taber, R. J. Herr, D. M. Gleave, *J. Org. Chem.* **1997**, *62*, 194-198 b. H. C. Brown, C. A. Brown, *J. Am. Chem. Soc.* **1963**, *85*, 1005-1006.

formation of product **4.147**. This result prompted us to employ stoeichiometric quantities of the catalyst.

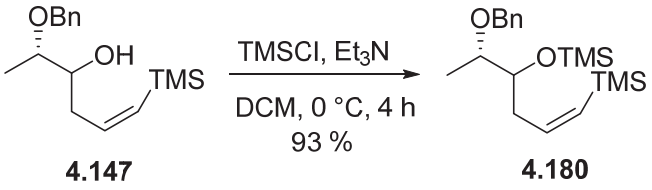
To our delight, pure vinyl-silane **4.147** was isolated in 80 % yield (scheme 86).



Scheme 86

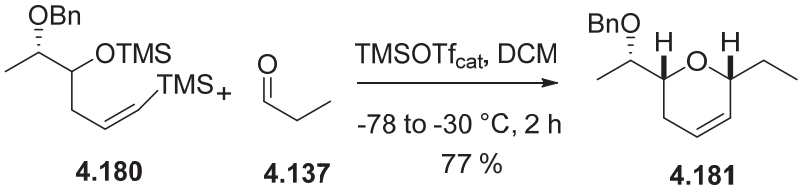
This reaction proceeds efficiently, is highly reproducible and the yields vary from 80 to 89 %.

The rest of the sequence was carried out as described in the previous section. Silylation of the free alcohol was accomplished in excellent yield (scheme 87).



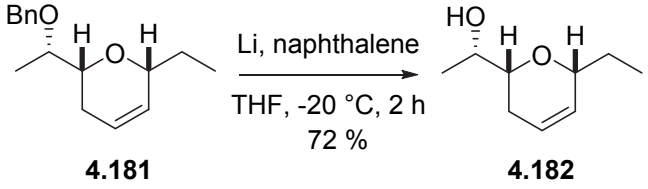
Scheme 87

ISMS cyclisation with propionaldehyde, in the presence of a catalytic amount of TMSOTf, produced the protected DHP **4.181** in 77 % yield (scheme 88).



Scheme 88

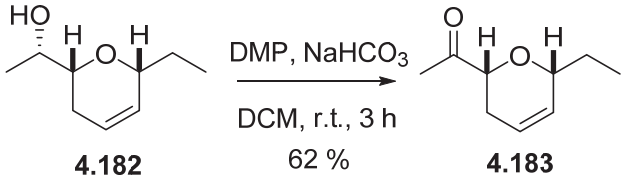
Debenzylation using the Li-naphthalenide protocol generated the corresponding secondary alcohol **4.182** in good yield (scheme 89).



Scheme 89

Once again, the two diastereomers of **4.182** could be separated by silica gel column chromatography at this step.

Oxidation of the mixture of two diastereomers to the corresponding ketone was performed extremely carefully since we surmise that this compound, like its methylated analogue, should be highly volatile. These precautions allowed us to isolate **4.183** in good yield (scheme 90).



Scheme 90

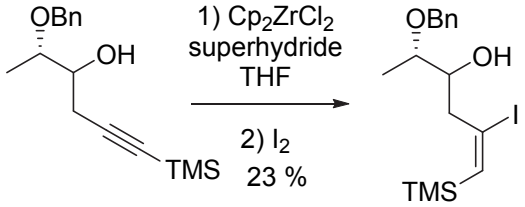
In conclusion, DHP **4.183** can be synthetized in 8 steps with an overall yield of 18 % starting from commercially available (*S*)-ethyl lactate.

II.4. Other analogues

II.4.1. Hydrozirconation of the free alcohol

During our studies on the optimisation of the hydrozirconation of alkyne **4.112**, product **4.157** could be isolated when the alcohol function was not protected. This adduct looks interesting in the context of the generation of diversely substituted DHP systems and the construction of modified jerangolid analogues. Therefore, it was decided to take advantage of this adduct to synthetize an analogue with the methyl group at position C4 instead of C3.

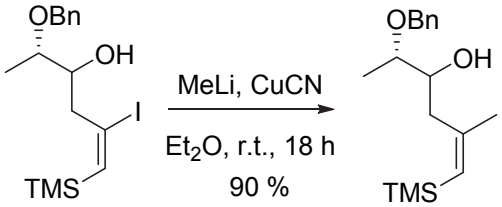
Substrate **4.112** was thus reacted again with Schwartz reagent to afford adduct **4.157** in low yield (scheme 91).



4.112 **4.157**

Scheme 91

Further methylation afforded compound **4.184** in excellent yield. Vinylsilane **4.184** was sufficiently pure to be engaged in the subsequent step without further purification (scheme 92).

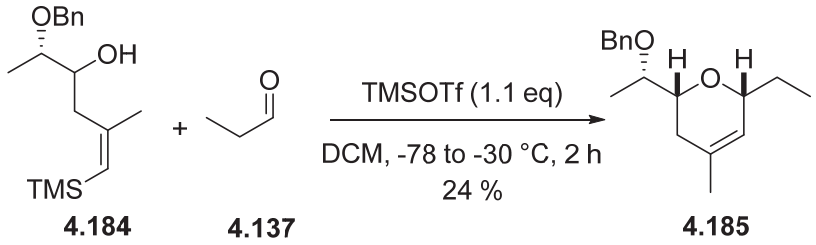


4.157 **4.184**

Scheme 92

It should be noted however that this compound is very sensitive to acids and decomposes rapidly in their presence. NMR spectra have to be taken in basified deuterated chloroform and the next step should be carried out as quickly as possible after obtention of **4.184**.

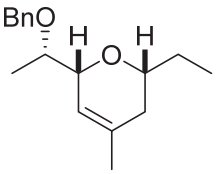
The ISMS cyclisation was perfomed directly on adduct **4.184** in the presence of 1.1 equivalents of TMSOTf to afford DHP **4.185** in modest yield (scheme 93). It is possible that the sensitivity of **4.184** towards acids is responsible for the low yield.



4.184 **4.137** **4.185**

Scheme 93

The regioisomeric adduct **4.186** was also detected in this reaction. It originates from the isomerisation of the double bond, probably induced by the presence of traces of TfOH formed during the reaction (figure 7). The temperature during the ISMS cyclisation should therefore be controlled very carefully to avoid this isomerisation.

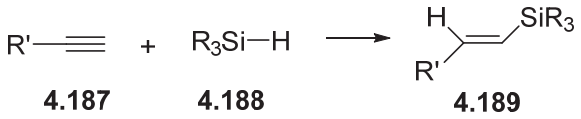


4.186

Figure 7

II.4.2. Hydrosilylation

The hydrosilylation of alkenes and alkynes describes the addition of Si-H bonds across carbon-carbon double or triple bonds respectively (scheme 94).



Scheme 94

Metal-catalyzed hydrosilylation of alkynes is the most straightforward, atom-economical access to vinylsilanes. The stereochemical outcome of this transformation strongly depends upon different parameters such as the metal employed, its ligands, the substituents on both the alkyne and the silane, the solvent, the temperature[69]... A large number of metals and systems have been described in the literature. For example, the group of Trost reported a highly regioselective, ruthenium-based system, which promotes *trans* addition to internal and terminal alkynes to afford the corresponding α isomers **4.190** and **4.191**[70]. Ruthenium[71] and Rhodium[72] catalysis allow the access to the *trans* addition product **4.192** β-(*Z*). On the other hand, the platinum-catalyzed hydrosilylation of alkynes has shown to proceed by *cis* addition to form exclusively adducts **4.190**, **4.193** β-(*E*) and **4.194** (scheme 95)[73].

---

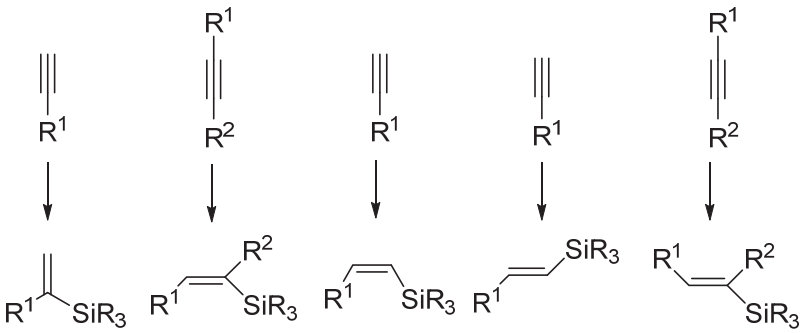
[69] S. Dierick, PhD Thesis, UCL **2013**

[70] B. M. Trost, Z. T. Ball, *J. Am. Chem. Soc.* **2005**, *127*, 17644-17655.

[71] Y. Na, S. Chang, *Org. Lett.* **2000**, *2*, 1887-1889.

[72] M. P. Doyle, K. G. High, C. L. Nesloney, J. W. Clayton, J. Lin, *Organometallics* **1991**, *10*, 1225-1226.

[73] L. N. Lewis, K. G. Sy, G. L. Bryant, P. E. Donahue, *Organometallics* **1991**, *10*, 3750-3759.



Scheme 95

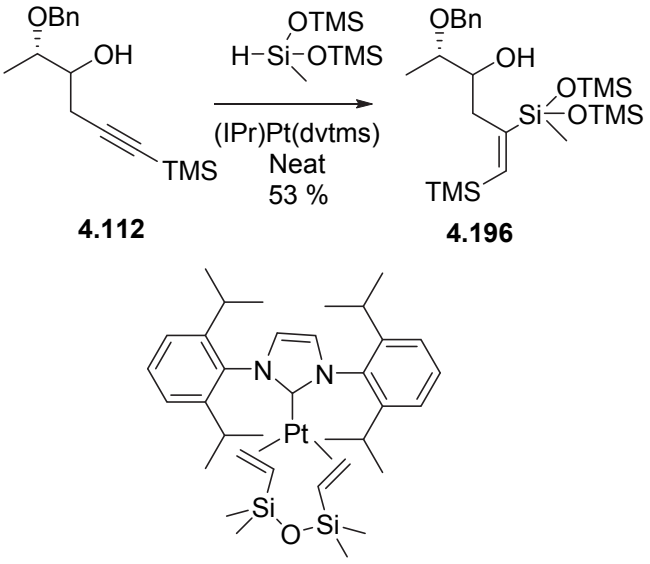
Our group has developed a series of *N*-heterocyclic carbenes platinum(0) complexes that are excellent catalysts for the hydrosilylation of alkynes to form the *β*-(E) isomer **4.193** as the major product in excellent yields[74].

Based on further work on the hydrosilylation of alkynes currently on-going in our group, we decided to apply this methodology to homopropargylic alcohol **4.112** to form yet another analogue of the dihydropyran portion of jerangolid D.

Hydrosilylation in the presence of our platinum catalyst **4.195** and bis-trimethyl silyloxysilane (kindly given by Dr F. Chellé) afforded compound **4.196** in good yield (scheme 96).

---

[74] a. G. de Bo, G. Berthon-Gelloz, B. Tinant, I. E. Markó, *Organometallics* **2006**, *25*, 1881-1890. b. G. Berthon-Gelloz, J-M. Schumers, G. de Bo, I. E. Markó, *J. Org. Chem.* **2008**, *73*, 4190-4197.



Scheme 96

The regiochemistry was determined by ^{1}H NMR analyses. If compound **4.184** was formed, proton 4 would appear as a doublet of doublet and a strong correlation between protons 3 and 4 would be observed in COSY experiment. In our case, proton 2 is a singlet and no correlation is observed between protons 1 and 2 in COSY NMR (figure 8). As for the configuration of the alkene, it is assumed that the (*Z*)-isomer is formed based upon the mechanism of the reaction. However, this was not proved unambigously.

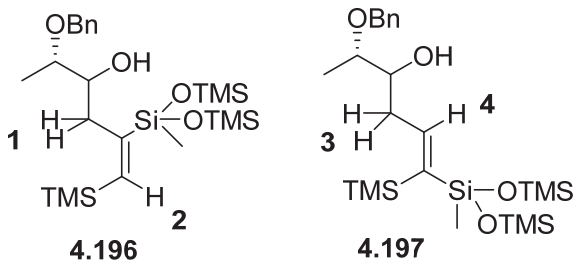
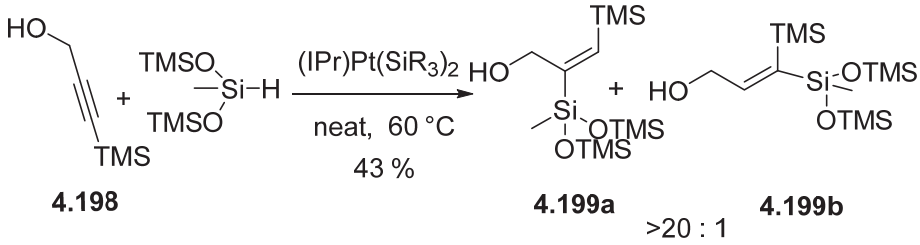


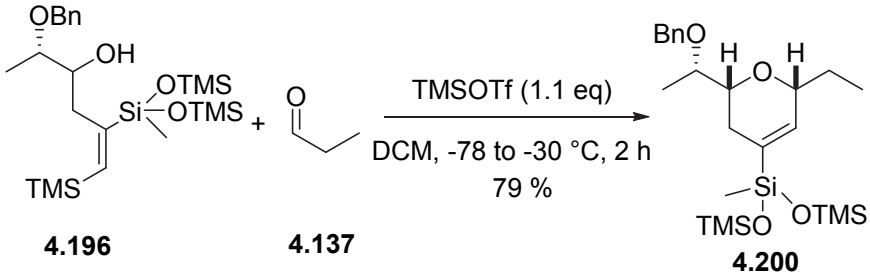
Figure 8

Morover, this result is in agreement with the results described by Dr. Steve Dierick during his PhD thesis. When homopropargylic alcohol **4.198** was hydrosilylated, the major product was the β isomer **4.199a** (scheme 97)[69].



Scheme 97

ISMS cyclisation in the presence of 1.1 equivalents of TMSOTf afforded the desired DHP **4.200** in good yield (scheme 98).

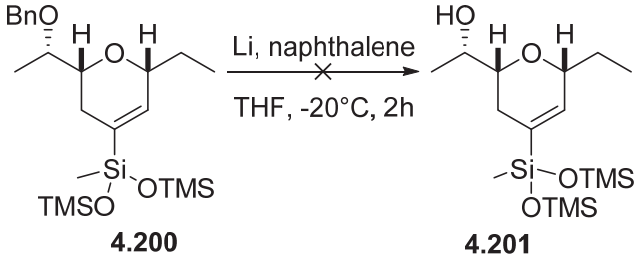


Scheme 98

As a note of caution, it is important to quench the reaction with a dilute solution of acid (0.1M HCl) if DHP **4.200** is to be obtained in good yields.

Indeed, when a more concentrated acidic solution is used, some desilylation product is observed, thus leading to a reduced yield.

Debenzylation was finally attempted using lithium naphthalenide. Unfortunately, in this case, degradation was observed and no single product could be isolated (scheme 99).

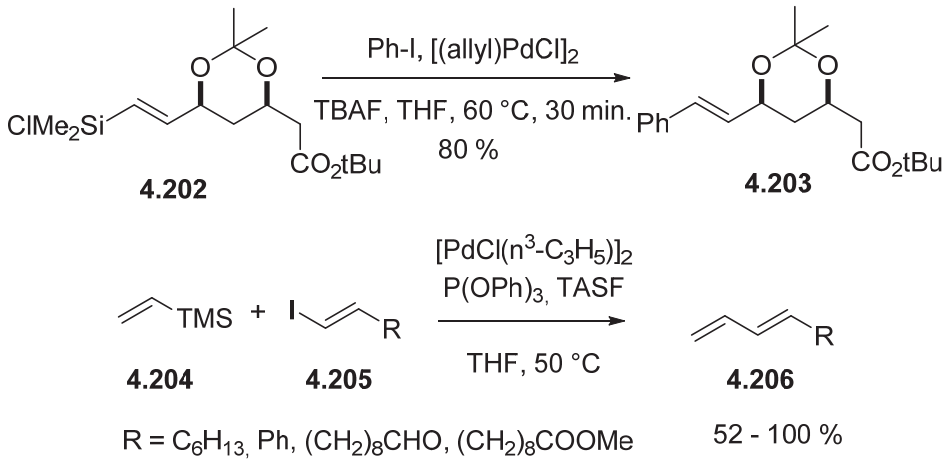


4.200 **4.201**

Scheme 99

Nevertheless, whilst adduct **4.201** cannot be directly incorporated into jerangolid analogues, it is a useful intermediate since the presence of the silyl group should enable further functionalisations at that particular position. These could include Hiyama cross-coupling reactions with a variety of aromatic, vinylic or acetylenic partners (scheme 100)[75].

[75] a. K. Takahashi, T. Minami, Y. Ohara, T. Hiyama, *Tetrahedron Lett.* **1993**, *51*, 8263-8266. b. Y. Hatanake, T. Hiyama, *J. Org. Chem.* **1988**, *53*, 918.



Scheme 100

The reactions described in this last paragraph can clearly benefit from some optimization but the results already obtained appear to be quite promising.

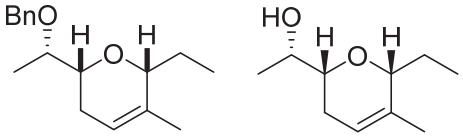
In conclusion, we have developed a general method to access various dihydropyrans starting from the same substrate, the homopropargylic alcohol **4.112**, by modifying in a diverse manner, its carbon-carbon triple bond.

In the next chapter, we will present our results on the modifications performed on the dihydropyran's double bond to reach various tetrahydropyrans, and especially the right-hand portion of jerangolids B, E and H.

MODIFICATIONS AND SYNTHESIS OF NEW ANALOGUES

I. Synthesis of the right-hand part of Jerangolids B, E and H

In the previous chapter, we discussed the synthesis of dihydropyran **4.138** and its deprotected version **4.099b** which corresponds to the right-hand fragment of jerangolid D (figure 1).



4.138 **4.099b**

Figure 1

With our desired dihydropyrans in hand, we started to functionalize the double bond in order to construct the right-hand fragment of jerangolids B, E and H (figure 2). Indeed, in these compounds, the stereochemistry at C14 is still unknown.

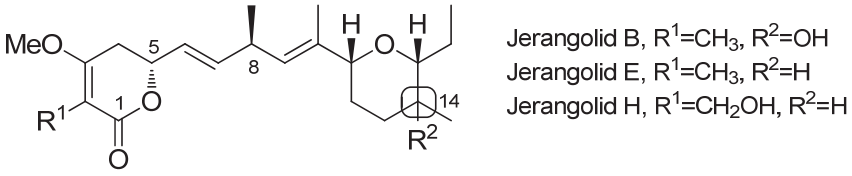


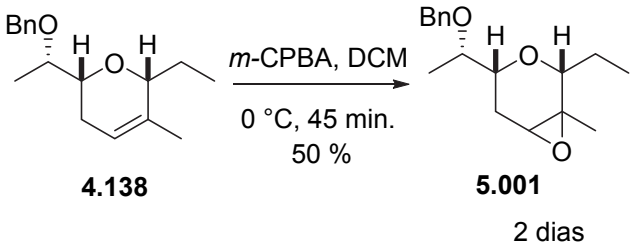
Figure 2

For that purpose, introduction of the –OH function in a stereoselective and regioselective manner was envisaged. Reduction of the trisubstituted double bond of **4.138** should afford the right-hand subunit of jerangolid E.

I.1. Right-hand subunit of jerangolid B

I.1.1. Epoxidation on benzylated DHP

Dihyropyran **4.138** was epoxidized with *m*-CPBA to yield two diastereomers in moderate yield (scheme 1).



Scheme 1

The epoxides were separated by silica gel column chromatography and noesy experiments were performed on each one. They confirmed that the stereochemistry at C2-C6 is *syn* in both molecules (figure 3).

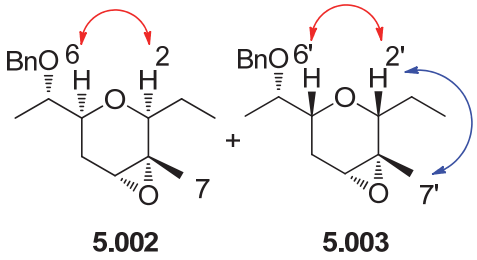


Figure 3

We think that the stereochemistry of these epoxides is the one depicted in figure 3. In fact, there is a strong Noe correlation between H2' and H7' in compound **5.003** which is not present in compound **5.002**. Still, this does not tell us the absolute stereochemistry and the epoxides that were formed could as well be the ones depicted in figure 4.

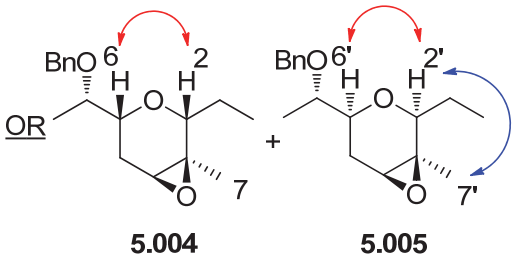
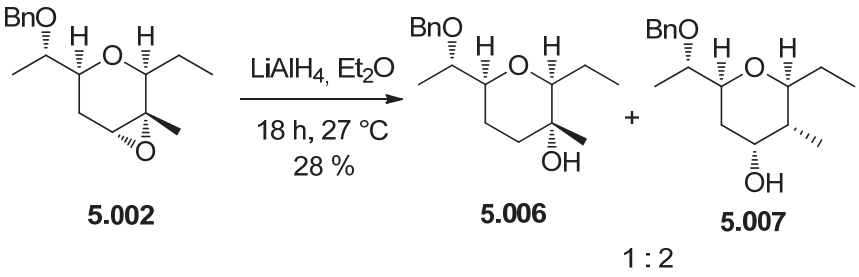


Figure 4

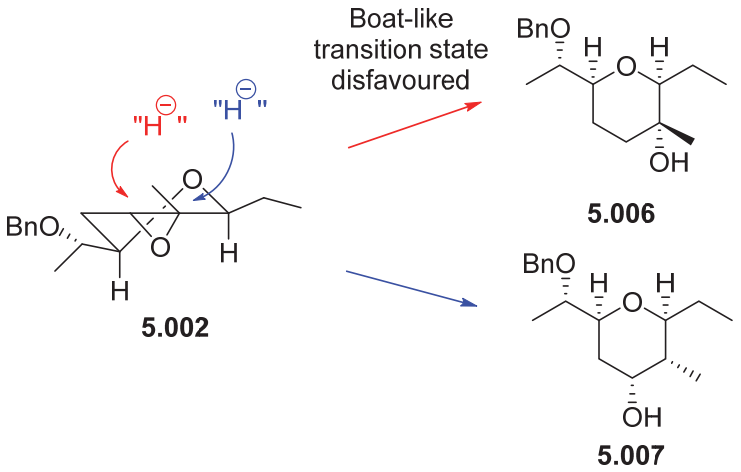
Unfortunately, noesy experiments did not enable us to confirm that unambigously. At this point, for the clarity of the reader, we will consider arbitrarily that epoxides **5.002** and **5.003** were the ones obtained.

Each epoxide was then opened with lithium aluminium hydride. Opening of **5.002** led to a mixture of two products which would not separate. After analysis, it was shown that the hydride opened the epoxide at the C4 position as expected, leading to **5.006**, but also at the C3 position to form THP **5.007** in a 1:2 ratio in favour of the latter (scheme 2).



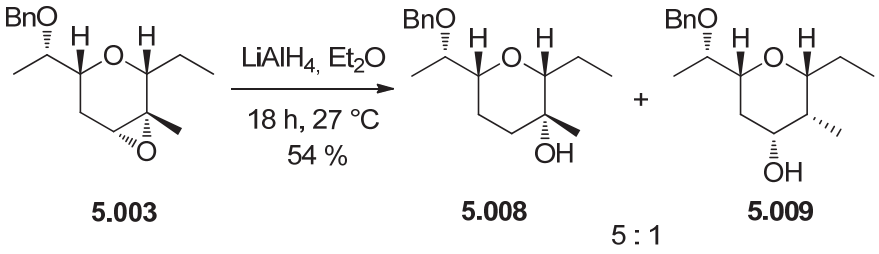
Scheme 2

The preferential formation of THP **5.007** can be explained by the fact that the generation of **5.006** would require the passage through a higher energy boat-like transition state (scheme 3).



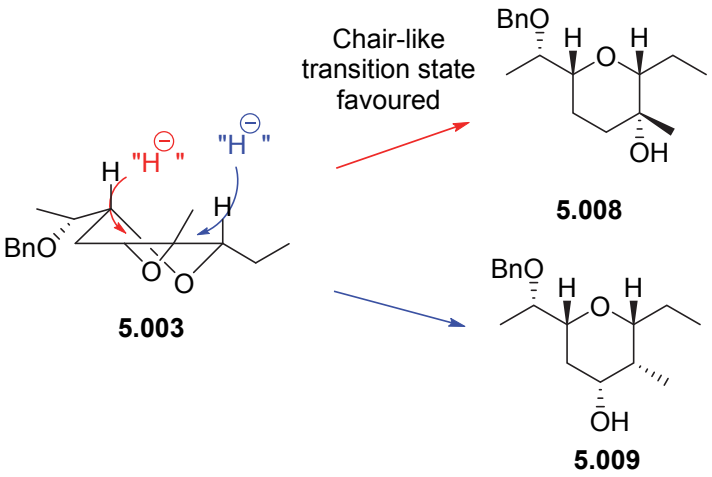
Scheme 3

Opening of **5.003** also led to a mixture of two products in a 5:1 ratio, this time in favour of THP **5.008** which is the desired one. This THP was isolated after silica gel column chromatography in 54 % yield (scheme 4).



Scheme 4

In this case, opening of the epoxide at the C4 position is favoured because it goes through a chair-like transition state, which explains the opposite selectivity from above (scheme 5).



Scheme 5

A Noe effect between the proton at C2 and the methyl group (CH3)7' confirmed their cis relationship, hence the stereochemistry depicted in figure 5.

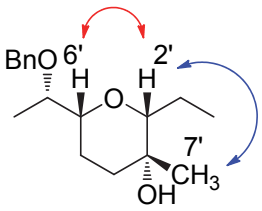


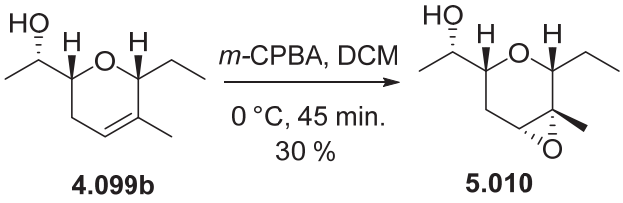
Figure 5

In order to verify the stereochemistry proposed in this section, it was necessary to carry out the same reactions on one single diastereomer.

I.1.2. Epoxidation on one diastereomer

Epoxidation was carried out on the deprotected diastereomer **4.099b** using the same conditions as above (scheme 6). Once again, a major epoxide

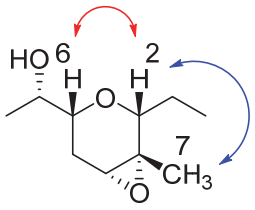
isomer was observed that could be easily isolated in 30 % yield. The ratio was calculated in the crude NMR and is 3.5:1.



4.099b **5.010**

Scheme 6

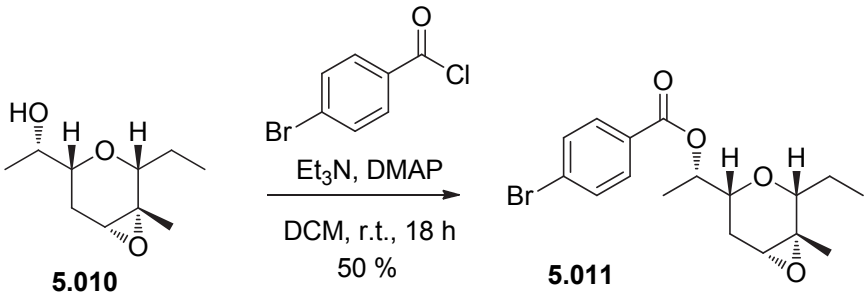
Noesy experiments confirmed once again that the 2,6 protons are *syn* and showed a correlation between H2 and methyl (CH_3)7 suggesting that the epoxide is pointing down (figure 6).



5.010

Figure 6

In order to confirm unambiguously that stereochemistry, the free alcohol was esterified with *p*-bromobenzoyl chloride in the presence of Et_3N and DMAP leading to the desired benzoate **5.011** in moderate yield (scheme 7).



5.010 **5.011**

Scheme 7

Fortunately, ester **5.011** proved to be nicely crystalline. Recrystallisation of the white solid enabled us to obtain a single crystal which was submitted to an X-ray diffraction structure analysis (figure 7).

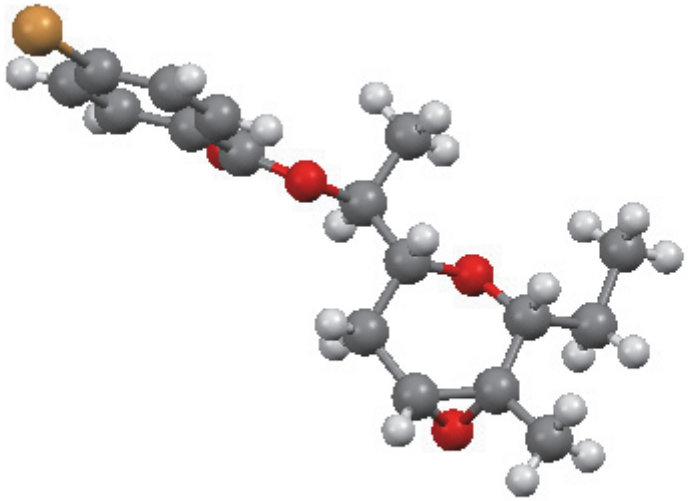


Figure 7

This study confirmed that the epoxide is pointing toward the α-face of the molecule, i.e. *anti* to the 2,6 hydrogens. This was a rather unexpected result since axial approach on the half-chair form of **4.099b** should be little discriminating and if so, should favor the β-epoxide. The selectivity can be explained by the presence of the hydroxyl group, which probably directs the approach of the peracid on the α-face of the alkene (figure 8).

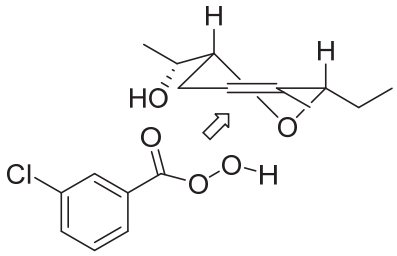
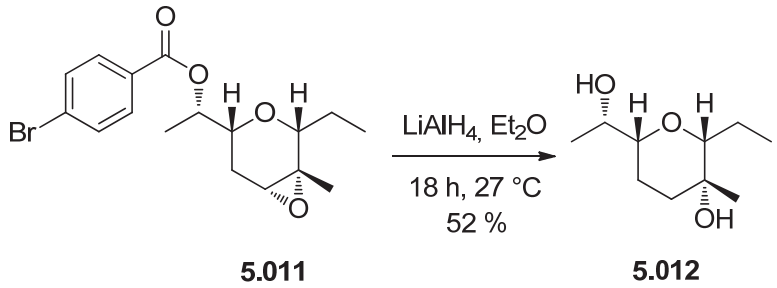


Figure 8

In addition to the stereochemistry of the epoxide, this analysis confirmed all the absolute stereochemistry of the chiral centres present in this molecule, proving unambiguously the 2,6-*syn* stereochemistry and the fact that no epimerization occured during the whole sequence to form this DHP.

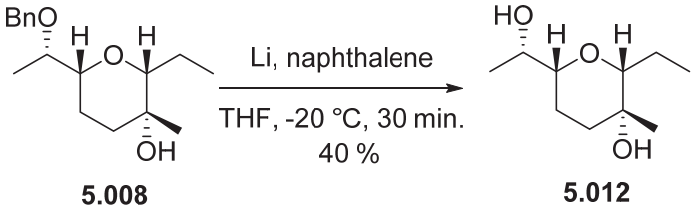
Opening of the epoxide with $LiAlH_4$ afforded the corresponding diol and cleaved ester **5.012** in 52 % yield (scheme 8).



5.011 **5.012**

Scheme 8

At this point, we know unambigously the absolute stereochemistry of compound **5.012**. If compound **5.008** has the stereochemistry we proposed in section 1.I.1, after deprotection, it should be the exact same compound as **5.012**. This experiment was therefore carried out using lithium naphthalenide in moderate yield (scheme 9).

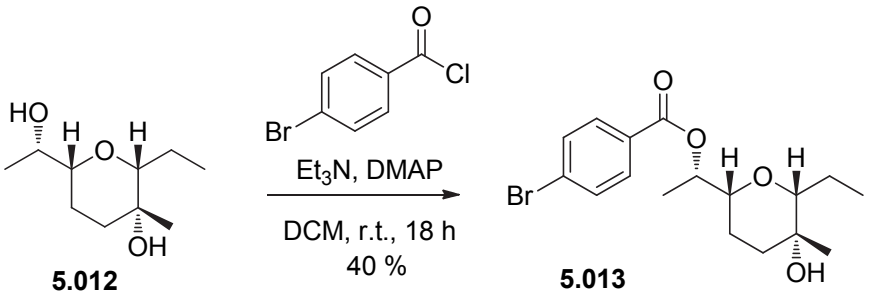


5.008 **5.012**

Scheme 9

Gratifyingly, the exact same compound was obtained, thus confirming the stereochemistry that we proposed earlier. These results prompt us to confirm that the epoxidation of our dihydropyrans using *m*-CPBA is directed by the oxygen as described in figure 8.

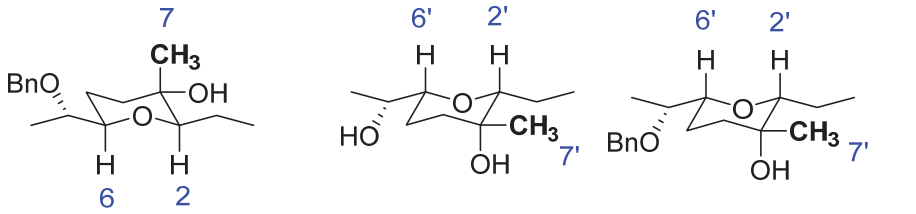
Benzoylation of the secondary alcohol was attempted but the quantities were too small and no single crystal could be obtained (scheme 10).



5.012 **5.013**

Scheme 10

Comparison of the NMR spectra of compounds **5.006**, **5.008** and **5.012** shows that **5.008** and **5.012** have the same relative stereochemistry between hydrogens H2' and H6' and the methyl substituent (CH3)7'; the latter one occupying an equatorial positon (figure 9).



5.006
Me7 = 20.43 ppm ($CDCl_3$)
20.00 ppm (MeOD)

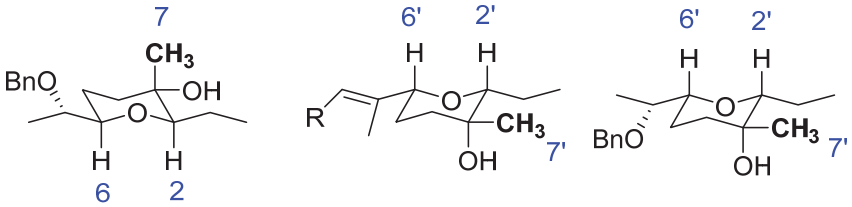
5.012
Me7' = 24.53 ppm ($CDCl_3$)

5.008
Me7' = 24.40 ppm $(CDCl)_3$
25.68 ppm (MeOD)

Figure 9

The methyl group in **5.012** is equatorial. The chemical shift for that equatorial methyl is 24.53 ppm in $CDCl_3$. The chemical shifts for the methyl group in **5.008** are 25.68 ppm in MeOD and 24.40 ppm in $CDCl_3$ respectively, which is thus also equatorial. In contrast, the chemical shift for the methyl of **5.006** is 20.00 ppm in MeOD and 20.43 ppm in $CDCl_3$, thus being axial.

NMR data for natural Jerangolid B describe a chemical shift for that same methyl group of 25.83 ppm in MeOD. Moreover, the values for H2' and C3' in **5.008** are similar to the ones in Jerangolid B (figure 10).



5.006
Me7 = 20.00 ppm
H2 = 87.7 ppm
C3 = 70.43 ppm

Jerangolid B
Me7' = 25.83 ppm
H2' = 86.92 ppm
C3' = 69.28 ppm

5.008
Me7' = 25.68 ppm
H2' = 86.87 ppm
C3' = 69.46 ppm

All these values are in MeOD

Figure 10

These values prompt us to suggest that the methyl group in jerangolid B occupies an equatorial position whilst the –OH function is axial, as indicated in figure 11.

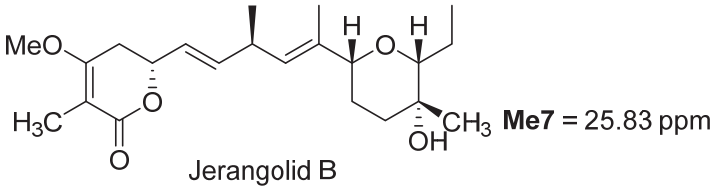
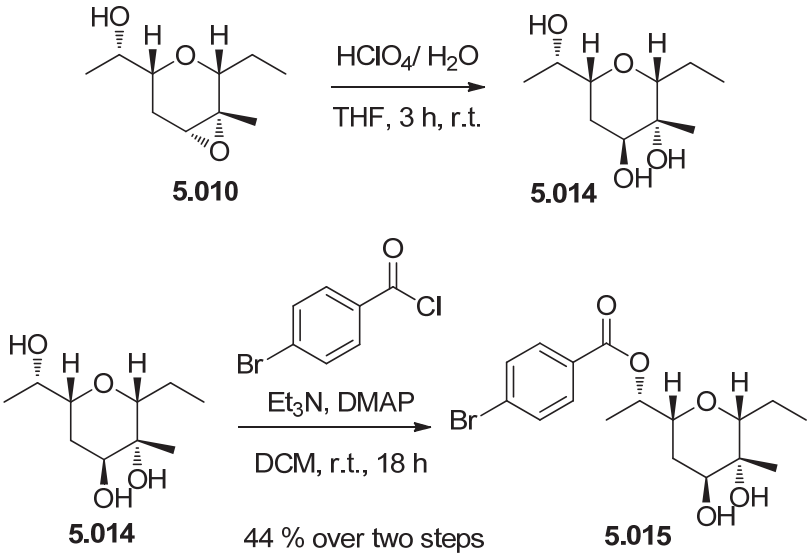


Figure 11

Opening of the epoxide was also carried out using $HClO_4$ in water[1]. Further benzoylation with *para*-bromobenzoyl chloride afforded the desired product as a white solid in 44 % yield over the two steps (scheme 11).

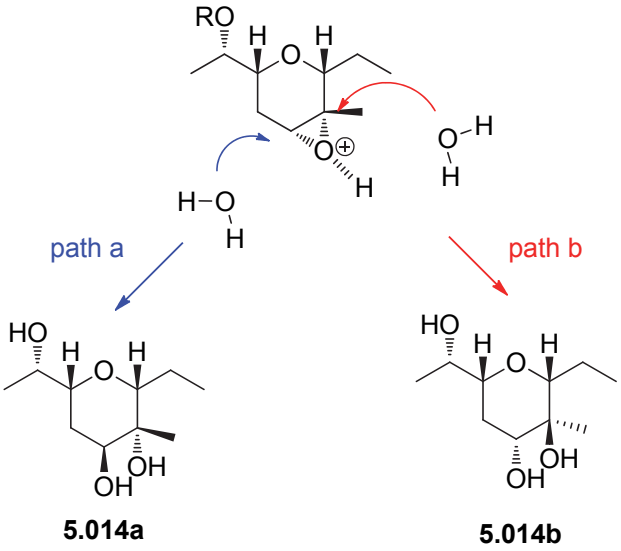


Scheme 11

However, the stereochemistry obtained for diol **5.014** and its derived ester **5.015** was the opposite of what was expected based upon the mechanism of

[1] I. C. González, C. J. Forsyth, *J. Am. Chem. Soc.* **2000**, *122*, 9099-9108.

this reaction (scheme 12). In fact, in acidic media, the reaction mechanism goes through the formation of a carbocation, which is favoured on tertiary carbon centers. For that reason, path b was expected.



5.014a **5.014b**

Scheme 12

If compound **5.014b** was formed, a large axial-axial coupling constant between H4' and H5' should be observed. However, the very small coupling constant (J = 2.85Hz) between H4 and H5 indicates that H4 can not be axial, thus should be equatorial with the secondary alcohol *anti* to the tertiary one (figure 12).

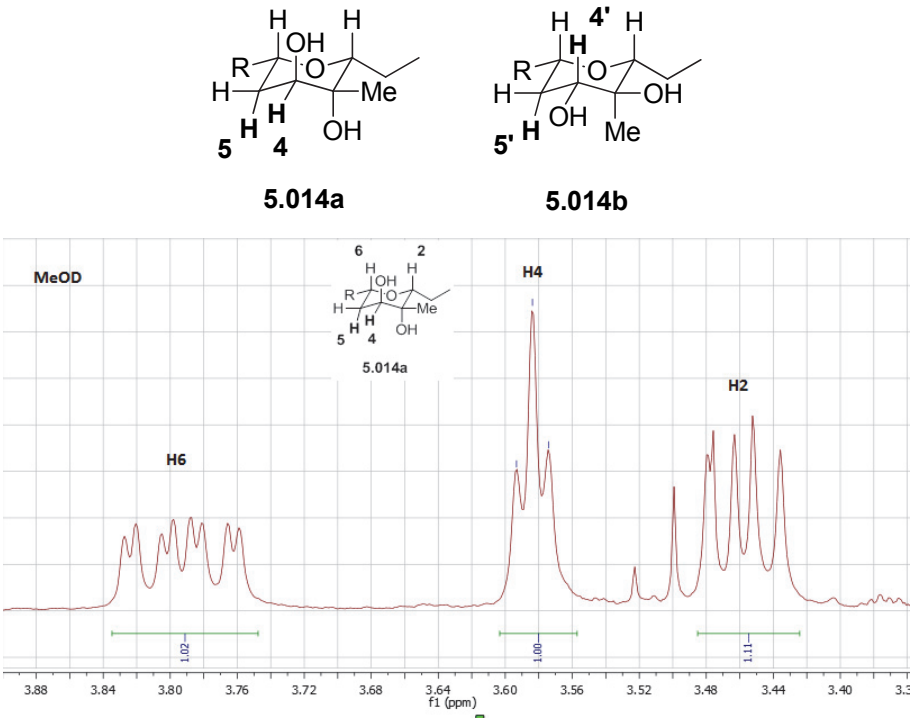
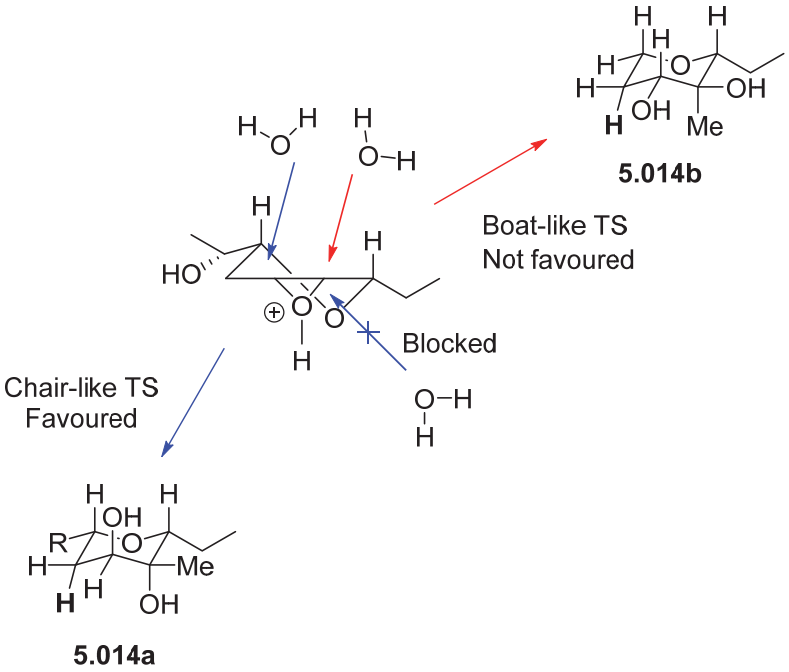


Figure 12

This selectivity can be explained by the fact that this molecule is a rigid system and the Furst-Platner rule can be applied (scheme 13). The approach going through a chair-like transition state is favoured, thus leading to the formation of compound **5.014a**.



