Asymmetric synthesis of 2,2-disubstituted chromanols

- Novel approaches to Vitamin E analogues.

Inauguraldissertation

zur

Erlangung der Würde eines

Doktors der Philosophie

Vorgelegt der

Philosophisch-Naturwissenschaftlichen Fakultät

der

Universität Basel

von

Julien Chapelat

aus Paris, France

Basel, 2009

Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät der Universität Basel auf Antrag von

Prof. Dr. Wolf-D. Woggon

Prof. Dr. Andreas Pfaltz

Basel, den 9 Dezember 2008

Prof. Dr. Eberhard Parlow (DEKAN)

POUR

Carole et Annabelle

Acknowledgments and Thanks

First of all, I would like to thank my Ph. D. supervisor, Prof. Dr. Wolf-D. Woggon, for his guidance and help during the preparation of this work and for his counsel regarding matters of a scientific and also a non-scientific nature, which has made this research a real pleasure and helped me to envisage my future career. Also many thanks to Pr. Dr. Antoinette Chougnet and Dr. Urs Hengartner for their constant support during the past 4 years.

I sincerely thank Pr. Dr. Andreas Pfaltz for his function as co-referee.

I would like to acknowledge Dr. Daniel Haeussinger and Dr. Klaus Kulicke for NMR measurements and analyses. I appreciate Dr. Markus Neuburger and Dr. Silvia Schaffner for determination of X-ray structure, Dr. Nadig for EI-MS and M. Kirsch for elemental analyses.
I would also like to thank the technical staff of the Institute of Organic Chemistry, especially Mr. M. Maier, Mr. A. Koller, Mr. F. Cabrera and Mr. M. Hermida of the „Werkstatt“ and Mr. R. Lips, Mr. A. Pfiffner, Mr. A. Schauble, Mr. F. Stehlin and Mr. M. Hauri from the „Materialausgabe“, without whom none of the work presented here would have been possible.

It has been a pleasure to work in a team with such a pleasant atmosphere, and my sincere thanks are given to all past members of the Woggon group whom I worked with during the past four years, and Dr. Hao Wang, Dr. Guoqi Zhang and Sandro Gabutti in particular. Many thanks to Dr. A. Buss for the collaboration in the “anti-Baldwin” story.

Thank Swiss National Science Foundation (SNF) and Novartis Institute for Biomedical Research (NIBR) for financial support, as well as Dr. Thomas Netscher (DSM) for helpful discussions and generous gifts.

My love and thanks go to my family and friends, and especially to my wife Carole and our lovely daughter Annabelle, for their continual understanding and support.

Finally, my sincere thoughts go to Dr. Pierre Acklin.

Julien Chapelat
Basel, 2008

Contents

THEORITICAL PART

1. Introduction

1.1. Structure and importance of 2,2-disubstituted chromanols in natural products.

Since the beginning of the last century, chromanols have been isolated from natural sources exhibiting a broad spectrum of biological and medicinal activities. In particular the structural motif of 2,2-disubstituted chromanols (*figure 1*), can be found in many important natural products, and made them of interest for organic chemists.

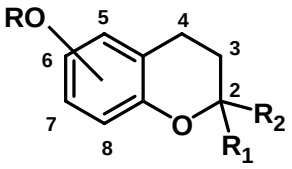


Figure 1: Structure of 2,2-disubstituted chromanols.

In 1948, Hughes et al. have isolated acronycine **1** from *Acronychia baueri* Schott (*Rutaceae*),[1] as depicted on figure 2. It exhibited a broad spectrum of activity against numerous solid tumors such as sarcoma, myeloma, carcinoma and melanoma, however, clinical trials only gave poor results. Several years later, the epoxide derivative **2** was isolated and led to the hypothesis of bioactivation by transformation of the double bond.[2] In 2000, Costes et al. reported the synthesis of a novel class of derivatives,[3] including diester **3** which was more potent and more active in vivo than acronycine **1**, and was active on P388 leukemia and induces tumor regression of the resistant C38 adenocarcinoma.

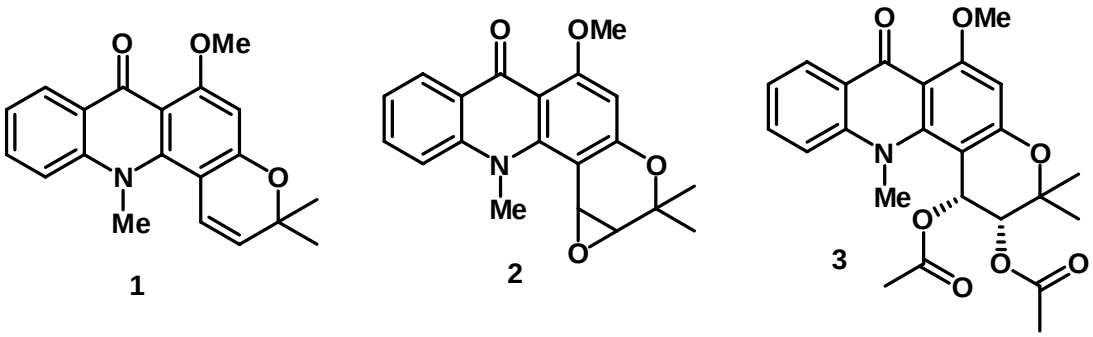
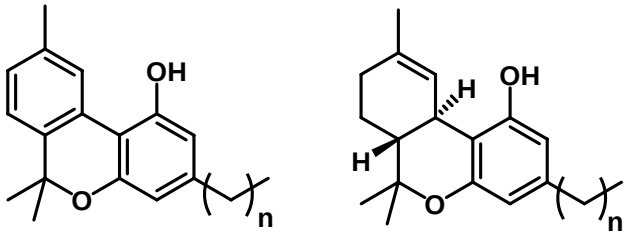


Figure 2: Acronycine **1** and related derivatives **2**-**3**.

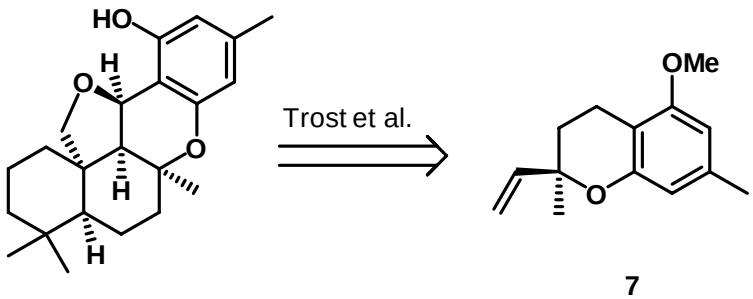
In the 1940's, cannabinoids such as **4** were identified and isolated from *Cannabis sativa* L (Cannabis), followed by Δ^9-tetrahydrocannabinols **5** (Δ^9-THC) 20 years later (*figure 3*).[4] These compounds exhibit strong psychoactive properties, in particular THC having analgesic and neuroprotective abilities. At least 66 cannabinoids have been isolated so far from the cannabis plant, and most of them include a 2,2-disubstituted chromanol unit.



4 (n=0..4) **5 (n=3..4)**

Figure 3: Cannabinoids compound: cannabinols **4** and tetrahydrocannabinols **5**.

(-)-Siccanin **6** was isolated and its structure elucidated in 1962 by Ishibashi (*scheme 1*).[5] **6** exhibits potent anti-fungal activity, particularly against the pathogenic fungi *Trichophyton interdigitale* and *Trichophyton asteroids*, as well as *Epidermophytyon* and *Mycosporum*.[6] Extensive studies allowed the isolation of other related analogues, siccanochromenes A-H by Hirai et al.,[7] and recently, Trost et al. reported the first biomimetic enantioselective total synthesis of **6** from vinyl chroman **7**.[8]



6 **7**

Scheme 1: Structure of (-)-siccanin **6** and its biomimetic precursor **7**.

The dried leaves of the plant *Rhododendron dauricum* known as "Manshanfong" have been employed since the 1970's in the northern part of China as an expectorant to treat acute-chronic bronchitis. Recently MeOH extracts were founds to display significant anti-HIV activity ($EC_{50} \leq 20$ μg/mL).[9] Two novel isomeric chromanol derivatives were isolated, rhododaurichromanic acid A **8** and B **9**, together with daurichromenic acid **10** (*figure 4*).

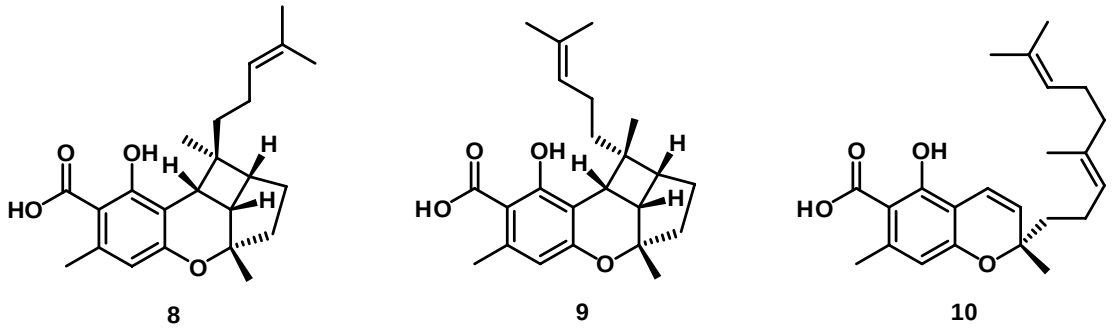


Figure 4: Compounds isolated from *Rhododendron dauricum* (Ericaceae).

Interestingly, though **8** and **10** were potent anti-HIV compounds (EC_{50} = 0.37 μg/mL and 5.67 ng/mL respectively), **9** did not exhibit any activity. Syntheses of these compounds were achieved in 2003 by Kang et al. and Kurdyumov et al. as enantiomeric mixtures.[10] Numerous other polycyclic chromanols have been isolated and characterized over the last decades, such as Clusiacyclol A **11**, Clusiacyclol B **12**, Eriobrucinol **13** and Murrayamine M **14** (figure 5).[11]

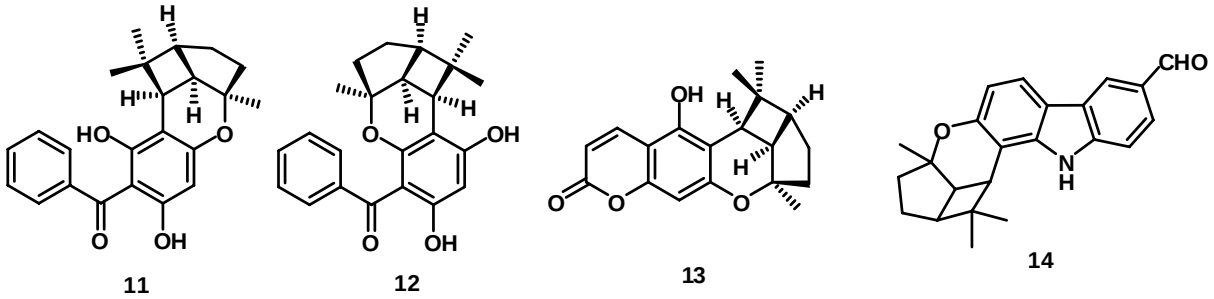


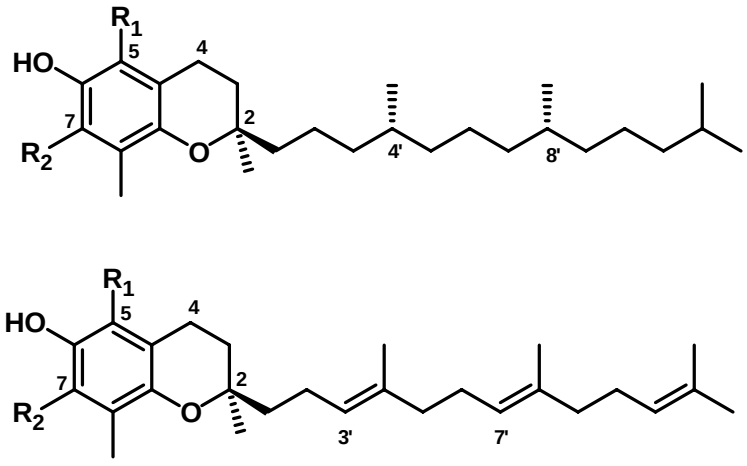
Figure 5: Polycyclic chromanol type natural compounds **11**-**14**.

The chromanols belonging to the vitamin E family have been investigated for more than 60 years mainly because of their potent antioxidant activity in tissues. Structures, biological availability and antioxidant properties of these compounds will be described in the following chapter, as well as its biosynthesis and more recent progress regarding its asymmetric synthesis.

1.2. Vitamin E – A highly potent radical chain-breaking antioxidant

1.2.1. History, structure, and natural sources.

The existence of Vitamin E was first discovered in 1922 by Evans and Bishop,[12] during a study on female rat fertility. Upon a typical diet, rats became fertile and they were able to cure it by the administration of fresh green leaves of lettuce. The presence of a novel factor, called substance 'X', was believed to be responsible for the recovery of fertile rats, and in 1925, Evans and Burr described it as Vitamin E.[13] They discovered that Vitamin E was present in rather high concentrations in some cereals, in particular in wheat germ, from which they isolate a biologically active yellow, viscous oil. Characterization and structure elucidation of this novel factor was initiated by Evans et al. in 1935,[14] who isolated a phenol which was named α-tocopherol (**15)**, from *tokos* (childbirth) and *phero* (to bear). In 1938, Fernholz proposed a structure by empirical deductions,[15] and in the following years, three new Vitamin E constituents were described, β-, γ- and δ-tocopherol **16-18**.[16] Complete elucidation of the configuration of the three chiral centers was accomplished thirty years later by Mayer et al.,[17] who claimed that natural α-tocopherol was (*R*)-configurated. The Vitamin E family complemented by four related compounds, which have an unsaturated, long aliphatic chain, the α-, β-, γ- and δ-tocotrienols **19-22** (*figure 6*).



	R_1	R_2	
15	CH_3	CH_3	α
16	CH_3	H	β
17	H	CH_3	γ
18	H	H	δ

	R_1	R_2	
19	CH_3	CH_3	α
20	CH_3	H	β
21	H	CH_3	γ
22	H	H	δ

Figure 6: Structure of tocopherols **15-18** and tocotrienols **19-22**, constituents of Vitamin E.

The eight vitamin E compounds are widely distributed in nature; the richest sources are latex lipids (8% w/v), followed by edible plant oils. Sunflower seeds contain almost exclusively α-tocopherol (59.5 mg/g of oil), oil from soybeans contains the γ-, δ- and α-tocopherols (62.4, 20.4, and 11.0 mg/g oil), and palm oil contains high concentrations of tocotrienols (17.2 mg/g oil) and α-tocopherol (18.3 mg/g oil).[18]

1.2.2. Bio-availability, metabolism and anti-oxidant activity.

Commercially available vitamin E supplements usually contain only racemic α-tocopherol. Since the free phenol is less stable, it is commonly available as its acetate, succinate or nicotinate ester. For optimal absorption, the esters are hydrolyzed by a pancreatic esterase, leading to tocopherol.[19]

Vitamin E is incorporated in the intestine into chylomicrons, lipoproteins made of phospholipids and apolipoproteins, together with cholesterol and other lipids, and could then enter to lymphatic system (*figure 7*). The absorption rate is generally incomplete and could reach up to 70%. One important enzyme in chylomicron catabolism is a lipoprotein lipase, which is bound to the endothelial lining of capillaries. This enzyme hydrolyses triglycerides, and also acts as a transfer protein.

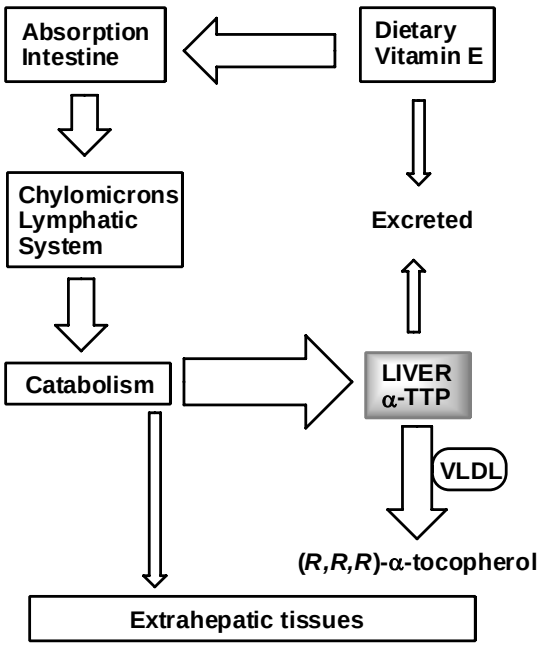
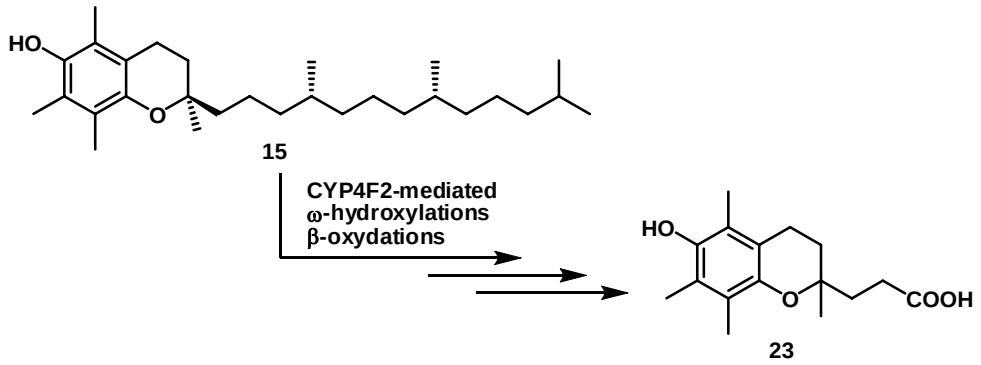


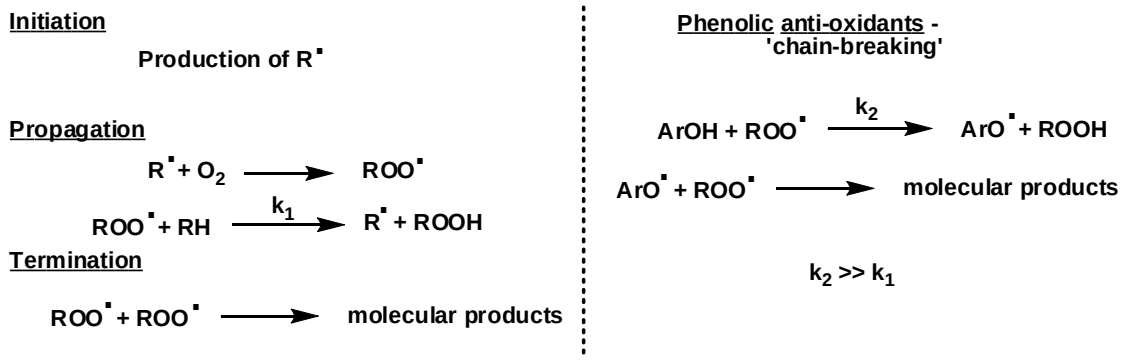
Figure 7: Vitamin E: transport to extrahepatic tissues[19] [VLDL=very low density lipoprotein, α-TTP=α-tocopherol transfer protein]

Thus, during chylomicron lipolysis, part of vitamin E is distributed to tissues (adipose tissue, muscle, skin), whereas the other part is captured by the liver.[20] In the liver, α-tocopherol is specifically recognized by the 32 kDa α-tocopherol transfer protein (α-TTP), incorporated into very low density lipoproteins (VLDL), released into human plasma and consequently delivered to peripheral tissues.[21] Remarkably, this protein also has a preference for (2*R*)-α-tocopherols, and recognizes only compounds having the phytyl-side chain. The other forms of vitamin E such as (2*S*)-isomers, γ-tocopherol or tocotrienols are excreted as bile, or by the urine.[22] Concerning the urine excretion pathway, it has been established that ω-hydroxylation of **15**, followed by β-oxidation, catalyzed by cytochrome P_{450} CYP4F2 produced α-carboxyethyl hydroxychroman (α-CEHC) **23**, one of the main degradation product observed (*scheme 2*). A similar mechanism was discovered for tocotrienols degradation, together with a reduction of the unsaturated chain by CoA-reductases.[22]



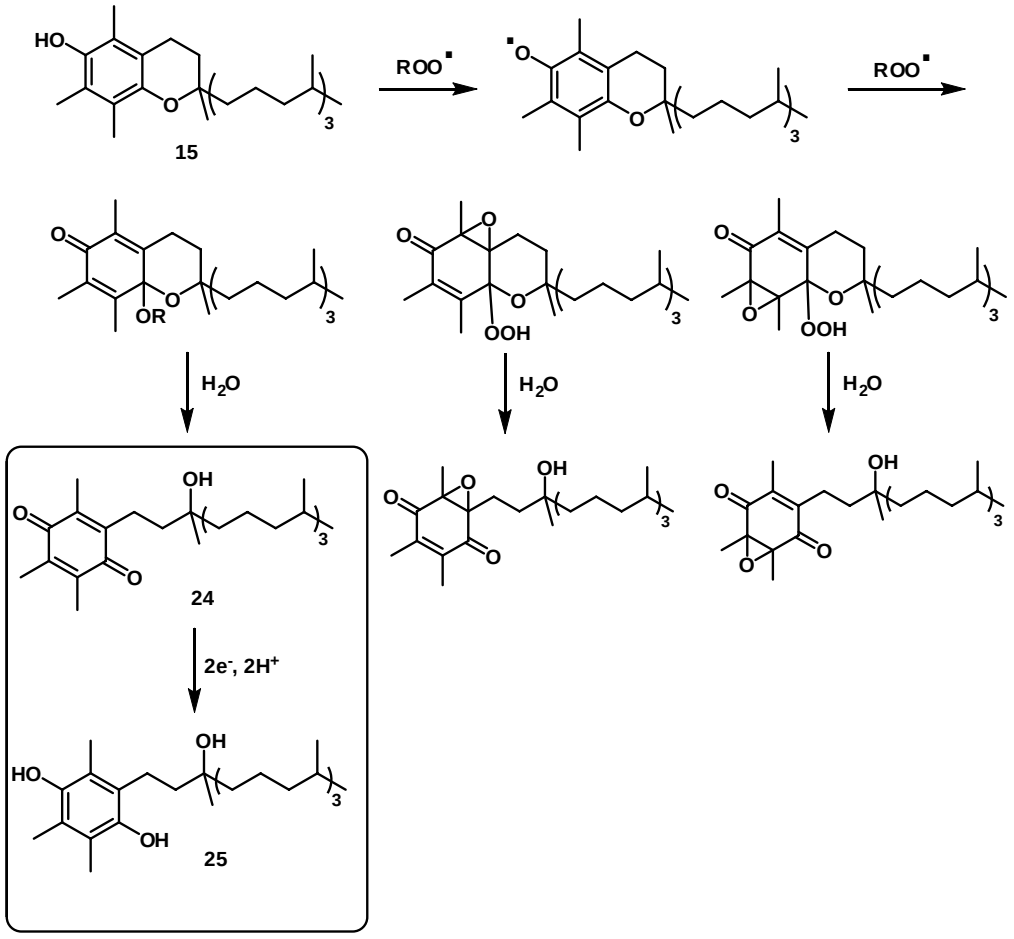
Scheme 2: Elimination of α-tocopherol **15** by the urinary excretion of α-CEHC **23**.

The other products usually observed in the urine are α-tocopheryl quinone **24**, α-tocopheryl hydroquinone **25** and α-tocopheronic acid (Simon metabolites[23]). These products are directly related to the anti-oxidant function of vitamin E.[24] Indeed, it has been reported in the 1980's by Burton and Ingold that tocopherols are highly potent radical-chain breaking anti-oxidants, and react much faster with free radicals than other phenols lacking the fused 6-membered heterocyclic ring.[25] Lipids can be easily oxidized and its peroxidations involve a free radical chain having three steps: initiation, propagation and termination, as depicted on scheme 3. The production of $R^{\cdot}$ could be a non-enzymatic single-electron transfer (SET) or an enzymatic SET, and it reacts rapidly with oxygen to afford the peroxyl radical, which could then attack another lipid molecule (RH).



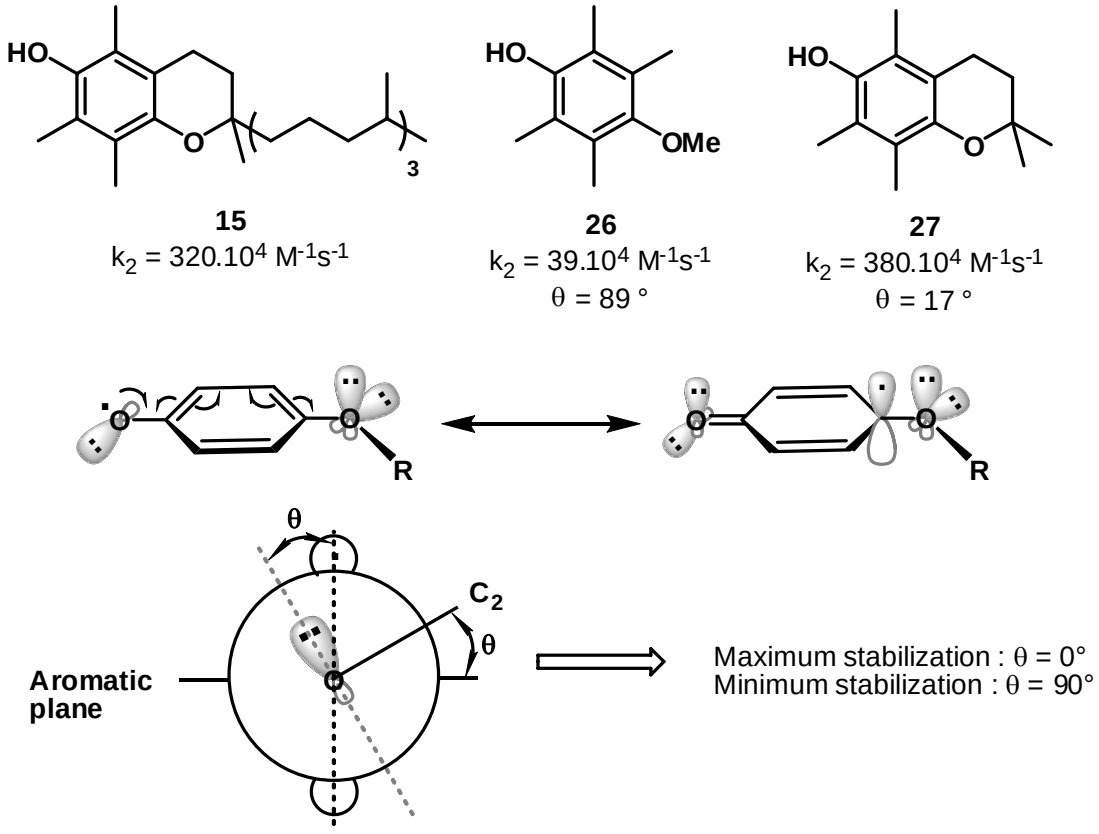
Scheme 3: Lipid peroxidation process – Free radical chain mechanism.

Chain-breaking antioxidants interfere in one or more propagation steps, and this is the case for most phenols, since the 'chain-carrying' peroxyl radicals are trapped.[26] The phenoxyl radicals thus formed are resonance stabilized and usually proceed to the termination step, by reacting with another peroxyl radical. In 1996, Liebler et al. analysed the oxidation products of vitamin E by gas chromatography, and proposed the reaction with R-OO· and subsequent formation of tocopherol metabolites as shown (*scheme 4*).



Scheme 4: Oxidation of α-tocopherol **15** by peroxyl radicals.

The ability of tocopherols as antioxidants is a consequence of their fused 6-membered heterocyclic ring, as demonstrated by Burton and Ingold in 1986.[25] During their studies determined the rate constant k_2 of the reaction of peroxyl radical with tocopherols and simple phenols (see *scheme 3*) and found out that the best values should be obtained for 4-methoxy-phenol, and that the best pattern for the other positions was achieved by four methyl groups. However, 4-methoxy-2,3,5,6-tetramethylphenol **26**, which was expected to show a high k_2 value, was ten times lower that of α-tocopherol. This difference was explained by the greater stabilization of the phenoxyl radical formed from α-tocopherol, due to the better overlapping of the lone pair orbital of the oxygen para to the OH, with the semi-occupied molecular orbital (SOMO) in the radical (*scheme 5*). Maximum stabilization is reached when the angle θ between the lone pair and the SOMO approaches 0°, and minimum stabilization corresponds to θ = 90°. X-ray analysis of **26** revealed that θ = 89° meaning that its radical was not stabilized by the oxygen lone pairs. It would explain the low rate constant k_2 in comparison to α-tocopherol and simple chromanol **27** that showed an angle θ = 17°, which could be extrapolated to **15**.



Scheme 5: The importance of the chromanol motif in the anti-oxidant activity of vitamin E.

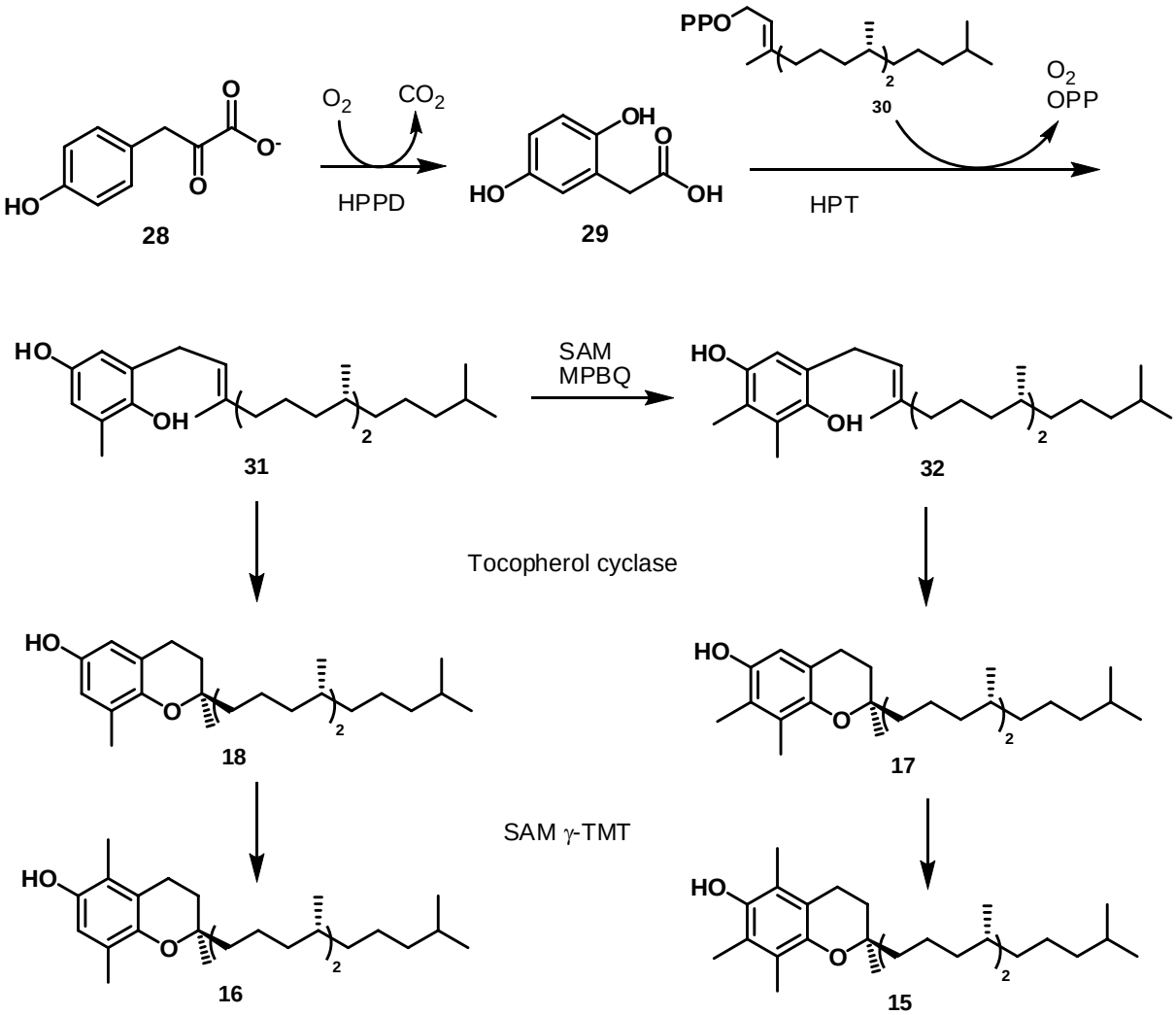
The aromatic substitution pattern, the nature of the aliphatic side chain and the configuration at C-2 play an important role in the anti-oxidant activity, as depicted on table 1, (2*R*,4'*R*,8'*R*)-α-tocopherol being the best one (100%).

Tocopherols / Tocotrienols		α-Tocopherols stereoisomers	
(*R*,*R*,*R*)-**15**	100%	(*R*,*R*,*R*)-**15**	100%
(*R*,*R*,*R*)-**16**	30%	(*R*,*R*,*S*)-**15**	90%
(*R*,*R*,*R*)-**17**	10%	(*R*,*S*,*S*)-**15**	73%
(*R*,*R*,*R*)-**18**	1%	(*S*,*S*,*S*)-**15**	60%
all-*E*-(*R*)-**19**	30%	(*R*,*S*,*R*)-**15**	57%
all-*E*-(*R*)-**20**	3%	(*S*,*R*,*S*)-**15**	37%
all-*E*-(*R*)-**21**	-	(*S*,*R*,*R*)-**15**	31%
all-*E*-(*R*)-**22**	-	(*S*,*S*,*R*)-**15**	21%

Table 1: Relative *in vivo* antioxidant activity of tocopherols and tocotrienols.[18b]

1.2.3. Biosynthesis of tocopherols – The tocopherol cyclase.

The biosynthesis of tocopherols by photosynthetic organisms has been investigated over the last 30 years, and the pathway, depicted on scheme 6, has been accepted. Homogentisic acid **29**, formed from p-hydroxyphenyl pyruvate **28** by the cytosolic enzyme HPP dioxygenase (HPPD),[27] undergoes a condensation with phytyl diphosphate **30** catalyzed by homogentisate phytyltransferase (HPT),[28] a membrane-bound chloroplast enzyme firstly discovered by Soll et al. in 1987.[29]

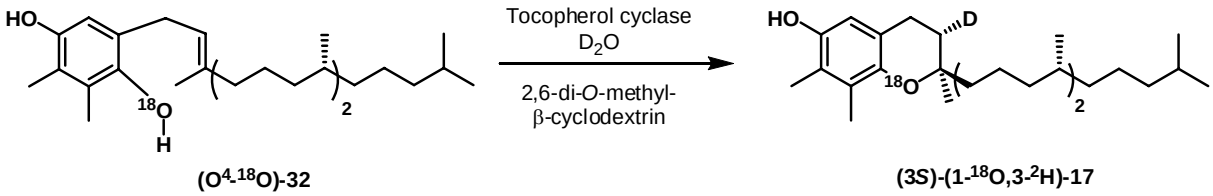


Scheme 6: Biosynthesis of tocopherols in photosynthetic organisms.

2-Methyl-6-phytyl-1,4-benzoquinol **31** (MPBQ) can be further methylated to afford 2,3-dimethyl-6-phytyl-1,4-benzoquinol **32** (DMPBQ), via the S-adenosyl-methionine MPBQ methyl-transferase (SAM MPBQ).[29,30]

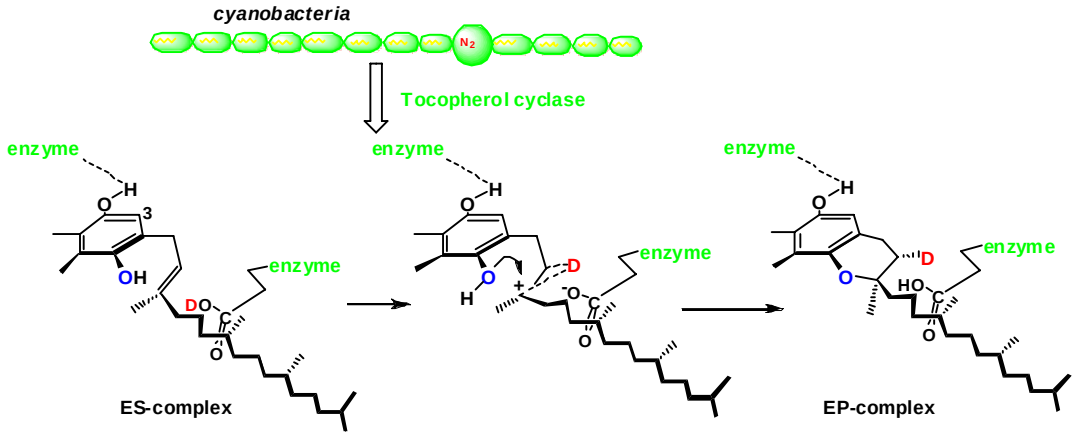
Cyclisation of **31** and **32** by the tocopherol cyclase, isolated from *Anabaena variabilis* Kützing (*Cyanobacteria*) by Woggon et al. in 1993,[31] led to γ- and δ-tocopherol **17** and **18**. The cyclisation affords exclusively the (*R*)-configuration at C-2. Finally, S-adenosyl-methionine γ-tocopherol methyl transferase (SAM γ-TMT)[32] catalyzed the methylation of **17** and **18**, leading to α- and β-tocopherol **15** and **16** respectively. The biosynthesis of tocotrienols is believed to be similar to the one of tocopherol, except that it starts from geranylgeranyl diphosphate, and is condensed with homogentisic acid by the homogentisic acid geranylgeranyl transferase (HGGT).[33]

The mechanism of the cyclisation promoted by tocopherol cyclase has been studied and reported by Woggon et al. in 1994,[31b] using labeled compounds. Indeed, (O^4-^{18}O)-**32** was synthesized and allowed to incubate with tocopherol cyclase in D_2O, affording (3*S*)-(1-^{18}O,3-^{2}H)-**17** (*scheme 7*).



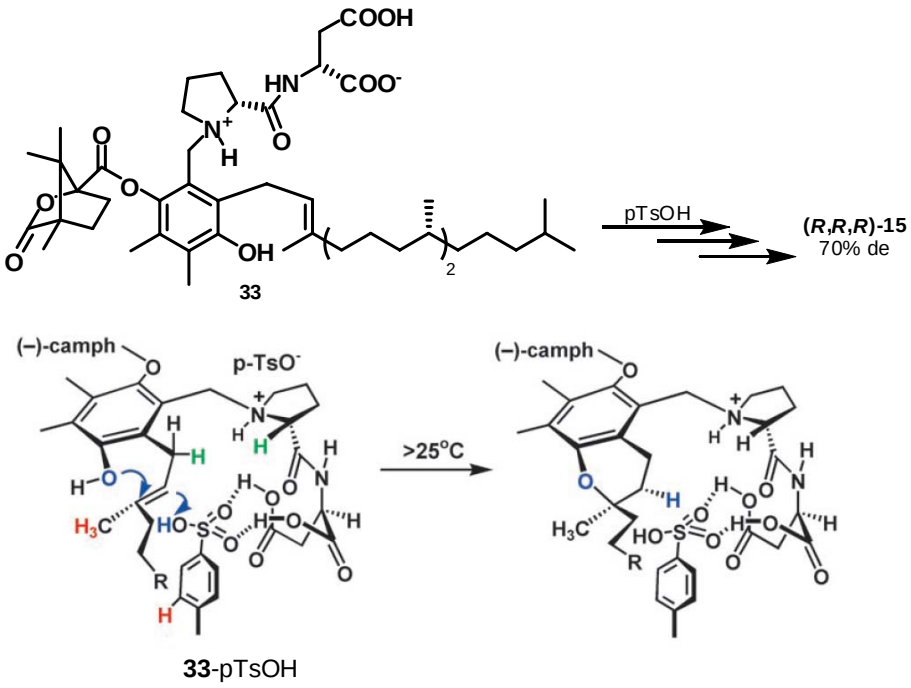
Scheme 7: Cyclisation of labeled γ-tocopherol precursor in presence of tocopherol cyclase.

This result suggested that tocopherol cyclase operates by *si*-protonation of the double bond of **32** and concomitant *re*-attack of the phenolic oxygen, the proposed mechanism is depicted on scheme 8.



Scheme 8: Tocopherol cyclase mechanism as proposed by Woggon et al. [E=enzyme, S=substrate, P=product]

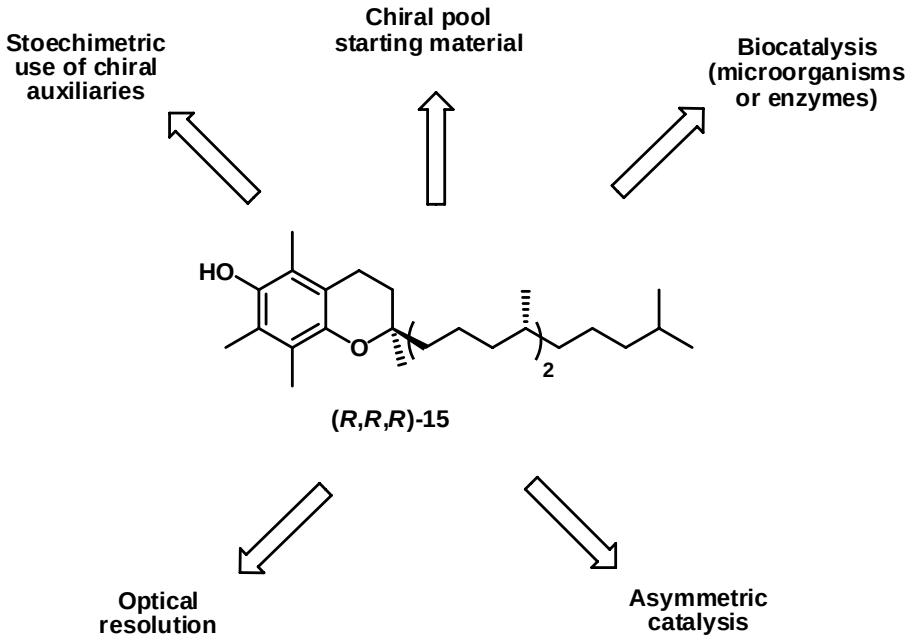
Based on this mechanism, a biomimetic synthesis has been developed in our group, by Woggon et al. in 2006,[34] involving a chiral peptide auxiliary, covalently bound to the phytylhydroquinone unit that mimic the enzyme tocopherol cyclase in the *si*-protonation step (*scheme 9*). Indeed, it was believed that the Brönsted acid p-toluene sulfonic acid (pTsOH), was activated by the chiral peptide, thus leading to the *si*-protonation of the double bond of **33**, followed by *re*-attack of the phenolic oxygen leading to diastereo-enriched chromanol. After removal of the auxiliary, (*R*,*R*,*R*)-α-tocopherol **15** was finally obtained in 70% de, being the first diastereoselective biomimetic synthesis of tocopherols.



Scheme 9: Biomimetic synthesis of α-tocopherol, using a chiral auxiliary.

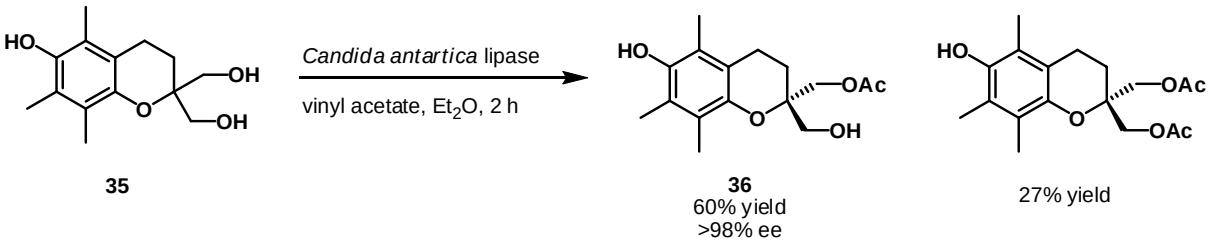
1.2.4. Recent progress in asymmetric synthesis of α-tocopherols.

Though the industrial production of vitamin E, manufactured in about 35,000 tons per year worldwide, leads to (all-*rac*)-α-tocopherol,[35] the synthesis of optically active α-tocopherols has been of great interest for organic and bioorganic chemists over the last decades, and an excellent review by Netscher covers the reported synthesis of vitamin E analogues until 2007.[35] Herein, we would like to report the most recent progresses done in the development of asymmetric synthesis of (*R*,*R*,*R*)-α-tocopherol **15**. Several pathways were envisaged to reach optically active tocopherols, and are depicted on scheme 10.



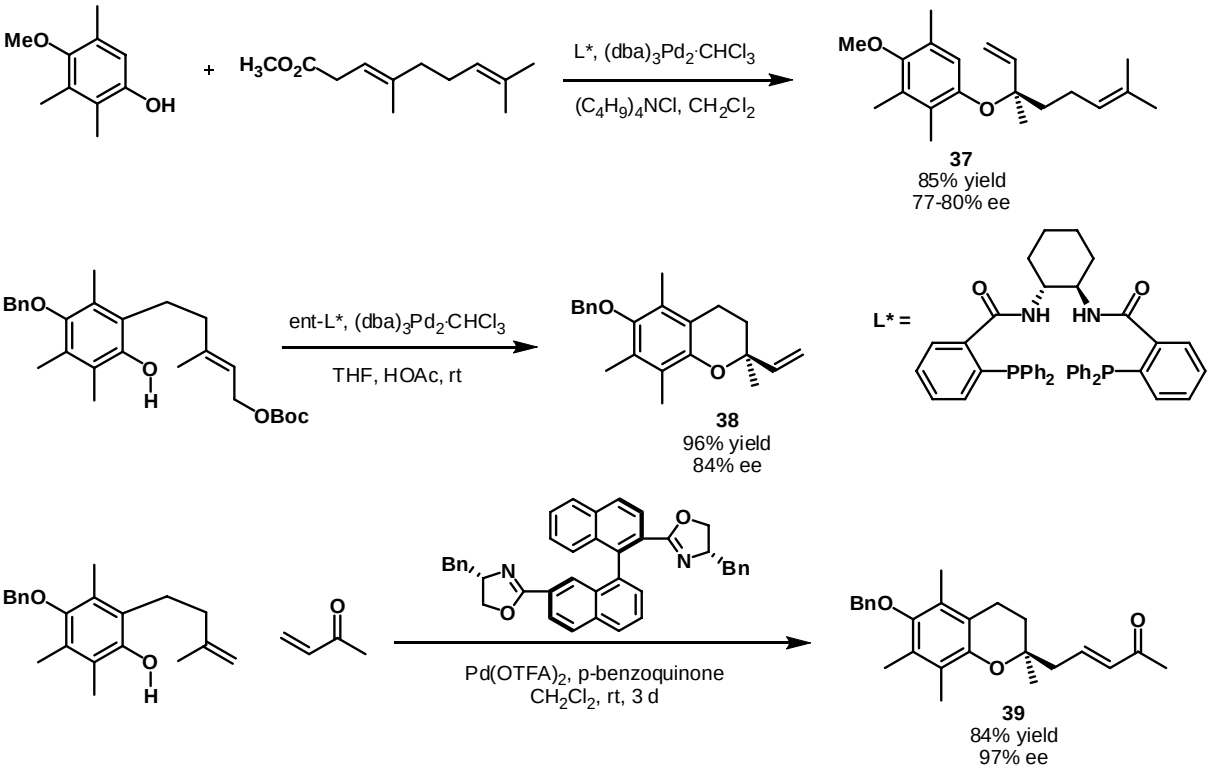
Scheme 10: Possible strategies for the synthesis of optically active α-tocopherol **15**.[35]

Three main problems were addressed separately in most reports, i) the synthesis of chiral chromans, ii) the introduction of the side-chain chiral centers, and iii) the coupling between these two building blocks. Synthesis of the chiral side chain usually started from natural *E*-(*R*,*R*)-phytol **34** and derivatives, and synthesis of chiral chromans was extensively studied. Indeed, in the 1970's, optical resolution was the first method employed,[36] followed by an important contribution from the area of bio-catalysis. Lipases were successfully used over the last 30 years,[37] giving access to functionalized precursor with high enantiomeric excess, as recently described by Chênevert and Courchesne in 2002 (*scheme 11*),[38] leading to chroman **36** in >98% ee.



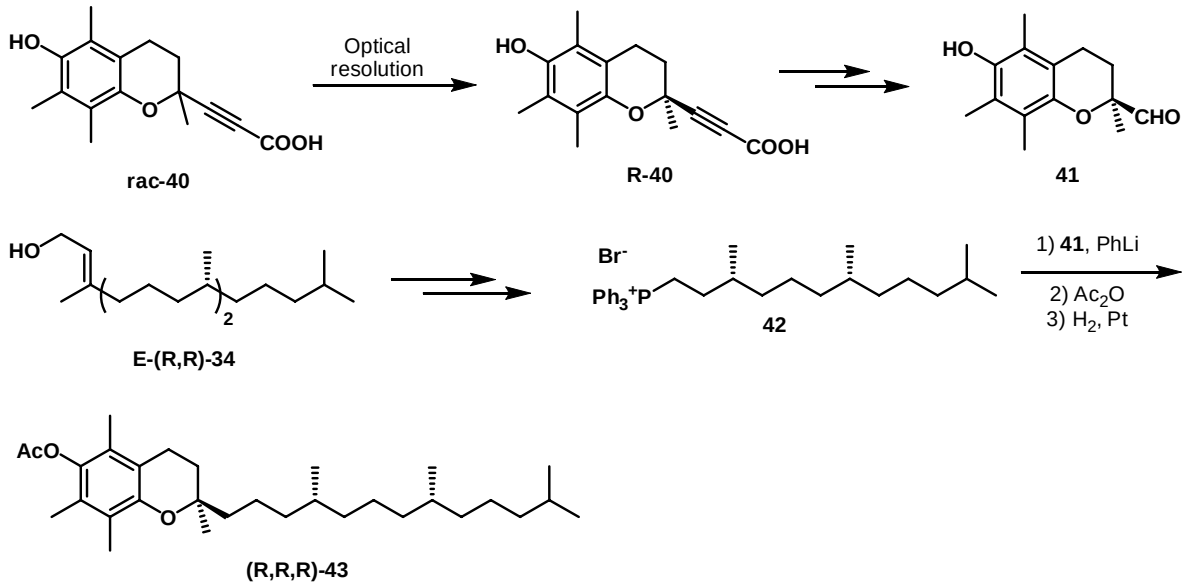
Scheme 11: Enzymatic desymmetrization of chroman **35** using *Candida antartica* lipase.

