UNIVERSITÀ DEGLI STUDI DI PAVIA

DOTTORATO IN SCIENZE CHIMICHE E FARMACEUTICHE

XXXI CICLO

Coordinatore: Chiar.mo Prof. Mauro Freccero

Synthesis of 5-membered heterocycles as natural product scaffolds and useful tools for PET probe

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SUMMARY

1. INTRODUCTION TO THE PhD THESIS

Heterocycles are ubiquitous molecular scaffolds in biologically-active natural products, including polyketides, alkaloids, steroids, and terpenes.[1] Due to their occurrence in many biologically active compounds such as the acetogenins,[2] lignans,[3] macrodiolides[4] and polyether ionophores[5], oxygen-containing heterocycles (e.g.,tetrahydrofurans) represent important synthetic targets. Several examples of natural products containing tetrahydrofuran cores are depicted in Figure 1.1.[6] Haterumalide NA **1** was isolated from the Okinawan sponge Ircinia sp. in 1999, and displays cytotoxicity against numerous cancer cell lines.[7] This molecule consists of a 2,5-disubsituted-3-hydroxytetrahydrofuran, a Z-chloroolefin, a trans-bridged 14-membered lactone, and contains five stereogenic centres, which make this compound particularly challenging as a target for total synthesis. Kumausallene **2** is a member of a class of halogenated nonisoprenoid sesquiterepenes that contains a cis-fused tetrahydrofuran unit halogenated at the C3 position and a bromoallene moiety.[8] Another example of a tetrahydrofuran-containing natural product is elatenyne **3**, which was isolated in 1983 from Laurencia elata and possesses a 2,2 -bifuranyl core and six stereocenters.[9] Jaspine B **4** and (+)-goniothalesdiol **5** are additional examples of tetrahydrofuran containing natural products.

In addition to oxygen-containing saturated heterocycles, heterocycles containing nitrogen atoms are also found in a variety of biologically relevant compounds. Among them, 5-membered ring heterocycles, such as pyrrolidines, are widely prevalent and compounds that incorporate this moiety have demonstrated a range of applications, including use as organocatalysts,[10] chiral ligands[11] or in pharmaceutical agents.[12,13] Pyrrolidines are also found in nature as components of pyrrolizidine and indolizidine alkaloids.[14] Some examples of natural products containing the pyrrolidine moiety include

[1] K.C. Majumdar, S.K. Chattopadhyay; Heterocycles in Natural Product Synthesis, 2011, 3-7
[2] A. Bermejo, B. Figadere, M.C. Zafra-Polo, I. Barrachina, E. Estornell, D. Cortes; Nat. Prod. Rep., 2005, 696, 269-272
[3] M. Saleem, H.J. Kim, M.S. Ali, Y.S. Lee; Nat. Prod. Rep., 2005, 696, 17-20
[4] E.J. Kang, E. Lee; Chem. Rev., 2005, 105, 4348-4352
[5] M.M. Faul, B.E. Huff; Chem. Rev., 2000, 100, 2407-2418
[6] G. Strobel, J.Y. Li, F. Sugawara, H. Koshino, J. Harper, W.M. Hess; Microbiology, 1999, 145, 3557-3561
[7] N. Takada, H. Sato, K. Suenaga, H. Arimoto, K. Yamada, K. Ueda, D. Uemura; Tetrahedron Lett., 1999, 40, 6309-6312
[8] T. Suzuki, K. Koizumi, M. Suzuki, E. Kurosawa; Chem. Lett., 1983, 12, 1639-1644
[9] J.G. Hall, J.A. Reiss; Aust. J. Chem., 1986, 39, 1401-1409
[10] A.J.B. Watson, D.W.C. MacMillan; Catalysis Asymmetric Synthesis, 2010, 39-57
[11] C.A. Caputo, N.D. Jones; Dalton Trans., 2007, 0, 4627-4640
[12] (a) C.V. Galliford, K.A. Scheidt; Angew. Chem. Int. Ed., 2007, 46, 8748-8758; (b) M.E. Hensler, G. Bernstein, V. Nizet, A. Nefzi; Biorg. Med. Chem. Lett., 2006, 16, 5073-5079; (c) L.R. Whitby, Y. Ando, V. Setola, P.K. Vogt, B.L. Roth; J. Am. Chem. Soc. 2011, 133, 10184-10194; (d) A. Raghuraman, E. Ko, L.M. Perez, T.R. Ioerger, K.J. Burgess; J. Am. Chem. Soc., 2011, 133, 12350-12353
[13] K. Tamazawa, H. Arima, T. Kojima, Y. Isomura, M. Okada, S. Fujita, T. Furuya, T. Takenaka, O. Inagaki, M. Terai; J. Med. Chem., 1986, 29, 2504-2511
[14] (a) J.R. Liddell; Nat. Prod. Rep., 2002, 19, 773-781; (b) P.J. Michael; Nat. Prod. Rep., 1999, 16, 675-696

hyacinthacine A4 **6**, an inhibitor of various carbohydrate processing enzymes,[15] (-)-kianic acid **7** disease and epilepsy,[16,17] (+)-preussin **8**, an antifungal agent isolated from a liquid fermentation broth of Aspergillus ochraceus,[18,19] and (-)-swainsonine **9**, a potent-mannosidase inhibitor.[20]

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

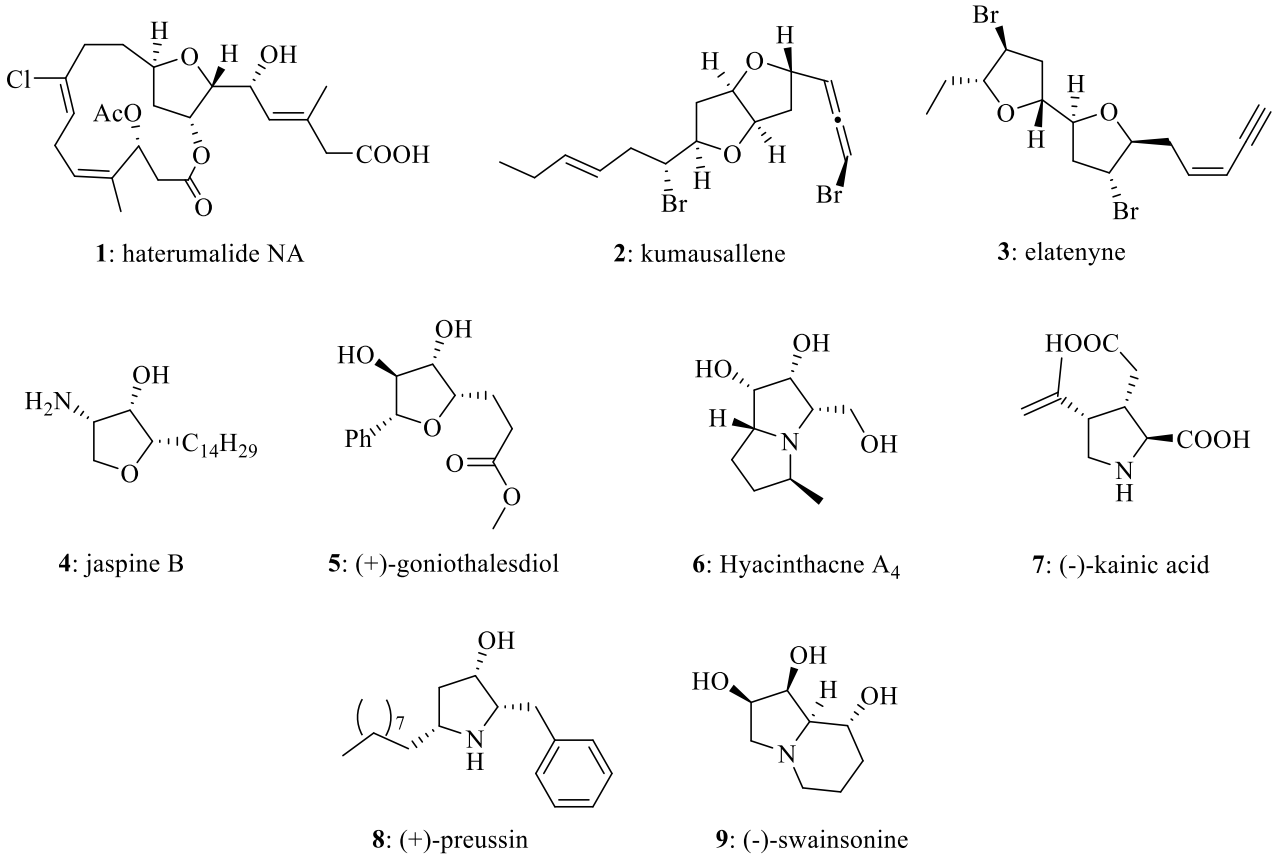


Figure 1.1. Representative Natural Products Containing a Tetrahydrofuran and a Pyrrolidine Core.

Starting from this background, the aim of the first part of the PhD Thesis deals with the implementation of the methodology previously developed to new tetrahydrofuran systems and subsequent application of the best outcome to the total synthesis of a bioactive THF-containing

[15] T. Yamashita, K. Yasuda, H. Kizu, Y. Kameda, A.A. Watson, R.J. Nash, G.W.J. Fleet, N.J. Asano; Nat. Prod. 2002, 65, 1875-1881

[16] S. Murakami, T. Takemoto, Z. Shimizu; J. Pharm. Soc. Jpn; 1953, 73, 1026-1028

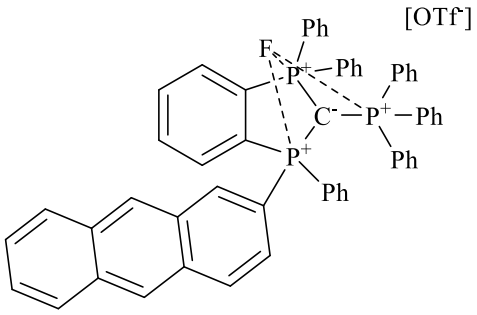
[17] (a) D.R. Hampson, J.L. Manalo; Nat. Toxins, 1998, 6, 153-158; (b) M.R. Gluck, E. Jayatilleke, S. Shaw, A.J. Rowan, V. Haroutunian; Epilepsy Res., 2000, 39, 63-71

[18] R.E. Schwartz, J. Liesch, O. Hensens, L. Zitano, S. Honeycutt, G. Garrity, R.A. Fromtling, J. Onishi, R.J. Monaghan; Antibiot., 1988, 41, 1774-1779

[19] J.H. Johnson, D.W. Phillipson, A.D. Kahle; J. Antibiot., 1989, 42, 1184-1185

[20] (a) P.R. Dorling, C.R. Huxtable, S.M. Colegate; Biochem. J., 1980, 191, 649-651; (b) A.D. Elbein, R. Solf, P. Dorling, K. Vosbeck; Proc. Natl. Acad. Sci., 1981, 78, 7393-7397

molecule (Part 1). Then, the thesis moves on the extension of the methodology to the synthesis of the pirrolidine via dehydrative amination of allylic alcohol mediated by a Gold(I) catalyst (Part 2). Finally, the last part of this work (Part 3), that was performed in the group led by Professor Jan J. Weigand (Dresden, Germany), is focused on the development of a new synthetic strategy toward a 5-membered heterocycle containing a triphonium dication for capturing F^- (figure 1.2).



10[OTf][F]

Figure 1.2 triphonium dication for capturing F^-

Part 1. SYNTHETIC STUDIES TOWARD ORTHODIFFENES

2. Introduction

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

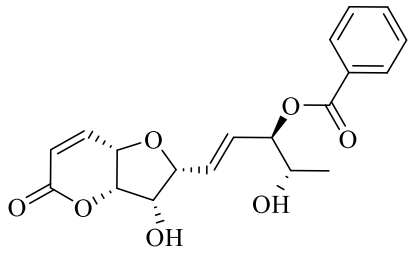
These substances possess a wide range of biological activities including: anti-microbial, anti-tumor, anthelmintic, anti-malarial and anti-protozoal.

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

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[21].

The 3,4-dihydroxy-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 Orthodiffene A (figure 2.1) due to its pharmacological interest.[22]



11
Orthodiffene A

Figure 2.1 Orthodiffene A **11**

The synthesis was developed keeping in mind the necessity of a cheap and easy-to-get starting material.

The purpose was also to limit the use of protective groups and rather exploit the reactivity of the already present functions.

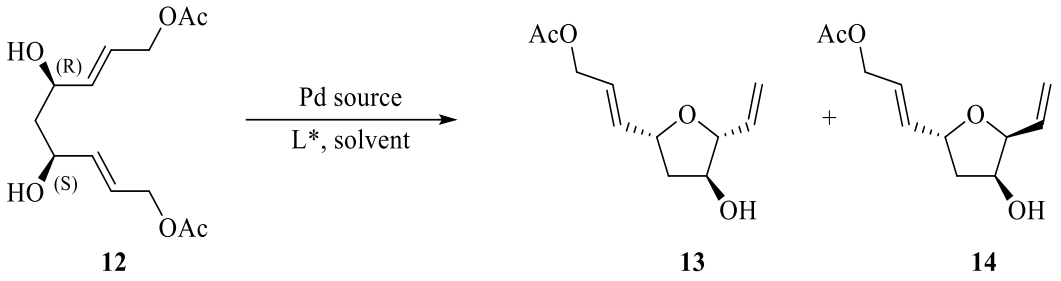
[21] P. Wolfe, M.B. Hay; Tetrahedron, 2007, 63, 261-265

[22] H. Holla, Y. Srinivas, A. Majhi, G. Srinivasulu, B. Sridhar, A. S. Krishna, J. V. Rao, B. Das; Tetr. Lett., 2011, 52, 49-52

To this general scope, the attention was primarily focused on the building of the tetrahydrofuran ring which contains four adjacent stereogenic centres. Among all the various possible strategies reported in literature, the organo-palladium Tsuji-Trost Asymmetric Allylic Etherification has been chosen.[23] This reaction has been widely studied by the research group in which this work has been carried out and presents a versatile way of constructing functionalized THF cores. Optimizing reaction conditions, outstanding levels of enantio- and diastereo- selectivity can be reached.[23,24,25,26]

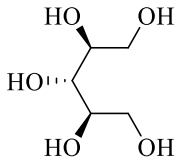
For these reasons, the Tsuji-Trost reaction can be considered the key step reaction of this Orthodiffene A synthesis.

We therefore based our retrosynthetic analysis on the previous outcomes of the meso diol **12** (Scheme 2.1). Diastereoisomers **13** or **14** can be obtained preferentially using different ligands and reaction conditions).[25]



Scheme 2.1 Stereochemical outcome of Tsuji-Trost reaction on meso diol **12**

Initially, the sugar alcohol Xylitol **15** (Figure 2.2) was identified as starting material because its sterochemical configuration is allegedly required by the key reaction, as well as of its readily availability and low cost.



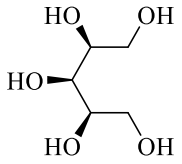
15
Xylitol

Figure 2.2 Xylitol **15**

[23] UNIVERSITÀ DEGLI STUDI DI PAVIA, DOTTORATO IN SCIENZE CHIMICHE E FARMACEUTICHE; A.A.2015/2016; Tutor Prof. Alessio Porta, thesis of Mattia Fredditori
[24] B. M. Trost, F. D. Toste; J. Am. Chem. Soc., 1999, 121, 4545-4554
[25] L. Jiang, S. D. Burke; Org. Lett., 2002, 4, 3411-3414
[26] M. Valli, P. Bruno, D. Sbarbada, A. Porta, G. Vidari, G. Zanoni; J. Org. Chem., 2013, 78, 5556-5567

However, subsequent studies[27] carried out in the laboratory had shown that the use of Xylitol as starting material doesn't afford the desired THF in high diastereomeric ratio and enantiomeric excess as required by the total synthesis (further details are present in the paragraph 7.5). Despite this warning, we decided to tackle the total synthesis starting from racemic THF.
Indeed, addition of a chiral-pool-derived building block to the racemic THF core allowed us to achieve the total synthesis of two enantiopure diasteromers of Orthodiffene A.
Subsequently, we passed to consider an alternative, possibly more selective synthetic pathway to Orthodiffene A via modification of the precursor of the Tsuji-Trost reaction.

Indeed, we found that adonitol **16** (Figure 2.3) is a relatively cheap starting material suitable for the scope.



16
Adonitol

Figure 2.3 Adonitol **16**

The similarity of the starting material **15** and **16** for the synthesis of Orthodiffene A readily implies two analogous synthetic strategies starting from either sugar alcohol. This first part of the manuscript is dedicated to the development of the total synthesis of Orthodiffene A using either Xylitol **15** and Adonitol **16**.

[27]Studi sintetici sull'Orthodiffene A, UNIVERSITÀ DEGLISTUDI DI PAVIA; undergraduate thesis. A.A. 2012/2013; Tutor Prof. G. Zanoni, Thesis of Martina Paro

Orthodiffenes were isolated and characterized from the extracts of the aromatic plant *Orthosiphon diffusus*, from which it owes its name.[22]

Orthosiphon diffusus, of family Lamiaceae, is a small, perennial, aromatic herb.[28] The genus *Orthosiphon*(Benth), in tribe Ocimeae, comprises 40 species of annual or perennial herbs, under shrubs or shrubs generally 30-120 cm in height and normally are erect herbs. They were recorded from the Old World: in tropical and Southern Africa, Madagascar and tropical or subtropical Asia. The species usually occurs in grassland, woodland, or forest margins. Essential oil from members of Lamiaceae has been used for medicinal values[28] as well as for their aromatic properties as spices and perfumes.

Species belonging to the Lamiaceae family produce a great variety of secondary metabolites, but are especially renowned for their essential oils, which are produced in glandular hairs on the surfaces of leaves and inflorescences.

The volatile oils in this family mainly consist of monoterpenoids, e.g. menthone in *Mentha* and thymol in *Thymus*, sesquiterpenoids such as caryophyllene, and sometimes volatile phenylpropanoidssuchas eugenol and methyl chavicol.

Important to notice that there is often a considerable infraspecific variation in essential oils.[28]

Figure 3.1 Inflorescences of different *Orthosiphon* species, from left to right: *O. Diffusus*, O. Thymifloreus,*O. Aristatus*

Various species of the genus *Orthosiphon* are known for their medicinal properties (figure 3.1).[29] For example, decoction of *Orthosiphon glabratus* is is used to cure diarrhea and piles, while leaves are applied to cuts and wounds. *Orthosiphon aristatus* is one of the popular traditional folk medicines used extensively in Southeast Asia for the treatment of a wide range of diseases. It possesses diuretic properties and is used in treating urinary lithiasis, oedema, eruptive fever, influenza, rheumatism, hepatitis and jaundice. In Japan, it is consumed as a healthy Java Tea to facilitate body detoxification.

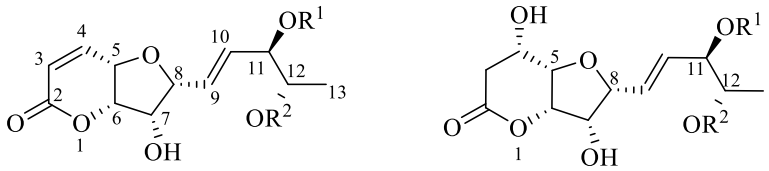
[28] R.M. Harley, S. Atkins, A. Budantsev, P.D. Cantino, B. Conn, R.J. Grayer, M.M. Harley, R. De Kok, T. Krestovskaja, A. Morales, A.J. Paton, O. Ryding, T. Upson; The Familie and Genera of Vascular Plants, Springer, 2004, VII, 167-275

[29] U. Singh, A.M. Wadhwani, B.M. Johri; Dictionary of economic plants in India., 1983, 159-169

In India a decoction of the plant *Orthosiphon thymiflorus* (Roth), *Orthosiphon glabratus*(Benth), *Orthosiphon tomentosus* or *Orthosiphon diffusus* is given to cure diarrhea and piles. A decoction of leaves cures fever.[30,31,32]

If the medical properties of the genus Orthosiphon are traditionally known, chemical studies on these species remain limited.

The phytochemical analysis of essential oil of *O. aristatus* reveals that sesquiterpenes are the main components, including β- elemene, β–caryophyllene and its oxide, β-selenene, cadinene, humulene, and α-guayene.[33,34] It has been demonstrated that the inflorescence of *O. aristatus* contains a benzopirane derivative, the metalripariocromeno[35] while studies on the essential oil of *O. diffuses* show the presence of t-caryophyllene, octocosane and limonene, but most important for their biological activity four very characteristic molecules were isolated from its extracts, they all show a furo-piranic core and have been called Orthodiffene A, B, C and D (respectively **11**, **17**, **18**, **19**).[35] More recent studies extend the Orthodiffene family shwing the existence of other two compounds analogues to Orthodiffene D **19**, called Orthodiffene AM-1 and AM-2 **(**respectively **20**, **21**)[36].



11 R^1=OBz; R^2=H
17 R^1=OBz; R^2=Ac
18 R^1=H; R^2=OBz

19 R^1=OBz; R^2=OAc
20 R^1=H; R^2=OBz
21 R^1=OBz; R^2=H

Figure 3.2 Atom numbering was assigned by Holla et al.[22] Subsequent derivates maintain those notations

The whole family presents the same carbon backbone and stereochemistry. Moreover, all these six molecules feature a tetra-substituted THF core with all the substituents facing the same side in an all-syn configuration: a rarity in Nature and a challenge for the synthetic chemist.

Orthodiffene A **11** and C **18** are very similar and differentiated just by the position of the benzoyl ester at C-11 and C-12, respectively. The presence of these two isomers suggests the involvement of

[30] S.P. Ambasta; The useful Plants of India, CSIR, 1986, 505
[31] P.T. Eisai; Medicinal Herb Index in Indonesia, Indonesia ed, 1995, 203
[32] N.D. Prajapati, S.S. Purohit, A.K. Sharma, T. Kumar; Agrobios, 2003, 373-374
[33] G.A. Schut, J.H. Zwaving; Planta Med., 1986, 52, 240-241
[34] E.S. Fernandes, G.F. Passos, R. Medeiros, F.M. da Cunha, J. Ferreira, M.M. Campos, L.F. Pianowski, J.B. Calixto; Eur. J. Pharmacol., 2007, 569, 228-236
[35] H.P. Guerin, P. Reveillere, L. Ducrey, A. Toupet; J. Nat. Prod., 1989, 52, 171-173
[36] A. Majhi, H. Holla, S. Shinde, G. Srinivasulu, A.S. Krishna, J.V. Rao, B. Das; Indian J. Of Chemistry, 2017, 56, 855-861

esterases in the course of the biosynthesis that can operate an interconversion in the natural biosynthetic process so that one could be converted into the other right at the end of its synthesis.[37,38]

Orthodiffene B **17** has both hydroxyl moieties on the olefinic side chain esterified: C-11 as a benzoyl ester, C-12 as an acetyl ester.

Orthodiffenes D **19**, AM-1 **20**, AM-2 **21** have the double bond of the α,β-unsaturated δ-lactonic system of Orthodiffenes A-C hydrated with the Hydroxyl function falling on C-4.

Orthodiffene D **19** presents both the Hydroxyl function on the olefinic side chain Esterified the same way they are in Orthodiffene B. Orthodiffene AM-1 **20** and AM-2 **21** are benzoylated respectively on C-12 and C-11 while the adjacent hydroxyl function is free, closely related to Orthodiffenes A and C.

[37] J. Liu, Y. Liu, X. Zhang, C. Zhang, Y. Gao, L.L. Wang, Y. Du; J. Org. Chem., 2012, 77, 9718-9723

[38] For examples of the transformation of natural products based on the intramolecular transesterification reaction, see: (a) Thuggacins A−C: H. Steinmetz, H. Irschik, B. Kunze, H. Reichenbach, G. Hofle, R. Jansen; Chem.Eur. J., 2007, 13, 5822-5832; (b) Chondropsins A and D: M.A. Rashid, C.L. Cantrell, K.R. Gustafson, M.R. Boyd; J. Nat. Prod., 2001, 64, 1341-1344; (c) Salvinorins D and E: L.M. Kutrzeba, X.C. Li, Y. Ding, D. Ferreira, J.K. Zjawiony; J. Nat. Prod., 2010, 73, 707-708

3. Biological activity

Two different studies have investigated the antitumor activity of the Orthodiffenes by studying their cytototoxicity.[36] While the later discovered Orthodiffenes AM-1 and AM-2 as well as Orthodiffene D don't shown any relevant activity, Orthodiffenes A-C are more promising.

Holla et al.[36] performed a cytotoxic assay of the compounds **11**, **17**, **18**. The cytotoxicity of these compounds was determined on Jurkat and HL-60 cells using modified MTT assay3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide).[39]

Jurkat cells are a human immortalized T lymphocyte cell line established in the late 1970s from the peripheral blood of a 14 year old boy with T cell leukemia.[40] They have been used to study T-cell leukemia, T-cell signaling, and cancer cell sensitivity to drug treatments.[41] These small, round cells grow readily in suspension and have also been used as a model system for various cell viability and apoptosis assays as in this case.

HL-60 is a promyelocytic cell line derived by Collins et al. in 1977.[40] Peripheral blood leukocytes were obtained by leukopheresis from a 36-year-old Caucasian female with acute promyelocytic leukemia. The HL-60 cultured cell line provides a continuous source of human cells for studying the molecular events of myeloid differentiation and the effects of physiologic, pharmacologic, and virologic elements on this process.[42,43]

All these compounds show significant cytotoxic activities against these two cell lines using camptothecin, a known antitumoral molecule, as a positive control.[44]

Noteworthy, Orthodiffene A and Orthodiffene B show comparable activity to camptothecin against HL-60 and Jurkat cells, respectively (Table 4.1).

Compound	Jurkat	HL-60
Camptothecin[b]	1.30	3.65
11	10.94	3.66
17	1.76	4.59

[39] J.A. Plumb, R. Milroy, S.B. Kaye; Cancer Res., 1989, 49, 4435-4440
[40] U. Schneider, H.U. Schwenk, G. Bornkamm; Int. J. Cancer, 1977, 19, 621-626
[41] R.T. Abraham, A. Weiss; Nat. Rev. Imm, 2004, 4, 301-308
[42] R. Gallagher, S. Collins, J. Trujillo, K. McCreie, M. Ahearn, S. Tsai, R. Metzgar, G. Aulakh, R. Tinh, F. Ruscetti, R. Gallo; Blood, 1979, 54, 713-735
[43] S.J. Collins, F.W. Ruscetti, C. Gallo; Proc. Nati. Acad. Sci., Medical Sciences, 1978, 75, 2458-2462
[44] M.E. Wall, C.E. Wani, C. Cook, K.H. Palmer, A.T. McPhail, G.A. Sim; J. Am. Chem. Soc., 1966, 88, 3888-3890.

18	13.40	19.75

[a]Control experiments were performed with carrier solvents alone
[b]Positive control.

Table 4.1 In vitro cytotoxic activity of Orthodiffenes A–C (**11**, **17**, **18**) (IC_{50}-µg/mL)[a]

4. Previous synthesis of the target

A synthesis of the enantiomers of the natural occurring Orthodiffenes A and C is already known in letterature.[37]

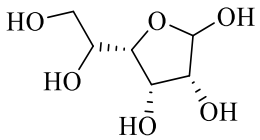
Liu et al[37] synthesized these molecules from the same precursor and transformed one to each other under a controlled benzoyl migration reaction.

Stereochemistry of the target derives from that of the starting L-Mannofuranoside **24'** (Figure 5.1), since it already incorporates the all-syn configuration of three of the four stereogenic centers on the THF core. Due to the prohibitive cost of L-mannose and the unknown absolute configurations of Orthodiffenes, they were interested in synthesizing either the natural (**11 - 18**) or unnatural enantiomers (**11′ - 18′**) for structural determination and further biological studies. Being D-mannose a readily available natural carbohydrate much cheaper than its enantiomeric counterpart, these authors decided to use it as the starting material.

At the end of the synthesis the optical measurement they assigned to their synthesized compounds was opposite in sign with respect to that obtained with the same measurement performed on the natural molecules, this way the absolute configuration of Orthodiffenes A and C was disclosed.

The absolute configuration of Orthodiffenes A and C is then illustrated in molecules **11** and **18**.

The synthesis here illustrated can in principle be carried out in the same way starting from the enantiomer L-(-)-Mannose but with the limitation of using a very expensive starting material, for instance 1 g of L-(-)-Mannose ≥99% to date is sold by Sigma-Aldrich® at 326,5 €[45]**.** Therefore, this strategy does not represent a practical way for the synthesis on gram scale.

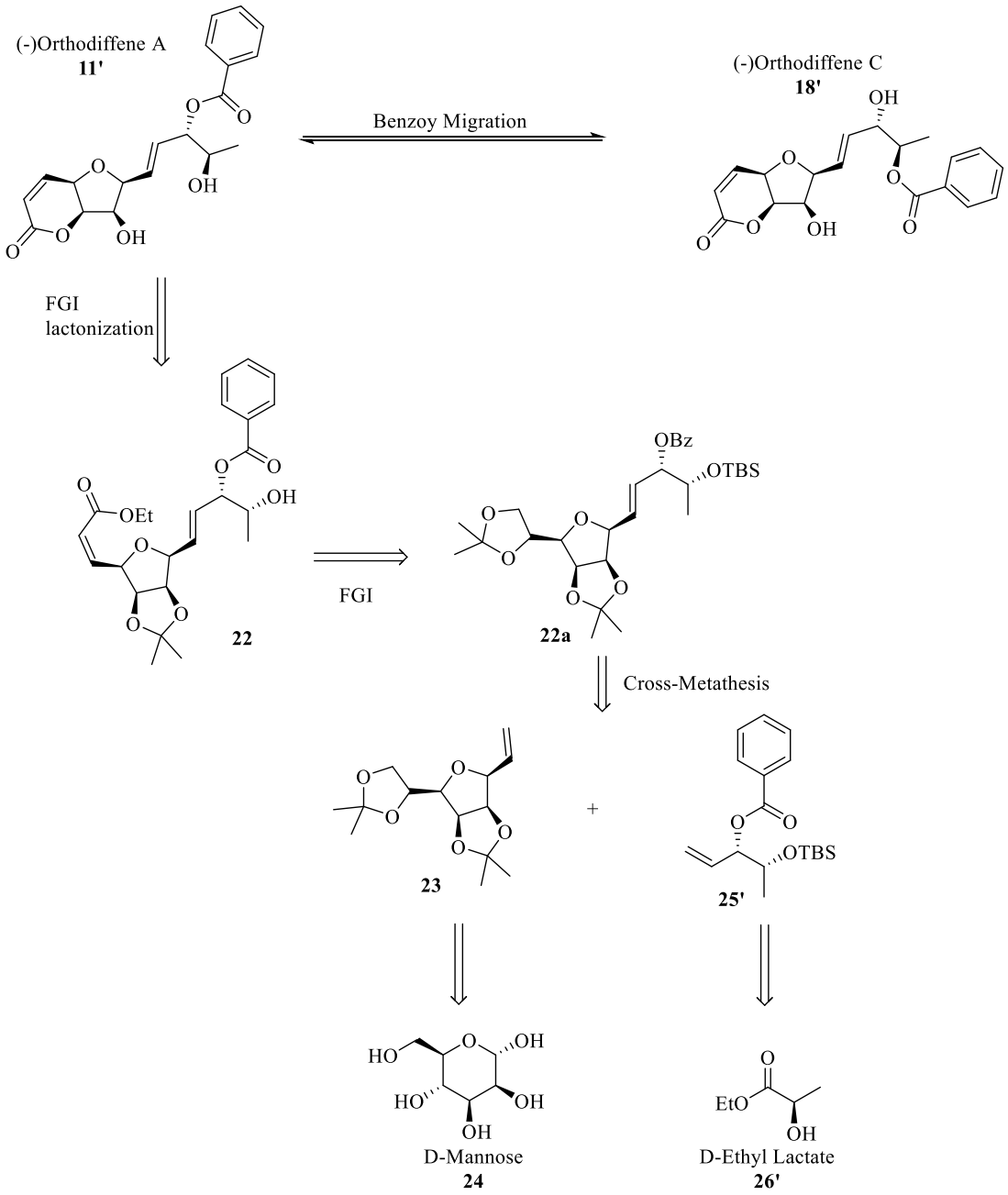


24'

Figure 5.1 L-Mannofuranoside from L-Mannose

The retrosynthetic analysis is herein reported in Scheme 5.1:

[45] www.sigmaaldrich.com



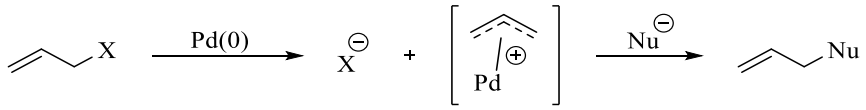
Scheme 5.1 Retrosynthetic analysis for the synthesis of (-)Orthodiffenes A and C starting from D-Mannose and D-Ethyl Lactate

The target molecule was easily reconducted to D-Mannose **24 and** D-Ethyl lactate **26'** through two key disconnections.

The former corresponding to a lactonization reaction of compound **22** to give (-)-Orthodiffene A **11'** the latter being an alkene cross-metathesis of compounds **23** and **25'** to give molecule to be lactonized **22**.

5. Novel synthetic approach to Orthodiffenes: retrosynthetical analysis

Considering the tetrahydrofuran core of our target molecule and the great effort carried out by our team during the last few years[26] to exploit the asymmetric allylic Trost etherification capitalizing on this useful strategy to plan this new synthesis seamed to us the most natural choise.
The Tsuji-Trost reaction in its most general form consists in the allylation of a nucleophile (originally carbon based) by means of an allylic system under Pd(0) catalysis (scheme 6.1).

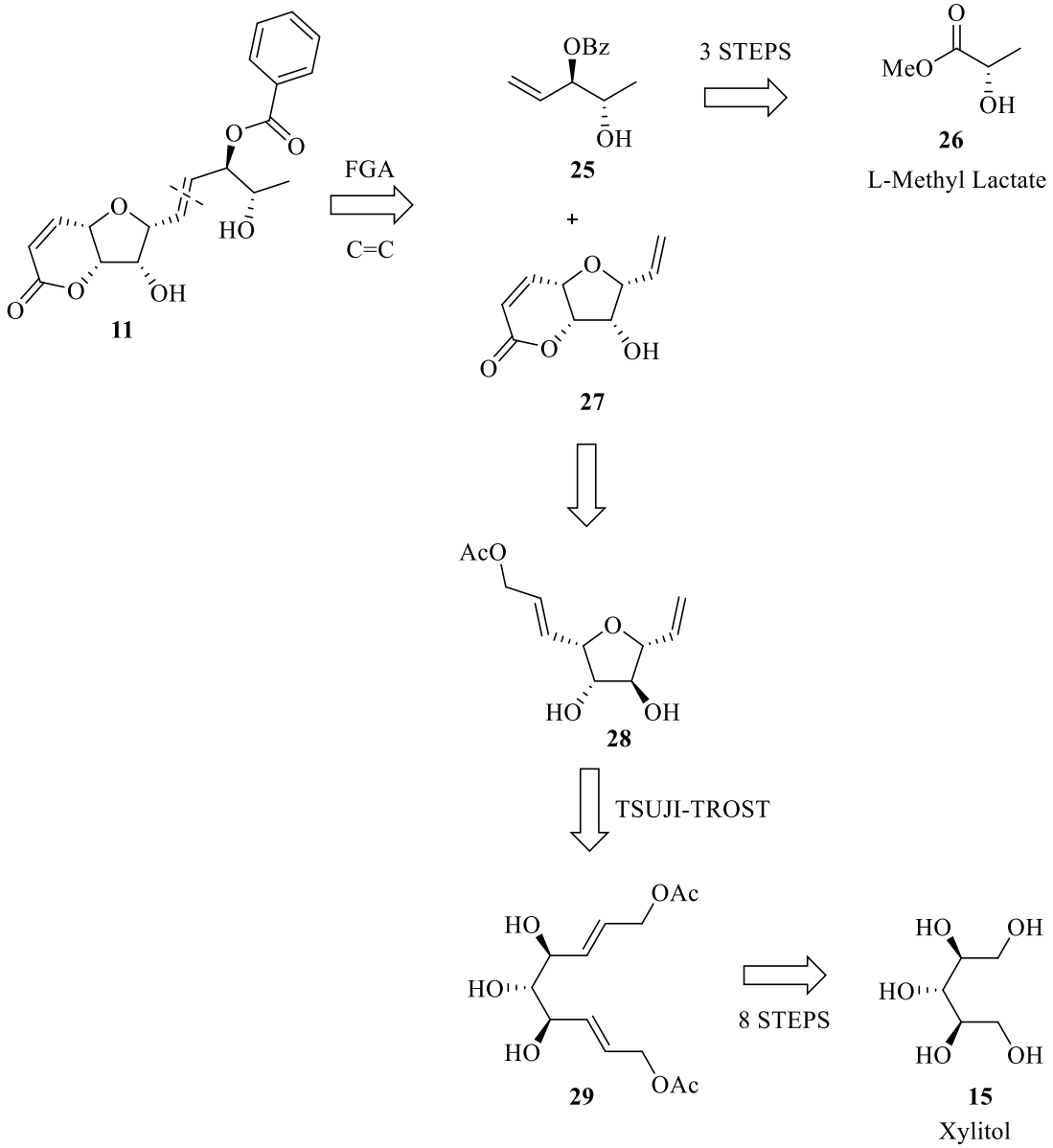


Scheme 6.1 Reaction scheme of a general Pd-catalyzed Tsuji-Trost reaction

The interest in applying this reaction for the building of polysubstituted THF cores is due to the diastero and enantioselective control achievable, and thus the possibility of efficiently synthesize numerous families of natural molecules that possess this heterocyclic motif, which include the Orthodiffenes class.

6.1 Identification of the intermediates: first approach

The initial retrosynthetic approach to orthodiffenes was devised is outlined in scheme 6.1.1.



Scheme 6.1.1 Retrosynthetic analysis for the synthesis of Orthodiffene A starting from Xylitol **15** with the Tsuji-Trost reaction as key step

With the proviso of the introduction of a suitable protective group for the hydroxyl function of the lateral chain of Orthodiffene A C=C disconnection though cross-metathesis allows to identify the intermediates **27** and **25**.[37]

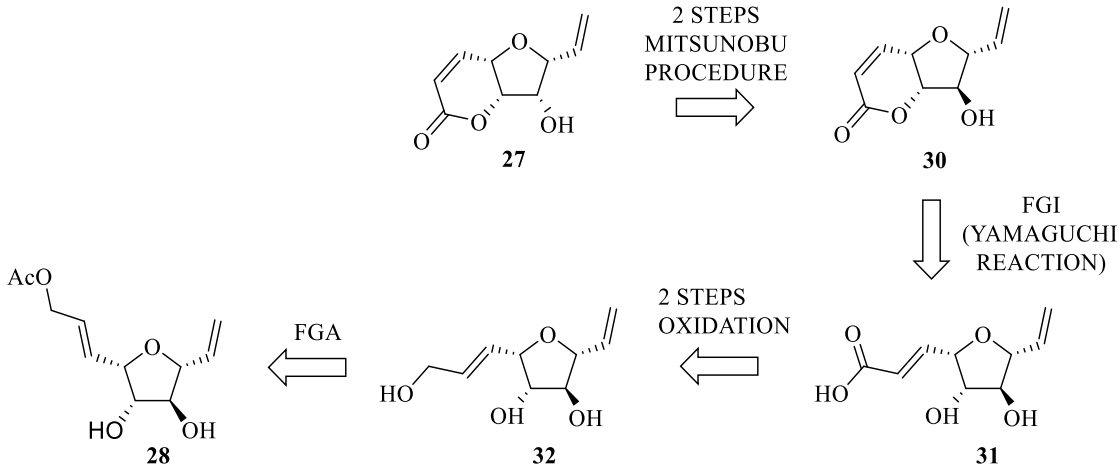
25 can in turn be reconducted to natural L-Lactate via an already known three-step synthesis.

Compound **27** can be reconducted, with some basic manipulation of the THF core, to unsaturated diol **28**, which is a plausible product of an asymmetric Tsuji-Trost allylic etherification of triol **29**.[23]

Finally, **29** can be synthesized *via* standard olefination procedures from the readily available sugar alcohol Xylitol **15**.[46]

This approach requires the inversion of the stereochemistry of the free hydroxyl function at C-7 on the THF core **28** derived from the cyclization reaction. The undesired outcome of the Tsuji-Trost asymmetric etherification is because the TS for the formation of the all-syn configuration is much higher than the one leading to compound **28**, as demonstrated via computational methods on the closely related meso diol **12** (see paragraph 7.1.1).[23]

Considering more in detail the conversion of compound **28** into **27**, the retrosynthetic analysis is reported in Scheme 6.1.2.



Scheme 6.1.2. Retrosynthetic analysis to relate molecule **27** to **28**

The inversion of the hydroxyl function of molecule **27** can be achieved with a Mitsunobu procedure applied right after the formation of the fused bicyclic core, hence passing from **30** to **27** in a two-step procedure. A very similar reaction reported for a structurally related substrate supports this plan.[47] Compound **30** is reconducted to compound **31** through a Yamaguchi lactonization reaction with concomitant E/Z double bond isomerization.[48] The isomerization should be possible due to the presence of pyridine which adds in a Michael fashion on the conjugate double bond allowing it to rotate, and once the double bond is isomerized, the lactonization reaction in the presence of the Yamaguchi Reagent (2,4,6-trichlorobenzoyl chloride) can take place.

[46] K. Toshima, K. Ohta, K. Yanagawa, T. Kano, M. Nakata, M. Kinoshita, S. Matsumura**;** J. Am. Chem. Soc., 1995, 117, 10825-10831

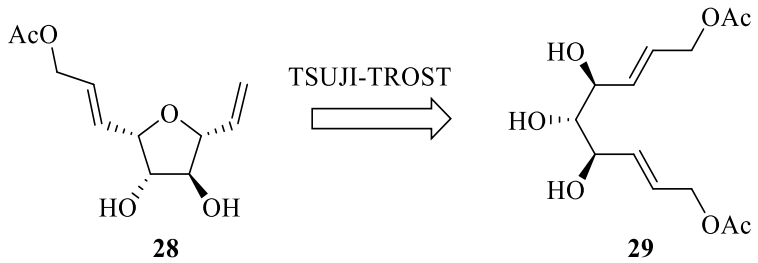
[47] J. G. Gillhouley, T. K. M. Shing; Chem. Commun., 1988, 0, 976-978

[48] R. Sunagawa, H. Yamada, M. Naito, E. Yasui, M. Mizukami, M. Miyashita, S. Nagumo; Tetr. Lett., 2015, 56, 6693-6695

The acidic moiety of compound **31** could be introduced with a two-step oxidation of compound **32**: forming the α,β-unsaturated aldehyde by treatment of the allylic alcohol with MnO_2[49], then oxidizing the thus formed aldehyde with a Pinnick reaction.[50]

This two-step approach has been envisaged because we needed a milder condition than the, usually harsh, conditions needed for the direct oxidation of alcohols to acids. Indeed, the Pinnick reaction has been frequently used in various total synthesis featuring sensitive functional groups.[51]

Compound **32** can be obtained by deacetylation of **28**, in turn deriving from the key Tsuji-Trost reaction (scheme 6.1.3).



28 **29**

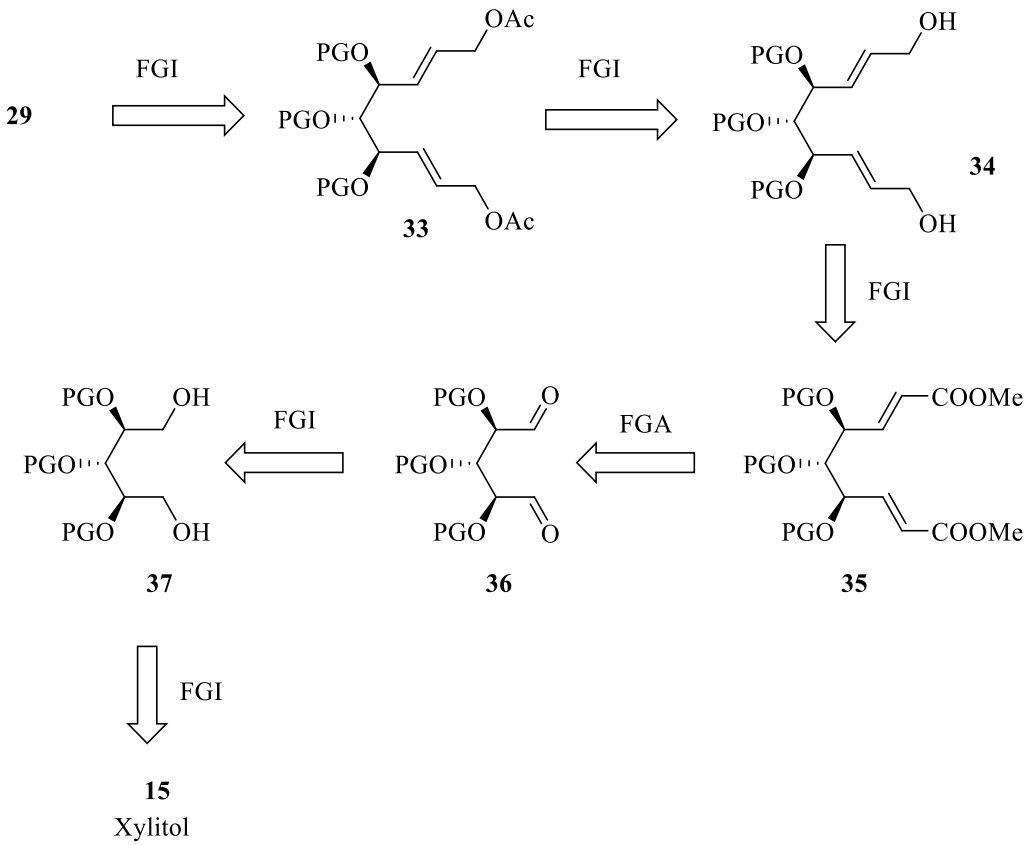
Scheme 6.1.3 Tsuji-Trost retrosynthetic hypothesis reaching compound **29** from **28**

Previous studies had shown that the cyclization performed on the meso diol **12** lead to a stereo defined THF core with optimal e.e. and d.r (d.r ST:AC = 80:20, e.e ST = 96 %).[23]

We surmised that the presence of the additional central OH in **29** was not expected to negalively affect the reactivity as well as the selectivity.[26]

Synthesis of compound **29** is reported in Scheme 6.1.4.