Scheme 13

Noesy experiments confirmed this stereochemistry. Correlation between H2 and H6 as well as between H2 and Me3 confirms their *syn* relationship. H4 correlates with Me3 which is normal because they are both in equatorial position (figure 13).

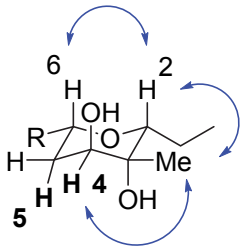
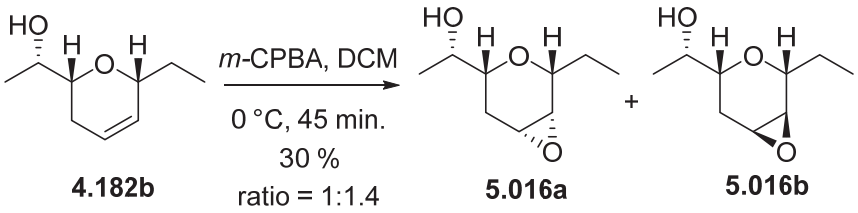


Figure 13

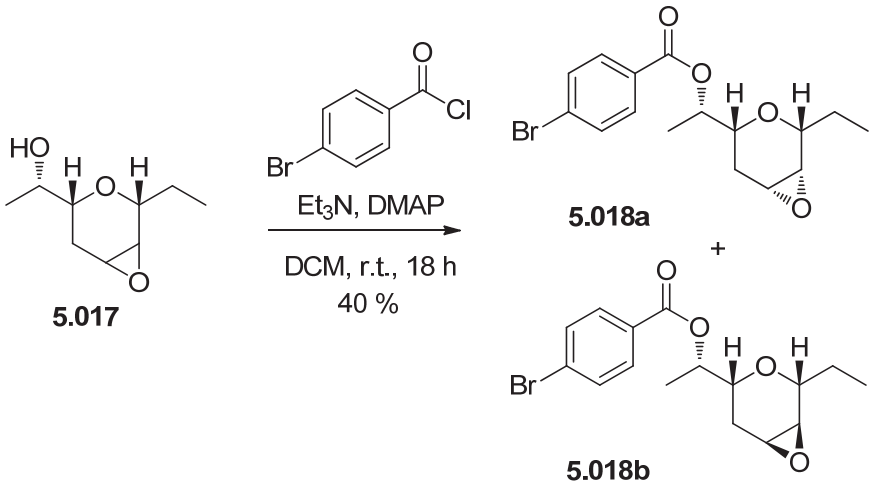
Epoxidation was also carried on DHP **4.182b** bearing no methyl group at position C3. In this case, the yield was low and the ratio between the two epimers of the epoxide is 1:1.4 (scheme 14). At this stage, compounds **5.016a** and **5.016b** could not be separated.



4.182b **5.016a** **5.016b**

Scheme 14

The mixture of the two diastereomers was then benzoylated in moderate yield and the resulting esters were easily separated by silica gel column chromatography (scheme 15).



5.017 **5.018a** **5.018b**

Scheme 15

Comparison of the ^{1}H NMR spectra of epoxides **5.018a** and **5.018b** gave us some information about the stereochemistry of the epoxides. Unfortunately, the coupling constants did not help us because in both molecules, H4 and H9 do not see each other. However, when examining H7, there is a difference of

chemical shift between the equatorial and the axial protons between the two compounds. In **5.018a**, H7eq has a chemical shift of 2.16 ppm and H7ax of 1.76 ppm whilst in **5.018b**, H7'eq has a chemical shift of 1.95 ppm and H7ax of 1.83 ppm (figure 14). Comparison of these values with the ones obtained for epoxide **5.003** which has been demonstrated earlier to be α , in which H7eq has a chemical shift of 2.14 ppm and H7ax of 1.75 ppm prompt us to propose that epoxide **5.018a** is also α.

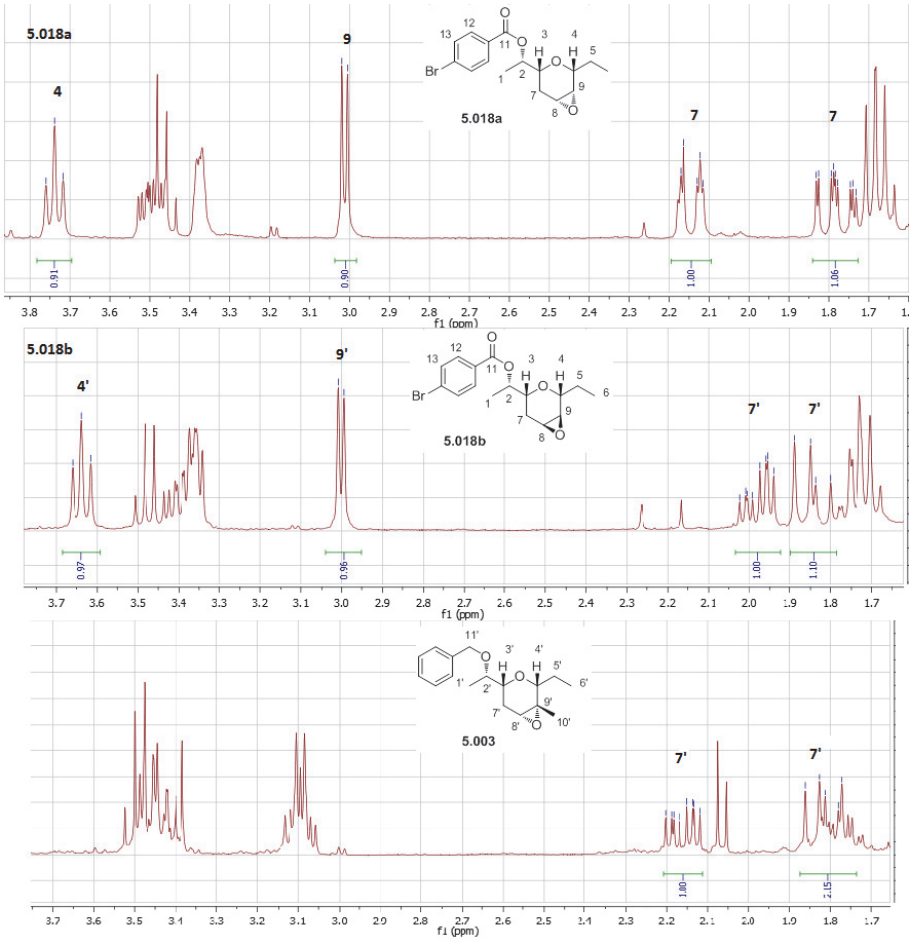


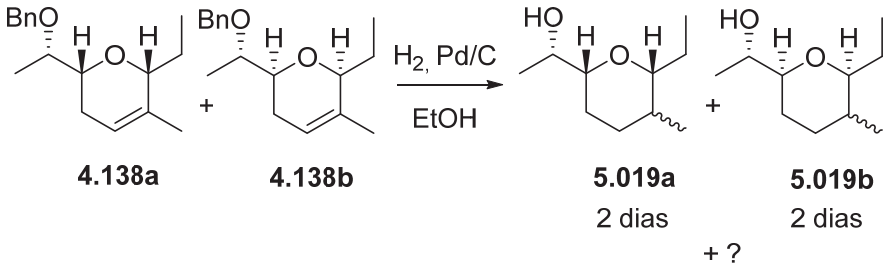
Figure 14

Recrystallisation of each diastereomer was attempted to confirm the absolute stereochemistry of both epoxides but unfortunately, no single crystals could be obtained.

We then turned our attention to the synthesis of the right-hand THP of jerangolid E and H through hydrogenation of the double bond of DHP **4.138**.

I.2. Right-hand subunit of jerangolid E and H

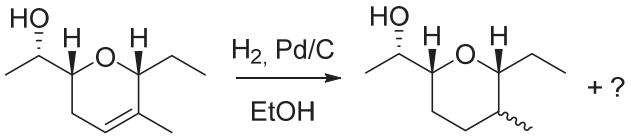
Dihydropyran **4.138a** and its isomer **4.138b** were therefore hydrogenated in the presence of palladium on charcoal. If the reaction is not stereoselective, four diastereomers are expected. Much to our surprise, five isomers were observed in ^{1}H and ^{13}C NMR. Each product contains the free alcohol (scheme 16).



Scheme 16

Chiral GC analysis, after purification by silica gel column chromatography, confirmed the presence of five different molecules.

In order to understand what happened and to simplify the spectra, hydrogenation was carried out using the same conditions as described above, but on the pure diastereomer **4.099b** (scheme 17).



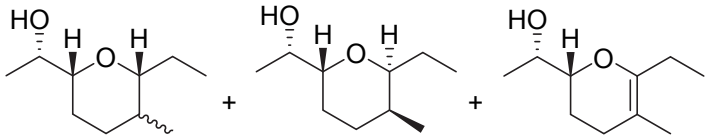
4.099b **5.019a**

2 dias

Scheme 17

In this case, three diastereomers were observed and isolated as well as a compound containing a tetrasubstituted double bond **5.021** (figure 15).

The free alcohol was then oxidized to the corresponding ketone in a NMR tube to remove the chiral centre at C8. The resulting mixture of products was analyzed by chiral GC analysis and three different diastereomers were still present, showing that the third product did not come from epimerization at C8. The three diastereomers are thus the ones drawn in figure 14.



5.019 **5.020** **5.021**

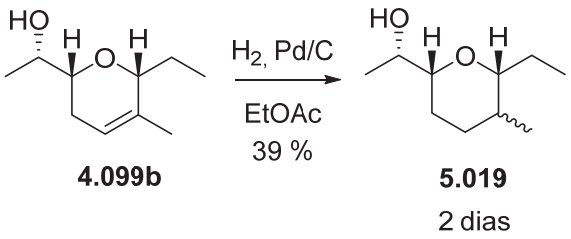
Figure 15

These hydrogenation conditions thus appear to promote the migration of the double bond to the C2-C3 position which can migrate back and then further be hydrogenated, leading to the observed epimerization at the C2 position in compound **5.020**.

To avoid this problem, ethanol was replaced by ethyl acetate as the solvent of the reaction[2]. To our delight, changing the solvent led to the formation of only two diastereomers though in low yield (scheme 18).

---

[2] N. K. Garg, D. D. Caspi, B. M. Stoltz, *J. Am. Chem. Soc.* **2004**, *126*, 9552-9553.



Scheme 18

The two epimers could not be separated by silica gel column chromatography. However, careful analysis of the NMR spectra allowed us to attribute the signals to each diastereomer. This attribution enabled us to define the stereochemistry at the newly formed chiral centre for each isomer. The methyl group Me7 displays very different chemical shifts between the two compounds in ^{13}C NMR. Me7 has a chemical shift of 11.46 ppm in $CDCl_3$ whilst Me7' appears at 17.88 ppm (figure 16).

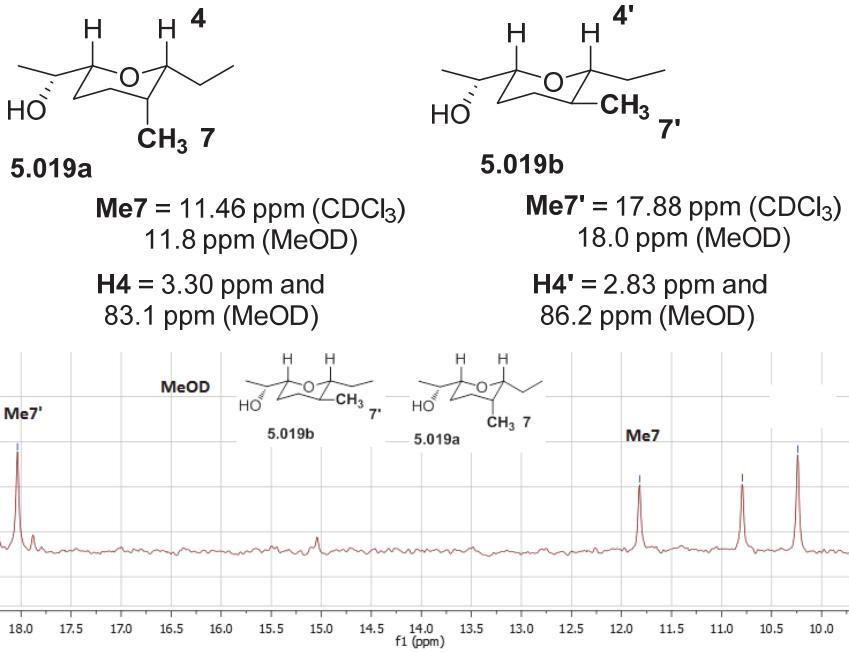


Figure 16

A literature search enabled us to find two examples describing the same types of THP rings. In the total synthesis of tetronomycin, the group of Yoshii synthesized the two epimers at C3 of THP **5.022** and **5.023**[3] (figure 17).

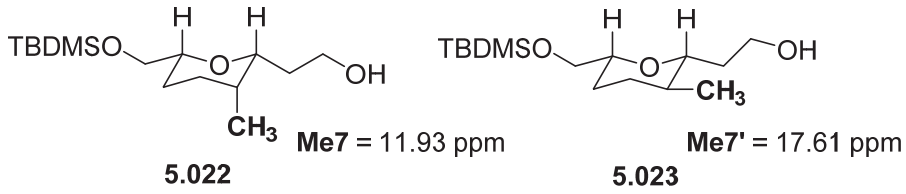


Figure 17

The axial methyl substituent possesses a chemical shift of 11.93 ppm whilst the equatorial methyl appears at 17.61 ppm in $CDCl_3$.

Schneider also synthetized highly substituted THP rings[4]. In the case of compounds **5.024** and **5.025**, the axial methyl group has a chemical shift of 12.6 ppm whilst the equatorial methyl group is present at 17.5 ppm in $CDCl_3$ (figure 18).

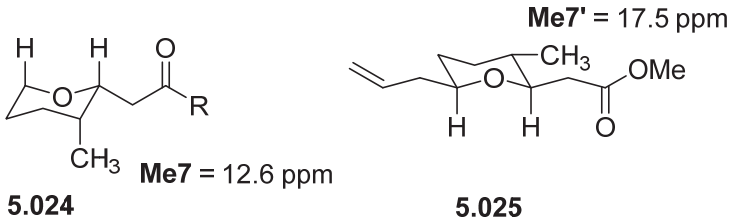


Figure 18

In jerangolid E, the chemical shift for the methyl group at C14 is 17.98 ppm in MeOD. NMR spectra of coumpounds **5.019a** and **5.019b** were also

---

[3] K. Hori, N. Hikage, A. Inagaki, S. Mori, K. Nomura, E. Yoshii, *J. Org. Chem.* **1992**, *57*, 2888-2902.

[4] C. Schneider, A. Schuffenhauer, *Eur. J. Org. Chem.* **2000**, 73-82.

measured in MeOD and the chemical shifts were 11.81 ppm and 18.03 ppm, respectively.

Moreover, as shown in figure 15, H4' in **5.019a** has a chemical shift of 3.30 ppm in ^{1}H and 83.1 ppm in ^{13}C NMR in MeOD whilst H4 in **5.019b** (in which the methyl is equatorial) has a chemical shift of 2.83 ppm in ^{1}H and 86.19 ppm in ^{13}C NMR in MeOD. In Jerangolid E, the same proton has a chemical shift of 2.87 ppm in ^{1}H and 85.92 ppm in ^{13}C NMR in MeOD.

All these informations prompt us to propose that the methyl group in jerangolid E occupies the equatorial position. The full structure of jerangolid E is thus shown in figure 19.

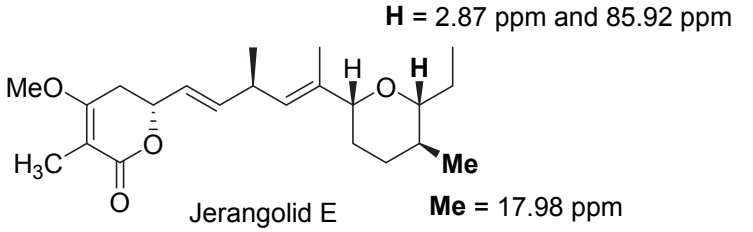


Figure 19

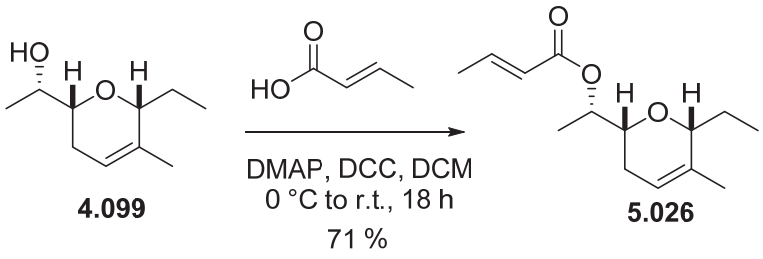
In conclusion, the modifications we have performed on our previously prepared DHPs have allowed us to determine the absolute stereochemistry of jerangolid B, E and H as well as to synthetize new analogues of the right-hand part of the jerangolids.

II. Esterifications

As stated in the objectives, since the dihydropyran moiety is also present in ambruticin, we wanted to synthetize different esters starting from DHP **4.099** in order to mimic the rest of the molecule.

The strategy is always the same, using DCC and DMAP as coupling agents between alcohol **4.099** and different commercially available acids.

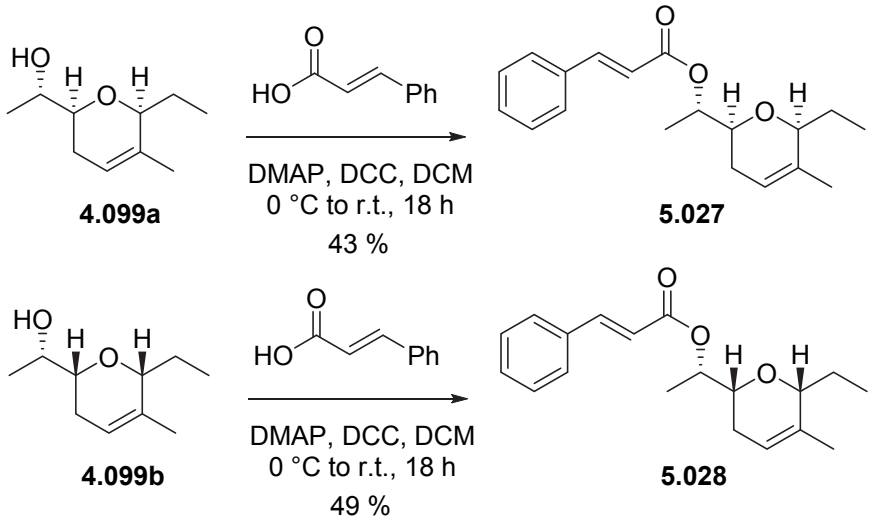
Coupling with crotonic acid afforded the desired DHP **5.026** in good yield (scheme 19).



Scheme 19

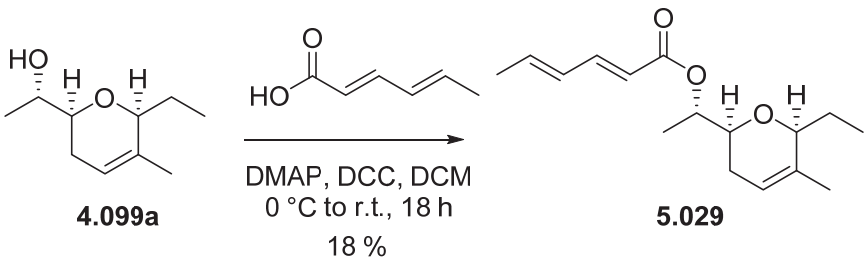
The two diastereomers were then separated by silica gel column chromatography.

Cinnamic acid was also used as the coupling agent and the reaction was performed on each diastereomer separately (scheme 20).



Scheme 20

Finally, diastereomer **4.099a** was coupled with hexa-2,4-dienoic acid in low yield after two purifications by silica gel column chromatography (scheme 21).

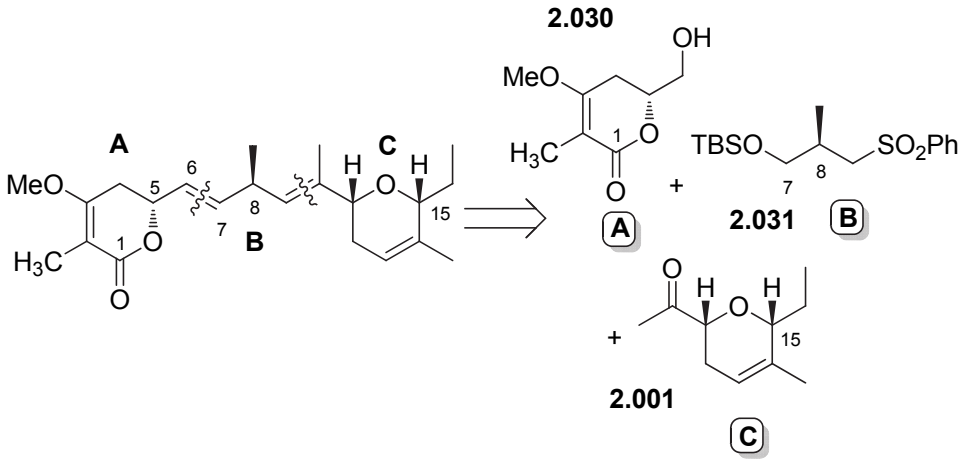


Scheme 21

In conclusion, five new molecules, mimics of jerangolid D, have been successfully synthetized. These compounds shall be submitted to biological evaluation in order to estimate their potential antifungal activities.

LACTONE SYNTHESIS

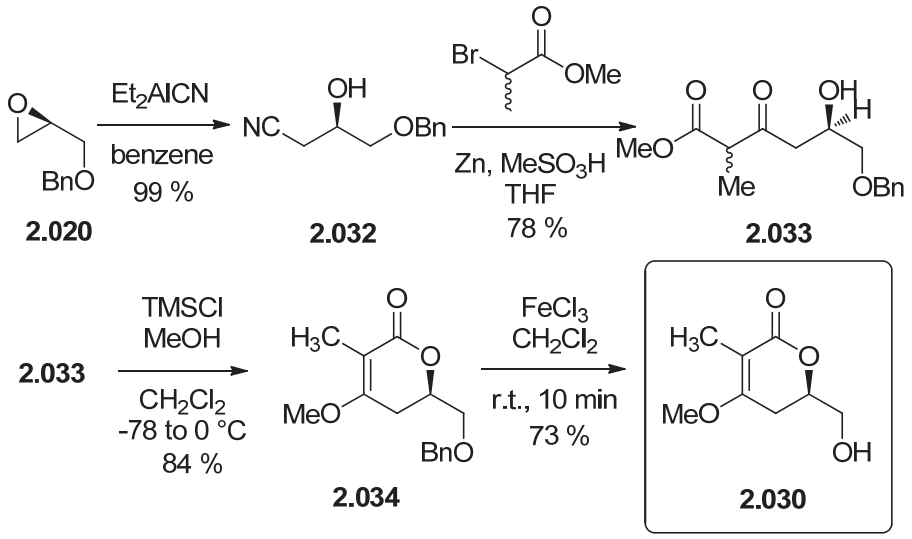
At this point, numerous subunits of Dihydropyran **C** have been obtained. It was thus time to prepare lactone **A** in order to possess both fragments that are needed to assemble the jerangolids and their analogues.



Scheme 1

I. Lactone synthesis

The route we followed to access lactone **2.030** for our total synthesis of jerangolid D was described in chapter two and is presented again in scheme 2.



Scheme 2

A couple of modifications had to be made to this strategy for the following reasons:

- (*R*)-benzylated glycidol is particularly expensive.
- Et_2AlCN is no longer commercially available.

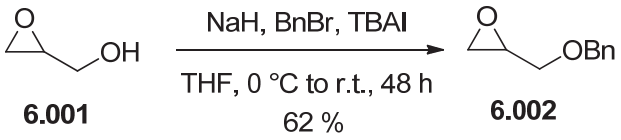
For these reasons, (*S*)-glycidol was protected using benzyl bromide and Et_2AlCN was replaced by KCN. Moreover, the setup and optimisation of the sequence was first carried out with racemic glycidol before being applied to the optically pure starting material.

Each step will be described in this section. It should be noted that this work has been done in collaboration with two master students, Sophie Moreau and Jean-François Body. The Blaise reaction was subsequently optimized by Damien Dewez.

I.1. Glycidol protection

Racemic glycidol **6.001** was deprotonated with sodium hydride (NaH). The resulting alkoxide was reacted with benzyl bromide (BnBr) in the presence

of tetrabutylammonium iodide (TBAI)[1] to afford protected glycidol **6.002** in 62% yield (scheme 3). Addition of TBAI is believed to lead to the *in situ* generation of benzyl iodide by substitution of the bromine atom by iodide (Finkelstein reaction), which is a better leaving group. The SN_2 reaction should thus be facilitated.



6.001 **6.002**

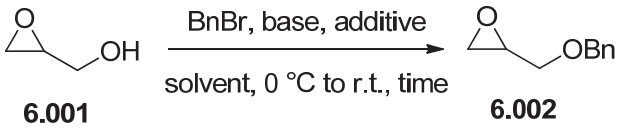
Scheme 3

Due to the moderate yield in ether **6.002**, some modifications were implemented. First, THF was replaced by DMF[2] (table 1, entry 2). The use of this polar solvent reduced the reaction time to 16 hours but did not alter the yield. Removal of TBAI lowered the yield to 38 % (table 1, entry 3), whilst changing the base to NaHMDS only gave 48 % yield (table 1, entry 4).

---

[1] S. Czernecki, C. Georgoulis, C. Provelenghiou, *Tetrahedron Lett.* **1976**, *17*, 3535-3536.

[2] R. Barbe, J. Hasserodt, *Tetrahedron* **2007**, *63*, 2199-2207.



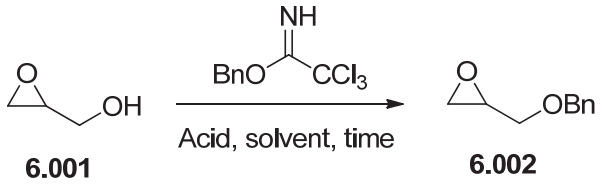
6.001 **6.002**

Entry	Additive	Base	Solvent	Time (h)	Yield (%)
1	TBAI	NaH	THF	48	62
2	**TBAI**	**NaH**	**DMF**	**16**	**62**
3	/	NaH	DMF	16	38
4	TBAI	NaHMDS	DMF	16	48

Table 1

Unfortunately, we were not able to further improve the yield under basic conditions.

In order to protect the glycidol under acidic conditions, benzyl bromide was replaced by trichloro acetamide, this reagent, in conjunction with an acid catalyst, has been employed in chapter 4 for the protection of ethyl lactate (table 2).



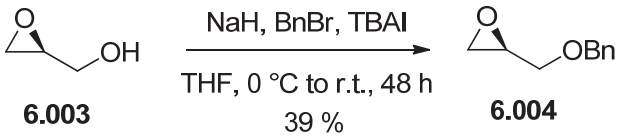
6.001 **6.002**

Entry	Solvent	Acid	Time (h)	Yield (%)
1	EP	$MeSO_3H$	48	0
2	DCM	$MeSO_3H$	16	0
3	DCM / EP (1 : 1)	TfOH	18	0

Table 2

Surprisingly, these conditions did not afford the desired product **6.002**. In all cases, the starting material was recovered at the end of the reaction.

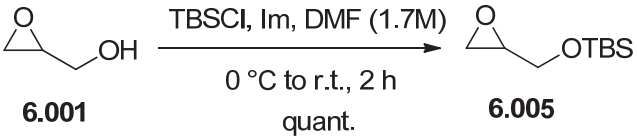
Finally, the former system was kept and used to protect enantiomerically pure glycidol **6.003** (scheme 4). Nonetheless, for some unknown reason, the yield was even lower than in the case of racemic glycidol.



6.003 **6.004**

Scheme 4

Glycidol was also protected with a TBS group in quantative yield as an alternative to the moderate yield obtained with the benzyl group (scheme 5).



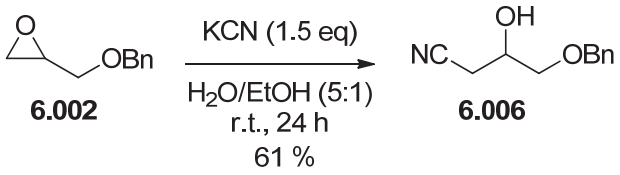
6.001 **6.005**

Scheme 5

I.2. Opening of the epoxide

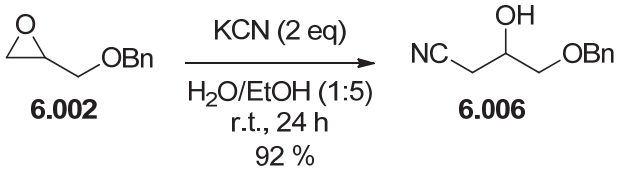
As mentioned earlier, new conditions for the opening of the epoxide had to be found since Et_2AlCN is no longer commercially available. The use of KCN in a mixture of $EtOH/H_2O$ afforded the corresponding nitrile **6.006** in moderate yield[3] (scheme 6).

[3] A. Kamal, G. B. Ramesh Khanna, *Tetrahedron: Asymm.* **2001**, *12*, 405-410.



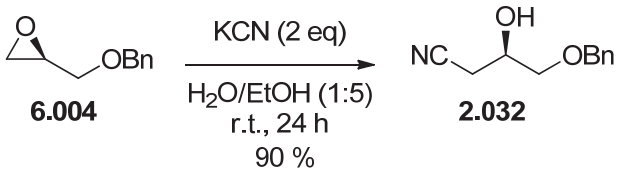
Scheme 6

Changing the ratio of solvent and increasing the number of equivalents of KCN led to a remarkable increase in the yield and nitrile **6.006** could be isolated in up to 92 % (scheme 7).



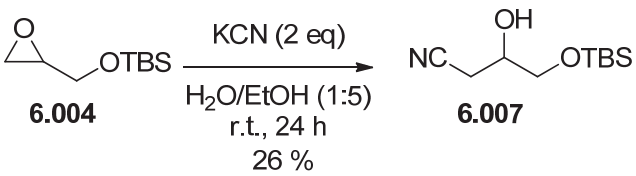
Scheme 7

These conditions were then applied to the enantiomerically pure epoxide **6.004**. Again, adduct **2.032** was obtained with an excellent yield (scheme 8).



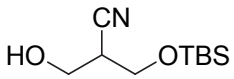
Scheme 8

The TBS protected glycidol was also treated under the same conditions. However, product **6.007** was isolated in moderate yield (scheme 9).



Scheme 9

Alcohol **6.008** was identified as a minor side product but its formation does not explain the low recovery of **6.007** (figure 1). One plausible explanation lies in the deprotection of the TBS group under these conditions, leading to glycidol **6.001**, which is extremely soluble in water, and would be lost during the work-up.



6.008

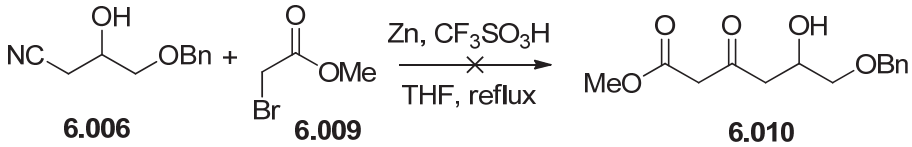
4%

Figure 1

Nitrile **6.006**, being readily prepared, can now be used in the next step which is a Blaise reaction. This transformation involves the addition of an organozinc reagent on a nitrile, affording, after hydrolysis, a β-ketoester.

I.3. Blaise reaction

The reaction was first carried out using methyl bromoacetate under the conditions described in scheme 10. Methanesulfonic acid was replaced by trifluoromethanesulfonic acid which should play the same activating role for zinc[4]. Unfortunately, the β-ketoester was not formed at all and the starting material was recovered (scheme 9).

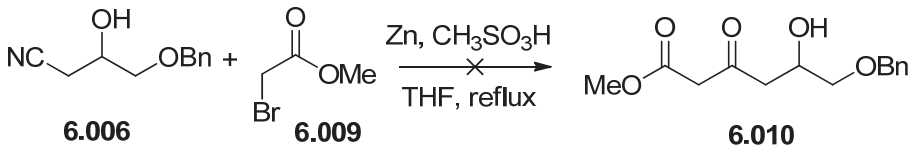


6.006 **6.009** **6.010**

Scheme 10

[4] H. Shin, B. S. Choi, K. K. Lee, H.-w. Choi, J. H. Chang, K. W. Lee, D. H. Nam, N.-S. Kim, *Synthesis* **2004**, 2629-2632.

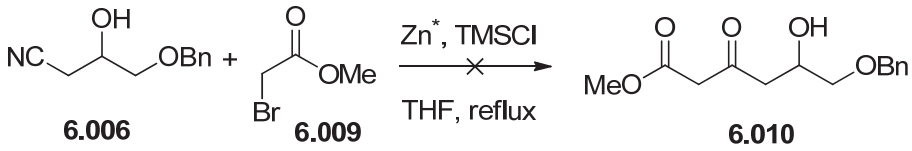
From this result, it appears that changing the acid might not have been a good idea. Thus, we repeated the reaction, using methanesulfonic acid and 20 mesh zinc[5]. Once again, the starting material was recovered (scheme 11).



6.006 **6.009** **6.010**

Scheme 11

The literature provides numerous methods for the activation of zinc to be used in the generation of organozinc derivatives. Among these, a procedure describing a pre-activation of the zinc by HCl was selected[6]. These conditions were then applied to our substrate but once again failed to deliver the desired product (scheme 12).



6.006 **6.009** **6.010**

Scheme 12

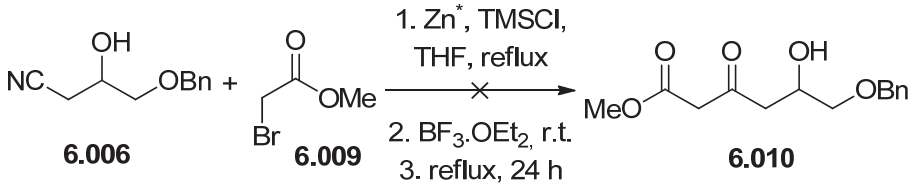
After having changed different parameters such as the granulometry of zinc, the activation method and the reaction time, we suspected a problem in the activation of the nitrile. For that reason, the use of BF_3-etherate, a Lewis acid known to bind to the nitrogen atom of nitriles[7], and hence make them more electrophilic was attempted. Unfortunately, no conclusive result could be obtained (scheme 13).

---

[5] 20 mesh is the granulometry of the zinc.

[6] X. Gao, M. Nakadai, B. B. Snider, *Org. Lett.* **2003**, *5*, 451-454.

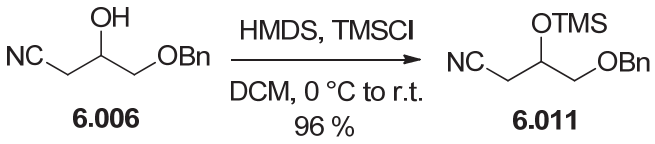
[7] J. L. Fry, R. A. Ott, *J. Org.Chem.* **1981**, *46*, 3333-3335.



Scheme 13

In desperation, we wondered if the free alcohol present on the nitrile might interfere with the reaction, by preventing the formation of the zincate or by protonating it before it has time to react. Indeed, although a couple of reactions are described in the literature in which a free alcohol is present in the substrate[8], in the majority of cases, the function is initially first protected with a TMS[4,9] or TBS[10] group.

Thus, alcohol **6.006** was protected with a TMS group almost quantitatively as described in scheme 14.



Scheme 14

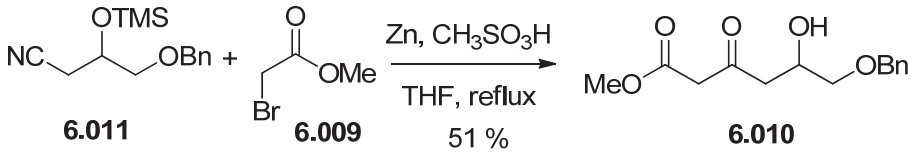
Conditions reported in the literature[4] were applied to nitrile **6.011**. Gratifyingly, the desired compound **6.010** could be obtained, though in moderate yield (scheme 15).

---

[8] a. F.-D. Wang, J.-M. Yue, *Synlett* **2005**, 2077-2079 b. T. Kyoko, M. Tatsuya, O. Yoshio, H. Tamejiro, *Tetrahedron Lett.* **1993**, *34*, 8263-8266.

[9] J. Syed, S. Förster, F. Effenberger, *Tetrahedron: Asymm.* **1998**, *9*, 805-815.

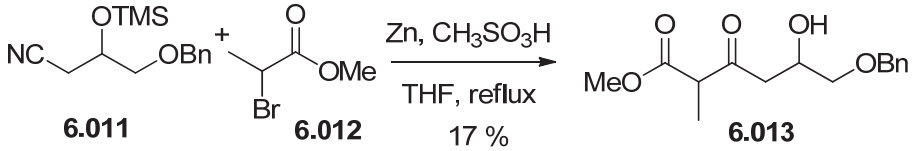
[10] J. H. Kim, H. Shin, S.-g. Lee, *J. Org. Chem.* **2012**, *77*, 1560-1565.



6.011 **6.009** **6.010**

Scheme 15

Encouraged by this result, we tested these conditions with 2-methyl bromopropanoate **6.012**. The desired β-ketoester **6.013**, necessary for the synthesis of the natural product, was formed but the yield was poor (scheme 16) and an important quantity of the deprotected nitrile was recovered.

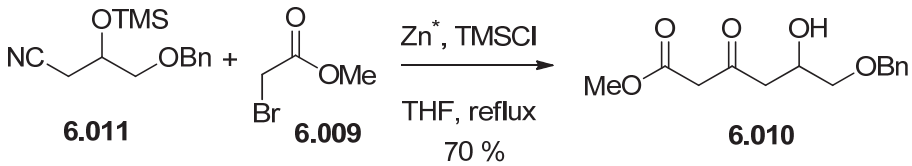


6.011 **6.012** **6.013**

Scheme 16

Different tests were then performed to evaluate the reproducibility of this key-transformation. A decrease in the yield indicates that these conditions are not optimal for the preparation of compound **6.013**. This can be explained by the fact that the TMS group is sensitive towards very acidic conditions. Therefore, if an important quantity of acid (useful for the activation of zinc) remains in the reaction, the silyl ether can be deprotected, leading to the free alcohol, which inhibits the process, as described earlier. To solve this problem, the zinc was pre-activated using HCl and then washed carefully with water, ethanol and diethyl ether to remove any traces of acid then dried under vacuum.

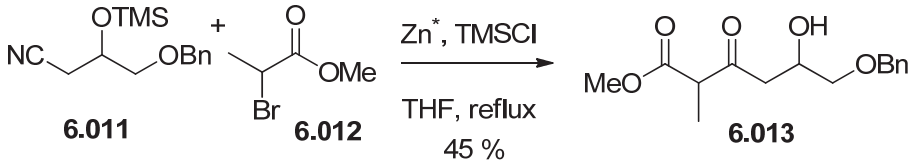
These precautions enabled us to prepare β-ketoester **6.010** in 70 % yield (scheme 17).



6.011 **6.009** **6.010**

Scheme 17

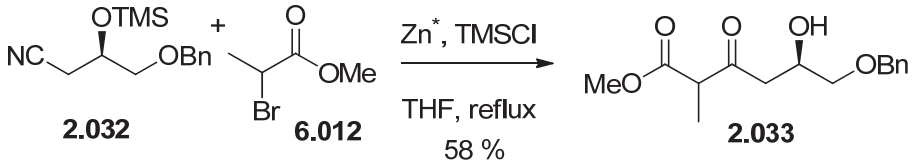
These conditions were subsequently applied to the coupling between substrate **6.011** and the less reactive α-bromopropanoate **6.012**. As expected, compound **6.013** was formed in moderate yield (scheme 18).



6.011 **6.012** **6.013**

Scheme 18

Optimisation of the workup as well as neutralising the silica before purification allowed us to isolate the desired product in 57 % yield reproducibly and on several grams scale. These conditions were successfully applied to the enantiomerically pure nitrile **2.032** to afford the desired β-ketoester **2.033** needed for the total synthesis of jerangolid D in 58 % yield (scheme 19).



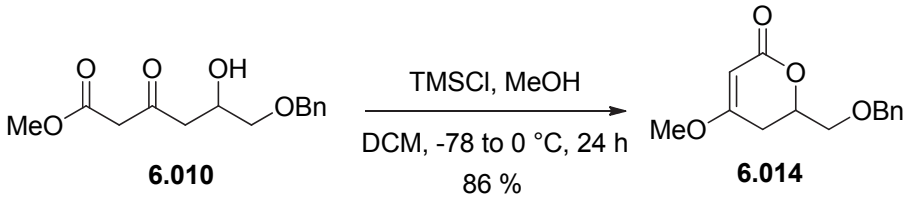
2.032 **6.012** **2.033**

Scheme 19

The β-ketoesters were finally engaged in the next step in order to accomplish the cyclisation and thus obtain the desired protected lactones akin to the western subunit of jerangolid D and its analogues.

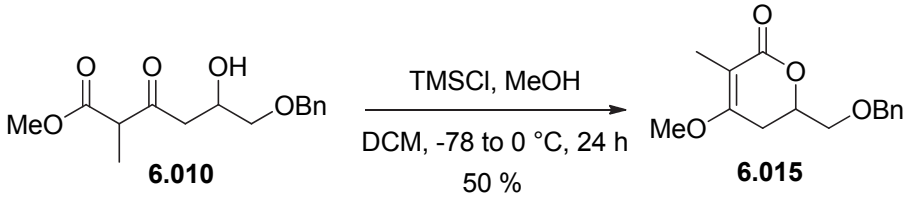
I.4. Lactonization and deprotection

β-ketoester **6.010** was cylised in the presence of TMSCl and an excess of methanol to afford lactone **6.014** in 86 % yield (scheme 20).



Scheme 20

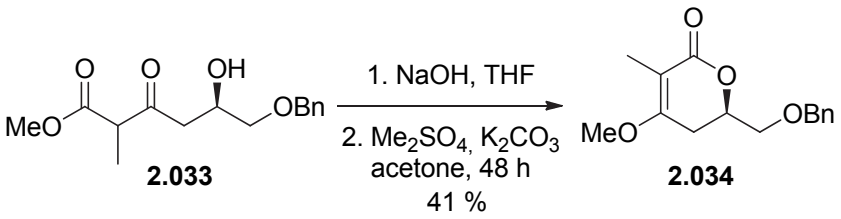
Substrate **6.013** was also cyclized under these conditions to form lactone **6.015**, though in a lower yield (scheme 21).



Scheme 21

Other conditions were also investigated to cyclise β-ketoester **2.033**. For example, lactonization using sodium hydroxide, followed by methylation of the resulting β-ketolactone with dimethyl sulfate and potassium carbonate[11] afforded lactone **2.034** in 41 % yield (scheme 22).

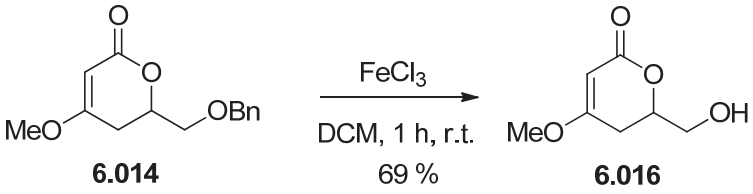
[11] H. Hagiwara, K. Kimura, H. Uda, *J. Chem. Soc., Perkin Trans. 1* **1992**, 693-700.