Enantioselective catalysis also offered a promising approach, and several methods were successfully used, such as Sharpless epoxidation[39] or Sharpless dihydroxylation.[40] More recently, Trost et al. developed the use of a chiral palladium catalyst in enantioselective intermolecular and intramolecular allylic substitutions,[41] leading to precursor **37** and chroman core **38** in high ee's (*scheme 12*). In the mean time, Tietze et al. reported a powerful domino palladium-catalyzed Wacker-Heck reaction leading to chroman unit **39**, in up to 97% ee.[42]



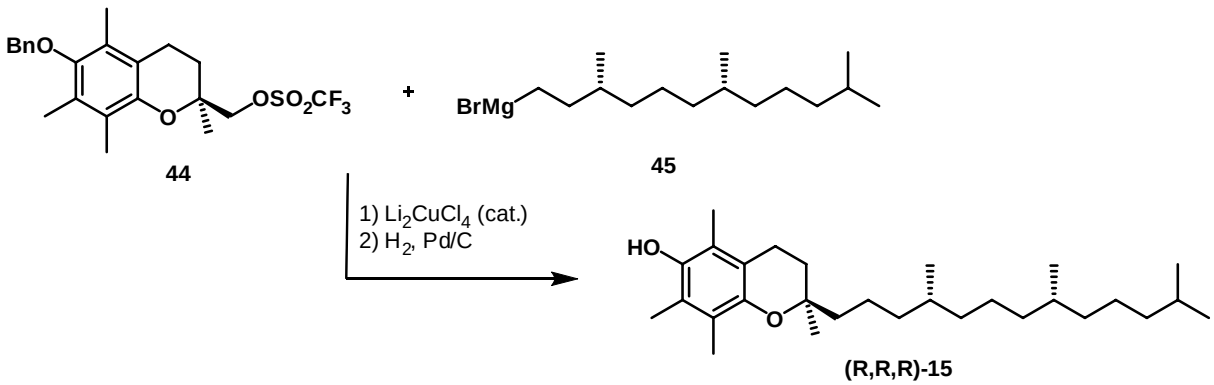
Scheme 12: Pd-catalyzed entioselective formation of compounds **37-39**.

The first synthesis of **(*R,R,R*)-15** was reported by Mayer et al. in 1963,[36c] starting from *E*-(*R,R*)-phytol **34** and optically resolved carboxylic acid ***R*-40** (*scheme 13*). Chiral aldehyde **41** and phosphonium salt **42** were successfully coupled via a Wittig reaction to afford the acetate derivative **(*R,R,R*)-43**.



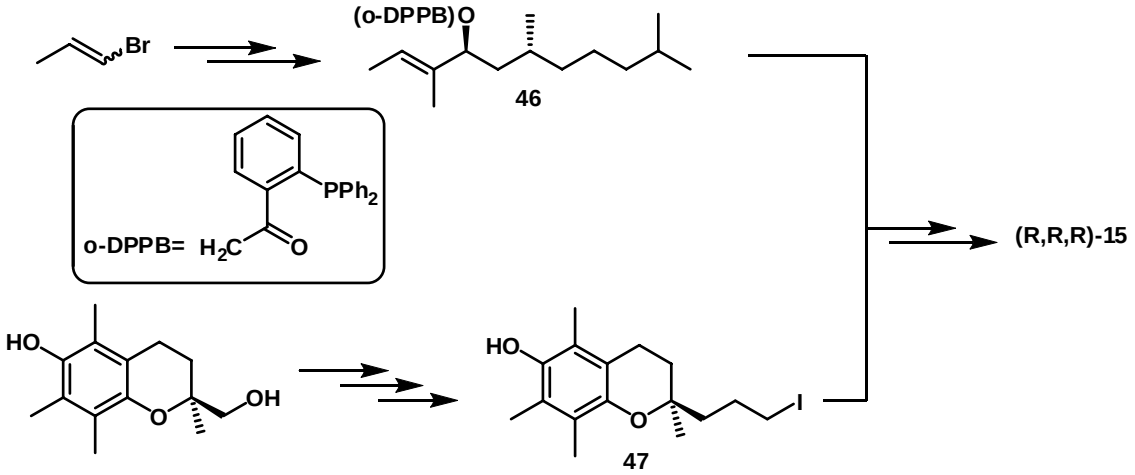
Scheme 13: The first synthesis of (*R*,*R*,*R*)-α-tocopherol by Mayer et al.

This general approach has been used for most coupling of chiral chromans and chiral side-chains, and Trolox, its corresponding aldehyde **41**, olefin **38** or sulfone **44** are very often key intermediates towards enantiomerically enriched **15** as recently reported by Netscher et al. in 2003 (*scheme 14*).[43] Indeed, triflate **44**, which synthesis was initiated in 1999 by Outten et al.,[44] could react with magnesium bromide **45**, derived from natural phytol, leading in excellent yields to ***(R,R,R)*-15**.



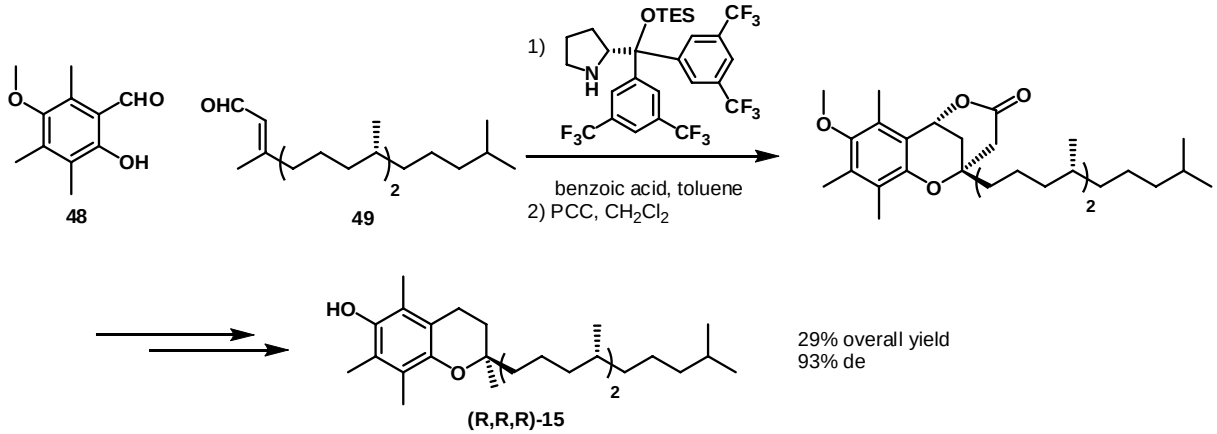
Scheme 14: Synthesis of ***(R,R,R)*-15** via a Grignard reaction.

In 2007, Breit et al. took advantage of the o-DPPB-directed allylic substitution methodology developed in their group,[45a] and applied it in the synthesis of ***(R,R,R)*-15** (*scheme 15*).[45b] Construction of the side-chain was performed by highly enantio- and diastereoselective steps, leading to **46**, which was coupled with **47**[44] in a o-DPPB-directed copper-mediated allylic substitution.



Scheme 15: o-DPPB-directing group – Application to the total synthesis of **(*R*,*R*,*R*)-15**.

Efforts in our group lead to the first biomimetic synthesis of α-tocopherol, using a chiral peptide auxiliary (*scheme 9 – section 1.2.3*), and in 2008, Woggon et al. reported the highly stereoselective domino aldol/oxa-Michael reaction between aromatic aldehyde **48** and *E*-(*R*,*R*)-phytal **49**, using a proline catalyst (*scheme 16*).[46] **(*R*,*R*,*R*)-15** was finally obtained in 93% de, and in an overall yield of 29%, being one of the shorter routes to **15** described so far.

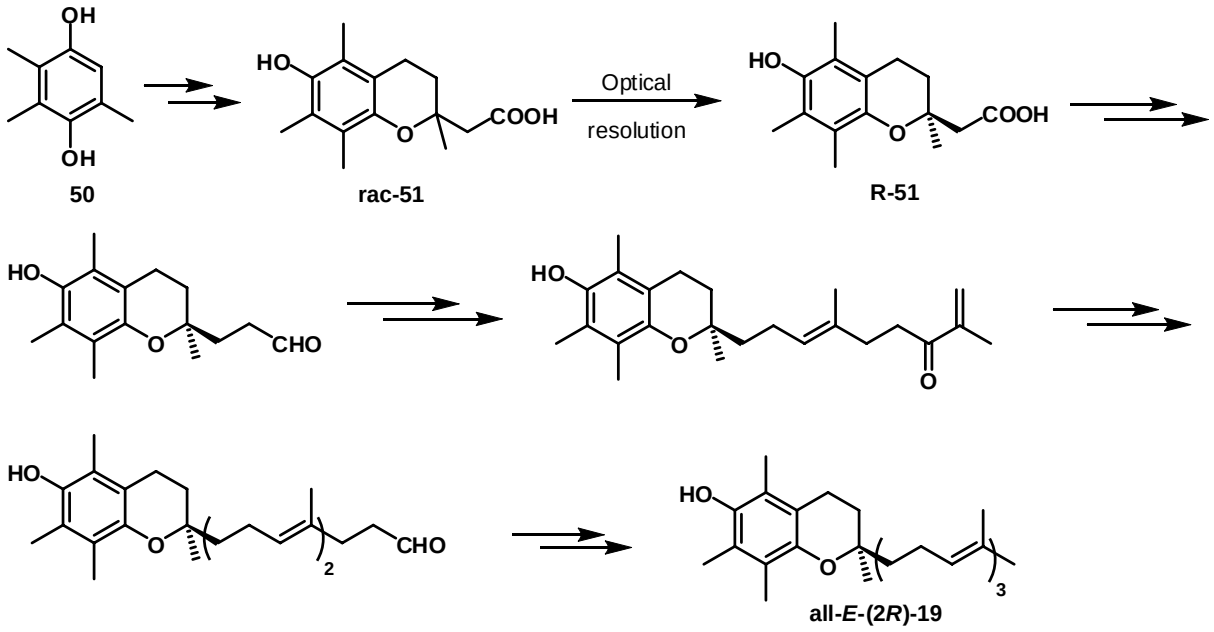


Scheme 16: Synthesis of **(*R*,*R*,*R*)-15** via a domino aldol/oxa-Michael reaction.

1.2.5. Synthesis of all-*E*-(2*R*)-α-tocotrienol **19**.

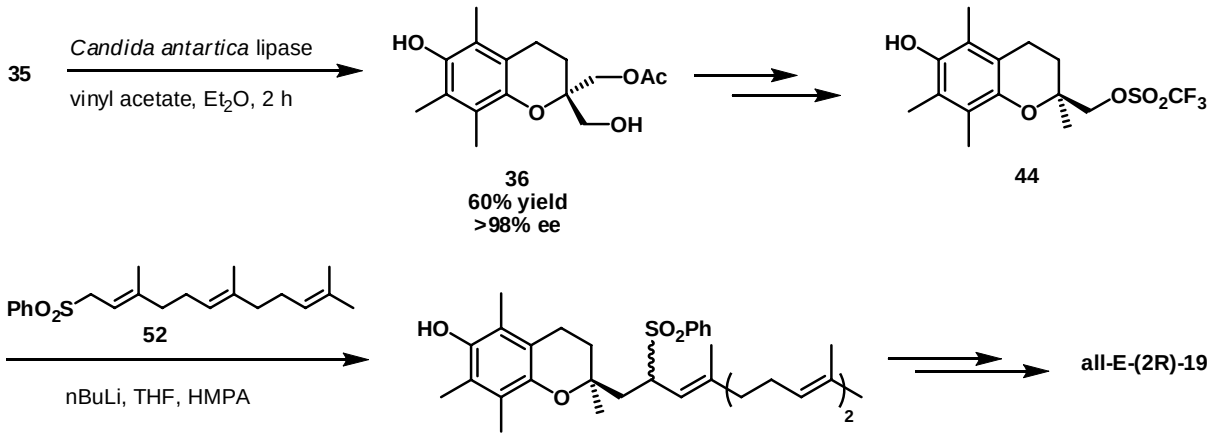
In comparison to its tocopherols analogue, all-*E*-(2*R*)-α-tocotrienol **19** has not been extensively studied, and only few examples of asymmetric synthesis have been reported. The first total synthesis of naturally occurring α-tocotrienol was published in 1976 by Scott et al.[47]

and was based on the optical resolution of acid **51**, gained from trimethylhydroquinone **50** (*scheme 17*) and using known methodologies for the stereoselective synthesis of trisubstituted olefins.



Scheme 17: First total synthesis of all-*E*-(2*R*)-α-tocotrienol **19**.

More recently, Chênevert et al. reported in 2006 the use of their chromanol building block **36** (*scheme 11*),[48] and successfully coupled it with sulfone **52** to afford **all-*E*-(2*R*)-19**, after desulfonylation using $LiBHEt_3$ in the presence of $PdCl_2$(dppp) as catalyst (*scheme 18*).

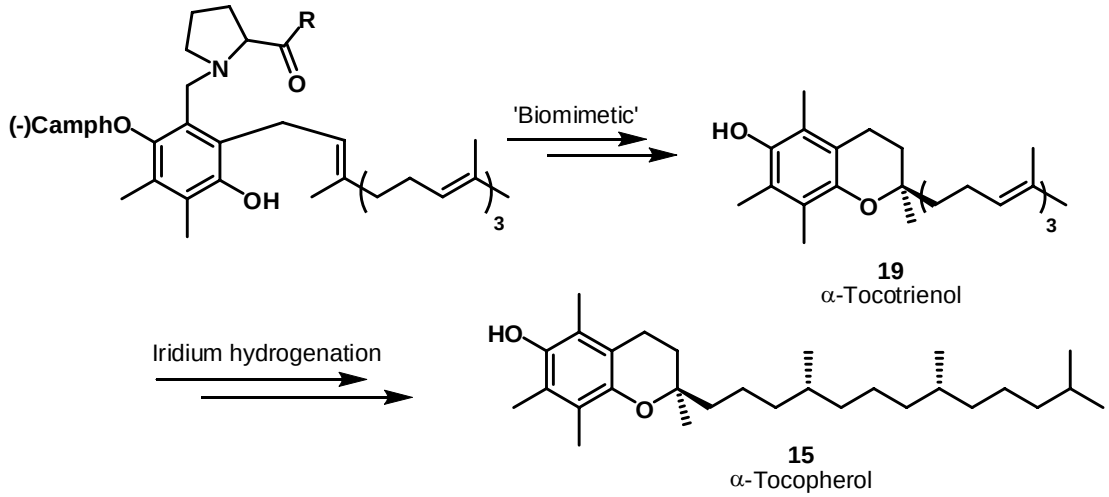


Scheme 18: Application of the lipase-catalyzed resolution of **35** to the synthesis of **all-*E*-(2*R*)-19.**

2. Aim of this work

The main goal of this work concerned the development of new methods for the synthesis of optically active tocopherols and tocotrienols, in particular addressing the problem of chirality at C-2.

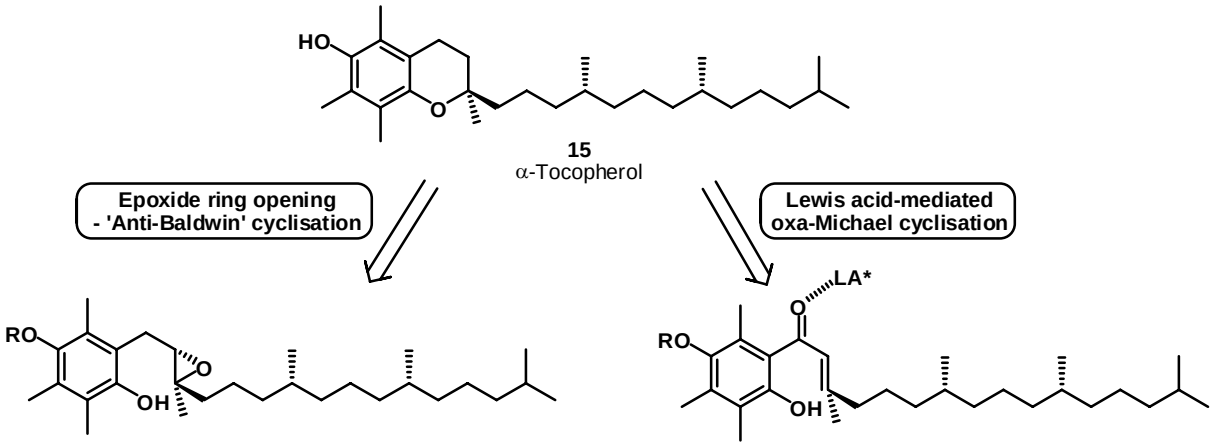
The first part was inspired by the work in our group by Woggon et al.,[34] regarding the application of the biomimetic synthesis of α-tocopherol, to the synthesis of α-tocotrienol **19**. Since the biosynthesis of tocotrienols has been reported to proceed in the same manner as for tocopherols,[33] meaning that there should be an equivalent of the tocopherol cyclase that promote the cyclisation to tocotrienols, we expected a similar *si*-protonation of the double bond, followed by a *re*-attack of the phenolic oxygen. By using a chiral peptide auxiliary, we should be able to form enantio-enriched α-tocotrienol **19** under acidic treatment (*scheme 19*).



Scheme 19: Proposed common route for α-tocotrienol **19** and α-tocopherol **15**. [R = OH, Amino acid]

In combination with the work done by Pfaltz et al. concerning the asymmetric hydrogenation of olefins using chiral Iridium catalysts,[49] a common synthetic route leading to α-tocotrienols and α-tocopherols was proposed. Finally, we expected to get important informations concerning the pro-asp-driven chromanol cyclisation, in order to explain the moderate diastereoisomeric excess observed, see page 19.

The second part of this work was directly oriented to the direct asymmetric synthesis of (*R*,*R*,*R*)-α-tocopherol **15** using two distinct strategies, based on the chromanol formation: (1) via an intramolecular epoxide ring opening, that would proceed under inversion of configuration, (2) by an asymmetric Lewis acid mediated oxa-Michael cyclisation (*scheme 20*).



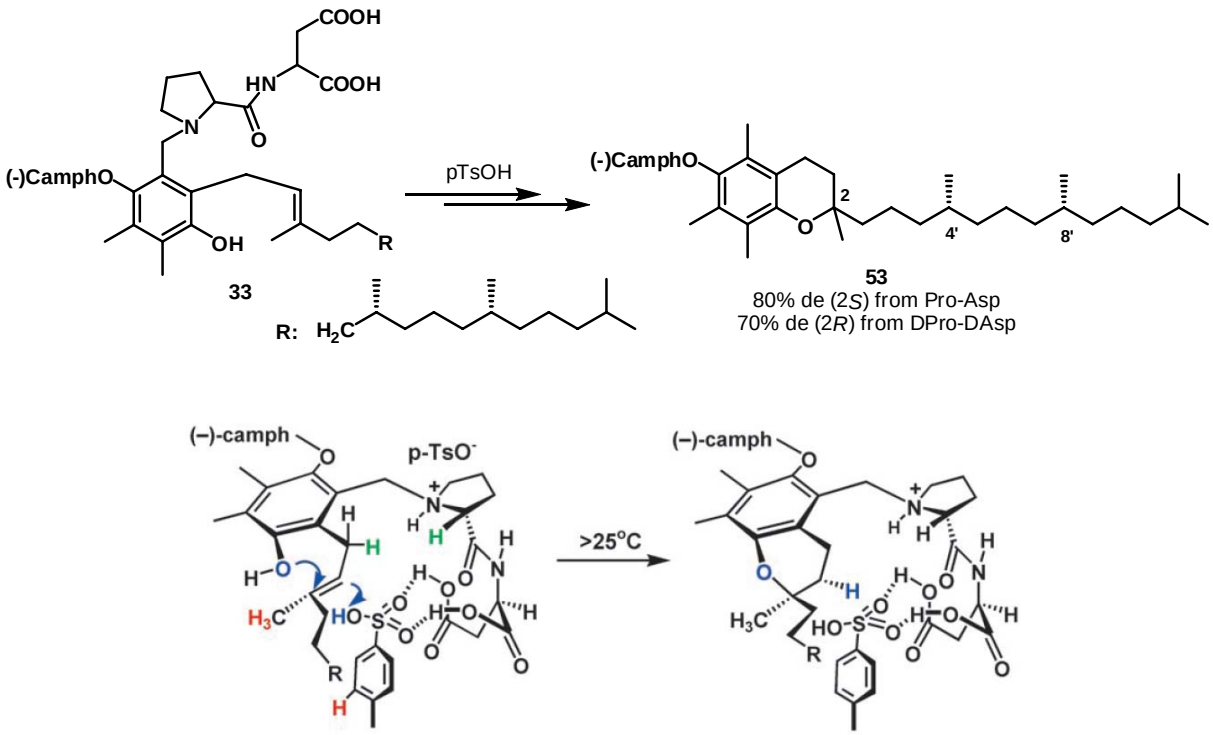
Scheme 20: Possible approaches for the diastereoselective chromanol ring formation.[LA=Lewis acid]

3. Results and Discussions

3.1. Biomimetic chromanol cyclisation: a common route to α-tocotrienol and α-tocopherol.

3.1.1. Design of the synthesis.

The biomimetic synthesis of α-tocopherol reported by Woggon et al.[34] in 2006 was based on the mechanism of chromanol formation catalyzed by the enzyme tocopherol cyclase from *Cyanobacteria*[31] (*scheme 8 – Section 1.2.3)*. Using a (*S*)-proline-(*S*)-aspartic acid dipeptide, chromanol ring **53** was formed with 80% de (2*S*), and 70% de (2*R*) when starting from DPro-DAsp peptide (*scheme 21*).

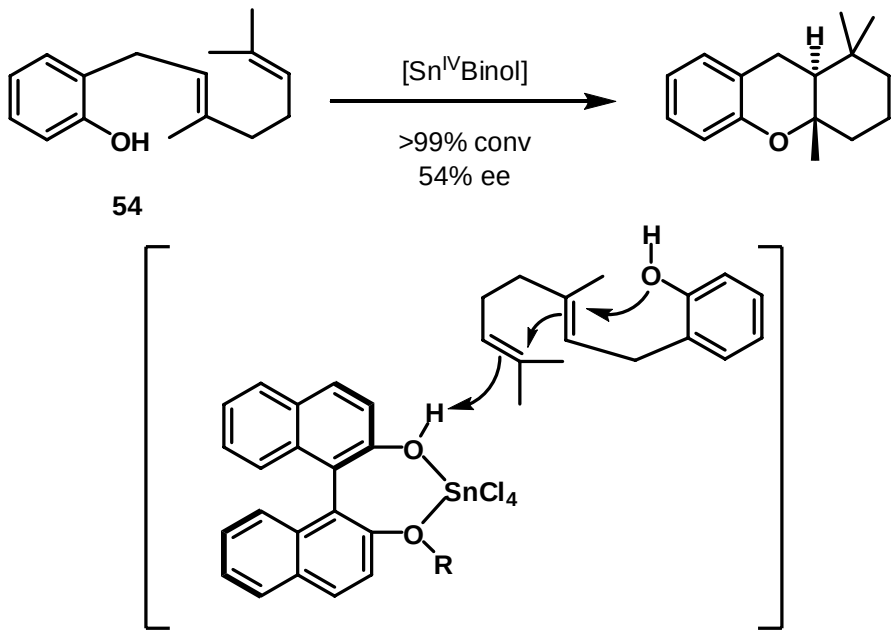


33-pTsOH

Scheme 21: Biomimetic cyclisation of **33** described by Woggon et al.

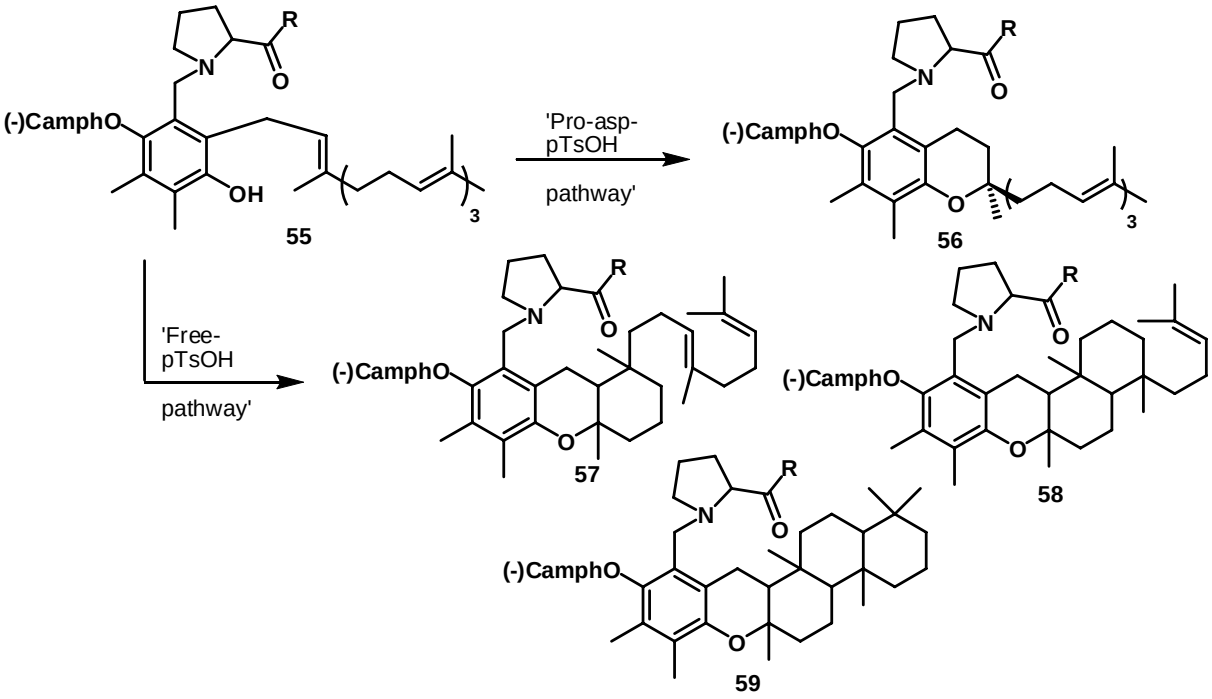
In the mechanism proposed by Woggon et al.,[34] the p-toluene sulfonic acid (pTsOH) is activated by hydrogen bonding of the asp moiety, thus leading in an increased acidity of its hydrogen. The chirality of the peptide is then transferred to the chromanol ring, leading to diastereo-enriched compounds (*scheme 21*).

The moderate (70% de) to good (80% de) diastereoisomeric excess in the reaction **33** → **53** suggested: i) a background reaction catalyzed by the excess of pTsOH without participation of the didpeptide linker and ii) the pro-asp residue is not absolutely efficient in creating a high-energy-conformation of the phytyl-hydroquinone which cyclises to a chroman system with >90% enantiomerical purity at C-2. Both aspects are important with respect to the plan of using the dipeptide linker for the synthesis of tocotrienols. In this context the experiment published by Yamamoto[50] are briefly discusses. This group reported the use of a chiral [Sn^{IV}-BINOL] catalyst in the cascade asymmetric cyclisation of o-geranyl phenol **54**, leading to the polycyclic product in >99% conversion and 54% ee (*scheme 22*). The mechanism of cyclisation, a "Lewis acid assisted, Bronsted acid supported reaction"[51] resembles to some extend, to the one proposed in the tocopherol biomimetic cyclisation, a "Bronsted acid assisted, Bronsted acid supported reaction".[34]



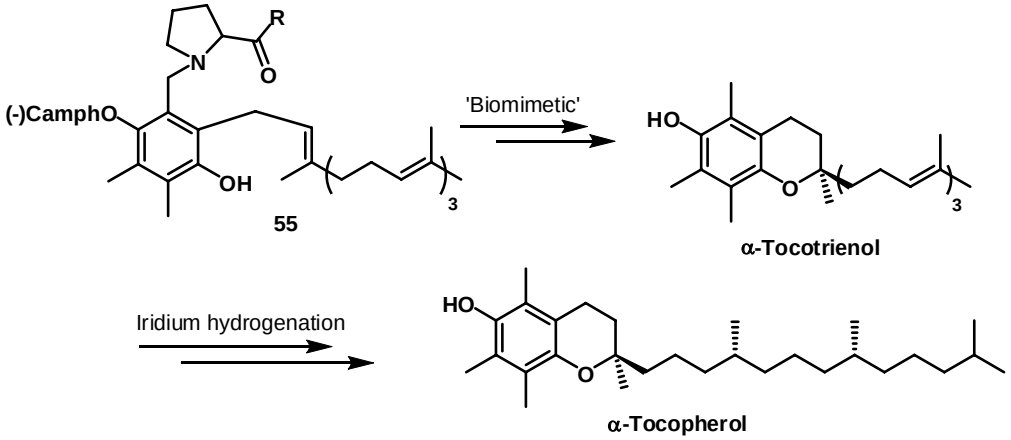
Scheme 22: Biomimetic cyclisation of o-geranyl phenol **54**, using a chiral Sn^{IV} catalyst.

Using this information for cyclisation experiments with **55** one can predict a pro-asp triggered ring closure to the desired **56** or / and a mixture of polycylic compounds **57**-**59** that would be produced by a Yamamoto-type cyclization of the unsaturated side-chain of **55** (*scheme 23*). The product distribution of the reaction of **55** in the presence of excess pTsOH would then allow us to estimate the participation of "free pTsOH" in the reaction which led to α-tocotrienol, see page 29.

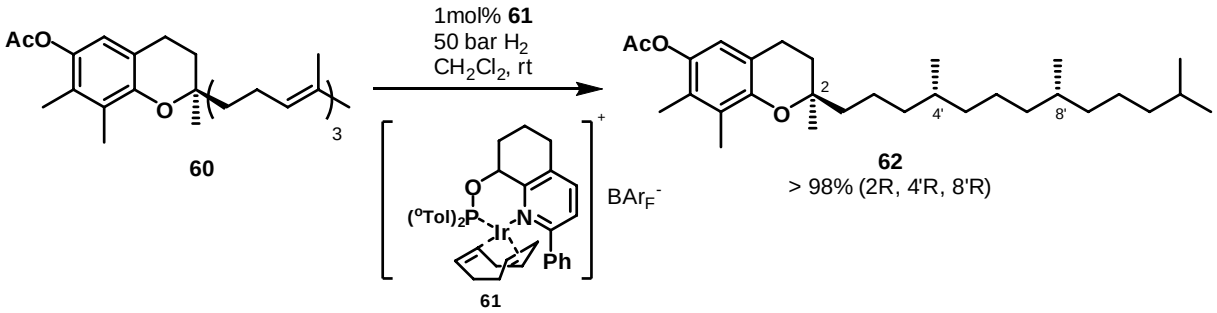


Scheme 23: Possible product distribution of cyclisation reaction of **55**. [R = OH, Amino acid]

Further, cyclisation of **55** → **56** would enable us to prepare both α-tocotrienol **19** through removal of the chiral auxiliary (*scheme 24*) and α-tocopherol **15** by asymmetric iridium hydrogenation, based on the work reported by Pfaltz et al. in the hydrogenation of γ-tocotrienyl acetate **60** with iridum catalyst **61** (scheme 25).[52]



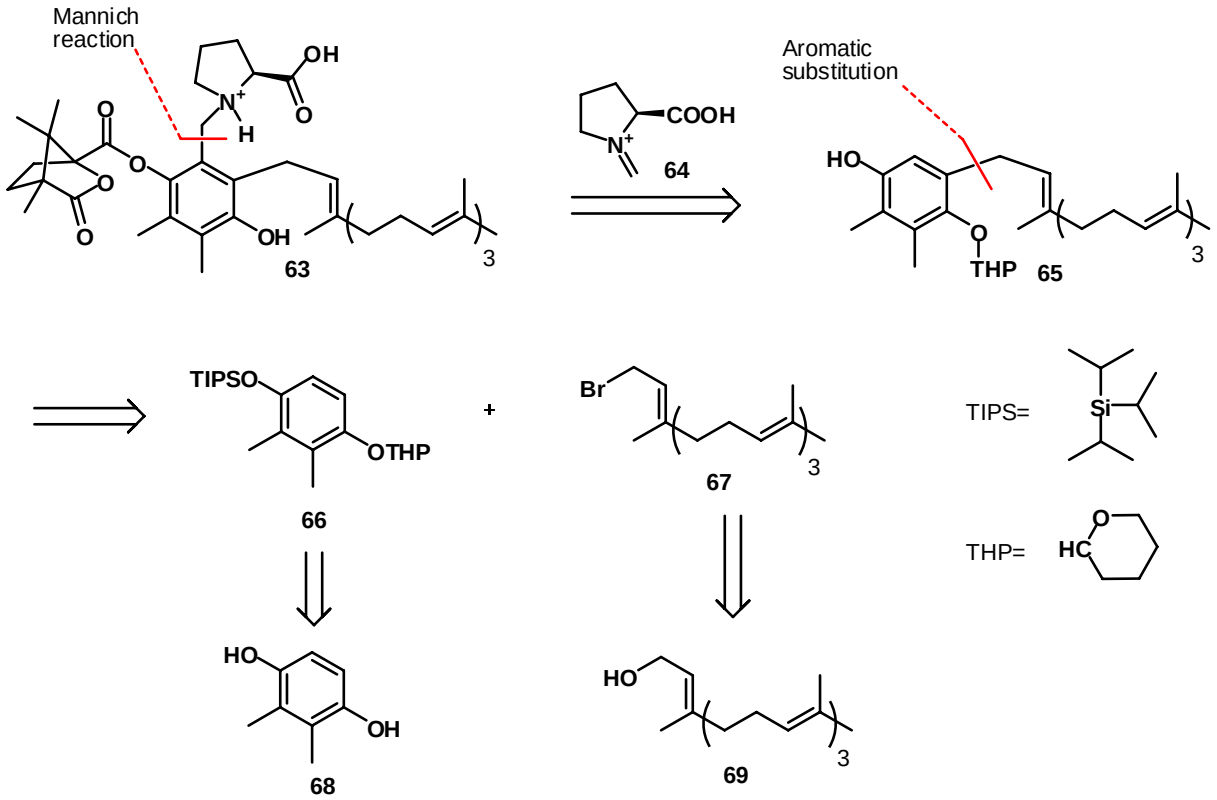
Scheme 24: Planned synthesis of α-tocotrienol and α-tocopherol in a common route.



Scheme 25: Asymmetric hydrogenation of γ-tocotrienyl acetate **60** with Iridium catalyst **61**.

3.1.2. Synthesis of proline precursors **63**.

The key intermediate for cyclisation experiments with **55** is the all-*E*-geranyl-geranyl-hydroquinone derivative **63** which can be obtained as shown in scheme 26.

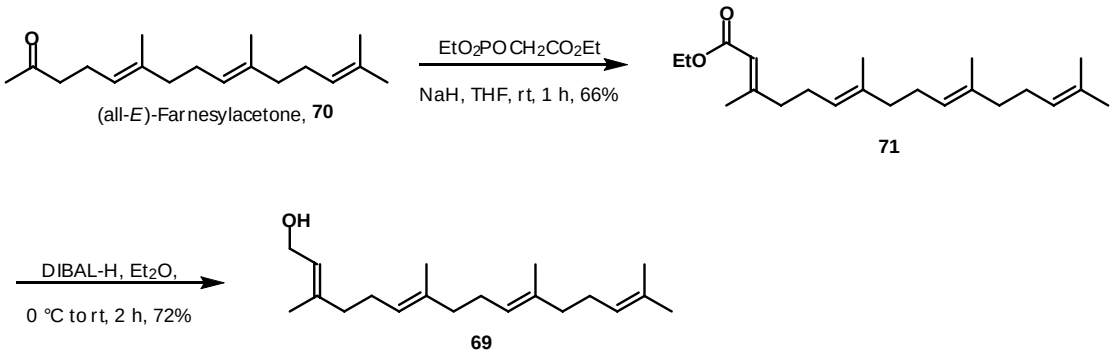


Scheme 26: Retrosynthetic approach to the synthesis of precursors **63**.

Accordingly, the proline can be attached by a Mannich reaction with the iminium salt **64** to the aromatic partner **65**, which can be formed by an aromatic substitution of bis-protected hydroquinone **66**, and geranyl geranyl bromide **67**. For the preparation of **66** and the Mannich reaction with **64**, we took advantage of earlier work[34], and since no mismatch was observed, (-)-camphanoyl ester was used for the phenol protection.

3.1.2.1. Synthesis of (all-*E*)-geranyl geraniol **69**. (Based on Pr. Chougnet work)

The synthesis of the long unsaturated chain started from (all-*E*)-farnesyl acetone **70** (DSM Nutritional Products), which was converted to its ethylester derivative **71**, by a Horner-Wadsworth-Emmons reaction (*scheme 27*). Pure *E*-compound was obtained in 66% yield, and finally reduced to furnish desired (all-*E*)-geranyl geraniol **69** in 72% yield.

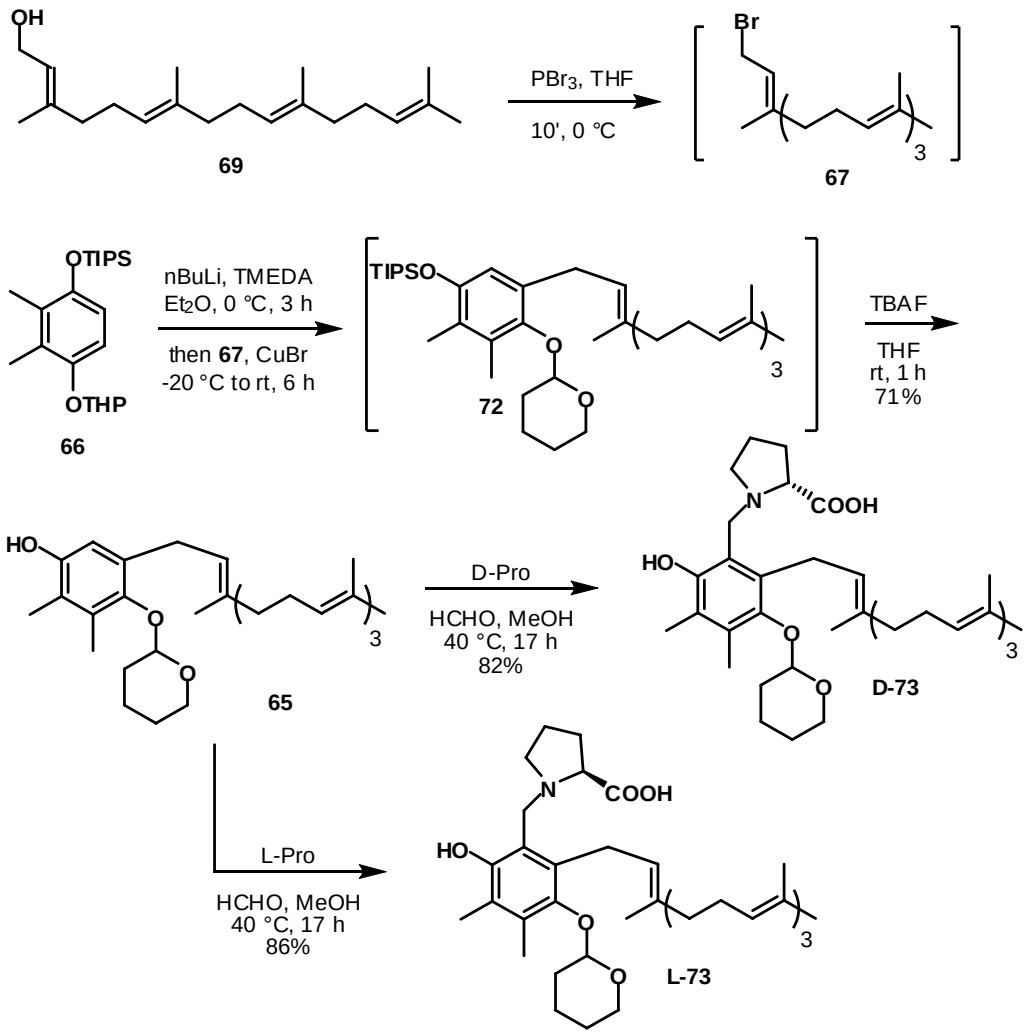


Scheme 27: Synthesis of (all-*E*)-geranyl geraniol **69**.

3.1.2.2. Coupling with the aromatic partner **66** – Mannich reaction.

(all-*E*)-Geranyl geraniol **69** was converted to its bromide derivative **67**, and directly coupled with bis-protected hydroquinone **66** to afford **72**, which was not purified but mono-deprotected to give easily separable products, affording **65** in 71% from **66**.

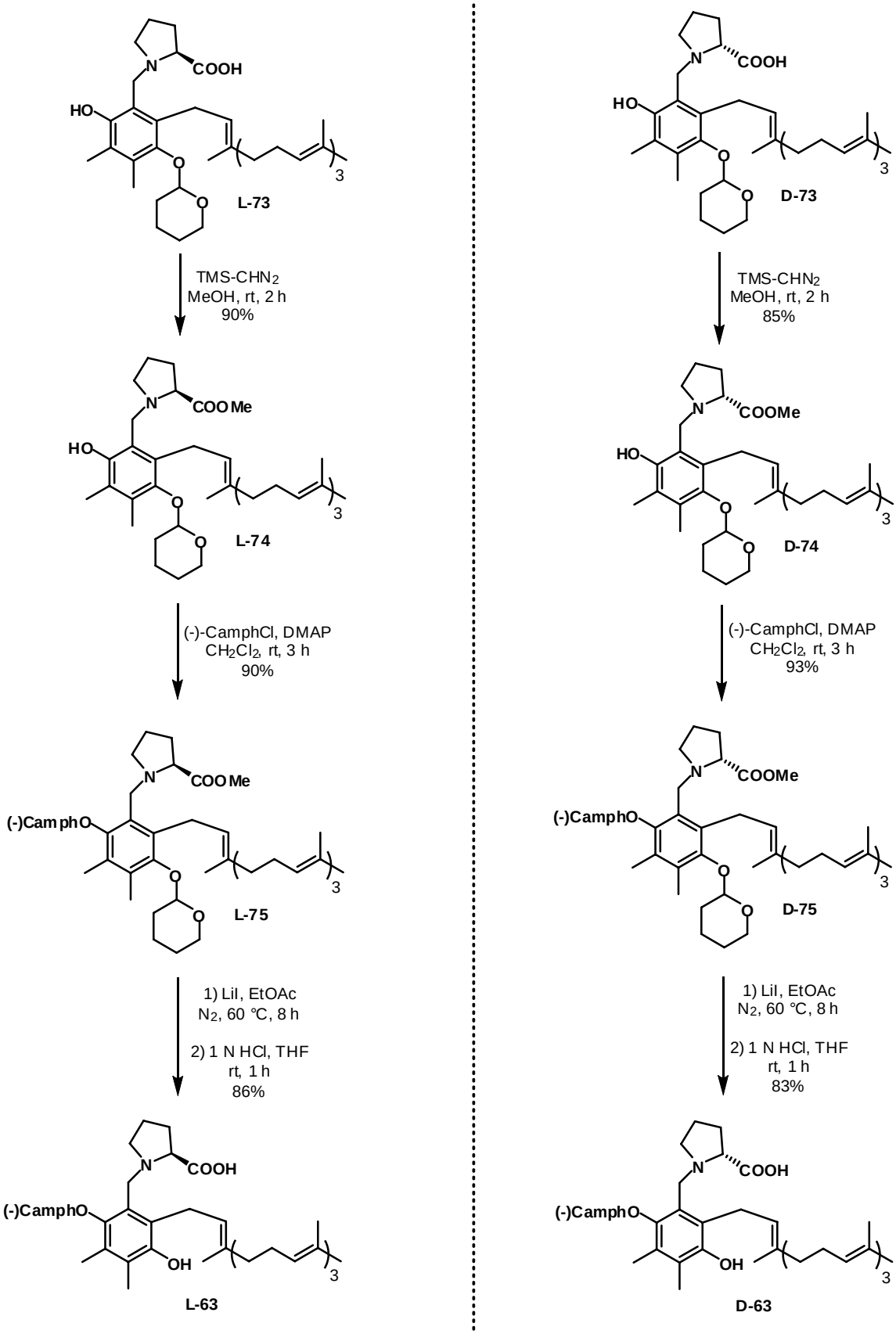
Finally, Mannich reagents of L-proline and D-proline were generated in situ by reaction with formaldehyde in MeOH, and then reacted with hydroquinone **65**, to yield **L-73** and **D-73** in 86% and 82% respectively.



Scheme 28: Synthesis of LProOH **L-73** and DProOH **D-73**.

3.1.2.3. Synthesis of cyclisation precursors **L-63** and **D-63**.

Final steps leading to desired precursors **L-63** and **D-63** consisted in the protection of the free phenol and the removal of the THP protecting group. Direct protection of the phenol was not possible in the presence of the free acid, which was firstly converted to its methyl ester derivatives. Then treatment with trimethylsilyl diazomethane in MeOH afforded **L-74** and **D-74**, in 90% and 85% yield respectively (*scheme 29*), subsequently protected with (-)-camphanoyl chloride to yield **L-75** (90%) and **D-75** (93%). The difficult methyl ester cleavage was then performed by using LiI under a constant flow of N_2, to eliminate the MeI formed and to drive the reaction to completion. The THP group was not stable under these conditions, and was partially cleaved. Hydrolysis was completed to afford desired cyclisation precursors **L-63** in 86% yield, and **D-63** in 83% over two steps.

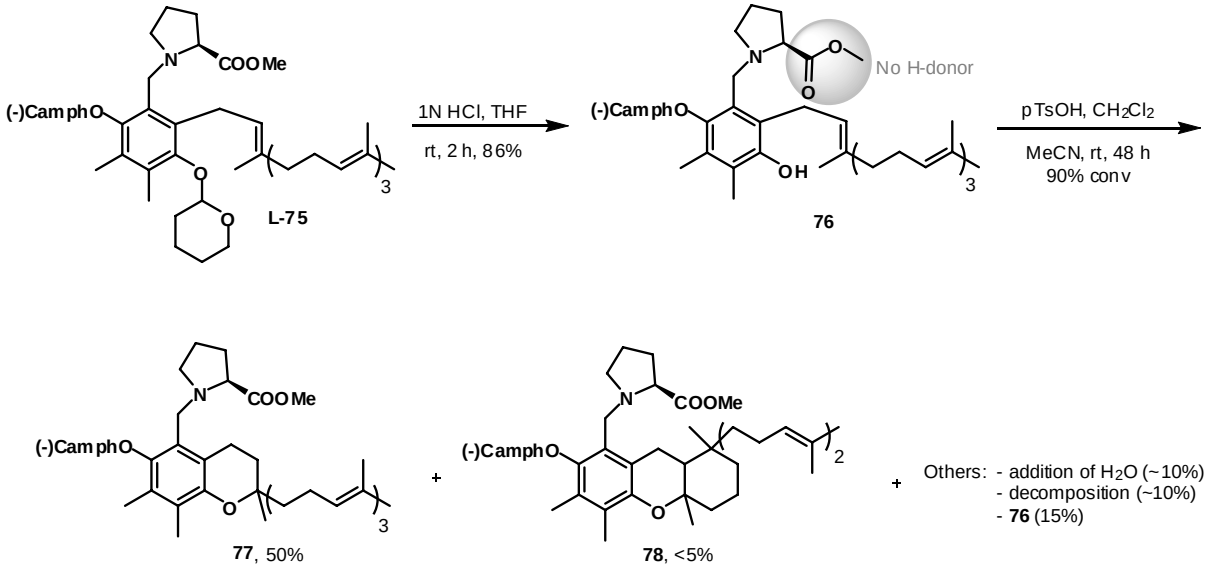


Scheme 29: Synthesis of **L-63** and **D-63**.

3.1.3. Yamamoto's products and background reaction.

In order to determine the importance of the "background" reaction in the biomimetic cyclisation, we tried to isolate and quantify the products resulting from a cascade cyclisation (*scheme 23*), involving the "non-chiral" pTsOH pathway. Since this pathway would be favoured in the absence of the dipeptide and a masked proline, preliminary experiments were conducted with protected LPro(OMe) precursor **76** (*scheme 30*).

The synthesis went smoothly from **L-75**, by treatment with 1N HCl in THF, to yield **76** in 86% yield. Cyclisation of **76** using established conditions, pTsOH in CH_2Cl_2:MeCN, showed a nice 70-80% conversion, but only <5% of a polycyclic compound.



Scheme 30: Cyclisation of **76** using pTsOH·H_2O – Only <5% of Yamamoto's products formed.

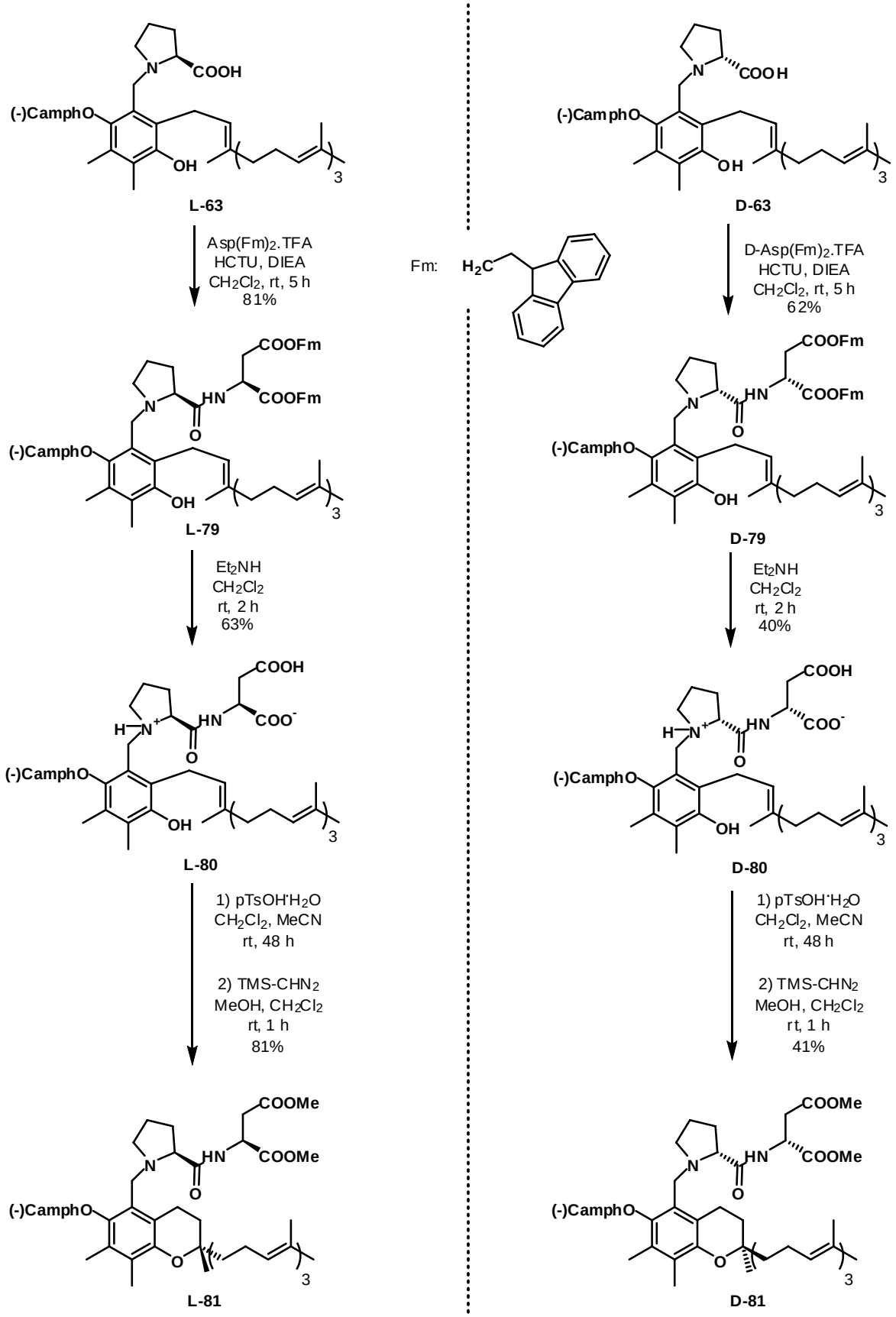
Indeed, the main product isolated was the chroman derivative **77** in 50% yield, under the "chiral pathway", and unreacted precursor **76** (15%). A further product (10%) displayed spectroscopic data (NMR/ESI-MS) corresponding to structure **77** with one H_2O added to one of the double bonds of the side chain. Due to the limited amount of material the regioselectivity of water addition could not be determined.