[49] J. A. Marshall, M. P. Bourbeau; J. Org. Chem., 2002, 67, 2751-2754
[50] B.S. Bal, W.E. Childers, W. Pinnick; Tetrahedron, 1981, 37, 2091-2096
[51] G. Tojo, M. Fernandez; Oxidation of Primary Alcohols to Carboxylic Acids: A Guide to Current Common Practice, Springer, 2007.



Scheme 6.1.4 Retrosynthetic analysis for the construction of triol **29** from available Xylitol **15**

Key disconnection is the cleavage of the C=C double bonds of the allylic alcohols moieties. This can be achieved by a retro Wittig transform[52].

Following the retrosynthetic scheme 6.1.4:

Deacetylation of **33** revealed the primary alcohol function, successive FGI of these hydroxyls into ester moieties lead to compound **35**.

C=C cleavage of compound **35** in a retro Wittig fashion affords the dialdehyde **36**, FGI from aldehyde to hydroxyl function gives compound **37** that disclosed all its similarity to the sugar alcohol Xylitol.

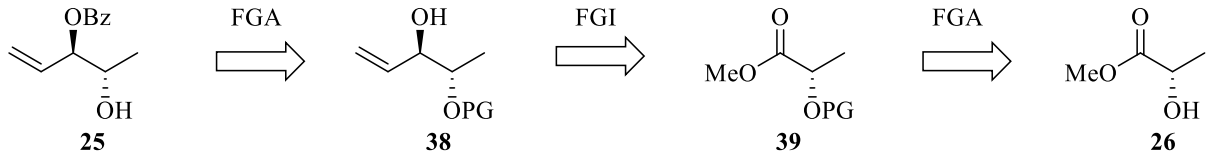
According to this synthetic strategy, it was evident that the secondary alcohol functions were to be protected from the start. Since it was not possible their selective protection by direct treatment of Xylitol **15** an already known protocol from literature that exploits the orthogonal deprotective conditions of silyl ether and ester protective groups was conceived. For instance, the primary

[52] The Wittig reaction of stabilized ylides with α-alkoxy or β-alkoxy aldehydes can stereoselectively form (Z)-α,β-unsaturated ester in alcoholic solvents, and the correlation between the structure of the starting carbonyl compound and the stereoselectivity of the reaction was also well established. For communications, see: (a) J.M. Tronchet, B. Gentile; Helv. Chim. Acta, 1979, 62, 2091-2098; (b) N. Minari, S.S. Ko, Y. Kishi; J. Am. Chem. Soc., 1982, 104, 1109-1111. (c) S. Valverde, M. Martin-Lomas, B. Herradon, S. Garcia; Tetrahedron, 1987, 43, 1895-1901; (d) F. Sanchez, S. Valverde, B. Herradon; Tetrahedron Asymmetry, 1996, 7, 3209-3246. For a comprehensive review, see: (e) B.E. Maryanoff; A.B. Reitz; Chem. Rev., 1989, 89, 863-927. For the synthesis of natural products involving the reactions, see: (f) L.J. Baird, M.S. Timmer, P.H. Teesdale, J.E. Harvey; J. Org. Chem., 2009, 74, 2271-2277; (g) H.K. Lee; J.S. Chun; J. Pak; J. Org. Chem., 2003, 68, 2471-2474

hydroxyls functions could be selectively protected by treatment with a hindered acyl chloride. Following protection of the remaining alcoholic functions with a silyl ether and then selective deprotection of the initially introduced terminal ester moieties seemed a good protocol to convert Xylitol **15** into diol **37** ready for the C-C bond formation protocol.

It is important to notice that an appropriate selective protection of the secondary OH for example as silyl ether was needed both for the oxidation to aldehyde of compound **37** as well as for the selective conversion of the primary hydroxyl functions to acetic ester required in the cyclization substrate **29**.

The synthesis of key intermediate **25** was already reported in literature.[37]



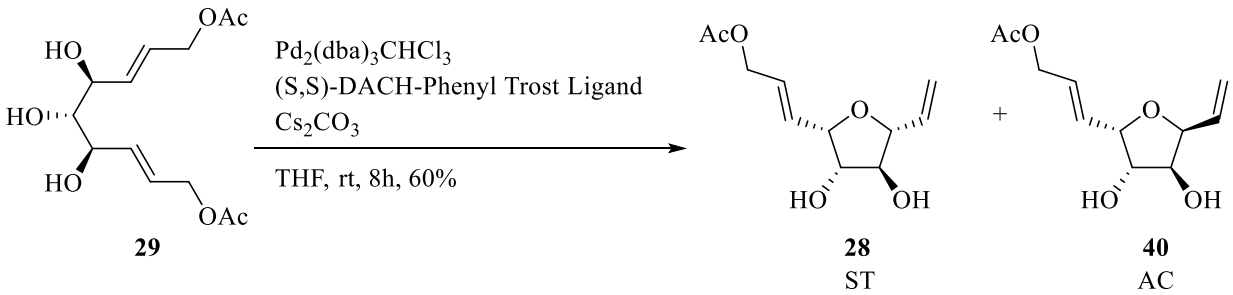
Scheme 6.1.5 Retrosynthetic analysis of alkene **25**

Retrosynthtical removal of the benzoyl function gives molecule **38**. (see scheme 6.1.5)

This latter is obtained from nucleophilic addition of a vinyl organometallic reactant to the aldehyde in turn obtained after controlled reduction of ester **39** with DIBAL-H.

Finally, removal of the protective group from compound **39** reveals the starting L-Methyl lactate **26**.

Unfortunately, the key Tsuji-Trost allylic etherification on **29** gave neither good diastereoselectivity nor good enantioselectivity (for further details and clarification on the nomenclature see paragraph 7.1).[27]



Scheme 6.1.6 Stereochemical outcome of the Tsuji-Trost reaction applied to Xylitol derived substrate **29**

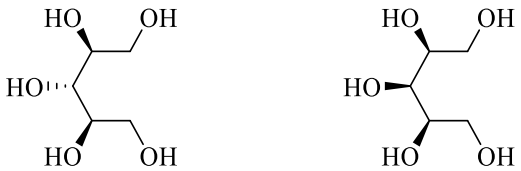
The best result obtained was: ST/AC=22/78; STe.e. = 73%; ACe.e. = 74%; yield = 60%

To exploit this reaction for the construction of the all syn THF core of Orthodiffene A was to be found another suitable substrate with the aim to obtain better stereochemical outcomes.

Anyway, as it was only a matter of changing starting sugar alcohol, this strategy remained a useful track for the successive developed synthesis and the main diastereomer obtained after the cyclization a good model to study the last reaction to be applied.

6.2 Identification of the intermediates: a new proposal

The unsatisfactory data for the cyclization of the Xylitol derivative lead us to try the same approach on a different sugar alcohol derivative.



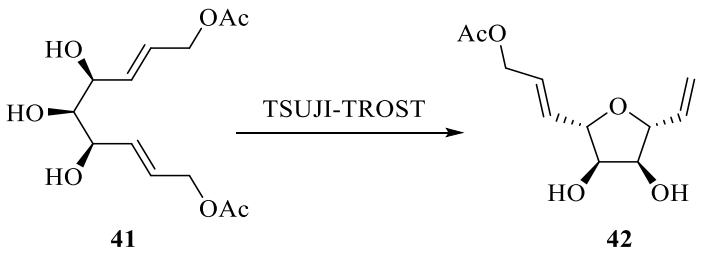
15 Xylitol **16** Adonitol

Figure 6.2.1 Structures of Xylitol **15** and Adonitol **16**

A quick perusal of the possible pentitols led us to choose adonitol **16**.

Adonitol is an epimer at C3, of Xylitol (figure 6.2.1). One first drawback is that it is more expensive then Xylitol. Nonetheless, it is affordable as starting material for a total synthesis, from Alfa Aesar® online catalog: 100g of Xylitol ≥ 99% costs 23.4 € while 5g of Adonitol ≥ 99% costs 22.7 €.[53]

The cyclization reaction hypothesized is outlined in scheme 6.2.2.

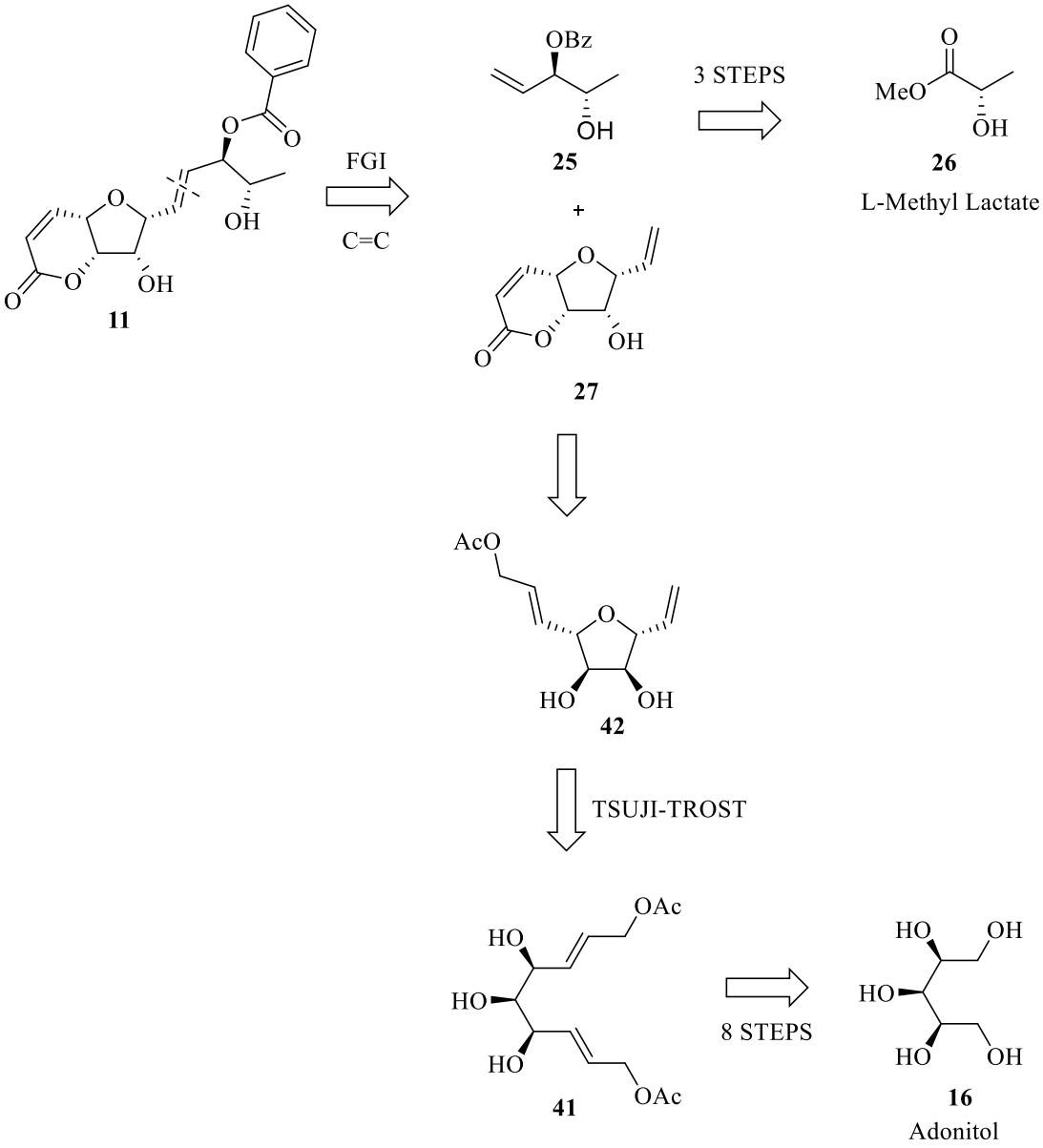


41 **42**

Scheme 6.2.1 Stereochemical outcome of the planned Tsuji-Trost reaction on the adonitol derivative **41**.

Aiming to apply this cyclization strategy to the Orthodiffene A synthesis, the same retrosynthetic analysis as applied to the xylitol derivative was followed.

[53] www.alfa.com

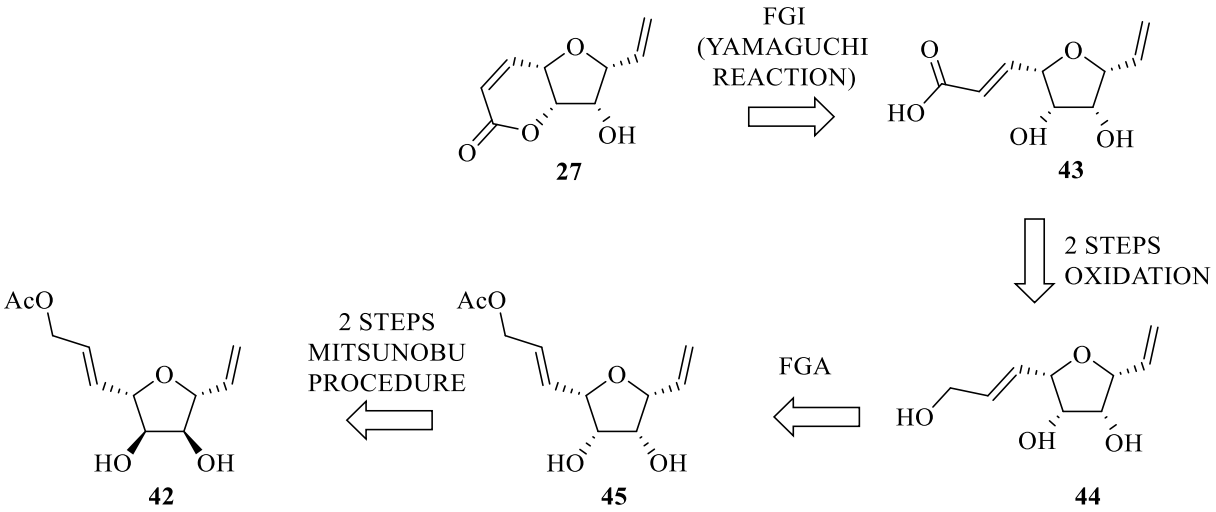


Scheme 6.2.2 Retrosynthetic analysis for the synthesis of Orthodiffene A starting from Adonitol **16** with the Tsuji-Trost reaction as key step

As in the previous approach, the target molecule was reconducted to compounds **25** and **27**.

Compound **25** was synthesized with the strategy outlined before starting from an L-Lactate (scheme 6.1.5).

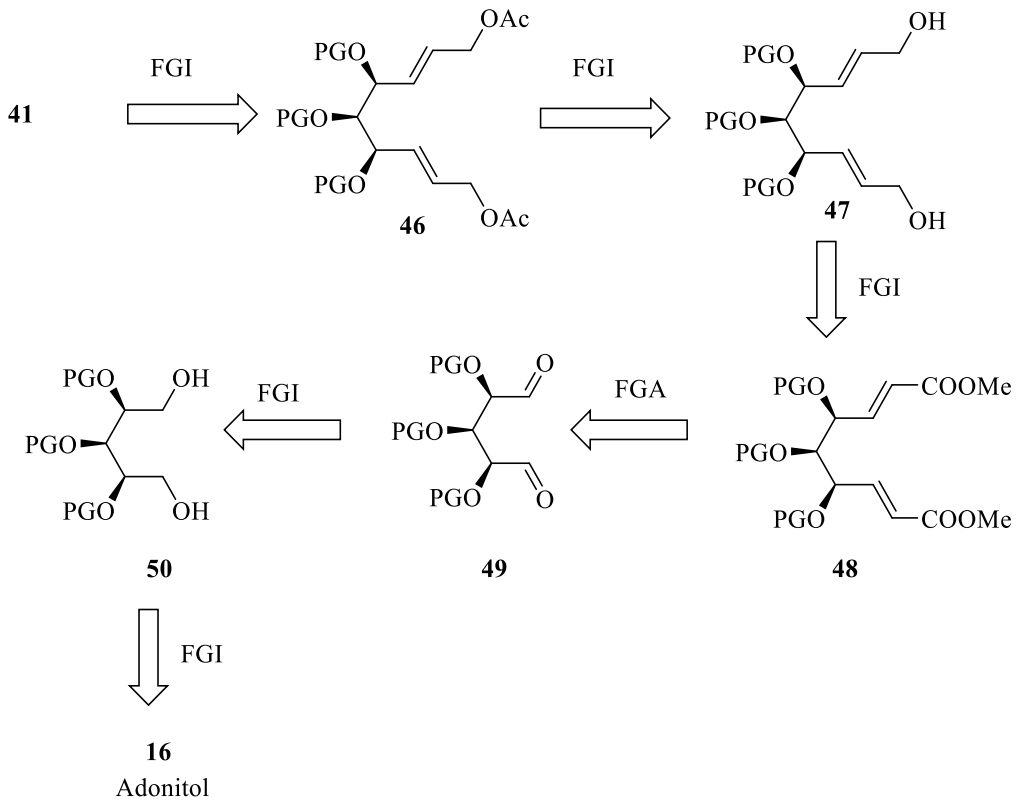
Compound **27** can be reconducted to diol **42** with the strategy outlined in scheme 6.2.3. This retrosynthtic analysis reveals a second drawback of this new approach: the need to invert both the hydroxyl groups of lactone **27**.



Scheme 6.2.3 Retrosynthetic analysis to relate molecule **27** to **42**

The synthetic pathway is analogous to the one already applied for the synthesis of THF core **28** differing from it because the Mitsunobu protocol to achieve the inversion of both the hydroxyl functions on the heterocycle must be applied right after the cyclization step and not at the end of the sequence done to reach the construction of molecule **27**.

The synthesis of **41**, precursor for the Tsuji-Trost cyclization, was started from Adonitol in the same way as carried out on Xylitol, as depicted in Scheme 6.2.4.



Scheme 6.2.4 Construction of diacetate **41**, substrate for the Tsuji-Trost reaction, starting from Adonitol **16**

7. The methodological approach

7.1 Early studies

During the last few years our team devoted a considerable attention to the asymmetric allylic Trost etherification in the total synthesis of natural derivatives[26] as anticipated in the paragraph 6.

The Tsuji-Trost reaction in its most general form consists in the allylation of a nucleophile (originally carbon based) by means of an allylic system under Pd(0) catalysis.

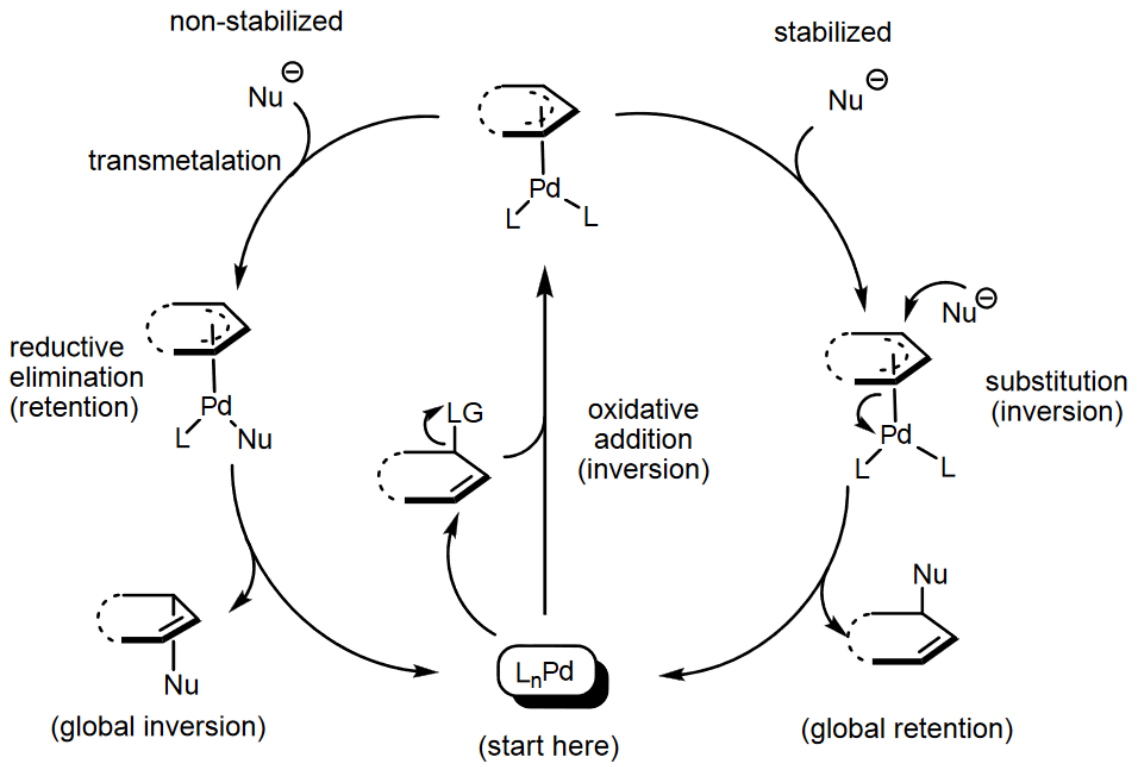
The nucleophiles that can be used in allylic substitution reactions generally belong to two classes[54]. For both classes, during the oxidative addition, the leaving group is ionized with inversion of configuration (the Pd complex approaches from the opposite side of the leaving group) then the pathway differs:

(I) "Hard" nucleophiles, defined as those derived from conjugate acids whose pKa > 25, normally effect such reactions by attachment of the nucleophile to the metal followed by reductive elimination. Therefore, the overall substitution take place with inversion of configuration.

(II) "Soft" nucleophiles, defined as those derived from conjugate acids whose pKa < 25, attack outside the coordination sphere of the Pd complex to give overall substitution with retention of configuration.

The two general mechanistic pathway are summerized in the scheme 7.1.1.

[54] G. Poli, G. Prestat, F. Liron, C. Kammerer-Pentier; Top Organomet Chem., 2012, 38, 1-64



Scheme 7.1.1 General mechanism of Pd-allylic alkylation reactions with stabilized and non-stabilized nucleophiles

Each step of the catalytic cycle offers opportunities for enantioselection. Therefore, several mechanisms for enantiodiscrimination are available to the Pd-catalyzed reaction.

In the ionization phase (formation of the Pd-substrate complex), enantiodiscrimination can happen either by (a) differentiating enantiotopic faces of the alkene double bond of the substrate or (b) by discriminating between enantiotopic leaving groups.

In the alkylation phase, asymmetric induction can happen by (c) recognition of two enantiotopic termini of a meso-π-allyl intermediate or (d) through enantioface exchange in the η^3-allyl complex: the metal can switch between the enantiofaces of the allylic fragment through a η^3-η^1-η^3 isomerization mechanism (scheme 7.2.4) or (e) through enantioface discrimination by prochiral nucleophiles or equilibrating mixtures of racemic nucleophiles. In the case of a pro-chiral metal-allyl complex and a pro-chiral nucleophile, diastereoselectivity becomes the issue.

Decomplexation of the metal from the olefinic product cannot change the stereochemistry of the product.

The extent of enantiodiscrimination depends on how the transition metal and, particularly, its ligands transmit their stereochemical information to the bond–breaking or –forming events during the stereodetermining step.

A plethora of chiral ligands have been developed for the Tsuji-Trost reaction. The symmetric C_2 class of ligands based on 2-(diphenyl-phosphino)benzoic acid as DACH-Trost ligand and ANDEN-Trost ligand are known to permit high ee with different substrates.[55]

The configuration of these ligands generates Pd fragments which allow the palladium-ligand complex to embrace the allyl function of the substrate forming a chiral pocket (figure 7.1.1).

The ultimate goal of such configuration is to restrict the number of degrees of freedom in the phosphine-metal complex favouring a specific transition state in the enantiodetermining step, thus assuring only a single product (enantiomer).

With this concept, Trost developed a model which allows predicting the product stereochemistry depending on the DPPBA chiral ligand used[56]. In this model, the asymmetric induction is established on steric interactions between the "wall" (phenyl substitutents of the chiral ligand) and the incoming nucleophile.

Depending on how the ligand "sits" on the allyl substrate, one terminus of the chiral environment should be favored for nucleophilic attack. In the figure below 7.1.1, for example, the back right and front left quadrants are effectively blocked.

However, in recent research it has been demonstrated that these ligands are forming oligomers making the reaction mechanism difficult to elucidate.[57]

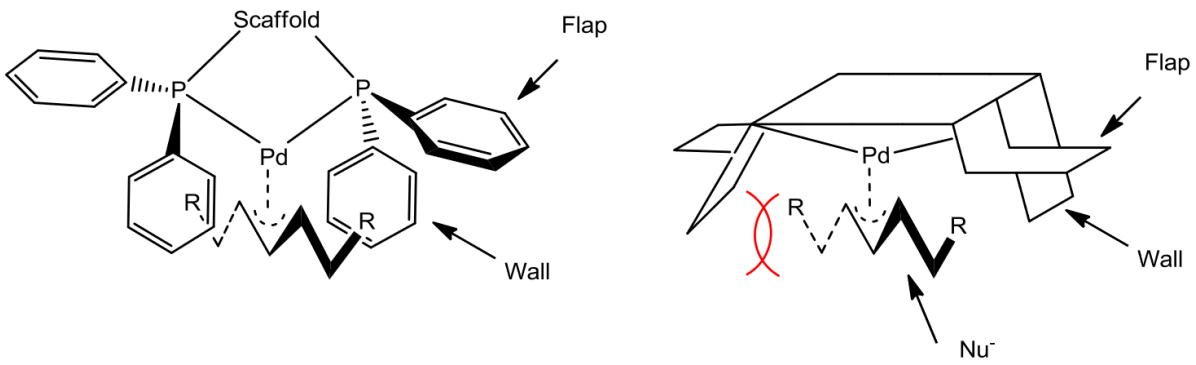


Figure 7.1.1 Model developed by Trost

An early work performed by our research group investigated the Pd(0)-asymmetric allylic etherification of meso diol **12** aiming to find a valid methodology for the formation of polysubstituted THF rings in the frame of the total synthesis of 7-*epi*-ST-Δ^8-10-Neurofuran.[26]

[55] B.M. Trost, D.L. Van Vranken, C. Binge1; J. Am. Chem. Soc., 1992, 114, 9327-9343
[56] B. M. Trost, M. R. Machacek, A. Aponick; Acc. Chem. Res., 2006, 39, 747-760
[57] J. Eastoe, I. J. S. Fairlamb, J. M. Hernandez, E. Filali, J. C. Jeffery, G. C. Jones, A. Martorell, A. Meadowcroft, P.O. Norrby, T. Riis-Johannessen, D. A. Sale, P. Tomlin; Faraday Discuss., 2010, 145, 27-47

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 can be *syn* (S) or *anti* (A), and the relation between the hydroxyl group and the C_2 substituent, that can be *cis* (C) or *trans* (T). All possible combinations are shown in figure 7.1.2.

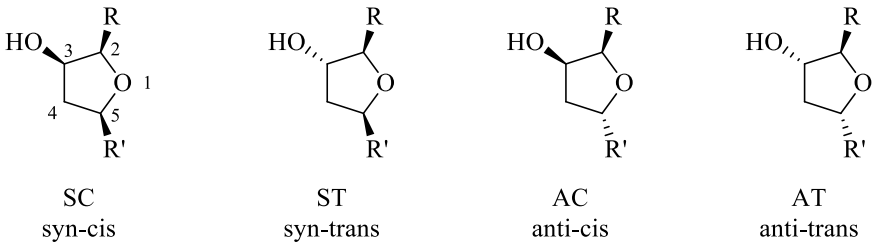
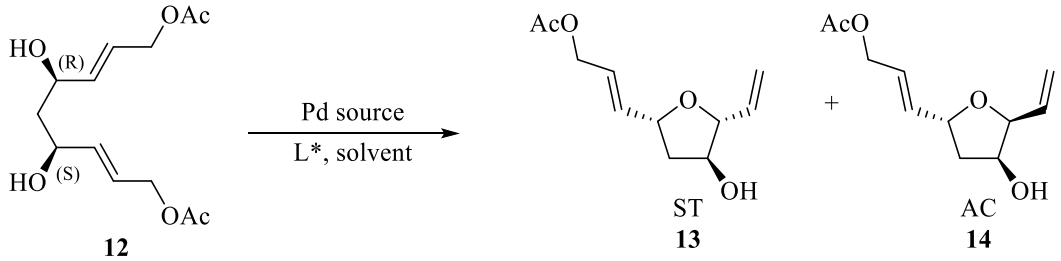


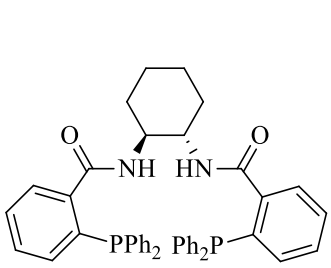
Figure 7.1.2 Nomenclature of all the possible diastereoisomers of 2,3,5-trisubstituted THF cores

To the stereochemical outcome of the cyclization, we can anticipate that, due to the symmetry features of the molecule, only two diasteroisomers can be formed (Scheme 7.1.2).



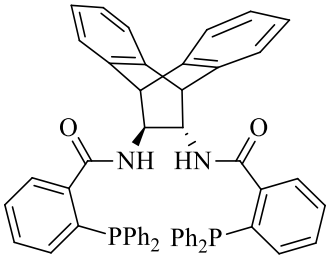
Scheme 7.1.2 Stereochemical features of the Tsuji-Trost reaction applied on meso diol **12** (L* represents a chiral ligand): not all the possible diasteroisomers are achievable with this strategy

At the beginning, cyclization of compound **12** 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.



(S,S)-**L1**

(S,S)-DACH-phenyl Trost ligand



(R,R)-**L2**

(R,R)-ANDEN-Phenyl Trost Ligand

Figure 7.1.3 Commercial name and stereochemistry of the chiral ligand utilized for this preliminar study

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 **12** (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.

Table 7.1.1 Stereochemical study on the stereochemical outcome of the Tsuji-Trost reaction on meso diol **12** using different ligands and reactions conditions

Under these conditions, a mixture of two tetrahydrofurans, ST-like **13** (94% ee) and AC-like **14** (11% ee), was obtained in 61% isolated yield and 61:39 dr (HPLC) (table 7.1.1, entry 1). This result was unexpected since the significant formation of **14** was not reported in the original work.[4]

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 **13** was obtained in 80:20 *d.r* ST:AC (HPLC) and 96% *ee*, accompanied by the AC-diastereomer **14** (3% *ee*), in an overall yield of 86% (table 7.1.1, entry 2).

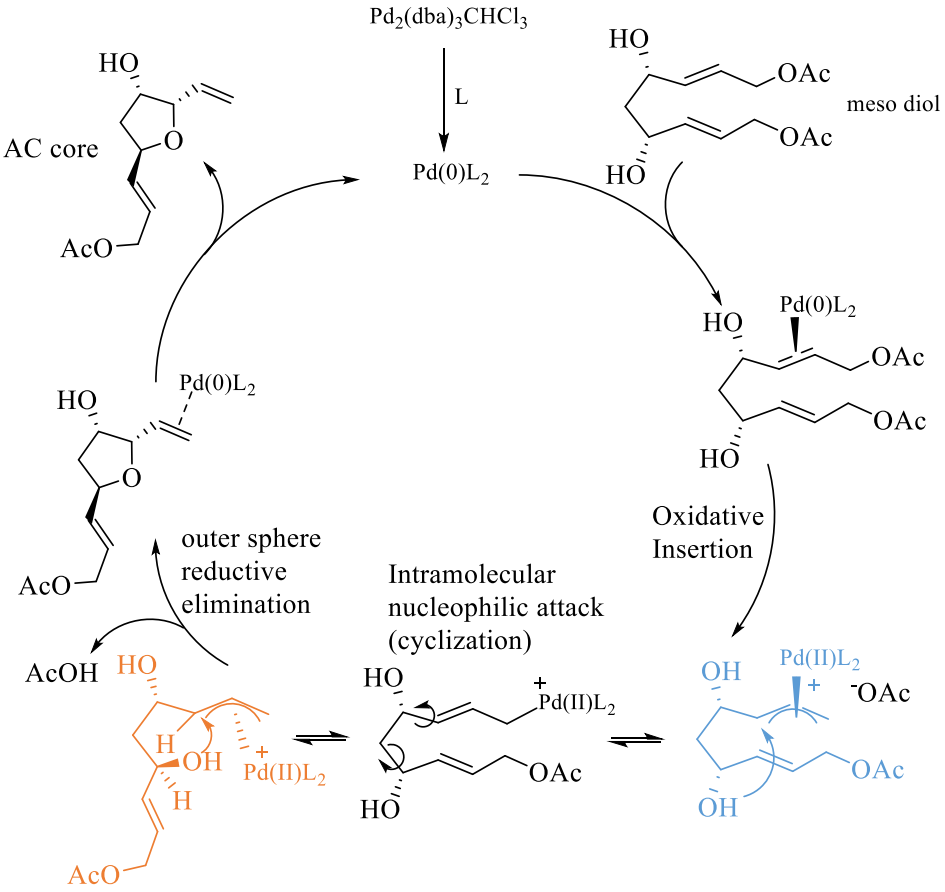
The two compounds **13** and **14** could not be separated by preparative column chromatography. For this reason, reaction conditions were optimized to achieve an improvement of the diastereoselectivity. Although no significant *d.r* enhancement was obtained, an unanticipated inversion in the diastereomeric products distribution in favor of AC-THF **14** was observed simply by using the anthracenyldiamine-derived ligand (*R,R*)-**L2** instead of (*S,S*)-**L1**.

Absolute configuration of 2*R*,3*S*,5*R* for **13** and 2*S*,3*S*,5*R* for **14** were established by studies of the corresponding Mosher esters and n.O.e NMR spectra[58].

7.2 Stereochemical features of the reaction

The reaction is characterized by the following steps[55] (Scheme 7.2.1)

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

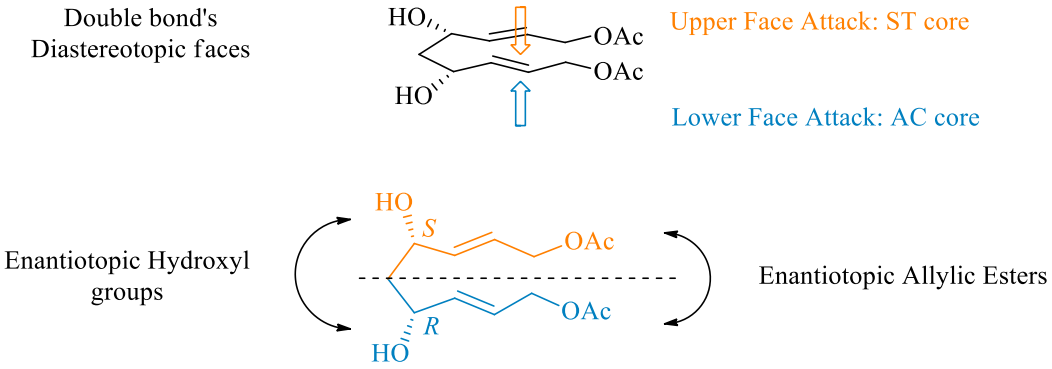


Scheme 7.2.1 Mechanism of Tsuji-Trost allylation

The achiral substrate **12** loses its symmetry (reflection plane) during the cyclization, thus chiral tetrahydrofuran systems are formed.

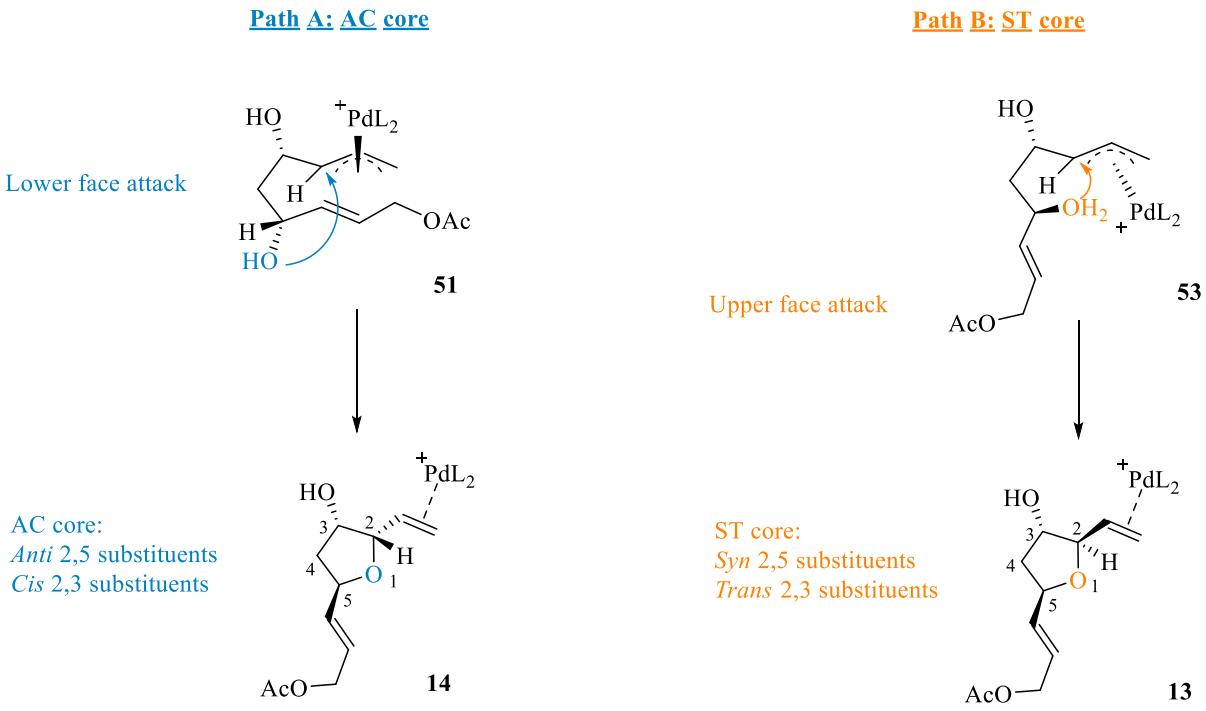
[58] R.J. Capon, R.A. Barrow, S. Rochfort, M. Jobling, C. Skene, E. Lacey, J.H. Gill, T. Friedel, D. Wadsworth; Tetrahedron, 1998, 54, 2227-2242

By analyzing the stereochemical features of compound **12** 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 π-allyl system, resulting in the two different diastereomeric rings AC and ST respectively.



Scheme 7.2.2 Stereochemical features of *meso* diol **12**

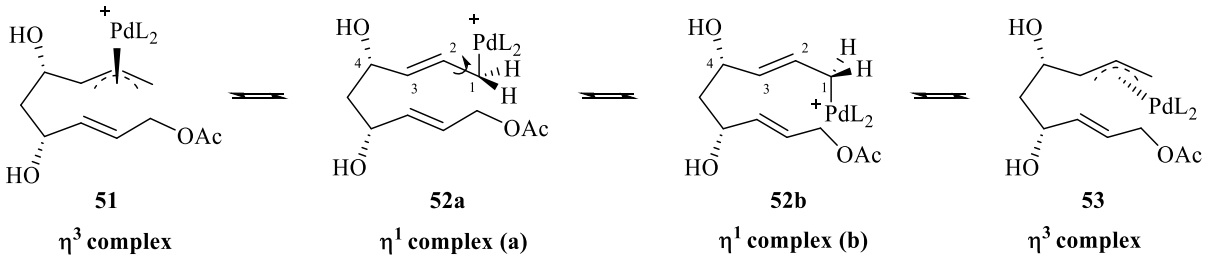
Scheme 7.2.2 reports the two competitive pathways of the Tsuji-Trost AAA on *meso* diol **12**.
The only new stereocenter that is created in the final product is the one bearing the vinyl substituent (C_2), the other two centers (C_3 and C_5), become automatically stereogenic because of the reflection 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 (Figure 7.1.1)
Moreover, the substrate contains a symmetry plane. Therefore, the hydroxyls functions and the two allyl esters are enantiotopic each other. Therefore, 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 7.2.3 Reaction pathways towards AC and ST cores

It is important to note that the two diastereoisomeric η^3-allyl complexes **51** and **53** (scheme 7.2.3) can be in equilibrium through the corresponding η^1- allyl complex **52** which can free rotate around its C_1-C_2 bond.

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



Scheme 7.2.4 equilibration between $\eta^3\pi$-allyl complexes

Equilibration is strongly influenced by temperature, solvent polarity and stereo-electronic features of the catalyst. Moreover, although the counteranion in η^3-complex lies outside the metal coordination sphere, usually as a tight ion-pair, in η^1-complex it is in the metal coordination sphere.[54]

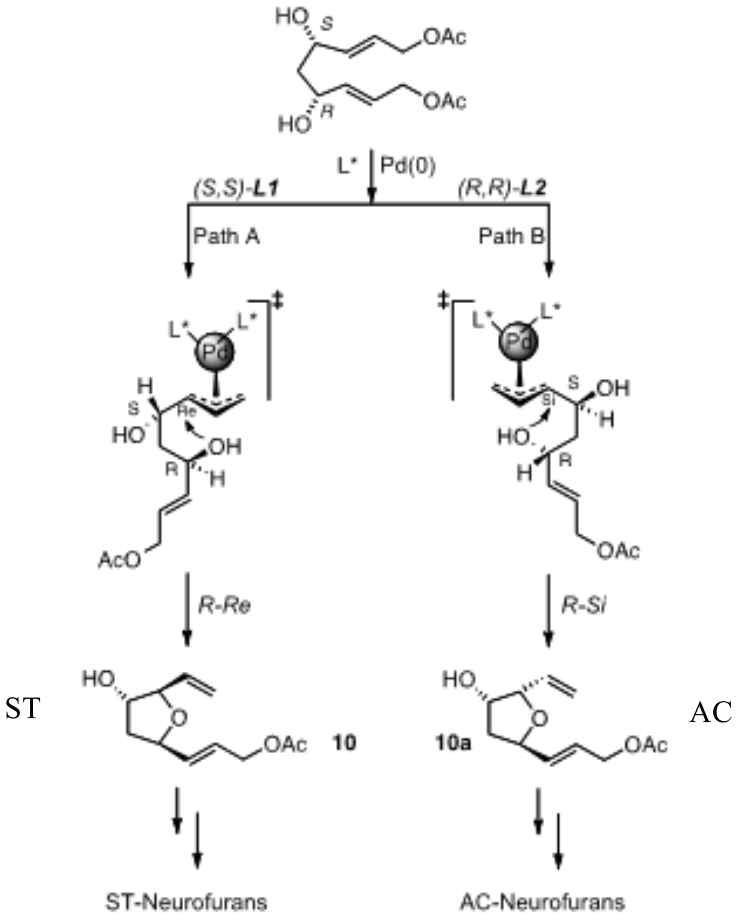
The stereochemical control of the Pd(0)-catalyzed asymmetric allylic etherification of *meso* diol **12** depends by working on two different selectivity levels. The diastereoselectivity, which is expressed

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.

Based on the outcomes showed in table 7.1.1, and according to the asymmetric induction model proposed by Trost for the Pd-catalyzed asymmetric allylic alkylation (AAA)[24,59], it was speculated that the stereoisomer **13** (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 7.2.3).

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 **13** (scheme 7.2.3, path A).



