UNIVERSITÀ DEGLI STUDI DI PAVIA

DOTTORATO IN SCIENZE CHIMICHE E FARMACEUTICHE

XXIX CICLO

Coordinatore: Chiar.mo Prof. Mauro Freccero

Asymmetric synthesis of chiral oxygenated five-membered rings: from mechanism to total synthesis

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a.a. 2015-2016

Summary

Introduction of the PhD Thesis

Research activities of our group were focused on the total synthesis of natural compounds and in the development of methodology for the stereoselective construction of widespread structural motifs.

In particular, during the last years, a growing interest has been devoted to the synthesis of tetrahydrofuran containing metabolites, involving the Tsuji-Trost allylic etherification as key step of the entire approach.

Starting from this background, the aim of the first part of the PhD Thesis is the implementation of the methodology previously developed to new tetrahydrofuran systems and then apply the best outcome to the total synthesis of a bioactive THF-containing molecule.

Remaining within the same line of research, the second part of this work, that was performed at the group leaded by Professor Stephen Hanessian (Montreal, Canada), was focused on the development of a new synthetic strategy toward an antioxidant γ-butyrolactone lignan isolated from *Acer saccharum*.

Our idea was to employ two different stereoselective approaches for the construction of oxygenated heterocycle moieties. In particular, the strategy proposed in the first part of the Thesis's work is based on a single step reaction for the preparation of trisubstituted THF ring with high diastero and enantioselectivity starting from an achiral substrate, while in the second part, the stereocenters of a trisubstituted γ-butyrolactone core are introduced one by one involving the inductive effect of chiral intermediates.

The main results achieved during the three years of PhD school can be considered as milestones for future developments in the field of oxygenated-five membered rings, especially because they led to the stereoselective construction of precious synthetic key intermediates which can be involved for the synthesis of several bioactive natural metabolites.

PART 1

3-hydroxy-2,5-trans-disubstituted THF rings: from methodology to total synthesis

CHAPTER 1: Overview of natural THF-containing metabolites

1.1 Introduction

Several natural products and biologically active compounds present oxygenated five-membered rings as characteristic structural motif. In particular, substituted tetrahydrofurans are commonly occurring substructures found both within terrestrial and marine metabolites.

These substances possess a wide range of biological activities including: anti-microbial, anti-tumor, anthelmintic, anti-malarial and anti-protozoal.

For these reasons, during the last years, considerable efforts have been devoted toward the development of efficient and completely stereoselective strategies for the construction of substituted THF rings[1].

The principal classes of natural products containing tetrahydrofuran systems are: acetogenins from annonaceous plants, lignans and marine macrolides.

1.2 Natural metabolites containing substituted THF moiety

1.2.1 Annonaceous acetogenins[2]

Annonaceous acetogenins (ACGs) represent a group of secondary metabolites isolated from *Annonaceous* spp, typical plants of tropical and subtropical areas.

[1] P. Wolfe and M. B. Hay, *Tetrahedron,* **2007**, 63, 261
[2] A. Bermejo, B. Figadere, M. Polo, I. Barrachina and D. Cortes, *Nat. Prod. Rep*, **2005**, 22, 269

The common framework generally is characterized by an unbranched C_{32} or C_{34} fatty acid chain, with a terminal γ-lactone moiety (figure 1.1)

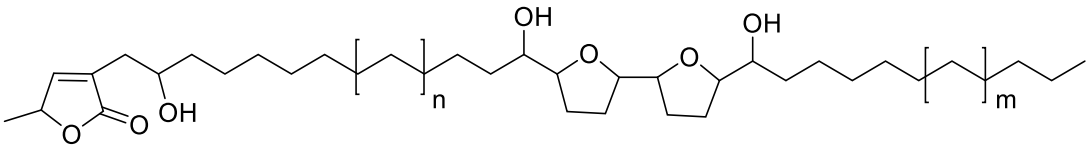


Figure 1.1: general structure of acetogenins

Different types of ACG have been isolated and characterized, and the classification is based on the kind of functional groups present within the chain. In most cases, these substituents are oxygenated functions such as hydroxyl groups, ketones, epoxides, tetrahydrofuran rings (THF) and tetrahydropyran rings (THP) but also double and triple bonds were found.

Acetogenins exhibit a wide range of biological activities, in particular some of them exibits properties such as anti-cancer, cytotoxic, anti-parasitic, pesticidal, anti-microbial and immunosuppressive agents.

Previous studies revealed that the mechanism of action of acetogenins is based on the ability of these compounds to strongly inhibit the mitochondrial respiratory chain complex I[3].

The biosynthesis of such metabolites remains still unknown, but a probable biogenetic pathway has been postulated.

At first, the terminal γ-lactone moiety is generated on a long polyunsaturated fatty acid chain, then THF and THP rings are introduced by enzymatic oxidation of specific double bonds, followed by opening and closing reactions[4].

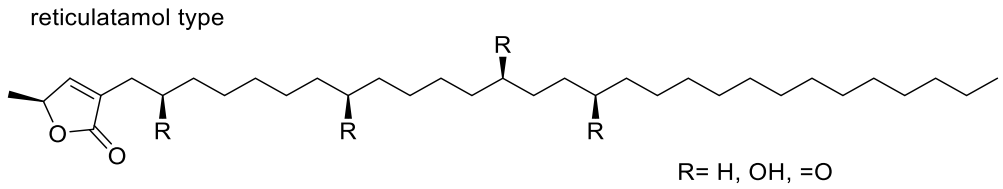
The extraction and purification of these metabolites were performed by following the classic protocol, based on successive solvent extractions with increasingly polar solvents or by liquid/liquid partition from an initial alcoholic extract.

[3] R. Tormo, T. Gallardo, M.C. Gonzales and E. Estornell, *Curr. Top. Phytochem.*, **1999**, 2, 69.
[4] M. Polo, B. Figadere, T. Gallardo, J.R. Tormo and D. Cortes, *Phytochemistry*, **1998**, 48, 1087.

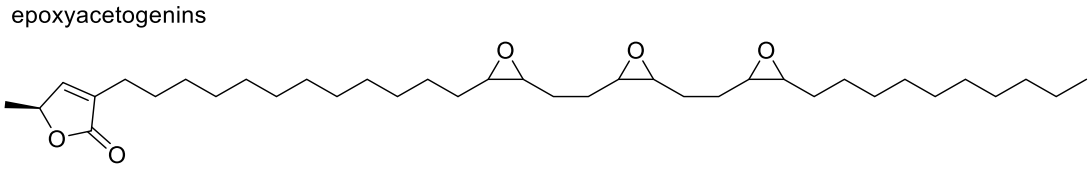
The separation of all the components of the crude mixture was carried out by preparative HPLC[5].

On the basis of their general structure and the nature of the substituents, acetogenins are divided into 6 groups:

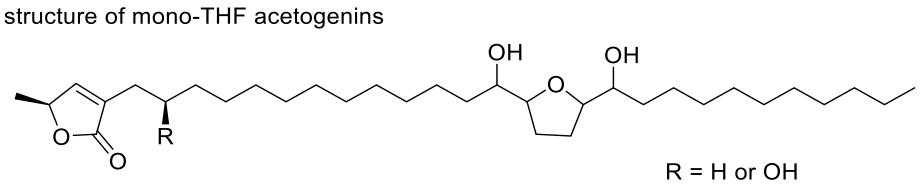
- Linear acetogenins: these compounds do not show any cyclic system within the chain, except the terminal γ-lactone. They are considered as the biogenetic precursor of epoxy and THF ACGs. Linear acetogenins are divided into 4 subgroups depending on the degree of unsaturation and hydroxylation of the alkyl chains. These subgroups are: vicinal dihydroxylated and olefinic acetogenins (giganin type), hydroxylated (or ketonic) linear acetogenins (reticulatamol type), olefinic and acetylenic acetogenins (muridienin-1 type) and bis-lactonic linear acetogenins (rollicosin type).



- Epoxy acetogenins: they originate from the oxidation of linear and olefinic acetogenins and are characterized by the presence of epoxide rings.



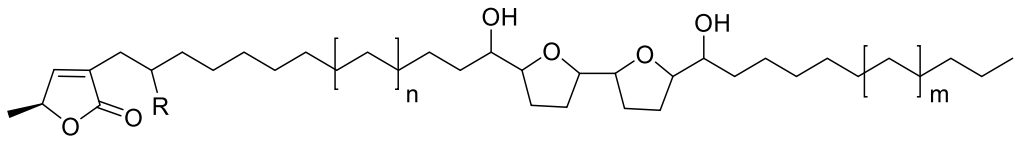
- Mono-THF acetogenins: this is the bigger class of acetogenins, all the compounds show a 2,5-disubstituted THF ring, and sometimes a hydroxyl on the C3 of the THF ring occur.



[5] L. Zeng, Q. Ye, N.H. Oberlies, G. Shii and J.L. McLaughing, *Nat. Prod. Rep.*, **1996**, 13, 275.

- Bis-THF acetogenins: these compounds show two THF rings that can be adjacent or not adjacent.

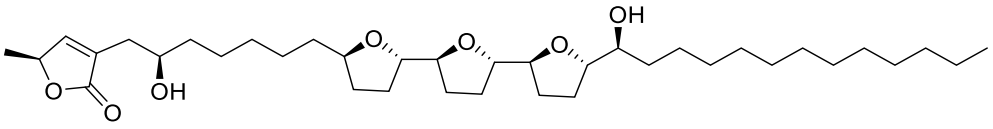
Structure of bis-THF acetogenins



R = H, OH or =O

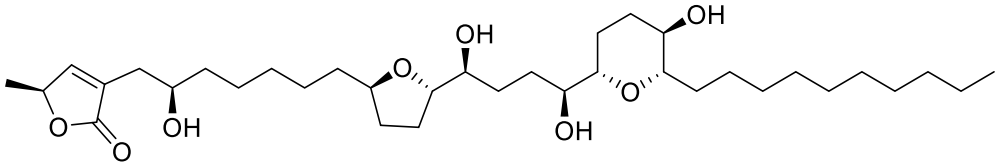
- Tri-THF acetogenins: only one compound is included in this group, goniocin

goniocin type



- THP-acetogenins: in this class, tetrahydropyran-containing acetogenins are included.

example of mono-THP acetogenins

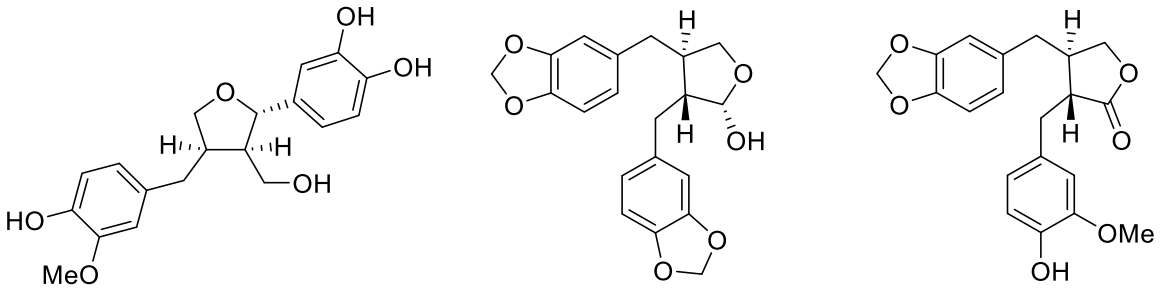


1.2.2 Lignans[6]

Lignans represent a large class of secondary metabolites produced by plants. These substances derive from oxidative dimerization of two phenylpropanoid units.

Despite their molecular framework consists only of two simple building blocks (C6-C3), lignans exhibit an enormous structural diversity. Most of them contain at least one oxygenated five-membered ring, such as substituted tetrahydrofuran moieties [(+)-taxyresinol)], γ-butyrolactol [(-)-cubebin] and γ-butyrolactone systems [(-)-Pluviatolide] (fig. 1.2).

[6] M. Saleem, H. Kim, M. Ali and Y.S. Lee, *Nat. Prod. Rep.* **2005,** 22, 696.



(+)-Taxiresinol (-)-cubebin (-)-pluviatolide

Figure 1.2

Within this class, several compounds showed very important biological activities, in particular anti-cancer, anti-inflammatory, anti-microbial, anti-oxidative and immunosuppressive properties. For this reason, during the last years, several efforts have been taken in order to develop stereoselective total synthesis of such molecules.
A more detailed section concerning lignans, their structures, biosynthesis and their properties will be discussed in chapter 6.

1.2.3 Tetrahydrofuran – containing marine macrolides[7]

Marine organisms have produced several structurally diverse secondary metabolites with important biological activities as a defense against the various aggressions typical of their environment.

This structural diversity makes marine natural products excellent candidates for the investigation of new bioactive molecules with high pharmacological potential[8].

A significant number of metabolites have been isolated in the last years from sponges, algae, dinoflagellate and other marine invertebrates, characterized by their structural novelty. From a

[7] A. Lorente, J. Merketegi, F. Albericio and M. Alvarez, *Chem. Rev*. **2013**, 113, 4567.
[8] I. Bhatnagar, S.K. Kim. *Mar Drugs* **2010**, 8, 2702.

chemical structure point of view, most of them are highly oxygenated and with complex stereochemical features.

The determination of biological activity, mechanism of action, and further medical applications of these compounds is few of the main challenges, because their isolation from natural sources often furnishes very small sample amounts. Thus, synthesis is necessary to further development of these molecules not only in terms of their supply, but also for structural and stereochemical assignments.

Large molecular size tetrahydropyran (THP)-containing polyketide macrolides are a class of marine macrolides with diverse and interesting biological activities. Some of them have reached the clinical trial stage, as in the case of the promising anti-cancer agent eribulin[9] (fig.1.3).

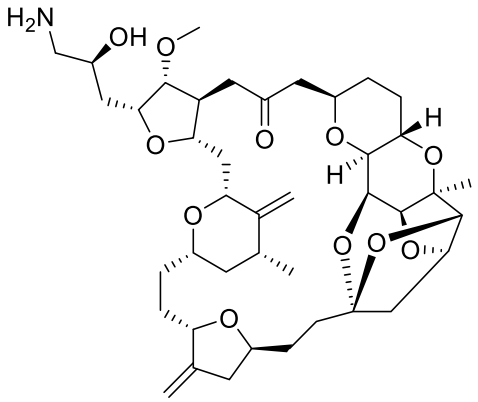


Figure 1.3: structure of eribulin

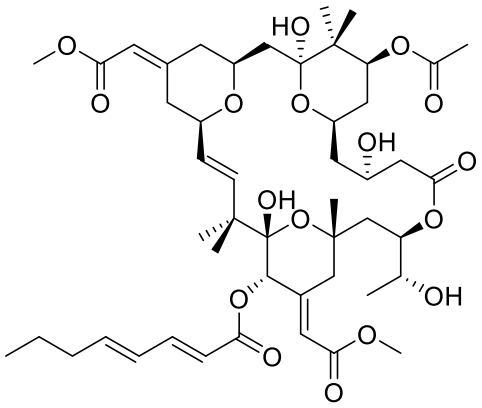
Large molecular size THP-containing macrolides rarely include tetrahydrofuran (THF) rings in their structure.

Nevertheless, some natural compounds are found where both systems are included, such as the pectenotoxins, the family of the halistatins and the above reported eribulin.

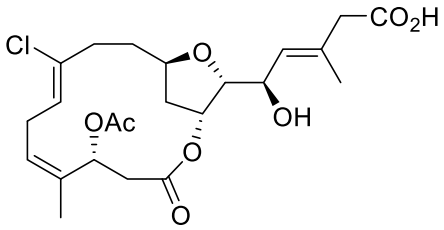
More recently, THF rings instead of THP rings, have occurred in structures of new bioactive compounds.

[9] K.L. Jackson, J.A. Henderson, A.J. Phillips *Chem. Rev*. **2009**, 109, 3044

Large molecular size macrolides containing THP and THF rings in their structure, were the first THF-containing macrolides reported in literature. Over the last 20 years more THF-containing polyketide macrolides have been described, and their potential as drug candidate has increased exponentially. It is worth mentioning that THF containing macrolides are often of small molecular weight and less complex than their THP congeners (fig. 1.4).



Briostatin 1



Haterumalide NA

Figure 1.4: structures of briostatin 1 and haterumalide NA, these examples show how generally THP-containing macrolides have a more complex structure than THF-containing ones.

1.2.4 Biosynthesis of macrolides

According to their biological origin, metabolites are divided into six principal classes: ribosomal and non-ribosomal peptides, alkaloids, phenylpropanoids, polyketides, terpenes and steroids, and carbohydrates. Ribosomal peptides and carbohydrates are primary metabolites: they are fundamental for execution of base activity of the normal life of the organism and they are the simplest structures. The other categories are secondary metabolites, that change from species to species, and they are involved in secondary biological activities. These last categories are characterized by much more complicated biosynthetic pathways that involve many other simpler molecules[10].

Polyketides are a big class of natural products including fatty acids, polyacetylenes,

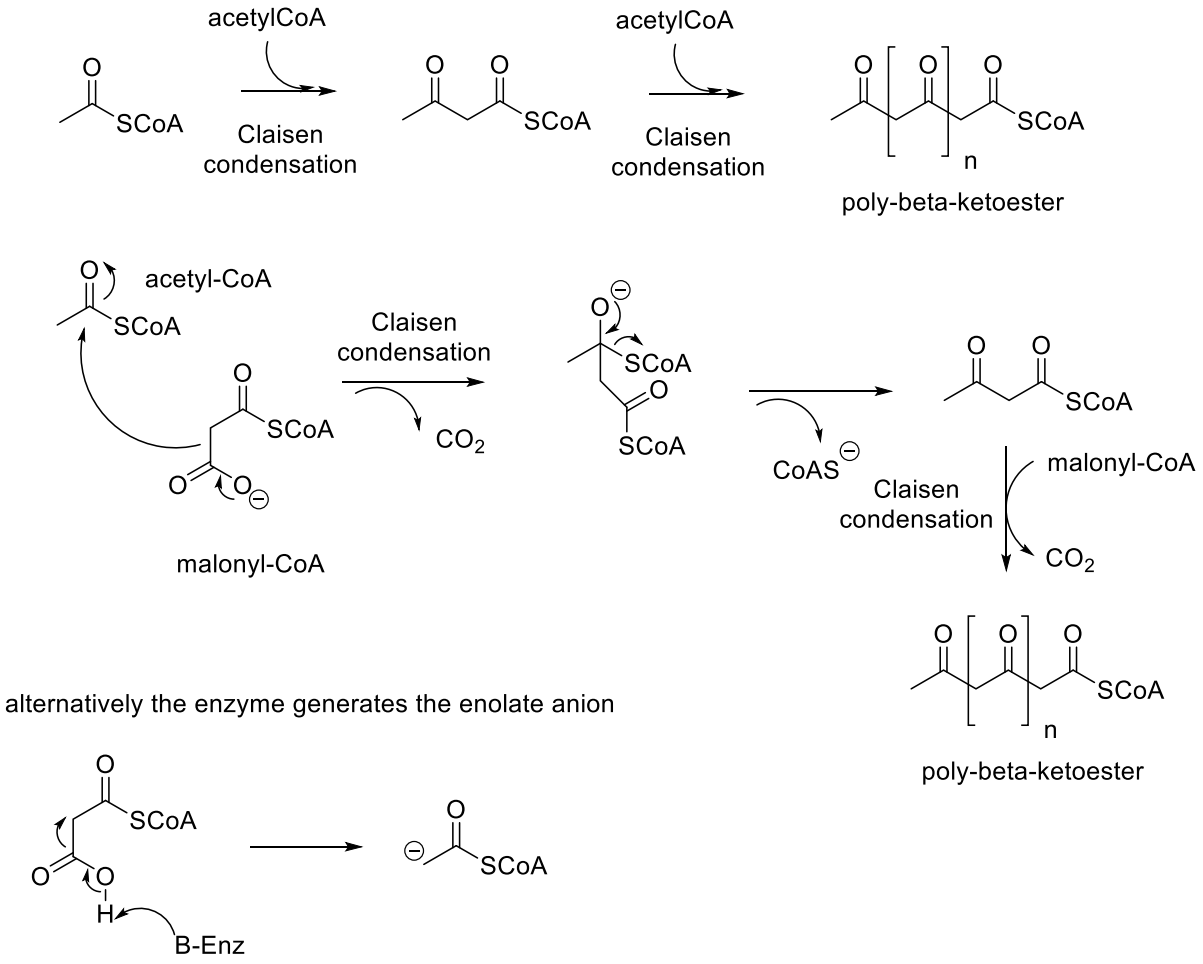
[10] Dewick, P. M. *Medicinal Natural Products: A Biosynthetic Approach*; Wiley: New York, **2001**.

prostaglandins, macrolides and some aromatic compounds. All these natural products are characterized by their common biosynthetic origin: they are synthetized, through the acetate pathway, by big proteic complexes: the PKS's (polyketide synthase). These proteins catalyze consecutive Claisen condensations in order to build poly-β-ketonic chains that undergo further transformations to give the final products. The simplest method to outline the reaction for the formation of the carbon skeleton is to imagine two identical molecules of acetyl-CoA that condense with a Claisen reaction to give an acetoacetyl-CoA; this reaction is repeated many times, to build a poly-β-ketonic chain (scheme 1.1). The first scientist who supposed this mechanism was Arthur Birch in the '50's. He experimentally verified his theory by using ^{14}C marker in a culture of an organism that produces polyketides[11].

However, the real mechanism of the reaction is a little more complex: initially a carboxylation of acetyl-CoA to malonyl-CoA takes place. In this way, there is an improvement of the acidity of the α hydrogen of the carboxylic group, in order to provide a better nucleophile for the Claisen condensation. It is important to note that in the biosynthesis, the derivate of the acylation of the malonic acid is not observed, nor any atom resulted from the ^{14}C marked bicarbonate is incorporated. Thus, the carboxylic group introduced in the malonyl-CoA is immediately lost by decarboxylation during the condensation. Another hypothesis is that the decarboxylation is essential in order to generate the acetyl enolate anion without using a strong base.

Different families of PKS synthetize various types of polyketides; currently, the knowledge concerning the relation between the structure and the catalytic mechanism of the PKSs, allows to obtain many variants of the original natural products through the genetic manipulation of the synthetic processes[12]. However, the basic mechanism is the same: the chain is built through consecutive Claisen condensations that use malonyl-CoA (or methylmalonyl-CoA) as fundamental unit of extension, and the acetyl-CoA (or propionyl-CoA) as starting unit. Every condensation produces a β-Ketoester that can be, or not, reduced before the following step. The PKS's have different domains showing different functions in the synthetic chain: the ketosynthetic domain (KS), the ketoreducting domain (KR), the dehydrating domain (DH), enolreducting domain (ER) and acyltranferasing (AT).

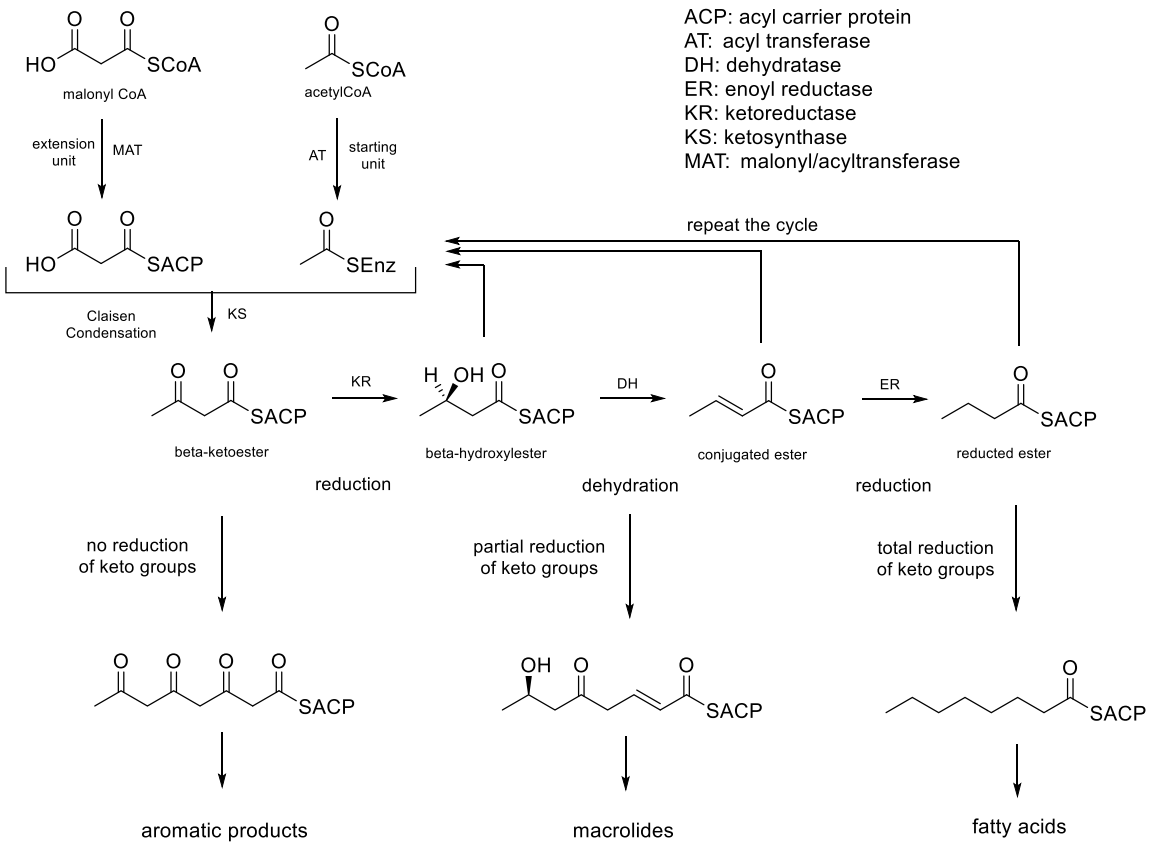
[11] A. J. Birch, P. A. Massy-Westropp, C. J. Moye, *Aust. J. Chem.* **1955**, 8, 539.
[12] C. R. Hutchinson, R. McDaniel, *Curr. Opin. Investig. Drugs*, **2001**, 2, 1681



Scheme 1.1: formation of poly-beta-ketoester

If no reduction of carbonyl functions takes place, the product is a poly-β-ketoester with alternated methylene and ketonic functions. As reported in scheme 1.2, this highly reactive intermediate can undergo enzyme catalyzed intramolecular cyclizations, that lead to aromatic products. On the contrary, if all the keto groups are reduced, the product is a fatty acid. In this case, the reduction proceeds through three-steps: reduction of the ketone to alcohol, dehydration to a conjugated ester and reduction of the double bond. On the other hand, if the β- polyketo chain undergoes a partial reduction of the carbonylic functions, the result is a carbon skeleton where, hydroxyl, double bond, methylene and carbonyl functions are alternated. This is the case of macrolides.

The reduction degree of the product and the distributions of the various functions depend on how active the domains of the enzyme are during the process.



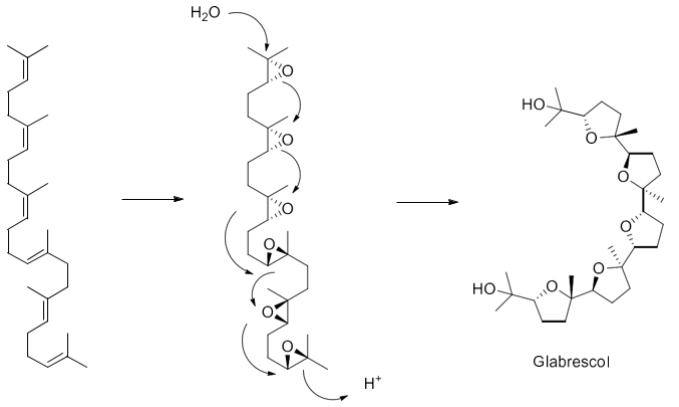
Scheme 1.2. PKS mechanism of action

It is possible to distinguish three different groups of PKS's: the type I are big multifunction proteins with individual functional domains and they are found in bacteria and fungi, the type II are composed by an individual multifunction protein complex and they are found in bacteria, while the type III are homodimeric proteins and they are found in plants, bacteria and fungi. The PKS's type I can be further divided in two more classes, iterative and non- iterative: the first group uses periodically their functional domains to synthetize a polyketide, while the second group has a dedicated active site for each step. The PKS's type II are non- iterative. Both those systems use ACP (acyl carrier protein) as acyl-CoA activating agent. The type I enzymes catalyze the macrolide synthesis, to whom little variation of the single steps bring a high structural diversity. Type II PKS catalyzes the synthesis of aromatics polyketides, while flavonoids and stilbenes are synthetized by type III enzymes. The last one uses esters of the CoA instead of the ACP and only one active site is used for a series of decarboxylations, condensations and cyclizations.

Despite the differences observed in the molecular structure of the PKS's in the kind of extension units employed, the chain synthesis is substantially the same. All the natural products cited are synthetized by the acetate pathway (apart from the flavonoids, that derive as from the acetate pathway as from the shikimate pathway, in fact the starting unit involved is the cumaryl-CoA, a shikimate pathway metabolite).

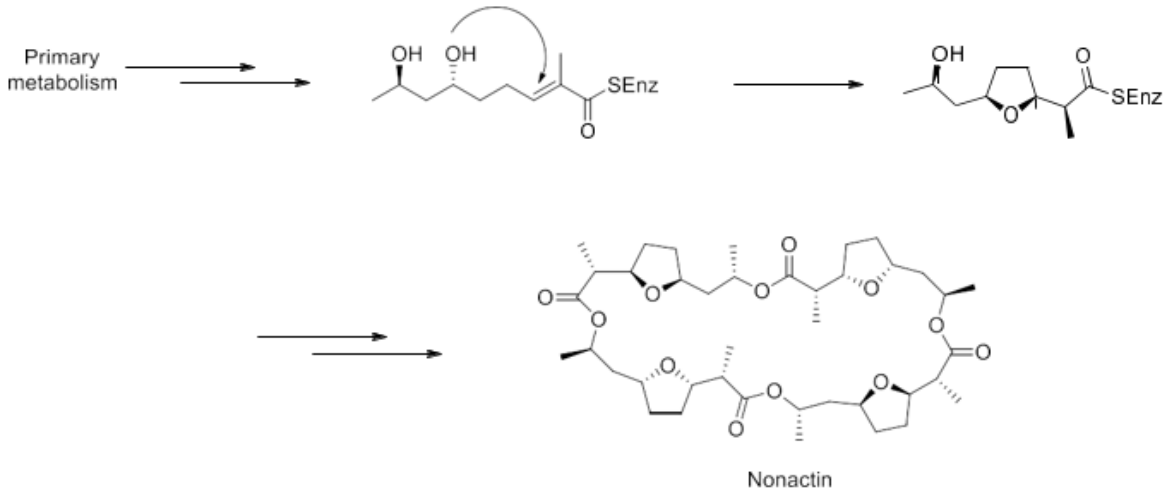
1.2.5 Biosynthetic pathways toward tetrahydrofuran rings

The cyclic ether ring formation is a normal modification in the post-PKS activity. The synthesis of these rings is not direct, but nature has developed different methods to obtain these structures with high efficiency and, if necessary, with high enantioselectivity and regioselectivity[13]. Some enzymes, like the peroxidase and the alkene monooxydase (AMO), show the property to build epoxides from double bonds. The consecutive opening of these epoxide rings results in the cyclic ethers. In some cases, this process happens with a "cascade" mechanism, and leads to the formation of polycyclic natural products: this is the case of the biosynthesis of Glabrescol[14] (scheme 1.3). Another approach to the synthesis of oxygenated heterocycles is the addition of a hydroxyl group to an activated double bond, a Michael enantioselective intramolecular addition, like in the case of the anti-cancer agent Nonactine[15] (scheme 1.4).



Scheme 1.3: THF rings' biosynthesis by epoxides opening

[13] P. Domínguez de María, R.W. Van Gemert, A.J. Straathof, U. Hanefeld, *Nat. Prod. Rep.* **2010**, 27, 370.
[14] Y. Morimoto, T. Iwai, T. Kinoshita, *J. Am. Chem. Soc*. **2000**, 122, 7124.
[15] A. J. Woo, W.R. Strohl, N.D. Priestley, *Antimicrob. Agents Chemother*. **1999**, 43, 1662.



Scheme 1.4: THF rings' biosynthesis by intramolecular Michael addition.

1.2.6 Amphidinolides[16]

Amphidinolides are members of a secondary metabolites class isolated from *Amphidinium sp*.

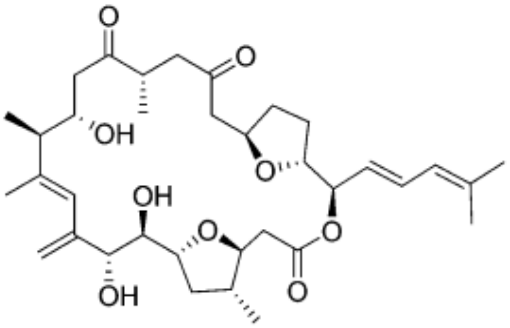
Despite around forty members of this big class of macrolides have been isolated up to 2010, only 15 of them show an additional fused or bridged THF in the macrolactone framework.

Typical features of such molecules are the presence of exomethylene units, polyene side chains and oxygenated five-membered rings.

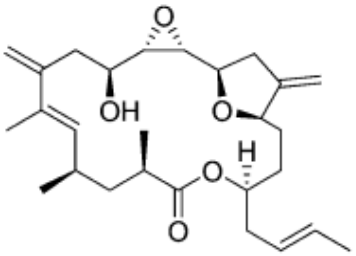
One of the most interesting members of Amphidinolides is Amphidinolide C that exhibits strong cytotoxicity in the nanomolar range against murine lymphoma L1210 (IC_{50} = 5,8 ng/mL) and human epidermoid carcinoma KB cells in vitro (IC_{50} = 4,6 ng/mL).

Figure 1.5 reports the structures of some of the most important amphidinolides.

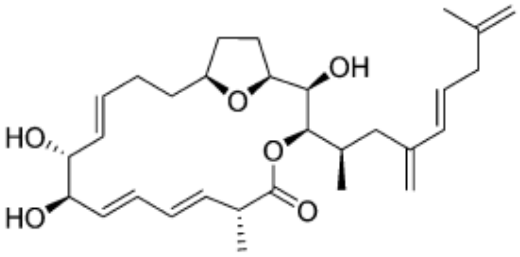
[16] J. Kobayashi, *J. Antibiot.*, **2008**, 61**,** 271.



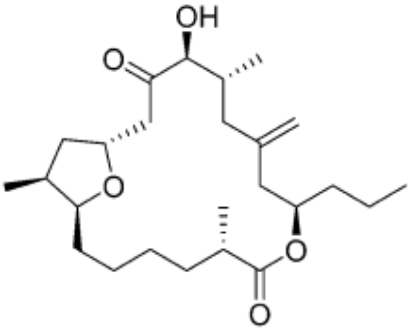
amphidinolide F



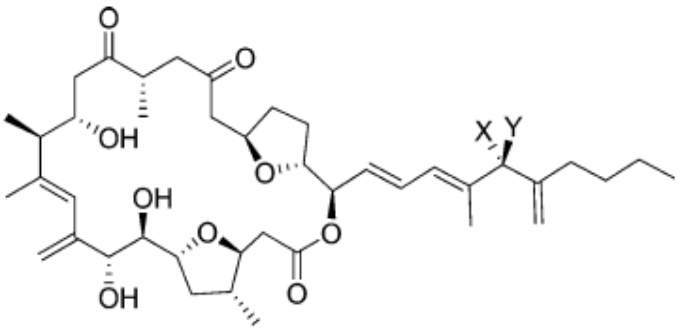
amphidinolide K



amphidinolide E



amphidinolide T1



X = H, Y = OH, amphidinolide C1
X = H, Y = OAc, amphidinolide C2

Figure 1.5: some examples of THF-containing amphidinolides

1.2.7 Haterumalides, Oocidin A and Biselides[17]

Haterumalides consists in a group of chlorinated macrolides isolated in 1999 from an Okinawan sea sponge of the species *Ircinia* and Okinawan ascidian *Lissoclinum* sp. The most important member of this class is Haterumalide NA (figure 1.4), that showed strong cytotoxicity against leukemia cell lines.

Oocydin A is a natural diastereomer of Haterumalide NA, that was isolated from the South American epiphyte *Serratia marcescens*, while biselides are oxygenated analogs of haterumalides that were extracted from the Okinawan ascidian *Didemnidae sp*.

From a structural point of view, all these compounds possess intriguing moieties in their complex backbone, for example the THF ring bridged with a macrocyclic lactone, a *Z*-chlorovinyl function, two allylic alcohols and several stereogenic centers.

1.2.8 Caribenolide I[18]

Caribenolide I is an interesting marine secondary metabolite obtained from cultured cells of *Amphidinium sp*. From a pharmacological point of view it is considered as a cytotoxic agent against the human colon carcinoma cell line (HCT 116) and it was found to be 100 times more potent than amphidinolide B.

It shows a new type of macrocyclic lactone, which contains one α-methylidene epoxide, one disubstituted THF, one tetrasubstituted THP ring, one keto group, one *E*-double bond, four hydroxyl groups and one butyl lateral chain.

[17] Ueda, K.; Hu, Y. *Tetrahedron Lett*. **1999**, 40, 6305

[18] Bauer, I.; Maranda, L.; Young, K. A.; Shimizu, Y. Fairchild, C.; Cornell, L.; MacBeth, J.; Huang, S. *J. Org. Chem.* **1995**, 60, 1084

CHAPTER 2: Stereoselective syntheses of tetrahydrofurans

Due to the importance of biological active compounds containing oxygenated five-membered rings, considerable efforts have been devoted during the last years, toward the development of stereoselective strategies for the construction of substituted tetrahydrofuran systems[19].

In this section, we will focus the attention on those methods involving the formation of the C-O bond as key step (except for the nucleophilic capture of oxocarbenium ions that involves a C-C bond formation), because they can be compared with the methodology developed in this PhD thesis that will be discussed in chapter 4.

The strategies reported in literature can be summarized in the following list:

- Nucleophilic substitution processes
- Nucleophilic capture of oxocarbenium ions
- Conjugate addition/anion capture
- Oxidation of alkenes, diene and polyenes
- Alkene carboetherification
- Ring closure via allyl transition metal intermediates

2.1 Nucleophilic substitution processes

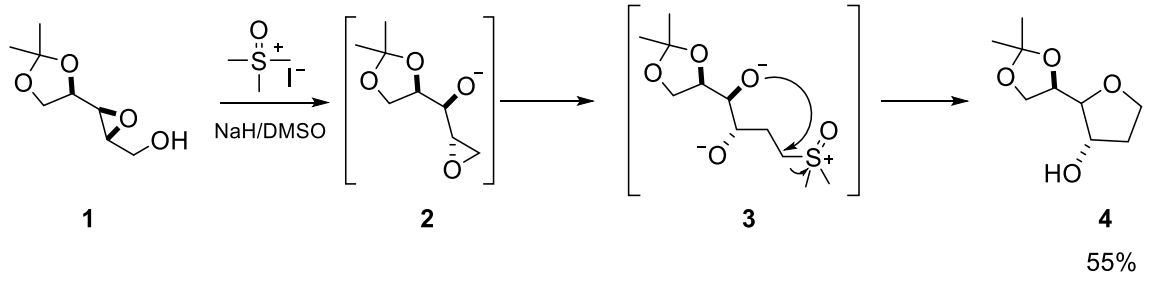
Nucleophilic substitution reactions have been employed in several strategies for stereoselective THF ring construction. Most of them involve intramolecular S_N2 processes between a hydroxyl group and a tethered leaving group, for example halides or sulfonates.

Scheme 2.1 shows that by treating compound **1** with trimethylsulfoxonium iodide under basic

[19] P. Wolfe and M. B. Hay, *Tetrahedron,* **2007**, 63, 261

conditions[20], a Payne rearrangement of epoxide **2** takes place followed by nucleophilic attack of a sulfoxonium ylide to give **3**, which subsequently undergoes S_N2 ring closure to afford hydroxytetrahydrofuran **4**. Excellent results were obtained with epoxides bearing ether substitution at C4, C5 or C6.

Most of the substrates employed in the nucleophilic substitution approaches come from the natural chiral pool and contain all the stereocenters of the product.



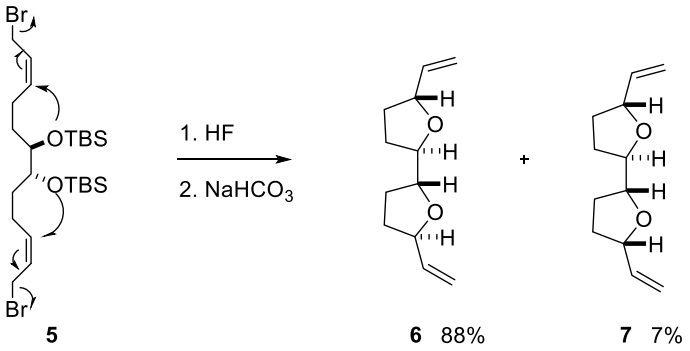
Scheme 2.1

However, some examples of approaches in which stereocenters are generated from achiral substrates, have also been reported in literature.

Zhao[21], reported the use of a double S_N2' reaction to generate 2-vinyltetrahydrofurans with installation of a new stereocenter on each newly formed ring (scheme 2.2).

The double cyclization of **5** proceeds with 13:1 diastereoselectivity and afforded the major 2,5-*trans*-2,5-*trans* isomer **6** in 88% yield.

[20] Schomaker, J. M.; Pulgam, V. R.; Borhan, B. *J. Am. Chem. Soc.* **2004**, 126, 13600
[21] Li, P.; Yang, J.; Zhao, K. *J. Org. Chem*. **1999**, 64, 2259.



5 **6** 88% **7** 7%

Scheme 2.2

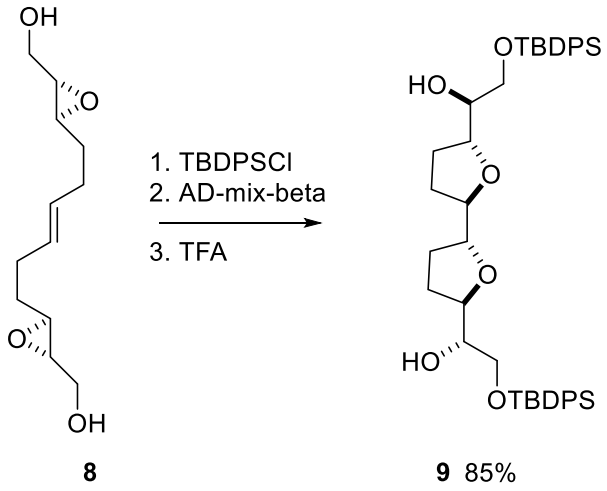
According to the authors, hydrogen bonding between hydroxyl groups may play an important role to determine the diastereoselectivity.

Another way to generate oxygenated rings through substitution processes is represented by intramolecular addition of alcohols to epoxides.

Different methods for *in situ* generation of epoxide rings have been carried out, including biocatalytic epoxidations, transition metal-catalyzed epoxidations and S_N2 epoxide formations from 1,2 diol derivatives. Cascade reactions have also been reported, in which an alkene containing two epoxide rings undergoes dihydroxylation followed by double cyclization.

For example, the bis-tetrahydrofuran core found in several acetogenins (see chapter 1, fig 1.1), can be achieved by TBDPS-protection and Sharpless asymmetric dihydroxylation of **8**, followed by addition of trifluoroacetic acid. Compound **9** is obtained as single diastereoisomer in 85% yield[22] (scheme 2.3)

[22] Hoye, T. R.; Ye, Z. *J. Am. Chem. Soc*. **1996**, 118, 1801



8 **9** 85%

Scheme 2.3

2.2 Nucleophilic capture of oxocarbenium ions

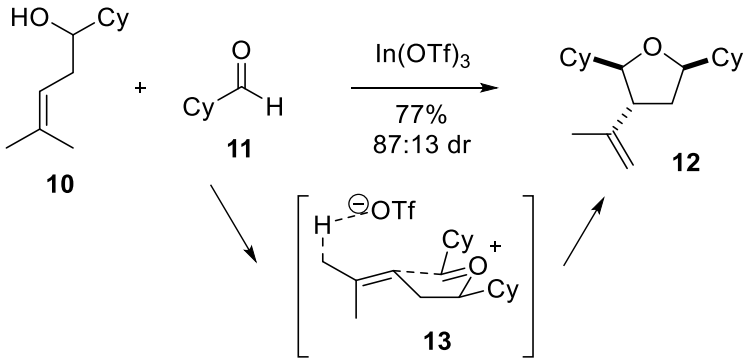
Several approaches toward the stereoselective construction of tetrahydrofurans are characterized by generation of reactive oxocarbenium ion intermediates that undergo intramolecular capture by a tethered nucleophilic alkene.

For example, scheme 2.4 shows that tetrahydrofuran **12** can be achieved in 77% yield, with 87:13 dr through $In(OTf)_3$-mediated coupling of alcohol **10** and aldehyde **11**, as reported by Loh[23]. Oxocarbenium ion **13** is the intermediate of the reaction.

The stereoselectivity observed, is the consequence of the pseudoequatorial orientation of the cyclohexyl substituents in the transition state (scheme 2.4).

Petasis[24] has described the conversion of substituted 1,3-dioxolan-4-ones to tetrahydrofuran products through methylenation and Lewis-acid mediated rearrangement.

[23] Loh, T.-P.; Hu, Q.-Y.; Tan, K.-T. ;Cheng, H.-S. *Org. Lett*. **2001**, 3, 2669.
[24] Petasis, N. A.; Lu, S.-P. *J. Am. Chem. Soc*. **1995**, 117, 6394.

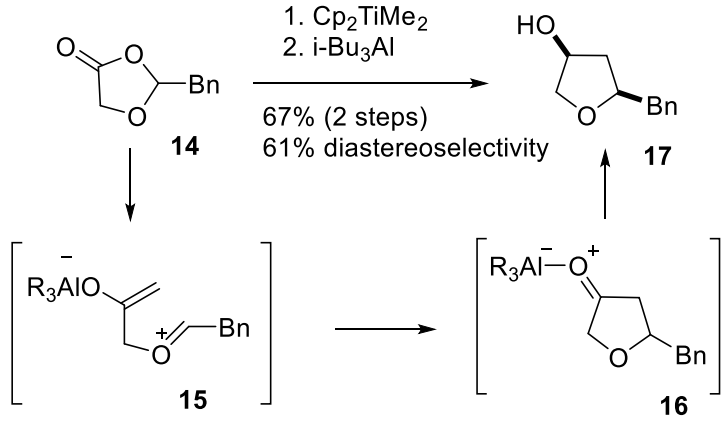


Scheme 2.4

Modest stereoselectivity has been achieved when compound **14** was treated with dimethyltitanocene followed by triisobutylaluminium to give tetrahydrofuran **17** (scheme 2.5).

The reaction proceeds via rearrangement of oxocarbenium ion **15** followed by *in situ* reduction of the resulting trialkylaluminium-ketone complex **16**.

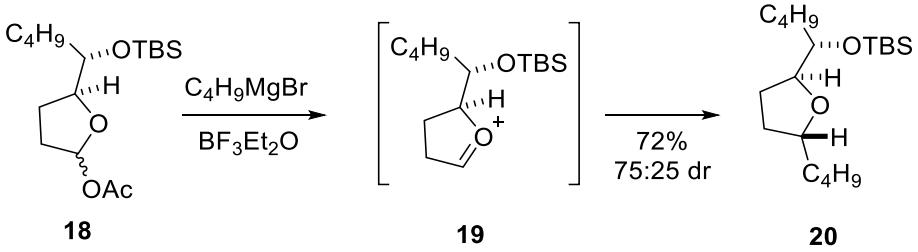
Moreover, oxocarbenium ions derived from γ-lactol derivatives have been widely employed for the stereoselective synthesis of THF rings, because they can undergo addition of nucleophiles like Grignard reagents and organozinc species.



Scheme 2.5

A useful example of such strategy, is the one reported in scheme 2.6[25], where acetoxytetrahydrofuran **18** was converted to substituted ring **20** in 72% yield and a diastereomeric ratio of 75:25.

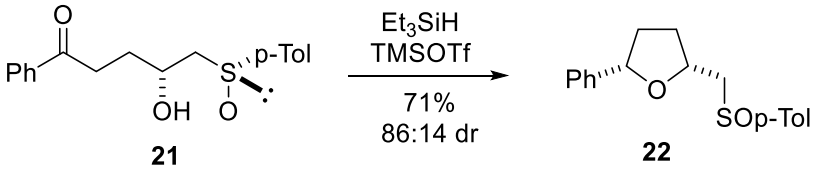
Reaction conditions involved BF_3Et_2O and butylmagnesium bromide.



Scheme 2.6

The example illustrated in scheme 2.7, describes a *cis* selective asymmetric synthesis of a 2,5-disubstituted tetrahydrofuran system, involving the reduction of an oxocarbenium ion generated *in situ* from a γ-hydroxyketone bearing a sulfoxide function[26].

The enantiopure substrate **21** is obtained by addition of the lithium anion deriving from [*(S)-R*]-methyl-*p*-tolylsulfoxides to succinic anhydride and subsequent conversion of the resulting carboxylic acid to ketone.



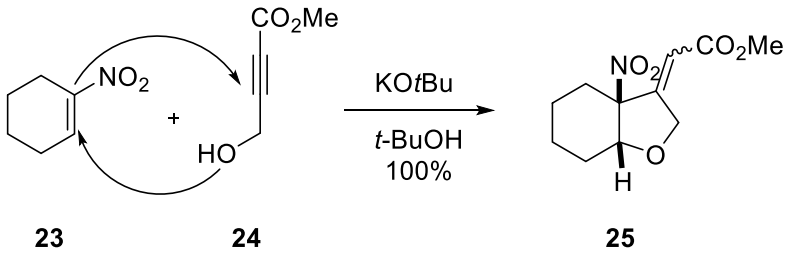
Scheme 2.7

[25] Franck, X.; Hocquemiller, R.; Figadere, B. *Chem. Commun*., **2002**, 160.
[26] Carreno, M. C.; Des Mazery, R.; Urbano, A.; Colobert, F.; Solladie, G. *J. Org. Chem.* **2003**, 68, 7779.

2.3 Conjugate addition /anion capture

Several stereoselective methods for THF ring construction reported in literature showed as key step a tandem conjugate addition of an allylic or propargylic alcohol to a Michael acceptor resulting in the capture of the intermediate stabilized anion. Nitroalkenes were widely used as electrophilic acceptors within this approach, followed by trapping via a second conjugate addition, radical cyclization or dipolar cycloaddition.

Scheme 2.8 reports that treatment of nitroalkene **23** with propargylic alcohol **24** in the presence of tBuOK, affords tetrahydrofuran **25** quantitatively as a mixture of *Z/E* olefin[27].

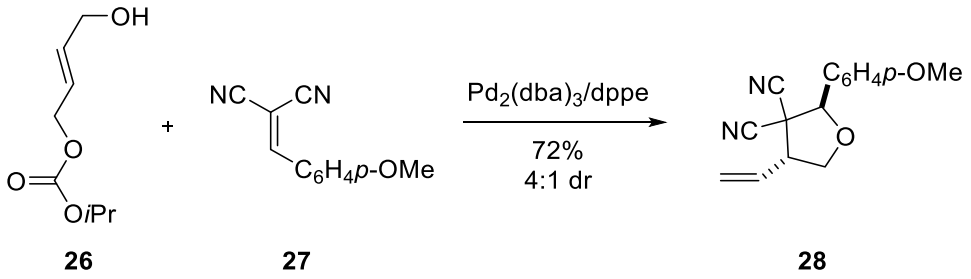


Scheme 2.8

Yamamoto employed Pd-catalyzed reaction of allylic alcohols containing allylic carbonate functionality at C4 with alkylidene malonate derivatives for the construction of highly substituted 3-vinyl-THF derivatives. The outcomes showed high yields but moderate levels of stereocontrol.

For example (scheme 2.9), treatment of allylic alcohol **26** with compound **27** in the presence of a Pd-dppe catalyst provided THF **28** in 72% yield and 4:1 *dr*[28].

[27] Yakura, T.; Tsuda, T.; Matsumura, Y.; Yamada, S.; Ikeda, M. *Synlett* **1996**, 985.
[28] Sekido, M.; Aoyagi, K.; Nakamura, H.; Kabuto, C.; Yamamoto, Y. *J. Org. Chem*. **2001**, 66, 7142.



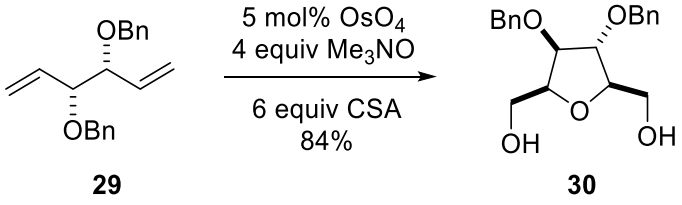
Scheme 2.9

2.4 Oxidation of alkenes, dienes and polyenes

The oxidative cyclization of 1,5-dienes to hydroxylated tetrahydrofuran derivatives is another way to achieve polysubstituted tetrahydrofuran systems that are often employed for the synthesis of complex molecules.

An issue concerning this approach is of course the use of stoichiometric amount of highly toxic strong oxidant such as $KMnO_4$ and OsO_4. Anyway, during the last years several efforts have been devoted to the development of catalytic version of these protocols.

For example, Donohoe has reported[29] (scheme 2.10) the conversion of **29** into **30** in 84% yield as a single diastereoisomer, by involving catalytic OsO_4 and excess trimethylamine N-oxide under acidic conditions.



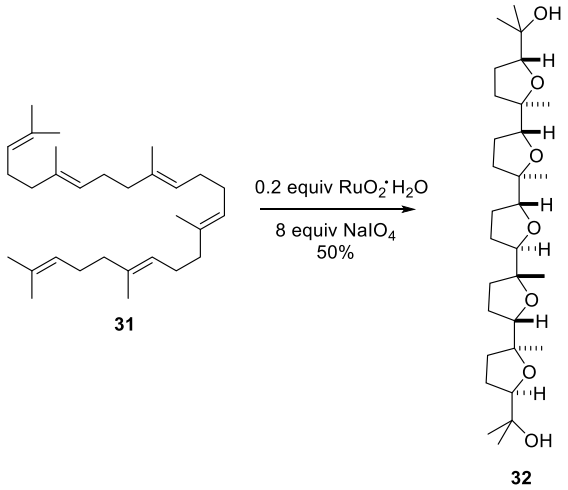
Scheme 2.10

Also the stereoselective construction of bis-, tris- and penta-THF systems has recently been reported.

An impressive example of such strategy (scheme 2.11), is the RuO_4-catalyzed oxidation of

[29] Donohoe, T. J.; Butterworth, S. *Angew. Chem., Int. Ed*. **2003**, 42, 948.

squalene **31**[30], that leads to penta-THF **32** in 50% yield. It's very intriguing that during the reaction, 12 bonds and 10 stereocenters are generated in a single step.



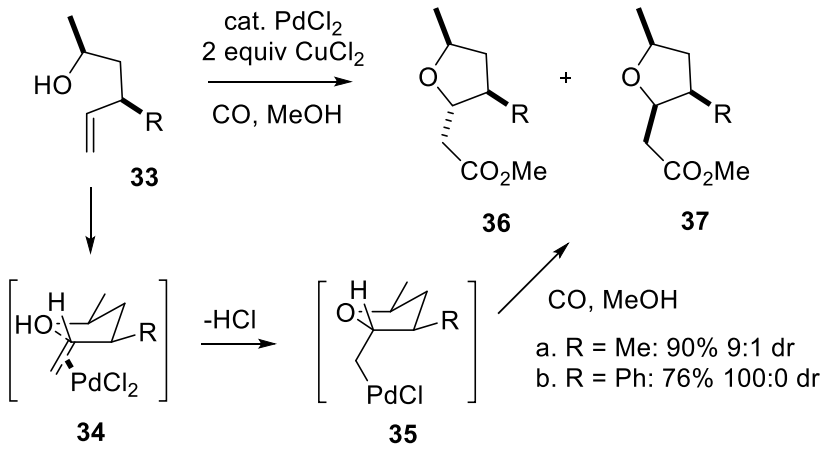
Scheme 2.11

2.5 Alkene carboetherifications

Reactions that generate both a carbon-oxygen and a carbon-carbon bond are much less common.

A strategy based on a Pd-catalyzed Wacker-type carbonylation reaction of unsaturated alcohols has been developed by Semmelhack[31] and is reported in scheme 2.12. Treatment of compound **33** with a catalytic amount of $PdCl_2$ in the presence of an excess of $CuCl_2$, under a CO atmosphere in methanol, results in a 9:1 mixture of **36** and **37** in 90% yield.

[30] Caserta, T.; Piccialli, V.; Gomez-Paloma, L.; Bifulco, G., *Tetrahedron,* **2005**, 61, 927.
[31] Semmelhack, M. F.; Bodurow, C. *J. Am. Chem. Soc.* **1984**, 106, 1496.



Scheme 2.12

As reported in scheme 2.12, this reaction leads to ring closure and installation of ester functionality at C1' position in one step through activation of the alkene by the metal to give **34**, followed by nucleophilic attack of the tethered alcohol resulting in **35**. The corresponding alkylpalladium complex then undergoes CO insertion and reductive elimination to give the tetrahydrofuran products **36** and **37**.

2.6 Ring closure via allyl transition metal intermediates

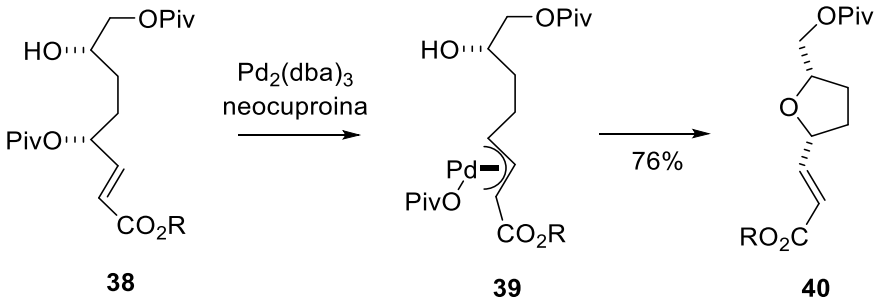
Several stereoselective tetrahydrofuran syntheses are based on a strategy involving nucleophilic capture of intermediate allyl transition metal complexes. Highly diastereoselectivity and enantioselectivity have been achieved when chiral enantiopure catalysts have been used.

For example, Rein[32] has reported the construction of THF **40** (scheme 2.13) in 76% yield as a single diastereoisomer via Pd-catalyzed intramolecular allylic alkylation of compound **38**.

In contrast to S_N2 allylation reactions, the Pd-catalyzed allylation occurs with complete retention of stereochemistry, as both the generation and trapping of the allylpalladium complex

[32] Vares, L.; Rein, T. *Org. Lett.* **2000**, 2, 2611.

proceed with inversion of configuration (scheme 2.13).

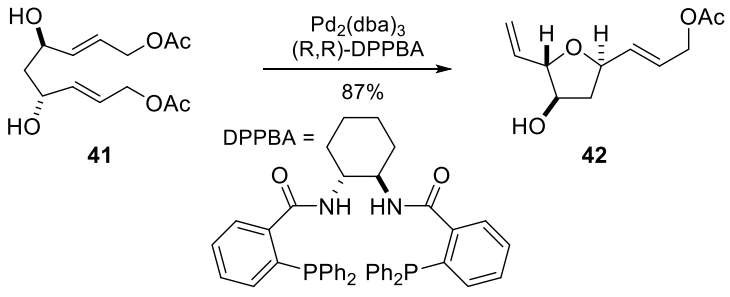


Scheme 2.13

Burke employed a desymmetrization strategy[33] using Pd(0)-catalyzed allylation reaction for the conversion of *meso* or C_2-symmetric diols to highly substituted THF cores (scheme 2.14).

In a representative example, treatment of **41** with a catalytic amount of $Pd_2(dba)_3$ and the chiral Trost ligand DPPBA, generated trisubstituted THF **42**.

Commonly, the intermediate allyl-palladium complex is generated via oxidative addition of an allylic acetate or related compounds. Anyway, some examples of allylpalladium species that are generated through formal transmetalation reactions have also been reported. For example,

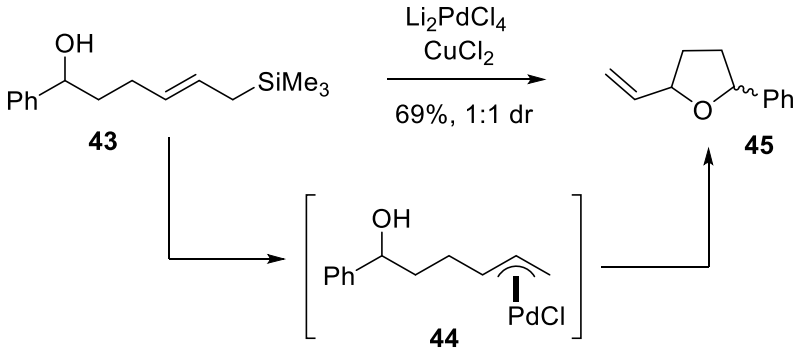


Scheme 2.14

[33] Jiang, L.; Burke, S. D. *Org. Lett.* **2002**, 4, 3411.

Szabo and coworkers[34] have performed the Pd-catalyzed conversion of hydroxyl-substituted allylsilane **43** to THF **45** in 69% yield but with poor diastereoselectivity (1:1) (scheme 2.15).

This reaction requires the use of stoichiometric amounts of Cu(II) salts, which are needed to reoxidize Pd(0) to Pd(II) after the cyclization and provide an alternative strategy to obtain 2-vinyl-tetrahydrofurans.



Scheme 2.15

[34] Macsari, I.; Szabo, K. *J. Chem. Eur*. J. **2001**, 7, 4097.

CHAPTER 3: Synthetic study toward Oxylipids from *Notheia anomala*

3.1 Introduction and previous synthesis of the target

The 3-hydroxy-2,5-disubstituted tetrahydrofuran ring is an important structural feature found in several biologically active natural compounds.

In this PhD thesis, we decided to focus our attention to nematocidal oxylipid **46**, isolated from the Australian brown algae *Notheia anomala*[35], that has been targeted for synthesis for the past three decades due to its strong anthelmintic activity.

Anthelmintics are drugs employed to rid host animals of parasites. In particular, parasitism by nematodes (unsegmented worms which constitute the phylum *Nematoda*), represents a major source of lost production to the commercial livestock industry. Despite the availability of excellent commercial anthelmintics, growing levels of resistance to key structure classes (macrolides, benzimidazoles…), need a progressive search for new bioactive agents.

Despite the presence of 4 stereocenters (three on the THF ring and one on the unsaturated side chain), only 2 of the 16 possible isomers of the molecule have been isolated and characterized from the brown algae, and they are the ones shown in figure 3.1.

One of the aims of this PhD Thesis is to develop an efficient, highly enantioselective synthetic strategy towards oxylipid **46**.

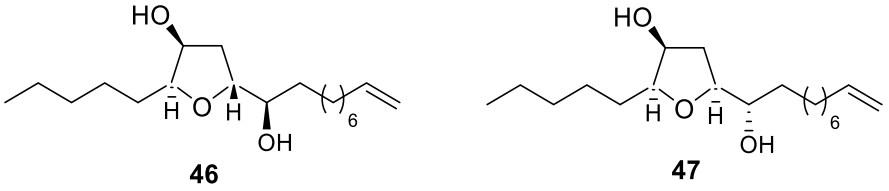


Figure 3.1: structures of oxylipids isolated from *Notheia anomala*

[35] (a) Warren, R. G. Wells, R. J. and Blount, J. F., *Aust. J. Chem*., **1980**, 33, 891, (b) Capon, R. J.; Barrow, R. A.; Rochfort, S.; Jobling, M.; Skene,C. *Tetrahedron,* **1998**, 54, 2227

During this long period, the synthetic strategies toward oxylipids **46** and **47** have evolved with improvement in methodology, in particular in THF core generation.

The first total synthesis of both diastereoisomers was reported by William et al in 1984[36], and is composed of 11 steps with an overall yield of 17%. Subsequently also a racemic biomimetic synthesis of **46** and **47** has been developed[37].

By analyzing the literature we found that nine enantioselective total synthesis of **46** have been proposed, with overall yields between 2 and 26% and five enantioselective synthesis of **47** with yields between 2 and 37%.

Moreover, three of these strategies can lead to both naturally occurring isomers.

The methodology we developed for the stereoselective construction of 3-hydroxy-2,5-disubstituted THF core is based on a C-O bond formation method, accordingly we will focus the attention on the most recent strategies that involve such disconnection approach for the cyclization step.

In 2009, Britton and coworkers proposed a concise synthesis of both isomers of oxylipids from *Notheia anomala*[38].

Scheme 3.2 shows the entire synthesis of the 2,5-*trans*-disubstituted isomer, that can be achieved in 6 steps with an overall yield of 26%.