These experiments clearly show that under conditions that favour polycyclization only a negligible amount of trycyclic compound such as **78** is produced. These results suggest that the excess of pTsOH used in cyclization experiment leading to the tocopherol or tocotrienol structure is not related to the moderate diastereoisomeric excess. It seems that the obtained de is indeed a result of limited conformationally control of the chiral auxiliary in an adduct such as **33**-pTsOH (*see scheme 21*), which explains the requirement of two equivalent of pTsOH.

3.1.4. Synthesis and cyclisation of ProAsp and DProDAsp precursors.

Our efforts were then focused on the biomimetic synthesis of enantio-enriched α-tocotrienol using ProAsp / DProDAsp as chiral auxiliaries.

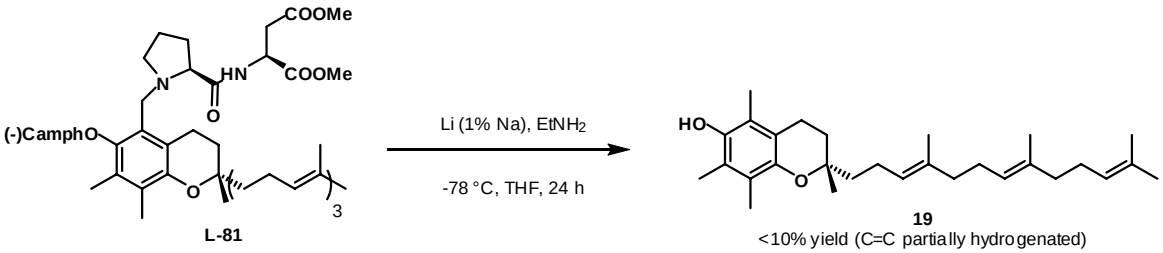
The synthesis started from proline derivatives **L-** and **D-63**, which reacted with Fm-protected aspartic acids, as its TFA salts, using classical peptide chemistry (*scheme 31*), to afford **L-79** and **D-79** in 81% and 62% yield respectively. Subsequent deprotection with Et_2NH in CH_2Cl_2, afforded the free acids **L-80** (63%) and **D-80** (40%), which COOH groups made purification on silica gel difficult. Cyclisation of **L-** and **D-80** went smoothly, in the presence of 2 equivalents of pTsOH, to afford the corresponding chromanols, which were directly protected as their bis-methyl esters **L-81** and **D-81**, in 81% and 41% yield respectively. Determination of the diastereoselectivity was not possible at this stage, since no suitable methods gave relevant results but was checked latter on. Nevertheless, we anticipated that **L-81** would have a *S* configuration at C-2, whereas **D-81**, should have a *R* configuration at C-2 as shown in scheme 31.



Scheme 31: Synthesis and cyclisation of ProAsp **L-80** and DProDAsp **D-80** chromanols.

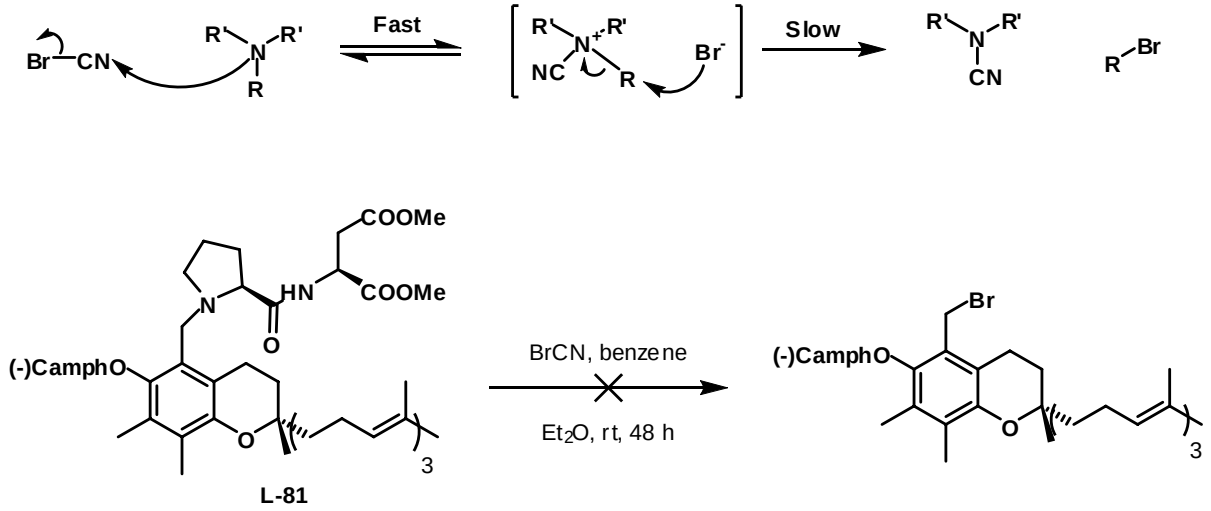
3.1.5. Synthesis of α-tocotrienol – Benzyl amine cleavage.

Synthesis of α-tocotrienol **19** required the removal of the chiral auxiliary, i.e. the cleavage of the C-N bond. It is usually achieved by reductive hydrogenation,[34] in the presence of palladium catalysts, however this method was obviously not compatible with substrate **81**, since the olefins would also be hydrogenated. Several alternatives were envisaged, such as the Birch reduction[53], but treatment of **L-81** by a mixture of Li (1% Na) in $EtNH_2$:THF (20:1) never afforded the desired product in yields higher than 10%, and the olefins were also partially hydrogenated (*scheme 32*).



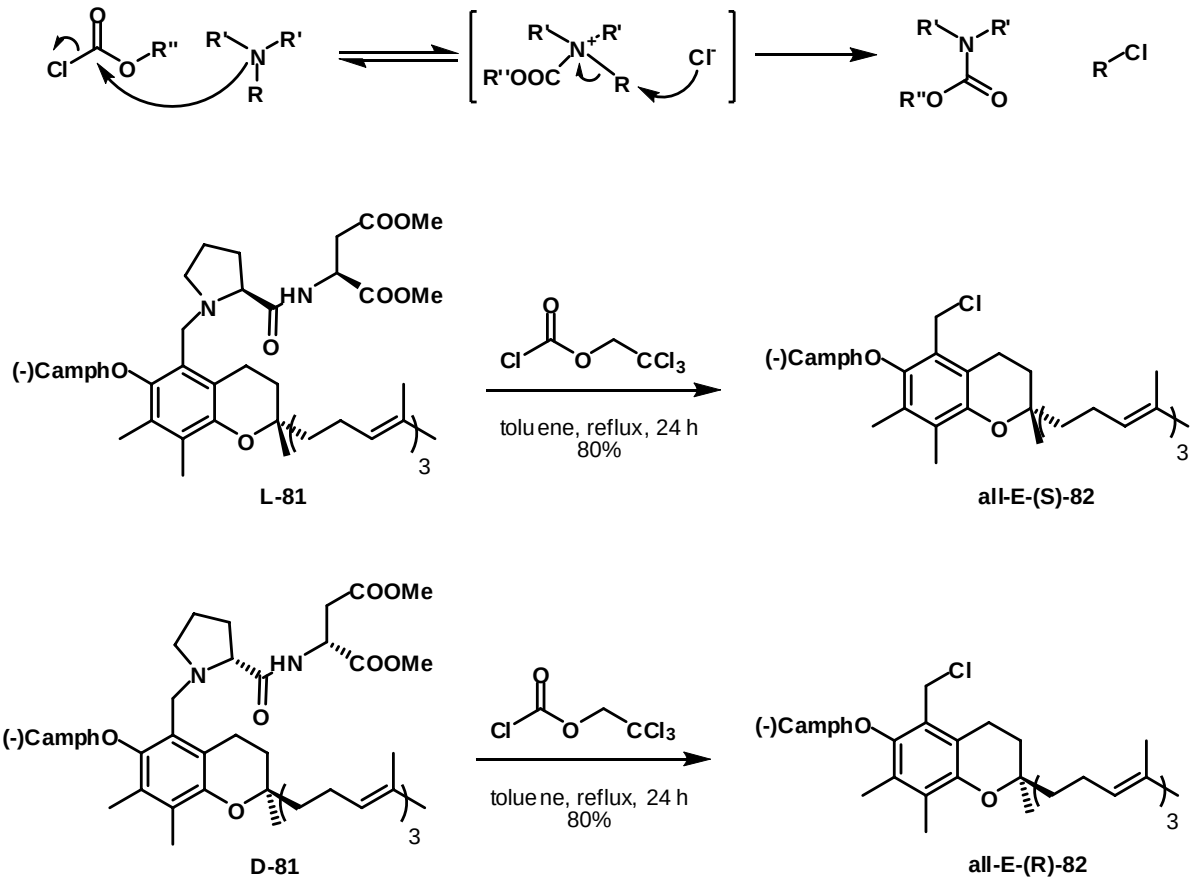
Scheme 32: Birch reduction of **L-81** in the presence of Li and $EtNH_2$.

The Von Braun reaction[54] appeared to be a promising alternative, being unreactive towards alkene functionalities (*scheme 33*). Accordingly to the mechanism of this reaction the amine moiety reacts on the cyanogen bromide, displacing the bromine atom, which then reacts to form the corresponding cyanamide and alkyl bromide.



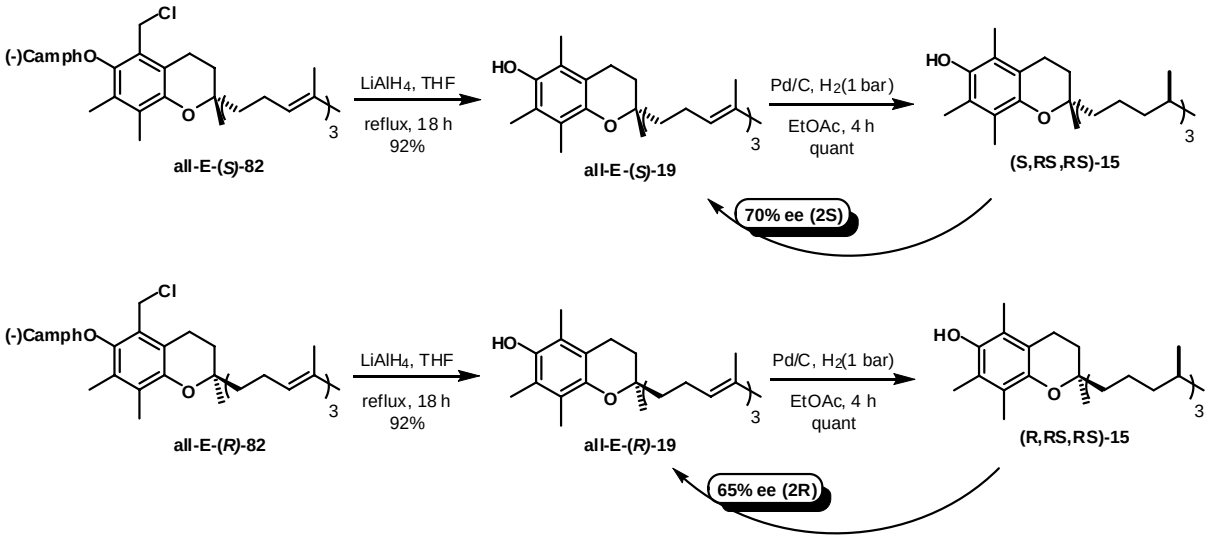
Scheme 33: Von Braun reaction mechanism and application to **L-81**.

However, treatment of **L-81** with BrCN was unsuccessful and the starting material was completely recovered. The Von Braun reaction have been studied extensively during the past century,[55] but its limitations led to several modifications, such as the use of chloroformate reagents[56], which are more reactive than BrCN. The reaction mechanism is similar, thus leading to alkyl chloride, and carbamate after two successive nucleophilic substitutions (*scheme 34*).



Scheme 34: Benzyl amine cleavage by using chloroformate reagents.

Thus treatment of **L-81** and **D-81** by an excess of 2,2,2-trichlorethyl chloroformate afforded the corresponding benzyl chloride **all-*E*-(*S*)-82** and **all-*E*-(*R*)-82** in 80% yield. The choice of the formate reagent is crucial, since dramatic decrease in yield was observed by using benzyl- or allyl- chloroformate (52% and <10% yield respectively). Tandem reductive elimination of the chlorine, and cleavage of (-)-camphanate ester by $LiAlH_4$ finally yielded all-*E*-(*S*)-α-tocotrienol **19**, and all-*E*-(*R*)-α-tocotrienol **19** in 92% yield (*scheme 35*).



Scheme 35: Final steps to α-tocotrienols – Determination of ee's after hydrogenation.

The enantiomeric excesses were then determined on the hydrogenated tocopherols, by treatment with Pd/C under H_2 in EtOAc, which formed (4'*RS*,8'*RS*)-α-tocopherols. HPLC analysis using a chiral column (Chiracel OD-H) allowed the separation of the (2*S*) and (2*R*) isomers,[57] leading to 70% ee (2*S*) for **all-*E*-(*S*)-19**, and 65% ee (2*R*) for **all-*E*-(*R*)-19** (*figure 8*).

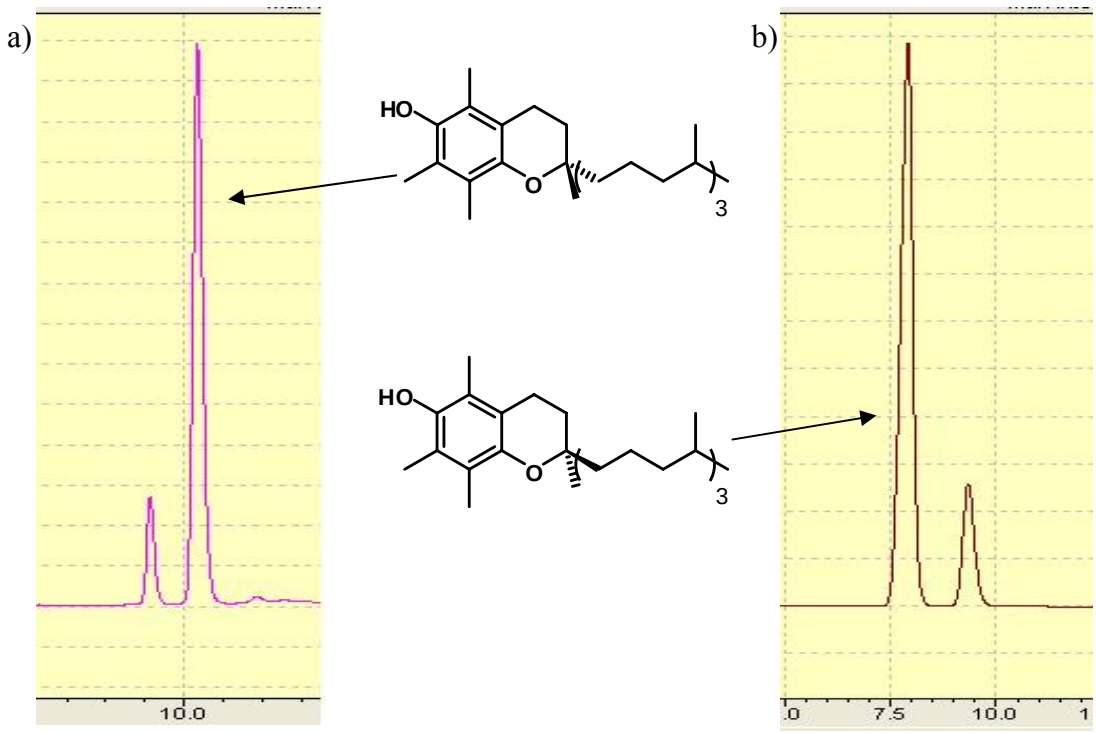
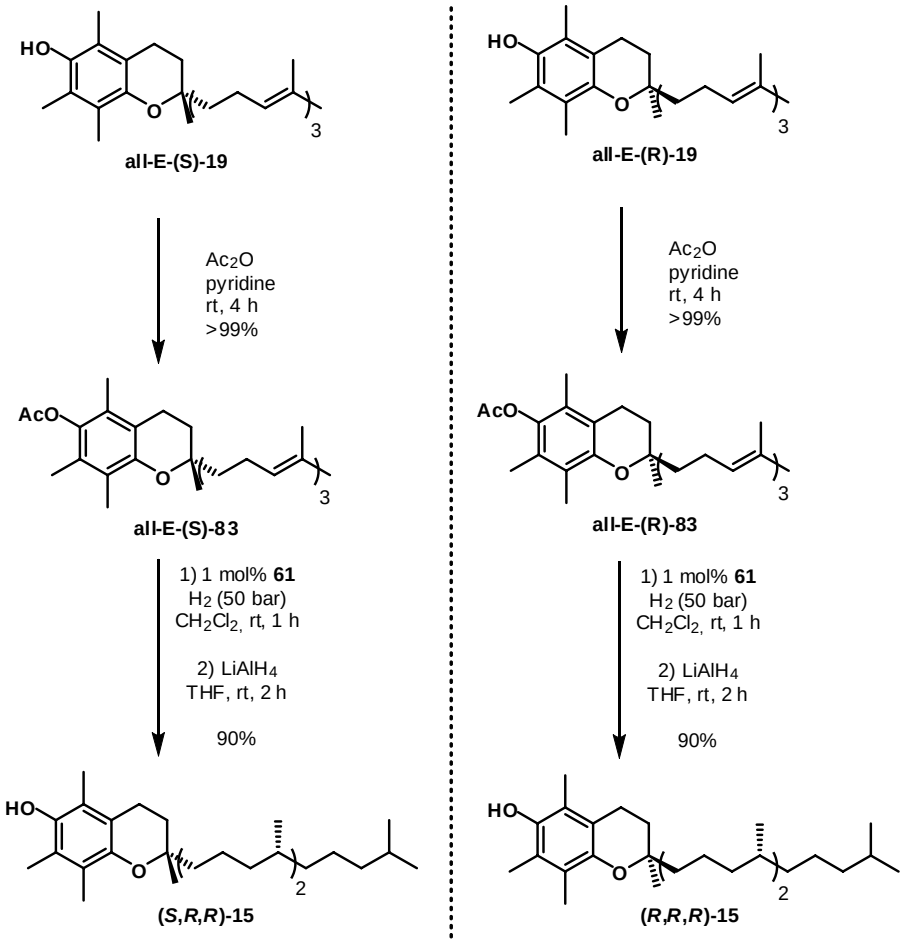


Figure 8: HPLC chromatogram of **(*S*,*RS*,*RS*)-15** and **(*R*,*RS*,*RS*)-15**. [Chiracel OD-H, 0.5% EtOH in n-hexane, 1mL/min, 220 nm, 25 °C]

Accordingly, the cyclization of **L-80** with the natural configuration of the chiral auxiliary yields predominantly the (2S) configuration at the chromanol of **19**, whereas **D-80** leads to the (2R) configuration.

3.1.6. Asymmetric hydrogenation of α-tocotrienol – Synthesis of α-tocopherol.

According to Pfaltz al.,[52] the asymmetric hydrogenation of α-tocotrienol with Iridium catalyst was performed on the acetylated derivatives **83** (*scheme 36*). Iridium catalyst **61** was then applied to enantiomerically enriched α-tocotrienyl acetates **all-*E*-(*S*)-83** and **all-*E*-(*R*)-83**, easily obtained by treatment with acetic anhydride in pyridine. Hydrogenation went smoothly to afford α-tocopheryl acetates, directly reduced to desired α-tocopherols **(*S,R,R*)-15** and **(*R,R,R*)-15** in excellent yields.



Scheme 36: Asymmetric hydrogenation of α-tocotrienyl acetates **83**.

The ratio of the 8 possible diastereoisomers was determined by a combination of HPLC analysis of α-tocopherols and GC analysis of α-tocopheryl methylethers.[57] As already discussed earlier, it was possible to separate (2*S*, 4'*RS*, 8'*RS*)-α-tocopherol and (2*R*, 4'*RS*, 8'*RS*)-α-tocopherol on chiral HPLC (*figure 8*). On the other hand, GC analysis of α-tocopheryl methylether allowed the separation of 4 couples of enantiomers, as depicted on figure 9.

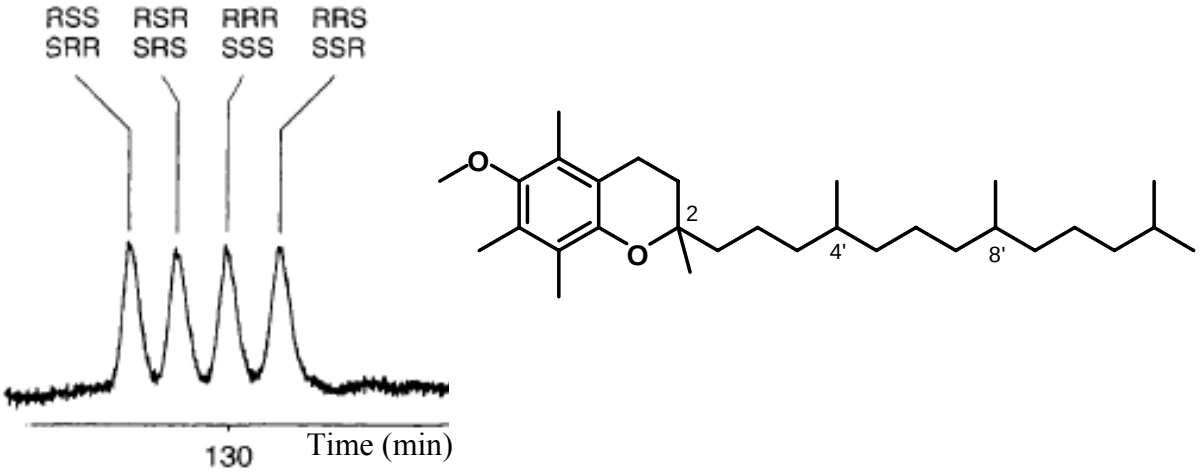


Figure 9: GC analysis of α-tocopheryl methylether. [CP-Sil-88 column, 50m x 0.25 mm, 0.25 μm; split injector (1:30), injector temp. 280 °C; FID detector, detector temp. 250 °C, carrier gas: H_2, 90 kPa; 170 °C, 140 min]

Combination of both analyses led to simple equations which would give the ratio of all 8 stereoisomers, as depicted on figure 10.

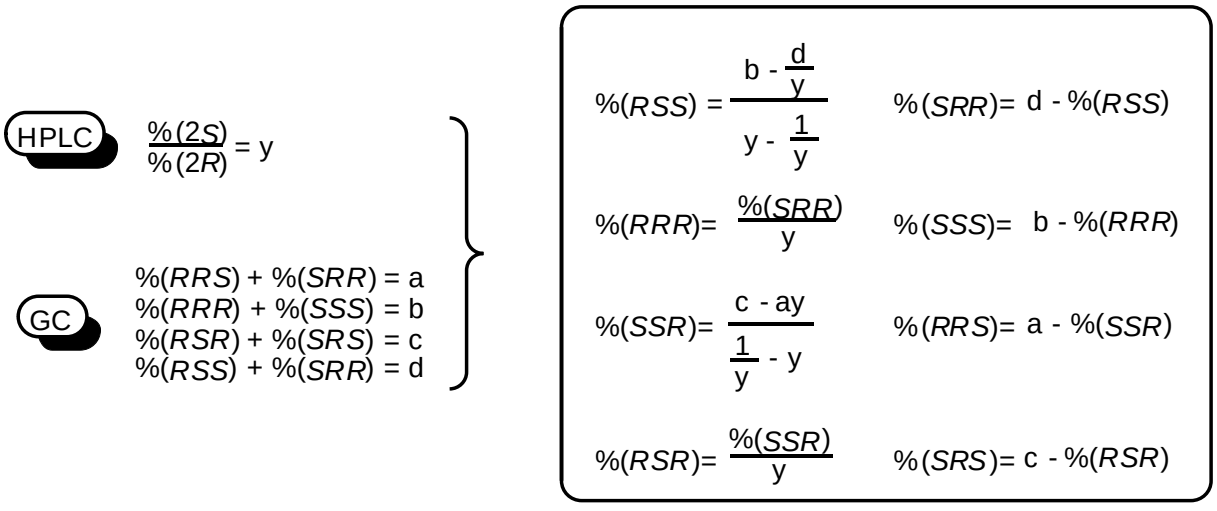
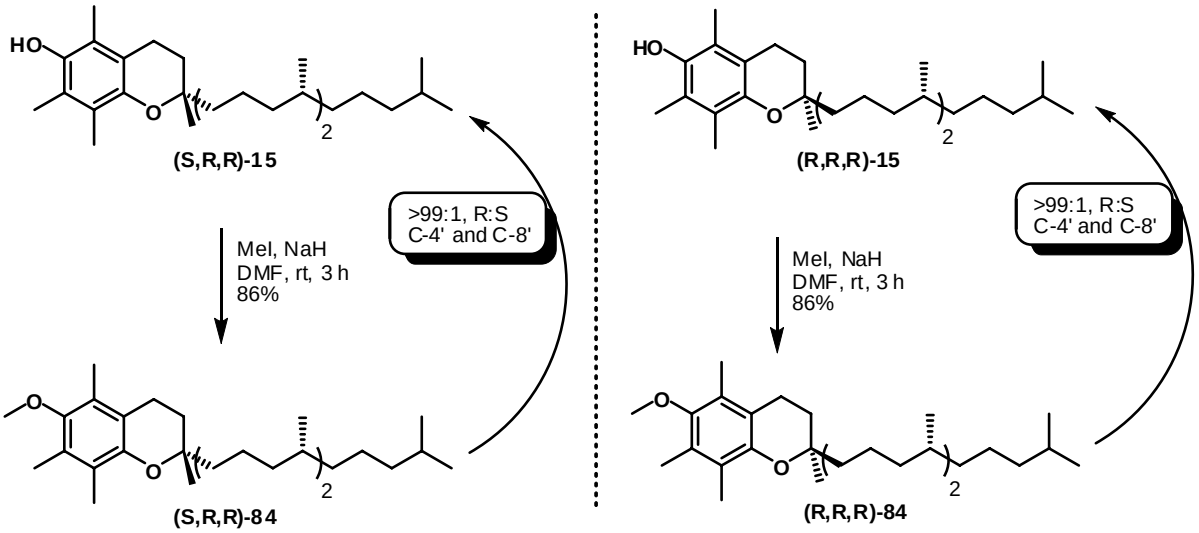


Figure 10: Calculations used for determination of diastereoisomers ratio.

Finally, α-tocopherols **15** were converted to their corresponding methyl ethers derivatives **84** (*scheme 37*), and GC analysis showed, in both case, an excellent *R*:*S* ratio up to >99:1 at C-4' and C-8'.

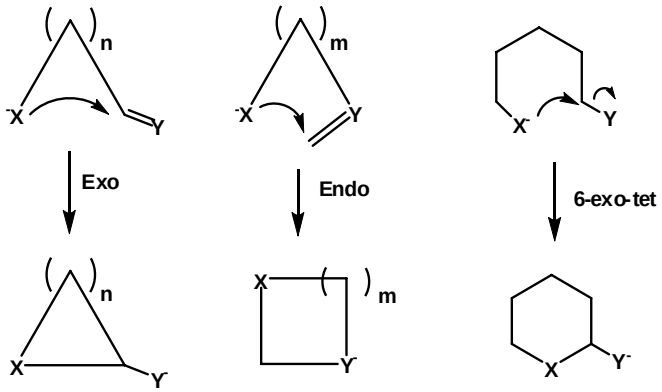


Scheme 37: Methyl ether protection – Selectivity of Ir-hydrogenation at C-4' and C-8'.

3.2. From Baldwin's Rules to the design of a novel chromanol ring formation

3.2.1. Design and retrosynthetic approach.

In 1976, Jack E. Baldwin described rules related to ring-closure reaction.[58] These rules, based on empirical results, allowed predicting favoured and disfavoured processes, depending on the nature of the cycle formed. Each reaction could be named using three parameters (*scheme 38*): (1) the size of the ring formed, (2) whether the breaking bond would be endocyclic (*Endo*) or exocyclic (*Exo*), (3) the geometry of the reacting carbon: *Tet* (tetrahedral), *Trig* (trigonal) or *Dig* (digonal).



Scheme 38: Baldwin's nomenclature in ring-closure reactions [n=1..5; m=0..4].

Indeed, depending on the geometry of the carbon atom undergoing the cyclisation, three rules were established (*table 2*). It relied on stereoelectronic requirements of transition state in ring-closure mechanisms, which referred to the angle α and the distance between the reacting atom and the reacting site (*figure 11*).

	Ring Size	Tet	Trig	Dig		Ring Size	Tet	Trig	Dig
Exo	3	✓	✓	×	Endo	3	?	×	✓
	4	✓	✓	×		4	?	×	✓
	5	✓	✓	✓		5	×	×	✓
	6	✓	✓	✓		6	×	✓	✓
	7	✓	✓	✓		7	?	✓	✓

Table 2: Baldwin's rules. [✓ : favour, × : disfavour, ? : not known]

Thus, for tetrahedral systems, favoured transition states should correspond to α = 180°, as established by Walden et al.;[59] for trigonal systems, Dunitz and Bürgi[60] reported an angle of 109°, specially on addition reactions to carbonyl group; and empirical observations showed that digonal systems required an α of 120°.

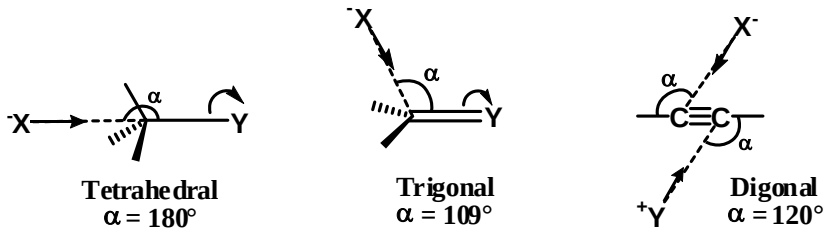
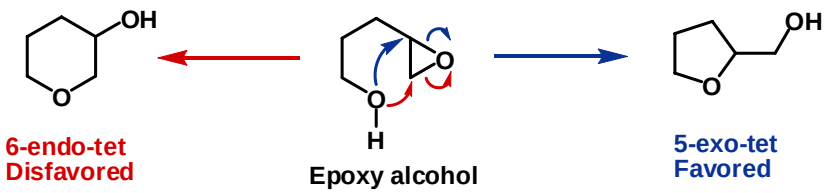


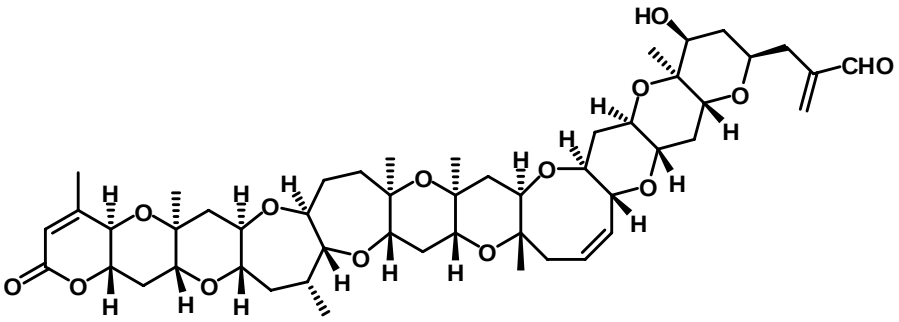
Figure 11: Transition state requirements that defined Baldwin's rules. [X=nucleophile]

Since 'disfavoured' do not necessarily imply 'impossible', several efforts have been published over the past decades, to circumvent these rules, and in particular in the case of γ-epoxy alcohol cyclisations. Two products could be formed, a 5-membered 'furan' ring (*5-exo-tet*), and a 6-membered 'pyran' ring (*6-endo-tet*), being the disfavoured cycle, as depicted on scheme 39.

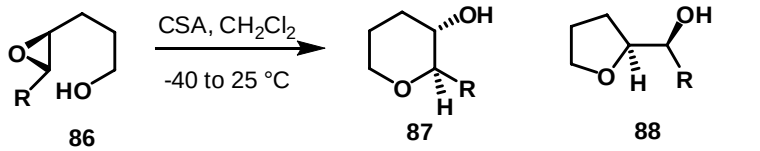


Scheme 39: γ-Epoxy alcohol cyclisations.

Marin natural products were the starting point of many studies in regioselective γ-epoxy alcohol cyclisations, since these types of compounds are usually constituted of several 'pyran'-type rings. In 1985, Nicolaou et al.[61] described first the use of directing groups in order to favour the 6-membered ring formation in the synthesis of brevetoxin B **85** (*scheme 40)*. Indeed, in the presence of camphorsulfonic acid (CSA), cyclisation of epoxy alcohol **86** could be driven to the 'pyran' product **87** by using allylic substituents, which have the ability to weaken the adjacent C-O bond, and to stabilize the positive charge formed.



Brevetoxin B, **85**

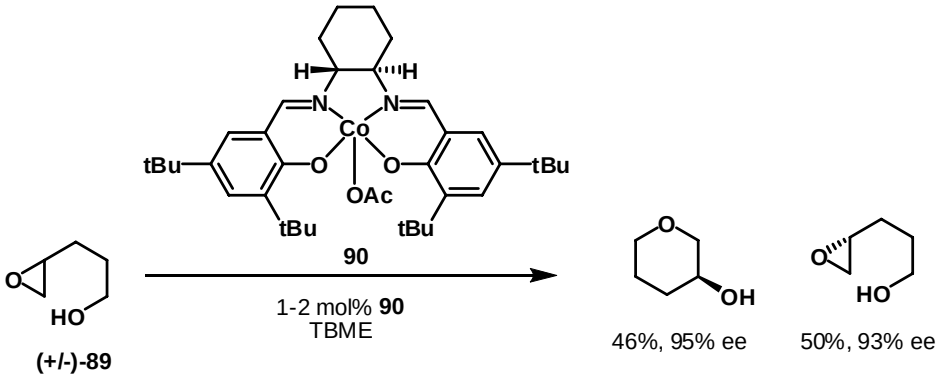


86 **87** **88**

R= $CH_2CH_2CO_2Me$, **87:88** = 0:100
R= $CH{=}CH_2$, **87:88** = 100:0

Scheme 40: Directing group for the regioselective 'pyran' ring formation in Brevetoxin B.

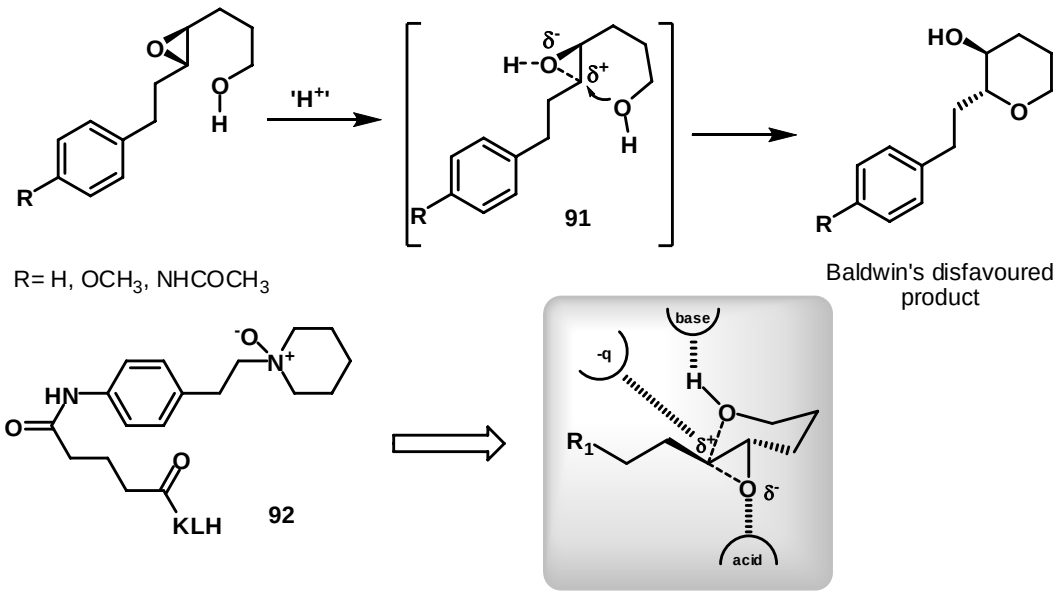
Based on this principle, several marine product syntheses have been accomplished over the last twenty years,[62] using a variety of different directing groups. Meanwhile, metal catalysts became more and more popular, and were also employed to direct regioselective cyclisation of epoxy alcohols. In 1994, Hanaoka et al.[63] reported the use of Co^{III} catalysts and later, Murai et al.[64] described the use of La^{III} metal complexes which directed the 6-endo pathway. Nevertheless, specific binding sites on substrates were necessary and these conditions thus suffered of difficult and long chemical modifications. But in 1999, Jacobsen et al.[65] reported the regio- and enantioselective cyclisation of epoxy alcohols, by using a chiral [Co^{III}(salen)] complex **90** (*scheme 41*), ending in a highly enantioselective kinetic resolution. Bio-inspired chemistry also gave good results, especially in the field of antibody catalysts, as reported by Lerner et al. in 1993[66] and Wilson et al. in1999.[67]



Scheme 41: [Co^{III}(salen)] catalyst: kinetic resolution of epoxy alcohol **89**.

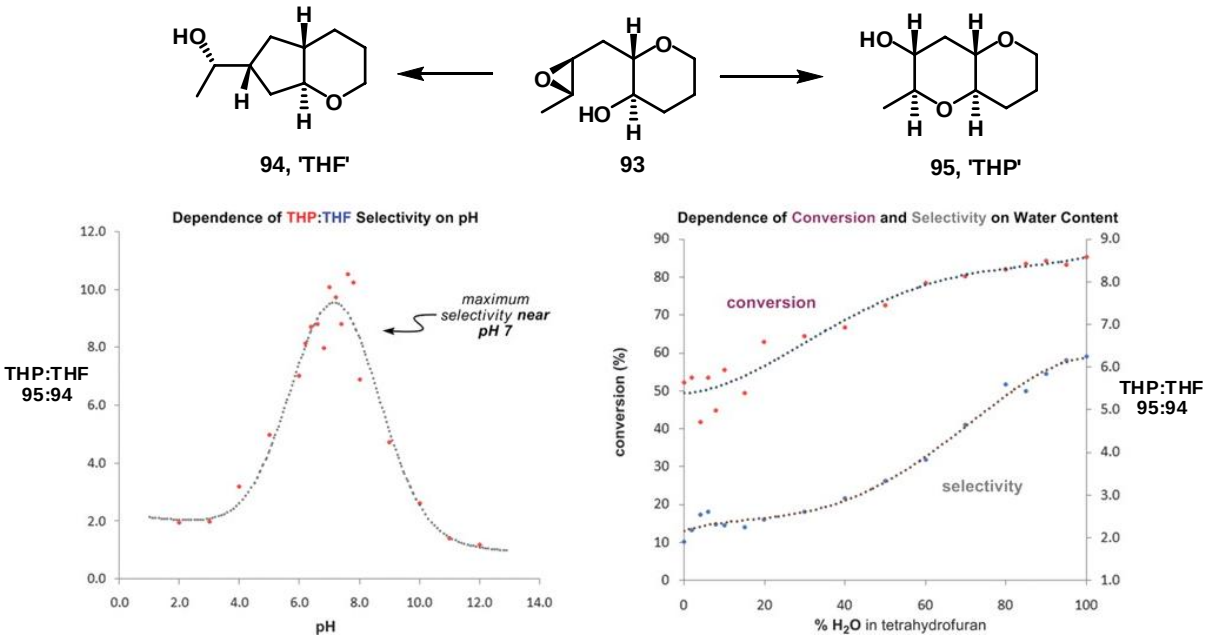
Hapten **92** was designed to mimic the disfavoured transition state **91** of the endo reaction and was used to induce corresponding antibodies. The cationic nitrogen was supposed to induce one or more amino acid residues that stabilize the carbocation appearing in the transition state **91**, while the anionic oxygen atom may induce positively charged amino acids to assist in the acid-catalyzed ring opening of the epoxyde (*scheme 42*). Induced antibody catalysts were screened and several gave excellent regioselectivity as well as stereoselectivity.

Recently, Jamison et al. published an epoxide-opening cascade for the construction of ladder polyether marine natural products,[68] such as brevetoxin B (*scheme 40*).



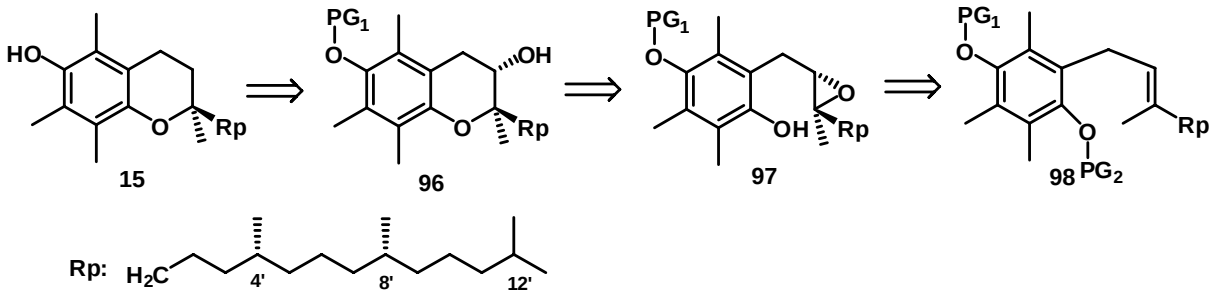
Scheme 42: Hapten **92** used to mimic transition state **91** and induce antibody catalysts [KLH = keyhole limpet hemocyanin].

Under optimized conditions in water at pH = 7.0, a ration of 11:1 in favour of the pyran product **95** was accomplished (*scheme 43*). Though the epoxy alcohol **93** used in this study is templated towards pyran formation, it remains a rare example in which neither directing groups nor metal/antibody catalysts were used.



Scheme 43: Cyclisation of templated epoxy alcohol **93** – pH and solvent optimization.

From this last report, we were encouraged to envisage chromanol formation via an epoxide ring opening, which led to a retrosynthetic approach depicted on scheme 44. α-Tocopherol **15** could then be obtained via hydroxy chromanol **96**, endo product of the cyclisation of chiral epoxide **97**, which could be formed from the allylic precursor **98**.

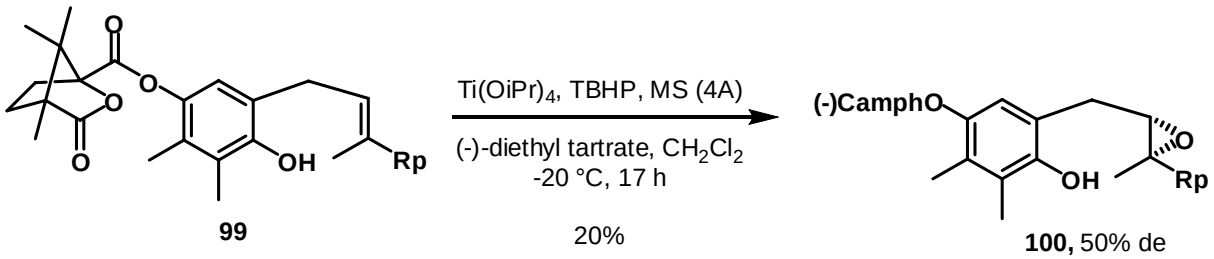


Scheme 44: Retrosynthetic proposal leading to α-tocopherol **15**. [PG_1, PG_2=protecting groups]

In all following schemes, figures and tables, Rp=(4'R,8'R)-4',8',12'-trimethyltridecanyl.

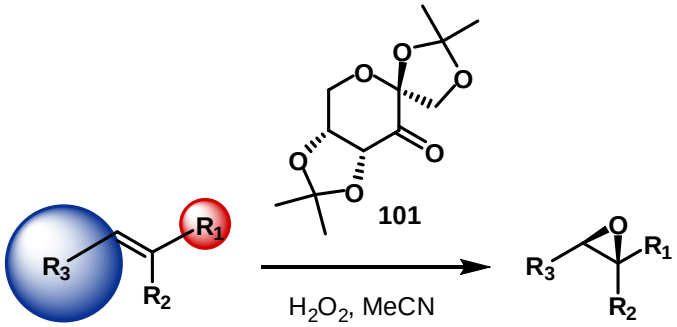
First of all, this approach required the asymmetric epoxidation of a trisubstituted, unfunctionalized olefin. The stereoselective synthesis of epoxides has been extensively investigated[69] including the direct asymmetric epoxidation of alkenes.[70] But most of these methods are substrate dependent, and hence were not considered to be suitable for our strategy.

It was the case of Sharpless epoxidation,[70a] which needed an allylic alcohol to induce high stereoselectivities, in the presence of a chiral titanium complex. Nevertheless, precursor **99**, easily available from our fridges, was submitted to Sharpless conditions, using TBHP as oxidant (*scheme 45*), that afforded epoxide **100** with a moderate 50% de. We expected the titan complex to bind to the phenolic oxygen, which was obviously too far away from the double bond to induce a reasonable de.



Scheme 45: Sharpless epoxidation of **99**.

In 1997, Shi et al. reported the use of a chiral fructose-derived **101** catalyst in the epoxidation of trans disubstituted and trisubstituted olefins[71,72] (*scheme 46*). The wide scope of reactive olefin substrates made it the catalyst of choice.



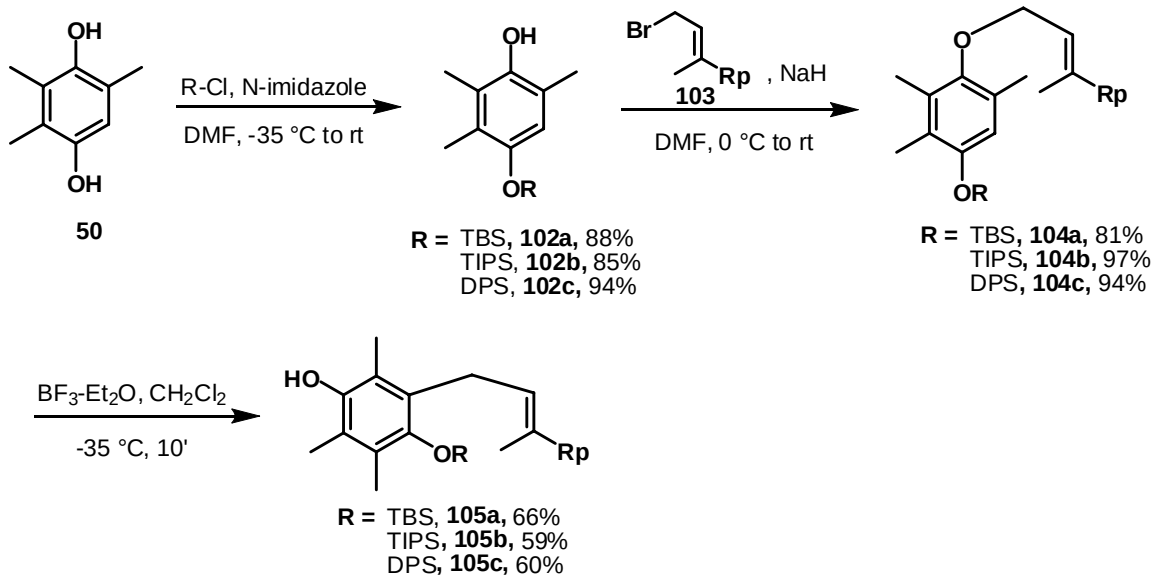
Scheme 46: Shi epoxidation in MeCN, using H_2O_2 as a co-oxidant.

Several factors govern the selectivity of this reaction, in particular the size of the olefin substituents is significant such that small R_1 and large R_3 groups gave the best enantioselectivities.[71]

Further, Shi's mechanism based correlation[71] between catalyst configuration and product stereochemistry suggested that we could obtain the desired epoxide using **ent-101** rather than the commercially available **101**.[73] In view of the given structure of our synthetic intermediate variation of the protecting groups at the hydroquinone was the only choice to enhance the difference in size of the substitutents at the trisubstituted double bond.

3.2.2. Synthesis of allylic precursors **106**.

Precursors for the asymmetric epoxidation were synthesized starting from commercially available hydroquinone **50**, and E-(*R*,*R*)-phytol **34** (>98.5:1.5 *E*:*Z*, DSM Nutritional Products). Monoprotection of **50** with bulky silylethers[74] were accomplished in high yields to afford **102a**, **102b** and **102c**, which could then react with phythyl bromide **103** (formed *in situ* from **34**), yielding **104a** (81%), **104b** (97%) and **104c** (94%), as depicted on scheme 47. Double Claisen rearrangement of phytyl ethers[75] produced corresponding mono-protected phenols **105a**, **105b** and **105c**, in moderate yields, due to isomerisation of double bond.