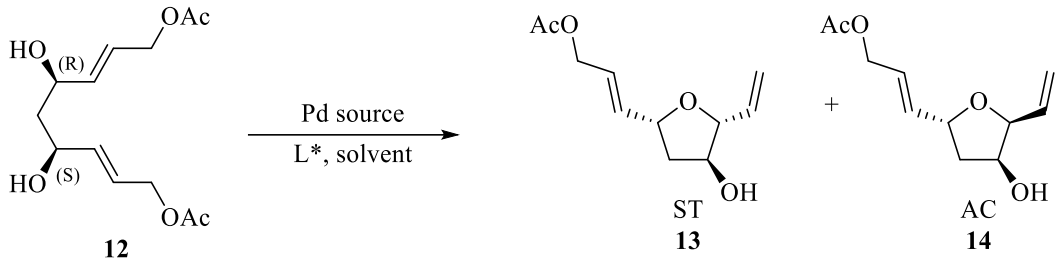
Scheme 7.2.5 Stereochemical picture of asymmetric allylic Pd-mediated cyclization of *meso* diol **12**

[59] (a) B.M. Trost, D.L. Van Vranken; Chem. Rev., 1996, 96, 395-422; (b) B.M. Trost, B.M. Machacek, M.R. Aponick; Acc. Chem. Res., 2006, 39, 747-760

On the contrary, it was assumed that the (*R,R*)-**L2**-Pd complex delivered preferentially the corresponding *trans*-diastereoisomer **14** (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 7.2.3, path B).
Not unexpectedly by using the enantiomers of ligands **L1** and **L2** namely (*R,R*)-**L1** and (*S,S*)-**L2**, the corresponding enantiomers of **13** and **14** were achieved with the same enantio- and diastereomeric excess.
Previous studies in our laboratory[23] have been focusing on:

- The investigation of the factors that can control the diastereoselectivity of the process through the screening of different kinds of solvents, temperature and achiral ligands for the Pd catalyst;
- Exploitation of the result obtained from the previous screening for the test of chiral ligands for the reaction
- Investigation of the role of the leaving group of the substrate in the stereochemical outcome of the reaction.

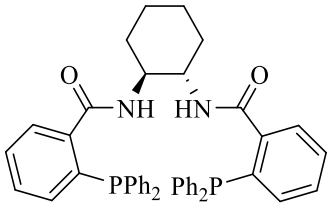
The main data obtained from the systematic study previously performed in our laboratory[23] are summarized in the following table 7.2.1 where the leaving group **A** is an acetyl, **B** is a Pivaloyl, **C** is a 4-Methoxybenzoyl. The ligand (S,S)-**L1**, (R,R)-**L2** and (S,S)-**L3** are hereby summarized.



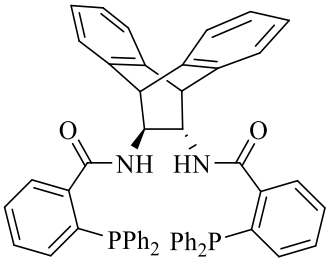
12 **13** **14**

ENTRY	LEAVING GROUP	LIGAND	SOLVENT	BASE	T (°C)	D.R. (ST:AC)	EE_{ST} %	EE_{AC} %	Y %	P-PD-P ANGLE
1	**A**	(R,R)-**L2**	DCM	/	-30	17:83	95	92	65	113
2	**A**	(R,R)-**L2**	PhMe	/	25	30:70	98	95	74	113
3	**A**	(S,S)-**L3**	PhMe	/	25	7:93	39	64	86	110
4	**A**	(S,S)-**L3**	PhMe	/	-30	5:95	99	87	80	110
5	**A**	(S,S)-**L3**	PhMe	$BaCO_3$	-30	5:95	98	84	85	110
6	**A**	(S,S)-**L3**	DCM	$BaCO_3$	-30	6:94	99	80	63	110
7	**A**	(S,S)-**L1**	DCM	/	25	80:20	96	3	86	117
8	**B**	(R,R)-**L2**	PhMe	/	25	31:69	91	94	70	113
9	**B**	(S,S)-**L3**	PhMe	/	25	1:>99	/	77	64	110
10	**C**	(S,S)-**L3**	PhMe	$BaCO_3$	-30	1:>99	/	92	70	110

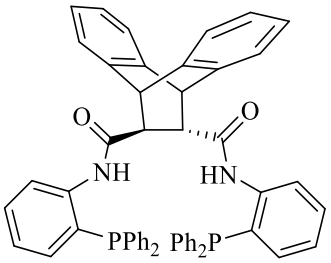
Table 7.2.1 Chiral ligand utilized in the systematic study. Reactions 1-10 were carried out with $Pd_2(dba)_3 \cdot CHCl_3$ (3 mol%), ligand (8 mol %) and solvent (0.1 M).
d.r. and e.e. were determined by chiral HPLC on Chiralpak AS-H.



(S,S)-**L1**



(R,R)-**L2**



(S,S)-**L3**

The best solvent for the reaction turned out to be toluene, because it allows a good solubilization of most of the ligands.

The ligand features that can affect the reaction course are both steric and electronic as the Tolman electronic parameter, Tolman cone angle, the plane angle P-Pd-P.

Donor ligands such as phosphines are necessary to enrich palladium atom and thus allow the oxidative addition step to take place. More precisely, moderately donor phosphine ligands are those that allow the fastest turnovers. Indeed, although electron-withdrawing phosphines render the allyl complex more electrophilic, they also favor ion-pair return (the inversion process of the oxidative insertion) more than exogenous nucleophile attack.[54]

Normally, the parameter employed to measure the electron donor power of a phosphine is the Tolman electronic parameter.[60]

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 (figure 7.2.1).

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

[60] C.A. Tolman; Chem. Rev., 1977, 77, 313-348.

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.

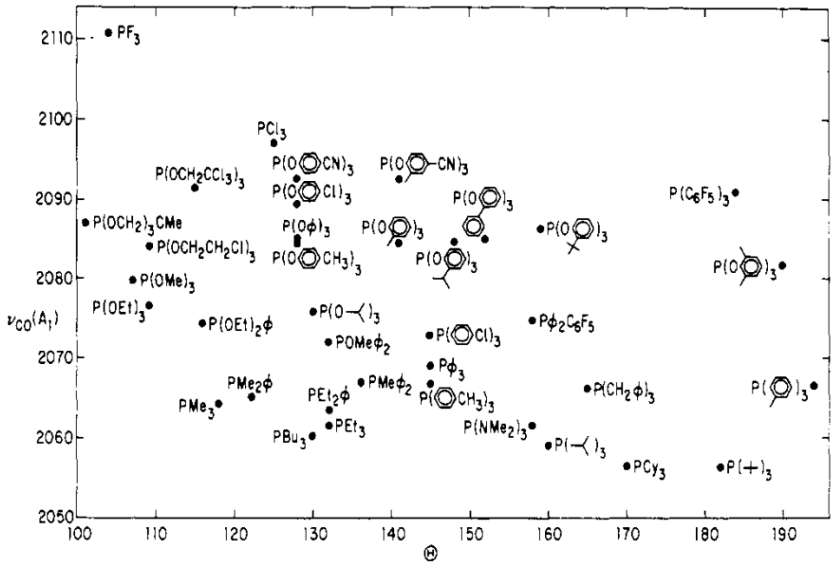


Figure 7.2.1: Tolman diagram about steric (θ angle) and electronic (ν_{CO}) effect of different phosphines (figure taken from ref 57)

Electronic and steric properties of the ligand are closely interlinked. Another important parameter that must be considered is the plane angle P-Pd-P (β angle), that can modify the electronic density of the metal.

This structural feature, that is present not only for bidentate phosphines but for monodentate too, can affect the electronic features of a coordinated moiety, and pi-allyl is related to the different orbital overlap between filled phosphorous ion pair and empty Pd "d" 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[61], we anticipate that by tightening the angle P-Pd-P, the electron density of a coordinated moiety pi-allyl will increase.

It is generally observed that by tightening the plane angle P-Pd-P, the AC:ST ratio enhances.

This result 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. Thus, making the cyclization step slower. As a result, equilibration between the two possible η^3 complexes (scheme 7.2.4) becomes more significant and the amount of AC product increases. In fact, previous computational studies[62] demonstrated that in all the ligands screened, the TS leading to the AC core is more stable than the one leading to the ST core.

[61] M. Ogasawara, K. Takizawa, T. Hayashi; Organometallics, 2002, 21, 4853-4861
[62] Sbarbada D., PhD thesis, 2014

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

(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 7.2.1).

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 7.2.1)

A deep computational study confirmed this catalytic scenario.[62]

The leaving group plays also a key role. In 2012, Gandon and Roulland[63] 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.

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.

By increasing the steric hindrance of the leaving group, coordination becomes more difficult and reaction would slow down as above noticed. If cyclization rate decreases, the intermediate pi-allyl system has more time to equilibrate and the amount of AC -THF core rises, as shown in table 7.2.1.

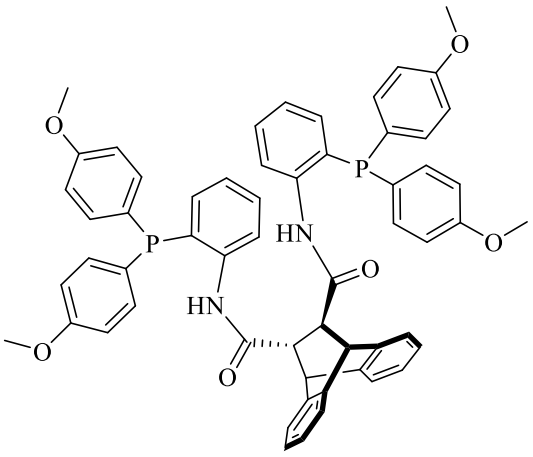
Pivalate and p-methoxybenzoate are the leaving groups that were tested. Both show a higher steric hindrance than the acetate.

In view of the above considerations, we decided to use the acetate as leaving group which would also be the most atom economical leaving group.

In view of the results of table 7.2.1, it was decided to increase the electron density of the pi-allyl complex by increasing the electron density on the ligand (S,S)-**L3** through the insertion of electron donating groups.

We came out then with (S,S)-**L4** (figure 7.2.2).

[63] M. Arthuis, R. Beaud, V. Gandon, E. Roulland; Angew. Chem. Int. Ed., 2012, 51, 10510-10514.



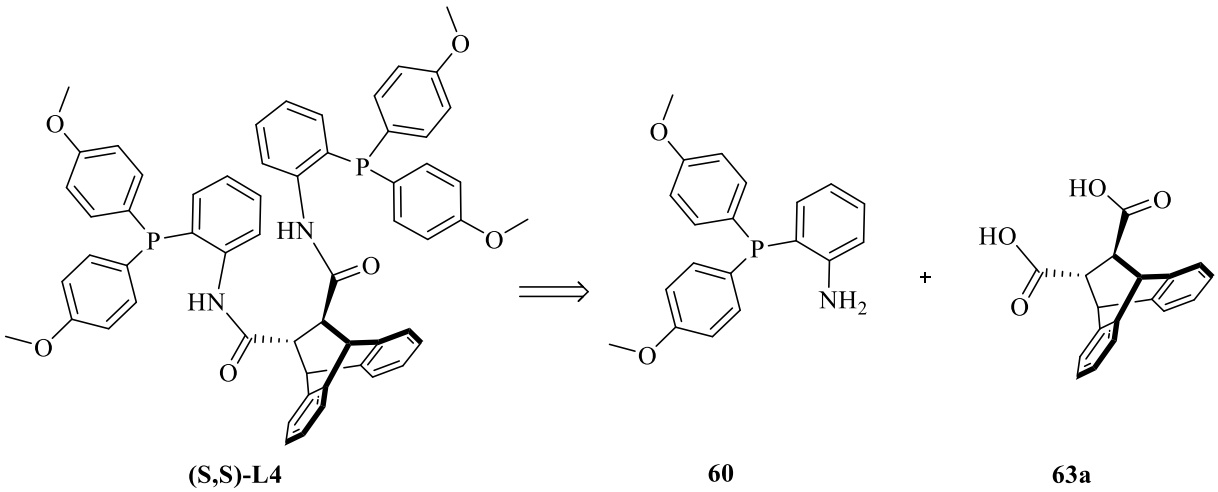
(S,S)-**L4**

Figure. 7.2.2. Stereochemical configuration of (*S,S*)-**L4**

7.3 Synthesis of (S,S)-L4

From a structural point of view, *(S,S)*-**L4** is very similar to *(S,S)*-**L3**, the only difference lies in the presence of the methoxy groups on the aromatic ring in para to the phosporous. The presence of such electron donating groups was expected to increase the stereoselectivity of the model reaction by increasing the electron density on the phosphorous atom.

The approach followed for the synthesis of *(S,S)*-**L4** is based on the disconnection of the amide bond that leads to the corresponding chiral *(S,S)*-dicarboxylic acid **63a** and phosphine **60** (Scheme 7.3.1).



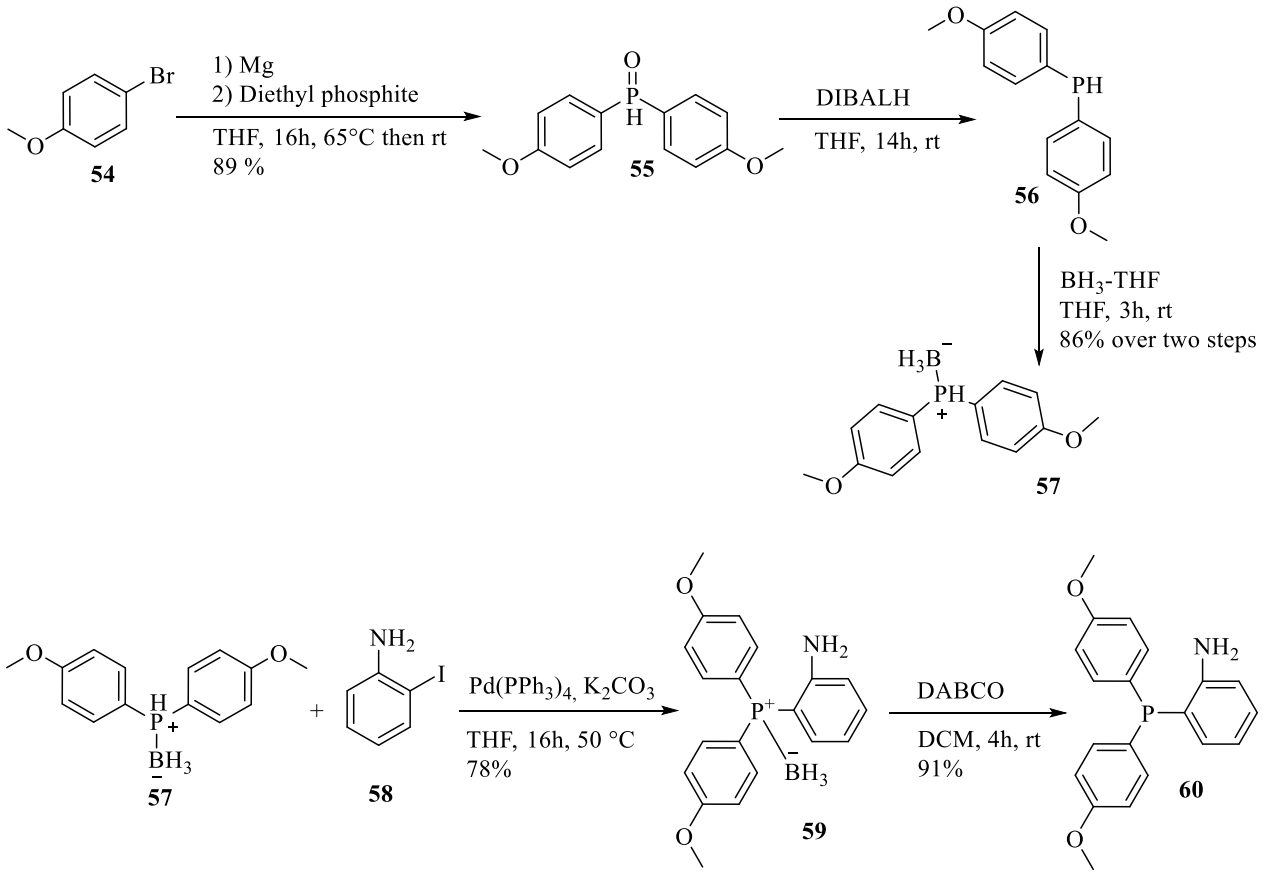
(S,S)-L4 **60** **63a**

Scheme 7.3.1 Retrosynthetic analysis leading to **(S,S)-L4**

The synthesis of phosphine **60** revealed troublesome. However, after several attempts, it was synthetized following a protocol[64] for similar compounds. We exploited as the key step a Pd-catalyzed P-C coupling between 2-iodoaniline and the secondary phosphine **57** protected as borane adduct (scheme 7.3.2).

The reaction is of broad applicability and compatible with electron donor or electron acceptor substituents in ortho, meta or para position to the halogen in the aromatic ring systems. It may be performed in protic and aprotic solvents.[64]

57 was synthesized using a known procedure in literature.[65]



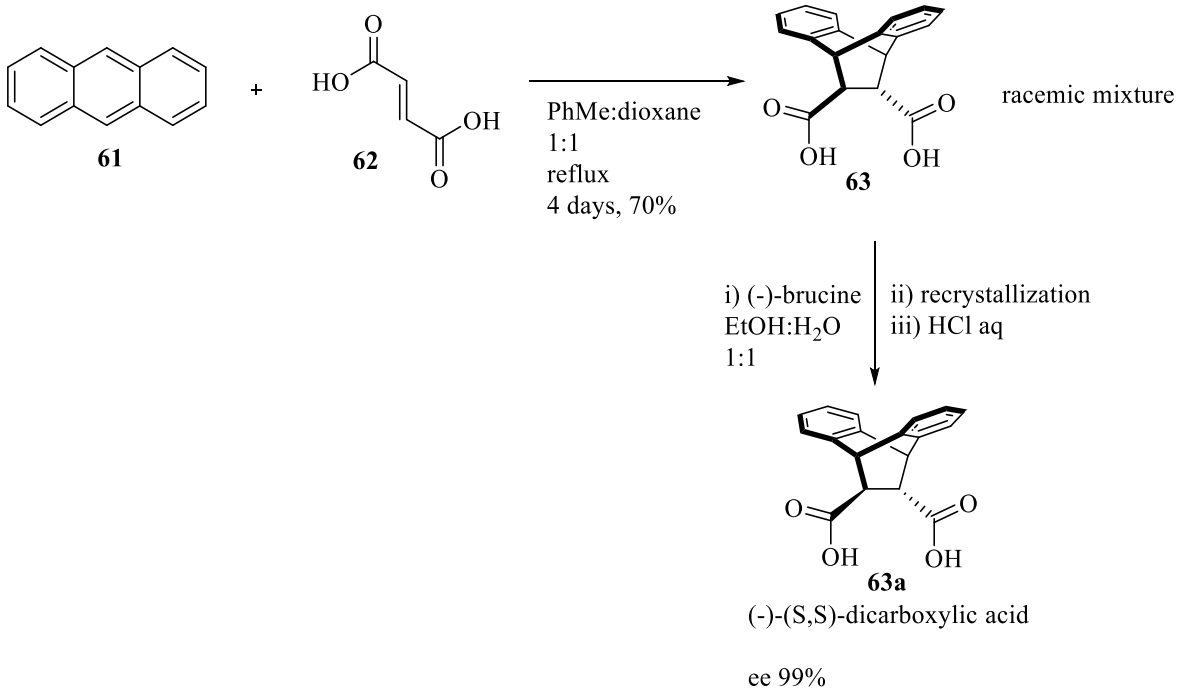
Scheme 7.3.2. Synthetic pathway to **60**

The approach used for the synthesis of the chiral *(S,S)*-dicarboxylic acid **63a** is based on classical resolution of the racemic diacid **63**, obtained from Diels-Alder reaction between anthracene **61** and fumaric acid **62** (Scheme 7.3.2).

(-) Brucine was used as resolving agent and *(S,S)*-dicarboxylic acid **63** was achieved with 99% *ee*.

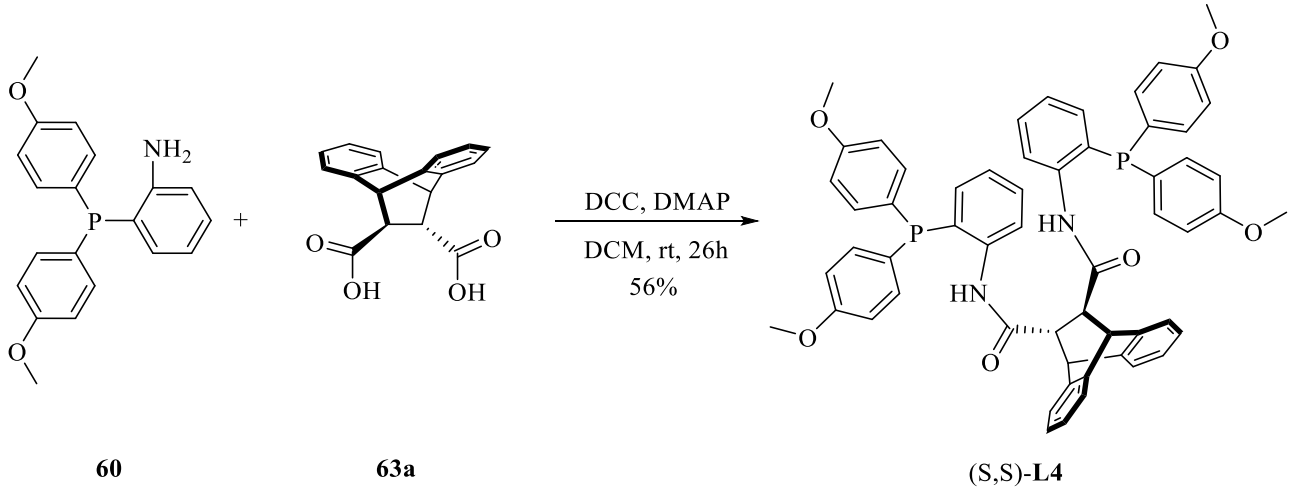
[64] D.J. Brauer, M. Hingst, K.W. Kottsieper, C. Liek, T. Nickel, M. Tepper, O. Stelzer; Journal of Organometallic Chemistry, 2002, 1, 14-26

[65] C.A. Busacca, J.C. Lorenz, N. Grinberg, N. Haddad, M. Hrapchak, B. Latli, H. Lee, P. Sabila, A. Saha, M. Sarvestani, S. Shen, R. Varsolona, X. Wei, C.H. Senanayake; Org. Lett., 2005, 7, 4277-4280



Scheme 7.3.2 Synthetic pathway to **63a**

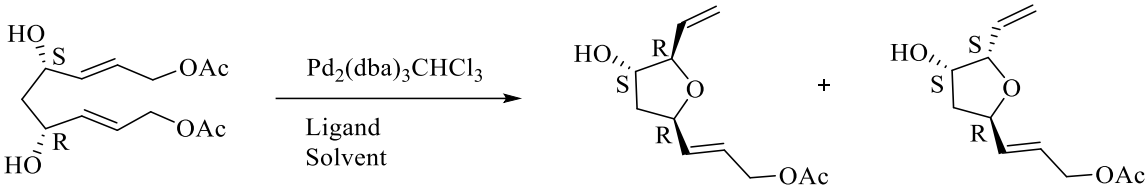
Finally, the enantiopure diacid **63a** was coupled with the amino-phosphine **60** via DCC leading to the synthesis of (*S*,*S*)-**L4** as depicted in scheme 7.3.3.



Scheme 7.3.3 Condensation between **60** and **63a** leading to the synthesis of (S,S)-**L4**

7.4 Test of (S,S)-**L4** on the meso diol **12**

Once synthesized, (*S*,*S*)-**L4** was tested on the cyclization of meso diol **12**.



12 ST **13** AC **14**

ENTRY	LIGAND	SOLVENT	BASE	T (°C)	D.R. (ST:AC)	EE_{ST} %	EE_{AC} %	Y %	TIME
1	(S,S)-**L4**	PhMe	/	-30	5:95	99	84	62	7h
2	(S,S)-**L3**	PhMe	/	-30	5:95	99	87	80	24h
3	(S,S)-**L4**	DCM	$BaCO_3$	-30	3:97	99	73	76	10h
4	(S,S)-**L3**	DCM	$BaCO_3$	-30	6:94	99	80	63	24h
5	(S,S)-**L4**	PhMe	/	25	<1:>99	/	1	91	15min
6	(S,S)-**L3**	PhMe	/	25	7:93	39	64	86	4h

Table 7.4.1 Reactions 1-6 were carried out with $Pd_2(dba)_3 \cdot CHCl_3$ (3 mol%), ligand (8 mol %) and solvent (0.1 M). d.r. and e.e. were determined by chiral HPLC on Chiralpak AS-H.

The reactions of entries 1-4 (table 7.4.1) were carried out at -30°C because it is the lowest temperature at which the complex maintains its activity (at lower temperature the conversion of the reaction drop dramatically down by using both the ligands).

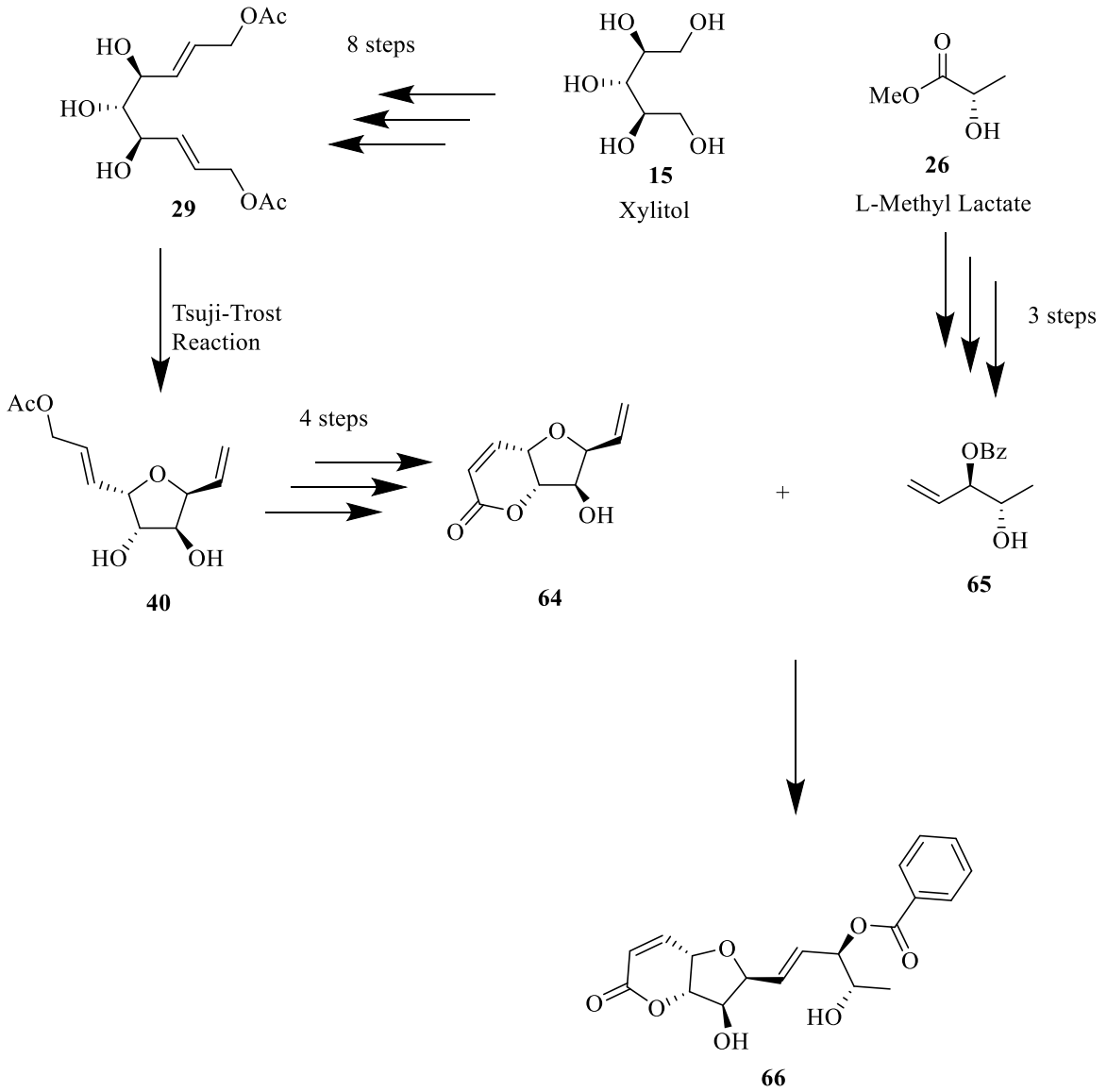
At room temperature the reaction was totally diasteroselective with (*S*,*S*)-**L4** but the AC core resulted racemic. The presence of these EDG groups on the ligand are expeted to cause a faster oxidative insertion with (*S*,*S*)-**L3**: this step is so fast that there is no discrimination between the two allylic fragments (no ee observed), at the same time the use of (*S*,*S*)-**L4** slows down the step of cyclization (reductive elimination) making possible the equilibration between the two η^3-complexes resulting in the formation only of the thermodinamic product (the AC core).

By comparing entries 1 with entry 2 and entry 3 with entry 4 it is possible to compare the effect of such ligands at -30°C. The low temperature slows down the reaction: this time the reaction doesn't produce a racemic AC core by using (*S*,*S*)-**L4.** Anyway, the ee_{AC} obtained with this ligand is slightly less then that obtained by carring out the reaction with (*S*,*S*)-**L3**. Again, the oxidative insertion is expected to be faster in presence of EDG groups on the ligand resulting in the decrease of the ee.

It could be expected a d.r.(ST:AC) of <1:>99 even at -30°C in the entry 1 and 3. Anyway, the formation of the ST core at low temperature could be explained on a major effect of the temperature on the step of equilibration compared to the step of cyclization: we speculate that the energy of the TS of the reductive elimination is lower then the two TS in the equilibration of the two η^3-complexes. With this observations, no further studies were carried out with the (*S*,*S*)-**L4** ligand.

7.5 A model study: approaching the synthesis of Orthodiffene starting from Xylitol **15**

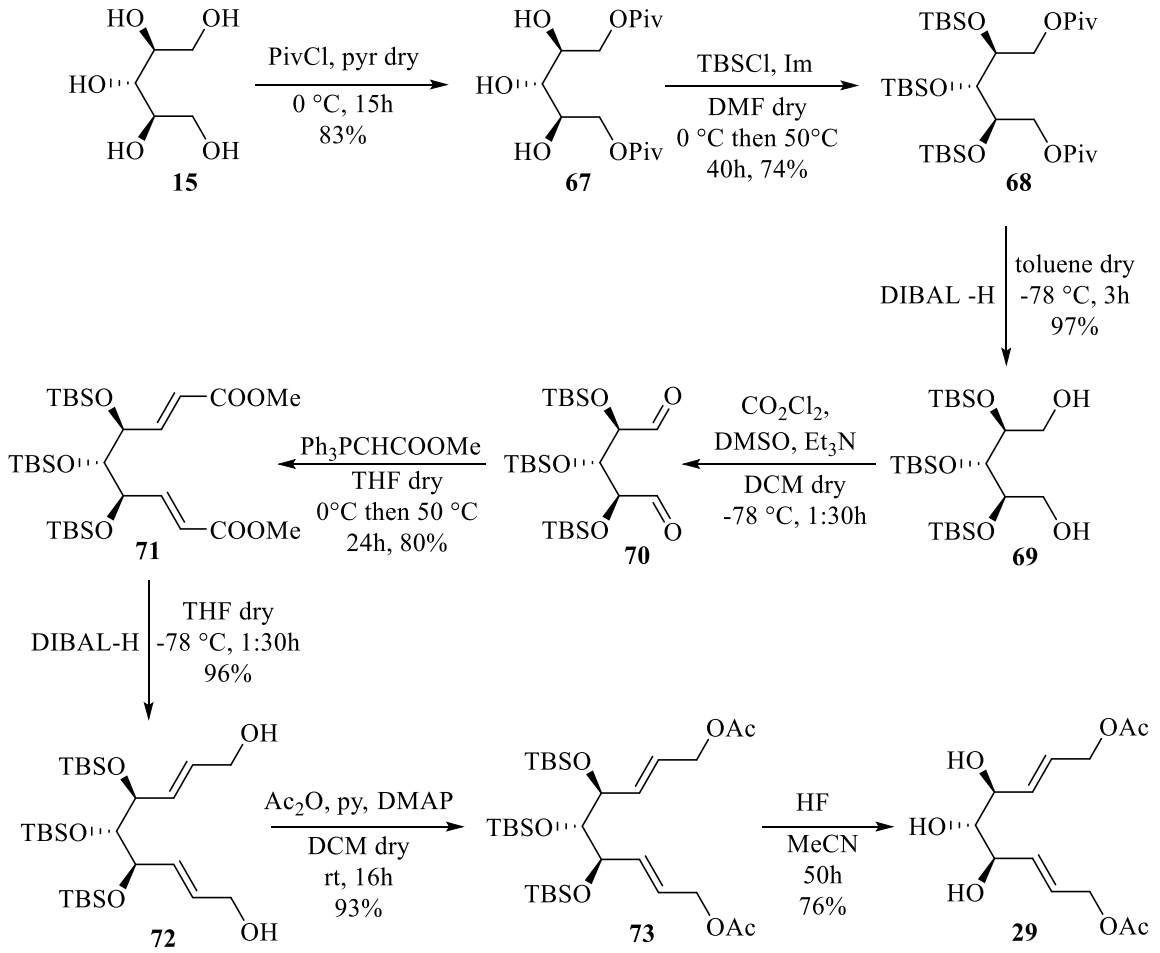
Following the retrosynthetic analysis previously described (see paragraph 6.1) a first approach to the total synthesis of Orthodiffene A retraced the strategy used starting from Xylitol **15** and L-Methyl Lactate **26** (scheme 7.5.1).



Scheme 7.5.1 Scheme of the synthetic study done towards Orthodiffene A construction starting from Xylitol **15**

7.5.1 Synthesis of the triol **29** precursor of the THF core

The synthetic sequence followed to obtain triol **29** starting from Xylitol is reported in the scheme 7.5.1.1



Scheme 7.5.1.1 Synthetic procedure scheme followed for the construction of triol **29** starting from Xylitol **15**

Treatment of Xylitol **15** with pivaloyl chloride in dry pyridine afforded the selective protection of the two primary alcohols as pivaloyl esters, **67**. This type of ester was chosen as protective group since it is orthogonal to the TBS moiety and it is sufficiently bulky to allow the selective protection of the primary hydroxyl functions.

Triol **67** was then treated with TBSCl in dry DMF to afford the trisilylated derivative **68**, which was converted to the diol **69** by reduction with DIBAL-H. Swern Oxidation to the corresponding dialdeyde and subsequent Wittig reaction with the stabilized ylide Ph_3PCHCO_2Me successfully led to diester **71** in good yield.

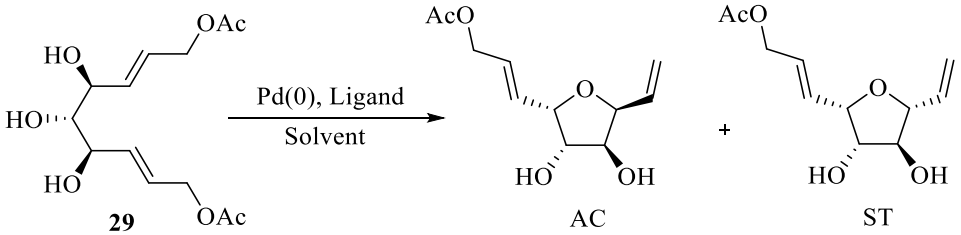
Followed the reduction of the terminal ester moieties of compound **71** with DIBAL-H, protection of the newly generated alcohol functions as acetates by treatment of **72** with acetic anhydride in pyridine. Finally, hydrolysis of the silyl ether **73** by treatment with concentrated aqueous HF solution in acetonitrile afforded the desired meso cyclization precursor **29**.

7.5.2 Optimization of the Tsuji-Trost reaction: the methodological study

This section reports some results achieved in our laboratory before the beginning of this work.

With triol **29** in hands its Tsuji-Trost cyclization was studied.

By virtue of our prevision in the study of the cyclization of meso diol **12**, it was speculated that using the chiral phosphine (S,S)-DACH Trost Ligand ((S,S)-L1 in Table 7.2.1) analogous cyclization of **29** would have produced preferentially the ST diastereoisomer. As table 7.5.2.1 shows, this expectation was not confirmed. Indeed, **29** diol cyclizes to the corresponding cyclic ether, but forming the AC isomer. In any case, it was verified that the presence of the extra hydroxy group did not compromise cyclization.



Ligand	Solvent	%Pd	T (°C)	Base	ST:AC	ee ST	ee AC	Yield
[a](S,S)-L1	DCM	8%	25	Cs_2CO_3	/	/	/	22%
[a](S,S)-L1	THF	8%	25	/	22:78	73	74	60%
[b]PPh_3	THF	8%	25	/	1:99	/	/	55%

[a] Conditions were $Pd_2(dba)_3CHCl_3$ adduct (8 mol%), chiral ligand L* (20 mol%), substrate **29** (1 mmol), solvent (5 ml, 0.2 M). If present: Cs_2CO_3 (1.05 equiv)

[b] Conditions were: $Pd(PPh_3)_4$ (8 mol%), substrate **29** (1 mmol), solvent (5 ml, 0.2 M). d.r. ST:AC was determined by HPLC. Enantiomeric excess was determined by chiral HPLC, on chiral pack AS-H 250-4, isocratic elution: eptane/isopropanole = 7/3, UV detection: λ=204nm

Table 7.5.2.1 Stereochemical output of the Tsuji-Trost reaction applied on triol **29** with different reaction conditions

Chromatogram I (Figure 7.5.2.1) shows the reaction products of the cyclization in presence of PPh_3 (entry 3 Table 7.5.2.1). Comparing the respective retention times of the three peaks with those observed from the corresponding cyclization of meso diol **12** obtained (using the same column and the same elution method) it was possible assign to peak 1 and 2 as the enantiomers of the stereoisomer AC.

In the experiment of entry 1, using ligand **(S,S)-L1**, use of Cs_2CO_3 as base gave a low yield, suggesting that the base may hinder the π-allyl complex formation. For this reaction neither diastereomeric ratio nor enantiomeric excesses were calculated since its low yield made the reaction anyway unfeasible.

This was the only trial with DCM as solvent since it was noted that the complex between ligand and catalyst was not formed because of the lack of the characteristic color variation associated with the complexation.

Chromatogram III shows the retention times of triphenylphosphine and triphenylphosphinoxide alone to use as reference. Indeed, both compounds could be present even after the preparative column chromatography done for isolating the reaction products before the analysis.

This allowed to identify the peak at 7 minutes of chromatogram I as triphenylphosphinoxide. A second experiment carried out without base in THF using the chiral (S,S)-DACH phenyl Trost Ligand gave unexpectedly, a 22:78 ST:AC ratio of the cyclized products which was unfortunately, the major AC product is not the one needed for the synthesis of Orthodiffene A.

This is clearly shown by the chromatograms I – III.

Peaks 2 and 4 of chromatogram II and peaks 1 and 2 of chromatogram I were assigned as the enantiomers of the AC core by comparison with the retention times obtained from the chromatogram on the cyclization products of the meso diol **12**. Peaks 1 and 3 were assigned as the ST core enantiomers. The ratio of the peak areas on chromatogram II, relative to the reaction with (S,S)-**L1** in THF without base, gave ST:AC in ratio 22:78.

The study on the Tsuji-Trost cyclization of the Xylitol derived triol was concluded at this point, without any assessment about the relative configuration of the cyclized products: NOE experiment were inconclusive in unveiling the relative stereochemistry and derivatization with Mosher's salts was impracticable.

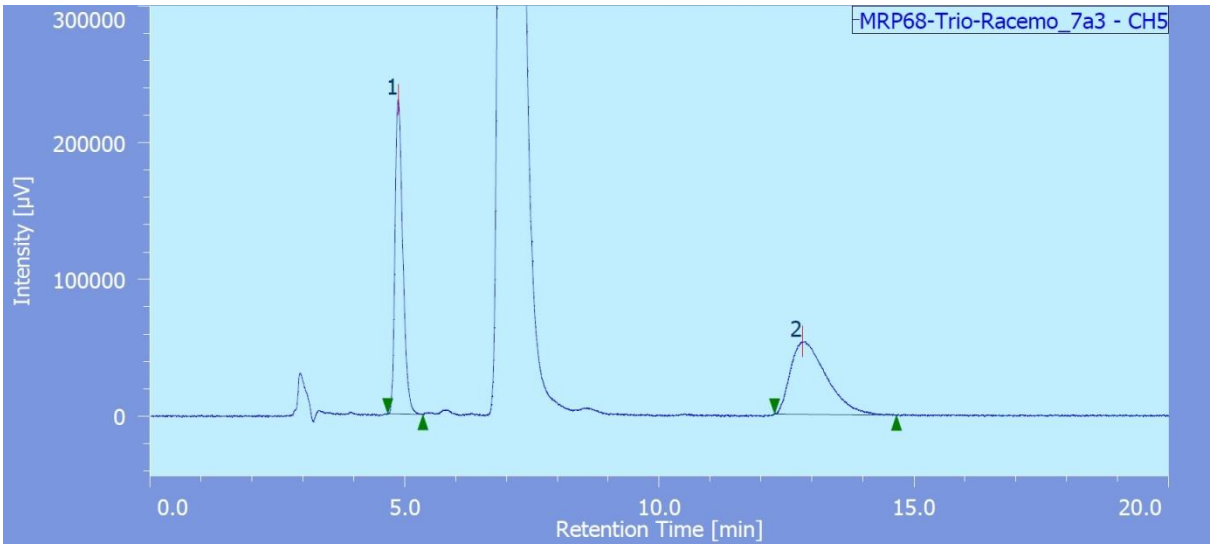


Figure 7.5.2.1 Cromatogram I (reaction product of entry 2 in Table 7.5.2.1)

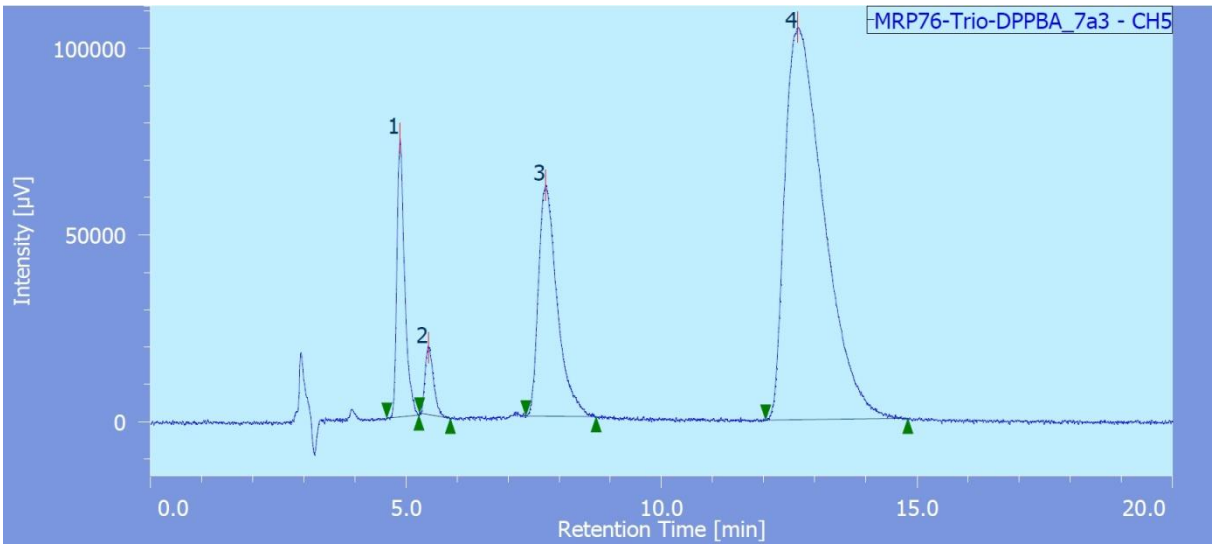


Figure 7.5.2.2 Cromatogram II (reaction product of entry 3 in Table 7.5.2.1)

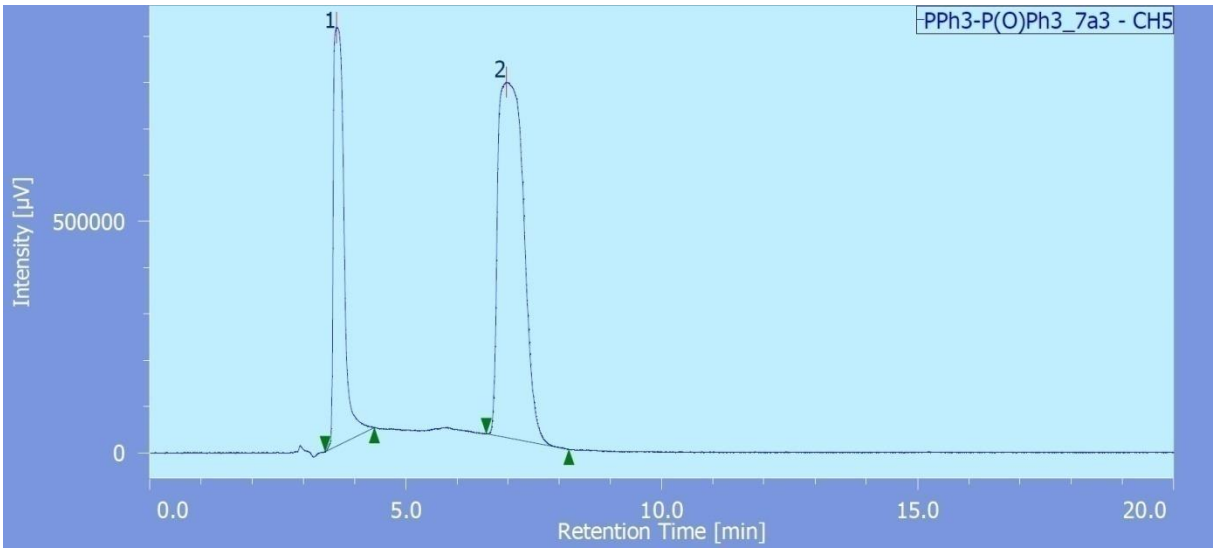


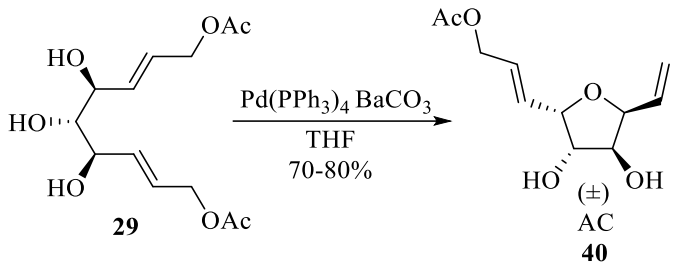
Figure 7.5.2.1 Cromatogram III obtained with HPLC elution of Ph_3PO and PPh_3

7.5.3 Conversion of THF core **40** into compound **64**

Even though the Xylitol approach has been proven unsuitable for the synthesis of Orthodiffene A, the cyclized AC THF core **40** was the starting point for a preliminary analysis on the transformations that the THF core should undergone anyway.