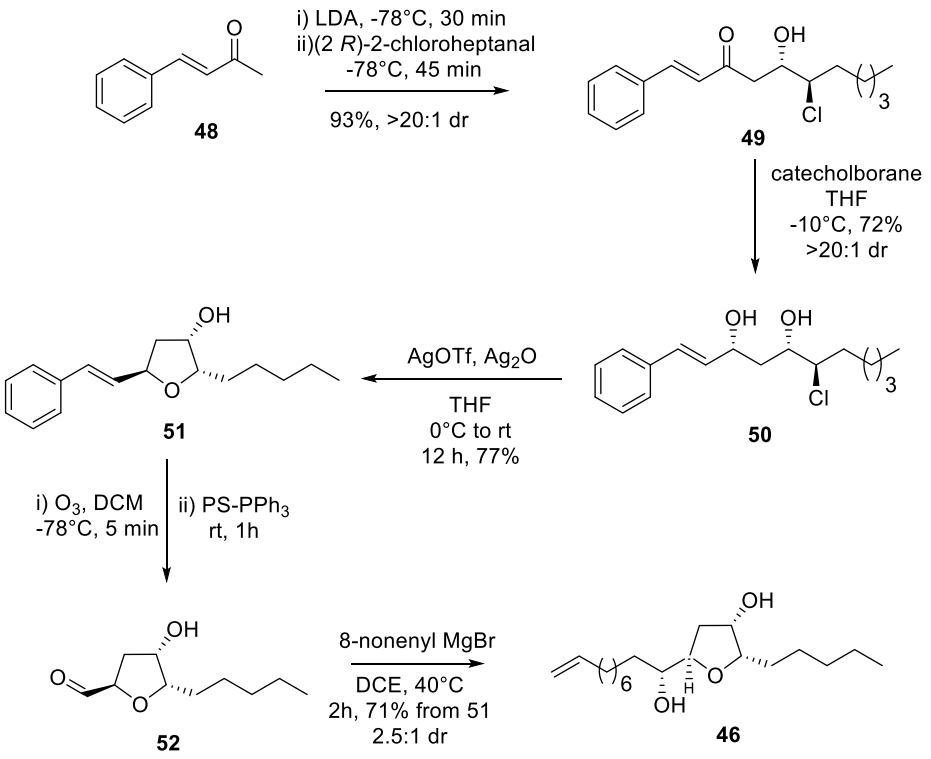
The aldol adduct **49** can be easily prepared in high yield, by treating (2*R*)-2-chloroheptanal with the lithium enolate deriving from 4-phenylbuthen-2-one **48**. The *anti* chlorohydrin **49** is obtained with a *dr* > 20:1. Subsequent stereoselective reduction of the ketone function with either catecholborane or DIBAL-H provides the 1,3- *syn* diol **50** with good yields.

The key cyclization step, is carried out by treating the chlorodiol **50** with stoichiometric amount of Ag_2O and AgOTf, in THF from 0°C to rt.

Silver triflate plays a fundamental role in this stereoselective approach because it can form an intermediate silver alkoxide in which the coordination between silver and chlorine would

[36] Williams, D. R.; Harigaya, Y.; Moore, J. L. *J. Am. Chem. Soc*. **1984**, 106, 2641
[37] Capon, R. J.; Barrow, R. A. *J. Org. Chem.* **1998**, 63, 75
[38] Kang, B.; Mowat, J.; Pinter, T.; Britton, R. Org. Lett. **2009**, 11, 1717

generate a wrong conformation for epoxide formation and at the same time it activates the chloromethane function to S_N2 by the distal hydroxyl group.



Scheme 3.2 Britton synthesis of oxylipid **46**

Ozonolysis and following treatment with polymer supported PPh_3 leads to aldehyde **52** and finally addition of 8-nonenylmagnesium bromide in DCE at 40°C gives the final oxylipid **46** in 71% yield from **51** with 2.5:1 *dr*.

In order to achieve the 2,5-*cis*-disubstituted isomer **47**, the same synthetic plan was followed but, instead of the 1,3- *syn* diol **50**, the 1,3-*anti* diol has been used. It can be prepared in 10:1 *dr*, by stereoselective reduction of ketone **49** with $Me_4NBH(OAc)_3$ in AcOH:MeCN (1:1.5) at -40°C.

In 2012, Roy *at al*, reported another approach for the total synthesis of both isomers of oxylipids from *Notheia anomala*[39].

In this case, the key steps for the substituted THF ring construction employ a combination of alkene cross methatesis and Pd(0)-catalyzed cyclization.

By careful choice of the coupling partners (e.g. **56** and **60**), in the cross methatesis step, any of the two possible 3-hydroxy-2,5-disubstituted THF motifs can be obtained.

Scheme 3.3 shows the strategy adopted for *syn* diol **57** synthesis. D-Proline catalyzed nitrosoaldol condensation of heptaldehyde **53** led to the α-aminoxy aldehyde **54**, which subsequently was treated with allyl magnesium chloride to give the *syn* diol **55** in 75% total yield.

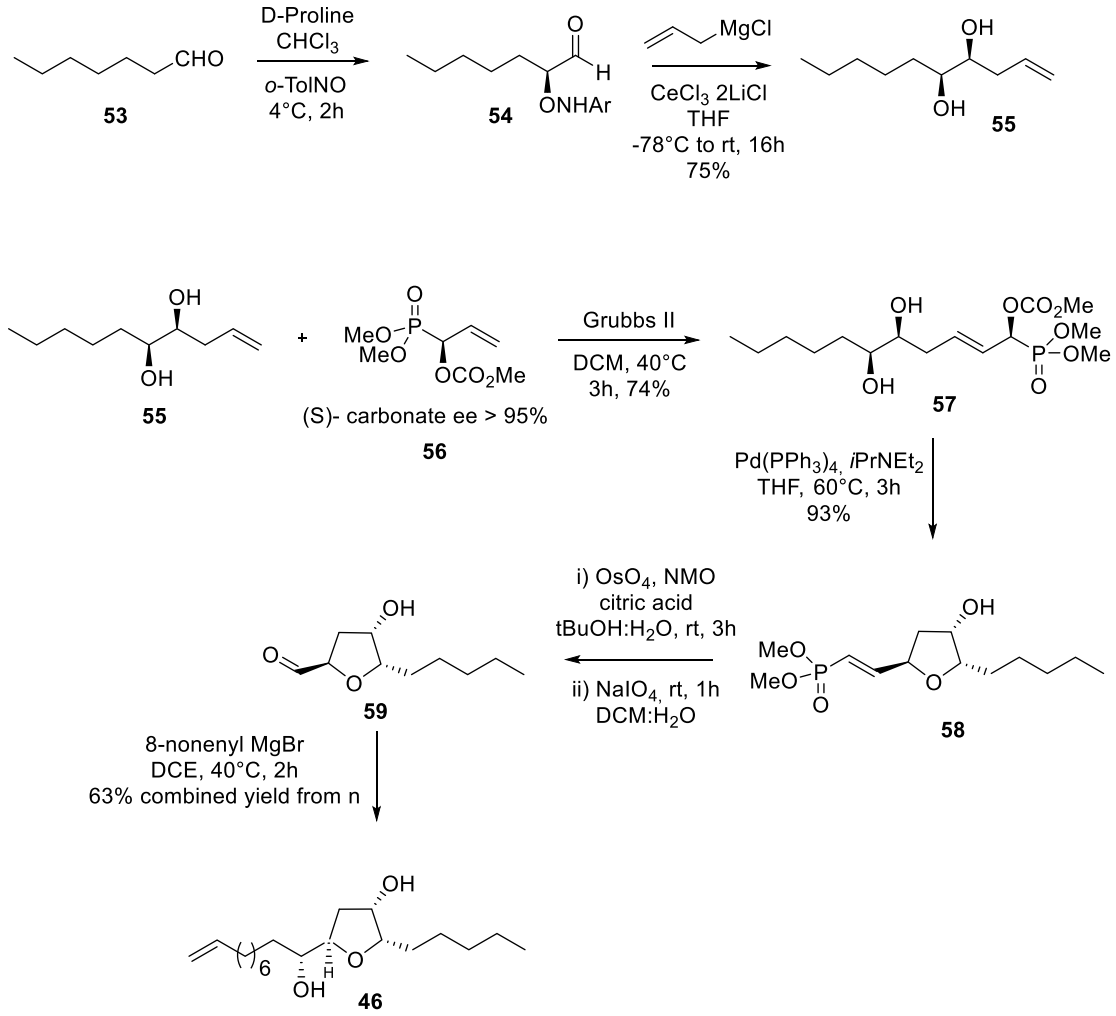
Grubbs II catalyzed cross methatesis of *syn* diol **55** and (S)-Carbonate **56** resulted in alkene **57** with 74% overall yield and subsequent Pd(0)-catalyzed cyclization gave the 2,5-*trans*-tetrahydrofuranyl-(*E*)-vinyl phosphonate **58** in 93% isolated yield.

The oxidative cleavage of the vinyl phosphonate **58** using $OsO_4/NaIO_4$ double step protocol furnished the aldehyde **59**.

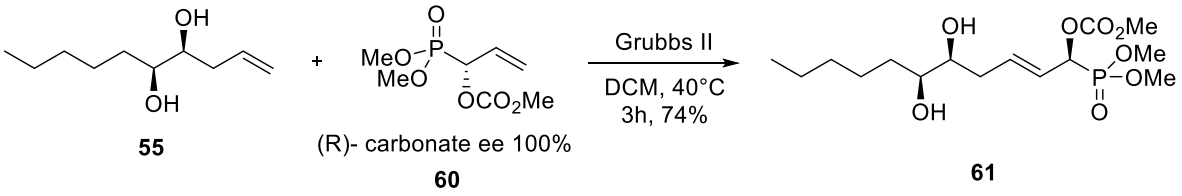
By treating the unstable aldehyde **59** with 8-nonenylmagnesium bromide (same conditions employed by Britton and coworkers), the *trans*-THF containing oxylipid **46** was achieved along with its epimer in a 2.5:1 *dr* and 63% total yield.

The *cis*-THF containing oxylipid **47** was prepared by following the same strategy, but *syn* diol **61** was used instead of *syn* diol **57**. It can be obtained through cross methatesis of diol **55** with (*R*)-carbonate **60**.

[39] S. Roy and C.D. Spilling, *Org. Lett.*, **2012**, 9, 2230



Scheme 3.3: Roy synthesis of 2,5-*trans*-THF oxylipid **46**



Scheme 3.4: synthesis of precursor for 2,5-*cis*-THF oxylipid **47**

3.2 Aim of the work

Since the method developed in our lab, which will be discussed in chapter 4, leads to 3-hydroxy- 2,5-*trans*-disubstituted THF rings with high stereoselectivity (>99:1 *dr* and 92% *ee*), we decided to employ such strategy for the development of a total synthesis. The molecule we chose is the *trans*-THF oxylipid from *Notheia anomala* **46**, because it contains the same structural motif that can be generated by Pd(0)-catalyzed asymmetric allylic etherification of *meso* diol systems.

One of the main advantages that characterizes this approach, making it different from the others reported for the same molecule, is the single step, highly stereoselective construction of the trisubstituted THF core that contains three of the four overall stereocenters of the target, starting from an achiral substrate. On the contrary, along the strategies developed by Roy and Britton, the stereocenters are generated one by one, starting from chiral commercially available substrates or by involving stereoselective reactions that result in mixtures of diastereoisomers requiring separation.

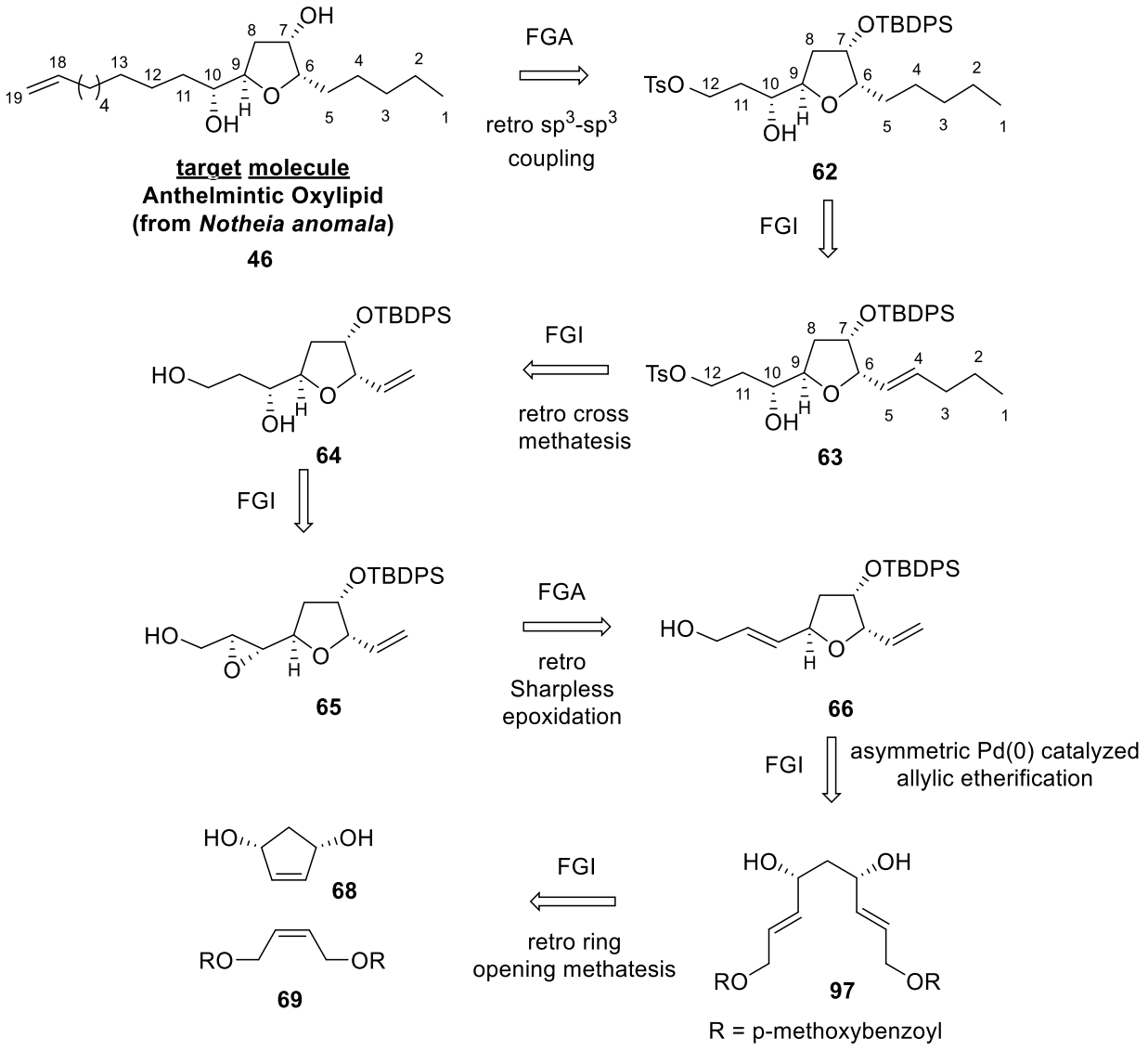
Moreover, the enantiopure THF compound obtained through our methodology, due to the presence of a vinyl and allyl acetate side chains, can be easily functionalized. In this way it represents a very useful key intermediate for the total synthesis of a wide range of natural THF containing molecules.

In the next section we will discuss our synthetic plan towards oxylipid **46**.

3.3 Retrosynthetic analysis of the marine oxylipid **46**

The retrosynthetic approach we proposed for the total synthesis of C_{19} marine oxylipide **46**, is characterized by two key steps: the first one is the construction of the 3-hydroxy-*trans*-2,5 disubstituted tetrahydrofuran core through a catalytic stereoselective reaction, the seconds one is represented by the installation of the two side chains.

Scheme 3.5 shows the entire retrosyntetic plan envisioned for the synthesis of **46**.



Scheme 3.5: retrosynthetic plan for the C_{19} marine oxylipid **46**

The first disconnection at the level of C_{12}-C_{13} bond identifies an sp^3-sp^3 coupling, the target molecule **46** might be obtained from the intermediate **62**. A retro hydrogenation step brings to the olefin **63**, this intermediate could be prepared starting from **64** by disconnecting the C_4-C_5 bond with a cross-methatesis approach.

Compound **64** should be considered as the key intermediate of the entire synthetic strategy because it is the first intermediate that contains all the stereocenters of the final target.

Subsequently, the totally stereoselective insertion of the C_{10} hydroxyl function could be performed *via* reductive opening of the epoxy alcohol **65**, that can be obtained by Sharpless epoxidation of the allylic alcohol **66**.

The C_6-O disconnection of the heterocyclic system, might be carried out through a Pd(0)-catalyzed asymmetric allylic etherification, which identifies the meso diol **97** as starting material. This is the most crucial step of the retrosynthetic plan because it allows to form the 3-hydroxy-*trans*-2,5-disubstituted tetrahydrofuran ring starting from a *meso* substrate, with a total control of the absolute and relative stereochemistry of three stereocenters, through a one pot reaction.

Finally, the *meso* diol **97** could be prepared starting from the *meso* cyclopentendiol **68** and the bis allyl ester **69**.

3.4 Synthesis of the key intermediate **64**

The first part of the oxylipid total synthesis has been devoted to the preparation of the key intermediate diol **64** that contains all the stereocenters of the final molecule.

This compound is considered as the key intermediate because it serves as starting point for the following side chains installations. It has a very high synthetic value because its synthesis requires two catalytic and almost complete stereoselective reactions: the Sharpless epoxidation and the Pd(0) - catalyzed asymmetric allylic etherification.

For this reason, we have worked simultaneously on the synthesis of such intermediate and were carried out preliminary tests on readily available substrates, structurally similar to the key intermediate **64**, aimed at finding efficient strategies for the side chains installation. These studies will be discussed in the next section of the thesis.

Scheme 3.6 shows all the reactions performed to synthetize the diol **64**.

Firstly, the *meso* diol **97** undergoes the Pd(0)-catalyzed asymmetric allylic etherification.

The choice of such substrate and reaction conditions, in particular the chiral ligand involved and the leaving group on the *meso* diol, are the results of a careful methodological study applied to the intramolecular asymmetric Tsuji-Trost reaction (see chapter 4)

This reaction has been studied for a long time by our research group, and it has been applied, in another version, to the total synthesis of other THFs containing natural products such as neurofurans[40].

The methodological study showed that the optimized reaction conditions in terms of yield, diastereo and enantioselectivity are those reported in the scheme 3.6.

As can be seen, the best substrate is found to be the one with p-methoxybenzoate as leaving group, and the chiral ligand for the metal is represented by the bis-amide diphosphine showed on the arrow, that has been synthetized as part of the methodological study (see chapter 4). $Pd_2(dba)_3CHCl_3$ has been employed as Pd(0) source.

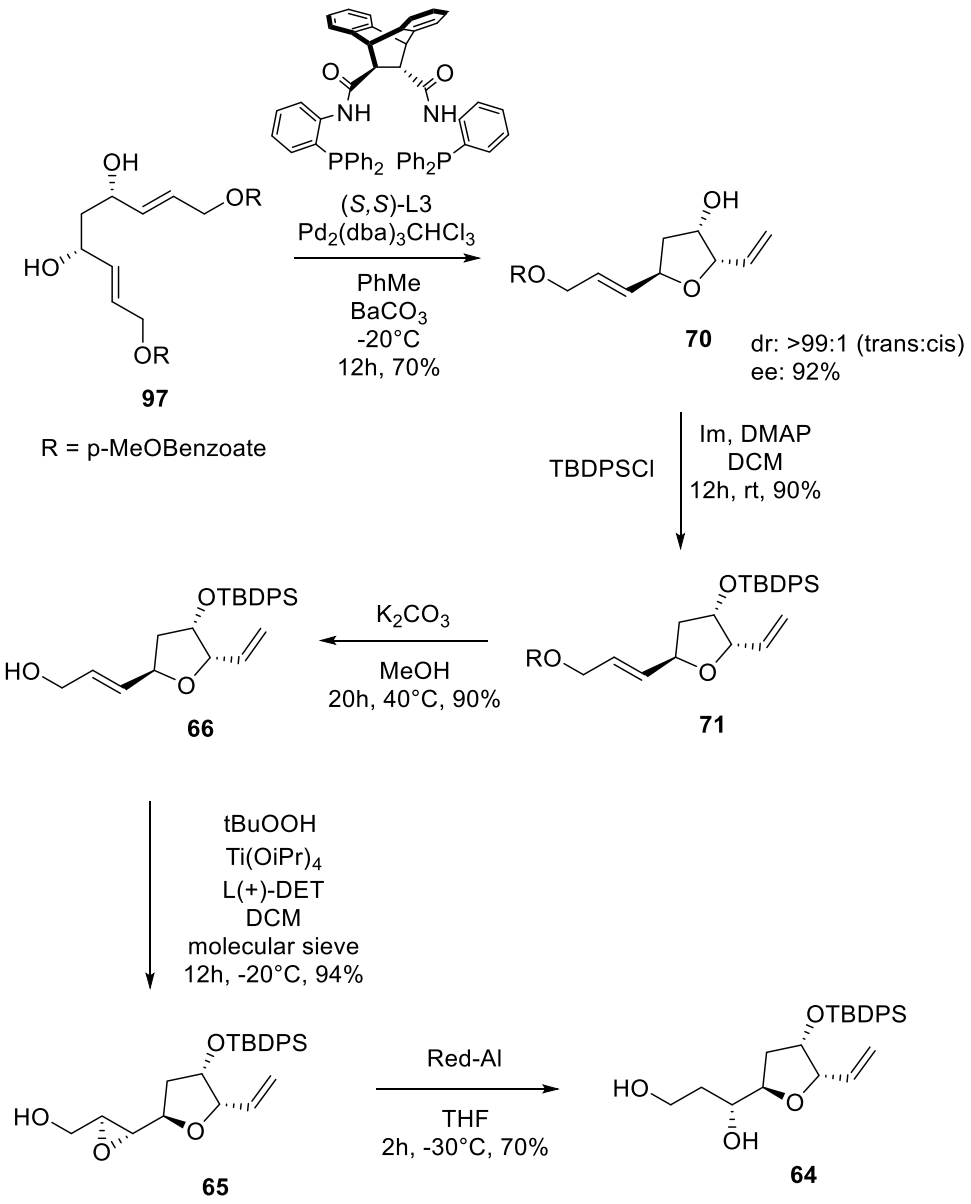
The previous study carried out by our research group demonstrated that the addition of stoichiometric amount of inorganic bases, such as $BaCO_3$, allows to neutralize the free p-metoxybenzoic acid that is formed during the reaction, which could destroy the catalytic complex. The addition of this additive increases the turnover number of the catalyst.

The 3-hydroxy-*trans*-2,5-disubstituted tetrahydrofuran is thus obtained with a complete diastereoselectivity (respect to the 3-hydroxy-*cis*-2,5disubstituted tetrahydrofuran diastereoisomer) and 92 % of enantiomeric excess.

The main advantages of such approach surely are: high control of the relative and absolute stereochemistry of three stereocenters in a single step reaction, use of catalytic amount of metal species, use of catalytic amount of expensive chiral ligand, in this way the chiral information is directly transferred from the catalyst to the product. Moreover, the possibility to obtain both the enantiomers of the product by simply changing the absolute configuration of the chiral

[40] M. Valli, P. Bruno, D. Sbarbada, A. Porta, G. Vidari and G. Zanoni, *J. Org. Chem,* **2013,** 78, 5556.

ligand and, finally, the high synthetic versatility of the tetrahydrofuran intermediate, due to the different reactivity of the vinyl and allyl acetate side chains.



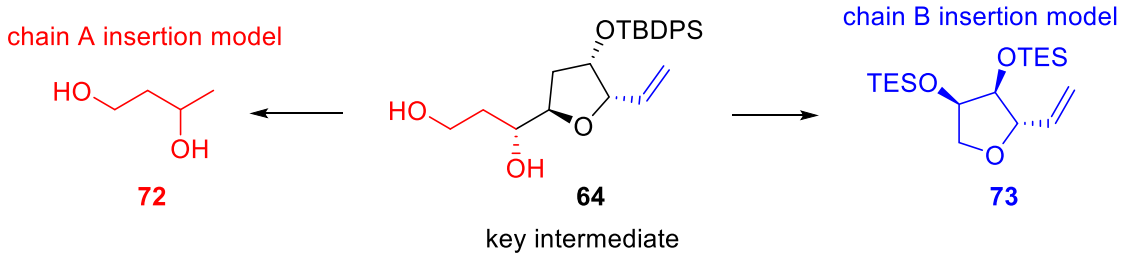
Scheme 3.6: synthesis of the key intermediate **64**

Next step, is represented by the protection of the secondary hydroxyl function on the THF ring as TBDPS ether (**71**). Hydrolysis of the p-methoxybenzoic ester is performed by using K_2CO_3 in methanol at 40°C for 20 hours and, subsequently, the Sharpless asymmetric epoxidation of the allylic alcohol **66** is achieved using tBuOOH, $Ti(OiPr)_4$ and L (+)-DET as chiral ligand.

Finally, the epoxide **65** is converted into the diol **64** by reductive opening of the epoxide ring via Red-Al.

3.5 Side chains installation: preliminary tests on structural models

In order to develop an efficient strategy for the side chains connection to the tetrahydrofuran intermediate **64**, two models have been used (scheme 3.7), one for the unsaturated C_{10} chain (chain A, model **72**) and one for the saturated C_5 chain (chain B, model **73**).



Scheme 3.7

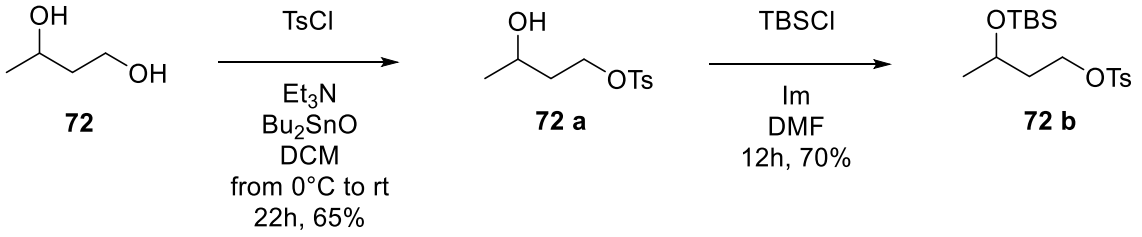
3.6 Tests for Chain A installation

Oxylipid **46**'s chain A is represented by a C_{10} chain which contains a terminal double bond between C_{18} e C_{19} and a secondary hydroxyl function on the stereogenic centre C_{10}. Following the retrosynthetic plan proposed, it should be generated from the intermediate **64**, by connecting a C_7 chain with the C_3 chain of the starting diol.

The presence of a primary hydroxyl function on the C_3 fragment of **64** suggested to involve it, after converting the hydroxyl moiety into a good leaving group, as electrophilic synthon and to attach a C_7 nucleophilic synthon that leads to the C_{10} chain.

The 1,3-butanediol **72** is a cheap and readily commercially available compound that can be a structural model of the dihydroxy-side chain of **64**. So, it has been used as starting point to find the strategy for chain A installation.

The selective activation of primary alcohol can be obtained by converting it into the corresponding tosylate[41] (scheme 3.8). It is in fact reported in literature[42] that primary tosylate can be employed to perform sp^3-sp^3 coupling with organocopper reagents.



Scheme 3.8: Activation of primary alcohol and protection of secondary alcohol.

In the first type of synthetic approach, the coupling reaction has been tested after protection of secondary alcohol as TBS ether (**72 b**), because it was thought that the free hydroxyl function could interfere with the right generation of the organometallic complex.

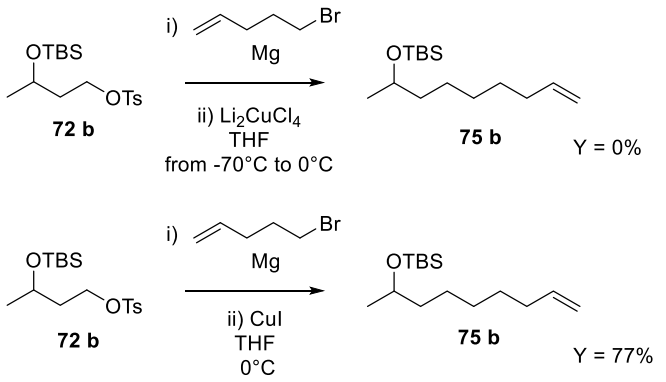
Scheme 3.9 shows the results obtained by coupling tests on the TBS protected chain A model **72 b**.

1-pentenylbromide has been used as precursor of the corresponding Grignard reagent, the resulting organomagnesium reagent was subsequently used for the generation of the organocopper reagent.

When the reaction was carried out by using catalytic amount of Li_2CuCl_4 (Kochi's catalyst), the coupling did not take place, but as it can be seen, in the second attempts, if stoichiometric amount of CuI is employed to generate the organocopper complex from Grignard reagent, sp^3-sp^3 coupling proceeds with good yields and without by-products.

[41] M. Martinelli, N. Nayyar, E. Moher, U. Dhokte, J. Pawlak and R. Vaidyanathan, *Org. Lett.*, **1999**, 1, 447.

[42] C.R. Johnson and G.A. Dutra, *J. Am. Chem. Soc.*, **1973**, *95*, 7777.

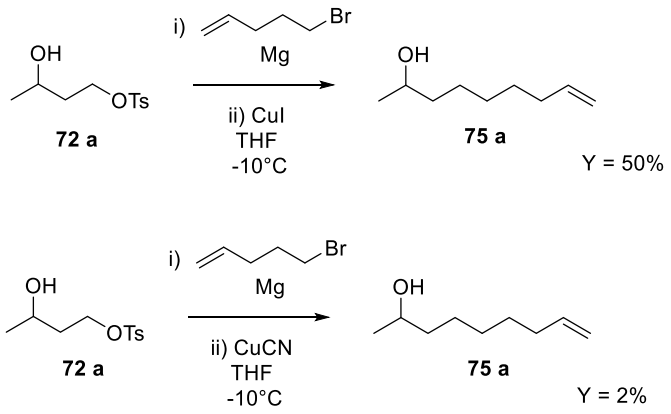


Scheme 3.9: sp^3-sp^3 coupling tests on TBS-protected chain A model

The secondary hydroxyl group protection, would lengthens the total synthesis of one step, for this reasons it has been decided to test the coupling reaction on the free alcohol.

The main results are shown in scheme 3.10. By employing the same reaction conditions used for the protected alcohol coupling, reaction worked and desired product was obtained with satisfactory 50% overall yield. Even if it is lower than the yield reported for the protected one (77%), with this strategy would be possible to remove the protection step from the total synthesis and increase the atom economy of the strategy.

In order to increase the yield of the coupling reaction, CuCN has been used instead of CuI, but the resulting reaction yield was very low (2%).



Scheme 3.10: sp^3-sp^3 coupling tests on free secondary alcohol chain A model

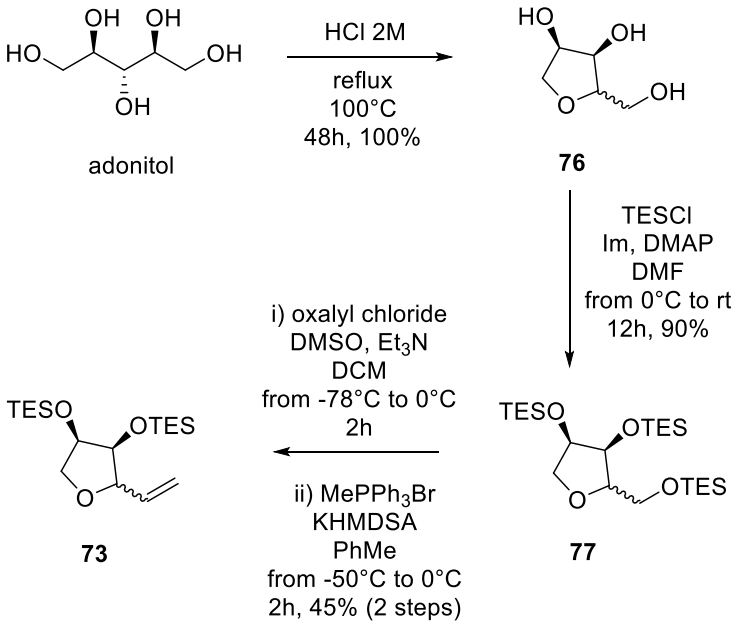
In conclusion, preliminary tests on the chain A model suggested to try to perform the sp^3-sp^3 coupling on the free secondary alcohol substrate, by using stoichiometric organocopper complexes deriving from Grignard reagents and CuI as copper source. This part of the Thesis sets one of the most important milestones for the total synthesis of oxylipid **46**. With these results, the synthetic studies were focused on installation of the other side chain.

3.7 Tests for Chain B installation

The structural motif inside chain B of the marine oxylipid, is a C_5 saturated chain. As it can be seen in the retrosynthetic scheme 3.5, it has been proposed to build this chain starting from the key intermediate **64**.

The transformation of the C_2 vinyl chain into a C_5 saturated chain is one of the most important endeavours of this thesis.

Compound **73** has been chosen as model for the chain B insertion, due to the similarity with the key intermediate and the low number of steps necessary to synthetize it.

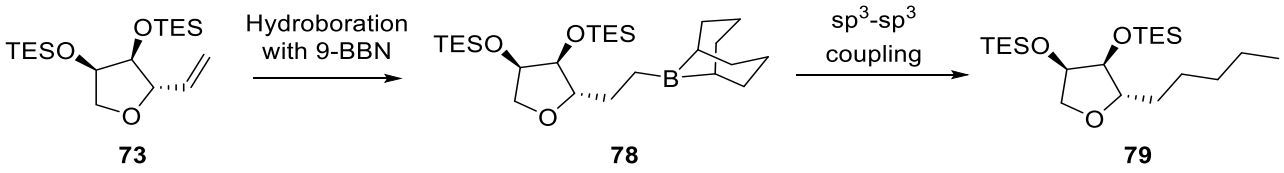


Scheme 3.11: chain model **73** synthesis

Scheme 3.11, shows how the model can be prepared in good amount through 4 reactions, starting from commercially available adonitol.

Adonitol has been refluxed with 2 M HCl and quantitatively converted into the tetrahydrofuran triol **76**[43]. Protection of hydroxyl groups as TES ethers and subsequent selective oxidation of primary hydroxyl function using Swern protocol and followed by Wittig reaction with methyl triphenylphosphonyum ylide, gave chain B model **73**.

At first, the strategy proposed for the construction of the C_5 saturated chain (scheme 3.12), was based on a sp^3-sp^3 Suzuki coupling[44], via hydroboration of the vinyl function with readily commercially available 9-BBN.

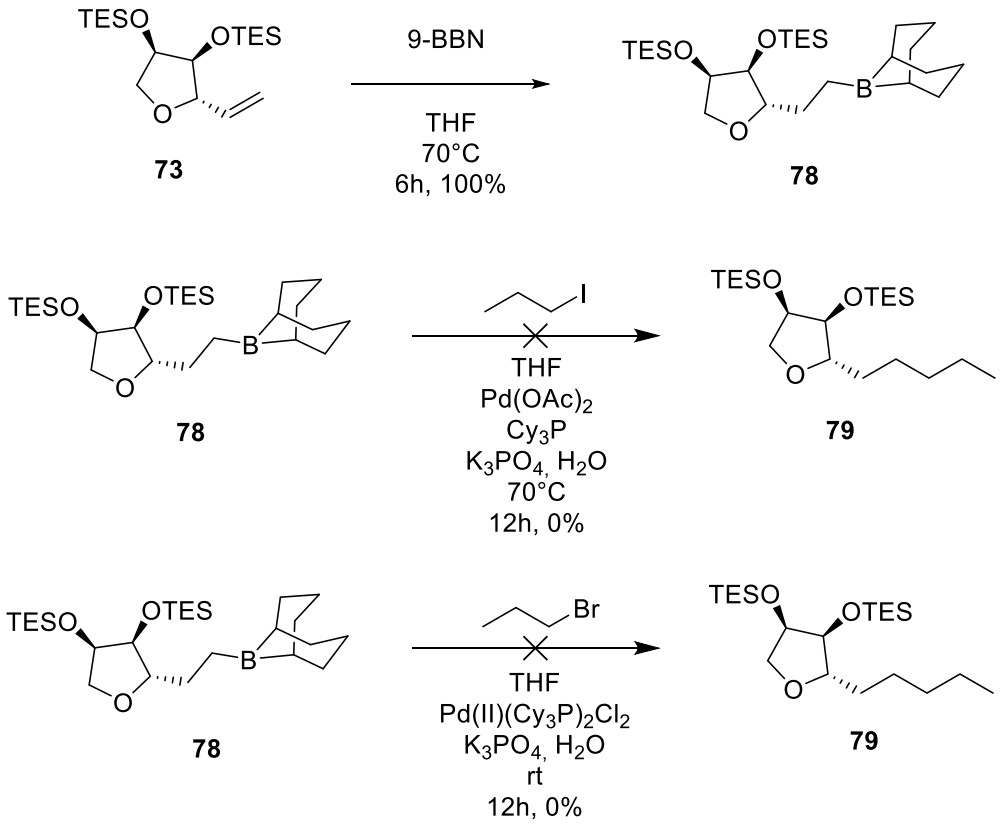


Scheme 3.12: synthetic approach for chain B installation

Unfortunately, as can be seen in scheme 3.13 the sp^3-sp^3 coupling strategy did not work.

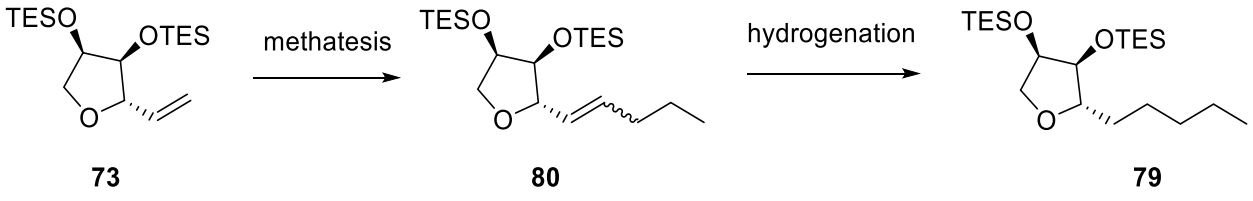
In spite of the formation of the borane intermediate **78**, the subsequent Pd (0) catalyzed coupling with propyl iodide (Suzuki version) or propyl bromide (Fu version)[45] did not take place at all. For this reason, it has been necessary to change the strategy for chain installation.

[43] Skorupa, E.; Dmochowska, B.; Pellowska-Januszek, L.; Wojnowski, W.; Chojnacki, J.; Wisniewski, A.; *Carbohyd. Res*, **2004**, *339*, 2355
[44] Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A., *Chemistry Letters,* **1992**, *4*, 691
[45] Netherton, M. R. , Dai, C., Neuschütz, K., and Fu, G.C. *J. Am. Chem. Soc.*, **2001**, *123*, 10099.



Scheme 3.13: unsuccessful attempts of Suzuki sp^3-sp^3 coupling

The presence of a vinyl function on the key intermediate, prompted to adopt a methatetic approach in order to connect the C_3 fragment on the side chain (scheme 3.14). The following hydrogenation of the resulting double bond should generate the saturated C_5 side chain.



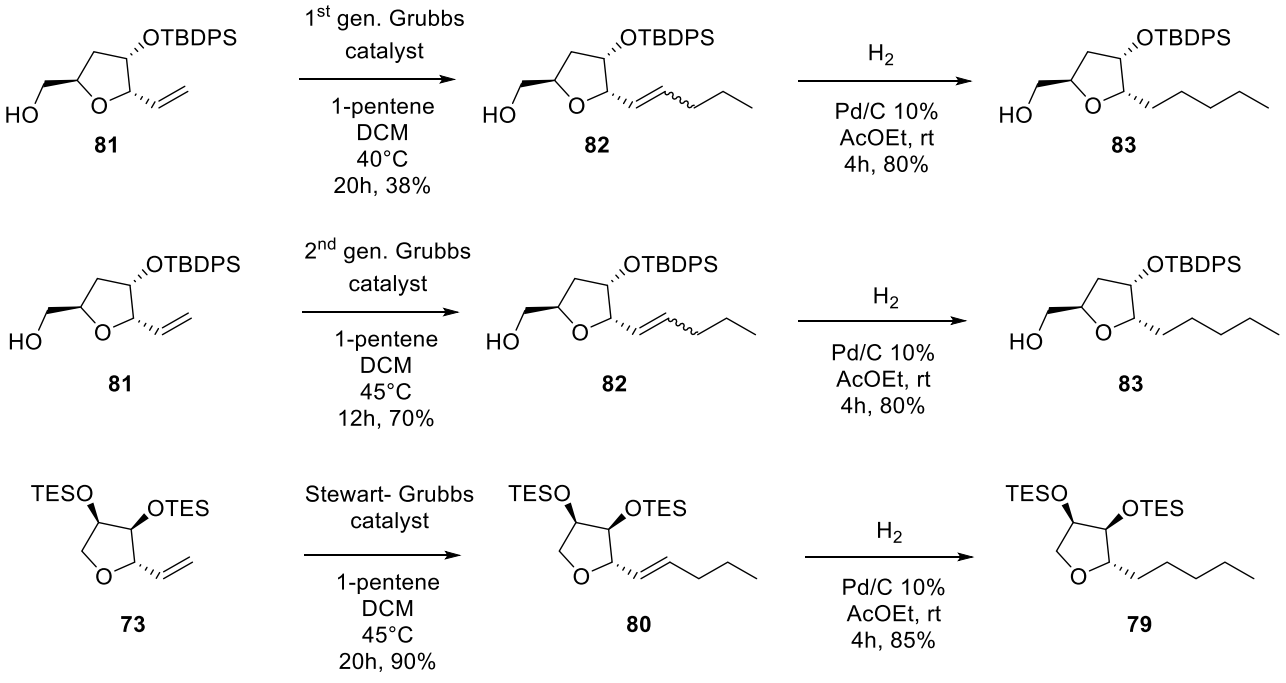
Scheme 3.14: methatetic approach for chain B installation

Some of the chain B installation tests have been performed on a structural model more similar to the key intermediate **64**, that is the one shown in the first and second examples of scheme 3.15.

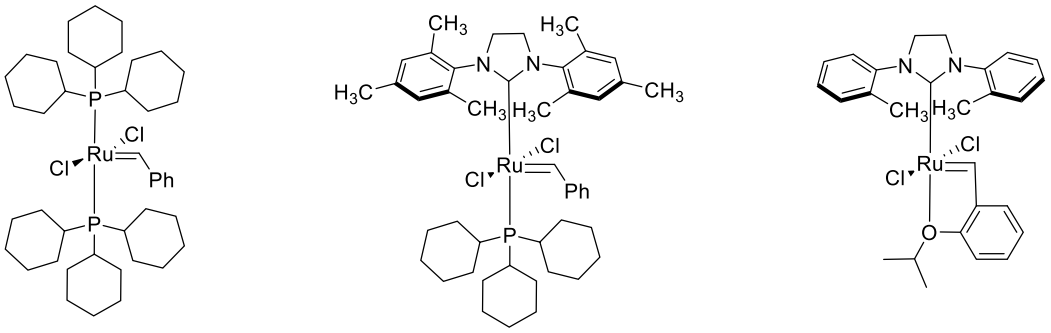
All the reactions have been carried out in DCM, at 40-45°C (in a sealed vial), with 1-pentene as reactant and three different kinds of catalysts: 1st generation Grubbs catalyst, 2nd generation Grubbs catalyst and finally Stewart-Grubbs catalyst.

The last one gone the best result, with 90 % of total yield. The subsequent hydrogenation of the double bond with H_2 on Pd/C leads to the saturated C_5 side chain.

Schemes 3.15 and 3.16 show reaction conditions and catalysts' structures respectively.



Scheme 3.15: methatesis/hydrogenation tests on chain B models



Scheme 3.16: structures of the catalysts employed for methatesis tests

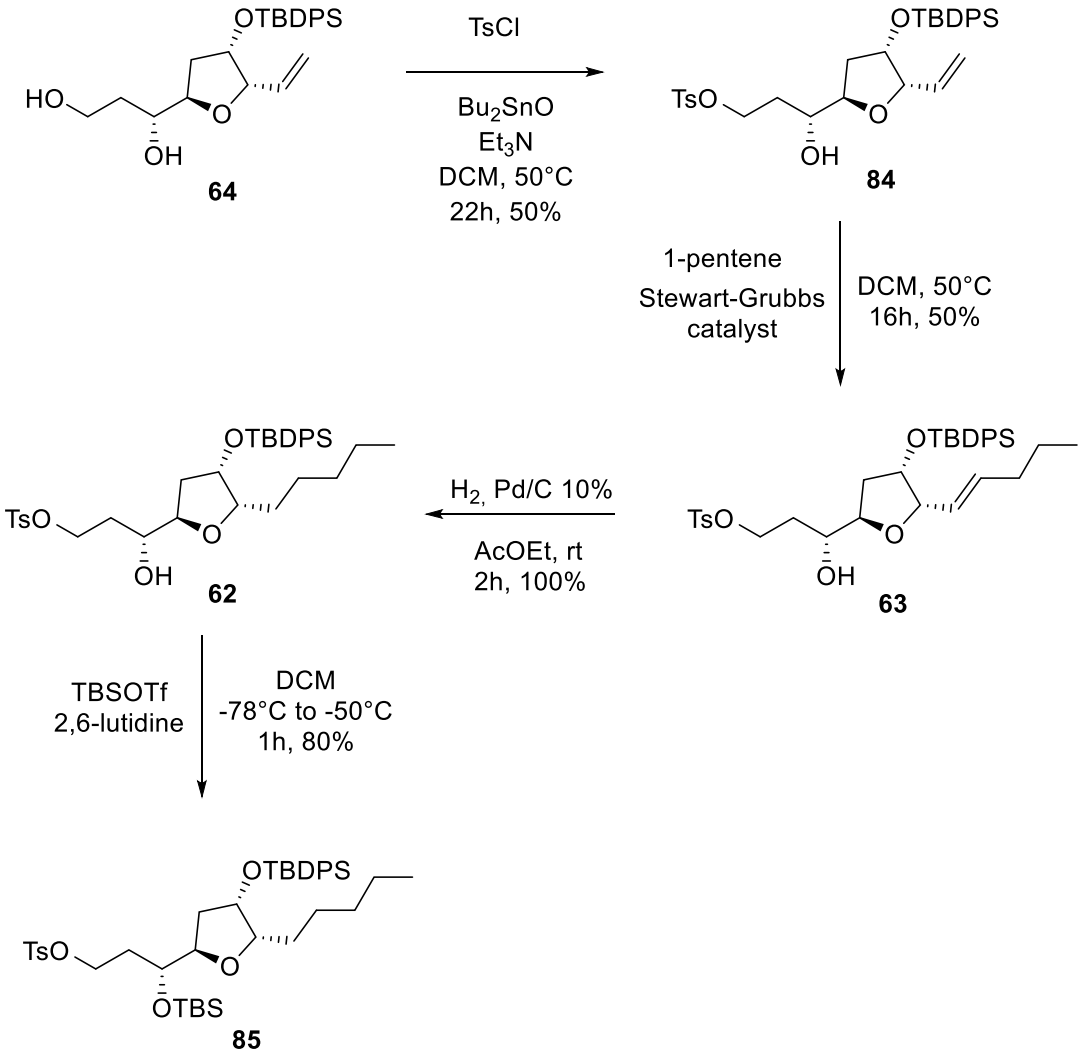
In conclusion, all the tests done on the structural models have been fundamental in order to settle the strategy for chain A and chain B installation. The same approaches will be applied subsequently on the more synthetically valuable intermediates for the oxylipid synthesis.

3.8 From the key intermediate **64** toward the marine oxylipid **46**

Once synthetized the key intermediate **64**, as reported in scheme 3.6, it has been possible to proceed with the synthetic plan towards the oxylipid **46**.

Previous tests performed on structural models, have paved the way for the strategies that must be adopted in order to install the THF side chains.

Scheme 3.17 shows the reactions carried out.



Scheme 3.17. From the key intermediate **64** toward the oxylipid **46**

At first, primary hydroxyl function of the key diol **64** has been selectively protected and activated as tosylate, by using catalytic Bu_2SnO and Et_3N. Subsequently, the cross methatesis approach developed on the model has been applied on the intermediate **84**. It is possible to observe that the yield of the Stewart Grubbs catalyzed cross methatesis in this case, is lower than the one reported during the tests on the model. Probably this is due to the structural differences between the model **73** and the intermediate **64**. Anyway, with the following step, the double bond has been quantitatively hydrogenated using Pd/C 10% and the saturated C_5 chain has been obtained in good overall yield.

Even if previous tests for the chain A installation showed that sp^3-sp^3 coupling could be carried out in spite of the presence of a free secondary alcohol, it was initially decided to try the coupling reaction on the protected one. So, by treating the intermediate **62** with TBSOTf and 2,6-lutidine, the hydroxyl function has been protected as TBS ether.

Unfortunately, the first attempt of sp^3-sp^3 coupling on the intermediate **85**, did not work as in the model **72 b** (scheme 3.9). The reaction has been carried out with the same conditions employed as for the model. Heptenyl magnesium bromide and CuI have been used to generate the organocopper reagent but when the tosylate **85** was added, the coupling did not take place and the starting material was recovered unalterated.

At this moment, studies are underway to try the coupling again and possibly find a new strategy. Anyway, the principal aims of the synthetic study, that were to develop an efficient diastereo and enantioselective process to the 3-hydroxy-*trans*-2,5 disubstituted tetrahydrofuran ring of the oxylipide **46** and the stereoselective insertion of the C_{10} hydroxyl group on the side chain, were successfully achieved. In this way, all the stereocenters of the metabolite were fixed, moreover a useful strategy for the saturated C_5 chain construction was developed.

The key intermediate **64**, can be considered as starting building block for the total synthesis of several 3-hydroxy-*trans*-2,5 disubstituted tetrahydrofuran containing natural molecules. Therefore, the above results can be used for many total syntheses of THFs natural products.

CHAPTER 4: methodological study toward 3-hydroxy-*trans*-2,5-disubstituted THF cores

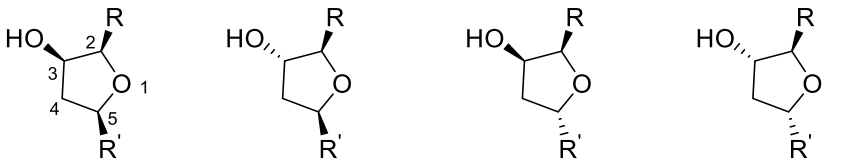
4.1 Background on Pd(0)-asymmetric allylic etherification on *meso* diol systems

Pd(0)-asymmetric allylic etherification of *meso* diol **86** (table 4.1) towards polysubstituted THF ring formation, has been subject of study by our research group, since it was employed as key step in the total synthesis of 7-*epi*-ST-Δ^8-10-Neurofuran[40]

To define the stereochemistry of such trisubstituted THF cores, the method employed for neurofurans is adopted.

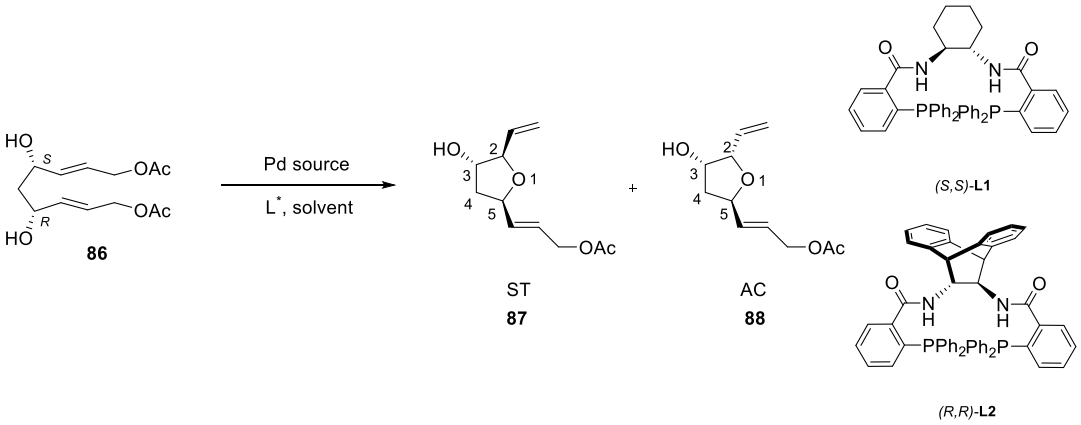
It considers the relative position of the two side chains on C_2 and C_5, that could be *syn* (S) or *anti* (A), and the relation between the hydroxyl group and the C_2 substituent, that could be *cis* (C) or *trans* (T).

All possible combinations are shown in scheme 4.1.



Scheme 4.1

Table 4.1: chiral ligands tests on meso diol **86**



Entry	Ligand	Solvent	Yield (%)	dr ST:AC	ee ST (%)	ee AC (%)
1[a]	(*S,S*)-L1	THF	61	61:39	94	11
2	(*S,S*)-L1	DCM	86	80:20	96	3
3	(*R,R*)-L2	DCM	70	34:66	93	88
4[b]	(*R,R*)-L2	DCM	65	17:83	95	92

Unless otherwise noted, reactions were carried out at room temperature, with $Pd_2(dba)_3CHCl_3$ adduct (3 mol%), chiral ligand L^* (8 mol%), substrate **86** (0.2 mmol), Cs_2CO_3 (1.05 equiv), solvent (2 ml, 0.1 M). d.r. ST:AC was determined by HPLC. Enantiomeric excess was determined by chiral HPLC, on Chiralpak AS-H and AS-3 columns. (a) Cs_2CO_3 was not used; $Pd_2(dba)_3CHCl_3$ adduct (8 mol%) and chiral ligand L^* (31 mol%) were employed. (b) reaction was carried out at -20°C.

At the beginning, cyclization of compound **86** could be only promoted by using 8 mol% of $Pd_2(dba)_3CHCl_3$ as Pd source and 31 mol% of cyclohexyldiamine -derived ligand (*S,S*)-L1 in THF at rt.

Under these conditions, a mixture of two tetrahydrofurans, ST-like **87** (94% ee) and AC-like **88** (11% *ee*), was obtained in 61% isolated yield and 61:39 *dr* (HPLC) (table 4.1, entry 1). This result was unexpected since the significant formation of **88** was not reported in the original work[33].

Catalyst loading could be reduced to 8 mol % of ligand and 3 mol % of Pd-precatalyst, by adding Cs_2CO_3 and using DCM as solvent. Under these conditions ST-tetrahydrofuran **87** was obtained in 80:20 *dr* ST:AC (HPLC) and 96% *ee*, accompanied by the AC-diastereomer **88** (3% *ee*), in an overall yield of 86% (table 4.1, entry 2).

The two compounds **87** and **88** could not be separated by preparative column chromatography, for this reason reaction conditions were changed in order to achieve an improvement of the diastereoselectivity.

Although no significant *dr* enhancement was obtained, un unanticipated inversion in the diastereomeric products distribution in favor of AC-THF **88** was observed, simply by using the anthracenyldiamine-derived ligand (*R,R*)-L2 instead of (*S,S*)-L1.

In fact, the *dr* ST:AC was 34:66 when the reaction was carried out at rt (table 4.1, entry 3), the two diastereomers being obtained in 93% and 88% *ee*, respectively. Moreover, lowering the reaction temperature to -20°C resulted in an increase of the *dr* ST:AC to 17:83 with a concomitant improvement of the enantiomeric excess of both **87** and **88** to 95 and 92% respectively (table 4.1, entry 4).

Absolute configuration of 2*R*,3*S*,5*R* for **87** and 2*S*,3*S*,5*R* for **88** were established by studies of the corresponding Mosher esters and n.O.e NMR spectra[46]. The Mosher method for enantioenriched **87** and **88**, has been applied on the products of entry 2 and entry 4, while NOE studies were carried out on chromatographically separated O-TBDPS ethers of **87** and **88**.

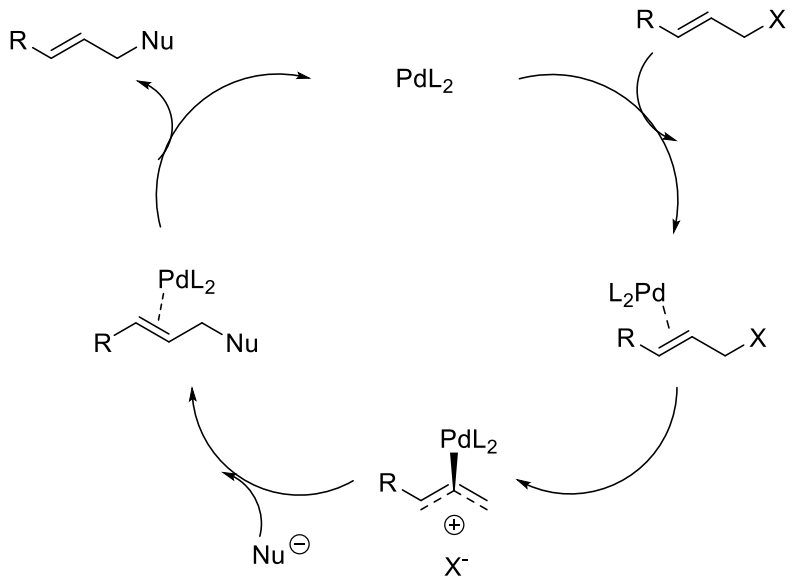
[46] Capon, R. J.; Barrow, R. A.; Rochfort, S.; Jobling, M.; Skene, C.; Lacey, E.; Gill, J. H.; Friedel, T.; Wadsworth, D. *Tetrahedron* **1998**, 54, 2227

4.2 Stereochemical features of the reaction

The key reaction of this methodological study is represented by the Tsuji-Trost allylic etherification of *meso* diol **86**.

The reaction is characterized by the following steps (scheme 4.2)

- Coordination of Pd (0) catalyst to the double bond of the allylic ester
- Oxidative addition of Pd (0) to the C-O bond and pi-allyl complex formation
- Intramolecular nucleophilic attack of the hydroxyl group on the pi-allyl complex and reductive elimination of Pd catalyst
- Decomplexation

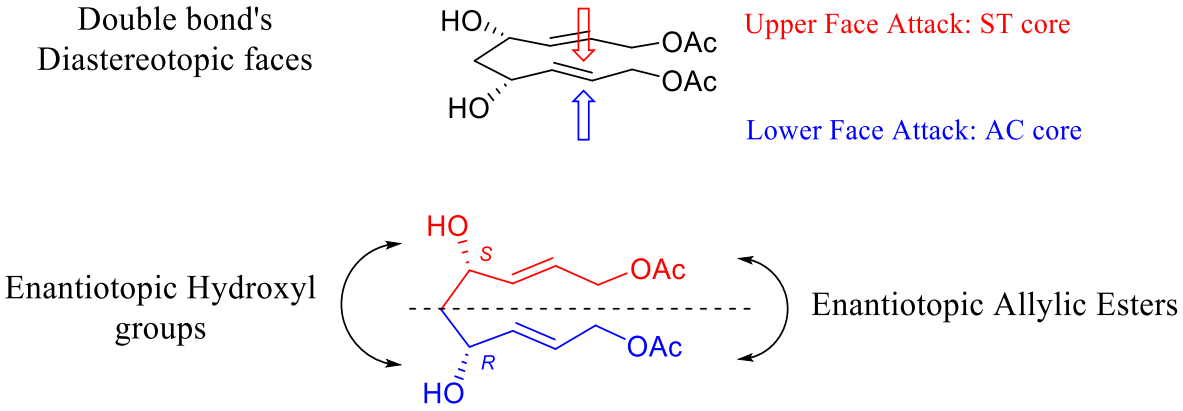


Scheme 4.2: mechanism of Tsuji-Trost allylation

The achiral substrate **86** loses its symmetry (reflection plane) during the cyclization, thus chiral tetrahydrofuran systems are formed.

By analyzing the stereochemical features of compound **86** it is possible to find that each double bond presents two diastereotopic faces. When cyclization takes place, the hydroxyl group can

attack both the lower and upper face of the intermediate pi-allyl system, resulting in the two different diastereomeric rings AC and ST respectively (scheme 4.3)



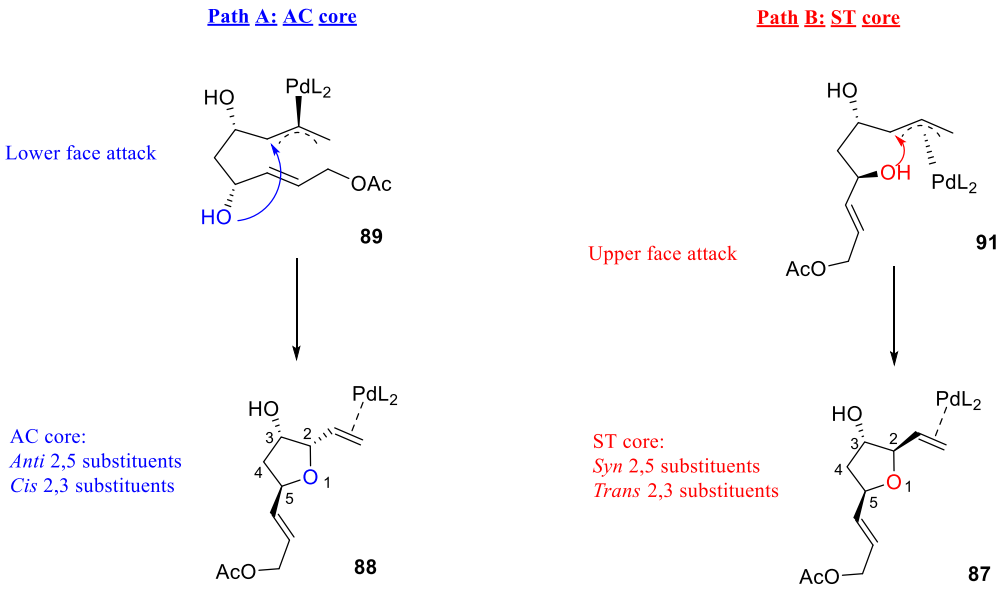
Scheme 4.3: stereochemical features of *meso* diol **86**

Scheme 4.4 reports the two competitive pathways of the Tsuji-Trost AAA on *meso* diol **86**.

The only new stereocenter that is created in the final product is the one bearing the vinyl substituent (C_2), the other two centers (C_3 and C_5), become automatically stereogenics as a result of the reflection plane loss.

For this reason, only two of the four possible diastereoisomers of the product can be formed. The ST type and the AC type (scheme 4.1)

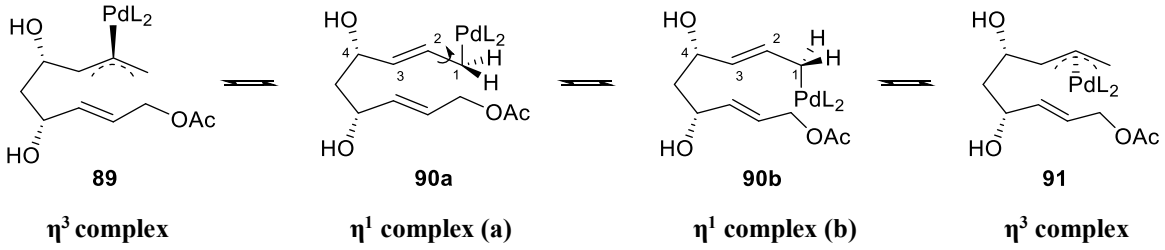
Moreover, the substrate contains a symmetry plane that divides the molecule into two identical parts, causing the hydroxyls functions and allyl esters to be enantiotopic groups. As a consequence of that, depending on which of the two enantiotopic hydroxyl groups will attack the opposite pi-allyl system, two different enantiomers of the product can be obtained.



Scheme 4.4: reaction pathways towards AC and ST cores

It is important to note that, the two diastereoisomeric η^3-allyl complexes **89** and **91** (scheme 4.5) can be in equilibrium through the corresponding η^1- allyl complex **90** which can free rotate around its C_1-C_2 bond.

This fluxional phenomenon is called equilibration of the pi-allyl system.



Scheme 4.5: equilibration between η^3 pi-allyl complexes

Equilibration is strongly influenced by temperature, solvent polarity and stereo-electronic features of the catalyst.

The stereochemical control of the Pd(0)-catalyzed asymmetric allylic etherification of *meso* diol **86** can be achieved by working on two different selectivity levels at the same time. The diastereoselectivity, which is expressed by the diastereomeric ratio between AC and ST compounds and the enantioselectivity, which is expressed by the *ee* of both AC and ST derivatives.

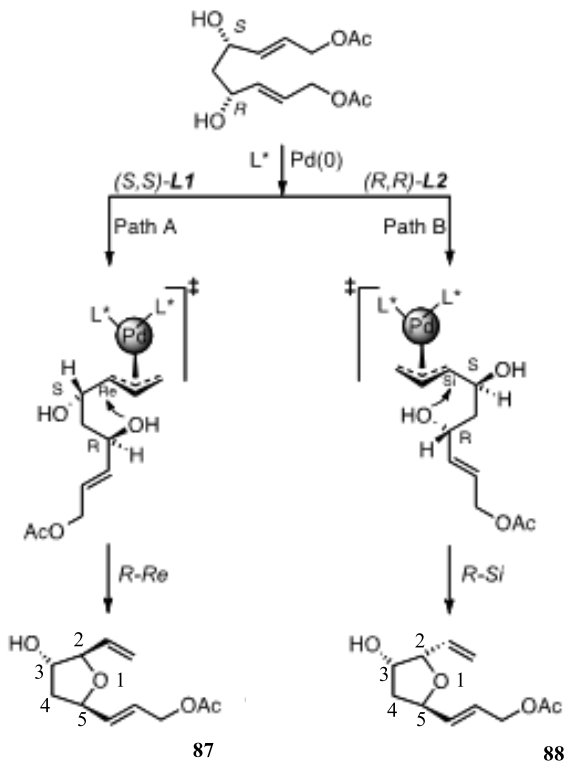
Factors that can affect the stereochemical outcomes are: solvent, temperature, chiral catalyst's structure and leaving group nature on the substrate.