Scheme 47: Synthesis of **105a**, **105b** and **105c** via a double Claisen rearrangement.

A ratio of 9:1 *E*:*Z* was observed on the crude materials, but purification of *E*-isomers was difficult and led to the loss of materials. Nevertheless, pure *E*-compounds were necessary to investigate asymmetric epoxidation, and thus *E*:*Z* ratio determinations were carefully done either by ^{1}H NMR for **105a** and **105b**, or by HPLC for **105c** (*figure 12*). Three successive column chromatography allowed the isolation of pure E-isomer (>98.5:1.5, E:Z).

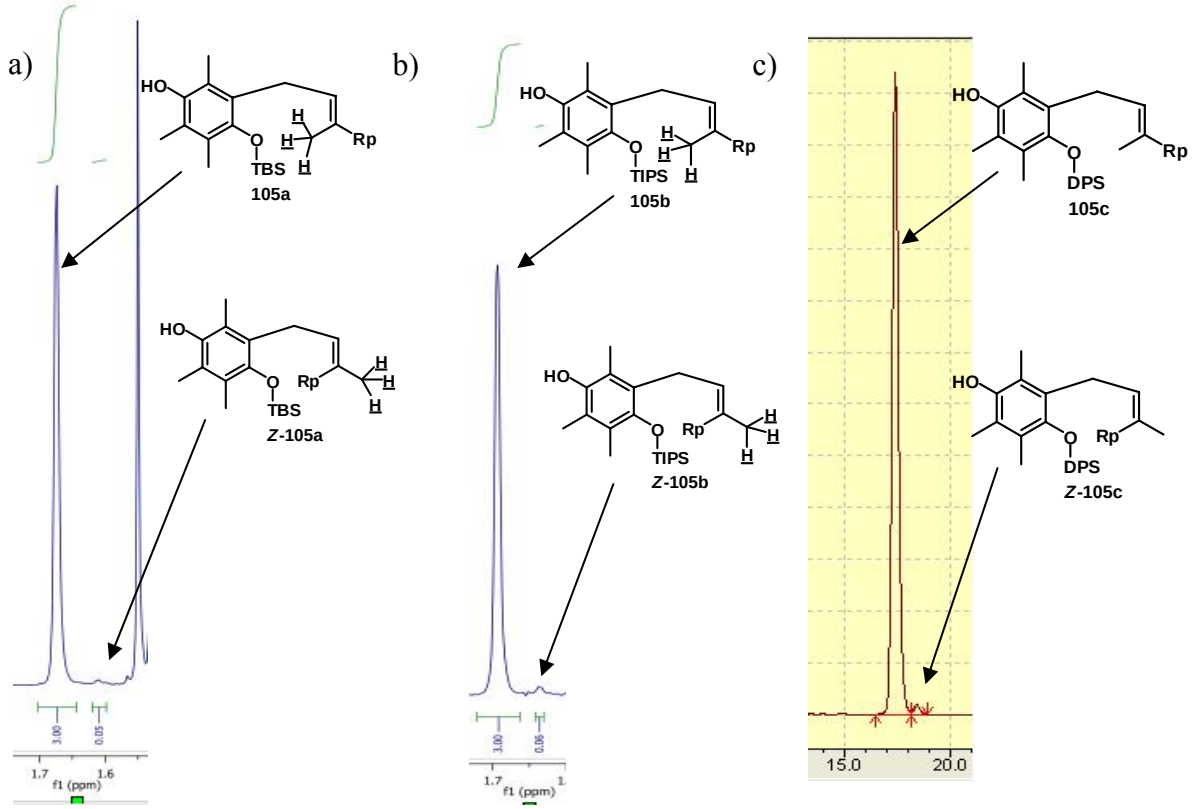
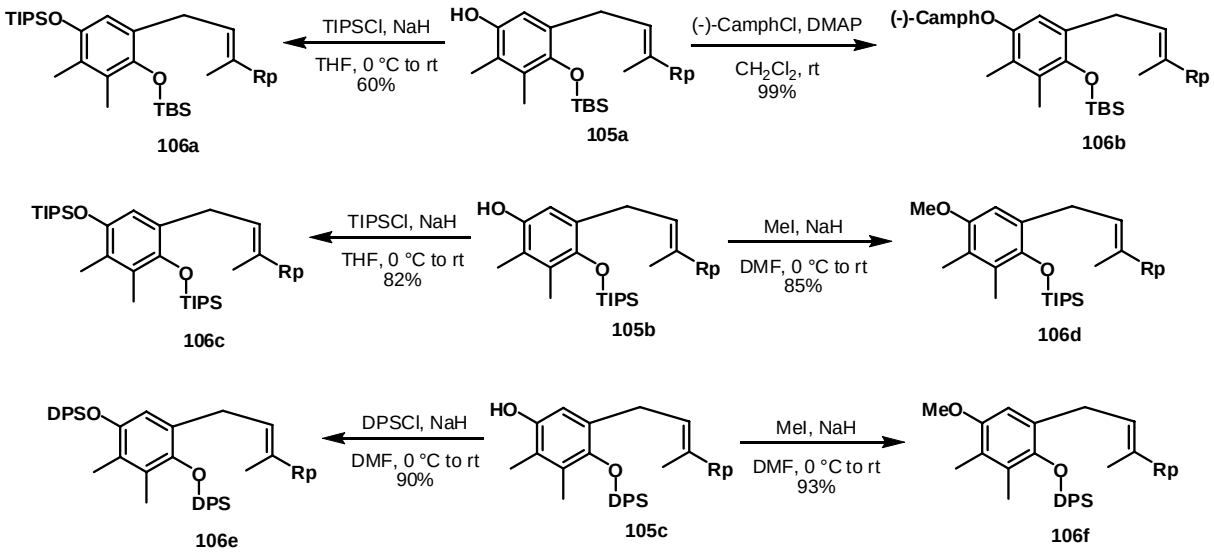


Figure 12: Determination of *E*/*Z* ratio. a) ^{1}H NMR of **105a**, δ(C_9-C$\underline{H}_3$), b) ^{1}H NMR of **105b**, δ(C_9-C$\underline{H}_3$), c) HPLC of **105c**.

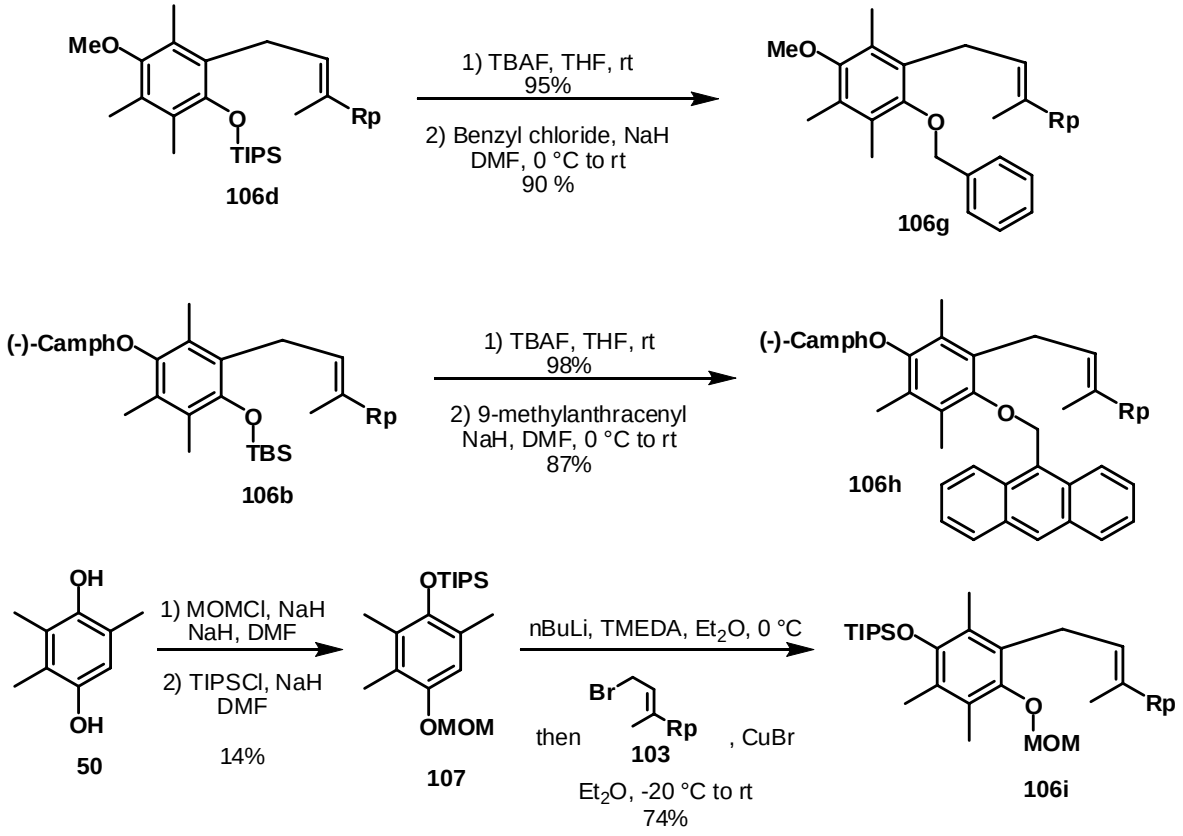
Various modifications at the remaining phenol were possible, giving access to different precursors, as shown on scheme 48. Protection of **105a** with TIPS- silyl ether, afforded **106a** in 60% yield, whereas same procedure on **105b** afforded **106c** in 82% yield.



Scheme 48: Synthesis of precursors **106a-f**. [Camph=camphanoyl]

(-)-Camphanoyl ester **106b** was also envisaged, and formed from (-)-camphanoyl chloride in almost quantitative yield. Small protecting groups were also investigated, and protection of **105b** and **105c** to their methyl ethers afforded **106d** and **106f** in 85 % and 93% yield respectively. Finally, bis-DPS precursor **106e** was formed in good yield from **105c**.

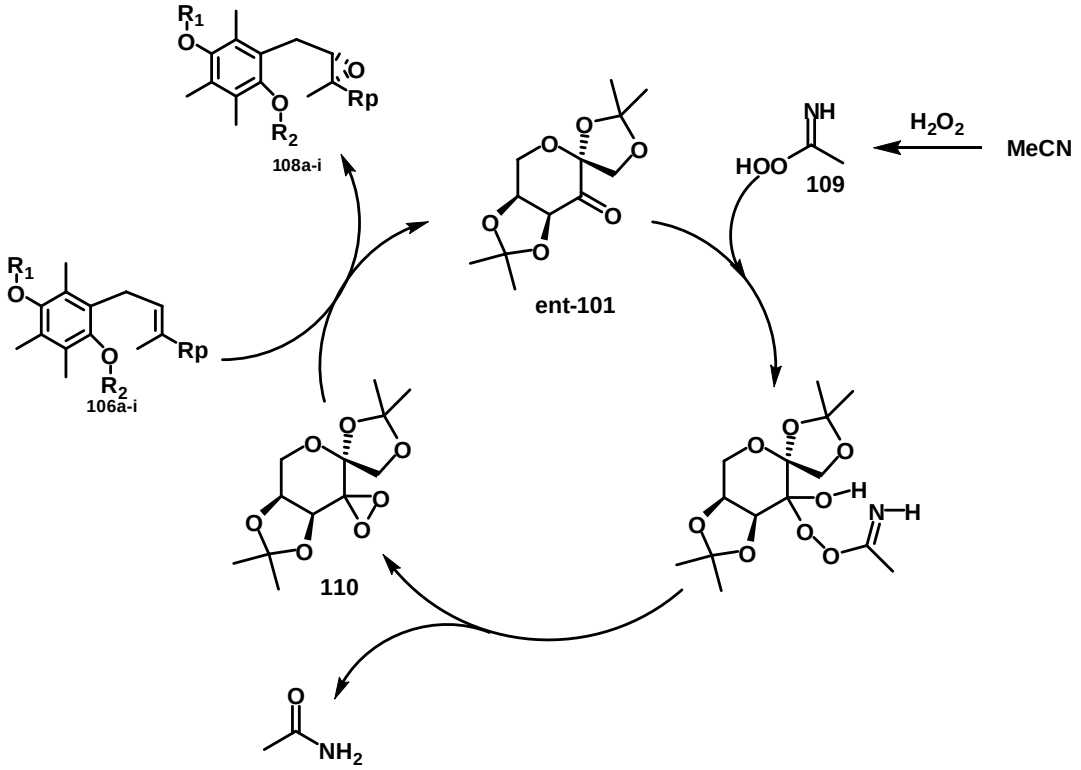
Other variations at the hydroquinone were synthesized, such as benzyl ether derivative **106g**, obtained from TIPS-deprotection of **106d**, followed by reaction with benzyl chloride (*scheme 49*). 9-Methylanthracenyl derivative **106h** was synthesized from **106b**, after TBS-deprotection using TBAF, and coupling with 9-methylanthracenyl chloride. Finally, MOMO-/TIPSO- precursor **106i** was obtained via mono-protection of hydroquinone **50** with MOMCl, followed by protection with TIPSCl to afford **107** in 14%. Finally, coupling of phytyl bromide **103**, on the lithiated bis-protected hydroquinone,[34] yielded **106i** in 74% (*scheme 49*).



Scheme 49: Synthesis of **106g**, **106h** and **106i**.

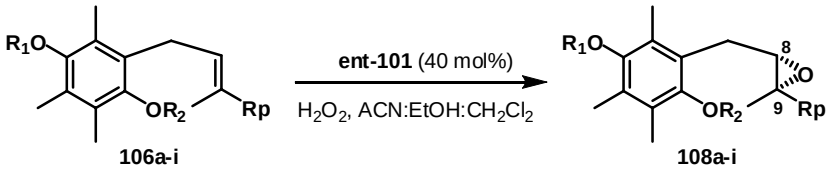
3.2.3. Asymmetric epoxidation of precursors **106**. (Based on Dr. A. Buss work)

In order to synthesize α-tocopherol **15** R-configured at C-2 the preparation of the epoxide **108** must be accomplished. According to systematic experiments by Shi, the organocatalyst **ent-101** was considered to be suitable.[71] The synthesis of **ent-101** has been described by Shi et al. in 2006,[73] starting from *L*-sorbose. Precursors **106a-i** were then submitted to Shi epoxidation procedure and converted to the corresponding epoxides **108a-i**, using hydrogen peroxide as co-oxidant in acetonitrile (*scheme 50*). It was proposed that perimidic acid **109**, generated from the reaction between MeCN and H_2O_2, is the actual oxidant, thus producing dioxirane **110**.



Scheme 50: Shi epoxidation mechanism – Epoxidation of **106a-i** to **108a-i**.

Results are presented in table 3, showing moderate to good yields, and good to excellent diastereoisomeric excesses. Two trends could be outlined from these results, relative to the size of the protecting groups: higher de's were observed with (i) small R_1 and (ii) bulky R_2. Thus, DPS- and MeO- ethers gave an excellent 97% de, in 81% yield (*entry 6*). Note that the diastereoisomeric excesses were determined by comparison with references racemic at the epoxide, prepared by mCPBA epoxidation of **106a-i** in CH_2Cl_2.



106a-i 108a-i

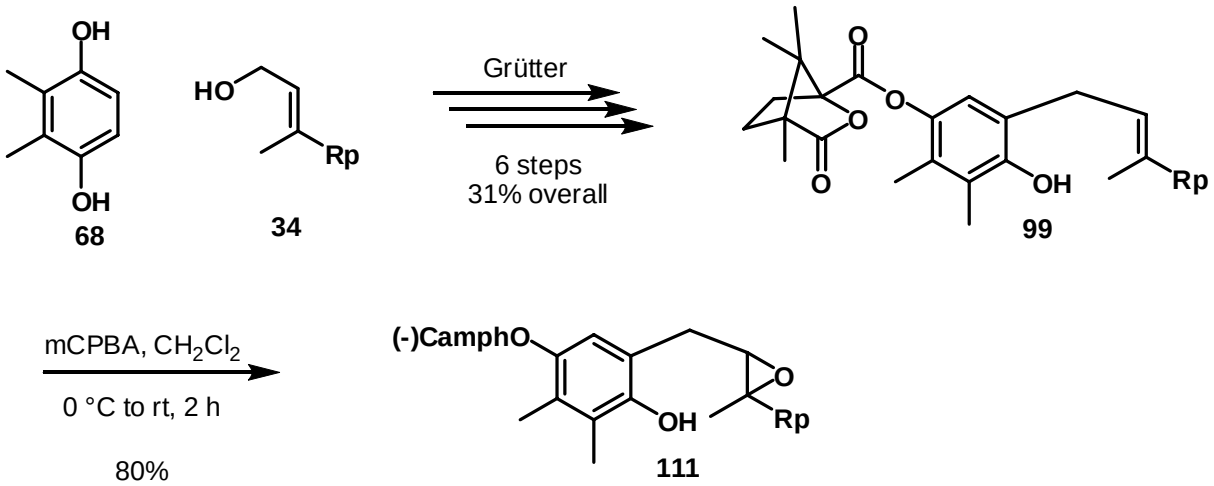
entry	epoxide	R_1	R_2	yield[a] (%)	de[b] (%)
1	**108a**	TIPS	TBS	76	73
2	**108b**	(-)-Camph[c]	TBS	73	79
3	**108c**	TIPS	TIPS	75	82
4	**108d**	Me	TIPS	78	85
5	**108e**	DPS	DPS	81	91
6	**108f**	**Me**	**DPS**	**81**	**97**
7	**108g**	Me	Benzyl	87	73
8	**108h**	(-)-Camph[c]	Anthr[d]	76	74
9	**108i**	TIPS	MOM	62	66

Table 3: Shi epoxidation of **106a-i**. [General conditions: 1 equiv **106**, 0.4 equiv **ent-101**, 5.4 equiv H_2O_2 (30% aq) in a buffered (2 M K_2CO_3 / EDTA) mixture of MeCN:EtOH:CH_2Cl_2 (1:1:2) at 0 °C, for 10 h. [a] Isolated yields. [b] Determined by chiral HPLC (8*S*,9*S*). [c] (-)-camphanoyl. [d] 9-methylanthracenyl.]

3.2.4. "Anti-Baldwin" epoxide ring opening.

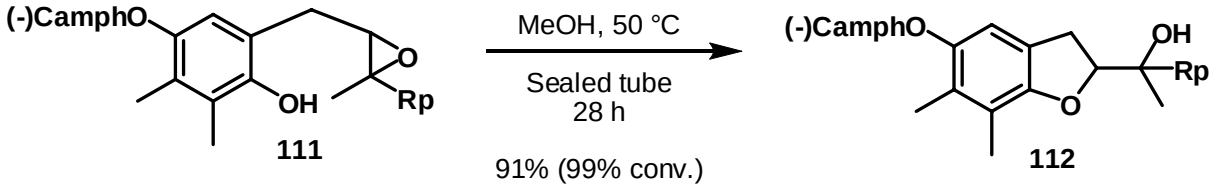
3.2.4.1. Preliminary studies on γ-tocopherol precursor.

We initially started our studies on easily the available precursor **111**,[76] and took advantage of the chiral (-)-camphanoyl group for HPLC analysis of different products and isomers that could be formed during cyclisation (*scheme 51*). 2,3-Dimethylhydroquinone **68** and E-(*R*,*R*)-phytol **34** were then converted to **99** in 6 steps, with 30% overall yield. Finally, treatment of **99** with mCPBA in CH_2Cl_2, afforded **111** in 80% yield, as a 1:1 mixture of diastereoisomers at the epoxide.



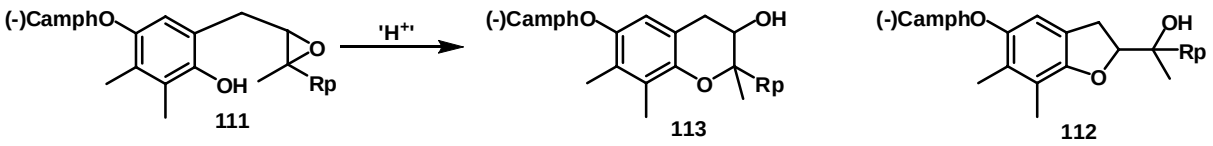
Scheme 51: Synthesis of cyclisation precursor **111**.

Jamison's conditions were firstly considered,[68b] and **11** was heated at 50 °C in MeOH, in a sealed tube for 18 h (*scheme 52*). Full conversion of epoxide was observed, but to our surprise, the 5-membered ring **112** was almost exclusively formed, in 91% yield (99% conversion by HPLC), following Baldwin's rules.



Scheme 52: Cyclisation of epoxide **111** under Jamison's conditions.

Basic conditions would probably also led to the 'furan' product, and hence we turned to acidic medias. Several conditions were screened in order to favour the 'pyran' product as presented in table 4. The different products formed were analysed by HPLC (Protonsil® 120-5-CN, 3% iPrOH in n-heptane, 1 mL/min, 280 nm, 25 °C), which allowed a clean separation of epoxide **111** (15.1 and 15.9 min), pyran product **113** (22.9, 23.3, 24.3 and 25.8 min) and furan product **112** (17.5 and 18.4 min). In general, the 6-membered ring was favoured, and several conditions gave remarkable regioselectivity (*entries 6, 11, 15, 18, 19, 20, 21*) with excellent yields.

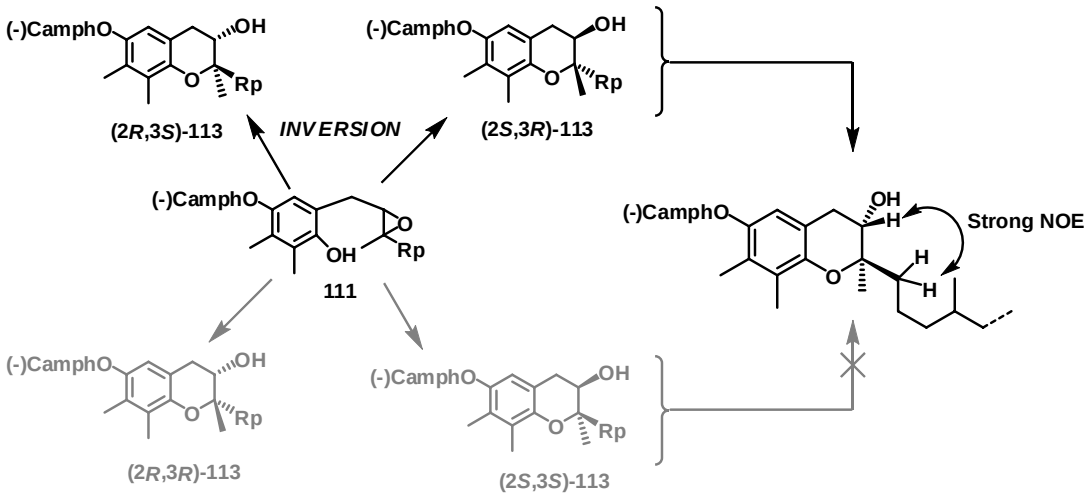


entry	acid	solvent	conversion[a] (%)	ratio **113**:**112**[a]
1[b]	none	MeOH	99	7:93
2	1N HCl_{aq}	MeOH:H_2O (2:1)	75	84:16
3	1N HCl_{aq}	MeOH:H_2O (3:1)	75	82:18
4	1N HCl_{aq}	MeOH:H_2O (4:1)	75	82:18
5	1N HCl_{aq}	EtOH:H_2O (1:1)	45	75:25
6	**1N HCl_{aq}**	**PC[c]:H_2O (3:1)**	**93**	**90:10**
7	1N HCl_{aq}	DMF:H_2O (3:1)	69	82:18
8	1N HCl_{aq}	THF:H_2O (3:1)	69	79:21
9	1N HCl_{aq}	Aceton:H_2O (3:1)	77	84:16
10	1N HCl_{aq}	Toluene:H_2O (3:1)	11	57:43
11	**1N HCl_{aq}**	**MeCN:H_2O (3:1)**	**90**	**89:11**
12	6N HCl_{aq}	MeCN:H_2O (3:1)	73	89:11
13	TFA (20%mol)	CH_2Cl_2	83	74:26
14	TFA (20%mol)	MeCN	<10	nd
15	**TFA (20%mol)**	**MeCN:H_2O (3:1)**	**85**	**89:11**
16	(+)-CSA[d] (1 eq.)	CH_2Cl_2	99	59:41
17	(+)-CSA (20%mol)	CH_2Cl_2	99	57:43
18	**(+)-CSA (1 eq.)**	**MeCN**	**99**	**94:6**
19	**(+)-CSA (1 eq.)**	**MeCN:H_2O (3:1)**	**99**	**89:11**
20	**$AlCl_3$ (0.8 eq.)**	**CH_2Cl_2**	**91**	**93:7**
21	**$Cu(OTf)_2$ (0.2 eq.)**	**CH_2Cl_2**	**95**	**95:5**

Table 4: Screening of acidic conditions to favour pyran **113**. [General conditions: 10.5 μmol **111**, 3 mL solvent, RT, 24h. [a] Determined by HPLC at 280 nm. [b] Reaction carried out at 50 °C for in a sealed tube. [c] propylene carbonate. [d] camphorsulfonic acid.]

It is important to note that not only the formation of the 6-membered ring is required but also inversion of configuration during epoxide opening. This aspect was investigated by correlation of NOESY experiments and HPLC analysis of the 6-membered ring product **113**. Cyclisation of **111** to its pyran product could afford 4 diastereoisomers, as depicted in scheme 53. Entry 3 (*table 4*) was firstly investigated, and **113** was isolated and submitted to NOESY experiments. It revealed a weak NOE between CH_3 at C-2 and H at C-3, versus a strong NOE between proton at C-1' and H at C-3, indicating a trans relationship of the hydroxyl group and the side chain (*scheme 53*).

This result indicates that the reaction mainly proceeded with inversion of configuration, since only **(2*S*,3*R*)-113** and **(2*R*,3*S*)-113** would fit with the NOESY results.



Scheme 53: Cyclisation of **111** to its 4 possible diastereoisomers – NOESY experiments revealed that **(2*S*,3*R*)-113** and **(2*R*,3*S*)-113** are mainly formed, under inversion of configuration.

HPLC chromatogram showed 4 peaks in the region of 25.0 min, which would correspond to the 4 diastereoisomers of **113** (*figure 13*). In correlation to the NOESY experiment, peaks at 24.3 and 25.8 min were assigned to **(2*S*,3*R*)-113** and **(2*R*,3*S*)-113**, whereas peaks at 22.9 and 23.3 min were assigned to **(2*R*,3*R*)-113** and **(2*S*,3*S*)-113**. Accordingly, ≥96% of the reaction proceeded by inversion of configuration

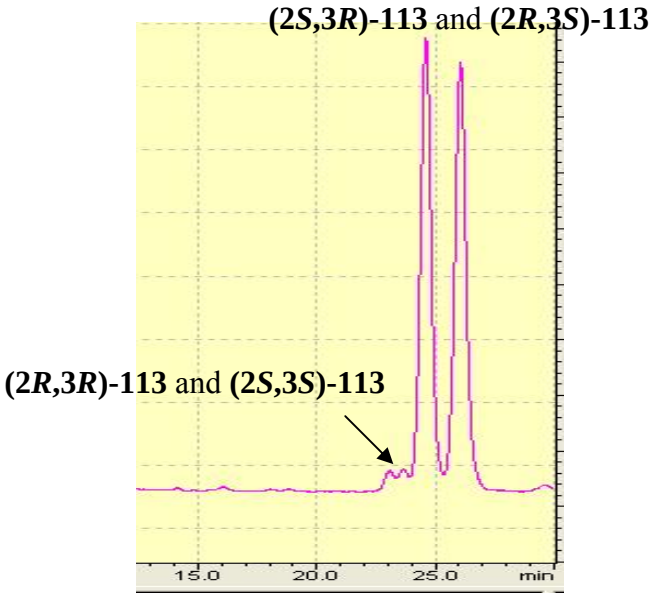
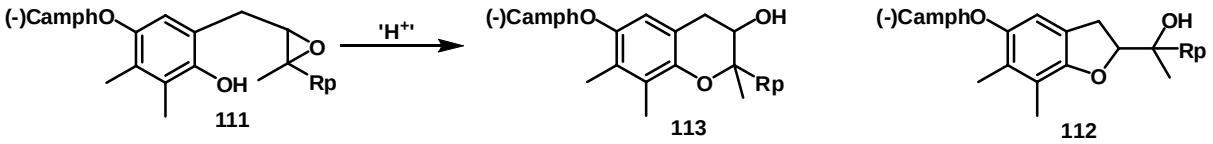


Figure 13: HPLC chromatogram of **113** (*table 4 - entry 3*).

Coming back to our first screening, the ratio between **(2*S*,3*R*)/(2*R*,3*S*)-113** and **(2*S*,3*S*)/(2*R*,3*R*)-113** were re-investigated by HPLC, especially for entries 6, 11, 15, 18, 19, 20 and 21 (*table 4*) which gave excellent regioselectivities (*table 5*).



entry	acid	solvent	conversion[a] (%)	ratio **113**:**112**[a]	ratio **(2*S*,3*R*)/(2*R*,3*S*)** : **(2*S*,3*S*)/(2*R*,3*R*)**
6	**1N HCl_{aq}**	**PC[b]:H_2O (3:1)**	**93**	**90:10**	**92 :8**
11	**1N HCl_{aq}**	**MeCN:H_2O (3:1)**	**90**	**89:11**	**92 :8**
15	TFA (20%mol)	MeCN:H_2O (3:1)	85	89:11	90 :10
18	(+)-CSA[c] (1 eq.)	MeCN	99	94:6	70 :30
19	**(+)-CSA (1 eq.)**	**MeCN:H_2O (3:1)**	**99**	**89:11**	**92 :8**
20	$AlCl_3$ (0.8 eq.)	CH_2Cl_2	91	93:7	90 :10
21	$Cu(OTf)_2$ (0.2 eq.)	CH_2Cl_2	95	95:5	68 :32

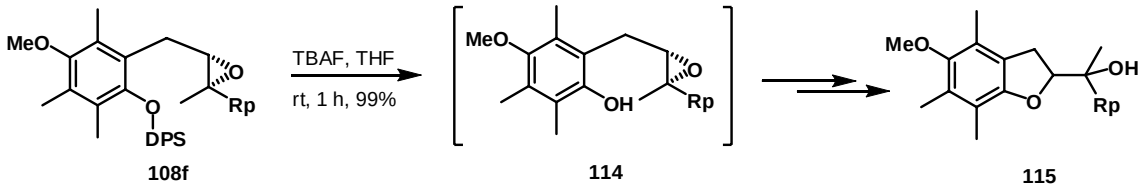
Table 5: Investigation relative to the inversion of configuration. [General conditions: 10.5 µmol **111**, 3 mL solvent, RT, 24h. [a] Determined by HPLC at 280 nm. [b] propylene carbonate. [c] camphorsulfonic acid.]

The main feature that could be outlined from this table concerned the importance of water in the reaction: under anhydrous conditions, the amount of reaction which proceeded with inversion of configuration dramatically decreased – the worst case was reached for the most regioselective Lewis acid (*entry 21*). It was clearly illustrated when using (+)-CSA in dry MeCN (*entry 18*), leading to a ratio **(2*S*,3*R*)/(2*R*,3*S*)**:**(2*S*,3*S*)/(2*R*,3*R*)** of 7:3, and compared with a similar reaction performed in MeCN:H_2O (*entry 19*), which gave a ratio of 92:8.

3.2.4.2. Application to the cyclisation of epoxide from **108f**.

The results shown in Table 5 led us to apply conditions as entry 11 to the cyclisation of epoxide originating from **108f**. Deprotection of the bulky DPS silylether was first attempted using usual conditions, that are TBAF in THF (*scheme 54*). To our surprise, deprotection occurred, but the free phenol **114** directly cyclized to the furan ring **115**, in 99% yield. It was not possible to isolate or 'see' **114** on TLC during the reaction, even by lowering the reaction temperature to 0 °C or above.

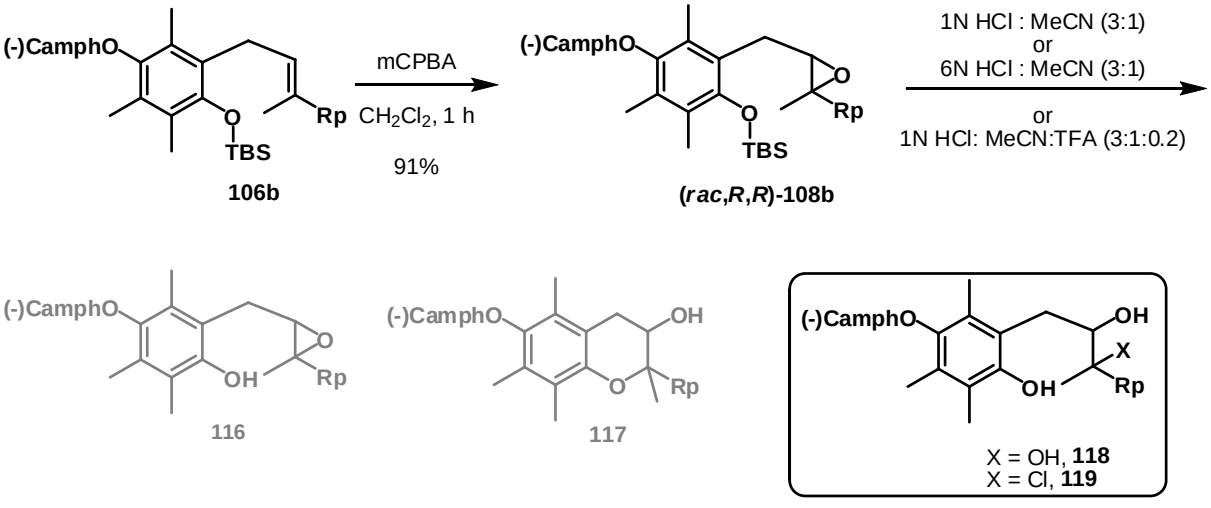
Though in principle chiral **115** is an interesting product it was not useful for our purpose, inter alia since the anti-oxidant activity of such benzo-dihydro-furans were estimated by Smith et al.[77] to be only 5% of that of α-tocopherol.



108f **114** **115**

Scheme 54: TBAF deprotection of **108f** : direct cyclisation to furan product **115**.

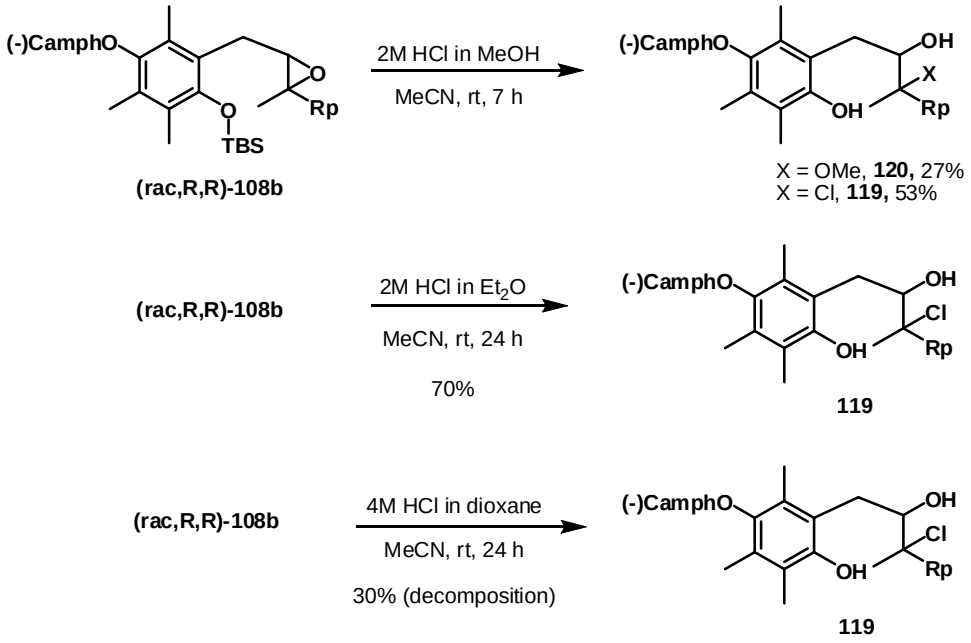
To avoid the cyclisation to the undesired 5-membered ring, acidic conditions were envisaged, to yield the desired pyran product. Two recent publications from Nicolaou et al.[78] and Ye et al.[79] reported the use of HCl for silylether deprotection of aromatic substrates, and substrate **106b**, having chiral (-)-camphanoyl ester, was used to test these conditions. Treatment with mCPBA afforded **(*rac*,*R*,*R*)-108b**, in 91% yield, racemic at the epoxide (*scheme 55*). Aqueous HCl was used in MeCN, but neither the free phenol **116** nor the pyran product **117** were obtained, and despite a fast cleavage of the TBS group, the epoxide was not stable under these conditions. Indeed, **118** and **119** were mainly observed, in different ratios, resulting in the epoxide opening by Cl^- or H_2O (*scheme 55*).



106b (*rac*,*R*,*R*)-108b 116 117

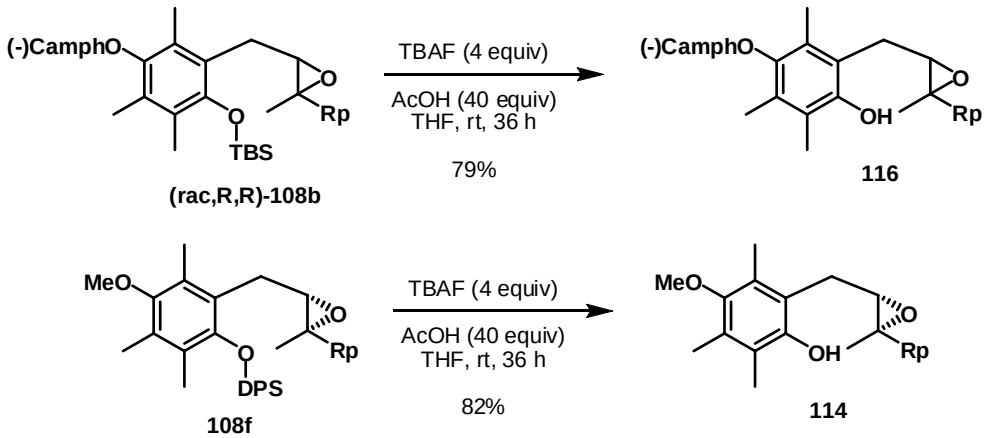
Scheme 55: Attempts for deprotection of silylether under acidic conditions.

Hydrochloric acid solution in anhydrous organic solvents such as MeOH, dioxane or Et_2O were then tested, but the epoxide was also unstable, and reactions led to epoxide opening, either by addition of Cl^- or MeOH (*scheme 56*).



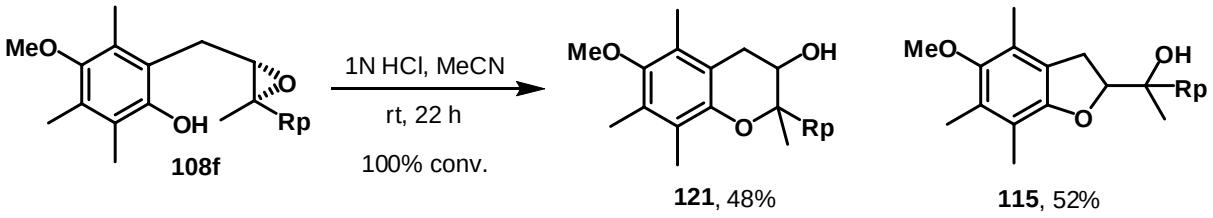
Scheme 56: TBS- deprotection using anhydrous HCl.

Finally, Barrett et al.[80] reported in 2007 the use of acetic acid in combination with TBAF, in a 1:1 ratio, for the deprotection of aromatic TBSO- groups on resorcinarenes, which gave excellent results in our case, after a slight optimization of the conditions. Then, treatment of ***(rac,R,R)*-108b** with TBAF:AcOH (1:10), in THF at rt, afforded the free phenol **116** in 79% yield (*scheme 57*). This procedure was applicable to chiral epoxide **108f**, which was successfully deprotected to afford **114** in 82% yield.



Scheme 57: Deprotection of TBS and DPS group using TBAF:AcOH (1:10)

Best cyclisation conditions were tested on **114** (*table 4, entry 11*), but despite an excellent regioselectivity in preliminary case, treatment with 1N HCl : MeCN (1:3) afforded a mixture of pyran **121** and furan **115**, in a 1:1 ratio (*scheme 58*).

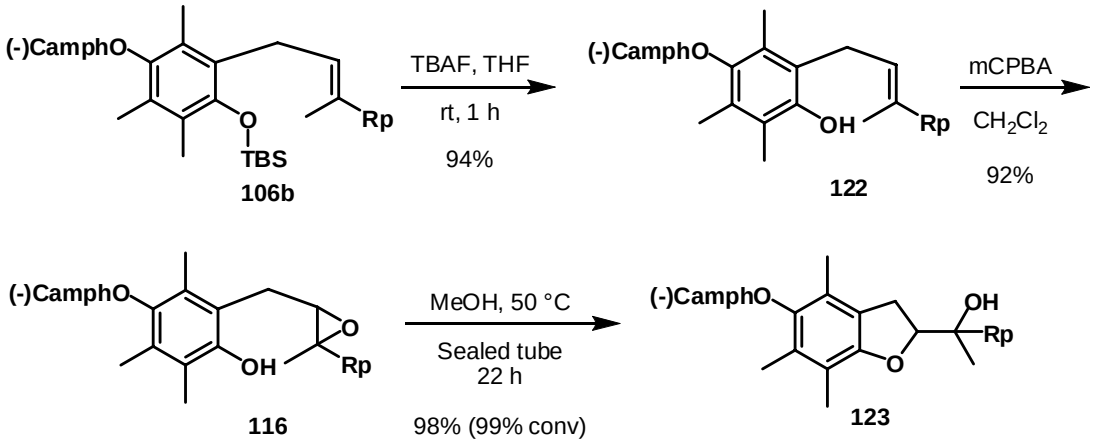


Scheme 58: Cyclisation of **114** using optimized conditions.

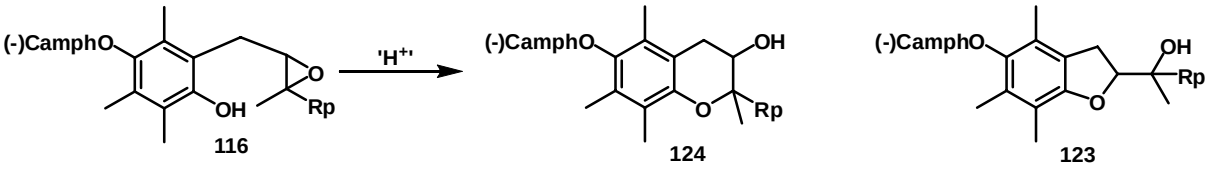
This result, unlikely predictable, could be input to the additional aromatic methyl of the α-tocopherol series, in comparison to the γ-tocopherol precursor **111**, used for our initial screening. It implied that an additional investigation to favour the "anti-Baldwin" product in the α-tocopherol series was necessary to get reasonable selectivity.

3.2.4.3. Optimisation of conditions in the cyclisation of α-tocopherol precursor **116**.

The epoxide **116** was then synthesized starting from **106b**, which was treated with TBAF in THF, to afford free phenol **122** in 94% yield (*scheme 59*), which epoxidation using mCPBA in CH_2Cl_2 yielded **116** in 92%, racemic at the epoxide. Jamison's conditions (MeOH, 50 °C), which were furan-driving in the preliminary case, were tested with precursor **116**, and with no surprise, produced the 5-membered ring **123** in 98% yield (99% conversion). Acidic conditions were then screened, in aqueous or anhydrous medias, and are reported in table 6.



Scheme 59: Synthesis and screening of precursor **116**.



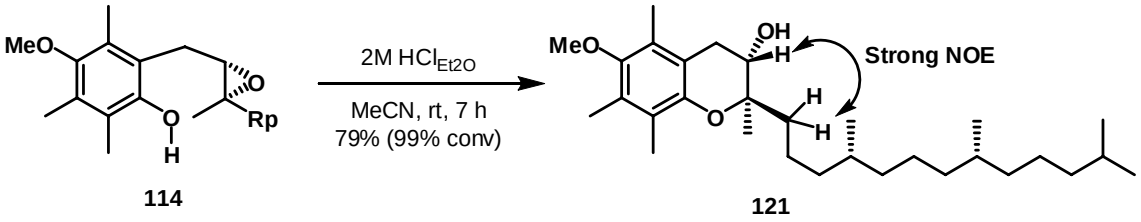
Entry	acid (A)	solvent (S)	conv[a] (%)	ratio **123**:**124**[a]
1[b]	none	MeOH	99	98:2
2	1N HCl_{aq}	MeCN:H_2O (3:1)	94	51:49
3	1N HCl_{aq}	THF:H_2O (3:1)	90	67:33
4	1N HCl_{aq}	MeOH:H_2O (3:1)	92	56:44
5	1N HCl_{aq}	Aceton:H_2O (3:1)	92	58:42
6	1N HCl_{aq}	PC[c]:H_2O (3:1)	97	51:49
7	1N HCl_{aq}	DMF:H_2O (3:1)	90	57:43
8	1N HCl_{aq}	CH_2Cl_2:H_2O (3:1)	95	80:20
9	6N HCl_{aq}	MeCN:H_2O (3:1)	92	35:65
10	12N HCl_{aq}	MeCN:H_2O (3:1)	94	37:67
11	TFA (20%mol)	MeCN:H_2O (3:1)	99	49:51
12	TFA (20%mol)	CH_2Cl_2	99	72:28
13	(+)-CSA[d] (1 equiv)	MeCN:H_2O (3:1)	99	47:53
14	(+)-CSA (0.5 equiv)	MeCN	99	40:60
15	(+)-CSA (1 equiv)	MeCN	99	40:60
16	(+)-CSA (2 equiv)	MeCN	99	38:62
17	2M HCl_{MeOH}	MeOH	98	62:38
18	2M HCl_{Et2O}	CH_2Cl_2	92	54:46
19	0.5M HCl_{Et2O}	MeCN	95	26:74
20	1M HCl_{Et2O}	MeCN	97	26:74
21	**2M HCl_{Et2O}**	**MeCN**	**98**	**23:77**

Table 6: Screening of acidic conditions to favour pyran **124**. [General experimental conditions: 5 µmol **116**, 1 mL of a S:A (3:1), rt, 15 h. [a] Determined by HPLC, not identified side products were <1% in each case. [b] Reaction carried out at 50 °C for 15 h in a sealed tube. [c] Propylene carbonate. [d] Camphorsulfonic acid.]

Aqueous hydrochloric acid did not exhibit any regioselectivity, independent of the solvent used (*entry 2-10*), and even favoured the furan product **123** under biphasic conditions (*entry 8*). Organic acids such as TFA or (+)-camphorsulfonic acid (CSA) did not improve the selectivity, despite an excellent conversion of epoxide **116** (*entries 11-16*). Finally, anhydrous HCl was envisaged, either in MeOH or Et_2O, and we were pleased to improve the formation of the pyran ring **124**, reaching a **124**:**123** ratio of 77:23 and 98% conversion (*entry 21*). It is important to note the Table 5 and 6 are only distinct due to difference of one methyl group in the structure of the epoxide. Having in hand an efficient method for "anti-Baldwin" cyclisation of γ-epoxy alcohols of type **116**, synthesis of α-tocopherol was completed.

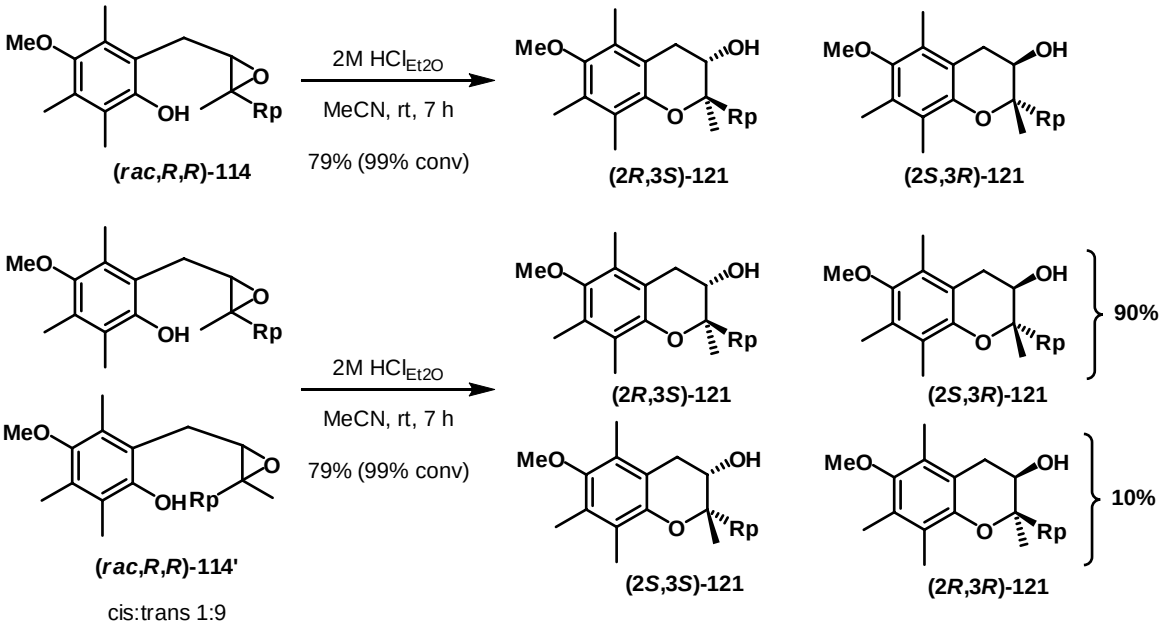
3.2.5. Synthesis of (*R*,*R*,*R*)-α-tocopherol **15**.

Chiral epoxide **114** was treated with our optimized conditions (*table 6, entry 21*), to afford pyran product **121** in 79% yield and 99% conversion (*scheme 60*). NOESY experiment of **121** also revealed a weak NOE between CH_3 at C-2 and H at C-3, versus a strong NOE between proton at C-1' and H at C-3, indicating a trans relationship of the hydroxyl group and the side chain.



Scheme 60: Cyclisation of chiral epoxide **114** – NOESY experiments indicated a trans relationship between the hydroxyl group and the side chain.

In addition, HPLC analysis of **121** allowed the separation of the 4 possible diastereoisomers, which identity was confirmed by the cyclisation of ***(rac,R,R)*-114**, racemic at the epoxide, and the cyclisation of ***(rac,R,R)*-114'**, racemic at the epoxide, with a ratio trans:cis 9:1 (*scheme 61*).