We therefore used compound **40** as model for the "achiral synthesis" of **27.**

Cyclization of triol **29** (its synthesis is analogue to **31** and will described in section 7.6.1) with achiral ligand triphenylphosphine was performed by treatment of compound **29** in THF with the $Pd(PPh_3)_4$ complex and Barium carbonate as base obtaining almost selectively compound 40, which bears the AC core as a racemic mixture.

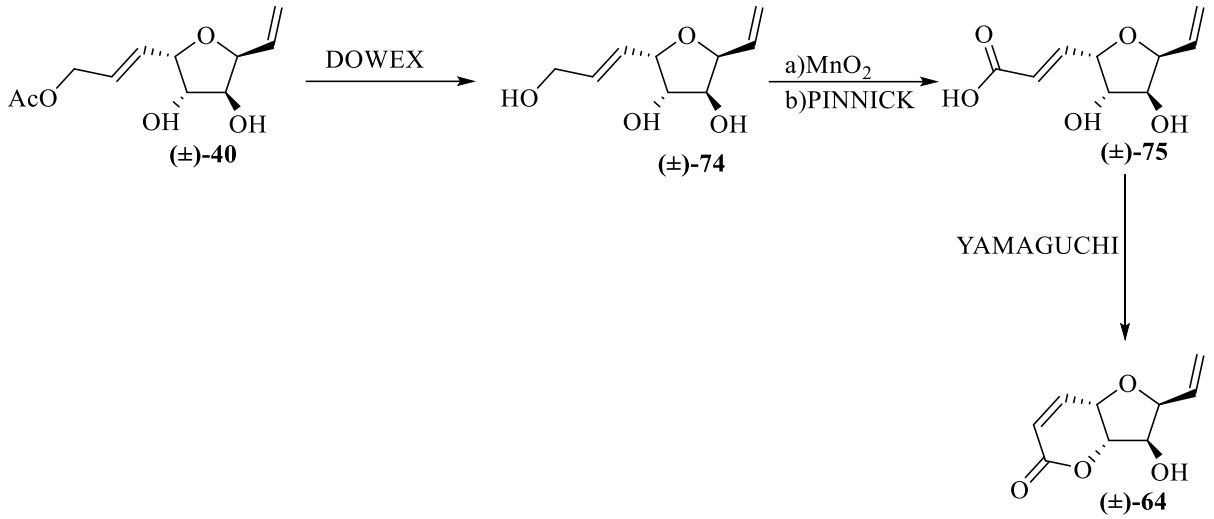


Scheme 7.5.3.1 Tsuji-Trost etherification applied on substrate **29**

The use of barium carbonate as base gave better yields than the cyclization performed in the same reaction condition but without any base addition (Table 7.2.1 entry three). This increase in yield has been ascribed to the Barium cation that coordinates the acetoxy anion (the leaving group of the etherification step). The effect is an increase of the catalyst turn over number by preventing the acetoxy anion to complex the catalyst and passivate it.

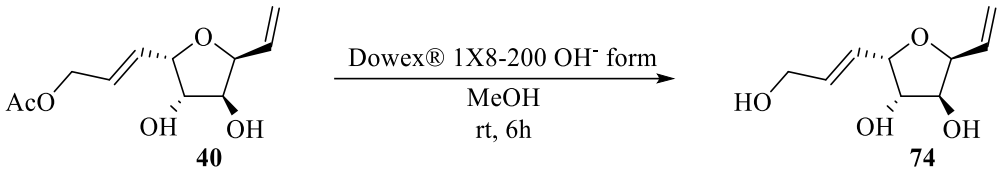
Barium forms also, with carbonate, a ionic couple with very low solubility: this feature is vital to prevent the hydrolysis in basic conditions of acetate ester groups, present both on reagent and products.

To reach compound **64** from the AC THF core the following synthetic procedure was planned.



Scheme 7.5.3.2 Synthetic procedure applied to reach compound **64**.

Hydrolysis of the acetal moiety was performed under mild conditions using the anionic exchange resin Dowex® 1X8-200 in its activated OH^-form.[66]



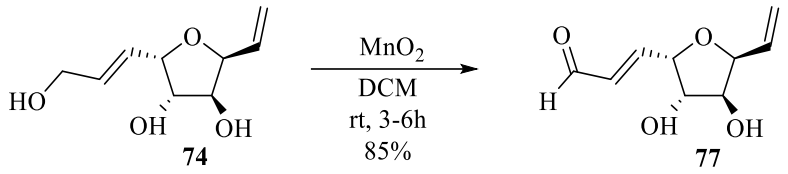
Scheme 7.5.3.3 Dowex® 1X8-200 anion exchange resin hydrolysis protocol

The resin in its Cl^- form was first exchanged in its OH^-activated form by repeated treatment with NaOH 0,1M solution followed by water washes.

Then, treatment of compound **40** in MeOH at room temperature with the activated resin under air afforded after 6h compound **74** in quantitative yield.

Oxidation of the thus obtained allylic alcohol into the corresponding acid revealed troublesome. However, two-step protocols were developed, both starting with the prior oxidation of the alcohol to aldehyde in a separate step (Scheme 7.5.3.5).

[66] G. Zanoni, S. Re, A. Meriggi, F. Castronovo, G. Vidari; Tetrahedron Asymmetry, 2001, 12, 1785-1792

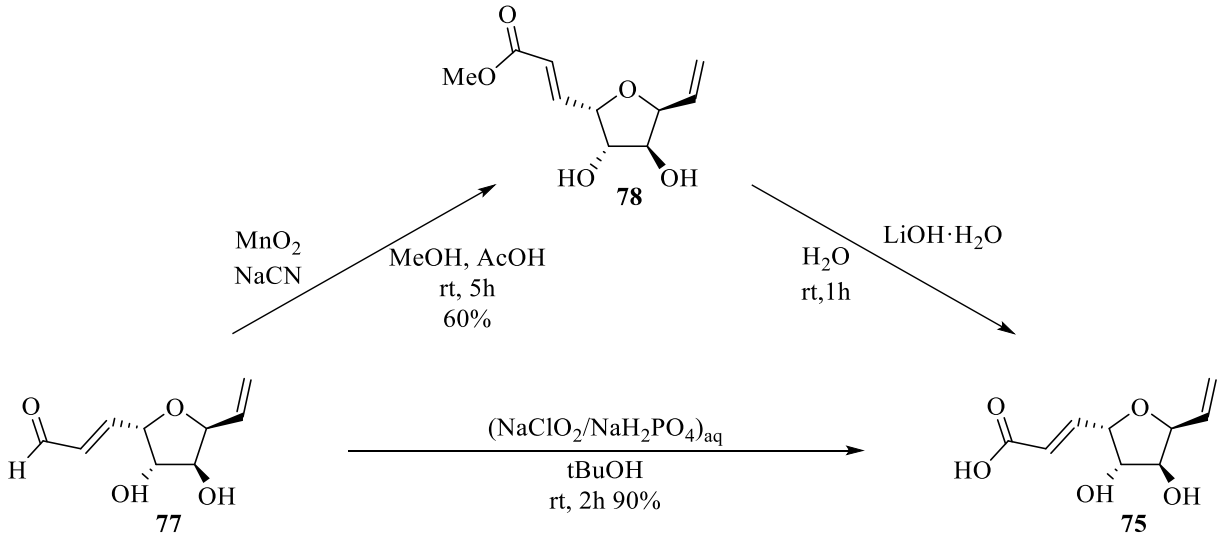


Scheme 7.5.3.4 Oxidation protocol with MnO_2 for the conversion of alcohol **74** into aldehyde **77**

Treatment of triol **74** with 30 equiv of Manganese dioxide added in six portions (over 4h) in DCM afforded in three to six hours aldeyde **77** with good yields.

The need to add MnO_2 in portions it is probably due to its passivation under the reaction conditions. Without this precaution, the conversion and the yield drops drastically.

Once obtained aldehyde **77,** two possible paths to the acid are practicable.[67]



Scheme 7.5.3.5 Two different approaches to the oxidation of aldehyde **77** to acid **75**

First, we tried to obtain the acid via the intermediate ester formation.

Addition by portions of 30 equiv of MnO_2 to the reaction flask where the aldehyde **77** was dissolved in methanol and acetic acid afforded in 5h the ester **78 (**Corey-Gilman-Ganem Oxidation).[68] Subsequenttreatment with 2 equivalents of Lithium hydroxide in water gave rapidly and quantitatively acid **75**.

In a later study we found that the less toxic (avoiding NaCN) Pinnick oxidation allows us to directly achieve the acid **75** from aldeyde **77** in a more efficient way.

[67] H. Kwart, T.J. George; J. Org. Chem., 1979, 44, 162-164

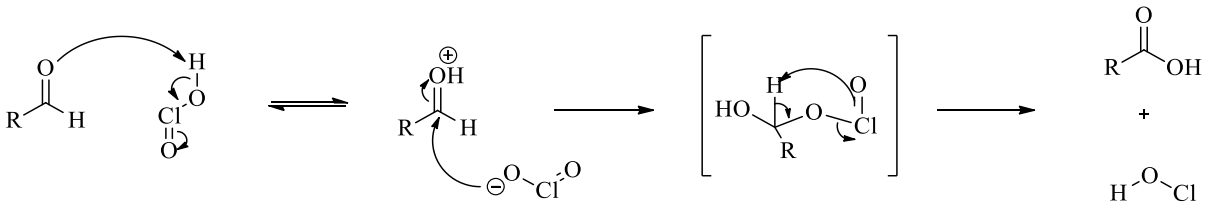
[68] Z. Wang; Comprehensive Organic Name Reactions and Reagents, Wiley & Sons, Inc, 2010

The Pinnick reaction is based on the oxidizing power of chlorous acid formed from chlorite anion under sufficiently acidic conditions, in this case monosodium phosphate is used as acidifying agent and the following equilibrium results active in the reaction solvent[69]

$$ClO_2^- + H_2PO_4^- \rightleftharpoons HClO_2 + HPO_4^{2-}$$

Once formed $HClO_2$ can oxidize an α,β-unsaturated aldehyde into the corresponding acid without touching the unsaturation. In some cases, the drawback of the Pinnick reaction could be the concurrent chlorination reaction.

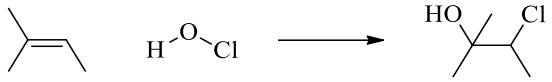
The following mechanism has been proposed for this step of the reaction



Scheme 7.5.3.6 Reaction mechanism for the Pinnick reaction

ClOH formed as byproduct then can consume $NaClO_2$ lowering yields or reacting with other compounds present in the reaction mixture. A scavenger sometimes is added to consume ClOH before it can react with the product.[50]

Here 2-methyl-2-butene is chosen, the mechanism by which this scavenger acts is illustrated in scheme below.



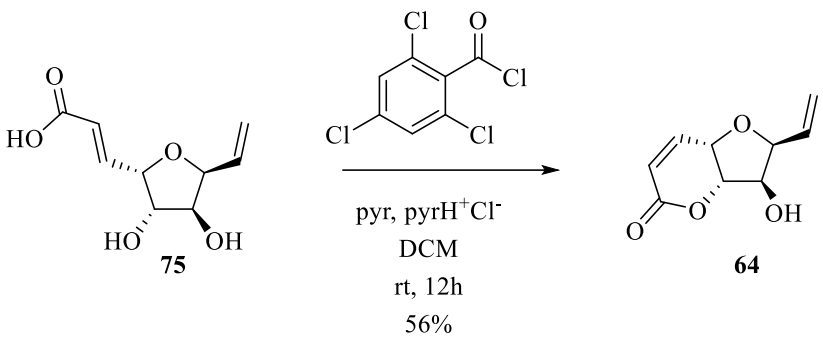
Scheme 7.5.3.7 Scavenger behavior of 2-methyl-2-butene towards ClOH

In both cases the carboxylic acid was hard to extract from the aqueous phase, even after multiple extraction steps including acidification of the medium. Then, the crude reaction mixture was absorbed on silica gel and purified via column chromatography in pure EA acidified with 3% formic acid. Following this method we could isolate the pure acid **75**.

For the lactonization reaction we found a convenient strategy utilizing a modified version of the Yamaguchi esterification.[70]

[69] E. Dalcanale, F. Montanari; J. Org. Chem, 1986, 51, 567-569

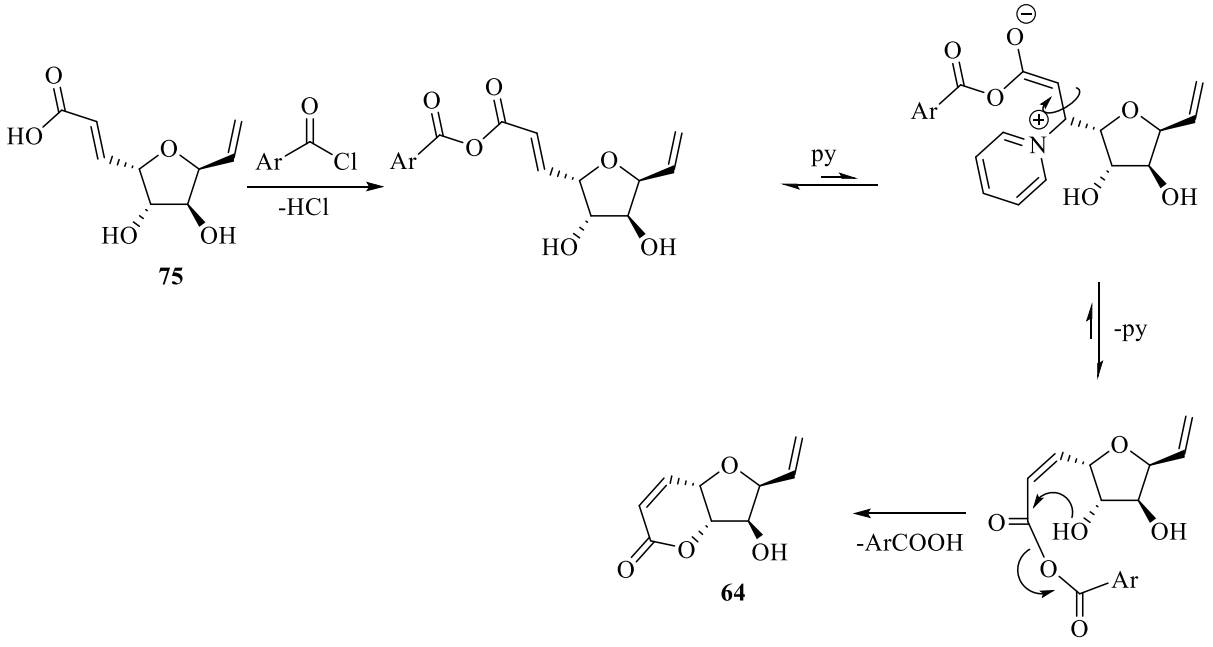
[70] S. Sunagawaa, H. Yamada, M. Naito, E. Yasui, M. Mizukami, M. Miyashita, S. Nagumo; Tetrahedron Letters, 2015, 56, 6693-6695



Scheme 7.5.3.8 Yamaguchi protocol applied for the lactonization of compound **75** to achieve **74**

This reaction provided a practical way to achieve both the lactonization and isomerization of the double bond conjugated to the carboxylic function. Treatment of compound **75** in dry pyridine as solvent and pyridine hydro-chloride as buffer with the Yamaguchi reagent 2,4,6-trichlorobenzoyl chloride afforded compound **64** with 56% yield. The noteworthy mechanism was convincingly proved by Ono et al.[71]

Considering the conditions in which we performed the reaction, the following mechanism has been proposed:



Scheme 7.5.3.9 Yamaguchi reaction mechanism illustrated on substrate **75**

[71] M. Ono, X.Y. Zhao, Y. Shidab, H. Akitab; Tetrahedron, 2007, 63, 10140-10148

First, the Yamaguchi reagent,4,6-trichlorobenzoyl chloride is attacked by the carboxylic acid with the formation of a mixed anhydride, much more reactive towards carbonyl substitution than the starting compound acid **75**.

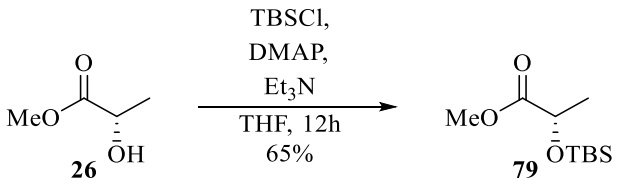
Pyridine used as solvent can act as soft nucleophile leading a Michael-type addition, thus allowing the free rotation of the α,β C-C bond. This zwitterionic species is very energetic. So, it tends to restore its original α,β-conjugated moiety. In case the nucleophile exits restoring the E configuration of the double bond, the reaction just goes back on the other end, when it exits generating the double bond in its Z configuration the thus formed α,β-unsaturated anhydride can be trapped by the hydroxy function at C3, affording irreversibely lactone **64**. Pyridine-hydrochloride is used as buffer.

With the compound **64** in hand, we chose not to perform a Mitsunobu protocol for the inversion of the hydroxyl function. Indeed, the literature already reports examples of this reaction applied on (very) similar substrates[47,72] and, most importantly, this was just a model study, using an achiral phosphine.

7.5.4 Synthesis of the terminal alkene **65**

We started the synthesis of alkene **65** from Methyl L-lactate **26.** We did not use ethyl lactate, as described in literature[37] because the methyl ester is cheaper. The s-absolute configuration was chosen because it is the right configuration for the synthesis of the natural (+)-Orthodiffene A.

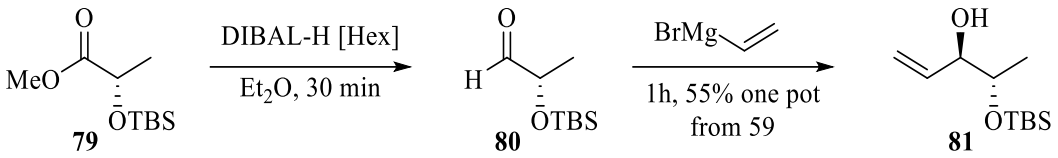
We started protecting the alcohol as TBS ether, which was achieved under standard protocol.



Scheme 7.5.4.1 Protection of s-methyl lactate **26** as TBS ether **79**

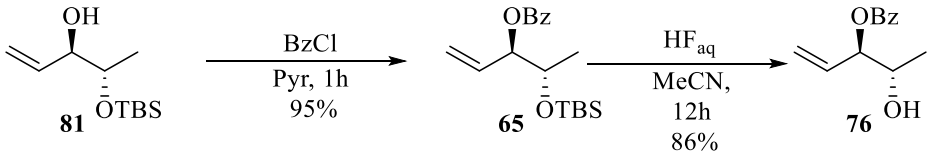
Thus, treatment of Methyl L-lactate **26** with TBSCl in dry THF in the presence of DMAP as nucleophile catalyst and Et_3N as base and buffer gave the corresponding TBS ether in 65% yield. A selective ester to aldehyde reduction followed by in-situ Grignard addiction was planned (scheme 7.5.4.2)[73]

[72] T.K.M. Shing, J.G. Gillhouley; Tetrahedron, 1994, 50, 8685-8698
[73] B. Schmidt, A. Biernat; Chem. Eur. J., 2008, 14, 6135-6141



Scheme 7.5.4.2 One-pot reduction of Ester **79** to aldehyde **80** and subsequent in-sityu addiction of vinyl Grignard

To achieve the reduction of ester **79** to the corresponding aldehyde, 1 equiv of DIBAL-H in hexane was added. After stirring for an hour at -78 °C, vinyl magnesium bromide was added to the reaction flask and the reaction temperature was allowed to reach room temperature. After 6 hours, the reaction was finished, and we were able to isolate compound **81** in 55% yield over two steps.
The allylic alcohol **81** was then finally benzoylated via standard procedure as depicted in scheme 7.5.4.3

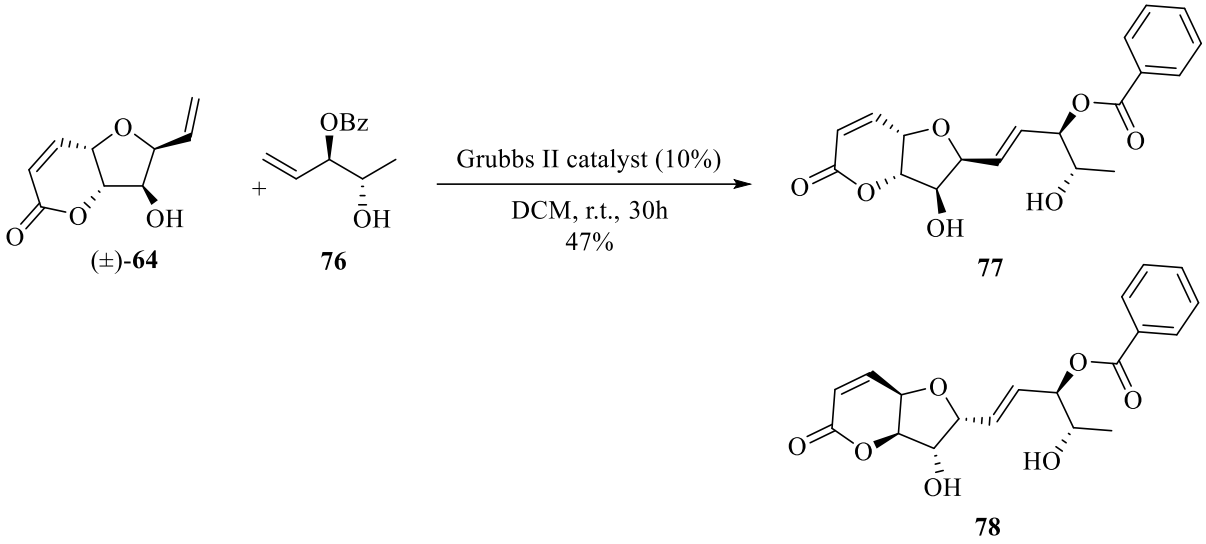


Scheme 7.5.4.3 Benzoylation of allylic alcohol **81** and subsequent TBS ether deprotection

Treatment of **81** with benzoyl chloride in pyridine gave the corresponding benzoyl ester **65** in 95% yield. Finally, deprotection of the silyl moiety *via* HF led to the formation of the desired compound **76**.

7.5.5 Cross-metathesis between alkenes **64** and **76**

With compound **76** and **64** synthesized, we tried to perform the metathesis reaction



(±)-**64** **76** **77** **78**

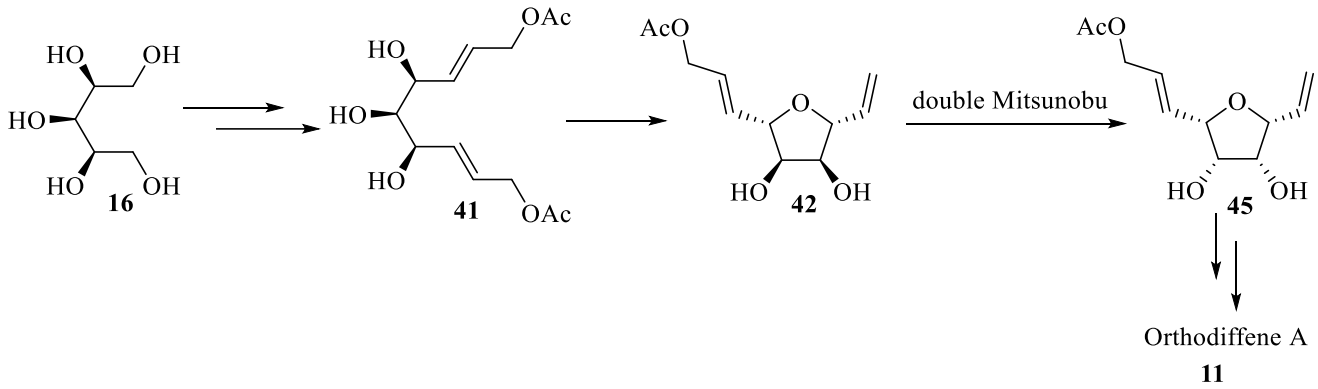
Scheme 7.5.5.1 Reaction scheme for the Methathesis reaction on **64** and **76** using the Grubbs II.

The reaction was successful and treating compounds **64** and **76** afforded the product in 47% yield as an inseparable mixture of two diastomers **77** and **78**.

7.6 Synthetic approach to Orthodiffene A starting from Adonitol 16

Following the retrosynthetic study outlined and in the light of the model study done to reach the construction of the lactofuranic core, the synthetic strategy we tried to apply is reported in scheme 7.6.1.

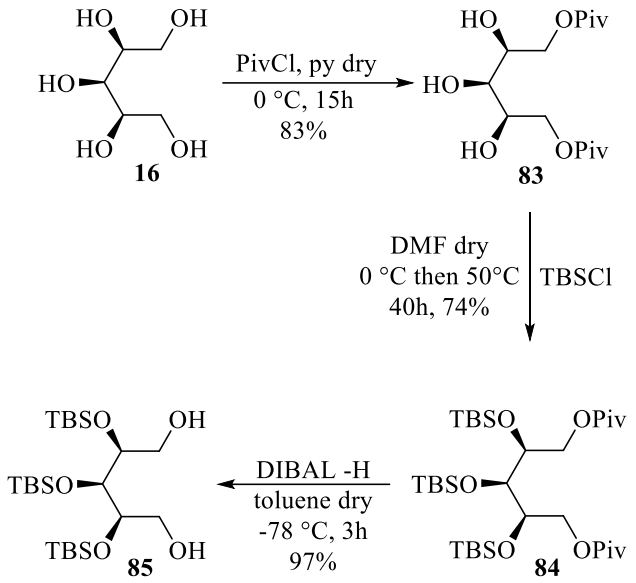
The first eight steps to reach key intermediate triol **41** starting from Adonitol **16** were carried out in the same way as they were done on Xylitol. Once synthesized compound **41** we achieved its enantio selective conversion to THF core. Then, the plan was to invert right after the cyclization the two stereocenters bearing the hydroxyl function of the THF core with a double Mitsunobu procedure.



Scheme 7.6.1 Rection scheme for the total synthesis of Orthodiffene A starting from Adonitol **16** and using the Tsuji-Trost etherification reaction as key reaction.

The synthesis started from the sugar alcohol Adonitol and proceeds exactly as with its epimer Xylitol. The first three steps of this synthesis followed a procedure already known in literature (scheme 7.6.2).[74]

[74] K. Toshima, K. Ohta, K. Yanagawa, T. Kano, M. Nakata, M. Kinoshita, S. Matsumura; J. Am. Chem. Soc., 1995, 117, 10825-10831



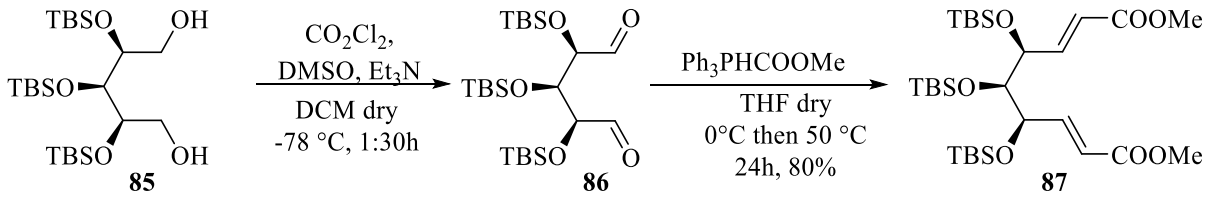
Scheme 7.6.2 Protocol for the selective protection of the secondary alcohols of Adonitol **16**

Adonitol **16** was first reacted with pivaloyl Chloride in dry pyridine at 0°C to afford compound **83** selectively pivaloylated at the two primary alcohols functions.

Triol **83** was then converted to compound **84** with TBSCl in dry DMF, hence introducing the silyl ether protection on the secondary alcoholic functions.

Selective deprotection of the ester function was achieved by reaction with 4.3 equivalents of DIBAL-H in dry toluene. Excess of this reagent was used to prevent the possible incomplete reduction of the pivaloyl ester to the corresponding aldehyde which would have possibly caused the formation of unwanted acetal byproducts.

With the secondary alcohols selectively protected, we could proceed to the carbon chain extension.

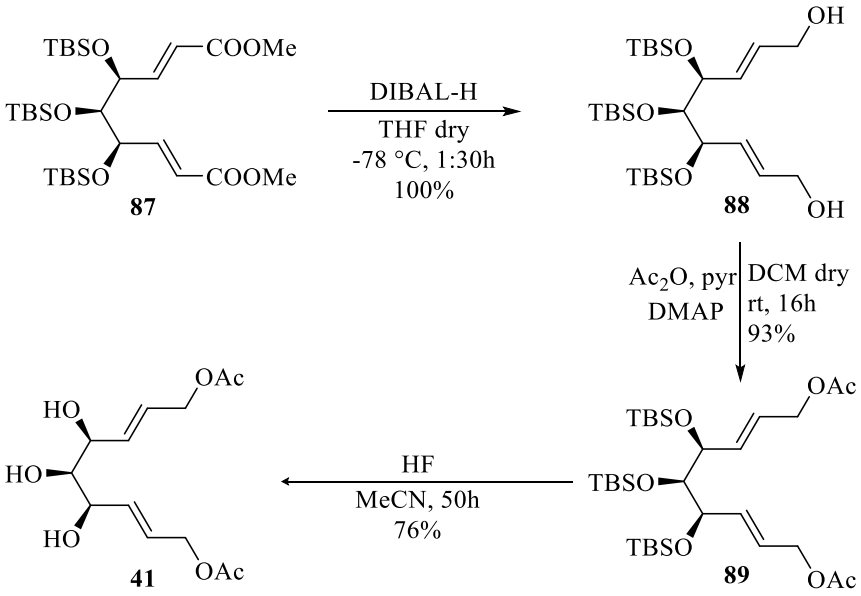


Scheme 7.6.3 Oxidation of primary hydroxyl functions and C-C bond forming on the obtained aldehyde **86** via a Wittig procedure

To this aim, we chose the well known elongation sequence (Scheme 7.6.3): Swern Oxidation to aldehyde, E-selective Wittig olefination with the stabilized ester ylide,[52] and DIBALH reduction to the corresponding allylic alcohols.[75]

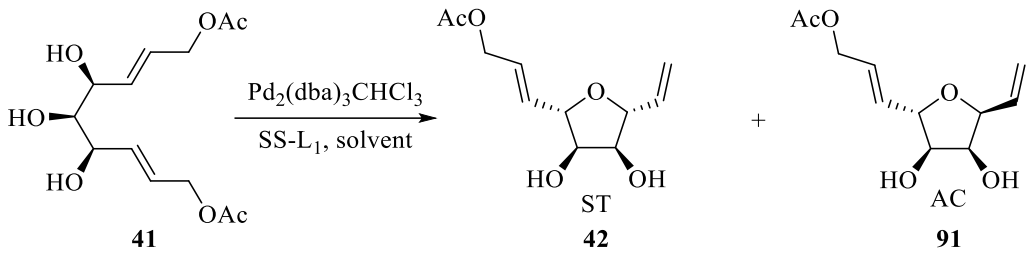
[75] R. Robiette, J. Richardson, V. K. Aggarwal, J. N. Harvey; J. Am. Chem. Soc., 2006, 128, 2397-2403

Hence, compound **85** was oxidized to the dialdehyde **86** utilizing a typical Swern oxidation reaction. Aldehyde **86** was then treated with $Ph_3PHCOOMe$ in dry THF, affording compound **87**.
At this point, compound **87** was converted into compound **41** via a three-step process (scheme 7.6.4) First, **87** was treated with DIBAL-H in dry THF to afford diol **88**.
The terminal hydroxyl functions of **88** were then acetylated using acetic anhydride in DCM with pyridine as buffer and DMAP as an efficient nucleophilic catalyst.



Scheme 7.6.4 Conversion of esters moieties of compound **87** into acetylated hydroxyls and successive silyl ether deprotection of secondary alcohols to reach compound **41**.

Subsequent treatment of diacetate **89** with HF in acetonitrile afforded the substrate **41,** ready for the cyclization step. With triol **41** in hand, we started to investigate the Tsuji-Trost asymmetric allylic etherification. The stereochemical outcome of the cyclization were extremely promising. Therefore, we decided to perform a methodological study on the reaction conditions to optimize our results.



Scheme 7.6.5 Stereochemical outcome of the Tsuji-Trost reaction on triol **41** using (S,S)DACH-Phenyl Trost Ligand and $Pd_2(dba)_3CHCl_3$ as Palladium source, reaction conditions were varied accordingly with table 7.6.1

N°	Solvent	Ligand	Pd	T (°C)	ST:AC	eeST	eeAC	Yield	Conv%
1	THF	31%	8%	r.t.	78/22	90.1%	35%	53%	100%
2	THF	21%	8%	r.t.	79/21	93%	22%	61%	100%
3	THF	21%	8%	0 °C	77/23	97%	41%	81.8%	100%
4	THF	13%	5%	r.t.	77/23	98%	12%	72.5%	100%
5	THF	13%	5%	0°C	77/23	95%	19%	55%	98%
6	THF	8%	3%	r.t.	78/22	96%	9%	83%	98%
7	THF	8%	3%	0 °C	80/20	98%	26%	60%	85%
8	**[a]THF**	**8%**	**3%**	**0° C**	**80/20**	**99%**	**20%**	**71%**	**84%**
9	**[a]THF**	**13%**	**5%**	**0° C**	**79/21**	**99.5%**	**/**	**74%**	**100%**
10	[b]THF/ DCM	13%	5%	0° C	79/21	99.1%	/	58%	89%
11	[c]THF	8%	3%	0°C	77/23	98%	27%	62%	82%
12	[d]THF	13%	5%	r.t.	58/42	/	/	76%	96%

Unless otherwise noted, reactions were carried out on substrate **41** (0.7 mmol), without base, solvent (7 ml, 0.1 M); d.r. ST:AC was determined by HPLC. Enantiomeric excess was determined by chiral HPLC, on Chiralpak AS-H columns. (a) 1.1 equivalents of $BaCO_3$ base were added to the reaction mixture. (b) 1.1 equiv of $BaCO_3$, solvent THF/DCM 7/3. (c) (R,R)DACH-phenyl Trost Ligand (d) (±)DACH-Phenyl Trost Ligand racemic.

Table 7.6.1 Methodological study for the Tsuji-Trost reaction to substrate **41** using the chiral ligand the (S,S)DACH-Phenyl Trost

We chose again the chiral (S,S)DACH-phenyl Trost Ligand ((S,S)-**L1**)), since it was expected to favor the ST core formation. Indeed, all the experiments tested showed the desired diastereoselectivity in favor of the ST core.

In the hope to increase the catalyst turnover, we tested a THF:DCM 7:3 mixture as solvent (see table 7.6.1 entry 10). However, this solvent mixture did not show satisfactory results. Toluene and DCM were not tried due to the insolubility of the substrate in those solvents.

We were also able to lower the catalyst loading to 3% achieving even better diastereomeric ratios and enantiomeric excess.

The use of Ba_2CO_3 as the lowering of temperature to 0°C significantly improved enantiomeric excesses as well as diastereomeric ratios.

The best reaction conditions were found to be THF as solvent with 5% catalyst loading at 0°C. Under these reaction conditions e.e.and d.r. were found to be 99.5% and AC:ST 79/21 respectively, with 75% total yield and complete conversion of the substrate.

In Figure 7.6.1 is reported the chromatogram of the best reaction conditions using the least Pd loading (entry 8 of Table 7.6.1).

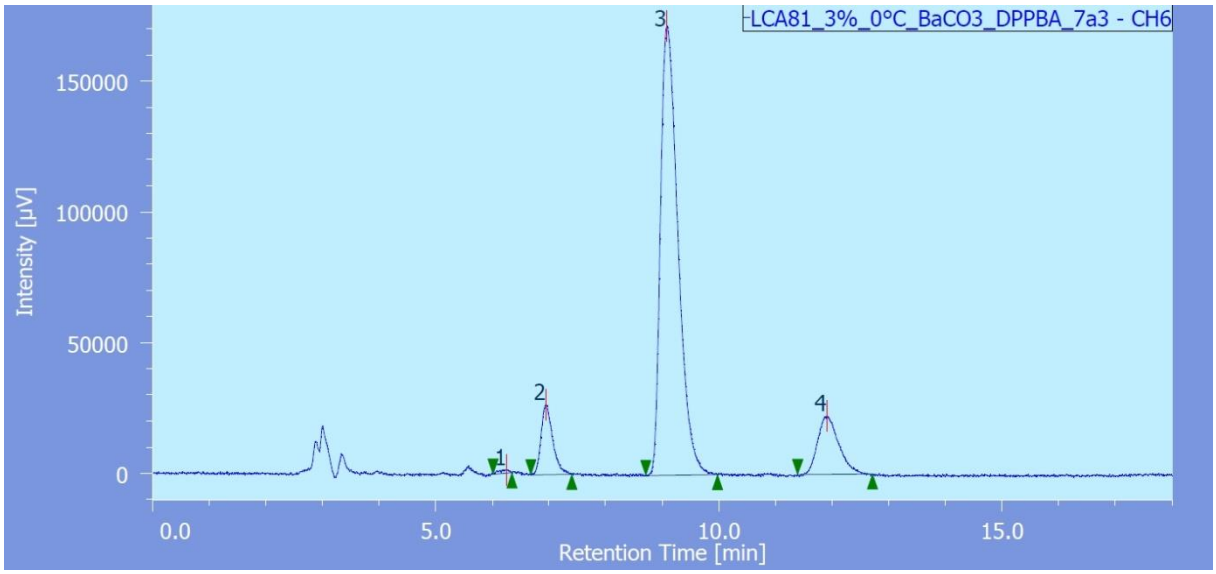


Figure 7.6.1 Chromatogram I relative to entry 8, Table 7.6.1.

Chromatogram II, Figure 7.6.2, shows the enantiomeric ratio obtained with ligand (R,R)-DACH-phenyl Trost Ligand (entry 11 Table 7.6.1) which clearly shows how the high d.r. is retained as well as the e.e of the ST core, but this time favouring the opposite configuration.

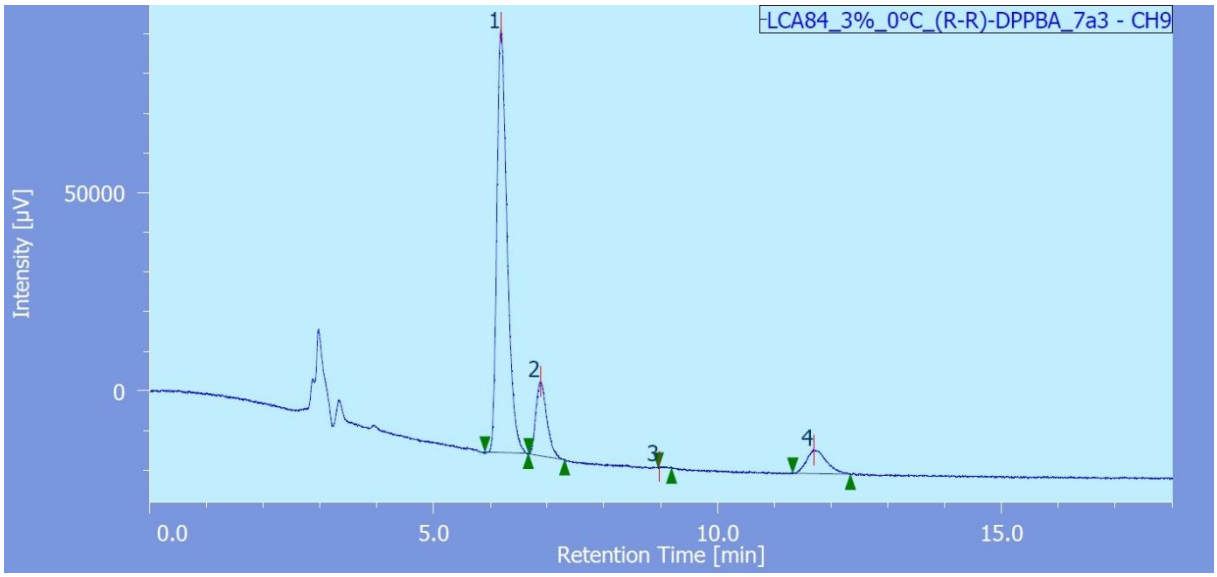


Figure 7.6.2 Chromatogram II relative to entry 11, Table 7.6.1 using (R,R)-DACH-phenyl Trost Ligand as ligand.

Figure 7.6.3 shows the chromathogram relative to the reaction conducted using racemic DACH-phenyl Trost Ligand. Although loss of enantioselectivity was, of course, expected, loss of diastereoselectivity was less trivial to anticipate.

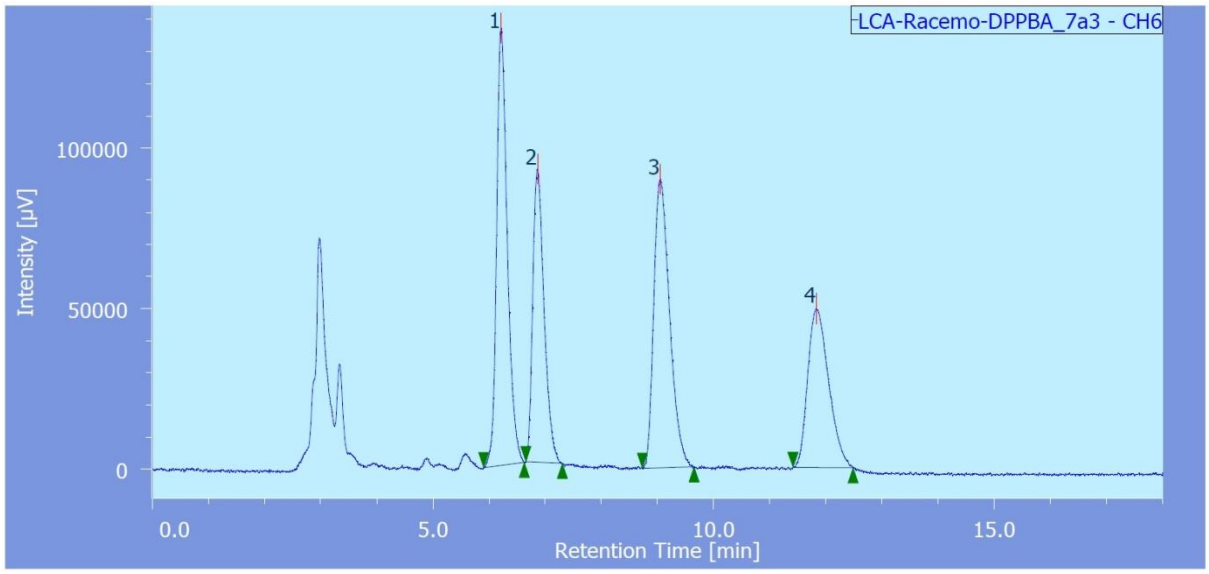


Figure 7.6.3 Chromatogram III registered on product entry 12, table 7.6.1 using as ligand for the cyclization racemic (±)DACH-Phenyl Trost Ligand

The major ST diasteromer **42**, from entry 9 was purified via silica gel chromathography (figure 7.6.4) and submitted to hydrolysis using a Dowex resin.