The aim of this work, is to find a highly stereoselective strategy to obtain one of the two possible enantiomers of the AC-THF core, which subsequently will be involved as key intermediate for the synthesis of marine oxilipid **46** (chapter 2).

Based on the outcomes showed in table 4.1, and according to the asymmetric induction model proposed by Trost for the Pd-catalyzed AAA[47], it was speculated that the stereoisomer **87** (ST core) would be produced by the preferential coordination of the (*S,S*)-L1-Pd complex on the *Si* face of the allyl moiety close to the newly created *S*-configured carbinol carbon atom (scheme 4.6).

Furan ring closure would thus result from preferential intramolecular *anti* attack of the (*R*)-OH group on the *Re* face of the allylic Pd-complex, affording the prevalent (2*R*,3*S*,5*R*) stereochemistry observed for **87** (scheme 4.6, path A).

[47] (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev*. **1996**, *96*, 395. (b) Trost, B. M.; Machacek, B. M.; Aponick, M. R. *Acc. Chem. Res.* **2006**, 39, 747. (c) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc*. **1999**, *121*, 4545.



Scheme 4.6[40] Stereochemical picture of asymmetric allylic Pd-mediated cyclization of *meso* diol **86**

On the contrary, it was assumed that the (*R,R*)-L2-Pd complex delivered the corresponding *trans*-diastereoisomer **88** as preferentially the (2*S*,3*S*,5*R*) enantiomer through nucleophilic addition of the (*R*)-OH onto the *Si* face of the (η^3-allyl)palladium complex intermediate (scheme 4.6, path B).

It's interesting to note that, by using the enantiomers of ligands L1 and L2 namely (*R,R*)-L1 and (*S,S*)-L2, the corresponding enantiomers of **87** and **88** were achieved with the same enantio- and diastereomeric excess.

4.3 Aim of the methodological study

In order to find an efficient strategy for the construction of the 3-hydroxy-2,5-*trans*-disubstituted-THF motif contained in the marine oxylipid **46**, we decided to employ the preliminary results obtained from the previous methodological study on the Pd(0)-catalyzed asymmetric allylic etherification[40], as starting point for the development of a new methodology aiming to the stereoselective construction of the AC-THF core with high diastereo and enantioselectivity.

The best outcome achieved from the previous study is the one shown in entry 4 (table 4.1), in which the AC core is obtained in 17:83 *dr* (ST:AC) and 92% *ee* in a 65% overall yield.

Our principal aims are:

- Investigate which factors can control the diastereoselectivity of the process through the screening of different kinds of solvents, temperature and achiral ligands for the Pd catalyst.
- Employ the results obtained from the previous screening in order to test new chiral ligands for the reaction.
- Investigate the role of the leaving group of the substrate in the stereochemical outcome of the reaction.
- Use the best result achieved for the total synthesis of marine oxylipid **46** (chapter 2)

4.4 Synthesis of *meso* diol systems

The *meso* diol systems employed as substrates for the reaction, can be prepared from cyclopentendiol **93** by two different synthetic approaches, depending on the nature of the leaving groups of the final compound.

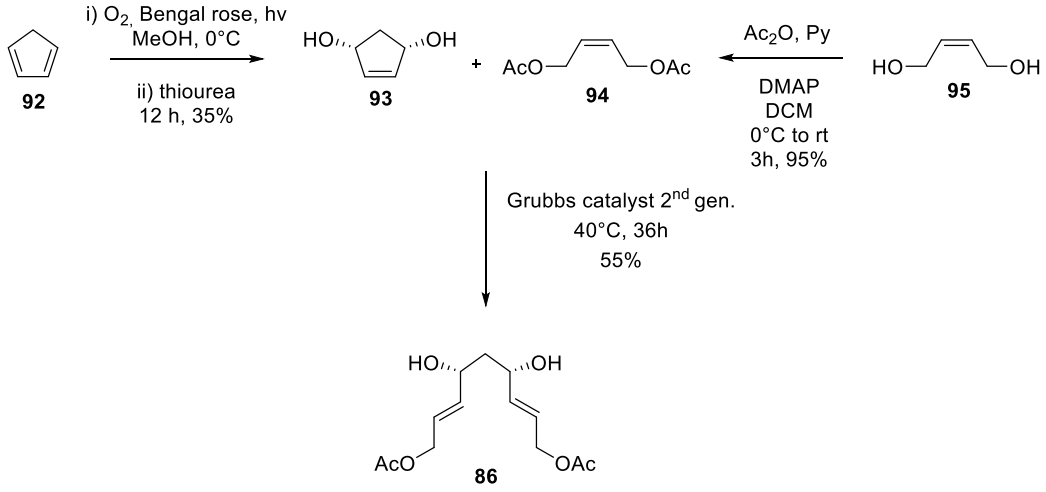
Cyclopentendiol **93** is commercially available, but as it is quite expensive, it was decided to synthetize it through an oxygen photocycloaddition on cyclopentadiene, by employing Bengal rose as photosensitizer and by irradiating with Hg lamp[48] (scheme 4.7).

After decomposition of the intermediate endoperoxide, by treating with thiourea as reducing agent, *syn*-1,3-cyclopentendiol **93** was achieved with moderate yield.

To obtain the *meso* diol substrate **86** with acetate as leaving groups, it is possible to employ a short strategy, based on a cross ring opening methatesis (CROM) with olefin **94**, that directly leads to the desired product.

Compound **94** was prepared through acetylation of *(Z)*-2-buthen-1,4-diol **95**.

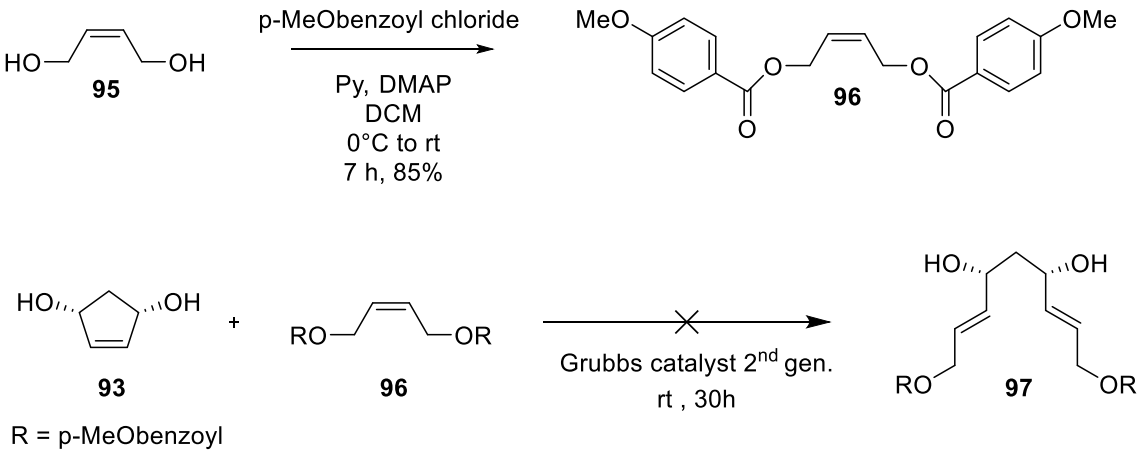
The ring opening methatesis between cyclopentendiol **93** and (*Z*)-1,4-diacetoxy-2-buthene **94** was catalyzed by 2nd generation Grubbs catalyst.



Scheme 4.7: synthesis of *meso* diol **86** via CROM

In order to avoid homo-coupling processes of substrate **93**, olefin **94** was used as solvent. In this way, polymerization reactions do not take place and the excess of the diacetate pushes the equilibrium to the right.

[48] Gurjar, Mukund K.; Reddy, Challa Nageswar; Kalkote, Uttam R.; Chorghade, Mukund S., *Heterocycles*, **2009**, 77, 2 ,909.



Scheme 4.8: approach to *meso* diol **97** synthesis

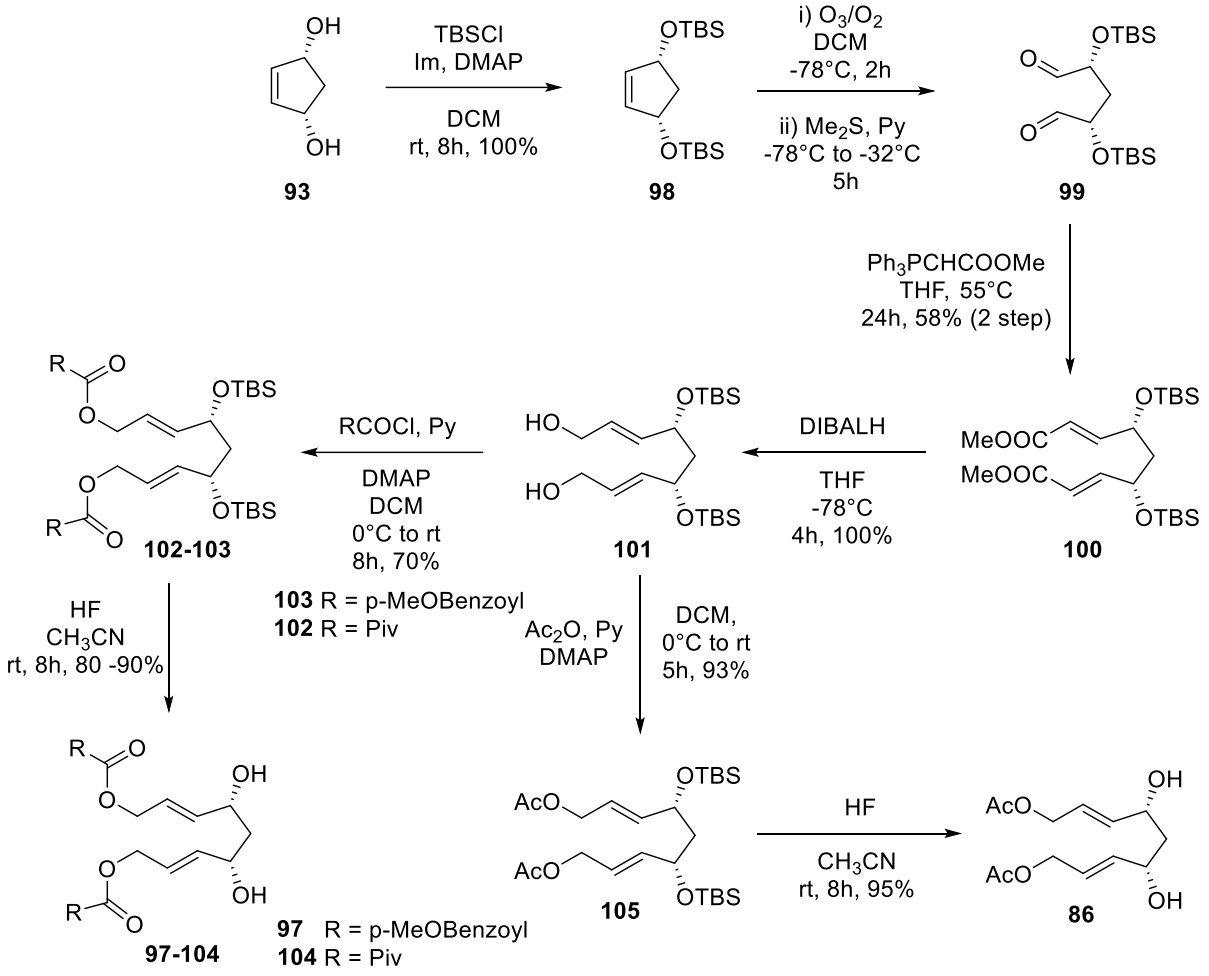
When extension of the same reaction was tried on olefins bearing different ester functionalities, it did not work at all. For instance, it was tested on compound **96** to obtain the *meso* diol system **97** showing (R = para-methoxybenzoate). After 1 day no trace of product was detected (scheme 4.8).

One of the troubles related to this approach is that alkene **96** is a solid compound, very difficult to solubilize in reaction solvent.

For this reason, a different approach was necessary in order to synthetize different *meso* diol substrates for the subsequent methodological study.

The synthetic plan that is going to be described, is a general method to obtain compounds like **86**. Even if it is longer than the methatetic approach, it allows to include different types of ester function on the final *meso* compound.

Scheme 4.9, shows all the reactions employed in such synthetic plan.



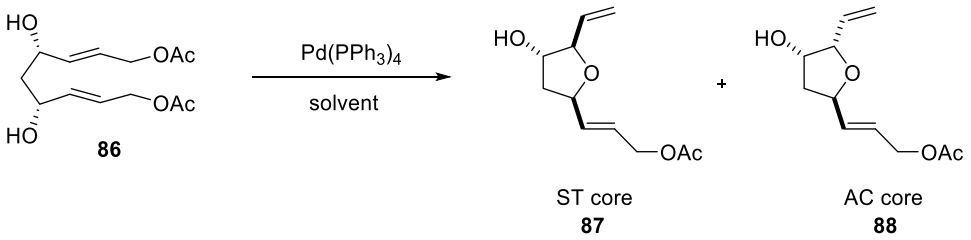
Scheme 4.9. Synthesis of *meso* diol compounds

After protection of the secondary hydroxyl functions as TBS ether, cyclopentendiol **93** is converted into the dimethylester **100** through an ozonolysis/Wittig sequence. Then, diol **101** is obtained after reduction with DIBAL-H. Then, esterification followed by removal of the silyl protecting groups led to the desire products **86**, **97** and **104**.

4.5 Screening of achiral phosphines

At first, reaction has been tested by using achiral phosphines as Pd (0) ligands, in order to understand the role of solvents and ligand stereo-electronic features on the yields and diastereoselectivity.

Table 4.2: solvent effect on yield and diastereoselectivity



Entry	Ligand	Solvent	Yield (%)	dr (AC:ST)
1	PPh_3	PhMe	97	88:12
2	PPh_3	DCM	92	92:8
3	PPh_3	THF	95	95:5

Unless otherwise noted, reactions were carried out at room temperature, with $Pd_2(dba)_3CHCl_3$ adduct (3 mol%), phosphine ligand L (8 mol%), substrate **86** (0.2 mmol), solvent (2 ml, 0.1 M). D.r. ST:AC was determined by HPLC.

Table 4.2 shows the results obtained by testing the reaction with $Pd(PPh_3)_4$ in different solvents. All the attempts are characterized by very high yields and as it can be seen, when solvent polarity increases, the diastereomeric ratio AC:ST gets higher.

Despite the outcomes above, when chiral ligands have been employed, the best solvent for the reaction turned out to be toluene, because it allows a good solubilization of most of the ligands.

Subsequently a complete screening of different achiral phosphine has been performed and table 4.3 shows the principal results.

These kinds of ligands were chosen after taking in exam other methodological studies done on other Pd-catalyzed reactions.

The ligand features that can affect the reaction course are both steric and electronic.
Normally, the parameter employed to measure the electron donor power of a phosphine is the Tolman electronic parameter[49].

Tolman studied the effect of a phosphine ligand on the frequency of the CO triple bond, when it is coordinated to a metal centre. Generally, nickel tethracarbonyl is used, because it shows a clear and strong CO stretching band in the IR spectrum. Moreover, CO is a small molecule, so steric effects are minimized.

After coordination to a metal center, ν_{CO} decreases compared to the one of the free CO. This is due to the electrons π back donation from the metal *d* orbitals to the ligand empty π^* orbital. This results in a stronger metal-CO bond and a weaker C-O that causes a IR CO frequency lowering.
Now, if another ligand (e.g. phosphine) binds to the metal, it can increase the electron density, weakening the C-O bonds, or it can compete with the CO for the back donation. In the former case the ν_{CO} will decrease while in the latter it will increase.
By considering these effects, an electron donor power scale of the ligands can be achieved.

Another important parameter is the Tolman cone angle (θ), which is defined as the solid angle formed with the metal at the vertex and the hydrogen atoms at the perimeter of the cone. Tertiary phosphine ligands are commonly classified using this parameter, but the method can be applied to any ligand. It is considered as a measure of the ligand size.

Figure 4.1 shows a diagram that compares the electron donor power (ν_{CO}) and the Tolman cone angle of different phosphines.

[49] Tolman, C.A. *Chem Rev*, **1977**, 77, 313.

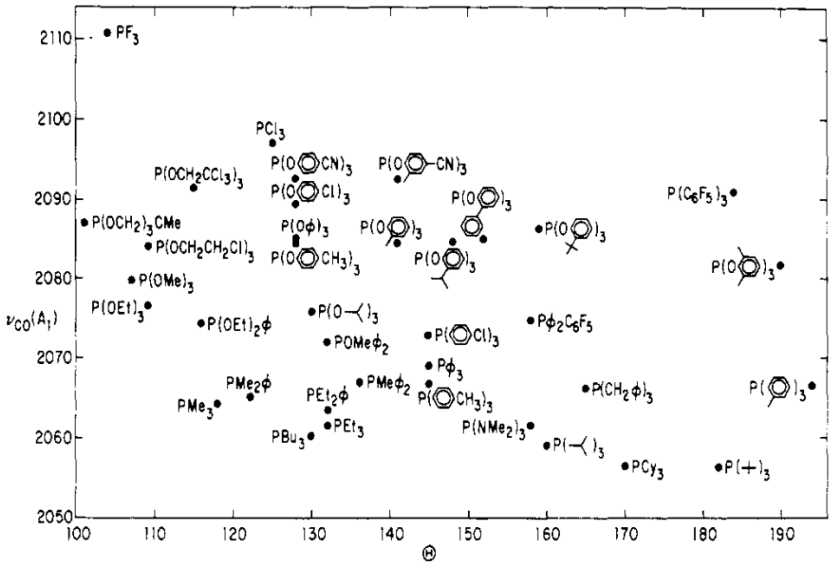


Figure 4.1[48]: Tolman diagram about steric (θ angle) and electronic (ν_{CO}) effect of different phosphines

Electronic and steric properties of the ligand are closely interlinked. In fact, another important parameter that must be taken into account is the plane angle P-Pd-P (β angle), that can modify the electronic density of the metal.

This structural feature is present not only for bidentate phosphines but for monodentate too. Figure 4.2 shows the β angle P-Pd-P for the two types of phosphine ligands.

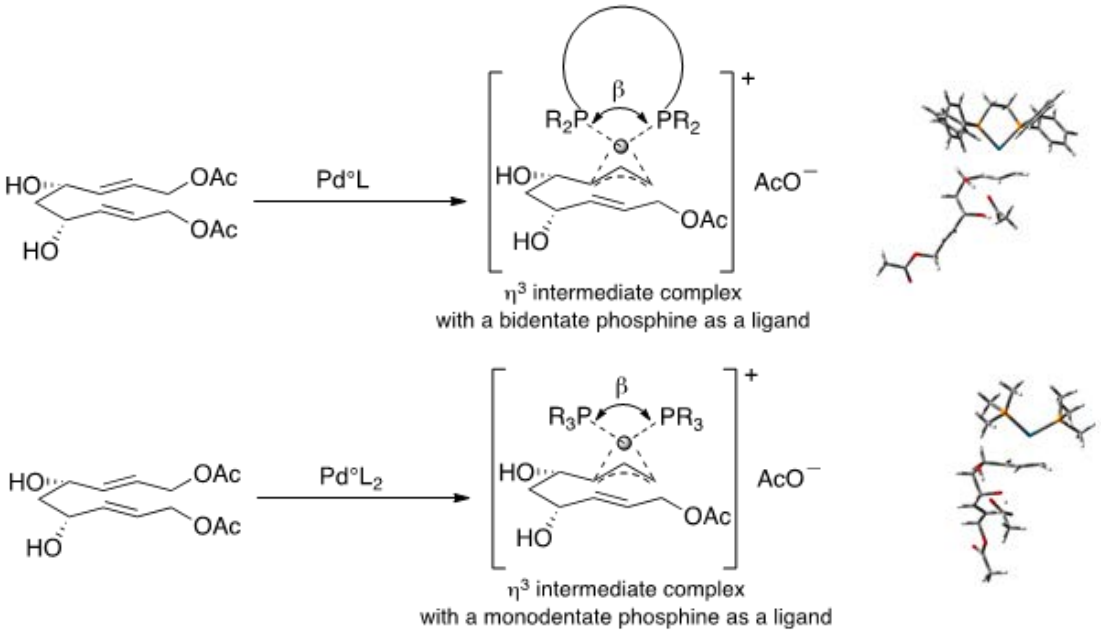


Figure 4.2: β angle. DPPE ligand for bidentate and PMe_3 ligand for monodentate phosphine.

All computations studies for determination of P-Pd-P angle (bite angle in case of bidentate ligands) were performed with Gaussian '09 software package.[50] Optimizations of complexes were carried out in gas-phase using the DFT-B3LYP functional. The P, C, H and O atoms were described with 6-31+G(d,p) basis set, and Pd atom with LANL2DZ[51,52] relativistic effective core potential (ECP) basis set implemented in Gaussian 09 software suite. Vibrational frequencies were computed at the same level of theory to verify that the optimized structures were minima.

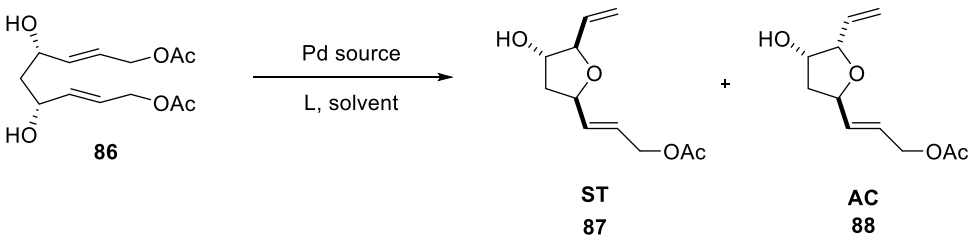
The effect of the β angle on the electronic fetaures of the pi-allyl complex is related to the different type of orbital overlapping between filled phosphorous orbitals and empty Pd orbitals. Essentially, by considering the outcomes of the studies performed by Hayashi and coworkers on the effect of bidentate phosphine ligands on *syn-anti* isomerization in pi-allylpalladium complexes[53], we anticipate that by tightening the angle P-Pd-P, the electron density of the pi-allyl complex will increase.

Table 4.3 shows the main results obtained from the achiral phosphines screening on the Pd(0)-catalyzed allylic etherification of *meso* diol **86**.

At first, it's important to note that by enhancing the Tolman cone angle, the steric hindrance of the ligand on the Pd center increases and when it becomes too high, like in entry 3 and 4, phosphine coordination to the metal is impossible and the reaction does not take place.
By comparing entry 6,7 and 5 with entry 1, the effect of electron donor (ED) and electron withdrawing (EWD) substituents may be shown.
It was observed that with electron-rich $P(p\text{-}MeOC_6H_4)_3$ and trifurylphosphine the reaction proceeds with higher yields if compared with PPh3 (91 % and 93% versus 83%), on the contrary with electron-poor $P(C_6F_5)_3$ a lower yield was reported if compared with PPh3 (22% versus 83%).

[50] Gaussian 09, Revision D.01, Gaussian, Inc., Wallingford CT, **2013**.
[51] (a) W. R. Wadt and P. J. Hay, *J. Chem. Phys.*, **1985**, *82*, 270
(b) W. R. Wadt and P. J. Hay, *J. Chem. Phys*., **1985**, *82,* 299
[52] W. R. Wadt and P. J. Hay, *J. Chem. Phys*., **1985**, *82,* 284
[53] M. Ogasawara, K. Takizawa, T. Hayashi*, Organometallics*, **2002**, *21*, 4853

Table 4.3: achiral phosphines screening



Entry	Ligand	Solvent	Yield (%)	dr AC:ST	Tolman cone angle (°)	P-Pd-P angle (°) (β angle)
1	PPh_3	PhMe	83	88:12	145	106.6
2	PBu_3	PhMe	65	65:35	130	109.2
3	PCy_3	PhMe	0	/	175	110.8
4	P(o-Tolyl)$_3$	PhMe	0	/	194	115.4
5	$P(C_6F_5)_3$	PhMe	22	89:11	/	111.6
6	P(p-$MeOC_6H_4$)$_3$	PhMe	91	91:9	145	111.8
7	P(furyl)$_3$	PhMe	93	91:9	133	107.5
8	Xantphos	PhMe	83	45:55	/	115
9	dppe	PhMe	92	97:3	/	87.1
10	dppp	PhMe	86	9:1	/	93
11	dppb	PhMe	86	9:1	/	100

Unless otherwise noted, reactions were carried out at room temperature, with $Pd_2(dba)_3CHCl_3$ adduct (3 mol%), phosphine ligand L (8 mol%), substrate **86** (0.2 mmol), solvent (2 ml, 0.1 M). D.r. ST:AC was determined by HPLC.

It's intriguing to observe how the stereo-electronic features can influence the diastereoselectivity of the reaction. Passing from $P(C_6F_5)_3$ to P(p-$MeOC_6H_4$)$_3$ and trifurylphosphine, the diastereomeric ratio AC:ST increases from 89:11 (entry 5) to 91:9 (entry 6 and 7).

Moreover, generally by tightening the plane angle P-Pd-P, the AC:ST ratio enhances. This effect can be observed by comparing the outcomes obtained with Xantphos (entry 8), PPh_3

(entry 1) and dppe (entry 9), and by looking at the series of bidenthate ligands dppe-dppp-dppb (entries 9,10,11).

The results reported above, can be explained by considering that, with electron rich phosphines and when the P-Pd-P angle is tighter, the electron density of the η^3-pi allyl complex increases(rif). The electron rich catalyst, reverberates its electronic features on the pi-allyl system that forms during the Tsuji-Trost reaction, making the cyclization step slower. Thus, equilibration between the two possible η^3 complexes (scheme 4.5) becomes more significant and the amount of AC product increases. In fact, previous computational studies[54] demonstrated that with all the ligands screened, the TS involved in the cyclization process leading to the AC core is more stable than the one leading to the ST core.

Table 4.4 summarizes the outcomes achieved from the achiral phosphine screening and highlights the role of plane P-Pd-P angle on the diastereoselectivity.

Going down the column, P-Pd-P angle decreases and an enhancement of the AC-THF amount was observed. When electron donor substituents are contained in the ligand scaffold, as for example in the case of $P(p\text{-}MeOC_6H_4)_3$ (table 4.5 entry 2), the effect due to the P-Pd-P angle tightening was amplified by the presence of the donor group and the quantity of AC derivative greatly rises.

Table 4.4: effect of P-Pd-P angle on diastereoselectivity

Entry	Ligand	Solvent	Yield (%)	dr (AC:ST)	P-Pd-P angle (°)
1	Xantphos	PhMe	83	45:55	115
2	$P(pMeOC_6H_4)_3$	PhMe	91	91:9	111.8
3	PBu_3	PhMe	65	65:35	109.2
4	PPh_3	PhMe	83	88:12	106.6
5	$P(furyl)_3$	PhMe	93	91:9	107.5
6	dppe	PhMe	92	97:3	87.1

Unless otherwise noted, reactions were carried out at room temperature, with $Pd_2(dba)_3CHCl_3$ adduct (3 mol%), phosphine ligand L (8 mol%), substrate **86** (0.2 mmol), solvent (2 ml, 0.1 M). D.r. ST:AC was determined by HPLC.

[54] Sbarbada D., PhD thesis, **2014**

The initial screening of achiral phosphines showed that, in order to enhance the yield and the diastereomeric ratio AC:ST of the THF products, electron density of the pi-allyl complex has to be increased. To do that, two strategies can be applied: insertion of electron donor group on the ligand scaffold and tightening of the P-Pd-P angle.

4.6 From achiral phosphines to chiral phosphines

4.6.1 Background

Previous screening of chiral ligands for the asymmetric allylic etherification of *meso* diol **86** revealed that *(S,S)*-L1 and *(R,R)*-L2, belonging to the series of the modular Trost ligands[55], are the best in order to obtain high diastereo and enantio selectivity (table 4.1).

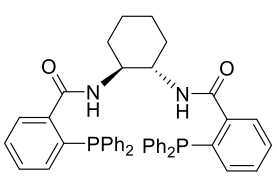
(S,S)-L1 ligand, which derives from the coupling reaction between enantiopure cycloesandiamine and diphenylphosphino benzoic acid, affords a pi-allyl complex which undergoes a fast cyclization process (compared to the η^3-η^1-η^3 equilibration) delivering the ST-THF ring with 80:20 *dr* and 96% *ee* (table 4.5, entry 2)

On the other hand, with the anden chiral scaffold of *(R,R)*-L2, cyclization becomes slower allowing the two diastereomeric pi-allyl-complexes to equilibrate. In this case the more abundant pi-allyl complex cyclizes on the opposite diastereotopic face respect to the *(S,S)*-L1 ligand, delivering the AC-THF core (*dr* ST:AC 17:83) with high enantioselectivity (*ee* AC: 92%) (table 4.5, entry 5)
A deep computational study confirmed this catalitic scenario[54].

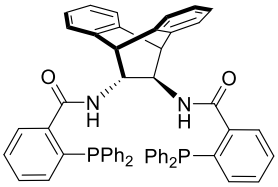
Also *(S,S)*-L5 was tested[40] (table 4.6 entry 4). It showed the same diastereoselectivity of (*R,R*)-L2, characterized by the preferential formation of AC core, but the enantioselectivity was definitely worse (*ee* AC 28%).

[55] Trost, B. M.; Van Vranken, D. L. *Angew. Chem. Int Ed.* **1992**, *31*, 228.

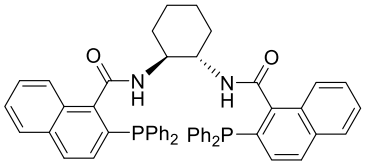
Table 4.5: Modular Trost ligands screening on *meso* diol **86**



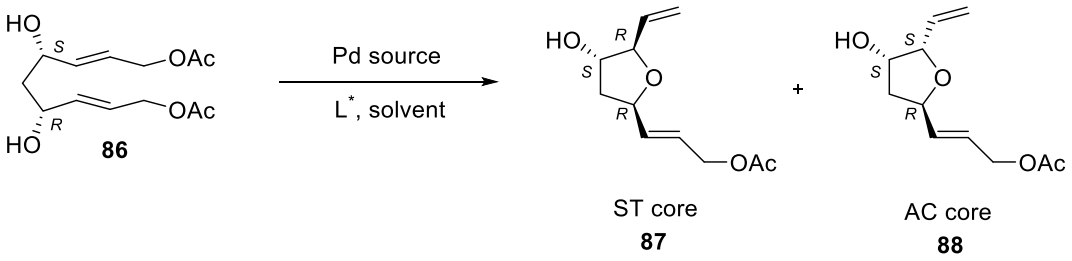
(S,S)-**L1**



(R,R)-**L2**



(S,S)-**L5**



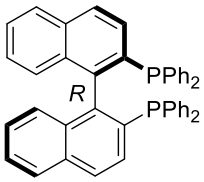
Entry	Ligand	Solvent	Yield (%)	dr ST:AC	ee ST (%)	ee AC (%)
1[a]	(*S,S*)-L1	THF	61	61:39	94	11
2	(*S,S*)-L1	DCM	86	80:20	96	3
3	(*R,R*)-L2	DCM	70	34:66	93	88
4	(*S,S*)-L5	DCM	82	37:63	89	28
5[b]	(*R,R*)-L2	DCM	65	17:83	95	92

Unless otherwise noted, reactions were carried out at room temperature, with $Pd_2(dba)_3CHCl_3$ adduct (3 mol%), chiral ligand L^* (8 mol%), substrate **86** (0.2 mmol), solvent (2 ml, 0.1 M), Cs_2CO_3 1.05 eqv. D.r. ST:AC was determined by HPLC. Enantiomeric excess was determined by chiral HPLC, on Chiralpak AS-H and AS-3 columns. (a) Cs_2CO_3 was not used, $Pd_2(dba)_3CHCl_3$ (8 mol%), ligand (31 mol%) were employed. (b) reaction was carried out at – 20°C

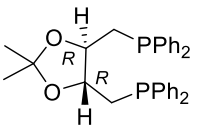
An interesting unresolved question about chiral ligands is that *(S,S)*-L1 and *(R,R)*-L2, despite the opposite absolute configurations, leads to the same enantiomer of the product.

Different types of chiral ligands, such as (*R*)-BINAP, (*R,R*)-DIOP, (*R*)-TUNEPHOS and (*R,S*)-L6 were used for the reaction, but none showed interesting outcomes (table 4.6). Some of them resulted in very low yield (entries 3 and 4), others did not show good enantioselectivity (entries 1 and 2).

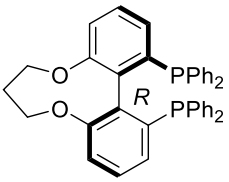
Table 4.6 Chiral ligand screening on *meso* diol **86**



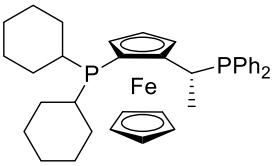
(*R*)-BINAP



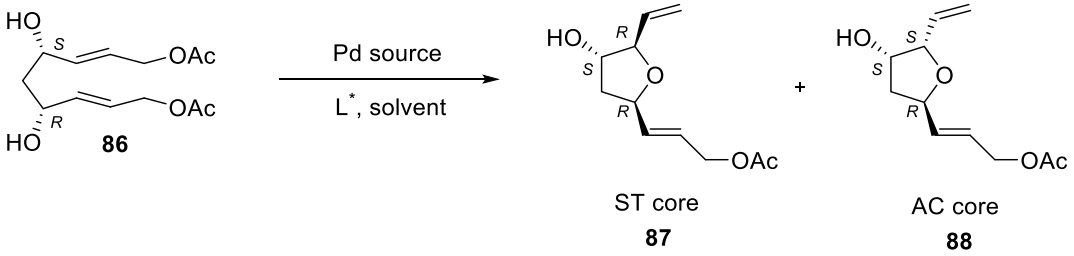
(*R,R*)-DIOP



(*R*)-TUNEPHOS



(*R,S*)-L6



Entry	Ligand	Solvent	Yield (%)	dr ST:AC	ee ST (%)	ee AC (%)
1	(*R*)-BINAP	DCM	58	10:90	92	0
2	(*R,R*)-DIOP	DCM	87	10:90	0	0
3	(*R*)-TUNEPHOS	DCM	10	9:91	87	8
4[a]	(*R,S*)-L6	DCM	17	11:89	5	40

Unless otherwise noted, reactions were carried out at room temperature, with $Pd_2(dba)_3CHCl_3$ adduct (3 mol%), chiral ligand L^* (8 mol%), substrate **86** (0.2 mmol), solvent (2 ml, 0.1 M), Cs_2CO_3 1.05 eqv. D.r. ST:AC was determined by HPLC. Enantiomeric excess was determined by chiral HPLC, on Chiralpak AS-H and AS-3 columns. a) the corresponding enantiomers of AC and ST were obtained.

Pd (0) sources commercially available are represented by $Pd(dba)_2$ (**C1**), $Pd_2(dba)_3CHCl_3$ (**C2**) and $(allyl\text{-}Pd\text{-}Cl)_2$ (**C3**). Despite literature data showed that **C1** and **C3** should be more reactive than **C2**, most of the reactions tested in this PhD work were performed with $Pd_2(dba)_3CHCl_3$ because of its stability to the air and moisture.

4.6.2 Work plan

Starting from the best outcomes obtained for the AC core synthesis (entry 5, table 4.5), it was decided to modify reaction conditions in order to optimize the stereoselectivity. In particular, the *dr* needs to be increased from the starting value of 17:83 (ST:AC) because we want to use the product as intermediate for total synthesis of 3-hydroxy-*trans*-2,5-disubstituted THF containing molecules.

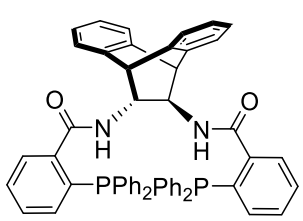
The strategies adopted include:

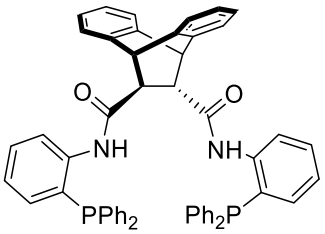
- Modification of chiral ligand structure
- Modification of leaving group on the substrate

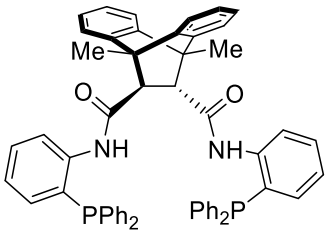
Achiral phosphines screening suggested us how to operate in order to increase AC:ST ratio. Now, we know that electron density of the catalyst needs to be enhanced and this can be done by introducing electron donor substituents on the chiral scaffold or by tightening the plane P-Pd-P angle (β angle).

At first, we decided to work on the latter parameter, finding new chiral catalysts that show a tighter P-Pd-P angle.

Previous experiments showed that *(R,R)*-L2 exhibits high enantioselectivity, so we thought that similar ligands *(S,S)*-L3 and *(R,R)*-L4 (scheme 4.10) could be interesting to be tested.







	(R,R)-**L2**	*(S,S)*-**L3**	*(R,R)*-**L4**
P-Pd-P angle (°)	**113**	**110**	**110**

Scheme 4.10. Structures of anden chiral ligands employed for the methodology

The choice of these ligands is due to the high similarity with the active anden ligand *(R,R)*-L2 and in particular because computational studies revealed that they possess a tighter P-Pd-P angle.

All computations studies for determination of P-Pd-P angle (bite angle in case of bidentate ligands) were performed with Gaussian '09 software package.[50] Optimizations of complexes were carried out in gas-phase using the DFT-B3LYP functional. The P, C, H and O atoms were described with 6-31+G(d,p) basis set, and Pd atom with LANL2DZ[51,52] relativistic effective core potential (ECP) basis set implemented in Gaussian 09 software suite. Vibrational frequencies were computed at the same level of theory to verify that the optimized structures were minima.

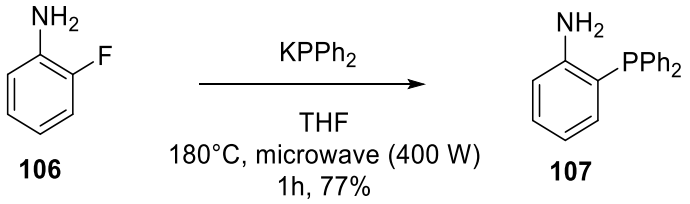
(R,R)-L2 shows a 113° bite angle as *(S,S)*-L3 and *(R,R)*-L4 show a 110° angle.

4.6.3 Synthesis of *(S,S)*-L3

From a structural point of view, *(S,S)*-L3 is very similar to *(R,R)*-L2, the only difference lies in the inversion of the amide function that causes the variation of the bite angle when it binds the metal center.

The approach followed for the synthesis of *(S,S)*-L3 is based on the disconnection of the amide bond that leads to the corresponding chiral *(S,S)*-dicarboxylic acid and phosphine **107**.

Phosphine **107**, was synthetized following the procedure reported by Seipel and coworkers[56], that employs a microwave assisted nucleophilic aromatic substitution on 2-fluoro-aniline **106** with potassium diphosphinide.



106 **107**

Scheme 4.11

To obtain the chiral dicarboxylic acid, at first, the approach proposed by Thunberg and Allenmark was run[57].

The strategy is based on a diastereoselective Diels-Alder reaction between fumarate ester **111** and anthracene.

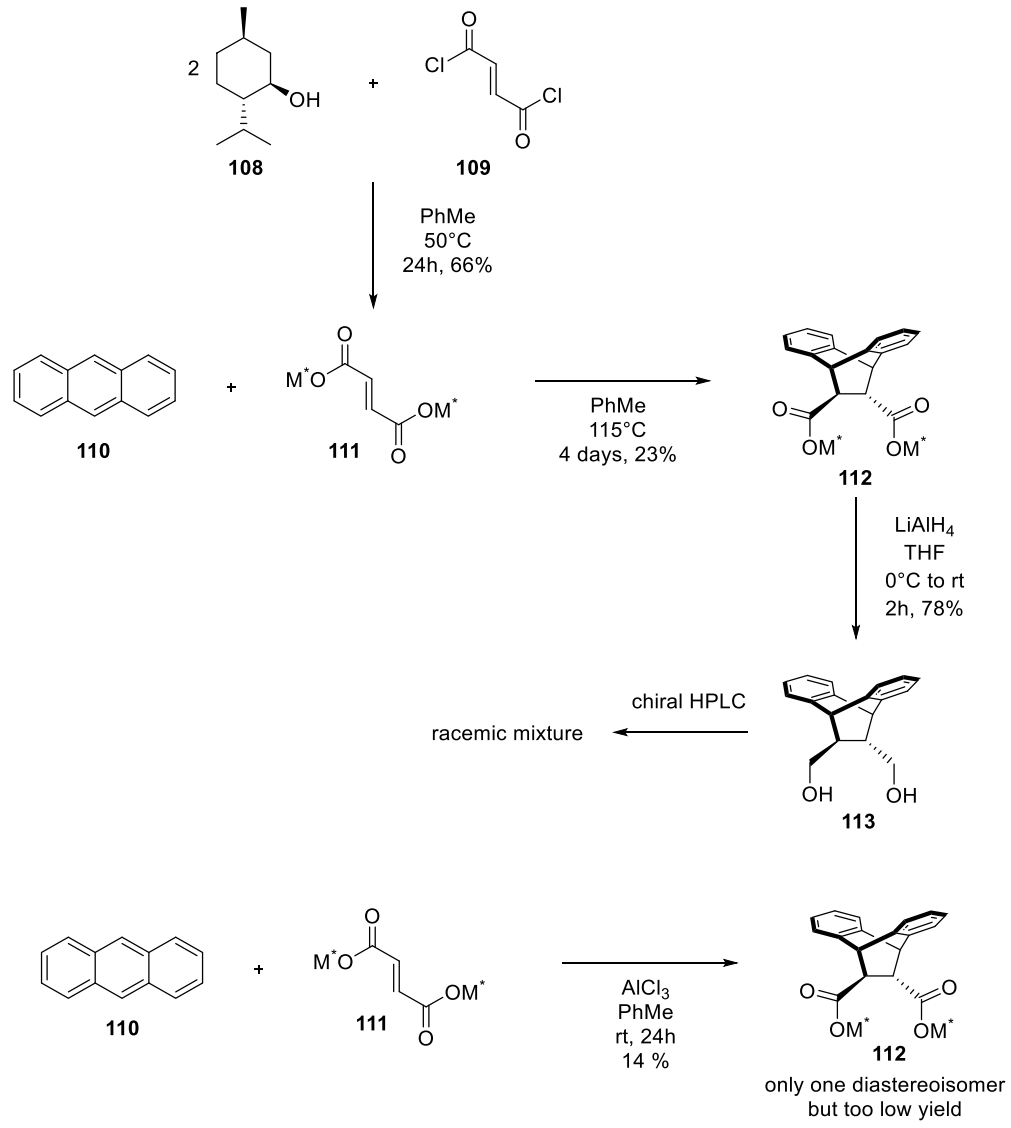
[56]K. R. Seipel, Z. H. Platt, M. Nguyen and A. W. Holland, *JOC*, **2008** , *73*, 4291.
[57] L. Thunberg, S. Allenmark, *Tet. Asymm.*, **2003**, *14,* 241.

(-)-Menthol **108** was used as chiral auxiliary, because it would lead to the *(S,S)* - enantiomer of the diacid with good yields.

Chiral fumarate **111** was obtained from reaction between fumaryl chloride **109** and (-)-menthol **108.**

Subsequently, it has been used for the Diels-Alder reaction.

Scheme 4.12 shows the results achieved. When reaction is performed in toluene at 115°C for 4 days, 23% yield is obtained and a 50:50 mixture of diastereoisomers has formed. In fact, after reduction of the ester functions with $LiAlH_4$, the corresponding diol **113** was used to measure enantiomeric excess by chiral hplc and it resulted in a racemic mixture.



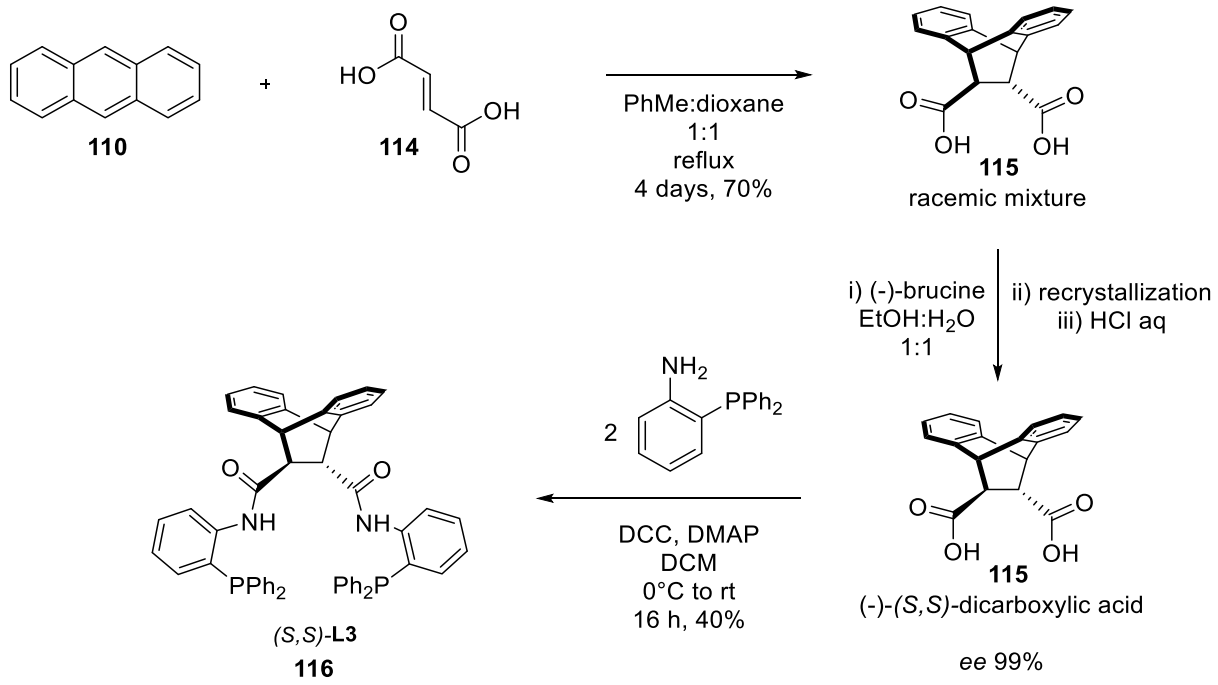
Scheme 4.12: first attempt for (*S,S*)-L3 synthesis

But when the Diels-Alder reaction was performed by using stoichiometric $AlCl_3$ (scheme 4.12), only one of the two possible diastereoisomers has formed. Unfortunately, the total yield of the reaction was too low, around 14%, thus the strategy was changed.

The last approach is based on classical resolution of the racemic diacid **115**[58], obtained from Diels-Alder reaction between anthracene **110** and fumaric acid **114** (scheme 4.13).

(-) Brucine was used as resolving agent and *(S,S)*-dicarboxylic acid **115** was achieved with 99% *ee*.

Finally, the enantiopure diacid **115** was coupled with the amino-phosphine **107**.



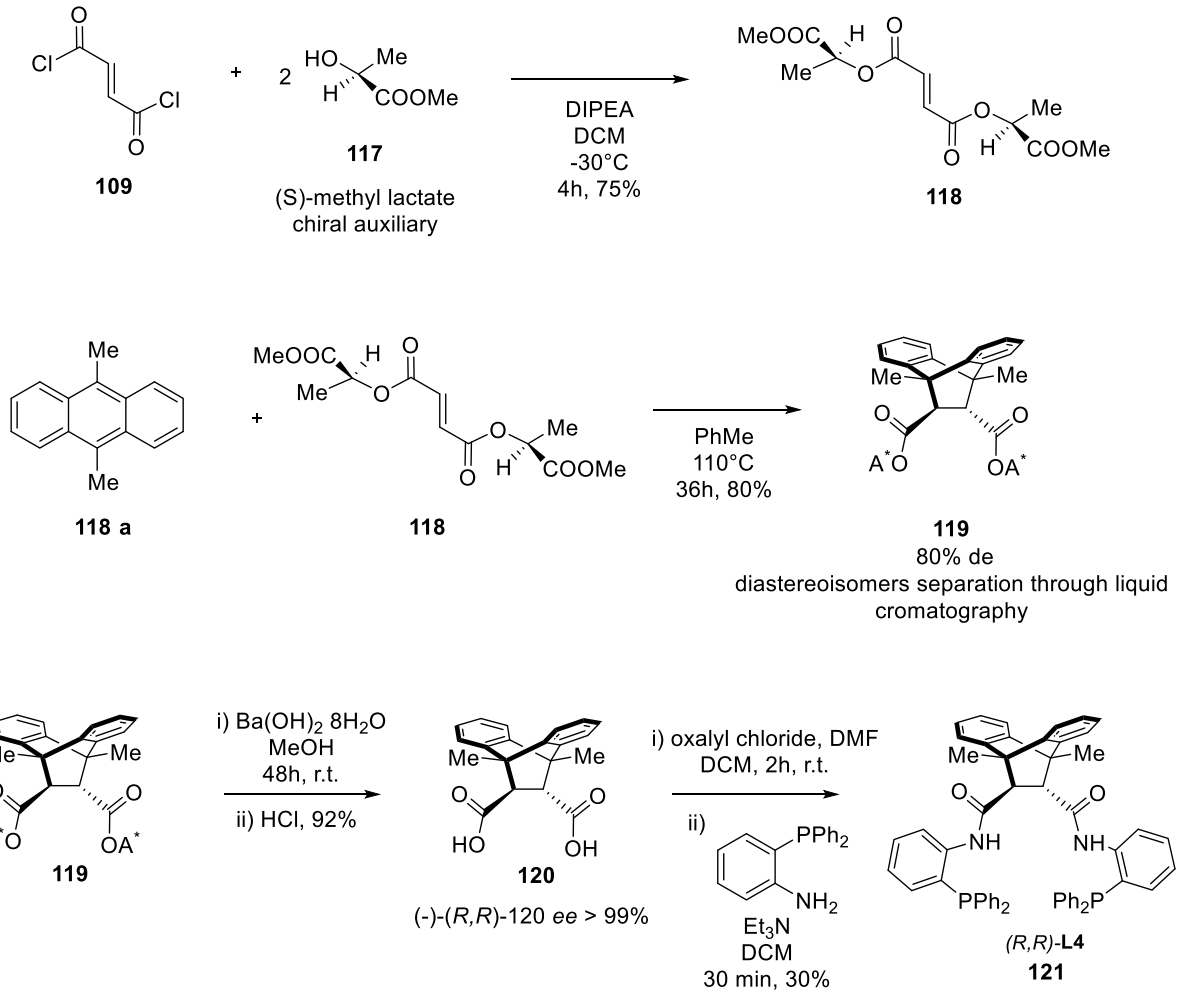
Scheme 4.13: synthesis of (*S,S*)-L3

[58] M.J. Brienne, J. Jacques, *Bull. Soc. Chim. Fr.*, **1973**, *1*, 190.

4.6.4 Synthesis of *(R,R)*-L4

(R,R)-L4 ligand is the dimethyl homologue of *(S,S)*-L3 and as it can be seen in scheme 4.10, they possess the same bite angle (110°).

To the best of our knowledge, there are no reported classical resolution protocols with chiral agents for the dicarboxylic acid precursor of *(R,R)*-L4.



Scheme 4.14: *(R,R)*-L4 synthesis

For this reason, we decided to follow another approach, based on a stereoselective Diels Alder reaction with chiral auxiliaries.

As reported for *(S,S)*-L3 synthesis, (-)menthol **108** does not work, because it leads to very low yields.

Thus, we employed the procedure suggested by Zacconi[59] for a similar compound, that involves (*S*)-methyl lactate **117** as chiral auxiliary (scheme 4.14).

Chiral fumarate ester **118**, was prepared starting from fumaryl chloride **109** and (*S*)-methyl lactate **117**.

Subsequently, Diels Alder reaction between the chiral dienophile **118** and 9,10-dimethylanthracene **118 a** led to the cycloadduct **119** with 80% *dr* (determined by NMR). After chromatographic separation, the main diasteroisomer was hydrolyzed with $Ba(OH)_2$ $8H_2O$ and resulted in (*R,R*)-diacid **120** with 99% *ee*.

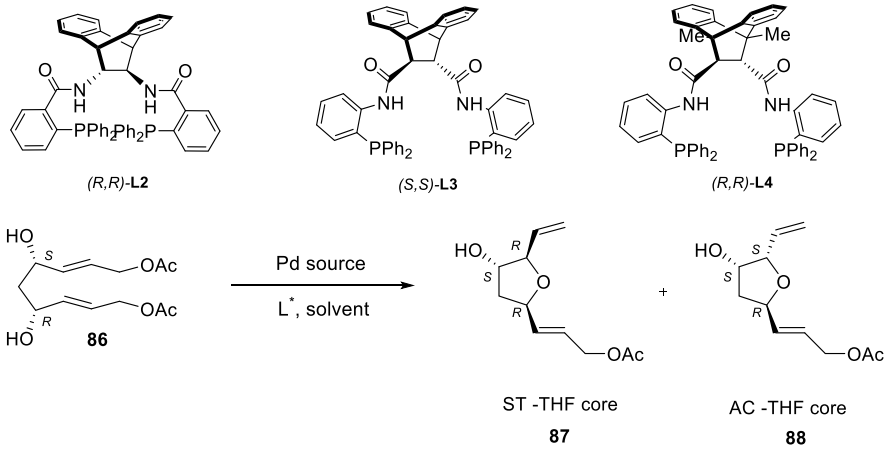
Last step is represented by the coupling of the enantiopure diacid **120** with the amino-phosphine **107**.

[59] Zacconi, F.C., Koll, L.C., Podestà, J.C., *Tet. Asymm.*, **2011**, *22*, 40

4.6.5 Chiral ligand tests on *meso* diol **86**

Once synthetized, *(S,S)*-L3 and *(R,R)*-L4 were tested on the cyclization of *meso* diol **86**.

Table 4.8: chiral ligands tests on *meso* diol **86**



Entry	Ligand	Solvent	Yield (%)	dr AC:ST (88:87)	*ee* ST (%)	*ee* AC (%)	P-Pd-P angle (°)
1[a]	(R,R)-L2	DCM	65	83:17	95	92	113
2	(R,R)-L2	PhMe	74	70:30	98	95	113
3	(S,S)-L3	PhMe	86	93:7	39	64	110
4[a]	(S,S)-L3	PhMe	80	95:5	99	87	110
5[b]	(S,S)-L3	PhMe	85	95:5	98	84	110
6[b]	(S,S)-L3	DCM	63	94:6	99	80	110
7	(R,R)-L4	PhMe	75	75:25	15	40	110

Unless otherwise noted, reactions were carried out at room temperature, with $Pd_2(dba)_3CHCl_3$ adduct (3 mol%), chiral ligand L* (8 mol%), substrate **86** (0.2 mmol), solvent (2 ml, 0.1 M). D.r. ST:AC was determined by HPLC. Enantiomeric excess was determined by chiral HPLC, on Chiralpak AS-H and AS-3 columns. (a) reaction was carried out at -30°C, (b) reaction was carried out at -30°C with 1.1 eqv of $BaCO_3$.

Unless otherwise noted, reactions were carried out with $Pd_2(dba)_3CHCl_3$ adduct (3 mol%), chiral ligand (8 mol%), solvent (0.1M). Diastereomeric ratio was determined by HPLC, enantiomeric excess was determined by chiral HPLC on Chiralpak AS-H columns.

By comparing entries 2 and 3 it is possible to see that when *(S,S)*-L3 is used instead of *(R,R)*-L2 in PhMe at rt, diastereomeric ratio AC:ST goes from 70:30 to 93:7. This confirms our idea concerning the importance of the P-Pd-P angle on the reaction diastereoselectivity. *(S,S)*-L3 has a tighter bite angle than *(R,R)*-L2 and this is reflected on a higher electron densisty of the corresponding pi-allyl intermediate system, resulting in a higher amount of AC type core.
Enantioselectivity is not high (*ee* AC 64%), if compared with the one achieved with *(R,R)*-L2 in the same conditions (*ee* AC 95%).

For this reason, temperature was decreased to -30°C, which is the lowest temperature at which the complex maintains its activity. In these conditions reaction rate decreases and to complete the process 24 hours are necessary, while at room temperature reaction lasts 3 hours.
Entry 4 shows that at -30°C overall stereoselectivity is improved, diastereomeric ratio AC:ST goes from 93:7 to 95:5 and AC enantiomeric excess rises from 64% to 87%.
Addition of a base ($BaCO_3$), increases the catalyst turnover number and even if it does not change the stereoselectivity, a slight improvement of the yield is achieved, from 80 to 85% (entry 5).
When reaction is performed in DCM (entry 6), the yield decreases and also the enantioselectivity is negatively affected. By comparing entry 5 and entry 6 we can say that PhMe is the best reaction solvent when *(S,S)*-L3 is employed.
It's intriguing that the enantiomeric excess of the minority product ST is very high in all cases (entries 4,5 and 6).
When *(R,R)*-L4 is employed with the same reaction conditions adopted for *(S,S)*-L3 in entry 3, the diastereomeric ratio AC:ST achieved is around 75:25, definitely worse than the one obtained with *(S,S)*-L3 (entry 3) and only slightly better than the one reached with *(R,R)*-L2 (entry 2). AC enantiomeric excess is 40 %.
This outcome suggests that, despite *(R,R)*-L4 has the same bite angle of *(S,S)*-L3, it does not possess the same ability to increase the diastereomeric ratio of the products. At the moment,

we can not explain this phenomenon, especially because of the high structural similarity that exists between the two chiral ligands.
Another curious fact to which we have not so far been able to explain is why by changing the absolute configuration of the stereocenters, from *(R,R)*-L2 to *(S,S)*-L3 the absolute configuration of the products does not change. In both cases, the same enantiomers of substituted THF cores were obtained.

4.6.6 Tests on different *meso* diol systems

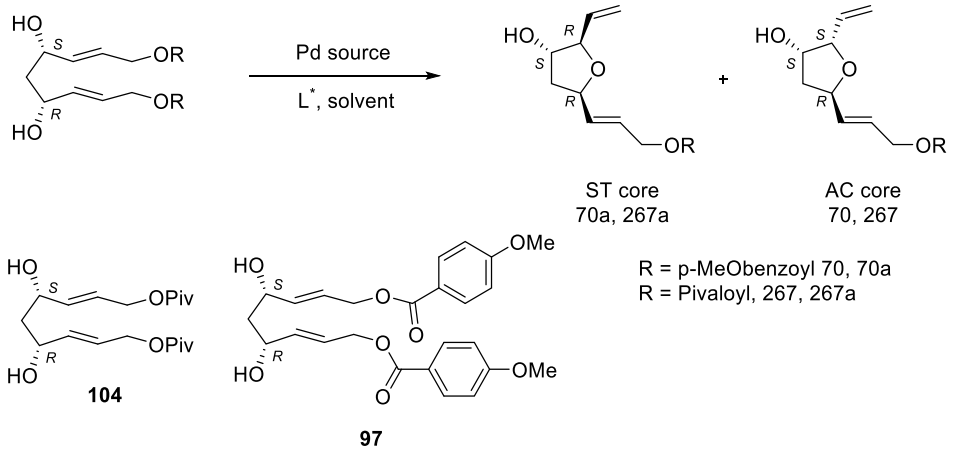
In order to further improve the good results achieved within the cyclization of *meso* diol **86** with *(S,S)*-L3, other structural variations were introduced in the system.
In section 4.2, it was explained that when electron density of the pi-allyl intermediate increases, the cyclization step becomes slower and the equilibration process between η^3 complexes, that interchanges the diastereotopic faces, becomes more significant. As a consequence of that, the amount of AC product rises.
It is for these reasons that *(S,S)*-L3 and *(R,R)*-L4 were synthetized.
Subsequently, we noticed that cyclization rate could be reduced also by changing substrate's structural features and not only catalyst's ones.
In 2012, Gandon and Roulland[60] demonstrated, with computational analysis support, that the leaving group of the substrate, plays a key role in Pd (0)-catalyzed cyclization toward 3-hydroxy-2,5-disubstituted THF rings.
In particular they observed that, the carboxylate anion of the leaving group, coordinates both the hydroxyl group by hydrogen bonding and the cationic pi-allyl system by electrostatic interaction. In this way it drives the cyclization step.
For this reason, we thought that by changing the stereoelectronic features of the leaving group, it could be possible to modulate these interactions. Probably, if steric hindrance of the leaving group will be increased, coordination becomes more difficult and reaction would slow down.
If cyclization rate decreases, the intermediate pi-allyl system will have more time to equilibrate, as we told above, and the amount of AC -THF core will rise.

[60] M. Arthuis, R. Beaud, V. Gandon and E. Roulland, *Angew. Chem. Int. Ed.* **2012**, 51, 10510.

Pivalate and p-methoxybenzoate are the leaving groups that were tested. Both show a higher steric hindrance than the acetate.

When cyclization was performed on *meso* diol **104**, by using *(R,R)*-L2 (entry 1, table 4.9) with the same conditions adopted for *meso* diol **86** (entry 2 table 4.8), the overall stereoselectivity did not change significantly, diastereomeric ratio AC:ST was around 70:30 and AC *ee* was 94%.

Table 4.9: Chiral ligands tests on different *meso* diol systems



Entry	Substrate	Ligand	Solvent	Yield (%)	dr AC:ST	*ee* ST (%)	*ee* AC (%)	P-Pd-P angle (°)
1	104	(R,R)-L2	PhMe	70	69:31	91	94	113
2	104	(S,S)-L3	PhMe	64	>99:1	99	77	110
3[a]	97	(S,S)-L3	PhMe	70	>99:1	0	92	110
4	97	(R,R)-L4	PhMe	73	78:22	0	45	110

Unless otherwise noted, reactions were carried out at room temperature, with $Pd_2(dba)_3CHCl_3$ adduct (3 mol%), chiral ligand L* (8 mol%), substrate **97-104** (0.2 mmol), solvent (2 ml, 0.1 M). D.r. ST:AC was determined by HPLC. Enantiomeric excess was determined by chiral HPLC, on Chiralpak AS-H and AS-3 columns. (a) reaction was carried out at -30°C with 1.1 eqv of $BaCO_3$.

But, when *(S,S)*-L3 was tested (entry 2, table 4.9), surprisingly AC:ST ratio rose to >99:1, and AC enantiomeric excess settled around 77%.
This result, proves what has been speculated about the effect of the leaving group.
Moving from bis pivalate **104** to bis p-methoxybenzoate **97** (entry 3, table 4.9) we observed that diastereomeric ratio reached the highest value ever observed, with a complete diastereoselectivity in AC core synthesis (*dr* AC:ST >99:1).
(R,R)-L4 was tested on *meso* diol **97** (entry 4, table 4.9), but despite diastereoselectivity and enantioselectivity were slightly enhanced in comparison with the result achieved when the same ligand was tested on *meso* diacetate **86** (entry 7, table 4.8), the overall stereochemical outcomes remained poor (*dr* AC:ST 78:22, *ee* AC 45%).
With >99:1 *dr* AC:ST and 92% *ee* AC, entry 3 represents the best way to obtain 3-hydroxy-*trans*-2,5-disubstituted tetrahydrofuran rings with high diastereo and enantioselectivity.

4.6.7 Conclusion

The improvement of the methodology concerning Pd(0)-catalyzed asymmetric allylic etherification of *meso* diol compounds (**86**, **97**, **104**), was planned in order to find an efficient stereoselective strategy to synthetize 3-hydroxy-*trans*-2,5-disubstituted tethraydrofuran cores, that could be involved as key intermediates for total synthesis of several THF containing natural molecules. In particular, we employed the best result for the synthesis of the marine oxylipid **46**.
By considering reaction's mechanism and starting from the results of the previous work[40], it was speculated to modify those parameters that could increase the diastereoselectivity and enantioselectivity towards the desired stereoisomer (AC core).
At first, a screening of achiral ligands was done in order to detect which parameters affect the yield and the diastereoselectivity. We supposed that by increasing the electron density of the pi-allyl intermediate, the amount of *trans*-2,5-disubstituted product (AC core) would rise as a consequence of the enhancement of the equilibration process that interconverts the two possible η^3-pi allyl complexes.

To achieve this purpose, two approaches could be run: the insertion of electron donor substituents on the ligand scaffold and tightening the plane P-Pd-P angle. We focused our attention on the latter aspect.

After that, the considerations concernings the achiral ligands were moved to the chiral ligands, thus *(S,S)*-L3 and *(S,S)*-L4 were synthetized and tested on *meso* diacetate **86**.

We found that *(S,S)*-L3 works better than *(R,R)*-L4 providing a good enhancement of the diastereoselectivity.

Another structural feature that can affect AC:ST distributions is the steric hindrance of the leaving group.

What we discovered is that hindered leaving groups slow down the cyclization step, causing an improvement of the diastereoselectivity toward the AC isomer.

The best outcome was achieved by combining catalyst's and substrate's modifications.