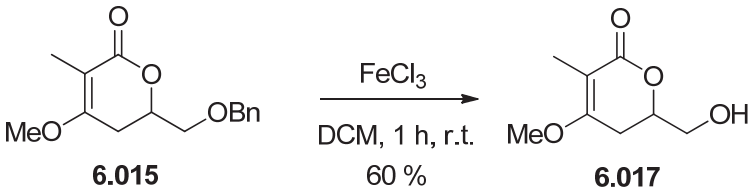
Scheme 22

In summary, protected lactone **2.034**, a direct precursor of the lactone fragment of jerangolid D, has been synthetized in four steps with an overall yield of 15.5 %.

These lactones could be further deprotected, using iron trichloride, as described in our total synthesis of jerangolid D. These conditions enabled us to isolate the corresponding hydroxy lactones **6.016** and **6.017** in good yields (schemes 23 and 24).



Scheme 23



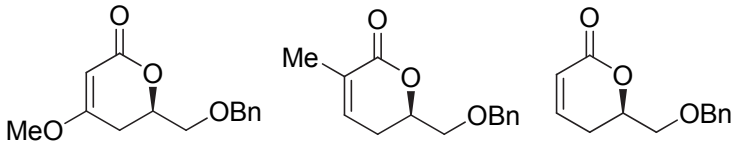
Scheme 24

These conditions still need to be applied to lactone **2.034** but should not be a problem.

These lactones could then be oxidized and coupled to the rest of the molecule using a Julia-Kocienski olefination.

II. Lactone analogues

As stated in the objectives, we wanted to synthesise three analogues of the lactone moiety of jerangolid D (figure 2). The racemic version of lactone **3.009** has already been prepared during our study of the Blaise reaction.



3.009 **3.010** **3.011**

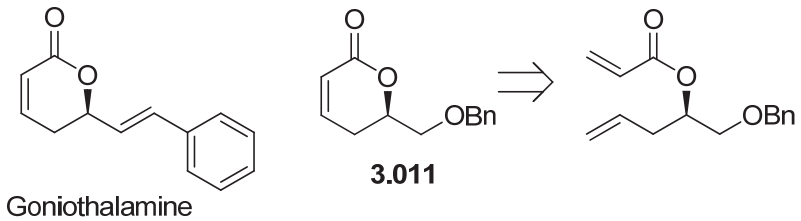
Figure 2

The syntheses of lactones **3.010** and **3.011** will be described in this section.

II.1. Synthesis of lactone 3.011

II.1.1. Via ring closing metathesis

Our approach to the synthesis of lactone **3.011** is based on a strategy used for the total synthesis of the natural product goniothalamine **6.018** by Dr. Pospisil[12] (figure 3). The key step of this sequence is a ring closing metathesis.



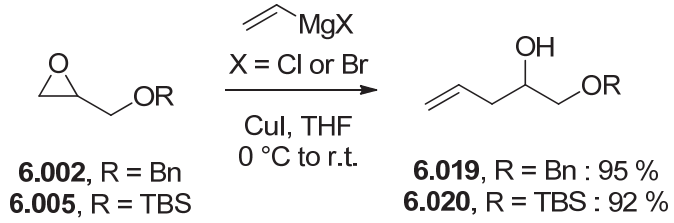
Goniothalamine
6.018

3.011

Figure 3

[12] J. Pospíšil, I. E. Markó, *Tetrahedron Lett.* **2006**, *47*, 5933-5937.

The synthesis begins from the protected epoxides **6.002** and **6.005** described at the beginning of this chapter. The oxirane function of protected glycidols **6.002** and **6.005** was opened with a vinyl Grignard in the presence of a copper (I) salt to form the homoallylic alcohols **6.019** and **6.020** in excellent yields (scheme 25).



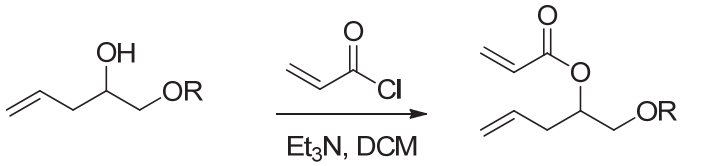
6.002, R = Bn
6.005, R = TBS

6.019, R = Bn : 95 %
6.020, R = TBS : 92 %

Scheme 25

Copper iodide is added to the reaction in catalytic quantities to form the corresponding cuprate. The latter is more nucleophilic and less basic than the Grignard reagent, reacting regioselectively, through an SN_2 mechanism, on the less substituted carbon centre of the oxirane function. Moreover, the nature of the halogen in the Grignard reagent is of no importance since both of them afford the desired product in similar yields.

Esterification of both homoallylic alcohols with acryloyl chloride in the presence of Et_3N leads to the formation of dienes **6.021** and **6.022** in good yields (scheme 26).

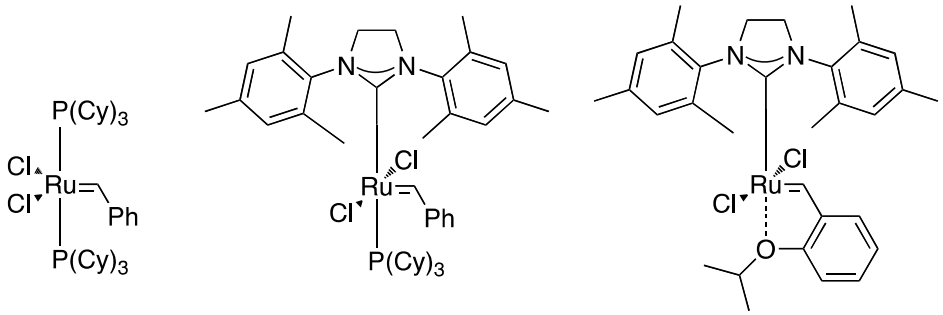


6.019, R = Bn
6.020, R = TBS

6.021, R = Bn : 70 %
6.022, R = TBS : 85 %

Scheme 26

Ring closing metathesis using Grubbs catalyst allows the cyclisation of the dienes to the corresponding protected lactones. Three different catalysts have been tested to optimize the reaction: Grubbs first generation **6.023** (Grubbs I), Grubbs second generation **6.024** (Grubbs II) and Hoveyda-Grubbs **6.025** (figure 4).



6.023 **6.024** **6.025**

Figure 4

As shown in table 3, the Grubbs second generation complex is the best catalyst for this cyclisation: the yield is higher and the conversion is complete after only one hour. When Grubbs first generation or Hoveyda-Grubbs catalysts were employed, the reaction was significantly slower and a complete conversion could not be achieved.

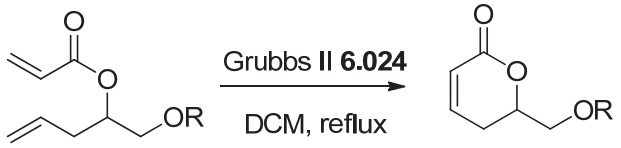
Molecule	Catalyst (mol%)	Time (min)	Conversion[a]	Yield (%)
6.021	**6.023** (8)	960	Incomplete	34
6.021	**6.024** (3)	60	Complete	56
6.021	**6.025** (3)	60	Incomplete	nd[b]
6.022	**6.024** (4)	60	Complete	78

[a]Observed on TLC : starting material's spot has disappeared or not

[b]nd = not determined

Table 3

These optimized conditions were then applied to both dienes. Gratifyingly, the two protected lactones **6.026** and **6.027** were isolated in good yields (scheme 27).



6.021, R = Bn
6.022, R = TBS

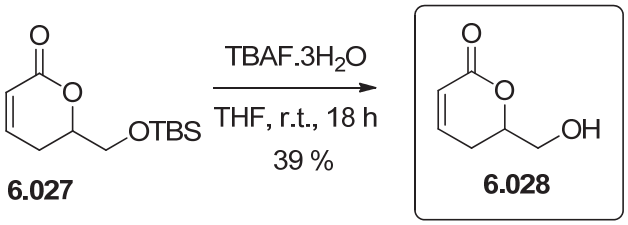
6.026, R = Bn = 56 %
6.027, R = TBS = 78 %

Scheme 27

The best results were obtained with Grubbs II catalyst **6.024**. This observation can be explained by the higher reactivity of this species as compared to its first generation analogue **6.023**. In fact, the presence of an NHC ligand accelerates the dissociation of the phosphine ligand whilst rendering the ruthenium more electrophilic. Addition of the complex on the more electron rich double bond is thus a faster process. Moreover, this

catalyst is more thermally stable and less degradation or dimerisation reactions can be observed, as compared to the Grubbs I reagent.

Finally, lactone **6.027** was deprotected using tetrabutylammonium fluoride in THF[13], affording the primary alcohol **6.028** in 39 % yield (scheme 28).



Scheme 28

Overall, lactone **6.028** was synthetized in five steps and 24 % overall yield from commercially available glycidol.

This lactone **6.028** is of great interest because it can be further modified to form new compounds similar to jerangolid D. In fact, the double bond enables the introduction of a wide range of new functionalities thus giving rise, after coupling, to various analogues.

However, the synthesis described here cannot be transposed on a larger scale due to the high cost of the Grubbs catalyst. For this reason, another pathway for the synthesis of this lactone was developed.

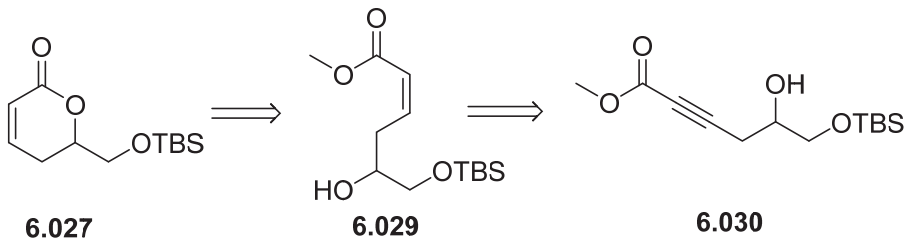
II.1.2. Via intramolecular esterification

To avoid the use of Grubbs catalyst, an intramolecular esterification of an intermediate such as **6.029** in order to generate the lactone moiety has been envisioned[14] (scheme 29).

---

[13] X.-L. Wang, W.-F. Huang, X.-S. Lei, B.-G. Wei, G.-Q. Lin, *Tetrahedron* **2011**, *67*, 4919-4923.

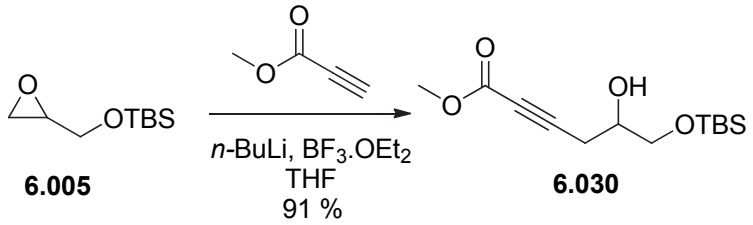
[14] Only lactone **6.027** has been synthetized with this pathway



6.027 **6.029** **6.030**

Scheme 29

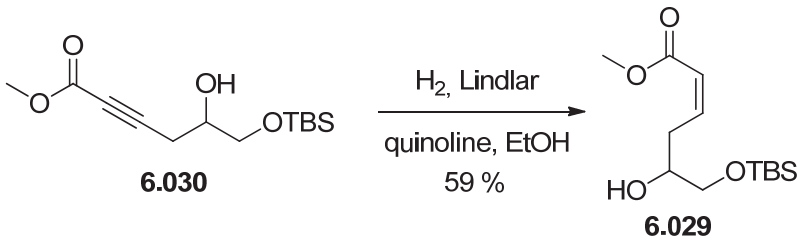
Opening of the oxirane with the *in situ* generated anion of methyl propiolate, in the presence of BF_3-etherate, allows the formation of homopropargylic alcohol **6.030** in excellent yield[15] (scheme 30).



6.005 **6.030**

Scheme 30

Partial hydrogenation of the triple bond to the corresponding (*Z*)-double bond, using Lindlar's catalyst and quinoline, leads to compound **6.029** in good yield (scheme 31).



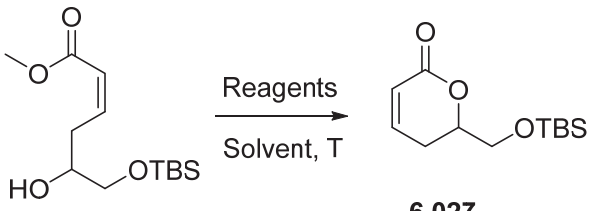
6.030 **6.029**

Scheme 31

---

[15] R. J. Maguire, S. P. Munt, E. J. Thomas, *J. Chem. Soc., Perkin Trans. 1* **1998**, 2853-2864.

Different conditions have been tried to access the desired protected lactone **6.027** from this intermediate **6.030**. These are described in table 4.



6.029 **6.027**

Entry	Reagents	Solvent	Temperature (°C)	Yield (%)
1	TMSCl, MeOH	DCM	0 then r.t.	Degradation
2	TMSCl, MeOH	DCM	-78 then r.t.	Degradation
3	PPTS[16]	MeOH	0 then r.t.	SM
4	NaH	DMF	r.t.	SM + Degradation

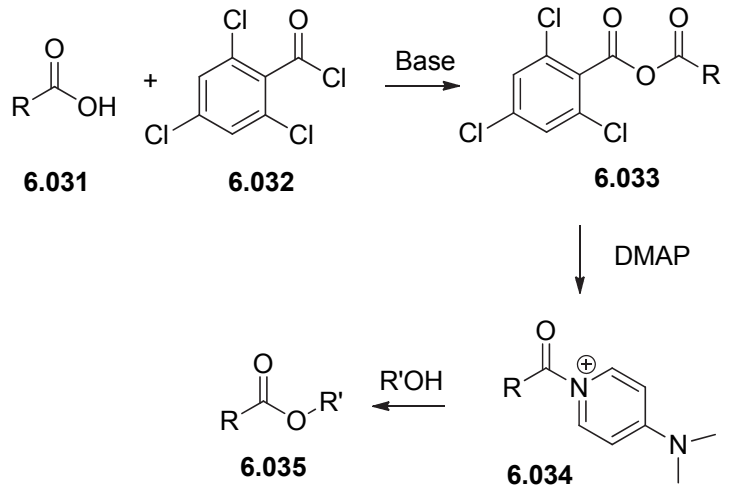
Table 4

Unfortunately, none of these conditions led to the formation of the desired product. A search in the literature reveals that the Yamaguchi reaction is one of the most powerful methods for the intramolecular esterification of hydroxyacids. It was thus decided to apply it in our case.

The mechanism of this reaction is described in scheme 32. After deprotonation, the carboxylate of **6.031** attacks 2,4,6-trichlorobenzoyl chloride to form the mixed anhydride **6.033**. DMAP then adds to the more accessible carbonyl function to generate the corresponding acyl pyridinium salt **6.034**. Addition of the alcohol to the activated carbonyl is fast and leads, after deprotonation, to the formation of the desired ester **6.035**.

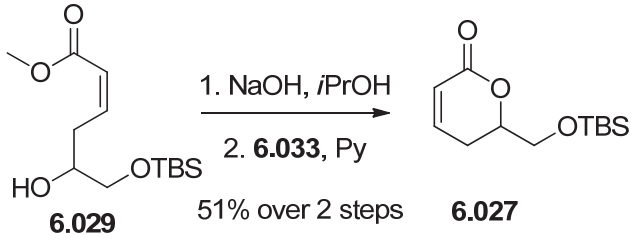
---

[16] B. Das, S. Nagendra, C. Ravindra Reddy, *Tetrahedron: Asymm.* **2011**, *22*, 1249-1254.



Scheme 32

Ester **6.029** was thus transformed into the corresponding acid, which was then reacted with Yamaguchi's reagent **6.032** and pyridine (instead of DMAP) to yield the desired lactone (scheme 32).



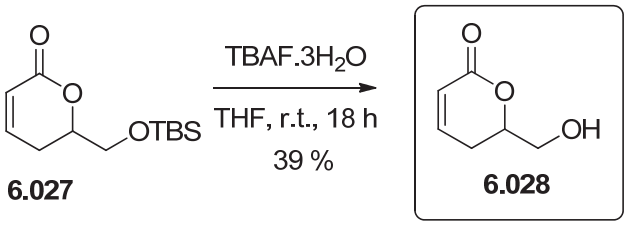
Scheme 33

During saponification of ester **6.029**, formation of lactone **6.027** is already observed in a ratio lactone/acid of 1:7. It would therefore be interesting to modulate these conditions in order to directly access the desired lactone and in good yield by a simple base-catalyzed process.

The conditions for Yamaguchi's reaction have been slightly modified compared to the literature, by replacing DMAP with pyridine. In this case, the latter plays a triple role: solvent, base and leaving group. Moreover, it

has been shown that the use of pyridine results in the isomerization of the double bond[17]. The two isomers of the acid can thus be cyclised into the same lactone, thus obviating the need for a selective reduction of the triple bond.

Finally, deprotection of the TBS group with TBAF afforded lactone **6.028** in 39 % yield (scheme 34).



Scheme 34

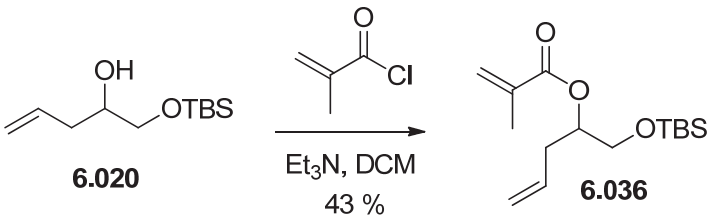
Compound **6.028** has been prepared in six steps with an overall yield of 11%, which is lower than the one obtained with the first sequence. However, a bigger amount of lactone can be sythetised with this more economical pathway and some steps can still be optimised.

II.2. Synthesis of lactone 3.010

The strategy for the synthesis of this lactone is the same as the one used for lactone **3.011**: ring-closing metathesis to cyclise the diene and form the trisubstituted lactone.

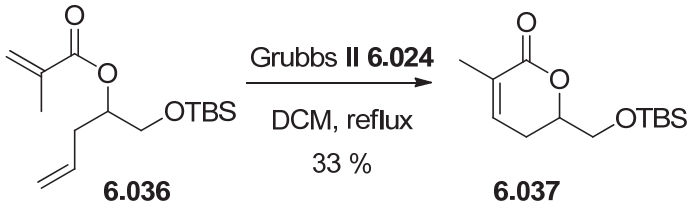
Starting from the same intermediate **6.020**, esterification with methacryloyl chloride led to diene **6.036** in moderate yield (scheme 35).

[17] M. Ono, X. Y. Zhao, Y. Shida, H. Akita, *Tetrahedron* **2007**, *63*, 10140-10148.



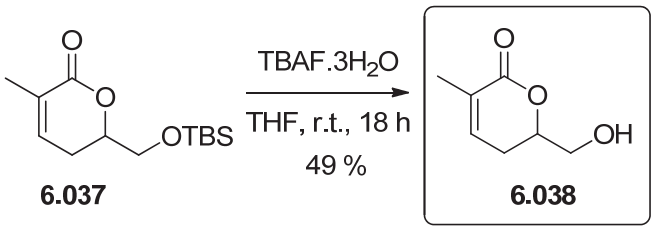
Scheme 35

The conditions for the ring-closing metathesis had been optimised earlier and were reproduced without further modifications. Unfortunately, the yield is much lower in this case (scheme 36). This can be explained by the presence of a methyl group on the more electrophilic double bond which increases the steric hindrance and disfavours the ring closing metathesis. This reaction is indeed very sensitive to steric hindrance.



Scheme 36

Finally, lactone **6.037** was deprotected using TBAF to deliver the corresponding primary alcohol in 49 % yield (scheme 37).



Scheme 37

Overall, lactone **6.038** was obtained in five steps with a global yield of 6 %, staring from commercially available glycidol. The three last steps can definitely be further optimized to increase the overall yield.

In summary, the lactone present in jerangolid D has been successfully synthesized along with three new analogues in moderate to good yields. The synthesis of these new analogues still needs to be applied to the enatiomerically pure starting material but that should not be a problem.

CENTRAL FRAGMENT SYNTHESIS

I. Central fragment synthesis

As stated in the objectives, it would be interesting to modify the central part of the jerangolid family. Some examples are presented in figure 1.

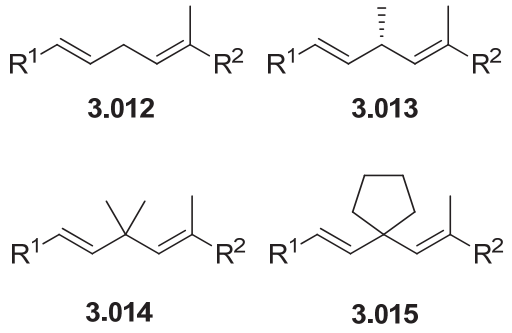


Figure 1

In order to form these olefins using two Julia olefinations, it is necessary to prepare the corresponding sulfones. In this chapter, we describe the synthesis of four intermediates that were synthetized by Sophie Moreau during her master thesis (figure 2).

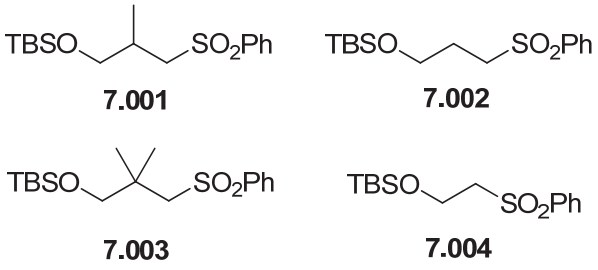
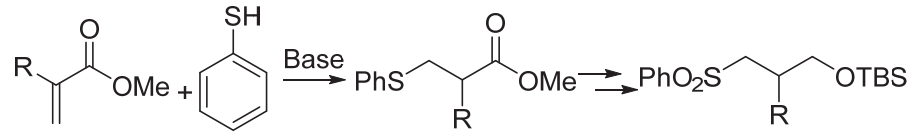


Figure 2

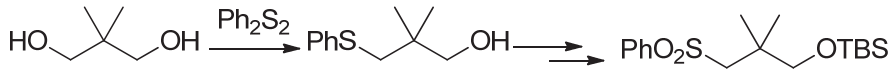
The strategy developed for the synthesis of **7.001** and **7.002** starts with the 1,4 addition of thiophenol to methyl acrylate or methacrylate. The ester function can further be reduced to the corresponding alcohol followed by protection with a TBS group. Finally, the sulfides can be oxidized to the desired sulfones (scheme 1).



R=H: **7.005** R=Me **7.006** **7.008** R=H: **7.009** R=Me: **7.010** R=H: **7.002** R=Me: **7.001**

Scheme 1

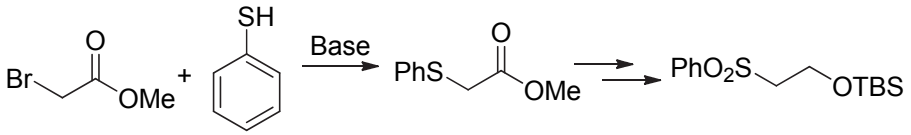
The intermediate **7.012** can be reached by transforming one –OH function in diol **7.011** into the corresponding sulfur derivative. The remaining alcohol can be protected with a TBS group and finally the sulfur can be oxidized to afford fragment **7.003** (scheme 2).



7.011 **7.012** **7.003**

Scheme 2

Finally, addition of thiophenol to bromoester **7.013** would allow the formation of derivative **7.014**. The ester function can then be reduced to the corresponding alcohol followed by its protection with a TBS group. Oxidation of the sulfur would lead to the desired sulfone **7.004** (scheme 3).



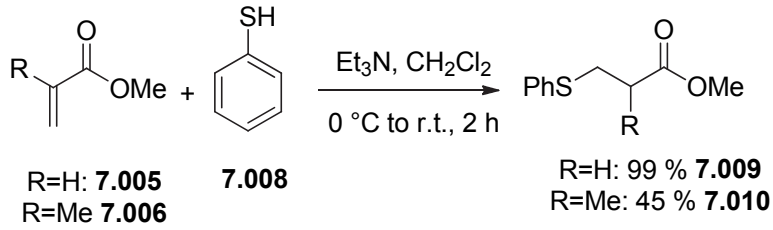
7.013 **7.008** **7.014** **7.003**

Scheme 3

These syntheses are described in the following sections. The main objective was to try to couple these fragments with dihydropyran **2.001** which is the reason why the steps in these syntheses have not been optimized.

I.1. Synthesis of esters 7.009, 7.010, 7.014

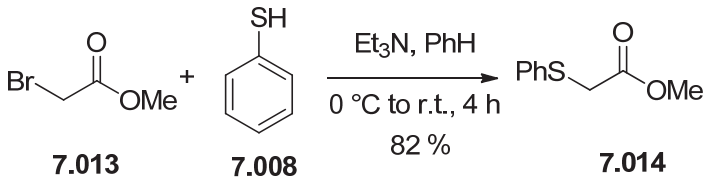
Esters **7.009** and **7.010** were prepared using a procedure described in the literature[1].



Scheme 4

Thiophenol was stirred with methyl acrylate or methyl methacrylate in the presence of triethylamine to furnish compounds **7.009** and **7.010** in 99 % and 45 % yields respectively. The moderate yield obtained for compound **7.010** can be explained by the loss of the product during the workup of the reaction.

In the case of ester **7.014**, thiophenol was stirred with bromoester **7.013** in the presence of triethylamine to afford the desired compound in very good yield[2] (scheme 5).



Scheme 5

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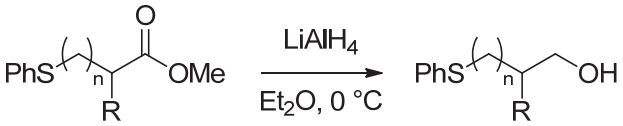
[1] P. Bakuzis, M. L. Bakuzis, *J. Org. Chem.* **1981**, *2*, 235-239.

[2] K. Miura, N. Fujisawa, H. Saito, D. Wang, A. Hosomi, *Org. Lett.* **2001**, *16*, 2591-2594.

I.2. Reduction of the ester functions

The most commonly used method to reduce esters to the corresponding alcohols employs lithium aluminium hydride. This technique has thus been applied to our substrates[3] (scheme 6).



n=1 R=H: **7.009**
n=1 R=Me: **7.010**
n=0 R=H **7.014**

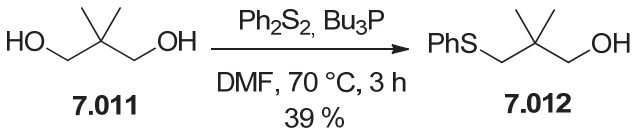
n=1 R=H: 92 % **7.016**
n=1 R=Me: 97 % **7.017**
n=0 R=H 88 % **7.018**

Scheme 6

After treatment and filtration of the crude mixture, the alcohols are obtained in excellent yields without purification.

I.3. Synthesis of alcohol 7.012

Alcohol **7.012** was obtained by treating diol **7.011** with Ph_2S_2 in the presence of tributyl phosphine in moderate yield[4] (scheme 7).



7.011 **7.012**

Scheme 7

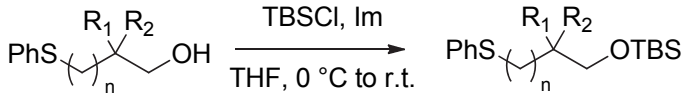
I.4. Protection of the alcohol functions

The four alcohols were then protected with a TBS group in the presence of imidazole in good yields (scheme 8).

---

[3] T. Hirie, H. Tanida, *J. Org. Chem.* **1980**, *24*, 4961-4965.

[4] K. J. Hale, M. Frigerio, S. Manaviazar, *Org. Lett.* **2001**, *23*, 3791-3794.



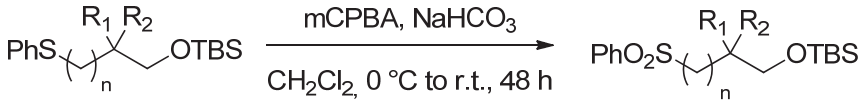
n=1 R_1=R_2=H **7.016**
n=1 R_1=Me, R_2=H **7.017**
n=0 R_1=R_2=H **7.018**
n=1, R_1=R_2=Me **7.012**

n=1 R_1=R_2=H: 70 % **7.019**
n=1 R_1=Me, R_2=H: 67 % **7.020**
n=0 R_1=R_2=H: 62 % **7.021**
n=1, R_1=R_2=Me: 80 % **7.022**

Scheme 8

I.5. Oxidation into sulfones

A classical method employing two equivalents of *m*CPBA in the presence of $NAHCO_3$ has been used to oxidize sulfurs into the corresponding sulfones (scheme 9).



n=1 R_1=R_2=H **7.019**
n=1 R_1=Me, R_2=H **7.020**
n=0 R_1=R_2=H **7.021**
n=1, R_1=R_2=Me **7.022**

n=1 R_1=R_2=H: 47 % **7.002**
n=1 R_1=Me, R_2=H: 39 % **7.001**
n=0 R_1=R_2=H: 50 % **7.004**
n=1, R_1=R_2=Me: 32 % **7.003**

Scheme 9

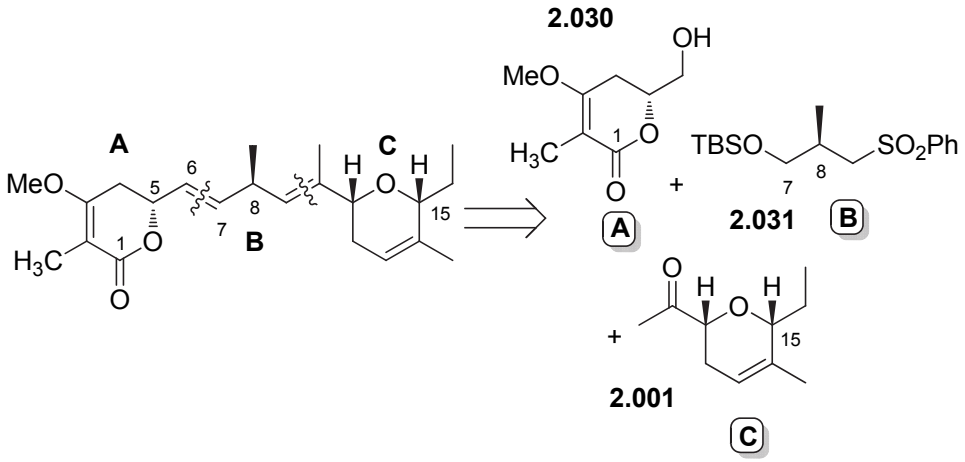
The yields are moderate which could come from the low purity of mCPBA used for these reactions.

These fragments are now ready to be coupled with dihydropyran **2.001**. A couple of tests were run but the results were not encouraging. Because of a shortage of time, these experiments were abandoned but hopefully, Kevin Debrus will find a practical methodology to couple all these fragments easily during his PhD thesis.

GENERAL CONCLUSIONS AND PERSPECTIVES

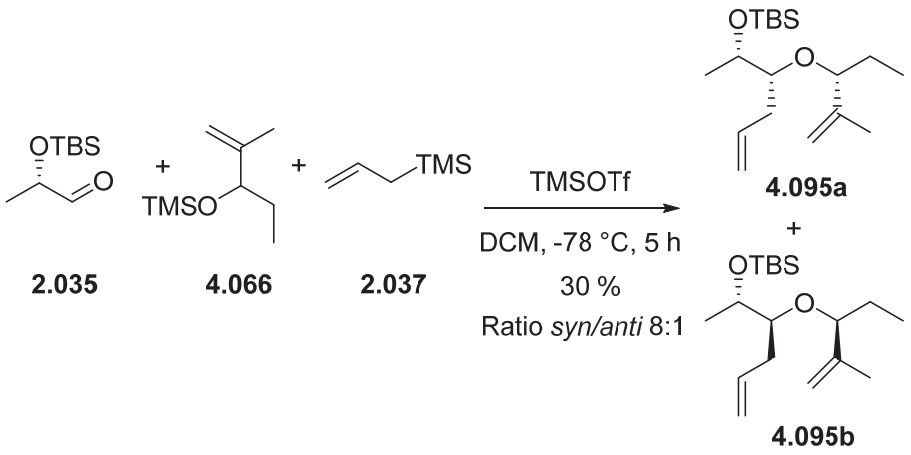
I.1. General conclusions and perspectives

At the beginning of this work, we were interested in the synthesis of jerangolid D and some new analogues based on the retrosynthesis in scheme 1.

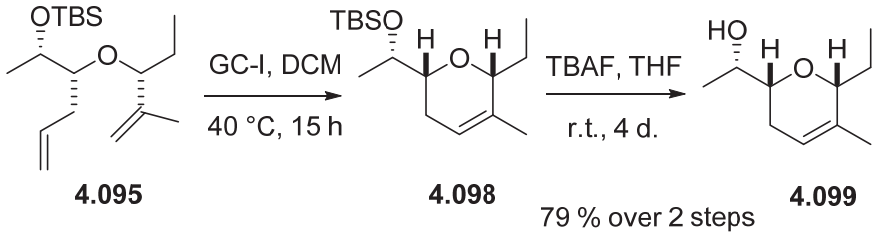


Scheme 1

We started our work with the synthesis of dihydropyran **C**, based on the strategy developed by Dr J. Pospisil during his Ph.D. thesis. Unfortunately, in our case, the yield and the selectivity for the SMS reaction were much lower (scheme 2). Despite the low yield, we were able to isolate the desired product **4.095** and to continue the sequence. Ring-closing metathesis, followed by TBAF deprotection, yielded dihydropyran **4.099** in 79 % over two steps (scheme 3).



Scheme 2



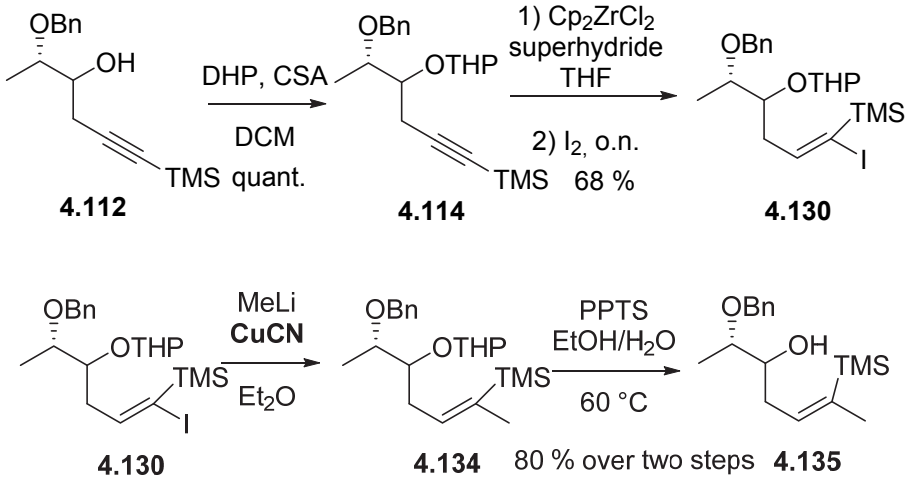
Scheme 3

At this point, in view of the disappointing results obtained with the direct three-components SMS reaction or the acetal formation, and since the optimization and study of this reaction was not the main goal of this thesis, we decided to move on to another approach and synthetize our fragments *via* a different sequence.

This new sequence has two key steps: the reduction of an alkyne to the corresponding substituted (*Z*)-alkene and an ISMS cyclyzation.

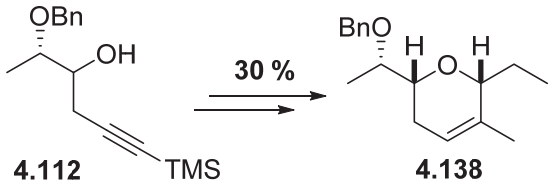
After many optimizations, we were able to develop a synthesis to access the desired dihydropyran **C** in good yields and excellent reproducibility. It includes the reduction of alkyne **4.112** *via* a hydrozirconation/methylation

process to the (*Z*)-vinylsilane **4.135** and its subsequent cyclization to the corresponding DHP **4.138** (scheme 4).



Scheme 4

Gratifyingly, this approach enabled us to obtain the desired protected DHP **4.138** in 30 % overall yield starting from adduct **4.112** in a reproducible manner (scheme 5)!



Scheme 5

In addition, starting from the same compound **4.112**, we employed other reducing agents to form original (*Z*)-vinylsilanes which were further cylized, *via* an ISMS cyclization, to form new dihydropyrans analogues with interesting structures in moderate to excellent yields (figure 1).

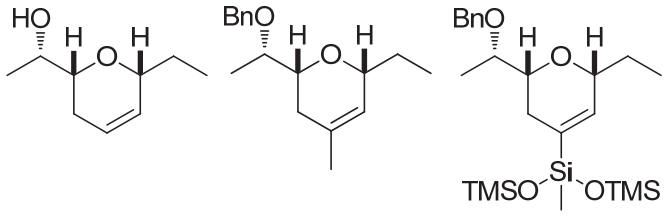
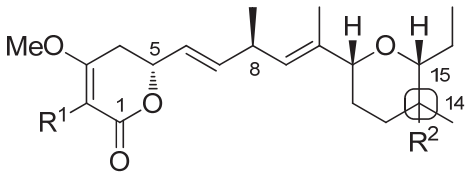


Figure 1

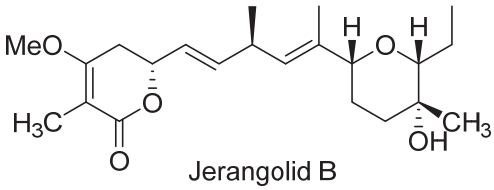
The second part of this work was devoted to the synthesis of the right-hand part of jerangolids B, E and H in which the stereochemistry at C14 is still unknown (figure 2).



Jerangolid B, $R^1=CH_3$, $R^2=OH$
Jerangolid E, $R^1=CH_3$, $R^2=H$
Jerangolid H, $R^1=CH_2OH$, $R^2=H$

Figure 2

Starting from our previously synthetized DHP **4.099b**, we were able to reach the right-hand part of jerangolids B and H through the epoxidation of the double bond and the opening of this epoxide. Therefore, we proposed that the methyl group in jerangolid B occupies an equatorial position whilst the –OH function is axial, as indicated in figure 3.



Me7 = 25.83 ppm

Figure 3

Hydrogenation of the same double bond enabled us to access the right-hand part of jerandolid E. Thus, we suggested that the methyl group in jerangolid

E occupies the equatorial position. The full structure of jerangolid E is thus shown in figure 4.

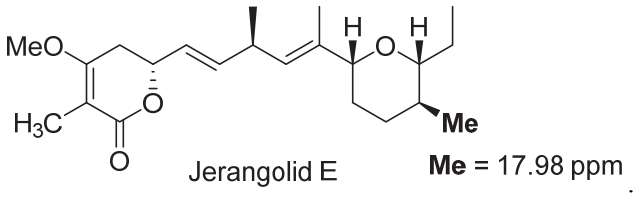
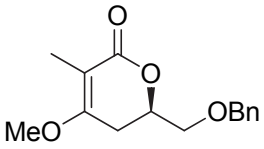


Figure 4

On the other hand, the synthesis of the left-hand lactone **A** of jerangolid D was completed in good yields and in a reproducible manner (figure 5).

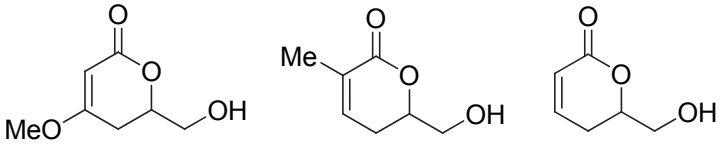


2.034

Figure 5

This lactone **2.034** still needs to be deprotected to complete the sequence.

Three new analogues of this lactone were also prepared in their racemic version (figure 6).



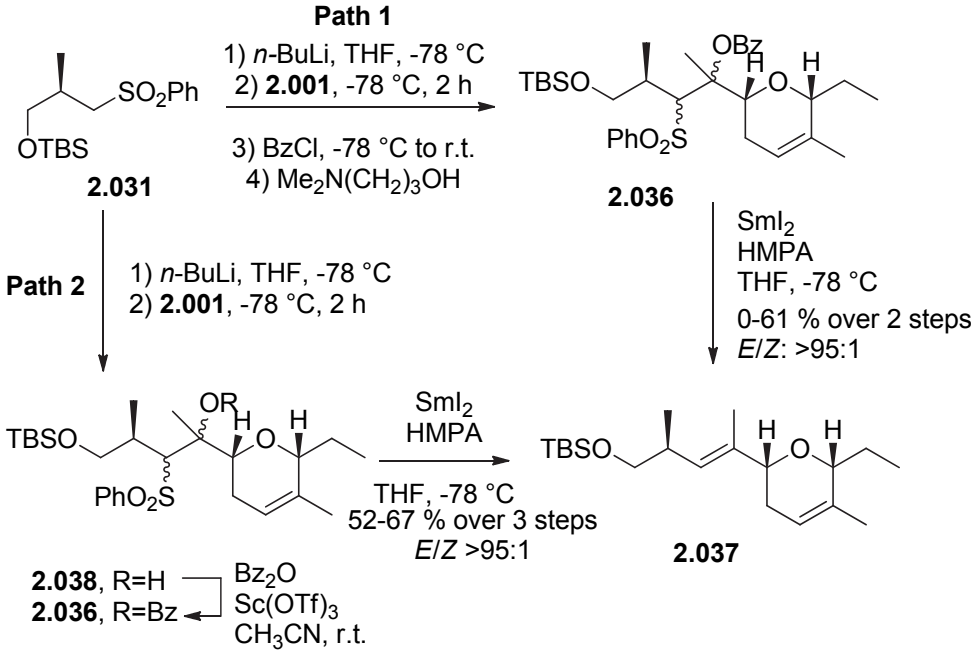
6.016 **6.038** **6.028**

Figure 6

These syntheses also have to be transposed to the enatiomerically pure version.

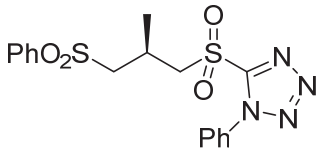
Finally, four different sulfones mimicking the central fragment **B** were prepared in moderate yield.

At the end of this work, we have synthetized a variety of compounds, analogues of each fragment of the family of jerangolids. The next step would naturally be, after oxidation, to couple them in order to form a library of new analogues of jerangolid D. One way to couple them would be to use the strategy developed by Dr J. Pospisil, using two subsequent Julia olefination (scheme 6).



Scheme 6

However, this approach is long, not always reproducible and there are a lot of fragments to couple. For these reasons, it would be interesting to develop an easy one-pot process using a double Julia olefination with a bis-sulfone such as **8.001** (figure 7).



8.001

Figure 7

All these compounds that we prepared should as well be submitted to biological evaluation in order to estimate their potential antifungal activities.

EXPERIMENTAL PART

I. Instrumentation and chemicals

Unless otherwise noted, all manipulations were performed under an argon atmosphere using standard glassware. Diethyl ether and THF were distilled on sodium/benzophenone under argon atmosphere. Dichloromethane, triethylamine and trimethylsilyl chloride were distilled on CaH_2. Solvents used for work-up were of technical grade. Commercial reagents were purchased from Acros, Sigma-Aldrich, ABCR, TCI or Fluorochem and used as received unless stated otherwise. Infrared spectra (IR) were recorded on a Shimadzu FTIR-8400S spectrometer. Wave numbers are given in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on BRUKER Avance II (300 MHz for ^{1}H and 75 MHz for ^{13}C). ^{1}H and ^{13}C NMR chemical shifts are reported relative to $CDCl_3$ (7.26, 77.16 ppm). Chemical shifts (δ) and coupling constants are respectively reported in ppm and Hertz (Hz). If necessary, the structures were confirmed by 2 dimensional analyses (COSY, HMQC and HMBC). ^{1}H spectra are described as explained below: chemical shift (multiplicity, integration, attribution, coupling constant(s) Hz). ^{13}C spectra are described as explained below: chemical shift (attribution). Multiplicity is given as follows: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, m = multiplet, dd = doublet of doublet, td = triplet of doublet, qd = quartet of doublet and br = broad. When the compound is present as a mixture of two diastereomers, the attribution is written H_x for one diastereomer and $H_{x'}$ for the other one. High resolution Mass Spectra (HRMS) and Mass Spectra (MS) were obtained from a Thermo Scientific Qexactive, with accurate mass reported for the molecular ion $[M+H]^+$ or suitable fragment ions. Spectra are described in the following way: m/z (intensity, %), [Fragmentation]. GC analyses were recorded on a Thermo Finningan Trace GC apparatus with a CHIRALSIL-DEX CB (25m, 0.25

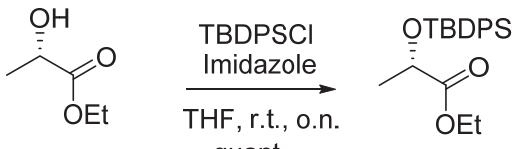
mm, 25 µm) column. Column chromatography was carried out on silica gel (ROCC 60, 40-63 µm). TLC analyses were performed on commercial aluminum plates bearing a 0.25 mm layer of Merck Silica gel 60F254.