Scheme 61: Cyclisation of ***(rac,R,R)*-114** and ***(rac,R,R)*-114'**, if the reaction proceeded with inversion of configuration.

Indeed, if the reaction would be with inversion of configuration, cyclisation of **(*rac*,*R*,*R*)-114** should have mainly formed 2 products, whereas cyclisation of **(*rac*,*R*,*R*)-114'**, should have produced 2 additional compounds, corresponding to 10% of cis-epoxide. On the other hand, if the reaction wouldn't be with inversion of configuration, the 4 diastereoisomers should all have been observed in both cases. HPLC analysis finally corresponded to the first case, meaning that the epoxide ring opening proceed with inversion of configuration (*figure 14*). The diastereoisomeric excess of **121** was then determined to be 93%, slightly lower than for epoxide **108f**, due to the extent carbenium formation during the epoxide ring opening.

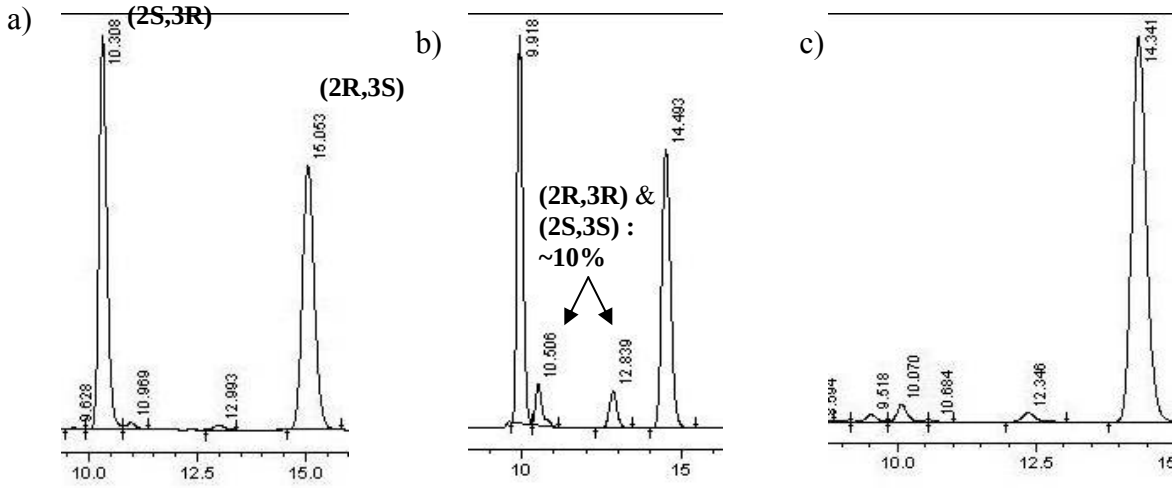
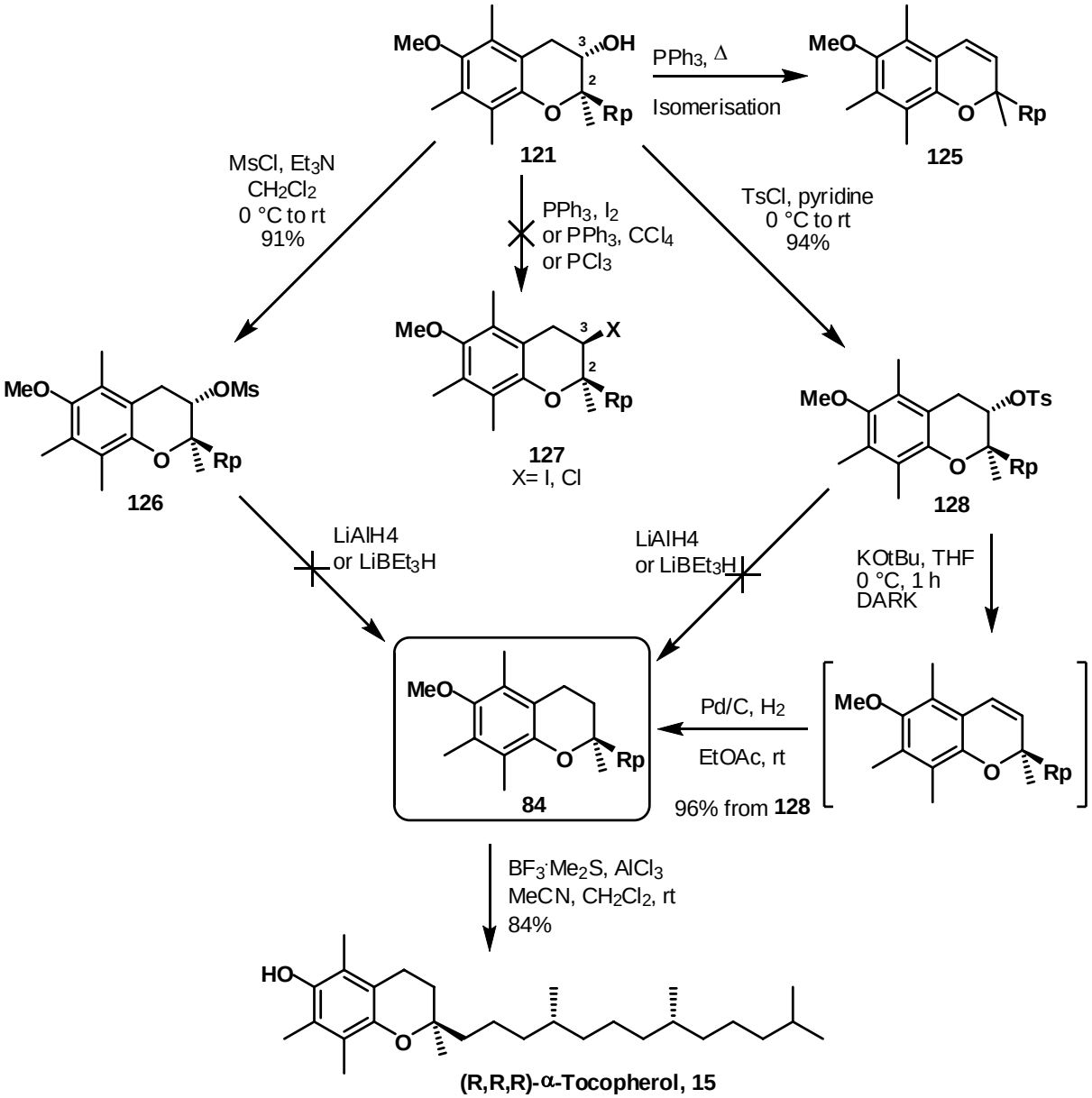


Figure 14: HPLC chromatograms from: a) cyclisation of **(*rac*,*R*,*R*)-114**; b) cyclisation of **(*rac*,*R*,*R*)-114'**; c) cyclisation of **114**.

Removal of the hydroxyl group was firstly envisaged by reductive elimination with hydrides. Pyran **121** was then converted to its mesylate derivative **126**, or to its tosylate derivative **128**, in good yields (*scheme 62*). But unfortunately, none of them could be cleaved either by using $LiAlH_4$ or superhydride® ($LiBEt_3H$), as already reported by Woggon et al.[31] This result could be explained by the steric hindrance through the adjacent tertiary ether, which blocks the reacting side. Inversion of the configuration at C-3 was envisaged, to unblock the reactivity of hydrides, but conversion of the hydroxyl group to its chloride or iodide analogues was not possible, since elimination of triphenylphosphine oxide occurred, yielding chromene **125**, as a major side-product. The main disadvantage of chromene such as **125**, comes from the isomerisation at chiral C-2, due to a Cope rearrangement which can be induced by T > 250 °C and/or light.

Nevertheless, milder conditions, that are low temperature and absence of light, were applied, and elimination of TsO^- with KOtBu at 0 °C in the dark, followed by Pd/C-hydrogenation, afforded **84** in 96% yield from **128**, with 93% de (2*R*,4'*R*,8'*R*). Finally, cleavage of the methoxy ether could be performed without any loss in chirality, by means of $BF_3{\cdot}Me_2S/AlCl_3$,[46] giving (*R*,*R*,*R*)-α-tocopherol **15**.



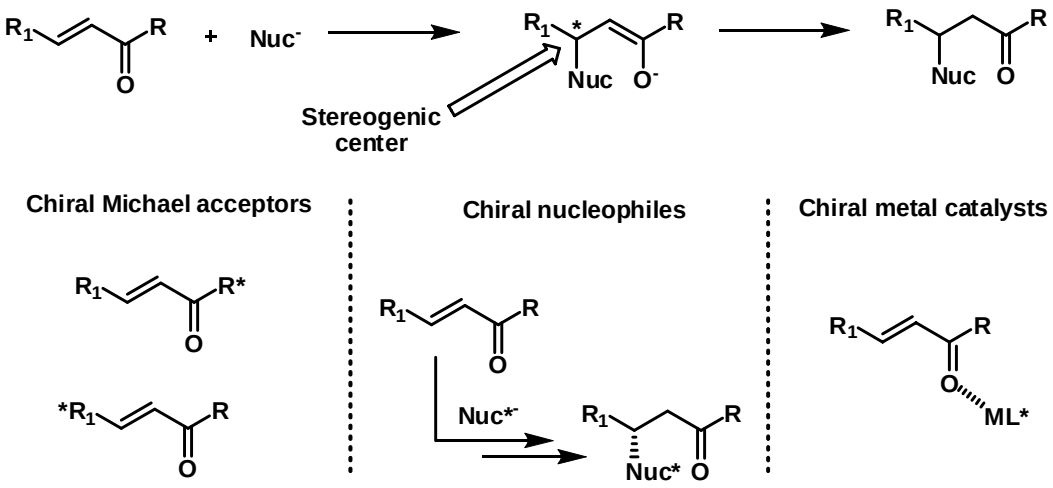
Scheme 62: Removal of the hydroxyl group - Tandem TsO^- elimination / hydrogenation of **128**.

3.3. Lewis acid mediated cyclisation – 1,4-oxa-addition.

3.3.1. Introduction

3.3.1.1. Asymmetric Michael reactions.

The well known Michael reaction, i.e. the addition of a nucleophile to an α,β-unsaturated carbonyl acceptor, belongs to the classical carbon-carbon bond forming reactions (*scheme 63)*. Since newly formed compounds present a stereogenic center, considerable efforts were devoted to the development of efficient stereoselective methods, either by starting from chiral Michael acceptor, like Oppolzer's chiral bornane sultam auxiliaries,[81] by using a chiral nucleophile such as chiral cuprates,[82] or, more recently, by the use of chiral catalysts.[83]



Scheme 63: Michael reaction – Possible strategies for asymmetric additions [Nuc = nucleophile].

Over the past years, several groups have focused in the development of new and efficient chiral metal complexes, able to promote high enantio- and diastereo-selectivities in Michael reactions. Various transition metals were tested and successfully used, such as nickel,[84] cobalt,[85] rhodium,[86] aluminium[87] or heterobimetallic complexes,[88] but copper remained the most noted, together with a broad variety of chiral ligands. Three main families of ligands used in copper-catalyzed 1,4-additions could be described: binaphtalene-derived ligand (*figure 15*), TADDOL-derived ligands (*figure 16*), and oxazoline-derived ligands (*figure 17*).

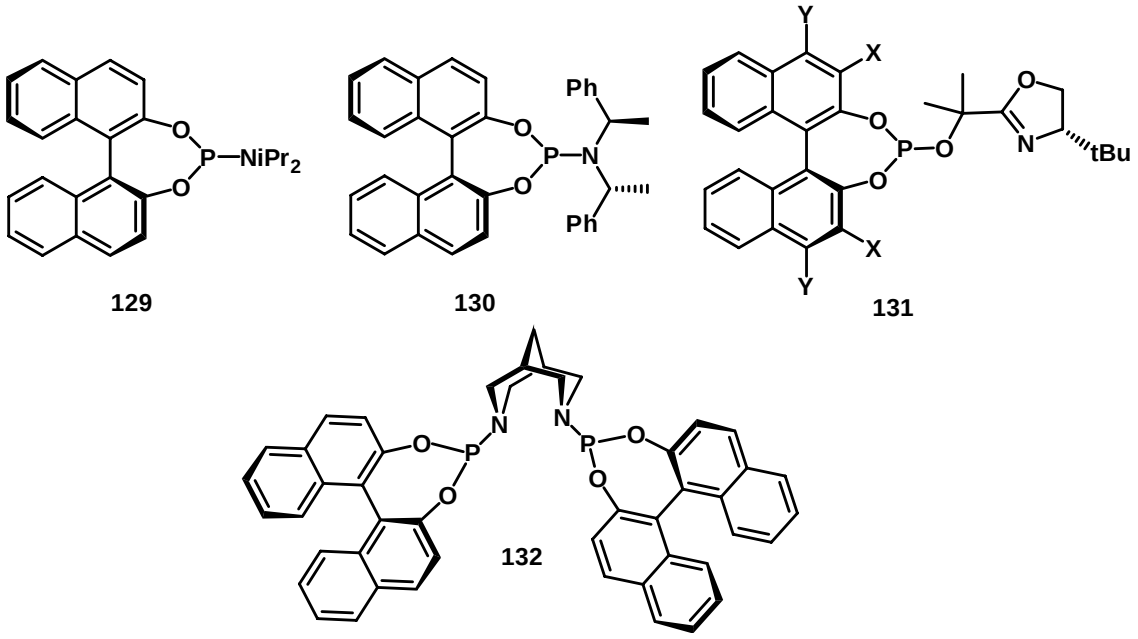


Figure 15: Binaphtalene-derived ligands.

Although 1,1'-binaphtalene-2,2'-diol (BINOL) and 2,2'-bis(diphenylphosphino)-1,1'-binaphtalene (BINAP) belong to the most frequently used chiral ligands, several binaphtalene derived ligand have been synthesized, such as **129** and **130**, by Feringa et al.[89] in the 1990's, which were, in combination with a Cu^{II} salt, the first systems giving high enantioselectivities with acyclic Michael acceptors. BINOL oxazoline phosphites of type **131**, by Pfaltz et al. in 1997,[90] and bis-phosphorous amidate **132**, by Waldmann et al.[91] in 2000 have also proven to be really efficient ligands.

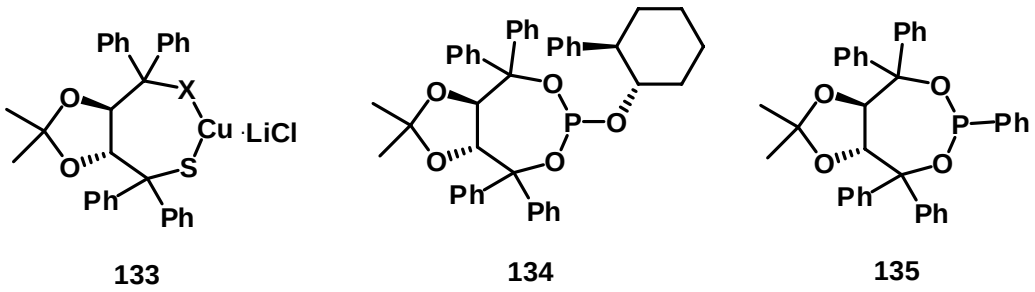


Figure 16: TADDOL-derived ligands.

TADDOLs ligands (α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanols) such as **133** were initially used in 1997 by Seebach et al.,[92] catalyzing the addition of an alkyl magnesium chloride to a cyclic Michael acceptor. Alexakis et al. exploited these scaffolds in the late 1990's,[93] thus leading to **134** and **135**.

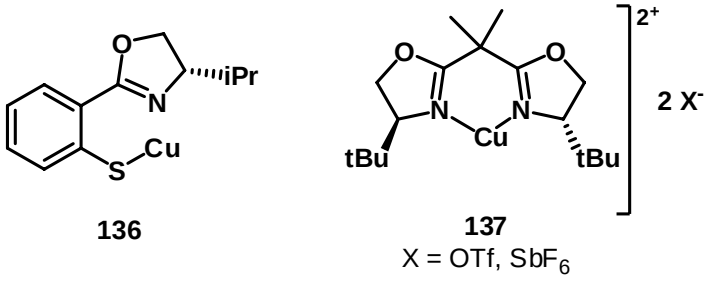
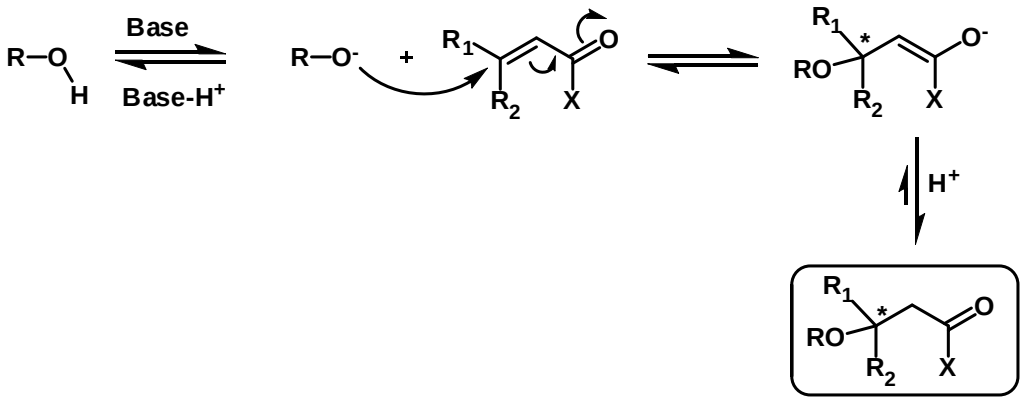


Figure 17: Oxazoline-derived ligands.

Chiral oxazolines, readily available from their corresponding natural or unnatural amino acids, were firstly used in 1993, when Pfaltz et al.[94] employed the Cu-thiophenolate **136** for addition reactions to cyclic enones, realizing enantiomeric excesses up to 87% ee. One of the most versatile ligand used in asymmetric Michael reactions was bis-oxazoline **137**, which was introduced by Scolastico et al. in 1996,[95] and extensively studied by Evans et al.[96] in 1999 and 2000.

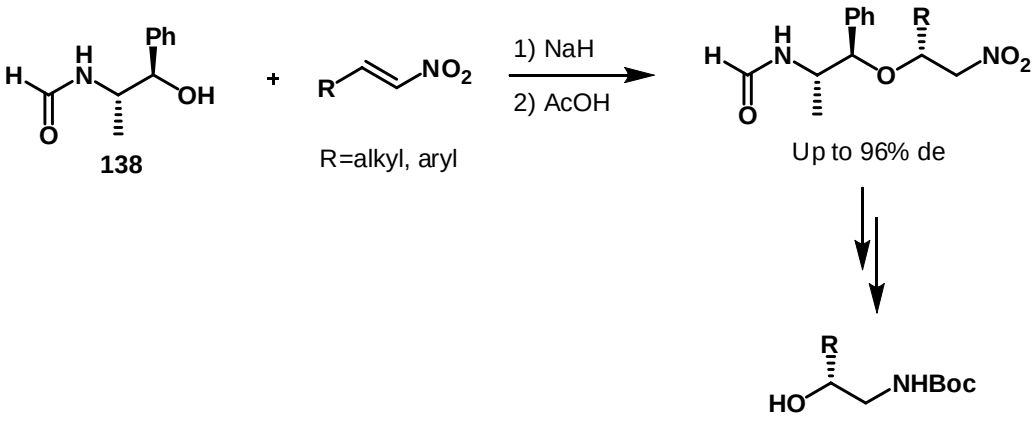
3.3.1.2. The oxa-Michael addition.[97]

In contrast to the important work related to C-C Michael additions, less attention has been shown for the hetero-Michael version, such as addition of amines,[98] thiols,[99] phosphorous[100] and alcohols as nucleophiles. This holds especially true for the oxa-Michael addition (*scheme 64*), despite the first example was reported by Loyld in his work towards the synthesis of malic acid in 1878.[101]



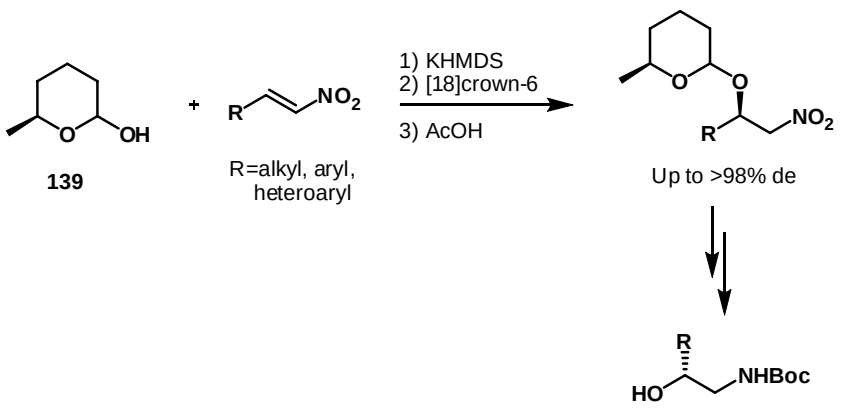
Scheme 64: Mechanism of the oxa-Michael reaction.

Nevertheless, considerable progress has been made in the development of asymmetric oxa-Michael reactions within the past years, reaching high levels of chiral inductions. One way of achieving such a reaction consists of the use of chiral hydroxide equivalents. Enders and co-workers, pioneers in this field, reported the use of chiral N-formylnorephedrine **138** as auxiliary,[102] which could react on a variety of nitroalkenes, further transformed in 2-amino alcohols, important chiral scaffold in natural products (*scheme 65*).



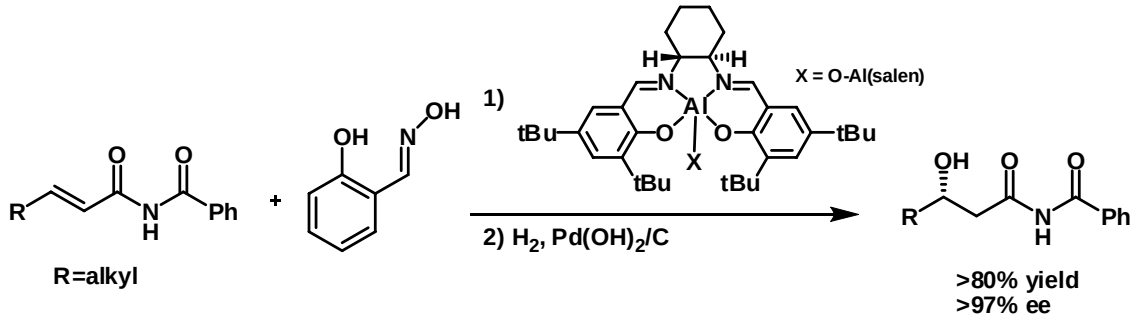
Scheme 65: Oxa-Michael addition of N-formylnorephedrine **138** on nitroalkenes.

Recently, Dixon et al. developed another alternative to the synthesis of these valuable amino alcohols,[103] by the use of 6-alkyl-δ-lactol **139** (*scheme 66*). Indeed, addition of **139** to nitroalkenes, in the presence of [18]crown-6, afforded the corresponding Michael products in high yields and up to >98% de. Although this reaction was originally developed for nitroalkenes as acceptors, it was recently extended to other systems such as α,β-malonate esters, unsaturated α-keto esters, α,β-disubstituted nitroolefins and activated α,β-unsaturated esters.



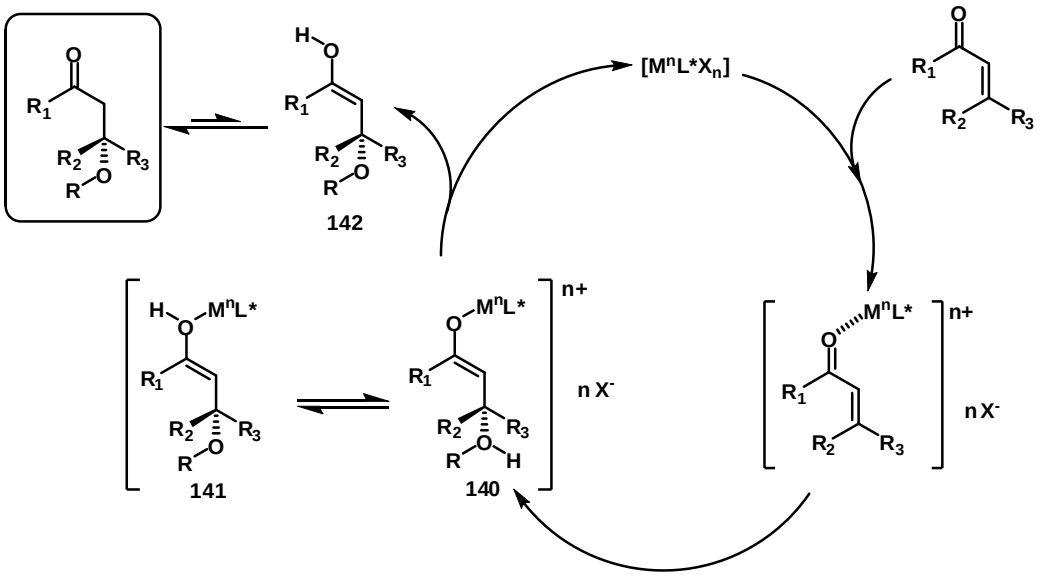
Scheme 66: Additions of 6-alkyl-δ-lactol **139** to nitroalkenes.

As an alternative to the use of chiral auxiliaries, catalytic enantioselective oxa-Michael reactions offer another straightforward strategy. Despite the rapid development of efficient organocatalysts in intermolecular[104] as well as in intramolecular[105] oxa-Michael reactions, examples of chiral Lewis acid remain rare. Jacobsen et al. applied their well-established (salen)aluminium complexes to the addition of oximes on α,β-unsaturated imides,[106] as depicted on scheme 67.



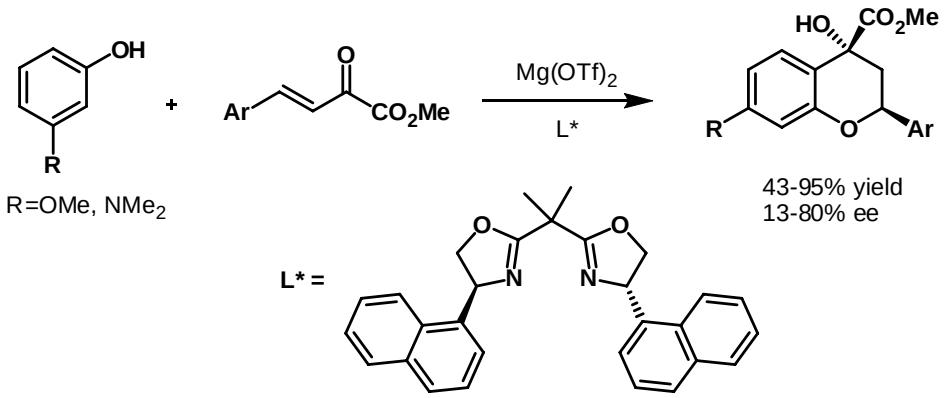
Scheme 67: Addition of oximes to α,β-unsaturated imides, using (salen)aluminium complexes.

The general mechanism of Lewis acid mediated oxa-Michael reaction is depicted on scheme 68. Coordination of the metal to the carbonyl group occurs and increases the reactivity of the Michael acceptor. The nucleophile can then react to form **140**, in a prototropic equilibrium with **141**, finally leading to enol **142** and regenerating the chiral metal complex.



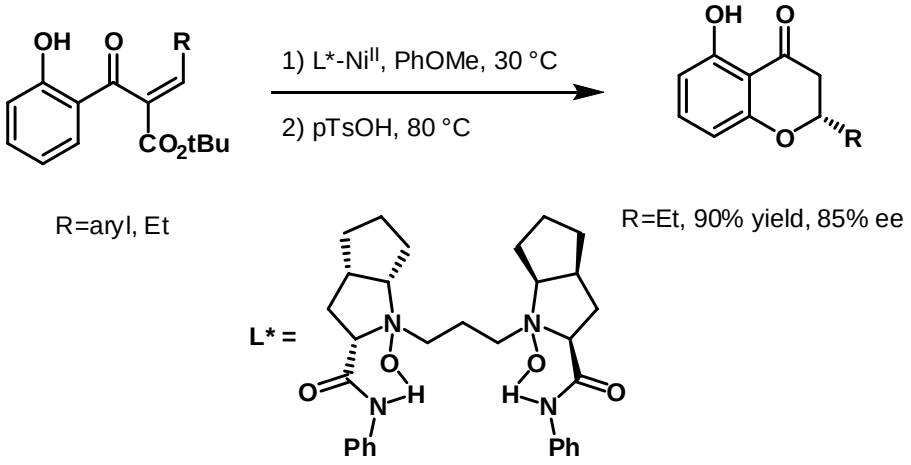
Scheme 68: Proposed mechanism for the Lewis acid catalyzed oxa-Michael reaction.

Recently, Joergensen et al. also developed the asymmetric synthesis of chromans by embedding an oxa-Michael reaction in a domino process,[107] using a bis-oxazoline magnesium complex (*scheme 69*). Nevertheless, substrate scope was limited since both an electron donating group on the phenol and the aromatic moiety on the acceptor were essential for high yield and enantioselectivity.



Scheme 69: Synthesis of chiral chromans, using a bis-oxazoline magnesium catalyst.

Recently, Wang et al. reported a chiral N,N'-dioxide-Ni^{II} complex for the highly enantioselective synthesis of flavanones[108] (*scheme 70*). The great advance by this group concerned the wide scope of substrate tolerated by this catalyst, especially aliphatic substituents at the double bond, being one of the first example that afforded high yield and enantioselectivity.

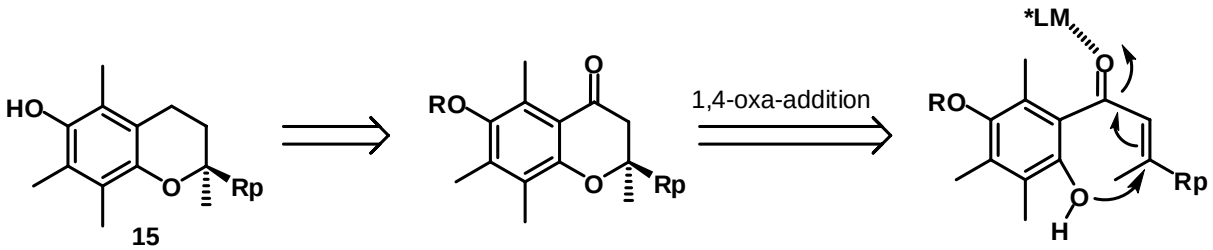


Scheme 70: Chiral N,N' dioxide Ni^{II} complex – Synthesis of flavanones.

However, no asymmetric oxa-Michael reaction leading to 2,2-disubstituted chromans or flavanones have been reported yet, and, in all the cases described herein, catalysts were substrate dependent.

3.3.1.3. Design of the synthesis.

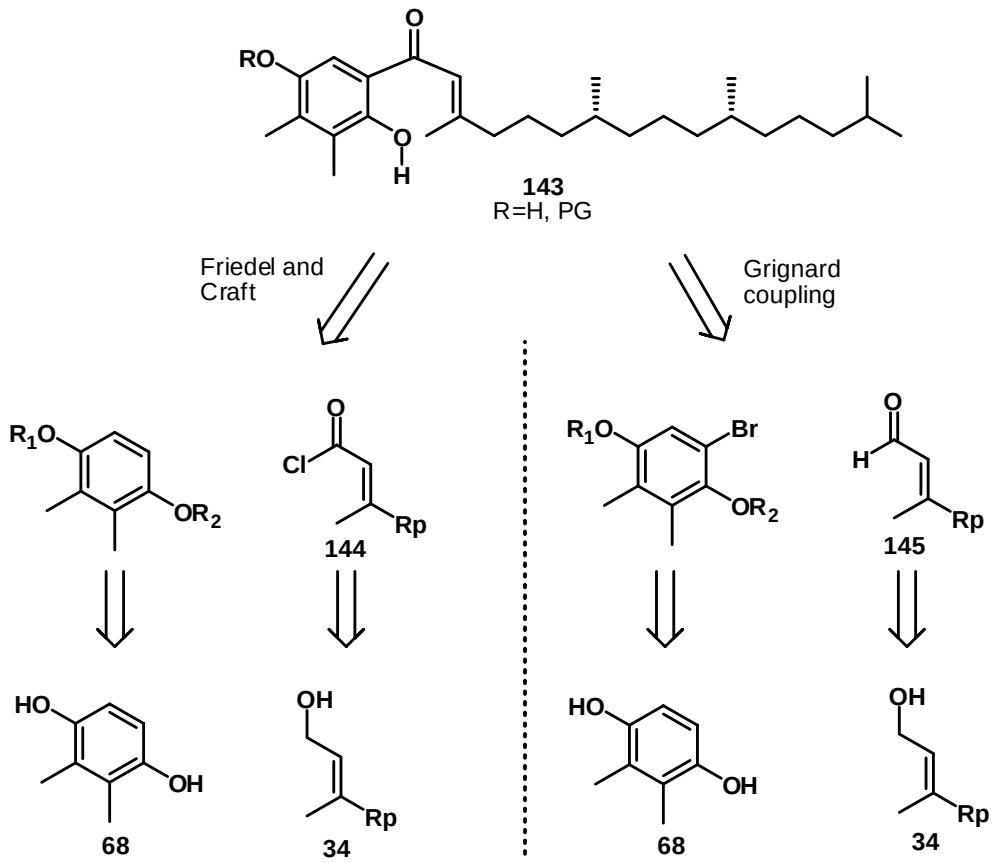
Based on this reaction, and on the broad literature available on chiral Lewis acid catalysts, we designed a retrosynthetic approach to the formation of the chromanol ring, as shown on scheme 71. It was based on a diastereoselective 1,4-oxa-addition on the α,β-unsaturated carbonyl derivative, the phenol acting as nucleophile. By using a chiral metal complex, we expected a complexation at the oxygen of the carbonyl group, leading in a stereoselective addition of the phenol.



Scheme 71: Retrosynthetic design via a diastereoselective oxa-Michael addition. [M = metal, L* = chiral ligand, R = protecting group, Rp=(4'R,8'R)-4',8',12'-trimethyltridecanyl]

3.3.2. Synthesis of cyclisation precursor.

Initial studies were conducted in the γ-tocopherol series, and cyclisation precursor **143** was firstly envisaged. Its synthesis was designed from 2,3-dimethylhydroquinone **68** and *E*-(*R*,*R*)-phytol **34**, and two coupling strategies were considered: (1) a Friedel-Crafts (F-C) acylation, (2) a Grignard reaction (*scheme 72)*. The acylation route would need a bis-protected hydroquinone and the acyl chloride **144** derived from phytol **34**, whereas the Grignard pathway would require the bromo-hydroquinone and *E*-(*R*,*R*)-phytal **145**.

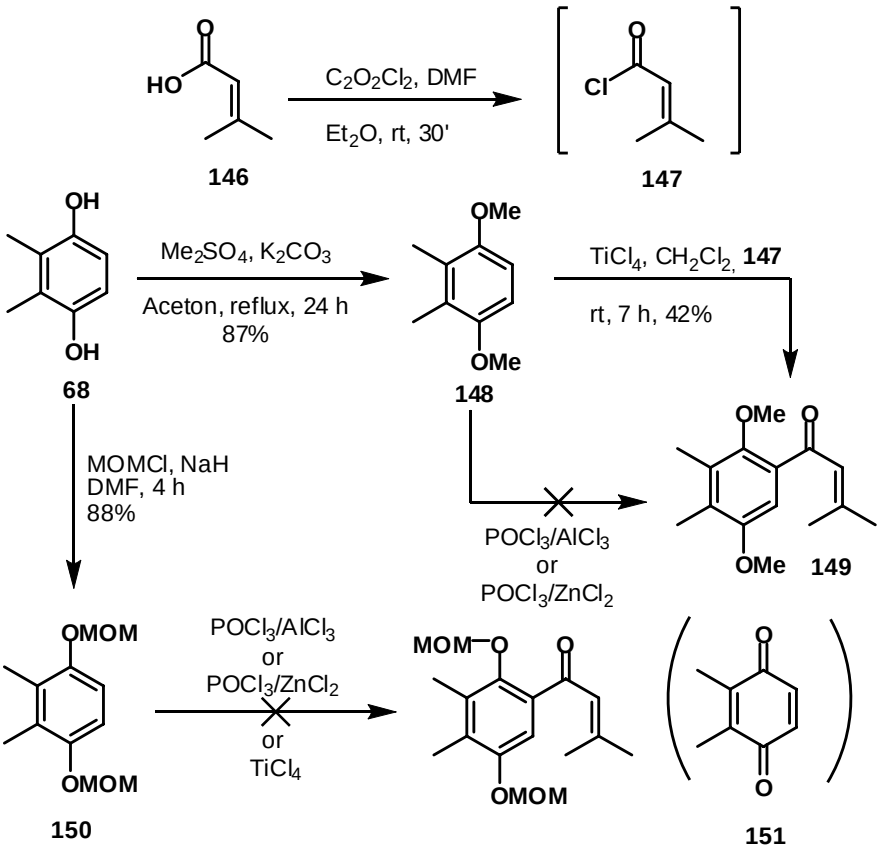


Scheme 72: Retrosynthetic strategies for the formation of **143**. [PG, R^1, R^2=protecting groups]

Orthogonal protection of the hydroquinone would be advantageous to selectively unprotect the phenolic oxygen involved in the cyclisation; however, first investigations were conducted on symmetric protected hydroquinone, i.e. R_1=R_2.

3.3.2.1. Friedel-Crafts acylation

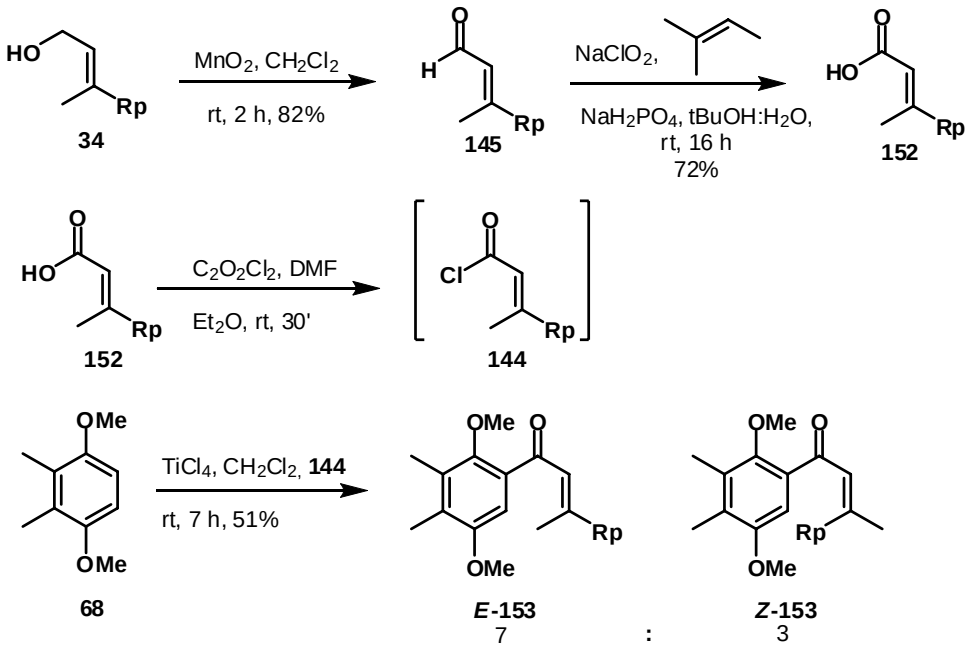
The well known Friedel-Crafts acylation, discovered in 1877,[109] consists on the addition of an acyl chloride to an aromatic moiety, catalyzed by a Lewis acid. As the product contains a carbonyl group, it deactivates the aromatic ring, and avoids successive acylations. A model substrate was firstly envisaged, in order to test the synthetic route, and commercially available 3-methyl-crotonic acid **146** was selected (*scheme 73*). Hydroquinone **68** was easily protected to its bis-methylether **148** and to its bis-MOM ether **150**, in 87% and 88% yield respectively, and different F-C acylation methods were screened.



Scheme 73: Synthesis of bisprotected hydroquinones **148** and **150**, and its F-C coupling.

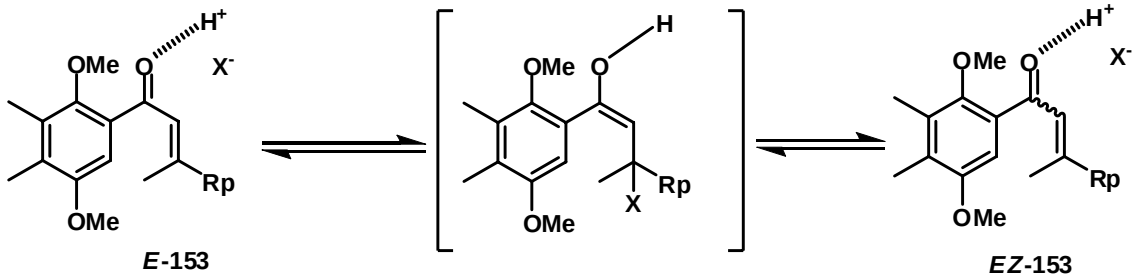
Acyl chloride **147** was generated *in situ* from reaction between acid **146** and oxalyl chloride in diethylether,[110] and allowed to react with bis-protected hydroquinones using different Lewis acids. In both cases, it turned out that the use of $POCl_3/ZnCl_2$[111] or $POCl_3/AlCl_3$[112] was not successful and led to unreacted starting materials, or unidentified side-products. Despite these disappointing results, by switching to $TiCl_4$ in CH_2Cl_2,[113] the desired bis-OMe product **149** was obtained in 42% yield, but surprisingly, reaction with bis-MOM hydroquinone **150** led to several byproducts and no F-C coupling was observed. One of the major side-product, 2,3-dimethyl quinone **151**, probably came from the cleavage of the MOM- ether that could be achieved in the presence of a strong Lewis acid.[114]

Having found conditions that allowed the formation of the bis-OMe F-C product **149**, it was applied to *E*-(*R*,*R*)-phytylic acid **152**, which was synthesized from *E*-(*R*,*R*)-phytol **34**. Oxidation with activated MnO_2 in CH_2Cl_2 afforded *E*-(*R*,*R*)-phytal **145** in 82% yield, further oxidized to the acid, using a mixture of $NaClO_2$ and NaH_2PO_4 in tBuOH:H_2O, that yielded **152** in 72%, as a single isomer (*scheme 74*).



Scheme 74: Synthesis of phytylic acid **152** and F-C coupling with bis-OMe hydroquinone **68**.

Thus, F-C coupling of **68** with *in situ* formed acyl chloride **144**, in the presence of a slight excess of $TiCl_4$, afforded the desired product **153** in 51% yield as a mixture of *E*- and *Z*-isomers. It could be rationalized by a possible equilibrium, catalyzed by a Brönsted or Lewis acid, as depicted on scheme 75.



Scheme 75: Possible equilibrium that explains the isomerisation observed.

Separation of both ***E*-153** and ***Z*-153** was possible by SiO_2 chromatography, and NOESY experiments allowed the assignment of each isomer. It appeared that ***E*-153** and ***Z*-153** were highly sensitive to acids, and NMR samples in d^1-chloroform directly isomerized to the original 7:3, *E*/*Z* ratio upon standing (*figure 18*). Filtration of $CDCl_3$ over a pad of basic aluminium oxide solved the problem and avoided the fast isomerisation of **153**.

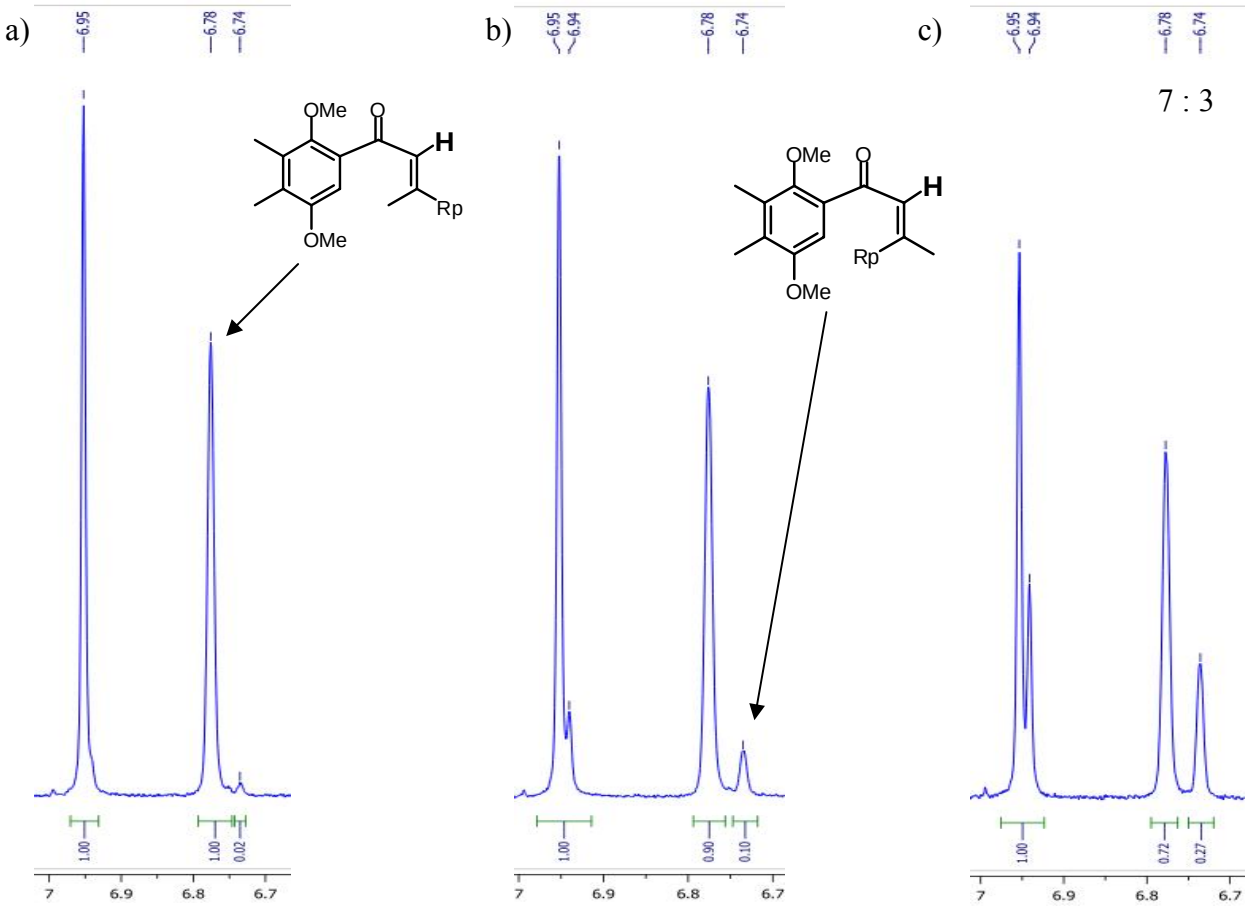
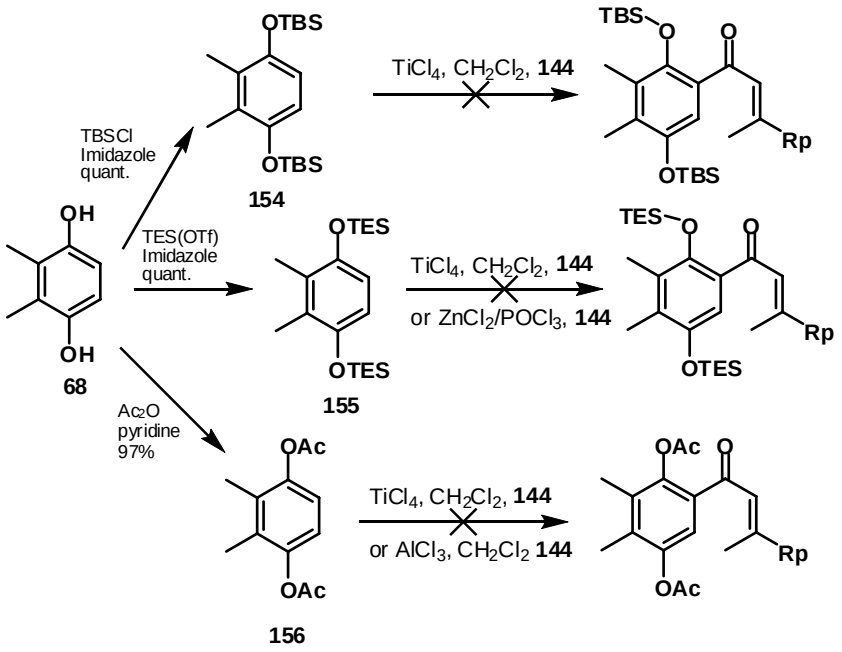


Figure 18: ^{1}H NMR (400 MHz) spectra of ***E*-153** at -C=CH-: a) directly after purification, b) upon standing for 17 h, c) upon standing for >24 h.