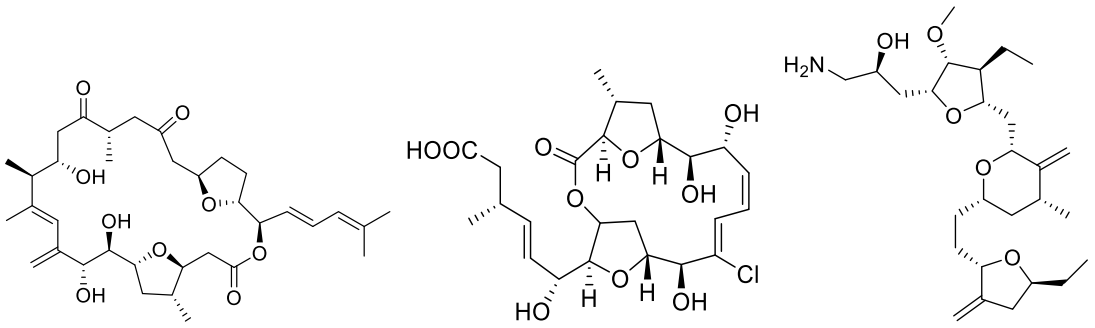
With *(S,S)*-L3 and p-methoxybenzoate as leaving group, AC core was formed with complete diastereoselectivity and 92% *ee*.

Future perspectives will be oriented towards modification of the substitution pattern of the ligands, for instance by introducing electron donor and electron withdrawing groups and of course towards studies aimed to detect which factors can affect the enantioselectivity.

CHAPTER 5: Toward tetrasubstituted THF rings

5.1 Introduction

Among the highly cytotoxic marine metabolites reported in literature[7], there are molecules that contain tetrahydrofuran systems bearing carbon substituents, such as C-C double bonds or methyl groups, on the ring. For example, Amphydinolide F and Chagosensine are characterized by the presence of a methyl tetrahydrofuran ring while Eribulin contains a carbon-carbon double bond on the C_3 position of the THF ring (figure 5.1).



Amphidinolide F Chagosensine Fragment of Eribulin

Figure 5.1.

For this reason, it seems be interesting to find a strategy that allows to obtain such substituted tetrahydrofuran rings.

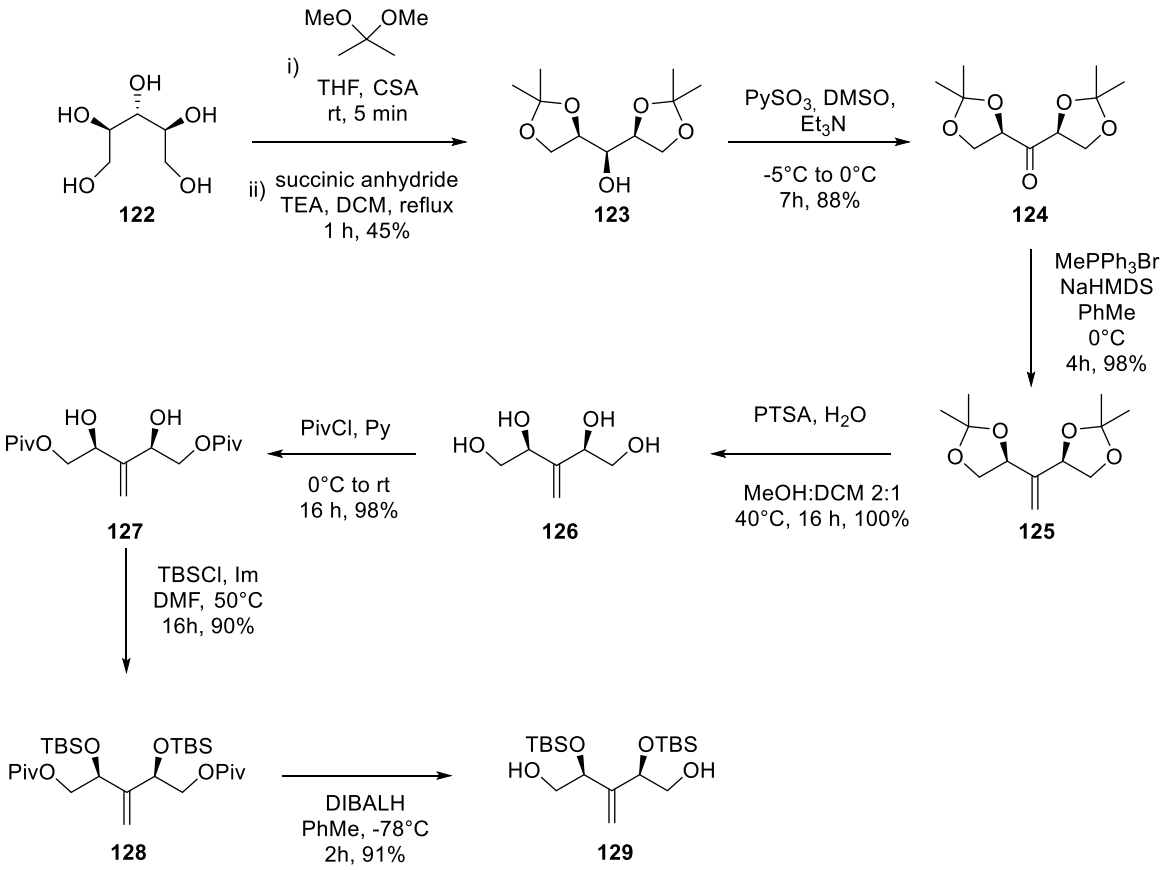
Following the approach developed in this PhD thesis, based on the Pd(0)-catalyzed asymmetric allylic etherification for the THF ring building, two choices are available for substituent insertion: the carbon substituent can be inserted on the THF system after the cyclization step, for instance, by substitution of the hydroxyl group on the C_3 position, otherwise it would be possible to functionalize the starting *meso* diol and then cyclize it.

5.2 Synthesis of methylidene *meso* diol **141**

At first, it has been decided to synthetize a *meso* diol system with a carbon-carbon double bond on the central carbon. This compound can be possibly converted into the methyl derivative by hydrogenation, so it acts as common precursor for methyl and exocyclic methylene THF rings.

Scheme 5.1 reports the first approach towards the synthesis of methylidene *meso* diol **141**.

Xylitol **122**, has been used as a readily available starting material because it contains two *syn*-hydroxyl functionalities on C_2 and C_4 positions, like in the final product.

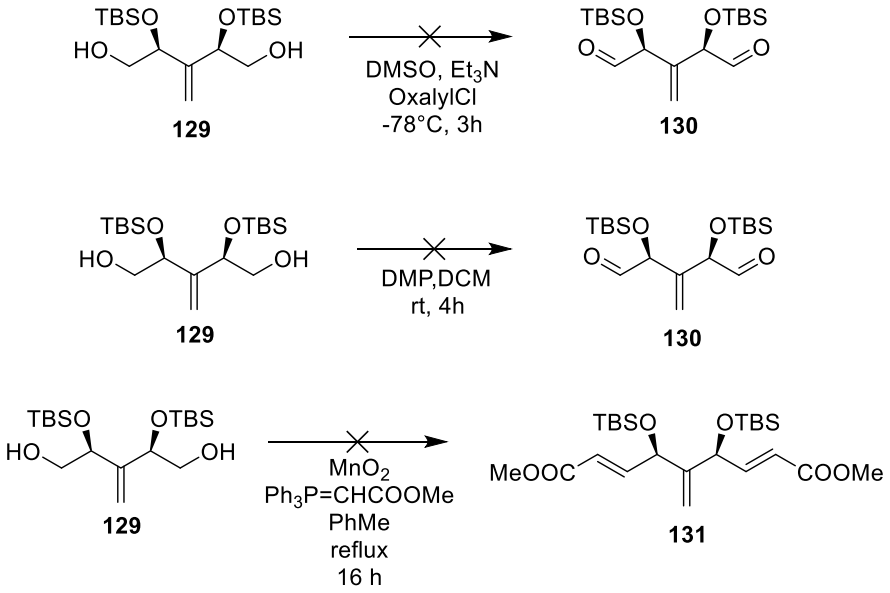


Scheme 5.1: first synthetic approach to *meso* diol **141**

At first, xylitol **122** has been protected as bis-isopropyliden acetal **123**, in order to single out central OH group. Subsequently oxidation of the alcohol **123** to ketone **124** and Wittig reaction led to intermediate **125**. In this way carbon-carbon double bond has been included in the *meso* compound.

Tetraol **126** can be prepared in good yield by Bronsted acid catalyzed deprotection of the acetal **125**, then primary hydroxyl functions have been protected as pivaloate esters **127** and secondary hydroxyl functions as TBS ethers **128**.

Reduction with DIBAL-H gave diol **129** with free primary alcohols.



Scheme 5.2: unproductive oxidation test of diol **129**

At this point, the synthetic protocol envisages the oxidation of the intermediate **129** to dialdehyde **130** and the subsequent Wittig reaction necessary to elongate the side chains.

Scheme 5.2 shows the attempts performed for the oxidation. Swern reaction, Dess Martin periodinane and MnO_2 were employed but none of these approaches worked, thus a change of strategy was needed.

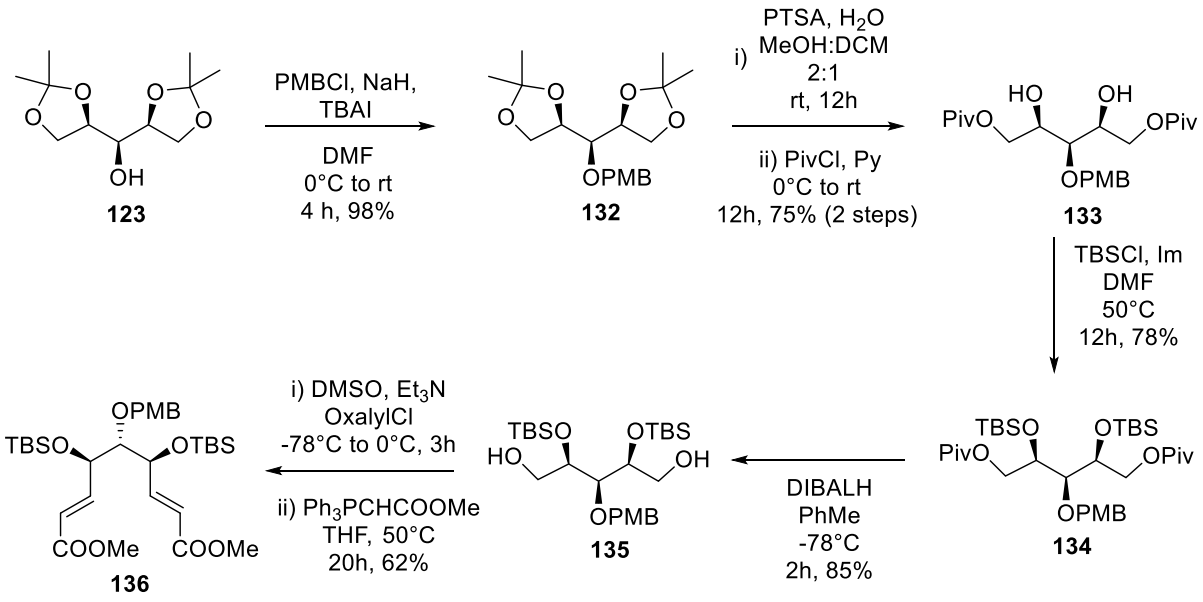
The main issue concerning the oxidation of **129**, seemed to be related to the presence of the central double bond, it is for this reason that in the second synthetic plan the oxidation step was done before the Wittig reaction. Schemes 5.3 and 5.4 show the entire new strategy.

Hydroxyl function at C_3 of bis-isopropylidene acetal **123** has been converted into the PMB ether **132**, then acid catalyzed deprotection led to the corresponding tetraol. Selective protection of secondary alcohols has been done employing the same reactions sequence of the first synthetic route that includes pivaloate functionalization, silylation and selective removal of pivaloate esters.

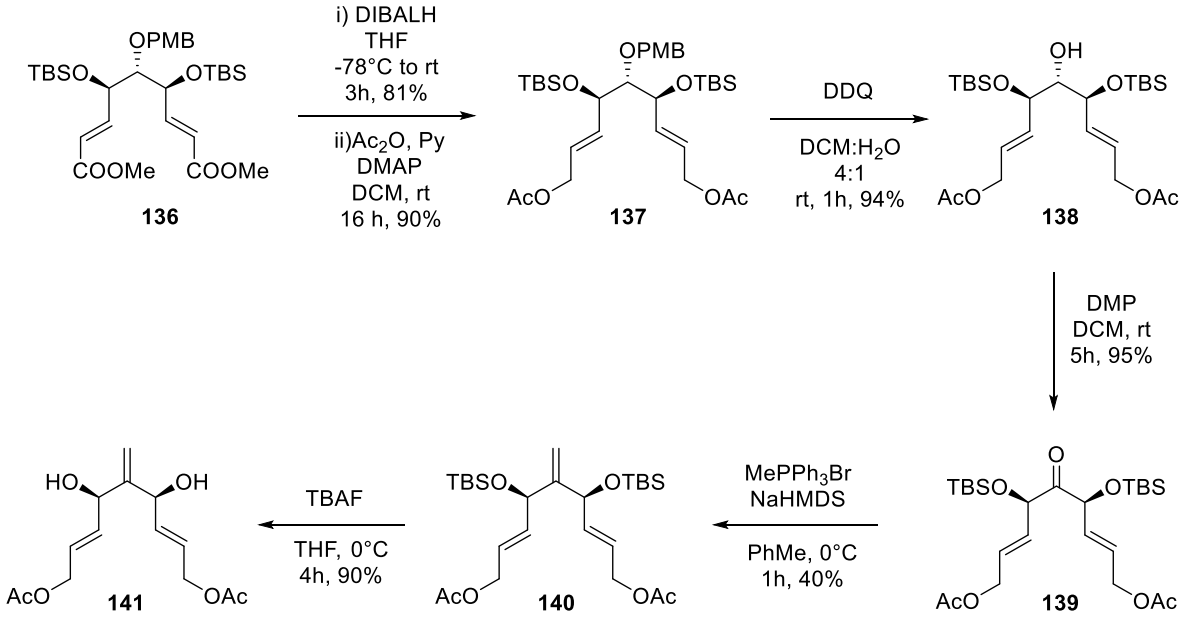
The intermediate **136** has been achieved through Swern oxidation and Wittig reaction. Reduction of methyl esters and subsequently acetylation gave the intermediate **137** (scheme 5.4).

At this point, central hydroxyl function has selectively removed through oxidative cleavage. Oxydation of the alcohol **138** led to ketone **139**, that was converted into olefin **140** by Wittig reaction.

Last step is represented by deprotection of secondary hydroxyl functions and produces the methylidene *meso* diol **141**.



Scheme 5.3: synthesis of *meso* diol **141**, part 1



Scheme 5.4: synthesis of *meso* diol **141**: part 2

5.3 Cyclization of methylidene *meso* diol **141**

The synthetic strategy worked fine but with very low overall yield due to the high number of reactions involved, in particular it contains several protection and deprotection steps.

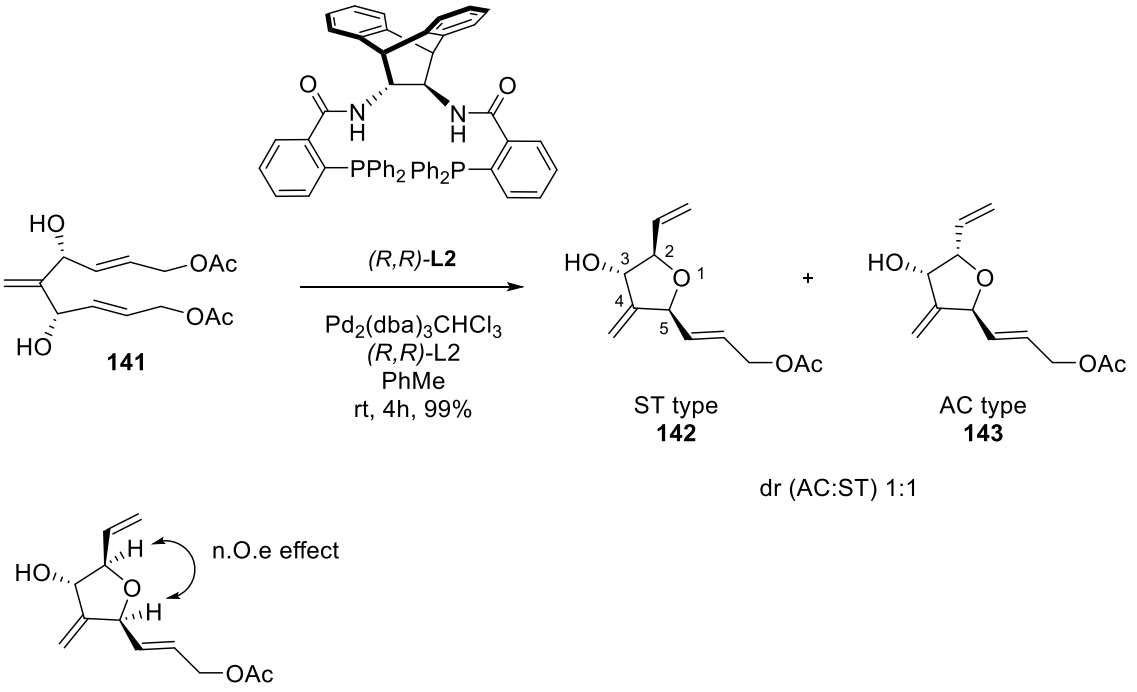
Of course, one of the future perspectives is to find a new synthetic plan easier and less challenging than the first one, aimed to obtain larger amounts of *meso* diol **141**.

With the first synthetic route, at the end of the synthesis, only 10 mg of compound **141** were available for the subsequent cyclization tests. This quantity was enough just to run one experiment, so it has been decided to test the commercially available chiral ligand (*R,R)*-L2, with the same reaction conditions employed for the classic *meso* diol **86** (see chapter 4).

The purpose of this first cyclization attempt was just to observe if the methodology developed for the Pd(0) catalyzed asymmetric allylic etherification of *meso* diol **86** could be extended on a compound with an extra carbon-carbon double bond on the central position.

Scheme 5.5 shows the reaction conditions employed.

It is very interesting to note that the extra double bond on the *meso* diol system **141** (that generates a bis allylic alcohol) does not affect the cyclization process. Indeed, the corresponding tethrahydrofuran containing product was isolated. It shows an exocyclic carbon-carbon double bond on the C_4 position and a hydroxyl function on the C_3 position, the side chains are obviously represented by a vinyl and an allyl acetate groups.



Scheme 5.5: cyclization of *meso* diol **141**

By considering the mechanism of the Tsuji-Trost reaction, also in this case, two different diastereoisomeric tetrahydrofuran rings can be obtained. One with the *anti* relative stereochemistry of the 2,5 chains (AC type ring **143**) and one with the *syn* relative stereochemistry of the same chains (ST type ring **142**).

The two diastereoisomers were separated by liquid chromatography and NOESY experiments allowed to assign the relative stereochemistry of the side chains. Diastereomeric ratio was determined by chromatographic separation of the isomers.

As can be seen in scheme 5.5, stereoselectivity is not very high, AC type and ST type rings were formed with approximately 1:1 ratio.

Although only one test was performed, the results obtained, that show the possibility of cyclize *meso* diol **141**, pave the way to a future methodological study which will involve the screening of different ligands and different leaving groups on the substrate. For example, in chapter 4, it was reported that electron donor leaving groups (such as p-methoxybenzoate) and ligands with tighter P-Pd-P angle increase the diastereoselectivity toward AC type ring.

Moreover, both the diastereoisomers resulting from the reaction are very useful synthetic intermediates, because they can be easily functionalized on all the ring's positions.

5.4 Towards methyl substituted *meso* diol systems

Once synthesized and tested *meso* diol **141**, our attention has shifted to *meso* diol systems bearing a methyl substituent on the central carbon (figure 5.2). In fact, we have seen earlier that many marine metabolites contain methyl substituted tetrahydrofuran cores (figure 5.1)

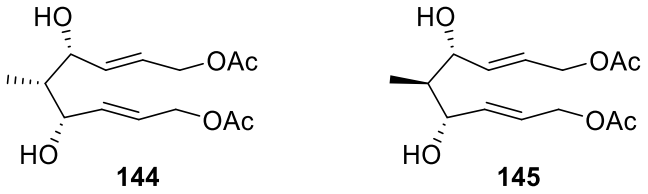


Figure 5.2: *meso* diol systems bearing a methyl substituent on central carbon

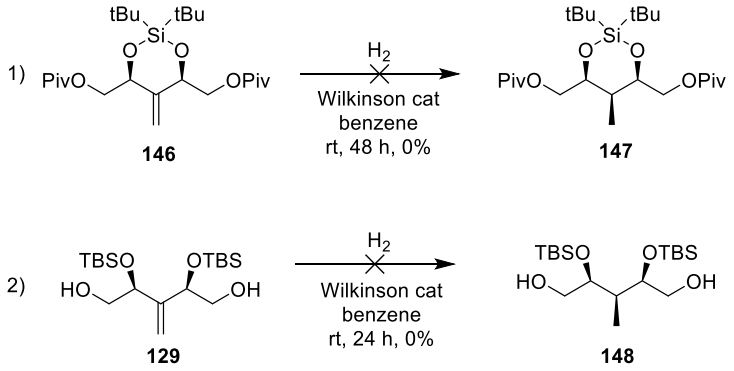
The idea of including the methyl group on the core already cyclized through substitution of the hydroxyl group (such as Mitsunobu reaction) has not proved effective. The few attempts have led to the elimination of the alcohol group with formation of the double bond within the ring.

For this reason, it was decided to try to synthetize *meso* diol compounds bearing a methyl group and subsequently cyclize them.

5.4.1 Hydrogenation approach

It's important to note that the methyl group may be both *syn* and *anti* to the hydroxyls. At first we focused on the one with *syn* geometry because, due to sterochemical features of starting material, it could be obtained through hydrogenation of the carbon-carbon double bond contained in some intermediates of the previous synthesis (see scheme 5.1).

Scheme 5.6 shows the results achieved for the hydrogenation of two intermediates derived from the synthesis of *meso* diol **141**. The reaction was firstly carried out on those intermediates in which the secondary hydroxyl functions are protected with bulky silyl substituents, with the hope to improve the *syn* steroselectivity. However, with these silyl protections and these reaction conditions, hydrogenation did not take place at all (scheme 5.6).



Scheme 5.6: hydrogenation tests part 1

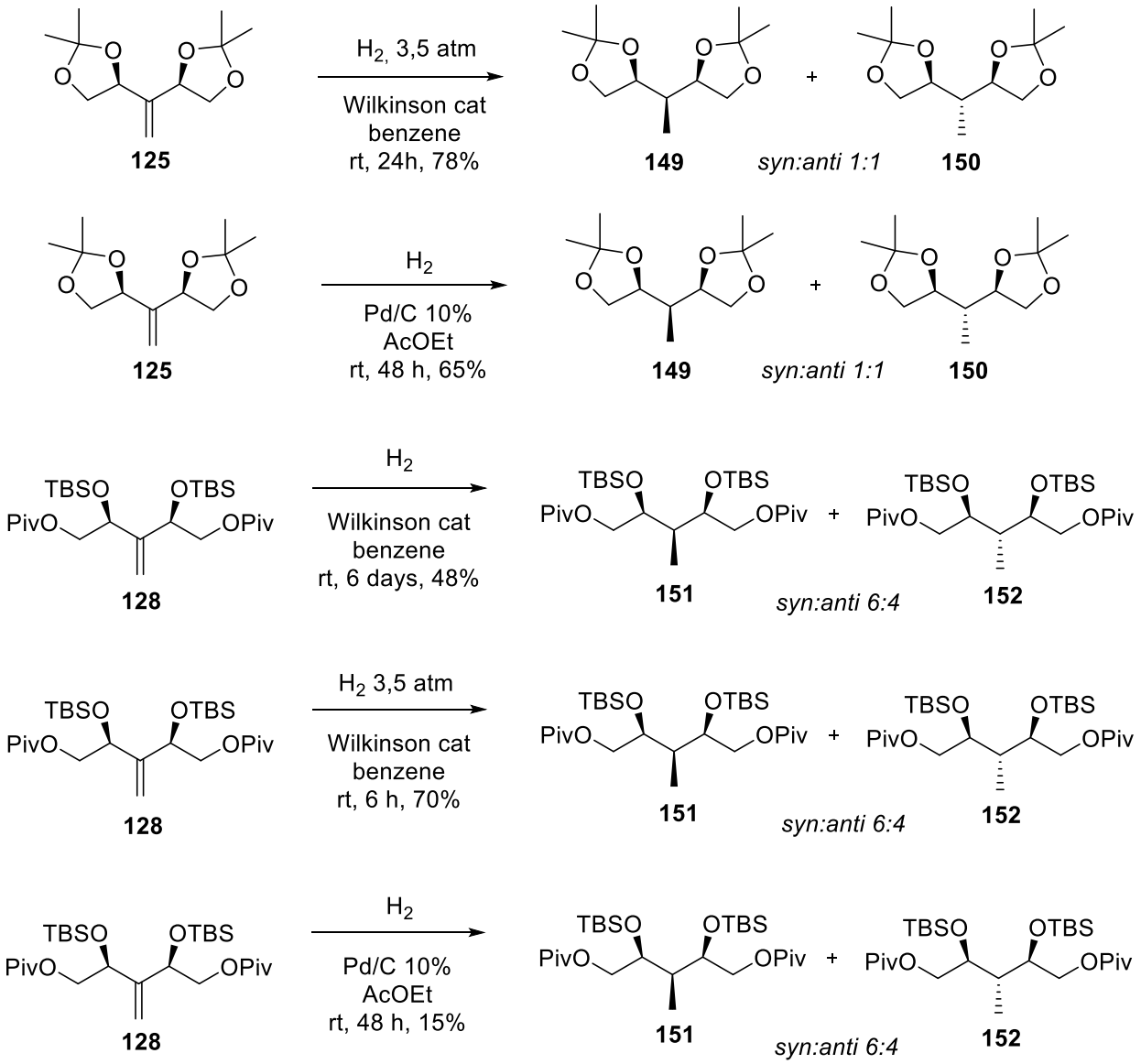
For these reasons, hydrogenation was performed on different intermediates and reaction conditions have been modified. In particular, both hydrogen pressure and reaction time were increased.

When compound **125** was tested, due to reduced sterical hindrance, the reaction worked but without any type of stereocontrol. 50:50 *syn:anti* ratio was obtained both with homogeneous and heterogeneous catalysis.

Surprisingly, the reaction carried out over compound **128**, that presents bulky protecting groups on primary hydroxyl groups and free secondary hydroxyl groups, gave an increased *syn:anti* ratio, 6:4 both with homogeneous and heterogeneous catalysis.

Although no reaction was found to be completely stereoselective, in all the examples reported in scheme 5.7, *syn* and *anti* diastereoisomers were separated by liquid chromatography, thus each single diastereoisomer can be used for the following steps.

This brief methodological study will serve as starting point for the future total synthesis of methyl *meso* diol systems.



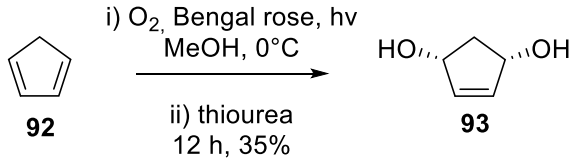
Scheme 5.7: hydrogenation tests, part 2

5.4.2 Photocycloaddition approach

Looking at the synthetic scheme 4.7 (chapter 4) for *meso* diol **86** which was employed for the methodological study, it was decided to run the same approach in order to obtain the methyl derivative.

The initial challenge was to find a way to synthetize a *meso* 1,3-cyclopenten diol containing a carbon substituent on the central carbon.

Oxygen photocycloaddition is one of the best approach to obtain *syn*-cyclopent-4-ene-1,3-diol systems (scheme 5.8), but if the reaction works very well with 1,3-cyclopentadiene, when C_5 substituted cyclopentadienes are used, the same strategy shows some problems because of the strong tendency of these molecules to isomerize to the more substituted alkene.



Scheme 5.8: photocycloaddition of oxygen to cyclopentadiene

In 1998, Fleming and Terret[61] reported the synthesis of 5-methylcyclopenta-1,3-diene from cyclopentadienyl anion. In this procedure, reaction temperature was kept at -40°C and once the product is formed, it was quickly distilled at -10°C and directly used for the next step, because otherwise it easily isomerizes into the corresponding 1-methylcyclopenta-1,3-diene.
For this reason, the use of 5-methylcyclopenta-1,3-diene in the photocycloaddition approach is critical, because the Diels-Alder step is a slow reaction that must be performed at -5°C-0°C and in such conditions a significant isomerization (1,3-hydrogen shift) of the substrate could take place.

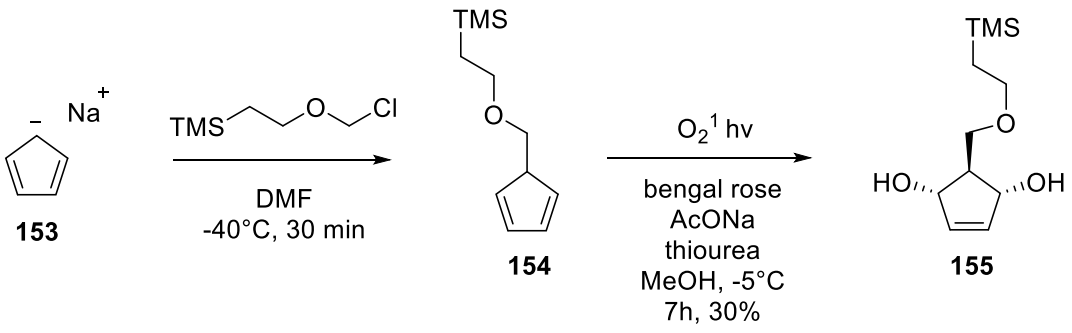
In 1994, Bradley[62] reported the synthesis of a cyclopentadiene bearing a $TMSCH_2CH_2OCH_2$ as substituent on C_5 position. To the best of our knowledge, this is one of the few methods to

[61] Fleming, I. Terrett, N. K., *Journal of the Chemical Society - Perkin Transactions 1*, **1998** , 17, 2645.
[62] Bradley K. Goering, Bruce Ganem, *Tet. Lett.*,**1994**, 35, 6997.

introduce a methyl substituent on C_5 position of cyclopentadiene that would results in a quite stable compound.

Compound **154** can be prepared by treating sodium cyclopentadienyl with trimethylsylil etoxy methyl chloride (SEM-Cl) at -40°C. Then, the resulting alkylated 1,3-cyclopentadiene **154** is converted into the corresponding *syn* diol **155** by singlet oxygen photocycloaddition (see scheme 5.9). It's interesting to point out that this approach is completely diastereoselective, with the central substituent *anti* to the hydroxylic functions. In this way it is possible to consider this strategy as a complementary method to the hydrogenation approach discussed in the previous section (5.4.1), that should provide access to the diastereoisomer with a *syn* geometry between hydroxyls and the central substituent.

Moreover, the $TMSCH_2CH_2OCH_2$ substituent can be converted into a hydroxymethyl function by removing the protecting group. Subsequently, deoxygenation would lead to the methyl derivative, while dehydration would form a carbon-carbon double bond. Thus, the strategy could be applied to the synthesis of both methyl and methyliden *meso* diol.



Scheme 5.9: photocycloaddition approach towards cyclopenthendiol **155**

Removal of the protecting group on the central carbon, represents one of the biggest issue of this approach.

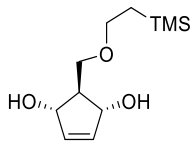
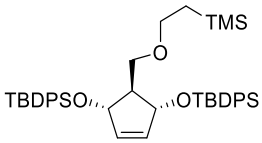
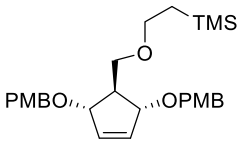
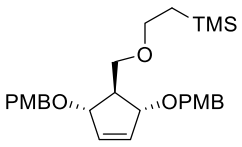
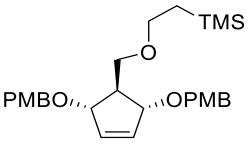
In order to convert the central substituent into a methyl group or an exocyclic double bond, it is fundamental to find an efficient deprotection strategy for the hydroxymethyl function, by removing the trimethylsilyl ethyl fragment.
Trimethylsilylethoxymethylchloride is generally used to protect alcohols as SEM derivative. This protecting group can be removed by treatment with fluoride sources or Lewis acid that cause the Si-C cleavage followed by release of ethylene, formaldehyde and the corresponding alcohol.
Compound **155** contains a modification of the classical SEM group, that is missing the acetal bridge.
In this case, deprotection would release only TMS and ethylene but not formaldehyde.
From the best of our knowledge, a few examples involving this protection are reported in literature, and they employed BF_3Et_2O or fluoride sources[63] for the cleavage.

Table 5.1 reports all the deprotection strategies adopted and the relative yields.

As it can be seen, the protecting group removal is quite tricky, also very strong reaction conditions did not work, and the best result is represented by entry 5 with a total yield of 9 %. Different kinds of fluoride sources like TBAF, KF and CsF combined with high reaction temperature were employed, and also strong lewis acid like BF_3Et_2O. But C-O cleavage it has proved difficult. At the moment we are looking for other protecting strategies for the central OH group.

[63] Goering, Bradley K.; Ganem, Bruce, *Tetrahedron Letters*, **1994**, 6997.

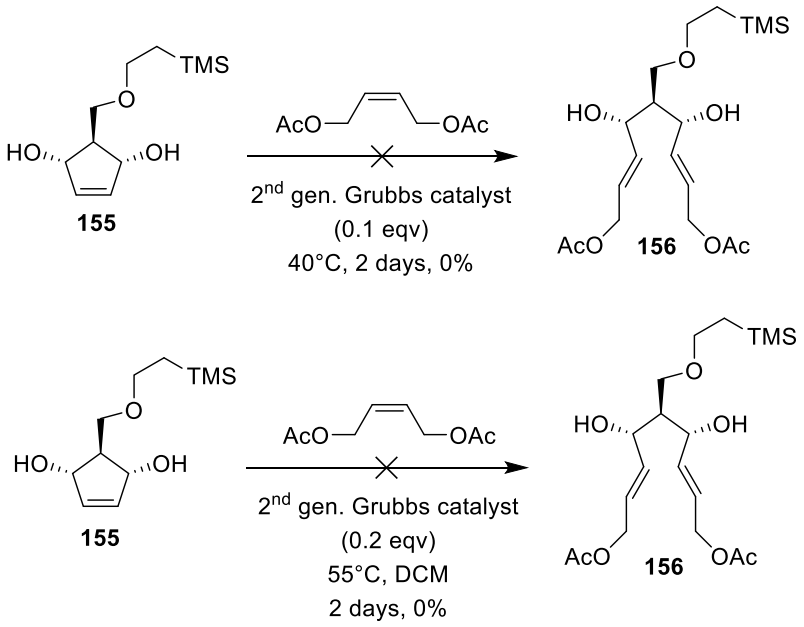
Table 5.1

	Substrate	Conditions	Yield
1		KF, TBAF THF, 18-crown-6 55°C, 24 h	Reaction did not work
2		BF_3Et_2O DCM 0°C to 25°C, 3h	Reaction did not work
3		BF_3Et_2O DCM 0°C to 25°C, 3h	Reaction did not work
4		CsF, DMF 130°C, 2 days	Reaction did not work
5		TBAF, THF 60°C, 2 days	9%

Once synthetized, intermediate **155** had to be converted into the corresponding *meso* diol to be used as a substrate for cyclization.

At first, the faster approach has been tried, by using ring opening/cross methatesis (ROM-CM) approach with *cis*-2-buthen-1,4 diacetate and 2nd generation Grubbs catalyst. This is the same method employed for the synthesis of the unsubstituted *meso* diol **86** (see chapter 4).

Scheme 5.10 shows the main results obtained. In both cases reactions did not start and no traces of desired product have been isolated. Within the first attempt, the acyclic olefin was used as reaction solvent and temperature was keep at 40°C. These are exactly the same conditions used for *meso* diol **86** (see scheme 4.7). However, after 2 days no traces of product have been detected and the starting material was recovered.
Subsequently, the amount of catalyst was doubled and reaction temperature was increased at 55°C, but despite the strongest conditions, after two days reaction was not started yet.



Scheme 5.10: methatetic approach towards *meso* diol **156**

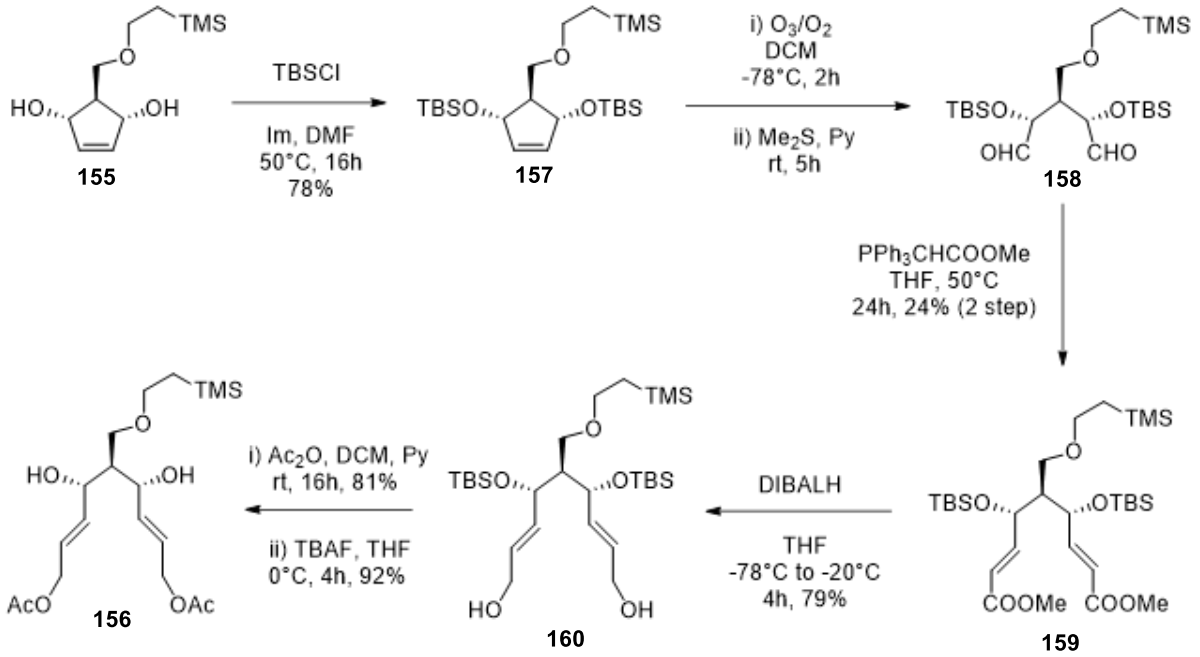
The reason for the methatesis failure remains unknown, but it was demonstrated by our research group that, when the same reaction was tested on the cyclopentendiol **93** bearing TBS

groups on the secondary hydroxyl functions it did not work at all. Thus, it can be assumed that structural modification of the original molecule can negatively affect the reaction course.

At that point, the synthetic approach was completely changed and the plan reported in scheme 5.11 was run.

Secondary hydroxyl groups were protected as TBS ether, then, endocyclic double bond of *meso* diol **157** was opened by ozonolysis, and the corresponding dialdehyde **158** was rapidly converted into the bis-unsaturated methylester **159** through Wittig reaction.

DIBAL-H reduction of **159** led to the bis-allylic alcohol **160**, which was subsequently acetylated. Removal of TBS groups gave the final compound **156**.



Scheme 5.11: synthetic plan to *meso* diol **156**

The process has a 11% overall yield starting from compound **155** and furnished around 50 mg of final product that were used to perform two cyclization tests.

5.4.3 Cyclization tests of *meso* diol **156**

Although the amount of final *meso* diol **156** obtained from the previous synthetic pathway was very low, it was sufficient to try a few cyclization tests, that could serve as starting point for future development of such methodology study.

Therefore, the remarks of this exploratory reactions should be considered as preliminary results, useful to prove if the envisioned approach could work or not.

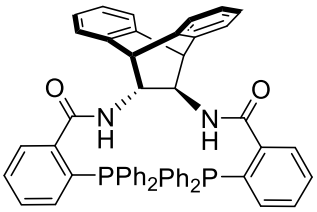
Looking at the outcomes of the study performed on *meso* diol **86**, it has been decided to try the commercially available ligands (*R,R)*-L2 and (*S,S)*-L1, that shown selectivity for AC core and ST core, respectively.

Scheme 5.12 reports reaction conditions and stereochemical outcomes.

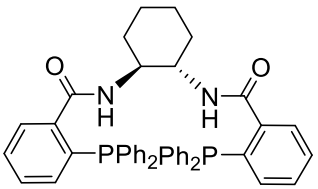
In both cases cyclization took place and the corresponding tetrasubstituted THF rings have been formed. The absolute configuration of C_3 and C_4 is inalterable. So the two diastereoisomers which can be achieved are AC type **161** and ST type **162**.

It is interesting to note that, as might be expected, with (*R,R)*-L2 ligand, AC type ring is selectively formed, with 67: 33 AC:ST *dr* and 96% *ee*.

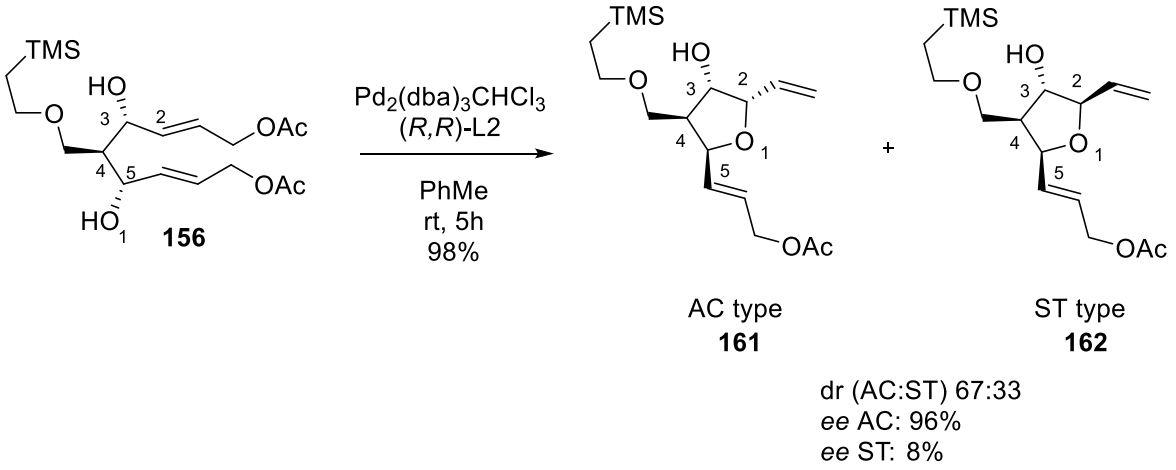
On the other hand, with (*S,S)*-L1 ligand, ST type is the main diastereoisomers, with 24:76 AC:ST *dr*, but overall enantioselectivity was worse than the reaction above. AC type showed 33% *ee* as ST type only 22%.

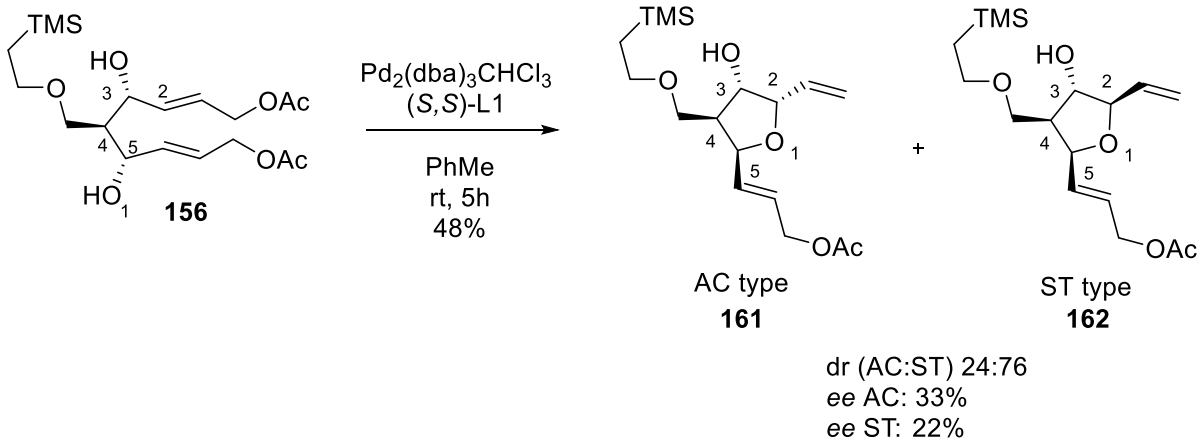


(R,R)-**L2**



(S,S)-**L1**





Scheme 5.12 cyclization tests of meso diol **156**

The absolute configuration of the stereocenters was assigned by analogy with the previous studies concerning the cyclization of *meso* diol **86** (see chapter 4) that were performed through studies of the corresponding Mosher esters and n.O.e NMR spectra.

To conclude this section, it is possible to say that cyclization of alkyl substituted *meso* diol systems can take place. In particular, when *meso* diol **156** is employed with (*R,R)*-L2 ligand, good diastereomeric ratio and high enantiomeric excess can be achieved. Future perspectives will consider the screening of different kind of ligands and different leaving groups on the substrate, in order to further increase the diastereomeric ratio.

However, despite the promising outcomes, the difficult cleavage of the protecting group will require to find a different protection strategy.

PART 2: *Synthetic studies on tetrasubstituted γ-butyrolactone lignans*

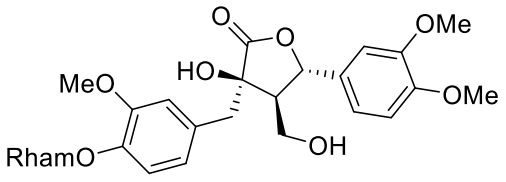
Scope of the project

The aim of this PhD thesis' section, that has been accomplished in Professor Stephen Hanessian Lab. (Montreal, Canada), consists into the development of a stereoselective strategy toward the antioxidant γ-butyrolactone lignan **163** from *Acer saccharum* that tries to compete with the corresponding reported syntheses.

The project, is included in the overall topic of this PhD thesis, aimed at finding stereoselective strategies for the construction of polysubstituted oxygenated five-membered rings.

Instead of the 3-hydroxy-2,5-disubstituted tetrahydrofuran moiety, typical of marine metabolites discussed in chapter 1 and 2, in this section the efforts are focused on the synthesis of 3,4,5-trisubstituted- γ-butyrolactone cores found in lignans.

Moreover, while the general approach followed in the first section, based on the asymmetric intramolecular Tsuji-Trost allylic etherification, involved the construction of the entire chiral scaffold within a single catalytic reaction, in this part of the work, different approaches will be took in consideration, in particular those involving the steric effect of the substrate for the stereoselective introduction of the substituents.



163

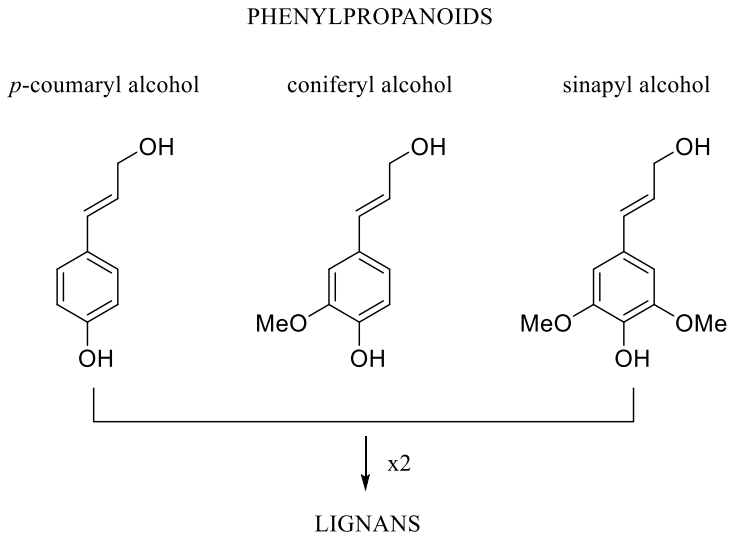
Figure 1: new γ-butyrolactone lignan from *Acer saccharum*

CHAPTER 6: Lignans in nature

6.1 Introduction

In 2003, Umezawa reported an interesting work[64], concerning the diversity in lignan biosynthesis, that we're going to use as starting point to introduce the topic.

Lignans are phenylpropanoid dimers (scheme 6.1), in which the phenylpropane scaffolds are linked by the central carbon (C_8) of their side chains. They represent exclusive secondary metabolites of the plant kingdom, synthetized within the shikimate pathway. The biosynthesis of lignans has been found to be closely related to but distinct from those of other phenylpropanoids, for example lignins, norlignans and neolignans. Moreover, while lignins are ubiquitous in plants, lignans are not. For this reason, they can be good subjects for studying the evolution of secondary metabolism.



Scheme 6.1: principal phenylpropanoid units found in lignans.

[64] Umezawa, T., *Phytochem. Rev.,* **2003,** *2*, 371.

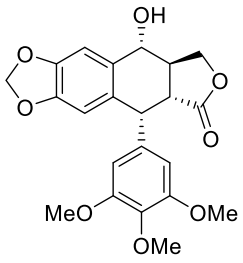
Despite the common basic carbon pattern, lignans are diversified by the oxidation level, substitution framework, and the general chemical structure.

Moreover, this class of natural compounds show considerable diversity in terms of enantiomeric composition, biosynthesis, and phylogenetic distribution.

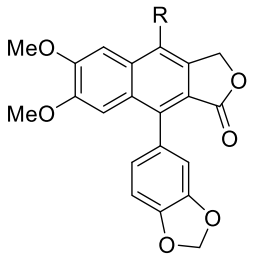
Due to their high number of relevant biological activities[65], lignans have received particular attention in many fields. Some of them have proved to be excellent anti-tumor, anti-mitotic, and anti-viral agents.

For instance, Podophyllotoxin (figure 6.1) and related lignans, which have been isolated from the roots of *Podophyllum* species (Berberidaceae) showed clinically useful cytotoxic and anti-cancer activity[10], while lignans from *Justicia procumbens* (figure 6.1) and their glycosides (justicidins A and B, diphyllin, diphyllin apioside) showed strong anti-viral activity against vesicular stomatitis virus[66].

Furthermore, due to the phenolic part, it is known that lignans play an important role in the anti-oxidant activity of food and plants[67].



podophyllotoxin



R = OMe	Justicidin A
R = H	Justicidin B
R = OH	Diphyllin
R = O,	Diphyllin apioside

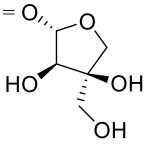


Figure 6.1: anti-cancer (podophyllotoxin) and anti-viral lignans

[65] J. Zhanga, J. Chenb, Z. Lianga and C. Zhao, *Chemistry and biodiversity*, **2014**, 11,
[66] J. Asano, K. Chiba, M. Tada, T. Yoshi, *Phytochemistry*, **1996**, *42*, 713
[67] S. Yamauchi, Y. Hayashi, T. Kirikihira, T. Masuda. *Biosci. Biotechnol. Biochem*., **2005**, *69*, 113

During the last years, several efforts have been made in order to develop stereoselective synthesis of such molecules with the aim of obtaining enough quantitites of products for the subsequent biological tests.

6.2 Nomenclature of lignans

In 1936, Haworth introduced the term lignan to describe a class of phenylpropanoid dimers in which the two phenylpropane units were connect by the central carbon of the C_3 side chains.

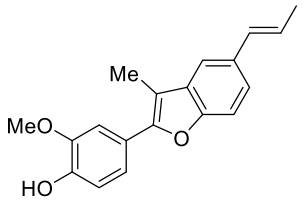
In 1969, McCredie and coworker suggested to extend the term to all low molecular weight natural compounds that derive primarily from the oxidative coupling of p-hydroxyphenylpropene units.

Neolignans were introduced in 1972 by Gottlieb, to indicate all those compounds in which the phenylpropane units are linked in a different fashion (figure 6.2).

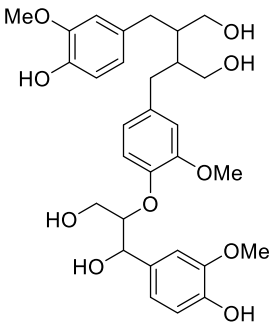
However, later neolignans have redefined as the dimers of allyl- and/or propenylphenyl monomers, while lignans were regarded as the dimers of cinnamyl alcohols and/or cinnamic acids.

However, in 2000, IUPAC adopted the Haworth's definition of lignans and Gottlieb former definition for neolignans.

Some analogs of lignans characterized by three and four phenylpropane units are called sesquilignans and dilignans respectively, but IUPAC chose for theme the terms sesquineolignans and dineolignans respectively.



eupomatenoid-5: example of neolignan



secoisolariciresinol guaiacylglycerol ether: example of sesquilignan

Figure 6.2: examples of neolignan and sesquilignan

6.3 Lignans classification

Lignans are divided into eight classes based on the cyclization pattern and the way in which oxygen is incorporated into the structure.

These classes are: furofuran, furan, dibenzylbutane, dibenzylbutyrolactone, aryltetralin, arylnaphtalene, dibenzocyclooctadiene and dibenzylbutyrolactol (figure 6.3).

The differences between each group concern the oxidation level of both the aromatic rings and propyl side chains. Some lignans of furan, dibenzylbutane and dibenzocyclooctadiene don't show any oxygen at C_9 (C_9'), but at the same time some of them possess extra hydroxyl groups at C_7 (C_7') or C_8 (C_8').

About the aromatic rings, the most frequently occurring are: 3-methoxy-4-hydroxyphenyl (guaiacyl), 3,4-dimethoxyphenyl (veratryl), 3,4-methylenedioxyphenyl (piperonyl), 3,5-dimethoxy-4-hydroxyphenyl (syringyl), and 3,4,5-trimethoxyphenyl (figure 6.3). Rarely, 4-hydroxyphenyl and 3,4-dihydroxyphenyl lignans have been identify.

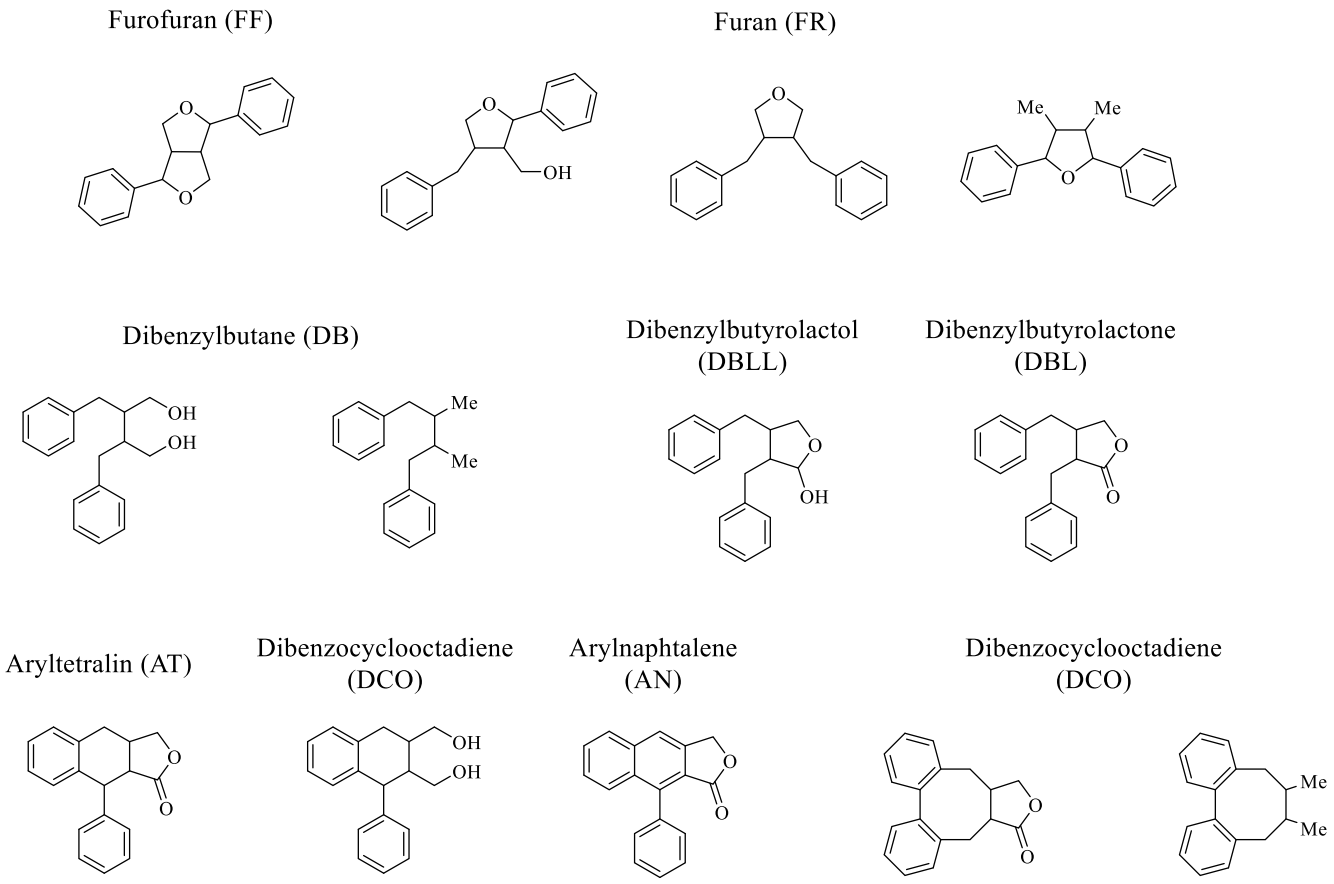
6.4 Stereochemical features of lignans

From a stereochemical point of view, lignans found in plants can exist both as one enantiomer and as enantiomeric mixture with different enantiomeric composition. Sometimes also racemic lignans have been found to occur.

Furofuran and furan lignans always have been isolated as enantiomeric mixture. For example, pinoresinol (figure 6.4), isolated from *Wikstroemia sikokiana,* is composed by a mixture in which (-) isomer is more abundant than (+) isomer (74% *ee*).

On the other hand, it's intriguing that all dibenzylbutyrolactone lignans, that have been studied for many years, have been found to be optically pure (*ee* > 99%) but with different configuration depending on the plants. For example, secoisolariciresinol (figure 6.4), belonging the class of dibenzylbutane lignans, from *Forsythia spp*, is optically pure in favor of the (-)-enantiomer, and the same lignans from *Phyllanthus sp*, is almost optically pure but dextrorotatory.

A. Principal subgroups of lignan



B. Principal aromatic structures of lignans

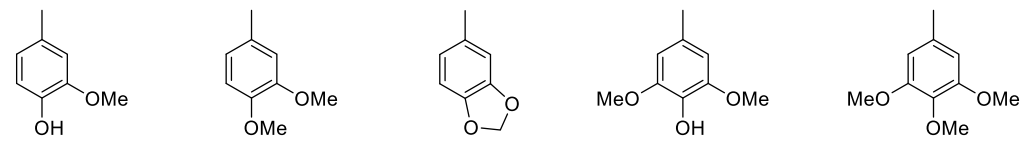
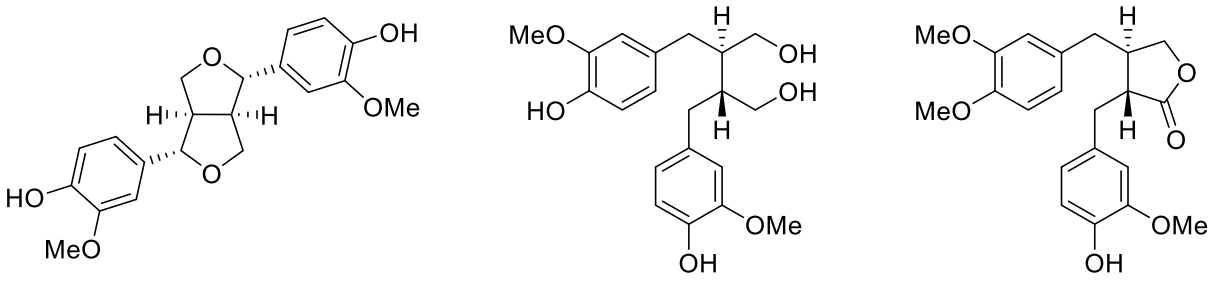


Figure 6.3: principal classes of lignans and relative aromatic structures

In contrast, when this lignan was isolated from *W. sikokiana* and *Arctium lappa*, it resulted in a mixture of enantiomers with (-) > (+) and 45% *ee*.

Moreover, within a single plant species the absolute configuration of predominant lignan enantiomers can vary. For example, (+)-arctigenin (figure 6.4) and (+)-pinoresinol, isolated from *Wikstroemia indica,* show opposite absolute configurations to each other at C_8 and C_8'.



(+)-Pinoresinol (-)-Secoisolariciresinol (-)-Arctigenin

Figure 6.4.

To summarize, Umezawa found that lignans' stereochemical features can be described with four propositions:

- Furofuran and furan lignans are mixture of both enantiomers with different compositions, while dibenzylbutyrolactone lignans are optically pure (*ee*>99%).
- Generally, dibenzylbutyrolactone lignans are levorotatory, except in rare cases (Thymelaeaceae plants and *S. doederleinii* are dextrorotatory).
- Most abundant enantiomers of furofuran, furan and dibenzylbutane lignans change among plant species and also within different organs in a single plant species.
- The absolute configuration of the predominant enantiomers of several lignans isolated from a single plant species sometimes are different.

6.5 Biosynthesis of lignans

The biosynthetic route of most of the classes of lignans described above have been studied and established, nevertheless, the biosynthesis of some of them is still unknown.

Studies in a wide range of gymnosperms and angiosperms revealed the presence of a common lignan biosynthetic pathway.

In 1933, Erdtman first proposed that the basic lignan framework was derived from the coupling of two phenylpropanoid monomer units.

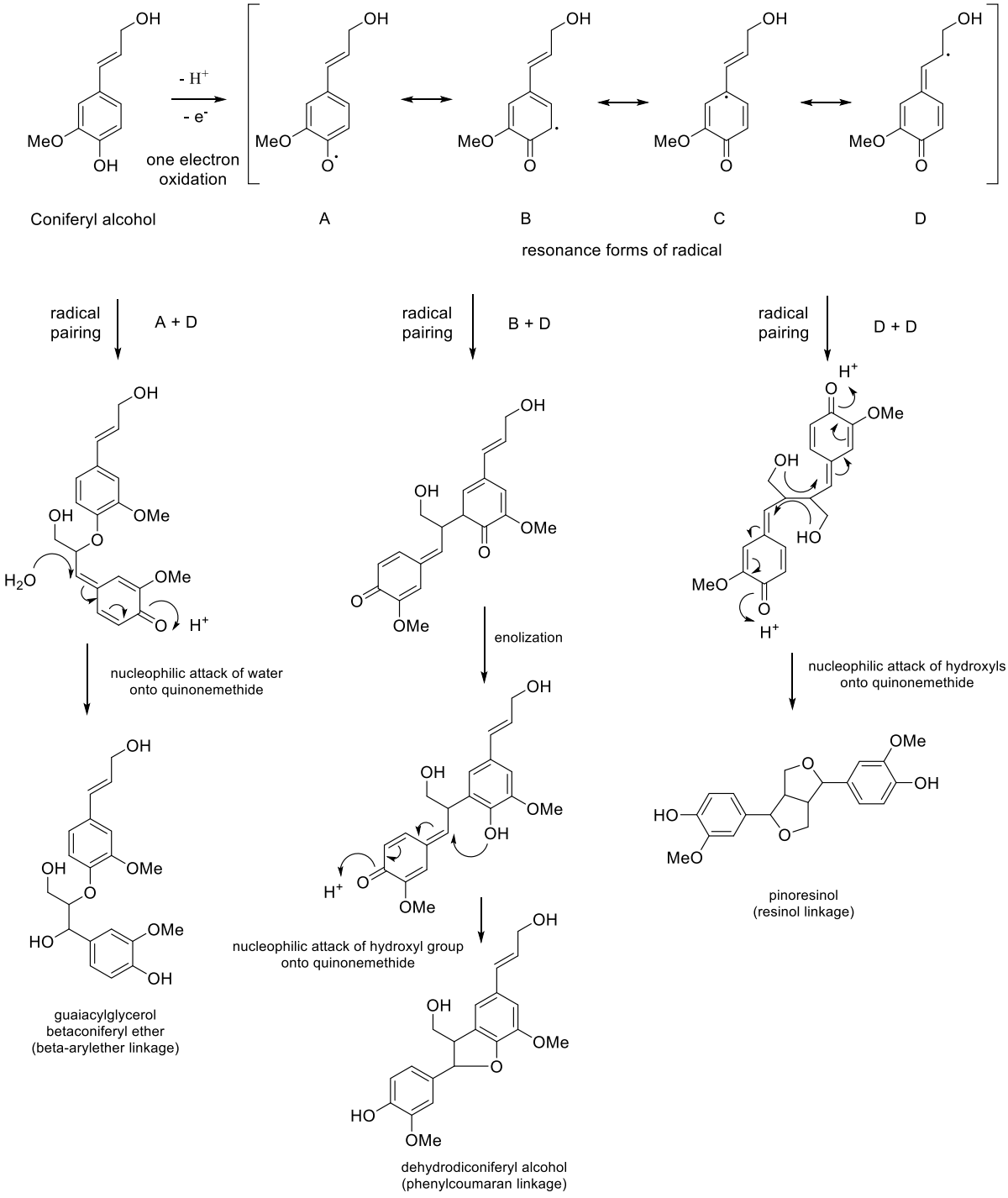
This assumption was subsequently confirmed by isotope tracer experiments.