II. Chapter 4: Dihydropyran synthesis

II.1. Substrates synthesis

II.1.1. Synthesis of esters 4.063, 4.087 and 4.094

II.1.1.1.Ester 4.063

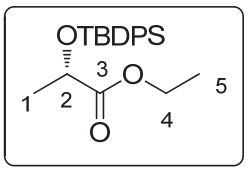


4.062 **4.063**

To a solution of (*S*)-ethyl lactate (15 g, 127 mmol) and imidazole (5 g, 42 mmol) in THF (0.5 M) at 0°C was added TBDPS-Cl (14 g, 51 mmol) carefully. The reaction mixture was stirred at room temperature overnight. Water was then added and the aqueous phase was extracted with ethyl acetate. The organic phases were combined, washed with water and brine and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The product was obtained without purification as a slightly yellow oil; yield: 15 g (quantitative).

- (*S*)-ethyl 2-((*tert*butyldiphenylsilyl)oxy)propanoate **4.063**[1]

[1] Jiri Pospisil, PhD thesis, UCL **2006**



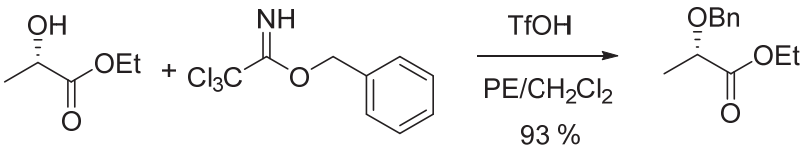
CAS number: [102732-44-5]

^{1}H NMR (300MHz, $CDCl_3$): δ 7.70-7.65 (m, 4H, H_{ar}) 7.41-7.35 (m, 6H, H_{ar}), 4.26 (q, 1H, H_2, J=6.9 Hz), 4.02 (q, 2H, H_4, J=7.2 Hz), 1.36 (d, 3H, H_1, J=6.9 Hz), 1.14 (t, 3H, H_5, J=7.2 Hz), 1.08 (bs, 9H, H_{tbu}).

^{13}C NMR (75MHz, $CDCl_3$): δ 173.9 (C_3), 136.0-135.8-134.9-133.7-133.3-129.9-127.8-127.7-127.6 (C_{ph}), 69.1 (C_2), 60.7 (C_4), 26.9 (C_{tbu}), 21.4 (C_{tbu}), 19.4 (C_1), 14.2 (C_5).

Data are in agreement with literature values.

II.1.1.2.Ester 4.087

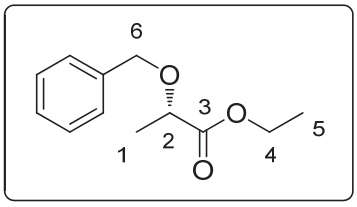


4.063 **4.086** **4.087**

To a solution of (*S*)-ethyl lactate (10 g, 85 mmol) and benzyl trichloroimidate (26 g, 102 mmol) in petroleum ether (260 mL) was added triflic acid (0.3 mL) dropwise. The resulting mixture was stirred at room temperature overnight. The precipitate was then filtered and the filtrate was concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (eluent: PE/Et_2O 100:1) to afford the pure product as a colorless oil; yield: 16.33 g (93 %).

- (*S*)-ethyl 2-(benzyloxy) propanoate **4.087**[2]

[2] Enders D., von Berg S., Jandeleit B. *Org. Synth.* **2002**, *78*, 177



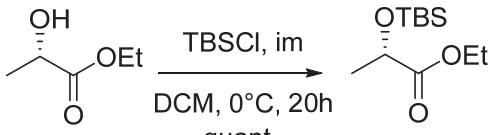
CAS number : [54783-72-1]

^{1}H NMR (300MHz, $CDCl_3$) : δ 7.40-7.29 (m, 5H, H_{ar}), 4.70 (d, 1H, H_6 J=12 Hz), 4.45 (d, 1H, H_6, J=12 Hz), 4.22 (q, 2H, H_4, J=9 Hz), 4.05 (q, 1H, H_2, J=6 Hz), 1.44 (d, 3H, H_1, J=6 Hz), 1.30 (t, 3H, H_5, J=9 Hz).

^{13}C NMR (75MHz, $CDCl_3$) : δ 173.2 (C_3), 136.6-128.4-127.9-127.8 (C_{ar}), 74.0 (C_2), 71.9 (C_4), 60.8 (C_6), 18.7 (C_1), 14.2 (C_5).

Data are in agreement with literature values.

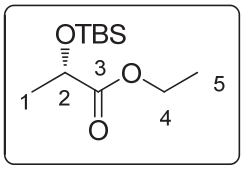
II.1.1.3.Ester 4.094



4.062 **4.094**

To a solution of (S)-ethyl lactate (15 g, 127 mmol) and imidazole (13 g, 190 mmol) in DCM (0.5 M) at 0°C was added TBS-Cl (21 g, 140 mmol) carefully. The reaction mixture was stirred at room temperature overnight. Water was then added and the aqueous phase was extracted with dichloromethane. The organic phases were combined, washed with brine and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The product is obtained without purification as a colorless oil; yield: 30 g (quantitative).

- (*S*)-ethyl 2-((*tert*butyldimethylsilyl)oxy)propanoate **4.094**[3]



CAS number : [105198-38-7]

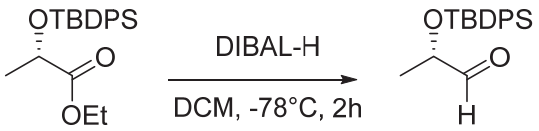
^{1}H NMR (300MHz, $CDCl_3$) : δ 4.29 (q, 1H, H_2, J=6.6 Hz), 4.21-4.10 (m, 2H, H_4), 1.37 (d, 3H, H_1, J=6.9 Hz), 1.26 (t, 3H, H_5, J=7.2 Hz), 0.88 (s, 9H, H_{TBS}), 0.08 (s, 3H, H_{TBS}), 0.05 (s, 3H, H_{TBS}).

^{13}C NMR (75MHz, $CDCl_3$): δ 174.2 (C_3), 68.6 (C_2), 60.8(C_4), 25.8 (C_{TBS}), 21.4 (C_{TBS}), 18.4 (C_1), 14.3 (C_5), -4.8 (C_{TBS}), -5.2 (C_{TBS}).

Data are in agreement with literature values.

II.1.2. Synthesis of aldehydes 4.061, 4.111 and 2.035

II.1.2.1.Aldehyde 4.061



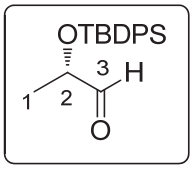
4.063 **4.061**

To a solution of silylated ester (5 g, 14 mmol) in DCM (0.1M) was added DIBAL-H (15.4 ml, 15.4 mmol) dropwise at -78°C. The reaction mixture was stirred at -78°C for 3 hours. Acetone was added to quench the remaining DIBAL-H. HCl 1 M was then added dropwise at -78°C and then the reaction mixture was allowed to warm up to 0°C. The aqueous phase was extracted twice with dichloromethane. The organic phases were combined, washed with $NaHCO_{3\ sat}$ and brine, dried over Na_2SO_4, filtered and carefully

[3] Joly, G. D.; Jacobsen, E. N. *Org. Lett.* **2002**, *4*, 1795.

concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (eluent: PE/Et_2O 35:1) to afford the pure product as a colorless oil; yield: 4.1 g (93 %).

- (*S*)-ethyl 2-((*tert*butyldiphenylsilyl)oxy)propanal **4.061**[4]



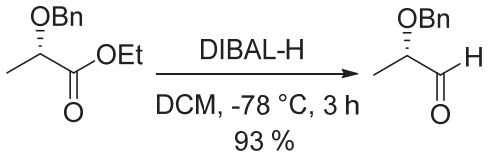
CAS number: [135367-18-9]

^{1}H NMR (300MHz, $CDCl_3$): δ 9.64 (s, 1H, H_3), 7.67 (m, 4H, H_{Ar}), 7.60 (m, 6H, H_{Ar}), 4.12 (qd, 1H, H_2, J=6.9 Hz, J=1.2 Hz), 1.23 (d, 3H, H_1, J=6.9 Hz), 1.10 (s, 9H, H_{TBu}).

^{13}C NMR (75MHz, $CDCl_3$): δ 204.0 (C_3), 138.5-127.7 (C_{ph}), 77.4 (C_2), 27.1 (C_{tBu}), 19.4 (C_{tBu}), 18.5 (C_1).

Data are in agreement with literature values.

II.1.2.2.Aldehyde 4.111



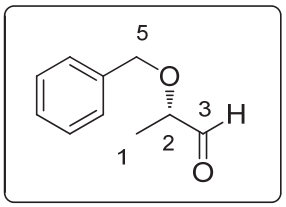
4.087 **4.111**

To a solution of benzylated ester (5 g, 24 mmol) in DCM (240 mL) was added DIBAL-H (1 M in DCM, 26.4 ml, 26.4 mmol) dropwise at -78°C. The reaction mixture was stirred at -78°C for 3 hours. Acetone was added to quench the remaining DIBAL-H. HCl 1M was then added dropwise at -78°C and the reaction mixture was allowed to warm up to 0°C. The aqueous

[4] Baudrenghien L., Master thesis UCL **2009**

phase was extracted with dichloromethane (3x). The organic phases were combined and washed with $NaHCO_{3\ sat}$ and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (eluent: PE/Et_2O 35:1) to afford the pure product as a colorless oil; yield: 4.1 g (93 %).

- (*S*)-ethyl 2-(benzyloxy) propanal **4.111**[2]



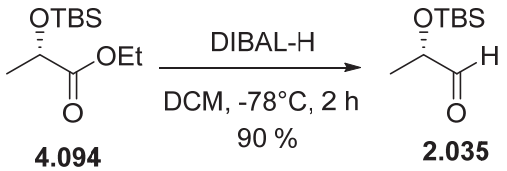
CAS number: [81445-44-5]

^{1}H NMR (300MHz, $CDCl_3$): δ 9.68 (s, 1H, H_3), 7.38-7.31 (m, 5H, H_{ar}), 4.66 (d, 1H, H_5, J=12 Hz), 4.60 (d, 1H, H_5, J=12 Hz), 3.90 (qd, 1H, H_2, J=9 Hz, 3Hz), 1.33 (d, 3H, H_1, J=9 Hz).

^{13}C NMR (75MHz, $CDCl_3$): δ 203.4 (C_3), 137.3-128.6-127.9 (C_{ar}), 79.4 (C_2), 72.0 (C_5), 15.5 (C_1).

Data are in agreement with literature values.

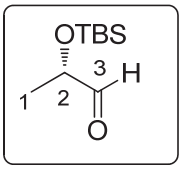
II.1.2.3.Synthesis of aldehyde 2.035



To a solution of silylated ester (6 g, 26 mmol) in DCM (0.1 M) was added DIBAL-H (28 ml of 1M solution, 28.4 mmol) dropwise at -78°C. The reaction mixture was stirred at -78°C for 2 hours. Acetone was added to quench the remaining DIBAL-H. HCl 1 N was then added dropwise at -78°C

and then the reaction mixture was allowed to warm up to 0°C. The aqueous phase was extracted twice with dichloromethane. The organic phases were combined and washed with $NaHCO_{3\ sat}$ and brine, dried over Na_2SO_4, filtered and carefully concentrated under vacuum. The crude mixture was purified by silica gel column chromatography (eluent: PE/Et_2O 35:1) to afford the pure product as a colorless oil; yield: 4.5 g (93 %).

- (*S*)-ethyl 2-((*tert*butyldimethylsilyl)oxy)propanal **2.035**[3]



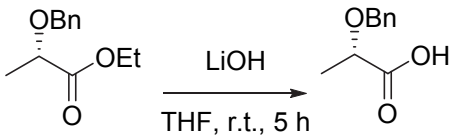
CAS number: [87727-28-4]

^{1}H NMR (300MHz, $CDCl_3$): δ 9.61 (s, 1H, H_3), 4.09 (qd, 1H, H_2, J=6.9Hz, J=0.9Hz), 1.27 (d, 3H, H_1, J=6.9Hz), 0.91 (s, 9H, H_{TBS}), 0.1 (s, 3H, H_{TBS}), 0.09 (s, 3H, H_{TBS}).

^{13}C NMR (75MHz, $CDCl_3$): δ 204.4 (C_3), 74.0 (C_2), 25.9 (C_{TBS}), 18.6 (C_{TBS}), 18.3 (C_1), -4.8 (C_{TBS}), -4.6 (C_{TBS}).

Data are in agreement with literature values.

II.1.3. Synthesis of lactic acid 4.088

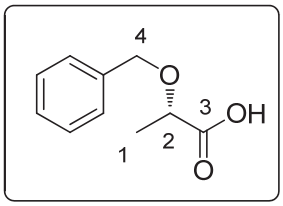


4.087 **4.088**

To a solution of benzylated ester (3.9 g, 18.6 mmol) in THF (0.1 M) at 0°C was added a solution of lithium hydroxide (1.6 g, 37.2 mmol) in water (0.2 M). The resulting solution was warmed up to room temperature and stirred for five hours. It was then quenched with a 1M solution of HCl and extracted with dichloromethane (4x). The organic phases were combined, washed with

brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The pure product was obtained as a white solid; yield: 3.2 g (95 %).

- (*S*)-2-benzyloxypropionic acid **4.088**[5]



CAS number : [33106-32-0]

^{1}H NMR (300MHz, $CDCl_3$) : δ 7.37-7.32 (m, 5H, H_{ar}), 4.70 (d, 1H, H_4, J=11.7 Hz), 4.54 (d, 1H, H_4, J=11.7 Hz), 4.11 (q, 1H, H_2, J=6.9 Hz), 1.49 (d, 3H, H_1, J=6.9 Hz).

^{13}C NMR (75MHz, $CDCl_3$): δ 178.1 (C_3), 137.5-128.6-127.8-127.4 (C_{ar}), 77.2 (C_2), 71.8 (C_4), 16.2 (C_1).

Data are in agreement with literature values.

II.1.4. Synthesis of racemic allylic alcohols 4.065, 4.068 and 4.071

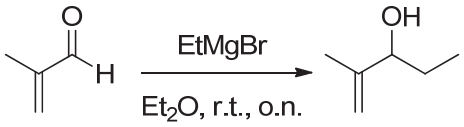
II.1.4.1. General procedure

To a suspension of activated magnesium (1.4 eq) in diethyl ether (1 M) under inert atmosphere was added a crystal of iodine (solution turn to yellow) and then a few drops of ethyl bromide to start forming the Grignard reagent. Once the reaction went from yellow to colorless, the rest of the ethyl bromide (1.2 eq) was carefully added dropwise. The reaction was exothermic and went quickly to diethyl ether reflux which was controlled with an ice bath. The reaction mixture was stirred for an hour. Aldehyde (1

[5] Hoppe, I.; Schöllkopf, U. *Lieb. Ann. Chem.* **1983**, *1983*, 372.

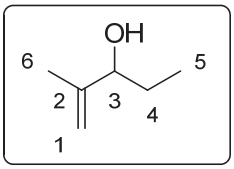
eq) was then added dropwise at 0°C and the reaction mixture was stirred overnight. NH_4Cl_{sat} was added and the aqueous phase was extracted three times with diethyl ether. The organic phases were combined, washed with brine, dried over Na_2SO_4, filtered and carefully concentrated under reduced pressure.

II.1.4.2.Synthesis of 4.065



4.064 **4.065**

- 2-methylpent-1-en-3-ol **4.065**[6]



The reaction was carried out on 243 mmol (17 g).

The crude mixture was purified by distillation (T_{eb} 110-120°C) to afford the pure product as a colorless oil; yield: 18.6 g (77 %).

CAS number: [2088-07-5]

^{1}H NMR (300MHz, $CDCl_3$): δ 4.93 (bs, 1H, H_1), 4.84 (bs, 1H, H_1), 4.00-3.95 (m, 1H, H_3), 1.71 (s, 3H, H_6), 1.58-1.54 (m, 2H, H_4), 0.89 (t, 3H, H_5, J= 7.5 Hz).

^{13}C NMR (75MHz, $CDCl_3$): δ 147.2 (C_2), 111.1 (C_1), 77.2 (C_3), 27.6 (C_4), 17.4 (C_6), 9.7 (C_5).

Data are in agreement with literature values.

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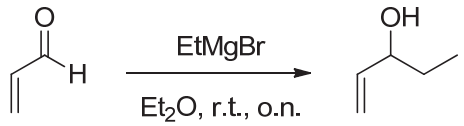
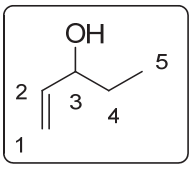
[6] J. Cossy, D. Bauer, V. Bellosta, *Tetrahedron* **2002**, *58*, 5909.

II.1.4.3.Synthesis of 4.068



4.067 88 % **4.068**

- 1-penten-3-ol **4.068**[7]



The reaction was carried out on a 50 mmol scale (2.8 g of acrolein).

The crude mixture was purified by distillation (T_{eb} 100-110 °C) to afford the pure product as a colorless oil; yield: 4.31 g (88 %)

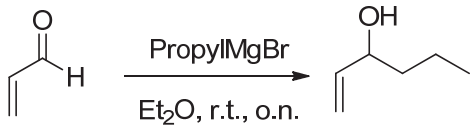
CAS number: [616-25-1]

^{1}H NMR (300MHz, $CDCl_3$): δ 5.91-5.80 (m, 1H, H_2), 5.22 (d, 1H, J=17.1 Hz, H_1), 5.11 (d, 1H, J=10.5 Hz, H_1), 4.02 (m, 1H, H_3), 1.56 (m, 2H, H_4), 0.92 (t, 3H, J=6 Hz, H_5).

^{13}C NMR (75MHz, $CDCl_3$): δ 141.1 (C_2), 114.9 (C_1), 74.7 (C_3), 30.0 (C_4), 9.7 (C_5).

Data are in agreement with literature values.

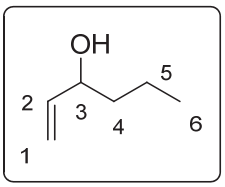
II.1.4.4.Synthesis of 4.071



4.070 97 % **4.071**

[7] V. N. Odinokov, R. R. Vakhidov, R. N. Shakhmaev, V. V. Zorin, *Chem. Nat. Compd.* **1996**, *32*, 912.

- Hex-1-en-3-ol **4.071**[8]



The reaction was carried out on 89 mmol (5 g).

The crude mixture was purified by distillation (T_{eb} 135-140°C) to afford the pure product as a colorless oil; yield: 8.65 g (97 %).

CAS number: [4798-44-1]

^{1}H NMR (300MHz, $CDCl_3$): δ 5.91-5.80 (m, 1H, H_2), 5.20 (d, 1H, H_1, J=17.2 Hz), 5.08 (d, 1H, H_1, J= 11.3 Hz), 4.13-4.06 (m, 1H, H_3), 1.53-1.46 (m, 2H, H_4), 1.43-1.35 (m, 2H, H_5), 1.19 (t, 3H, H_6, J=9 Hz).

^{13}C NMR (75MHz, $CDCl_3$): δ 141.3 (C_2), 114.4 (C_1), 72.9 (C_3), 39.1 (C_4), 18.5 (C_5), 13.9 (C_6).

Data are in agreement with literature values.

II.1.5. Silylation of allylic alcohols with TMS-Cl

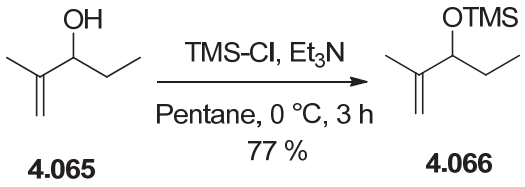
II.1.5.1. General procedure

To a solution of allylic alcohol (1 eq) in pentane (0.2 M) under inert atmosphere at 0°C was added Et_3N (1 eq) dropwise. The mixture was stirred for 5 minutes after which TMS-Cl (1 eq) was added dropwise. The reaction mixture was allowed to warm up to room temperature and stirred for 2h30. It was then filtered and the solid was rinsed thoroughly with pentane. The combined solutions were carefully removed under reduced pressure without heating.

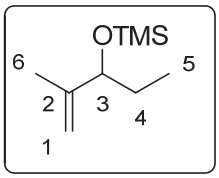
---

[8] W. F. Bailey, X. L. Jiang, *J. Org. Chem.* **1994**, *59*, 6528.

II.1.5.1.Synthesis of silyl ether 4.066



- Trimethyl(2-methylpent-1-en-3-yloxy)silane **4.066**[4]



The reaction was carried out on 30 mmol (3 g).

The crude mixture was purified by silica gel column chromatography (eluent: PE/Et_2O 50:1) to afford the pure product as a colorless oil; yield: 4 g (77 %).

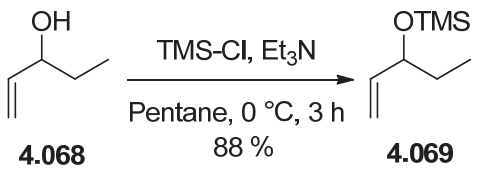
CAS number: [902769-00-0]

^{1}H NMR (300MHz, $CDCl_3$): δ 4.85-4.83 (m, 1H, H_1), 4.76-4.74 (m, 1H, H_1), 3.91 (t, 1H, H_3, J= 6.3 Hz), 1.66 (s, 3H, H_6), 1.49 (q, 2H, H_4, J=7.5 Hz), 0.83 (t, 3H, H_5, J=7.5 Hz), 0.09 (s, 9H, H_{TMS}).

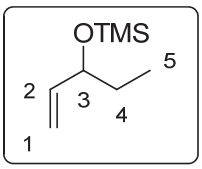
^{13}C NMR (75MHz, $CDCl_3$): δ 147.7 (C_2), 110.8 (C_1), 78.3 (C_3), 29.0 (C_4), 17.3 (C_6), 10.3 (C_5), 0.2 (C_{TMS}).

Data are in agreement with literature values.

II.1.5.2.Synthesis of silyl ether 4.069



- 3-(trimethylsilyloxy)-1-pentene **4.069**[9]



The reaction was carried out on 23 mmol (2 g).

The crude mixture was purified by silica gel column chromatography (eluent: PE/Et_2O 50:1) to afford the pure product as a colorless oil; yield: 3.26 g (88 %).

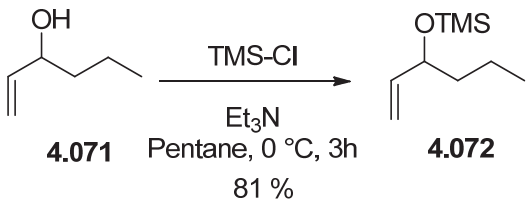
CAS number: [18388-22-2]

^{1}H NMR (300MHz, $CDCl_3$): δ 5.86-5.76 (m, 1H, H_2), 5.13 (d, 2H, J=17.1 Hz, H_1), 5.03 (d, 1H, J=10.2 Hz, H_1), 3.98 (m, 1H, H_3), 1.27 (m, 2H, H_4), 0.88 (t, 3H, J=6.2 Hz, H_5), 0.11 (s, 9H, H_{TMS}).

^{13}C NMR (75MHz, $CDCl_3$): δ 141.6 (C_2), 113.8 (C_1), 75.3 (C_3), 30.9 (C_4), 10.03 (C_5), 0.35 (TMS).

Data are in agreement with literature values.

II.1.5.3.Synthesis of silyl ether 4.072

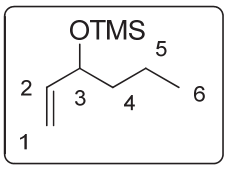


- 3-(trimethylsilyloxy) hex-1-ene **4.072**[10]

---

[9] a. M. J. Brown, T. Harrison, L. E. Overman, *J. Am. Chem. Soc.* **1991**, *113*, 5378. b. R. J. Fessenden, M. D. Coon, *J. Org. Chem.* **1964**, *29*, 1607.

[10] T. Hayashi, M. Konishi, K. I. Yokota, M. Kumada, *J. Organomet. Chem.* **1985**, *285*, 359.



The reaction was carried out on 30 mmol (3 g).

The crude mixture was purified by silica gel column chromatography (eluent: PE/Et_2O 50:1) to afford the pure product as a colorless oil; yield: 4.2 g (81 %).

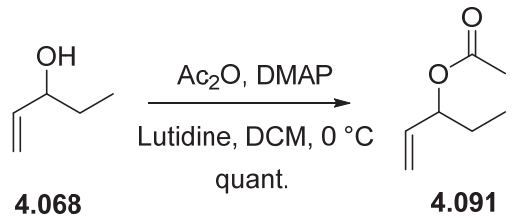
CAS number: [17869-38-4]

^{1}H NMR (300MHz, $CDCl_3$): δ 5.86-5.75 (m, 1H, H_2), 5.16-5.00 (m, 2H, H_1), 4.09-4.01 (m, 1H, H_3), 1.50-1.26 (m, 4H, $H_{4\ and\ 5}$), 0.87 (t, 3H, J=6.9 Hz, H_6), 0.09 (s, 9H, H_{TMS}).

^{13}C NMR (75MHz, $CDCl_3$): δ 138.8 (C_2), 115.7 (C_1), 74.9 (C_3), 31.4 (C_4), 16.4 (C_5), 10.5 (C_6), 0.41 (C_{TMS}).

Data are in agreement with literature values.

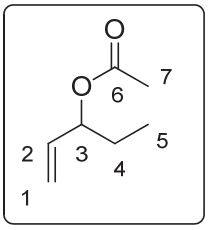
II.1.6. Acylation



4.068 **4.091**

To a solution of alcohol (1 g, 11.6 mmol), lutidine (1.62 mL, 13.9 mmol) and DMAP (0.028 g, 11.1 mmol) in DCM (116 mL) at 0°C was added Ac_2O (1.32 mL, 13.9 mmol). The resulting mixture was stirred at 0°C for 4 hours and quenched with a saturated solution of $NaHCO_3$, extracted with DCM (3x), washed with brine and filtered over a pad of silica gel to remove the remaining lutidine; yield: 1.2 g (quant.).

- Pent-1-en-3-yl acetate **4.091**[11]



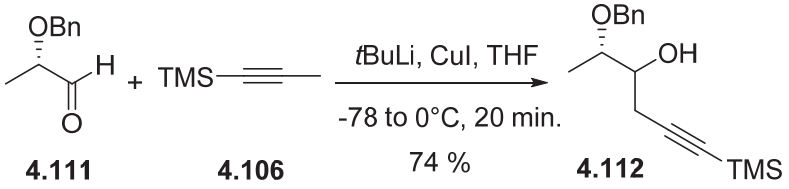
CAS number: [10500-11-5]

^{1}H NMR (300MHz, $CDCl_3$): δ 5.82-5.70 (m, 1H, H_2), 5.29-5.14 (m, 3H, $H_{1,3}$), 2.06 (s, 3H, H_7), 1.66-1.58 (m, 2H, H_4), 0.89 (t, 3H, H_5, J=7.5 Hz).

^{13}C NMR (75MHz, $CDCl_3$): δ 170.5 (C_6), 136.4 (C_2), 116.8 (C_1), 76.1 (C_3), 27.3 (C_7), 21.3 (C_4), 9.5 (C_5).

Data are in agreement with literature values.

II.1.7. Triple bond addition to aldehyde

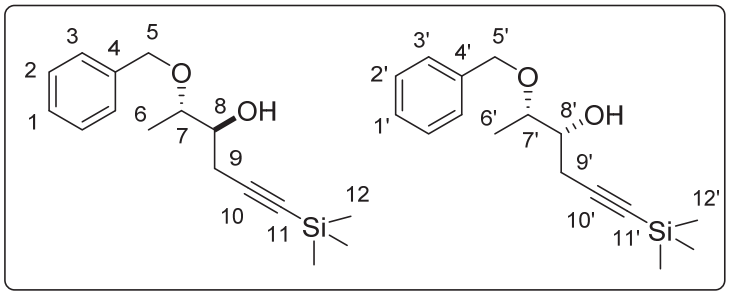


To 51 mL of THF at -78°C, was added tBuLi (1.9M in pentane, 14.8 mL, 28 mmol) dropwise followed by trimethylsilyl prop-1-yne (4.15 mL, 28 mmol). The resulting mixture was stirred at -78 °C for 2h30 and then copper(I) iodide (2.9 g, 15.3 mmol) was added. The acetone/dry ice bath was replaced with an ice bath (0°C) for 30 minutes; the solution became dark red. The solution was once again lowered to -78°C and aldehyde **4.111** (2.4 g, 12.7 mmol) was added dropwise. The reaction mixture was stirred for 2h at -78°C

[11] Z. Rappoport, S. Winstein, W. G. Young, *J. Am. Chem. Soc.* **1972**, *94*, 2320.

and was added on a saturated NH_4Cl solution at 0°C and stirred overnight. The aqueous phase was extracted with EtOAc (5x). The organic phases were combined and washed with a saturated solution of NH_4Cl (4x), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (eluent: PE/Et_2O 30:1) to afford the pure product as a yellow oil and a mixture of 2 diastereomers (1:1); yield: 3.0 g (74 %).

- (2S)-2-(benzyloxy)-6-(trimethylsilyl)hex-5-yn-3-ol **4.112**



The two diastereomers were differentiated in NMR but the absolute stereochemistry at C8 is unknown. It has been attributed arbitrarely for the clarity of the spectra analysis.

^{1}H NMR (300MHz, $CDCl_3$): δ 7.38-7.28 (m, 10H, H_{ar}), 4.69-4.46 (m, 4H, $H_{5,5'}$), 3.82-3.78 (m, 1H, H_8), 3.67-3.60 (m, 3H, $H_{8',7,7'}$), 2.59-2.44 (m, 4H, $H_{9,9'}$), 1.24 (d, 3H, J= 9 Hz, H_6), 1.22 (d, 3H, J=9 Hz, $H_{6'}$), 0.15 (s, 18H, H_{12}, $H_{12'}$).

^{13}C NMR (75MHz, $CDCl_3$): δ 138.4 (C_4), 138.3 ($C_{4'}$), 128.6-128.5 (C_2,$C_{2'}$), 127.9-127.8 (C_1,$C_{1'}$,C_3,$C_{3'}$), 103.3 ($C_{10'}$), 103.8 (C_{10}), 87.4 ($C_{11'}$), 87 (C_{11}), 76.5 ($C_{7'}$), 76.2 (C_7), 73.3 ($C_{8'}$), 72.1 (C_8), 71.3 ($C_{5'}$), 71.1 (C_5), 25.0 ($C_{9'}$), 24.4 (C_9), 15.7 ($C_{6'}$), 14.5 (C_6), 0.2 ($C_{12,12'}$).

IR (film, cm^{-1}): 698, 732, 777, 840, 970, 1002, 1072, 1249, 1454, 2175, 2970.

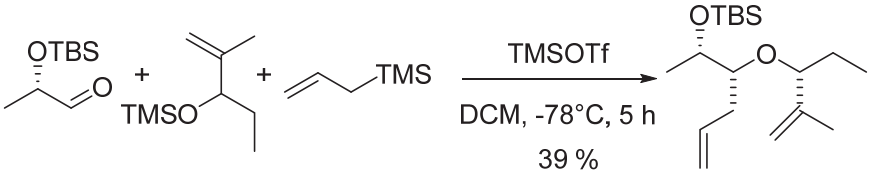
MS (ESI) *m/z* (%): 277.16 (32) $[M+1]^+$, 299.14 (100) $[M+Na]^+$.

HRMS *m/z*: calculated for $C_{16}H_{25}O_2Si$: 277.16205. Found: 277.16183.

II.2. Synthesis of DHP 4.099

II.2.1. Sequence via SMS reaction

II.2.1.1.SMS reaction

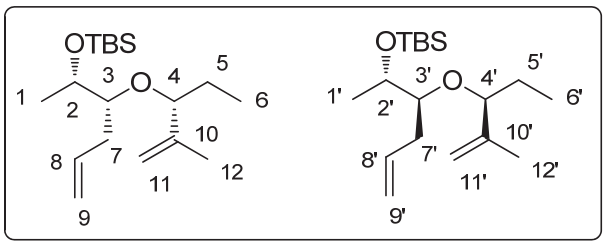


2.035 **4.066** **2.037** **4.095**

2 major dias (1:1)

To a solution of aldehyde (0.31 g, 1.63 mmol) and silylated allylic alcohol (0.30 g, 1.75 mmol), in DCM (8.2 mL) was added allylsilane (0.21 mL, 1.80 mmol). The reaction mixture was refrigerated to -78°C and TMSOTf was added (0.03 mL, 0.16 mmol). The resulting mixture was stirred at -78°C for 3 hours then diisopropylamine was added at the same temperature to quench the reaction. Temperature was allowed to rise to room temperature and the mixture was then concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (Eluent: PE/DCM 20:1 → 5:1) to afford the desired product as a mixture of 2 diastereomers; Yield 0.19 g (39 %).

- *Tert*-butyldimethyl(((2S,3R)-3-(((R)-2-methylpent-1-en-3-yl)oxy)hex-5-en-2-yl)oxy)silane and *Tert*-butyldimethyl(((2S,3S)-3-(((S)-2-methylpent-1-en-3-yl)oxy)hex-5-en-2-yl)oxy)silane **4.095a** ans **4.095b**[1,4]

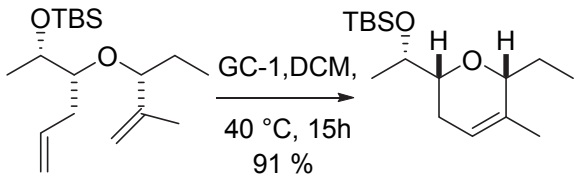


^{1}H NMR (300MHz, $CDCl_3$): δ 5.83-5.77 (m, 2H, $H_{8 \text{ and } 8'}$), 5.05-4.83 (m, 8H, $H_{9, 9', 11 \text{ and } 11'}$), 3.98-3.92 (m, 2H, $H_{4 \text{ and } 2'}$), 3.90-3.79 (m, 1H, H_2), 3.60 (t, 1H, $H_{4'}$, J=7.2Hz), 3.36-3.31 (m, 1H, H_3), 3.27-3.24 (m, 1H, $H_{3'}$), 2.42-2.07 (m, 4H, $H_{7 \text{ and } 7'}$), 1.63 (s, 3H, H_{12}), 1.58 (s, 3H, $H_{12'}$), 1.40-1.58 (m, 4H, $H_{5 \text{ and } 5'}$), 1.13 (d, 3H, H_1, J=6.3 Hz), 1.08 (d, 3H, $H_{1'}$, J=6.3Hz), 0.88-0.83 (m, 24H, $H_{6, 6', \text{ and TBS}}$), 0.04 (s, 12H, H_{TBS}).

^{13}C NMR (75MHz, $CDCl_3$): δ 145.1 (C_{10}), 144.9 ($C_{10'}$), 137.3 (C_8), 136.0 ($C_{8'}$), 116.4-115.8-114.2-113-9 ($C_{9, 9', 11, 11'}$), 85.6 (C_4), 84.2 ($C_{4'}$), 80.4 (C_3), 79.0 ($C_{3'}$), 70.6 (C_2), 67.1 ($C_{2'}$), 36.7 (C_7), 33.2 ($C_{7'}$), 26.5 (C_5), 26.3 ($C_{5'}$), 26.0-25.9 (C_{TBS}), 22.7 (C_{TBS}), 18.5 (C_1), 18.1 ($C_{1'}$), 17.2 (C_{TBS}), 16.6 (C_{12}), 16.4 ($C_{12'}$), 10.5 (C_6), 10.4 ($C_{6'}$), -4.3/-4.5/-4.6 (C_{TBS}).

Data are in agreement with literature values.

II.2.1.2.Grubbs metathesis

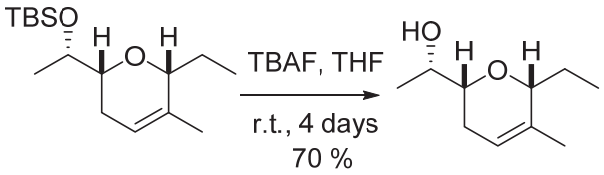


4.095 **4.099**

To a solution of substrate (1 g, 3.2 mmol) in DCM (32 mL) was added Grubbs-I catalyst (0.132 g, 0.16 mmol). The mixture was stirred at 40°C overnight and then concentrated under reduced pressure. The crude solution

was filtered on silica gel, rinsed with DCM and used without further purification in the next step.

II.2.1.3.TBAF deprotection

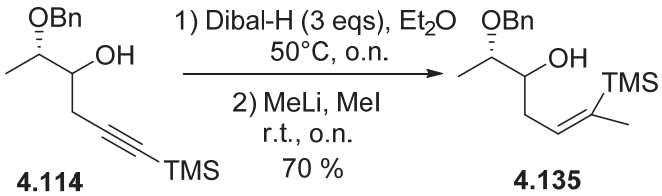


4.098 **4.099**

To a solution of substrate (1 g, 3.5 mmol) in THF (18 mL) was added TBAF (1 M in THF) (7 mL, 7 mmol). The reaction mixture was stirred at room temperature for 4 days, quenched with water and extracted with Et_2O (3x). The organic phases were combined, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (Eluent PE/Et_2O 5:1) to afford the desired product as a mixture of 2 diastereomers. Yield: 0.43g (79 % over two steps). (See page 251 for analysis).

II.2.2. Sequence via ISMS

II.2.2.1.Hydroalumination

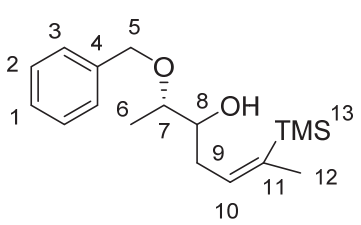


4.114 **4.135**

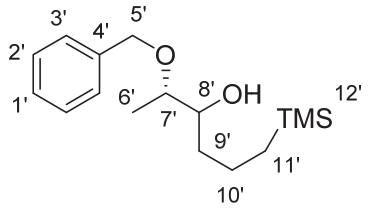
To a solution of homopropargyl alcohol (1 g, 3.6 mmol) in THF (0.3 mL) and Et_2O (12 mL) at 0°C was added dropwise DIBAL-H (1 M in hexane) (10.8 mL, 10.8 mmol). The resulting solution was stirred at 50°C for 24 hours. The reaction mixture was then cooled to 0°C and MeLi (1.6 M in

Et_2O) (6.8 mL, 10.8 mmol) was added dropwise. After stirring at room temperature for 30 minutes, methyl iodide (1.1 mL, 18.1 mmol) was added. The resulting solution was stirred at room temperature for 48 hours. The solution was poured onto HCl/ice and filtered over celite. The aqueous phase was extracted with Et_2O (3x). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography to afford the desired product inseparable from the side-product.

- (2*S*,*Z*)-2-(benzyloxy)-6-(trimethylsilyl)hept-5-en-3-ol **4.135** and (2*S*)-2-(benzyloxy)-6)(trimethylsilyl)hexan-3-ol **4.144**



4.135



4.144

^{1}H NMR (300MHz, $CDCl_3$): δ 7.36-7.28 (m, 10H, H_{ar}), 6.11-5.99 (m, 1H, H_{10}), 4.70-4.42 (m, 4H, $H_{5 \text{ and } 5'}$), 3.81-3.72 (m, 1H, H_7), 3.55-3.39 (m, 3H, $H_{7', 8 \text{ and } 8'}$), 2.31-2.26 (m, 2H, H_9), 1.78 (s, 3H, H_{12}), 1.51-1.32 (m, 4H, $H_{10' \text{ and } 9'}$), 1.22-1.14 (m, 6H, $H_{6 \text{ and } 6'}$), 0.57-0.41 (m, 2H, $H_{11'}$), 0.13 (s, 9H, H_{13}), 0.03 (s, 9H, $H_{12'}$).

^{13}C NMR (75MHz, $CDCl_3$): δ 138.5 (C_{10}), 137.8 ($C_{4 \text{ and } 4'}$), 128.5-127.8-127.7 ($C_{1,2,3,1',1',3'}$), 78.7 (C_8), 74.9-73.5-72.8 ($C_{8',7,7'}$), 71.1-70.9 ($C_{5,5'}$), 36.9-36.0 ($C_{9',10'}$), 34.4 (C_9), 24.8 (C_{12}), 16.7 ($C_{11'}$) 15.4 ($C_{6,6'}$), 0.37- -1.56 ($C_{13, 12'}$)

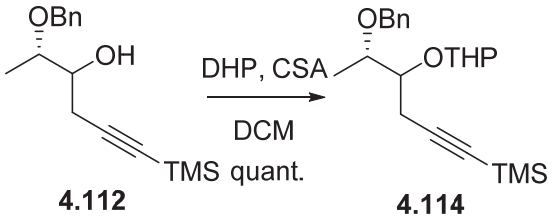
MS (ESI) *m/z* (%): 303.17 (23) $[M'+Na]^+$, 315.17 (100) $[M+Na]^+$

HRMS *m/z*: calculated for $C_{17}H_{28}O_2SiNa$: 315.17554. Found: 315.17508.

IR (film, cm^{-1}): 696, 735, 837, 1074, 1088, 1248, 1373, 1454, 1616, 2906.

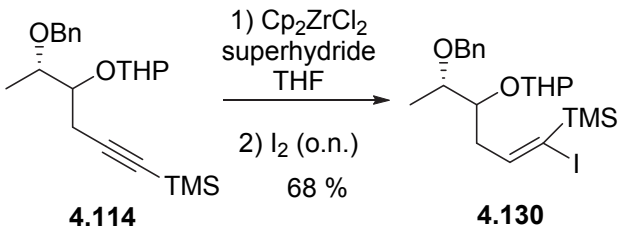
II.2.2.2.Hydrozirconation

II.2.2.2.1. Protection with THP



To a solution of substrate (1 g, 3.62 mmol) in DCM (18 mL) were added DHP (0.49 mL, 5.43 mmol) and CSA (0.08 g, 0.36 mmol). The resulting solution was stirred at room temperature for 18 hours. It was quenched with a saturated solution of K_2CO_3 and extracted with DCM (3x). The organic phases were combined, washed with a saturated solution of $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The product was used without further purification in the next step.

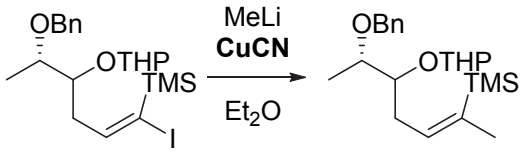
II.2.2.2.2. Hydrozirconation



To a solution of Cp_2ZrCl_2 (0.41 g, 1.38 mmol) in THF (4.6 mL) was added Et_3BHLi (1.38 mL, 1.38 mmol) dropwise very slowly. The resulting white opaque solution indicates that Schwartz reagent is formed. The mixture was stirred for 1 hour hidden from light. A solution of substrate **4.114** (0.2 g, 0.55 mmol) in THF (3 mL) was added dropwise and the resulting mixture was heated to 55°C for 1 hour. After cooling down, a solution of I_2 (0.5 g) in THF (2 mL) was added dropwise and the mixture was stirred at room

temperature for 18 hours. The solution was then quenched with a saturated solution of $Na_2S_2O_3$ and extracted with EtOAc (3x). The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent: PE/Et_2O → 20:1) to afford the desired product as a mixture of 4 diastereomers. Yield: 0.185 g (68 %).