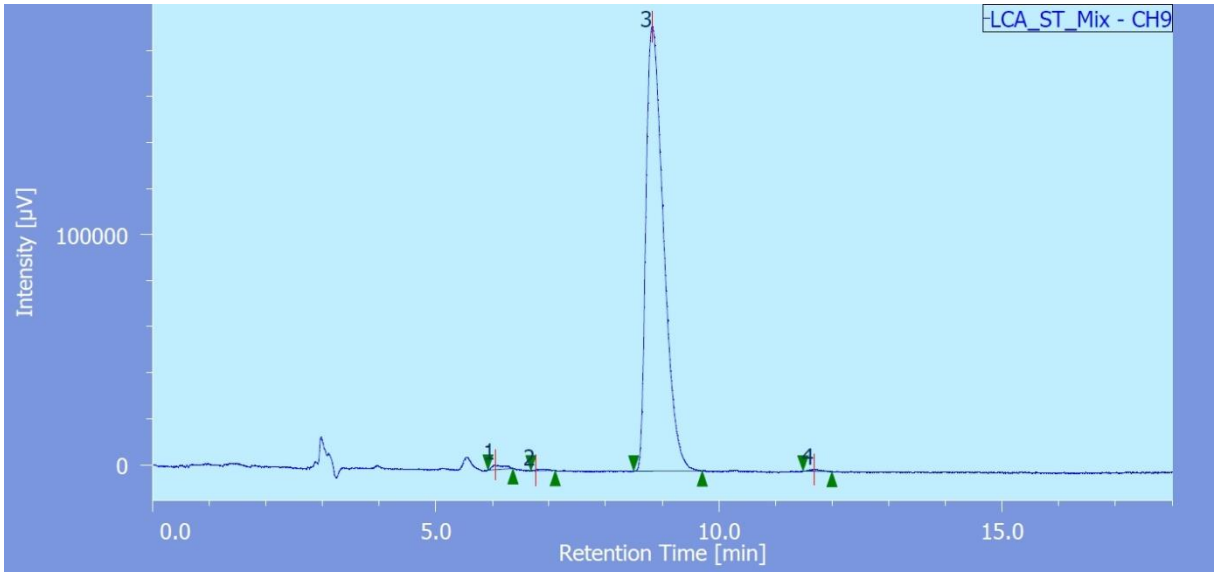
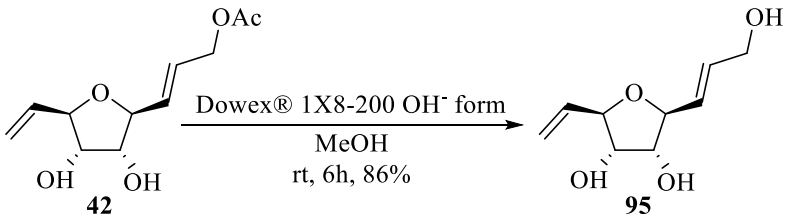


Figure 7.6.4 Chromatogram IV registered after column separation of diastereoisomers AC and ST

The resulting solid, triol **95**, was, after column chromathography, crystallized by slow diffusion of pentane into a solution of **95** in DCM. A simple crystal of the triol was submitted to X-ray diffraction analysis. The collected data are shown in the experimental section and the model of the molecule is represented in the Figure 7.6.5.



Scheme 7.6.6. Hydrolysis of **42** leadind to **95**.

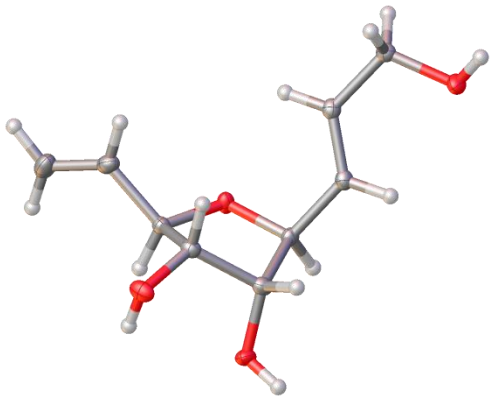
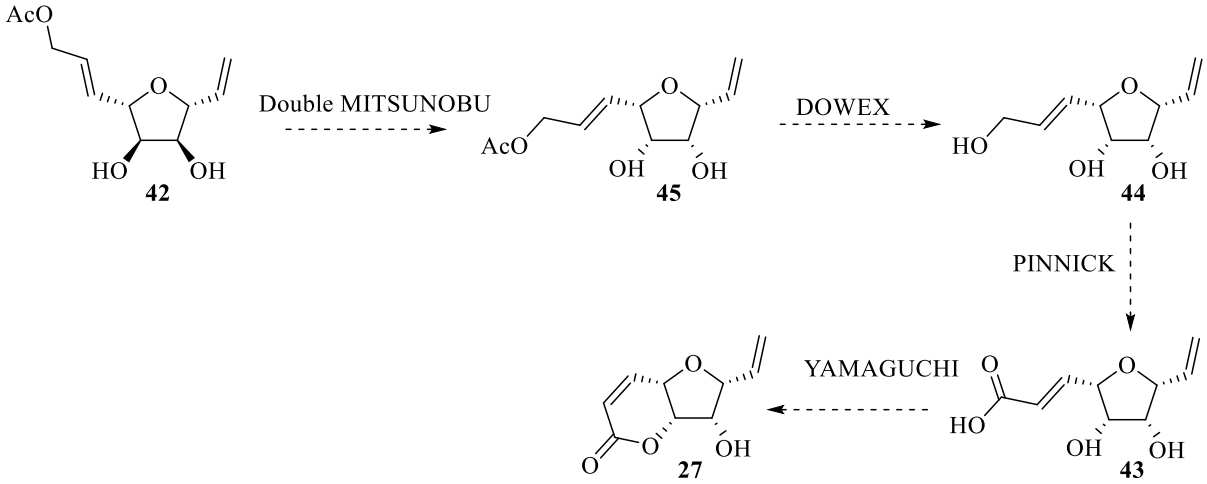


Figure 7.6.5 3D model of molecule **95** calculated via X ray diffraction measurements

Once obtained analytically pure ST core **42** we then proceeded with its chemical derivatization aiming to obtain compound **27**. The planned synthetic strategy is shown in the scheme 7.6.7.



Scheme 7.6.7 Planned synthetic strategy to convert diol **42** into lactone **27** according to our previous retrosynthetical analysis

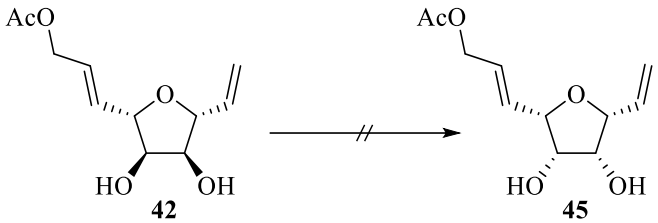
First, we hypothesized a double Mitsunobu reaction to invert both the adjacent hydroxyl groups in the THF core.

In case of success, we planned to continue our synthesis appling the same sequence as developed on the Xylitol derivative AC core **40**, i.e: a) acetate hydrolysis, b) MnO_2 oxidation to aldehyde, c) Pinnick oxidation to acid, d) Yamaguchi lactonization.

Unfortunately, the double Mitsunobu reaction failed.

Various Mitsunobu reaction procedures were applied changing phosphine, nucleophile, solvent and diazocompound but none achieved the double S_N2 on the two THF carbon atoms bearing the alcoholic functions.

Table 7.6.3 resumes all the conditions tested:



Solvent	Phosphine	Diazocompound	Nu-H	Protocol
THF[a]	PPh_3	DEAD	*p*NO_2PhCOOH	1
THF	$P(nBu)_3$	DEAD	*p*NO_2PhCOOH	1
THF	$P(nBu)_3$	DIAD	*p*NO_2PhCOOH	1

THF	$P(nBu)_3$	DIAD	$ClCH_2COOH$	2
THF	$P(nBu)_3$	DEAD	$pNO_2PhCOOH$	2
Toluene	PPh_3	DEAD	$pNO_2PhCOOH$	3
Toluene[b]	PPh_3	DEAD	$pNO_2PhCOOH$	3

[a] only reaction that didn't permitted to obtain the monosubstituted products

[b] the reaction was carried out on the monosubstituted mixture

Table 7.6.2 Trials done to perform a Mitsunobu reaction on substrate **42**

Protocol 1 consisted into adding the phosphine and the Nu-H one after the other to the stirred solution of alcohol **42** in THF under static Argon atmosphere, cooling the reaction flask to -78 °C and then adding the diazocompound dropwise. After the addition, the temperature was let to reach room temperature and stirring continued for 12 to 36 hours, depending on the case.[76]

Utilizing the $P(nBu)_3$, a less hindered phosphine than PPh_3, we were able to achieve the randomly monosubstituted compounds on one of the two hydroxyl functions. The use of DIAD instead of DEAD was of little improvement, although the reaction was certainly cleaner.

We so decided to follow another protocol, (protocol 2):[77]

To a solution of phosphine in THF the diazocompound was added dropwise at -20°C. To this first flask a solution of H-Nu in THF was cannulated. Lastly to resulting mixture was added the solution of the alcohol. The reaction was then allowed to reach room temperature and kept stirred for 12 to 24h depending on the case. This second protocol also failed, despite the use of additional more acidic nucleophiles.

Protocol 3[78] consisted in the dropwise addiction of DEAD to a suspension of triphenylphospine, 4-nitrobenzoic acid and alcohol **42** in toluene at 50°C.

Isolation and characterization of the products at the H-200 NMR showed in this case random mixture of both the monosubstituted compounds was effectively formed. We thus decided to redo the reaction from the monosubstituted mixture. Unfortunately, this mixture revealed to be unreactive.

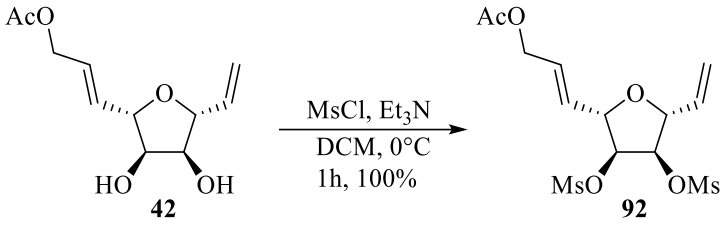
We concluded that the Mitsunobu reaction was unfeasible due to the steric hindrance experimented by the carbon atoms on the ring bearing the hydroxyl substituents.

We then planned to functionalize the hydroxyl functions as mesyl groups and then effect a double S_N2 with the rather unhindered oxygen-based nucleophile.

The double mesylation reaction took place uneventufully, and treatment at 0°C of the THFcore **42** with mesylchloride in DCM in presence of triethylamine base afforded mesylated compound **92** in

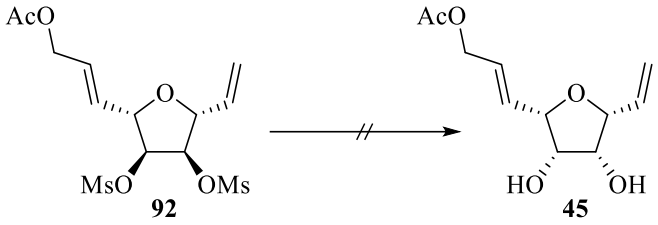
[76] Y. J. Shi, D. L. Hughes, J. M. McNamara; Tetrahedron Lett., 2003, 44, 3609-3611
[77] L. E. Overman, K. L. Bell, R. Ito; J. Am. Chem. Soc., 1984, 106, 4192-4201
[78] J. Harris, G. Doherty; Tetrahedron, 2001, 57, 5161-5171

quantitative yield. Purification via column chromatography on silica gel was not performed since the mesylate **92** was found to decompose in the column.



Scheme 7.6.8 Standard mesylation procedure applied on compound **42**

The substitution reaction on the mesylate **92** was then tried. Table 7.6.4 resumes all the reaction carried out.



REACTANT	COUNTER ANION	COMPLEXANT	SOLVENT	YIELD
KO_2		18-Crown-6	DMSO	/
KOH		18-Crown-6	DMSO/DME	/
KOAc		18-Crown-6	DMF	/
CsOAc		/	CH_3CN	/

Table 7.6.3 S_N2 tests on compound **70** different reaction with different reaction mechanism were involved

Counter anion complexant 18-Crown-6 was used with potassium as to have a naked charged nucleophile to favor the S_N2 mechanism. However, this strategy mt with failure.

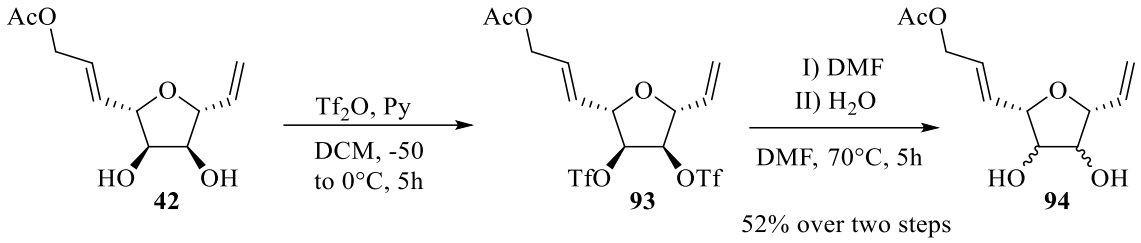
None of the protocols above outlined worked either at rt and 60°C. When using potassium superoxide and hydroxide we always obtained untractable crude mixtures, while with both acetates the reaction substrate **92** was still untouched after a week of stirring.

By increasing the temperature at 100°C with KOAc in DMF we could only observe the formation of the product of double elimination (the furan core).

We then came out with a different strategy outlined in the scheme 7.6.9.

We converted both hydroxy groups into the corresponding triflates and then we tried to perform the nucleophilic substitution by using the not basic DMF as nucleophile. Unfortunately, we observed in

the ^{1}H-NMR of the product many signals splitted. We ascribed this result as presence of a mixture of diastereomers of the desired product due to a concomintant S_N1 and S_N2 mechanism of the reaction.



Scheme 7.6.9. Concomintant process S_N1 and S_N2 in the formation of **94**.

8. Conclusions

Due to the difficulties encountered during the inversion of the stereocenters on the THF core **42** we couldn't complete the synthesis of the target molecule Orthodiffene A.

Nevertheless, the Tsuji-Trost reaction on triol **41** was successful to achieve outstanding levels of diastero and enantioselectivity making it a convenient method for the building of tetrasubstituted THF cores of the type of molecule **42.** This core can be used as key synthetic intermediates for the construction of other natural molecules than Orthodiffene A, a research line that is currently in development in our laboratory.

We achieved anyway the synthesis of two new enantiopure diastereoisomers of Orthodiffene A **77** and **78** by performing a "racemic" cyclization on the meso triol system **29** followed by a cross-metathesis with a chiral enantiopure terminal alkene obtained from L-lactate. The two diasteromers obtained **77** and **78** could be separated by preparative HPLC to evaluate their biological activity.

Part 2. PYRROLIDINE VIA DESYMMETRIZATION OF DIAMINOMESO

9. Desymmetrization of diaminomeso via Au(I) catalysis

In the last years a considerable effort has been devoted to develop chiral gold catalysts. There are in this field intrinsic difficulties ascribed to the linear coordination favored by Au(I): the chiral ligand (L*) and the substrate are on opposite sides of the metal center; therefore, the substrate is displaced from the chiral environment, at the same time both, the L*-Au bond and Au-substrate bond retain free rotation and unrestricted bonding. Additionally, gold-catalyzed addition reactions of nucleophiles to π-bonds are generally proposed to proceed through outer-sphere pathways.
To overcome such intrisic difficulties, three main strategies have been successfully implemented in the development of homogeneous gold-catalyzed enantioselective reactions[79]:

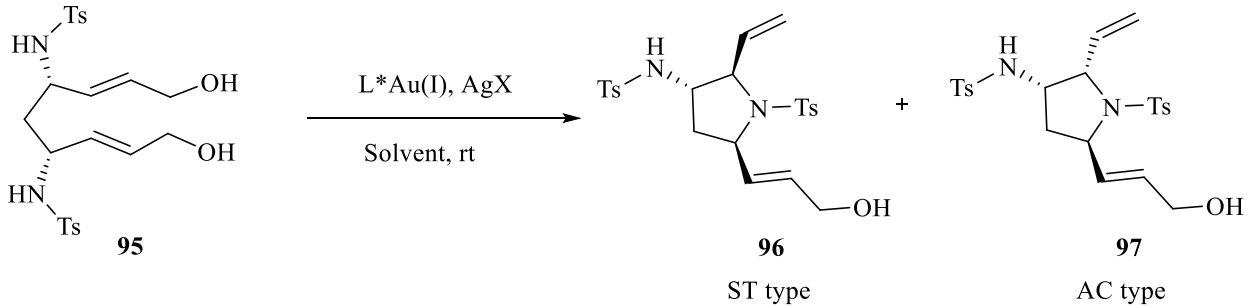
- Bimetallic gold complexes with atropisomeric bisphosphines ligands. Although it remains unclear whether aurophilic interactions between the individual gold centers play a role in the asymmetric induction, it is clear that the second phosphine gold center is essential for enantioselectivity and chiral induction.
- Monodentate phosphoramidite-type ligands have been employed in enantioselective gold catalysis.
- Chiral counteranions to achiral cationic gold(I) catalysts.

Dramatic differences in reactivity favoring alkynes and allenes over alkenes, is generally observed in gold-catalyzed hydrofunctionalization reactions of π-bonds. However, allylic alcohols exhibit enhanced reactivity toward nucleophilic addition. The alkylgold species generated form nucleophilic addition to the π-bond of allylic alcohols can undergo a β-hydroxyl elimination, thereby circumventing the requirement for an unfavorable protodeauration of an alkylgold species.[79] The mild reaction conditions of gold(I)-catalyzed transformation of allylic alcohols make them ideal substrates for enantioselective gold catalysis. Bandini and co-workers disclosed the first report on enantioselective gold-catalyzed alkylation of indoles with allylic alcohols.[80] In 2012, the same group reported a detailed mechanism for this reaction.[81] The DFT calculation support a stepwise S_N2' process, involving antiauroindolination of the olefin, proton-transfer, and a subsequent anti-

[79] W. Zi, F. D. Toste; Chem. Soc. Rev., 2016, 45, 4567-4589
[80] (a) M. Bandini, A. Gualandi, M. Monari, A. Romaniello, D. Savoia, M. Tragni; Journal of Organometallic Chemistry, 2011, 696, 338-347; (b) P. Mukherjee, R. A. Widenhoefer; Angew. Chem. Int. Ed., 2012, 51, 1405-1407
[81] M. Bandini, A. Bottoni, M. Chiarucci, G. Cera, G. P. Miscione; J. Am. Chem. Soc., 2012, 134, 20690-20700

elimination. The triflate counterion was shown to play a pivotal role in the reaction by forming strong H-bonds with the indole NH and the allylic hydroxyl group and assisting in the proton transfer process. Aside from indole and alcohol, the amine group has also been employed as the nucleophile in the gold-catalyzed allylic substitution reactions. Widenhoefer and co-workers worked on the dehydrative amination of allylic alcohols with carbamates forming five- and six-membered nitrogen heterocycles with 90% ee and 91% ee, respectively.[80]

We decided then to investigate this synthetic pathway for the synthesis of the core **96** and **97** by the desymmetrization of the meso tosyldiamine system **95** in order to obtain a highly functionalizable pyrrolidine core (scheme 9.1).

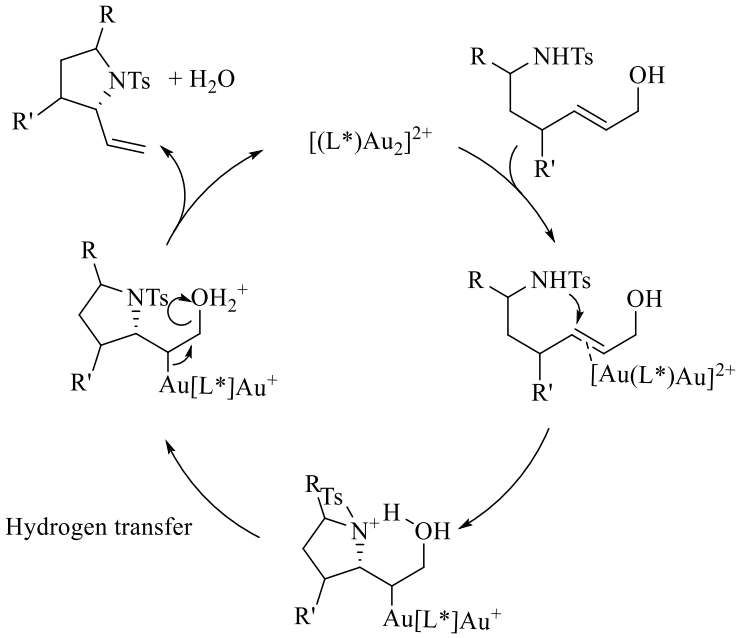


Scheme 9.1 desymmetrization of the meso tosyldiamine system **95**

9.1 Stereochemical features of the reaction

We thus decided to study the gold(I)-catalyzed allylic amination of the meso diamine **95**.

According to closely reported reactions,[80] the mechanism of this reaction is expected to involve an S_N2' mechanism, as illustrated in scheme 9.1.1.



Scheme 9.1.1. mechanism proposed for the Au(I) catalyzed key step.

The key steps are hereby summarized:

- π-complexation of the alkene on the gold(I) complex
- outer-sphere anti-addition of the nucleophile and anti-elimination of the hydroxy group, perhaps facilitated by an intramolecular N-H-O hydrogen bond, which is proposed to be crucial for the proton transfer step
- anti-gold elimination with the simultaneous decomplexation

Alternatively, syn-substitution is also consistent with a mechanism involving σ-activation of the hydroxy group followed by concerted S_N2' displacement can be considered. Indeed, Toste et al. have demonstrated the formation of σ-complexes of cationic gold with σ-donor ligands generating a chiral Brønsted acid activated by complexation with gold.[82] However, the failure of either triflic acid or $BF_3 \cdot OEt_2$ (10 mol %, 25°C, 48 h) to catalyze the cyclization of **95** argues against a σ-activation pathway for this allylic amination.

9.2 Synthesis of *meso* diamine system

The Scheme 9.2.1 shows the pathway leading to the synthesis of the meso diamine system **95**. Cyclopentendiol **99** is commercially available, but as it is quite expensive, we decided to synthetize

[82] C. H. Cheon, O. Kanno, F. D. Toste; J. Am. Chem. Soc., 2011, 133, 13248-13251

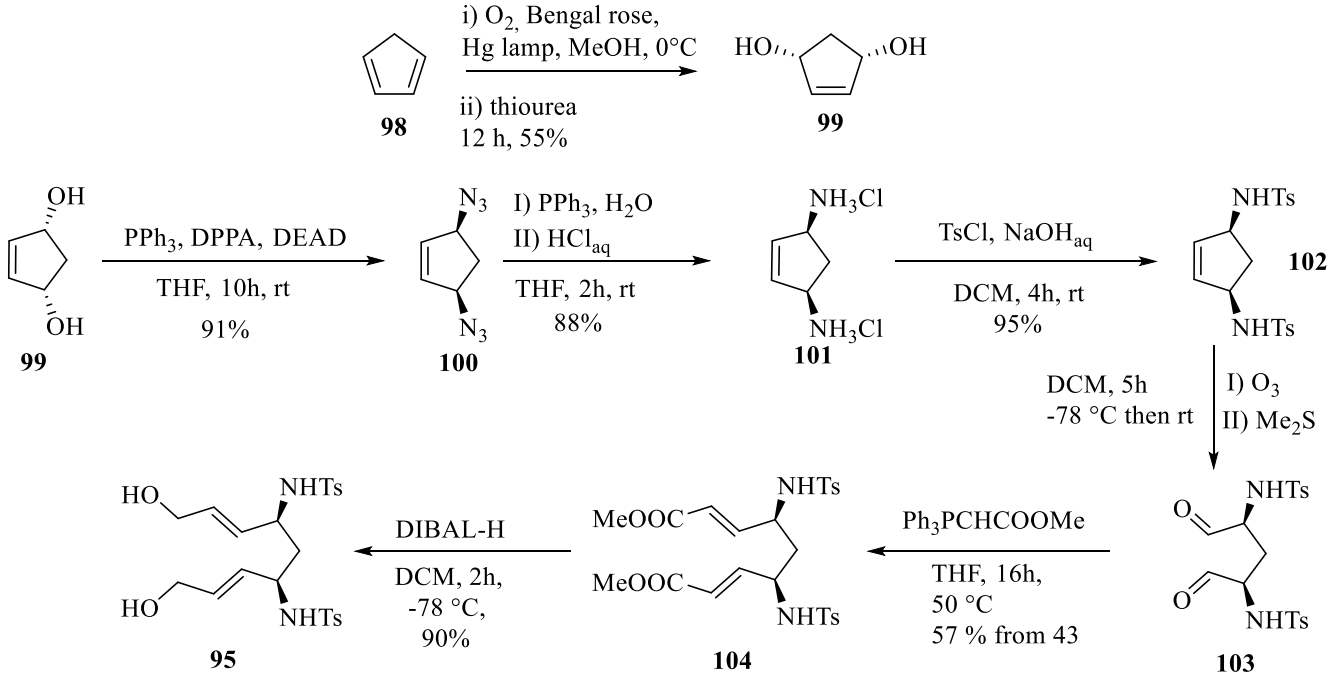
it through an oxygen photocycloaddition on cyclopentadiene, by employing Bengal rose as photosensitizer and by irradiating with Hg lamp.[83]

After decomposition of the intermediate endoperoxide, by treating with thiourea as reducing agent, we obtained the desired *syn*-1,3-cyclopentendiol **99** in moderate yield.

In order to convert the two hydroxyl functions into the corresponding amino functions we decided to follow a sequence of azidation/azido-to-amine reduction.

Accordingly, we converted then the cyclopentendiol **99** into the corresponding diazide derivative **100** in a Mitsunobu-like fashion by using the DPPA-DBU method.[84]

As to the azide reduction, we chosed the Staudinger reduction as it takes place under mild conditions. Accordingly, triphenylphosphine reacted with the azide **100** to generate a phosphazide, which loses N_2 to form the corresponding iminophosphorane. Aqueous work up led to the amine and the very stable phosphine oxide. We chose to convert the amine to the corresponding hydrochloride salt **101** for practical reasons: analytical pure product could be obtaneid just by recrystallization from methanol. Treatment of the dihydrochloride **101** with TsCl/NaOH gave the ditosyl derivative **102,** which was converted into the dimethylester **104** through an ozonolysis/Wittig sequence. Finally, the desired meso ditosylamine **95** was obtained after reduction with DIBAL-H.



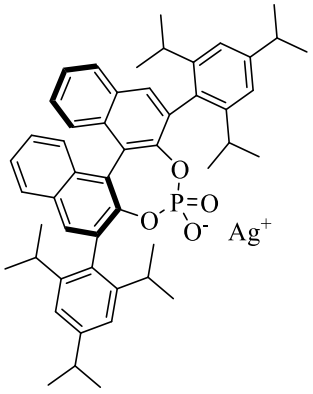
Scheme 9.2.1. Reaction sequence leading to the diamine meso system **95**.

[83] K. Mukund, R.D. Nageswar, M. Chorghade, S. Mukund; Heterocycles, 2009, 77, 909-925

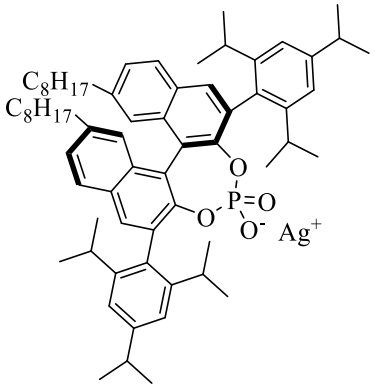
[84] T. Shioiri, S. Ninomiya, S. Yamada; J. Am. Chem. Soc., 1972, 94, 6203-6205

9.3 Screening of the reaction conditions

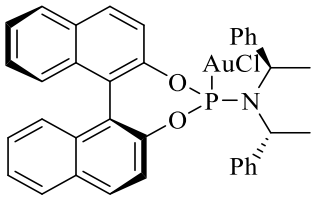
In order to evaluate the applicability of the asymmetric gold catalysis to the planned cyclization, we undertook a survey of reaction conditions (ligand, gold-source, counterion). In the following tables are summerized the data of the methodological study. The ligands used here below are commercially available by Sigma-Aldrich.



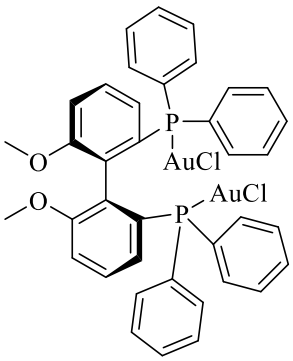
Ag[105]



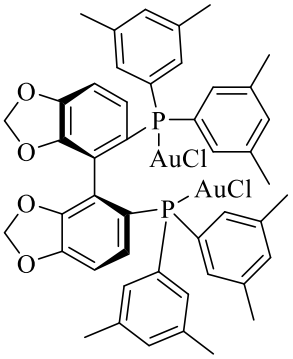
Ag[106]



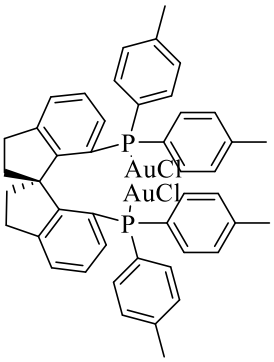
107(AuCl)



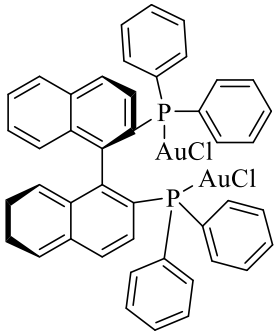
108(AuCl)$_2$



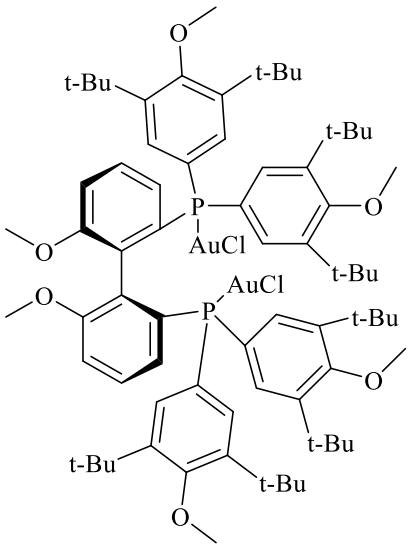
109(AuCl)$_2$



110(AuCl)$_2$

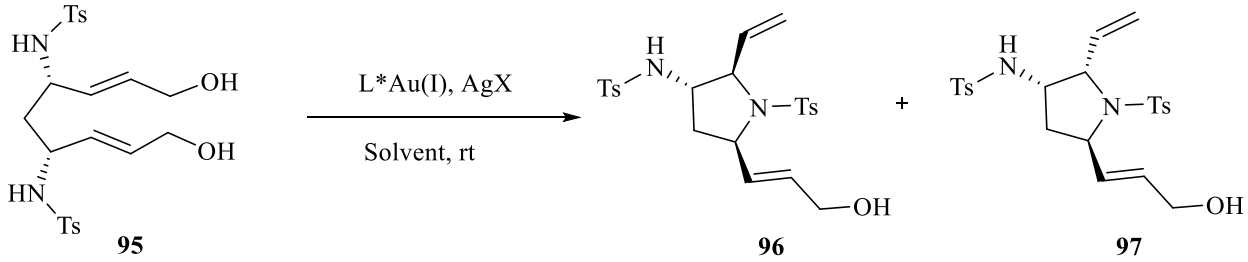


111(AuCl)$_2$



112(AuCl)$_2$

[(S)-3,5-t-Bu-4-MeO-MeOBIPHEP](AuCl)$_2$



95 **96** ST type **97** AC type

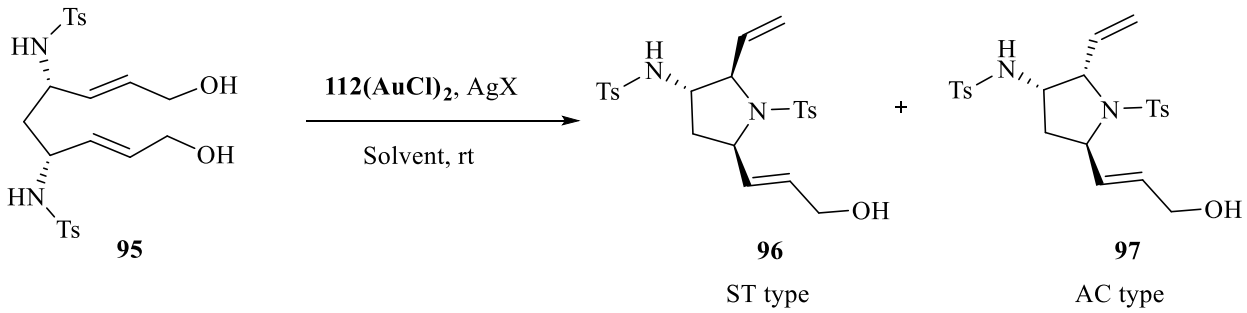
Entry	Au	Ag	Solvent	Y	dr(ST:AC)	ee (ST)
1	Ph_3PAuCl	AgOTf	DCM	75%	100:0	/
2	Ph_3PAuCl	**Ag[105]**	PhMe	No reaction	/	/
3	Ph_3PAuCl	**Ag[106]**	PhMe	No reaction	/	/
4	**108(AuCl)$_2$**	AgOTf	DCM	78%	100:0	43%
5	**109(AuCl)$_2$**	AgOTf	DCM	70%	100:0	26%
6	**110(AuCl)$_2$**	AgOTf	DCM	75%	100:0	34%
7	**111(AuCl)$_2$**	AgOTf	DCM	84%	100:0	28%
8	**107(AuCl)**	AgOTf	DCM	/	/	/
9	**112(AuCl)$_2$**	**AgOTf**	**DCM**	**95%**	**100:0**	**76%**

Unless otherwise noted, reactions were carried out at room temperature, Au catalyst (5 mol%), Ag counteranion (10 mol%), substrate **95** (0.2 mmol), solvent (2 ml, 0.1 M). d.r.(ST:AC) and enantiomeric excess was determined by chiral UHPLC, on Kromasil 3-AmyCoat RP. Elution (isocratic): Water (0,2% HCOOH)/MeCN (0,2% HCOOH) = 65/35, UV detection: λ = 204 nm.

Table 9.3.1 Stereochemical study on the stereochemical outcome of the desymmetrization of the meso diamine **95** using different ligands, counterion and solvents.

First, we considered three types of chiral environments: a) chiral C_2 symmetric phosphine ligands (**108**, **109**, **110**, **111**, **112**), b) a monodentate phosphoramidite-type ligand (**107**), c) chiral counteranions (Ag-TRIP derivatives **105** and **106**). Surprisingly, only the dinuclear gold complexes formed by the chiral C_2 symmetric ligands were able to promote the ring-closure of **95**.

It turned out that the (S)-3,5-tBu-4-MeO-MeOBIPHEP **112** proved to be the best ligand, probably due to the bulkiness, leading to the diasteroselective formation of the ST core in 95% yield and ee_{ST} = 76% (entry 9, table 9.3.1). The relative configuration was demostrated by the 2D-NMR NOESY. Then, we proved the crucial role of the solvent and of the counterion for both reaction rate and stereoinduction, with NTf_2^- (bis(trifluoromethanesulfonyl)imide) acting as the best not coordinated counterion. NTf_2^- is also the conjugate base of the strongest acid used. (entry 9, table 9.3.2).

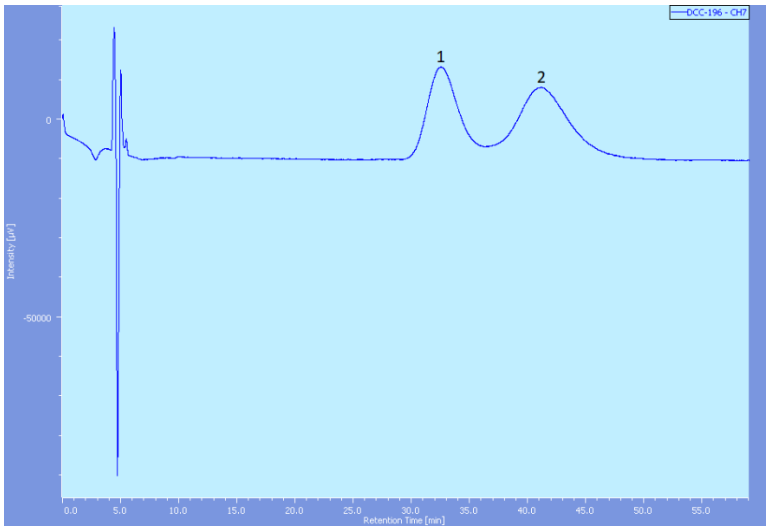


Entry	Ag (I)	Solvent	Y	dr(ST:AC)	ee (ST)
1	AgOTf	DCM	95%	100:0	76%
2	AgOTf	DME	<5%	/	/
3	AgOTf	PhMe	70%	100:0	78%
4	AgOTf	Dioxane	85%	100:0	64%
5[a]	$AgClO_4$	Dioxane	>99%	100:0	87%
6	$AgClO_4$	Dioxane	78%	100:0	88%
7	$AgClO_4$	DCM	>99%	100:0	24%
8	$AgClO_4$	THF	29%	/	/
9	$AgNTf_2$	Dioxane	>99%	100:0	91%
10	AgOTs	Dioxane	<5%	/	/

Unless otherwise noted, reactions were carried out at room temperature, **112(AuCl)$_2$** catalyst (5 mol%), Ag counteranion (10 mol%), substrate **95** (0.2 mmol), solvent (2 ml, 0.1 M). d.r.(ST:AC) and enantiomeric excess was determined by chiral UHPLC, on Kromasil 3-AmyCoat RP. Elution (isocratic): Water (0,2% HCOOH)/MeCN (0,2% HCOOH) = 65/35, UV detection: λ = 204 nm. (a) $AgClO_4$ (20 mol%) was employed.

Table 9.3.2 Stereochemical study on the stereochemical outcome of the desymmetrization of the meso diamine **95** using different ligands, counterion and reactions conditions.

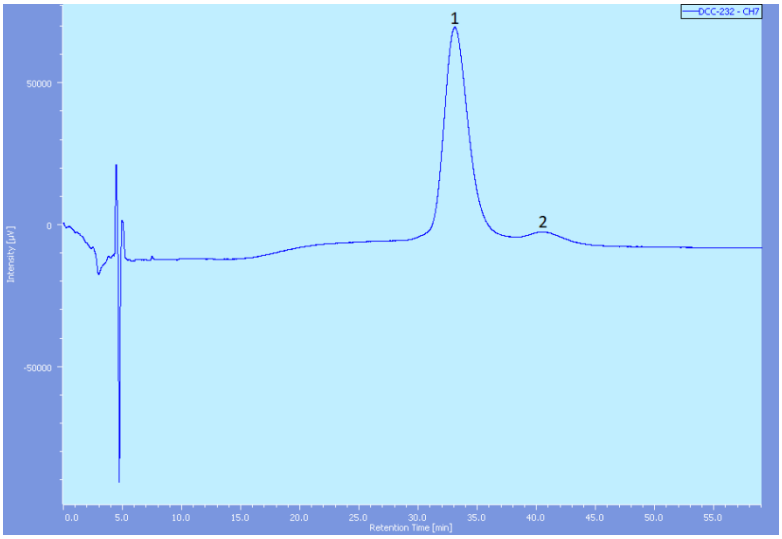
Chromatogram I, Figure 9.3.1 shows the enantiomeric profile of the reaction product obtained in achiral conditions (entry 1, Table 9.3.1).



Peak number	Description	A%
1	ST enantiomer 1	50.4
2	ST enantiomer 2	49.6

Figure 9.3.1 Chromatogram I registered on the product of entry 1, Table 8.3.1.

Chromatogram II, Figure 9.3.1 shows the enantiomeric profile of the reaction product obtained in the best conditions found (entry 9, Table 9.3.2).



Peak number	Description	A%
1	ST enantiomer 1	95.6
2	ST enantiomer 2	4.4

Figure 9.3.2 Chromatogram II registered on the product of entry 9, Table 8.3.2.

10. Conclusions

The study of the Au(I)-catalyzed asymmetric allylic etherification of *meso* diamine **95** was undertaken, to find an efficient stereoselective strategy to a functionalized pyrrolidine core that can be used as key intermediates for the total synthesis of pyrrolidine containing natural molecules such us **6**, **7**, **8**.

The parameters were optimized to increase the diastereoselectivity and enantioselectivity towards a stereoisomer (ST core).

First, a screening of the chiral ligands or counteranion was done to detect the best ligand/counterion. Subsequently, we focused to optimize the other reaction conditions.

Notably, in all the cases studied only the ST-diastereoisomer core could be observed, whose relative configuration was demostrated by 2D-NMR NOESY.

Future perspectives will be oriented toward the total synthesis of a secondary metabolite containing such core and the study of the desymmetrization of meso diamines by Pd(0) catalyzed Tsuji-Trost allylic aminations.

Part 3. DIPHOSPHONIUM TRICATION FOR CAPTURING F^-

11. Positron Emission Tomography (PET)

PET is a non-invasive diagnostic imaging technique producing images of radioactivity distribution in human body sections, following the administration of a radiopharmaceutical to the patient under examination. PET employes positron emitting radioisotopes, listed in Table 11.1. These radioisotopes have a short half-life, of the order of minutes, which implies the need for a cyclotron for their production in the proximity of the PET scanner. The costs related to such instrumentation and its complexity explain the limited diffusion of PET with respect to other imaging techniques. On the other hand, PET radioisotopes make possible the synthesis of radioactive bioactive molecules, whose kinetics can be assessed in vivo by external detection of the emitted radiations. By measuring radioactivity concentration in the organ under study, PET allows metabolic functions and biochemical reactions to be quantitatively measured in vivo, thus representing a unique feature of PET.

Isotope	**Decay**			
	Decay Product	$t^{1/2}$ (min)	β^+ (%)	$E^{\beta+}$ max (MeV)
^{18}F	^{18}O	109.8	96.9	0.69
^{11}C	^{11}B	20.4	99.8	0.96
^{13}N	^{13}C	10.0	100	1.19
^{15}O	^{14}N	2.0	99.9	1.72

Table 11.1 Most common radionuclides for PET applications

PET imaging agents are radiolabeled with positron emitting radionuclides, which dacay by the emission of a positevely charged particle, the positron (e^+). After travelling a short distance in the electron rich tissue, the positron recombines with an electron in a process called annihilation: the masses of both positron and electron are converted in two high-energy photons (511keV γ radiations) which are approximately 180° placed and allow to approximate location of the emitting source within the organism by the detectors of a PET scanner.[85]

The longer is the distance traveled by positron before annihilation, the larger is the loss in spatial resolution.[86]

[85] T. J. Wadas, E. H. Wong, G. R. Weisman, C. J. Anderson; Chem. Rev., 2010, 110, 2858-2902
[86] R. Gong, X. Cheng, W. Han; Imaging, 2005, 32, 325-345

A PET scanner (figure 11.1) consists of a number of adjacent rings of scintillator detectors connected by a temporal coincidence circuitry.

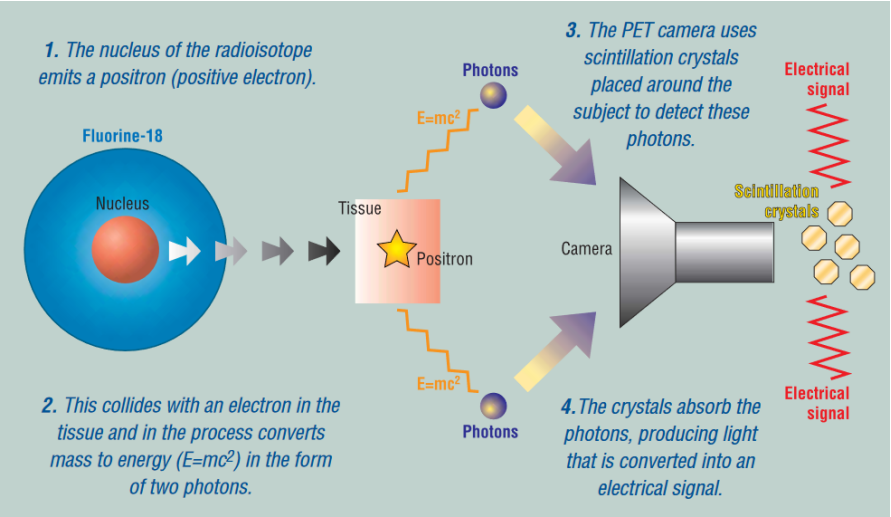


Figure 11.1 Principle of operation of a PET scanner[87]

Among the radionuclides cited, ^{18}F is the most useful due to its physical and chemical characteristics. $^{18}F^-$ can be produced through different nuclear reactions;[88] The most widely used involves the $^{18}O(p,n)^{18}F$ reaction. This compact notation is equivalent to the following nuclear conversion:

$$p + {}^{18}O \rightarrow {}^{19}F^* \rightarrow {}^{18}F + n + \Delta$$

where p is a proton, n a neutron, Δ the mass excess.

It consists in bombarding a target liquid material of H_2O enriched in ^{18}O (>95%) with a beam of protons with an energy of 16 MeV. This production method is the most advantageous for reaching high yields of reaction, high specific activity and because any radioactivity produced is potentially usable for the marking of the desired ligand[89] the only drawback is the cost of the target material, which is rather high and needs recycling of enriched water after entrapment of ^{18}F.