The first step in lignan biosynthesis[10] is represented by the oxidative dimerization of two identical or different phenylpropanoid units. The enzymatic complexes that control the pathway are able to implement a one-electron oxidation of the conjugate system of substrate like coniferyl alcohol (scheme 6.2), through a single electron transfer followed by deprotonation. The resulting resonance stabilized radical is a highly reactive species in which the radical site can be delocalized on different atoms of the conjugated scaffold. In particular on the phenolic oxygen, on the *ortho* and *para* position of the ring (respect to the OH) and on the C_2 carbon of the side chain.

Subsequently, a radical pairing reaction takes place leading to different kinds of connections based on which radical sites interact each other. Scheme 6.2 reports some possibility of radical combination.

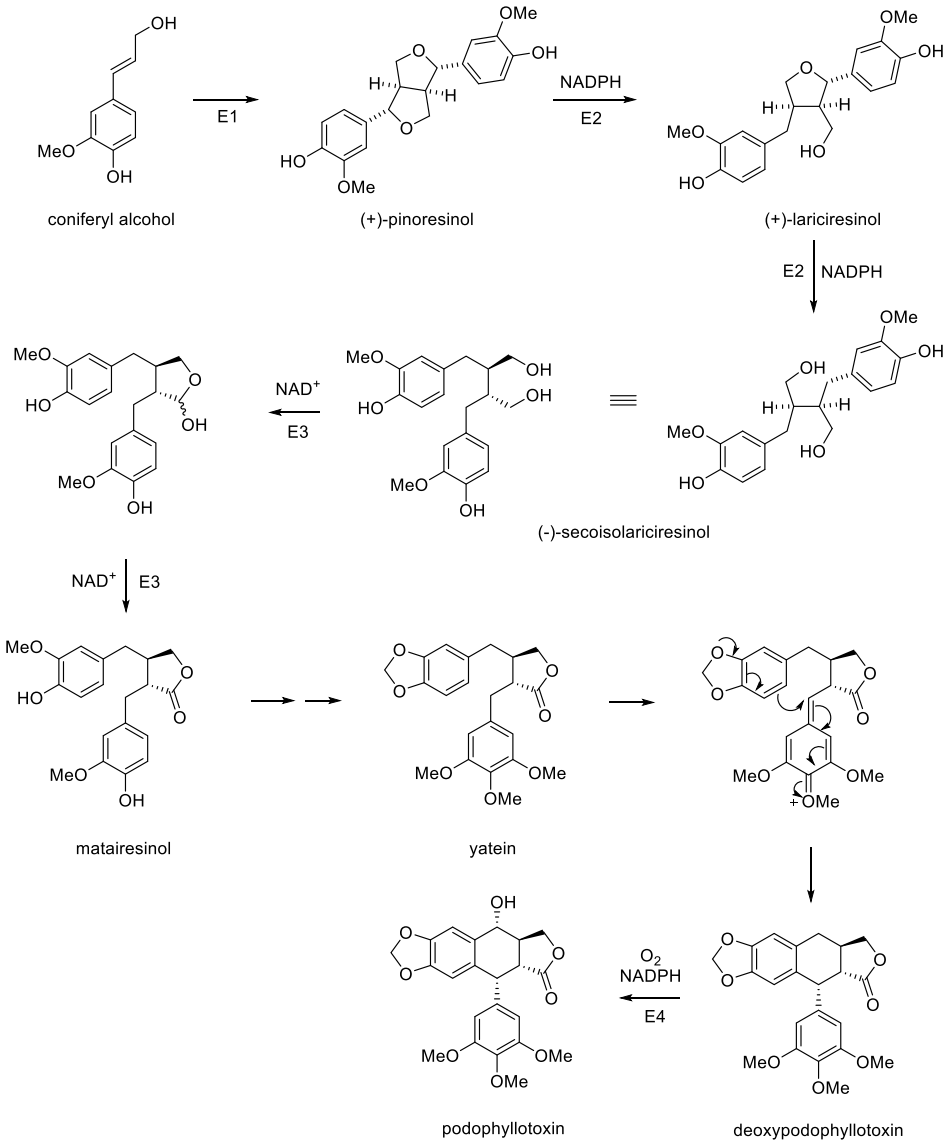
The direct product of radical pairing contains a highly reactive quinonemethide system that quickly undergoes a reaction aimed at restoring the lost aromaticity. These reactions generally are:

- Nucleophilic attack of water onto quinonemethide, that leads to hydroxyl introduction on the side chain.
- Intramolecular nucleophilic attack of hydroxyl group onto quinonemethide, that leads to five-membered oxygenated heterocycles' formation.
- Enolization, followed by one of the processes reported above.



Scheme 6.2[10]: biosynthesis of lignans: examples.

For instance, pinoresinol (scheme 6.2), a simple furofuran lignan extracted from *Stirax sp*, derives from homo radical coupling of coniferyl alcohol units (D+D pairing). The resulting double quinonemethide system, undergoes a double intramolecular nucleophilic attack by the primary alcohol. In this way the furofuran scaffold, consisting of two fused tetrahydrofuran rings, is obtained.



Scheme 6.3: biosynthesis of podophyllotoxin

Further enzymatic modifications of the basic lignan scaffolds are responsible of the biosynthesis of more complex lignans. For example, furofuran framework, is the starting point for aryltetralin lactone synthesis. It can be observed in scheme 6.3, where the conversion of pinoresinol into podophyllotoxin is shown[10].

NADPH promoted reductive cleavage of the tetrahydrofuran moieties of (+)-pinoresinol brings to (-)- secoisolariciresinol. Then, oxidation of primary alcohol to aldehyde and intramolecular hemiacetalyzation form the lactol core, that is subsequently oxidized to lactone (matairesinol).

Various modification of the aromatic rings substitution pattern leads to yatein, that after oxidation to quinone methide and cyclization lead to deoxypodophyllotoxin. Last step is an enzymatic benzylic oxidation that gives podophyllotoxin.

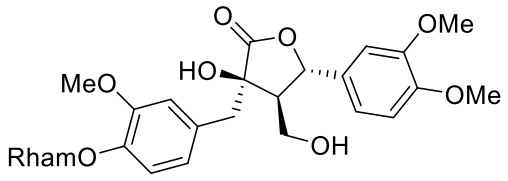
CHAPTER 7: γ-butyrolactone lignans from *Acer saccharum*: description and previous syntheses

7.1 Lignans and aromatic compounds from *Acer saccharum*

Acer saccharum, also known as sugar maple or rock maple, is a species of maple native to the hardwood forest of eastern Canada, from Nuova Scotia west through Quebec and Southern Ontario to southeastern Mannitoba around Lake of the Woods, and the northern parts of the Central and eastern United States, from Minnesota eastward to the highlands of the eastern state.

This plant is famous all over the world for its spectacular autumnal foliage and because it is the primary source of maple syrup.

In 2011, Yoshikawa and coworkers reported[68] the extraction and complete characterization of a novel lignan glycoside 5-(3'',4''-dimethoxyphenyl)-3-hydroxy-3-(4'-hydroxy-3'-methoxybenzyl)-4-hydroxymethyl-dihydrofuran-2-one 4'-O-a-L-rhamnopyranoside **163** (figure 7.1) and other seven known compounds including: koaburside, icariside E4, cleomiscosin C, cleomiscosin D, scopoletin, and 5'-demethylaquillochin.
All these secondary metabolites were isolated from the EtOH extract of the wood of *Acer saccharum*.



163

Figure 7.1: new lignan from *Acer saccharum*

The wood of the plant, was exhaustively extracted with ethanol at room temperature for 45 days.

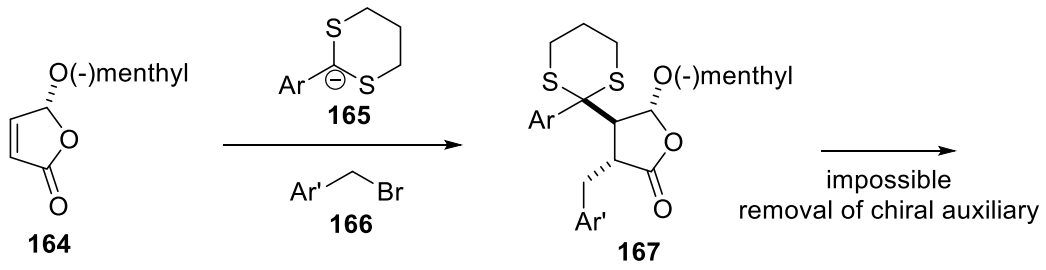
[68] Yoshikawa, K., Kawahara, Y., Arihara, S., Hashimoto, T., *J Nat Med,* **2011**, *65*, 191.

Subsequently, the raw mixture was separated by ordinary phase silica gel and reversed phase silica gel to give the new lignan glycoside **163** as a colorless oil and all the other compounds reported above.

The characterization was performed by 1D and 2D nuclear magnetic resonance, including DEPT, COSY, NOESY, ROESY, HMBC and HMQC and by mass spectroscopy analysis.
All the compounds extracted have shown antioxidant activity that was tested in superoxide dismutase (SOD)-like assay. Vitamin C was used as a positive control (IC_{50} 66.2 μM).

7.2 Previous syntheses of compound **163**

In 2006, Raffaelli and coworkers[69] developed a general approach for the asymmetric synthesis of several 7'-hydroxylignano-9,9'-lactones, together with the synthesis of two lignans that was necessary to clarify the absolute configuration of naturally occurring (-)-parabenzlactone.
Within the strategy proposed, the authors reported the formation of a novel hydroxylactone core, arising from a rearrangement process during a hydride ketone reduction. Such new γ-butyrolactone core, which they obtained just as reaction's byproduct, contains exactly the same structural motif of our target **163**.
Initially, the authors tried to develop a strategy based on the well known tandem Michael addition-alkylation sequence (scheme 7.1), by involving a lithiated dithiane (**165**) as nucleophile, 5-(-)-menthyloxybutenolide **164** as Michael acceptor functionalized with a chiral auxiliary and a substituted benzylic bromide (**166**) as alkylating agent.
The corresponding adduct, was achieved in 56 % yield as a single isomer, but it has been impossible to remove the chiral auxiliary.



Scheme 7.1

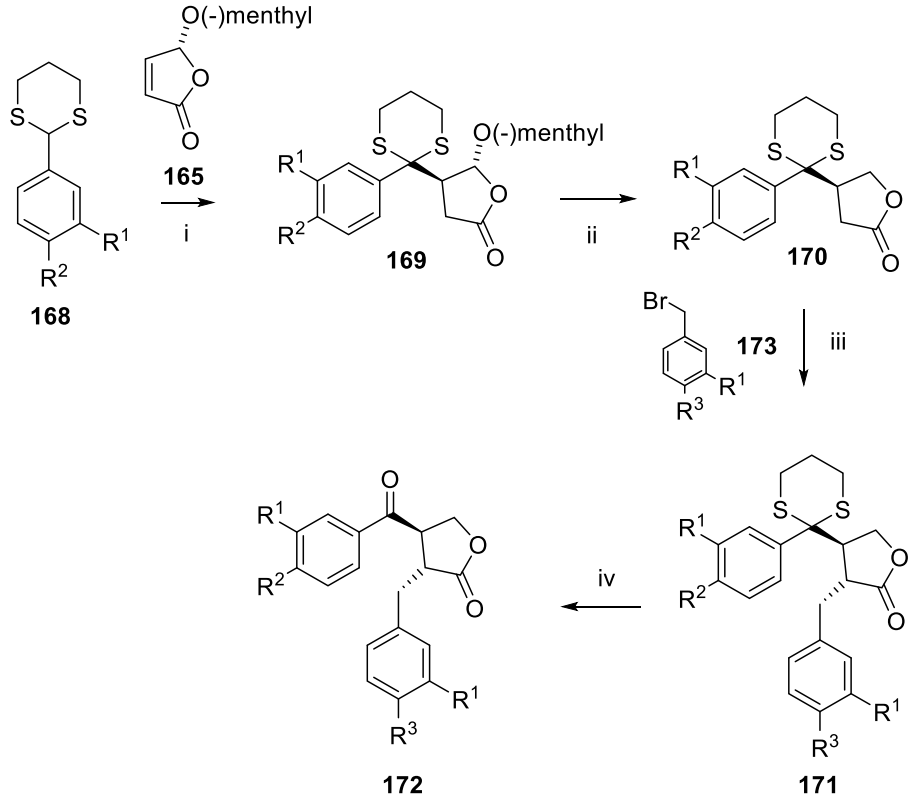
For this reason, they decided to remove the menthyloxy auxiliary before the alkylation step (scheme 7.2).
The conjugate addition of lithiated dithianes (**168**) to the chiral butenolide **165** led to compound **169** in 75-88% yield as a single isomer. Subsequently, the menthyloxy function was easily detached by a basic lactone hydrolysis followed by *in situ* reduction of the intermediate aldehyde with $NaBH_4$, that give the chiral lactones **170** in 60-82% yield.

[69] Raffaelli, B., Wahala*, K. and Hase, T., *Org. Biomol. Chem.*, **2006**, *4*, 331.

By using the appropriate benzylic bromides (**173**), alkylation of **170** resulted in lignanolactone derivatives **171** in acceptable yields (66-78%) and with *trans* 8*R*/8'*R* configuration.

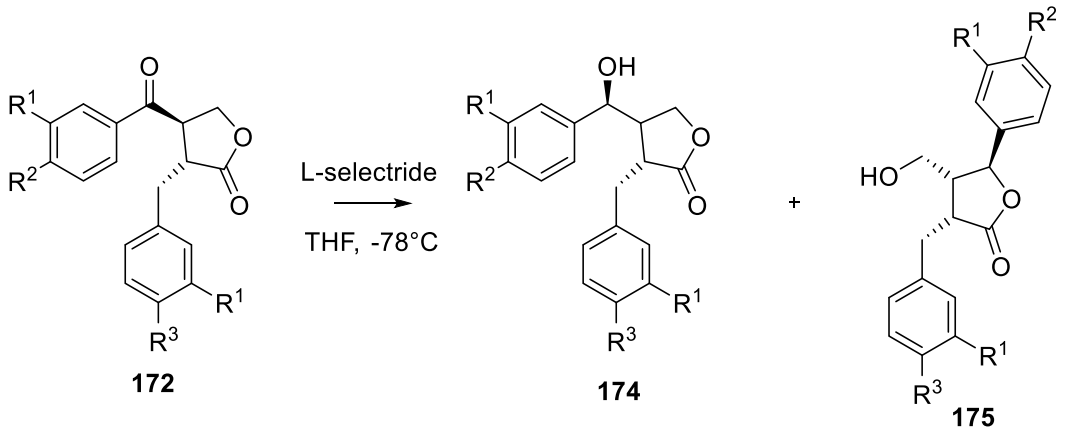
The deprotection of the C_7 carbonyl function, was carried out by $(CF_3CO_2)_2IPh$ and leads to oxolignanolactones **172** in 50-80% yield.

For the subsequent reduction of ketone moiety, L-Selectride was employed (scheme 7.3). The hydride attacks from the less hindered face of the carbonyl, giving compounds **174** in high enantiomeric excess.



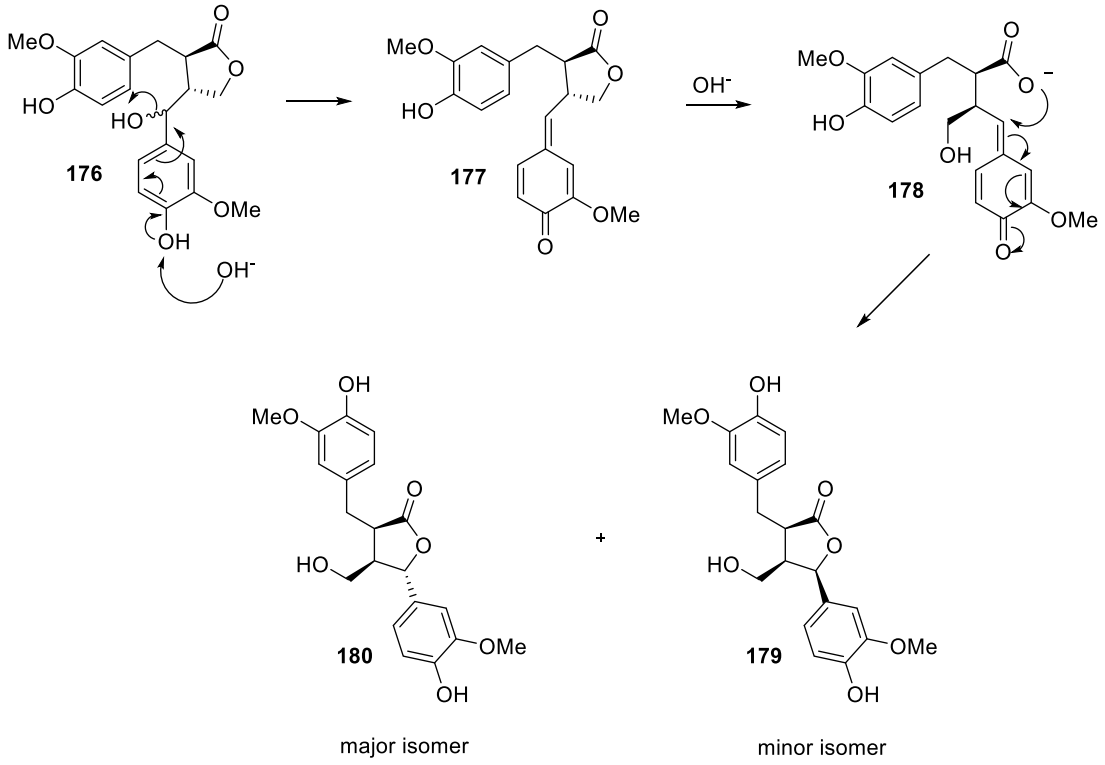
Scheme 7.2: reagents and conditions: (i) *n*-BuLi, THF, DMPU, -78°C; (ii) (a) $NaBH_4$, KOH, EtOH, 0°C, then rt. (b) 0.1N HCl, (pH 5-6); (iii) LDA, THF, DMI, -78°C to rt; (iv) $(CF_3COO)_2IPh$, MeCN-H_2O, rt.

During this reduction, hydroxylactone **175** was isolated by the authors as byproduct in 10% yield, and it may be considered as the result of a translactonization reaction, in which the 7'-alkoxyborane from the L-Selectride reaction acts as nucleophile towards the lactone ring, leading to the appearance of a primary hydroxyl function. Such compound shows the same structural motif of our synthetic lignan target **163**.



Scheme 7.3 Stereoselective reduction of ketones **172**

At the same time, Eklund and coworkers[70], reported the isolation and characterization of two lariciresinol type lactone lignans (**179** and **180**, scheme 7.4) as result of the treatment of 7'-hydroxymatairesinol **176** with base.



Scheme 7.4: hydroxylactone rearrangement of **176** via quinonemethide intermediate.

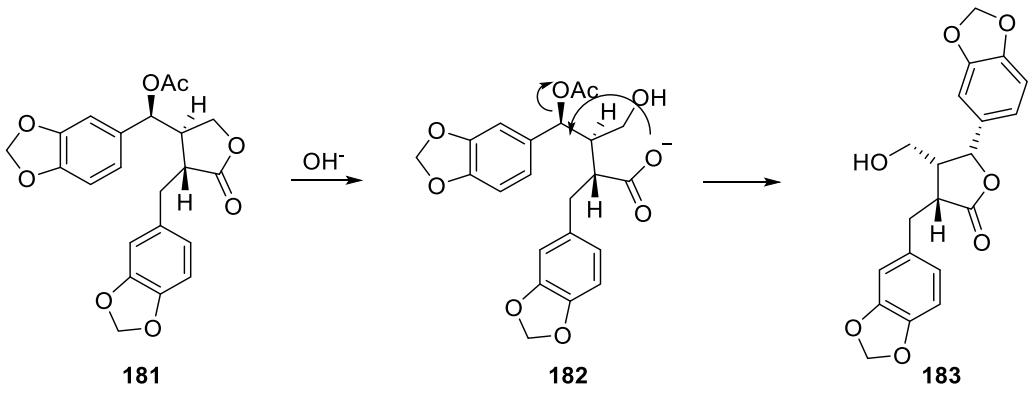
[70] P. C. Eklund, S. M. Willf or, A. I. Smeds, F. J. Sundell, R. E. Sjoholm and B. R. Holmbom, *J. Nat. Prod.*, **2004**, *67*, 927

The mechanism proposed by Eklund for the lactones **179** and **180** formation is shown in scheme 7.4, and involves a *p*-quinonemethide intermediate (**177**), that can be generated only when a free *p*-phenol group is present.
Moreover, in this way the carboxylate can attack both the diasterotopic faces of the intermediate's double bond, resulting in the formation of a mixture of isomers.

This hypothesis of mechanism can't be applied to the case of Raffaelli because the phenol was protected as TBDMS ether.

By analyzing the literature, it has been found that also Niwa *et al*. in 1976[71] and Moritani later in 1996[72], reported the formation of a rearranged compound like hydroxylactone **175**, but the mechanisms they proposed are different than the one thought by Eklund.

The rearrangement observed by Niwa (scheme 7.5), was the result of the treatment of natural occurring acetylparabenzlactone **181** with KOH.
The presence of an acetate group, led to the lactone ring hydrolysis, with the resulting formation of a carboxylic function and a primary alcohol. With these conditions, the carboxylate generated can act as nucleophile and bring to an S_N2 reaction on the 7' center with simultaneous detachment of the AcO group and inversion of configuration.

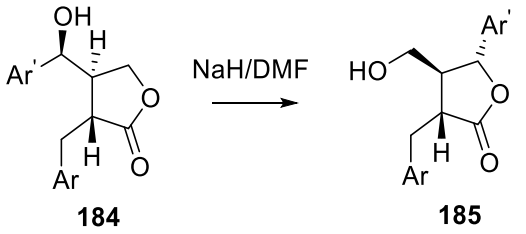


Scheme 7.5: Niwa's rearranged lactone and possible mechanism of formation of **183**

[71] M. Niwa, M. Iguchi, S. Yamamura and S. Nishibe, *Bull. Chem. Soc.Jpn.*, **1976**, *49*, 3359.
[72] Y. Moritani, C. Fukushima, T. Ukita, T. Miyagishima, H. Ohmizu and T. Iwasaki, *J. Org. Chem.*, **1996**, *61*, 6922.

Moritani and coworkers[72] observed the rearranged lactone **185** by treating compound **184** with NaH in DMF.

The mechanism proposed is similar to the one suggested by Raffaelli and is based on the translactonization operated by the benzylic alcoholate formed from compound **184** after treatment with NaH. In contrast with Raffaelli, in this case the rearrangement showed a high yield, in fact the reaction was employed for the stereoselective synthesis of a class of lignans very similar to the target of this thesis.



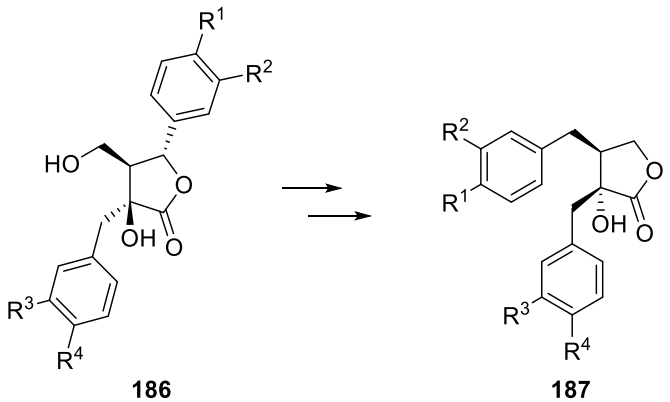
184 **185**

Scheme 7.6: Lactone isomerization reported by Moritani *et al.*

7.3 Moritani's approach to tetrasubstituted γ-butyrolactone lignans

In 1996, Moritani and coworkers[72] developed a general stereoselective strategy toward γ-butyrolactones lignans, while they were working on the total syntheses of *cis* and *trans*-isomers of α-hydroxy-α,β-dibenzyl-γ-butyrolactone lignans (**187**, scheme 7.7).

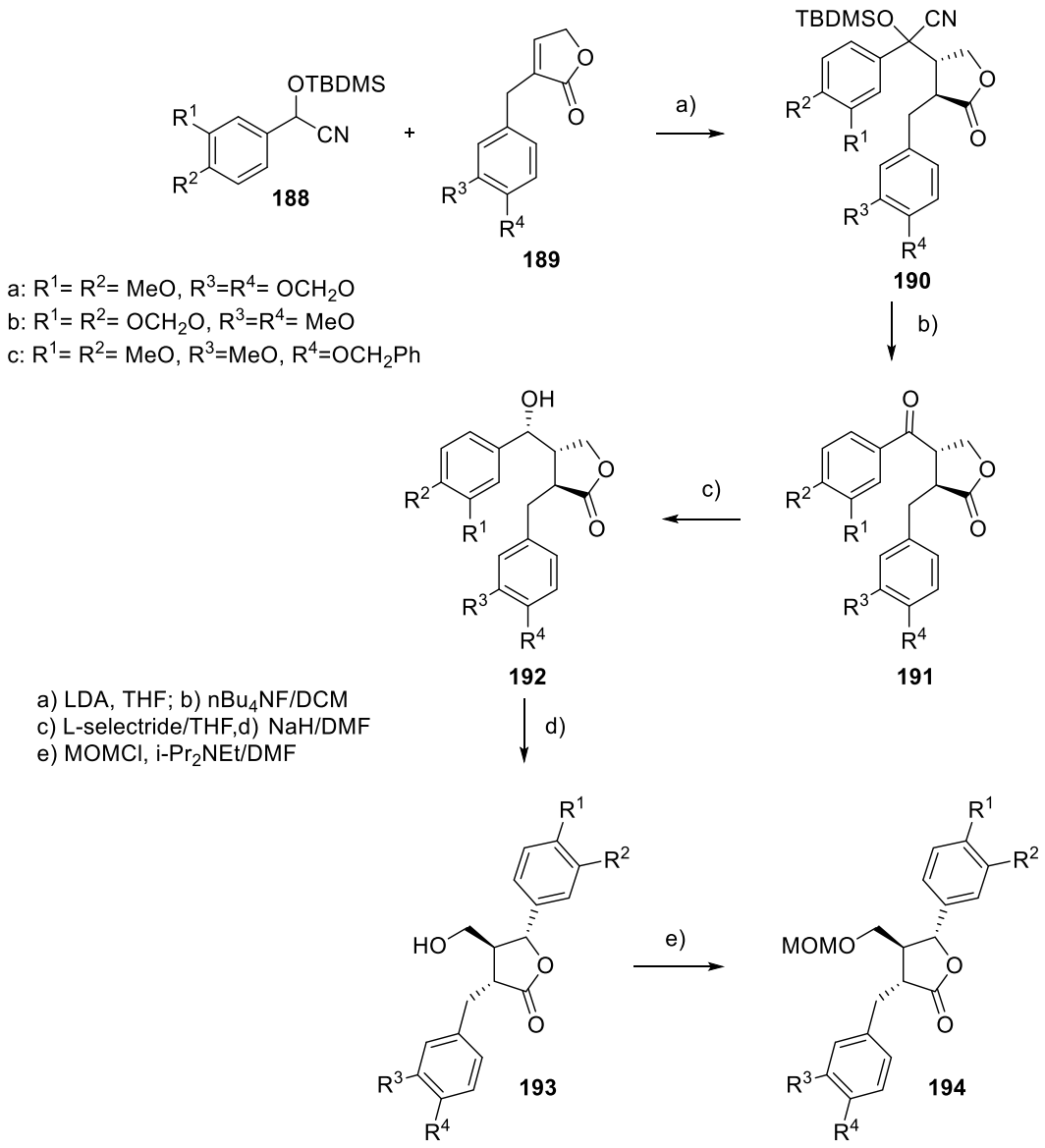
The key reactions of such approach are represented by the translactonization described in the previous chapter and the stereoselective electrophilic hydroxylation of metal enolates.



186 **187**

Scheme 7.7

The preparation of the γ-butirolactone **186**, started from O-silylated cyanohydrin **188** (scheme 7.8).



Scheme 7.8: Moritani's synthesis of lignan **193**.

The Michael addition of the lithium enolate of **188** to 2(5H)-furanone **189** at -78°C led to intermediate **190**.

Subsequently, the crude mixture was treated with tetrabutylammonium fluoride to give the *trans*-γ-butyrolactone **191**.

After carbonyl reduction with L-Selectride, alcohol **192** was quantitatively achieved. The hydride attacks mainly from the sterically less hindered face.

At this point, alcohol **192** was treated with NaH in DMF and γ-butyrolactone **193** was obtained as a consequence of the translactonization rearrangement.

The structure of compound **193** was determined by X-ray crystallographic analysis and a complete epimerization of the α carbon of **192** was observed.

Finally, the primary hydroxyl function of **193** was protected as MOM derivative. The total yield of rearrangement and protection reaction was around 80%.

At this point, the authors employed the substrates previously prepared in order to test the stereoselectivity of the α-alkylation of the corresponding metal enolates.

Several reactions concerning the alkylation of the metal enolates of γ- and δ-lactones have been reported in literature and it is well known that an electrophilic attack on the metal enolates of β-substituted γ-butyrolactones is completely controlled by the substituent on the β position, that leads to the *trans* addition product[73].

The aim of Moritani *et al*. was to demonstrate that the shielding effect of the phenyl group of the α-benzyl moiety, due to 1,3-allylic strain, would drive the electrophilic attack on the metal enolates of **194** predominantly from the sterically less hindered upper face in spite of the presence of the β-substituent.

In order to verify such hypothesis, electrophilic addition experiments on the enolates of compound **194** were carried out. Table 7.1 shows the main outcomes.

The potassium enolate was generated by reaction of **194** with KHMDS in THF at -78°C. Subsequently, MeI, D_2O, EtI and MoOPH were used as alkylating agents.

In all the attempts, good yields (80-90%) and excellent selectivity (>99/1) were achieved, but the most interesting results are the hydroxylations showed in entries 4,5 and 6 because the corresponding α-hydroxylated lactones possess the same structure of our target lignan **163**.

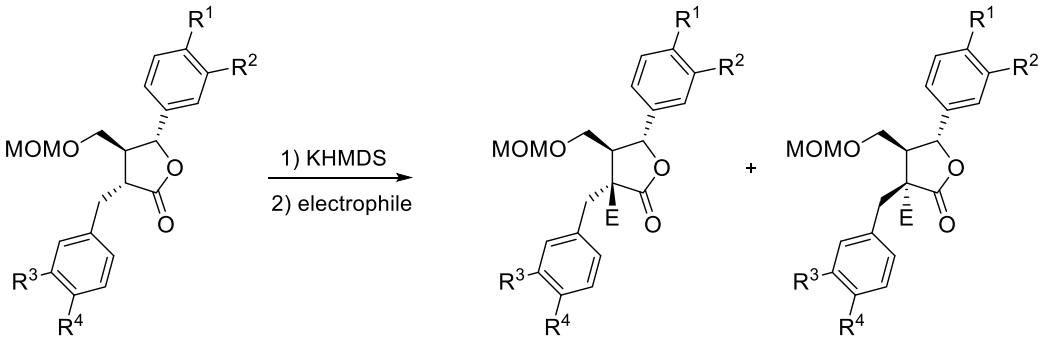
The only difference is the substitution pattern of one of the aromatic ring.

From the best of our knowledge, Moritani's work is the only one that reported a complete synthesis of racemic lignans very similar to our synthetic target.

[73] (a) Hannesian, S.; Murray, P. *J. Can. J. Chem.* **1986**, *64*, 2231., (b) Hannesian, S.; Murray, P. J. *J. Org. Chem.* **1987**, *52*, 1170.

The aim of this section of the thesis is to develop an alternative efficient enantioselective strategy toward molecule **163**, by involving catalytic processes for the lactone ring building and stereoselective reactions for the substituents insertion.

Table 7.1: reaction of metal enolates of **194** with electrophiles.



194 **195** **196**

a: R^1= R^2= MeO, R^3=R^4= OCH_2O E = OH
b: R^1= R^2= OCH_2O, R^3=R^4= MeO E = OH
c: R^1= R^2= MeO, R^3=MeO, R^4=OCH_2Ph E = OH
d: R^1= R^2= MeO, R^3=R^4= OCH_2O E = D
e: R^1= R^2= MeO, R^3=R^4= OCH_2O E = Me
f: R^1= R^2= MeO, R^3=R^4= OCH_2O E = Et

entry	substrate	electrophile	E	% yield[b] (195+196)	Selectivity (195/196)
1	194 a	MeI	Me	87	>99/1[d]
2	194 a	D_2O	D	92	>99/1[c]
3	194 a	EtI	Et	89	>99/1[d]
4	194 a	MoOPH	OH	89	>99/1[d]
5	194 b	MoOPH	OH	83	>99/1[d]
6	194 c	MoOPH	OH	81	>99/1[d]

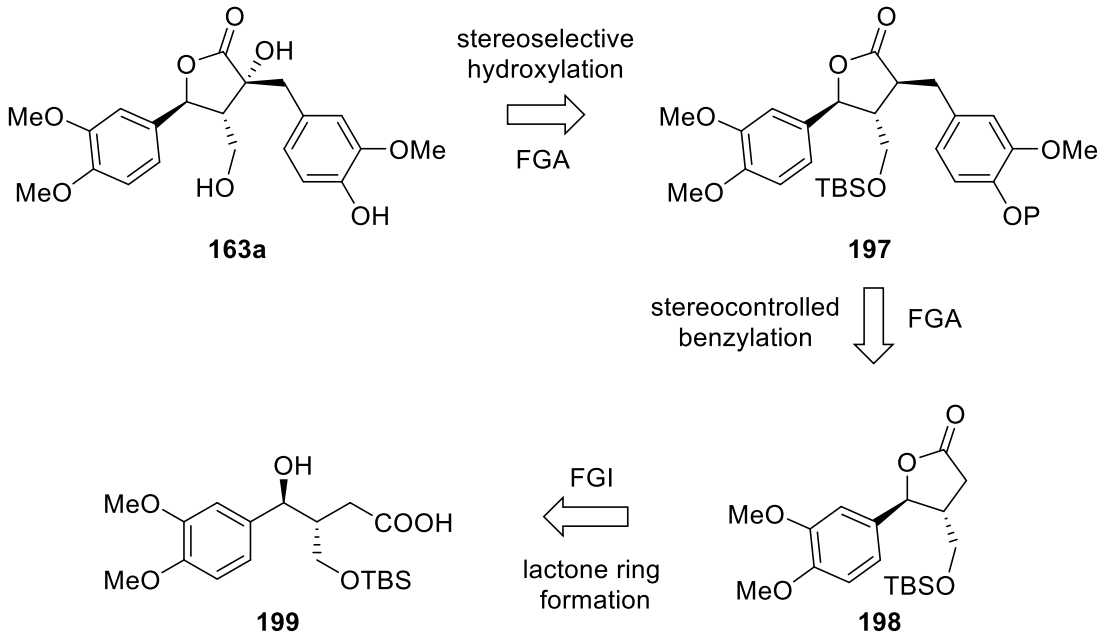
a)Reaction was carried out in THF at -78°C, using KHMDS as a base. b) Isolated yield. c) the ratio was determined by ^{1}H NMR, d) the ratio was determined by HPLC (CAPCELL PAK C_{18}).

CHAPTER 8: Synthetic strategies to γ-butyrolactone lignan 163 from *Acer saccharum*

8.1 First route to γ-butyrolactone lignan **163**

In order to develop the synthesis of γ-butyrolactone lignan **163**, the first strategy that was proposed is the one showed in scheme 8.1.

Starting from the aglycone **163a** and by disconnecting the C-OH bond on the alpha position of the lactone core, intermediate **197** is achieved. The approach followed for the hydroxylation reaction is the one reported in literature by Moritani et al[72], that employed MoOPH as source of electrophilic hydroxyl group (table 7.1, chapter 7). It's important to note that the relative stereochemistry of the benzyl substituent on the alpha position is not fundamental in order to achieve a stereoselective hydroxylation, because the reaction employs deprotonation and resulting enolate formation with loss of the stereochemical information. The subsequent OH insertion is driven by the group on the β position.

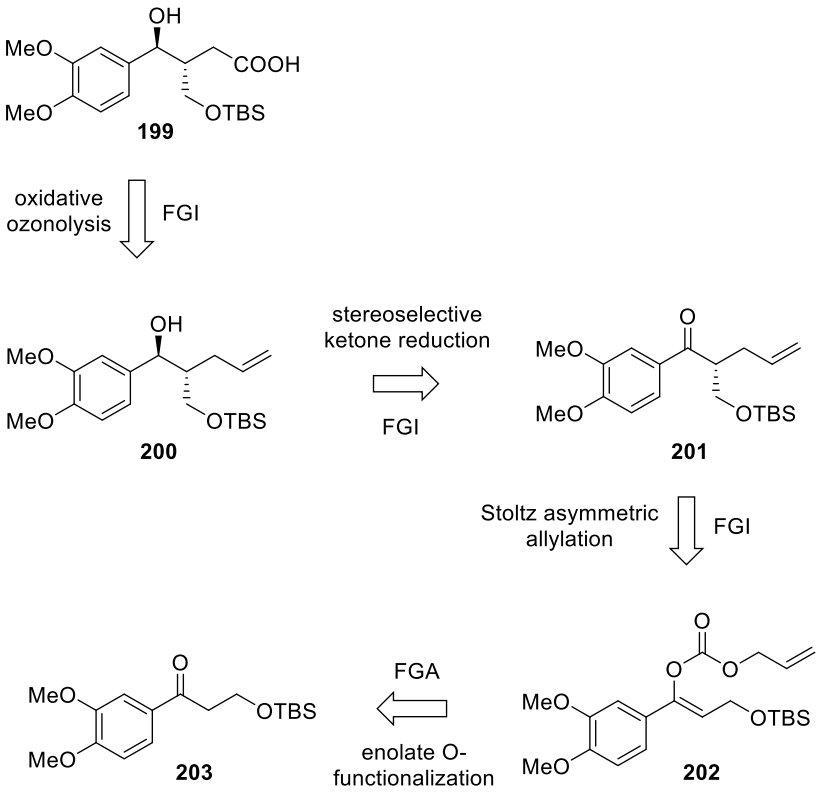


Scheme 8.1: first route to γ-butyrolactone lignan **163**

Compound **197** leads to the intermediate **198** by disconnection of the α – benzylic chain, that we initially supposed to run through a benzylation approach based on the alpha alkylation of the lactone core via benzyl bromide derivative. We supposed that the steric hindrance due to the -CH_2OTBS group on the beta carbon should drive the attack on the opposite side of the ring.

Lactone **198** can be derived from lactonization of hydroxyacid **199**, which can in turn derive from olefin **200** (scheme 8.2) through an oxidative ozonolysis strategy.

Enantiopure benzylic alcohol **200** can be obtained through a stereoselective carbonyl reduction of ketone **201**. Different enantioselective strategies are reported in literature, such as CBS catalysts[74] and a variety of chiral Lewis acids can be used to activate the carbonyl group within reduction's protocols.

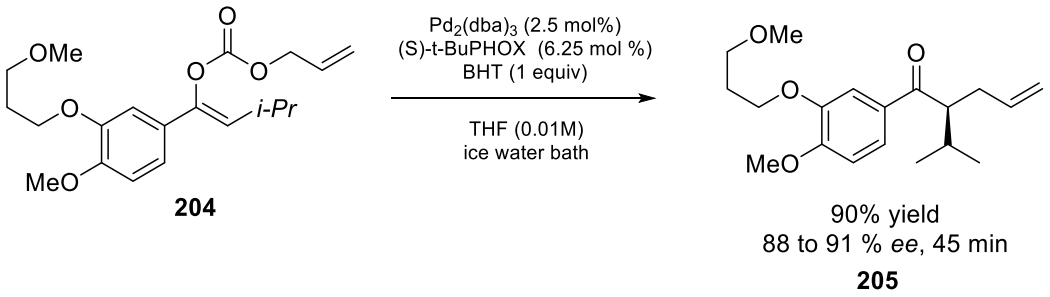


Scheme 8.2: first route to γ-butyrolactone lignan **163**

[74]Yoshida, M., Shoji, Y. and Shishido, K., *Org. Lett.,* **2009**, *11*, 1441.

However, the key step of this first retrosynthesis is represented by the Stoltz palladium-catalyzed asymmetric allylation[75] that converts enol-allyl carbonate **202** into ketone **201**.

This method was proposed by Hanessian in 2012[76] for the synthesis of peptidomimetic renin inhibitors. As can be seen in scheme 8.3, the reaction allows to enantioselectively introduce an allyl substituent on the alpha carbon of the ketone with high *ee*.



Scheme 8.3[75]: Stoltz palladium-catalyzed asymmetric allylation

Hanessian developed this methodology on substrates like **204**, that in all the cases showed a terminal isopropyl chain. Our challenge was to extend this procedure to an alternative substrate, in particular to intermediate **202**, which bears a CH_2OTBS group instead of the isopropyl.

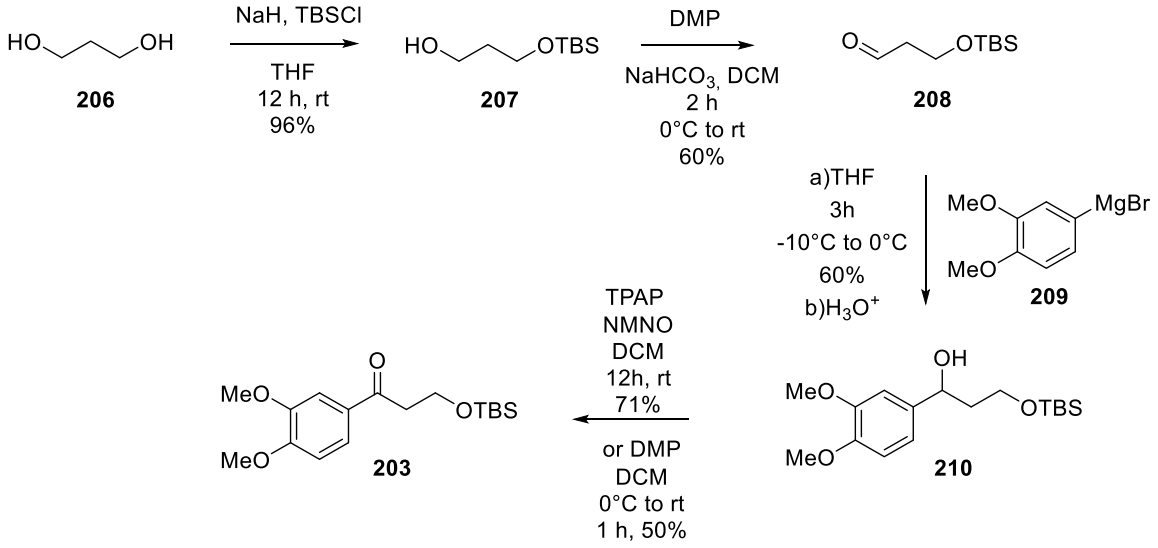
[75] Mohr, J. T., Stoltz, B. M., *Chem. Asian. J.*, **2007**, 2, 1476
[76] Hanessian, S. and Chénard, E., *Org. Lett.*, **2012**, 14, 3222

8.1.1 Synthesis of ketone **203**

To test our first approach to γ-butyrolactone lignan **163**, substrate **203** needed to be synthetized first.

This latter represented the appropriate precursor to apply the Stoltz palladium-catalyzed asymmetric allylation, key reaction of the entire synthetic plan.

Scheme 8.4 reported all the reactions employed.



Scheme 8.4: synthesis of substrate **203**

Commercially available 1,3-propane diol (**206**) was selectively functionalized with TBSCl and NaH on one of the two primary hydroxyl functions.

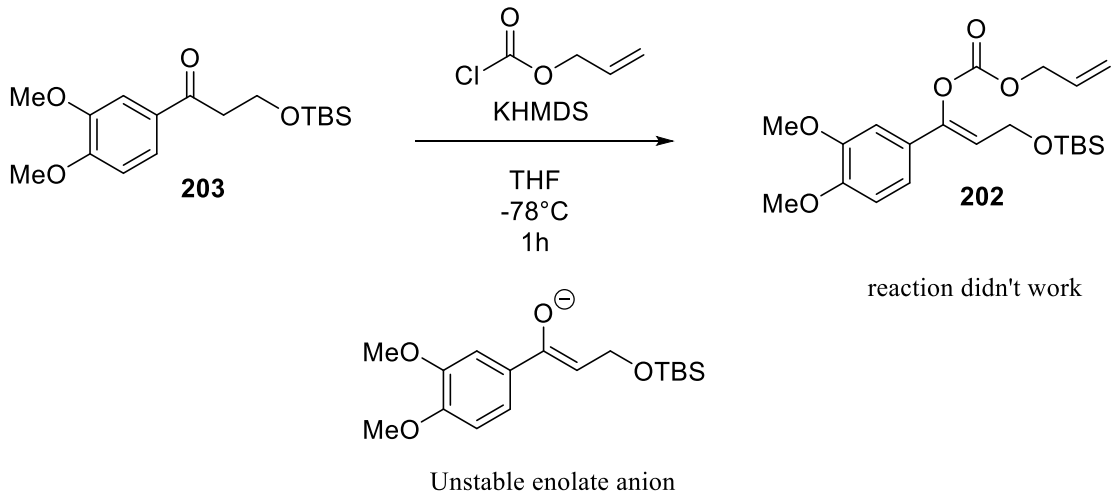
Subsequently, the free hydroxyl group was oxidized to aldehyde **208** with Dess-Martin periodinane. Then, 3,4-dimethoxyphenyl magnesium bromide (**209**) was added to aldehyde **208** to give racemic benzylic alcohol **210**.

Oxidation of the hydroxyl function to give the corresponding ketone **203** was performed both with Dess Martin periodinane and TPAP/NMNO. In the former test (scheme 8.4), the yield obtained was around 50 %, while in the latter it was more than 70%.

8.1.2 Generation of the enol-allyl carbonate **202**

In order to test the Stoltz palladium-catalyzed asymmetric allylation, aryl ketone **203** has to be converted into the corresponding enol-allyl carbonate **202**.

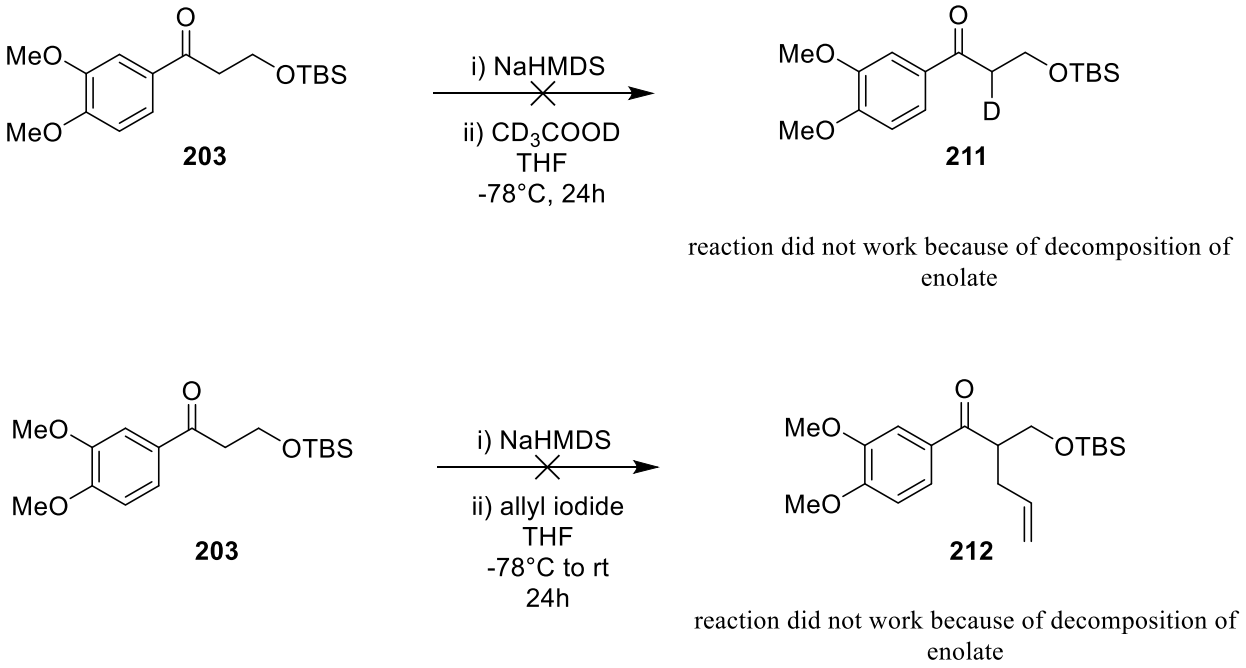
The reaction needed prior generation of the enolate anion, by treating with strong bases like KHMDS, and subsequent functionalization of the oxygen with allyl chloro carbonate.



Scheme 8.5: attempted synthesis of enol-allyl carbonate **202**

Scheme 8.5 reports the first attempt performed. Unfortunately, no traces of product were observed, likely due to the instability of the corresponding enolate. In fact, after addition of the base, reaction mixture became viscous with concomitant formation of several unknown compounds.

We supposed that the reason of such instability was due to the presence of a -OTBS group on the beta position of the ketone, that could cause elimination processes on the enolate.



Scheme 8.6: enolate's formation tests

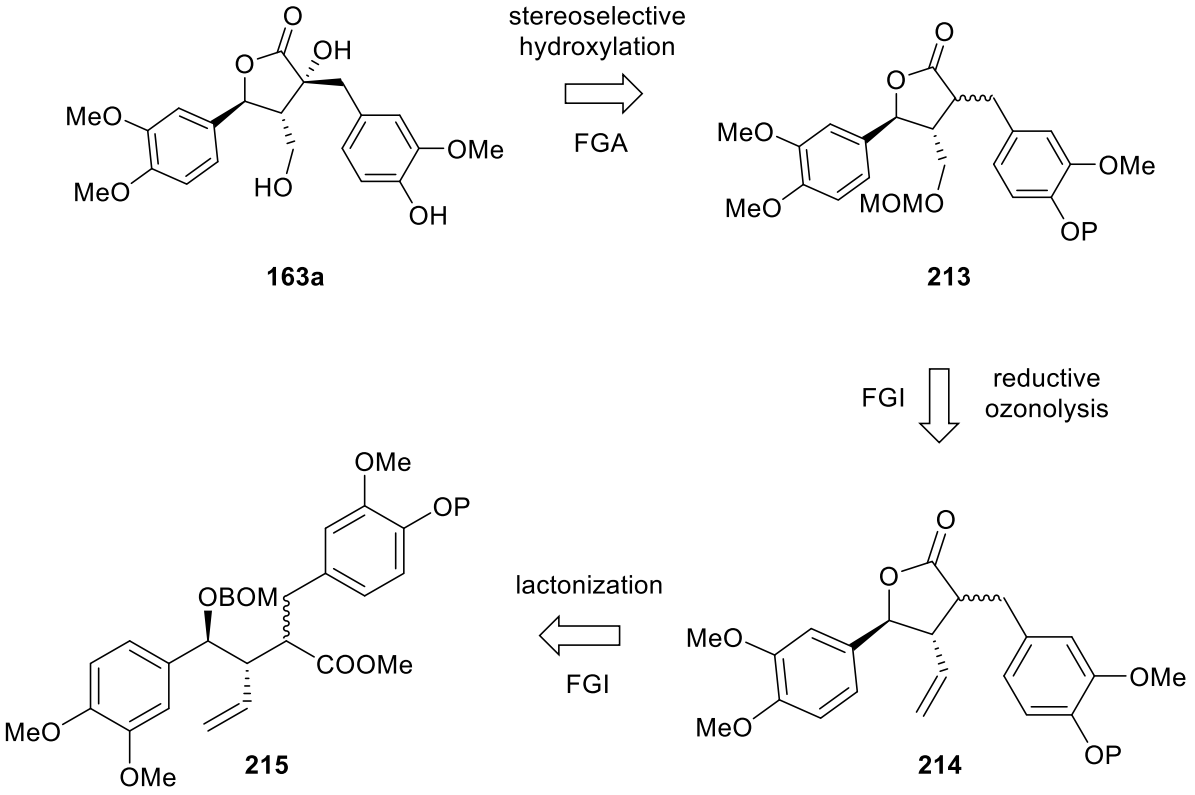
To prove the above hypothesis, an alpha deuteration with CD_3COOD and an alpha allylation reaction with allyl iodide were attempted on the same substrate (scheme 8.6). In both cases we observed decomposition of the enolate.

In conclusion, the Stoltz palladium-catalyzed asymmetric allylation approach, can't be applied on beta silyloxy aryl ketones because of their instability to bases. Thus, the first route has been abandoned and a new one has been proposed.

8.2 Second route to γ-butyrolactone lignan **163**

Because of the problem found within the enolate formation, the first strategy towards γ-butyrolactone lignan **163** had to be changed.

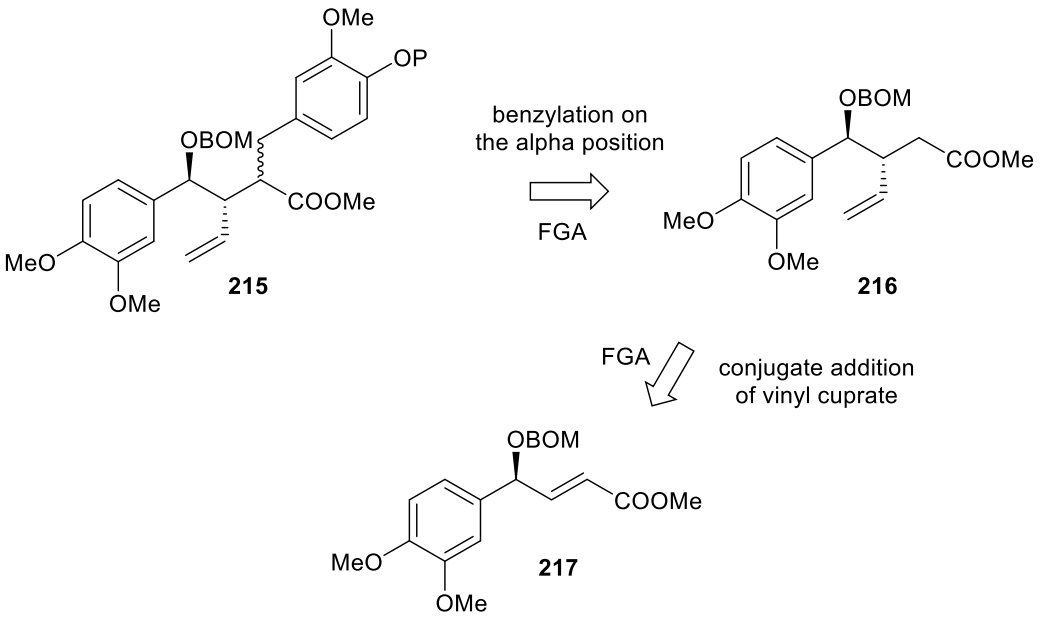
The second synthetic plan we proposed is the one shown in scheme 8.7.



Scheme 8.7: second route to γ-butyrolactone lignan **163**

The first disconnection is the same reported in the previous approach, that is based on the Moritani's procedure for stereoselective hydroxyl insertion.

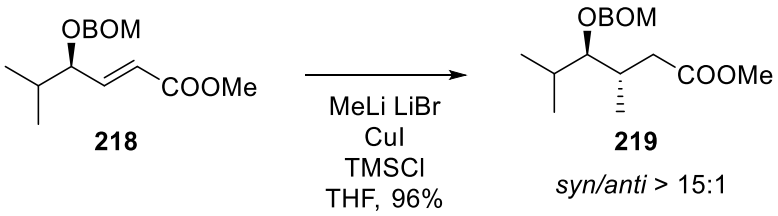
Intermediate **213** derives from olefin **214**, by considering that the beta hydroxymethyl substituent can be obtained by reductive ozonolysis of the corresponding vinyl function. Subsequently, **214** can be obtained via lactonization after deprotection of BOM ether **215**.



Scheme 8.8: second route to γ-butyrolactone lignan **163**

By disconnecting the benzyl substituent on the alpha position, compound **216** is achieved which can be derived from the α-β-unsaturated ester **217** through a diastereoselective conjugate addition of a vinyl moiety.

An analogous strategy was recently exploited by Hanessian and coworkers[77] in the synthesis of contiguous deoxypropionate units (scheme 8.9).



Scheme 8.9[76]: stereoselective methyl addition on unsaturated ester **218**

[77] Hanessian, S., Chahal, N., Giroux, S., *J. Org. Chem*, **2006**, *71*, 7403.

The stereoselectivity of the conjugate addition is guaranteed by the steric hindrance associated to the benzyloxymethyl substituent that drives the attack on the opposite side of the double bond and results in the preferential formation of one of the two possible diastereoisomers (see scheme 8.9).

For the same reasons cited in the previous paragraph about the first route (paragraph 8.1), the stereoselectivity of the subsequent benzylation on the alpha position to the ester is not relevant because the final configuration of the stereocenter is controlled by the last stereoselective hydroxylation.

8.2.1 Synthesis of key intermediate **217**

Alpha-beta unsaturated ester **217**, represents the key intermediate of the second approach to the target.

It is possible to consider it as starting point for the installation of vinyl C_4 chain and benzyl C_3 chain (figure 8.1).

Vinyl substituent acts as precursor of the hydroxymethyl function and it could be inserted through a stereoselective Michael addition of vinyl cuprate, while benzyl chain can be connected to the core by classical enolate alkylation. As reported by Hanessian[76], the stereoselectivity of the double functionalization should be controlled by the hindered BOM protecting group.

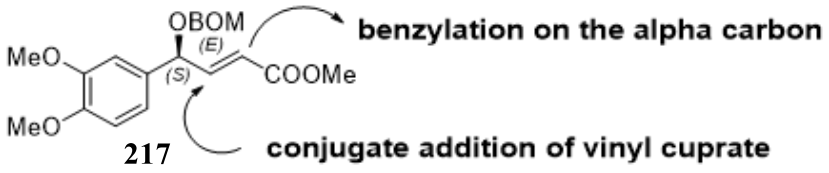
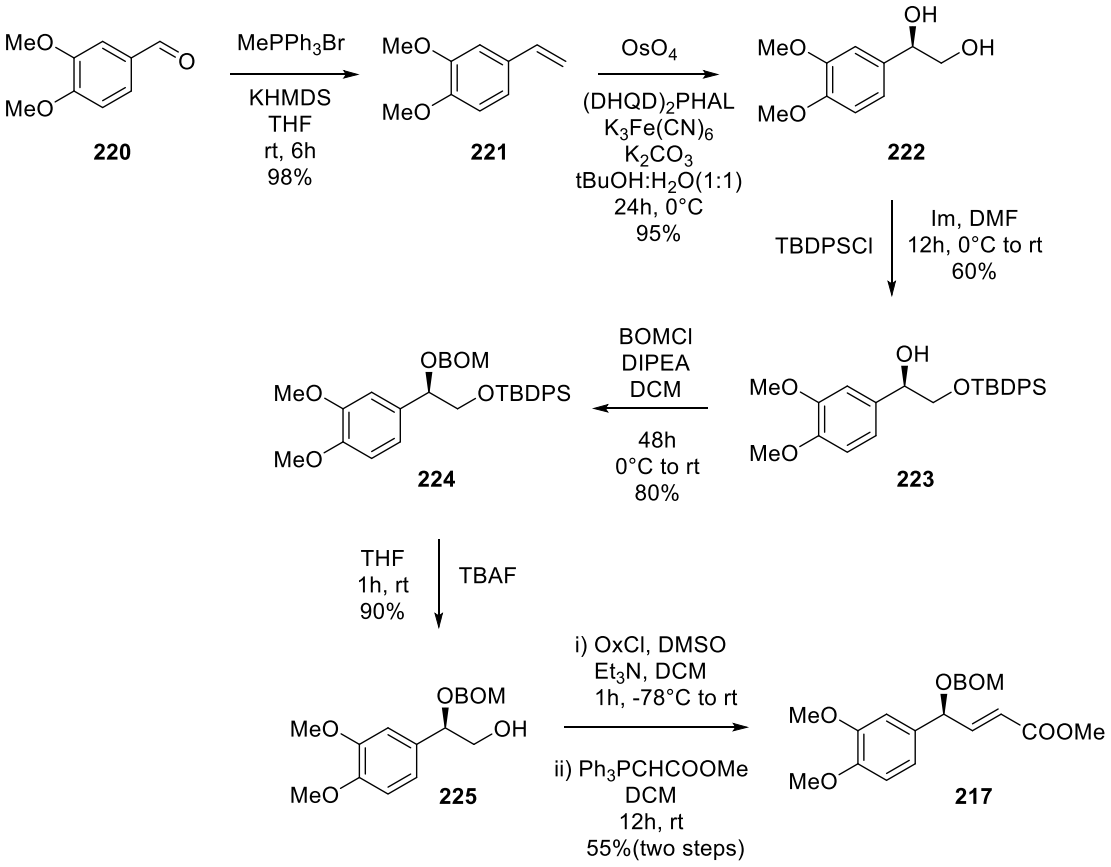


Figure 8.1

For this reason, in order to develop an entire enantioselective strategy, it is fundamental to find a way to intermediate **217**, bearing the (*S*) configuration at the benzylic substituent.

The approach followed for this purpose is based on the Sharpless asymmetric dihydroxylation (AD) and is reported in scheme 8.10.

Commercially available 3,4-dimethoxybenzaldehyde (**220**) was quantitatively converted into 3,4-dimethoxystyrene (**221**) through a classic Wittig reaction. At this point, the double bond was dihydroxylated by following the Sharpless AD protocol, which in this case required $(DHQD)_2PHAL$ as chiral catalyst in order to obtain the desired (*R*) enantiomer. The enantiopurity was confirmed by comparing the $[\alpha]_D$ of the product with the data reported in literature[78].Subsequently, the primary hydroxyl function was selectively protected as TBDPS ether (**223**), and the secondary one was functionalized as BOM ether (**224**).



Scheme 8.10. Synthesis of key intermediate **217**

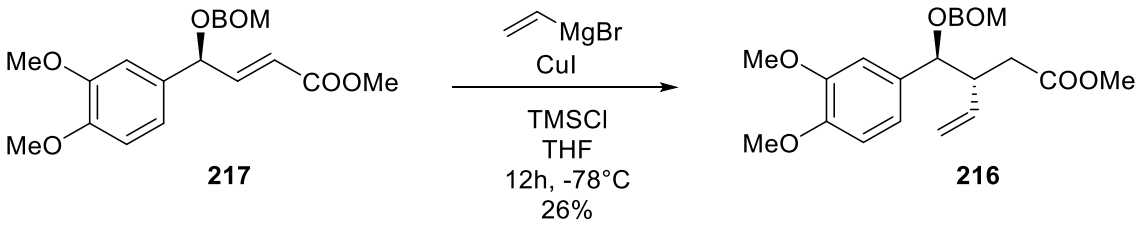
[78] Pradeep K., Rajesh K. U., and Rajesh K. P., *Tetrahedron: Asymmetry,* **2004,** *15*, 3955.

Selective removal of silylether with TBAF, led to compound **225** that finally was oxidized to the corresponding aldehyde through Swern protocol and converted into the alpha-beta unsaturated ester **217** by Wittig reaction.

8.2.2 Alkylation of α,β-unsaturated ester **217**

The vinyl conjugate addition on the α,β-unsaturated ester **217** was performed by using vinyl magnesium bromide and CuI (2:1) in THF, with TMSCl as Lewis acid catalyst[79], as we expected (scheme 8.11), the reaction was completely stereoselective (from NMR analysis), but the yield was not so good (around 26%).

Subsequently, the benzylation reaction on the alpha position was run by using benzyl bromide as tester, in order to observe which yield and which stereoselectivity could be achieved.

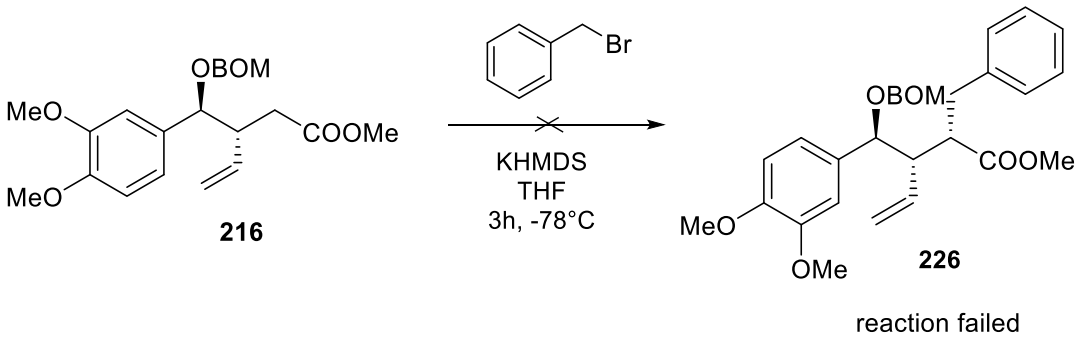


Scheme 8.11: Stereoselective vinyl addition on α,β-unsaturated ester **217**

Unfortunately, the reaction did not work, and even after more than 24 hours, no traces of benzylated product were found (scheme 8.12).