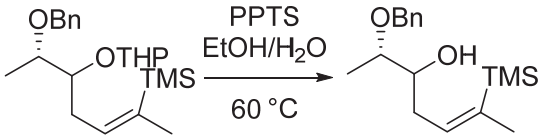
II.2.2.2.3. Methylation



4.130 **4.134**

To a solution of CuCN (0.07 g, 0.83 mmol) in Et_2O (1.3mL) at 0°C was added MeLi (0.7 mL of 1.6 M solution in Et_2O, 1.14 mmol) dropwise. It was stirred for 15 minutes at 0°C and then the substrate (0.185 g, 0.38 mmol) was added dropwise. The resulting solution was stirred at 0°C for 24 hours. The mixture was then quenched with water and extracted with Et_2O (3x). The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was used without further purification in the next step.

II.2.2.2.4. Deprotection

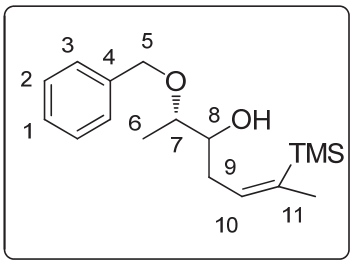


4.134 80 % over two steps **4.135**

The crude product (0.115 g, 0.235 mmol) was taken up in a mixture EtOH/ H_2O (2.1/0.2 mL). PPTS was added (0.006 g, 0.024 mmol) and the resulting

solution was stirred at 65°C for 18 hours. It was then quenched with a saturated solution of NH_4Cl and extracted with Et_2O (3x). The organic phases were combined, washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent: PE/Et_2O →20:1) to afford the desired product as a yellow oil and a mixture of 2 diastereomers (1:1). Yield: 0.079 g (88 %). (80 % over two steps).

- (2*S*,*Z*)-2-(benzyloxy)-6-(trimethylsilyl)hept-5-en-3-ol **4.135**



^{1}H NMR (300MHz, $CDCl_3$): δ 7.33-7.29 (m, 10H, H_{ar}), 6.08-5.98 (m, 2H, $H_{10 \text{ and } 10'}$), 4.68-4.43 (m, 4H, $H_{5 \text{ and } 5'}$), 3.75-3.71 (m, 1H, H_8), 3.54-3.49 (3H, $H_{7, 7' \text{ and } 8'}$), 2.32-2.25 (m, 4H, $H_{9 \text{ and } 9'}$), 1.78 (s, 6H, $H_{11 \text{ and } 11'}$), 1.23 (t, 6H, $H_{6 \text{ and } 6'}$, J=6Hz), 0.13 (s, 18H, H_{TMS}).

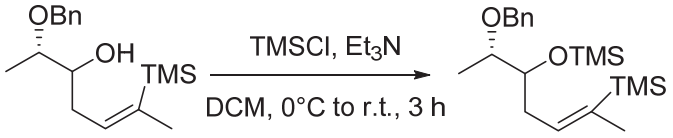
^{13}C NMR (75MHz, $CDCl_3$): δ 138.6-138.4-138.3-138.0-137.9-137.6 ($C_{4, 4',10,10',11,11'}$), 128.5-127.9-127.7 ($C_{2,2',3,3',4,4'}$), 77.8 (C_7) , 77.3 ($C_{7'}$), 75.1 (C_8), 73.5 ($C_{8'}$), 71.1 (C_5), 70.9 ($C_{5'}$), 35.3 (C_9), 34.7 ($C_{9'}$), 25.0 (C_{11}), 24.9 ($C_{11'}$), 15.7 (C_6), 14.0 ($C_{6'}$), 0 (C_{TMS}).

MS (ESI) *m/z* (%): 315.17 (100) $[M+Na]^+$, 331.15 (22) $[M+K]^+$, 607.36 (76) $[2M+Na]^+$.

HRMS *m/z*: calculated for $C_{17}H_{28}O_2NaSi$: 315.17515. Found: 315.17508.

IR (film, cm^{-1}): 652, 696, 735, 752, 835, 997, 1028, 1074, 1132, 1248, 1373, 1454, 2854, 2869, 2926, 2951, 3498.

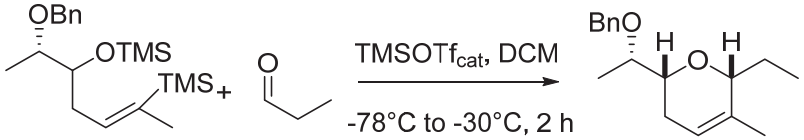
II.2.2.3.Silylation



4.135 **4.136**

To a solution of alcohol (0.58 g, 2 mmol) and TMSCl (0.3 mL, 2.4 mmol) in DCM (10 mL) at 0°C was added dropwise Et_3N (0.35 mL, 2.6 mmol). The reaction mixture was stirred at room temperature overnight. Saturated $NaHCO_3$ was added and the aqueous phase was extracted with dichloromethane (3x). The organic phases were combined, washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was used without further purification in the next step.

II.2.2.4.ISMS



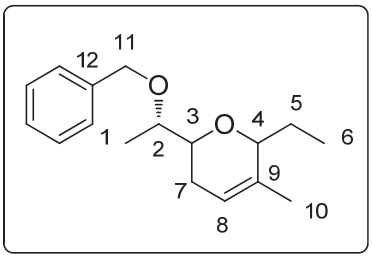
4.136 **4.137** **4.138**

To a solution of substrate (0.32 g, 0.88 mmol) and propionaldehyde (0.07 mL, 0.97 mmol) in DCM (4.4 mL) at -78°C was added TMS-OTf (0.06 mL, 0.35 mmol). The resulting mixture was stirred for 2 hours and allowed to warm up to -30°C. Quench was performed at -30°C with pyridine followed by a saturated solution of $NaHCO_3$. The aqueous phase was extracted with DCM (3x). The organic phases were combined, washed with 1M HCl, dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (eluent: PE/Et_2O 30:1) to

afford the pure product as a yellow oil, mixture of 2 diastereomers (1:1); yield 0.18g (79%).

- 2-((S)-1-(benzyloxy)ethyl)-6-ethyl-5-methyl-3,6-dihydro-2H-pyran

4.138



^{1}H NMR (300MHz, $CDCl_3$): δ 7.37-7.26 (m, 5H, H_{ar}), 5.56 (bs, 1H, H_8), 4.70-4.57 (m, 2H, H_{11}), 4.09-3.95 (m, 1H, H_4), 3.60-3.47 (m, 1H, H_2), 3.45-3.38 (m, 1H, H_3), 2.08-2.05 (m, 2H, H_7), 1.80-1.72 (m, 1H, H_5), 1.58 (s, 3H, H_{10}), 1.53-1.39 (m, 1H, H_5), 1.22 (d, 3H, H_1, J=6 Hz,), 0.90 (t, 3H, H_6, J=6 Hz).

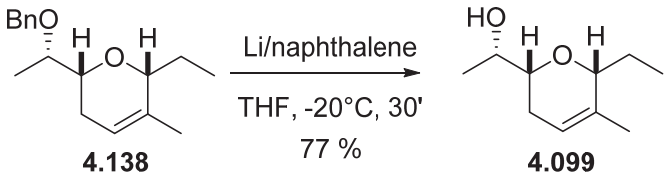
^{13}C NMR (75MHz, $CDCl_3$): δ 139.2 (C_{12}), 135.4 (C_9), 128.4-127.8-127-5 (C_{ph}), 120.7 (C_8), 78.5 (C_4), 77.4 ($C_{2\ and\ 3}$), 71.4 (C_{11}), 27.3 (C_7), 25.9 (C_5), 19.1 (C_{10}), 16.7 (C_1), 8.9 (C_6).

MS (ESI) *m/z* (%): 91.05 (18), 261.18 (76) $[M+1]^+$, 283.16 (100) $[M+Na]^+$.

HRMS *m/z*: calculated for $C_{17}H_{25}O_2$: 261.18496. Found: 261.18491.

IR (film, cm^{-1}): 696, 733, 845, 910, 927, 1028, 1059, 1089, 1095, 1207, 1371, 1454, 2897.

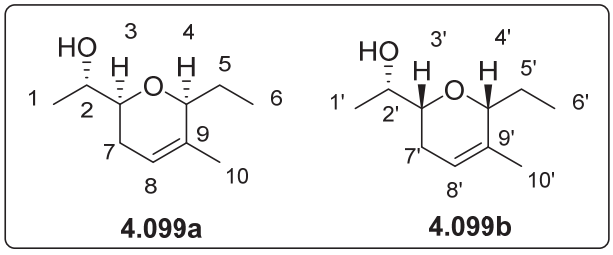
II.2.2.5.Debenzylation



4.138 **4.099**

To a solution of naphthalene (1.77 g, 13.8 mmol) in THF (6 mL) was added lithium (0.1 g, 13.8 mmol). The solution was stirred at room temperature for 2 hours and turned dark green after a few minutes. The substrate (0.72 g, 2.77 mmol) was then added at -20°C and the solution was stirred at that temperature for 30 minutes. The resulting mixture was quenched with water and extracted with EtOAc (3x). The organic phases were combined, washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent: PE/Et_2O 8:1) to afford the 2 separated diastereomers as colorless oils; yield:0.363 g (77 %).

- (*S*)-1-((2*S*,6*S*)-6-ethyl-5-methyl-3,6-dihydro-*2H*-pyran-2-yl)ethanol **4.099a** and (*S*)-1-((2*R*,6*R*)-6-ethyl-5-methyl-3,6-dihydro-*2H*-pyran-2-yl)ethanol **4.099b**



4.099a **4.099b**

Dia **4.099a**

^{1}H NMR (300MHz, $CDCl_3$): δ 5.53 (bs, 1H, H_8), 4.03 (bs, 1H, H_4), 3.67-3.60 (m, 1H, H_2), 3.26-3.20 (m, 1H, H_3), 2.89 (s, 1H, -OH), 1.91-1.88 (m, 2H, H_7), 1.81-1.72 (m, 1H, H_5), 1.60 (s, 3H, H_{10}), 1.59-1.43 (m, 1H, H_5), 1.15 (d, 3H, H_1, J=6 Hz), 0.91 (t, 3H, H_6, J=9 Hz).

^{13}C NMR (75MHz, $CDCl_3$): δ 135.6 (C_9), 120.0 (C_8), 78.2 ($C_{4\ and\ 3}$), 70.6 (C_2), 27.5 (C_7), 25.7 (C_5), 19.0 (C_{10}), 18.0 (C_1), 8.8 (C_6).

MS (ESI) *m/z* (%): 71.08 (100), 95.08 (33), 109.10 (41), 135.11 (41), 153.12 (55) (-OBn), 171.14 (80) $[M+1]^+$, 193.12 $[M+Na]^+$

HRMS *m/z*: calculated for $C_{10}H_{19}O_2$: 171.13818. Found: 171.13796

IR (film, cm^{-1}): 739, 845, 870, 888, 927, 991, 1026, 1057, 1082, 1115, 1260, 1367, 1377, 1464, 2933, 3441.

$[\alpha]_D^{20}$ = -73.3 (c=1.6 M, $CHCl_3$)

Dia **4.099b**[1]

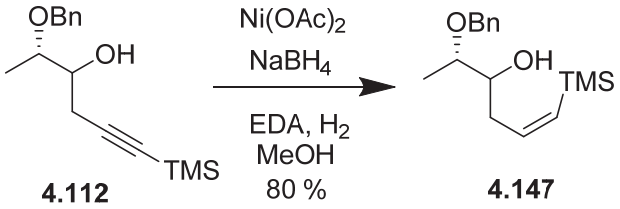
^{1}H NMR (300MHz, $CDCl_3$): δ 5.58 (bs, 1H, $H_{8'}$), 4.09 (bs, 1H, $H_{4'}$), 3.93-3.90 (m, 1H, $H_{2'}$), 3.49-3.39 (m, 1H, $H_{3'}$), 2.20-2.11 (m, 1H, $H_{7'}$),1.85-1.80 (m, 1H, $H_{7'}$), 1.78-1.70 (m, 1H, $H_{5'}$), 1.60 (s, 3H, $H_{10'}$), 1.56-1.44 (m, 1H, $H_{5'}$), 1.15 (d, 3H, $H_{1'}$, J=6 Hz), 0.88 (t, 3H, $H_{6'}$, J=9 Hz).

^{13}C NMR (75MHz, $CDCl_3$): δ 135.2 ($C_{9'}$), 120.5 ($C_{8'}$), 78.2 ($C_{4'}$), 76.1 ($C_{3'}$), 69.3 ($C_{2'}$), 25.7 ($C_{7'}$), 24.3 ($C_{5'}$), 19.0 ($C_{10'}$), 17.5 ($C_{1'}$), 8.5 ($C_{6'}$).

Data are in agreement with literature values.

II.3. Synthesis of DHP 4.182

II.3.1. P2-nickel[12]



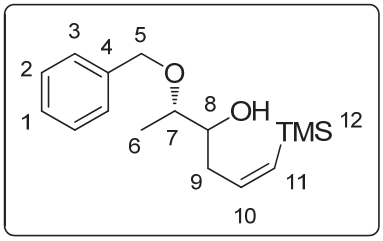
4.112 **4.147**

To a solution of $Ni(OAc)_2.4H_2O$ (0.13 g, 0.7 mmol) in MeOH (1 mL) was added carefully $NaBH_4$ (0.06 g, 1.4 mmol); the solution turned black. The reaction vessel was evacuated and backfilled with hydrogen for 5 minutes. Ethylenediamine was added (0.2 mL, 2.8 mmol) followed by the substrate (0.4 g, 1.4 mmol). The resulting mixture was stirred for 18 hours under hydrogen. It was then filtered over silica gel and washed with MeOH. After

[12] D. F. Taber, R. J. Herr, D. M. Gleave, *J. Org. Chem.* **1997**, *62*, 194.

concentration under reduced pressure, the residue was diluted in PE/EtOAc (1:1) and washed with water and brine. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the desired product as a yellow oil, mixture of 2 diastereomers; yield: 0.16 g (80 %).

- (2*S*,*Z*)-2-(benzyloxy)-6-(trimethylsilyl)hex-5-en-3-ol **4.147**



^{1}H NMR (300MHz, $CDCl_3$): δ 7.34-7.25 (m, 10H, H_{ar}), 6.44-6.30 (m, 2H, $H_{10,10'}$), 5.66 (d, 1H, H_{11}, J=9 Hz), 5.62 (d, 1H, $H_{11'}$, J=9 Hz), 4.68-4.42 (m, 4H, $H_{5,5'}$), 3.78-3.75 (m, 2H, $H_{8,8'}$), 3.55-3.49 (m, 2H, $H_{7,7'}$), 2.35-2.16 (m, 4H, $H_{9,9'}$), 1.20 (t, 6H, $H_{6,6'}$, J=6 Hz), 0.11 (s, 18H, $H_{12,12'}$).

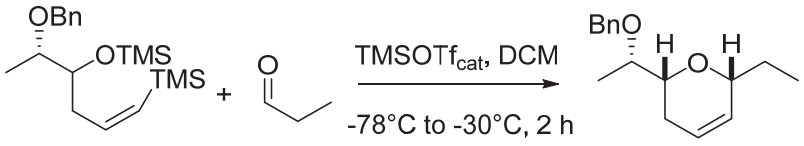
^{13}C NMR (75MHz, $CDCl_3$): δ 144.6 (C_{10}), 144.5 ($C_{10'}$), 138.6 (C_4), 138.4 ($C_{4'}$), 132.4-132.4-131.7 ($C_{2,2'}$), 127.8-127.7 ($C_{1,1',3,3'}$), 77.1 (C_7), 74.7 ($C_{7'}$), 73.2 ($C_{8,8'}$), 71.1 (C_5), 70.9 ($C_{5'}$), 36.7 (C_9), 36.1 ($C_{9'}$), 15.6 (C_6), 14.0 ($C_{6'}$), 0.2 ($C_{12,12'}$).

MS (ESI) *m/z* (%): 277.16 (32) $[M-1]^+$, 301.16 (100) $[M+Na]^+$.

HRMS *m/z*: calculated for $C_{16}H_{26}O_2SiNa$: 301.15939. Found: 301.15943.

IR (film, cm^{-1}): 696, 734, 761, 850, 993, 1027, 1072, 1247, 1375, 1454, 1496, 1604, 2180, 2921, 2954.

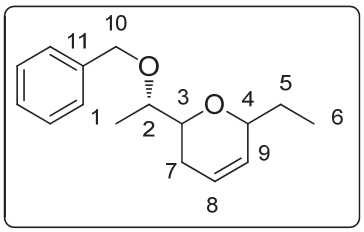
II.3.2. ISMS



4.180 **4.137** **4.181**

To a solution of substrate (1 g, 2.97 mmol) and propionaldehyde (0.26 mL, 3.56 mmol) in DCM (15 mL) at -78 °C was added TMS-OTf (0.21 mL, 0.5 mmol). The resulting mixture was stirred for 2 hours and allowed to warm up to -30 °C. Quench was performed at -30°C with pyridine followed by a saturated aqueous solution of $NaHCO_3$. The aqueous phase was extracted with DCM (3x). The organic phases were combined, washed with 1M HCl, dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (eluent (PE/Et_2O 30:1) to afford the pure product as a yellow oil and a mixture of 2 diastereomers(1:1); yield 0.54 g (74 %).

- 2-((*S*)-1-(benzyloxy)ethyl)-6-ethyl-3,6-dihydro-*2H*-pyran **4.181**



^{1}H NMR (300MHz, $CDCl_3$): δ 7.37-7.26 (m, 10H, H_{Ar}), 5.85-5.78 (m, 2H, H_8), 5.66-5.59 (m, 2H, H_9), 4.71-4.56 (m, 4H, H_{10}), 4.09-4.03 (m, 2H, H_4), 3.67-3.46 (m, 4H, $H_{2\ and\ 3}$), 2.17-1.91 (m, 4H, H_7), 1.61-1.50 (m, 4H, H_5), 1.25 (d, 3H, H_1, , J=6 Hz), 1.17 (d, 3H, $H_{1'}$, J=6 Hz), 1.01-0.93 (m, 6H, H_6).

^{13}C NMR (75MHz, $CDCl_3$): δ 139.4 (C_{11}), 139.1 ($C_{11'}$), 130.5 (C_9), 130.2 ($C_{9'}$), 128.4-127.9-127.8-127.5-127.4 (C_{ar}), 124.8 (C_8), 124.5 ($C_{8'}$), 77.4 (C_4

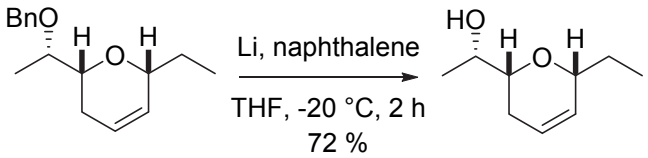
and 4'), 76.3-76.2 ($C_{3,3',2,2'}$), 72.1 (C_{10}), 71.4 ($C_{10'}$), 28.7 (C_5), 28.6 ($C_{5'}$), 27.3 (C_7), 26.8 ($C_{7'}$), 16.6 (C_1), 15.8 ($C_{1'}$), 9.8 (C_6), 9.6 ($C_{6'}$).

MS (ESI) *m/z* (%): 91.05 (46), 175.11 (100), 247.16 (28) $[M+1]^+$, 269.15 (100) $[M+Na]^+$.

HRMS *m/z*: calculated for $C_{16}H_{23}O_2$: 247.16916. Found: 247.16926.

IR (film, cm^{-1}): 675, 696, 732, 1027, 1064, 1184, 1373, 1454, 2923.

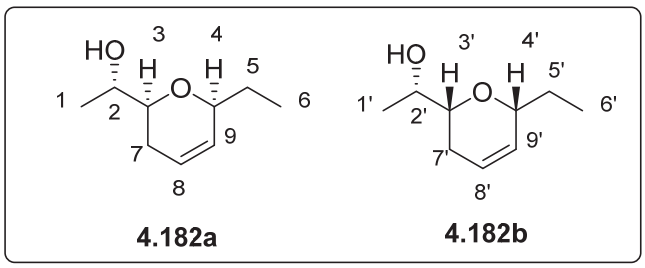
II.3.3. Deprotection



4.181 **4.182**

To a solution of naphthalene (1.52 g, 11.9 mmol) in THF (18.5 mL) was added lithium (0.08g, 11.9 mmol). The solution was stirred at room temperature for 2 hours and turned dark green after a few minutes. The substrate (0.62 g, 2.38 mmol) was then added at -20°C and the solution was stirred at that temperature for 30 minutes. The resulting mixture was quenched with water and extracted with EtOAc (3x). The organic phases were combined, washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent: PE/Et_2O 8:1) to afford the 2 separated diastereomers (1:1) as colorless oils; yield: 0.29 g (72 %).

- (*S*)-1-((2*S*,6*S*)-6-ethyl-3,6-dihydro-*2H*-pyran-2-yl)ethanol **4.182a** and (*S*)-1-((2*R*,6*R*)-6-ethyl-3,6-dihydro-*2H*-pyran-2-yl)ethanol **4.182b**



4.182a **4.182b**

Dia **4.182a**

^{1}H NMR (300MHz, $CDCl_3$): δ 5.83-5.78 (m, 1H, H_8), 5.67-5.63 (m, 1H, H_9), 4.08-4.05 (m, 1H, H_4), 3.70-3.61 (m, 1H, H_2), 3.37-3.29 (m, 1H, H_3), 2.93 (bs, 1H, -OH), 1.98-1.92 (m, 2H, H_7), 1.65-1.53 (m, 2H, H_5), 1.16 (d, 3H, H_1, J=6 Hz), 0.96 (t, 3H, H_6, J=9 Hz,).

^{13}C NMR (75MHz, $CDCl_3$): δ 130.2 (C_9), 124.1 (C_8), 78.7 (C_3), 76.0 (C_4), 70.6 (C_2), 28.5 (C_5), 27.3 (C_7), 17.9 (C_1), 9.6 (C_6).

$[\alpha]_D^{20}$ = -1.1 (c=1.1 M, $CHCl_3$)

Dia **4.182b**

^{1}H NMR (300MHz, $CDCl_3$): δ 5.87-5.82 (m, 1H, H8'), 5.67-5.59 (m, 1H, $H_{9'}$), 4.10 (m, 1H, $H_{4'}$), 3.94-3.91 (m, 1H, $H_{2'}$), 3.53-3.47 (m, 1H, $H_{3'}$), 2.27-2.17 (m, 1H, $H_{7'}$), 1.98-1.88 (m, 1H, $H_{7'}$), 1.58-1.43 (m, 2H, $H_{5'}$), 1.15 (d, 3H, $H_{1'}$, J=6 Hz), 0.92 (t, 3H, $H_{6'}$, J=9 Hz).

^{13}C NMR (75MHz, $CDCl_3$): δ 129.9 ($C_{9'}$), 124.6 ($C_{8'}$), 77.2 ($C_{3'}$), 76.0 ($C_{4'}$), 69.3 ($C_{2'}$), 28.5 ($C_{5'}$), 24.2 ($C_{7'}$), 17.6 ($C_{1'}$), 9.4 ($C_{6'}$).

$[\alpha]_D^{20}$ = +14 (c=1.8 M, $CHCl_3$).

MS (ESI) *m/z* (%): 139.11 (16), 157.12 (6) $[M+1]^+$, 179.10 (100) $[M+Na]^+$

HRMS *m/z*: calculated for $C_9H_{17}O_2$: 157.12224. Found: 157.12231.

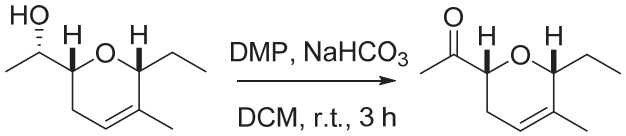
IR (film, cm^{-1}): 790, 1075, 1353, 1485, 1650, 2922, 3440.

II.4. Oxidation of DHP 4.099 and 4.182

II.4.1. General procedure

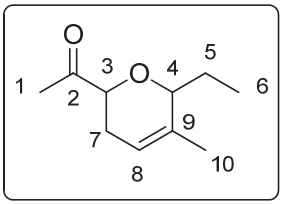
To a solution of substrate (1 eq) in DCM (0.2 M) was added dry $NaHCO_3$ (4 eqs). Dess-Martin periodane (1.2 eq) was then added at 0°C and the reaction was warmed up to room temperature and stirred for 3 hours. The reaction was filtered through a pad of celite and rinsed with Et_2O (3x). The solvent was carefully concentrated. The products are highly volatile.

II.4.2. Synthesis of ketone 4.170



4.099 **4.170**

- 1-(6-ethyl-5-methyl-3,6-dihydro-*2H*-pyran-2-yl)ethanone **4.170**



The reaction was carried out on 1.6 mmol (0.27 g).

The crude mixture was purified by silica gel column chromatography (eluent: PE/Et_2O 10:1) to afford the desired product as a clear oil and a racemic mixture of two enantiomers; yield: 0.047 g (18 %).

^{1}H NMR (300MHz, $CDCl_3$): δ 5.56 (bs, 1H, H_8), 4.08 (bs, 1H, H_4), 3.98 (dd, 1H, H_3, J=3 Hz, J=9 Hz), 2.24 (s, 3H, H_1), 2.13-2.08 (m, 2H, H_7), 1.86-1.74 (m, 1H, H_5), 1.59 (s, 3H, H_8), 1.55-1.47 (m, 1H, H_5), 0.94 (t, 3H, H_6, J=9 Hz).

^{13}C NMR (75MHz, $CDCl_3$): δ 210.2 (C_2), 135.8 (C_9), 119.7 (C_8), 78.9 (C_3), 78.5 (C_4), 27.5 (C_7), 25.9 (C_4), 25.8 (C_1), 19.0 (C_{10}), 8.8 (C_6).

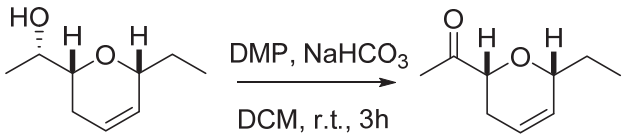
MS (ESI) *m/z* (%): 141.12 (13), 169.12 (24) $[M+1]^+$, 191.10 (100) $[M+Na]^+$.

HRMS *m/z*: calculated for $C_{10}H_{17}O_2$: 169.12229. Found: 169.12231.

IR (film, cm^{-1}): 748, 850, 921, 1052, 1115, 1248, 1347, 1452, 1720, 2879, 2935, 2966.

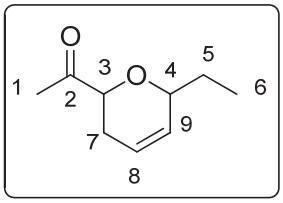
Chiral GC: T=50°C (2 min) to 120°C (2 min); 10°C/min – T=120°C to 140 °C (10 min); 5°C/min – T=140°C to 160°C (3 min); 30°C/min; t_r : 14.4 min and 14.9 min.

II.4.3. Synthesis of ketone 4.183



4.182 **4.183**

- 1-(6-ethyl-3,6-dihydro-*2H*-pyran-2-yl)ethanone **4.183**



The reaction was carried out on 1.25 mmol (0.19 g).

The pure product was isolated as a racemic mixture of two enantiomers without purification; yield: 0.12 g (62%).

^{1}H NMR (300MHz, $CDCl_3$): δ 5.85-5.66 (m, 1H, H_8), 5.66-5.61 (m, 1H, H_9), 4.14-4.10 (m, 1H, H_4), 3.99 (dd, 1H, H_3, J=4.5 Hz), 2.24 (s, 3H, H_1), 2.19-2.11 (m, 2H, H_7), 1.62-1.54 (m, 2H, H_5), 0.97 (t, 3H, H_6, J=7.4 Hz).

^{13}C NMR (75MHz, $CDCl_3$): δ 209.8 (C_2), 130.3 (C_9), 123.8 (C_8), 79.2 (C_3), 76.3 (C_4), 28.4 (C_5), 21.2 (C_7), 25.9 (C_1), 9.5 (C_6).

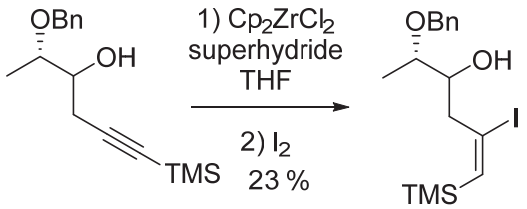
MS (ESI) *m/z* (%) : 95.01 (59), 177.09 (100) $[M+Na]^+$.

HRMS *m/z*: calculated for $C_9H_{14}O_2Na$: 177.08862. Found: 177.08860.

IR (film, cm^{-1}): 733, 910, 1095, 1355, 1463, 1718, 2852, 2823, 2962.

II.5. Synthesis of other DHPs

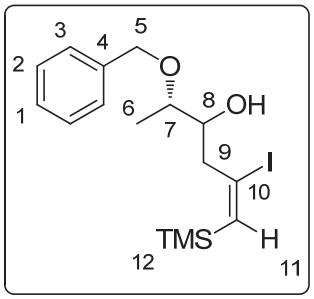
II.5.1. Hydrozirconation



4.112 **4.157**

To a solution of Cp_2ZrCl_2 (1.69 g, 5.79 mmol) in THF (15 mL) was added Et_3BHLi (5.8 mL, 5.79 mmol) dropwise very slowly. The resulting white opaque solution indicates that Schwartz reagent is formed. It was stirred for 1 hour hidden from light. A solution of substrate **4.112** (0.5 g, 1.81 mmol) in THF (5 mL) was added dropwise and the solution was heated to 55°C for 1 hour. After cooling down, a solution of I_2 (1.5 g) in THF (6 mL) was added dropwise and the mixture was stirred at room temperature for 18 hours. It was then quenched with a saturated aqueous solution of $Na_2S_2O_3$ and extracted with EtOAc (3x). The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent: PE/Et_2O → 30:1) to afford the desired product as a mixture of 2 diastereomers (1:1). Yield: 0.17 g (23 %).

- (2*S*,*E*)-2-(benzyloxy)-5-iodo-6-(trimethylsilyl)hex-5-en-3-ol **4.157**



^{1}H NMR (300MHz, $CDCl_3$): δ 7.33-7.27 (m, 10H, H_{ar}), 6.53 (bs, 2H, $H_{11,11'}$), 4.69-4.44 (m, 4H, $H_{5,5'}$), 4.07-3.98 (m, 1H, $H_{8,}$), 3.92-3.85 (m, 1H, $H_{8'}$), 3.65-3.57 (m, 1H, H_7), 3.56-3.48 (m, 1H, $H_{7'}$), 2.65-2.43 (m, 4H, $H_{9,9'}$), 2.20 (d, 1H, -OH, J=6 Hz,), 1.98 (d, 1H, -OH', J=6 Hz,), 1.25 (d, 3H, H_6, J=6 Hz,), 1.20 (d, 3H, $H_{6'}$, J=6 Hz,), 0.12 (s, 18H, $H_{12,12'}$).

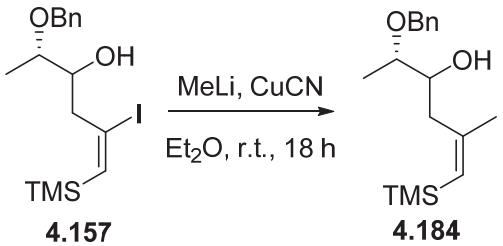
^{13}C NMR (75MHz, $CDCl_3$): δ 147.8 (C_{11}), 147.4 ($C_{11'}$), 138.5 (C_4), 138.3 ($C_{4'}$), 128.5-127.9-127.8 ($C_{1,2,3,1',2',3'}$), 115.5 (C_{10}), 115.4 ($C_{10'}$), 77.0 ($C_{7,7'}$), 73.8 (C_8), 73.0 ($_{8'}$), 71.1 ($_{5,5'}$), 48.3 ($_9$), 47.2 ($C_{9'}$), 15.7 (C_6), 15.1 ($C_{6'}$), 0.3 ($C_{12,12'}$).

MS (ESI) *m/z* (%): 427.05 (85) $[M+Na]^+$

HRMS *m/z*: calculated for $C_{16}H_{25}O_2INaSi$: 427.05629. Found: 427.05607

IR (film, cm^{-1}): 696, 733, 841, 908, 972, 1028, 1072, 1088, 1248, 1377, 1454, 1585, 2851, 2898, 2921, 2954.

II.5.2. Methylation

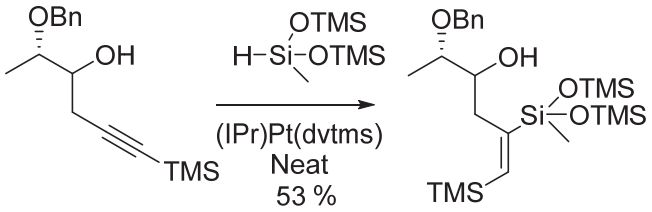


4.157 **4.184**

To a solution of CuCN (0.08 g, 0.92 mmol) in Et_2O (2 mL) at 0°C was added MeLi (0.8 mL of 1.6 M solution in Et_2O, 1.26 mmol) dropwise. It was stirred

for 15 minutes at 0°C and then the substrate (0.17 g, 0.42 mmol) was added dropwise. The resulting solution was stirred at 0°C for 24 hours. It was then quenched with water and extracted with Et_2O (3x). The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was used without further purification in the next step.

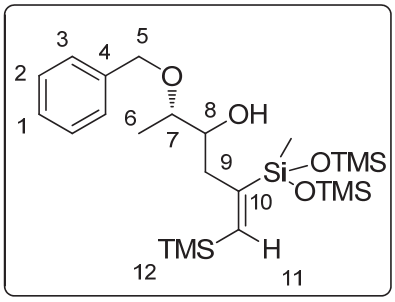
II.5.3. Hydrosilylation



4.112 **4.196**

A mixture of substrate (0.50 g, 1.81 mmol), MD'M (0.40 g, 1.81 mmol) and (IPr)Pt(dvtms) (0.056 g, 0.072 mmol) was stirred at 75 °C for 30 minutes. It was then cooled down to room temperature and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent PE/Et_2O 98:2) to afford the desired product as a clear oil and a mixture of two diastereomers (1:1); yield: 0.48 g (53 %).

- (2*S*,*E*)-2-(benzyloxy)-5-(1,1,1,3,5,5,5-heptamethyltrisiloxan-3-yl)-6-(trimethylsilyl)hex-5-en-3-ol **4.196**



^{1}H NMR (300MHz, $CDCl_3$): δ 7.37-7.28 (m, 10H, H_{ar}), 6.33 (s, 1H, H_{11}), 6.32 (s, 1H, $H_{11'}$), 4.69-4.50 (m, 4H, $H_{5,5'}$), 3.84-3.78 (m, 2H, $H_{8,\ 8'}$), 3.55-3.47 (m, 2H, $H_{7,7'}$), 2.60-2.35 (m, 5H, $H_{9,\ 9',\ OH}$), 2.21 (d, 1H, $H_{OH'}$, , J=3 Hz), 1.23 (d, 6H, H_6, J=6 Hz), 0.15-0.10 (m, 60H, H_{TMS}).

^{13}C NMR (75MHz, $CDCl_3$): δ 159.4 ($C_{10,10'}$), 147.3 (C_{11}), 146.9 ($C_{11'}$), 139.05 ($C_{4,4'}$), 128.4-127.8-127.8-127.5 (C_{ar}), 78.1 ($C_{7,7'}$), 73.3 (C_8), 73.2 ($C_{8'}$), 71.2 (C_5), 71.1 ($C_{5'}$), 38.8 (C_9), 38.5 ($C_{9'}$), 15.4 (C_6), 15.2 ($C_{6'}$), 2.0-0.5-0.0 (C_{TMS}).

MS (ESI) *m/z* (%):102.13 (18), 171.12 (23), 229.11 (16), 306.29 (13), 337.16 (28), 385.26 (40), 409.20 (55) $[M\text{-}OTMS]^+$, 499.25 (100) $[M+1]^+$, 521.24 (62) $[M+Na]^+$

HRMS *m/z*: calculated for $C_{23}H_{47}O_4Si_4$: 499.25471. Found: 499.25459.

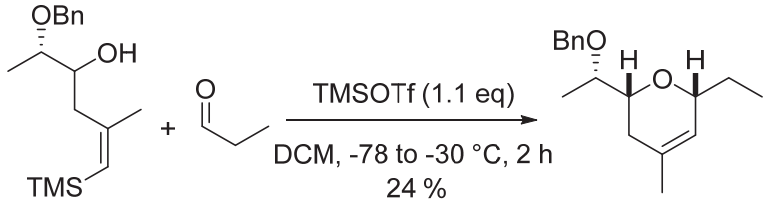
IR (film, cm^{-1}): 696, 742, 754, 785, 839, 1041, 1064, 1250, 2955.

II.5.4. ISMS

II.5.4.1.General procedure

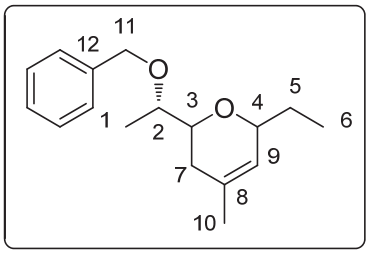
To a solution of substrate (1 eq) and propionaldehyde (1.2 eq) in DCM (0.2 M) at -78°C was added TMS-OTf (1.1 eq). The resulting mixture was stirred for 2 hours and let to warm up to -30°C. It was then quenched at that temperature with pyridine followed by a saturated aqueous solution of $NaHCO_3$. The aqueous phase was extracted with DCM (3x). The organic phases were combined, washed with 0.1 M HCl, dried over Na_2SO_4, filtered and concentrated under vacuum.

II.5.4.2.Synthesis of DHP 4.185



4.184 **4.137** **4.185**

- 2-((*S*)-1-(benzyloxy)ethyl)-6-ethyl-4-methyl-3,6-dihydro-*2H*-pyran **4.185**



The reaction was carried out on 0.4 mmol (0.12 g).

The crude product was purified by silica gel column chromatography (eluent: PE/Et_2O → 30:1) to afford the desired product as a mixture of 2 diastereomers (1:1). Yield: 0.026 g (24 %).

^{1}H NMR (300MHz, $CDCl_3$): δ 7.38-7.29 (m, 10H, H_{ar}), 5.34-5.31 (m, 2H, $H_{9,9'}$), 4.72-4.57 (m, 4H, $H_{11,11'}$), 3.98-3.96 (m, 2H, $H_{4,4'}$), 3.60-3.54 (m, 2H, $H_{2,2'}$), 3.49-3.43 (m, 2H, $H_{3,3'}$), 2.08-1.93 (m, 5H, $H_{7,7',5}$), 1.71 (s, 6H, $H_{10,10'}$), 1.55-1.49 (m, 3H, $H_{5,5'}$), 1.25 (d, 3H, H_2, J=6.2 Hz), 1.18 (d, 3H, $H_{2'}$, J=6.1 Hz), 0.98-0.93 (m, 6H, $H_{6,6'}$)

^{13}C NMR (75MHz, $CDCl_3$): δ 139.4 ($C_{12'}$), 139.1 (C_{12}), 132.5 (C_8), 132.1 ($C_{8'}$), 128.4-127.9-127.8-127.5 (C_{ar}), 124.2 ($C_{9'}$), 123.8 (C_9), 77.7 ($C_{3,3'}$)77.4 ($C_{2,2'}$), 76.3 (C_4), 76.2 ($C_{4'}$), 72.1 ($C_{11'}$), 71.4 (C_{11}), 31.9 (C_7), 31.5 ($C_{7'}$), 28.9 ($C_{5,5'}$), 23.3 ($C_{10,10'}$), 16.7 (C_1), 15.8 ($C_{1'}$), 9.9 ($C_{6'}$), 9.7 (C_6).

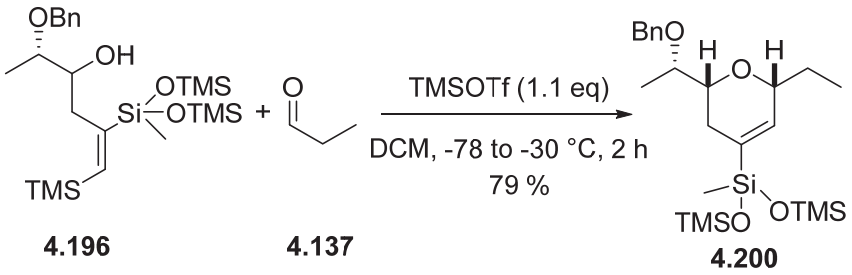
MS (APCI) *m/z* (%): 85.06 (44), 137.13 (10), 151.11 (13), 261.18 (13) $[M+1]^+$, 283.16 (100) $[M+Na]^+$.

MS2: 81.07 (11), 91.05 (100), 95.08 (26), 105.07 (10), 131.08 (6), 137.13 (23), 143.08 (15), 171.11 (12), 199.15 (11), 225.16 (14), 261.18 (23).

HRMS *m/z*: calculated for $C_{17}H_{25}O_2$: 261.18492. Found: 261.18491.

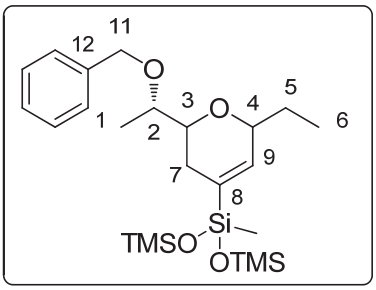
IR (film, cm^{-1}): 696, 735, 781, 814, 881, 987, 1011, 1028, 1090, 1161, 1207, 1377, 1454, 2854, 2875, 2926, 2962.

II.5.4.3.Synthesis of DHP 4.200



4.196 **4.137** **4.200**

- 3-(2-((*S*)-1-(benzyloxy)ethyl)-6-ethyl-3,6-dihydro-*2H*-4-yl)-1,1,1,3,5,5,5-heptamethyltrisiloxane **4.200**



The reaction was carried out on 0.36 mmol (0.18 g).

The crude product was purified by silica gel column chromatography (eluent: PE/Et_2O → 30:1) to afford the desired product as a mixture of 2 diastereomers (1:1). Yield: 0.13 g (79 %).

^{1}H NMR (300MHz, $CDCl_3$): δ 7.36-7.29 (m, 10H, H_{ar}), 5.95-5.93 (m, 2H, $H_{9,\,9'}$), 4.69-4.55 (m, 4H, $H_{11,11'}$), 4.04-4.01 (m, 2H, $H_{4,4'}$), 3.59-3.49 (m, 3H, $H_{2,2',3'}$), 3.43-3.38 (m, 1H, H_3), 2.27-1.93 (m, 5H, $H_{7,7',5'}$), 1.61-1.50 (m, 3H,

$H_{5,5'}$), 1.24 (d, 3H, $H_{1'}$, J=6.2Hz), 1.17 (d, 3H, H_1, J=6.1Hz), 1.00-0.92 (m, 6H, $H_{6,6'}$), 0.09-0.07 (m, 42H, H_{TMS}).

^{13}C NMR (75MHz, $CDCl_3$): δ 139.5 ($C_{9'}$), 139.2 (C_9), 135.3 ($C_{8,\ 8'}$), 128.4-127.9-127.8-127.5 (C_{ar}), 76.1-75.9-75.3 ($C_{2,2',3,3',4,4'}$), 72.1 ($C_{11'}$), 71.4 (C_{11}), 28.4-27.7 ($C_{7,7',5,5'}$), 16.6 (C_1), 15.9 ($C_{1'}$), 9.9 ($C_{6'}$), 9.7 (C_6), 2.0 (C_{OTMS}), -1.0 (C_{TMS})

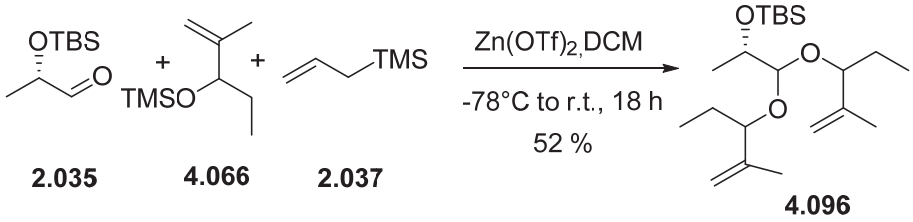
MS (APCI) *m/z* (%): 171.12 (6), 211.15 (9), 239.10 (8), 377.20 (14), 467.25 (100) 468.25 (41) 469.25 (11) $[M+1]^+$

MS2: 91.05 (100), 121.10 (8), 205.07 (6), 221.08 (18), 239.08 (46), 359.19 (4).