Furthermore, the maximum energy associated with the positron emitted by ^{18}F is only 0.633 MeV, which translates into an avarage radius of tissue penetration of 0.6 mm (the lowest among all radionuclides normally used) making it the radionuclide which gurantees the highest image resolution.[90]

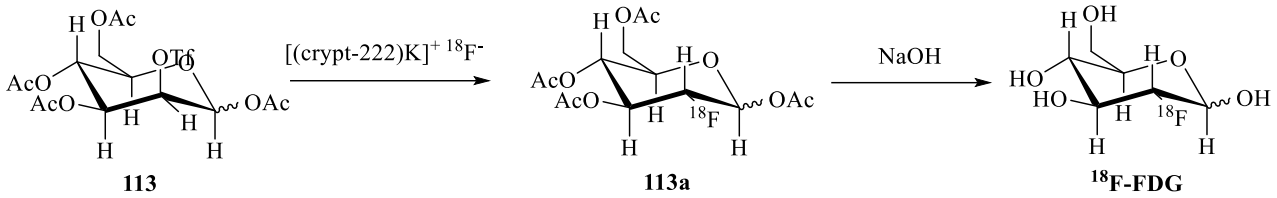
[87] A. Berger A; Brit. Med. J., 2003, 326, 1449
[88] M. Yigit; Annals of Nuclear Energy, 2014, 69, 44-50
[89] S. M. Ametamey, M. Honer, P. A. Schubiger; Chem. Rev., 2008, 1503-1508
[90] O. Jacobsen, D. O. Kiesewetter, X. Chen; Bionconjugate Chem., 2015, 26, 1-18

The half-life of ^{18}F being 109 minutes, makes it ideal to monitor many biological processes even with slow kinetics. The most widely used PET-tracer with ^{18}F is an analogue of glucose: the 2-[F-18] Fluoro-2-Deoxy-D-glucose (FDG). FDG is retained by cells through glucose transporters and is a substrate for hexokinase, an enzyme that phosphorylates gluocse at position 6. As FDG doesn't bear the hydroxyl group at C-2, it cannot continue the matabolic process of glucose degradation and remains mainly trapped in the cancer cells, characterized by higher consumption of glucose, and will be revealed.[91]

[91] E. Bustamante, P.L. Pederson, PNAS, 2005, 74, 3735-3739

12. Synthesis of ^{18}F-FDG

Many attempts have been made to develop a nucleophilic substitution for the synthesis of ^{18}F-FDG. This included the use of ^{18}F-CsF, ^{18}F-Et_4NF, and ^{18}F-KHF.[92] But the major breakthrough was reported in 1986 by Hamacher et al. who had used Kryptofix 222™ as a catalyst (Scheme 12.1).[93]



Scheme 12.1 Synthesis of ^{18}F-FDG starting from protected mannose triflate **113**

In the synthesis of **^{18}F-FDG**, the precursor is the mannose triflate **113** in which the hydroxy groups at position 1,3,4,6 position are protected as acetyl group, while the OH group at C-2 is functionalized as Tf-. The reaction has a consistent yield of over 50% starting from **113** and the reaction time was shortened to 50 min. The reaction takes place with Walden inversion at C-2 due to the S_N2 nature of the reaction. In presence of Kryptofix 222™ as catalyst and acetonitrile as solvent, $^{18}F^-$ ion approaches the mannose triflate at the 2-carbon, while the triflate group leaves the protected mannose molecule to form ^{18}F-FDG. The synthesis of ^{18}F-FDG can be carried out in different computer-controlled automatic synthesizers in which the main stages are:

12.1 Removal of $^{18}F^-$ from the ^{18}O-water coming out from the cyclotron target

As described above, the fluoride ion has a high hydration energy. Thus, water is not a suitable solvent in this synthesis. Polar aprotic solvent such as acetonitile should be used in an S_N2 nucleophilic substitution reaction. Since $^{18}F^-$ is produced by a ^{18}O(p,n) $^{18}F^-$ reaction, it is necessary to isolate the $^{18}F^-$ ion from its aqueous environment. The most convenient way to isolate it, is to use a quaternary ammonium anion exchange column. The $^{18}F^-$ is retained by or via an ion-exchange reaction and allowed the ^{18}O-water to flow through. The retained $^{18}F^-$ is then eluted with an acetonitrile solution of Kryptofix and potassium carbonate.

[92] P.A. Beeley, W.A. Szarek, G.W. Hay, M.M. Perlmutter; J. Chem, 1984, 62, 2709-2711
[93] K. Hamacher, H.H. Coenen, G. Stocklin; J. Nucl. Med., 1986, 27, 235-238

Kryptofix 222^{TM} is a cyclic crown ether which binds the potassium ion, preventing the formation of ^{18}F-KF.

12.2 Evaporation of residual ^{18}O-water

After the $^{18}F^-$ is eluted into reaction vessel, it is necessary to evaporate any residual water from the solution. The benefit of using acetonitrile as the eluting solvent is that it forms an azeotropic mixture with water.

12.3 Addition of mannose triflate into the $^{18}F^-$ with acetonitrile

The nucleophilic substitution takes place at this stage. After the evaporation of any residual water, the sugar precursor is added to the $^{18}F^-$. The choice of precursor depends on the ease of preparation, ease of producing the final product, consistency, yields, and so on. The most commonly used precursor molecule in synthesis of ^{18}F-FDG is 1,3,4,6-O-Acetyl-2-O-trifluoro-methanesulfonyl-beta-D-mannopyranose (mannose triflate). After the nucleophilic replacement of the triflate group by $^{18}F^-$ via a S_N2 mechanism, the acetyl groups can be easily removed by hydrolysis to give ^{18}F-FDG. In the synthesis of 18F-FDG, triflates produces a yield at about 50 to 60%.[94]

12.4 Hydrolysis to remove the protective acetyl groups to form ^{18}F-FDG

The final step of the synthesis is to remove the protective acetyl groups on the 1,3,4,6 position carbons. This can be accomplished by either using hydrochloric acid (acid hydrolysis) or sodium hydroxide (basic hydrolysis). Acid hydrolysis requires a longer time and higher temperature. Basic hydrolysis, which is more commonly used currently, is faster and takes place at room temperature. One of the improved basic hydrolysis is to adsorb the 1,3,4,6 acetyl protected ^{18}F labelled 2-deoxyglucose in a C-18 reverse phase column. All other impurities can be removed by rinsing heavily with water. Sodium hydroxide is added to the column so that the base hydrolysis occurs on the column surface. The final ^{18}F-FDG product can be eluted with water while the unhydrolysed or partially hydrolysed 1,3,4,6 acetyl protected ^{18}F labelled 2 deoxyglucose remains on the column.[95]

[94] D.J. Schlyer, Ann. Acad. Med. Singapore, 2004, 33, 146-154
[95] G.B. Saha GB. NY Springer Publishing, 2005, 97-116

12.5 Purification of the final ^{18}F-FDG product

Purification of the final ^{18}F-FDG can be performed with a series of anion exchange column, C-18 reverse phase column and alumina column.

13. Phosphonium cations for the complexation of F^-

The synthesis described shows some drawback, such us the necessity to remove water *via* an ion exchange resin in order to avoid competitive reaction in the nucleophilic substitution, as the time play also a key role, considering the short $t_{1/2}$.

Moreover, the complexation and recognition of fluoride ions by molecular receptors is an intensively investigated field of research.[96]

F^--complexation in the presence of water is challenging, owing to the high polarizing effects of the F^- anion, especially associated with the high hydration energy, (515 $kJ*mol^{-1}$),[97] as mentioned before.

To overcome this problem, a series of main group Lewis acids were introduced for the binding of F^- ions. Boranes in particular are effective Lewis acids. Gabbaï and co-workers demonstrated the application of several boron-based receptors which detect F^- ions at the ppm level in aqueous media.[98] Some of the boranes are, however, only stable in acidic media, due to competitive reaction with OH^- ions.

Certain phosphonium cations also possess a high F^- affinity,[99] when hypercoordination is possible.[100] As they are environmentally benign species, they are interesting targets for F^- capture. Furthermore, ^{31}P as NMR active nucleus would also allow to follow F^- complexation by NMR spectroscopy. To prepare water-stable phosphonium based salts that are capable of F^- complexation, a significantly enhanced Lewis acidity is required. The implementation of electron withdrawing substituents and/or the increase of the overall charge of the cations by the introduction of onium-substituents are suitable concepts to achieve this goal (figure 13.1).[101] Furthermore, the Lewis acidity can furthermore be enhanced by the incorporation of strained rings[102] and/or by using bidentate Lewis acids.[103]

[96] D. J. M. Snelders, G. van Koten, R. J. M. Klein Gebbink; Chem. Eur. J. 2011, 17, 42-57
[97] J.S. Fowler, T. Ido; Semin. Nucl. Med., 2002, 32, 6-12
[98] (a) H. Zhao, L. A. Leamer, F. P. Gabbaï; Dalton Trans. 2013, 42, 8164-8178. (b) Y. Kim, F. P. Gabbaï; J. Am. Chem. Soc. 2009, 131, 3363-3369. (c) M. H. Lee, T. Agou, J. Kobayashi, T. Kawashima, F. P. Gabbaï; Chem. Commun., 2007, 0, 1133-1135
[99] D.O. Kiesewetter, W.C. Eckelman, R.M. Cohen; Int. J. Appl. Radiat., 1986, 37, 1181-1188
[100] S. Levy, E. Livni, D. Elmaleh W. Curatolo; Chem. Commun., 1982, 0, 972-973
[101] J. J. Weigand, N. Burford, A. Decken, A. Schulz; Eur. J. Inorg. Chem., 2007, 32, 4868-4872
[102] W. Szarek, G.W. Hay, M.M. Perlmutter; Chem. Commun., 1982, 0, 1253-1254
[103] C. Lemaire, P.H. Damhaut, B. Lauricella, C. Mosdzianowski, J.L. Morelle, M. Monclus, J. Van Naemen, E. Mulleneers, J. Aerts, A. Plenevaux, C. Brihaye, A. Luxen; J. Labelled Comp. Radiopharm., 2002, 45, 435-447

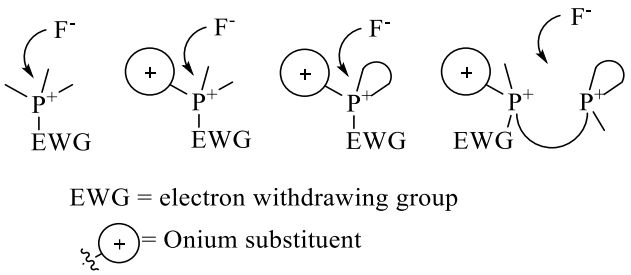


Figure 13.1 Enhancement of fluoride affinity via onium centered Lewis acidity.

The reactivity of the resulting cationic phosphanes strongly depends also on the nature of the attached oniium-substituents. Nitrogen-based (*N*-based) onium-substituted phosphanes are very reactive due to the labile P–N bond, which has been found to be useful for molecular transformation reactions.[104] However, their high reactivity towards protic compounds impede applications in catalysis and exclude their use in protic media.[105] Carbon-based (*C*-based) onium-substituted phosphanes are more robust, due to the less reactive P–C bond, thus, enabling in comparison to *N*-based derivatives a much diverse chemistry.[106] Particularly, phosphonium cations are gaining strong reputation as very potent Lewis acids[107] representing potential organocatalysts[108] and reagents for molecule transformations.[109] Applications of phosphonium-substituted boron based molecular receptors for anion complexation in protic media are also reported.[98] Imidazoliumyl-, cyclopropeniumyl-, pyridiniumyl- and di(phosphonium)methanidyl- represent some suitable *C*-based onio-substituents for the preparation of phosphorus based cations. For such reasons, we decided to evaluate the the affinity of **[122]OTf$_2$** to the fluoride ion (Figure 13.2). Interestingly, such compound could be amenable to a further functionalization via a Diels-Alder reaction with a dienophile on the anthracenyl moiety.

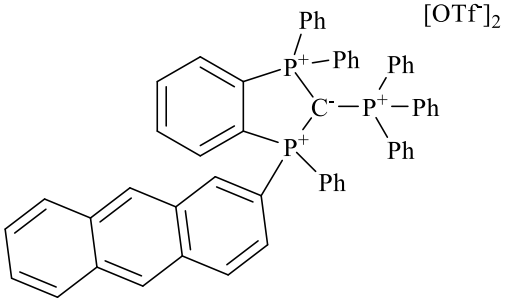


Figure 13.2 triphosphonium dication **122[OTf]$_2$**

[104] (a) K.O. Feldmann, J. J. Weigand; Angew. Chem. Int. Ed., 2012, 51, 6566-6568; (b) J. J. Weigand, K.O. Feldmann, A. K. C. Echterhoff, A. W. Ehlers, K. Lammertsma; Angew. Chem. Int. Ed., 2010, 49, 6178-6181; (c) K.O. Feldmann, J. J. Weigand; Angew. Chem., 2012, 124, 7663-7667; (d) S. S. Chitnis, A. P. M. Robertson, N. Burford, B. O. Patrick, R. McDonald, M. J. Ferguson; Chem. Sci., 2015, 6, 6545-6555
[105] T. Koizumi, P. Haake; J. Am. Chem. Soc., 1973, 95, 8073-8079
[106] M. Alcarazo; Acc. Chem. Res., 2016, 49, 1797-1805
[107] J. M. Bayne, D. W. Stephan; Chem. Soc. Rev., 2016, 45, 765-774
[108] M. Pérez, L. J. Hounjet, C. B. Caputo, R. Dobrovetsky, D. W. Stephan; J. Am. Chem. Soc., 2013, 135, 18308-18310
[109] D. Winkelhaus, M. H. Holthausen, R. Dobrovetsky, D. W. Stephan; Chem. Sci., 2015, 6, 6367-6372

13.1 Synthesis of the trionium-substituted phosphane and complexation

Carbodiphosphoranes are divalent carbon(0) compounds featuring four-electron donation with σ- and π-symmetry (figure 13.1.1).

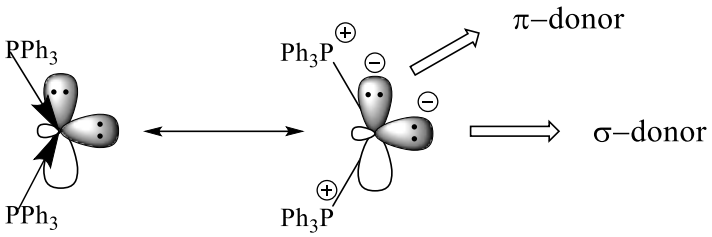
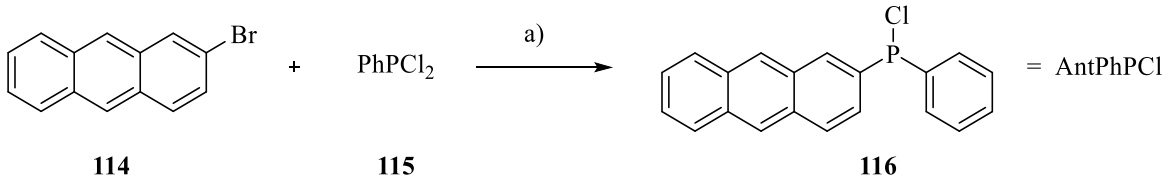


Figure 13.1.1 $(Ph_3P)_2C$ as four electron donor with σ- and π-symmetry.

This unusual situation allows for example $(Ph_3P)_2C$ to be doubly protonated. Moreover, $(Ph_3P)_2C$ is capable to coordinate one- or two gold chloride fragments at the same donor atom.[110] This coordination behavior of the carbodiphosphoranes have proven to contribute in the stabilization of especially electron deficient bonding situations in certain compounds (like the coordinatively saturated group 13 complexes, *e.g.* BH_3, $AlBr_3$, $GaCl_3$).[111]

The implementation of a phosphanyl moiety into the carbodiphosphorane $(Ph_3P)_2C$ was already reported in 1966 as a result of the reaction of $(Ph_3P)_2C$ with Ph_2PCl.[112]

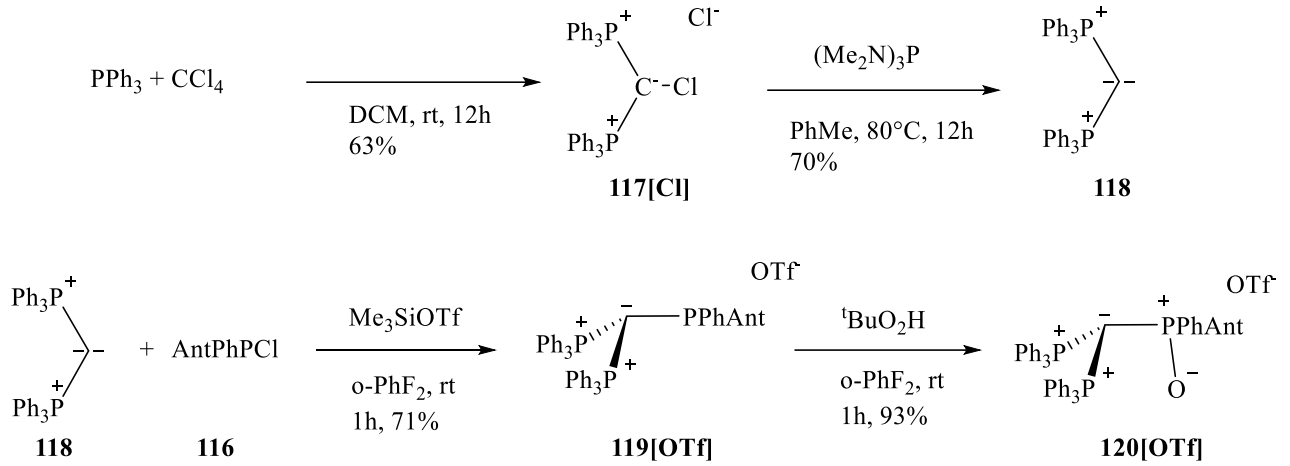
Following an analogous reasoning, we prepared an anthracenyl chlorophosphine, suitable for further funcionalization *via* a Diels-Alder reaction, for example (Scheme 13.1.1).



Scheme 13.1.1 Synthesis of **116**. a) Grignard generation of **114**: Mg, THF, 50°C, o.n. Following reaction: addition of **115**, THF, -78°C, 1h, then rt, 14h, 69%.

Then, carbodiphorane **118** was synthesized by the reaction between triphenylphosphine and carbon tetrachloride, followed by the reduction of the intermediate **117[Cl]** with tris(dimethylamino)phoshine.[113]

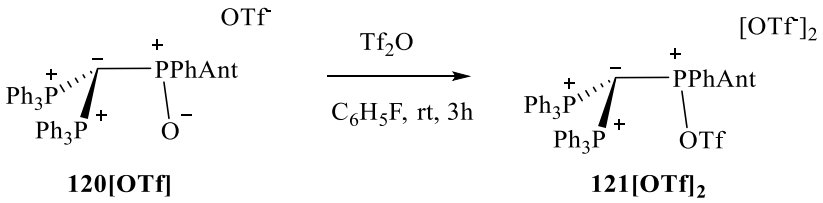
[110] J. Vicente, A. R. Singhal, P. G. Jones; Organometallics, 2002, 21, 5887-5900
[111] W. Petz; Coord. Chem. Rev., 2015, 291, 1-27
[112] G. H. Birum, C. N. Matthews; J. Am. Chem. Soc., 1966, 88, 4198-4203
[113] R. Appel, F. Knoll, H. Schöler, H.D. Wihler; Angew. Chem., 1976, 88, 769-770



Scheme 13.1.2 Preparation of **104[OTf]** and **105[OTf]**

119[Cl] was obtained via nucleophilic substitution of **118** on **116**. This intermediate was conveniently converted into the triflate salt *via in situ* addition of Me_3SiOTf. **119[OTf]** was obtained as a yellow and air-stable powder in good yields (71%, Scheme 13.1.2).

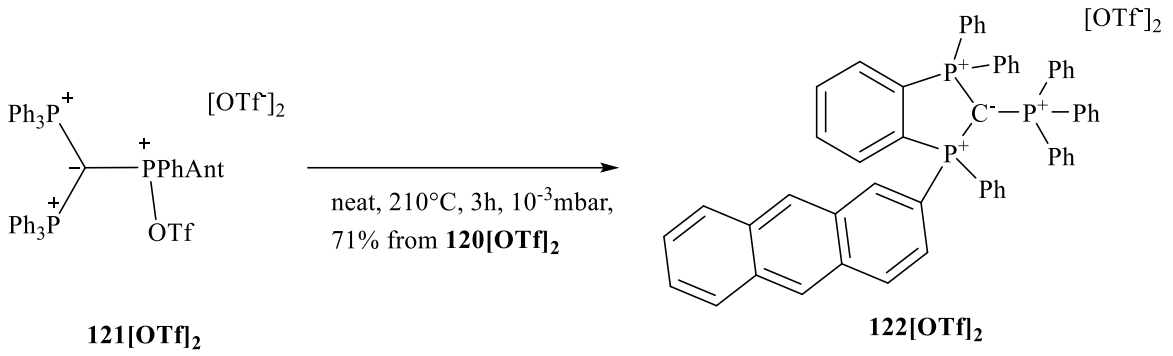
119[OTf] was then oxidezed with $^tBuO_2H$ leading to the phosphane oxide triflate salt **120[OTf]** (yield: 93% Scheme 13.1.2)



Scheme 13.1.3 Preparation of **121[OTf]$_2$**

The reaction of **120[OTf]** with one equivalent of triflic anhydride (Tf_2O) led to the formation of the highly moisture sensitive triflyloxyphosphonium triflate salt **121[OTf]$_2$** in excellent yield (98%, Scheme 13.1.3). The (additional) π-donor ability of the $(Ph_3P)_2C$ moiety leads to a sufficient stabilization of the triflyloxyphosphonium cation **121**$^{2+}$ by increasing electron density at the P atom of the PhAnt moiety, which consequently enhances the Lewis basicity of the oxygen of the triflate moiety.

Dication **121**$^{2+}$ was a suitable reaction platform for the synthesis of functionalized phosphonium salts,[95] enabling ideally the isolation of various carbodiphosphorane-substituted halo- and *pseudo*halophosphonium dications.

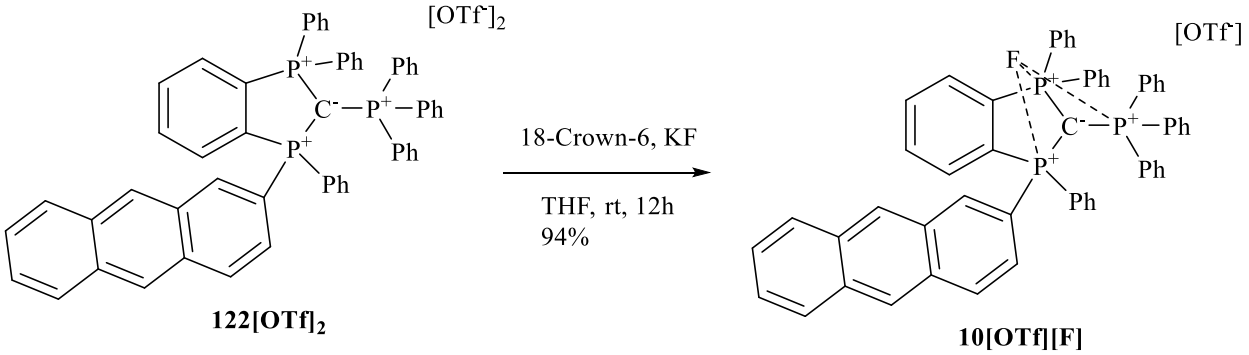


Scheme 13.1.4 Synthesis of **122[OTf]₂** *via* an intramolecular electrophilic aromatic substitution (S_EAr) reaction.

Similar functionalization was obtained when dication **121**$^{2+}$ is heated to 210 °C for 2 h under dynamic vacuum (≈10^{-3} mbar) resulting in an intramolecular C–H activation followed by a phosphonionation reaction to yield the cyclic tri(phosphonio)methanide salt **122[OTf]₂** as air and moisture stable solid in good yields (71% over two steps, Scheme 13.1.4).

The reaction mechanism proposed for the formation of **122[OTf]₂** is an intramolecular electrophilic aromatic substitution (S_EAr) following the same pathway for a close related compound containing a phenyl unit instead of the anthracenyl moiety.[114]

No reaction was observed by reacting **122[OTf]₂** with BH_3·THF and [AuCl(tht)], this elucidates the absence of nucleophilicity of the compound due to the *π*-conjugation from the p-type lone pair at the formally negative charged C into the σ*(P-C_{Ph}) orbitals.



Scheme 13.1.5 Complexation of F- by **122[OTf]₂**

In contrast, the reaction of **122[OTf]₂** with a source of F^- anions (e.g. KF, AgF, [Bu_4N]F) gave quantitatively the fluoride salt as a result of the addition of a F^- anion to one of the electrophilic P atoms (Scheme 13.1.5).

[114] S. Yogendra, F. Hennersdorf, A. Bauzá, A. Frontera, R. Fischer, J. J. Weigand; Angew. Chem. Int. Ed., 2017, 56, 7907-7911

10[OTf][F] showed a good stability towards moisture and was conveniently prepared by reacting **122[OTf]$_2$** under standard reaction conditions using KF as fluoride source. No special care needed to be taken and the starting materials could be used without prior drying.

10[OTf][F] was obtained as colorless and air stable solid in excellent yield.

Then **10[OTf][F]** was reacted with a solution of 10eq of H_2O in CH_3CN (0.05 M) and the reaction mixture was stirred for 12 h at ambient temperature. ^1H and ^{31}P NMR spectra showed no decomposition of **10[OTf][F]**.

10 eq. of the salt NaN_3, KCN, $[Ph_4P]Cl$, [Bu4N]I, K_2CO_3 were also independently added to a solution of **122[OTf]$_2$** in CH_3CN (1 mL). The reaction suspension in case of NaN_3, KCN and K_2CO_3 and reaction solution in case of [Bu4N]I and $[Ph_4P]Cl$ were sonicated for 30 min. The ^{31}P NMR spectra of all reactions showed **122[OTf]$_2$** as the only detectable species, proving the selectivity of this triphosphonium dication toward F^-.

14. Conclusions

The phosphonium cations are gaining strong reputation as very potent Lewis acids representing potential organocatalysts and reagents for molecule transformations.

We came out then with the synthesis of the dication **122[OTf]$_2$** and we proved the selectivity of such compound in binding F^-. Noteworthy, the synthesis of the trisphonium dication **122[OTf]$_2$** was achieved in 7 steps without any purification by column chromathography.

Further studies are required to evaluate the reversibility of the F^- complexation, the ability to catch the fluoride from an acquous solution, as a source of anydrous fluoride and the labelling of the complex with a biomolecule via a Diels Alder reaction on the anthracenyl moiety.

EXPERIMENTAL SECTION

Materials and methods

Within the experimental section the following materials and instruments were employed.
For the characterization of compounds:

- Spectrometer NMR Bruker, 300, 400 and 500 MHz. All ^{13}C NMR spectra were exclusively recorded with composite pulse decoupling. Reported numbers assigning atoms in the ^{13}C spectra, if present, were indirectly deduced from the cross-peaks in 2D correlation experiments (HMBC, HSQC). Chemical shifts were referenced to δ_{TMS} = 0.00 ppm (^{1}H, ^{13}C), δ_{CHCl3} = 0.00 ppm (^{19}F, externally) and $\delta_{H3PO4(85\%)}$ = 0.00 ppm (^{31}P, externally). Chemical shifts (δ) are reported in ppm. Coupling constants (J) are reported in Hz. The designation of the spin systems is performed by convention. The furthest downfield resonance is denoted by the latest letter in the alphabet and the furthest upfield by the earliest letter.
- Polarimeter Perkin-Elmer 241;
- Spectrometer FT-IR Perkin Elmer Paragon 100 PC. The intensities, if present, are reported relative to the most intense peak and are given in parenthesis using the following abbreviations: vw=very weak, w=weak, m=medium, s=strong, vs=very strong
- ESI-MS Thermo LTQ
- Bruker Vertex 70 instrument equipped with a RAM II module (Nd:YAG laser, 1064 nm)
- Suitable single crystal was coated with Paratone-N oil, mounted using either a glass fibre or a nylon loop and frozen in the cold nitrogen stream. Crystals were measured at 100K on a Bruker Kappa APEX II system using Mo K_α radiation (λ=0.71073Å) generated by a fine-focus sealed tube. The data reduction and absorption correction was performed with the Bruker SADABS. Using Olex2 the structures were solved with SHELXS/T by direct methods and refined with SHELXL by least-square minimization against F^2 using first isotropic and later anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms were added to the structure models on calculated positions using the riding model. Images of the structure were produced with Olex2 software.

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), vanillin 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 an oven.

Most of the reaction solvents were dried by distillation on appropriate drying agents, under Ar atmosphere. 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

Boc: tert-butyloxycarbonyl

BRINE: sodium chloride saturated solution

ROCHELLE salt solution: sodium potassium tartrate saturated solution

DCM: dichloromethane

DET: diethyltartrate

DME: dimethyether

DMF: dimethylformamide

DMP: Dess-Martin Periodinane

DMSO: dimethylsulfoxide

DMS: dimethylsulfide

DPPA: diphenylphosphoryl azide

DPPBA: diphenylphosphino benzoic acid

Im: imidazole

Py: pyridine

DMAP: 4-dimethylaminopyridine

KHMDS: potassium hexamethyldisilylamide

NaHMDS: sodium hexamethyldisilylamide

MTBE: methyl *t*-Butyl ether

Piv : pivaloyl

pTSA: para-toluenesulfonic acid

TBAF: tetrabutyl ammonium fluoride

TES: Triethylsilyl

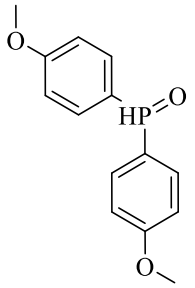
TBS: *t*-Butyl dimethylsilyl

TBDPS: *t*-Butyl diphenylsilyl

Ts: Tosyl

THF: tethrahydrofuran

Synthesis of 55

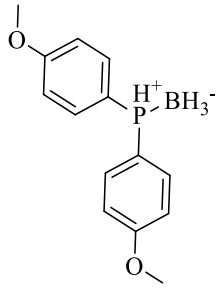


A Schlenk flask was charged under inert conditions with 4-methoxyphenylmagnesium bromide (10mL, 0.5M in THF, 5.0mmol, 3.3 eq.), and the solution cooled to 0°C. A solution of diethylphosphite (0.137mL, 1.5mmol, 1.0 eq) in THF (5mL) was then added dropwise over 15 minutes. The mixture was stirred for 15 minutes at 0°C, then the bath was removed, and the mixture stirred for additional fivw hours at rt, then cooled again to 0°C. 10mL of 0.1M HCl was then added dropwise over 20 minutes, then 75 mL MTBE was added, and the mixture agitated well for 5 minutes. The upper organic phase was decanted from the gel and saved. To the remaining gel was added DCM (20mL), and the mixture agitated well for 5 minutes. The resultant mixture was then filtered through a Celite pad, washing the pad with DCM. The filtrate phases were separated, and the organic phase combined with the first organic phase, dried over $MgSO_4$, and the solvents removed in vacuo. The crude product was purified by flash column chromathography (2% MeOH in DCM) yielding **55** as analytically pure, colorless and air stable powder.

Yield: 226mg (58%).

The spectroscopical data match with those reported in literature.[65]

Synthesis of 57

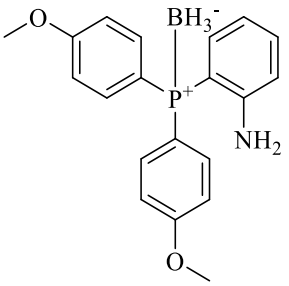


A Schlenk flask was charged under inert conditions with DIBAL-H (6.0mL, 1M in THF, 6mmol, 5eq). A solution of **55** (394mg, 1.5mmol, 1eq) in THF (5mL) was then added dropwise over a period of 15 minutes. The resulting mixture was then stirred 0.5h at rt then 10mL of MTBE was added dropwise over 10minutes. Then the mixture was extracted with 5mL of 2M NaOH under inert condions followed by 10 mL of Brine. The organic phase was then transferred under inert condions in a flask containing $MgSO_4$. The dried organic mixture was filtered *via* Schelenk frit. The solid was washed with further 10mL of MTBE. The combined organic phases were used in the following step without further purifications. BH_3 (4mL, 1M in THF, 4mmol, 2.7eq) was then added to the organic mixture containing the crude product over a period of 20min. The solution was then cooled to 0°C, then 7mL 1M HCl was added dropwise. The phases were separated, and the aqueous phase reextracted with 5mL MTBE. The combined organics were washed with satured $NaHCO_3$ (10mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to give a colorless solid which was purified by column chromathography (30% EtOAc in Hexane) yielding **57** as analytically pure, colorless and air stable powder.

Yield: 260mg (67%).

The spectroscopical data match with those reported in literature.[65]

Synthesis of 59



A two necked flask equipped with a condenser was charged under inert conditions with **57** (180mg, 0.692 mmol, 1eq), 2-iodoaniline (303mg, 1.4mmol, 2eq), $Pd(PPh_3)_4$ (80mg, 0.07mmol, 0.1eq), K_2CO_3 (191mg, 1.38mmol, 2eq). The mixture was suspended in THF (5mL) and left to react at 50°C o.n. The mixture was concentrated *in vacuo* and purified by column chromathography (15% EtOAc in Hexane) yielding **59** as analytically pure, colorless and air stable powder.

Yield: 170mg (70%).

^{1}H NMR ($CDCl_3$, 300 K, in ppm): δ 7.53 (m, 4H), 7.28 (td, *J* = 7.5, 1.5 Hz, 1H), 6.99 (dd, *J* = 8.8, 1.9 Hz, 4H), 6.80 (ddd, *J* = 12.0, 7.7, 1.6 Hz, 1H), 6.68 (m, 2H), 4.60 (s, 2H), 3.86 (s, 6H), 1.37 (d, J = 15Hz, 3H)

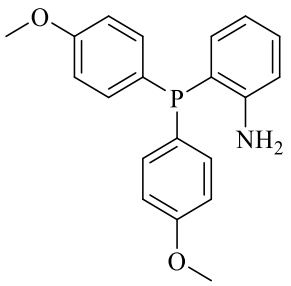
^{13}C{^{1}H} NMR ($CDCl_3$, 300 K, in ppm): δ 162.04 (C, d, *J* = 2.5Hz, 2C), 150.25 (C, d, J = 8.8Hz, 1C), 134.79 (CH, d, J = 8.8Hz, 4C), 134.40 (CH, d, J = 8.8Hz, 1C), 132.61 (CH, d, J = 2.5Hz, 1C), 119.15 (C, d, J = 64.3Hz, 2C), 117.85 (CH, d, J = 8.8Hz, 1C), 116.70 (CH, d, J = 6.3Hz, 1C), 114.52 (CH, d, J = 11.3Hz, 4C), 110.82 (C, d, J = 58.0Hz, 1C), 55.33 (CH_3, s, 6C)

^{31}P{^{1}H} NMR ($CDCl_3$, 300 K, in ppm): δ 12.81 (d, *J* = 77.9 Hz, 1P)

^{11}B NMR ($CDCl_3$, 300 K, in ppm): -36.74 (m, 1B)

IR (300 K, ATR, in cm^{-1}): 3442, 1639, 1597, 1502, 1292, 1254, 1181, 1112, 1064, 1027, 892, 736, 579, 525.

Synthesis of 60



In a Schlenk flask was dissolved **59** (355mg, 1mmol, 1eq) in DCM (4mL) followed by the addiction of DABCO (460mg, 4mmol, 4eq). The solution obtained was left to stir o.n. and then concentrated *in vacuo*. The crude product was purified by column chromathography (20% EtOAc in Hexane) by using previously degassed solvents. The collection of the fractions yielded **60** as analytically pure and colorless powder.

Yield: 303mg (90%).

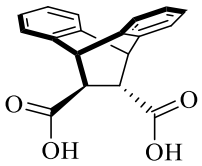
^{1}H NMR ($CDCl_3$, 300 K, in ppm): δ = 7.29 (4H, *pseudo*-t, J_{HH} = 7.7 Hz), 7.19 (1H, dt, J_{HH} = 7.2 Hz, J_{HP} = 1.6 Hz), 6.93 (4H, d, J_{HH} = 8.3 Hz), 6.73 (3H, m), 4.07 (2H, brs), 3.84 (6H, s).

^{13}C{^{1}H} NMR ($CDCl_3$, 300 K, in ppm): δ = 160.46(C, s), 135.17 (CH, d, J_{CP} = 27.3 Hz), 133.80 (C, d, J_{CP} = 15.2 Hz), 133.52 (CH, s), 130.17 (CH, s), 125.16 (CH, s), 119.12 (CH, s), 115.89 (C, d, J_{CP} = 10.2 Hz), 114.31 (CH, d, J_{CP} = 11.1 Hz), 113.97 (C, d, J_{CP} = 17.2 Hz), 55.09 (CH_3, s).

IR (300 K, ATR, in cm^{-1}): 3363, 3059, 3008, 2957, 2926, 2836, 1612, 1593, 1567, 1497, 1475, 1462, 1442, 1402, 1285, 1247, 1177, 1095, 1029, 827, 797, 751, 737, 703, 529.

m.p.: 134 °C

Synthesis of 63a



*Synthesis of racemic acid **63***

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 **63** as analytical pure racemic diacid.

Yield: 5,74g (70%)

*Resolution of racemic diacid **63***

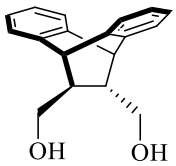
In a beaker, diacid **63** (5.74 g, 19.5 mmol, FW=294.31) was dissolved in a mixture of water (185 mL) and EtOH (115 mL). Brucine (18.3 g, FW = 394.45, 46.4 mmol, 2.38 eqv) was added and the mixture was stirred for one minute. The resulting white solid was filtered on buchner (washing with water), recrystallized 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 **63a** (>99% *ee*) were achieved.

Spectroscopic data agree with the literature[115]

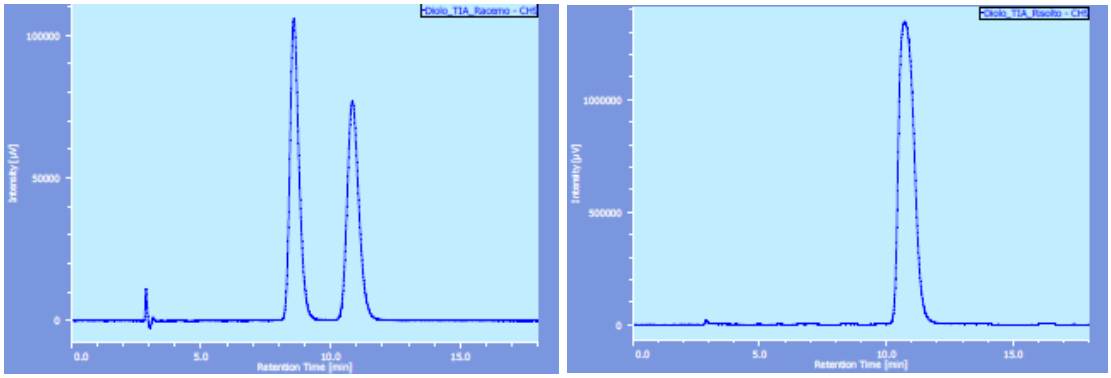
To determine the *ee*, a small amount of diacid **63** was reduced with $LiAlH_4$ to the corresponding diol **113**, that subsequently was analyzed by chiral HPLC.

[115] N. Jain, A.V. Bedekar; Tetrahedron Asymmetry, 2011, 22, 1176-1179

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 **113**



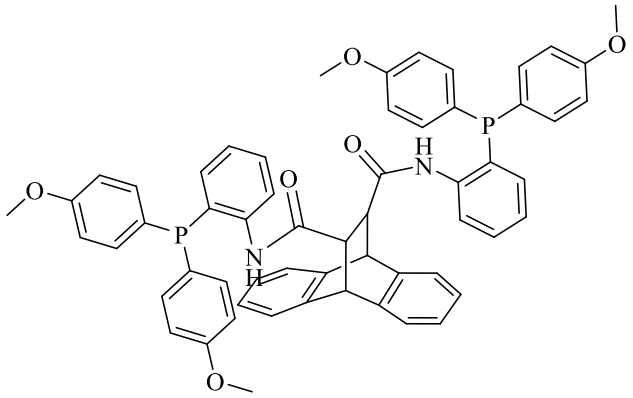
Analysis of racemic diol **113** (left chromatogram)

Peak number	Description	A%
1	(*R*,*R*)-enantiomer	49.3
2	(*S*,*S*)-enantiomer	50.7

Analysis of resolved diol **113** (right chromatogram)

Peak number	Description	A%
1	(*S*,*S*)-enantiomer	>99

Synthesis of (S,S)-L4



A two necked flask was charged under inert conditions with **60** (130mg, 0.387 mmol, 2.2eq), **63a** (51.4mg, 0.172mmol, 1.0eq), DMAP (10.8mg, 0.0880mmol, 0.5eq). DCM was then added (5mL) followed by DCC (90.8mg, 0.440mmol, 2.5eq). The solution was left to stir at rt for 36h. The mixture was concentrated *in vacuo* and purified by column chromathography (30% EtOAc in Hexane) yielding (S,S)-**L4** as analytically pure, colorless powder.

Yield: 89.9 mg (56%)

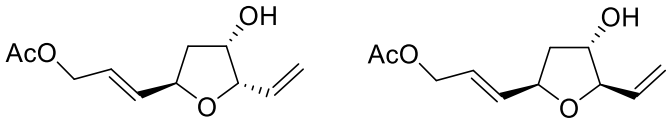
^{1}H NMR ($CDCl_3$, 300 K, in ppm): δ = 8.53 (d, *J* = 6.4 Hz, 2H), 8.04 (dd, *J* = 8.2, 4.4 Hz, 2H), 7.40 – 7.18 (m, 12H), 7.15 – 6.93 (m, 12H), 6.87 (dd, *J* = 12.7, 7.4 Hz, 6H), 4.28 (s, 2H), 3.83 (d, *J* = 2.1 Hz, 12H), 2.94 (s, 2H).

^{13}C{^{1}H} NMR ($CDCl_3$, 300 K, in ppm): δ = 160.82 (C), 160.67 (C), 142.33 (C), 140.30 (C), 140.07 (C), 139.83 (C), 135.63 (CH), 135.35 (CH), 135.27 (CH), 135.00 (CH), 132.97 (CH), 129.64 (CH), 127.75 (C), 126.01 (CH), 125.93 (CH), 125.31 (CH), 124.96 (CH), 124.68 (CH), 122.88 (CH), 122.81 (CH), 114.72 (CH), 114.60 (CH), 114.49 (CH), 55.18 (CH_3), 55.11 (CH_3), 49.62 (CH), 46.76 (CH).

IR (300 K, ATR, in cm^{-1}): 3390, 3346, 3055, 3010, 2960, 2942, 2837, 2535, 1896, 1693, 1593, 1572, 1498, 1436, 1403, 1286, 1249, 1179, 1096, 1029, 910, 829, 798, 762, 736, 703, 628, 567, 532, 501.

m.p.: 127 °C

General procedure for cyclization of *meso* diol **12** leading to **13** and **14**



14 **13**

(S,S)-**L4** (8 mol%) and $Pd_2(dba)_3CHCl_3$ (3 mol%) were 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 was completed. The solution switched from violet to yellow/orange. In another flask, the *meso* diol was dissolved in dry solvent (DCM or toluene, 0.1 M) under Argon atmosphere and the catalyst containing solution previously prepared was cannulated.

The mixture was stirred till the reaction was completed.

If necessary, $BaCO_3$ (1.1 eqv) was added to the solution containing the substrate before cannulation.

If necessary, reaction mixture was cooled at -30°C before cannulation of the catalyst solution and was kept at the same temperature till the end.

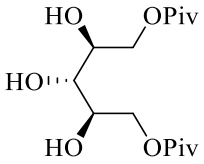
Reaction was monitored by TLC and when it was completed it was quenched by addition of silica and filtration on a silica pad by washing with EtOAc.

The resulting crude material was 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.

Spectroscopical data match with those previously reported.[23]

Synthesis of 67

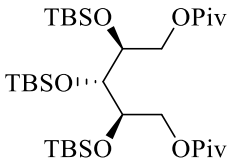


In a two necked round bottomed flask, under static Argon atmosphere, were placed xylitol **15** (4.0g, 26.3 mmol, 1eq) and pyridine (61 mL). The solution was than cooed to 0°C and PivCl (8.1 mL, 65.5 mmol, 2.5eq) was slowly added. After 15 minutes the reaction was allowed to reach room temperature and stirred overnight. The reaction was monitored via TLC (toluene:acetone 3:1) and was completed in 15h. The volatiles were then removed *in vacuo* and then diluted in H_2O and extracted with ethyl acetate. The collected organic phases were washed with brine, dried over Na_2SO_4 and brought to dryness. The crude product was purified via column chromatography on silica gel (toluene:acetone 3:1) yieldin analytically pure, colorless product **67.**

Yield: 7.03g (83%)

Spectroscopical data match with those previously reported.[62]

Synthesis of 68



In a two neck round bottomed flask under static Argon atmosphere compound **67** (2.0g, 2.25mmol, 1eq), imidazole (0.75g, 11.3mmol, 5eq) and DMAP (0.098g, 0.8 mmol, 0.3eq) were dissolved in dry DMF (62mL). The solution was cooled to 0°C and TBSCl (1.6 g, 10.1 mmol, 4.5eq), was slowly added. After the addition the reaction was allowed to reach room temperature and then heated with an oil bath to 50 °C for two days keeping it constantly stirred.