Probably, the steric hindrance of the BOM group on the substrate hampered approach of the benzyl bromide to the enolate.
Because of the high number of synthetic steps employed to obtain α,β-unsaturated ester **217**, the amount of such compound was very low (around 50 mg) and it was enough to perform just one attempt. As a consequence of the not promising outcome of the first trial, it was decided to change the strategy.

[79] Mulzer, J. and Riether, D., *Tetrahedron Letters*, **1999**, *40*, 6197.

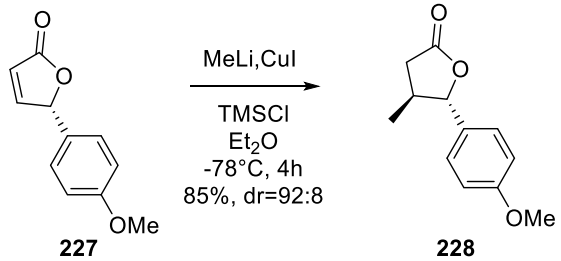


Scheme 8.12: Benzylation test on intermediate **216**

The new approach is characterized by the same key concept as the previous one, i.e. the tandem stereoselective conjugate vinyl addition followed by alpha benzylation. However, a shorter synthetic route leads to the key intermediate. Moreover, this intermediate needs to be less hindered than the BOM derivative employed in scheme 8.11.
Starting from these concepts, the third synthetic plan was developed.

8.3 Third route to γ-butyrolactone lignan **163**

By analyzing the literature concerning stereoselective conjugate addition on α,β-unsaturated esters, we found that in 1996, Mandville and coworkers[80] have performed a highly diastereoselective methyl addition on α,β-unsaturated lactone **227**.



Scheme 8.13[79]: stereoselective methyl addition on α,β-unsaturated lactone **227**

[80] Mandville, G. , Ahmar, M. and Bloch, R., *J. Org. Chem.*, **1996**, *61*, 1122

This outcome suggested us to employ the same approach as developed for the second route, based on the steric effect of a vicinal bulky substituent, but in this case applied on a cyclic system, in particular on α,β-unsaturated lactone **230** (figure 8.2).

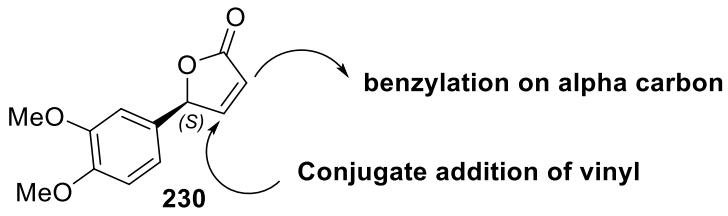


Figure 8.2

Within such strategy, the stereochemical course of the vinyl insertion is regulated by the hindered 3,4-dimethoxyphenyl group on C_5.

As reported in scheme 8.14, until intermediate **214**, the third retrosynthetic plan is very similar to the second one, and all the steps were discussed in the previous paragraph.

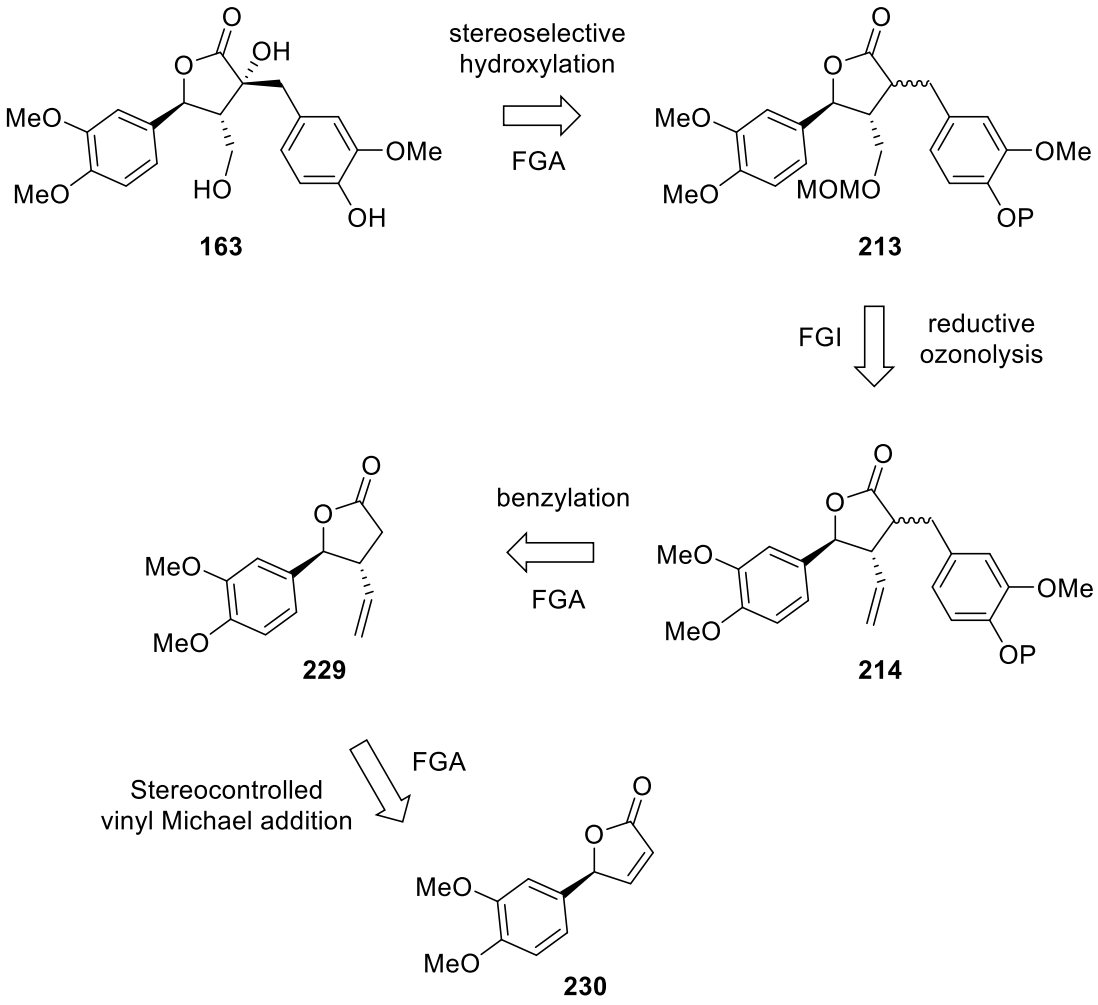
8.3.1 Synthesis of cyclic key intermediate **230**

Initially, the aim of the third approach was to synthetize enantiopure compound **230**, that represents the key intermediate of such synthetic plan.

For this purpose, three different strategies were run, but just the last one allowed us to reach the α,β-unsaturated lactone **230** in a few easy steps and with good yields.

The first two approaches were based on the C_1-O disconnection of the lactone ring, while the last one, involved the disconnection of the conjugated C-C double bond.

Obviously, all the ways proposed were characterized by an enantioselective step for the generation of the C_5 stereocenters.

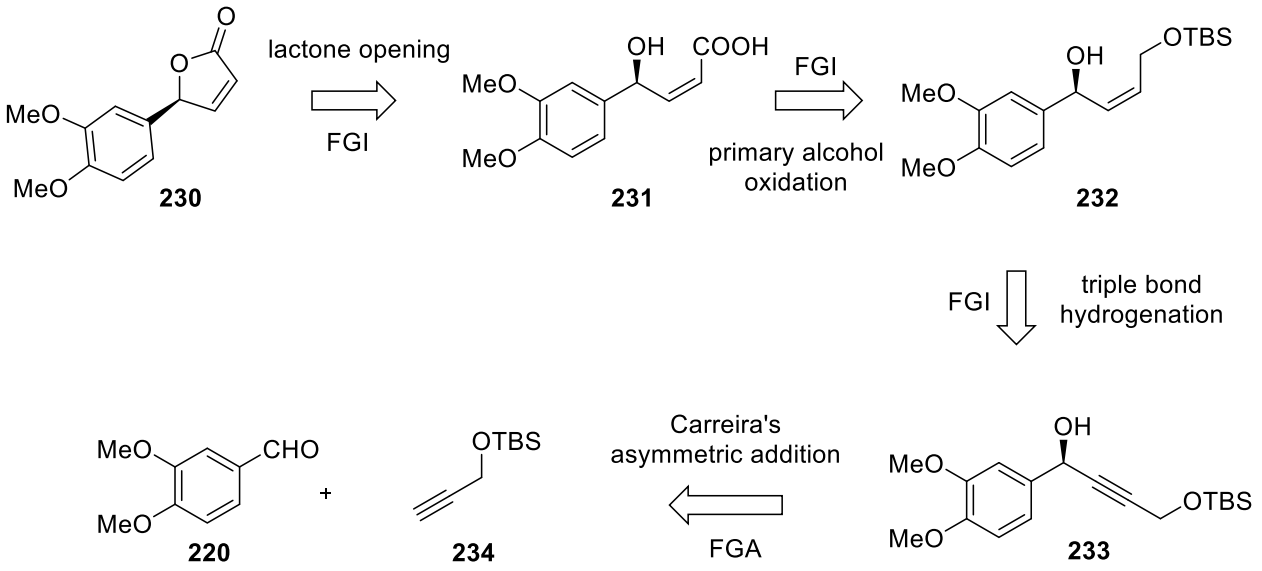


Scheme 8.14: Third retrosynthetic plan for γ-butyrolactone lignan **163**

8.3.2 First synthetic plan to α,β-unsaturated lactone **230**: Carreira's approach

Highly enantioselective alkynylzinc additions to both aliphatic and aromatic aldehydes were performed by Carreira and co-workers[81]. For this reason, we decided to involve this approach for the synthesis of the α,β-unsaturated lactone **230**. The restrosynthetic plan we proposed is shown in scheme 8.15.

[81] Boyall, D., Frantz, D. E. and Carreira, E.M. *Org. Lett.*, **2002**, *4*, 2605.



Scheme 8.15: First retrosynthetic plan to cyclic intermediate **230**

By disconnecting the ester bond of the lactone ring, the *Z*-configured α,β-unsaturated carboxylic acid **231** is obtained. We thought to obtain such intermediate, through selective oxidation of the primary alcoholic function of the (*Z*)-alkene **232**. Since it is an allylic alcohol, it should be easily oxidized to aldehyde with MnO_2 and then to the corresponding carboxylic acid through Pinnick reaction.

The *cis* geometry of the double bond, can be reached by hydrogenation of the alkyne **233** with Lindlar's catalyst.

But the most significant reaction of the entire approach surely is represented by the enantioselective addition of the alkyne **234** on 3,4-dimethoxy benzaldehyde (**220**).

By analyzing all the data published by Carreira and co-workers, we found that generally when aromatic aldehydes were employed, the yields were lower than the ones achieved with aliphatic aldehydes[82]. Moreover, methoxy- substituted benzaldehydes were never used.

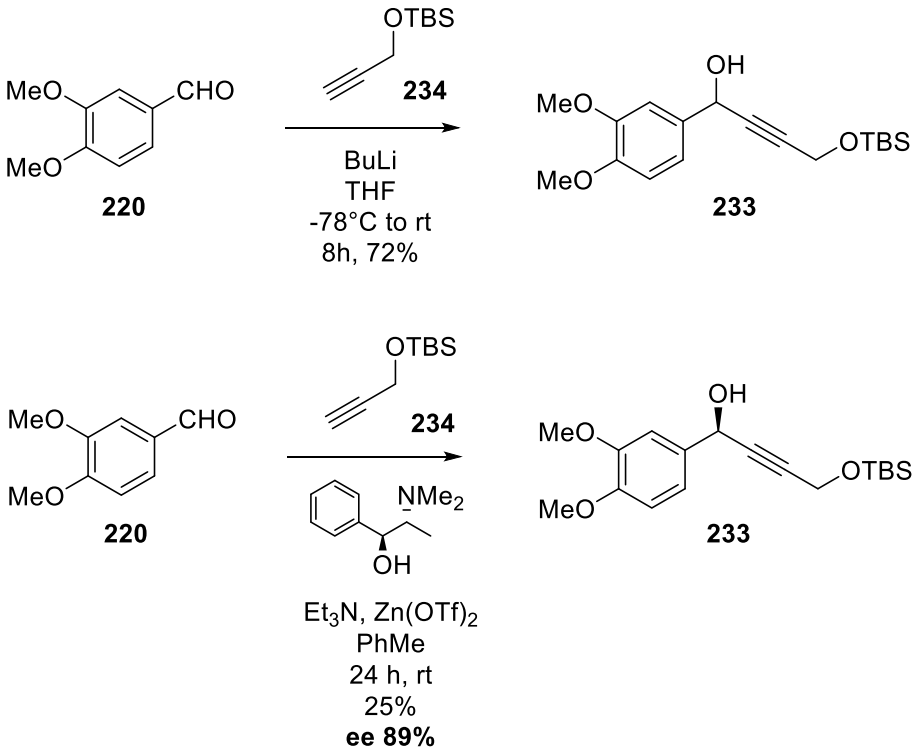
[82] D. E. Frantz , R. Fässler and E. M. Carreira, *J. Am. Chem. Soc.*, **2000**, *122*, 1806.

The TBS protected propargyl alcohol **234**[83] was added to the aliphatic c-C_6H_{11}-CHO with good yield and *ee*, thus we decided to use it within our strategy.

8.3.3 Enantioselective addition of alkyne **234** on 3,4-dimethoxybenzaldehyde.

Our initial aim, was to try to carry out an enantioselective addition of alkyne **234** on 3,4-dimethoxybenzaldehyde by following the Carreira's approach.

At first, the reaction was tested in a non stereoselective way, just to check if the product can be formed or not, and scheme 8.16 shows that racemic propargylic alcohol **233** was obtained with 72% of yield, by treating alkyne **234** with BuLi in presence of aldehyde **220**. Then the enantioselective version was performed.



Scheme 8.16

[83] K. Anand, E. M. Carreira, *J Am Chem Soc.* **2001**, *123*, 9687.

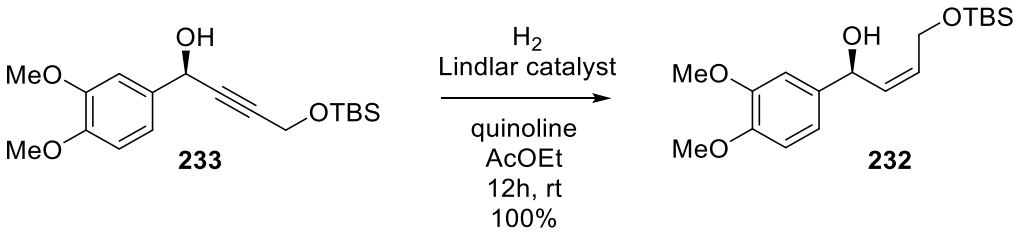
A stoichiometric amount of chiral amino alcohol, N-methylephedrine, was used to control the stereoselectivity of the process.

The typical procedure was run, a toluene solution of the 3,4-dimethoxybenzaldehyde and alkyne, was treated with 1.1 equivalents of $Zn(OTf)_2$, 1.2 equivalents of Et_3N and 1.2 equivalents of chiral base.

The reaction took 24 hours to complete and the resulting enantioselectivity was good. The (*R*)-enantiomer of the propargylic alcohol **233** was obtained in 25% of yield and 89% *ee*.

The absolute configuration of the stereocenter was defined by comparison with the results reported in literature for reaction on similar substrates[81-82] employing the same enantiomer of chiral ligand, and *ee* was determined by chiral HPLC (Chiralcel OD, Heptane:iPrOH 90:10).

Subsequently, hydrogenation of the triple bond with Lindlar's catalyst led to the (*Z*)-alkene **232** in quantitatively yields.



Scheme 8.17

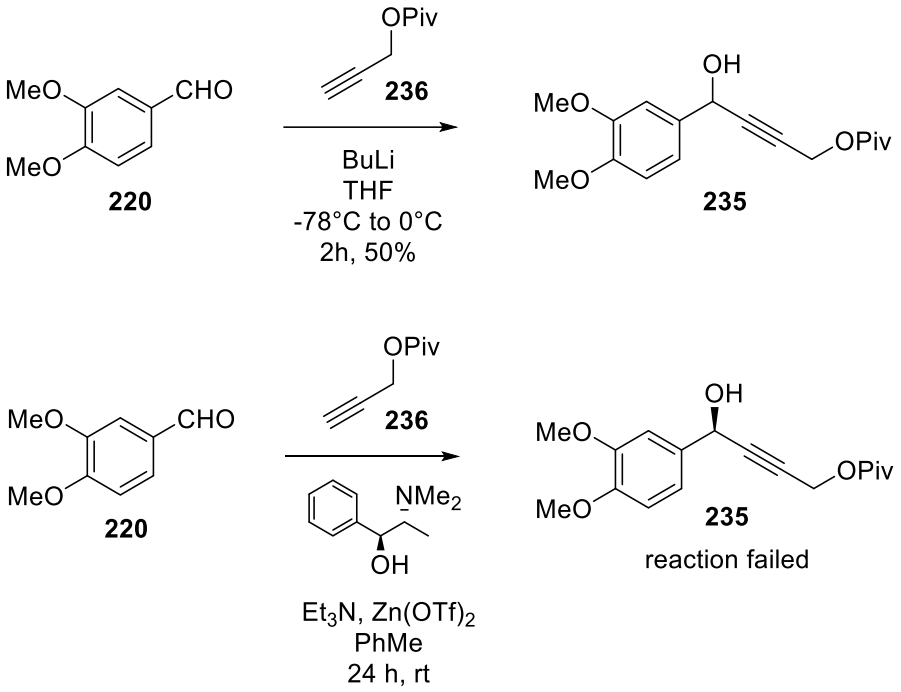
Despite the good enantioselectivity found, the addition showed a low yield, thus we decided to try other strategies.

The Carreira's reaction was tested on the same aldehyde (**220**), by changing the alkyne. Scheme 8.18 reported the attempt performed with the pivalic ester of 2-propyn-1-ol (**236**).

In the non stereoselective version, the product **235** was obtained with 50% of yield because of the partial decomposition of alkyne **236** under reaction conditions.

Unfortunately, the asymmetric version of the same reaction, that was carried out with the Carreira's procedure, didn't work because in this case the reaction was slower than the non stereoselective one and probably all the alkyne **236** decomposed during the experiment.

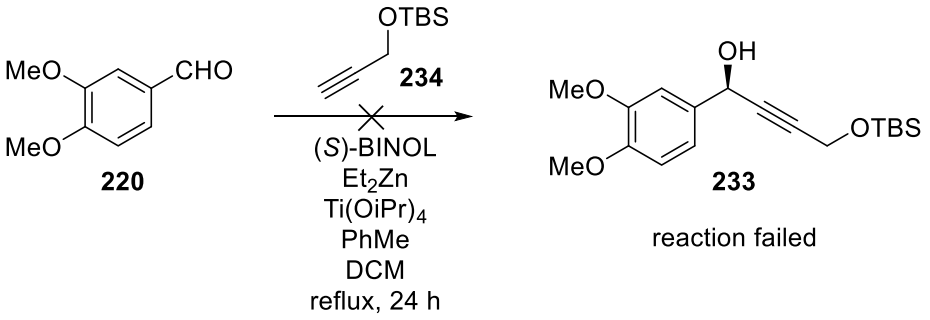
In 2002, Moore and coworkers, proposed a BINOL-catalyzed highly enantioselective terminal alkyne additions on aromatic aldehydes[84]. Within this work, phenylacetylene was added to different kinds of substituted aromatic aldehydes with high yields and *ee*.



Scheme 8.18

By following Moore approach, we tried to add alkyne **234** on 3,4-dimethoxybenzaldehyde, but no traces of product were observed (scheme 8.19).

[84] Moore, D. and Pu, L., *Org. Lett.,* **2002**, *4*, 1855.



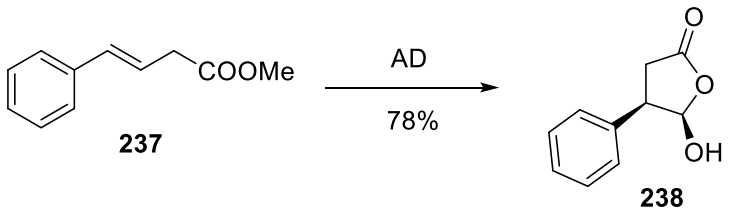
Scheme 8.19

In conclusion, the Carreira's approach we proposed to achieve intermediate **230** led to good enantioselectivty when conditions reported in scheme 8.16 were employed. Unfortunately, the highest yield observed was around 25%. So, for this reason, we decided to change the strategy towards a new more efficient one.

8.3.4 Second synthetic plan to α,β-unsaturated lactone **230**: Sharpless approach

Also the second route to the cyclic intermediate **230** was based on the disconnection of the C_1-O bond, but in this case, the enantioselective key step was represented by the Sharpless asymmetric dihydroxylation.

In 2006, Eissler and coworkers reported a strategy for Cryptophycin unit A total synthesis[85] that employed compound **238** as intermediate (scheme 8.20). We thought to use such strategy, in order to obtain α,β-unsaturated lactone **230**.

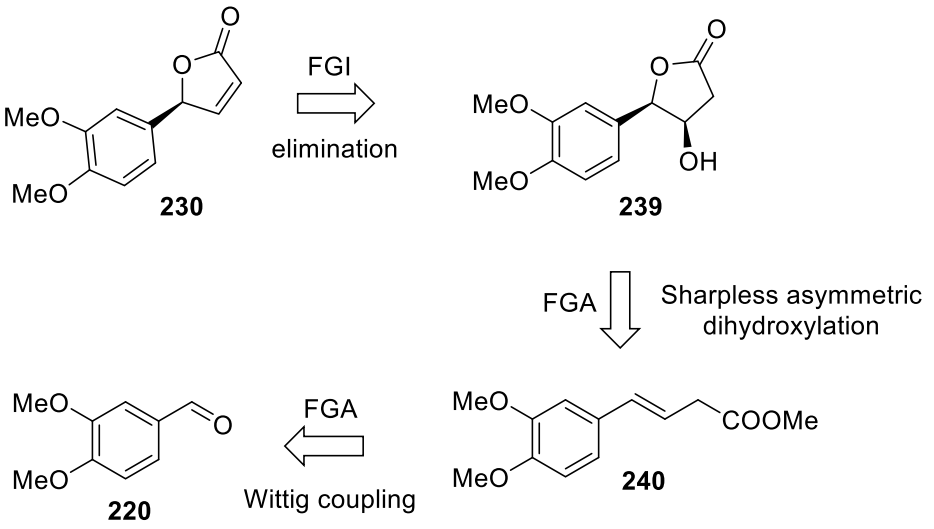


Scheme 8.20

[85] Eissler, S., Nahrwold, M., Neumann, B., Stammler, H.G. and Sewald, N., *Org. Lett.*, **2007**, *9*, 817.

Scheme 8.21 illustrates the entire synthetic plan. Lactone **230** can be generated from the alcohol **239**, through an elimination reaction. The driving force of this process should be the conjugation of the resulting double bond with the carboxylic function.

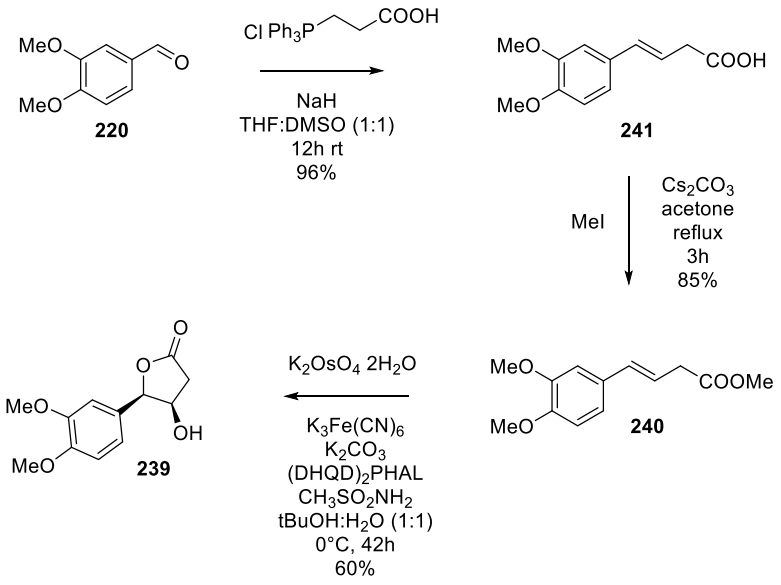
A Sharpless asymmetric dihydroxylation, allows to derive compound **239** from the unsaturated ester **240**. It's important to note that the corresponding enantiopure diol cyclizes as soon as it is formed.



Scheme 8.21: Second retrosynthetic plan to cyclic intermediate **230**

By disconnecting the C-C double bond through a Wittig reaction, alkene **240** may be derived from the commercially available 3,4-dimethoxybenzaldehyde.

All the reaction conditions of this strategy are shown in scheme 8.22



Scheme 8.22

Unsaturated carboxylic acid **241** was synthetized starting from aldehyde **220** by using the commercially available phosphonium salt reported on the arrow (scheme 8.22) with high yield.

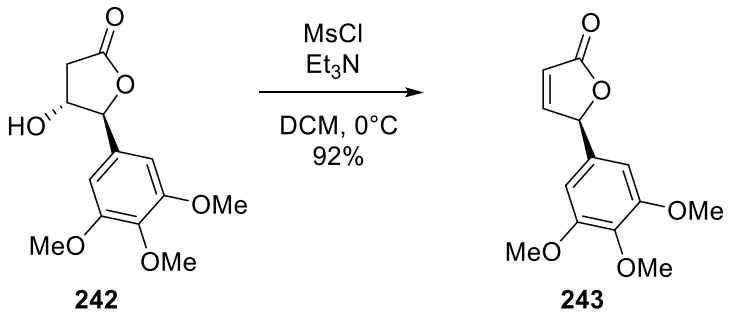
Methylation of the carboxylic function with iodomethane gave methylester **240**, that subsequently was cyclized through Sharpless AD to obtain alcohol **239** with good yield[86].

In this case, K_2OsO_4 was used instead of the most common OsO_4, because it shows less toxicity and is easier to handle.

For the elimination of the hydroxyl function, initially we followed the procedure reported by Wu and coworkers[87] on a very similar substrate (scheme 8.23).

The alcohol is activated as mesilate ester and in presence of a base like Et_3N it quickly undergoes elimination to the corresponding α,β-unsaturated lactone with high yields.

[86] Eissler, S ; Nahrwold, M.; Neumann, B.; Stammler, H.; Sewald, N., *Organic Letters*, **2007** , *9*, 817
[87] X. Wu, M. Li, and P. Wang, *Org. Lett.*, **2007**, *9*, 817.



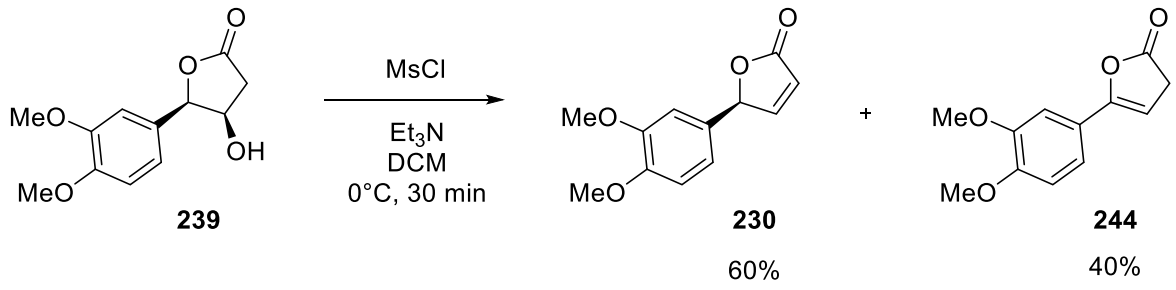
Scheme 8.23

When the same reaction protocol was applied on intermediate **239**, only 60% of right product **230** was formed. Moreover, the reaction was not reproducible, sometimes it gave lower yields even if the reaction conditions was always the same.

We supposed that this problem was related to the relative stereochemistry of the hydroxyl group and the hydrogen on C_5.

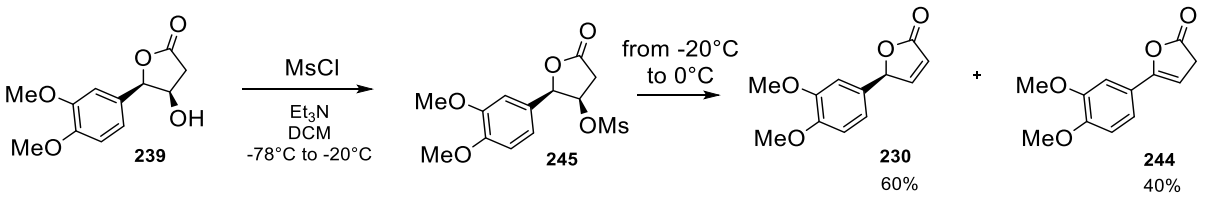
In the experiment reported by Wu, such stereochemistry is *syn*, thus, the C_5 hydrogen does not possess the correct *anti* orientation necessary to have elimination. The hydrogen that shows antiperiplanar orientation to the leaving group is on C_3, so the only possible product is the one having the double bond conjugated with the carboxylic function.

On the contrary, compound **239** shows an *anti* geometry between the hydroxyl function and the C_5 hydrogen. In this way, the base can extract the hydrogen both from C_3 and C_5, making possible the formation of the double bond conjugated with the aromatic ring.



Scheme 8.24

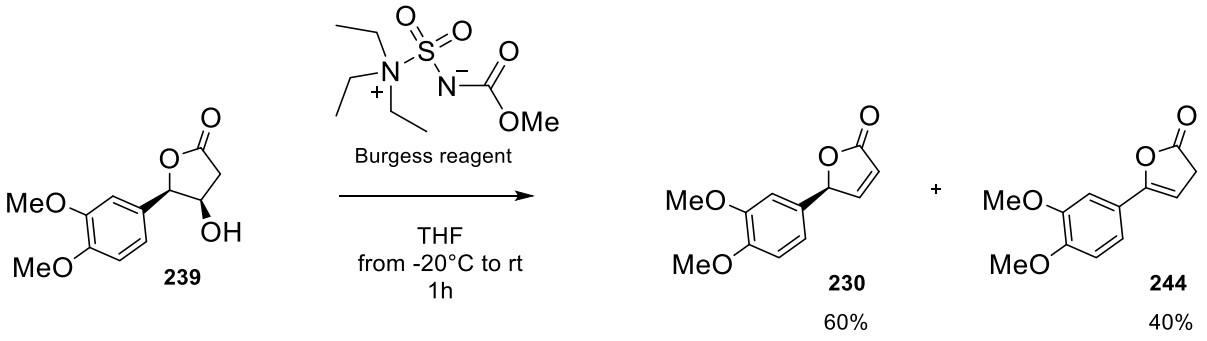
This is actually what's happened when we tried the elimination for the first time (scheme 8.24). Two different products were isolated and, after characterization, we found that the major compound was the desired α,β-unsaturated lactone **230**, while the minor one, was the compound in which the double bond was conjugated with the phenyl substituent (**244**) . Moreover, the ratio of the isomers was different every time the reaction was tried.



Scheme 8.25

As reported in scheme 8.25, the elimination was run also at lower temperature, in order to observe if the isomer ratio could be controlled. From -78°C to -20°C, the intermediate mesilate was quite stable and didn't undergo the elimination. But when the temperature was slowly raised to 0°C, the elimination quickly took place and around 40 % of the product was the wrong isomer.

It's intriguing that even when Burgess reagent was used (scheme 8.26), around 40% of the alkene product showed the double bond conjugated with the aromatic substituent, despite with that reagent, elimination takes place with *syn* elimination.



Scheme 8.26. Burgess approach to lactone **230**

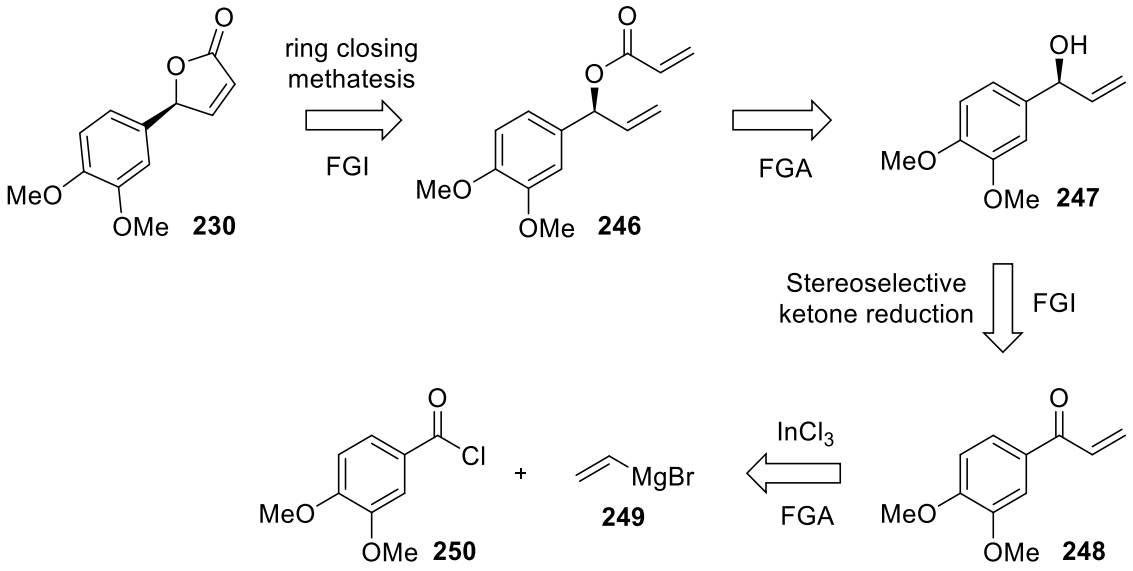
In conclusion, the poor reproducibility of the elimination prompted us to look for a more efficient way to the product.

8.3.5 Third synthetic plan to α,β-unsaturated lactone **230**: methatetic approach

The last approach followed for α,β-unsaturated lactone **230** synthesis, is based on the disconnection of the C_3-C_4 double bond.

The key reaction of such strategy is represented by the ring closing methatesis on the dialkenes **246** (scheme 8.27), catalyzed by 2nd generation Grubbs catalyst[88]. The driving force, of course, is the formation of a five-membered ring containing a conjugated double bond.

In contrast to the second approach, in this case compound containing double bond conjugated with the aromatic ring can't be formed.

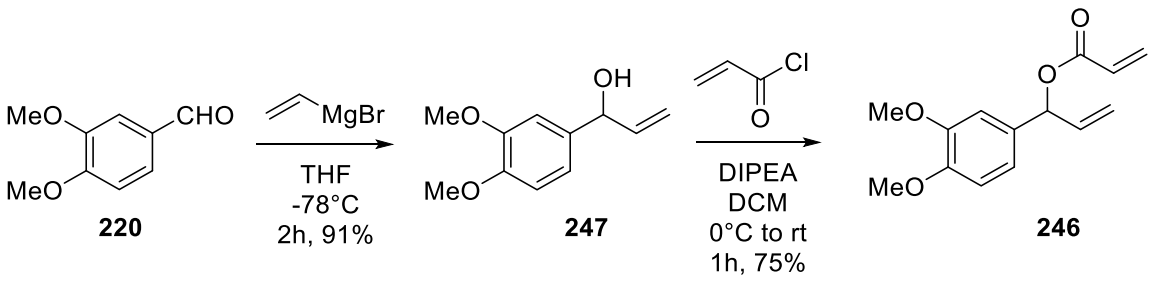


Scheme 8.27: third retrosynthetic plan to α,β-unsaturated lactone **230**

[88] S. Krehl, D. Geißler, S. Hauke, O. Kunz, L. Staude and B. Schmidt, *Beilstein J. Org. Chem.* **2010,** *6,* 1188.

Scheme 8.27 shows the entire retrosynthetic plan. Chiral dialkene **246** can be prepared from benzylic alcohol **247**, which can be derived from the unsaturated ketone **248** through a stereoselective reduction of carbonyl function.

Finally, compound **248** can be easily obtained from commercially available 3,4-dimethoxybenzoyl chloride and vinyl magnesium bromide.



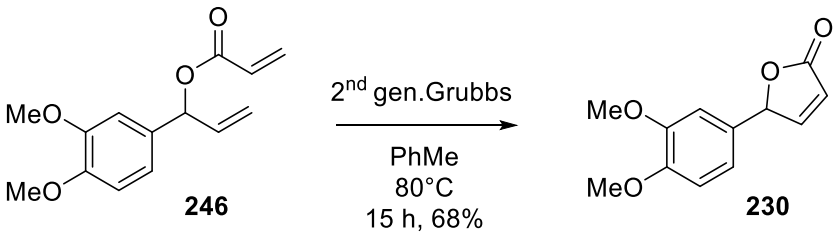
Scheme 8.28

The first attempts of cyclization were performed on the racemic substrate **246** because we wanted to verify if the reaction could take place or not.

So, by following the procedure reported in scheme 8.28, the dialkene **246** was synthetized.

3,4-dimethoxybenzaldehyde (**220**) was treated with vinyl magnesium bromide, and racemic benzyl alcohol **247** was obtained. Acylation with acryloyl chloride led to compound **246** with good yield.

Subsequently, ring closing methatesis was run, by following the procedure reported by Krehl and coworkers on a similar substrate[87], that involved toluene as solvent, 2nd generation Grubbs catalyst and a reaction temperature of 80°C.



Scheme 8.29. Methatetic approach to lactone **230**

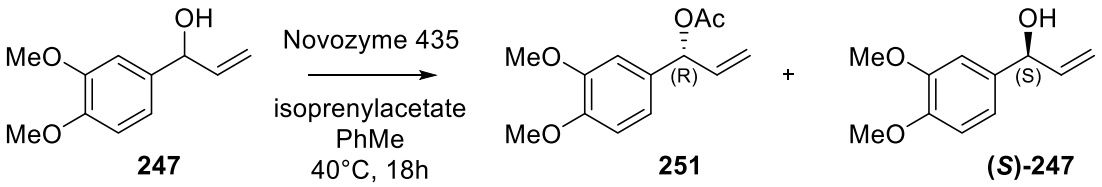
High dilution conditions were necessary in order to avoid intermolecular coupling. After 1.5 hours reaction was completed with good yields.

8.3.6 Toward enantiopure α,β-unsaturated lactone 230

In order to develop an enantioselective total synthesis of lignan **230**, based on the ring closing methatesis approach discussed above, it's fundamental to find a way to obtain benzyl alcohol **247** with the right configuration of the stereocenter.

To reach this goal, we can follow two different approaches, one based on the resolution of the racemic mixture and the other based on an enantioselective reaction.

By analyzing the literature, we found that in 2008, Stambasky and coworkers[89] developed an enzymatic resolution of the alcohol **247** (scheme 8.30), that allows to obtain (*S*)-enantiomer through selective acetylation of the (*R*)-enantiomer.



Scheme 8.30: enzymatic resolution of alcohol **247**

The resulting pure (*S*)-enantiomer **247** will be used for the subsequent steps of the synthetic plan.

An issue associated with this strategy is that half of the starting material, the (*R*)-enantiomer, can not be employed in the synthetic path, thus we decided to look for an enantioselective

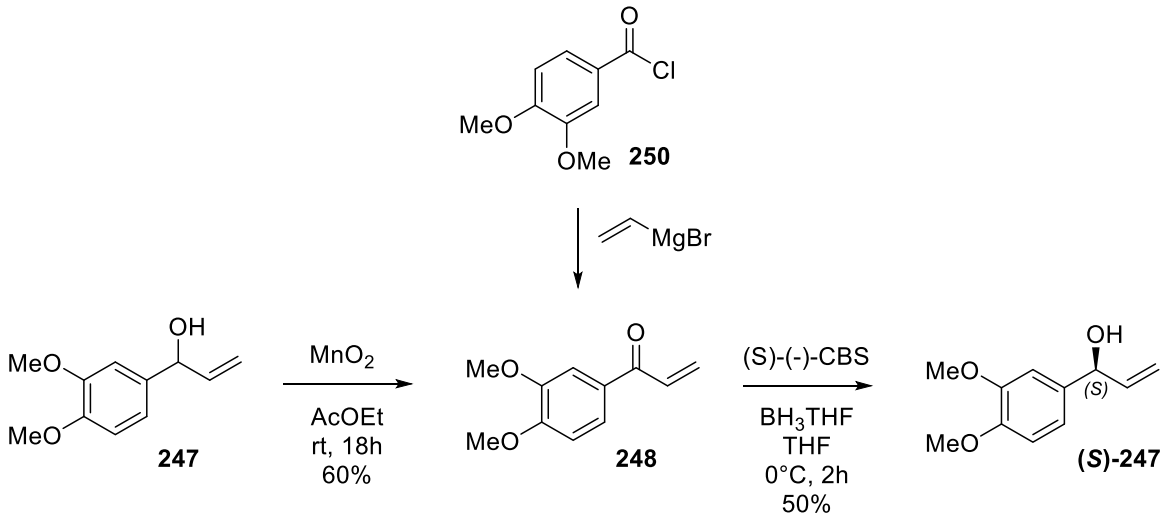
[89] Stambasky, J., Malkov, A.V. and Kovsky, P., *J. Org. Chem.* **2008**, *73*, 9148.

reaction that allows to achieve directly (*S*)-enantiomer starting from an achiral substrate. By looking at the literature, we decided to try the reaction involving CBS catalyst[90].

Oxidation of racemic benzylic alcohol **247** leads to achiral ketone **248** (scheme 8.31). Anyway, it can be prepared in a single step reaction starting from 3,4-dimethoxy benzoyl chloride and vinyl magnesium bromide[91], transforming the Grignard reagent into the corresponding $R_4InMgCl$ reagent.

As reported in scheme 8.31, reduction of the carbonyl function with BH_3 and (*S*)-(-)-CBS as chiral catalyst led to enantioenriched benzylic alcohol **247** in 50% of yield. The $[\alpha]_D$ value of the mixture, $[\alpha]_D$ -9 (c 2.78, PhH), showed that the (*S*)- enantiomer is the most abundant one (by comparison with the value reported in literature, $[\alpha]_D$ -10.8 (c 2.78, PhH)[92].

Unfortunately, this promising result was achieved at the end of the period spent in the laboratory of Professor Hanessian, so we can just say that it paved the way to an enantioselective route toward lignan **247**.



Scheme 8.31: Stereoselective reduction of ketone **248**

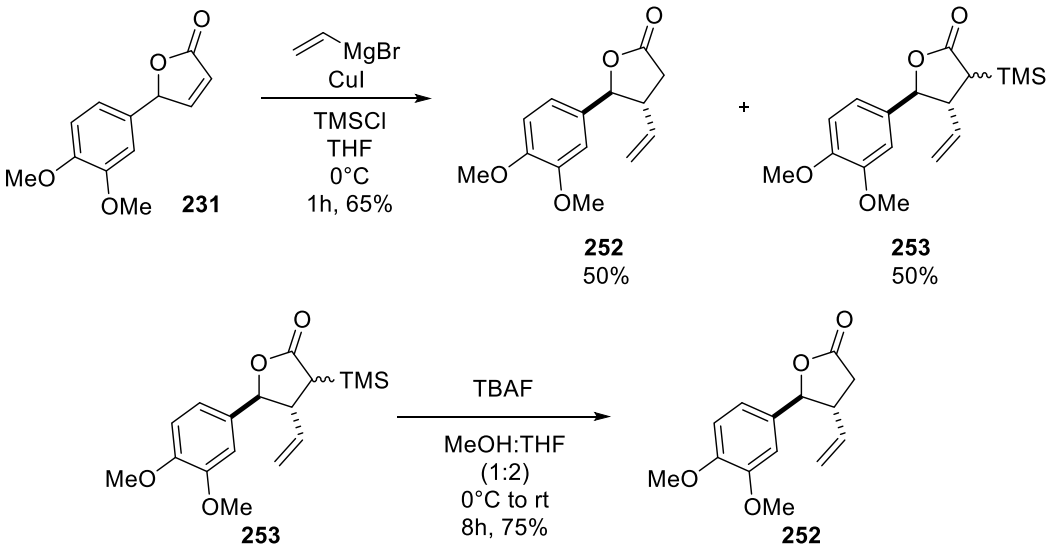
[90] Wang, G.Y.; Liu, X.Y.; Zhao, G., *Synlett*, **2006** , *8* , 1150.
[91] Lee, P. H.; Lee, S.W. ; Seamon, D., *Organic Letters*, **2003**, 4963
[92] J. Stambasky, A. V. Malkov and P. Kovsky, *J. Org. Chem.* **2008**, *73*, 9148

8.4 Towards the synthesis of γ-butyrolactone lignan **163**

8.4.1 Stereoselective conjugate addition of vinyl cuprate

Once synthetized, racemic lactone **230** was involved for the total synthesis of γ-butyrolactone lignan **163**, by following the third synthetic approach proposed (see paragraph 8.3.1).

At first, stereoselective Michael addition of vinyl cuprate was tested. Reaction conditions employed, were the same found in literature for similar substrates, that involved vinyl magnesium bromide and CuI (2:1) for the organocuprate generation and TMSCl as stoichiometric Lewis acid[75].



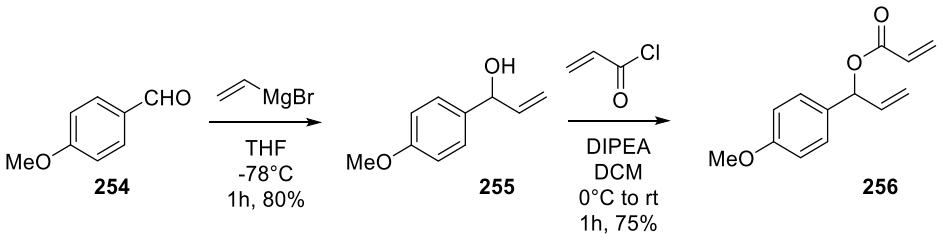
Scheme 8.32. Stereoselective vinyl addition on lactone **230**

As can be seen in scheme 8.32, the addition proceeded with complete stereoselectivity, with the vinyl group showing *anti* geometry respect to the phenyl substituent (stereoselectivity was evaluated by NMR analysis). The total yield of alkylated lactone was 65%, but around 50 % of the product showed the TMS group on the alpha position. This did not represent a big problem, because by treating the silyl derivative with TBAF, the TMS group can be easily removed.

While we were working on the lactone **230** synthesis, we thought that probably the ortho-dimethoxy pattern on the aromatic ring could be a problem when metallic species were involved in the reactions, because of the ability that such system possess, to act as bidentate coordinating agent for metals.

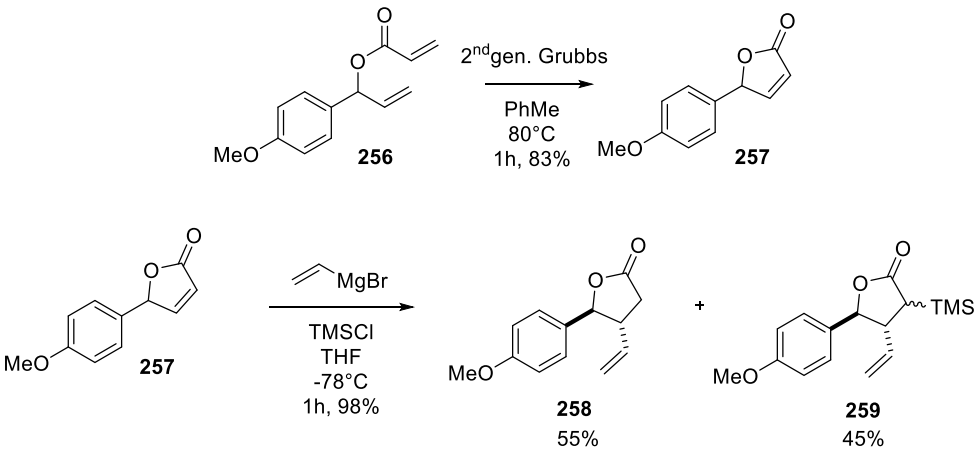
For this reason, the 4-methoxy derivative **256** was synthetized (scheme 8.33) and tested on the same reactions involved in lactone **230** path, in order to see if the reaction course could be positively affected by the lack of the chelating system.

It can be observed that both the methatesis and the vinyl addition on the mono-methoxy derivative showed higher yields than the ones reported for the ortho-dimethoxy derivative.



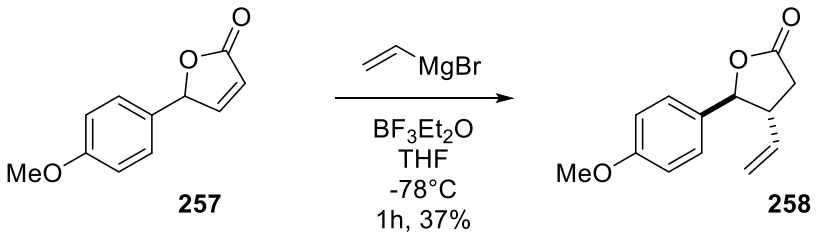
Scheme 8.33. Synthesis of 4-methoxy derivative **256**

Both the reactions involve the use of metals; catalytic amount of ruthenium is employed for the methatesis, while copper iodide and vinyl magnesium bromide are used for the conjugate addition. Thus, we supposed that, the coordination of the ortho-dimethoxy system to the metal could negatively affect the reaction's outcome.



Scheme 8.34: tests on mono-methoxy derivatives

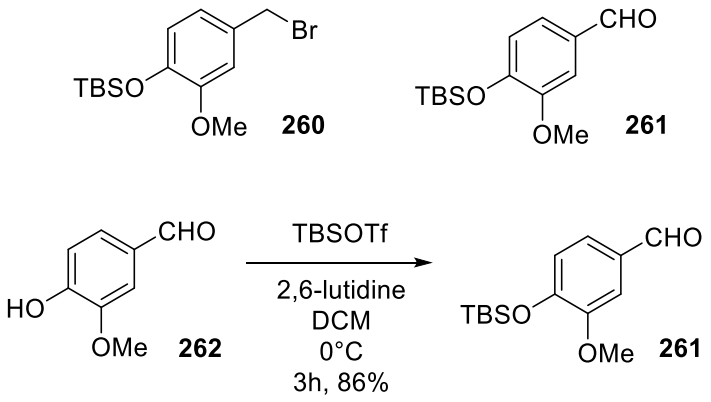
Also when the monomethoxy derivative was employed, the conjugate addition proceeded with the formation of around 45% of alpha-TMS lactone **259**. For this reason, we decided to test the reaction by using BF_3Et_2O as Lewis acid, but the total yield was worse than the one reported with TMSCl, because most of the substrate underwent polymerization.



Scheme 8.35. BF_3Et_2O catalyzed vinyl conjugate addition

8.4.2 Benzylation on the alpha position

To attach the benzyl substituent on the alpha position, the strategy we decided to run is based on an aldol condensation followed by deoxygenation, by using TBS-protected aldehyde **261** as alkylating agent. This approach seemed to be easier than the one involving 3-methoxy-4-hydroxybenzyl bromide **260**, that is more difficult to prepare than aldehyde **261** (scheme 8.36).

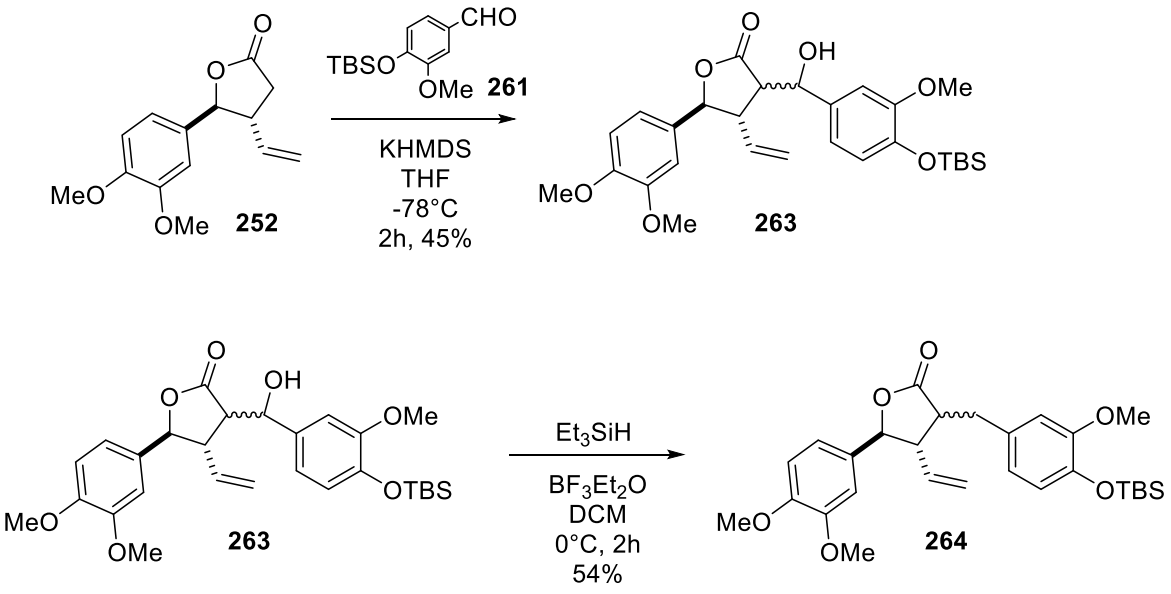


Scheme 8.36

Scheme 8.37 reports the outcomes of the preliminary tests performed on substrate **252**.

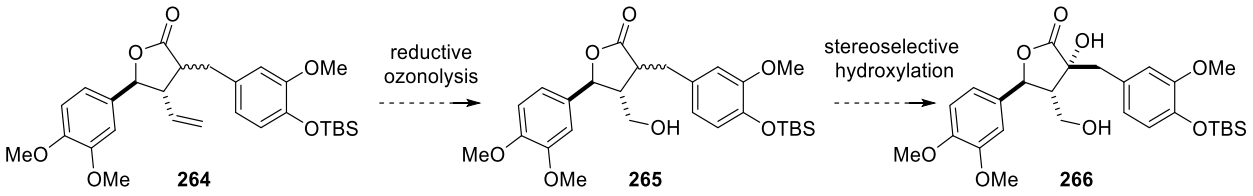
By treating lactone **252** with KHMDS and aldehyde **261**, condensation took place in 45% yield. The resulting product was a complex mixture of isomers, but that did not represent a problem because the following deoxygenation removed one of the stereocenters and the last stereoselective hydroxylation is not affected by the configuration of the alpha benzyl substituent (Moritani approach, paragraph 7.3).

The hydroxyl group removal was carried out by using Et_3SiH and BF_3Et_2O with 54% of yield. In this way compound **264** was achieved.



Scheme 8.37. Preliminary benzylation test on racemic **252**.

Due to lack of time, it has been impossible to continue with the strategy proposed, that requires ozonolysis of the vinyl function and stereoselective hydroxylation on the alpha position in order to get the final compound core (scheme 8.38).



Scheme 8.38.

Anyway, after several attempts, we can claim to have paved the way toward the γ-butyrolactone lignan **163**, by outlining a strategy for the construction of the 3,4,5-trisubstituted lactone core **264**. Moreover, the last stereoselective hydroxylation is already reported in literature on a very similar substrate.

At this time, at the laboratory of Professor Stephen Hanessian, work is underway aimed at ending the synthesis as soon as possible.

Conclusion of the Thesis and future perspective

By summarizing all the work done within this PhD Thesis, it is possible to say that the main goals achieved are:

- The development of an efficient, highly stereoselective strategy, for the construction of 3-hydroxy-*trans*-2,5-disubstituted tetrahydrofuran cores, showing an excellent synthetic versatility.

- The application of the previous methodology to the construction of a very useful synthetic intermediate (diol **64**) and the development of a synthetic strategy toward the anthelmintic oxylipide **46** from *Notheia anomala.*

- The extension of the methodology to alternative *meso* diol systems bearing an extra-substituent on the central carbon (compounds **141** and **156**), that provided preliminary results towards the implementation of a stereoselective strategy for tetrasubstituted THF cores.

- The development of a stereoselective route towards γ-butyrolactone lignan **163** from *Acer saccharum*.

At the moment, work is in progress in order to improve what was achieved whitin this PhD Thesis, in particular, the principal future perspectives are:

- To find an efficient strategy for the installation of the unsaturated side chain of oxylipide **46.**

- To improve the cyclization conditions for substituted meso diol systems **141** and **156** and involve the best result for the development of a new total synthesis.

- To extend the methodology to oxygenated six-membered rings and to nitrogen containing heterocycles.

EXPERIMENTAL SECTION

Materials and methods

Within the sperimental section of the Thesis, the following materials and instrumensts were employed.

For the characterization of compounds:

- Spectrometer NMR Bruker, 200, 300 and 400 MHz;
- Polarimeter Perkin-Elmer 241;
- Spectrometer FT-IR Perkin Elmer Paragon 100 PC;
- ESI-MS Thermo LTQ

For the chromatographic purification of compounds:

- Kieselgel 60 Merck (230-400 mesh) for flash chromatography;
- Isolera One Biotage Flash Chromatography Purification System with Uv-Vis detector for automatic preparative chromatographic purification;
- HPLC/UV: Jasco PU-2080 Plus, detector UV-2075 Plus
- TLC (direct phase) : silica gel GF-254 Merck (0.25 mm)
- For TLC development: Lamp (254 nm and 366 nm), vanilline solution (0.5% H_2SO_4-EtOH); Phosphomolibdic acid (20 % in EtOH); $KMnO_4$ in acetone, Hanessian stain.

All the reactions requiring dry and static atmosphere and involving moisture and oxygen sensitive reagents, were performed under Argon atmosphere, in dry glass stored at 120°C inside a hoven.

Most of the reaction solvents were dried by distillation on appropriate drying agents, under Ar atmosphere. In particular, THF and Et_2O were dried on sodium/benzophenone, toluene on metallic sodium, DCM and pyridine on calcium hydride and methanol on molecular sieves.

Common abbreviations involved in the procedures:

Ac: acetyl

BRINE: sodium chloride saturated solution

ROCHELLE salt solution: sodium potassium tartrate saturated solution

DCM: dichloromethane

DET: diethyltartrate

DMF: dimethylformamide

DMP: Dess-Martin Periodinane

DMSO: dimethylsulfoxide

DMS: dimethylsulfide

Im: imidazole

Py: pyridine

DMAP: 4-dimethylaminopyridine

KHMDS: potassium hexamethyldisilylamide

NaHMDS: sodium hexamethyldisilylamide

MTBE: methyl *t*-Butyl ether

Piv : pivaloyl

TBAF: tetrabutyl ammonium fluoride

TES: Triethylsilyl

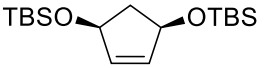
TBS: *t*-Butyl dimethylsilyl

TBDPS: *t*-Butyl diphenylsilyl

Ts: Tosyl

THF: tethrahydrofuran

Synthesis of (3*R*,5*S*)-3,5-bis((tert-butyldimethylsilyl)oxy)cyclopent-1-ene (**98**)



Chemical Formula: $C_{17}H_{36}O_2Si_2$
Molecular Weight: 328.64

Imidazole (2.72 g, FW=68.08, 39.95 mmol, 8 eq) and DMAP (61 mg, FW = 122.17, 0.5 mmol, 0.1 eq) were solubilized in dry DCM (9 ml) under Ar atmosphere. A solution of diol **93** (500 mg, FW=100.12, 5 mmol, 1 eq) in DMF (500 µL) was added dropwise via syringe. The mixture was cooled to 0°C, then TBSCl (2.00 g, 95%, FW=150.73, 13.0 mmol, 2.6 eq) was quickly added. After 5 minutes, temperature was spontaneously raised to rt and the solution was kept under vigorous stirring.

Reaction was monitored via TLC, (dichloromethane: methanol 95:5). It was quenched with water (9 ml), diluted with diethyl ether (20 ml). The aqueous layer was extracted one time with 30 ml of diethyl ether and the combined organic layers were washed with water (20 ml) and brine (20 ml), then dried on Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the resulting crude oil was purified by flash chromatography on silica gel (Hex:Et_2O 99/1 then 95/5).

1.72 g of pure product were obtained (FW=328.64, Y=100%)

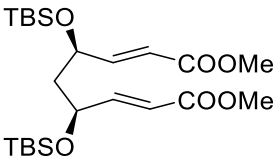
IR (liquid film): ν_{max}: 2956, 2912, 2878, 1370, 1238, 1080, 1040, 1007, 824, 742 cm^{-1}

LC-MS (HESI probe): $[M+H]^+$ 329.78, $[M+Na]^+$ 351.79.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm)= 5.68 (s, 2H), 4.10 (m, 2H), 2.00-1.50 (m, 2H), 0.91 (s, 18H), 0.1 (s, 12H)

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 131.96, 65.91, 28.60, 25.79, 18.09, -4.68

Synthesis of dimethyl (2*E*,4*R*,6*S*,7*E*)-4,6-bis((tert-butyldimethylsilyl)oxy)nona-2,7-dienedioate (**100**)



Chemical formula: $C_{23}H_{44}O_6Si_2$
Molecular weight: 472.77

Alkene **98** (4.90 g, FW=328.64, 15 mmol, 1 eq) was solubilized in dry DCM (125 ml). The solution was cooled to -78°C and a O_3/O_2 mixture was bubbled in it until the color became blue. The excess of ozone was eliminated by bubbling oxygen in the solution that was kept at -78°C. The mixture became colorless, then Ar was bubbled in order to remove the oxygen.

Under vigorous stirring, at -78°C, a solution of pyridine (3 drops) in dimethyl sulfide (11 ml, d=0.846 g/cm^3, FW=62.13, 126.72 mmol, 8 eq) was added dropwise to the mixture and the temperature was slowly raised to -32°C. After 2 hours, the temperature was spontaneously increased at rt, then the solvent was removed under reduced pressure.

The crude oil was directly dissolved in dry THF (10 ml) under Ar atmosphere and subsequently it was transferred via cannula into a round bottom flask containing a THF solution (65 ml) of methyl(triphenylphosphoranyliden)acetate ($Ph_3PCHCOOMe$, 15.030 g, FW=334.36, 45 mmol) that was kept under vigorous stirring.

After 30 minutes, the temperature was raised at 50°C and the mixture was stirred for 20 hours. The reaction was monitored by TLC (Hex:AcOEt 9:1). It was quenched through addition of NH_4Cl saturated aqueous solution (60 ml) and diluted with H_2O (100 ml). Phases were separated, then the aqueous one was extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with water (2 x 250 mL) and Brine (250 mL), dried on Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the resulting crude material was filtered on a silica gel pad (45 g) by washing with Hex:AcOEt 8:2. Finally, the raw compound was purified by flash chromatography on silica gel (450 g, Hex:AcOEt from 96:4 to 9:1).

4.10 g of pure compound were achieved (FW= 472.77, 8.65 mmol, Y=58%).

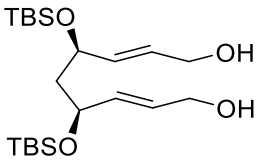
IR (liquid film): ν_{max}: 2955, 2879, 1731, 1300, 1277, 1166, 1128, 1007, 980, 729 cm^{-1}

LC-MS (HESI probe): $[M+H]^+$ 473.90, $[M+Na]^+$ 495.80.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm)= 7.10-6.90 (dd, J_1=15.6, J_2=5.1, 2H), 6.10-5.95 (dd, J_1=15.6, J_2=1.5, 2H), 4.90-4.40 (m, 2H), 3.76 (s, 6H), 1.95-1.50 (m, 2H), 0.90 (s, 18H), 0.1 (d, J=8Hz, 12H)

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 166.9, 150.5, 119.7, 68.3, 52.6, 45.5, 28.8, 18.09, -4.68

Synthesis of (2*E*,4*R*,6*S*,7*E*)-4,6-bis((tert-butyldimethylsilyl)oxy)nona-2,7-diene-1,9-diol (**101**)



Chemical Formula: $C_{21}H_{44}O_4Si_2$
Molecular Weight: 416.75

In a double neck round bottom flask equipped with a pressure equalizing funnel, ester **100** (3.0 g, FW=472.76, 6.63 mmol, 1 eq), was dissolved in dry THF (50 ml) under Ar atmosphere.

The funnel was charged with DIBAL-H (1M solution in hexane, 31.5 mL, 31.5 mmol, 4.7 eq) and the reaction mixture was cooled to -78°C. The DIBAL-H solution was added dropwise and under vigorous stirring, to the ester solution.

Reaction was monitored by TLC (Hex:EtOAc 7:3) and it was completed after 1.5 hours.

To quench, the mixture was diluted with Et_2O (50 ml) and subsequently saturated Rochelle salt solution (80 mL) and water (50 mL) were slowly added to the -78°C solution.

Temperature was spontaneously raised to rt while the double phases system was kept under vigorous stirring until two clear layers were obtained.

After separation, the aqueous phase was extracted with Et_2O (3 x 150 mL). The combined organic layers were washed with water (100 mL) and Brine (100 mL), then dried on Na_2SO_4, filtered and the solvent was removed under reduced pressure.

The crude oil was purified by flash chromatography on silica gel (Hex:AcOEt 7:3).