HRMS *m/z*: calculated for $C_{23}H_{43}O_4Si_3$: 467.24694. Found: 467.24637.

IR (film, cm^{-1}): 696, 733, 754, 783, 841, 868, 980, 1051, 1148, 1252, 1375, 1454, 2852, 2922, 2959.

II.6. Synthesis of acetal 4.096

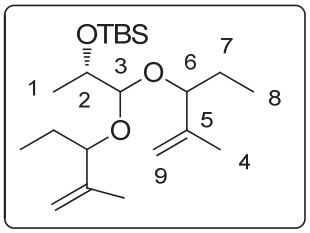


2.035 **4.066** **2.037** **4.096**

To a solution of aldehyde (0.3 g, 1.59 mmol), silyl ether (0.29 g, 1.70 mmol) and allylsilane (0.28 mL, 1.75 mmol) in DCM (8 mL) was added $Zn(OTf)_2$ (0.06 g, 0.16 mmol) at -78 °C. The reaction was then warmed up to room temperature and stirred for 24 hours. The mixture was quenched with 0.1M HCl and extracted with DCM. The organic phases were combined, washed with a saturated solution of $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by

silica gel column chromatography (eluent PE/EtOAc 30:1) to afford the desired product as clear oil; yield: 0.26 g (52 %).

- (((2*S*)-1,1)bis((2-methylpent-1-en-3-yl)oxypropan-2-yl)oxy)(*tert*-butyl)dimethylsilane **4.096**



The reaction was carried out on 1.59 mmol of aldehyde (0.3 g).

^{1}H NMR (300MHz, $CDCl_3$): δ 4.91-4.83 (m, 4H, H_9), 4.30-3.64 (m, 4H, $H_{2, 3 \text{ and } 6}$), 1.72-1.48 (m, 10H, $H_{7 \text{ and } 4}$), 1.16 (t, 3H, H_1, J=6 Hz), 0.92-0.80 (m, 15H, $H_{8 \text{ and TBS}}$), 0.10-0.1 (m, 6H, H_{TBS}).

^{13}C NMR (75MHz, $CDCl_3$): δ 145.4, 145.0, 144.9, 144.5 (C_5), 114.3, 114.1, 114.0 (C_9), 101.4-101.9 (C_3), 85.1-84.4-82.7-81.7 (C_6), 71.6-70.3 (C_2), 26.0-25.9 (C_{TBS}), 18.6-18.5-18.3-18.2-16.8-16.7-16.5-16.4 ($C_{7 \text{ and } 4}$), 14.3 (C_1), 10.4-10.3-10.2 (C_8), -4.5, -4.7 (C_{TBS}).

MS (ESI) *m/z* (%):118 (16), 188 (7), 271 (4), 335 (5), 393 (100) $[M=Na]^+$, 409 (62) $[M+K]^+$.

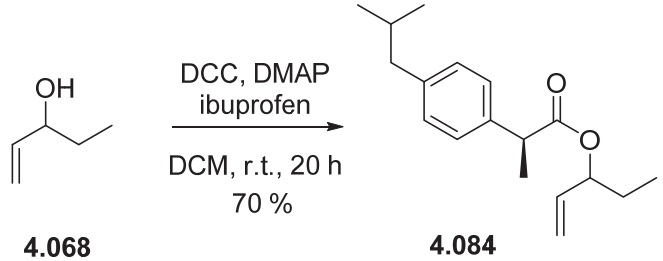
HRMS *m/z*: calculated for $C_{21}H_{42}O_3NaSi$: 393.27954. Found: 393.27954.

II.7. Esterification with DMAP/DCC

II.7.1. General procedure[13]

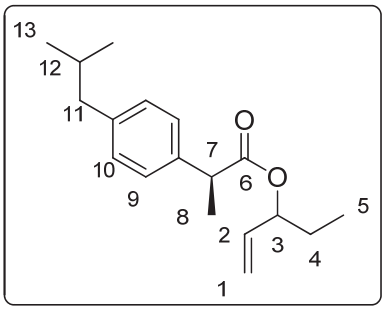
To a solution of substrate (1 eq), DCC (1.1 eq) and DMAP (0.1 eq) in DCM (0.2M) was added naproxene or ibuprofen (1.1 eq). The resulting solution was stirred at room temperature for 20 hours. Mixture was then filtered and washed with DCM (3x). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure.

II.7.2. Synthesis of ester 4.084



4.068 **4.084**

- (2*S*)-pent-1-en-3-yl 2-(4-isobutylphenyl)propanoate **4.084**



The reaction was carried out on 2.32 mmol (0.2 g).

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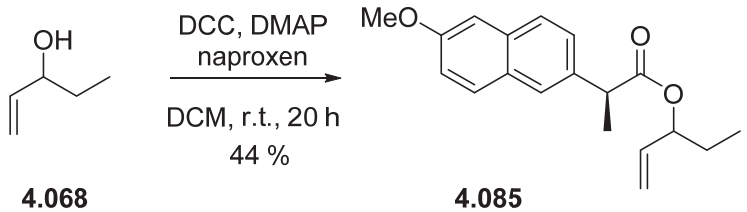
[13] B. Linclau, A. J. Boydell, R. S. Timofte, K. J. Brown, V. Vinader, A.C. Weymouth-Wilson, *Org. Biomol. Chem.* **2009**, *7*, 803.

The crude product was purified by silica gel column chromatography (eluent: PE/AcOEt 50:1→5:1) to afford the desired product as a mixture of 2 diastereomers (1:1). Yield: 0.45 g (70 %).

^{1}H NMR (300MHz, $CDCl_3$): δ 7.20 (d, 4H, $H_{9,9'}$, J=8.0 Hz), 7.07 (d, 4H, $H_{10,10'}$, J=8.1 Hz), 5.80-5.59 (m, 2H, $H_{2,2'}$), 5.20-4.92 (m, 6H, $H_{1,1',3,3'}$), 3.74-3.66 (m, 2H, $H_{7,7'}$), 2.43 (d, 4H, $H_{11,11'}$, J=7.2 Hz), 1.87-1.78 (m, 2H, $H_{12,12'}$), 1.62-1.47 (m, 10H, $H_{4,4',8,8'}$), 0.88-0.66 (m, 18H, $H_{13,13',5,5'}$).

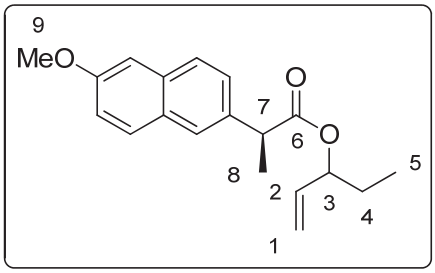
^{13}C NMR (75MHz, $CDCl_3$): δ 174.2 (C_6), 174.1 ($C_{6'}$), 140.5 (C_{ar}), 137.0 (C_{ar}), 136.4 (C_2), 136.2 ($C_{2'}$), 129.3-127.3-127.2 ($C_{9,9',10,10'}$), 116.6 (C_1), 116.1 ($C_{1'}$), 76.1-75.8 ($C_{11,11',7,7'}$), 30.3 ($C_{12,12'}$), 27.3 (C_4), 27.2 ($C_{4'}$), 22.4 ($C_{13,13'}$), 18.5 (C_8), 18.3 ($C_{8'}$), 9.4 (C_5), 9.2 ($C_{5'}$).

II.7.3. Synthesis of ester 4.085



4.068 **4.085**

- (2*S*)-pent-1-en-3-yl 2-(6-methoxynaphthalen-2-yl)propanoate **4.085**



The reaction was carried out on 2.3 mmol (0.2 g).

The crude product was purified by silica gel column chromatography (eluent: PE/acetone 95:5→90:10) to afford the desired product as a mixture of 2 diastereomers (1:1). Yield: 0.3 g (44 %).

^{1}H NMR (300MHz, $CDCl_3$): δ 7.70-7.68 (m, 6H, H_{ar}), 7.43-7.41 (m, 2H, H_{ar}), 7.15-7.11 (m, 4H, H_{ar}), 5.81-5.58 (m, 2H, $H_{2,2'}$), 5.22-4.98 (m, 6H, $H_{1,1',7,7'}$), 3.91 (s, 6H, $H_{9,9'}$), 3.88-3.82 (m, 2H, $H_{3,3'}$), 1.62-1.51 (m, 10H, $H_{4,4',8,8'}$), 0.89-0.84 (m, 3H, H_5), 0.70 (t, 3H, $H_{5'}$, J=7.5 Hz).

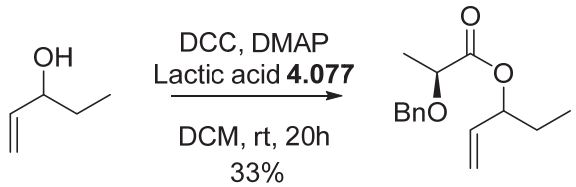
^{13}C NMR (75MHz, $CDCl_3$): δ 174.1 (C_6), 157.7 (C_{ar}), 136.4-136.1-136.0-135.9 (C_{ar}), 133.7 (C_2), 129.4-129.0-127.1-126.5-126.1-119.0 (C_{ar}), 116.8 (C_1), 116.5 ($C_{1'}$), 105.7 (C_{ar}), 77.1 (C_7), 55.4 (C_9), 45.8 (C_3), 27.3 (C_4), 27.2 ($C_{4'}$), 18.7 (C_8), 18.6 ($C_{8'}$), 9.5 (C_5), 9.3 ($C_{5'}$).

MS (EI) *m/z* (%): 91 (16), 141 (10), 170 (8), 185 (100), 298 (37) [M]

HRMS *m/z*: calculated for $C_{19}H_{22}O_3$: 298.15635. Found: 298.15677.

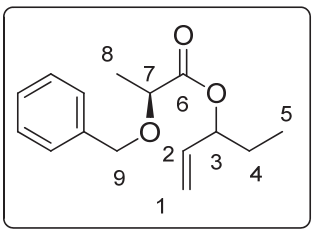
IR (film, cm^{-1}): 671, 746, 783, 810, 892, 921, 989, 1030, 1055, 1087, 1120, 1151, 1176, 1217, 1230, 1263, 1319, 1375, 1392, 1418, 1440, 1483, 1504, 1604, 1728, 2873, 2933.

II.7.4. Synthesis of ester 4.089



4.068 **4.089**

- (2*S*)-pent-1-en-3-yl 2-(benzyloxy)propanoate **4.089**



The reaction was carried out on 11.6 mmol (1 g).

The crude product was purified by silica gel column chromatography (eluent: PE/AcOEt 50:1) to afford the desired product as a mixture of 2 diastereomers. Yield: 0.5 g (33 %).

^{1}H NMR (300MHz, $CDCl_3$): δ 7.38-7.26 (m, 10H, H_{ar}), 5.82-5.73 (m, 2H, $H_{2,2'}$), 5.31-5.18 (m, 6H, $H_{1,1',3,3'}$), 4.72 (d, 1H, H_9, J=11.7 Hz), 4.70 (d, 1H, $H_{9'}$, J=11.4 Hz), 4.44 (d, 2H, $H_{9,9'}$, 11.7 Hz), 4.06 (q, 2H, $H_{7,7'}$, J=6.6 Hz), 1.73-1.46 (m, 4H, $H_{4,4'}$), 1.46-1.43 (m, 6H, $H_{8,8'}$), 0.92 (t, 6H, $H_{5,5'}$).

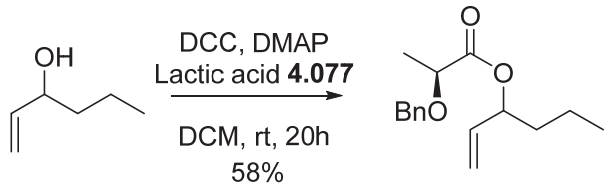
^{13}C NMR (75MHz, $CDCl_3$): δ 172.7 (C_6), 137.7 (C_2), 136.1 ($C_{2'}$), 136.0 (C_{ar}), 128.5-128.1-127-9 (C_{ar}), 117.4 (C_5), 117.2 ($C_{5'}$), 77.0 ($C_{3,3'}$), 74.3 ($C_{7,7'}$), 72.1 ($C_{9,9'}$), 27.4 ($C_{4,4'}$), 19.0 (C_8), 18.9 ($C_{8'}$), 9.6 ($C_{5,5'}$).

MS (CI) *m/z* (%): 159 (10), 179 (45), 181 (100), 207 (34), 249 (12) $[M+1]^+$.

HRMS *m/z*: calculated for $C_{15}H_{21}O_3$: 249.14907. Found: 249.14951.

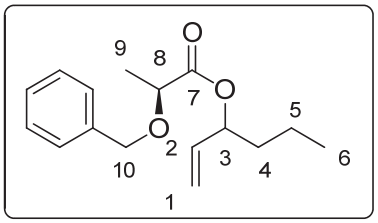
IR (film, cm^{-1}): 698, 734, 891, 933, 989, 1022, 1063, 1128, 1142, 1194, 1265, 1454, 1732, 1747, 2904, 2916, 2966.

II.7.5. Synthesis of ester 4.090



4.071 **4.090**

- (2*S*)-hex-1-en-3-yl 2-(benzyloxy)propanoate **4.090**



The reaction was carried out on 5 mmol (0.5 g).

The crude product was purified by silica gel column chromatography (eluent: PE/AcOEt 50:1) to afford the desired product as a mixture of 2 diastereomers. Yield: 0.76 g (58 %).

^{1}H NMR (500MHz, $CDCl_3$): δ 7.36-7.28 (m, 10H, H_{ar}), 5.84-5.75 (m, 2H, $H_{2,2'}$), 5.29-5.35 (m, 2H, $H_{3,3'}$), 5.26 (dd, 2H, $H_{1,1'}$, J=8.8 Hz, J=1.5 Hz), 5.18 (dd, 2H, $H_{1,1'}$, J=6.3 Hz, J=1.4 Hz), 4.71 (d, 1H, H_{10}, J=7.0 Hz), 4.69 (d, 1H, $H_{10'}$, J=6.9 Hz), 4.43 (d, 1H, $H_{10,10'}$, J=7.0 Hz), 4.05 (q, 2H, $H_{8,8'}$, J=6.0 Hz), 1.68-1.64 (m, 2H, $H_{4,4'}$), 1.62-1.58 (m, 2H, $H_{4,4'}$), 1.45 (m, 6H, $H_{9,9'}$), 1.39-1.34 (m, 4H, $H_{5,5'}$), 0.8-0.97 (m, 6H, $H_{6,6'}$).

^{13}C NMR (75MHz, $CDCl_3$): δ 172.7 ($C_{7,7'}$), 137.7 ($C_{2'}$), 136.4 (C_2), 128.5-128.1-128.0-127.9 (C_{ar}), 117.2 ($C_{1'}$), 116.9 (C_1), 75.2 ($C_{3,3'}$), 75.6 ($C_{8'}$), 75.2 (C_8), 72.1 (C_{10}), 72.0 ($C_{10'}$), 36.4 ($C_{4,4'}$), 18.9-18.8-18.5 ($C_{5,5',9,9'}$), 13.9 ($C_{6,6'}$).

MS (CI) *m/z* (%): 83 (13), 91 (46), 132 (5), 159 (6), 173 (26), 179 (34), 181 (100), 263 (5) $[M+1]^+$.

HRMS *m/z*: calculated for $C_{16}H_{22}O_3$: 263.16472. Found: 263.16473.

IR (film, cm^{-1}): 696.2, 738.7, 923.8, 956.6, 989.4, 1018.3, 1062.7, 1089.7, 1112.8, 1139.8, 1193.8, 1267.1, 1371.3, 1454.2, 1732.0, 1743.5, 2858.3, 2925.8.

III. Chapter 5: modifications and analogues

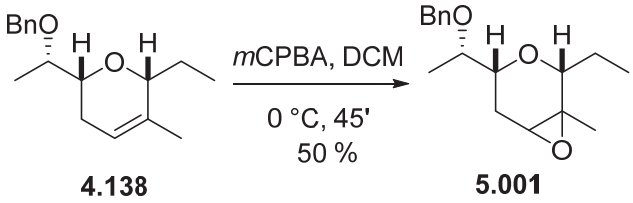
III.1. Epoxidation

III.1.1. General procedure

To a solution of DHP (1 eq) in DCM (0.4M) at 0°C was added *m*CPBA (1.5 eq). The resulting mixture was stirred at 0°C for 45 minutes. The solution was quenched with saturated aqueous solution of K_2CO_3. The aqueous phase was extracted with DCM (3x). The organic phases were combined, washed

with saturated aqueous K_2CO_3, dried over Na_2SO_4, filtered and concentrated under reduced pressure.

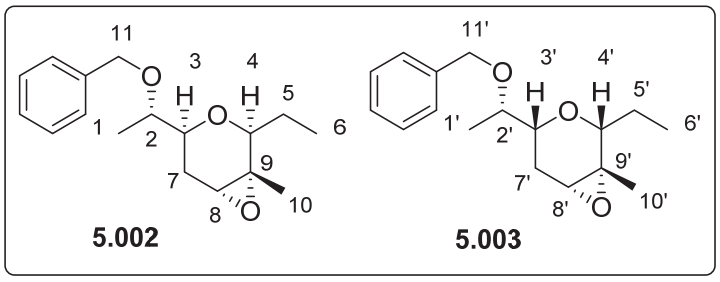
III.1.2. On the mixture of two diastereomers



4.138 **5.001**

2 dias

- (1*S*,2*R*,4*R*,6*S*)-4-((*S*)-1-(benzyloxy)ethyl)-2-ethyl-1-methyl-3,7-dioxabicyclo[4.1.0]heptane **5.002** and (1*S*,2*S*,4*S*,6*S*)-4-((*S*)-1-(benzyloxy)ethyl)-2-ethyl-1-methyl-3,7-dioxabicyclo[4.1.0]heptane **5.003**



5.002 **5.003**

The reaction was carried out on 1.15 mmol (0.3 g).

The crude product was purified by silica gel column chromatography (eluent: PE/Et_2O 30:1) to afford the desired product as a clear oil and a mixture of two diastereomers (1:1); yield: 0.16 g (50 %).

Dia **5.002:**

^{1}H NMR (300MHz, $CDCl_3$): δ 7.34-7.28 (m, 5H, H_{ar}), 4.62 (d, 1H, H_{11}, J=12 Hz), 4.55 (d, 1H, H_{11}, J=12 Hz), 3.65 (dd, 1H, H_4, J= 9 Hz, J=3 Hz), 3.49-3.46 (m, 1H, H_2), 3.38-3.33 (m, 1H, H_3), 3.15-3.12 (m, 1H, H_8), 2.21-

2.16 (m, 1H, H_7), 1.88-1.83 (m, 1H, H_7), 1.75-1.50 (m, 2H, H_5), 1.28 (s, 3H, H_{10}), 1.16 (d, 3H, H_1, J=6 Hz), 1.02 (t, 3H, H_6, J=6 Hz).

^{13}C NMR (75MHz, $CDCl_3$): δ 139.1 (C_{ar}), 128.4-127.7-127.5 (C_{ar}), 79.8 (C_4), 77.18 (C_2), 73.7 (C_3), 71.3 (C_{11}), 59.8 (C_8), 59.5 (C_9), 27.6 (C_7), 26.0 (C_5), 20.3 (C_{10}), 16.7 (C_1), 10.7 (C_6).

$[\alpha]_D^{20}$ = +37 (c=1.8M, $CHCl_3$)

Dia **5.003:**

^{1}H NMR (300MHz, $CDCl_3$): δ 7.33-7.28 (m, 5H, H_{ar}), 4.62 (d, 1H, $H_{11'}$, J=12 Hz), 4.47 (d, 1H, $H_{11'}$, J=12 Hz), 3.49-3.39 (m, 2H, $H_{4' \text{ and } 2'}$), 3.12-3.06 (m, 2H, $H_{3' \text{ and } 8'}$), 2.18-2.11 (m, 1H, $H_{7'}$), 1.85-1.52 (m, 3H, $H_{7' \text{ and } 5'}$), 1.27 (s, 3H, $H_{10'}$), 1.22 (d, 3H, $H_{1'}$, J=6 Hz), 1.02 (t, 3H, $H_{6'}$, J=6 Hz).

^{13}C NMR (75MHz, $CDCl_3$): δ 138.8 (C_{ar}), 128.5-128.0-127.7 (C_{ar}), 78.7 ($C_{4' \text{ or } 2'}$), 77.6 ($C_{2' \text{ or } 4'}$), 77.0 ($C_{3'}$), 71.2 ($C_{11'}$), 58.1 ($C_{8'}$), 56.4 ($C_{9'}$), 27.2 ($C_{7'}$), 23.7 ($C_{5'}$), 18.7 ($C_{10'}$), 16.6 ($C_{1'}$), 10.4 ($C_{6'}$).

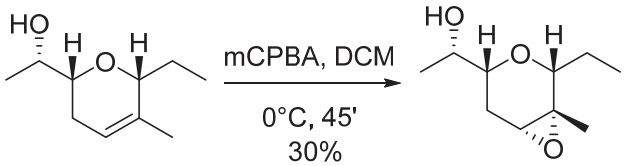
$[\alpha]_D^{20}$ = +32 (c=2.6M, $CHCl_3$)

MS (ESI) *m/z* (%): 299.16 (100) $[M+Na]^+$, 575.33 (28) $[2M+1]^+$

HRMS *m/z*: calculated for $C_{17}H_{25}O_3$: 277.17988. Found: 277.17982.

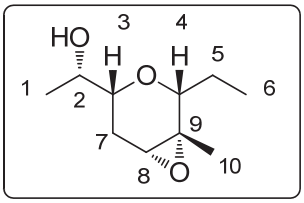
IR (film, cm^{-1}): 696, 732, 1029, 1110, 1367, 1379, 1454, 2850, 2873, 2921.

III.1.3. On one diastereomer



4.099b **5.010**

- (*S*)-1-((1*R*,2*R*,4*R*,6*R*)-2-ethyl-1-methyl-3,7-dioxabicyclo[4,1,0]heptan-4-yl)ethanol **5.010**



The reaction was carried out on 0.54 mmol (0.09 g).

The crude product was purified by silica gel column chromatography (eluent: PE/Et_2O 10:1 → 1:1) to afford the desired product as a clear oil and a major diastereomer (3.5:1); yield: 0.03 g (30 %).

^{1}H NMR (300MHz, $CDCl_3$): δ 3.87-3.78 (m, 1H, H_2), 3.51 (dd, 1H, H_4, J=9 Hz,J=3 Hz), 3.18-3.09 (m, 2H, $H_{3\ and\ 8}$), 2.01-1.71 (m, 2H, H_7), 1.63-1.42 (m, 2H, H_5), 1.27 (s, 3H, H_{10}), 1.11 (d, 3H, H_1, J=6 Hz), 1.01 (t, 3H, H_6, J=6 Hz).

^{13}C NMR (75MHz, $CDCl_3$): δ 78.3 (C_4), 76.6 (C_3), 69.2 (C_2), 57.9 (C_8), 56.3 (C_9), 23.9 (C_7), 23.7 (C_5), 18.7 (C_{10}), 18.0 (C_1), 10.4 (C_6).

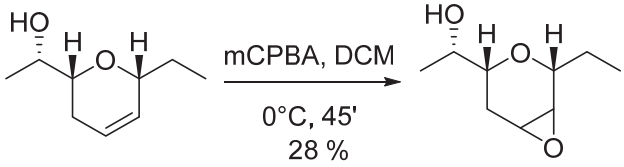
MS (ESI) *m/z* (%): 187.13 (28) $[M+H]^+$, 209.11 (100) $[M+Na]^+$, 395.24 (28) $[2M+Na]^+$

HRMS *m/z*: calculated for $C_{10}H_{19}O_3$: 187.13296. Found: 187.13287

IR (film, cm^{-1}): 714, 854, 889, 947, 1034, 1049, 1059, 1090, 1116, 1297, 1377, 1456, 1668, 2852, 2923, 2962, 3390.

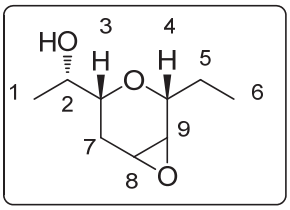
$[\alpha]_D^{20}$ = +47 (c=1.1M, $CHCl_3$).

III.1.4. On DHP 5.026



4.182b **5.016**

- (1*S*)-1-((2*R*,4*R*)-2-ethyl-3,7-dioxabicyclo[4.1.0]heptan-4-yl)ethanol **5.016**



The reaction was carried out on 0.51 mmol (0.08 g).

The crude product was purified by silica gel column chromatography (eluent: PE/Et_2O 15:1 → 0:1) to afford the desired product as a clear oil and a mixture of two diastereomers (1:1.4); yield: 0.025 g (28 %).

^{1}H NMR (300MHz, $CDCl_3$): δ 4.07-3.95 (m, 3H, $H_{2,2',4'}$), 3.85 (t, 1H, H_4, J=9 Hz), 3.63-3.61 (m, 2H, $H_{8,8'}$), 3.58-3.53 (m, 1H, $H_{3'}$), 3.43 (dt, 1H, H_3, J=9 Hz, J=3 Hz), 3.27 (d, 2H, $H_{9,9'}$, J=3 Hz), 2.33-2.12 (m, 4H, $H_{7,7'}$), 2.10-1.99 (m, 4H, $H_{5,5'}$), 1.50-1.46 (m, 6H, $H_{1,1'}$), 1.43-1.37 (m, 6H, $H_{6,6'}$).

^{13}C NMR (75MHz, $CDCl_3$): δ 77.2 (C_3), 76.2 ($C_{4'}$), 75.5 (C_4), 72.9 ($C_{3'}$), 69.1 (C_2), 69.0 ($C_{2'}$), 54.8 ($C_{9'}$), 51.9 ($C_{8'}$), 51.7 (C_9), 50.4 (C_8), 27.1 ($C_{5'}$), 26.0 (C_5), 24.4 ($C_{7'}$), 23.0 (C_7), 18.0 (C_1), 17.6 ($C_{1'}$), 10.1 (C_6), 9.7 ($C_{6'}$).

MS (ESI) *m/z* (%): 155.11 (8), 195.09 (100) $[M+Na]^+$, 367.21 (17) $[2M+Na]^+$

HRMS *m/z*: calculated for $C_{10}H_{16}O_3Na$: 195.09928. Found: 195.09917

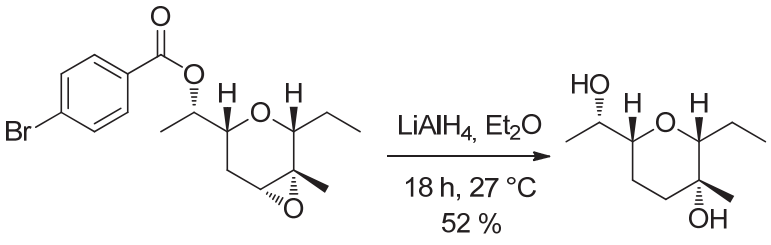
IR (film, cm^{-1}): 861, 862, 875, 892, 1035, 1088, 1142, 1365, 1464, 2852, 2874, 2922, 2964, 3406.

III.2. Epoxide opening

III.2.1. General procedure

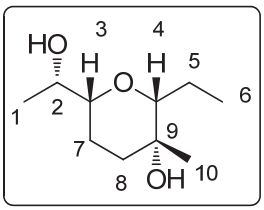
To a solution of substrate (1 eq) in Et_2O (0.15 M) was added $LiAlH_4$ (3 eqs). The reaction was stirred at room temperature for 18 hours. It was carefully quenched with water and extracted with Et_2O (3x). The organic phases were combined, dried over Na_2SO_4 and concentrated under reduced pressure.

III.2.2. Synthesis of 5.012



5.011 **5.012**

- (2*R*,3*R*,6*R*)-2-ethyl-6-((*S*)-1-hydroxyethyl)-3-methyltetrahydro-*2H*-pyran-3-ol **5.012**



The reaction was carried out on 0.08 mmol (0.03 g).

The crude mixture was purified by silica gel column chromatography (eluent PE/EtOAc 5:1 →1:5) to afford the desired product as a yellow oil. Yield: 0.008 g (52%).

^{1}H NMR (300MHz, $CDCl_3$): δ 3.87-3.79 (m, 1H, H_2), 3.25-3.20 (m, 1H, H_3), 3.06 (dd, 1H, H_4, J=3 Hz, J=12 Hz), 1.93 (bs, 2H, -OH), 1.81-1.76 (m, 1H, H_8), 1.68-1.45 (m, 5H, $H_{8,7,5}$), 1.17 (d, 3H, H_1, J=6 Hz), 1.09 (s, 3H, H_{10}), 0.95 (t, 3H, H_6, J=6 Hz).

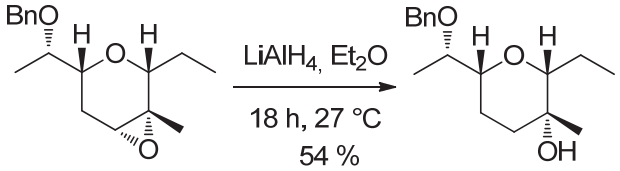
^{13}C NMR (75MHz, $CDCl_3$): δ 85.8 (C_4), 81.4 (C_3), 69.7 (C_2), 68.8 (C_9), 37.4 (C_8), 24.5 (C_{10}), 21.7-21.6 ($C_{7,5}$), 18.3 (C_1), 10.9 (C_6).

MS (ESI) *m/z* (%): 211.13 (100) $[M+Na]^+$, 399.27 (8) $[2M+Na]^+$

HRMS *m/z*: calculated for $C_{10}H_{20}O_3Na$: 211.13056. Found: 211.13047

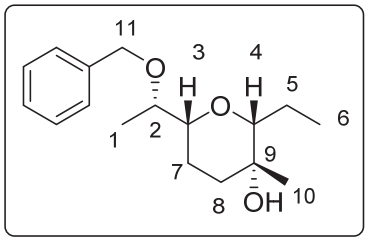
IR (film, cm^{-1}): 748, 762, 871, 998, 1055, 1060, 1355, 1464, 1650, 2852, 2921, 2955, 3310.

III.2.3. Synthesis of 5.008



5.003 **5.008**

- (2*S*,3*S*,6*S*)-6-((*S*)-1-(benzyloxy)ethyl)-2-ethyl-3-methyltetrahydro-*2H*-pyran-3-ol **5.008**



The reaction was carried out on 0.19 mmol (0.052 g).

The crude mixture was purified by silica gel column chromatography (eluent PE/EtOAc 10:1 → 5:1 →1:1) to afford the desired product as a clear oil; yield: 0.028 g (54 %).

^{1}H NMR (300MHz, $CDCl_3$): δ 7.36-7.27 (m, 5H, H_{ar}), 4.66 (d, 1H, H_{11}, J=11.8 Hz), 4.50 (d, 1H, H_{11}, J= 11.8 Hz), 3.50-3.43 (m, 1H, H_2), 3.21-3.15 (m, 1H, H_3), 3.02 (dd, 1H, H_4, J=10.1 Hz, J=2.9 Hz), 2.21 (bs, 1H, -OH), 1.86-1.74 (m, 2H, H_8), 1.59-1.52 (4H, $H_{5\ and\ 7}$), 1.25 (d, 3H, H_1, J=6.2 Hz), 1.09 (s, 3H, H_{10}), 0.97 (t, 3H, H_6, J= 7.4 Hz)

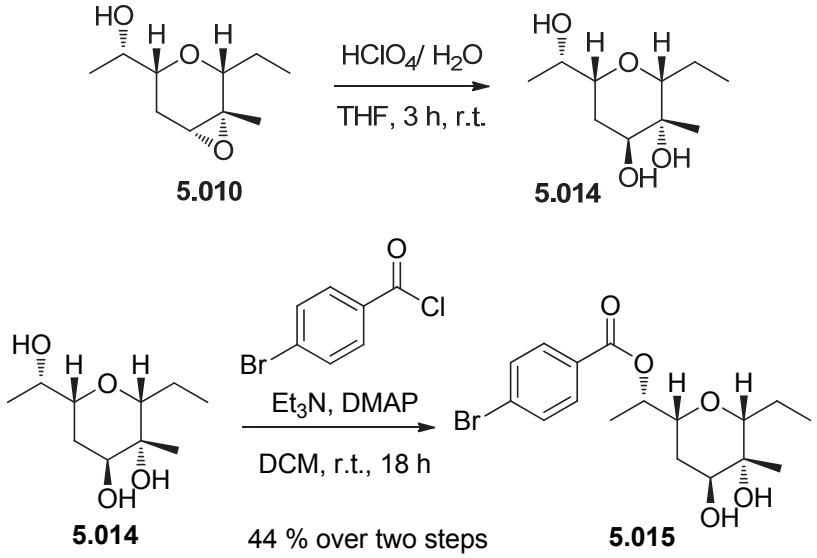
^{13}C NMR (75MHz, $CDCl_3$): δ 138.9 (C_{ar}), 128.5-127.8-127.6 (C_{ar}), 85.8 (C_4), 81.6 (C_3), 77.5 (C_2), 71.5 (C_{11}), 68.7 (C_9), 37.5 (C_8), 24.4 (C_{10}), 24.1 ($C_{7\ or\ 5}$), 21.6 ($C_{5\ or\ 7}$), 16.8 (C_1), 10.8 (C_6).

MS (ESI) *m/z* (%): 261.18 (16) $[M\text{-}OH]^+$, 296.22 (30), 301.17 (100) $[M+Na]^+$

HRMS *m/z*: calculated for $C_{17}H_{27}O_3$: 279.19550. Found: 279.19547

IR (film, cm^{-1}): 696, 733, 779, 796, 918, 976, 1022, 1074, 1097, 1188, 1207, 1269, 1296, 1369, 1454, 1784, 2852, 2823, 2962.

III.2.4. Opening with $HClO_4$ and benzoylation in situ

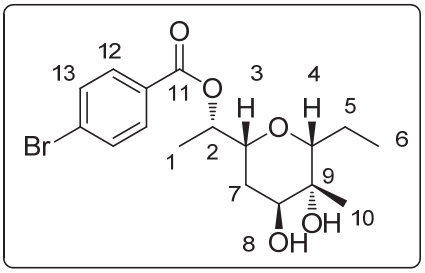


To a solution of epoxide (0.011 g, 0.059 mmol) in THF (0.5 mL) at 0°C was added $HClO_4$ in H_2O (0.65 mL of 0.1 M solution) dropwise. The resulting mixture was stirred at room temperature for 3 hours. Water and EtOAc were added. The layers were separated and the aqueous phase was extracted with EtOAc (5x). The organic phases were combined, washed with brine, dried over $MgSO_4$ filtered and concentrated under reduced pressure to afford the crude mixture.

The crude product was dissolved in DCM (0.9 mL) along with benzoyl chloride (0.04 g, 0.183 mL). To this solution were added Et_3N (0.024 mL, 0.2 mmol) and a catalytic amount of DMAP at 0°C. The resulting mixture was stirred overnight at room temperature. It was quenched with a saturated aqueous solution of NH_4Cl and extracted with DCM (3x). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated under

reduced pressure. The crude product was purified by silica gel column chromatography (eluent: PE/Et_2O 20:1→5:1) to afford the desired product as a white solid. Yield: 0.01 g (44 %).

- (*S*)-1-((2*R*,4*S*,5*R*,6*R*)-6-ethyl-4,5-dihydroxy-5-methyltetrahydro-*2H*-pyran-2-yl)ethyl 4-bromobenzoate **5.015**



^{1}H NMR (300MHz, MeOH-d4): δ 7.92 (d, 2H, H_{13}, J= 6.6 Hz), 7.66 (d, 2H, H_{12}, J=6.7 Hz), 5.04 (quint, 1H, H_2, J=6.4 Hz), 3.79 (ddd, 1H, H_3, J= 11.9 Hz, J=6.6 Hz, J=2.0 Hz), 3.58 (t, 1H, H_8, J= 2.8 Hz), 3.45 (dd, 1H, H_4, J=8.2 Hz, J=4.9 Hz), 2.00 (ddd, 1H, H_7, J=13.8 Hz, J=11.9 Hz, J=2.9 Hz), 1.68 (dt, 1H, H_7, J=13.7 Hz, 2.6 Hz),1.61-1.51 (d, 2H, H_5), 1.38 (d, 3H, H_1, J=6.4 Hz), 1.12 (s, 3H, H_{10}), 1.00 (t, 3H, H_6, J=7.3 Hz).

^{13}C NMR (75MHz, MeOH-d4): δ 166.5 (C_{11}), 132.9-132.6 ($C_{12 \text{ and } 13}$), 130.9-129.0 (C_{ar}), 81.4 (C_4), 75.3 (C_3), 74.9 (C_2), 73.4 (C_8), 71.7 (C_9), 32.6 (C_7), 22.4 (C_5), 22.1 (C_{10}), 16.9 (C_1), 11.3 (C_6).

MS (ESI) *m/z* (%): 123.09 (87), 296.22 (26), 301.17 (72), 352.32 (15), 387.08, 389.08 (62, 60) $[M+1]^+$, 409.06, 411.06 (100, 98) $[M+Na]^+$.

HRMS *m/z*: calculated for $C_{17}H_{24}O_5Br$: 387.08016. Found: 387.08016.

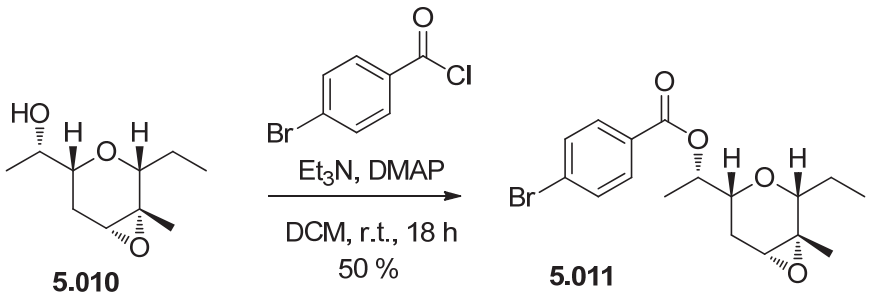
IR (film, cm^{-1}): 758, 850, 1012, 1055, 1103, 1240, 1375, 1456, 1589, 1759, 1770, 2926, 2955, 2993.

III.3. Benzoylation

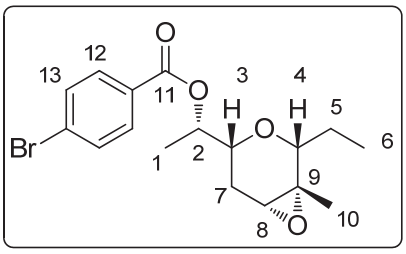
III.3.1. General procedure

To a solution of epoxide (1 eq) and benzoyl chloride (1.1 eq) in DCM (0.2M) at 0°C was added Et_3N (1.2 eq) and DMAP (0.1 eq). The resulting reaction mixture was stirred at room temperature overnight. Solution was quenched with a saturated aqueous solution of NH_4Cl and extracted with DCM (3x). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure.

III.3.2. Synthesis of 5.011



- (*S*)-1-((1*R*,2*R*,4*R*,6*R*)-2-ethyl-1-methyl-3,7-dioxabicyclo[4.1.0]heptan-4-yl)ethyl 4-bromobenzoate **5.011**



The reaction was carried out on 0.16 mmol (0.3 g).

The crude product was purified by silica gel column chromatography (eluent: PE/Et_2O 20:1→5:1) to afford the desired product as a white solid. Yield: 0.03 g (50 %).

^{1}H NMR (300MHz, $CDCl_3$): δ 7.87 (d, 2H, H_{13}, J=8.6 Hz), 7.57 (d, 2H, H_{12}, J=8.6 Hz), 5.02 (q, 1H, H_2, J=6.3 Hz), 3.50 (dd, 1H, H_4, J=9.7 Hz, J=2.9 Hz), 3.40-3.32 (m, 1H, H_3), 3.09 (d, 1H, H_8, J=5.6 Hz), 1.99-1.56 (m, 4H, $H_{5\ and\ 7}$), 1.35 (d, 3H, H_1, J=6.3 Hz), 1.28 (s, 3H, H_{10}), 1.03 (t, 3H, H_6, J=7.4 Hz).

^{13}C NMR (75MHz, $CDCl_3$): δ 165.2 (C_{11}), 131.8 (C_{13}), 131.2 (C_{12}), 129.5 (C_{ar}), 128.2 (C_{ar}), 78.7 (C_4), 75.4 (C_3), 73.5 (C_2), 57.6 (C_9), 56.1 (C_8), 26.7 (C_7), 23.7 (C_5), 18.7 (C_{10}), 16.1 (C_1), 10.4 (C_6).

MS (ESI) *m/z* (%): 369.07, 371.07 (100,96) $[M+H]^+$, 391.05, 393.05 (53,52) $[M+Na]^+$

HRMS *m/z*: calculated for $C_{17}H_{22}O_4Br$: 369.06988. Found: 369.06960

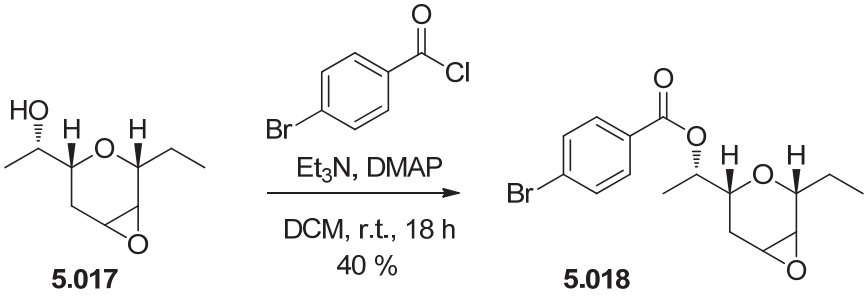
IR (film, cm^{-1}): 683, 719, 756, 849, 858, 1012, 1068, 1101, 1117, 1173, 1230, 1270, 1377, 1397, 1454, 1483, 1589, 1718, 2851, 2874, 2924, 2962, 2976.

X-ray: Crystal data and structure refinement

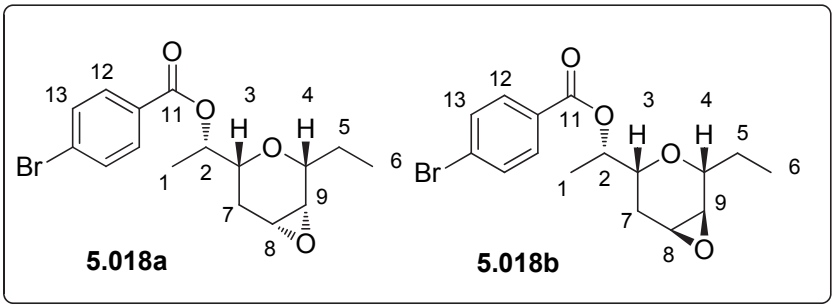
Identification code	hxg_09_020_01
Empirical formula	$C_{17}\ H_{21}\ Br\ O_4$
Formula weight	369.25
Temperature	293(2) K
Wavelength	0.7107 Å
Crystal system	Monoclinic
Space group	$P\ 2_1$
Unit cell dimensions	a = 11.6441(6) Å
	b = 5.8019(2) Å
	c = 13.7278(8) Å
	α= 90°.

	β= 111.601(6)°.
	γ = 90°.
Volume	862.28(7) $Å^3$
Z	2
Density (calculated)	1.422 g/cm^3
Absorption coefficient	2.398 mm^{-1}
F(000)	380
Crystal size	0.9 x 0.14 x 0.09 mm^3
Theta range for data collection	3.51 to 28.68°.
Reflections collected	6361
Independent reflections	3609 [$R_{(int)}$ = 0.0478]
Completeness to theta = 25.24°	99.3 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.30917
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3609 / 1 / 202
Goodness-of-fit on F^2	1.018
Final R indices [I>2sigma(I)]	R_1 = 0.0532, wR_2 = 0.0801
R indices (all data)	R_1 = 0.1273, wR_2 = 0.0988
Absolute structure parameter	0.006(13)
Largest diff. peak and hole	0.303 and -0.290 $e.Å^{-3}$

III.3.3. Synthesis of 5.018



- (1*S*)-1-(2*R*,4*R*)-2-ethyl-3,7-dioxabicyclo[4.1.0]heptan-4-yl)ethyl 4-bromobenzoate **5.018a** and **5.018b**



The reaction was carried out on 0.14 mmol (0.025 g).