The reaction was monitored via TLC (toluene/acetone 3/1 and Hexane/MTBE 95/5) and was completed in 40h.

Quenching with a mixture of ice, hexane and saturated $NaHCO_3$ was performed.

The aqueous layer was than separated from the organic phase and extracted three times with a solution of hexane:MTBE 9:1.

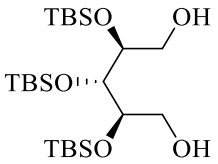
Organic extracts were reunited and washed with water and then brine, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure.

The crude product was purified over column chromatography on silica gel (Hexane:MTBE 98:2) yielding **68** as a colorless oil.

Yield: 3.05g (74%)

Spectroscopical data match with those previously reported.[62]

Synthesis of 69



In a two neck round bottomed flask under static Argon atmosphere compound **68** (1.45g, 2.19mmol, 1.0eq) was dissolved in toluene (22mL). The solution was cooled to -78°C, then DIBAL-H was added dropwise (9.4mL, 9.4mmol, 1.0M in hexane, 4.3eq).

The mixture was left to stir at -78°C, monitored *via* TLC (Hexane:MTBE 8:2) and was complete in 3h. The solution was then quenched by adding a solution of Rochelle's Salt at such temperature and left to stir overnight allowing it to reach room temperature.

The organic phase was than separated from the aqueous layer and extracted three time with ethyl acetate. Organic fractions were collected and washed with brine, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure.

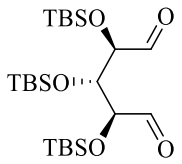
No further purification was performed.

The work up yielded **69** as analytically pure, colorless solid.

Yield: 1,05 g (97%)

Spectroscopical data match with those reported in literature.[62]

Synthesis of 70



In a two neck round bottomed flask under static Argon atmosphere oxalyl chloride (1.3 mL, 15.2mmol, 3.0eq) was dissolved in DCM (36mL). The solution was cooled to -78°C, then a solution of DMSO (1.4 mL, 20.3 mmol, 4.0eq) in DCM (3.6 mL) was slowly added. After 10 minutes a solution of **69** (2.51g, 5.07 mmol, 1.0eq) in DCM (15 mL) was added and kept stirred for 0.5h minutes. At this point Et_3N (7.0 mL) was added leading the appearance of an intense yellow coloration. After 10 minutes at -78°C, the reaction was allowed to reach room temperature.

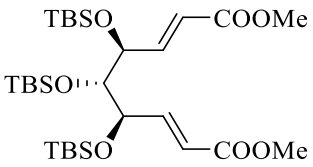
The reaction was controlled via TLC (Hexane:Acetate 9:1) and was complete in 1.5h.

It was then quenched with water and the layers separated. The aqueous layer was extracted 3 times with Hexane.

Organic moieties were collected and washed with a saturated solution of $NaHCO_3$, brine, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure.

The crude product **70** was used in the following step without further purifications.

Synthesis of 71



In a two neck round bottomed flask under static Argon atmosphere crude **70** (2.49g, 5.07mmol, 1eq) was dissolved in THF (51mL). The solution was cooled to 0°C and under vigorous stirring $Ph_3PCHCOOMe$ (8.48g, 25.4mmol, 5.0eq) was added. The reaction temperature was then allowed to reach room temperature and successively warmed to 50°C and left to stir overnight at this temperature.

The reaction was controlled via TLC (Hexane:MTBE 9:1) and was completed in 24h. It was quenched with a saturated NH_4Cl solution. The phases were separated, the aqueous layer was extracted with Et_2O.

Organic extracts were reunited and washed with water and then brine, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure.

The reaction crude was than purified with column chromatography on silica gel (gradient from Hexane:MTBE 99:1 to 96:4).

Analytically pure **71** was then obtained as a colorless solid.

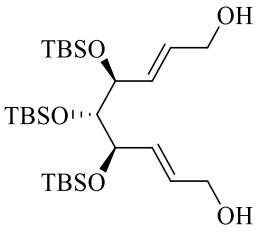
Yield: 2.45g (80%)

^{1}H NMR ($CDCl_3$, 300 K, in ppm): δ = 7.15 (dd, *J* = 15.7, 4.8 Hz, 2H), 5.95 (dd, *J* = 15.8 Hz, *J* = 1.8, 2H), 4.42 (m, 2H), 3.85 (s, 6H), 3.55 (t, *J* = 7.0 Hz, 1H), 0.89 (s, 18H), 0.84 (s, 9H), 0.08 (m, 18H).

^{13}C{^{1}H} NMR ($CDCl_3$, 300 K, in ppm): δ = 166.8 (C), 149.0 (CH), 120.2 (CH), 77.9 (CH), 72.5 (CH), 51.4 (CH_3), 25.8 (CH_3), 18.1 (C), -4.4 (CH_3), -4.5 (CH_3), -4.7 (CH_3).

IR (300 K, ATR, in cm^{-1}): 2954, 2859, 1732, 1660, 1472, 1436, 1362, 1258, 1166, 1122, 1007, 967, 938, 838, 813, 777, 666.

Synthesis of 72



In a two neck round bottomed flask under static Argon atmosphere compound **71** (3.4g, 5.6 mmol, 1eq) was dissolved in THF (43mL). The solution was cooled to -78°C and kept stirred while DIBAL-H (43.5mL, 43.5 mmol, 1.0M in hexane, 8eq) was added dropwise. The reaction was left to stir at 78°C for 1.5h. After completion via TLC (Hexane:Ethyl acetate 8:2), a saturated solution of Rochelle's Salt was added. The biphasic system was stir overnight at rt.

The organic phase was than separated from the aqueous layer and extracted three time with diethyl ether. Organic moieties were reunited and washed with brine, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure.

The crude product was purified *via* column chromatography on silica gel (hexane:ethylacetate 9:1). Analytically pure **72** was obtained in quantitative yield as a colorless oil.

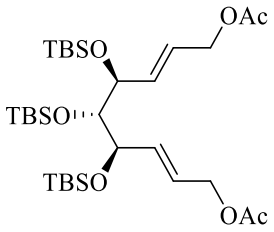
Yield: 2.95g (96%)

^{1}H NMR ($CDCl_3$, 300 K, in ppm): δ = 5.80 (m, 4H), 4.20 (m, 2H), 4.14 (d, J = 4.5 Hz, 4H), 3.50 (t, J = 4.6 Hz, 1H), 1.70 (brs, 2H), 0.90 (s, 9H), 0.85 (s, 18H), 0.10 (s, 12H), 0.01 (s, 6H).

^{13}C{^{1}H} NMR ($CDCl_3$, 300 K, in ppm): δ = 133.0 (CH), 128.9 (CH), 78.6 (CH), 74.0 (CH), 63.5 (CH_2), 25.8 (CH_3), 25.7(CH_3), 18.0 (C), 18.1 (C), -4.1 (CH_3), -4.3 (CH_3), -4.4 (CH_3).

IR (300 K, ATR, in cm^{-1}): 3340, 2929, 2857, 1472, 1462, 1362, 1255, 1096, 1048, 1006, 835, 775, 738, 666.

Synthesis of 73



In a two neck round bottomed flask under static Argon atmosphere compound **72** (2.9g, 5.4 mmol, 1eq) was dissolved in DCM (30mL). Under stirring were added pyridine (1.2 mL, 15mmol, 2.9eq), Ac_2O (1.2mL, 12.4mmol, 2.4eq) and DMAP (0.105g, 0.86mmol, 0.16eq). The reaction was then stirred overnight at room temperature. After completion, by monitoring *via* TLC (Hexane:Ethylacetate 9:1), the reaction was quenched by adding a saturated $NaHCO_3$ solution and the phases separated.

The organic layer was washed with a saturated solution of $CuSO_4$, water, brine, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure.

The crude product was purified via column chromatography on silica gel (Hexane:Ethylacetate 95:5). Analytically pure **73** was then obtained as a colorless oil.

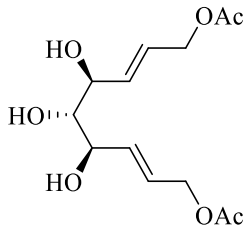
Yield: 3.17g (93%)

^{1}H NMR ($CDCl_3$, 300 K, in ppm): δ = 5.95 (dd, J = 15.6, 6.1 Hz, 2H), 5.70 (dt, J = 15.6, 6.1 Hz, 2H), 4.55 (d, J = 6.1 Hz, 4H), 4.20 (t, J = 5.5 Hz, 2H), 3.45 (t, J = 4.7 Hz, 1H), 2.05 (s, 6H), 0.90 (s, 9H), 0.85 (s, 18H), 0.10 (s, 6H), 0.05 (s, 6H), 0.01 (s, 6H).

^{13}C{^{1}H} NMR ($CDCl_3$, 300 K, in ppm): δ = 170.8 (C), 135.8 (CH), 123.8 (CH), 78.4 (CH), 73.5 (CH), 64.7 (CH_2), 26.0 (CH_3), 20.9 (CH_3), 18.1 (C), -4.2 (CH_3), -4.3 (CH_3), -4.4 (CH_3).

IR (300 K, ATR, in cm^{-1}): 2930, 2858, 1747, 1473, 1362, 1254, 1102, 1027, 970, 939, 837, 777, 666.

Synthesis of 29



In a Teflon recipient with double seal compound **73** (7.4g, 117 mmol, 1.0eq) was dissolved in MeCN (230mL). Under stirring HF was added (25mL, 690mmol, 47eq) and stirred overnight. The reaction was controlled via TLC (pure Ethyl acetate) and was completed in 50h.

Quenching was performed by careful addition of solid $NaHCO_3$ until the total consumption of the acid shown by the end of the effervescence.

The suspension was then filtered and the solvent removed under reduced pressure.

The crude product was purified via column chromatography on silica gel (Ethylacetate:Hexane 9:1). Analytically pure **29** was then obtained as a colorless oil.

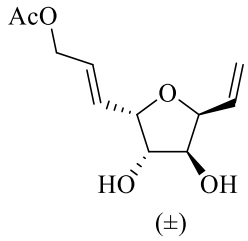
Yield: 3.2 g, (95%)

^{1}H NMR ($CDCl_3$, 300 K, in ppm): δ = 5.92 (m, 4H), 4.62 (d, J = 3.8 Hz, 4H), 4.29 (t, J = 3.7 Hz, 2H), 3.46 (t, J = 2.9 Hz, 1H), 2.96 (brs, 3H), 2.09 (s, 6H).

^{13}C{^{1}H} NMR ($CDCl_3$, 300 K, in ppm): δ = 170.7 (C), 132.8 (CH), 126.9 (CH), 75.4 (CH), 72.3 (CH), 63.9 (CH_2), 20.8 (CH_3).

IR (300 K, ATR, in cm^{-1}): 3432, 3058, 2939, 2890, 1736, 1655, 1439, 1383, 1365, 1243, 1133, 1083, 1027, 971, 886, 822, 735, 702.

Synthesis of 40



(±)

In a two neck round bottomed flask under static Argon atmosphere compound **29** (1.5g, 5.2mmol, 1.0eq) and $BaCO_3$ (1.2eq: 6.6 mmol, 1.3g) were suspended in dry THF (160ml). To the solution was then added $Pd(PPh_3)_4$ (0.49g, 0.42mmol, 0.08eq).

The reaction was controlled via TLC (Ethylacetate:Hexane 9:1) and it was completed in 1h.

The reaction was quenched by the addition of silica gel and then filtrated over silica gel. The solvent was evaporated under reduced pressure.

The crude product was purified *via* column chromatography on silica gel (Ethyl acetate:hexane 1:1)

Compound **40** was then obtained as an inseparable mixture of two diastomers (anti:syn 8:2).

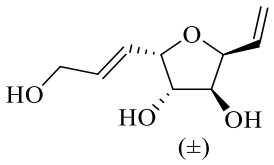
Yield: 932mg (80%)

^{1}H NMR ($CDCl_3$, 300 K, in ppm): δ = 6.04 (m, 1H), 5.90 (m, 2H), 5.59 (d, *J* = 16.3 Hz, 1H), 5.45 (d, *J* = 10.4 Hz, 1H), 5.25 (d, *J* = 10.5 Hz, 1H*), 4.83 (m, 2H), 4.66 (d, *J* = 5.5 Hz, 1H), 4.20 (m, 2H), 4.07 (m, 2H*), 2.10 (s, 3H), 2.07 (s, 3H*), 1.80 (brs, 1H), 1.61 (brs, 1H).

^{13}C{^{1}H} NMR ($CDCl_3$, 300 K, in ppm): δ = 170.7 (C), 136.4 (CH), 132.6 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 128.1 (CH), 119.0 (CH_2), 116.7 (CH_2), 86.1 (CH), 82.1 (CH), 81.5 (CH), 80.6 (CH), 79.1 (CH), 77.7 (CH), 77.3 (CH), 76.9 (CH), 64.1 (CH_2), 64.0 (CH_2), 20.8 (CH_3).

IR (300 K, ATR, in cm^{-1}): 3448, 3056, 1735, 1369, 1266, 1026, 934, 737.

Synthesis of 74



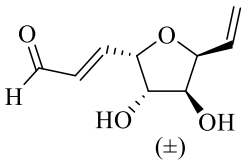
Acetate deprotection was performed by using the ion exchange resin Dowex IX8-200

Resin preparation:
1g of Dowex IX8-200 resin functionalized with Cl^- was placed in a round bottom flask with a NaOH 0.1 M solution (15mL). The mixture was stirred for 2h at room temperature than filtered, washed with 20mL of NaOH 0.1M and 30 mL of water. The washed resin was than suspended again in NaOH 0.1M (15mL) and kept stirred for other 2h. After that the resin was filtered again, washed with water and dried *in vacuo* overnight.

Compound **40** (180mg, 0.8mmol, 1eq) was dissolved in MeOH (15mL) and the activated resin (720mg) added under stirring.
The reaction was monitored *via* TLC (pure Ethylacetate) and was completed in 6h.
The reaction mixture was then filtered and the solvent removed under reduced pressure.
Compound **74** was obtained as a mixture of two inseparable diasteromers (anti:syn 8:2).

Yield: 130mg (90%)
^{1}H NMR (CD3OD, 300 K, in ppm): δ = 5.91 (m, 3H), 5.36 (dt, *J* = 17.1, 1.5 Hz, 1H), 5.30 (m, 1H*), 5.25 (m, 1H), 5.16 (m, 1H*), 4.62 (dd, *J* = 5.7, 3.3 Hz, 1H), 4.46 (m, 2H*), 4.12 (m, 2H), 4.08 (m, 1H*), 4.03 (m, 1H), 3.96 (m, 1H*), 3.88 (m, 1H*), 2.54 (brs, 2H), 2.09 (s, 3H).
^{13}C{^{1}H} NMR (CD3OD, 300 K, in ppm): δ = 139.0 (CH), 135.9 (CH), 135.0 (CH), 134.7 (CH), 128.2 (CH), 127.8 (CH), 118.5 (CH_2), 117.1 (CH_2), 88.3 (CH), 84.0 (CH), 83.5 (CH), 83.2 (CH), 80.9 (CH), 80.4 (CH), 80.3 (CH), 63.4 (CH_2).
IR (300 K, ATR, in cm^{-1}): 3370, 2924, 1645, 1428, 1026, 933, 877, 778.

Synthesis of 75



In a two necked round bottomed flask under static Argon atmosphere compound **74** (106mg, 0.57mmol, 1.0eq) was dissolved in dry DCM. Under stirring was added solid MnO_2 in 5 portions (2,0g, 23.0mmol, 40eq) over 2h.

The reaction was monitored via TLC (pure Ethyl acetate) and it was completed in 3h.

Quenching was performed by filtration over Celite with abundant washes and the solvent removed under reduced pressure.

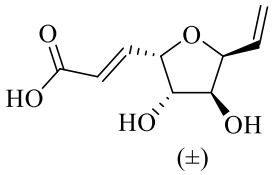
Crude 57 was then used in the following step without further purifications.

75 was obtained as a colorless solid.

Yield: 90mg (85%)

^{1}H NMR (CD_3OD, 300 K, in ppm): δ = 9.61 (d, J = 7.8, 1H), 6.89 (dd, J = 15.7, 4.8, 1H), 6.47 (ddd, J = 15.7, 7.8, 1.4 Hz, 1H), 5.91 (m, 1H), 5.56 (d, J = 17.3 Hz, 1H), 5.43 (d, J = 10.5 Hz, 1H), 5.00 (m, 1H), 4.84 (m, 1H), 4.40 (m, 1H), 4.16 (d, J = 1.6 Hz, 1H), 2.09 (brs, 1H), 1.97 (brs, 1H).

Synthesis of 75



In a round bottomed flask under room atmosphere compound **77** (50mg, 0.27mmol, 1.0eq) was dissolved in tBuOH (1.4mL) and 2-methyl-2-butene (115µL, 1.10mmol, 4eq) was added. Then 1.6mL of aqueous solution containing $NaClO_2$ (73.3mg, 0.810mmol, 3eq) and NaH_2PO_4 (128.6mg, 1.08mmol, 4eq) was added under stirring.

The reaction was monitored via TLC (Pure Ethyl acetate) and was completed in 3h.

The quenching was performed by adding silica gel to the reaction mixture than removing the solvent under reduced pressure.

Reaction crude so adsorbed over silica was purified via column chromatography on silica gel (Pure Ethyl acetate acidified with 3% HCOOH).

Analytically pure **75** was obtained as a colorless solid.

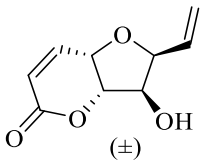
Yield: 37.6 mg (70%)

^{1}H NMR (CD_3OD, 300 K, in ppm): δ = 6.97 (dd, J = 15.6, 5.3 Hz, 1H), 6.02 (m, 2H), 5.46 (d, J = 16.9 Hz, 1H), 5.27 (d, J = 10.3 Hz, 1H), 4.79 (ddd, J = 5.5, 3.6, 1.5 Hz, 1H), 4.61 (dd, J = 7.3, 3.1 Hz, 1H), 4.19 (d, J = 2.9 Hz, 1H), 4.05 (d, J = 2.4 Hz, 1H), 2.17 (s, 2H).

^{13}C{^{1}H} NMR (CD_3OD, 300 K, in ppm): δ = 170.3 (C), 146.1 (CH), 135.6 (CH), 124.2 (CH), 118.7 (CH_2), 84.3 (CH), 81.9 (CH), 80.2 (CH), 80.1 (CH).

IR (300 K, ATR, in cm^{-1}): 3430, 3054, 2987, 2928, 2306, 1708, 1640, 1607, 1551, 1422, 1264, 1156, 1098, 1014, 896, 739.

Synthesis of 64



In a round bottomed flask under static argon atmosphere compound **75** (35mg, 0.175mmol, 1.0eq) was dissolved in 3.5 mL of DCM. Then were added under stirring pyridine (28µL, 0.450mmol, 2.0eq), pyridinium chloride (40.4mg, 0.350mmol, 2.2eq) and 2,4,6-Trichlorobenzoyl Chloride (55□L, 0.350mmol, 2.0eq).

The reaction was monitored via TLC (Pure Ethyl acetate) and was completed in 12h.

The reaction was quenched with a satured solution of $NaHCO_3$ and extracted with Ethyl Acetate. The collected organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure.

Reaction crude was purified via column chromatography on silica gel (hexane : ethyl acetate 6:4).

Analytically pure **64** was obtained as a colorless oil.

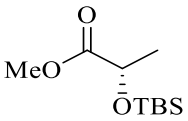
Yield: 17.8mg (56%)

^{1}H NMR (CD_3OD, 300 K, in ppm): δ = 7.02 (dd, *J* = 9.8, 5.3 Hz, 1H), 6.14 (d, *J* = 9.8 Hz, 1H), 5.98 (ddd, *J* = 17.4, 10.4, 7.0 Hz, 1H), 5.47 (d, *J* = 17.2 Hz, 1H), 5.27 (d, *J* = 10.3 Hz, 1H), 4.94 (dd, *J* = 4.5, 1.5 Hz, 1H), 4.70 (t, *J* = 4.9 Hz, 1H), 4.51 (dd, *J* = 7.1, 3.4 Hz, 1H), 4.32 (dd, *J* = 3.5, 1.5 Hz, 1H).

^{13}C{^{1}H} NMR (CD_3OD, 300 K, in ppm): δ = 163.6 (C), 143.3 (CH), 134.6 (CH), 123.5 (CH), 119.4 (CH_2), 87.0 (CH), 84.6 (CH), 78.8 (CH), 69.0 (CH).

IR (300 K, ATR, in cm^{-1}): 3434, 3082, 2923, 1723, 1638, 1429, 1387, 1363, 1251, 1155, 1085, 1048, 1013, 938, 880, 850, 824, 753.

Synthesis of 79



In a two necked round bottomed flask under static Argon atmosphere Methyl-L(-)Lactate (1.0mL, 10.5mmol, 1.0eq) was dissolved in 10.5 mL of THF. TBSCl (2.30g, 15mmol, 1.4eq), Et_3N (3.8mL, 27.0mmol, 2.6eq) and DMAP (0.130g, 1.0mmol, 0.1eq) were added to the reaction mixture and stirred at room temperature.

The reaction was controlled via TLC (Hexane:Ethyl acetate 7:3) and was completed in 12h.

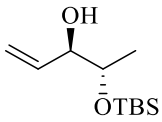
The reaction mixture was then filtrated over Celite and washed with DCM. The solvent was removed *in vacuo*.

The crude product was purified via column chromatography on silica gel (Ethyl acetate:hexane 9:1). Analytically pure **79** was obtained as a colorless oil.

Yield: 1.70g (75%)

Spectroscopical data match with those reported in literature.[37]

Synthesis of 81



In a two necked round bottomed flask under static Argon atmosphere compound **79** (630mg, 2.9mmol, 1.0eq) was dissolved in 11.5 mL of dry Et_2O and cooled to -78 °C. Then DIBAL-H (3.15mL, 3,15mmol, 1M in hexane, 1.1eq) was added dropwise to the vigorously stirred solution. Terminated the additions the reaction was kept at -78 °C for 15 minutes and controlled via TLC (hexane:ethyl acetate 7:3) to confirm the consumption of the reagent. Then vinyl magnesium bromide (9.1 mL, 6.37mmol, 0.7M in THF, 2.2eq) was added dropwise and the reaction was allowed to reach room temperature and stirred overnight.

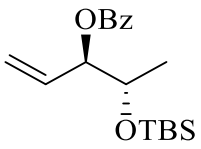
The reaction was then controlled via TLC (hexane:ethyl acetate 7:3) and it was completed in 12h. A saturated solution of Rochelle salts was added and stirred for 6h. The organic layer was isolated and the aqueous one was extracted with diethyl ether and washed with brine. The organic phases were reunited, dried over Na_2SO_4 and then the solvent removed under reduced pressure.

Reaction crude was purified via column chromatography on silica gel (ethyl acetate:hexane 95:5) yielding pure compound **81** as a colorless oil.

Yield: 345mg (55%)

Spectroscopical data match with those reported in literature.[37]

Synthesis of 65



In a two neck round bottomed flask under static Argon atmosphere to a 0.4M solution of 50 mg(0.23mmol) of crude allylic alcohol **81** in dry pyridine (0,6mL) was added BzCl (1.5 equiv: 40µL, 0.35mmol) at 0 °C. After 15 min, the solution was warmed to room temperature and stirred for a further 15 min.

The reaction is controlled via TLC (hexane/Ethylacetate 95/5) and is complete in 1 hour.

Thereaction was quenched by the addition of MeOH (0.5 mL) and adsorbed on silica gel removing the solvent under reduced pressure.

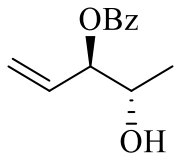
The adsorbed crude was then purified via column chromatography on silica gel (eluent: Hexane/Ether 99/1)

pure compound **65** was obtained.

Yield = 71mg (95%)

Spectroscopical data match with those reported in literature.[37]

Synthesis of 76



In a Teflon recipient with double seal compound **65** (200 mg, 0.62 mmol, 1eq) was dissolved in MeCN (2mL). Under stirring HF was added (340 µL, 9.3mmol, 27.6M in H_2O, 15eq) and stirred overnight.

The reaction was controlled via TLC (pure Ethylacetate) and was completed in 12h.

Quenching was performed by careful addition of solid $NaHCO_3$ until the total consumption of the acid shown by the end of the effervescence.

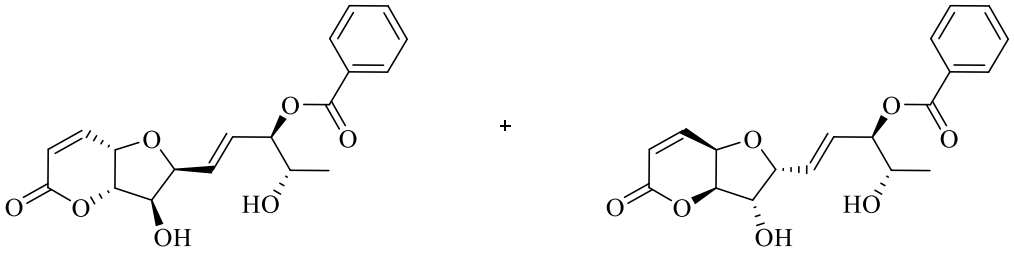
The suspension was then filtered and the solvent removed under reduced pressure.

The crude product was purified via column chromatography on silica gel (Ethylacetate:Hexane 8:2). Analytically pure **76** was then obtained as a colorless oil.

Yield: 110mg (86%)

Spectroscopical data match with those reported in literature.[37]

Synthesis of 77 and 78



77 **78**

In a vial, compound **64** (10 mg, 0.055 mmol, 1eq) was dissolved in dry degassed DCM (0.6 mL) under Ar atmosphere, then **76** (52 mg, 0,18 mmol, 3eq) was added, followed by Grubbs II catalyst (4.7 mg, 0.0055 mmol, 0.1 eq). Reaction mixture was kept under vigorous stirring at r.t. and was monitored by TLC (Hex:AcOEt 4:6). After 30 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 (gradient Hex:AcOEt from 6:4 to 2:8) to give product **77** and **78** as a mixture of two inseparable diastomers. Aspect: colorless oil.

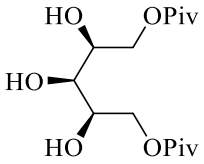
Yield: 12.1mg (47%)

^{1}H NMR (CDCl$_3$, 300 K, in ppm): δ = 8.13 - 7.99 (m, 2H), 7.68 - 7.37 (m, 3H), 7.02 - 6.84 (m, 1H), 6.21 - 6.03 (m, 2H), 5.85 (dd, *J* = 16.4, 5.9 Hz, 1H), 5.31 - 5.42 (m, 1H), 4.98 (d, *J* = 4.5 Hz, 1H), 4.86 - 4.66 (m, 2H), 4.38 (d, *J* = 2.9 Hz, 1H), 4.13 (d, *J* = 8.7 Hz, 1H),1.51 – 1.40 (m, 3H).

IR: 3436, 3064, 2954, 2929, 2893, 2856, 1721, 1379, 1360, 1315, 1270, 1252, 1153, 1086 1045, 1026, 1008, 974, 942, 835, 777, 713.

ESI MS $[C_{25}H_{34}O_7SiNa]^+$: 497.20 100%, 498.20 27%. **Found:** 497,17 100%, 498,17 27%

Synthesis of 82



In a two necked round bottomed flask, under static Argon atmosphere, were placed adonitol **16** (9.05g, 59.5 mmol, 1eq) and pyridine (140 mL). The solution was than cooed to 0°C and PivCl (18.3 mL, 150 mmol, 2.5eq) was slowly added. After 15 minutes the reaction was allowed to reach room temperature and stirred overnight. The reaction was monitored via TLC (toluene:acetone 3:1) and was completed in 15h. The volatiles were then removed *in vacuo* and then diluted in H_2O and extracted with ethyl acetate. The collected organic phases were washed with brine, dried over Na_2SO_4 and brought to dryness. The crude product was purified via column chromatography on silica gel (toluene:acetone 3:1) yieldin analytically pure, colorless product **82**.

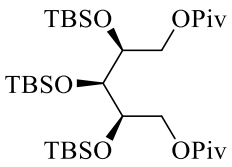
Yield: 15.1g (80%)

^{1}H NMR ($CDCl_3$, 300 K, in ppm): δ = 4.44 (dd, *J*= 12.0, 4.9 Hz, 2H), 4.34 (dd, *J* =12.0, 2.8 Hz, 2H), 3.88 (m, 2H), 3.43 (m, 4H), 1.25 (s, 18H).

^{13}C{^{1}H} NMR ($CDCl_3$, 300 K, in ppm): δ = 180 (C), 73(CH), 69.8(CH), 65,9 (CH_2), 32.9 (C), 27.1 (CH_3)

IR (300 K, ATR, in cm^{-1}): 3458, 2973, 2936, 2910, 2875, 1711, 1482, 1461, 1399, 1288, 1229, 1168, 1066, 1036.

Synthesis of 84



In a two neck round bottomed flask under static Argon atmosphere compound **82** (14.1g, 44mmol, 1eq), imidazole (15.0g, 220mmol, 5eq) and DMAP (1.6g, 13 mmol, 0.3eq) were dissolved in dry DMF (340mL). The solution was cooled to 0°C and TBSCl (30.0 g, 0.198 mmol, 4.5eq), was slowly added. After the addition the reaction was allowed to reach room temperature and then heated with an oil bath to 50 °C for two days keeping it constantly stirred.

The reaction was monitored via TLC (toluene/acetone 3/1 and Hexane/MTBE 95/5) and was completed in 40h.

Quenching with a mixture of ice, hexane and saturated $NaHCO_3$ was performed.

The aqueous layer was than separated from the organic phase and extracted three times with a solution of hexane:MTBE 9:1.

Organic extracts were reunited and washed with water and then brine, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure.

The crude product was purified over column chromatography on silica gel (Hexane:MTBE 98:2) yielding **84** as a colorless oil.

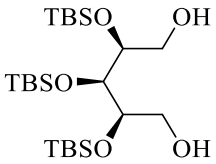
Yield: 26.7g (90%)

^{1}H NMR ($CDCl_3$, 300 K, in ppm): δ = 4.29 (dd, J= 11.8, 1.8 Hz, 2H), 4.0 (m, 5H), 1.23 (s, 18H), 0.90 (d, J = 9.9 Hz, 27H), 0.13 (m, 18H).

^{13}C{^{1}H} NMR ($CDCl_3$, 300 K, in ppm): δ =178.4 (C), 78.5 (CH), 71.5 (CH), 65.4 (CH_2), 38.7 (C), 27.2 (CH_3), 25.8 (CH_3), 25.5 (CH_3), 17.9 (C), -4.5 (CH_3).

IR (300 K, ATR, in cm^{-1}): 2958, 2931, 2886, 2858, 1732, 1472, 1462, 1362, 1283, 1255, 1154, 1110, 1092, 1036, 1021, 1005, 962, 830, 811, 778.

Synthesis of 85



In a two neck round bottomed flask under static Argon atmosphere compound **84** (14.9g, 2.25mmol, 1.0eq) was dissolved in toluene (225mL). The solution was cooled to -78°C, then DIBAL-H was added dropwise (80.5mL, 120mmol, 1.2M in hexane, 4.3eq).

The mixture was left to stir at -78°C, monitored *via* TLC (Hexane:MTBE 8:2) and was complete in 3h. The solution was then quenched by adding a solution of Rochelle's Salt at such temperature and left to stir overnight allowing it to reach room temperature.

The organic phase was than separated from the aqueous layer and extracted three time with ethyl acetate. Organic fractions were collected and washed with brine, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure.

No further purification was performed.

The work up yielded **85** as analytically pure, colorless solid.

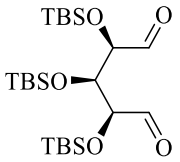
Yield: 10,87 g (97%)

^{1}H NMR ($CDCl_3$, 300 K, in ppm): δ = 3.90 (m, 3H), 3.68 (m, 4H), 2.00 (m, 2H), 0.95 (s, 27H), 0.15 (s, 18H)

^{13}C{^{1}H} NMR ($CDCl_3$, 300 K, in ppm): δ = 76.8 (CH), 73.4 (CH), 63.15 (CH_2), 25.8 (CH_3), 18.0 (C), -4.4 (CH_3)

IR (300 K, ATR, in cm^{-1}): 3361, 2953, 2929, 2886, 2857, 1471, 1388, 1360, 1255, 1125, 1075, 1032, 1005, 833, 777, 747.

Synthesis of 86



In a two neck round bottomed flask under static Argon atmosphere oxalyl chloride (4.5 mL, 53.5mmol, 3.0eq) was dissolved in DCM (128mL). The solution was cooled to -78°C, then a solution of DMSO (5 mL, 71.4 mmol, 4.0eq) in DCM (12.5 mL) was slowly added. After 10 minutes a solution of **85** (8.8g, 17.8 mmol, 1.0eq) in DCM (54 mL) was added and kept stirred for 0.5h minutes. At this point Et_3N was added leading the appearance of an intense yellow coloration. After 10 minutes at -78°C, the reaction was allowed to reach room temperature.

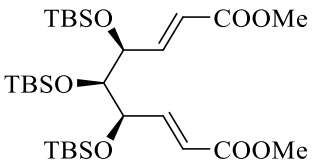
The reaction was controlled via TLC (Hexane:Acetate 9:1) and was complete in 1.5h.

It was then quenched with water and the layers separated. The aqueous layer was extracted 3 times with Hexane.

Organic moieties were collected and washed with a saturated solution of $NaHCO_3$, brine, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure.

The crude product **86** was used in the following step without further purifications.

Synthesis of 87



In a two neck round bottomed flask under static Argon atmosphere crude **86** was dissolved in THF (180mL). The solution was cooled to 0°C and under vigorous stirring $Ph_3PCHCOOMe$ (29.8g, 89.2mmol, 5.0eq) was added. The reaction temperature was then allowed to reach room temperature and successively warmed to 50°C and left to stir overnight at this temperature.

The reaction was controlled via TLC (Hexane:MTBE 9:1) and was completed in 24h. It was quenched with a saturated NH_4Cl solution. The phases were separated, the aqueous layer was extracted with Et_2O.

Organic extracts were reunited and washed with water and then brine, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure.

The reaction crude was than purified with column chromatography on silica gel (gradient from Hexane:MTBE 99:1 to 96:4).

Analytically pure **87** was then obtained as a colorless solid.

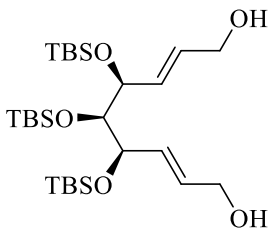
Yield: 8.5g (80%)

^{1}H NMR ($CDCl_3$, 300 K, in ppm): δ = 7.00 (dd, *J* = 15.7, 5.4 Hz, 2H), 6.02 (d, *J* = 15.7 Hz, 2H), 4.42 (*pseudo*-t, *J* = 5.1 Hz, 2H), 3.76 (s, 6H), 3.70 (t, *J* = 4.4 Hz, 1H), 0.89 (s, 18H), 0.84 (s, 9H), 0.08 (m, 18H).

^{13}C{^{1}H} NMR ($CDCl_3$, 300 K, in ppm): δ = 166.5 (C), 148.2 (CH), 127.9 (CH), 80.8 (CH), 73.1 (CH), 51.4 (CH_3), 25.8 (CH_3), 18.1 (C), -4.4 (CH_3), -4.7 (CH_3).

IR (300 K, ATR, in cm^{-1}): 2954, 2931, 2888, 2858, 1728, 1472, 1463, 1435, 1361, 1256, 1191, 1166, 1122, 1006, 980, 950, 939, 835, 813, 779.

Synthesis of 88



In a two neck round bottomed flask under static Argon atmosphere compound **87** (8.2g, 13.6 mmol, 1eq) was dissolved in THF (105mL). The solution was cooled to -78°C and kept stirred while DIBAL-H (109mL, 109 mmol, 1.0M in hexane, 8eq) was added dropwise. The reaction was left to stir at 78°C for 1.5h. After completion via TLC (Hexane:Ethyl acetate 8:2), a saturated solution of Rochelle's Salt was added. The biphasic system was stir overnight at rt.

The organic phase was than separated from the aqueous layer and extracted three time with diethyl ether. Organic moieties were reunited and washed with brine, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure.

The crude product was purified *via* column chromatography on silica gel (hexane:ethylacetate 9:1). Analytically pure **88** was obtained in quantitative yield as a colorless oil.

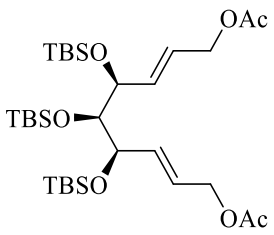
Yield: 7.4g, quantitative

^{1}H NMR ($CDCl_3$, 300 K, in ppm): δ = 5.72 (m, 4H), 4.18 (t, J = 5.4 Hz, 2H), 4.14 (d, J = 4.5 Hz, 4H), 3.62 (t, J = 4.5 Hz, 1H), 1.85 (brs, 2H), 0.90 (s, 18H), 0.85 (s, 9H), 0.06 (s, 12H), 0.03 (s, 6H).

^{13}C{^{1}H} NMR ($CDCl_3$, 300 K, in ppm): δ = 131.8 (CH), 131.3 (CH), 80.9 (CH), 74.2 (CH), 63.2 (CH_2), 25.9 (CH_3), 18.2 (C), 18.1 (C), -4.0 (CH_3), -4.3 (CH_3), -4.7 (CH_3).

IR (300 K, ATR, in cm^{-1}): 3330, 2954, 2929, 2887, 2857, 1471, 1462, 1388, 1361, 1252, 1084, 1048, 1005, 835, 777, 738, 678.

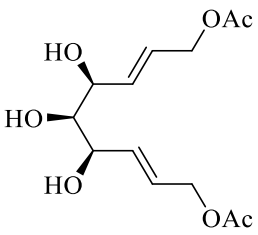
Synthesis of 89



In a two neck round bottomed flask under static Argon atmosphere compound **88** (8.2g, 15 mmol, 1eq) was dissolved in DCM (85mL). Under stirring were added pyridine (0.44mmol, 3.4mL, 2.9eq), Ac_2O (3.4mL, 46.0mmol, 2.4eq) and DMAP (0.30g, 2.5mmol, 0.16eq). The reaction was then stirred overnight at room temperature. After completion, by monitoring *via* TLC (Hexane:Ethylacetate 9:1), the reaction was quenched by adding a saturated $NaHCO_3$ solution and the phases separated.
The organic layer was washed with a saturated solution of $CuSO_4$, water, brine, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure.
The crude product was purified via column chromatography on silica gel (Hexane:Ethylacetate 95:5). Analytically pure **89** was then obtained as a colorless oil.

Yield: 9.2g (93%)
^{1}H NMR ($CDCl_3$, 300 K, in ppm): δ = 5.72 (m, 4H), 4.59 (m, 4H), 4.19 (dd, J = 6.2, 4.8 Hz, 2H), 3.59 (t, J = 4.7 Hz, 1H), 2.07 (s, 6H), 0.91 (s, 18 H), 0.85 (s, 9H), 0.06 (s, 12H), 0.03 (s, 6H).
^{13}C{^{1}H} NMR ($CDCl_3$, 300 K, in ppm): δ = 170.6 (C), 134.9 (CH), 126.0 (CH), 80.5 (CH), 73.9 (CH), 64.3 (CH_2), 25.9 (CH_3), 20.8 (CH_3), 18.2 (C), 18.1 (C), -4.1 (CH_3), -4.2 (CH_3), -4.7 (CH_3).
IR (300 K, ATR, in cm^{-1}): 2955, 2930, 2887, 2857, 1745, 1471, 1463, 1362, 1250, 1087, 1047, 1027, 1005, 973, 939, 835, 777, 680.

Synthesis of 41



In a Teflon recipient with double seal compound **89** (9.3g, 14.7 mmol, 1eq) was dissolved in MeCN (295mL). Under stirring HF was added (25mL, 690mmol, 27.6M in H_2O, 47eq) and stirred overnight. The reaction was controlled via TLC (pure Ethylacetate) and was completed in 50h.

Quenching was performed by careful addition of solid $NaHCO_3$ until the total consumption of the acid shown by the end of the effervescence.

The suspension was then filtered and the solvent removed under reduced pressure.

The crude product was purified via column chromatography on silica gel (Ethylacetate:Hexane 9:1). Analytically pure **41** was then obtained as a colorless oil.

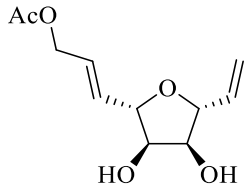
Yield: 3.3 g, (76%)

^{1}H NMR ($CDCl_3$, 300 K, in ppm): δ = 5.92 (m, 4H), 4.62 (d, J = 4.3 Hz, 4H), 4.29 (m, 2H), 3.62 (s, 2H), 2.73 (m, 2H), 2.57 (m, 1H), 2.09 (s, 6H).

^{13}C{^{1}H} NMR ($CDCl_3$, 300 K, in ppm): δ = 170.9 (C), 132.8 (CH), 127.0 (CH), 76.5 (CH), 73.2 (CH), 64.2 (CH_2), 20.9 (CH_3).

IR (300 K, ATR, in cm^{-1}): 3429, 3024, 2891, 1733, 1442, 1383, 1366, 1248, 1075, 1027, 972, 608.

Synthesis of 42



In a two neck round bottomed flask under static Argon atmosphere compound **41** (214mg, 0.742 mmol, 1.0eq) and $BaCO_3$ (180mg, 0.912mmol, 1.2eq) were suspended in dry THF (3.7mL). In a second two neck round bottomed flask were placed ligand (S,S)-DACH-phenyl Trost Ligand (47.4 mg, 0.0594mmol, 90%purity, 0.08eq) and $Pd_2(dba)_3CHCl_3$ (23.5mg, 0.0227mmol, 0.03eq), the solid mixture was dissolved in dry THF (4.1mL) under static Argon atmosphere, after 20 minutes from a brownish red coloration the solution started to became more of an intense yellow-orange color indicating the formation of the desired palladium-phosphine complex. After another 10 to 20 minutes the color became stable and it was cannulated under stirring at room temperature to the solution of substrate **41** in THF.

The reaction was controlled via TLC (Ethylacetate:Hexane 9:1) and it was completed in 1h.

Quenching was performed by addition of silica gel to the reaction mixture and then filtration over silica gel. The solvent was evaporated under reduced pressure.

The crude product was purified *via* column chromatography on silica gel (Ethylacetate:Hexane 1:1). Analytically pure **42** was then obtained as a colorless oil.

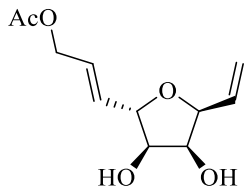
Yield: 116.2mg (70%)

^{1}H NMR ($CDCl_3$, 300 K, in ppm): δ = 5.88 (m, 3H), 5.42 (dt, *J* = 17.1, 1.5 Hz, 1H), 5.26 (dt, *J* = 10.4, 1.4 Hz, 1H), 4.62 (d, *J* = 5.7, 1H), 4.27 (q, *J* = 4.5 Hz, 2H), 3.92 (d, *J* = 1.8 Hz, 2H), 2.54 (brs, 2H), 2.09 (s, 3H).

^{13}C{^{1}H} NMR ($CDCl_3$, 300 K, in ppm): δ = 171.0 (C), 135.75 (CH), 131.72 (CH), 126.91 (CH), 117.5 (CH_2), 84.2 (CH), 82.8 (CH), 75.0 (CH), 64.0 (CH_2), 20.9 (CH_3).

IR (300 K, ATR, in cm^{-1}): 3408, 3086, 3013, 2985, 2931, 1736, 1645, 1428, 1367, 1240, 1108, 1059, 1025, 970, 932, 875, 735, 607.

Synthesis of 91



In a two neck round bottomed flask under static Argon atmosphere compound **41** (214mg, 0.742 mmol, 1.0eq) and $BaCO_3$ (180mg, 0.912mmol, 1.2eq) were suspended in dry THF (3.7mL). In a second two neck round bottomed flask were placed ligand (S,S)-DACH-phenyl Trost Ligand (47.4 mg, 0.0594mmol, 90%purity, 0.08eq) and $Pd_2(dba)_3CHCl_3$ (23.5mg, 0.0227mmol, 0.03eq), the solid mixture was dissolved in dry THF (4.1mL) under static Argon atmosphere, after 20 minutes from a brownish red coloration the solution started to became more of an intense yellow-orange color indicating the formation of the desired palladium-phosphine complex. After another 10 to 20 minutes the color became stable and it was cannulated under stirring at room temperature to the solution of substrate **41** in THF.

The reaction was controlled via TLC (Ethylacetate:Hexane 9:1) and it was completed in 1h.