2.13 g of pure product were achieved (FW=416.75, 6.1 mmol, Y = 100%)

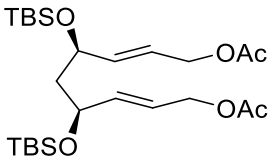
IR (liquid film): ν_{max}: 3340, 2955, 2913, 2877, 1459, 1415, 1239, 1088, 1005, 972, 739 cm^{-1}

LC-MS (HESI probe): $[M+H]^+$ 417.61 $[M+Na]^+$ 439.62

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 5.80-5.60 (m, 4H), 4.25-4.20 (m, 2H), 4.20-4.10 (d, J=4.4, 4H), 1.95-1.60 (m, 3H), 1.60-1.55 (m, 1H), 0.90 (s, 18H), 0.1 (d, J=8Hz, 12H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 134.7, 129.2, 70.0, 63.0, 47.1, 28.8, 18.09, -4.68

Synthesis of (2*E*,4*R*,6*S*,7*E*)-4,6-bis((tert-butyldimethylsilyl)oxy)nona-2,7-diene-1,9-diyl diacetate (**105**)



Chemical Formula: $C_{25}H_{48}O_6Si_2$
Molecular Weight: 500.82

In a round bottom flask, under Ar atmosphere, diol **101** (2.10 g, FW=416.74, 6.25 mmol, 1eq) was dissolved in dry DCM (25 mL). Pyridine (1.4 mL, FW=79, d=0.974 g/mL, 17.3 mmol, 2.8 eq) was subsequently added dropwise followed by acetic anhydride (1.35 mL, FW=102.09, d=1.081 g/mL, 14.3 mmol, 2.4 eq). Finally, DMAP (113 mg, FW=122.17, 0.95 mmol, 0.15 eq) was added.

Reaction was monitored by TLC (Hex:AcOEt 8:2) and after 3 hours it was finished.

Quenching was done by addition of saturated $NaHCO_3$ solution (35 mL) and when bubbling due to acetic anhydride decomposition stopped, the phases were separated. The aqueous one was extracted with Et_2O (3 x 80 mL). The combined organic layers were washed with water (80 mL), saturated solution of $CuSO_4$ (3 x 80 mL), again water (80 mL) and finally with Brine (100 mL). After drying on Na_2SO_4 and removal of the solvent at reduce pressure, the resulting crude oil was purified by flash chromatography (Hex:AcOEt from 95:5 to 9:1).

2.94 g of pure product (FW= 500.82, 5.8 mmol, Y=93%) were achieved.

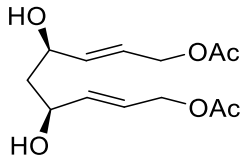
IR (liquid film): ν_{max}: 2955, 2914, 2878, 1745, 1366, 1237, 1085, 1006, 971, 745 cm^{-1}

LC-MS (HESI probe): $[M+H]^+$ 501.56 $[M+Na]^+$ 523.45

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 5.85-5.65 (m, 4H), 4.65-4.50 (d, J=5.3, 4H), 4.30-4.15 (m, 2H), 2.07 (s, 6H), 1.90-1.75 (dt, J_1= 13.5, J_2=6.8, 1H), 1.65-1.50 (dt, J_1= 13.5, J_2=6.3, 1H), 0.90 (s, 18H) 0.1 (d, J=8Hz, 12H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 170.7, 137.6, 123.9, 69.6, 64.3, 46.6, 20.09, 28.4, 18.3, -4.28

Synthesis of (2*E*,4*R*,6*S*,7*E*)-4,6-dihydroxynona-2,7-diene-1,9-diyl diacetate (**86**)



Chemical Formula: $C_{13}H_{20}O_6$
Molecular Weight: 272,30

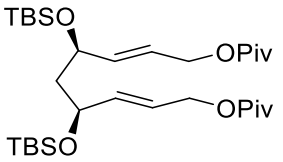
Substrate **105** (2.85g, FW=500.82, 5.78 mmol, 1 eq) was transferred in a Teflon flask equipped with magnetic stirrer and subsequently dissolved in MeCN HPLC grade (45 mL). After a few minutes, an aqueous solution of HF 48% p/p (6.3 mL, 27.6M,173.4 mmol, 30 eq), was slowly added to the reaction mixture. The flask was tightly closed in order to prevent the escape of acid vapor. The reaction was monitored by TLC (Hex: iPrOH 9/1) and it was quenched through addition of solid $NaHCO_3$ (14.65 g, FW=84.01, 173.4 mmol, 1 eq) till the bubbling due to CO_2 release stopped. The resulting mixture was filtered on a Celite pad and concentrated, finally, the crude was purified by flash chromatography on silica (Hex:EtOAc 4/6).

1.5 g (FW=272.30, 5.49 mmol, Y=95%) of pure product were achieved.

Spectroscopic data are in agreement with the literature[93].

[93] Jiang, L., Burke, S.D. *Org. Lett.,* **2002**, *4*, 3411

Synthesis of (2*E*,4*R*,6*S*,7*E*)-4,6-bis((tert-butyldimethylsilyl)oxy)nona-2,7-diene-1,9-diyl bis(2,2-dimethylpropanoate (**102**)



Chemical Formula: $C_{31}H_{60}O_6Si_2$
Molecular Weight: 584.98

In a round bottom flask, under Ar atmosphere, diol **101** (450 mg, FW=416.75, 1.08mmol,) was dissolved in dry DCM (8 mL). Pyridine (263 µL, FW=79, d=0.974 g/mL, 3.24 mmol, 3 eq) was subsequently added dropwise followed by trimethylacetyl chloride (319 µL, FW=120.58, d=0.980 g/mL, 2.59 mmol, 2.4 eq). Finally, DMAP (20 mg, FW=122.17, 0.16 mmol, 0.15 eq) was added.

Reaction was monitored by TLC (Hex:AcOEt 8:2) and after 8 hours it was finished.

Quenching was done by addition of saturated $NaHCO_3$ solution (8 mL), then the phases were separated. The aqueous one was extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with water (15 mL), saturated solution of $CuSO_4$ (3 x 15 mL), again water (15 mL) and finally with Brine (20 mL). After drying on Na_2SO_4 and removal of the solvent at reduce pressure, the resulting crude oil was purified by flash chromatography (Hex:AcOEt from 95:5 to 9:1).

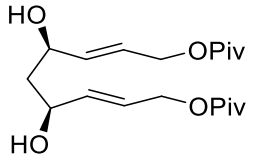
537 mg of pure product (FW= 584.98, 0.918 mmol, Y=85%) were achieved.

LC-MS (HESI probe): $[M+H]^+$ 585.32 $[M+Na]^+$ 607.43.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm)= 5.80-5.71 (m, 4H), 4.56-4.54 (d, J=4.56, 4H), 4.25-4.19 (m, 2H), 1.87-1.82 (m, 1H), 1.62-1.55 (m, 1H), 1.22 (s, 18H), 0.9 (s, 18H), 0.056-0.034 (d, J=6.35, 12 H)

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 178.05, 137.27, 124.23, 69.75, 64.09, 46.70, 38.63, 27.09, 25.75, 18.04, -4.19, -4.86

Synthesis of (2*E*,4*R*,6*S*,7*E*)-4,6-dihydroxynona-2,7-diene-1,9-diyl bis(2,2-dimethylpropanoate) (**104**)



Chemical Formula: $C_{19}H_{32}O_6$
Molecular Weight: 356.46

Substrate **102** (537 mg, FW=584.98, 0.918 mmol, 1 eq) was transferred in a Teflon flask equipped with magnetic stirrer and subsequently dissolved in MeCN HPLC grade (4 mL). After a few minutes, an aqueous solution of HF 48% p/p (1 mL, 27.6M, 27.5 mmol, 30 eq), was slowly added to the reaction mixture. The flask was tightly closed in order to prevent the escape of acid vapor. The reaction was monitored by TLC (Hex: iPrOH 9/1) and it was quenched through addition of solid $NaHCO_3$ (2.31 g, FW=84.01, 27.5 mmol, 1 eq) till the bubbling due to CO_2 release stopped. The resulting mixture was filtered on a Celite pad and concentrated, finally, the crude was purified by flash chromatography on silica (Hex:EtOAc 4/6).

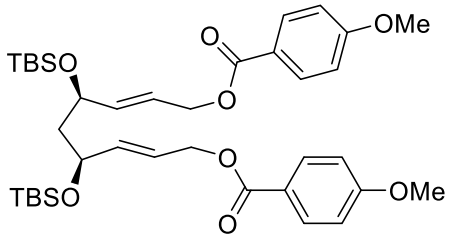
301 mg (FW=356.46, 0.844 mmol, Y=92%) of pure product were achieved.

LC-MS (HESI probe): $[M+H]^+$ 357.21 $[M+Na]^+$ 379.12

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 5.88-5.74 (m, 4H), 4.58-4.56 (d, J=4.12, 4H), 4.47-4.42 (m, 2H), 3.1 (s, 2H), 1.75-1.7 (m, 2H), 1.22 (s, 18H)

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 178.18, 135.50, 124.83, 71.97, 63.84, 42.86, 38.65, 27.08

Synthesis of (2*E*,4*R*,6*S*,7*E*)-4,6-bis((tert-butyldimethylsilyl)oxy)nona-2,7-diene-1,9-diyl bis(4-methoxybenzoate) (**103**)



Chemical Formula: $C_{37}H_{56}O_8Si_2$
Molecular Weight: 685.02

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In a round bottom flask, under Ar atmosphere, diol **101** (600 mg, FW=416.75, 1.44 mmol,) was dissolved in dry DCM (3 mL). At 0°C (water-ice bath), pyridine (700 µL, FW=79, d=0.974 g/mL, 8.64 mmol, 6 eq) was subsequently added dropwise followed by p-methoxybenzoyl chloride (448 µL, FW=170.6, d=1.260 g/mL, 3.31 mmol, 2.3 eq). Finally, DMAP (26 mg, FW=122.17, 0.22 mmol, 0.15 eq) was added.

Reaction was monitored by TLC (Hex:AcOEt 6:4) and after 8 hours it was finished.

Quenching was done by addition of saturated $NaHCO_3$ solution (8 mL), then the phases were separated. The aqueous one was extracted with DCM (3 x 15 mL). The combined organic layers were washed with water (15 mL), saturated solution of $CuSO_4$ (3 x 15 mL), again water (15 mL) and finally with Brine (20 mL). After drying on Na_2SO_4 and removal of the solvent at reduce pressure, the resulting crude oil was purified by flash chromatography (Hex:AcOEt 9:1).

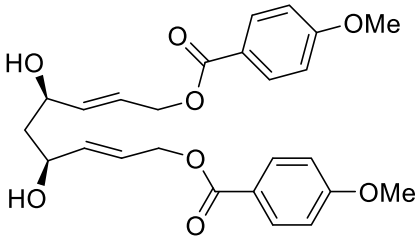
690 mg of pure product (FW= 685.02, 1.0 mmol, Y=70%) were achieved.

LC-MS (HESI probe): $[M+H]^+$ 686.02 $[M+Na]^+$ 708.02

^1H NMR (300 MHz, $CDCl_3$): δ (ppm)= 8.03-8.0 (d, J=8.94, 4H), 6.95-6.92 (d, J=9, 4H), 5.85-5.83 (m, 4H), 4.8-4.78 (d, J=4.2, 4H), 4.29-4.27 (m, 2H), 3.87 (s, 6H), 1.95-1.92 (m, 1H), 1.75-1.72 (m, 1H), 0.91 (s, 18H), 0.061-0.047 (d, J=4.2, 12H)

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 165.88, 137.48, 131.51, 124.20, 122.5, 113.48, 69.81, 64.40, 55.29, 46.68, 25.77, 18.05, -4.16, -4.87.

Synthesis of (2*E*,4*R*,6*S*,7*E*)-4,6-dihydroxynona-2,7-diene-1,9-diyl bis(4-methoxybenzoate) (**97**)



Chemical Formula: $C_{25}H_{28}O_8$
Molecular Weight: 456.49

Substrate **103** (494 mg, FW=685.02, 0.721 mmol, 1 eq) was transferred in a Teflon flask equipped with magnetic stirrer and subsequently dissolved in MeCN HPLC grade (3.6 mL). After a few minutes, an aqueous solution of HF 48% p/p (0.81 mL, 27.6M, 21.6 mmol, 30 eq), was slowly added to the reaction mixture. The flask was tightly closed in order to prevent the escape of acid vapor. The reaction was monitored by TLC (Hex: AcOEt 6:4) and it was quenched through addition of solid $NaHCO_3$ (1.82 g, FW=84.01, 21.63 mmol, 30 eq) till the bubbling due to CO_2 release stopped. The resulting mixture was filtered on a Celite pad and concentrated, finally, the crude was purified by flash chromatography on silica (Hex:EtOAc 6:4).

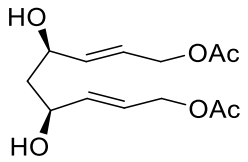
260 mg (FW=456.49, 0.56 mmol, Y=80%) of pure product were achieved.

LC-MS (HESI probe): $[M+H]^+$ 457.49 $[M+Na]^+$ 479.49

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 8.02-7.99 (d, J=9, 4H), 6.94-6.91 (d, J=9, 4H), 5.97-5.84 (m, 4H), 4.8-4.79 (d, J=3, 4H), 4.50-4.44 (m, 2H), 3.87 (s, 6H), 3.22 (s, 2H), 1.78-1.74 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 165.96, 136.0, 131.57, 124.75, 122.33, 113.52, 71.96, 64.19, 55.32, 42.83.

Synthesis of (2*E*,4*R*,6*S*,7*E*)-4,6-dihydroxynona-2,7-diene-1,9-diyl diacetate (**86**) (methatetic approach)



Chemical Formula: $C_{13}H_{20}O_6$
Molecular Weight: 272,30

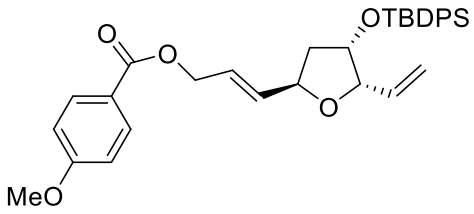
(Z)-2-buten-1,4-diyl diacetate (11868 mg, 69 mmol, 11 eq) and 1,3-*cis*-cyclopentendiol (600 mg, 6 mmol, 1 eq), were transferred in a round bottom flask under Ar atmosphere. The 2nd generation Grubbs catalyst (600 mg, 0.706 mmol, 0.11 eq) was added and the reaction mixture was kept under vigorous stirring at 40°C.

The reaction was monitored by TLC (Hex:AcOEt 7:3) and after 36 hours the temperature was lowered at rt, the mixture was diluted with DCM (15 ml) and air was bubbled inside for 10 minutes. DCM was removed at reduced pressure and the crude material was purified by liquid chromatography on silica gel (Hex:AcOEt 3:7).

898 mg (3.3 mmol, FW:272.3 Y=55%) of pure product were achieved.

Spectroscopic data are in agreement with the literature[93]

Synthesis of (*E*)-3-((2*R*,4*S*,5*S*)-4-((tert-butyldiphenylsilyl)oxy)-5-vinyltetrahydrofuran-2-yl)allyl 4-methoxybenzoate (**71**)



Chemical Formula: $C_{33}H_{38}O_5Si$
Molecular Weight: 542.75

Compound **70** (458 mg, FW=304, 1.5 mmol, 1 eqv) was dissolved in dry DCM (15 mL) in a round bottom flask under Ar atmosphere. Imidazole (255 mg, FW=68, 3.75 mmol, 2.5 eqv) was added, followed by TBDPSCl (468 µL, FW=274.86, d=1.057, 1.8 mmol, 1.2 eqv). Reaction mixture was kept under vigorous stirring at rt for 12 hours.

Reaction was monitored by TLC (Hex:AcOEt 8:2) and was quenched through addition of water (20 mL). The layers were separated and the aqueous one was extracted with DCM (3 x 20 mL). The organic phase was dried on $MgSO_4$, filtered and concentrate at reduced pressure.

The crude material was purified by liquid chromatography on silica gel (Hex:AcOEt 95:5).

732 mg (1.35 mmol, FW = 542.75, Y = 90%) of pure compound were obtained.

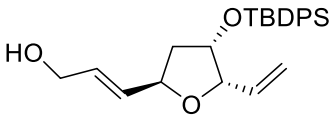
LC-MS (HESI probe): $[M+H]^+$ 543.72 $[M+Na]^+$ 566.74

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 8.03-8.00 (d, J=9, 2H), 7.72-7.66 (m, 4H), 7.46-7.37 (m, 6H), 6.95-6.92 (d, J=9, 2H), 6.25-6.15 (m, 1H), 6.0-5.75 (m, 2H), 5.36-5.26 (m, 2H), 4.83-4.76 (m, 3H), 4.49 (s, 1H), 4.49-4.32 (m, 1H), 3.88 (s, 3H), 1.97-1.91 (m, 1H), 1.68-1.58 (m, 1H), 1.11 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 165.88, 135.86, 135.72, 135.12, 134.53, 133.94, 133.19, 131.57, 129.71, 129.67, 127.58, 127.50, 125.60, 122.44, 117.80, 113.47, 84.42, 77.43, 77.37, 76.94, 76.52, 75.70, 64.21, 55.31, 41.79, 26.85, 19.22.

$[\alpha]^{21}_D$ = + 15.7 (CH_2Cl_2)

Synthesis of (*E*)-3-((2*R*,4*S*,5*S*)-4-((tert-butyldiphenylsilyl)oxy)-5-vinyltetrahydrofuran-2-yl)prop-2-en-1-ol (**66**)



Chemical Formula: $C_{25}H_{32}O_3Si$
Molecular Weight: 408.61

Compound **71** (730 mg, FW= 542.75, 1.34 mmol) was dissolved in MeOH (14 mL) and K_2CO_3 (10 mg, FW= 138.2, 0.067 mmol, 0.05 eqv) was added, then the mixture was kept under vigorous stirring at 40°C for 20 hours.

Reaction was monitored by TLC (Hex:AcOEt 8:2) and when it was completed, the mixture was filtered and the solvent was removed at reduced pressure.

The crude material was purified by liquid chromatography on silica gel (Hex:AcOEt 8:2).

490 mg (1.2 mmol, FW=408.61, Y=90%) of pure compounds were achieved.

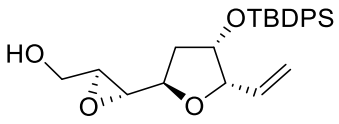
LC-MS (HESI probe): $[M+H]^+$ 409.76 $[M+Na]^+$ 431.65

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 7.71-7.65 (m, 4H), 7.43-7.39 (m, 6H), 6.25-6.15 (m, 1H), 5.89-5.83 (ddt, J= 15.4, 7.1, 1.4 Hz, 1H), 5.70-5.64 (m, 1H), 5.34-5.24 (m, 2H), 4.85-4.70 (m, 1H), 4.52-4.44 (m, 1H), 4.33-4.30 (m, 1H), 4.13-4.12 (d, J= 4.7, 2H), 1.95-1.88 (ddd, J=13.2, 6.1, 1.2 Hz, 1H), 1.64-1.56 (m, 1H), 1.54 (s, 1H), 1.1 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 136.88, 136.74, 136.17, 134.99, 134.22, 132.95, 131.83, 130.72, 130.68, 128.58, 128.52, 118.73, 85.34, 78.61, 77.94, 76.73, 63.84, 42.82, 27.87, 20.24

$[\alpha]^{21}_D$ = + 13.6 (CH_2Cl_2)

Synthesis of ((2*S*,3*S*)-3-((2*R*,4*S*,5*S*)-4-((tert-butyldiphenylsilyl)oxy)-5-vinyltetrahydrofuran-2-yl)oxiran-2-yl)methanol (**65**)



Chemical Formula: $C_{25}H_{32}O_4Si$
Molecular Weight:424.61

In a double neck round bottom flask, under Ar atmosphere, activated molecular sieves (4 Å, 10 mg) are transferred. Then dry DCM (4 mL) was added and the suspension was kept under vigorous stirring at room temperature. At this point, L-(+)-DET (4.4 µL, FW= 206.2, d=1.205, 0.15 eqv) and tBuOOH (125 µL, sol 5.5 M in nonane, 4 eqv) were added and the mixture was stirred at rt for 20 minutes.

Subsequently, the suspension was cooled at -20°C, Ti(O*i*Pr)$_4$ (5 µL, FW=284.22, d=1.205, 0.1 eqv) was added and the mixture was stirred at the same temperature for 20 minutes.

In another round bottom flask, compound **66** (71 mg, FW= 408.61, 0.17 mmol) was dissolved in dry DCM (4 mL), activated molecular sieves (4 Å, 10 mg) were added and the suspension was stirred at room temperature for 20 minutes. At this point, temperature was decreased at -20°C and the substrate's solution was cannulated inside the flask containing the catalyst.

Reaction was kept under vigorous stirring at -20°C for 12 hours and was monitored by TLC (Hex:AcOEt 6:4). After that, it was quenched by adding at -20°C, a 10% solution of (+)-tartaric acid (6 mL). Temperature was slowly raised at rt, then water (6 mL) was added till complete dissolution of molecular sieves. The phases were separated, then the aqueous one was extracted with DCM (3 x 15 mL), dried on Na_2SO_4, filtered and concentrated at reduced pressure.

The crude material was purified by liquid chromatography on silica gel (Hex:AcOEt 7:3) to give 68.3 mg (0.16 mmol, FW= 424.61, Y= 94%) of pure product.

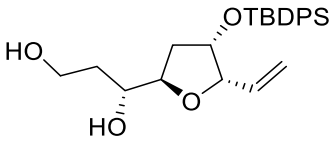
LC-MS (HESI probe): $[M+H]^+$ 425.83 $[M+Na]^+$ 447.64

^{1}H NMR (300 MHz, CD_2Cl_2): δ (ppm)= 7.71-7.66 (m, 4H), 7.44-7.40 (m, 6H), 6.25-6.15 (m, 1H), 5.37-5.23 (m, 2H), 4.50-4.48 (m, 1H), 4.4-4.25 (m, 2H), 3.9-3.85 (dd, J=12.6, 2.55 Hz, 1H), 3.61-3.55 (dd, J=12.6, 4.49 Hz, 1H), 3.02-3.0 (m, 1H), 2.95-2.93 (m, 1H), 1.84-1.80 (ddd, J=13.2, 6.1, 1.2 Hz, 1H), 1.74-1.70 (m, 1H), 1.1 (s, 9H).

^{13}C NMR (75 MHz, CD_2Cl_2): δ (ppm)= 136.80, 136.67, 136.15, 134.88, 134.19, 128.52, 128.46, 85.31, 77.20, 76.45, 62.26, 57.40, 55.04, 37.90, 27.56, 20.00

$[\alpha]^{21}_{D}$ = - 4.5 (CH_2Cl_2)

Synthesis of ((2*S*,3*S*)-3-((2*R*,4*S*,5*S*)-4-((tert-butyldiphenylsilyl)oxy)-5-vinyltetrahydrofuran-2-yl)oxiran-2-yl)methanol (**64**)



Chemical Formula: $C_{25}H_{34}O_4Si$
Molecular Weight:426.63

Epoxide **65** (68.3 mg, FW=424.61, 0.16 mmol) was dissolved in dry THF (2 mL) under Ar atmosphere and the solution was cooled at -30°C. The reaction mixture was kept under vigorous stirring and Red-Al (120 µL, 65% solution in toluene, 0.4 mmol, 2.5 eqv) was added dropwise. The stirring was continued for 2 hours at the same temperature and reaction was monitored by TLC (Hex:AcOEt 4:6).

When the process was completed, temperature was raised at 0°C, then saturated Rochelle salt solution (4 mL), water (8 mL) and Et_2O (4 mL) were slowly added and the stirring was continued till the temperature was spontaneously raised at rt. At this point, the phases were separated and the aqueous one was extracted with DCM (3 x 15 mL). The combined organic phases were dried on Na_2SO_4, filtered and concentrated at reduced pressure.

The crude material was purified by flash chromatography on silica gel (Hex:AcOEt 4:6) to give 46 mg (0.11 mmol, FW= 426.63, Y= 70%) of pure diol.

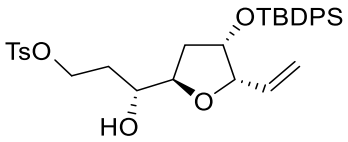
LC-MS (HESI probe): $[M+H]^+$ 427.81 $[M+Na]^+$ 449.64

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.70-7.65 (m, 4H), 7.46-7.39 (m, 6H), 6.25-6.15 (m, 1H), 5.33-5.25 (m, 2H), 4.5-4.46 (m, 1H), 4.27-4.24 (m, 2H), 4.04-4.01 (m, 1H), 3.84-3.80 (t, J=6.0, 2H), 1.84-1.80 (ddd, J=13.2, 6.1, 1.2 Hz, 1H), 1.72-1.48 (m, 3H), 1.1 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 135.83, 135.68, 135.04, 133.95, 133.16, 129.68, 127.51, 117.90, 85.02, 80.58, 77.11, 72.20, 61.55, 34.72, 33.93, 26.84, 19.22

$[\alpha]^{21}_D$ = + 8.9 (CH_2Cl_2)

Synthesis of (*R*)-3-((2*R*,4*S*,5*S*)-4-((tert-butyldiphenylsilyl)oxy)-5-vinyltetrahydrofuran-2-yl)-3-hydroxypropyl 4-methylbenzenesulfonate (**84**)



Chemical Formula: $C_{32}H_{40}O_6SSi$
Molecular Weight:580.81

In a round bottom flask, compound **64** (428 mg, FW=426.63, 1 mmol) was dissolved in dry DCM (5 mL) under Ar atmosphere and the mixture was cooled at 0°C. At this point, Bu_2SnO (5 mg, FW=248.94, 0.02 mmol, 0.02 eqv), freshly distilled Et_3N (153 µL, FW=101.19, d=0.728, 1.1 mmol, 1.1 eqv) and finally Tosyl chloride (210 mg, FW=190.65, 1.1 mmol, 1.1 eqv) were added. The mixture was stirred at 0°C for 10 minutes and then at room temperature for 22 hours.

Reaction was monitored by TLC (Hex:AcOEt 7:3) and was quenched by adding water (10 mL). The phases were separated, then the organic one was washed with water (15 mL) and brine (15 mL), dried on Na_2SO_4, filtered and concentrated at reduce pressure.

The crude material was purified by flash chromatography on silica gel (Hex:AcOEt 7:3) to give 464 mg (0.8 mmol, FW=580.81, Y=80%) of pure compound.

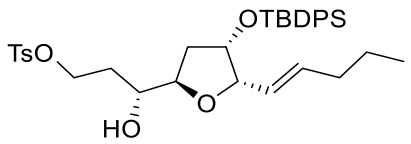
LC-MS (HESI probe): $[M+H]^+$ 581.94 $[M+Na]^+$ 603.84

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.95-7.92 (d, J=9 Hz, 2H), 7.70-7.65 (m, 4H), 7.46-7.39 (m, 8H), 6.25-6.15 (m, 1H), 5.33-5.25 (m, 2H), 4.5-4.46 (m, 1H), 4.27-4.24 (m, 2H), 4.04-4.01 (m, 1H), 3.84-3.80 (t, J=6.0, 2H), 2.43 (s, 3H), 1.84-1.80 (ddd, J=13.2, 6.1, 1.2 Hz, 1H), 1.72-1.48 (m, 3H), 1.1 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 144.42, 140.33, 134.72, 134.12, 130.65, 130.04, 129.55, 128.33, 119.25, 92.28, 78.84, 74.14, 70.48, 67.41, 37.13, 32.15, 30.47, 26.87, 21.35.

$[\alpha]^{21}_D$ = + 8.6 (CH_2Cl_2)

Synthesis of (*R*)-3-((2*R*,4*S*,5*S*)-4-((tert-butyldiphenylsilyl)oxy)-5-((*E*)-pent-1-en-1-yl)tetrahydrofuran-2-yl)-3-hydroxypropyl 4-methylbenzenesulfonate (**63**)



Chemical Formula: $C_{35}H_{46}O_6SSi$
Molecular Weight: 622.89

In a vial, compound **84** (113 mg, FW=580.81, 0.19 mmol) was dissolved in dry degassed DCM (2 mL) under Ar atmosphere, then 1-pentene (1 mL) was added, followed by Stewart-Grubbs catalyst (10 mg, FW=570.52, 0.0095 mmol, 5 mol%). Reaction mixture was kept under vigorous stirring at 50°C and was monitored by TLC (Hex:AcOEt 7:3). After 16 hours it was quenched by bubbling air inside the solution for 10 minutes and by removing the solvent at reduced pressure.

The crude material was purified by flash chromatography on silica gel (Hex:AcOEt 8:2) to give 60 mg (0.095 mmol, FW=622.89, Y = 50%).

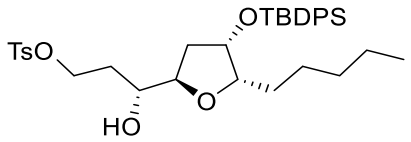
LC-MS (HESI probe): $[M+H]^+$ 623.95 $[M+Na]^+$ 645.81

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.95-7.92 (d, J=9 Hz, 2H), 7.70-7.65 (m, 4H), 7.46-7.39 (m, 8H), 5.84-5.67 (m, 2H), 4.5-4.44 (m, 1H), 4.43-4.23 (m, 4H), 3.96-3.9 (m, 1H), 2.43 (s, 3H), 2.15-1.98 (ddd, J=13.2, 6.1, 1.2 Hz, 1H), 1.94-1.46 (m, 7H), 1.1 (s, 9H), 0.96 (t, J=6.8, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 144.47, 140.31, 134.14, 131.67, 130.52, 130.05, 129.56, 128.31, 127.22, 92.04, 78.88, 74.47, 70.43, 67.41, 37.17, 37.15, 36.24, 32.15, 30.43, 26.88, 23.31, 21.37, 14.23

$[\alpha]^{21}_D$ = - 4.3 (CH_2Cl_2)

Synthesis of (*R*)-3-((2*R*,4*S*,5*S*)-4-((tert-butyldiphenylsilyl)oxy)-5-pentyltetrahydrofuran-2-yl)-3-hydroxypropyl 4-methylbenzenesulfonate (**62**)



Chemical Formula: $C_{35}H_{48}O_6SSi$
Molecular Weight: 624.91

In a round bottom flask, compound **63** (122 mg, FW=622.89, 0.196 mmol) was dissolved in degassed AcOEt (4 mL) and Pd/C 10% (20 mg, 15% w/w) was added. The mixture was vigorously stirred under hydrogen atmosphere for 2 hours at room temperature. It was monitored by TLC (Hex:AcOEt 8:2) and when it was completed it was filtered and the solvent was removed at reduced pressure.

The crude material wasn't purified and was directly used for the following step.

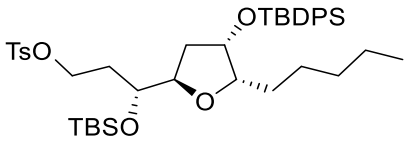
LC-MS (HESI probe): $[M+H]^+$ 625.97 $[M+Na]^+$ 647.92

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.95-7.92 (d, J=9 Hz, 2H), 7.70-7.65 (m, 4H), 7.46-7.39 (m, 8H), 4.25-4.2 (m, 1H), 4.2-4.0 (m, 3H), 3.82-3.78 (m, 1H), 3.68-3.62 (m, 1H), 2.43 (s, 3H), 2.15-1.98 (ddd, J=13.2, 6.1, 1.2 Hz, 1H), 1.85-1.41 (m, 9H), 1.1 (s, 9H), 0.96 (t, J=6.8, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 144.45, 140.34, 134.01, 130.44, 130.07, 129.51, 128.38, 86.24, 82.27, 80.66, 70.31, 67.38, 37.13, 32.28, 32.09, 30.47, 26.72, 26.34, 25.66, 22.58, 21.34, 14.11

$[\alpha]^{21}_D$ = + 9.6 (CH_2Cl_2)

Synthesis of (*R*)-3-((tert-butyldimethylsilyl)oxy)-3-((2*R*,4*S*,5*S*)-4-((tert-butyldiphenylsilyl)oxy)-5-pentyltetrahydrofuran-2-yl)propyl 4-methylbenzenesulfonate (**85**)



Chemical Formula: $C_{41}H_{62}O_6SSi_2$
Molecular Weight: 739.17

In a round bottom flask, compound **62** (122 mg, FW=624.91, 0.196 mmol) was dissolved in dry DCM (2 mL) under Ar atmosphere and the solution was cooled at -78°C. At this point, freshly distilled 2,6-lutidine (60 µL, FW=107.16, d=0.923, 0.49 mmol, 2.5 eqv) was added followed by TBSOTf (90 µL, FW=264.34, d=1.15, 0.4 mmol, 2 eqv). The latter must be added dropwise. Temperature was slowly raised at -50°C and the mixture was stirred at the same temperature for 1 hour.

Reaction was monitored by TLC (Hex:AcOEt 8:2) and when it was completed it was quenched by adding saturated solution of $NaHCO_3$ (8 mL). The layers were separated and the aqueous one was extracted with DCM (3 x 15 mL). The combined organic phases were dried on Na_2SO_4, filtered and then concentrated at reduced pressure.

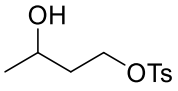
Purification of the crude material was performed by flash chromatography on silica gel (Hex:AcOEt 95:5) and resulted in 117.3 mg (0.16 mmol, FW=739.17, Y=81%) of pure compound.

LC-MS (HESI probe): $[M+H]^+$ 740.22 $[M+Na]^+$ 762.27

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.95-7.92 (d, J=9 Hz, 2H), 7.70-7.65 (m, 4H), 7.46-7.39 (m, 8H), 4.25-4.2 (m, 1H), 4.2-4.0 (m, 3H), 3.82-3.78 (m, 1H), 3.68-3.62 (m, 1H), 2.43 (s, 3H), 2.15-1.98 (ddd, J=13.2, 6.1, 1.2 Hz, 1H), 1.85-1.41 (m, 9H), 1.1 (s, 9H), 0.98 (s, 9H), 0.96 (t, J=6.8, 3H), 0.21 (s, 6H)

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 144.47, 140.31, 134.04, 130.57, 130.07, 129.42, 128.15, 86.16, 80.71, 79.58, 73.64, 67.51, 37.17, 32.22, 32.07, 31.51, 30.88, 26.74, 26.34, 25.83, 25.78, 22.65, 21.34, 14.11, -2.05

Synthesis of 3-hydroxybutyl 4-methylbenzenesulfonate (**72 a**)



Chemical Formula: $C_{11}H_{16}O_4S$
Molecular Weight: 244.30

In a round bottom flask, commercially available 1,3-butandiol (900 µL, FW=90.12, d=1.005, 10 mmol, 1 eqv) was dissolved in dry DCM (50 mL) under Ar atmosphere and the mixture was cooled at 0°C.

At this point, Bu_2SnO (50 mg, FW=248.94, 0.2 mmol, 0.02 eqv), freshly distilled Et_3N (1.5 mL, FW=101.19, d=0.728, 11 mmol, 1.1 eqv) and finally Tosyl chloride (2 g, FW=190.65, 11 mmol, 1.1 eqv) were added. The mixture was stirred at 0°C for 10 minutes and then at room temperature for 22 hours.

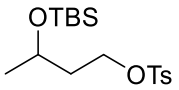
Reaction was monitored by TLC (Hex:AcOEt 4:6) and was quenched by adding water (50 mL). The phases were separated, then the organic one was washed with water (50 mL) and brine (50 mL), dried on Na_2SO_4, filtered and concentrated at reduce pressure.

The crude material was purified by flash chromatography on silica gel (Hex:AcOEt 1:1) to give 1.53 g (6.26 mmol, FW=244.31, Y=65%) of pure compound.

Spectroscopic data are in agreement with the literature[94].

[94] Steinmetz, H.; Li, J.; Fu, C.; Zaburannyi, N.; Kunze, B.; Harmrolfs, K.; Schmitt, V.; Herrmann, J.; Reichenbach, H.; Höfle, G.; Kalesse, M.; Müller, R., *Angewandte Chemie - International Edition*, **2016**, *34*, 10113.

Synthesis of 3-((tert-butyldimethylsilyl)oxy)butyl 4-methylbenzenesulfonate (**72 b**)



Chemical Formula: $C_{17}H_{30}O_4SSi$
Molecular Weight: 358.57

In a round bottom flask, compound **73** (245 mg, FW=244.30, 1 mmol, 1 eqv) was dissolved in dry DMF (2 mL) and imidazole (136 mg, FW=68.08, 2 mmol, 2eqv) was added. Temperature was lowered at 0°C, then TBSCl (181 mg, FW=150.72, 1.2 mmol, 1.2 eqv) was added in small portions and the mixture was kept under vigorous stirring while temperature was slowly raised at rt.

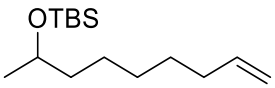
Reaction was monitored by TLC (Hex:AcOEt 1:1) and after 12 hours was quenched by adding water (10 mL) and Et_2O (10 mL). The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organic phases were dried on Na_2SO_4, filtered and the solvent was removed under reduced pressure.

The crude material was purified by flash chromatography on silica gel (Hex:AcOEt 9:1) to give 256 mg (0.71 mmol, FW=358.57, Y=71%) of pure compound.

Spectroscopic data are in agreement with the literature[95]

[95] Ramana; Suryawanshi, Sharad B.; Gonnade, Rajesh G., *J. Org. Chem.*, **2009** , *74*, 2842.

Synthesis of tert-butyldimethyl(non-8-en-2-yloxy)silane (**75 b**)



Chemical Formula: $C_{15}H_{32}OSi$
Molecular Weight: 256.50

Preparation of Grignard reagent

Magnesium turnings (70 mg, FW=24.30, 2.75 mmol, 2.5 eqv) was suspended in dry THF (10 mL) under Ar atmosphere and 5-Bromo-pentene (267 µL, FW=149.03, d=1.259, 2.2 mmol, 2 eqv) was added dropwise. The mixture was kept under vigorous stirring for 5 minutes, then 1,2-dibromoethane (5 µL) was added, temperature was raised at 50°C and was kept at the same value till activation of Mg. At this point, the mixture was cooled at rt and stirring was continued for 1 hour. The result was a pale yellow solution.

Preparation of organo-copper reagent

CuI (430 mg, FW=190.44, 2.2 mmol, 2 eqv) was suspended in dry THF (10 mL) under Ar atmosphere and temperature was lowered at -10°C. After 15 minutes, the Grignard reagent previously prepared was cannulated inside the CuI suspension and the mixture was stirred at -10°C for 30 minutes. The result was a black solution.

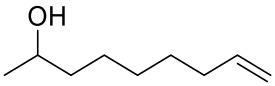
After that, a solution of compound **74** (394 mg, FW=358.57, 1.1 mmol, 1 eqv) in dry THF (5 mL) was cannulated inside the organo-copper solution and the temperature was raised at 0°C.

The reaction was monitored by TLC (Hex:AcOEt 1:1) and after 4 hours it was quenched by addition of NH_4Cl saturated solution (15 mL) and was kept under stirring for 20 minutes. The phases were separated, then the aqueous one was extracted with Et_2O (3 x 20 mL) and the combined organic layers were washed with brine (80 mL), dried on Na_2SO_4, filtered and concentrated at reduced pressure. The crude material was purified by flash chromatography on silica gel (penthane:Et_2O 6:4) to furnish 217 mg (0.85 mmol, FW= 256.50, Y = 77%)

Spectroscopic data are in agreement with the literature[96].

[96] Bonini, C.; Chiummiento, L.; Evidente, A.; Funicello, M., *Tetrahedron Letters*, **1995**, 36, 7285

Synthesis of non-8-en-2-ol (**75 a**)



Chemical Formula: $C_9H_{18}O$
Molecular Weight: 142.24

Preparation of Grignard reagent

Magnesium turnings (126 mg, FW=24.30, 5.17 mmol, 2.5 eqv) was suspended in dry THF (20 mL) under Ar atmosphere and 5-Bromo-pentene (490 µL, FW=149.03, d=1.259, 4.14 mmol, 2 eqv) was added dropwise. The mixture was kept under vigorous stirring for 5 minutes, then 1,2-dibromoethane (10 µL) was added, temperature was raised at 50°C and was kept at the same value till activation of Mg. At this point, the mixture was cooled at rt and stirring was continued for 1 hour. The result is a pale-yellow solution.

Preparation of organo-copper reagent

CuI (790 mg, FW=190.44, 4.14 mmol, 2 eqv) was suspended in dry THF (20 mL) under Ar atmosphere and temperature was lowered at -10°C. After 15 minutes, the Grignard reagent previously prepared was cannulated inside the CuI suspension and the mixture was stirred at -10°C for 30 minutes. The result is a black solution.

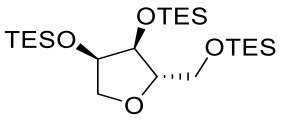
After that, a solution of compound **73** (505 mg, FW=244.3, 2.07 mmol, 1 eqv) in dry THF (5 mL) was cannulated inside the organo-copper solution and the temperature was kept at -10°C.

The reaction was monitored by TLC (Hex:AcOEt 8:2) and after 4 hours it was quenched by addition of NH_4Cl saturated solution (30 mL) and was kept under stirring for 20 minutes. The phases were separated, then the aqueous one was extracted with Et_2O (3 x 40 mL) and the combined organic layers were washed with brine (100 mL), dried on Na_2SO_4, filtered and concentrated at reduced pressure. The crude material was purified by flash chromatography on silica gel (pentane: Et_2O 7:3) to furnish 143 mg (1 mmol, FW= 142.24, Y = 50%).

Spectroscopic data are in agreement with the literature[97].

[97] Beekman, A. M.; Barrow, Russell A., *Aust. J. Chem.*, **2015** , *68*, 1583.

Synthesis of ((2*S*,3*S*,4*R*)-2-((triethylsilyl)methyl)tetrahydrofuran-3,4-diyl)bis(triethylsilane) (**77**)



Chemical Formula: $C_{23}H_{52}OSi_3$
Molecular Weight: 428.92

Commercially available adonitol (2 g, FW=152.15, 13.14 mmol, 1 eqv) was dissolved in 2 M HCl (50 mL) and the mixture was refluxed for 48 h. After that, the solution was concentrated at reduced pressure to give a white solid (1.95 g).

Subsequently, the crude material was dissolved in DMF (73 mL) and imidazole (9.9 g, FW = 68.08, 145 mmol, 10 eqv) was added followed by DMAP (160 mg, FW=122, 1.3 mmol, 0.09 eqv).

At 0°C, TESCl (12.2 mL, FW = 150.73, d=0.898, 72.7 mmol, 5 eqv) was slowly added dropwise, then temperature was raised at rt and the mixture was stirred for 12 hours.

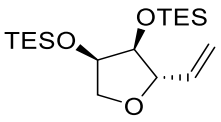
Reaction was monitored by TLC (Hex:AcOEt 98:2) and was quenched by pouring the mixture in a beaker containing ice, $NaHCO_3$ saturated solution (100 mL) and Hexane (100 mL). The phases were separated, then the aqueous one was extracted with Hex:MTBE 1:1 (3 x 200 mL).The combined organic layers were washed with water (2 x 200 mL) and brine (2 x 200 mL), then dried on Na_2SO_4, filtered and the solvent was removed at reduced pressure.

The crude material was purified by flash chromatography on silica gel (Hex: AcOEt 98:2) to give 5 g of pure product (11.8 mmol, FW = 428.92, Y = 90%).

LC-MS (HESI probe): $[M+H]^+$ 429.91 $[M+Na]^+$ 451.98

^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 4.40-4.35 (m, 1H), 4.08-3.75 (m, 6H), 1.0-0.82 (m, 27H), 0.76-0.51 (m, 18H)

Synthesis of ((3*S*,4*R*)-2-vinyltetrahydrofuran-3,4-diyl)bis(triethylsilane) (**73**)



Chemical Formula: $C_{18}H_{38}OSi_2$
Molecular Weight: 326.67

Swern oxidation

In a round bottom flask, oxalyl chloride (200 µL, FW = 126.93, d = 1.5, 2.36 mmol, 4.4 eqv) was dissolved in dry DCM (1 mL) under Ar atmosphere and temperature was lowered at -78°C. Subsequently, DMSO (330 µL, FW=78.13, d=1.10, 4.64 mmol, 8.8 eqv) was added dropwise and a solution of substrate **77** (252 mg, FW=428.92, 0.53 mmol) in dry DCM (3 mL) was cannulated. Reaction mixture was kept under vigorous stirring at -78°C for 20 minutes, then temperature was raised at -40°C and the mixture stirred for other 20 minutes.

At this point, temperature was lowered again at -78°C and Et_3N (1.1 mL, FW=101.19, d=0.728, 8 mmol, 15 eqv) was added dropwise. Reaction mixture was kept at 0°C for 30 minutes, then it was diluted with Et_2O (5 mL) and transferred in a separating funnel. The organic phase was washed with HCl 1 M (15 mL), water (20 mL) and $NaHCO_3$ saturated solution (20 mL), then it was dried on Na_2SO_4, filtered and finally the solvent was removed at reduced pressure.

Wittig reaction

In another round bottom flask, $MePPh_3Br$ (662.6 mg, FW=357.24, 1.85 mmol, 3.5 eqv) was suspended in dry toluene (4 mL) and KHMDS (3.6 mL, solution 0.5 M in toluene, 1.8 mmol, 3.4 eqv) was slowly added dropwise at rt. Reaction mixture was kept under vigorous stirring at the same temperature for 45 minutes, then, it was cooled at -50°C and a solution of the crude material previously prepared (320 mg) in dry toluene (2 mL) was cannulated.

Temperature was raised at 0°C and the mixture was stirred for 2 hours at the same temperature.

Reaction was monitored by TLC (Hex:AcOEt 95:5) and when it was completed it was quenched by addition of NH_4Cl saturated solution (10 mL). The layers were separated, then

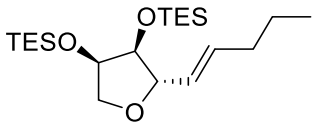
the aqueous one was extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with brine (20 mL), dried on Na_2SO_4, filtered and concentrated at reduced pressure.

The resulting crude material was purified by flash chromatography on silica gel (Hex: AcOEt 95:5) to give 75 mg of pure compound (0.23 mmol, FW= 326.67, Y=45%).

LC-MS (HESI probe): $[M+H]^+$ 327.70 $[M+Na]^+$ 349.74

^1H NMR (200 MHz, $CDCl_3$): δ (ppm) = 5.85-5.75 (m, 1H), 5.40-5.25 (dt, J = 17.1, 1.7 Hz, 1H), 5.25-5.05 (dt, J = 10.4, 1.4 Hz, 1H), 4.26-4.11 (m, 2H), 4.0-3.85 (m, 1H), 3.72-3.63 (m, 2H), 1.0-0.82 (m, 18H), 0.76-0.51 (m, 12H)

Synthesis of ((3*S*,4*R*)-2-(pent-1-en-1-yl)tetrahydrofuran-3,4-diyl)bis(triethylsilane) (**80**)



Chemical Formula: $C_{21}H_{44}OSi_2$
Molecular Weight: 368.75

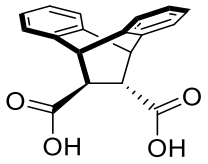
In a vial, compound **73** (50 mg, FW=326.67, 0.15 mmol) was dissolved in dry degassed DCM (2 mL) under Ar atmosphere, then 1-pentene (1 mL) was added, followed by Stewart-Grubbs catalyst (5 mg, FW=570.52, 0.0075 mmol, 5 mol%). Reaction mixture was kept under vigorous stirring at 50°C and was monitored by TLC (Hex:Et_2O 96:4). After 16 hours it was quenched by bubbling air inside the solution for 10 minutes and by removing the solvent at reduced pressure.

The crude material was purified by flash chromatography on silica gel (Hex:Et_2O 96:4) to give 50 mg (0.135 mmol, FW=368.75, Y = 90%).

LC-MS (HESI probe): $[M+H]^+$ 369.85 $[M+Na]^+$ 391.71

^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 5.81-5.7 (m, 1H), 5.41-5.28 (m, 1H), 4.2-4.05 (m, 2H), 4.0-3.85 (m, 1H), 3.75-3.62 (m, 2H), 2.13-1.98 (m, 2), 1.47-1.32 (m, 2H), 1.05-0.81 (m, 18H), 0.62-0.38 (m, 12H).

Synthesis of (11*S*,12*S*)-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid (**115**)



Chemical Formula: $C_{18}H_{14}O_4$
Molecular Weight: 294.31

Synthesis of racemic acid

In a round bottom flask, anthracene (5g, FW = 178.23, 28 mmol, 1 eqv), was suspended in a 1:1 mixture of xylene : dioxane (30mL+30mL) and fumaric acid (3.7 g, FW=116, 31.64 mmol, 1.13 eqv) was added. The suspension was refluxed for 4 days and was monitored by TLC (Hex:AcOEt 1:1).

Reaction quenching was performed by cooling the mixture to room temperature and by adding 50 mL of an aqueous solution of NaOH (1.5 g, FW=40, 37.5 mmol, 1.3 eqv). The phases were separated, then the aqueous one was treated with HCl 2M (50 mL). The resulting white insoluble solid was filtered on buchner and wash with water several times.

The raw material was subsequently purified by recrystallization from acetic acid (1mL of acetic acid per 0.5 g of crude) to give 5.74 g (19.5 mmol, FW=294.31, Y = 70%) of pure racemic diacid.

*Resolution of racemic diacid **115***

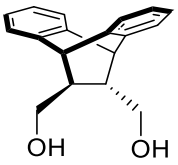
In a beaker, diacid **115** (5.74 g, 19.5 mmol, FW=294.31) was dissolved in a mixture of water (185 mL) and EtOH (115 mL). Brucine (18.3 g, FW = 394.45, 46.4 mmol, 2.38 eqv) was added and the mixture was stirred for one minute. The resulting white solid was filtered on buchner (washing with water), recrystallized from a mixture of water (115 mL) and EtOH (70 mL) and finally treated with HCl 1 M (70 mL). 2 g (6.79 mmol, FW=294.31) of pure (*S,S*)-diacid **115** (>99% *ee*) were achieved.

Spectroscopic data are in agreement with the literature[98]

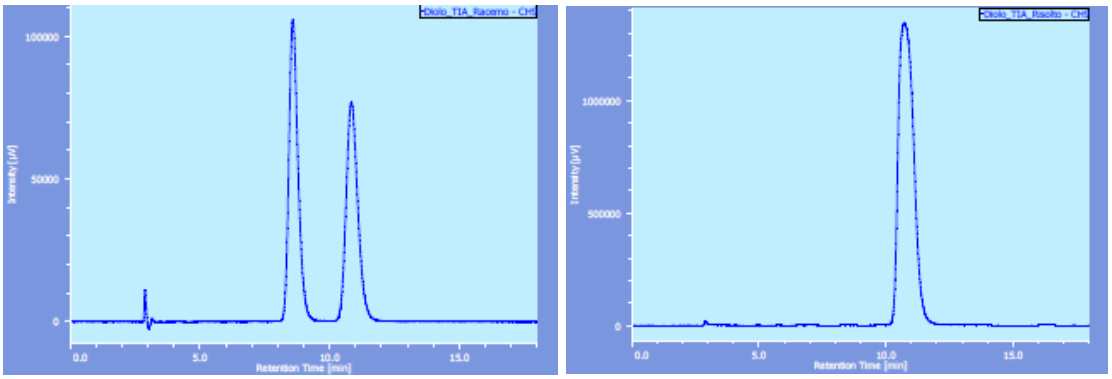
[98] Jain, N.; Bedekar, A.V., *Tetrahedron: Asymmetry*, **2011**, *22*, 1176.

In order to determine the *ee,* a small amount of diacid **115** was reduced with $LiAlH_4$ to the corresponding diol **268**, that subsequently was analyzed by chiral HPLC.

HPLC analysis: chiralpak AS-H 250 x 4.6 mm (ID), 70:30 n-Heptane:*i*PrOH, flow 1 mL/min, UV-DET: 230 nm



Diol 268



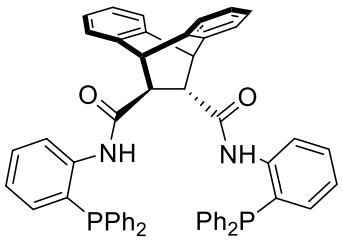
Analysis of racemic diol 268 (left chromatogram)

Peak number	Description	A%
1	(*R,R*)-enantiomer	49.3
2	(*S,S*)-enantiomer	50.7

Analysis of resolved diol **268** (right chromatogram)

Peak number	Description	A%
1	(*S,S*)-enantiomer	>99

Synthesis of (11*S*,12*S*)-N11,N12-bis(2-(diphenylphosphanyl)phenyl)-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxamide (**116**)



Chemical Formula: $C_{54}H_{42}N_2O_2P_2$
Molecular Weight: 812.89

In a round bottom flask, under Ar atmosphere, enantiopure diacid **115** (361 mg, FW = 294.31, 1.23 mmol, 1 eqv) and amine **107** (756 mg, FW=277.3, 2.7 mmol, 2.2 eqv) were dissolved in dry DCM (8 mL). Temperature was lowered at 0°C, then a solution of DCC (634 mg, FW=206.2, 3.075 mmol, 2.5 eqv) and DMAP (76 mg, FW=122.17, 0.615 mmol, 0.5 eqv) in dry DCM (2 mL) was cannulated and temperature was raised at 25°C. The mixture was stirred for 16 hours and was monitored by TLC (Hex:AcOEt 7:3). After 16 hours it was quenched by removing the solvent at reduced pressure.

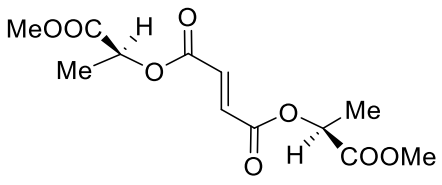
The resulting crude material was purified by flash chromatography on silica gel (Hex:AcOEt from 9:1 to 7:3) to give 398 mg (0.49 mmol, FW=812.89, Y= 40%) of pure product.

LC-MS (HESI probe): $[M+H]^+$ 813.94 $[M+Na]^+$ 835.97

^{1}H NMR (300 MHz, CD_2Cl_2): δ (ppm) = 8.07-8.03 (m, 2H), 7.43-6.95 (m, 36H), 4.25 (s, 2H), 2.87 (s, 2H).

^{13}C NMR (75 MHz, CD_2Cl_2): δ (ppm)= 170.84, 146.47, 143.43, 141.79, 135.64, 134.98, 134,62, 134.49, 134.36, 130.89, 130.10, 129.97, 129.72, 129.66, 129.62, 129.58, 129.53, 126.52, 126.45, 125.83, 123.60, 123.32, 120.87, 58.71, 55.02, 53.58, 45.18

Synthesis of (*R*)-1-methoxy-1-oxopropan-2-yl ((*S*)-1-methoxy-1-oxopropan-2-yl) fumarate (**118**)



Chemical Formula: $C_{12}H_{16}O_8$
Molecular Weight: 288.25

In a round bottom flask, (*S*)-methyl lactate (190 µL, FW=104.11, d=1.092, 2 mmol, 2 eqv) was dissolved in dry DCM (10 mL) under Ar atmosphere and temperature was decreased at -30°C. DIPEA (342 µL, FW=129.25, d=0.755, 2 mmol, 2 eqv) and then fumaryl chloride (108 µL, FW=152.97, d=1.413, 1 mmol, 1 eqv) were added dropwise. Reaction mixture was stirred for 4 hours at the same temperature and was monitored by TLC (Hex:AcOEt 1:1).

When reaction was completed, HCl 1 M was added (2 mL, 2 mmol, 2 eqv), followed by water (5 mL). The aqueous layer was extracted with DCM (3 x 15 mL) and the combined organic phases were dried on Na_2SO_4, filtered and concentrated at reduced pressure.

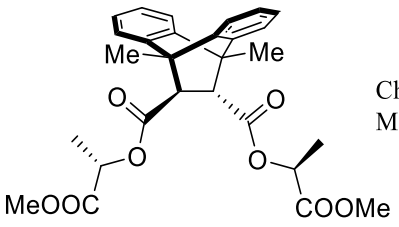
The crude material was purified by liquid chromatography on silica gel (Hex:AcOEt 8:2) to give 200 mg (0.7 mmol, FW=288.25, Y = 70%) of pure product.

LC-MS (HESI probe): $[M+H]^+$ 289.35 $[M+Na]^+$ 311.31

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.00 (s, 2H), 5.23-5.16 (q, J = 7.05, 2H), 3.74 (s, 6H), 1.54-1.52 (d, J = 7.07, 6H)

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 170.43, 163.81, 133.48, 69.25, 52.35, 16.75

Synthesis of bis((*S*)-1-methoxy-1-oxopropan-2-yl) (11*R*,12*R*)-9,10-dimethyl-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylate (**119**)



Chemical Formula: $C_{28}H_{30}O_8$
Molecular Weight: 494.19

In a round bottom flask, 9,10-dimethylanthracene (1.2 g, FW=206.28, 5.8 mmol, 1 eqv), and compound **118** (1.7 g, FW=288.25, 5.88 mmol, 1 eqv), were dissolved in dry toluene (20 mL) and temperature was raised at 110 °C. The mixture was kept under vigorous stirring for 36 hours and it was monitored by TLC (Hex:Et_2O 6:4).

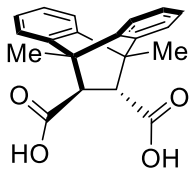
When reaction was completed, the solvent was removed at reduced pressure and the crude material was purified by liquid chromatography on silica gel (Hex:Et_2O 6:4). The product (2.3 g, FW=494.19, 4.65 mmol, Y = 80%) contains a mixture of diastereoisomers (80% *de* by chiral HPLC), that were subsequently separated by MPLC (ISOLERA) (Hex:MTBE 8:2) to give the most abundant isomer **118** (2 g, FW=494.19, 4.18 mmol).

LC-MS (HESI probe): $[M+H]^+$ 495.33 $[M+Na]^+$ 517.28

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.39-7.18 (m, 8H), 5.0-4.93 (q, J = 7.07 Hz, 2H), 3.74 (s, 6H), 3.03 (s, 2H), 2.15 (s, 6H), 1.36-1.34 (d, J = 7.07, 6H)

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 171.61, 170.73, 144.86, 142.28, 125.80, 122.55, 120.32, 68.76, 54.77, 52.13, 43.94, 16.72, 15.68

Synthesis of (11*R*,12*R*)-9,10-dimethyl-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid (**120**)



Chemical Formula: $C_{20}H_{18}O_4$
Molecular Weight: 322.36

In a round bottom flask, compound **119** (300 mg, FW=494.19, 0.6 mmol, 1 eqv) was dissolved in MeOH (6 mL), subsequently $Ba(OH)_2$ 8 H_2O (1.5 g, FW=315.5, 4.8 mmol, 8 eqv) was added and the mixture was stirred for 2 days at room temperature.

Reaction was monitored by TLC (Hex: Et_2O 6:4) and when it was completed it was diluted with water (10 mL), then MeOH was removed at reduced pressure. The aqueous phase was washed with DCM (2 x 20 mL), then HCl 1M (15 mL) was added till acid pH. The resulting acid aqueous solution was extracted with DCM (3 x 20 mL), dried on Na_2SO_4, filtered and concentrated at reduced pressure.

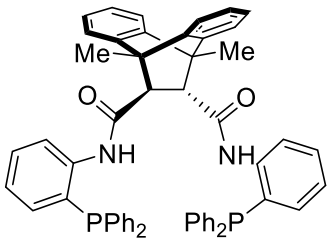
174 mg (0.54 mmol, FW=322.36, Y = 90%) of pure compound were achieved.

LC-MS (HESI probe): $[M+H]^+$ 323.44 $[M+Na]^+$ 345.46

^{1}H NMR (300 MHz, CD_2Cl_2): δ (ppm) = 7.39-7.2 (m, 8H), 2.94 (s, 2H), 2.06 (s, 6H)

^{13}C NMR (75 MHz, CD_2Cl_2): δ (ppm)= 178.71, 146.17, 142.80, 126.81, 123.46, 121.13, 55.46, 44.49, 16.73

Synthesis of (11*R*,12*R*)-N11,N12-bis(2-(diphenylphosphanyl)phenyl)-9,10-dimethyl-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxamide (**121**)



Chemical Formula: $C_{56}H_{46}N_2O_2P_2$
Molecular Weight: 840.94

In a round bottom flask, diacid **120** (192.5 mg, FW=322.36, 0.6 mmol, 1 eqv), was suspended in dry DCM (3 mL) and DMF (30 µL) was added. The mixture was cooled at 0°C and oxalyl chloride (152 µL, FW=126.93, d=1.5, 1.8 mmol, 3 eqv) was added dropwise in a period of 10 minutes.

The resulting yellow solution was stirred for 2 hours at room temperature, then the solvent was removed at reduced pressure.

The crude material was dissolved in dry DCM (3 mL), subsequently a solution of phosphine **107** (400 mg, FW=277.3, 1.44 mmol, 2.4 eqv) and Et_3N (250 µL, FW=101.19, d=0.728, 1.8 mmol, 3 eqv) in dry DCM (3 mL), was cannulated and the mixture was stirred for 30 minutes at room temperature.

Reaction was monitored by TLC (Hex:AcOEt 8:2) and was quenched by removing the solvent at reduced pressure.

The crude material was purified by flash chromatography on silica gel (Hex:AcOEt 8:2) to afford 150 mg (0.17 mmol, FW=840.94, Y=30%).

LC-MS (HESI probe): $[M+H]^+$ 841.98 $[M+Na]^+$ 863.91

^1H NMR (300 MHz, CD_2Cl_2): δ (ppm) = 8.07-8.03 (m, 2H), 7.43-6.95 (m, 36H), 2.75 (s, 2H), 1.68 (s, 6H).

^{13}C NMR (75 MHz, CD_2Cl_2): δ (ppm)= 170.84, 146.47, 143.43, 141.79, 135.64, 134.98, 134,62, 134.49, 134.36, 130.89, 130.10, 129.97, 129.72, 129.66, 129.62, 129.58, 129.53, 126.52, 126.45, 125.83, 123.60, 123.32, 120.87, 58.71, 55.02, 53.58, 45.18, 16.35

General procedure for cyclization of *meso* diol (**86**)

Ligand (8 mol%) and $Pd_2(dba)_3CHCl_3$ are dissolved in dry solvent (DCM or toluene, 0.02M) under Argon atmosphere and the mixture was stirred for 45 minutes at room temperature, till the formation of the chiral ligand is completed. The solution switch from violet to yellow/orange.

In another flask, the *meso* diol is dissolved in dry solvent (DCM or toluene, 0.1 M) under Argon atmosphere and the catalyst containing solution previously prepared is cannulated.

The mixture is stirred till the reaction is completed.

If necessary, $BaCO_3$ (1.1 eqv) is added to the solution containing the substrate before cannulation.

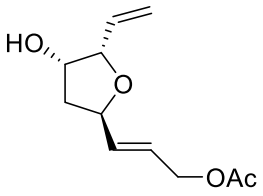
If necessary, reaction mixture is cooled at -30°C before cannulation of the catalyst solution and is kept at the same temperature till the end.

Reaction is monitored by TLC and when it is completed it is quenched by addition of silica and filtration on a silica pad by washing with EtOAc.

The resulting crude material is purified by liquid chromatography on silica gel to give the pure cyclized product.

d.r. ST:AC was determined by HPLC. Enantiomeric excess was determined by chiral HPLC, on Chiralpak AS-H.

Synthesis of (*E*)-3-((2*R*,4*S*,5*S*)-4-hydroxy-5-vinyltetrahydrofuran-2-yl)allyl acetate (**88**)



Chemical Formula: $C_{11}H_{16}O_4$
Molecular Weight: 212.24

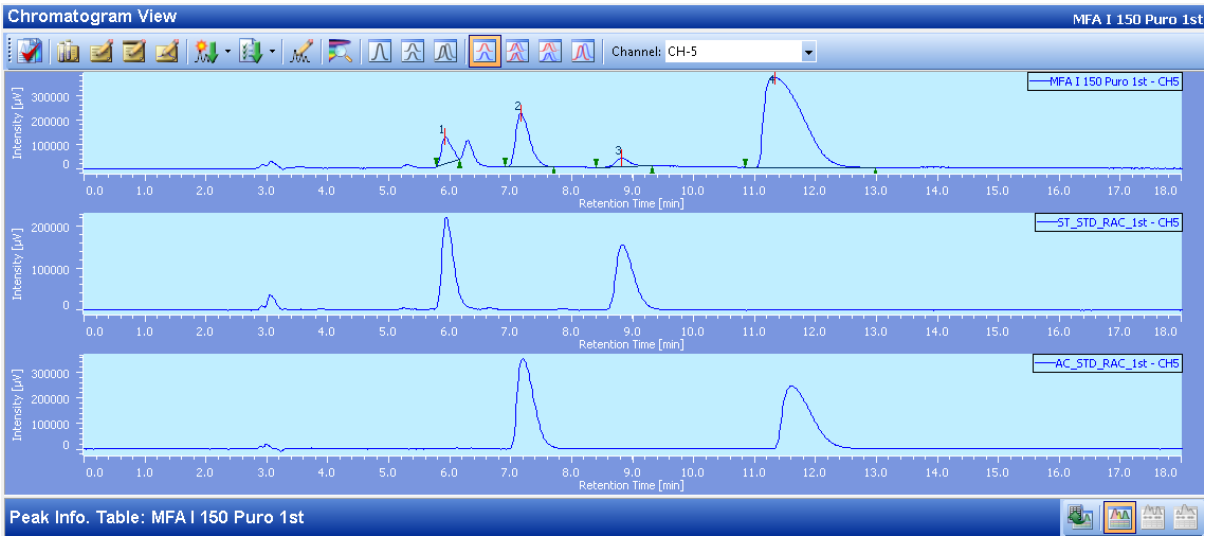
In a round bottom flask, meso diol **86** (53.6 mg, FW=272.3, 0.2 mmol, 1 eqv) was dissolved in dry toluene (1 mL). In another flask, (*S,S*)-L3 (13 mg, FW=812.27, 0.016 mmol, 8 mol%) and $Pd_2(dba)_3CHCl_3$ (6.2 mg, FW=1035.08, 0.006 mmol, 3 mol%) were dissolved in dry toluene (1 mL) under Ar atmosphere and the mixture was stirred at room temperature for 45 minutes. The solution switched from violet to orange.