The crude product was purified by silica gel column chromatography (eluent: PE/Et_2O 20:1→5:1) to afford the desired product and the 2 diastereomers were separated. Yield: 0.02 g (39 %).

5.018a

^{1}H NMR (300MHz, $CDCl_3$): δ 7.87 (d, 2H, H_{13}, J= 8.6 Hz), 7.57 (d, 2H, H_{12}, J=8.6 Hz), 5.04 (q, 1H, H_2, J=6.3 Hz), 3.74 (t, 1H, H_4, J=6.4 Hz), 3.53-3.47 (m, 1H, H_3), 3.38-3.36 (m, 1H, H_8), 3.01 (d, 1H, H_9, J=4.3 Hz), 2.17-2.12 (m, 1H, H_7), 1.83-1.79 (m, 1H, H_7), 1.77-1.63 (m, 2H, H_5), 1.32 (d, 3H, H_1, J= 6.4 Hz), 1.00 (t, 3H, H_6, J=7.4 Hz).

^{13}C NMR (75MHz, $CDCl_3$): δ 165.2 (C_{11}), 131.8 (C_{13}), 131.2 (C_{12}), 129.5 (C_{ar}), 128.2 (C_{ar}), 76.4 (C_4), 73.2 (C_2), 71.9 (C_3), 54.8 (C_9), 51.6 (C_8), 27.4 ($C_{7 \text{ or } 5}$), 27.1 ($C_{7 \text{ or } 5}$), 16.4 (C_1), 9.7 (C_6).

$[\alpha]_D^{20}$ = +16 (c=0.6 M, $CHCl_3$).

5.018b

^{1}H NMR (300MHz, $CDCl_3$): δ 7.87 (d, 2H, H_{13}, J=8.6 Hz), 7.57 (d, 2H, H_{12}, J=8.6 Hz), 5.01 (q, 1H, H_2, J=6.2 Hz), 3.64 (t, 1H, H_4, J=6.7 Hz), 3.39-3.34 (m, 2H, $H_{3 \text{ and } 8}$), 3.00 (d, 1H, H_9, J=4.1 Hz), 1.97-1.80 (m, 2H, H_7), 1.75-1.68 (m, 2H, H_5), 1.34 (d, 3H, H_1, J=6.4 Hz), 1.04 (t, 3H, H_3, J=7.4 Hz).

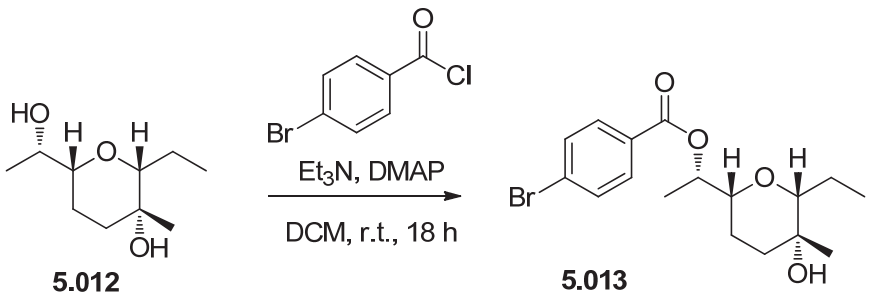
^{13}C NMR (75MHz, $CDCl_3$): δ165.2 (C_{11}), 131.8 (C_{13}), 131.2 (C_{12}), 129.4 (C_{ar}), 128.2 (C_{ar}), 75.8 (C_4), 75.4 (C_3), 73.4 (C_2), 51.6 (C_9), 50.07 (C_8), 25.8 ($C_{7 \text{ or } 5}$), 25.7 ($C_{7 \text{ or } 5}$), 16.0 (C_1), 10.1 (C_6).

MS (ESI) *m/z* (%): 137.09 (4), 155.01 (10), 337.0, 339.04 (6, 5), 335.05, 357.05 (100, 97) $[M+H]^+$

HRMS *m/z*: calculated for $C_{16}H_{20}O_4Br$: 355.05393. Found: 355.05395.

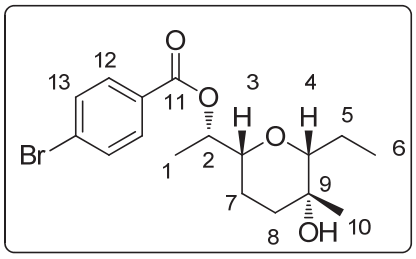
IR (film, cm^{-1}): 719, 734, 756, 756, 787, 848, 864, 880, 939, 1010, 1066, 1103, 1116, 1222, 1371, 1396, 1454, 1483, 1589, 1716, 2852, 2923, 2962.

III.3.4. Synthesis of 5.013



5.012 **5.013**

- (*S*)-1-(2*R*,5*R*,6*R*)-6-ethyl-5-hydroxy-5-methyltetrahydro-*2H*-pyran-2-yl)ethyl 4-bromobenzoate **5.013**



The reaction was carried out on 0.053 mmol (0.01 g).

The crude product was purified by silica gel column chromatography (eluent: PE/EtOAc 10:1) to afford the desired product; Yield: 0.008 g (40 %).

^{1}H NMR (300MHz, $CDCl_3$): δ 7.89 (d, 2H, H_{13}, J=8.6 Hz), 7.58 (d, 2H, H_{12}, J=8.6 Hz), 5.09 (q, 1H, H_2, 6.3 Hz), 3.47-3.40 (m, 1H, H_3), 3.07 (dd, 1H, H_4, J=10.1 Hz, J=2.9 Hz), 2.20 (bs, 1H, -OH), 1.82-1.76 (m, 1H, H_8), 1.65-1.57 (m, 5H, $H_{5,7,8}$), 1.53 (d, 3H, H_1, J=7.4 Hz), 1.11 (s, 3H, H_{10}), 0.97 (t, 3H, H_6, J=7.3Hz).

^{13}C NMR (75MHz, $CDCl_3$): δ 165.2 (C_{11}), 131.8 (C_{13}), 131.2 (C_{12}), 129.5 (C_{ar}), 128.2 (C_{ar}), 85.9 (C_4), 79.8 (C_3), 73.5 (C_2), 68.5 (C_9), 37.3 (C_8), 24.3 (C_5), 23.9 (C_{10}), 21.5 (C_7), 16.3 (C_1), 10.7 (C_6).

MS (ESI) *m/z* (%): 218.08 (14), 353.07, 355.07 (8) $[M\text{-}OH]^+$, 371.08, 373.08 (18) $[M+H]^+$, 395.05 (100) $[M+Na]^+$

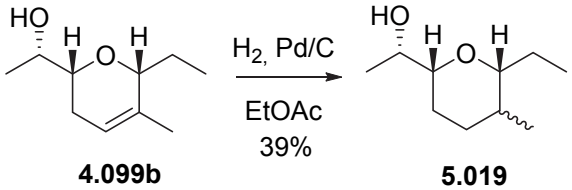
Ms2:81.07 (19), 95.08 (55), 109.10 (37), 135.12 (41), 153.13 (75), 182.94 (100), 371.28 (5).

HRMS *m/z*: calculated for $C_{17}H_{24}O_4Br$: 371.08543. Found: 371.08525.

IR (film, cm^{-1}): 734.8, 757.9, 777.3, 1012.6, 1062.7, 1103.2, 1116.7, 1269.1, 1284.5, 1452.3, 1589.2, 1718.4, 2927.7, 3493.2.

$[\alpha]_D^{20}$ = +16 (c=0.4M, $CHCl_3$).

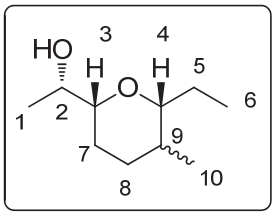
III.4. Hydrogenation



4.099b **5.019**

2 dias

- (1*S*)-1-((2*R*,6*R*)-6-ethyl-5-methyltetrahydro-*2H*-pyran-2-yl)ethanol **5.019**



To a solution of substrate (0.223 mmol, 0.038 g) in EtOAc (1.1 mL) was added Pd/C 10% w/w (0.033 mmol, 0.036 g). The reaction vessel was saturated with hydrogen and stirred overnight. The resulting mixture was filtered over a pad of silica/celite and rinsed with EtOAc. The crude product was purified by silica gel column chromatography to afford the desired product as a colorless oil and a mixture of two diastereomers (1:1). Yield: 0.015 g (39 %).

^{1}H NMR (300MHz, $CDCl_3$): δ 3.85-3.77 (m, 2H, $H_{2 \text{ and } 2'}$), 3.32-3.18 (m, 3H, $H_{3,3' \text{ and } 4'}$), 2.88 (td, 1H, H_4, J=9 Hz, J=3 Hz), 1.82-1.24 (m, 14H, $H_{5, 7, 8, 9, 5', 7', 8', 9'}$), 1.15-1.12 (m, 6H, $H_{1 \text{ and } 1'}$), 0.95-0.86 (m, 9H, $H_{6, 6' \text{ and } 10'}$), 0.80 (d, 3H, H_{10}, J=6.4 Hz).

^{13}C NMR (75MHz, $CDCl_3$): δ 84.6 (C_4), 81.9 ($C_{4'}$), 81.4 ($C_{3'}$), 80.6 (C_3), 69.8 ($C_{2 \text{ and } 2'}$), 34.9-32.6-30.8-30.2-26.3-26.0-25.5 ($C_{5, 7, 8, 9, 5', 7', 8' \text{ and } 9'}$), 19.6 ($C_{1 \text{ or } 1'}$), 17.9 ($C_{10}$), 17.8 ($C_{1 \text{ or } 1'}$), 11.5 ($C_{10'}$), 10.5 ($C_{6'}$), 9.7 ($C_6$).

MS (ESI) *m/z* (%): 137.13 (57), 155.14 (28) $[M-H_2O]^+$ 173.15 (6) $[M+1]^+$, 195.14 (100) $[M+Na]^+$

HRMS *m/z*: calculated for $C_{10}H_{21}O_2$: 173.15367. Found: 173.15361.

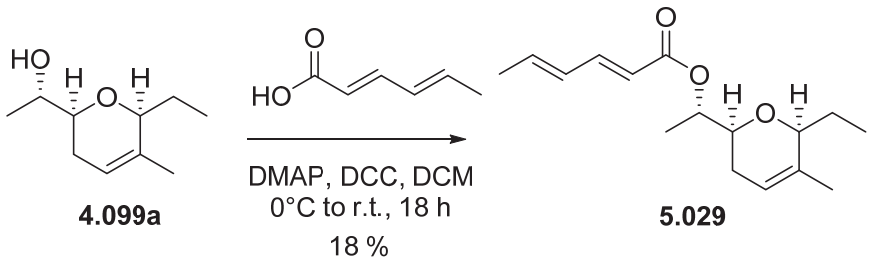
IR (film, cm^{-1}): 652, 958, 976, 1053, 1086, 1120, 1381, 1456, 2501, 2854.4, 2876, 2928, 2964, 3331.

III.5. Esterification

III.5.1. General procedure[13]

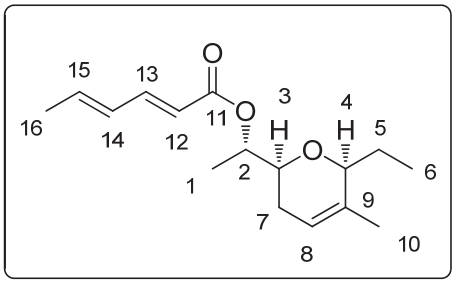
To a solution of substrate (1 eq), DCC (1.1 eq) and DMAP (0.1 eq) in DCM (0.2 M), was added the acid (1.1 eq). The resulting solution was stirred at room temperature for 20 hours. Mixture was then filtered and washed with DCM (3x). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure.

III.5.2. Synthesis of ester 5.029



4.099a **5.029**

- (2*E*,4*E*)-(*S*)-1-((2*S*,6*S*)-6-ethyl-5-methyl-3,6-dihydro-2*H*-pyran-2-yl)ethyl hexa-2,4-dienoate **5.029**



The reaction was carried out on 0.85 mmol (0.14 g).

The crude product was purified twice by silica gel column chromatography (eluent: PE/AcOEt 50:1) to afford the desired product as a clear oil. Yield: 0.04 g (18 %).

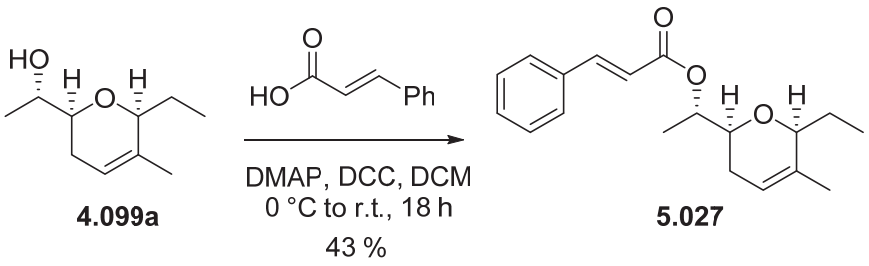
^{1}H NMR (300MHz, $CDCl_3$): δ 7.23-7.20 (m, 1H, H_{13}), 6.24-6.08 (m, 2H, $H_{14\ and\ 15}$), 5.80 (d, 1H, H_{12}, J=15.3 Hz), 5.52 (d, 1H, H_8, J=5.7 Hz), 5.05 (quint, 1H, H_2, J=5.7 Hz), 3.99-3.97 (m, 1H, H_4), 3.56-3.50 (m, 1H, H_3), 2.10-2.05 (m, 1H, H_7), 1.85 (d, 3H, H_{16}, J=5.7Hz), 1.79-1.70 (m, 2H, $H_{7\ and\ 5}$), 1.58 (s, 3H, H_{10}), 1.49-1.41 (m, 1H, H_5), 1.25 (d, 3H, H_1, J=6.6 Hz), 0.90 (t, 3H, H_6, J=6.8 Hz)

^{13}C NMR (75MHz, $CDCl_3$): δ 166.2 (C_{11}), 144.9 (C_{13}), 139.1 (C_{15}), 135.8 (C_9), 130.0 (C_{14}), 120.1 (C_{12}), 119.6 (C_8), 78.5 (C_4), 74.9 (C_3), 71.7 (C_2), 26.7 ($C_{7\ or\ 5}$), 25.7 ($C_{7\ or\ 5}$), 19.0 ($C_{16\ or\ 10}$), 18.8 ($C_{16\ or\ 10}$), 15.7 (C_1), 9.8 (C_6).

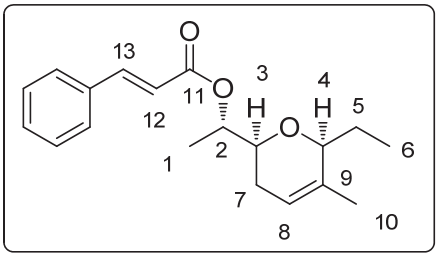
MS (CI) *m/z* (%):95 (13), 153 (24), 247 (17), 265 (100) $[M+H]^+$

HRMS *m/z*: calculated for $C_{16}H_{25}O_3$: 265.18037. Found: 265.17979.

III.5.3. Synthesis of esters 5.027 and 5.028



- (*S*)-1-((2*S*,6*S*)-6-ethyl-5-methyl-3,6-dihydro-*2H*-pyran-2-yl)ethyl cinnamate **5.027**

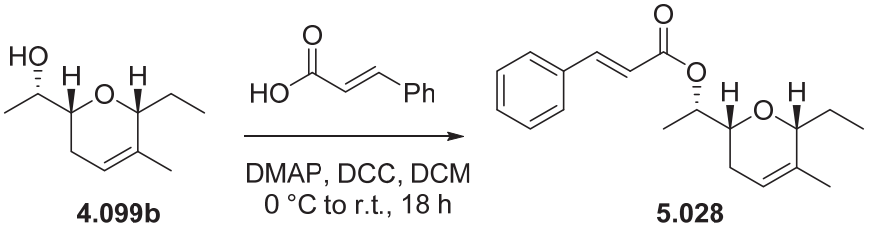


The reaction was carried out on 0.59 mmol (0.1 g).

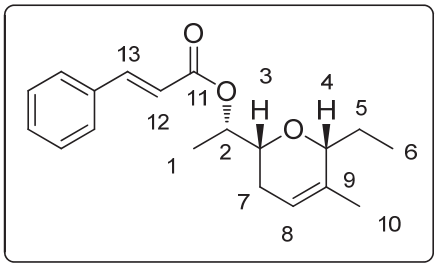
The crude product was purified by silica gel column chromatography (eluent: PE/AcOEt 50:1) to afford the desired product as a clear oil. Yield: 0.076 g (43 %).

^{1}H NMR (300MHz, $CDCl_3$): δ 7.68 (d, 1H, H_{12}, J=15.9 Hz), 7.54-7.51 (m, 2H, H_{ar}), 7.39-7.37 (m, 3H, H_{ar}), 6.46 (d, 1h, H_{13}, J=15.9 Hz), 5.55-5.54 (m, 1H, H_8), 5.03 (quint, 1H, H_2, J=6.6 Hz), 4.06-4.03 (m, 1H, H_4), 3.58-3.52 (m, 1H, H_3), 2.05-2.00 (m, 2H, H_7), 1.79-1.70 (m, 1H, H_5), 1.59 (s, 3H, H_{10}), 1.56-1.50 (m, 1H, H_5), 1.34 (d, 3H, H_1 , J=6.6 Hz), 0.88 (t, 3H, H_6, J=7.5 Hz)

^{13}C NMR (75MHz, $CDCl_3$): δ 166.3 (C_{11}), 144.7 (C_{12}), 135.6 ($C_{9\ or\ ar}$), 134.6 ($C_{9\ or\ ar}$), 130.3-129.0-128.2 (C_{ar}), 120.2 (C_8), 118.7 (C_{13}), 78.3 (C_4), 75.3 (C_3), 72.9 (C_2), 29.5 (C_5), 27.4 (C_7), 19.0 (C_{10}), 16.0 (C_1), 8.5 (C_6).



- (*S*)-1-((2*R*,6*R*)-6-ethyl-5-methyl-3,6-dihydro-2*H*-pyran-2-yl)ethyl cinnamate **5.028**



The reaction was carried out on 0.59 mmol (0.1 g).

The crude product was purified by silica gel column chromatography (eluent: PE/AcOEt 50:1) to afford the desired product as a clear oil. Yield: 0.085 g (49 %).

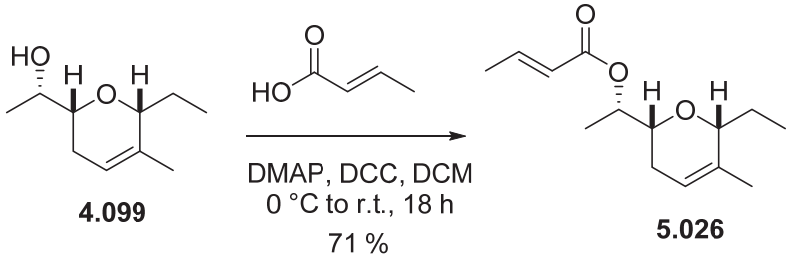
^{1}H NMR (300MHz, $CDCl_3$): δ 7.7 (d, 1H, H_{12}, J=15.9 Hz), 7.53-7.50 (m, 2H, H_{ar}), 7.39-7.37 (m, 3H, H_{ar}), 6.43 (d, 1H, H_{13}, J= 15.9 Hz), 5.49-5.47 (m, 1H, H_8), 5.02 (quint, 1H, H_2, J=6 Hz), 3.90 (t, 1H, H4, J=6.3 Hz), 3.74-3.67 (m, 1H, H_3), 2.08-2.03 (m, 2H, H_7), 1.64-1.61(m, 5H, $H_{5\ and\ 10}$), 1.36 (d, 3H, H_1, J=6.3 Hz), 1.03 (t, 3H, H_6, J=7.5 Hz).

^{13}C NMR (75MHz, $CDCl_3$): δ 166.5 (C_{11}), 144.8 (C_{12}), 136.2 ($C_{9\ or\ ar}$), 134.6 ($C_{9\ or\ ar}$), 130.3-129.0-128.2 (C_{ar}), 118.6 ($C_{13\ or\ 8}$), 118.5 ($C_{13\ or\ 8}$), 78.0 (C_4), 72.6 (C_2), 69.0 (C_3), 27.2 (C_7), 24.5 (C_5), 20.0 (C_{10}), 16.2 (C_1), 10.7 (C_6).

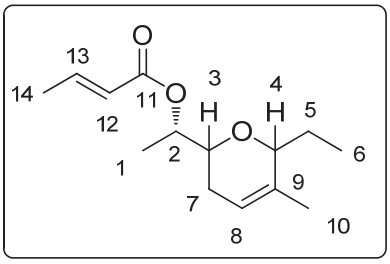
MS (CI) *m/z* (%): 153 (19), 283 (15), 301 (100) $[M+H]^+$.

HRMS *m/z*: calculated for $C_{19}H_{25}O_3$: 301.18037. Found: 301.18074.

III.5.4. Synthesis of ester 5.026



- (*E*)-(1*S*)-1-(6-ethyl-5-methyl-3,6-dihydro-*2H*-pyran-2-yl)ethyl but-2-enoate **5.026**



The reaction was carried out on 0.59 mmol (0.1 g).

The crude product was purified by silica gel column chromatography (eluent:PE/Et_2O 30:1) to afford the desired product as a clear oil and a mixture of two diastereomers. Yield: 0.079 g (71 %).

^{1}H NMR (300MHz, $CDCl_3$): δ 7.02-6.90 (m, 2H, $H_{13,13'}$), 5.84 (d, 2H, $H_{12,12'}$), 5.52-5.50 (m, 2H, $H_{8,8'}$), 5.03 (q, 1H, $H_{2'}$, J=6 Hz), 4.93 (q, 1H, H_2, J= 6 Hz), 4.02-3.97 (m, 2H, $H_{4,4'}$), 3.52-3.44 (m, 2H, $H_{3,3'}$), 2.03-1.90 (m, 4H, $H_{7,7'}$), 1.85 (d, 6H, $H_{14,14'}$, J=9 Hz), 1.78-1.67 (m, 2H, $H_{5,5'}$), 1.56 (s, 6H, $H_{10,10'}$), 1.49-1.41 (m, 2H, $H_{5,5'}$), 1.26 (d, 3H, H_1, J=6 Hz), 1.22 (d, 3H, $H_{1'}$, J=6 Hz), 0.85 (t, 6H, $H_{6,6'}$).

^{13}C NMR (75MHz, $CDCl_3$): δ 166.3 (C_{11}), 166.1 ($C_{11'}$), 144.6 (C_{13}), 144.4 ($C_{13'}$), 135.8 ($C_{9'}$), 135.5 (C_9), 123.2 (C_{12} **and** $_{12'}$), 120.1 (C_8), 120.0 ($C_{8'}$), 78.5 ($C_{4'}$), 78.2 (C_4), 75.3 (C_3), 74.9 ($C_{3'}$), 72.4 (C_2), 71.6 ($C_{2'}$), 27.4 (C_7), 26.6 ($C_{7'}$), 25.7 (C_5), 25.6 ($C_{5'}$), 19.0 (C_{10} and $_{10'}$), 18.1 (C_{14} and $_{14'}$), 16.1 (C_1), 15.6 ($C_{1'}$), 8.8 ($C_{6'}$), 8.5 (C_6).

MS (CI) *m/z* (%): 102(22), 135 (43), 153 (12), 239 (58) $[M+H]^+$, 261 (100) $[M+Na]^+$.

HRMS *m/z*: calculated for $C_{14}H_{23}O_3$:239.16410. Found: 239.16417

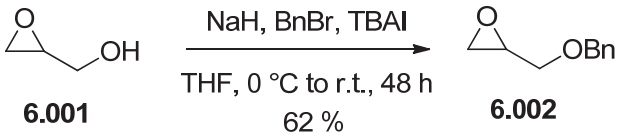
IR (film, cm^{-1}): 688, 737, 839, 918, 925, 968, 997, 1026, 1060, 1101, 1122, 1184, 1263, 1292, 1377, 1444, 1656, 1716, 2854, 2923, 2964.

IV. Chapter 6: lactone synthesis

IV.1. Substrates synthesis

IV.1.1. Glycidol protection

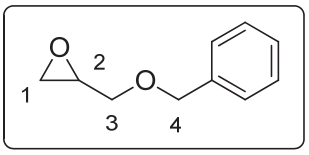
IV.1.1.1. With a benzyl group



6.001 **6.002**

To a solution of glycidol (2.0 ml, 30.0 mmol) in DMF (55 ml) was added NaH 60 % (1.8 g, 45.0 mmol) at 0°C. Benzyl bromide (14.4 ml, 120.0 mmol) and TBAI (1.11 g, 3.0 mmol) were then added. The solution was warmed up to room temperature and stirred for 72 hours. The reaction was quenched with water and the solution was diluted with EtOAc. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (PE/EtOAc 8:2) to afford the desired compound as a yellow oil; yield: 2.95 g (62 %).

- (±)-2-((benzyloxy)methyl)oxirane **6.002**[14]



CAS number : [2930-05-4]

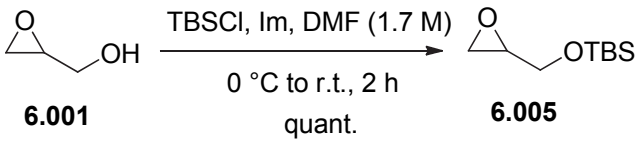
[14] Master thesis, Sophie Moreau, UCL **2012**

^{1}H NMR (300MHz, $CDCl_3$): δ 2.64 (dd, J=5.0 Hz, J=2.7 Hz, 1H, H_1), 2.81 (dd, J=5.0 Hz, J=4.2 Hz, 1H, H_1), 3.20 (m, 1H, H_2), 3.46 (dd, J=11.4 Hz ,J=5.8 Hz, 1H, H_3), 3.78 (dd, J=11.4 Hz, J=3.1 Hz, 1H, H_3), 4.58 (d, J=11.9 Hz, 1H, H_4), 4.63 (d, J=11.9 Hz, 1H, H_4), 7.28-7.37 (m, 5H, H_{ar}).

^{13}C NMR (75MHz, $CDCl_3$): δ 44.4 (C_1), 50.9 (C_2), 70.9 (C_3), 73.4 (C_4), 127.8-128.5-137.9 (C_{ar}).

Data are in agreement with literature values.

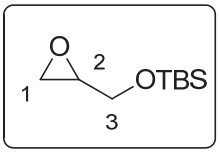
IV.1.1.2. With a TBS group



6.001 **6.005**

A solution of glycidol (1.33 ml, 20 mmol) and imidazole (2.18 g, 32 mmol) in DMF (12 ml) was stirred for 10 minutes at 0°C. TBSCl (3.92 g, 26.00 mmol) was then added at 0°C and the resulting mixture was stirred for 30 minutes. The reaction was then warmed up to room temperature and stirred for 2 hours. It was quenched with saturated brine and the mixture was stirred for 30 minutes. The solution was extracted with Et_2O. The combined organic layers were washed with brine and concentrated under redued pressure to afford the desired compound as a colorless oil; yield: 3.87 g (quant.).

- (±)-*Tert*-butyldimethyl(oxiran-2-ylmethoxy)silane **6.005**[15]



CAS number : [114413-26-2]

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[15] Donohoe, T. J.; Ironmonger, A.; Kershaw, N. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 7314.

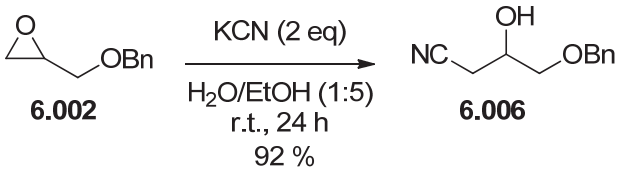
^{1}H NMR (300MHz, $CDCl_3$): δ 0.07 (s, 3H, H_{TBS}), 0.08 (s, 3H, H_{TBS}), 0.90 (s, 9H, H_{TBS}), 2.64 (dd, 1H, H_1, J=5.1 Hz, J=2.7 Hz), 2.77 (dd, 1H, H_1, J=5.1 Hz, J=4.1 Hz), 3.09 (m, 1H, H_2), 3.66 (dd, 1H, H_3, J=11.9 Hz, J=4.8 Hz), 3.85 (dd, 1H, H_3, J=11.9 Hz, J=3.2 Hz).

^{13}C NMR (75MHz, $CDCl_3$): δ -5.2 (C_{TBS}), -5.2 (C_{TBS}), 18.5 (C_{TBS}), 26.0 (C_{TBS}), 44.6 (C_1), 52.57 (C_2), 63.9 (C_3).

Data are in agreement with literature values.

IV.1.2. Opening of epoxides

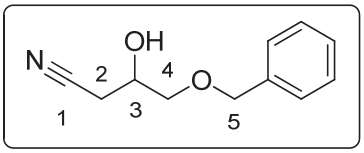
IV.1.2.1. Synthesis of nitrile 6.006



6.002 **6.006**

To a solution of substrate (2 g, 12.2 mmol) in a mixture of EtOH/H_2O (5:1, 80 ml) was added KCN (1.6 g, 24.4 mmol). The reaction was stirred overnight at room temperature. Water was added and the aqueous phase was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (PE/EtOAc 8:2) to afford the desired compound as a colorless oil; yield: 2.14 g (92 %).

- 4-(benzyloxy)-3-hydroxybutanenitrile **6.006**



CAS number : [137618-52-1]

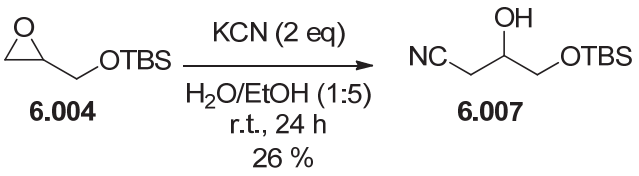
^{1}H NMR (300MHz, $CDCl_3$): δ 2.57 (dd, 1H, H_2, J=16.8 Hz, J=6.3 Hz), 3.01-3.03 (m, 1H, H_2), 3.53 (m, 2H, H_4), 4.07 (quint., 1H, H_3, J=5.4 Hz), 4.56 (s, 2H, H_5), 7.29-7.40 (m, 5H, H_{ar}).

^{13}C NMR (75MHz, $CDCl_3$): δ 22.5 (C_2), 66.5 (C_3), 72.2 (C_4), 73.7 (C_5), 117.4 (C_1), 127.9-128.1-128.6-127.3 (C_{ar}).

MS (EI) *m/z* (%): 84.0 (93), 91.1 (100), 191.1 (11) $[M]^+$

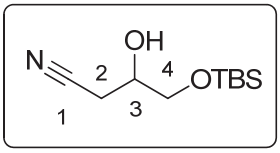
IR (film, cm^{-1}): 698, 738, 1091, 1454, 1496, 2250, 2860, 3440, 3745.

IV.1.2.2. Synthesis of nitrile 6.007



To a solution of substrate (1.3 g, 6.9 mmol) in a mixture of EtOH/H_2O (5:1, 18 ml) was added KCN (0.9 g, 13.8 mmol) at room temperature. The mixture was stirred for 6 hours. Then, water was added. The aqueous layer was extracted with EtOAc and the combined organic layers were directly concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (PE/EtOAc 9:1) to afford the desired compound as a colorless oil; yield: 0.370 g (26 %).

- 4-((*tert*-butyldimethylsilyl)oxy)-3-hydroxybutanenitrile **6.007**[14]



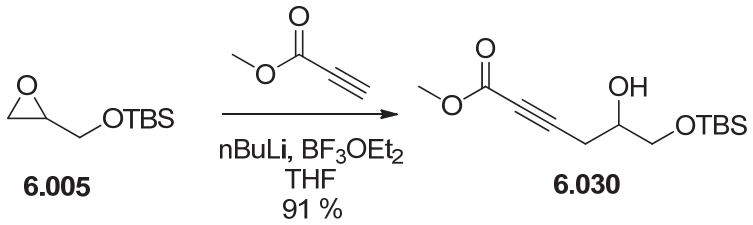
CAS number : [141096-18-6]

^{1}H NMR (300MHz, $CDCl_3$): δ 0.10 (s, 6H, H_{TBS}), 0.91 (s, 9H, H_{TBS}), 2.57 (dd, 2H, H_2, J=6.2 Hz, J=1.8 Hz), 3.65 (dd, 1H, H_4, J=10.2 Hz, J=5.2 Hz), 3.73 (dd, 1H, H_4, J=10.2 Hz, J=4.2 Hz), 3.99 (m, 1H, H_3).

^{13}C NMR (75MHz, $CDCl_3$): δ -4.7 and -4.7 (C_{TBS}), 18.1 (C_{TBS}), 23.0 (C_2), 25.8 (C_{TBS}), 65.6 (C4), 68.9 (C_3), 117.7 (C_1).

Data are in agreement with literature values.

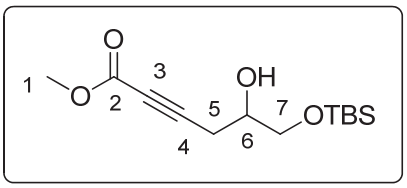
IV.1.2.3. Synthesis of homopropargylic alcohol 6.030



6.005 **6.030**

To a solution of methyl propiolate (2.50 ml, 28.1 mmol) in THF (100 ml) at -78°C was added *n*-BuLi ((2.5M solution in THF), 11.20 ml, 28.1 mmol). The mixture was stirred for 20 minutes, then, BF_3OEt_2 (3.50 ml, 28.1 mmol) was added at -78°C. The resulting solution was stirred for another 20 minutes. Finally, *tert*-butyldimethyl(oxiran-2-ylmethoxy)silane (1.53 g, 8.1 mmol) was added at -78°C. The mixture was warmed up to room temperature and stirred overnight. The solution was quenched with NH_4Cl, extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (PE/EtOAc 95:5) to afford the desired compound as a yellow oil; yield: 2.0 g (91 %)

- Methyl 6-(benzyloxy)-5-hydroxyhex-2-ynoate **6.030**[16]



[16] J. Maguire, R.; P. Munt, S.; J. Thomas, E. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2853.

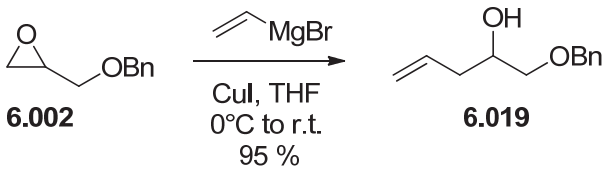
CAS number : [124067-07-8]

^{1}H NMR (300MHz, $CDCl_3$): δ 0.08 (s, 6H, H_{TBS}), 0.90 (s, 9H, H_{TBS}), 2.57 (d, 2H, H_5, J=6.4 Hz), 3.61 (dd, 1H, H_7, J=5.4 Hz, J=10.1 Hz), 3.72 (dd, 1H, H_7, J=3.7 Hz, J=6.4 Hz), 3.76 (s, 3H, H_1), 3.87 (m, 1H, H_6).

^{13}C NMR (75MHz, $CDCl_3$): δ -4.8 (C_{TBS}), 18.4 (C_{TBS}), 24.0 (C_5), 26.3 (C_{TBS}), 52.9 (C_1), 65.5 (C_7), 70.0 (C_6), 74.8 (C_3), 86.3 (C_4), 154.2 (C_2).

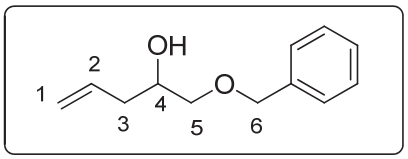
Data are in agreement with literature values.

IV.1.2.4. Synthesis of homoallylic alcohol 6.019



To a solution of vinyl magnesium bromide ((0.7 M solution in THF) 30.90 ml, 21.6 mmol) in THF (40 ml) was added CuI (0.343 g, 1.8 mmol) at 0°C. The solution was stirred for 15 minutes then, cooled to -15°C and 2-((benzyloxy)methyl)oxirane (2.955 g, 18.0 mmol) in THF (10 ml) was added dropwise. The reaction was warmed up to room temperature and stirred for 20 minutes. The mixture was quenched with NH_4Cl and extracted with Et_2O. The combined organic phases were washed with NH_4Cl and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (PE/EtOAc 9:1) to afford the desired compound as a yellow oil; yield: 3.24 g (95 %).

- 1-(benzyloxy)pent-4-en-2-ol **6.019**[1]



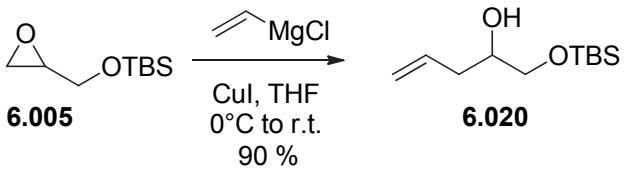
CAS number : [58931-16-1]

^{1}H NMR (300MHz, $CDCl_3$): δ 2.12 (bs, 1H, H_5), 2.27 (m, 2H, H_3), 3.38 (dd, 1H, H_5, J=9.5 Hz, J=7.4 Hz), 3.52 (dd, 1H, H_5, J=9.5 Hz, J=3.4 Hz), 3.89 (m, 1H, H_4), 4.56 (s, 2H, H_6), 5.12 (m, 2H, H_1), 5.83 (ddt, 1H, H_2, J=17.1 Hz, J=10.1 Hz, J=7.0 Hz), 7.30-7.37 (m, 5H, H_{ar}).

^{13}C NMR (75MHz, $CDCl_3$): δ 38.0 (C_3), 69.9 (C_4), 73.5 (C_2), 74.0 (C_6), 117.9 (C_1), 127.9-127.9-128.6-134.3-138.1 (C_{ar}).

Data are in agreement with literature values.

IV.1.2.5. Synthesis of homopropargylic alcohol 6.020

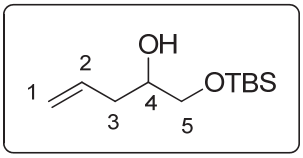


6.005 **6.020**

To a solution of vinyl magnesium chloride ((1.9 M solution in THF) 13.2 ml, 25.1 mmol) in THF (40 ml) was added CuI (0.398 g, 2.1 mmol) at 0°C. The solution was stirred for 30 minutes and tert-butyldimethyl(oxiran-2-ylmethoxy)silane (3.932 g, 20.9 mmol) was added to the solution at -15°C. The solution was warmed up to room temperature and stirred for 1 hour. It was quenched with NH_4Cl and extracted with EtOAc. The combined organic layers were washed with NH_4Cl and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The desired product was obtained as a brown oil; yield: 4.1 g (90 %).

- 1-((*tert*-butyldimethylsilyl)oxy)pent-4-en-2-ol **6.020**[17]

[17] D. Amans, V. Bellosta, C. Dacquet, A. Ktorza, N. Hennuyer, B. Staels, D. Caignard, J. Cossy, *Org. Biomol. Chem.* **2012**, *10*, 6169.



CAS number: [127793-63-9]

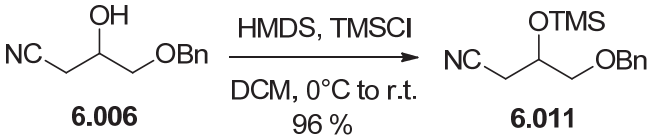
^{1}H NMR (300MHz, $CDCl_3$): δ 0.07 (s, 6H, H_{TBS}), 0.90 (s, 9H, H_{TBS}), 2.24 (m, 2H, H_3), 3.45 (dd, 1H, H_5, J=9.9 Hz, J=6.9 Hz), 3.63 (dd, 1H, H_5, J=9.9 Hz, J=3.7 Hz), 3.71 (m, 1H, H_4), 5.11 (m, 2H, H_1), 5.84 (m, 1H, H_2).

^{13}C NMR (75MHz, $CDCl_3$): δ -5.2 and -5.2 (C_{TBS}), 18.3 (C_{TBS}), 26.0 (C_{TBS}), 37.7 (C_3), 66.7 (C_5), 71.2 (C_4), 117.5 (C_1), 134.6 (C_2).

Data are in agreement with literature values.

IV.1.3. Protection with TMSCl

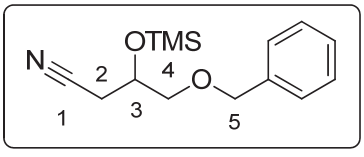
IV.1.3.1. Synthesis of 6.011



6.006 **6.011**

To a solution of 4-(benzyloxy)-3-hydroxybutanenitrile (0.86 g, 4.5 mmol) in DCM (10 mL) were added HMDS (0.57 mL, 2.7 mmol) and TMSCl (0.02 mL, 0.2 mmol) at 0°C. The solution was warmed up to room temperature and stirred overnight. It was quenched by adding saturated NH_4Cl, extracted with DCM and concentrated under reduced pressure to afford the desired compound as a colorless oil; yield: 1.139 g (96 %).

- 4-(benzyloxy)-3-((trimethylsilyl)oxybutanenitrile **6.011**



^{1}H NMR (300MHz, $CDCl_3$): δ 0.15 (s, 9H, H_{TMS}), 2.52 (dd, 1H, H_2, J=16.6 Hz, J=6.8 Hz,), 2.64 (dd, 1H, H_2, J=16.6 Hz, J=4.4 Hz), 3.39 (dd, 1H, H_4, J=9.6 Hz, J=6.9 Hz), 3.50 (dd, 1H, H_4, J=9.6 Hz, J=4.8 Hz), 4.07 (m, 1H, H_3), 4.54 (s, 2H, H_5), 7.30-7.39 (m, 5H, H_{ar}).

^{13}C NMR (75MHz, $CDCl_3$): δ 0.2 (C_{TMS}), 24.0 (C_2), 67.6 (C_3), 72.9 (C_4), 73.7 (C_5), 117.9 (C_1), 127.9-128.1-128.6-137.7 (C_{ar}).

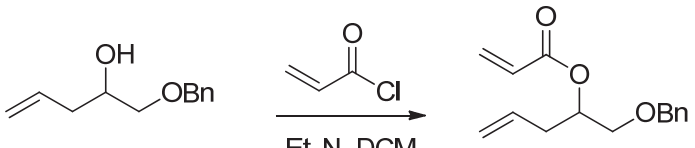
MS (APCI) *m/z* (%): 91.09 (59), 174.05 (100), 264.12 (100) [M+1].

HRMS *m/z*: calculated for $C_{14}H_{21}O_2NNaSi$: 286.12353. Found: 286.12338.

IR (film, cm^{-1}): 698, 736, 840, 1251, 1454, 2250, 2908.

IV.1.4. Esterifications

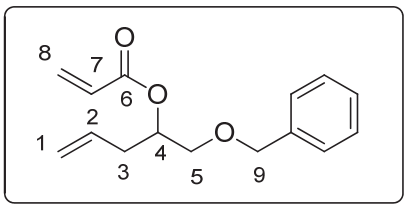
IV.1.4.1. Synthesis of 6.021



6.019 **6.021**

To a solution of 1-(benzyloxy)pent-4-en-2-ol (0.476 g, 2.5 mmol) in Et_2O (10 mL) was added Et_3N (0.28 mL, 3.5 mmol). The solution was cooled to 0°C and acryloyl chloride (0.28 mL, 3.5 mmol) was added dropwise. The solution was stirred for 1 hour, filtered, the solution was washed with PE/EtOAc (8:2) and the combined solutions were concentrated under reduced pressure. The product was purified by elution through a short silica gel column (PE/EtOAc 9:1) to afford the desired compound as a yellow oil; yield: 0.42 g (70 %).

- 1-(benzyloxy-pent-4-en-2-yl acrylate **6.021**[1]



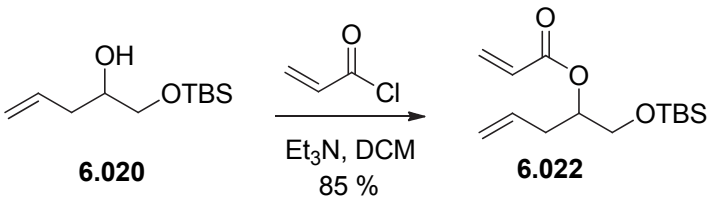
CAS number : [640298-47-1]

^{1}H NMR (300MHz, $CDCl_3$): δ 2.44 (m, 2H, H_3), 3.57 (d, 2H, H_5, J=4.9 Hz), 4.52 (d, 1H, H_9, J=12.1 Hz), 4.58 (d, 1H, H_9, J=12.1 Hz), 5.09 (m, 2H, H_1), 5.17 (m, 1H, H_4), 5.74 (m, 1H, H_2), 5.83 (dd, 1H, H_8, J=10.4 Hz, J=1.6 Hz), 6.14 (dd, 1H, H_7, J=17.3 Hz, J=10.3 Hz), 6.42 (dd, 1H, H_8, J=17.3 Hz, J=1.5 Hz), 7.28-7.36 (m, 5H, H_{ar}).