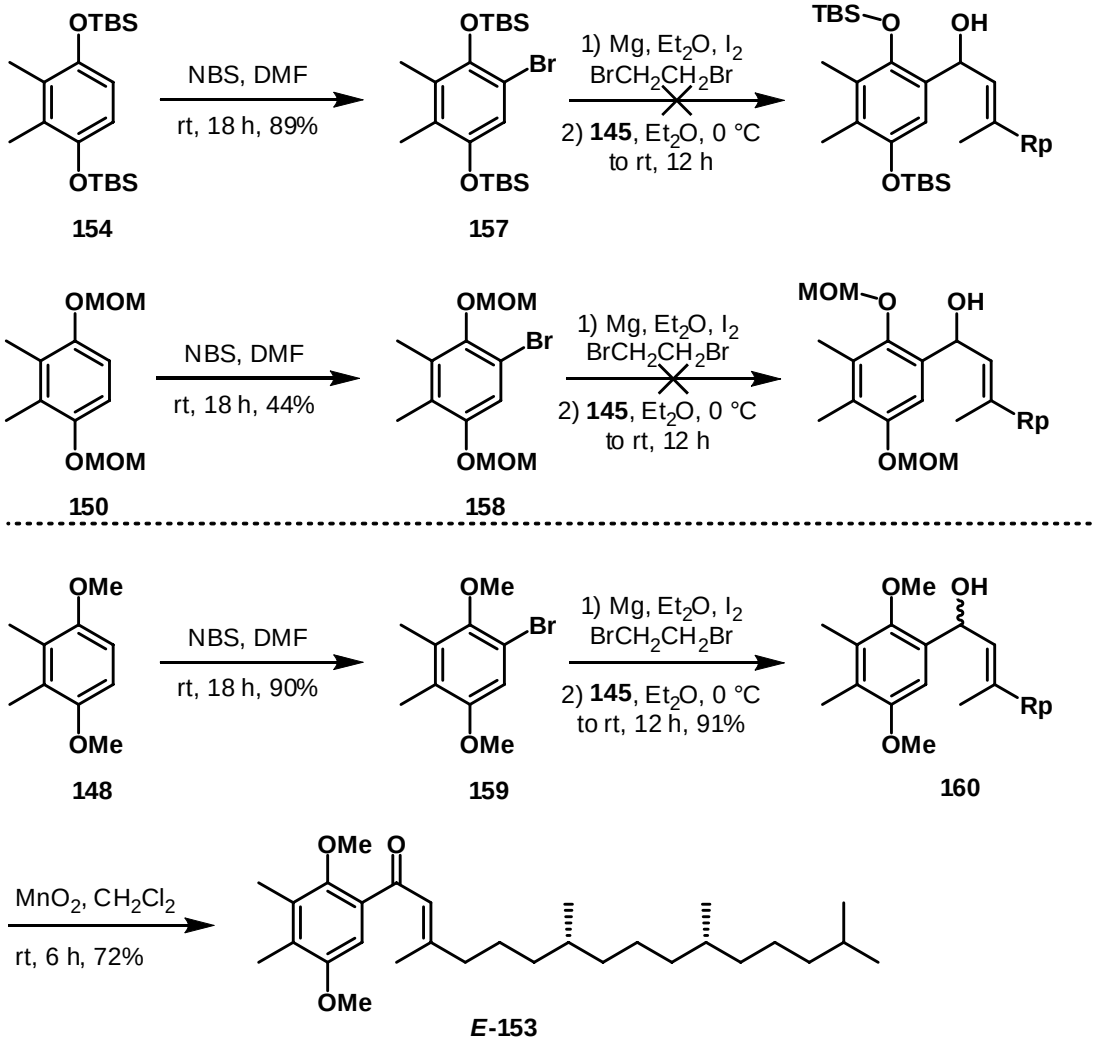
Several other protecting groups were envisaged at the hydroquinone, and synthesized from 2,3-dimethylhydroquinone **68** (*scheme 76*). Thus protection to TBS- and TES-silylethers went smoothly to afford **154** and **155** in quantitative yields, as well as bis-acetyl hydroquinone **156**, gained in 97% yield from acetic anhydride and pyridine. But unfortunately, none of them reacted with acyl chloride **144**, either in presence of $POCl_3/ZnCl_2$, $AlCl_3$ or $TiCl_4$, and investigations were then moved to Grignard coupling reaction.



Scheme 76: Synthesis of **154**, **155** and **156**, and F-C reaction with acyl chloride **144**.

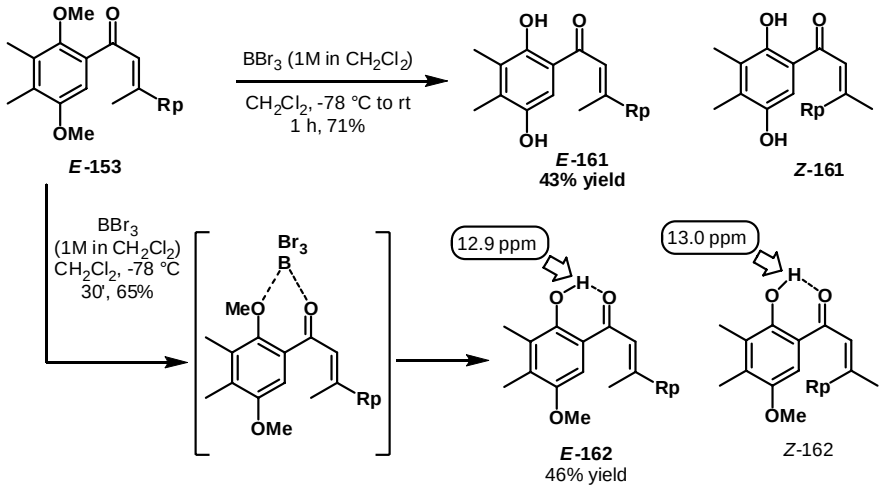
3.3.2.2. Grignard reaction on *E*-(*R*,*R*)-phytal **145**.

Several years after Friedel and Crafts reported the acylation of aromatics, Grignard described the use of magnesium in synthesis and in particular the reactivity of organomagnesium compound with carbonyl groups.[115] From the retrosynthetic proposal, we envisaged the coupling of an aromatic magnesium bromide with *E*-(*R*,*R*)-phytal **145**. Synthesis of the aldehyde partner has already been described in previous part, by an oxidation of *E*-(*R*,*R*)-phytol **34**, and bromination of the different bis-protected hydroquinones already used was necessary. To this end, *N*-bromosuccinimide was used as brominating agent, and showed excellent reactivities on hydroquinones **148**, **150** and **154** (*scheme 77*). Grignard reagents were formed *in situ* by reaction of aromatic bromides with Mg in Et_2O, in the presence of catalytic amounts of I_2 and dibromoethane, and were allowed to react with aldehyde **145**. Despite no reaction was observed in the case of TBS- and MOM- ethers and the aldehyde fully recovered, an excellent 91% yield was obtained for bis-methyl ether hydroquinone **159**. Steric hindrance could be responsible for the absence of reaction with **157** and **158**, due to the bulkiness of TBS- and MOM- protecting groups. Benzylic alcohol **160** was then obtained as a 1:1 mixture of diastereoisomers, giving two sets of signals on ^{1}H NMR analysis, and could be oxidized to ***E*-153**, using activated MnO_2, in 72% yield and pure *E*-isomer (*scheme 77*).



Scheme 77: Bromination of bis-protected hydroquinones - Grignard reaction with (*E*)-phytal **145**.

The advantage of this route in comparison with the F-C pathway described in previous part concerned the higher yields reached. Finally, deprotection of the methyl ether was investigated, and was based on a report of Vickery et al.[116] in the use of boron tribromide and iodotrimethylsilane for the selective O-demethylation of catechol ethers. Thus, treatment of ***E*-153** in the presence of 3 equivalents of BBr_3 in CH_2Cl_2 afforded the corresponding hydroquinone **161**, in 71% yield (*scheme 78*). But with no surprises, isomerisation of the double bond was also observed, giving a ratio of 6:4 *E*/*Z*, and isolation of pure ***E*-161** made dropped the yield to 43%. Influence of the temperature was checked in order to decrease the isomerisation of the double bond, but surprisingly, when the reaction was carried out at -78 °C and kept at this temperature, there was no influence on the isomerisation and mono-O-demethylation occurred, leading to ***E*-162** in 46% yield (65% conv, 7:3 *E*/*Z*).



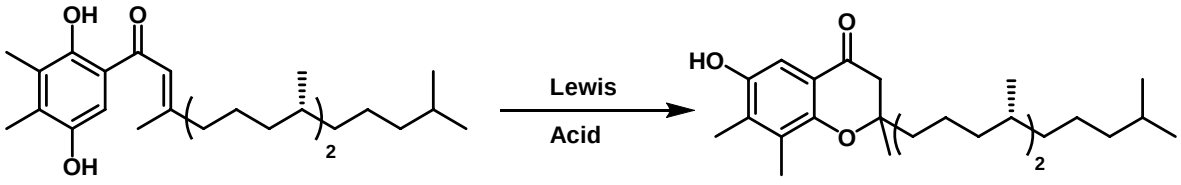
Scheme 78: O-Demethylation of ***E*-153** in the presence of BBr_3 – Influence of the temperature.

The difference in reactivity of the methyl ethers could be explained by the coordination of the boron to the carbonyl and to the *ortho*-methoxyether, thus leading in a regioselective deprotection at low temperatures. A similar H-bond was clearly observed on ^{1}H NMR spectrum since the hydroxyl proton was shift in low fields to δ = 12.9 ppm for the *E*-isomer, and δ = 13.0 ppm for the *Z*-isomer. Having in hand two precursors for the Lewis acid mediated cyclisation, several metal sources were screened.

3.3.3. Lewis-acid mediated cyclisation.

3.3.3.1. Screening of metal salts.

Precursor **E-161** was then submitted to different Lewis acid, and the cyclisation was followed by HPLC (Protonsil® 120-5-CN, 1% to 2% iPrOH in n-heptane, 1 mL/min, 270 nm, 25 °C), to determine the conversion to the desired product **163** (*table 7*). The first observation concerned the 'integrity' of the double bond since the unreacted starting material **161** was isolated as a *E*:*Z* mixture in some cases. It was obvious that Lewis acids that induced such isomerisations would not be considered as potential candidates for an asymmetric version of the reaction, since it would lead to the absence of diastereoselectivity. Several metals such as Cu^{II} and Fe^{III} gave good results (*entries 10, 15 and 16*), that were excellent reactivity and no isomerisation observed during the reaction period. Influence of the solvent was crucial in the case of $Cu(OTf)_2$, as its complete solubility in MeCN (*entry 16*) led to a fast and quantitative reaction.



***E*-161** **163**

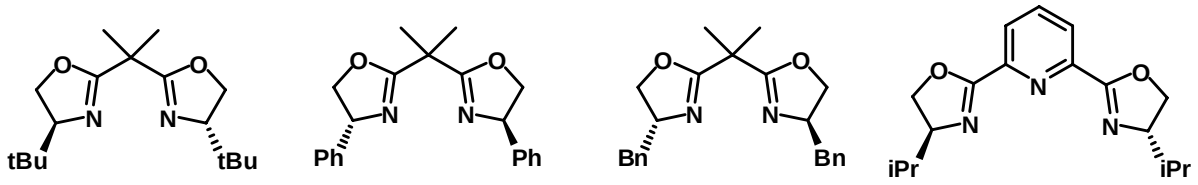
entry	Lewis acid (LA)	conversion[a] (%)	ratio ***E*-161**:***Z*-161**[b]
1	$AlCl_3$	0	7:3
2	$Al(ClO_4)_3$	0	7:3
3	$Al(OTf)_3$	0	7:3
4	$TiCl_4$	0	>98 :2
5	$ZnCl_2$	0	>98 :2
6	$Zn(BF_4)_2$	traces	>98 :2
7	$Zn(OTf)_2$	4	7:3
8	$CuCl_2$	3	7:3
9[c]	$Cu(OTf)_2$	52	>98 :2
10[d]	**$Cu(OTf)_2$**	**>99**	**>98 :2**
11	$NiCl_2$	0	8:2
12	$Ni(ClO_4)_2$	0	8:2
13[c]	$Sn(OTf)_2$	26	8:2
14	$SnCl_4$	4	7:3
15	**$FeCl_3$**	**>99**	**>98 :2**
16	**$Fe(ClO_4)_3$**	**>99**	**>98 :2**
17	$Fe(ClO_4)_2$	17	7:3
18	$CoCl_2$	0	8:2
19	$Co(BF_4)_2$	0	8:2
20	$La(OTf)_3$	traces	8:2

Table 7: Screening of Lewis acid for the intramolecular oxa-Michael reaction of ***E*-161**. [General conditions: 34.5 µmol ***E*-161**, 1.5 equiv LA, 1 mL CH_2Cl_2, RT, 15h. [a] Determined by HPLC at 270 nm. [b] *E*:*Z* ratio of unreacted **161**, determined by HPLC. [c] Complete conversion observed after >5 days. [d] Reaction performed in MeCN.]

From the two metals showing outstanding results, Cu^{II} was selected to envisaged a diastereoselective reaction, since it is one of the most commonly used metal for asymmetric Michael reaction (*see section 3.3.1.1 and references cited therein*) and literature offers a broad variety of chiral ligands.

3.3.3.2. Copper catalyzed asymmetric cyclisation.

A broad variety of chiral ligands were already described in copper catalyzed asymmetric reactions, of which several are commercially available and were used for preliminary experiments. C_2-Symmetric bisoxazoline (BOX) ligands such as **164**, **165** and **166** were selected, as well as pyridine bis-oxazoline (PyBOX) ligand **167** (*figure 19*), taking advantage of the work achieved by Evans and co-workers, on the formations, structures and applications of corresponding Cu^{II} complexes.[96]

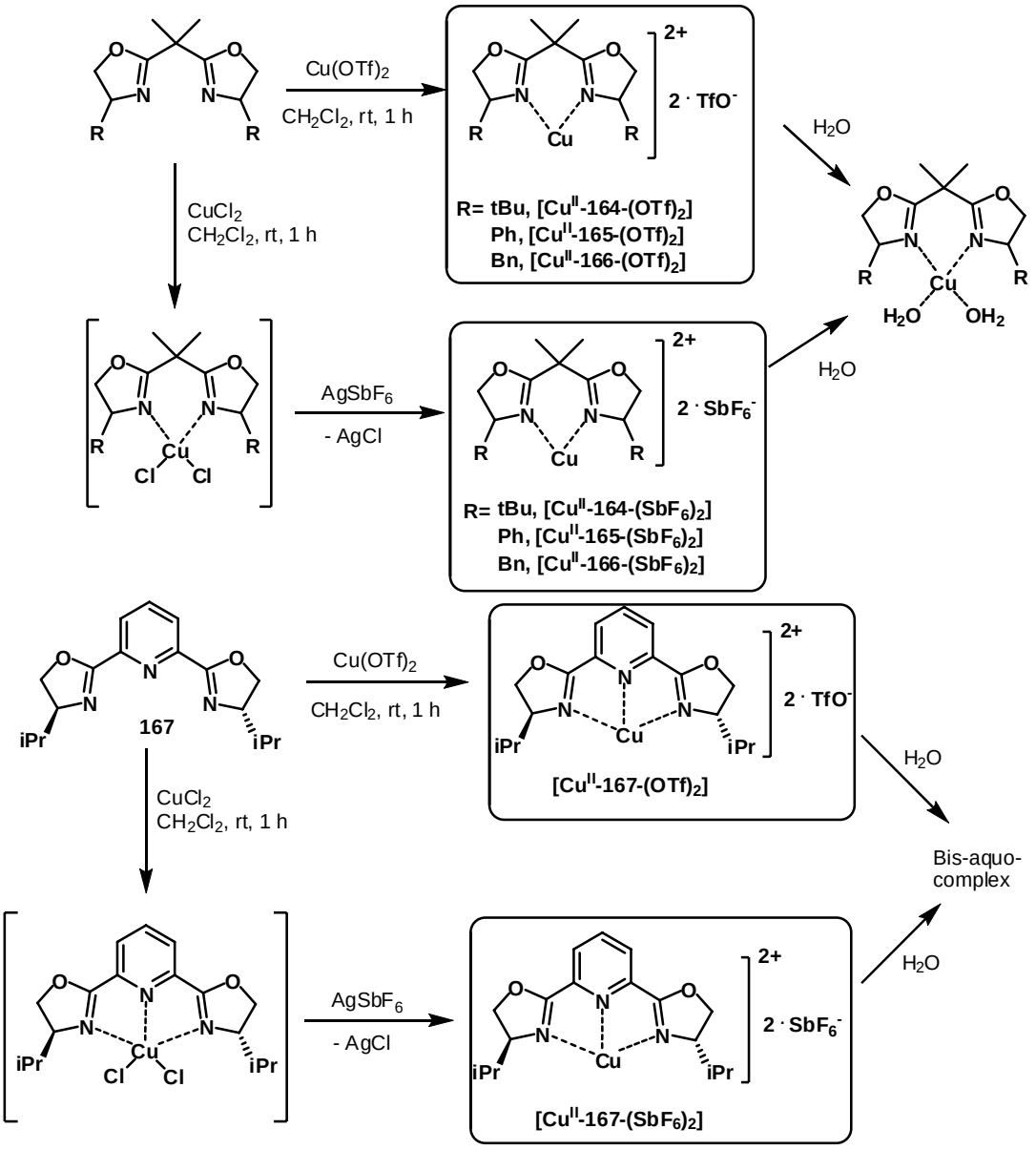


(*S*,*S*)-tBu-BOX **164** | (*R*,*R*)-Ph-BOX **165** | (*R*,*R*)-Bn-BOX **166** | (*S*,*S*)-iPr-PyBOX **167**

Figure 19: BOX and PyBOX ligands selected for preliminary experiments.

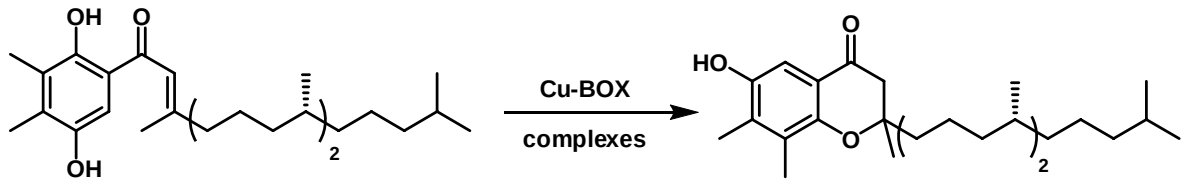
Several factors were reported to be critical for both reactivity and stereoselectivity, such as the solvent, the choice of the metal counterions, the temperature or the use of additives. In 1995, Evans et al. reported a study on the counterion influence in BOX-copper complexes [Cu^{II}-(BOX)X_2], for the enantioselective Diels-Alder reaction.[117] Four anions were tested, BF_4^-, TfO^-, PF_6^- and SbF_6^-, and a correlation between the coordination ability of the anion to the metal center and the efficiency of the copper catalyst was found: poor coordinating anions gave better results, SbF_6^- being the best. Accordingly, triflate (TfO^-) and hexafluoroantimonate (SbF_6^-) counterion were selected for the oxa-Michael cyclisation.

Formation of these copper-BOX complexes was intensively studied and reported by Evans et al.,[96] and could be achieved by simply stirring the chiral ligands in the presence of the copper salt, in CH_2Cl_2, under a strictly anhydrous atmosphere (*scheme 79*). In the case of SbF_6^- counterion, the bis-chloro-complexes were first produced by reacting $CuCl_2$ with the chiral ligands, followed by an anion exchange upon addition of $AgSbF_6$, thus precipitating AgCl. These complexes are highly sensitive to moisture, since H_2O could rapidly exchange with counterions, leading to the bis-aquo complexes.



Scheme 79: Formation of Cu^{II}-BOX complexes.

These complexes were then tested on the oxa-Michael cyclisation of precursor ***E*-161**, under different conditions, and results are presented in table 8. Note that the diastereoisomeric excesses were checked by comparison with a reference compound, racemic at C-2. Moderate conversions were observed and none of the chiral complexes showed diastereoisomeric excesses by chiral HPLC analysis (Chiralpak AD-H, 1% to 3% iPrOH in n-heptane, 0.5 mL/min, 270 nm, 25 °C). However, it clearly revealed that SbF_6^- counterion was necessary to promote the cyclisation, since no reaction was observed when TfO^--complexes were used. The use of an additive was also important, as reported by Kitajima et al. in 1997[118] that increased the turnover of the catalyst, and avoided side-reactions by trapping the enolate formed.



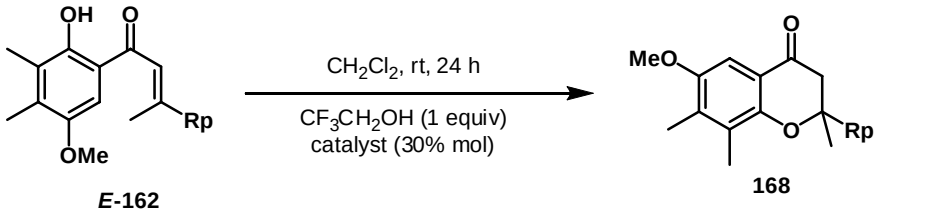
***E*-161** **163**

entry	catalyst	load. (mol%)	temp (°C)	solvent (S)	additive (A)	conv[a] (%)	de[a] (%)	ratio ***E*-161**:***Z*-161**[b]
1	[Cu-**164**-$(OTf)_2$]	100	rt	MeCN	-	0	-	>98:2
2	[Cu-**164**-$(OTf)_2$]	100	-78	MeCN	-	0	-	>98:2
3	[Cu-**164**-$(OTf)_2$]	100	rt	THF	-	0	-	>98:2
4	[Cu-**164**-$(OTf)_2$]	100	-78	THF	-	0	-	>98:2
5	[Cu-**164**-$(OTf)_2$]	100	rt	CH_2Cl_2	-	0	-	>98:2
6	[Cu-**164**-$(OTf)_2$]	100	-78	CH_2Cl_2	-	0	-	>98:2
7	[Cu-**166**-$(OTf)_2$]	100	rt	MeCN	-	0	-	>98:2
8	[Cu-**166**-$(OTf)_2$]	100	rt	CH_2Cl_2	-	0	-	>98:2
9	[Cu-**165**-$(OTf)_2$]	100	rt	MeCN	-	0	-	>98:2
10	[Cu-**165**-$(OTf)_2$]	100	rt	CH_2Cl_2	-	0	-	>98:2
11	[Cu-**165**-$(OTf)_2$]	15	rt	CH_2Cl_2	-	0	-	>98:2
12	[Cu-**165**-$(OTf)_2$]	15	rt	CH_2Cl_2	CF_3CH_2OH	0	-	>98:2
13[c]	[Cu-**167**-$(OTf)_2$]	100	rt	CH_2Cl_2	-	9	0	>98:2
14	[Cu-**165**-$(SbF_6)_2$]	30	rt	CH_2Cl_2	-	15	0	80:20
15	**[Cu-165-$(SbF_6)_2$]**	**30**	**rt**	**CH_2Cl_2**	**CF_3CH_2OH**	**38**	**0**	**80:20**
16	[Cu-**165**-$(SbF_6)_2$]	30	rt	MeCN	CF_3CH_2OH	0	-	>98:2
17	[Cu-**165**-$(SbF_6)_2$]	30	rt	CF_3CH_2OH	-	0	-	>98:2
18	[Cu-**165**-$(SbF_6)_2$]	30	rt	CH_2Cl_2	DNBA[c]	49	0	67:33
19	[Cu-**165**-$(SbF_6)_2$]	30	rt	CH_2Cl_2	PFP[d]	50	0	53:47
20	**[Cu-167-$(SbF_6)_2$]**	**10**	**rt**	**CH_2Cl_2**	**CF_3CH_2OH**	**20**	**0**	**90:10**
21	[Cu-**167**-$(SbF_6)_2$]	10	-78	CH_2Cl_2	CF_3CH_2OH	7	0	>98:2

Table 8: Asymmetric oxa-Michael cyclisation of ***E*-161** using chiral copper complexes. [General conditions: 34.9 μmol ***E*-161**, 1 mL S, 1 equiv A, 24 h. [a] Determined by chiral HPLC at 270 nm. [b] *E*:*Z* ratio of unreacted **161**, determined by chiral HPLC. [c] 2,4-dinitrobenzyl alcohol. [d] pentafluorophenol.]

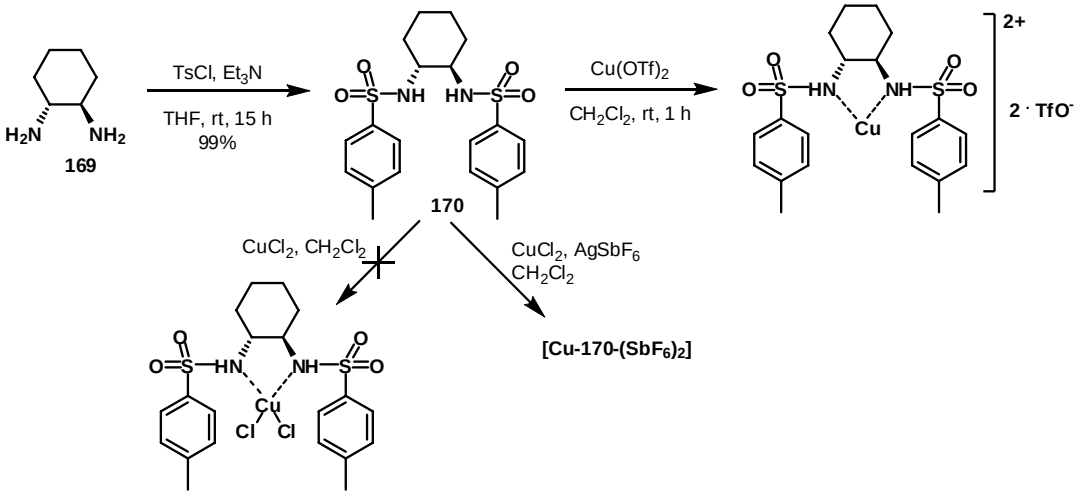
To this end, 2,2,2-trifluoroethanol was used and successfully enhanced the reactivity from 15% (*entry 14*) to 38% conversion (*entry 15*). Other alcohol derivatives were envisaged, such as 2,4-dinitrobenzyl alcohol (*entry 18*) and pentafluorophenol (*entry 19*), but despite an increase of the reactivity up to 50% conversion, isomerisation of the unreacted precursor **161** occurred in more than 30%, thus contributing in the absence of stereoselectivity. Different solvents were screened but none of them could promote a diastereoisomeric excess.

The influence of the free phenol was also checked, and cyclisation of ***E*-162** was performed with best conditions (*table 8 – entries 15 and 20*) and is depicted on scheme 80. The great advantage of **162** concerned the absence of isomerisation of the double bond, but the cyclisation did not occur in more than 10% conversion and no diastereoselectivity was observed by chiral HPLC analysis (Chiralpak AD-H, 0.5% to 5% iPrOH in n-heptane, 0.5 mL/min, 270 nm, 25 °C).



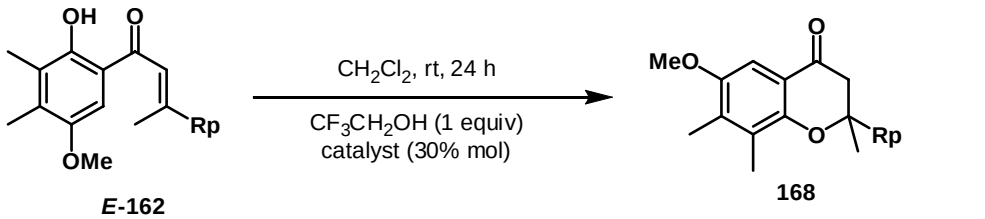
Scheme 80: Cyclisation of ***E*-162** using copper-BOX catalysts.

The Lewis acidity of the chiral catalyst was then considered in order to increase the reactivity toward **161** and **162**, and the choice of less electron donating ligands would be advantageous. Accordingly, we prepared bis-tosylated cyclohexyldiamine **170**, and expected the tosyl group to withdraw the electrons from the nitrogen lone pairs, thus increasing the acidity of the coordinating metal center (*scheme 81*). Synthesis went smoothly from commercially available (*R*,*R*)-cyclohexyldiamine **169**, which quantitatively afforded **170** upon treatment with tosyl chloride and triethylamine in THF.



Scheme 81: Synthesis of bis-tosylated cyclohexyldiamine **170** and formation of Cu^{II}-complexes.

[Cu-**170**-$(OTf)_2$] complex was then prepared by stirring **170** and $Cu(OTf)_2$ in CH_2Cl_2, producing a clear blue solution. Preparation of the SbF_6 analogue did not worked under Evans conditions, since no coordination occurred between $CuCl_2$ and **170** in CH_2Cl_2. However, stirring of a mixture of **170**, $CuCl_2$ and $AgSbF_6$ in CH_2Cl_2 for 4 h afforded a solid after filtration of silver salts and evaporation of solvent, which was used for cyclisation tests. Cyclisation of ***E*-162** showed promising results, as depicted on scheme 82, with up to 79% isolated yield. However, no stereoselectivities were obtained in both cases.



***E*-162** → **168**

[Cu-170-$(TfO)_2$], 24% yield, 0% de

[Cu-170-$(SbF_6)_2$], 79% yield, 0% de

Scheme 82: Cyclisation of ***E*-162** using Cu^{II}-**170** complexes

Investigations on the catalyst structures were attempted by mass spectroscopy, using electro-spray ionization (ESI), and MeCN solutions of [Cu-**170**-$(OTf)_2$] and [Cu-**170**-$(SbF_6)_2$] were analysed. The spectrum of the [Cu-**170**-$(OTf)_2$] complex presented 2 major signals at m/z = 358^+ and 557^+ (*figure 20*), showing the typical isotopic pattern of copper, and thus were attributed to $[Cu^{II}(MeCN)_2(OTf)]^+$ and an *in situ*-reduced[119] copper complex $[Cu^{I}$-**170**-$(H_2O)_4]^+$.

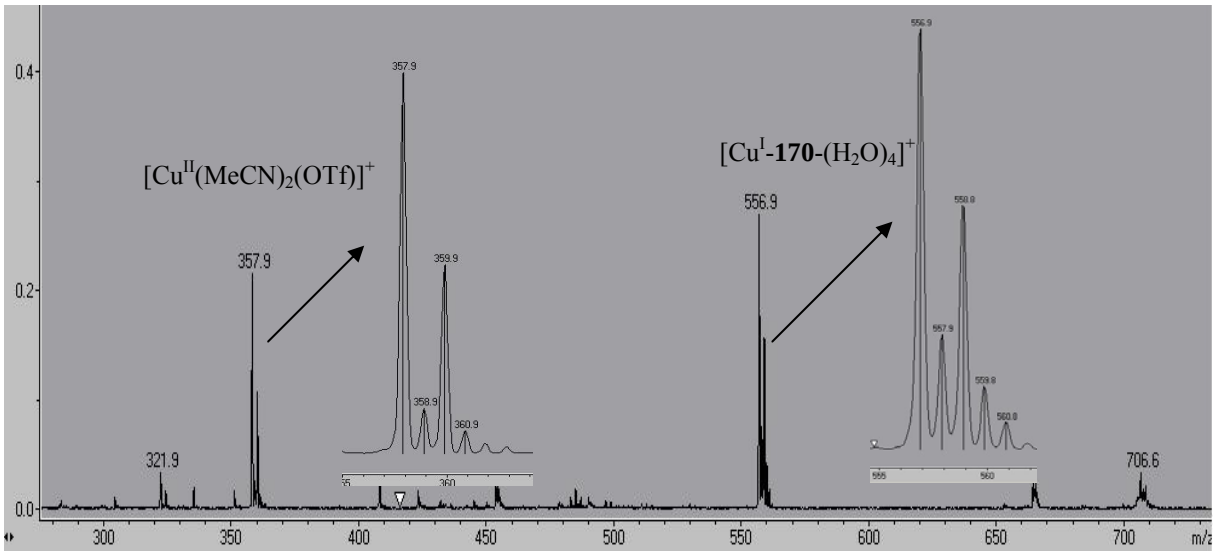


Figure 20: MS-ESI spectrum of [Cu-**170**-$(OTf)_2$] in MeCN.

Surprisingly, the MS-ESI spectrum of the expected [Cu-**170**-$(SbF_6)_2$] complex presented 2 main signals, at m/z = 529^+ and 951^+, but the isotopic pattern of the signals were rather corresponding to a silver complex than to a copper complex (*figure 21*). It clearly indicated that the complex formed and used for the cyclisation was a Ag^I complex since the signals were attributed to $[Ag^I$-**170**$]^+$ and the dimer $[Ag^I$-(**170**$)_2]^+$ respectively.

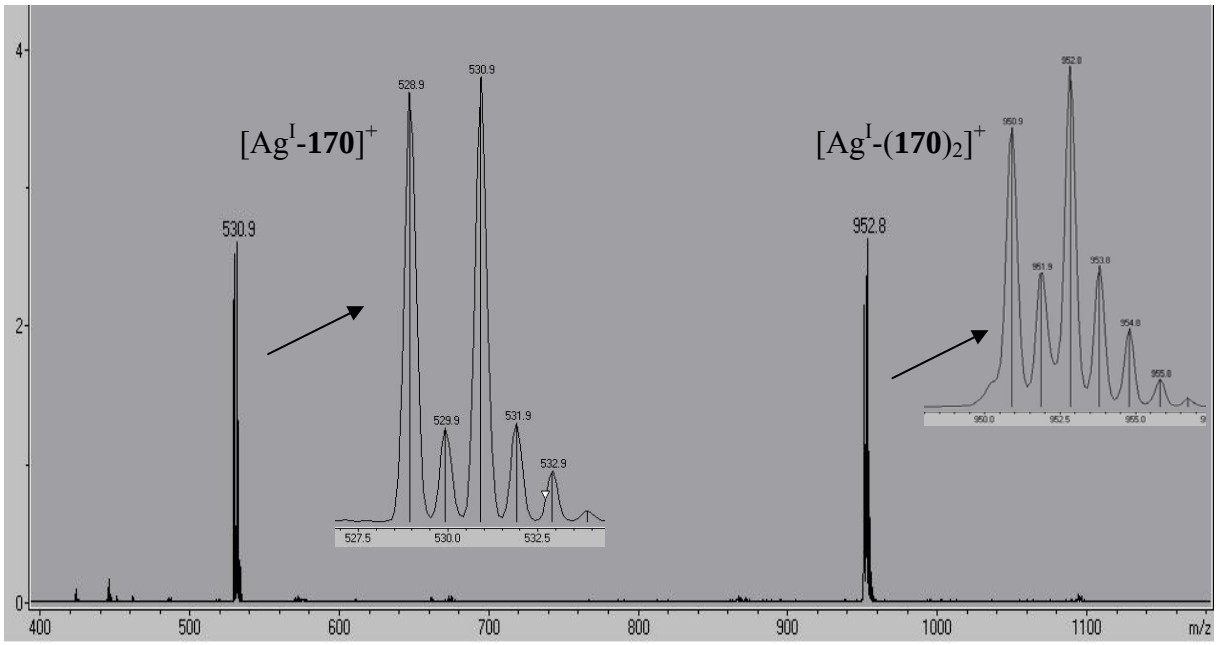


Figure 21: MS-ESI spectrum of [Cu-**170**-$(SbF_6)_2$] in MeCN – Formation of the Ag^I complex.

Coming back to results presented on scheme 82, the actual catalyst that promoted the cyclisation was [Ag^I-**170**-(SbF_6)] and thus the investigation of asymmetric silver-catalyzed cyclisation was considered.

3.3.3.3. Silver catalyzed asymmetric cyclisation.

Structure elucidation of the silver complex [Ag^I-**170**-(SbF_6)] was continued and ^1H NMR analysis was done to determine the nature of the coordination. A 1:1 ratio of **170** and $AgSbF_6$ was analysed in MeCN-d^3, and a typical shift of characteristic protons was observed, and is depicted on figure 22. The first important observation concerned the amine protons, which remained in the silver complex, indicating a non-covalent coordination at the nitrogen atoms.

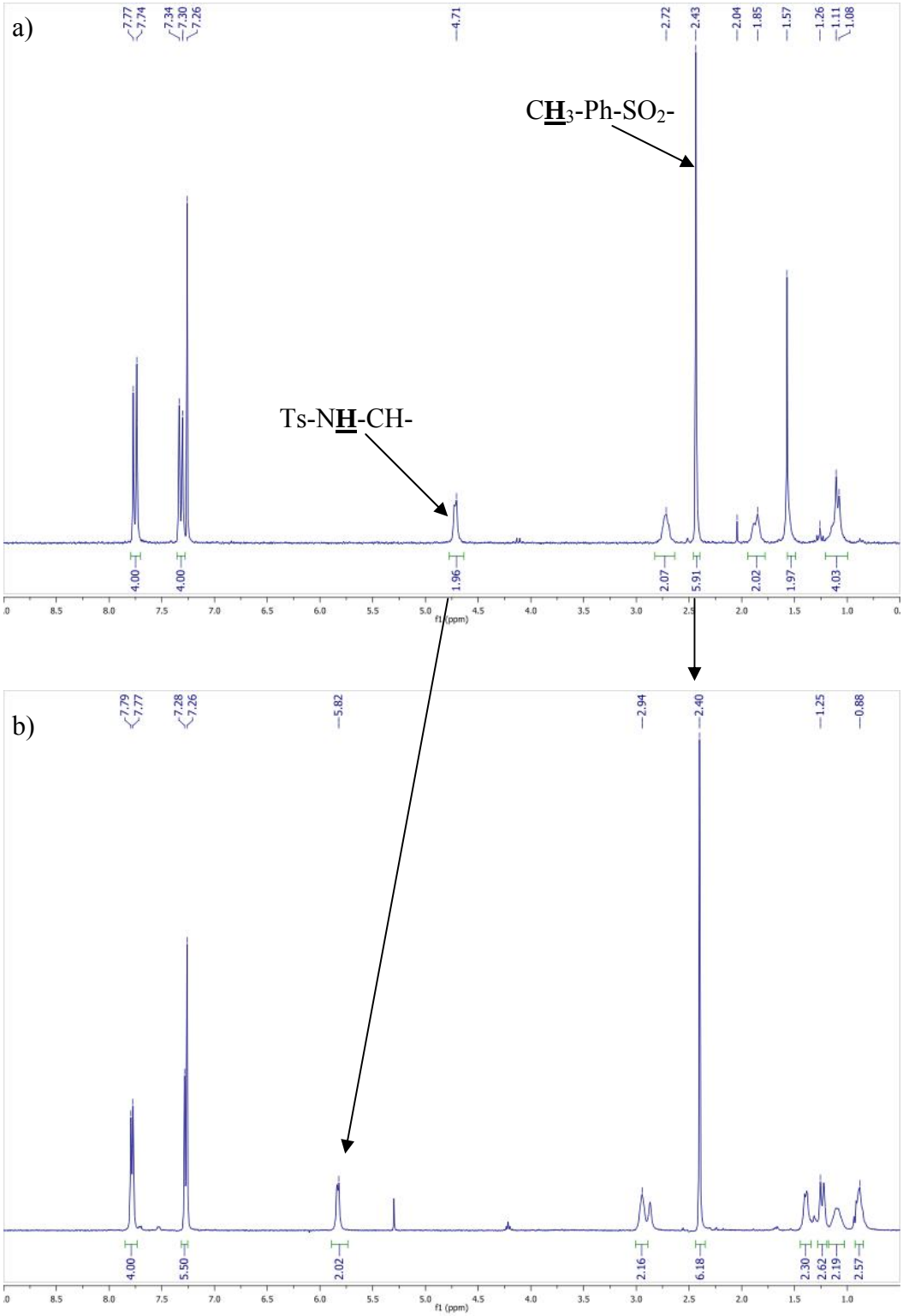


Figure 22: ^{1}H NMR in MeCN-d^{3} of: a) **170** alone, b) **170**:$AgSbF_6$ (1:1).

Moreover, a slight shift of the aromatic methyl as well as the aromatic protons was also observed, that could be explained by a coordination of the silver atom to the π-system of one or both aromatic rings.

A ^{1}H NMR titration revealed that it was most likely a 1:1 Ag^{I+} : **170** complex, which structure is tentatively drawn on figure 23. However, despite a good reactivity of this complex, no selectivity was observed in the cyclisation of ***E*-162** (*scheme 82*).

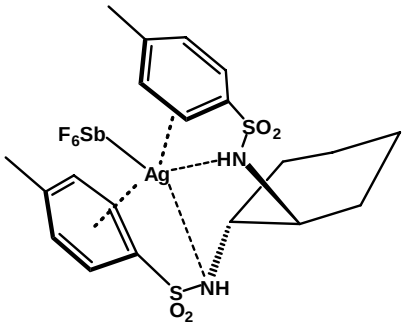
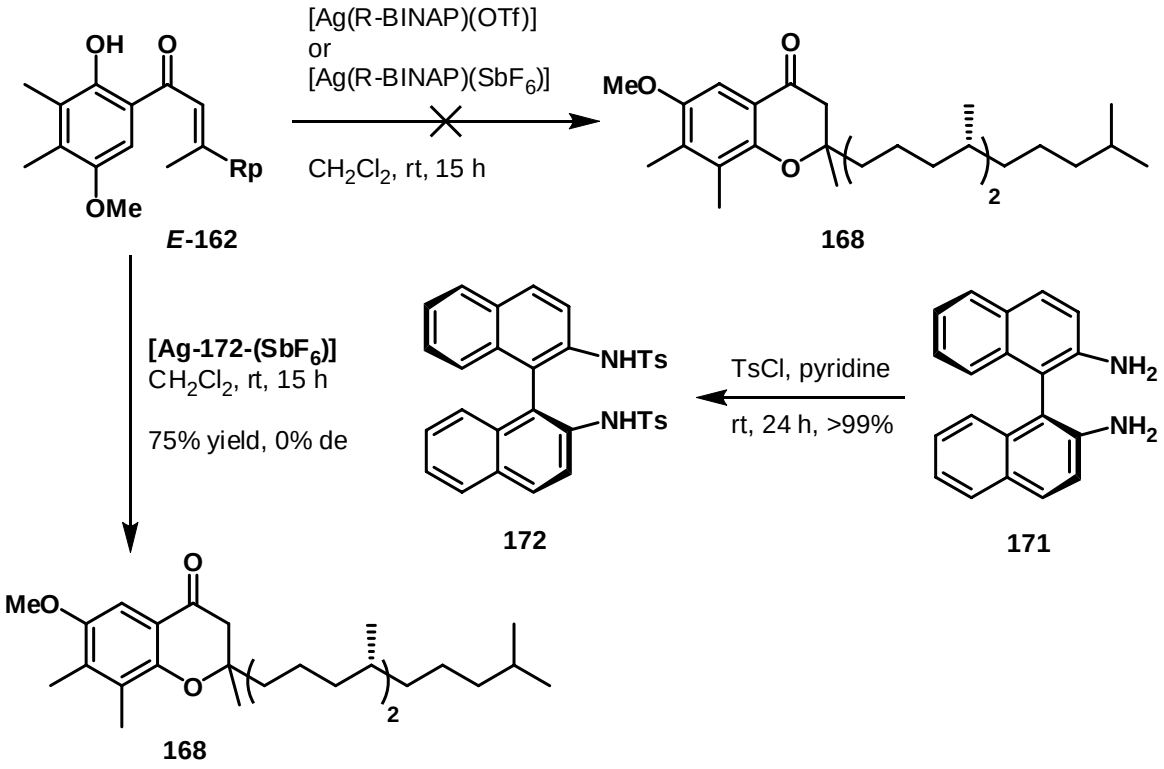


Figure 23: Proposed structure of [Ag^{I}-**170**-(SbF_6)] complex

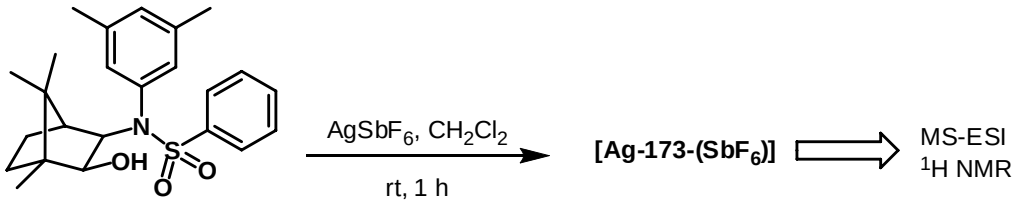
Other ligands were tested, such as commercially available (*R*)-BINAP, which silver complex was already described by Yamamoto et al. for aldol reactions[120] using triflate counterion. Cyclisation attempts using $AgSbF_6$ or AgOTf as silver sources, in a 1:1 ratio with the chiral ligand, were not successful and no reaction occurred (*scheme 83*).



Scheme 83: Cyclisation of ***E*-162** using binaphtalene derived ligands and Ag^{I}.

The Lewis acidity of the silver center was probably too weak due to the strong electron donating ability of the BINAP ligand. Using the same design as for **170**, bis-tosylated (*R*)-DABN **172** was synthesized from diamine **171**, and its silver complex was used in the cyclisation of ***E*-162**. The chromanol product was formed in 75% yield, but no diastereoselectivity was observed.

In the 1980's, Helmchen et al. reported the use of camphor derived chiral auxiliaries in the asymmetric addition of organocopper compounds to enoates,[121] in high diastereoselectivity. Readily available from our fridges, ligand **173** was envisaged for the silver catalyzed oxa-Michael cyclisation (*scheme 84*), and its silver complex, formed by stirring a CH_2Cl_2 solution of $AgSbF_6$ and **173**, in a 1:1 ratio, was characterized by MS-ESI and ^1H NMR analysis.



173

Scheme 84: 'Helmchen's ligand' **173** – Formation of [Ag-**173**-(SbF_6)] complex.

The MS-ESI analysis was performed on a MeCN solution of [Ag-**173**-(SbF_6)] complex, and several peaks were observed, at m/z = 519.9^+, 560.9^+ and 592.9^+, attributed to monomeric silver complexes $[Ag^I\text{-}\mathbf{173}]^+$, $[Ag^I\text{-}\mathbf{173}\text{-}(MeCN)]^+$ and $[Ag^I\text{-}\mathbf{173}\text{-}(MeCN)(MeOH)]^+$ respectively (*figure 24*).

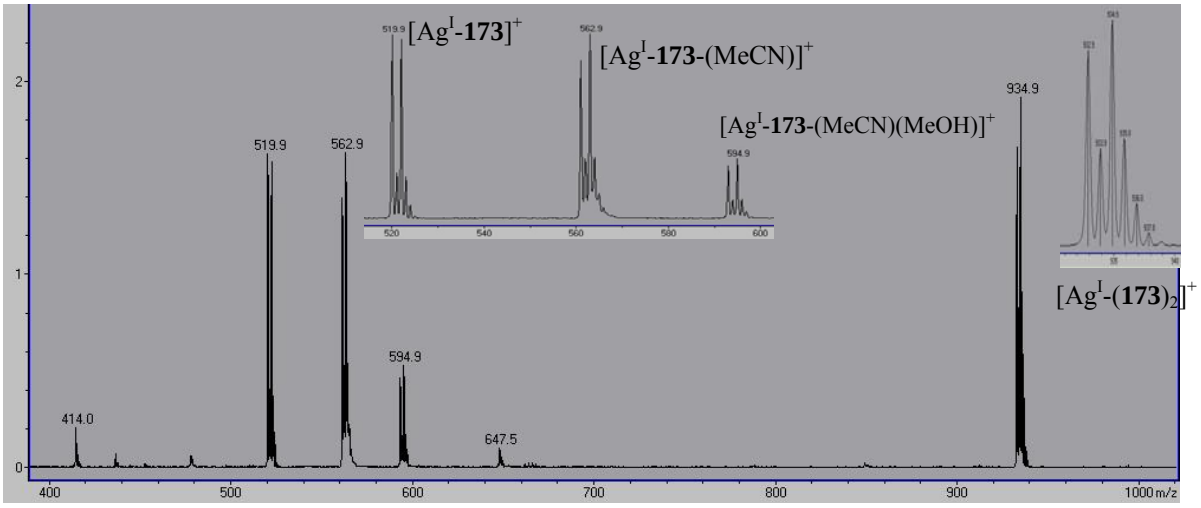


Figure 24: MS-ESI spectrum of [Ag-**173**-(SbF_6)] in MeCN.

Note that the MeOH-complex observed was probably due to residual traces of methanol in the spectrometer, commonly used solvent for MS-experiments. A dimer was also found at m/z = 932.9^{+}, attributed to $[Ag^{I}\text{-}(\mathbf{173})_2]^{+}$. ^{1}H NMR analysis of a 1:1 mixture of **173** and $AgSbF_6$ was performed in CD_2Cl_2-d^2, and a typical shift of characteristic protons was observed, and is depicted on figure 25.