At this point, the catalyst solution was cannulated into the substrate solution and stirring was continued for 3 hours.

Reaction was monitored by TLC (Hex:AcOEt 1:1) and was quenched by addition of silica gel (500 mg). The mixture was then filtered on a silica pad by washing with AcOEt and the solvent was removed at reduced pressure.

The crude material was purified by liquid chromatography on silica gel (Hex:AcOEt 1:1) to give 34 mg (0.16 mmol, FW=212.24, Y=80%) of pure compound.

HPLC analysis: chiralpak AS-H 250 x 4.6 mm (ID), 95:5 n-Heptane:*i*PrOH, flow 1 mL/min, UV-DET: 204 nm



Upper chromatogram: Analysis of compound **88** (table 4.8 entry 3)

Peak number	Description	A%
1	ST (2S,4R,5R) enantiomer	5.9
2	AC (2S,4R,5R) enantiomer	16.6
3	ST (2R,4S,5R) enantiomer	2.6
4	AC (2R,4S,5S) enantiomer	74.7

Median chromatogram: Analysis of racemic ST core

Peak number	Description	A%
1	ST (2S,4R,5R) enantiomer	48.9
2	ST (2R,4S,5R) enantiomer	51.1

Lower chromatogram: Analysis of racemic AC core

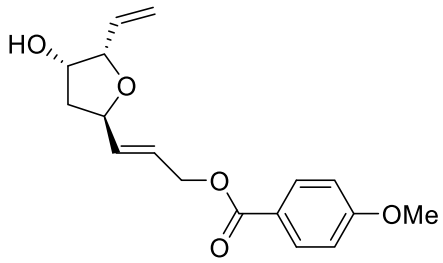
Peak number	Description	A%
1	AC(2S,4R,5R) enantiomer	49.3
2	AC (2R,4S,5S) enantiomer	50.7

LC-MS (HESI probe): $[M+H]^+$ 213.57 $[M+Na]^+$ 235.24

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 5.98-5.80 (m, 3H), 5.51 (dt, J=17.3, 1.7 Hz, 1H), 5.40 (dt, J=10.6, 1.6 Hz, 1H), 4.78 (dt, J=10.0, 5.2 Hz, 1H), 4.59 (d, J=5.1 Hz, 2H), 4.57-4.51 (m, 1H), 4.36 (m, 1H), 2.28 (ddd, J=13.2, 6.1, 1.2 Hz, 1H), 2.11-2.05 (s, 3H), 1.90 (m, 2H)

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 170.77, 134.84, 133.47, 125.32, 118.77, 83.41, 77.78, 73.65, 64.13, 41.66, 20.94.

Synthesis of (*E*)-3-((2*R*,4*S*,5*S*)-4-hydroxy-5-vinyltetrahydrofuran-2-yl)allyl 4-methoxybenzoate (**70**)



Chemical Formula: $C_{17}H_{20}O_5$
Molecular Weight: 304.34

In a round bottom flask, (*S,S*)-L3 (4.5 mg, FW=812.27, 0.0056 mmol, 8 mol%) and $Pd_2(dba)_3CHCl_3$ (2.2 mg, FW=1035.08, 0.0021 mmol, 3 mol%) were dissolved in dry toluene (1 mL) under Ar atmosphere and the mixture was stirred at room temperature for 45 minutes. The solution switched from violet to orange. In another round bottom flask, *meso* diol **97** (31.5 mg, FW= 450, 0.07 mmol, 1 eqv) was dissolved in dry toluene (2 mL), then $BaCO_3$ (15 mg, FW=197.35, 0.077 mmol. 1.1 eqv) was added and temperature was decreased at -30°C.

At this point, the catalyst solution was cannulated into the substrate solution and stirring was continued for 48 hours at -20°C.

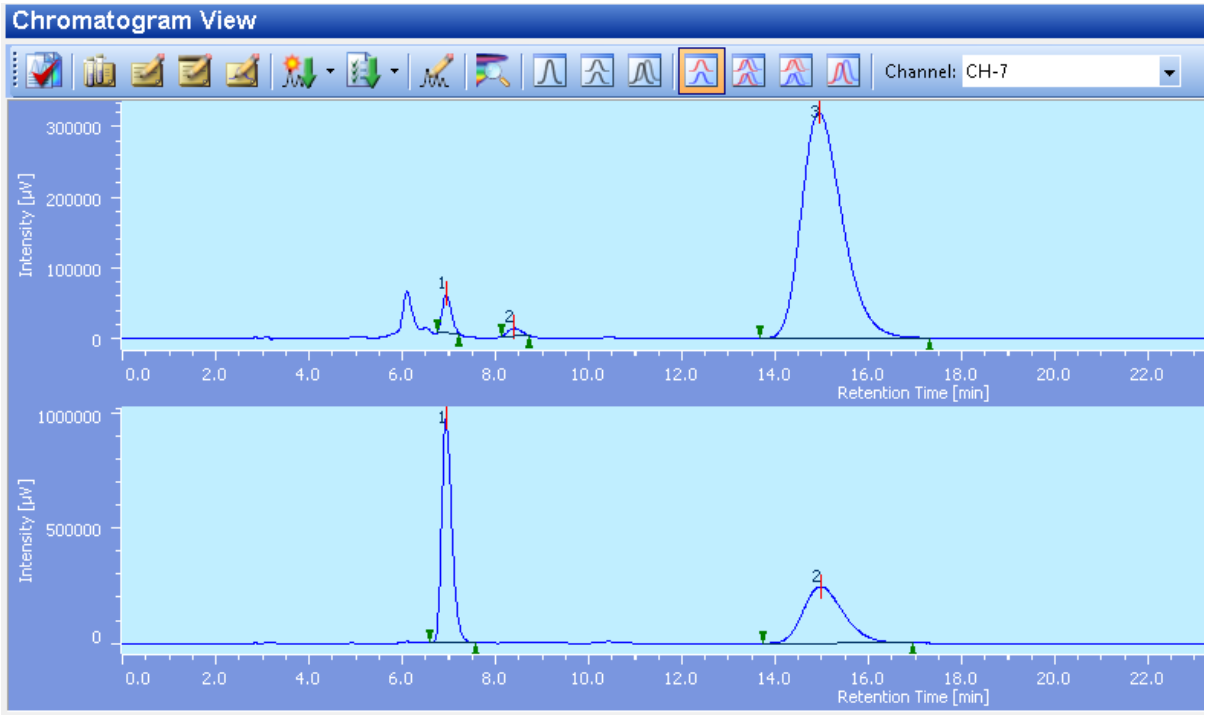
Reaction was monitored by TLC (Hex:AcOEt 1:1) and was quenched by addition of silica gel (500 mg). The mixture was then filtered on a silica pad by washing with AcOEt and the solvent was removed at reduced pressure.

The crude material was purified by liquid chromatography on silica gel (Hex:AcOEt 1:1) to give 15 mg (0.05 mmol, FW=304.34, Y=70%) of pure compound.

Diastereomeric ratio and enantiomeric excess were determined by chiral HPLC, ChiralPak AS-H.

Compound **70** was obtained in >99:1 *dr* (AC:ST) and 92% *ee*.

HPLC analysis: chiralpak AS-H 250 x 4.6 mm (ID), 70:30 n-Heptane:*i*PrOH, flow 1 mL/min, UV-DET: 230 nm



Upper chromatogram: analysis of compound 70 (table 4.9 entry 3)

Peak number	Description	A%
1	ST (2S,4R,5R) enantiomer	3.5
2	AC (2S,4R,5R) enantiomer	1.0
3	AC (2R,4S,5S) enantiomer	95.4

Lower chromatogram: analysis of racemic AC core

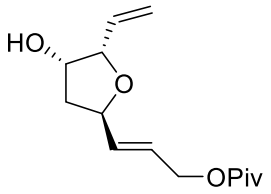
Peak number	Description	A%
1	AC (2S,4R,5R) enantiomer	50.0
2	AC (2R,4S,5S) enantiomer	50.0

LC-MS (HESI probe): $[M+H]^+$ 305.78 $[M+Na]^+$ 327.56

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 8.05-8.01 (d, J=9, 2H), 6.96-6.91 (d, J=9, 2H), 6.05-5.88 (m, 3H), 5.51 (dt, J=17.3, 1.7 Hz, 1H), 5.40 (dt, J=10.6, 1.6 Hz, 1H), 4.8-4.79 (m, 3H), 4.56-4.53 (m, 1H), 4.37 (s, 1H), 3.88 (s, 3H), 2.32-2.26 (ddd, J=13.2, 6.1, 1.2 Hz, 1H), 1.96-1.88 (m, 1H), 1.73 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 165.89, 134.32, 133.25, 131.58, 125.66, 122.42, 118.67, 113.49, 83.30, 77.70, 77.10, 73.54, 64.10, 55.32, 41.52, 29.59.

Synthesis of (*E*)-3-((2*R*,4*S*,5*S*)-4-hydroxy-5-vinyltetrahydrofuran-2-yl)allyl pivalate (**267**)



Chemical Formula: $C_{14}H_{22}O_4$
Molecular Weight: 254.33

In a round bottom flask, (*S,S*)-L3 (6.5 mg, FW=812.27, 0.008 mmol, 8 mol%) and $Pd_2(dba)_3CHCl_3$ (3 mg, FW=1035.08, 0.003 mmol, 3 mol%) were dissolved in dry toluene (1 mL) under Ar atmosphere and the mixture was stirred at room temperature for 45 minutes. The solution switched from violet to orange. In another round bottom flask, *meso* diol **104** (40 mg, FW= 388, 0.1 mmol, 1 eqv) was dissolved in dry toluene (2 mL), then $BaCO_3$ (22 mg, FW=197.35, 0.11 mmol. 1.1 eqv) was added and temperature was decreased at -30°C

At this point, the catalyst solution was cannulated into the substrate solution and stirring was continued for 48 hours at -20°C.

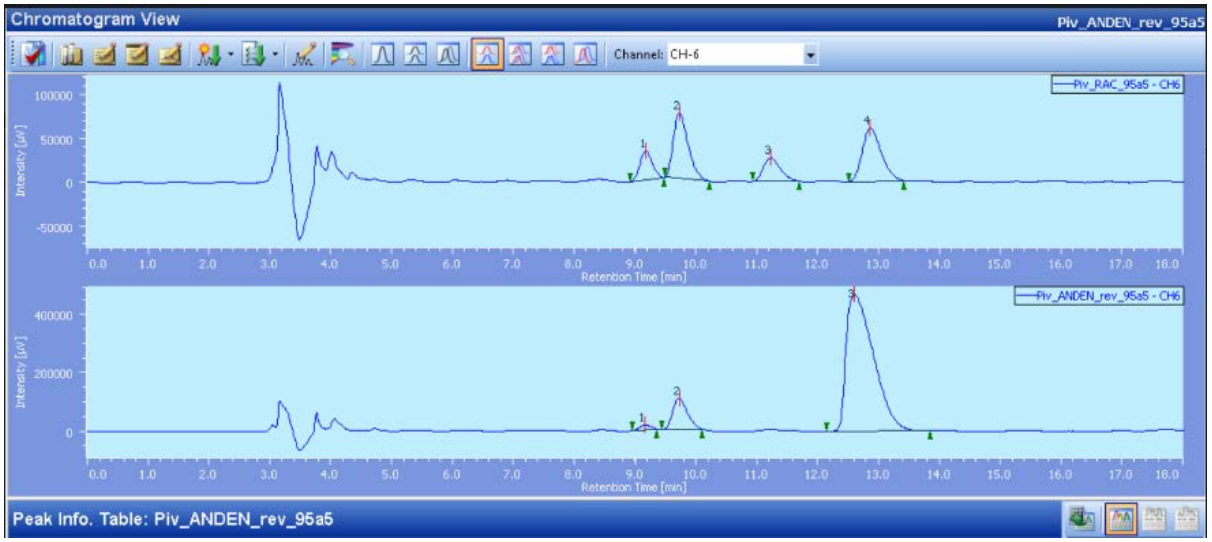
Reaction was monitored by TLC (Hex:AcOEt 4:6) and was quenched by addition of silica gel (500 mg). The mixture was then filtered on a silica pad by washing with AcOEt and the solvent was removed at reduced pressure.

The crude material was purified by liquid chromatography on silica gel (Hex:AcOEt 7:3) to give 17 mg (0.067 mmol, FW=254.33, Y=64%) of pure compound.

Diastereomeric ratio and enantiomeric excess were determined by chiral HPLC, ChiralPak AS-H.

Compound **267** was obtained with 99:1 *dr* (AC:ST) and 77% *ee.*

HPLC analysis: chiralpak AS-H 250 x 4.6 mm (ID), 95:5 n-Heptane:*i*PrOH, flow 1 mL/min, UV-DET: 204 nm



Upper chromatogram: Analysis on a racemic mixture of AC and ST core (dr 70:30 AC:ST)

Peak number	Description	A%
1	ST (2S,4R,5R) enantiomer	16.2
2	AC (2S,4R,5R) enantiomer	34.7
3	ST (2R,4S,5R) enantiomer	14.8
4	AC (2R,4S,5S) enantiomer	34.3

Lower chromatogram: Analysis of compound **267** (table 4.9 entry 2)

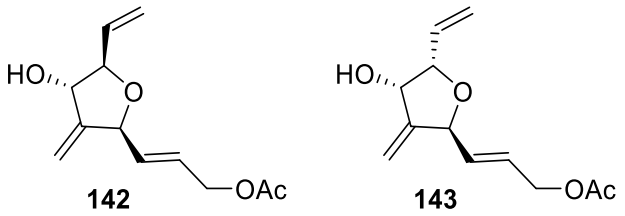
Peak number	Description	A%
1	ST (2S,4R,5R) enantiomer	1.2
2	AC (2S,4R,5R) enantiomer	10.8
3	AC (2R,4S,5S) enantiomer	88.0

LC-MS (HESI probe): $[M+H]^+$ 255.65 $[M+Na]^+$ 277.32

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 5.98-5.80 (m, 3H), 5.51 (dt, J=17.3, 1.7 Hz, 1H), 5.40 (dt, J=10.6, 1.6 Hz, 1H), 4.78 (dt, J=10.0, 5.2 Hz, 1H), 4.59 (d, J=5.1 Hz, 2H), 4.57-4.51 (m, 1H), 4.36 (m, 1H), 2.28 (ddd, J=13.2, 6.1, 1.2 Hz, 1H), 1.90 (m, 2H), 1.27 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 175.96, 134.74, 133.13, 129.12, 119.22, 91.04, 78.66, 74.67, 68.17 42.61, 38.84, 27.45

Synthesis of (*E*)-3-((2*S*,4*S*,5*R*)-4-hydroxy-3-methylene-5-vinyltetrahydrofuran-2-yl)allyl acetate (**142**) and (*E*)-3-((2*S*,4*S*,5*S*)-4-hydroxy-3-methylene-5-vinyltetrahydrofuran-2-yl)allyl acetate (**143**)



Chemical Formula: $C_{12}H_{16}O_4$
Molecular Weight: 224.25

In a round bottom flask, (*R,R)*-L2 (5.7 mg, FW=812.27, 0.007 mmol, 8 mol%) and $Pd_2(dba)_3CHCl_3$ (2.7 mg, FW=1035.08, 0.0025 mmol, 3 mol%) were dissolved in dry toluene (1 mL) under Ar atmosphere and the mixture was stirred at room temperature for 45 minutes. The solution switched from violet to orange. In another round bottom flask, meso diol **141** (21 mg, FW= 284.30, 0.07 mmol, 1 eqv) was dissolved in dry toluene (1 mL).

At this point, the catalyst solution was cannulated into the substrate solution and stirring was continued at room temperature for 4 hours.

Reaction was monitored by TLC (Hex: MTBE 6:4) and was quenched by addition of silica gel (100 mg). The mixture was then filtered on a silica pad by washing with AcOEt and the solvent was removed at reduced pressure.

The crude material was purified by liquid chromatography on silica gel (Hex:MTBE 6:4) to give 7.3 mg (0.032 mmol) of ST isomer **142** and 8.2 mg (0.036 mmol) of AC isomer **143** (total yield = 99%).

LC-MS (HESI probe): $[M+H]^+$ 225.46 $[M+Na]^+$ 247.31

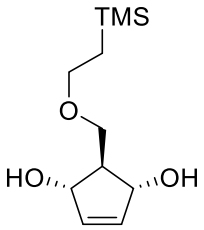
^{1}H NMR (**142**) (300 MHz, CD_2Cl_2): δ (ppm) = 6.10-5.91 (m, 2H), 5.4-5.25 (m, 3H), 5.07-4.97 (m, 2H), 4.82-4.75 (m, 1H), 4.61-4.59 (m, 2H), 4.28-4.25 (m, 1H), 3.99-3.96 (m, 1H), 2.08 (s, 3H).

^{13}C NMR (**142**) (75 MHz, CD_2Cl_2): δ (ppm) = 171.34, 150.28, 136.52, 129.54, 115.47, 109.32, 90.24, 87.21, 76.20, 65.11, 20.17

^{1}H NMR (**143**) (300 MHz, CD_2Cl_2): δ (ppm) = 6.17-5.98 (m, 2H), 5.32-5.15 (m, 3H), 5.01-4.91 (m, 2H), 4.83-4.77 (m, 1H), 4.61-4.59 (m, 2H), 4.15-4.12 (m, 1H), 3.62-3.59 (m, 1H), 2.06(s, 3H).

^{13}C NMR (**143**) (75 MHz, CD_2Cl_2): δ (ppm) = 175.32, 154.21, 136.53, 129.16, 114,22, 109.33, 94.12, 85.24, 77.20, 65.12, 20.14.

Synthesis of (1*R*,2*r*,3*S*)-2-((2-(trimethylsilyl)ethoxy)methyl)cyclopent-4-ene-1,3-diol (**155)**



Chemical Formula: $C_{11}H_{22}O_3Si$
Molecular Weight: 230.38

Part 1

In a round bottom flask, under Ar atmosphere, (2-(chloromethoxy)ethyl)trimethylsilane (4.6 mL, FW = 166.72, d = 0.942, 26 mmol, 1.3 eqv) was dissolved in dry DMF (40 mL) and temperature was lowered at -40°C. At this point, sodium cyclopentadienyle (10 mL, sol. 2M in THF, 20 mmol, 1 eqv), was added dropwise and the solution was stirred for 30 minutes at the same temperature. After that, the reaction mixture was poured in a separating funnel containing a 2:1 mixture of n-pentane: iced water (100 mL). The layers were separated, then the organic one was washed with iced water (3 x 100 mL), dried on Na_2SO_4 (by keeping temperature at 0°C), filtered and concentrated at 0°C at reduced pressure.

Part 2

The resulting crude material was dissolved in dry MeOH (180 mL) and transferred in a photochemical reactor (Hg lamp, 150 W). Thiourea (2 g), AcONa (100 mg) and Bengal Rose (70 mg) were added, temperature was lowered at -5°C, O_2 was bubbled into the solution and the mixture was irradiated under vigorous stirring for 7 hours.

Reaction was monitored by TLC (DCM :MeOH 95:5) and was quenched by removal of the solvent at reduced pressure. The raw material was diluted with AcOEt (50 mL) and was washed with water (2 x 100 mL). The organic phase was dried on Na_2SO_4, filtered and concentrated at reduced pressure.

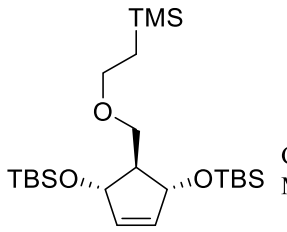
The crude material (1.35 g, 5.86 mmol, FW = 230.38, Y = 30%) wasn't purified because NMR analysis showed that it didn't contain any impurities.

LC-MS (HESI probe): $[M+H]^+$ 231.41, $[M+Na]^+$ 253.49

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 5.91 (s, 2H), 4.45-4.42 (d, J = 5.02 Hz, 2H), 3.65-3.55 (m, 4H), 2.11-2.07 (m, 1H), 0.98-0.93 (t, J = 8.4 Hz, 2H), 0.03 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 135.39, 77.70, 70.24, 68.51, 58.91, 18.07, -1.47

Synthesis of (((1*R*,2*r*,3*S*)-2-((2-(trimethylsilyl)ethoxy)methyl)cyclopent-4-ene-1,3-diyl)bis(oxy))bis(tert-butyldimethylsilane) (**157)**



Chemical Formula: $C_{23}H_{50}O_3Si_3$
Molecular Weight: 458.90

Imidazole (475 mg, FW=68.08, 6.96 mmol, 6 eq) was solubilized in dry DMF (11 ml) under Ar atmosphere. A solution of diol **155** (267 mg, FW= 230.38, 1.16 mmol, 1 eq) in DMF (3 µL) was added dropwise via syringe. The mixture was cooled to 0°C, then TBSCl (790 mg, FW=150.73, 5.22 mmol, 4.5 eq) was quickly added. After 5 minutes, temperature was spontaneously raised to rt and the solution was kept under vigorous stirring.

Reaction was monitored via TLC, (Hex:AcOEt 9:1). It was quenched by pouring the reaction mixture in a H_2O: $NaHCO_{3\ (sat\ sol)}$: hexane 1:1:1 (50 mL). The layers were separated, then the organic one was extracted with Hex:MTBE 1:1 (3 x 30 mL). The combined organic phases were washed with brine (50 mL) and water (50 mL), then dried on Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the resulting crude oil was purified by flash chromatography on silica gel (Hex:Et_2O 98:2).

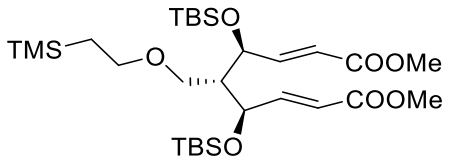
415 mg of pure product were obtained (0.9 mmol, FW = 230.38, Y= 78%).

LC-MS (HESI probe): $[M+H]^+$ 459.94, $[M+Na]^+$ 481.97.

^1H NMR (300 MHz, CD_2Cl_2): δ (ppm)= 5.76 (s, 2H), 4.59-4.57 (d, J = 5.7 Hz, 2H), 3.59-3.54 (m, 4H), 1.98-1.94 (m, 1H), 0.98-0.88 (s, 20 H), 0.11 (s, 12H), 0.04 (s, 9 H).

^{13}C NMR (75 MHz, CD_2Cl_2): δ (ppm)= 136.05, 76.99, 69.14, 67.89, 60.17, 54.30, 26.48, 18.97, -0.82, -4.12.

Synthesis of dimethyl (2*E*,4*R*,5*r*,6*S*,7*E*)-4,6-bis((tert-butyldimethylsilyl)oxy)-5-((2-(trimethylsilyl)ethoxy)methyl)nona-2,7-dienedioate (**159**)



Chemical Formula: $C_{29}H_{58}O_7Si_3$
Molecular Weight: 603.02

Alkene **157** (407 mg, FW=458.90, 0.89 mmol, 1 eq) was solubilized in dry DCM (9 mL). The solution was cooled to -78°C and a O_3/O_2 mixture was bubbled in it until the color became blue. The excess of ozone was eliminated by bubbling oxygen in the solution that was kept at -78°C. The mixture became colorless, then Ar was bubbled in order to remove the oxygen.

Under vigorous stirring, at -78°C, a solution of pyridine (2 mg, PM = 79, d = 0.98, 2 μL) in dimethyl sulfide (653 μL, d=0.846, FW=62.13, 8.9 mmol, 10 eq) was added dropwise to the mixture and the temperature was slowly raised to -32°C. After 2 hours, the temperature was spontaneously increased at rt, then the solvent was removed under reduced pressure.

The crude oil was directly dissolved in dry THF (2 mL) under Ar atmosphere and subsequently it was transferred via cannula into a round bottom flask containing a THF solution (9 ml) of methyl(triphenylphosphoranyliden)acetate ($Ph_3PCHCOOMe$, 1 g, FW=334.36, 3.11 mmol, 3.5 eqv) that was kept under vigorous stirring.

After 30 minutes, the temperature was raised at 50°C and the mixture was stirred for 24 hours. The reaction was monitored by TLC (Hex:Et_2O 9:1). It was quenched through addition of NH_4Cl saturated aqueous solution (15 ml) and diluted with H_2O (20 ml). Phases were separated, then the aqueous one was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with water (2 x 50 mL) and Brine (50 mL), dried on Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the resulting crude material was filtered on a silica gel pad (10 g) by washing with Hexane:Et_2O 7:3. Finally, the raw compound was purified by flash chromatography on silica gel (Hex:Et_2O 9:1).

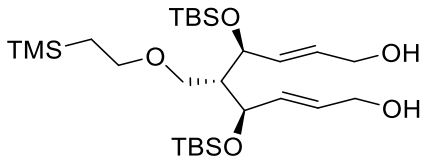
126 mg of pure compound were achieved (FW= 603.02, 0.2 mmol, Y=24%).

LC-MS (HESI probe): $[M+H]^+$ 604.05, $[M+Na]^+$ 626.05.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 7.12-6.92 (dd, J =15.5, 5.2 Hz, 2H), 6.03-5.88 (dd, J=15.6, 1.5 Hz, 2H), 4.70-4.20 (m, 2H), 3.81 (s, 6H), 3.49-2.69 (m, 4 H), 2.11-2.03 (m, 1H), 1.35-1.30 (t, J = 8.4 Hz, 2H), 0.97 (s, 18H), 0.15 (s, 21 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 166.52, 145.45, 123.22, 72.31, 68.18, 66.77, 50.31, 49.12, 31.14, 25.16, 23.82, 2.11, -1.95

Synthesis of (2*E*,4*R*,5*r*,6*S*,7*E*)-4,6-bis((tert-butyldimethylsilyl)oxy)-5-((2-(trimethylsilyl)ethoxy)methyl)nona-2,7-diene-1,9-diol (**160**)



Chemical Formula: $C_{27}H_{58}O_5Si_3$
Molecular Weight: 547.01

In a round bottom flask, ester **159** (126 mg, FW=603.02, 0.2 mmol, 1 eq), was dissolved in dry THF (1.5 ml) under Ar atmosphere.

The reaction mixture was cooled to -78°C, then DIBAL-H solution (1.2 M solution in toluene, 790 µL, 0.94 mmol, 4.7 eq) was added dropwise and under vigorous stirring, to the ester solution.

Reaction was monitored by TLC (Hex:Et_2O 7:3) and it was completed after 4 hours.

To quench, the mixture was diluted with Et_2O (3 ml) and subsequently saturated Rochelle salt solution (10 mL) and water (10 mL) were slowly added to the -78°C solution.

Temperature was spontaneously raised to rt while the double phases system was kept under vigorous stirring until two clear layers were obtained.

After separation, the aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with water (50 mL) and Brine (50 mL), then dried on Na_2SO_4, filtered and the solvent was removed under reduced pressure.

The crude oil was purified by flash chromatography on silica gel (Hex:AcOEt 7:3).

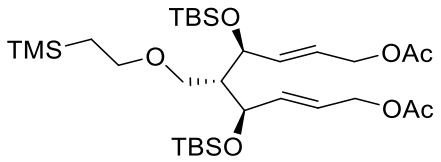
86.5 mg of pure product were achieved (FW=547.01, 0.16 mmol, Y = 79%)

LC-MS (HESI probe): $[M+H]^+$ 548.03, $[M+Na]^+$ 570.02

^1H NMR (300 MHz, $CDCl_3$): δ (ppm)= 5.82-5.62 (m, 4H), 4.27-4.22 (m, 2H), 4.21-4.11 (d, J=4.4 Hz, 4H), 3.15-2.92 (m, 4H), 1.91-1.83 (m, 1H), 1.37-1.32 (t, J = 8.4 Hz, 2H), 0.97 (s, 18H), 0.12 (s, 21 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 131.65, 127.31, 75.33, 70.24, 66.11, 60.23, 45.64, 30.28, 27.10, 24.34, 2.64, -1.91

Synthesis of (2*E*,4*R*,5*r*,6*S*,7*E*)-4,6-bis((tert-butyldimethylsilyl)oxy)-5-((2-(trimethylsilyl)ethoxy)methyl)nona-2,7-diene-1,9-diyl diacetate (**160a)**



Chemical Formula: $C_{31}H_{62}O_7Si_3$
Molecular Weight: 631.08

In a round bottom flask, under Ar atmosphere, diol **160** (86.5 mg, FW=547.01, 0.16 mmol, 1eq) was dissolved in dry DCM (2 mL). Pyridine (36 µL, FW=79, d=0.974 g/mL, 0.45 mmol, 2.8 eq) was subsequently added dropwise followed by acetic anhydride (40 µL, FW=102.09, d=1.081 g/mL, 0.38 mmol, 2.4 eq). Finally, DMAP (3 mg, FW=122.17, 0.026 mmol, 0.16 eq) was added.

Reaction was monitored by TLC (Hex:AcOEt 7:3) and after 16 hours it was completed.

Quenching was done by addition of saturated $NaHCO_3$ solution (5 mL) and when bubbling due to acetic anhydride decomposition stopped, the phases were separated. The aqueous one was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with water (30 mL), saturated solution of $CuSO_4$ (3 x 30 mL), again water (30 mL) and finally with Brine (30 mL). After drying on Na_2SO_4 and removal of the solvent at reduce pressure, the resulting crude oil was purified by flash chromatography (Hex:Et_2O 9:1).

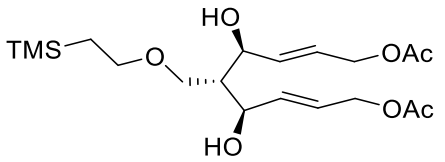
81.5 mg of pure product (FW= 631.08, 0.13 mmol, Y=81%) were achieved.

LC-MS (HESI probe): $[M+H]^+$ 632.19, $[M+Na]^+$ 654.28

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.85-5.65 (m, 4H), 4.66-4.51 (m, 2H), 4.30-4.15 (d, J=5.3, 4H) ,3.57-3.37 (m, 4H), 2.07 (s, 6H), 1.91-1.76 (m, 1H), 1.36-1.31 (t, J = 8.4 Hz, 2H), 0.97 (s, 18H), 0.12 (s, 21 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 171.32, 129.55, 128.16, 72.03, 70.91, 65.13, 64.17, 48.74, 31.12, 25.81, 23.12, 18.77, 2.15, -1.92

Synthesis of (2*E*,4*R*,5*r*,6*S*,7*E*)-4,6-dihydroxy-5-((2-(trimethylsilyl)ethoxy)methyl)nona-2,7-diene-1,9-diyl diacetate (**156**)



Chemical Formula: $C_{19}H_{34}O_7Si$
Molecular Weight: 402.56

In a round bottom flask, compound **160a** (81.5 mg, FW = 631.08, 0.13 mmol) was dissolved in THF (2 mL) and temperature was lowered at 0°C. At this point, TBAF (520 µL, sol 1 M in THF, 0.52 mmol, 4 eqv) was added dropwise and the mixture was stirred at the same temperature for 4 hours.

Reaction was monitored by TLC (Hex:AcOEt 7:3) and when it was completed it was quenched by addition of phosphate buffer (5 mL). The layers were separated, then the aqueous one was extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (50 mL), dried on Na_2SO_4, filtered and finally concentrated at reduced pressure.

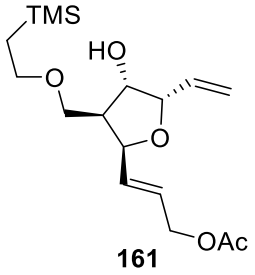
The crude material was purified by liquid chromatography on silica gel (Hex:AcOEt 6:4) to furnish 47 mg (0.12 mmol, FW = 402.56, Y = 92%) of pure compound.

LC-MS (HESI probe): $[M+H]^+$ 403.77, $[M+Na]^+$ 425.64

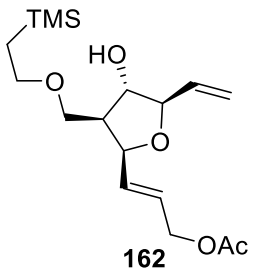
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.96-5.81 (m, 4H), 4.66-4.61 (d, J = 4.5 Hz, 4H), 4.50-4.41 (m, 2H), 3.79-3.72 (d, J = 5.2, 2H), 3.53-3.48 (t, J = 8.5 Hz, 2H), 2.1 (s, 6 H), 1.68-1.63 (m, 1H), 0.98-0.93 (t, J = 8.4 Hz, 2H), 0.09 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 171.15, 130.55, 128.18, 70.62, 68.45, 66.02, 62.12, 45.22, 22.14, 21.15, 2.32

Synthesis of (*E*)-3-((2*S*,3*S*,4*S*,5*R*)-4-hydroxy-3-((2-(trimethylsilyl)ethoxy)methyl)-5-vinyltetrahydrofuran-2-yl)allyl acetate (**161**) and (*E*)-3-((2*S*,3*S*,4*S*,5*S*)-4-hydroxy-3-((2-(trimethylsilyl)ethoxy)methyl)-5-vinyltetrahydrofuran-2-yl)allyl acetate (**162**).



161



162

Chemical Formula: $C_{17}H_{30}O_5Si$
Molecular Weight: 342.5

In a round bottom flask, (*R,R)*-L2 (3.38 mg, FW=812.27, 0.0042 mmol, 8 mol%) and $Pd_2(dba)_3CHCl_3$ (1.6 mg, FW=1035.08, 0.0016 mmol, 3 mol%) were dissolved in dry toluene (1 mL) under Ar atmosphere and the mixture was stirred at room temperature for 45 minutes. The solution switched from violet to orange. In another round bottom flask, meso diol **156** (21 mg, FW= 402.55, 0.052 mmol, 1 eqv) was dissolved in dry toluene (1 mL).

At this point, the catalyst solution was cannulated into the substrate solution and stirring was continued at room temperature for 5 hours.

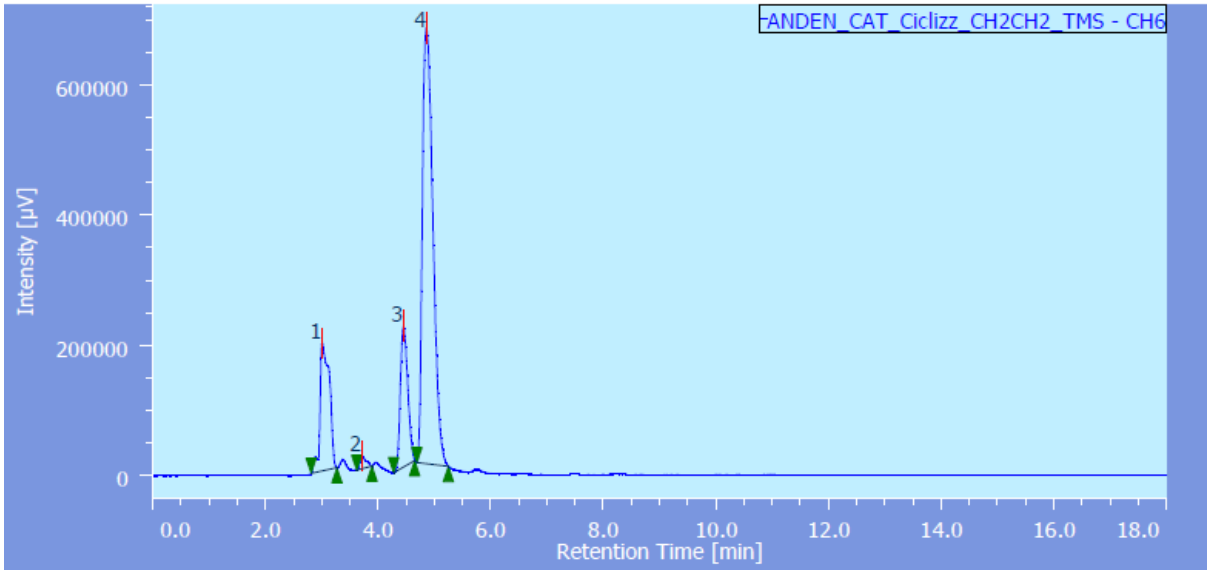
Reaction was monitored by TLC (Hex: AcOEt 8:2) and was quenched by addition of silica gel (100 mg). The mixture was then filtered on a silica pad by washing with AcOEt and the solvent was removed at reduced pressure.

The crude material was purified by liquid chromatography on silica gel (Hex:AcOEt 1:1) to give 17.5 mg (0.05 mmol, FW=342.5, Y=98%) of pure compound as mixture of AC and ST diastereoisomers.

LC-MS (HESI probe): $[M+H]^+$ 343.64 $[M+Na]^+$ 365.55

^1H NMR (200 MHz, CD_2Cl_2): δ (ppm) = 6.11-5.63 (m, 2.26 H), 5.52-5.19 (m, 1.85 H), 4.63-4.58 (m, 3H), 4.18-4.02 (t, J = 6.8, 1H), 3.97-3.81 (t, J = 6.7, 1H), 3.58-24 (m, 3.26 H), 2.58-2.39 (m, 1 H), 2.15 (s, 3.8 H), 1.01-0.89 (t, J = 7.4, 1.8 H), 0.16 (s, 6.7 H)

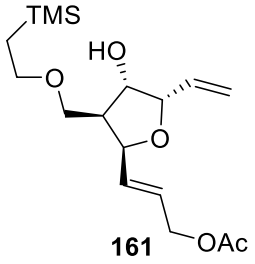
HPLC analysis: chiralpak AS-H 250 x 4.6 mm (ID), 80:20 n-Heptane:*i*PrOH, flow 1 mL/min, UV-DET: 204-208 nm



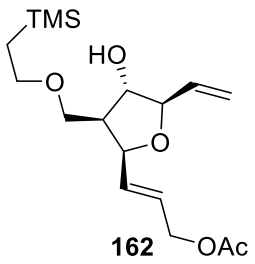
Peak number	Description	A%
1	ST (2R,3R,4R,5S) enantiomer	17.6
2	AC (2R,3R,4R,5R) enantiomer	1.1
3	ST (2S,3S,4S,5R) enantiomer	15.1
4	AC (2S,3S,4S,5S) enantiomer	66.2

The amount of substrate achieved from the synthesis was very low. For this reason, it was impossible to determine the absolute configuration of the stereocenters of each single stereoisomer. Due to the structural similarity between the THF products 161 and 162 and the ones obtained from the cyclization of the meso diols 86, 104 and 97, we simply assumed that, the peaks sequence in the chromatogram was the same in all the cases.

Synthesis of (*E*)-3-((2*S*,3*S*,4*S*,5*R*)-4-hydroxy-3-((2-(trimethylsilyl)ethoxy)methyl)-5-vinyltetrahydrofuran-2-yl)allyl acetate (**161**) and (*E*)-3-((2*S*,3*S*,4*S*,5*S*)-4-hydroxy-3-((2-(trimethylsilyl)ethoxy)methyl)-5-vinyltetrahydrofuran-2-yl)allyl acetate (**162**).



161



162

Chemical Formula: $C_{17}H_{30}O_5Si$
Molecular Weight: 342.5

In a round bottom flask, (*S,S)*-L1 (3.54 mg, FW=690.76, 0.00512 mmol, 8 mol%) and $Pd_2(dba)_3CHCl_3$ (2 mg, FW=1035.08, 0.0019 mmol, 3 mol%) were dissolved in dry toluene (1 mL) under Ar atmosphere and the mixture was stirred at room temperature for 45 minutes. In another round bottom flask, meso diol **156** (26 mg, FW= 402.55, 0.064 mmol, 1 eqv) was dissolved in dry toluene (1 mL).

At this point, the catalyst solution was cannulated into the substrate solution and stirring was continued at room temperature for 5 hours.

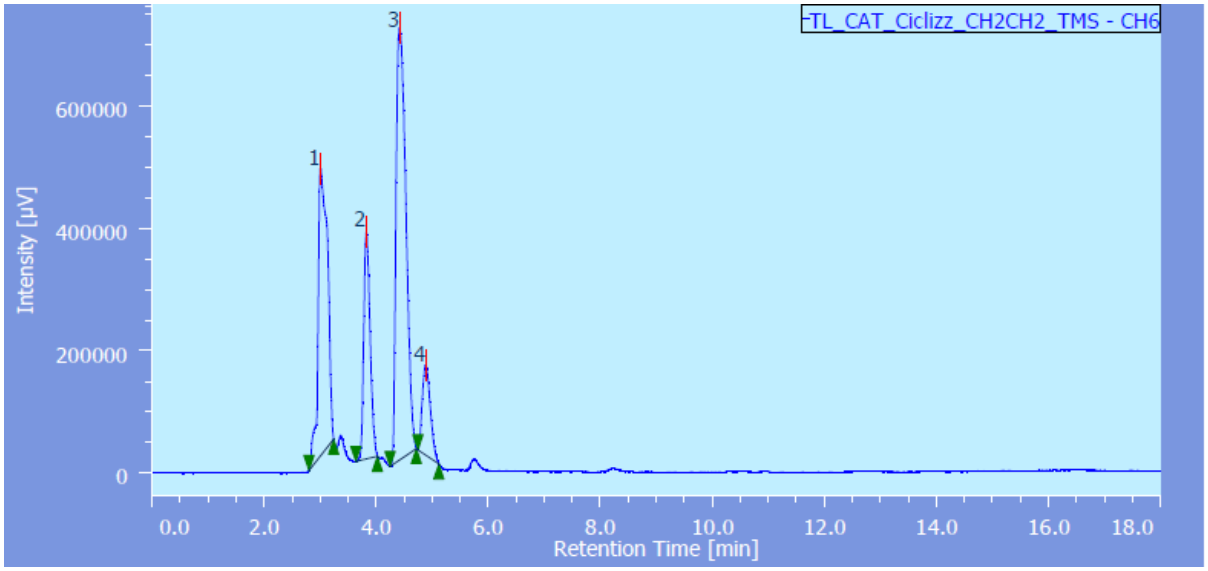
Reaction was monitored by TLC (Hex: AcOEt 8:2) and was quenched by addition of silica gel (100 mg). The mixture was then filtered on a silica pad by washing with AcOEt and the solvent was removed at reduced pressure.

The crude material was purified by liquid chromatography on silica gel (Hex:AcOEt 1:1) to give 10.5 mg (0.03 mmol, FW=342.5, Y=48%) of pure compound as a mixture of AC and ST diasteroisomers.

LC-MS (HESI probe): $[M+H]^+$ 343.64 $[M+Na]^+$ 365.55

^1H NMR (200 MHz, CD_2Cl_2): δ (ppm) = 6.11-5.63 (m, 3.6 H), 5.52-5.19 (m, 3.3 H), 4.63-4.58 (m, 4.1H), 4.18-4.02 (t, J = 6.8, 1H), 3.97-3.81 (t, J = 6.7, 1H), 3.58-24 (m, 5.3 H), 2.58-2.39 (m, 2.5 H), 2.15 (s, 3.8 H), 1.01-0.89 (t, J = 7.4, 3H), 0.16 (s, 10.9 H)

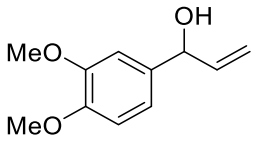
HPLC analysis: chiralpak AS-H 250 x 4.6 mm (ID), 80:20 n-Heptane:*i*PrOH, flow 1 mL/min, UV-DET: 204-208 nm



Peak number	Description	A%
1	ST(2R,3R,4R,5S) enantiomer	29.7
2	AC(2R,3R,4R,5R) enantiomer	15.8
3	ST(2S,3S,4S,5R) enantiomer	46.4
4	AC(2S,3S,4S,5S) enantiomer	8.0

The amount of substrate achieved from the synthesis was very low. For this reason, it was impossible to determine the absolute configuration of the stereocenters of each single stereoisomer. Due to the structural similarity between the THF products 161 and 162 and the ones obtained from the cyclization of the meso diols 86, 104 and 97, we simply assumed that, the peaks sequence in the chromatogram was the same in all the cases.

Synthesis of 1-(3,4-dimethoxyphenyl)prop-2-en-1-ol (**247**)



Chemical Formula: $C_{11}H_{14}O_3$
Molecular Weight: 194.23

In a round bottom flask, 3,4-dimethoxybenzaldehyde (997 mg, FW=166.17, 6 mmol, 1 eqv) was dissolved in dry THF (5 mL) under Argon atmosphere. Temperature was lowered at -78°C and vinyl magnesium bromide (6.6 mL, solution 1M in THF, 6.6 mmol, 1.1 eqv) was added dropwise, then the mixture was kept under vigorous stirring at 0°C for 2 hours.

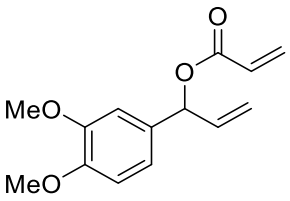
Reaction was monitored by TLC (Hex:AcOEt 7:3) and when it was completed it was quenched by addition of NH_4Cl saturated solution (10 mL) and diluted with EtOAc (10 mL). The organic layer was washed with brine (50 mL), dried on Na_2SO_4, filtered and concentrated at reduced pressure.

The crude material (1.066 g, 5.49 mmol, FW=194.23, Y= 91%) was directly used for the following step without any purification.

Spectroscopic data are in agreement with the literature[99].

[99] Swain, N.A., Brown, R. C. D. and Bruton, G., *J. Org. Chem.*, **2004** , *69*, 122.

Synthesis of 1-(3,4-dimethoxyphenyl)allyl acrylate (**246**)



Chemical Formula: $C_{14}H_{16}O_4$
Molecular Weight: 248.28

In a round bottom flask, compound **247** (500 mg, FW=194.23, 2.57 mmol, 1 eqv) was dissolved in dry and degassed DCM (50 mL), then DIPEA (1.27 mL, FW=129.25, d=0.742, 7.32 mmol, 2.85 eqv) was added dropwise and the mixture was cooled at 0°C.

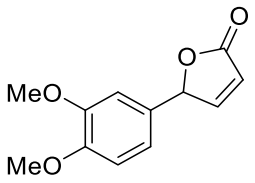
After 10 minutes, a solution of acryloyl chloride (501 µL, FW=90.51, d=1.114, 6.17 mmol, 2.4 eqv) in dry DCM (16 mL) was slowly cannulated and the mixture was gently warmed to room temperature and kept under vigorous stirring.

Reaction was monitored by TLC (Hex:AcOEt 7:3) and after 1 hour it was poured into water. The phases were separated and the aqueous one was extracted with DCM (3 x 80 mL). The combined organic phases were washed with brine (200 mL), dried on $MgSO_4$ and concentrated at reduced pressure.

The crude material was purified by flash chromatography on silica gel (Hex:AcOEt 9:1) to give 480 mg (1.93 mmol, FW=248.28, Y=75%) of pure product.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)= 6.99-6.97 (dd, J = 8.4, 2.0, 1H), 6.92-6.87 (m, 3H), 6.50-6.45 (dd, J = 17.2, 1.6, 1H), 6.34-6.32 (d, J = 5.6, 1H), 6.24-6.17 (dd, J = 17.2, 10.4, 1H), 6.11-6.03 (m, 1H), 5.89-5.86 (dd, J = 10.4, 1.6, 1H), 5.37-5.27 (ddd, J = 18.4, 10.8, 1.6, 1H), 3.88 (s, 3H), 3.86 (s, 3H).

Synthesis of 5-(3,4-dimethoxyphenyl)furan-2(5H)-one (**230**)



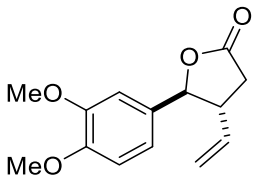
Chemical Formula: $C_{12}H_{12}O_4$
Molecular Weight: 220.22

In a round bottom flask, compound **246** (105 mg, FW=248.28, 0.42 mmol, 1 eqv) was dissolved in dry and degassed toluene (20 mL). Then 2nd generation Grubbs catalyst (18 mg, FW=848.97, 0.021 mmol, 5 mol%) was added and the reaction mixture was heated to 80°C.

Reaction was monitored by TLC (Hex: AcOEt 1:1) and after 15 hours it was quenched by lowering the temperature to rt and by bubbling air inside the solution for at least 15 minutes. After that, the solvent was removed at reduced pressure and the resulting crude material was purified by liquid chromatography on silica gel (Hex:AcOEt 1:1) to give 63.4 mg (0.29 mmol, FW=220.22, Y=68%) of pure product.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)= 7.55-7.53 (dd, J = 5.6, 1.6, 1H), 6.91-6.85 (m, 3H), 6.74-6.73 (d, J = 2, 1H), 6.27-6.25 (dd, J = 5.6, 2, 1H), 3.88 (s, 3H), 3.84 (s, 3H).

Synthesis of 5-(3,4-dimethoxyphenyl)-4-vinyldihydrofuran-2(3H)-one (**252**)



Chemical Formula: $C_{14}H_{16}O_4$
Molecular Weight: 248.28

In a round bottom flask under Ar atmosphere, CuI (220.9 mg, FW=190.45, 1.16 mmol, 4 eqv) was suspended in dry THF (6 mL) and temperature was lowered at -78°C. Then, vinyl magnesium bromide (2.3 mL, solution 1M in THF, 2.32 mmol, 8 eqv) was slowly added dropwise and the mixture was stirred at the same temperature for 1 hour. At this point, a solution of compound **230** (63.4 mg, FW=220.22, 0.29 mmol, 1 eqv) and TMSCl (55 µL, FW=108.64, d=0.856, 0.435 mmol, 1.5 eqv) in dry THF (2 mL) was cannulated and temperature was slowly increased at 0°C.

Reaction was monitored by TLC (Hex:AcOEt 7:3) and after 1 hour it was quenched by addition of an NH_4Cl saturated solution : NH_4OH (1:1) (10 mL). Phases were separated, then the aqueous one was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried on Na_2SO_4 and concentrated at reduced pressure.

The resulting crude material was purified by flash chromatography on silica gel (Hex:AcOEt 8:2) to give a mixture of compound n (22.3 mg, FW=248.28, 0.09 mmol) and the corresponding α-TMS derivative (31 mg, FW=320.46, 0.097 mmol). The overall yield is 65 %

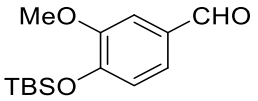
The TMS derivative (31 mg, FW=320.46, 0.097 mmol) was dissolved in a mixture MeOH:THF (1:2) (1 mL) and temperature was lowered at 0°C. At this point, TBAF (116 µL, solution 1M in THF, 0.116 mmol, 1.2 eqv) was added dropwise and the mixture was kept under vigorous stirring at room temperature for 8 hours.

Reaction was monitored by TLC (Hex:AcOEt 1:1) and was quenched by addition of Brine (5 mL), then it was diluted with EtOAc (5 mL). Phases were separated and the aqueous one was extracted with AcOEt (3 x 15 mL). The combined organic phases were washed with brine (50 mL), dried on Na_2SO_4, filtered and solvent was removed at reduced pressure.

The resulting crude material was then purified by flash chromatography (Hex:AcOEt 8:2) to give 18 mg (0.073, FW=248.28, Y=75%) of pure compound **252.**

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)= 5.86-5.78 (ddd, J = 16.4, 9.2, 7.2 Hz, 1H), 5.21-5.19 (d, J = 10 Hz, 1 H), 5.12-5.08 (d, J = 16.4 Hz, 1H), 5.08-5.06 (d, J = 9.2 Hz, 1H), 3.88 (s, 6H), 3.14-3.05 (m, 1H), 2.87-2.81 (dd, J = 17.6, 8.4 Hz, 1H), 2.67-2.59 (dd, J = 17.2, 11.2 Hz, 1H)

Synthesis of 4-((tert-butyldimethylsilyl)oxy)-3-methoxybenzaldehyde (**261**)



Chemical Formula: $C_{14}H_{22}O_3Si$
Molecular Weight: 266.41

In a round bottom flask, 500 mg of vanillin, were dissolved in dry DCM under Argon atmosphere, 2,6-lutidine was added and the mixture was cooled at 0°C. At this point, TBSOTf was slowly added dropwise and the mixture was kept at 0°C for 1 hour.

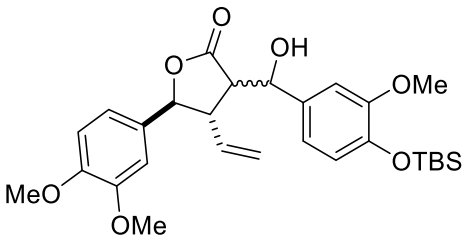
Reaction was monitored by TLC (Hex:AcOEt 6:4) and when it was completed it was quenched by addition of NH_4Cl saturated solution. The phases were separated and the aqueous one was extracted with DCM. The combined organic layers were washed with brine, dried on Na_2SO_4, filtered and finally concentrated at reduced pressure.

The crude material was purified by liquid chromatography on silica gel (Hex:AcOEt 9:1) to give 749 mg (2.81 mmol, FW=266.41, Y=86%) of pure compound n.

Spectroscopic data are in agreement with the literature[100].

[100] Castano, M.; Cardona, W.; Quinones, W.; Robledo, S.; Echeverri, F. *Molecules*, **2009**, *14*, 2491

Synthesis of 3-((4-((tert-butyldimethylsilyl)oxy)-3-methoxyphenyl)(hydroxy)methyl)-5-(3,4-dimethoxyphenyl)-4-vinyldihydrofuran-2(3H)-one (**263**)



Chemical Formula: $C_{28}H_{38}O_7Si$
Molecular Weight: 514.69

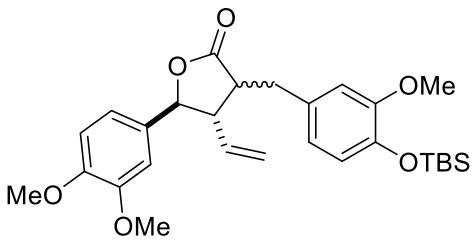
In a round bottom flask under Ar atmosphere, dry THF (1mL) was transferred and KHMDS (144 µL, solution 1M in THF, 0.144 mmol, 1.2 eqv) was added dropwise. The mixture was cooled to -78°C and a solution of compound **252** (30 mg, FW=248.24, 0.12 mmol, 1 eqv) in dry THF (500 µL) was cannulated. After 15 minutes of vigorous stirring, a solution of aldehyde n (50 mg, FW=266.41, 0.18 mmol, 1.5 eqv) in dry THF (250 µL) was cannulated and the mixture was stirred at the same temperature for 2 hours.

Reaction was monitored by TLC (Hex:AcOEt 7:3) and it was quenched by addition of NH_4Cl saturated solution (5 mL). The mixture was diluted with Et_2O (10 mL), the phases were separated and the organic one was dried on Na_2SO_4, filtered and solvent was removed at reduced pressure.

The crude was purified by flash chromatography on silica gel (Hex:AcOEt 7:3) to give 30 mg (0.058 mmol, FW=514.69, Y=48%) of pure product.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)= 6.87-6.76 (m, 6H), 5.47-5.32 (m, 2H), 4.95-4.93 (d, J = 8.8 Hz, 1H), 4.88-4.86 (d, J = 10.4 Hz, 1H), 4.70-4.66 (d, J = 17.2 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.80 (s, 3H), 3.09-3.0 (m, 2H), 1.69 (s, 1H), 1.05 (s, 9H), 0.15 (s, 6H).

Synthesis of 3-(4-((tert-butyldimethylsilyl)oxy)-3-methoxybenzyl)-5-(3,4-dimethoxyphenyl)-4-vinyldihydrofuran-2(3H)-one (**264**)



Chemical Formula: $C_{28}H_{38}O_6Si$
Molecular Weight: 498.69

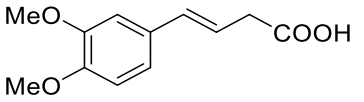
In a round bottom flask, under Ar atmosphere, compound **263** (27.4 mg, FW=514.69, 0.053 mmol, 1 eqv) was dissolved in dry DCM (2 mL) and temperature was lowered at 0°C. At this point, Et_3SiH (34 µL, FW=116.28, d = 0.728, 0.212 mmol, 4 eqv) was added dropwise followed by BF_3Et_2O (3.2 µL, FW=141.93, and reaction mixture was stirred at 0°C for 2 hours.

Reaction was monitored by TLC (Hex:AcOEt 7:3) and was quenched by adding $NaHCO_3$ saturated solution (10 mL). The layers were separated, then the organic one was washed with brine (10 mL), dried on Na_2SO_4, filtered and solvent was removed at reduced pressure.

The crude material was purified by flash chromatography on silica gel (Hex:AcOEt 8:2) to give 14.4 mg (0.029 mmol, FW=498.69, Y=54%) of pure compound n.

^1H NMR (400 MHz, $CDCl_3$): δ (ppm)= 6.79-6.56 (m, 6H), 5.71-5.62 (ddd, J = 16.4, 9.2, 7.2 Hz, 1H), 5.15-5.12 (d, J = 10Hz, 1H), 4.97-4.94 (d, J = 13.2, 1H), 4.94-4.92 (d, J = 9.6, 1H), 3.88 (s, 3H), 3.75 (s, 6H), 3.23-3.19 (m, 1H), 2.98-2.91 (m, 2H), 2.75-2.68 (m, 1H), 1.05 (s, 9H), 0.15 (s, 6H).

Synthesis of (*E*)-4-(3,4-dimethoxyphenyl)but-3-enoic acid (**241**)



Chemical Formula: $C_{12}H_{14}O_4$
Molecular Weight: 222.24

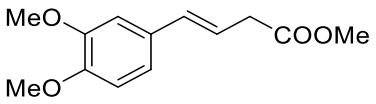
In a round bottom flask, under Ar atmosphere, (2-carboxyethyl)triphenylphosphonium chloride (742 mg, FW=370.81, 2 mmol, 2 eqv) was dissolved in a 1:1 mixture of THF and DMSO (2 mL + 2 mL), then, the solution was cooled at 0°C and NaH (154 mg, FW=24, 4.5 mmol, 4.5 eqv) was added in small portions. After 1 h of vigorous stirring, a solution of 3,4-dimethoxybenzaldehyde (167 mg, FW=166.17, 1 mmol, 1 eqv) in dry THF (2 mL) was cannulated and the mixture was stirred at room temperature for 12 hours.

Reaction was monitored by TLC (Hex:AcOEt 6:4) and when it was completed it was quenched by addition of HCl 1M (30 mL) solution till acid pH. The mixture was diluted with Et_2O (20 mL), then the layers were separated and the aqueous one was extracted with AcOEt (3 x 30 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried on Na_2SO_4 and concentrated at reduced pressure.

The crude material, was purified by liquid chromatography on silica gel (Hex:AcOEt 1:1 + 10% AcOH) to furnish 213 mg (0.96 mmol, FW=222.24, Y=96%) of pure compound.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)= 6.97-6.83 (m, 3H), 6.51-6.47 (d, J = 16, 1H), 6.22-6.14 (dt, J = 16.4, 6.4, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.33-3.31 (d, 7.2, 2H).

Synthesis of methyl (*E*)-4-(3,4-dimethoxyphenyl)but-3-enoate (**240**)



Chemical Formula: $C_{13}H_{16}O_4$
Molecular Weight: 236.27

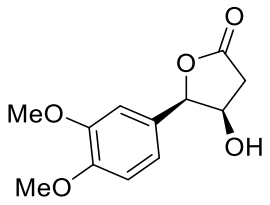
In a round bottom flask under Argon atmosphere, compound **241** (139.6 mg, FW=222.24, 0.63 mmol, 1 eqv) was dissolved in acetone (2 mL), then Cs_2CO_3 (103 mg, FW=325.82, 0.315 mmol, 0.5 eqv) was added followed by MeI (90 µL, FW=141.94, d=2.28, 1.38 mmol, 2.2 eqv).

The mixture was refluxed for 3 hours and was monitored by TLC (Hex:AcOEt 1:1). When it was completed, it was quenched by addition of DCM (5 mL) and brine (5 mL). The phases were separated, then the organic one was dried on Na_2SO_4 and solvent was removed under reduced pressure.

The crude product (124.6 mg, 0.53 mmol, Y=85%) was directly used for the following step.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)= 6.97-6.83 (m, 3H), 6.48-6.44 (d, J = 15.6, 1H), 6.23-6.15 (dt, J = 16, 6.8, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.58 (s, 3H), 3.28-3.26 (d, J = 7.2, 2H).

Synthesis of (4*R*,5*R*)-5-(3,4-dimethoxyphenyl)-4-hydroxydihydrofuran-2(3H)-one (**239**)



Chemical Formula: $C_{12}H_{14}O_5$
Molecular Weight: 238.24

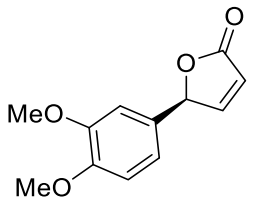
In a round bottom flask, K_2OsO_4 $2H_2O$ (2 mg, FW=368.45, 0.0053 mmol, 1 eqv), $K_3Fe(CN)_6$ (436 mg, FW=329.26, 1.325 mmol, 2.5 eqv), K_2CO_3 (220 mg, FW=138.21, 1.59 mmol, 3 eqv), $MeSO_2NH_2$ (50 mg, FW=95.12, 0.53 mmol, 1 eqv) and $(DHQD)_2PHAL$ (4 mg, FW=778.98, 0.0053 mmol. 0.01 eqv) were solubilized in tBuOH : H_2O 1:1 (5.4 mL) and the mixture was kept under vigorous stirring at 0°C.

At this point, a solution of compound **240** (124.6 mg, FW=236.27, 0.53 mmol, 1eqv) in tBuOH (2 mL) was added and reaction mixture was stirred at 0°C for 42 hours.

Reaction was monitored by TLC (Hex:AcOEt 3:7) and when it was completed, it was quenched by addition of a Na_2SO_3 (80 mg, FW= 126, 0.63 mmol, 1.2 eqv) solution in water (3 mL). The mixture was stirred for 2 hours at room temperature, then Et_2O (10 mL) was added, the phases were separated and the aqueous one was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried on Na_2SO_4, filtrated and concentrated at reduced pressure. The resulting solid, was solubilized in AcOEt (5 mL) and then filtrated on a silica pad by washing several times with AcOEt. The solvent was removed at reduced pressure and the crude material was purified by liquid chromatography on silica gel (Hex:AcOEt 3:7) to give pure product **239** (76 mg, FW=238.24, 0.318 mmol, Y=60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)= 6.97-6.83 (m, 3H), 5.52-5.51 (d, J = 3.6, 1H), 4.63-4.61 (m, 1H), 3.88 (s, 6H), 2.95-2.89 (dd, J = 17.2, 4.8, 1H), 2.83-2.79 (d, J = 17.2, 1H).

Synthesis of (*S*)-5-(3,4-dimethoxyphenyl)furan-2(5H)-one (**230**)



Chemical Formula: $C_{12}H_{12}O_4$
Molecular Weight: 220.22

In a round bottom flask, under Argon atmosphere, compound **239** (68 mg, FW=238.24, 0.28 mmol, 1 eqv) was dissolved in dry DCM (1 mL) and the solution was cooled at 0°C. At this point, Et_3N (110 µL, FW=101.19, d=0.726, 0.78 mmol, 2.8 eqv) and then MsCl (33 µL, FW=114.55, d=1.48, 0.42 mmol, 1.5 eqv) were added dropwise and the mixture was stirred at the same temperature for 30 minutes.

Reaction was monitored by TLC (Hex:AcOEt 3:7) and when it was completed it was quenched by addition of NH_4Cl saturated solution (5 mL). The aqueous layer was extracted with DCM (3 x 10 mL), then the combined organic phases were dried on Na_2SO_4, filtrated and the solvent was removed at reduced pressure.

The crude material was purified by liquid chromatography on silica gel (Hex:AcOEt 1:1) and 38.5 mg (0.17 mmol, FW= 220.22, Y=60%)of compound **230** were achieved.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)= 7.55-7.53 (dd, J = 5.6, 1.6, 1H), 6.91-6.85 (m, 3H), 6.74-6.73 (d, J = 2, 1H), 6.27-6.25 (dd, J = 5.6, 2, 1H), 3.88 (s, 3H), 3.84 (s, 3H).

Acknowledgements

Come to the end of the thesis, I would like to express my deepest thanks to all the people that supported me during the last three years and that allowed me to do all the work that has been achieved.
In particular, I really want to thank all the stuff of B2 laboratory of the University of Pavia. My tutor Prof Alessio Porta, Prof. Giuseppe Zanoni, Prof. Giovanni Vidari and Prof. Paola Vita Finzi. All my colleagues: Serena Bugoni, Andrea Gandini, Francesco Chiesa, Corrado Nicolini, Matteo Virelli and Davide Corriero and all the students.

I want to thank Prof. Stephen Hanessian and all his laboratory members of the University of Montreal for having me from January to July 2016 and finally all my family and my friends.