^{13}C NMR (75MHz, $CDCl_3$): δ 35.5 (C_3), 70.6 (C_5), 72.3 (C_4), 73.3 (C_9), 118.2 (C_1), 127.8-127.8-128.5 (C_{ar}), 128.7 (C_7), 131.0 (C_8), 133.3 (C_2), 138.1 (C_{ar}), 165.9 (C_6).

Data are in agreement with literature values.

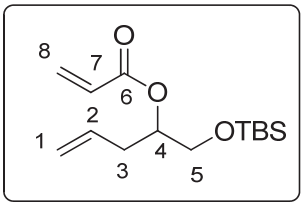
IV.1.4.2. Synthesis of 6.022



To a solution of 1-((*tert*-butyldimethylsilyl)oxy)pent-4-en-2-ol (0.769 g, 4.0 mmol) and Et_3N (0.83 mL, 6.0 mmol) in DCM (10 mL) was added dropwise acryloyl chloride (0.45 mL, 5.6 mmol) at 0°C. The solution was warmed up to room temperature and stirred for 15 minutes. The mixture was diluted with water and extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under

reduced pressure to afford the desired compound as a yellow oil; yield: 0.92 g (85 %).

- 1-((*tert*-butyldimethylsilyl)oxy)pent-4-en-2-yl acrylate **6.022**



^{1}H NMR (300MHz, $CDCl_3$): δ 0.05 (s, 6H, H_{TBS}), 0.88 (s, 9H, H_{TBS}), 2.40 (m, 2H, H_3), 3.69 (d, 2H, H_5, J=5.0 Hz,), 5.07 (m, 3H, H_1 and H_4), 5.80 (m, 2H, H_8 and H_2), 6.11 (dd, 1H, H_7, J=17.3 Hz, J=10.3 Hz), 6.40 (dd, 1H, H_8, J=17.3 Hz, J=1.1 Hz).

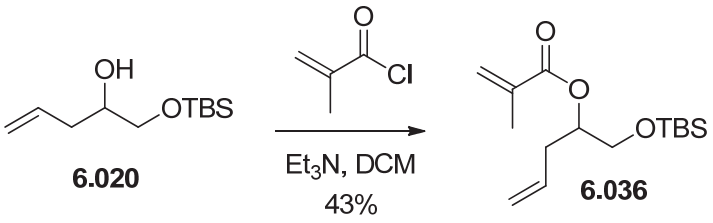
^{13}C NMR (75MHz, $CDCl_3$): δ -5.3 (C_{TBS}), 18.4 (C_{TBS}), 25.9 (C_{TBS}), 35.1 (C_3), 63.7 (C_5), 74.0 (C_4), 118.0 (C_1), 128.8 (C_7), 130.7 (C_8), 133.6 (C_2), 165.9 (C_6).

IR (film, cm^{-1}): 810, 833, 1103, 1191, 1253, 1406, 1471, 1637, 1726, 2856, 2927, 2952.

MS (ESI) *m/z* (%): 271.17 (25) $[M+H]^+$, 293.15 (100) $[M+Na]^+$

HRMS *m/z*: calculated for $C_{14}H_{27}O_3Si$: 271.17229. Found: 271.17240.

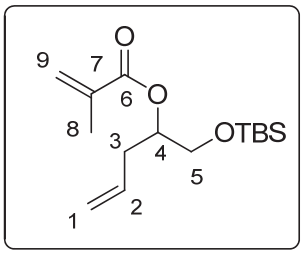
IV.1.4.3. Synthesis of 6.036



To a solution of 1-((*tert*-butyldimethylsilyl)oxy)pent-4-en-2-ol (1.961 g, 9.1 mmol) and Et_3N (1.89 mL, 13.6 mmol) in DCM (20 mL) was added methacryloyl chloride (1.24 mL, 12.7 mmol) at 0°C. The solution was

warmed up to room temperature and stirred for 15 minutes. Mixture was quenched with water and extracted with DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (PE/EtOAc 95:5) to afford the desired compound as a yellow oil; yield: 1.116 g (43 %).

- 1-((tert-butyldimethylsilyl)oxy)pent-4-en-2-yl methacrylate **6.036**



^{1}H NMR (300MHz, $CDCl_3$): δ 0.05 (s, 6H, H_{TBS}), 0.89 (s, 9H, H_{TBS}), 1.94 (dd, 3H, H_8, J=1.5 Hz, J=0.9 Hz), 2.42 (m, 2H, H_3), 3.69 (dd, 2H, H_5, J=5.0 Hz, J=1.1 Hz), 4.99 (m, 1H, H_4) 5.10 (m, 2H, H_1), 5.55 (m, 1H, H_9), 5.79 (m, 1H, H_2), 6.11 (dd, 1H, H_9, J=1.7 Hz, J=0.9 Hz).

^{13}C NMR (75MHz, $CDCl_3$): δ -5.2 (C_{TBS}), 18.7 (C_{TBS} and C_8), 26.0 (C_{TBS}), 35.3 (C_3), 63.9 (C_5), 74.3 (C_4), 118.0 (C_1), 125.6 (C_9), 133.9 (C_2), 137.0 (C_7), 167.1 (C_6).

MS (ESI) *m/z* (%): 285.19 (43) $[M+H]^+$, 307.17 (100) $[M+Na]^+$

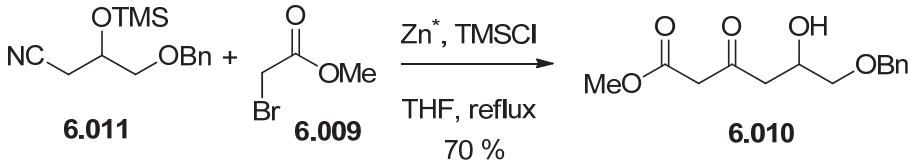
HRMS *m/z*: calculated for $C_{15}H_{29}O_3Si$: 285.18754. Found: 285.18805.

IR (film, cm^{-1}): 734, 775, 835, 1109, 1165, 1252, 1471, 1639, 1720, 2856, 2927.

IV.2. Synthesis of lactones 6.016 and 6.017

IV.2.1. Blaise reaction

IV.2.1.1. Synthesis of 6.010

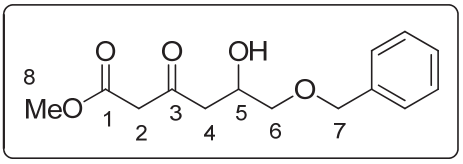


6.011 **6.009** **6.010**

Powdered zinc was activated with 3M HCl, rinsed with water, EtOH and Et_2O then dried under reduced pressure.

To a suspension of activated zinc dust (0.89 g, 13.7 mmol) in THF (6.8 mL) was added TMSCl (0.26 mL, 2.0 mmol). The solution was stirred for 20 minutes, treated with substrate **6.011** (1.8 g, 6.8 mmol) and the mixture was heated to reflux. Methyl bromoacetate (1.03 mL, 10.9 mmol) was then added dropwise over 90 minutes and the mixture was refluxed for 60 more minutes. The mixture was cooled to 0°C and 3M HCl (4 mL) was added dropwise. After 2 hours, the organic volatiles were removed under reduced pressure and the remaining mixture was extracted with EtOAc. The organic layer was washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: PE/EtOAC 85:15 →70:30) to afford the title product as a yellow oil; yield: 1.28 g (70 %).

- Methyl 6-(benzyloxy)-5-hydroxy-3-oxohexanoate **6.010**



^{1}H NMR (300MHz, $CDCl_3$): δ 2.76 (m, 2H, H_4), 3.50 (m, 2H, H_6), 3.51 (s, 2H, H_2), 3.74 (s, 3H, H_8), 4.29 (m, 1H, H_5), 4.56 (s, 2H, H_7), 7.27-7.33 (m, 5H, H_{ar})

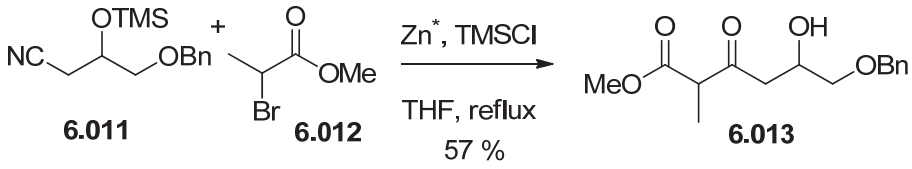
^{13}C NMR (75MHz, $CDCl_3$): δ 46.3 (C_4), 49.5 (C_8), 52.2 (C_2), 66.5 (C_5), 73.1 (C_6), 73.2 (C_7), 127.6-128.3-137.7 (C_{ar}), 167.4 (C_1), 202.2 (C_3).

MS (ESI) *m/z* (%): 91.13 (21), 249.04 (85), 266.83 (100) $[M]^+$, 283.94 (65).

HRMS *m/z*: calculated for $C_{14}H_{19}O_5$: 267.12278. Found: 267.12270.

IR (film, cm^{-1}): 736, 1078, 1454, 1712, 1745, 2918, 3420.

IV.2.1.2. Synthesis of 6.013

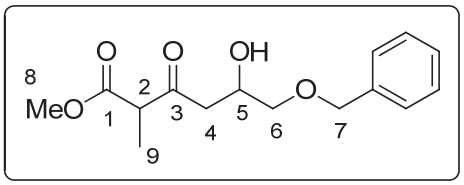


6.011 **6.012** **6.013**

Powdered zinc was activated with 3M HCl, rinsed with water, EtOH and Et_2O then dried under reduced pressure.

To a suspension of activated zinc dust (0.26 g, 4.0 mmol) in THF (2 mL) was added TMSCl (0.04 mL, 0.3 mmol). The solution was stirred for 20 minutes, treated with substrate **6.011** (1.8 g, 6.8 mmol) and the mixture was heated to reflux. Methyl bromoacetate (0.45 mL, 4 mmol) in THF (3 mL) was then added dropwise over 90 minutes and the mixture was refluxed for 2 more hours. The mixture was cooled to 0°c and added onto a solution of APTS (3 eqs)/H_2O (5 mL)/THF (5 mL) at 0°C and it was stirred for 1 hour. The solvent was then removed under reduced pressure. The residue was dissolved in EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: PE/EtOAC 1:1, 5 % Et_3N) to afford the title product as a clear oil; yield: 0.157 g (57 %).

- Methyl 6-(benzyloxy)-5-hydroxy-2-methyl-3-oxohexanoate **6.013**



^{1}H NMR (300MHz, $CDCl_3$): δ 1.34 (d, 3H, H_9, J=7.1Hz), 2.78 (m, 2H, H_4), 3.52 (m, 3H, $H_{2\ and\ 6}$), 3.72 (s, 3H, H_8), 4.29 (m, 1H, H_5), 4.56 (s, 2H, H_7), 7.27-7.39 (m, 5H, H_{ar}).

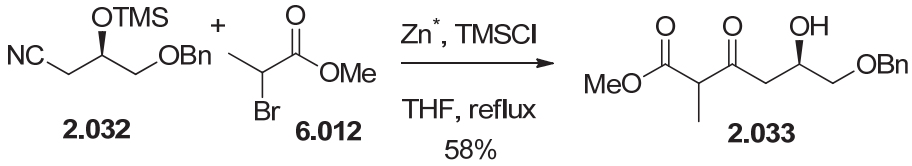
^{13}C NMR (75MHz, $CDCl_3$): δ 12.7 (C_9), 44.8 (C_4), 52.6 (C_8), 53.3 (C_2), 66.8 (C_5), 73.2 (C_6), 73.5 (C_7), 127.8-127.9-128.6-137.9 (C_{ar}), 170.8 (C_1), 205.6 (C_3).

MS (ESI) *m/z* (%): 303.12 (100) $[M+Na]^+$, 319.09 (14), 583.25 (11) $[2M+Na]^+$

HRMS *m/z*: calculated for $C_{15}H_{21}O_5$: 281.13862. Found: 281.13835.

IR (film, cm^{-1}): 700, 734, 1114, 1454, 1714, 1737, 3380.

IV.2.1.3. Synthesis of 2.033

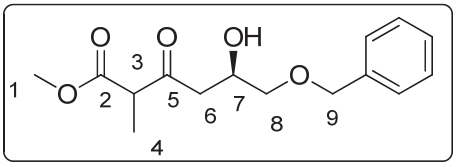


2.032 **6.012** **2.033**

To a suspension of activated Zn (10 mmol, 0.65 g) in THF (5 mL) was added TMSCl (0.75 mmol, 0.1 mL) dropwise and the resulting mixture was stirred for 20 minutes. Nitrile (0.66 g, 2.5 mmol) was added and the solution was heated to reflux (76°C). A solution of methyl-bromo acetate (10 mmol, 1.12 mL) in THF (7.5 mL) was added dropwise over 90 minutes and stirred for 2 more hours at reflux. The reaction mixture was cooled down to 0°C and poured on a solution of APTS (3eq)/H_2O(5 mL)/THF (5 mL) at 0°C and stirred for 1 hour. The solvent was evaporated under reduced pressure and the residue was taken in EtOAc. It was washed with brine, dried over

Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent: PE/EtOAc 1:1, 5 % Et_3N) to afford the pure product as a clear oil and a mixture of two compounds (1:1); yield: 0.41 g (58 %).

- (*R*)-Methyl 6-(benzyloxy)-5-hydroxy-2-methyl-3-oxohexanoate **2.033**[1]



CAS number : [934623-82-2]

^{1}H NMR (300MHz, $CDCl_3$): δ 7.35-7.29 (m, 5H, H_{ar}), 4.54 (s, 2H, H_9), 4.28 (quint., 1H, H_7, J=6Hz), 3.71 (s, 3H, H_1), 3.50-3.43 (m, 3H, $H_{3\ and\ 8}$), 2.76-2.73 (m, 2H, H_6), 1.32 (d, 3H, H_4, J=9Hz).

^{13}C NMR (75MHz, $CDCl_3$): δ 205.6 ($C_{5,5'}$), 170.9 ($C_{2,2'}$), 137.9-128.6-127.9 (C_{ar}), 73.5-73.2-73.1 ($C_{8,8',\ 9,9'}$), 66.9-66.8 ($C_{7\ and\ 7'}$), 53.4-53.3-52.7 ($C_{1,1',3,3'}$), 44.8-44.9 ($C_{6\ and\ 6'}$), 12.6-12.7 ($C_{4\ and\ 4'}$).

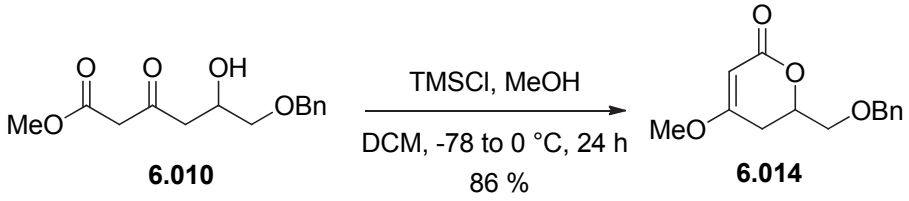
Data are in agreement with literature values.

IV.2.2. Lactonization

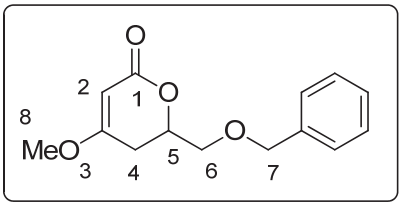
IV.2.2.1. General procedure

To a solution of substrate (1 eq) in DCM (0.1 M) was added MeOH (30 eqs). The resulting solution was cooled to -78°C and TMSCl (4 eqs) was added dropwise. The solution was allowed to warm up to 0°C and stirred 8 hours at 0°C. The mixture was placed in a refrigerator overnight. Saturated $NaHCO_3$ was added and the aqueous phase was extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure.

IV.2.2.2. Synthesis of 6.014



- 6-((benzyloxy)methyl)-4-methoxy-5,6-dihydro-*2H*-pyran-2-one **6.014**



The reaction was carried out on 4.67 mmol (1.2 g).

The crude mixture was purified by silica gel column chromatography (PE/EtOAc 85:15) to afford the title product as a yellow oil; yield: 1 g (86 %).

^{1}H NMR (300MHz, $CDCl_3$): δ 2.39 (dd, 1H, H_4, J=17.2 Hz, J=4.1 Hz), 2.73 (ddd, 1H, H_4, J=17.2 Hz, J=11.8 Hz, J=1.2 Hz), 3.70 (dd, 2H, H_6, J=4.8 Hz, J=1.8 Hz), 3.74 (s, 3H, H_8), 4.57 (m, 1H, H_5), 4.60 (s, 2H, H_7), 5.14 (d, 1H, H_2, J=1.2 Hz), 7.29-7.39 (m, 5H, H_{ar}).

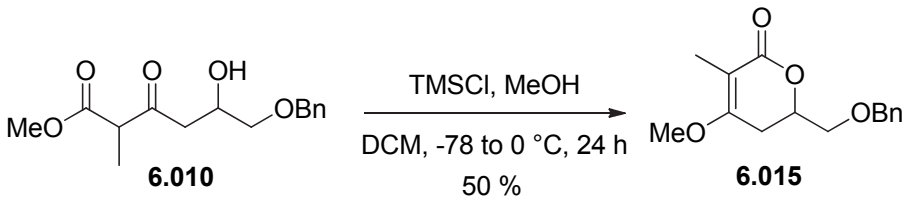
^{13}C NMR (75MHz, $CDCl_3$): δ 29.8 (C_4), 56.1 (C_8), 70.6 (C_6), 73.6 (C_5), 74.6 (C_7), 90.2 (C_2), 127.7-127.9-128.5-137.7 (C_{ar}), 166.7 (C_3), 172.8 (C_1).

MS (ESI) *m/z* (%): 249.11 (31) $[M+1]^+$, 271.09 (69) $[M+Na]^+$, 519 (100) $[2M+Na]^+$

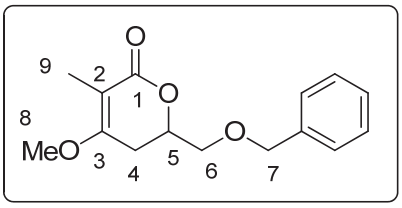
HRMS *m/z*: calculated for $C_{14}H_{17}O_4$: 249.11217. Found: 249.11214.

IR (film, cm^{-1}): 698, 736, 1051, 1224, 1390, 1454, 1622, 1697.

IV.2.2.3. Synthesis of 6.015



- 6-((benzyloxy)methyl)-4-methoxy-3-methyl-5,6-dihydro-*2H*-pyran-2-one **6.015**



The reaction was carried out on 2.79 mmol (0.78 g).

The crude mixture was purified by silica gel column chromatography (PE/EtOAc 85:15) to afford the title product as a yellow oil; yield: 0.37 g (50 %).

^{1}H NMR (300MHz, $CDCl_3$): δ 1.79 (s, 3H, H_9), 2.68 (m, 2H, H_4), 3.72 (m, 2H, H_6), 3.79 (s, 3H, H_8), 4.48 (m, 1H, H_5), 4.61 (s, 2H, H_7), 7.28-7.40 (m, 5H, H_{ar}).

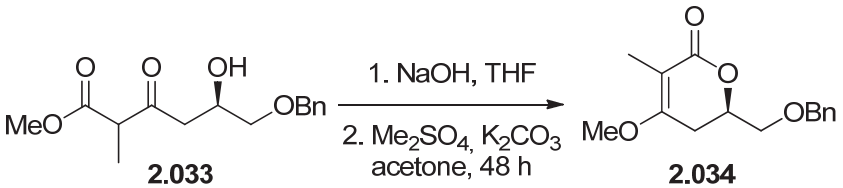
^{13}C NMR (75MHz, $CDCl_3$): δ 8.7 (C_9), 25.9 (C_4), 55.4 (C_8), 70.7 (C_6), 73.3 (C_5), 74.7 (C_7) 102.7 (C_2), 127.7-127.8-128.3-137.6 (C_{ar}), 165.6 (C_3), 171.1 (C_1).

MS (ESI) *m/z* (%): 263.13 (82) $[M+1]^+$, 285.11 (93) $[M+Na]^+$, 301.08 (48), 547.23 (100) $[2M+Na]^+$

HRMS *m/z*: calculated for $C_{15}H_{19}O_4$: 263.12779. Found: 263.12779.

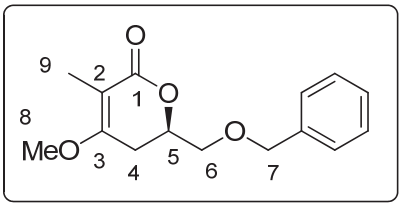
IR (film, cm^{-1}): 700, 736, 1099, 1238, 1454, 1643, 1693.

IV.2.2.4. Synthesis of 2.034



To a solution of βketoester (0.1 g, 0.36 mmol) in THF (4 mL) was added aqueous NaOH (1 M) (1.4 mL, 1.43 mmol). The mixture was stirred for 30 minutes and then quenched with saturated NH_4Cl followed by diluted HCl_{aq}. The aqueous phase was extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was diluted in acetone (3.4 mL). Me_2SO_4 (0.05 mL, 0.51 mmol) was added followed by K_2CO_3. The resulting mixture was stirred for 2 days. Mixture was quenched with water and extracted with Et_2O. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent PE/EtOAc 5:1 → 1:1) to afford the desired product as a clear oil; yield: 0.037 g (41 %).

- (*R*)-6-((benzyloxy)methyl)-4-methoxy-3-methyl-5,6-dihydro-2H-pyran-2-one **2.034**[1]



^{1}H NMR (300MHz, $CDCl_3$): δ 1.77 (s, 3H, H_9), 2.69-2.63 (m, 2H, H_4), 3.71 (dd, 2H, H_6, J=4.5 Hz, J=2.7 Hz), 3.78 (s, 3H, H_8), 4.50-4.45 (m, 1H, H_5), 4.59 (d, 2H, H_7, J=3.6 Hz), 7.29-7.39 (m, 5H, H_{ar}).

^{13}C NMR (75MHz, $CDCl_3$): δ 168.1 (C_1), 165.5 (C_3), 137.7-128.6-128.1-127.9 (C_{ar}), 103.3 (C_2), 73.9 (C_7), 73.4 (C_5), 70.9 (C_6), 55.6 (C_8), 26.3 (C_4), 9.0 (C_9).

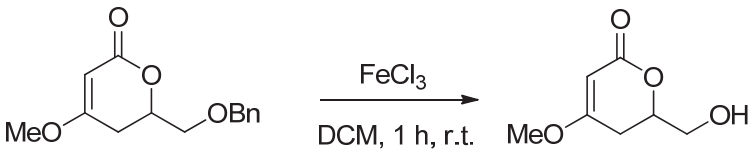
Data are in agreement with literature values.

IV.2.3. Deprotection

IV.2.3.1. General procedure

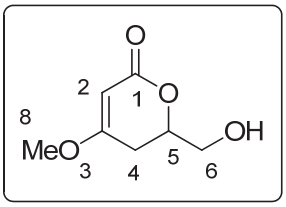
To a solution of substrate (1 eq) in DCM (0.1 M) was added $FeCl_3$ (3 eqs). The resulting suspension was stirred at room temperature for 1 hour. Water was added and the phases were separated. The aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure.

IV.2.3.2. Synthesis of 6.016



6.014 **6.016**

- 6-(hydroxymethyl)-4-5,6-dihydro-2H-pyran-2-one **6.016**



The reaction was carried out on 1.54 mmol (0.38 g).

The crude mixture was purified by silica gel column chromatography (PE/EtOAc 1:1 → 0:1) to afford the title product as a white solid; yield: 0.17 g (69 %).

^{1}H NMR (300MHz, $CDCl_3$): δ 2.27 (dd, 1H, H_4, J=17.1 Hz, J=3.9 Hz), 2.79 (ddd, 1H, H_4, J=17.2 Hz, J=12.6 Hz, J=1.6 Hz), 3.72 (dd, 1H, H_6, J=12.3 Hz, J=4.7 Hz), 3.77 (s, 3H, H_8), 3.91 (dd, 1H, H_6, J=12.3 Hz, J=3.9 Hz), 4.50 (m, 1h, H_5), 5.15 (d, 1H, H_2, J=1.6 Hz).

^{13}C NMR (75MHz, $CDCl_3$): δ 29.0 (C_4), 56.3 (C_8), 63.8 (C_6), 76.4 (C_5), 90.0 (C_2), 167.0 (C_3), 173.17 (C_1).

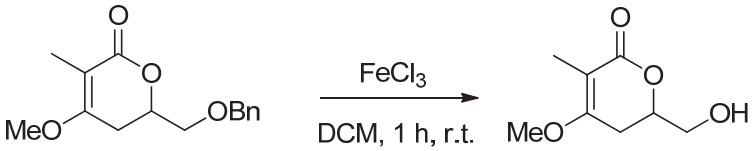
MS (ESI) *m/z* (%): 159.07 (57) $[M+1]^+$, 181.07 (100) $[M+Na]^+$

HRMS *m/z*: calculated for $C_7H_{11}O_4$: 159.06519. Found: 159.06569.

IR (film, cm^{-1}): 854, 997, 1033, 1226, 1382, 1620, 1681, 2918, 3377.

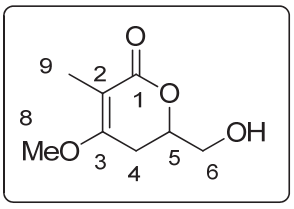
Mp (°C): 126-127°C.

IV.2.3.3. Synthesis of 6.017



6.015 **6.017**

- 6-(hydroxymethyl)-4-methoxy-3-methyl-5,6-dihydo-2H-pyran-2-one **6.017**



The reaction was carried out on 0.51 mmol (0.27 g).

The crude mixture was purified by silica gel column chromatography (PE/EtOAc 1:1 → 0:1) to afford the title product as a white solid; yield: 0.052 g (60 %).

^{1}H NMR (300MHz, $CDCl_3$): δ 1.75 (s, 3H, H_9), 2.54 (dd, 1H, H_4, J=17.1 Hz, J=3.7 Hz), 2.76 (t, 1H, H_4, J=17.2 Hz), 3.72 (dd, 1H, H_6, J=12.2 Hz, J=4.4

Hz), 3.79 (s, 3H, H_8), 3.89 (dd, 1H, H_6, J=12.2 Hz, J=3.5 Hz), 4.4 (m, 1H, H_5).

^{13}C NMR (75MHz, $CDCl_3$): 8.9 (C_9), 25.3 (C_4), 55.7 (C_8), 63.7 (C_6), 75.1 (C_5), 102.8 (C_2), 166.1 (C_3), 168.6 (C_1).

MS (ESI) *m/z* (%): 173.08 (100) $[M+1]^+$, 195.06 (69) $[M+Na]^+$, 367.13 (52) $[2M+Na]^+$

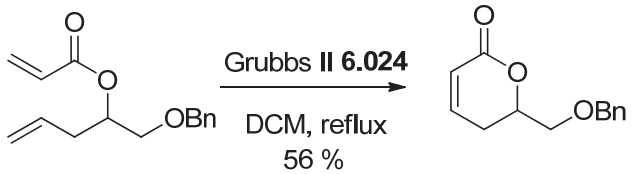
HRMS *m/z*: calculated for $C_8H_{13}O_4$: 173.08084. Found: 173.08114.

IR (film, cm^{-1}): 761, 997, 1132, 1236, 1326, 1386, 1463, 1639, 1672, 2921, 3346.

IV.3. Synthesis of lactone 6.028

IV.3.1. Via ring-closing metathesis

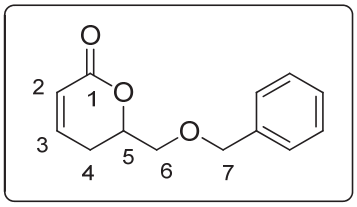
IV.3.1.1. Synthesis of 6.026



6.021 **6.026**

A solution of 1-(benzyloxy)pent-4-en-2-yl acrylate (0.250 g, 1.0 mmol) in DCM (35 mL) was heated to reflux. Grubb's II catalyst (0.02 g, 0.03 mmol) was added to the solution and the mixture was stirred for 1 hour. Then, a second portion of 10 mg (1.5 mol %) of Grubb's II catalyst was added to the solution which was stirred for another hour. The solution was concentrated and the crude mixture was purified by silica gel column chromatography (PE/EtOAc 8:2→ 0:1) to afford the desired compound as a brown oil; yield: 0.222 g (56 %).

- 6-((benzyloxy)methyl)-5,6-dihydro-*2H*-pyran-2-one **6.026**[1]

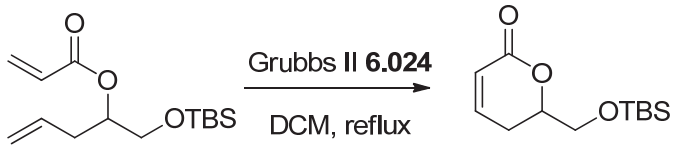


^{1}H NMR (300MHz, $CDCl_3$): δ 2.37 (dddd, 1H, H_4, J=18.5 Hz, J=5.8 Hz, J=4.4 Hz, J=1.2 Hz), 2.55 (ddt, 1H, H_4, J=18.6 Hz, J=11.5 Hz, J=2.6 Hz), 3.68 (d, 2H, H_6, J=4.7 Hz), 4.58 (m, 1H, H_5), 4.59 (d, 2H, H_7, J=1.4 Hz), 6.00 (ddd, 1H, H_2, J=9.7 Hz, J=2.7 Hz, J=1.1 Hz), 6.89 (ddd, 1H, H_3, J=9.7 Hz, J=5.91 Hz, J=2.6 Hz), 7.28-7.34 (m, 5H, H_{ar}).

^{13}C NMR (75MHz, $CDCl_3$): δ 31.8 (C_4), 70.9 (C_6), 73.7 (C_7), 76.8 (C_5), 121.2 (C_2), 127.9 (C_{ar}), 128.0-128.6-137.8 (C_{ar}), 145.3 (C_3), 163.9 (C_1).

Data are in agreement with literature values

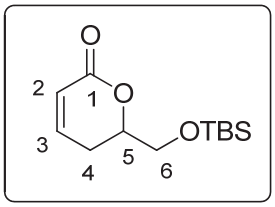
IV.3.1.2. Synthesis of 6.027



6.022 **6.027**

A solution of ((tert-butyldimethylsilyl)oxy)pent-4-en-2-yl acrylate (0.139 g, 0.51 mmol) in DCM (17 mL) was heated to reflux. Then, Grubbs II catalyst (0.017 g, 0.02 mmol) was added and the mixture was stirred under reflux for 1 hour. The solution was cooled to room temperature and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (PE/EtOAc 9:1) to afford the desired compound as an orange oil; yield: 0.098 g (78 %).

- 6-((benzyloxy)methyl)-5,6-dihydro-2H-pyran-2-one **6.027**[18]

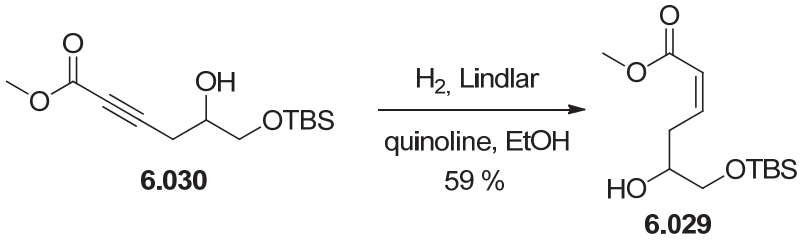


^{1}H NMR (300MHz, $CDCl_3$): δ 0.06 (s, 6H, H_{TBS}), 0.88 (s, 9H, H_{TBS}), 2.40 (m, 1H, H_4), 2.53 (m, 1H, H_4), 3.81 (dd, 2H, H_6, J=4.9 Hz, J=1.3 Hz), 4.47 (dq, 1H, H_5, J=10.5 Hz, J=5.2 Hz), 6.01 (d, 1H, H_2, J=9.7 Hz), 6.90 (ddd, 1H, H_3, J=9.7 Hz, J=5.7 Hz, J=2.8 Hz).

^{13}C NMR (75MHz, $CDCl_3$): δ -5.2 (C_{TBS}), 18.4 (C_{TBS}), 26.0 (C_{TBS}), 26.1 (C_4), 64.3 (C_6), 77.9 (C_5), 121.3 (C_2), 145.1 (C_3), 164.1 (C_1).

IV.3.2. Via intramolecular esterification

IV.3.2.1. Synthesis of 6.029

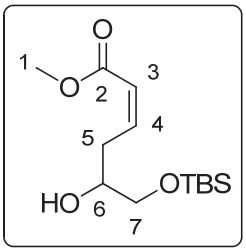


Hydrogen was bubbled into a solution of Lindlar catalyst (0.118 g, 1.11 mmol) and quinoline (0.26 mL, 2.21 mmol) in EtOH (6 mL) for 10 minutes and the mixture was stirred for 30 minutes. Then, methyl-6-((*tert*-butyldimethylsilyl)oxy)-5-hydroxyhex-2-ynoate (1.006 g, 3.69 mmol) was added to the heterogeneous mixture and the mixture was stirred overnight.

[18] A. Ahmed, E. K. Hoegenauer, V. S. Enev, M. Hanbauer, H. Kaehlig, E. Öhler, J. Mulzer, *J. Org. Chem.* **2003**, *68*, 3026.

EtOAc was added to the mixture which was filtered and the solid residue extracted several times with EtOAc. After concentration of the solution under reduced pressure, the crude mixture was purified by silica gel column chromatography (PE/EtOAc 9:1) to afford the desired compound as a yellow oil; yield: 0.597 g (59 %).

- (*Z*)-methyl 6-((*tert*-butyldimethylsilyl)oxy)-5-hydroxyhex-2-enoate **6.029**



^{1}H NMR (300MHz, $CDCl_3$): δ 0.08 (s, 6H, H_{TBS}), 0.91 (s, 9H, H_{TBS}), 2.68 (d, 1H, -OH, J=4.2 Hz), 2.82 (m, 2H, H_5), 3.50 (dd, 1H, H_7, J=6.9 Hz, J=10.0 Hz) , 3.65 (dd, 1H, H_7, J=10.0 Hz, J=4.0 Hz), 3.71 (s, 3H, H_1), 3.78 (m, 1H, H_6), 5.92 (dt, 1H, H_3, J=11.5 Hz, J=1.7 Hz), 6.43 (dt, 1H, H_4, J=11.5 Hz, J=7.5 Hz).

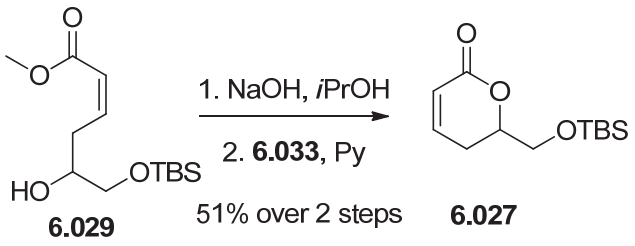
^{13}C NMR (75MHz, $CDCl_3$): δ -5.1 (C_{TBS}), 18.8 (C_{TBS}), 26.3 (C_{TBS}), 33.0 (C_5), 51.5 (C_1), 67.3 (C_8), 71.6 (C_6), 121.5 (C_3), 146.9 (C_4), 167.3 (C_2).

MS (ESI) *m/z* (%): 275.16 (18) $[M+H]^+$, 297.16 (75) $[M+Na]^+$

HRMS *m/z*: calculated for $C_{13}H_{27}O_3$: 275.16728. Found: 275.16731.

IR (film, cm^{-1}): 777, 835, 119, 1173, 1254, 1440, 1464, 1647, 1724, 2856.4, 2928, 2953.

IV.3.2.2. Synthesis of 6.027



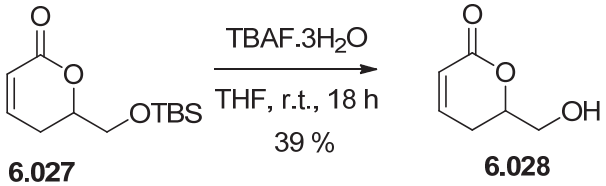
6.029 **6.027**

To a solution of (*Z*)-methyl 6-((tert-butyldimethylsilyl)oxy)-5-hydroxyhex-2-enoate (1.7 g, 4.19 mmol) in *i*PrOH (10 mL) was added NaOH ((1M aqueous solution) 8.39 mL, 8.39 mmol). The solution was stirred at room temperature for 1 hour then it was quenched with 1M HCl and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Pyridine (10 mL) was added to the resulting product and the solution was cooled to 0°C. Yamaguchi's reagent (1.42 g, 5.83 mmol) was then added and the reaction was stirred for 1 hour. The mixture was diluted with Et_2O, the organic layer was washed with 1M NaOH, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (PE/EtOAc 9:1) to afford the desired compound as an orange oil; yield: 0.52 g (46 %).

- 6-(((tert-butyldimethylsilyl)oxy)methyl)-5,6-dihydro-*2H*-pyran-2-one **6.027**

Cfr IV.3.1.2 for analyses.

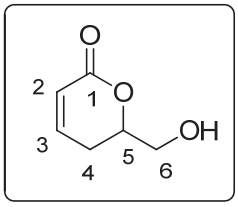
IV.3.3. Deprotection



6.027 **6.028**

To a solution of 6-(((*tert*-butyldimethylsilyl)oxy)methyl)-5,6-dihydro-2*H*-pyran-2-one (0.11 g, 0.46 mmol) in THF (2 mL) was added TBAF.$3H_2O$ (0.29 g, 0.92 mmol). The mixture was stirred overnight and quenched by adding saturated $NaHCO_3$. The mixture was extracted with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (PE/EtOAc 9:1) to afford the desired product as a colorless oil; yield: 0.02 g (39 %).

- 6-(hydroxymethyl)5,6-dihydro-*2H*-pyran-2-one **6.028**[19]



CAS number : [124918-95-2]

^{1}H NMR (300MHz, $CDCl_3$): δ 1.81 (bs, 1H, -OH), 2.32 (dddd, 1H, H_4, J=18.5 Hz, J=6.2 Hz, J=4.0 Hz, J=0.9 Hz), 2.63 (ddt, 1H, H_4, J=18.4 Hz, J=12.5 Hz, J=2.7 Hz), 3.76 (dd, 1H, H_6, J=12.4 Hz, J=4.9 Hz), 3.91 (dd, 1H, H_6, J=12.4 Hz, J=3.2 Hz), 4.53-4.61 (m, 1H, H_5), 6.05 (ddd, 1H, H_2, J=9.8 Hz, J=2.8 Hz, J=0.9 Hz), 6.95 (ddd, 1H, H_3, J=9.7 Hz, J=6.2 Hz, J=2.3 Hz).

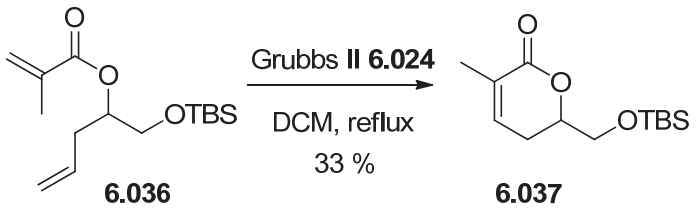
^{13}C NMR (75MHz, $CDCl_3$): δ 25.4 (C_4), 64.1 (C_6), 78.4 (C_5), 121.2 (C_2), 145.4 (C_3), 163.8 (C_1).

IV.4. Synthesis of lactone 6.038

IV.4.1. Via Grubbs metathesis

IV.4.1.1. Synthesis of 6.037

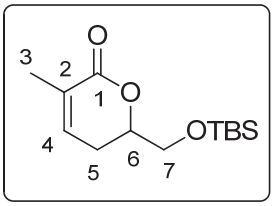
[19] K.S. Kumar, C. S. Reddy, *Org. Biomol. Chem.* **2012**, *10*, 2647.



6.036 **6.037**

To a solution of 1-((*tert*-butyldimethylsilyl)oxy)pent-4-en-2-yl methacrylate (0.515 g, 1.81 mmol) in DCM (60 mL) was added Grubb's II catalyst (0.031 g, 0.04 mmol) under reflux. The mixture was stirred for 1 hour. Then, a second amount (2 mol %) of Grubbs II catalyst was added. The reaction was stirred overnight before adding another 2 mol % of catalyst. The mixture was stirred for 6 more hours. Finally, a last addition of 2 mol% of Grubb's catalyst was done and the mixture stirred for another hour. The solution was concentrated under reduced pressure and the crude mixture was purified by silica gel column chromatography (PE/EtOAc 95:5) to afford the desired compound as a brown oil; yield: 0.155 g (33 %).

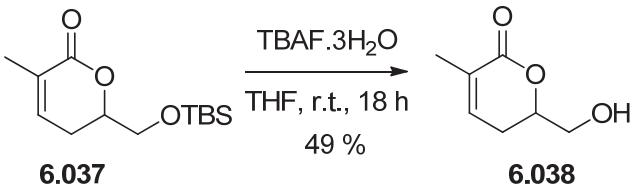
- 6-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-methyl-5,6-dihydro-*2H*-pyran-2-one **6.037**



^{1}H NMR (300MHz, $CDCl_3$): δ 0.09 (s, 6H, H_{TBS}), 0.90 (s, 9H, H_{TBS}), 1.93 (s, 3H, H_3), 2.42 (m, 2H, H_5), 3.80 (m, 2H, H_7), 4.42 (ddt, 1H, H_6, J=11.0 Hz, J=5.7 Hz, J=4.5 Hz), 6.60 (dd, 1H, H_4, J=5.9 Hz, J=2.8 Hz).

^{13}C NMR (75MHz, $CDCl_3$): δ -5.2 (C_{TBS}), 17.3 (C_3), 18.4 (C_{TBS}), 26.0 (C_{TBS}), 64.4 (C_7), 78.0 (C_6), 128.3 (C_2), 139.0 (C_4), 165.6 (C_1).

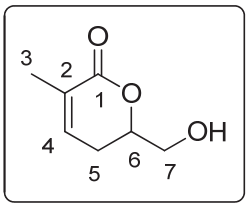
IV.4.1.2. Synthesis of 6.038



6.037 **6.038**

To a solution of 6-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-methyl-5,6-dihydro-*2H*-pyran-2-one (0.15 g, 0.59 mmol) in THF (2 mL) was added TBAF.$3H_2O$ (0.369 g, 1.17 mmol). The mixture was stirred overnight, quenched with saturated $NaHCO_3$ and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (PE/EtOAc 9:1) to afford the desired compound as a colorless oil; yield: 0.036 g (49 %).

- 6-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-methyl-5,6-dihydro-*2H*-pyran-2-one **6.038**



^{1}H NMR (300MHz, $CDCl_3$): δ 1.90 (s, 3H, H_3), 2.26 (m, 1H, H_5), 2.54 (ddd, 1H, H_5, J=18.1 Hz, J=12.6 Hz, J=2.6 Hz), 2.70 (bs, 1H, -OH), 3.71 (dd, 1H, H_7, J=12.3 Hz, J=5.0 Hz), 3.82 (dd, 1H, H_7, J=12.3 Hz, J=3.3 Hz), 4.45 (dq, 1H, H_6, J=12.4 Hz, J=4.3 Hz), 6.60 (m, 1H, H_4).

^{13}C NMR (75MHz, $CDCl_3$): δ 17.1 (C_3), 25.7 (C_5), 64.0 (C_7), 78.6 (C_6), 128.1 (C_2), 139.3 (C_4), 165.7 (C_1).

MS (ESI) *m/z* (%): 143.07 (33) $[M+H]^+$, 165.05 (100) $[M+Na]^+$

HRMS *m/z*: calculated for $C_7H_{11}O_3$: 143.07027. Found: 143.07027.

IR (film, cm^{-1}): 731, 1230, 1375, 1452, 1654, 1708, 2854, 2926, 3400.