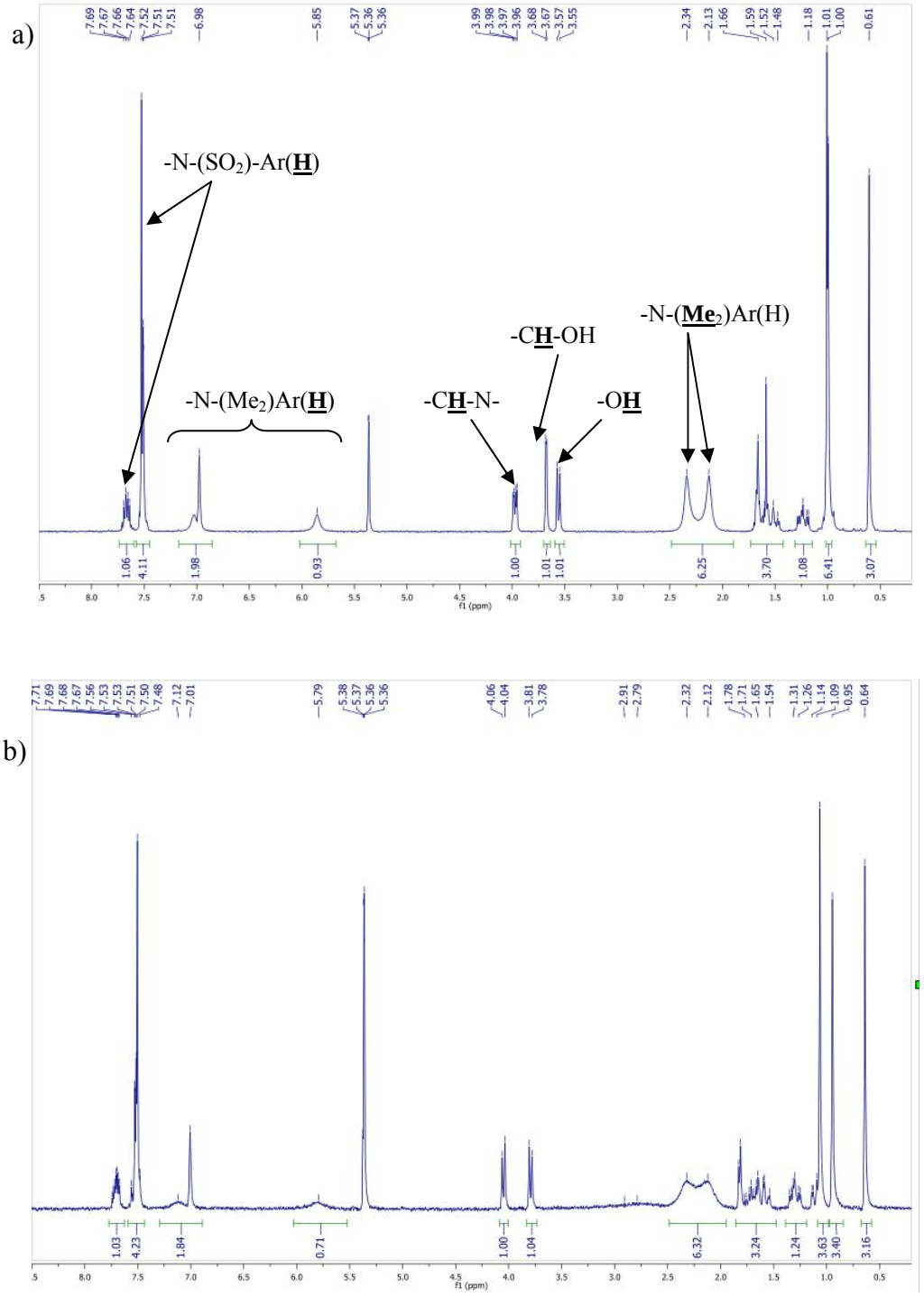
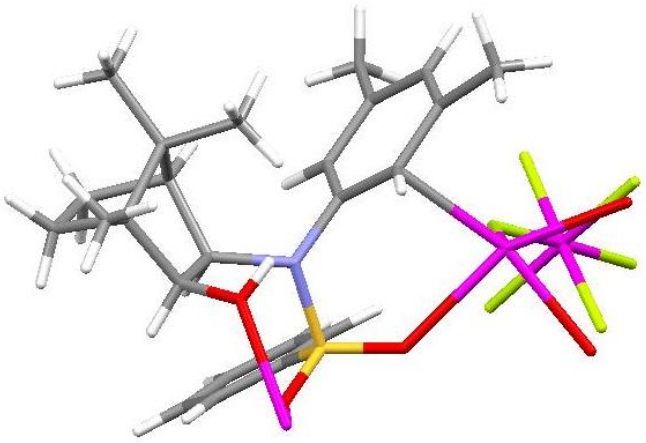


Figure 25: ^{1}H NMR in CD_2Cl_2-d^2 of: a) **173** alone, b) **173**:$AgSbF_6$ (1:1)

The first important observation was relative to the hydroxyl proton which gave a very broad signal upon addition of the silver salt. It suggested that the Ag^I would be coordinated at the oxygen lone pairs. Moreover, the protons of the dimethyl-phenyl ring were all shifted, as well as the two aromatic methyls, which suggested an interaction of the silver center with the π system of the phenyl ring. In addition, the second aromatic ring did not show any typical shifts, suggesting that there was no coordination of the metal. Single crystals were obtained from slow evaporation of CD_2Cl_2, which X-Ray analysis gave the polymeric structure depicted on figure 26.

a)



b)

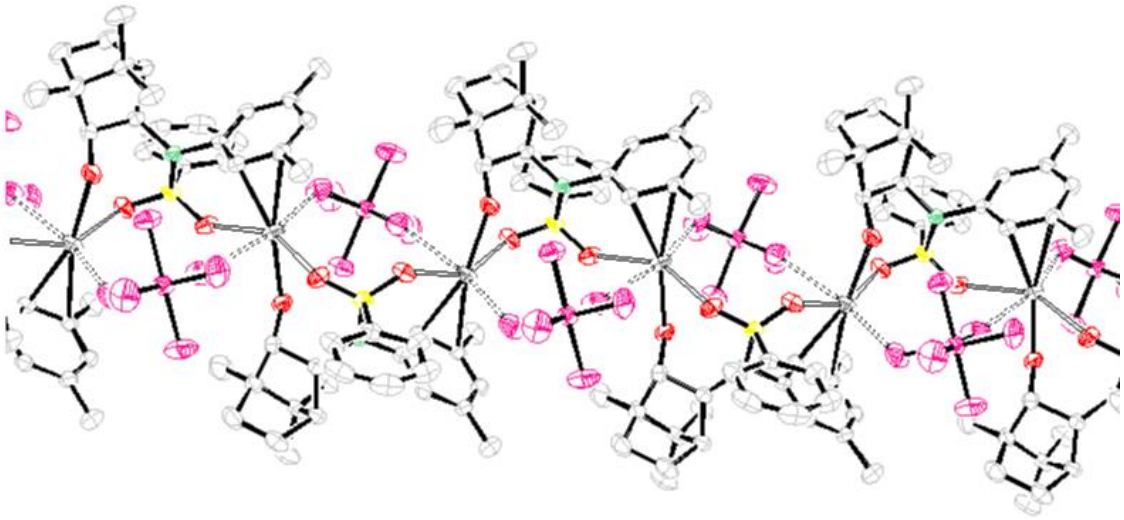
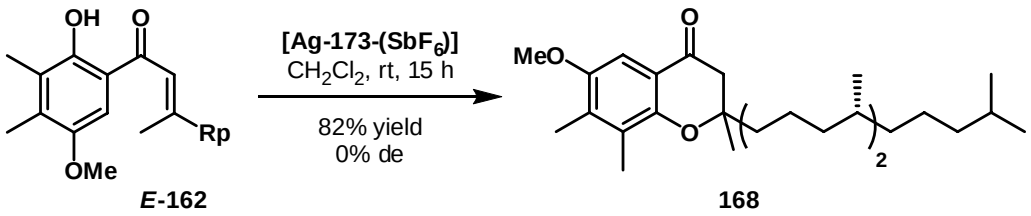


Figure 26: X-Ray structure of [Ag-**173**-(SbF_6)]. a) Monomeric unit, O=red, N=blue, S=yellow, F=green, Ag=pink. b) 1D polymeric structure, O=red, N=green, S=yellow, F=pink, Ag=grey.

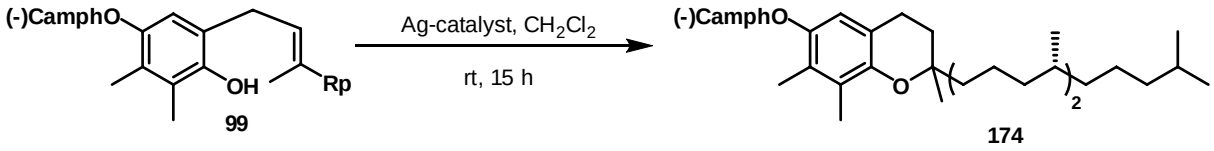
Interestingly, the silver atom coordinated to the hydroxyl group and to one oxygen atom of the sulfonamide. The other SO_2-oxygen atom was then coordinated to the silver of the next unit. Moreover, the observation concerning the interactions between Ag^I and the dimethyl phenyl ring was confirmed. Unfortunately, this silver complex was absolutely not diastereoselective in the oxa-Michael cyclisation of ***E*-162**, though the reactivity was excellent (*scheme 85*).



***E*-162** **168**

Scheme 85: Cyclisation of ***E*-162** using [Ag-**173**-(SbF_6)].

Silver being known to also coordinate at double bonds, the reactivity of these complexes were shortly investigated on precursor **99**, readily available and which synthesis has already been reported[34] (*scheme 86*). Reactivity was excellent and product **174** isolated in up to 94% yield, but no diastereoisomeric excesses were found.



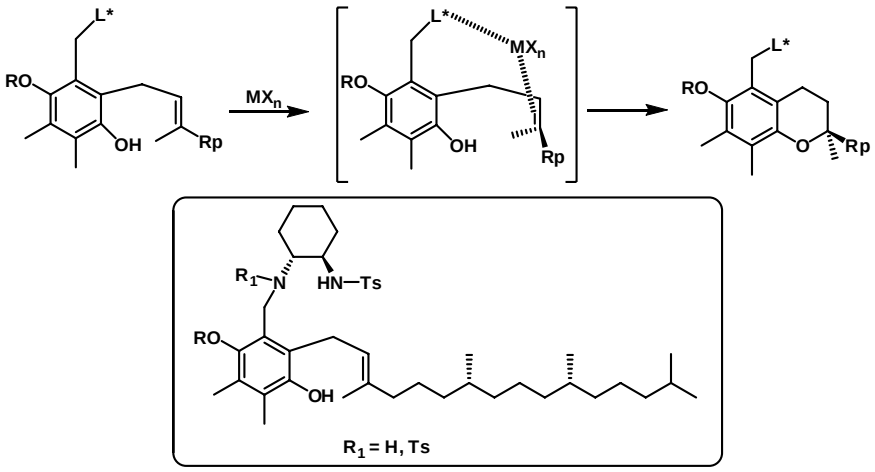
99 **174**

[Ag-170-(SbF_6)], 90% yield, 0% de

[Ag-173-(SbF_6)], 94% yield, 0% de

Scheme 86: Silver mediated cyclisation of **99**.

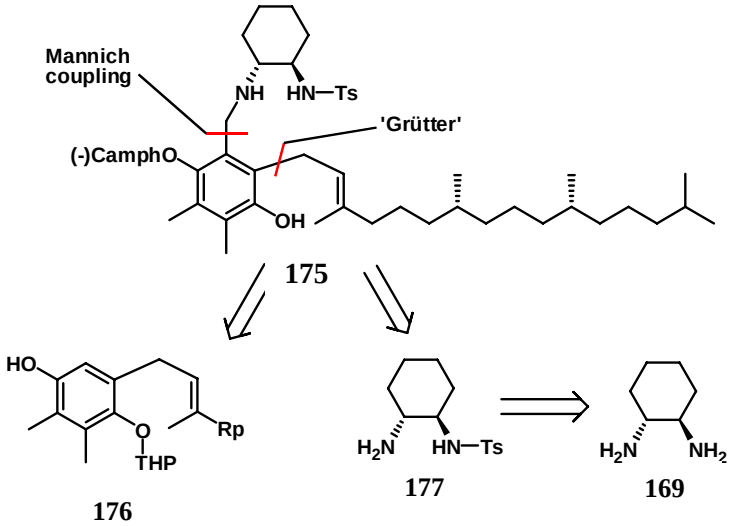
Since none of the chiral Lewis acids used have induced a diastereoselectivity in the oxa-Michael intramolecular cyclisation of **161** and **162**, a new approach was proposed in which the chiral ligand would be covalently attached to the substrate (*scheme 87*). The absence of selectivity in the original design could be explained by the single binding site, the carbonyl oxygen atom or the double bond, probably not sufficient to induce a preferred conformation of the substrate, thus leading to a non-stereoselective attack of the phenolic oxygen atom. An additional conformational strength was expected from the covalently attached ligand, and since best results were obtained with precursor **99**, binding at the C=C was preferred.



Scheme 87: New design using a covalently attached chiral ligand.

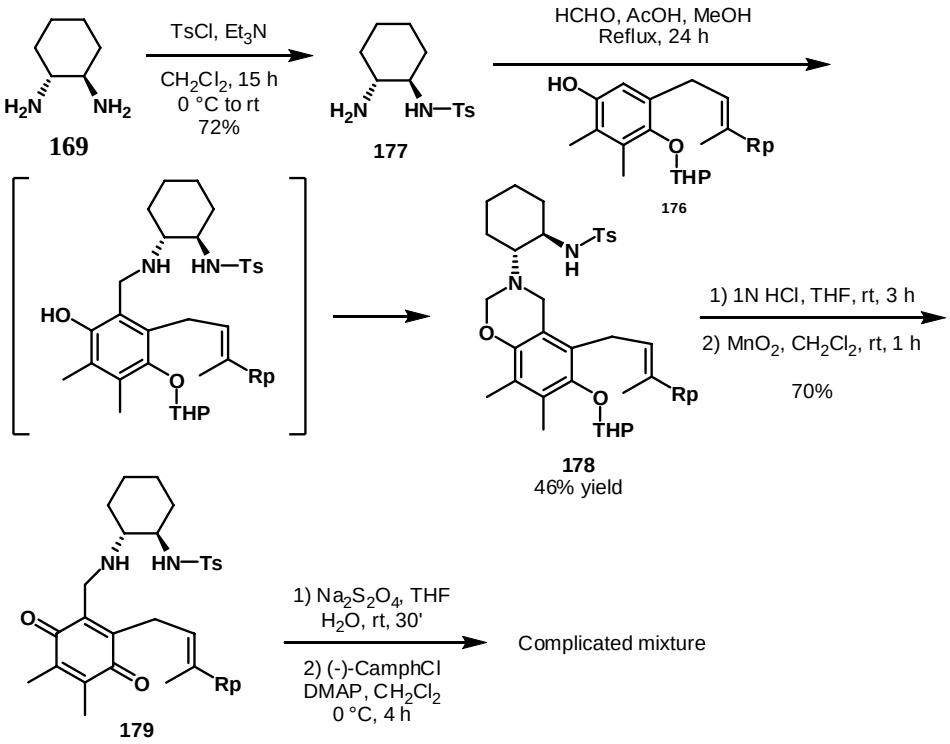
3.3.3.4. Intramolecular chiral ligand design.

The synthesis of **175** was inspired by the one developed in the biomimetic chromanol cyclisation (*see part 3.1.1*), and based on a Mannich coupling to attach the cyclohexyl diamine moiety, as depicted on scheme 88. The bulky (-)-camphanoyl ester was used for the same purpose, and the general remarks concerning the synthesis were kept. Mono-protected phytylhydroquinone **176**, which synthesis has already been described by Woggon et al.,[34] and cyclohexyl diamine **169** were the two initial building blocks.



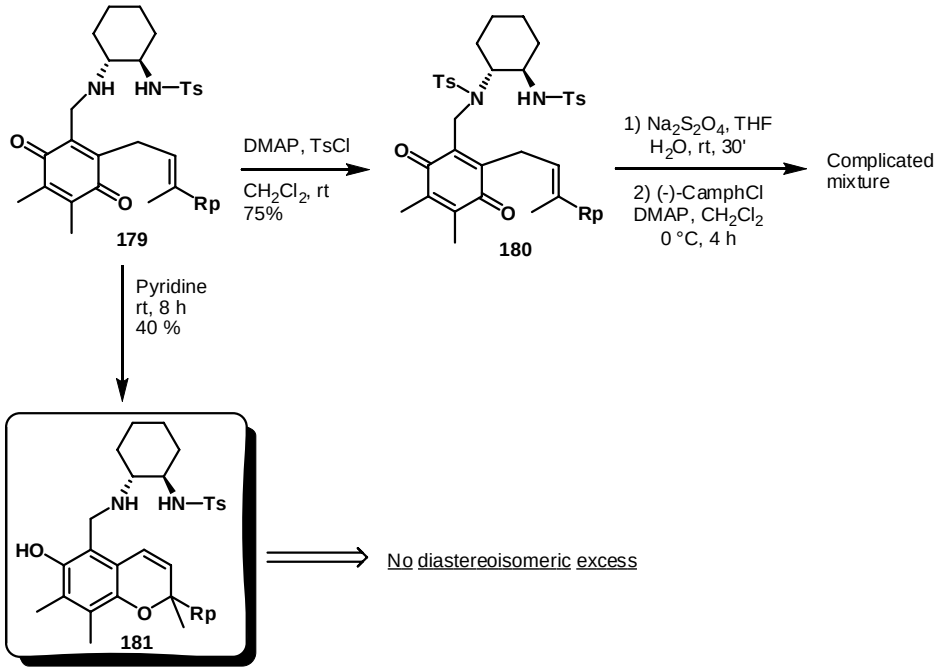
Scheme 88: Retrosynthetic design for the synthesis of precursor **175**.

Mono-tosylation of **169**, in the presence of TsCl and Et_3N, afforded **177** in 72% yield, after careful purification to ensure the complete removal of the base from the crystalline product (*scheme 89*). Having in hand the phytylhydroquinone **176**, Mannich coupling was attempted with formaldehyde and acetic acid in refluxing MeOH, but to our surprise, the expected product was not isolated, as a 'double Mannich' reaction took place, directly leading to **178**. The amino-acetal formed was then cleaved by acidic treatment with 1N HCl in THF, which conditions also cleaved the THP group (*scheme 89*). A hydroquinone / quinone mixture was obtained, and since it was the most stable compound, full oxidation to the quinone **179** was done with activated MnO_2. Protection of the phenol by the bulky (-)-camphanoyl group was investigated, by reduction of the quinone, directly followed by treatment with (-)-CamphCl and DMAP, but the reaction was not regioselective and a complicate mixture was obtained. Both hydroxyl groups probably reacted, as well as the secondary amine. In order to remove one reacting site, protection of the amine was envisaged, at the quinone stage.



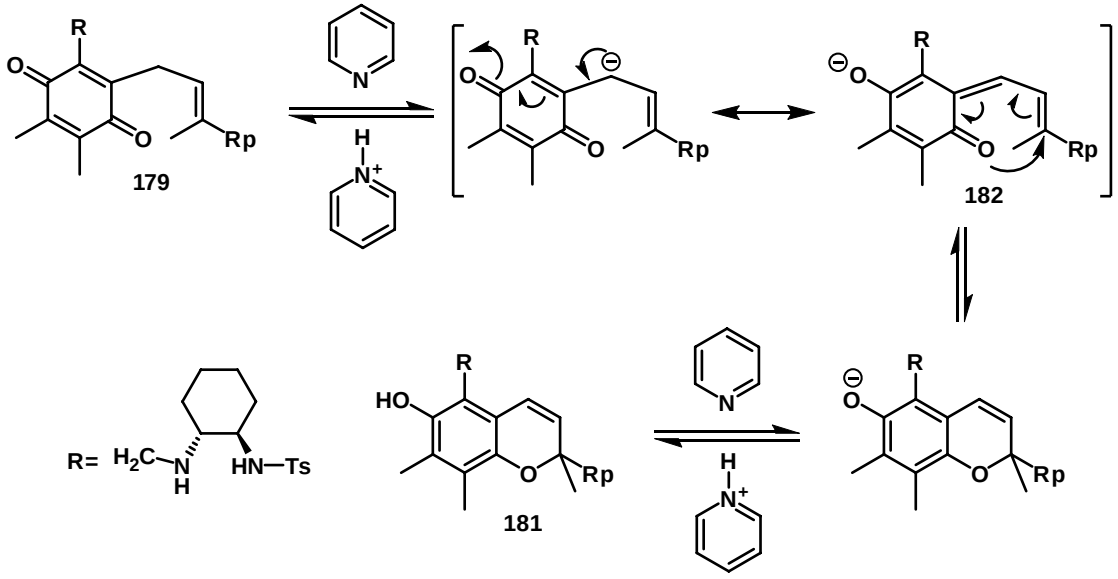
Scheme 89: Mono-tosylation of **168** and its Mannich coupling with **176**.

Accordingly, treatment of the quinone **179** with TsCl and DMAP in CH_2Cl_2, afforded the corresponding bis-tosylated precursor **180** in 75% yield (*scheme 90*). Reduction with sodium dithionite, directly followed by treatment with (-)-CamphCl and DMAP led also to a complicated mixture.



Scheme 90: Protection of the secondary amine – Electrocyclisation of quinone **179**.

During the first attempts of amine tosylation, pyridine has been used as base and solvent, and the chromene **181** was isolated as a side-product. A short investigation revealed that the pyridine was responsible of the cyclisation, and **181** could be isolated in 40% yield, but unfortunately, no diastereoisomeric excess was found. This type of 'electrocyclisation' was already reported in 1963 by Linn et al. in the cyclisation of coenzyme Q[122] and the proposed mechanism is depicted on scheme 91. After deprotonation at the benzylic position, rearrangement produced **182**, suitable for an electrocyclisation leading to chromene **181**.

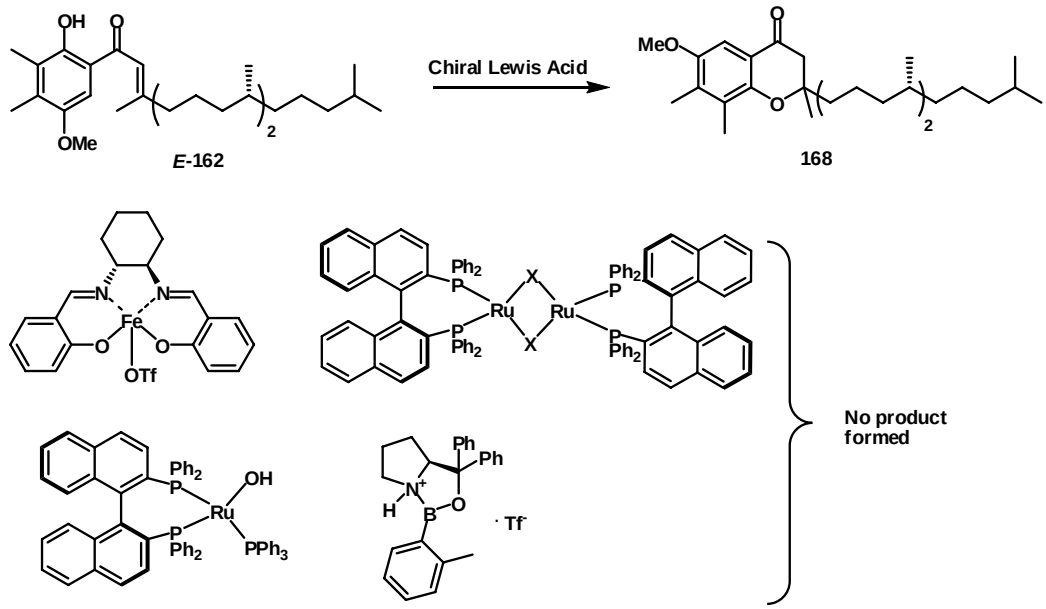


Scheme 91: Proposed mechanism of the electrocyclisation of **179**.

The use of chiral bases was shortly envisaged, but since the electrocyclisation went through intermediate **182**, any asymmetric deprotonation of **179** would not be useful. Finally, this route was not investigated and other chiral Lewis acids were screened

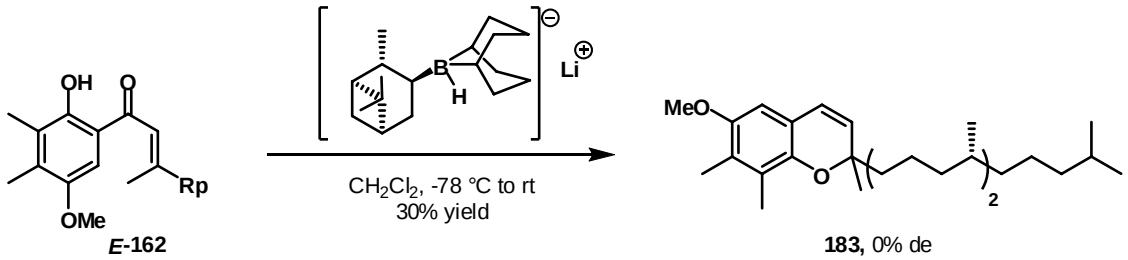
3.3.3.5. Miscellaneous chiral Lewis acids.

Some other usual chiral Lewis acids were tested on the cyclisation of ***E*-162**, and the results are presented on scheme 92. Corey catalyst[123] was applied but no reactivity was observed, as well as with a [Fe^{III}(OTf)SALEN] complex. Various rhodium complexes were synthesized, but none of them were efficient.



Scheme 92: Cyclisation of ***E*-162** using Fe^{III}, Rh^{I} and Corey's catalysts. [X=OH, Cl]

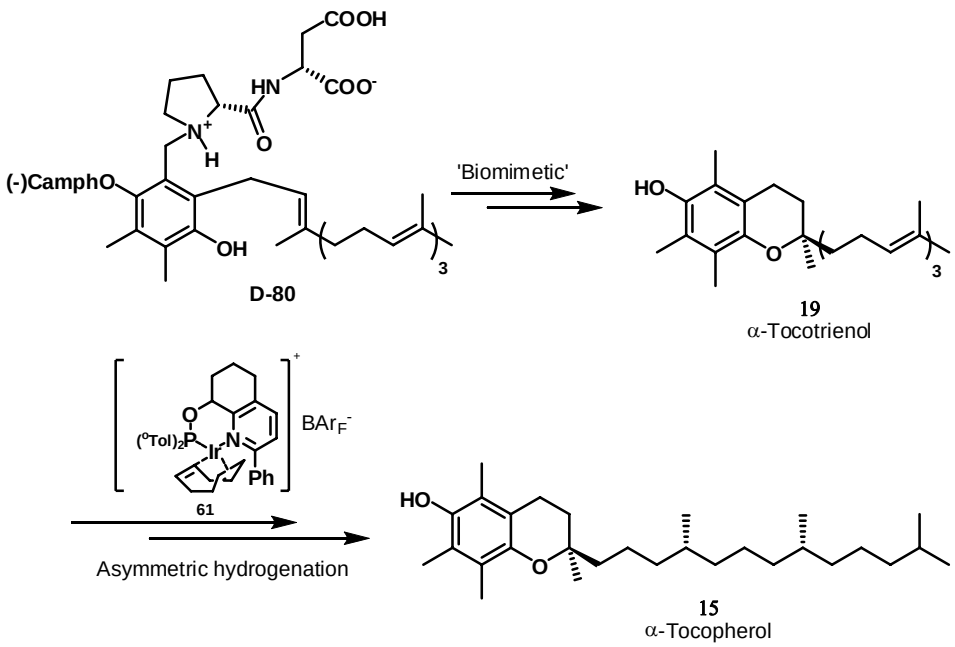
Finally, (R)-Alpine-hydride® promoted the cyclisation of ***E*-162** to chromene **183** in 30% yield, but no diastereoisomeric excess was found (*scheme 93*).



Scheme 93: Cyclisation of ***E*-162** using (R)-Alpine-hydride®.

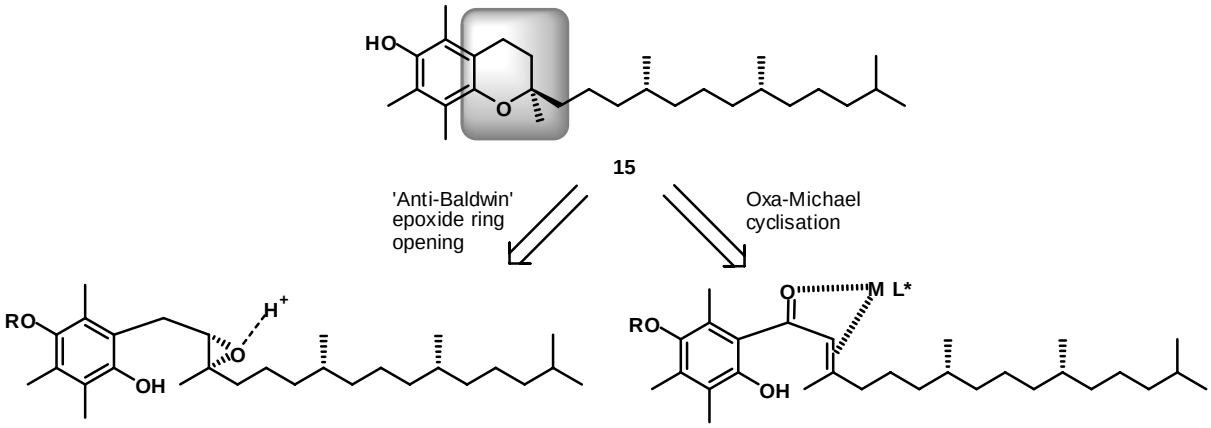
4. Summary and Conclusions

Based on the mechanism of tocopherol cyclase, isolated from *Cyanobacteria*, a biomimetic synthesis of α-tocopherol has already been developed in our group, using a covalently bonded peptide that mimicked the active site of the enzyme. Application of this strategy was presented in the first part, and allowed the synthesis of another important member of vitamin E family, α-tocotrienol **19**. Indeed, the chromanol ring formation was induced by a Brönsted acid assisted – Brönsted acid supported reaction, leading to enantio-enriched α-tocotrienols (*scheme 94*). The asymmetric hydrogenation of **19**, as described by Pfaltz et al. with Iridium catalyst **61**, furnished a common route for the synthesis of α-tocotrienols and α-tocopherols.



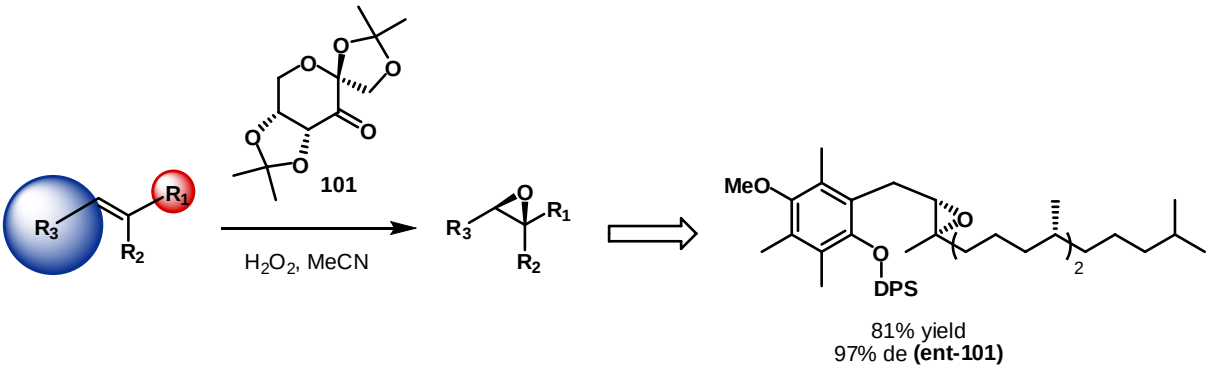
Scheme 94: Biomimetic synthesis of α-tocotrienols **19** and its asymmetric hydrogenation to α-tocopherols **15**.

In a second project, novel diastereoselective syntheses of α-tocopherol were investigated and a retrosynthetic analysis outlined two possible strategies (*scheme 95*), concerning the chromanol ring formation.



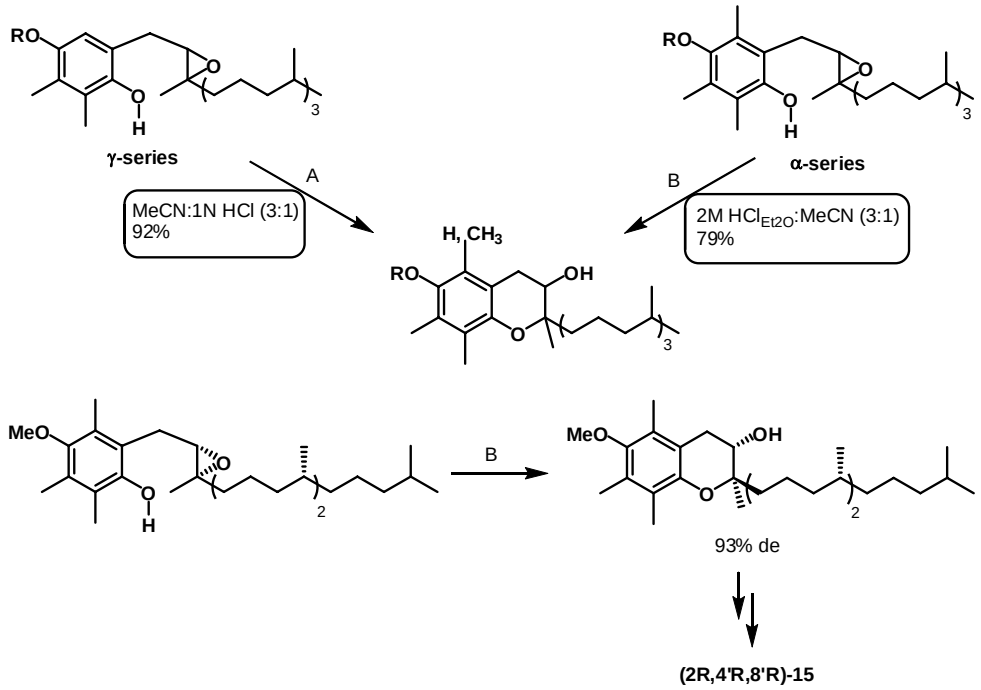
Scheme 95: Retrosynthetic approaches for the chromanol ring formation in α-tocopherol.

A first approach was designed based on an epoxide ring opening, in an 'anti-Baldwin' fashion. Taking advantage of the substrate scope of Shi catalyst **ent-101**, preparation of optically active epoxide **108f** was achieved in high yield and high diastereoselectivity (*scheme 96*).



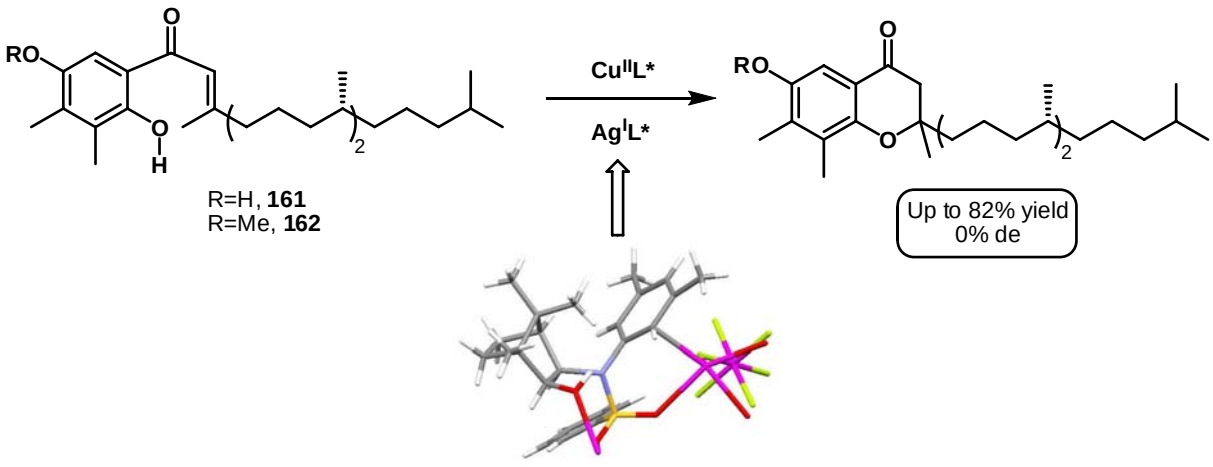
Scheme 96: Asymmetric Shi epoxidation – Synthesis of optically active epoxide **108f**.

The epoxide ring opening conditions were then screened and interestingly a strong influence of the aromatic substituents could be outlined, since completely different media were necessary for γ-tocopherol and α-tocopherol series to favour the pyran ring (*scheme 97*). Application of best conditions on chiral epoxide produced the chromanol ring in good yield, under inversion of configuration. (2*R*,4'*R*,8'*R*)-α-Tocopherol was finally reached in 93% de after removal of the hydroxyl group.



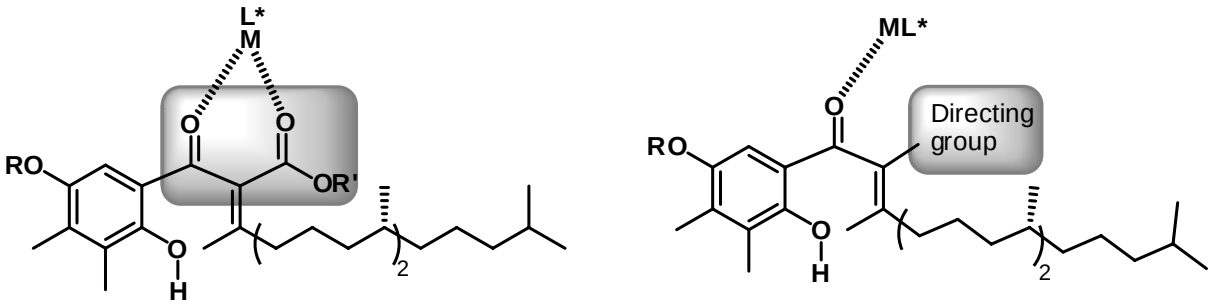
Scheme 97: "Anti-Baldwin" epoxide ring opening – Optimisation and application to the synthesis of α-tocopherol **15**.

The second approach was based on an oxa-Michael cyclisation, using chiral Lewis acids that could be bound to the carbonyl group or the olefin, and would induce an asymmetric cyclisation (*scheme 98*). However, though carbon-carbon bond forming Michael reactions have been extensively studied, its oxa-analogue obviously missed sound precedents. Nevertheless, known chiral copper complexes as well as novel silver Lewis acids were applied on **161** and **162**, but despite good reactivity up to 90%, none of them were diastereoselective.



Scheme 98: Lewis acid mediated oxa-Michael cyclisation of **161** and **162**.

This drawback could be explained by the lack of supplementary binding sites for the chiral metal complex that would allow a preferential conformation of the substrate, leading to a diastereoselective cyclisation. To this end, a 1,3-dicarbonyl may be necessary, or the use of a directing group, as depicted on scheme 99, and research in these directions could be investigated.



Scheme 99: Possible strategies to achieve a diastereoselective oxa-Michael cyclisation to α-tocopherol.

EXPERIMENTAL PART

5. Experimental part

5.1. General remarks

5.1.1. Solvents and reagents

Reagents were used as received from *Fluka AG*, *Acros AG*, *Merck AG* and *Aldrich* unless otherwise stated. Chemicals of the quality *purum*, *purum p. a*. or >98% were used without further purification.

Solvents for chromatography and extractions were distilled prior to use. Dry solvents used for reactions corresponded to the quality *puriss p. a.*, *abs.*, *over Molecular Sieves* from *Fluka AG*. HPLC-grade solvents were purchased and used for analytical LC and GC. For an inert atmosphere *Argon 6.0* from *PanGas AG* was used.

5.1.2. Materials and instruments

Solvents were removed with a *Büchi* rotary evaporator. For weighing compounds and reagents *Mettler* balances P360, AE163 and AX205 were used. A high-vacuum pump TRIVAC D5E from *Leybold Vakuum GmbH* was used for drying compounds and reagents. For all non-aqueous reactions, glassware were flame-dried under vacuum and the atmosphere was exchanged by three cycles of evacuating and flushing with argon. Melting points were determined on an apparatus by the *Werkstatt der Organischen Chemie der Universität Basel* and are uncorrected. Description: **m.p.** given in °C.

5.1.3. Chromatographic methods

Analytical thin layer chromatography (TLC) was performed on precoated glass plates 5x10 cm, silica gel 60 F_{254} from *Merck AG* and compounds were detected at 254 nm (UV), at 366 nm (fluorescence) or were revealed by a Cer-DIP solution. Preparative TLC were conducted on precoated glass plates 20x20 cm, silica gel 60 F_{254} from *Merck AG*. Column chromatography was performed on silica gel 60 from *Merck AG* (0.040-0.063 mm, 230-400 mesh).

Analytical HPLC were performed using a Protonsil 120-5-CN *Bischoff*, a Chiracel OD-H or a Chiralpak AD-H column, either on an *Agilent* 1100 series HPLC system with solvent degasser G1322A, BinPump G1312A, Autosampler G1313A, Thermostatic column housing G1316A, Diode array UV detector G1315B; or on a *Shimadzu* CBM-20A HPLC system with solvent degasser DGU-20A_3, BinPump LC-20AB, Autosampler SIL-20A, Fluorescence detector RF-10A_{XL}, Diode array UV detector SPD-M20A and a Fraction collector FRC-10A. Description: **HPLC** (conditions): retention times given in minutes.

Gas chromatography (GC-MS) was performed on a *Hewlett Packard* 5890 series II using a 25m dimethyl silane column coupled with a *Hewlett Packard* 5971 series mass selective detector. Description: **GC** (conditions).

5.1.4. Spectroscopic methods

Ultra violet-visible absorption spectra (UV-Vis) were recorded on an *Agilent* 8453 Diode Array spectrophotometer using optical 110 QS *Hellma* cuvettes (10 mm light path). Description: **UV** (solvent): wavelength of maxima (λmax) in nm.

Infrared spectra (IR) were measured on a FTIR-8400S spectrometer from *Shimadzu*. Description: **IR** (medium): wavenumbers of transmission maxima in cm^{-1}.

Electron impact mass spectra (EI) and fast atom bombardment mass spectra (FAB) were measured by Dr. H. Nadig on a Finnigan MAT 95Q spectrometer and Finnigan MAT 8400 spectrometer. Electron spray ionization mass spectra (ESI) were recorded on a Bruker Esquire 3000^{plus}. Description: **MS** (medium): mass peaks in m/z. (Fragmentation peaks were not considered)

^{1}H-Nuclear magnetic resonance spectroscopy (^{1}H NMR) was performed using either a *Bruker* av250 (250 MHz), *Bruker* DPX-NMR (400 MHz), *Bruker* DRX-500 (500 MHz) or *Bruker* DRX-600 (600 MHz) spectrometer. Solvents for NMR were obtained from *Cambridge Isotope Laboratories*. $CDCl_3$ was filtered through basic alumina prior to use. All spectra were recorded at room temperature. If necessary for the interpretation, correlated spectra like COSY and NOESY were also recorded. Description: **^{1}H NMR** (frequency,

solvent): δ_H in ppm relative to TMS or residual solvent peaks (peak multiplicity: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad; coupling constants *J* in Hertz).

^{13}C-Nuclear magnetic resonance spectroscopy (^{13}C NMR) was ^{1}H-decoupled and recorded on a Bruker DPX-NMR (100 MHz) or Bruker DRX-500 (125 MHz) spectrometer. For the assignment of carbons, DEPT, HMQC and HMBC experiments were carried out if necessary. Description: **^{13}C NMR** (frequency, solvent): δ_C in ppm relative to residual solvent peaks.

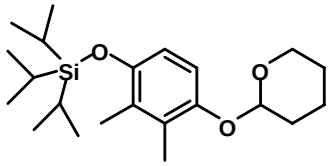
Single crystal *X*-ray structure was determined by Dr. Markus Neuburger and Dr. Silvia Schaffner in the chemical crystallography laboratory of the department. Data collection was carried out on a *Nonius KappaCCD* diffractometer using the COLLECT software suite. The usual corrections were applied. No absorption correction was determined. The structure was solved by direct method using the program DIRDIF-99. Anisotopic least-squares refinement was carried out on all non-hydrogen atoms using the program CRYSTALS. Hydrogen atoms were in calculated positions.

5.1.5. Miscellaneous

The elemental analysis (EA) was carried out by Mr. H. Kirsch at the institute on a Perkin-Elmer 240 Analyzer. Description: **anal. calcd.** for 'chemical formula': calculated abundance of C, H, O in %; found abundance of C, H, O in %.

Optical rotations were measured on a Perkin-Elmer polarimeter 341 at λ = 589nm with 100 mm cells, at 20 °C. Description: $\mathbf{[\alpha]_D^{20}}$ = given in °.

5.2. Syntheses



66

THPO-/TIPSO-hydroquinone 66.[76] To a solution of 2,3-dimethylhydroquinone **68** (23.0 g, 166.5 mmol) in THF (150 mL) at -5 °C, was added 2,3-dihydropyrane (16.7 mL, 183.1 mmol), followed by pTsOH (285.2 mg, 1.50 mmol) and the mixture was stirred at room temperature for 5 h. The mixture was quenched with saturated $NaHCO_3$ and extracted with TBME (3 ×). Combined organic phases were washed with H_2O, brine (2 ×), dried over Na_2SO_4, evaporated to dryness and the residue purified by column chromatography on SiO_2 (hexane – EtOAc, 5:1) to afford mono-OTHP hydroquinone (18.6 g, 50%) as a slight orange solid. Spectral data were identical to those already reported – Selected data.

m.p. = 92 - 94 °C;

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.60-1.70 (m, 3H, C$\underline{H}_2$-THP),1.85-1.95 (m, 2H, C$\underline{H}_2$-THP), 1.95-2.05 (m, 1H, C$\underline{H}_2$-THP), 2.17 (s, 3H, $C_{2/3}$-C$\underline{H}_3$), 2.20 (s, 3H, $C_{2/3}$-C$\underline{H}_3$), 3.62-3.65 (m, 1H, C$\underline{H}_2$-THP), 3.90-3.98 (m, 1H, C$\underline{H}_2$-THP), 4.42 (s, 1H, OH), 5.24 (t, 1H, J = 3.3 Hz, C$\underline{H}$-THP), 6.56 (d, 1H, J = 8.7 Hz, H_{Ar}), 6.84 (d, 1H, J = 8.7 Hz, H_{Ar}) ppm.

To a solution of mono-OTHP hydroquinone (2.63 g, 11.8 mmol) in THF (150 mL) at 0 °C, was added NaH (60% on mineral oil, 517.0 mg, 13.0 mmol), and the mixture stirred for 10 min. Triisopropylsilylchloride (3.0 mL, 14.2 mmol) was added dropwise at 0 °C, and the mixture further stirred at room temperature for 3 h. The mixture was quenched with saturated $NaHCO_3$ and extracted with TBME (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue purified by column chromatography on SiO_2 (hexane – EtOAc, 97:3) to afford **66** (3.77 g, 84%) as a white solid.

m.p. = 34 - 35 °C;

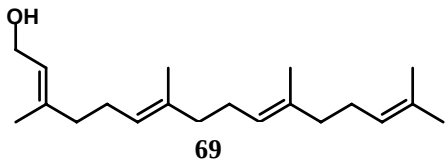
^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.10 (d, 18H, J = 6.5 Hz, C$\underline{H}_3$-TIPS), 1.21-1.33 (m, 3H, C$\underline{H}$-TIPS), 1.60-1.70 (m, 3H, C$\underline{H}_2$-THP), 1.84-1.95 (m, 2H, C$\underline{H}_2$-THP), 1.95-2.05 (m, 1H, C$\underline{H}_2$-THP), 2.17 (s, 3H, $C_{2/3}$-C$\underline{H}_3$), 2.18 (s, 3H, $C_{2/3}$-C$\underline{H}_3$), 3.57-3.62 (m, 1H, C$\underline{H}_2$-THP), 3.91-4.00 (m, 1H, C$\underline{H}_2$-THP), 5.23 (t, 1H, J = 3.3 Hz, C$\underline{H}$-THP), 6.57 (d, 1H, J = 8.8 Hz, H_{Ar}), 6.79 (d, 1H, J = 8.8 Hz, H_{Ar}) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.0, 13.4, 18.5, 19.6, 25.8, 31.2, 62.6, 97.9, 115.0, 115.4, 127.8, 128.3, 149.1, 149.5 ppm;

IR (KBr) υ_{max} 2942, 2866, 1540, 1477, 1384, 1247, 1091, 1038, 923, 883 cm^{-1};

UV (CH_2Cl_2) λ_{max} : 238 nm, 286 nm;

anal. calcd. for $C_{22}H_{38}O_3Si$: C 69.79, H 10.12; found: C 70.00, H 10.12.



69

(all-*E*)-Geranyl geraniol 69. To a suspension of NaH (60% on mineral oil, 430mg, 10.8 mmol) in THF (25 mL), was slowly added triethylphosphonoacetate (2 mL, 10.0 mmol), and the mixture was stirred at room temperature for 1 h. Farnesylacetone (1.86g, 7.1 mmol) in THF (3 mL) was then added, and the mixture further stirred for 16 h. The reaction was quenched with cold saturated brine, extracted with EtOAc, and the organic phase washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography on SiO_2 (hexane – Et_2O, 20:1) to afford (all-*E*)-geranyl geranoyl ethylester **71** (1.48 g, 66%) as a colourless oil. Spectral data were identical to those already reported[124] – Selected data.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.27 (t, 3H, J = 7.1 Hz, Et), 1.60 (s, 9H, C$\underline{H}_3$C=C), 1.68 (s, 3H, C$\underline{H}_3$C=C), 1.90-2.20 (m, 15H, C$\underline{H}_3$C=C, C$\underline{H}_2$), 4.14 (q, 2H, J = 7.2 Hz, Et), 5.09 (m, 3H, C$\underline{H}$=C), 5.66 (s, 3H, C=C$\underline{H}$COOEt) ppm;

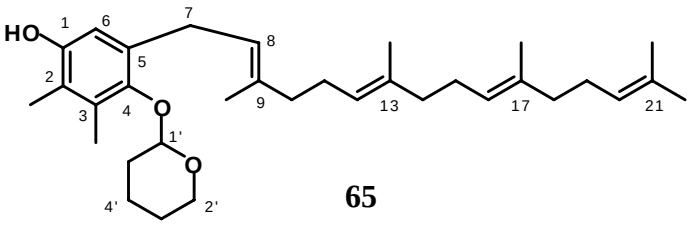
^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.7, 16.4, 18.1, 19.2, 26.1, 26.4, 27.0, 27.2, 40.1, 41.4, 59.8, 116.0, 123.3, 124.5, 124.8, 131.7, 135.4, 136.6, 160.2, 167.3 ppm;

GC (Optima-5 Ph-Me Si column, 25m x 0.2 mm, 0.35 μm; split injector (1:20), injector temp. 250 °C; FID detector, detector temp. 270 °C, carrier gas: H_2, 20 psi; 100°C to 270°C (6°C/min), 39 min): $t_{(Z,E,E,E)}$= 26.6 min, $t_{(E,E,E,E)}$ = 27.4 min, *E*:*Z* ratio: >99:1.

To a solution of (all-*E*)-geranyl geranoyl ethyl ester **71** (1.67 g, 5.25 mmol) in Et_2O (20 mL), was added DIBAL-H (0.7-1.3 M in hexane, 10.0 mL) dropwise at 0 °C, and the reaction further stirred at room temperature for 2 h. The mixture was quenched by addition of H_2O at 0 °C, extracted with EtOAc, and the organic phase washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. The residue was passed through a pad of SiO_2 (EtOAc) to afford (all-

E)-geranyl geraniol **69** (1.1 g, 72%) as a slightly yellow oil. Spectral data were identical to those of an original sample – Selected data.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.60 (s, 9H, C<u>H</u>$_3$C=C), 1.68 (s, 6H, C<u>H</u>$_3$C=C), 1.90-2.15 (m, 12H, C<u>H</u>$_2$), 4.15 (t, 2H, J = 6.1 Hz, C<u>H</u>$_2$OH), 5.10 (m, 3H, C<u>H</u>=C), 5.42 (m, 1H, C=C<u>H</u>CH$_2$OH) ppm.



65

Monoprotected hydroquinone 65. To a solution of *n*BuLi (1.6 M in hexane, 7.4 mL, 11.8 mmol) in Et_2O (40 mL) at 0 °C, was added TMEDA (1.7 mL, 11.4 mmol) together with **66** (4.3 g, 11.4 mmol) in Et_2O (10 mL). The mixture was stirred for 3 h at 0 °C, and cooled down to -20 °C. CuBr (530 mg, 3.6 mmol) was added, followed by geranyl geranylbromid **67**[76] (3.2 g, 9.11 mmol) in Et_2O (10 mL), and the mixture was stirred for 6 h at room temperature. The reaction was quenched with saturated $NaHCO_3$ and extracted with TBME (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue purified by column chromatography on SiO_2 (hexane – CH_2Cl_2, 3:1) to afford a mixture of **72** and **66** (5.33g).

To a solution of **72:66** (5.33g) in THF (70 mL), was added TBAF (1 M in THF, 10.5 mL, 10.5 mmol) and the mixture was stirred at room temperature for 1 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with TBME (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue purified by column chromatography on SiO_2 (CH_2Cl_2) to afford **65** (3.20 g, 98%) as a slight yellow oil.