Quenching was performed by addition of silica gel to the reaction mixture and then filtration over silica gel. The solvent was evaporated under reduced pressure.

The crude product was purified *via* column chromatography on silica gel (Ethylacetate:Hexane 1:1). Analytically pure **91** was then obtained as a colorless oil.

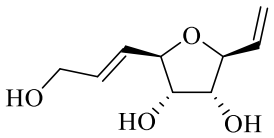
Yield: 29.0mg (18%)

^{1}H NMR ($CDCl_3$, 300 K, in ppm): δ = 5.90 (m, 3H), 5.41 (dt, *J* = 17.3, 1.2 Hz, 1H), 5.33 (dt, *J* = 10.6, 1.4 Hz, 1H), 4.57 (m, 3H), 4.28 (t, *J* = 5.8, 1H), 4.16 (t, *J* = 4.2 Hz, 1H), 4.00 (dd, *J* = 7.5, 4.3 Hz, 1H), 3.00 (brs, 2H), 2.07 (s, 3H).

^{13}C{^{1}H} NMR ($CDCl_3$, 300 K, in ppm): δ = 171.1 (C), 135.9 (CH), 131.6 (CH), 126.5 (CH), 117.5 (CH_2), 84.2 (CH), 82.1 (CH), 74.0 (CH), 64.6 (CH_2), 20.9 (CH_3).

IR (300 K, ATR, in cm^{-1}): 3422, 2924, 2854, 1735, 1654, 1431, 1385, 1370, 1244, 1131, 1064, 1023, 988, 969, 895, 844, 800, 735, 607.

Synthesis of 95



Acetate deprotection was performed by using the ion exchange resin Dowex IX8-200

Resin preparation:

1g of Dowex IX8-200 resin functionalized with Cl^- was placed in a round bottom flask with a NaOH 0.1 M solution (15mL). The mixture was stirred for 2h at room temperature than filtered, washed with 20mL of NaOH 0.1M and 30 mL of water. The washed resin was than suspended again in NaOH 0.1M (15mL) and kept stirred for other 2h. After that the resin was filtered again, washed with water and dried *in vacuo* overnight.

Compound **42** (153mg, 0.68mmol, 1eq) was dissolved in MeOH (13mL) and the activated resin (612mg) added under stirring.

The reaction was monitored *via* TLC (pure Ethylacetate) and was completed in 6h.

The reaction mixture was then filtered, and the solvent removed under reduced pressure.

Analytically pure **95** was obtained as a colorless solid.

Yield: 107mg (86%)

^{1}H NMR (CD_3OD, 300 K, in ppm): δ = 5.94 (m, 2H), 5.76 (ddd, *J* = 15.4, 6.6, 1.6 Hz, 1H), 5.37 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.20 (dd, *J* = 10.5, 1.5 Hz, 1H), 4.26 (m, 1H), 4.10 (d, *J* = 5.0 Hz, 1H), 3.82 (m, 1H).

^{13}C{^{1}H} NMR ($CDCl_3$, 300 K, in ppm): δ = 138.5 (CH), 133.7 (CH), 130.5 (CH), 117.2 (CH_2), 85.7 (CH), 84.9 (CH), 76.9 (CH), 76.8 (CH), 63.1 (CH_2).

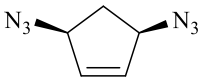
IR (300 K, ATR, in cm^{-1}): 3385, 2924, 2856, 2513, 1718, 1656, 1416, 1390, 1321, 1266, 1108, 1069, 992, 933, 712.

X-Ray diffraction data

Empirical formula	$C_9 H_{14} O_4$
Formula weightin (g mol^{-1})	186.20
Temperature in K	100.00
Crystal system	orthorhombic

Space group	P 2_1 2_1 2_1
a in Å	4.77758(4)
b in Å	11.23387(7)
c in Å	16.40742(14)
a in °	90
b in °	90
g in °	90
Volume in $Å^3$	880.598
Z	4
ρ_c in (g cm^{-3})	1.404
μ in mm^{-1}	0.924
F(000)	400
Crystal size in mm^3	0.45 x 0.306 x 0.011
$\lambda_{XK\alpha}$in Å (X = Cu)	1.54184
Θ_{min} in °	4.7660
Θ_{max} in °	76.4730
Index ranges	-4 ≤ h≤ 5 -14 ≤ k≤ 14 -20 ≤l ≤ 20
Reflectionscollected	1829
Independentreflections	1812
R_{int} / R_{sigma}	0.0301/ 0.0340
Data / restraints / parameters	1829 / 0 / 130
GooF on F^2	1.059
Final R indices (all data)	R_1 = 0.0236 wR_2 = 0.0626
Highest diff. peak and hole in (e $Å^3$)	0.188 and -0.136

Synthesis of 100



(1R,3S)-cyclopent-4-ene-1,3-diol (0.757g, 7.56mmol, 1.0eq) was solubilized in THF (15mL). The solution was cooled down to 0°C and DPPA (4mL, 18.2mmol, 2.4eq) and DBU (2.71mL, 18.2mmol, 2.4eq) were then added dropwise. The mixture was allowed to reach rt and left to stir overnight. The reaction was monitored with TLC (100% DCM). At the completion it was quenched by removing the solvent under reduced pressure and then directly purified by column chromatography on silica gel (Pentane:DCM 9:1).

Analytically pure **100** was then obtained as a colorless oil.

Yield: 1.05g (93%)

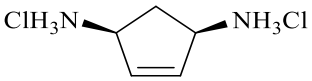
Molecular Weight:150,1450 **Found:** 150.02

^{1}H NMR ($CDCl_3$, 300 K, in ppm): δ = 6.08 (s, 2H), 4.35 (dd, J = 7.9, 4.2 Hz, 2H), 2.74 (ddd, J = 14.6, 8.2, 7.5 Hz, 1H), 1.83 (dt, J = 14.7, 4.2 Hz, 1H)

^{13}C{^{1}H} NMR ($CDCl_3$, 300 K, in ppm): δ = 133.60 (CH), 64.42 (CH), 36.55 (CH_2).

IR (300 K, ATR, in cm^{-1}): 3318, 3068, 2946, 2484, 2094, 1441, 1360, 1310, 1252, 1117, 1058, 990, 945, 773, 686, 557, 509.

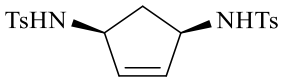
Synthesis of 101



In a two necked round bottomed flask under static Argon atmosphere compound **100** (4.10g, 27.3 mmol, 1.0eq) was solubilized in THF (130mL). PPh_3 (17.2g, 65.5mmol, 2.4eq) was then added and left to stir at rt for 4h. After that H_2O (1.18ml, 2.4eq, 65.5mmol) was added dropwise. The mixture was left to stir overnight. Quenching was performed by evaporating the solvent at the rotavap. The solid was solubilized in DCM (100mL), followed by the addiction of HCl_{aq} (50mL, 2M). The biphasic system was vigorously stirred for 10min, then the two phases were separated and the aqueous layer washed with DCM (4 x 100mL) and brought to dryness.
The crude product was recrystallized by MeOH.
Analytically pure **101** was then obtained as a colorless solid.

Yield: 3.53g (76%)
^{1}H NMR (D_2O, 300 K, in ppm): δ = 6.17 (s, 2H), 4.67 (s, 6H), 4.40 (dd, *J* = 8.3, 5.7 Hz, 2H), 2.99 (dt, *J* = 14.6, 8.3 Hz, 1H), 1.82 (dt, *J* = 14.7, 5.7 Hz, 1H)
^{13}C{^{1}H} NMR (D_2O, 300 K, in ppm): δ = 133.40 (CH), 54.90(CH), 32.86 (CH_2).
IR (300 K, ATR, in cm^{-1}): 3054, 2987, 1604, 1551, 1422, 1264, 1156, 896, 744.
m.p.: 248 °C (decomp)

Synthesis of 102



In a round bottomed flask under air **101** (3.53g, 20.6mmol, 1.0eq) was solubilized in $NaOH_{aq}$ (65mL, 2M), in a second flask under air was prepared a solution of TsCl (7.91g, 41.5mmol, 2.01eq) in DCM (350mL). The second solution was then transferred in the first flask. The biphasic system was left to stir vigorously at rt. The reaction was controlled via TLC (ethyl acetate:hexane 6:4) and was completed in 4h. The phases were then separated and the aqueous layer was extracted with DCM (3 x 100mL). Organic extracts were reunited and washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure.

The crude product was than purified by column chromatography on silica gel (ethyl acetate:hexane 1:1).

Analytically pure **102** was then obtained as a colorless solid.

Yield: 8.06g (96%)

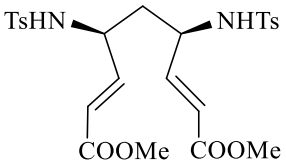
^{1}H NMR ($CDCl_3$, 300 K, in ppm): δ = 7.73 (d, J = 8.2 Hz, 4H), 7.31 (d, J = 7.64 Hz, 4H), 5.42 (m, 4H), 4.18 (td, J = 8.7, 4.9 Hz, 2H), 2.45 (m, 7H), 1.30 (m, 1H).

^{13}C{^{1}H} NMR ($CDCl_3$, 300 K, in ppm): δ = 143.47 (C), 137.57 (C), 133.61 (C), 129.69 (CH), 126.93 (CH), 57.27 (CH), 39.32 (CH_2), 21.47 (CH_3).

IR (300 K, ATR, in cm^{-1}): 3281, 3056, 2986, 2925, 1598, 1424, 1335, 1265, 1160, 1093, 1080, 1023, 906, 815, 738, 704, 666, 580, 550.

m.p.: 113-115 °C

Synthesis of 104



Alkene **102** (548mg, 1.35mmol, 1.0eq) was solubilized in dry DCM (25mL). 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 to remove oxygen.

Under vigorous stirring, at -78°C, a solution of pyridine (3 drops) in dimethyl sulfide (0.792mL, 10.8mmol, 8.0eq) was added dropwise to the mixture and the temperature was slowly raised to rt overnight. The solvent was then removed under reduced pressure.

The crude oil was directly dissolved in dry THF (10mL) under Ar atmosphere and subsequently it was transferred via cannula into a round bottomed flask containing a THF solution (10mL) of $PPH_3CHCOOMe$ (1.35g, 4.04mmol, 3.0eq) that was kept under vigorous stirring.

After 0.5h, the temperature was raised at 50°C and the mixture was stirred overnight. The reaction was monitored by TLC (hexane:ethyl acetate 4:6). It was quenched through addiction of NH_4Cl satured aqueous solution (5mL) and diluted with H2O (5mL). Phases were separated, then the aqueous one was extracted with THF (5 x 10mL). The combined organic layers were washed with Brine (5mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the resulting crude material was filtered on a silica gel pad by washing with hexane:ethyl acetate 4:6. Finally the raw product was purified by flash column chromatography on silica gel (hexane:ethyl acetate 6:4).

Analytically pure **104** was then obtained as a colorless solid.

Yield: 0.353g (48%)

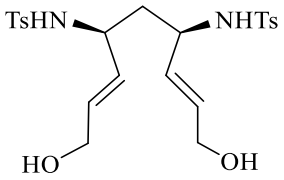
^{1}H NMR ($CDCl_3$, 300 K, in ppm): δ = 7.69 (d, J = 8.1 Hz, 4H), 7.26 (d, J = 8.1 Hz, 4H), 6.48 (dd, J = 15.7, 6.8 Hz, 2H), 5.87 (d, J = 9.2 Hz, 2H), 5.50 (dd, J = 15.7, 1.2 Hz, 2H), 3.99 (m, 2H), 3.65 (s, 6H), 2.39 (s, 6H), 1.89 (m, 2H).

^{13}C{^{1}H} NMR ($CDCl_3$, 300 K, in ppm): δ = 166.13 (C), 145.13 (CH), 143.63 (C), 137.28 (C), 129.62 (CH), 127.06 (CH), 121.93 (CH), 51.61 (CH_2), 51.39 (CH), 40.01 (CH_2), 21.34 (CH_3).

IR (300 K, ATR, in cm^{-1}): 3260, 3055, 2987, 1736, 1598, 1434, 1344, 1265, 1162, 1092, 1027, 896, 816, 739, 705, 670, 597, 552.

m.p.: 104-107 °C

Synthesis of 95



In a two necked round bottomed flask equipped with a preassure equalizing funnel, esther **104** (3.49g, 6.35mmol, 1.0eq), was dissolved in dry THF (120mL) under Ar atmosphere. The funnel was charged with DIBAL-H (38.1mL, 38.1mmol, 1M in THF, 6eq) and the reaction mixture was cooled down to -78°C. The DIBAL-H solution was added dropwise and under vigorous stirring, to the ester solution. Reaction was monitored by TLC (pure ethyl acetate) and it was completed after 2h.

The mixture was then quenched by the addiction of a satured Rochelle salt solution (300mL) and H_2O (100mL) at -78°C. The 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 THF (6 x 100mL). The combined organic layers were washed with Brine (100mL), then dried over Na_2SO_4, filtered and the solvent removed under reduced preassure. Finally the raw product was purified by flash column chromatography on silica gel (gradient hexane:ethyl acetate from 3:7 to 0:10).

Analytically pure **95** was then obtained as a colorless solid.

Yield: 2.86g (91%)

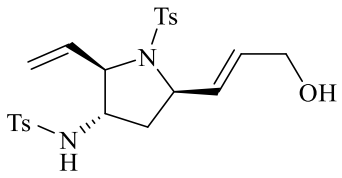
^{1}H NMR (CD_3OD, 300 K, in ppm): δ = 7.70 (d, J = 8.2 Hz, 4H), 7.30 (d, J = 8.2 Hz, 4H), 5.28 (m, 4H), 4.88 (s, 4H), 3.74 (m, 4H), 3.33 (m, 2H), 2.43 (s, 6H), 1.80 (m, 1H), 1.61 (m, 1H).

^{13}C{^{1}H} NMR (CD_3OD, 300 K, in ppm): δ = 144.67 (C), 140.35 (C), 133.19 (CH), 130.84 (CH), 130.40 (CH), 128.61 (CH), 62.90 (CH_2), 53.98 (CH), 43.89 (CH_2), 21.76 (CH_3).

IR (300 K, ATR, in cm^{-1}): 3200, 2954, 2923, 2854, 1459, 1377, 1276, 1261, 1155, 1081, 932, 764, 749, 724, 655, 543.

m.p.: 138 °C

General procedure to cyclization leading to **96**



Generally L(AuCl) (5 mol%) and AgX (5 mol%) were suspended in dry solvent (0.05M) in presence of molecular sieves 3Å and under Argon atmosphere. The mixture was stirred for 15 minutes at room temperature, till the formation of the complex was completed. The suspension switched from colorless to a slight violet.

In another flask, the *meso* diamine **95** was dissolved in dry solvent (0.1 M) under Argon atmosphere and the catalyst containing solution previously prepared was cannulated.

The mixture was stirred till the reaction was completed.

Reaction was monitored by TLC and when it was completed it was quenched by filtration on a silica pad by washing with EtOAc.

The resulting crude material was purified by liquid chromatography (EtOAc:Hexane 8:2) on silica gel to give analytical pure cyclized product.

Enantiomeric excess was determined by chiral UHPLC, on Kromasil 3-AmyCoat ReversePhase. Elution (isocratic): Water (0,2% HCOOH)/MeCN (0,2% HCOOH) = 65/35, UV detection: λ = 204 nm.

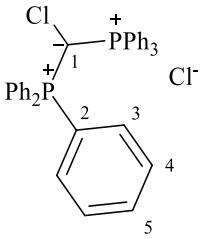
^{1}H NMR ($CDCl_3$, 300 K, in ppm): δ = 7.68 (t, *J* = 8.2 Hz, 4H), 7.32 (dd, *J* = 8.1, 4.8 Hz, 4H), 5.84 – 5.49 (m, 3H), 5.28 – 5.06 (m, 2H), 4.58 (d, *J* = 7.5 Hz, 2H), 4.24 (q, *J* = 7.6 Hz, 2H), 4.07 (dt, *J* = 6.9, 3.4 Hz, 1H), 3.51 (td, *J* = 6.0, 4.8, 2.7 Hz, 1H), 2.45 (s, 6H), 1.89 (d, *J* = 11.3 Hz, 2H).

^{13}C{^{1}H} NMR ($CDCl_3$, 300 K, in ppm): δ = 144.34 (C), 143.85 (C), 137.04 (C), 135.42 (CH), 134.85 (C), 133.84 (CH), 129.77 (CH), 129.70 (CH), 127.70 (CH), 126.93 (CH), 126.38 (CH), 117.81 (CH_2), 68.21 (CH), 63.68 (CH_2), 59.86 (CH), 57.21 (CH), 37.53 (CH_2), 21.50 (CH_3), 21.46 (CH_3).

IR (300 K, ATR, in cm^{-1}): 3260, 3054, 2987, 1600, 1422, 1348, 1264, 1163, 1092, 990, 896, 738, 704.

m.p.: 119-122 °C

Synthesis of 117[Cl]

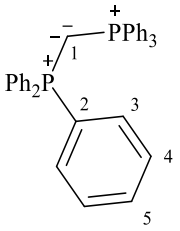


In a 3-necked round bottomed flask equipped with a condenser and dropping funnel was added PPh_3 (55.2g, 95%purity, 200mmol, 3eq) followed by DCM (150mL). To the resulting solution was added CCl_4 (12.9 mL, 133 mmol, 2eq) dropwise. The color of the solution shifted from colorless to yellow to dark red over a period of 3h. The mixture was left to stir o.n. After that, epoxy butane (12mL) was added very slowly so that the temperature did not exceed 40 °C. Next, 50 mL of Et_2O was added, until there was permanent opacity, upon further stirring, the precipitation was complete within 20min. After filtering, the residue was washed with Et_2O (3 x 30 mL). It was dried under vacuum at rt to give a pale brown product **117[Cl]**.

Yield: 25.5g (63%)

The spectroscopical data match with those reported in literature.[113]

Synthesis of $(PPh_3)_2C$ 118



117[Cl] (6.0 g, 10mmol, 1eq) was transferred into a Schleck flask. Then PhMe (25 mL) was added. To the suspension obtained, tris(dimethlamino)phosphane (1.8 mL, 10mmol, 1eq) was added. The mixture was then left to react at 80 °C o.n. While stirring, the suspension slowly turned yellow. The mixture was then brought to 100 °C and immediately filtered. On cooling, $(PPh_3)_2C$ **118** crystallized from the turbid filtrate, it was filtered off, washed with 20ml of PhMe, Et_2O (2 x 50 mL), and finally dried under vacuum at room temperature. Bright yellow crystals were obtained (of 92% purity by P-NMR). Analytically clean product was obtained by suspending the product in THF (50mL). The insoluble by-product was filtered off. The yellow solution was finally dried under vacuum at rt to give **118** as yellow and moisture sensitive powder.

Yield: 3.71g (70%).

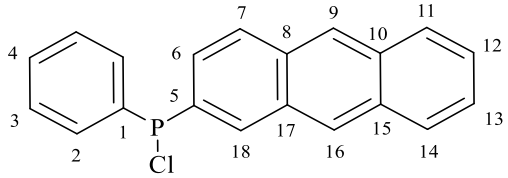
$^1H\{^{31}P\}$ NMR (THF-d_8, 300 K, in ppm): δ = 7.64 (12H, d, $^3J_{HH}$ = 7.3 Hz, C3-H), 7.28 (6H, t, $^3J_{HH}$ = 7.3 Hz, C5-H), 7.20 (12H, t, $^3J_{HH}$ = 7.3 Hz, C4-H).

$^{13}C\{^1H\}$ NMR (THF-d_8, 300 K, in ppm): δ = 138.41 (6C, *pseudo*-quint., $^1J_{CP}$ = 96.0 Hz, C2), 132.77 (12C, t, $^2J_{CP}$ = 5.2 Hz, C3), 129.63 (6C, s, C5), 127.97 (12C, t, $^3J_{CP}$ = 6.0 Hz, C4), 12.22 (1C, t, $^1J_{CP}$ = 127.4 Hz, C1).

$^{31}P\{^1H\}$ NMR (THF-d_8, 300 K, in ppm): δ = -4.7 (2P, s).

The spectroscopical data match with those reported in literature.[113]

Synthesis of AnPhPCl 116



Mg (110.2 mg, 4.53mmol, 1.1eq) and a catalytic amount of I_2 was suspended in THF (6mL) and heat to reflux. Then a solution of 2-Bromoanthracene (1.06 g, 4.12mmol, 1eq) in THF (40mL) was added dropwise in 40min at those temperature. The red solution was then left to stir at rt o.n. The day after the brown Grignard was added via a dropping funnel to a solution of *P,P*-Dichlorophenylphosphine (1.12 mL, 8.24 mmol, 2eq) in THF (18mL) at -78 °C. The yellow mixture was left to stir for 1h at -78 °C and then allowed to warm up gradually to rt. At the completion of the reaction by ^{31}P-NMR, dioxane (6mL) was added and stir for 1h. The white solid formed was removed by a Schlenk frit, and the yellow solution dried under inert conditions. The suspension obtained by the addiction of acetonitrile (10mL) was sonicated for 10min and then filtered by a Schlenk frit, washed two times with acetonitrile (4mL) and then dried to give **116** as pale yellow, air and moisture sensitive powder in a 3:1 mixture of chloride:bromide derivative (by ^{31}P-NMR). Analytically pure **116** was obtained by refluxing the product in PCl_3 (5mL) o.n. and then drying the mixture *in vacuo*.

Yield: 0.91g (69%)

^{1}H NMR (CD_2Cl_2, 300 K, in ppm): δ = 8.50 (1H, s, C16-H), 8.44 (1H, s, C9-H), 8.39 (1H, d, $^{4}J_{HP}$ = 11.4 Hz, C7-H), 8.03 (3H, m, C11-H C14-H C18-H), 7.67 (2H, m, C3-H), 7.53 (3H, m, C12-H C13-H C6-H), 7.44 (3H, m, C2-H C4-H).

^{13}C{^{1}H} NMR (CD_2Cl_2, 300 K, in ppm): δ = 139.04 (1C, d, $^{1}J_{CP}$ = 32.4 Hz, C1), 135.90 (1C, d, $^{1}J_{CP}$ = 32.4 Hz, C5), 134.82 (1C, d, $^{3}J_{CP}$ = 37.8 Hz, C7), 133.22 (1C, s, C15), 132.60 (1C, s, C10), 132.09 (1C, s, C8), 131.90 (2C, d, $^{3}J_{CP}$ = 23.1 Hz, C3), 130.98 (1C, d, $^{3}J_{CP}$ = 11.7 Hz, C17), 130.76 (1C, s, C4), 129.46 (1C, s, C11), 129.41 (1C, s, C14), 129.11 (2C, d, $^{2}J_{CP}$ = 6.6 Hz, C2), 128.63 (1C, d, $^{2}J_{CP}$ = 19.8 Hz, C18), 127.87 (1C, s, C16), 126.74 (1C, s, C9), 126.36 (2C, s, C12 C13), 125.96 (1C, d, $^{2}J_{CP}$ = 29.6 Hz, C6).

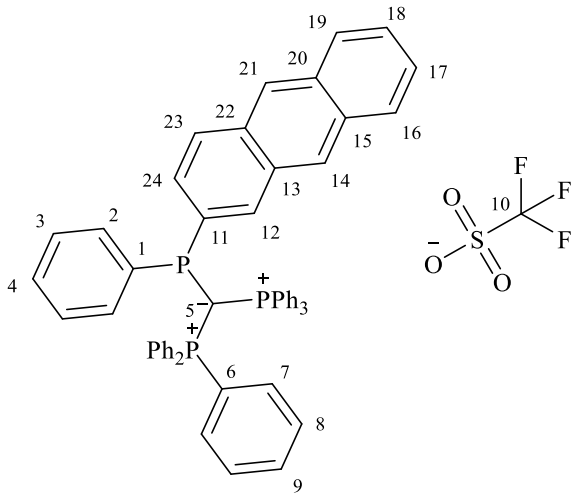
^{31}P{^{1}H} NMR (CD_2Cl_2, 300 K, in ppm): δ = 82.8 (1P, s).

Raman (100 mW, 100 scans, 300K, in cm^{-1}): 3056 (22), 1616 (4), 1584 (13), 1557 (29), 1472 (12), 1426 (4), 1405 (86), 1256 (15), 1186 (7), 1073 (7), 1027 (10), 998 (28), 756 (37), 462 (9), 393 (4)

IR (300 K, ATR, in cm^{-1}): 3051(vw), 2923(vw), 1454(m), 1433(w), 1300(vw), 1240(vw), 1184(vw), 1156(vw), 1093(vw), 1068(w), 958(w), 916(vw), 893(s), 805(vw), 742(vs), 691(s), 633(vw), 614(vw), 602(m), 554(vw), 522(w), 501(w).

m.p.: decomp.: > 147 °C

Synthesis of 119[OTf]



In a Schlenk flask $(PPh_3)_2C$ **118** (1.16 g, 2.2 mmol, 1eq) and AnPhPCl **116** (0.950 g, 3mmol, 1.4 eq) were suspended in 1,2-difluorobenzene (25mL) under inert conditions. The mixture was left to react for 1h at rt, then TMSOTf (0.525g, 2.4mmol, 1.1eq) was added dropwise at rt. The intensive red reaction mixture was stirred for additional 2h, the volatiles were then removed *in vacuo*. To the crude product was then added 1,2-difluorobenzene (5 mL). The suspension was filtered *via* Schlenk frit and the residue washed with 1,2-difluorobenzene (5mL) and Et_2O (2 x 10 mL) and dried *in vacuo* to give **119[OTf]** as analytically pure, yellow and air stable powder.

Yield: 2.05g (71%)

^{1}H NMR (CD_2Cl_2, 300 K, in ppm): δ = 8.42 (1H, s, C14-H), 8.04 (1H, dd, $^3J_{HH}$ = 6.7 Hz, C19-H), 8.00 (1H, m, C16-H), 8.00 (1H, s, C21-H), 7.87 (1H, d, $^3J_{HP}$ = 8.5 Hz, C12-H), 7.82 (1H, d, $^3J_{HH}$ = 8.9 Hz, C23-H), 7.56 (6H, t, $^3J_{HH}$ = 7.5 Hz, C9-H), 7.51 (14H, m, C7-H, C17-H, C18-H), 7.31 (12H, t, $^3J_{HH}$ = 7.6 Hz, C8-H), 7.28 (1H, t, $^3J_{HH}$ = 1.1 Hz, C4-H), 7.18 (2H, dt, $^3J_{HH}$ = 7.8 Hz, C3-H), 7.10 (2H, t, $^3J_{HH}$ = 7.7 Hz, C2-H), 7.07 (1H, dt, $^3J_{HH}$ = 6.7 Hz, $^4J_{HH}$ = 1.3 Hz, C24-H).

^{13}C{^{1}H} NMR (CD_2Cl_2, 300 K, in ppm): δ = 136.55 (1C, dt, $^1J_{CP}$ = 12.6 Hz, $^3J_{CP}$ = 5.7 Hz, C1), 134.3 (12C, dt, $^2J_{CP}$ = 1.8 Hz, $^4J_{CP}$ = 4.7 Hz, C7), 134.1 (1C, dt, $^1J_{CP}$ = 12.9 Hz, $^3J_{CP}$ = 5.7 Hz, C11), 133.3 (6C, s, C9), 132.8 (1C, d, $^2J_{CP}$ = 16.5 Hz, C12), 132.29 (1C, s, C20), 132.09 (1C, s, C15) 132.52 (2C, d, $^2J_{CP}$ = 19.8 Hz, C2), 132.2 (1C, d, $^1J_{CP}$ = 24.7 Hz, C1), 130.9 (1C, d, $^3J_{CP}$ = 5.7 Hz, C13), 130.85 (1C, s, C22), 129.1 (12C, *pseudo*-t, $^3J_{CP}$ = 6.1 Hz, C8), 128.4 (1C, s, C4), 128.37 (2C, d, $^3J_{CP}$ = 6.4 Hz, C3), 128.17 (1C, s, C19), 128.14 (1C, s, C16), 127.98 (1C, d, $^2J_{CP}$ = 24.3 Hz, C24), 127.65 (1C, d, $^3J_{CP}$ = 8.9 Hz, C23), 126.17 (1C, s, C14), 126.15 (6C, ddd, $^1J_{CP}$ = 93.1 Hz, $^3J_{CP}$ = 29.9 Hz, $^3J_{CP}$

= 30.7 Hz, C6), 125.91 (2C, s, C17, C18), 125.90 (1C, s, C21), 121.20 (1C, q, $^{1}J_{CF}$ = 321.6 Hz, C10), 8.73 (1C, dt, $^{1}J_{CP}$ = 63.5 Hz, $^{1}J_{CP}$ = 82.3 Hz C5).

^{19}F NMR (CD_2Cl_2, 300 K, in ppm): δ = -78.6 (3F, s, $^{1}J_{FC}$ = 322.5 CF_3).

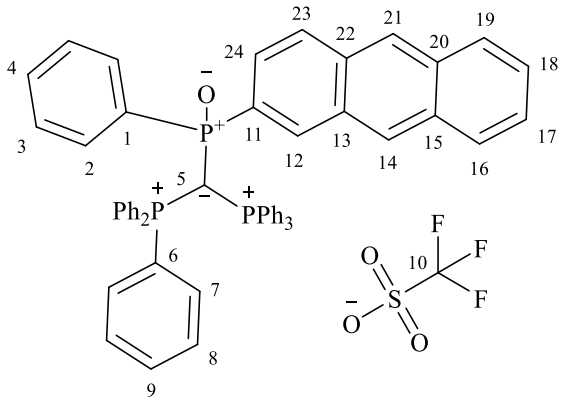
$^{31}P\{^{1}H\}$ NMR (CD_2Cl_2, 300 K, in ppm): δ = 26.5 (2P, d, $^{2}J_{PP}$ = 74.0 Hz), 0.5 (1P, t, $^{2}J_{PP}$ = 73.0 Hz).

Raman (100 mW, 100 scans, 300K, in cm^{-1}): 3058 (19), 1618 (7), 1587 (23), 1557 (6), 1471 (11), 1423 (11), 1405 (95), 1251 (10), 1187 (5), 1165 (4), 1098 (9), 1051 (9), 1030 (19), 1003 (44), 759 (18), 696 (4), 617 (6), 465 (6), 425 (4), 347 (5).

IR (300 K, ATR, in cm^{-1}): 3054(vw), 1615(vw), 1586(vw), 1483(vw), 1435(w), 1261(vs), 1222(vw), 1193(vw), 1144(s), 1096(m), 1029(m), 1001(vw), 963(m), 900(vw), 878(s), 742(s), 714(vw), 691(s), 635(vs), 615(vw), 570(vw), 553(vw), 529(vw), 502(s).

m.p.: decomp.: > 240 °C

Synthesis of 120[OTf]



To a solution of **119[OTf]**·o$C_6H_4F_2$ (1.09 g, 1mmol, 1eq) in DCM (20mL) was added $^tBuO_2H$ (200µl, 5.50M in *n*-decane, 1.1mmol, 1.1eq) and the reaction mixture was stirred for 1h at rt and then dried *in vacuo*, suspended in THF (2mL) and sonicated. The colorless solid formed was filtered *via* Schlenk frit, washed with THF (2 x 2mL), plentiful Et_2O (5 x 4mL) and finally dried *in vacuo* to give the product **120[OTf]** as analytically pure, colorless and air stable powder.

Yield: 2.68g (93%)

^{1}H NMR (CD_2Cl_2, 300 K, in ppm): δ = 8.27 (1H, s, C14-H), 8.13 (1H, s, C21-H), 8.07 (1H, d, $^3J_{HH}$, C23-H), 7.97 (2H, *pseudo*-t, $^3J_{HH}$ = 7.9 Hz, C16-H C19-H), 7.62 (13H, m, C12-H C7-H), 7.46 (10H, m, C9-H C2-H C17-H C18-H), 7.36 (1H, t, $^3J_{HH}$ = 8.9 Hz, C24-H), 7.29 (12H, t, $^3J_{HH}$ = 6.3 Hz C8-H), 7.15 (1H, t, $^3J_{HH}$ = 7.3 Hz, C4-H), 7.02 (2H, dt, $^3J_{HH}$ = 7.1 Hz, $^4J_{HH}$ = 2.0 Hz, C3-H).

^{13}C{^{1}H} NMR (CD_2Cl_2, 300 K, in ppm): δ = 136.30 (1C, d, $^3J_{CP}$ = 6.8 Hz, C23), 135.40 (1C, dt, $^1J_{CP}$ = 110.5 Hz, $^3J_{CP}$ = 2.6 Hz, C1), 135.13 (12C, t, $^2J_{CP}$ = 5.2 Hz, C7), 133.63 (6C, t, $^4J_{CP}$ = 1.3 Hz, C9), 133.30 (1C, s, C15), 132.31 (1C, d, $^5J_{CP}$ = 0.9 Hz, C20), 132.22 (2C, d, $^2J_{CP}$ = 9.0 Hz, C2), 131.45 (1C, dt, $^1J_{CP}$ = 108.6 Hz, $^3J_{CP}$ = 2.7 Hz, C11), 131.33 (1C, d, $^4J_{CP}$ = 2.2 Hz, C22), 130.98 (1C, d, $^4J_{CP}$ = 2.9 Hz, C4), 130.20 (1C, d, $^3J_{CP}$ = 13.9 Hz, C13), 129.18 (12C, t, $^3J_{CP}$ = 6.5 Hz, C8), 128.70 (1C, s, C16), 128.45 (2C, d, $^3J_{CP}$ = 12.4 Hz C3) 128.43 (1C, s, C19), 128.22 (1C, d, $^2J_{CP}$ = 11.9 Hz, C12), 128.12 (1C, m, C21), 126.83 (1C, s, C17), 126.38 (1C, d, $^4J_{CP}$ = 0.7 Hz, C14), 126.27 (1C, s, C18), 125.36 (6C, m, C6), 124.98 (1C, d, $^2J_{CP}$ = 10.5 Hz, C24), 121.70 (1C, q, $^1J_{CF}$ = 321.6 Hz, C10), 18.9 (1C, q, $^1J_{CP}$ = 77.1 Hz, C5).

^{19}F NMR (CD_2Cl_2, 300 K, in ppm): δ = -78.6 (3F, s, $^1J_{FC}$ = 323.4 CF_3).

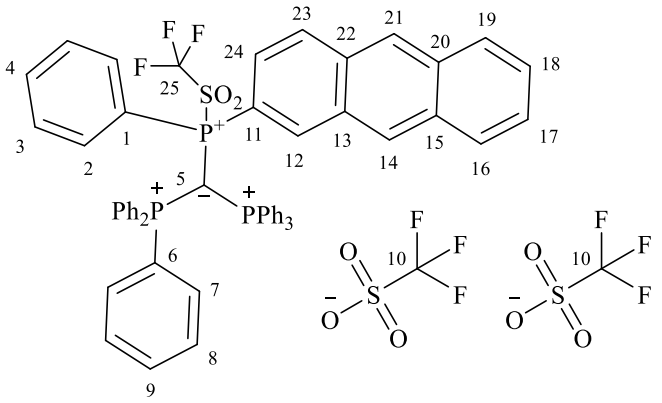
^{31}P{^{1}H} NMR (CD_2Cl_2, 300 K, in ppm): δ = 26.4 (2P, d, $^2J_{PP}$ = 18.2 Hz), 22.9 (1P, t, $^2J_{PP}$ = 18.2 Hz).

Raman (100 mW, 100 scans, 300K, in cm^{-1}): 3064 (28), 1617 (3), 1588 (24), 1558 (8), 1474 (13), 1406 (100), 1255 (9), 1189 (6), 1098 (8), 1072 (3), 1030 (23), 1003 (41), 758 (19), 706 (4), 617 (6).

IR (300 K, ATR, in cm^{-1}): 3055(vw), 1617(vw), 1587(vw), 1483(vw), 1436(w), 1262(s), 1221(vw), 1149(m), 1095(m), 1071(vw), 1029(w), 984(w) 944(vw), 909(s), 742(m), 716(vw), 686(m), 635(s), 614(vw), 562(w), 534(w), 517(vw), 503(s).

m.p.: decomp.: > 185 °C

Synthesis 121[OTf]$_2$



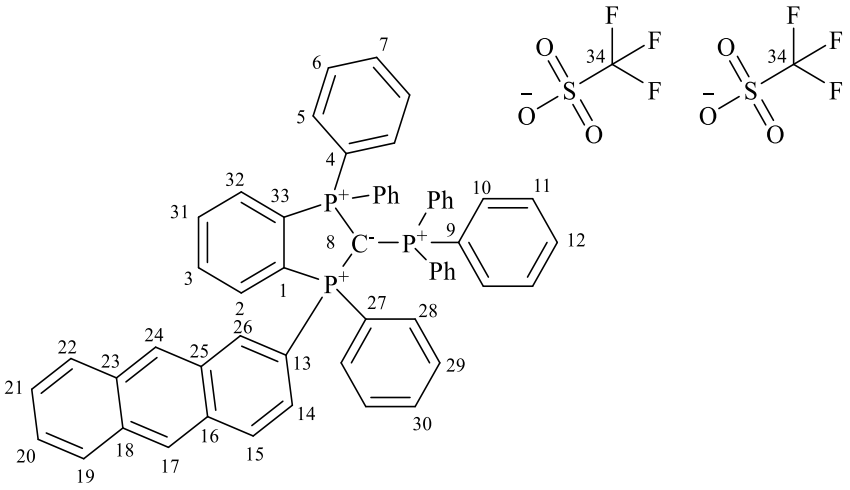
To a suspension of **120[OTf]** (480 mg, 0.486 mmol, 1eq) in PhF (5mL), Tf_2O (98µl, 0.535mmol, 1.2eq) was added at rt and the reaction mixture was stirred for 3h at rt. The suspension became a yellow solution upon the addiction of the anhydride. The mixture was then dried *in vacuo* and used in the following step without further purifications.

^{19}F NMR (CD_2Cl_2, 300 K, in ppm): δ = -71.8 (3F, s, $^1J_{FC}$ = 321.8 C25-F), -78.5 (6F, s, $^1J_{FC}$ = 320.4 CF_3-OTf).

^{31}P{^{1}H} NMR (CD_2Cl_2, 300 K, in ppm): δ = 86.2 (1P, t, $^2J_{PP}$ = 19.1 Hz), 25.8 (2P, d, $^2J_{PP}$ = 19.1 Hz).

m.p.: decomp.: > 170 °C

Synthesis of 122[OTf]$_2$



Solid **121[OTf]$_2$** (610mg, 0.486mmol) was heated to 210 °C under reduced pressure (10^{-3} mbar) for 2h. The color shifted from yellow to green. The resulting slightly oily material was suspended in THF (20 mL). The precipitated formed was filtered *via* Schlenk frit, washed once with THF (5 mL) and then with Et_2O (3 x 10 mL). The green precipitate was dried *in vacuo* to give **122[OTf]$_2$** as analytically pure, green, air and moisture stable powder.

Yield: 0.387 g (71% from **120[OTf]**, over two steps)

^{1}H NMR (CD_3CN, 300 K, in ppm): δ = 8.65 (1H, s, C24-H), 8.62 (1H, s, C17-H), 8.24 (2H, m, C15-H C26-H), 7.97 (2H, t, $^3J_{HH}$ = 8.2 Hz, C22-H C19-H), 8.04 (2H, m, C3-H C31-H), 7.98 (1H, m, C32-H), 7.93 (1H, m, C2-H), 7.80 (3H, m, C7-H C30-H), 7.62 (17H, m, C5-H C6-H C12-H C20-H C21-H), 7.37 (1H, dt, $^3J_{HH}$ = 9.2 Hz, $^3J_{HP}$ = 1.9 Hz, C14-H), 7.29 (12H, m, C10-H C11-H).

^{13}C{^{1}H} NMR (CD_3CN, 300 K, in ppm): δ = 141.65 (1C, d, $^3J_{CP}$ = 10.7 Hz, C15), 137.33 (2C, m, C3, C31), 136.45 (3C, m, C30 C7), 136.07 (3C, d, $^4J_{CP}$ = 2.7 Hz, C12), 135.77 (6C, d, $^3J_{CP}$ = 10.9 Hz, C11), 134.91 (6C, dt, $^3J_{CP}$ = 10.0 Hz, $^5J_{CP}$ = 1.6 Hz, C29, C6), 133.52 (1C, s, C18), 132.27 (2C, m, C2 C32), 132.79 (1C, d, $^5J_{CP}$ = 2.0 Hz, C23), 132.65 (1C, m, C13), 132.07 (1C, *pseudo*-dd, $^2J_{CP}$ = 10.5 Hz, $^4J_{CP}$ = 2.7 Hz, C26), 131.47 (1C, d, $^4J_{CP}$ = 2.1 Hz, C16), 131.31 (6C, d, $^2J_{CP}$ = 12.6 Hz, C5 C28), 130.52 (6C, d, $^2J_{CP}$ = 13.0 Hz, C10), 130.47 (1C, s, C17), 130.25 (1C, dd, $^3J_{CP}$ = 12.6 Hz, $^5J_{CP}$ = 2.5 Hz, C25), 129.68 (1C, s, C22), 129.20 (1C, s, C19), 129.04 (1C, s, C21), 128.08 (1C, s, C20), 127.95 (1C, s, C24), 124.91 (1C, d, $^2J_{CP}$ = 10.9 Hz, C14), 122.15 (2C, q, $^1J_{CF}$ = 321.2 Hz, C34), 121.6 (2C, m, C1 C33), 120.43 (3C, s, C4 C27), 119.69 (3C, s, C9), 9.88 (1C, ddd, $^1J_{CP}$ = 99.6 Hz, $^1J_{CP}$ = 98.9 Hz, $^1J_{CP}$ = 83.6 Hz C8).

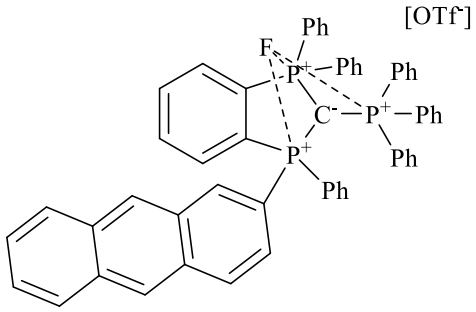
^{19}F NMR (CD_3CN, 300 K, in ppm): δ = -79.2 (6F, s, $^1J_{FC}$ = 321.7 CF_3).

$^{31}P\{^{1}H\}$ NMR (CD_3CN, 300 K, in ppm): δ = 37.84 (1P, d, $^{2}J_{PP}$ = 22.4 Hz), 37.78 (1P, d, $^{2}J_{PP}$ = 23.5 Hz), 19.69 (1P, t, $^{2}J_{PP}$ = 23.5 Hz).

IR (300 K, ATR, in cm^{-1}): 3062 (vw) 2970 (vw), 2867 (vw), 1484 (vw), 1437 (vw), 1403 (vw), 1271 (vw), 1257 (m), 1223 (vw), 1190 (vw), 1156 (w), 1100 (s), 1071 (m), 1030 (w), 998 (vw), 946 (m), 927 (s), 883 (w), 857 (w), 852 (vw), 745 (w), 722 (vw), 692 (vw), 667 (m), 636 (w), 595 (m), 572 (m), 563 (m), 543 (vs), 529 (w), 516 (m), 501 (s).

m.p.: decomp.: > 210 °C

Synthesis of 10[OTf][F]



To a suspension of **122[OTf]$_2$** (224 mg, 0.20 mmol, 1eq) and 18-crown-6 (10.6 mg, 0.04 mmol, 0.2eq) in THF (1.5 mL), KF (17.4 mg, 0.30 mmol, 1.5eq) was added and the reaction mixture stirred for 12 h at ambient temperature. The resulting suspension was filtered and the residue was washed with THF (0.5 mL). CH_2Cl_2 (5 mL) was added to the residue to dissolve the product. After removal of all volatiles *in vacuo* from the filtrate, **10[OTf][F]** was obtained as colorless powder.

Yield: 186 mg (94%).

^{1}H NMR (CD_3CN, 300 K, in ppm): δ = 8.65 (1H, s), 8.62 (1H, s), 8.24 (2H, m), 7.97 (2H, t, J = 8.2 Hz), 8.04 (2H, m), 7.71 (2H, t, J = 7.5 Hz), 7.65-7.59 (4H, m), 7.53-7.52 (6H, dt, J = 8.2, 7.9 Hz), 7.51-7.47 (4H, m), 7.44 (4H, m); 7.41-7.36 (3H, m), 7.35-7.30 (5H, m), 7.25 (2H, t, J = 7.16 Hz), 7.23-6.81 (4H, br), 6.63 (1H, m);

^{19}F NMR (CD_3CN, 300 K, in ppm): δ = 56.3 (1F, ddd, J = 542.2, 40.5, 31.2 Hz), –79.2 (3F, s);

^{31}P{^{1}H} NMR (CD_3CN, 300 K, in ppm): δ = 26.2 (1P, ddd, J = 52.4, 13.7, 40.5 Hz), 21.3 (1P, ddd, J = 67.1, 52.0, 31.2), −58.6 (1P, ddd, J = 542.1, 67.0, 13.4 Hz);

m.p.: >250°C