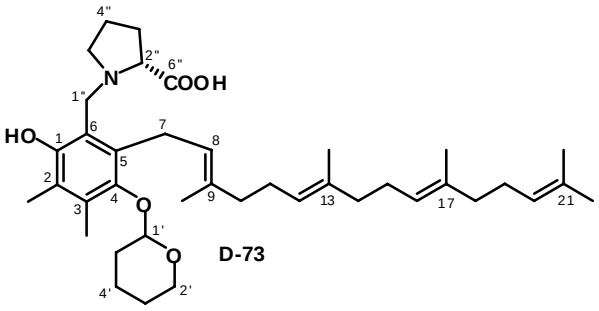
^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.48-1.63 (m, 12H, $H_{3'/4'}$, $C_{9/13/17}$-C<u>H</u>$_3$), 1.66-1.70 (dd, 6H, *J* = 5.7 and 1.0 Hz, C_{21}-C<u>H</u>$_3$), 1.77-1.87 (m, 1H, $H_{5'}$), 1.90-2.02 (m, 6H, $H_{14/18/3'/4'}$), 2.02-2.16 (m, 6H, $H_{10/11/15/19}$), 2.12 (s, 3H, C_2-C<u>H</u>$_3$), 2.21 (s, 3H, C_3-C<u>H</u>$_3$), 3.36 (d, 2H, *J* = 7.3 Hz, H_7), 3.44 (m, 1H, $H_{2'}$), 4.04 (m, 1H, $H_{2'}$), 4.49 (s, 1H, OH), 4.67 (m, 1H, $H_{1'}$), 5.05-5.17 (m, 3H, $H_{12/16/20}$), 5.29 (t, 1H, *J* = 6.9 Hz, H_8), 6.44 (s, 1H, H_6) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 11.9, 12.2, 14.0, 15.9, 16.0, 16.1, 17.6, 21.1, 25.1, 25.6, 26.5, 26.7, 28.4, 31.2, 39.6, 39.7, 65.1, 103.7, 112.9, 120.8, 122.8, 124.1, 124.3, 131.2, 132.7, 134.9, 136.1, 147.8, 149.6 ppm;

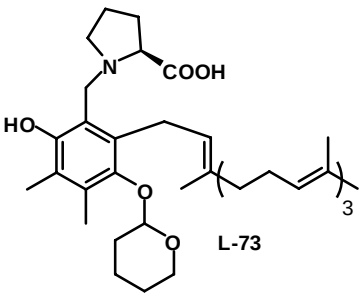
MS (ESI - MeOH): 571.4$^+$ $(M + Na)^+$;

IR (neat) υ_{max} 3401, 2922, 2852, 1442, 1379, 1200, 1074, 1034, 954, 910, 833, 651 cm^{-1};

UV (MeOH) λ_{max} : 209 nm, 285 nm.



D-73



L-73

Mannich reaction – General procedure. A solution of D-proline or L-proline (39.9 mmol) in formaldehyde (35% aq, 41.9 mmol) was stirred at 40 °C, under a flow of N_2, for 15 min. The sticky white solid was solved in MeOH (15 mL), and **65** (1.94 mmol) was added in MeOH (7 mL). The mixture was stirred at 40 °C for 17 h, and allowed to cool down to room temperature. The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue purified by column chromatography on SiO_2 (CH_2Cl_2 - MeOH, 9:1).

D-ProOH derivative D-73. 989 mg (82% yield) as a pinky oil.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.45-1.63 (m, 12H, $H_{3'/4'}$, $C_{9/13/17/21}$-C$\underline{H}_3$), 1.67 (s, 3H, $C_{9/13/17/21}$-C$\underline{H}_3$), 1.71-1.84 (m, 1H, $H_{5'}$), 1.75 (s, 3H, $C_{9/13/17/21}$-C$\underline{H}_3$), 1.84-2.00 (m, 8H, $H_{14/18/3'/4'/4''}$), 2.00-2.10 (m, 6H, $H_{10/11/15/19}$), 2.11-2.31 (m, 7H, $C_{2/3}$-C$\underline{H}_3$, $H_{3''}$), 2.39 (m, 1H, $H_{3''}$), 2.77 (m, 1H, $H_{5''}$), 3.25-3.52 (m, 3.5H, $H_{7/2'/5''}$), 3.57 (m, 0.5H, H_7), 3.76 (m, 1H, $H_{6''}$), 3.83-4.03 (m, 2H, $H_{2'/1''}$), 4.39 (m, 1H, $H_{1''}$), 4.59 (m, 1H, $H_{1'}$), 5.00-5.16 (m, 4H, $H_{8/12/16/20}$) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ= 12.9, 14.4, 14.5, 15.9, 16.0, 16.5, 17.6, 21.2, 23.5, 25.0, 25.6, 26.5, 26.7, 31.2, 39.6, 65.2, 65.4, 103.9, 123.7, 123.8, 124.0, 124.3, 131.2, 134.9, 135.0, 135.3, 147.4 ppm;

MS (ESI - MeOH): 622.8^{+} $(M + H)^{+}$, 644.5^{+} $(M + Na)^{+}$;

IR (neat) υ_{max} 2920, 2851, 1619, 1450, 1377, 1251, 1202, 1074, 1033, 907, 645, 587 cm^{-1};

UV (MeOH) λ_{max} : 207 nm, 290 nm;

anal. calcd. for $C_{39}H_{59}NO_5$: C 75.32, H 9.56, N 2.25; found: C 74.84, H 9.29, N 2.18.

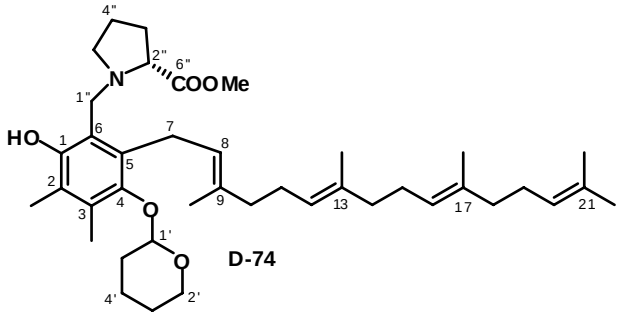
L-ProOH derivative L-73. 1.58 g (86% yield) as a pinky oil.

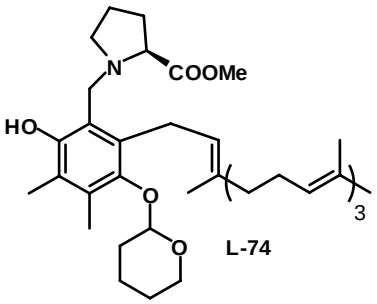
^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.45-1.62m, 12H, ($H_{3'/4'}$, $C_{9/13/17/21}$-C<u>H</u>$_3$), 1.67 (s, 3H, $C_{9/13/17/21}$-C<u>H</u>$_3$), 1.71-1.84 (m, 1H, $H_{5'}$), 1.75 (s, 3H, $C_{9/13/17/21}$-C<u>H</u>$_3$), 1.84-2.01 (m, 8H, $H_{14/18/3'/4'/4"}$), 2.02-2.10 (m, 6H, $H_{10/11/15/19}$), 2.12-2.30 (m, 7H, $C_{2/3}$-C<u>H</u>$_3$, $H_{3"}$), 2.38 (m, 1H, $H_{3"}$), 2.76 (m, 1H, $H_{5"}$), 3.21-3.51 (m, 3.5H, $H_{7/2'/5"}$), 3.56 (m, 0.5H, H_7), 3.75 (m, 1H, $H_{5"}$), 3.83-4.04 (m, 2H, $H_{2'/1"}$), 4.39 (m, 1H, $H_{1"}$), 4.59 (m, 1H, $H_{1'}$), 5.01-5.14 (m, 4H, $H_{8/12/16/20}$) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 12.9, 14.4, 14.5, 15.9, 16.0, 16.5, 17.6, 21.2, 23.5, 25.0, 25.6, 26.5, 26.7, 31.2, 39.6, 39.7, 65.2, 65.4, 103.9, 123.7, 123.8, 124.0, 124.3, 131.2, 134.9, 135.0, 135.3, 147.4 ppm;

MS (ESI - MeOH): 622.8^{+} $(M + H)^{+}$, 644.5^{+} $(M + Na)^{+}$;

anal. calcd. for $C_{39}H_{59}NO_5$: C 75.32, H 9.56, N 2.25; found: C 74.55, H 9.24, N 2.24.





<u>Methylester protection – General procedure.</u> To a solution of **73** (1.25 mmol) in MeOH (50 mL) was added trimethylsilyl diazomethane (2 M in hexanes, 16.29 mmol) dropwise, at room temperature. The mixture was stirred for 2 h, quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue purified by column chromatography on SiO_2 (CH_2Cl_2 - MeOH, 99.5:0.5).

D-ProOMe derivative D-74. 677.4 mg (85% yield) as a slight yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 1.45-1.64 (m, 12H, $H_{3'/4'}$, $C_{9/13/17/21}$-C<u>H</u>$_3$), 1.67 (s, 3H, $C_{9/13/17/21}$-C<u>H</u>$_3$), 1.74 (s, 3H, $C_{9/13/17/21}$-C<u>H</u>$_3$), 1.76-1.89 (m, 2H, $H_{5'}$), 1.89-2.00 (m, 8H, $H_{14/18/4'/3''/4''}$), 2.01-2.10 (m, 6H, $H_{10/11/15/19}$), 2.16 (s, 3H, C_2-C<u>H</u>$_3$), 2.17-2.26 (m, 4H, C_3-C<u>H</u>$_3$, $H_{3''}$), 2.34 (m, 1H, $H_{4''}$), 3.04 (m, 1H, $H_{4''}$), 3.24-3.34 (m, 2H, H_7), 3.36-3.55 (m, 2H, $H_{2'/2''}$), 3.61 (dd, 1H, *J* = 13.4 and 8.5 Hz, $H_{1''}$), 3.74 (s, 3H, C<u>H</u>$_3$O), 3.93 (dd, 1H, *J* = 13.4 and 10.83 Hz, $H_{1''}$), 4.01 (m, 1H, $H_{2'}$), 4.61(m, 1H, $H_{1'}$), 4.97-5.15 (m, 4H, $H_{8/12/16/20}$), 10.68 (s, 1H, OH) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 11.9, 14.1, 15.9, 16.5, 17.6, 21.3, 23.2, 25.1, 25.6, 25.7, 25.9, 26.6, 26.7, 29.5, 31.2, 39.6, 52.1, 52.5, 52.9, 53.2, 65.1, 65.2, 65.5, 65.7, 104.0, 104.1, 117.8, 117.9, 122.2, 124.0, 124.3, 129.9, 131.2, 134.3, 134.8, 134.9, 135.0, 146.4, 152.4, 173.8 ppm;

MS (ESI - MeOH): 636.6$^+$ $(M + H)^+$, 658.4$^+$ $(M + Na)^+$;

IR (neat) υ_{max} 2919, 2850, 1741, 1438, 1377, 1250, 1203, 1076, 1033 cm^{-1};

UV (MeOH) λ_{max} : 224 nm, 289 nm;

anal. calcd. for $C_{40}H_{61}NO_5$: C 75.55, H 9.67, N 2.20; found: C 75.38, H 9.42, N 2.03.

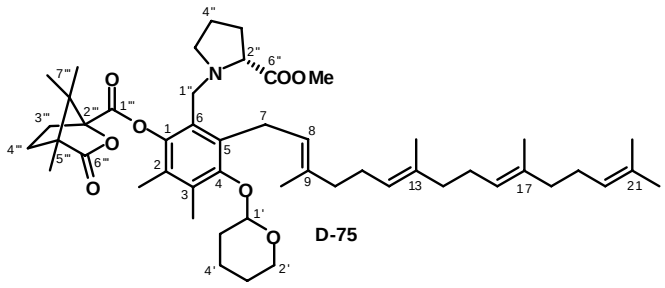
L-ProOMe derivative L-74. 1.16 g (90% yield) as a slight yellow oil.

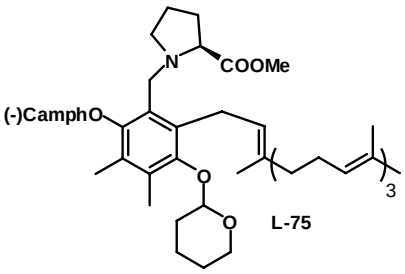
^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 1.45-1.63 (m, 12H, $H_{3'/4'}$, $C_{9/13/17/21}$-C<u>H</u>$_3$), 1.67 (s, 3H, $C_{9/13/17/21}$-C<u>H</u>$_3$), 1.74 (s, 3H, $C_{9/13/17/21}$-C<u>H</u>$_3$), 1.76-1.89 (m, 2H, $H_{5'}$), 1.89-2.00 (m, 8H, $H_{14/18/4'/3''/4''}$), 2.01-2.10 (m, 6H, $H_{10/11/15/19}$), 2.16 (s, 3H, C_2-C<u>H</u>$_3$), 2.17-2.26 (m, 4H, C_3-C<u>H</u>$_3$, $H_{3''}$), 2.34 (m, 1H, $H_{5''}$), 3.04 (m, 1H, $H_{5''}$), 3.24-3.34 (m, 2H, H_7), 3.36-3.55 (m, 2H, $H_{2'/2''}$), 3.61 (dd, 1H, *J* = 13.4 and 8.5 Hz, $H_{1''}$), 3.74 (s, 3H, C<u>H</u>$_3$O), 3.93 (dd, 1H, *J* = 13.4 and 10.83 Hz, $H_{1''}$), 4.01 (m, 1H, $H_{2'}$), 4.61(m, 1H, $H_{1'}$), 4.97-5.15 (m, 4H, $H_{8/12/16/20}$), 10.68 (s, 1H, OH) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ= 11.9, 14.1, 15.9, 16.5, 17.6, 21.3, 23.3, 25.1, 25.6, 26.6, 26.7, 29.5, 31.2, 34.9, 39.6, 52.0, 52.5, 63.6, 65.1, 65.2, 65.5, 65.7, 104.1, 117.9, 122.2, 124.0, 124.2, 124.3, 129.9, 130.0, 130.1, 131.2, 134.3, 134.9, 135.0, 146.4, 152.4, 173.8 ppm;

MS (ESI - MeOH): 636.6$^+$ $(M + H)^+$, 658.4$^+$ $(M + Na)^+$;

anal. calcd. for $C_{40}H_{61}NO_5$: C 75.55, H 9.67, N 2.20; found: C 75.28, H 9.41, N 2.36.





(-)-Camphanoyl protection – General procedure. To a solution of **74** (1.01 mmol) in CH_2Cl_2 (40 mL) was added DMAP (3.54 mmol), followed by (-)-camphanoyl chloride (3.84 mmol), at room temperature. The mixture was stirred for 3 h, quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue purified by column chromatography on SiO_2 (CH_2Cl_2 - MeOH, 99:1).

(-)-CamphanoylO-/THPO- D-ProOMe derivative D-75. 769.0 mg (93% yield) as a slight yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.10-1.22 (m, 9H, $C_{5'''/7'''}$-C$\underline{H}_3$), 1.46-1.63 (m, 12H, $H_{3'/4'}$, $C_{9/13/17/21}$-C$\underline{H}_3$), 1.67 (s, 3H, $C_{9/13/17/21}$-C$\underline{H}_3$), 1.69-1.87 (m, 7H, $C_{9/13/17/21}$-C$\underline{H}_3$, $H_{5'/3''/4'''}$), 1.88-2.00 (m, 9H, $H_{11/14/15/18/19/4'/5'/4''}$), 2.00-2.12 (m, 11H, C_2-C$\underline{H}_3$, $H_{10/11/15/19/3''/4'''}$), 2.18-2.33 (m, 4H, C_3-C$\underline{H}_3$, $H_{3'''}$), 2.36-2.70 (m, 2H, $H_{5''/3'''}$), 2.72-3.00 (m, 1H, $H_{5''}$), 3.15 (m, 0.5H, $H_{2''}$), 3.24-3.54 (m, 4.5H, $H_{7/2'/1''/2''/7''}$), 3.54-3.95 (m, 4H, $H_{7/1''/7''}$), 3.96-4.06 (m, 1H, $H_{2'}$), 4.71 (d, 1H, J = 5.8 Hz, $H_{1'}$), 4.97-5.13 (m, 4H, $H_{8/12/16/20}$) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 9.63, 13.7, 14.5, 15.9, 16.5, 17.0, 17.6, 21.1, 25.0, 25.6, 26.6, 26.7, 28.9, 31.2, 31.4, 39.6, 54.8, 64.4, 65.1, 90.9, 103.9, 124.1, 124.3, 126.6, 131.1, 134.8 ppm;

MS (ESI - MeOH): 816.6$^+$ $(M + H)^+$, 838.5$^+$ $(M + Na)^+$;

IR (neat) υ_{max} 2921, 2852, 1795, 1748, 1448, 1377, 1261, 1232, 1166, 1063, 1033, 632, 534 cm^{-1};

UV (MeOH) λ_{max} : 208 nm, 270 nm;

anal. calcd. for $C_{50}H_{73}NO_8$: C 73.59, H 9.02, N 1.72; found: C 72.82, H 8.72, N 1.65.

(-)-CamphanoylO-/THPO- L-ProOMe derivative L-75. 1.33 g (90% yield) as a slight yellow oil.

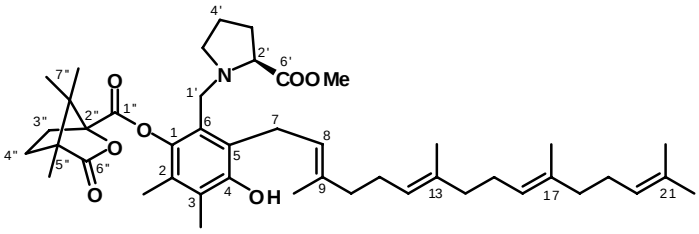
^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 1.12-1.21 (m, 9H, $C_{5'''/7'''}$-C$\underline{H}_3$), 1.46-1.63 (m, 12H, $H_{3'/4'}$, $C_{9/13/17/21}$-C$\underline{H}_3$), 1.67 (s, 3H, $C_{9/13/17/21}$-C$\underline{H}_3$), 1.71-1.88 (m, 7H, $C_{9/13/17/21}$-C$\underline{H}_3$, $H_{5'/3''/4'''}$),

1.88-2.00 (m, 9H, $H_{11/14/15/18/19/4'/5'/4"}$), 2.00-2.12 (m, 11H, C_2-C<u>H</u>$_3$, $H_{10/11/15/19/3"/4"'}$), 2.18-2.30 (m, 4H, C_3-C<u>H</u>$_3$, $H_{3"'}$), 2.36-2.66 (m, 2H, $H_{5"/3"'}$), 2.68-3.03 (m, 1H, $H_{5"}$), 3.15 (m, 0.5H, $H_{2"}$), 3.27-3.54 (m, 4.5H, $H_{7/2'/1"/2"/7"}$), 3.54-3.92 (m, 4H, $H_{7/1"/7"}$), 3.96-4.06 (m, 1H, $H_{2'}$), 4.71 (d, 1H, J = 5.8 Hz, $H_{1'}$), 4.97-5.15 (m, 4H, $H_{8/12/16/20}$) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 9.62, 13.6, 13.7, 14.5, 15.9, 16.5, 16.8, 17.6, 21.1, 21.2, 25.0, 25.4, 26.5, 26.6, 31.2, 39.6, 52.0, 54.2, 54.8, 65.1, 90.9, 103.9, 124.1, 124.3, 126.6, 131.1, 134.2, 134.8, 144.3, 152.7, 165.8, 174.5 ppm;

MS (ESI - MeOH): 816.6$^+$ $(M + H)^+$, 838.5$^+$ $(M + Na)^+$;

anal. calcd. for $C_{50}H_{73}NO_8$: C 73.59, H 9.02, N 1.72; found: C 73.02, H 8.82, N 1.64.



76

(-)-CamphanoylO-/OH, L-ProOMe derivative 76. To a solution of **L-75** (71.2 mg, 0.087 mmol) in THF (6 mL) was added 1N HCl (2.5 mL) at room temperature and the mixture was stirred for 4 h, quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue purified by column chromatography on SiO_2 (CH_2Cl_2 - MeOH, 98:2) to afford **76** (57.1 mg, 86%) as a slight yellow oil.

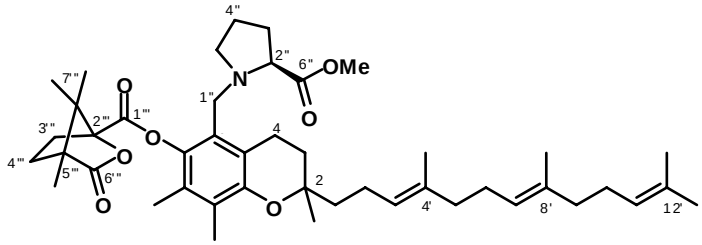
^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.11-1.21 (m, 9H, $C_{5"/7"}$-C<u>H</u>$_3$), 1.54-1.63 (m, 9H, $C_{9/13/17/21}$-C<u>H</u>$_3$), 1.67 (s, 3H, $C_{9/13/17/21}$-C<u>H</u>$_3$), 1.73-1.89 (m, 7H, $C_{9/13/17/21}$-C<u>H</u>$_3$, $H_{3'/4'/4"}$), 1.91-2.01 (m, 6H, $H_{14/18/4'}$), 2.01-2.13 (m, 13H, C_2-C<u>H</u>$_3$, $H_{3'/4''/10/11/15/19}$), 2.15 (s, 3H, C_3-C<u>H</u>$_3$), 2.23 (m, 0.5H, $H_{3"}$), 2.39 (m, 1H, $H_{5'}$), 2.57 (m, 1H, $H_{3"}$), 2.75 (m, 0.5H, $H_{5'}$), 2.90 (m, 0.5H, $H_{5'}$), 3.12 (m, 0.5H, $H_{1'}$), 3.26 (m, 0.5H, $H_{2'}$), 3.37 (m, 0.5H, $H_{2'}$),3.48-3.62 (m, 4H, COO<u>Me</u>, $H_{1'/7}$), 3.62-3.75 (m, 2H, COO<u>Me</u>, $H_{1'}$), 3.88 (m, 0.5H, $H_{1'}$), 5.00-5.10 (m, 3H, $H_{12/16/20}$), 5.15 (m, 1H, H_8), 5.38 (br, 1H, OH) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 10.1, 12.7, 16.4, 16.5, 16.7, 17.3, 18.1, 26.1, 26.7, 27.0, 27.2, 28.8, 40.0, 40.1, 55.3, 122.6, 123.9, 124.6, 124.8, 125.4, 131.6, 135.3, 136.1 ppm;

MS (ESI - MeOH): 732.5$^+$ $(M + H)^+$, 754.3$^+$ $(M + Na)^+$;

IR (neat) υ_{max} 3485, 1794, 1747, 1732, 1446, 1380, 1091, 1084 cm^{-1};

UV (MeOH) λ_{max} : 208 nm, 284nm.



77

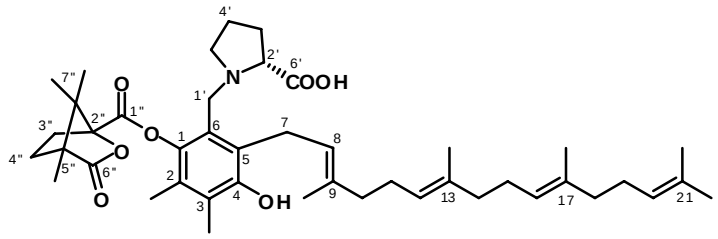
Yamamoto's cyclisation - Chromanol 77. To a solution of **76** (55.0 mg, 0.075 mmol) in CH_2Cl_2:MeCN (4:1, 5 mL) was added pTsOH (28.5 mg, 0.165 mmol) at room temperature and the mixture was stirred for 2 d, quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue purified by column chromatography on SiO_2 (hexane - TBME, 98:2) to afford **77** (26.2 mg, 50%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.11-1.21 (m, 9H, $C_{5'''/7'''}$-C<u>H</u>$_3$), 1.21-1.30 (m, 3H, C_2-CH_3), 1.54-1.63 (m, 11H, $C_{3/4'/8'/12'}$-C<u>H</u>$_3$), 1.68 (s, 3H, $C_{4'/8'/12'}$-C<u>H</u>$_3$), 1.70-1.84 (m, 4H, $H_{3''/4''/4'''}$), 1.91-2.12 (m, 18H, $C_{7/8}$-CH3, $H_{2'/5'/6'/9'/10'/3''/4'''}$), 2.24 (m, 1H, $H_{3'''}$), 2.37 (m, 1H, $H_{5''}$), 2.57 (m, 1H, $H_{3'''}$), 2.70-3.00 (m, 2H, $H_{4/5''}$), 3.08 (m, 1H, $H_{1''/5''}$), 3.24 (m, 0.5H, $H_{2''}$), 3.38 (m, 0.5H, $H_{2'}$), 3.44-3.62 (m, 2H, COO<u>Me</u>, $H_{1'}$), 3.62-3.75 (m, 2H, COO<u>Me</u>, $H_{1'}$), 3.83 (m, 0.5H, $H_{1'}$), 5.00-5.14 (m, 3H, $H_{3'/7'/11'}$) ppm;

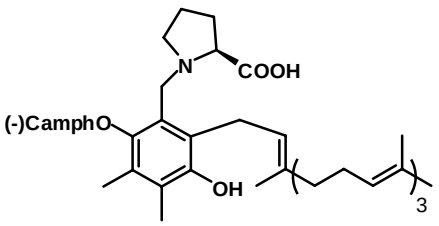
MS (ESI - MeOH): 732.6$^+$ $(M + H)^+$, 754.4$^+$ $(M + Na)^+$, 770.2$^+$ $(M + K)^+$;

IR (neat) υ_{max} 2996, 2854, 1794, 1747, 1446, 1377, 1242, 1164, 1091, 1043, 644 cm^{-1};

UV (MeOH) λ_{max} : 206 nm, 288nm.



D-63



L-63

<u>Cleavage of methylester and THP – General procedure.</u> To a solution of **75** (0.90 mmol) in EtOAc (7 mL), was added LiI (24.6 mmol). The solution was stirred at 60 °C under a flow of N_2 (addition of EtOAc, ca. 3 mL / h) for 8 h, then the reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue filtrated over a pad of SiO_2 (CH_2Cl_2 - MeOH, 99:1) to afford a crude oil used directly without further purification.

The crude material is solved in THF (60 mL) and 1 N HCl (30 mL) was added. The mixture was stirred 2 h at room temperature. The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue purified by column chromatography on SiO_2 (CH_2Cl_2 - MeOH, 99:1).

(-)-CamphanoylO-/OH D-ProOH derivative D-63. 531.4 mg (83% yield over two steps) as a slight yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.11-1.21 (m, 9H, $C_{5''/7''}$-C<u>H</u>$_3$), 1.54-1.63 (m, 9H, $C_{9/13/17/21}$-C<u>H</u>$_3$), 1.67 (s, 3H, $C_{9/13/17/21}$-C<u>H</u>$_3$), 1.73-1.89 (m, 5H, $C_{9/13/17/21}$-C<u>H</u>$_3$, $H_{4''}$), 1.91-2.01 (m, 6H, $H_{14/18/4'}$), 2.01-2.13 (m, 11H, C_2-C<u>H</u>$_3$, $H_{10/11/15/19}$), 2.17 (s, 3H, C_3-C<u>H</u>$_3$), 2.21-2.33 (m, 2H, $H_{3'/3''}$), 2.56 (m, 1H, $H_{3''}$), 2.88 (m, 1H, $H_{5'}$), 3.39 (m, 1H, $H_{5'}$), 3.42-3.61 (m, 2H, H_7), 3.62-3.75 (m, 1H, $H_{2'}$), 3.75-4.07 (m, 2H, $H_{1'}$), 5.00-5.20 (m, 4H, $H_{8/12/16/20}$) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 9.6, 12.5, 13.7, 15.9, 16.0, 16.4, 16.7, 17.1, 17.6, 24.3, 25.5, 25.6, 26.2, 26.3, 26.5, 26.7, 28.6, 29.6, 31.1, 39.5, 39.6, 54.8, 90.1, 90.7, 120.5, 123.3, 124.1, 124.3, 128.1, 131.1, 134.9, 135.7, 140.2, 151.8, 165.9, 177.5 ppm;

MS (ESI - MeOH): 718.6$^+$ $(M + H)^+$, 740.5$^+$ $(M + Na)^+$, 756.3$^+$ $(M + K)^+$;

IR (neat) υ_{max} 3537, 2916, 2853, 1794, 1755, 1635, 1448, 1381, 1311, 1240, 1161, 1090, 1034, 845, 735 cm^{-1};

UV (MeOH) λ_{max} : 205 nm, 288 nm;

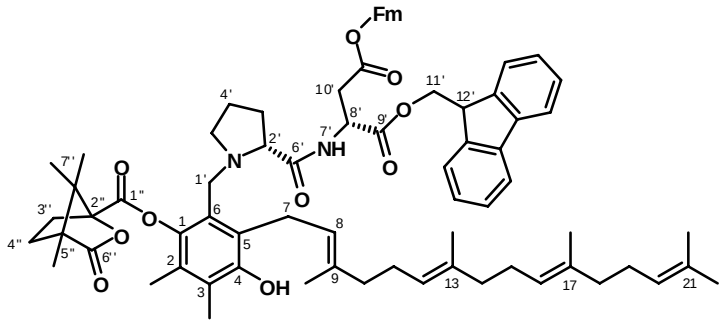
anal. calcd. for $C_{44}H_{63}NO_7$: C 73.61, H 8.84, N 1.95; found: C 72.55, H 8.86, N 1.80.

(-)-CamphanoylO-/OH L-ProOH derivative L-63. 821.6 mg (86% yield over two steps) as a slight yellow oil.

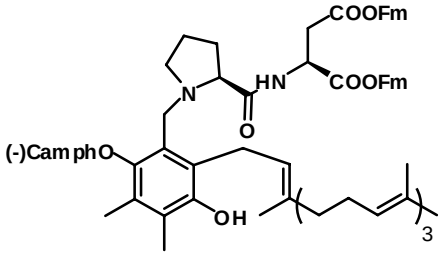
^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.12-1.19 (m, 9H, $C_{5''/7''}$-C<u>H</u>$_3$), 1.56-1.61 (m, 9H, $C_{9/13/17/21}$-C<u>H</u>$_3$), 1.67 (s, 3H, $C_{9/13/17/21}$-C<u>H</u>$_3$), 1.73-1.85 (m, 5H, $C_{9/13/17/21}$-C<u>H</u>$_3$, $H_{4''}$), 1.91-2.01 (m, 6H, $H_{14/18/4'}$), 2.01-2.15 (m, 11H, C_2-C<u>H</u>$_3$, $H_{10/11/15/19}$), 2.17 (s, 3H, C_3-C<u>H</u>$_3$), 2.21-2.33 (m, 2H, $H_{3'/3''}$), 2.54 (m, 1H, $H_{3''}$), 2.88 (m, 1H, $H_{5'}$), 3.35 (m, 1H, $H_{5'}$), 3.41-3.57 (m, 2H, H_7), 3.62 (m, 1H, $H_{2'}$), 3.73-3.95 (m, 2H, $H_{1'}$), 5.01-5.14 (m, 4H, $H_{8/12/16/20}$) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 9.6, 12.5, 13.6, 15.9, 16.0, 16.4, 16.7, 17.1, 17.6, 24.4, 25.6, 26.2, 26.3, 26.5, 26.7, 28.6, 29.6, 31.2, 39.5, 39.6, 54.0, 54.8, 90.6, 120.4, 123.3, 124.1, 124.3, 128.1, 131.2, 134.9, 135.7, 140.4, 141.1, 151.7, 162.7, 177.5 ppm;

MS (ESI - MeOH): 718.6^{+} $(M + H)^{+}$, 740.5^{+} $(M + Na)^{+}$, 756.3^{+} $(M + K)^{+}$;
anal. calcd. for $C_{44}H_{63}NO_7$: C 73.61, H 8.84, N 1.95; found: C 72.63, H 8.77, N 1.69.



D-79



L-79

Coupling of aspartic acid – General procedure. A solution of **63** (0.705 mmol) and HCTU (2.61 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 0.5 h. Then D-Asp(Fm)$_2$·TFA or L-Asp(Fm)$_2$·TFA (1.41 mmol) and DIEA (4.23 mmol) were added and the mixture stirred at room temperature for 5 h. The reaction was quenched with saturated NH_4Cl and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue purified by column chromatography on SiO_2 (CH_2Cl_2 - MeOH, 95:5).

(-)-CamphanylO-/OH D-Pro-D-Asp(Fm)$_2$ derivative D-79. 512.4 mg (62% yield) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ= 1.07-1.22 (m, 9H, $C_{5''/7''}$-C<u>H</u>$_3$), 1.49-1.62 (m, 9H, $C_{9/13/17/21}$-C<u>H</u>$_3$), 1.67 (s, 3H, $C_{9/13/17/21}$-C<u>H</u>$_3$), 1.69-1.86 (m, 5H, $C_{9/13/17/21}$-C<u>H</u>$_3$, $H_{4''}$), 1.86-2.34 (m, 23H, $C_{2/3}$-C<u>H</u>$_3$, $H_{10/11/14/15/18/19/3'/4'/3''}$), 2.35-2.70 (m, 3H, $H_{5'/3''}$), 2.70-2.98 (m, 2H, $H_{10'}$), 3.02-3.84 (m, 6H, $H_{7/1'/2'}$), 4.09-4.20 (m, 2H, $H_{12'}$), 4.25-4.55 (m, 4H, $H_{11'}$), 4.75-4.90 (m, 1H, $H_{8'}$), 4.93-5.15 (m, 4H, $H_{8/12/16/20}$), 5.21 (s, 1H, OH), 7.19-7.43 (m, 7H, H_{Ar}-Fm), 7.46-7.60 (m, 4H, H_{Ar}-Fm), 7.64-7.79 (m, 4H, H_{Ar}-Fm) ppm;
^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ= 9.6, 12.2, 13.5, 15.9, 16.0, 16.2, 16.8, 16.9, 17.6, 25.5, 25.6, 26.2, 26.5, 26.7, 28.8, 35.8, 39.5, 39.6, 46.5, 51.3, 54.7, 66.8, 70.5, 119.9, 121.1, 123.3, 124.1, 124.3, 124.9, 127.0, 127.2, 127.7, 131.1, 134.8, 135.7, 141.1, 143.4, 143.5, 151.2, 170.8 ppm;
MS (ESI - MeOH): 1190.7^{+} $(M + H)^{+}$, 1212.3^{+} $(M + Na)^{+}$, 1227.8^{+} $(M + K)^{+}$;

IR (neat) υ_{max} 3365, 2966, 2914, 1792, 1738, 1668, 1506, 1448, 1263, 1227, 1163, 1092, 1047, 739 cm^{-1};

anal. calcd. for $C_{76}H_{88}N_2O_{10}$: C 76.74, H 7.46, N 2.36; found: C 76.12, H 7.51, N 2.22.

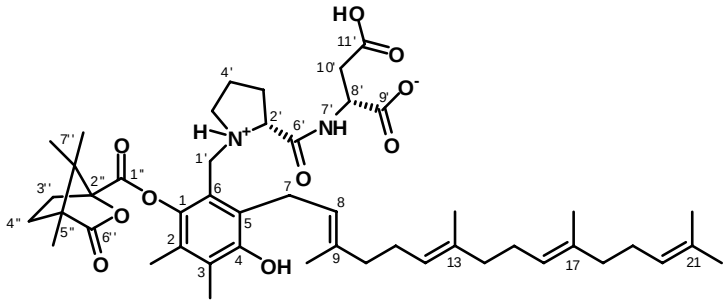
(-)-CamphanylO-/OH L-Pro-L-Asp(Fm)$_2$ derivative L-79. 368.5 mg (81% yield) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ= 1.13-1.24 (m, 9H, $C_{5''/7''}$-C<u>H</u>$_3$), 1.51-1.65 (m, 9H, $C_{9/13/17/21}$-C<u>H</u>$_3$), 1.67 (s, 3H, $C_{9/13/17/21}$-C<u>H</u>$_3$), 1.69-1.87 (m, 5H, $C_{9/13/17/21}$-C<u>H</u>$_3$, $H_{4''}$), 1.86-2.30 (m, 23H, $C_{2/3}$-C<u>H</u>$_3$, $H_{10/11/14/15/18/19/3'/4'/3''}$), 2.39-2.79 (m, 3H, $H_{5'/3''}$), 2.79-3.02 (m, 2H, $H_{10'}$), 3.02-3.24 (m, 1H, $H_{2'}$), 3.26-3.40 (m, 1H, $H_{1'}$), 3.41-3.67 (m, 3H, $H_{7/2'}$), 3.68-3.86 (m, 1H, $H_{1'}$), 4.08-4.23 (m, 2H, $H_{12'}$), 4.23-4.52 (m, 4H, $H_{11'}$), 4.53-4.74 (m, 0.5H, $H_{8'}$), 4.85-5.18 (m, 4.5H, $H_{8/12/16/20/8'}$), 5.25-5.41 (m, 1H, OH), 7.23-7.32 (m, 3H, H_{Ar}-Fm), 7.33-7.44 (m, 4H, H_{Ar}-Fm), 7.48-7.61 (m, 4H, H_{Ar}-Fm), 7.68-7.80 (m, 4H, H_{Ar}-Fm) ppm;

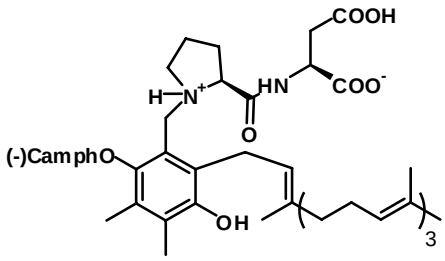
^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ= 9.7, 12.2, 14.3, 15.9, 16.0, 16.2, 16.9, 17.3, 17.6, 24.1, 25.7, 26.2, 26.6, 26.7, 28.9, 30.6, 30.9, 31.3, 31.6, 35.9, 39.6, 39.7, 46.5, 46.6, 48.3, 51.2, 53.4, 54.3, 54.9, 60.9, 66.8, 67.4, 120.0, 121.5, 123.4, 124.2, 124.3, 124.9, 125.0, 127.1, 128.3, 129.5, 131.2, 132.7, 134.9, 135.8, 141.2, 141.3, 143.3, 143.5, 166.6, 170.3, 174.7, 177.8 ppm;

MS (ESI - MeOH): 1189.7$^+$ $(M + H)^+$, 1212.3$^+$ $(M + Na)^+$, 1227.5$^+$ $(M + K)^+$;

anal. calcd. for $C_{76}H_{88}N_2O_{10}$: C 76.74, H 7.46, N 2.36; found: C 76.15, H 7.50, N 2.20.



D-80



L-80

Fm-deprotection – General procedure. To a solution of **79** (0.129 mmol) in CH_2Cl_2 (10 mL) was added Et_2NH (2.5 mL) and the mixture was stirred at room temperature for 2 h. Solvents were removed in vacuum, the crude product solved in CH_2Cl_2, and extracted with $KHSO_4$ (100 mg in 5 mL H_2O). The aqueous phase was washed with CH_2Cl_2 (3 ×), combined organic

phases were dried over Na_2SO_4, evaporated to dryness and the residue purified by column chromatography on SiO_2 (CH_2Cl_2 - MeOH, 75:25).

(-)-CamphanoylO-/OH D-Pro-D-Asp(OH)$_2$ derivative D-80. 42.9 mg (40% yield) as a colourless oil.

^{1}H NMR (600 MHz, DMSO, 25 °C): δ= 0.96 (s, 3H, $C_{5''/7''}$-C<u>H</u>$_3$), 1.00 (s, 3H, $C_{5''/7''}$-C<u>H</u>$_3$), 1.06-1.15 (s, 3H, $C_{5''/7''}$-C<u>H</u>$_3$), 1.44-1.51 (m, 9H, $C_{9/13/17/21}$-C<u>H</u>$_3$), 1.51-1.73 (m, 8H, $C_{9/13/17/21}$-C<u>H</u>$_3$, $H_{3'/4'/4''}$), 1.78-2.00 (m, 16H, C_3-C<u>H</u>$_3$, $H_{10/11/14/15/18/19/3'/4'}$), 2.00-2.33 (m, 6H, C_2-C<u>H</u>$_3$, $H_{3''/4''}$), 2.39 (m, 1H, $H_{5'}$), 2.46-2.62 (m, 1H, $H_{5'}$), 2.62-2.78 (m, 0.2H, $H_{8'}$), 2.93-3.63 (m, 7H, $H_{7/1'/2'/5'/10'}$), 3.69-4.17 (m, 0.8H, $H_{8'}$), 4.87-5.12 (m, 4H, $H_{8/12/16/20}$), 7.44-7.84 (m, 1H, NH), 7.98-8.68 (m, 2H, OH) ppm;

^{13}C NMR (125 MHz, DMSO, from 2D exp. HMQC/HMBC, 25 °C): δ= 9.1, 12.7, 13.0, 15.4, 16.2, 16.3, 17.2, 23.6, 25.1, 25.8, 26.2, 27.9, 30.8, 38.8, 39.1, 47.6, 49.9, 52.8, 53.9, 54.4, 55.3, 64.2, 66.4, 90.7, 123.7, 124.7, 125.6, 127.5, 130.6, 134.3, 140.7, 150.9, 177.8 ppm;

MS (ESI - MeOH): 834.0$^+$ $(M + H)^+$, 856.0$^+$ $(M + Na)^+$, 877.9$^+$ $(M + 2Na)^+$, 832.0$^-$ $(M - H)^-$;

IR (neat) υ_{max} 3353, 2968, 2918, 1795, 1751, 1595, 1423, 1416, 1238, 1163, 1091, 1048, 930 cm^{-1};

UV (MeOH) λ_{max}: 240 nm, 284 nm.

(-)-CamphanoylO-/OH L-Pro-L-Asp(OH)$_2$ derivative L-80. 154.8 mg (63% yield) as a slight yellow solid.

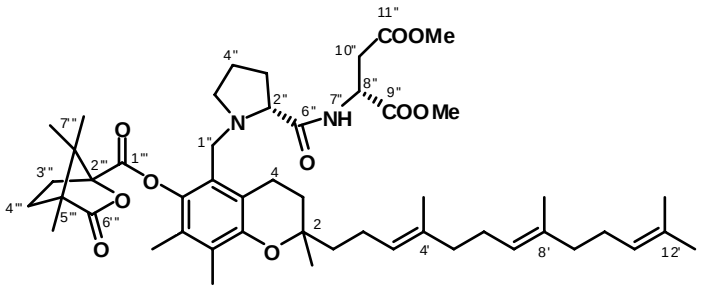
m.p. = 127-132 °C;

^{1}H NMR (500 MHz, DMSO, 25 °C): δ= 0.95-1.19 (m, 9H, $C_{5''/7''}$-C<u>H</u>$_3$), 1.41-1.56 (m, 9H, $C_{9/13/17/21}$-C<u>H</u>$_3$), 1.57-1.79 (m, 8H, $C_{9/13/17/21}$-C<u>H</u>$_3$, $H_{3'/4'/4''}$), 1.79-2.05 (m, 16H, C_3-C<u>H</u>$_3$, $H_{10/11/14/15/18/19/3'/4'}$), 2.05-2.26 (m, 5H, C_2-C<u>H</u>$_3$, $H_{3''/4''}$), 2.26-2.75 (m, 4.5H, $H_{5'/10'/3''}$), 2.89-3.89 (m, 5.9H, $H_{7/1'/2'/5'/8'}$), 3.92-4.44 (m, 0.6H, $H_{8'}$), 4.80-5.20 (m, 4H, $H_{8/12/16/20}$), 7.61-8.66 (m, 2H, OH, NH) ppm;

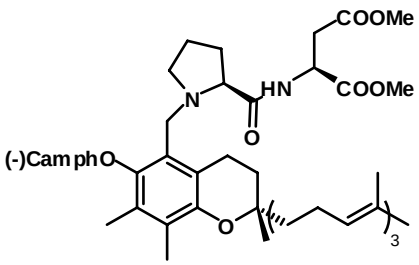
^{13}C NMR (125 MHz, DMSO, from 2D exp. HMQC/HMBC, 25 °C): δ= 9.1, 12.7, 13.0, 15.4, 16.2, 16.3, 17.2, 23.6, 25.1, 25.8, 26.2, 27.9, 30.8, 38.8, 39.1, 47.6, 49.9, 52.8, 53.9, 54.4, 55.3, 64.2, 66.4, 90.7, 123.7, 124.7, 125.6, 127.5, 130.6, 134.3, 140.7, 150.9, 177.8 ppm;

MS (ESI - MeOH): 833.5$^+$ $(M + H)^+$, 855.4$^+$ $(M + Na)^+$, 877.4$^+$ $(M + 2Na)^+$, 831.9$^-$ $(M - H)^-$;

anal. calcd. for $C_{48}H_{66}N_2O_{10}Na_2$: C 65.74, H 7.59, N 3.19; found: C 64.56, H 7.66, N 2.87.



D-81



L-81

Cyclisation and protection of diacid – General procedure. To a solution of **80** (40.82 μmol) in CH_2Cl_2 (35 mL) was added pTsOH·H_2O (85.7 μmol) in ACN (2 mL), and the mixture was stirred at room temperature for 48 h. The reaction is quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the crude oil was dried under high vacuum.

The residue was then solved in MeOH:CH_2Cl_2 (4:1, 2.5 mL) and trimethyl diazomethane (2 M in hexanes, 1.2 mmol) was added. The mixture was stirred at room temperature for 1 h, and the reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and purified by column chromatography on SiO_2 (CH_2Cl_2 - MeOH, 98.5:1.5).

(-)-Camphanoyl D-Pro-D-Asp(OMe)$_2$ cyclised derivative D-81. 15.2 mg (45% yield over two steps) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.10-1.32 (m, 9H, $C_{5'''/7'''}$-C$\underline{H}_3$), 1.49-1.89 (m, 23H, $C_{2/4'/8'/12'}$-C$\underline{H}_3$, $H_{3/1'/3''/4''/4'''}$), 1.89-2.31 (m, 19H, $C_{7/8}$-C$\underline{H}_3$, $H_{2'/5'/6'/9'/10'/3'''/3'''/4'''}$), 2.35-3.42 (m, 9H, $H_{4/2''/5''/10'/3'''/4'''}$), 3.53-3.89 (m, 8H, COOC$\underline{H}_3$, $H_{1''}$), 4.53-4.99 (m, 1H, $H_{8''}$), 5.00-5.23 (m, 3H, $H_{3'/7'/11'}$), 7.68-8.17 (m, 1H, NH) ppm;

^{13}C NMR (125 MHz, $CDCl_3$, from 2D exp. HMQC/HMBC, 25 °C): δ = 9.6, 12.2, 13.5, 17.0, 17.3, 21.3, 23.0, 25.5, 25.7, 28.7, 28.9, 30.8, 35.3, 39.4, 39.7, 52.2, 53.9, 55.2, 59.5, 61.4, 63.1, 64.6, 69.3, 74.2, 75.4, 77.2, 77.4, 85.7, 89.3, 90.8, 92.6, 124.3, 131.2, 134.9, 141.2, 143.2, 171.4, 178.1 ppm;

MS (ESI - MeOH): 861.8$^+$ $(M + H)^+$, 883.7$^+$ $(M + Na)^+$;

IR (neat) υ_{max} 3365, 2921, 2853, 1794, 1739, 1674, 1502, 1436, 1376, 1225, 1163, 1092, 1044 cm^{-1};

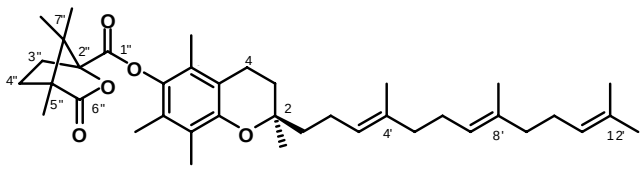
anal. calcd. for $C_{50}H_{72}N_2O_{10}$: C 69.74, H 8.43, N 3.25; found: C 69.23, H 8.36, N 3.15;

Determination of diastereoisomeric excess from HPLC analysis was not possible at this stage – peaks were not properly resolved.

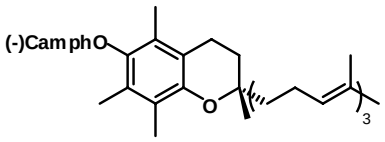
(-)-Camphanoyl L-Pro-L-Asp(OMe)$_2$ cyclised derivative L-81. 83.7 mg (81% yield over two steps) as a colourless oil. Spectral data were identical to those of **D-81**.

HPLC (Protonsil® 120-5-CN, 10% to 20% iPrOH in n-heptane, 1 mL/min, 25°C, 290 nm): $t_{(2S,3'E,7'E)}$ = 29.9 min (82.6%), $t_{(2R,3'E,7'E)}$ = 31.5 min (17.4%), Diastereoisomeric excess (overlapped peaks) = 65% (9*S*);

UV (MeOH) λ_{max} : 205 nm, 289 nm.



all-E-(*R*)-82



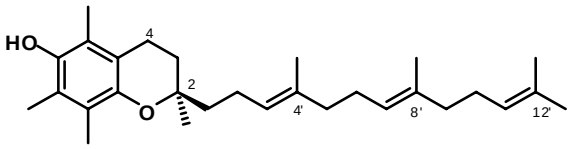
all-E-(*S*)-82

Cleavage of chiral peptide – Benzyl chlorides all-E-(*R*)-82 and all-E-(*S*)-82. To a solution of benzylic amine **81** (21.4 μmol) in benzene (2 mL) was added 2,2,2-trichlorethyl chloroformate (0.64 mmol). The solution was refluxed for 24 h, and the mixture was allowed to cool down to room temperature. The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and purified by column chromatography on SiO_2 (CH_2Cl_2) to afford benzyl chloride **82** as a colourless oil. (80% yield). Analytics were identical for both diastereoisomers.

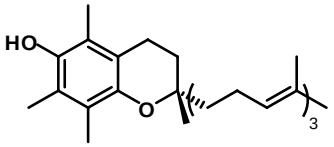
^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 1.14-1.29 (m, 9H, $C_{5"/7"}$-C<u>H</u>$_3$), 1.50-1.72 (m, 18H, $C_{2/4'/8'/12'}$-C<u>H</u>$_3$, $H_{1'/4"}$), 1.72-1.91 (m, 4H, $H_{3/5'/9'}$), 1.89-2.16 (m, 15H, $C_{5/7/8}$-C<u>H</u>$_3$, $H_{2'/5'/6'/9'/10'/4"}$), 2.29 (m, 1H, $H_{3"}$), 2.62 (m, 1H, $H_{3"}$), 2.82 (m, 2H, H_4), 4.36-4.67 (m, 2H, C<u>H</u>$_2$Cl), 5.05-5.17 (m, 3H, $H_{3'/7'/11'}$) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 9.6, 12.2, 13.2, 15.8, 15.9, 16.8, 17.6, 19.1, 22.0, 25.6, 26.5, 26.6, 28.9, 29.2, 30.6, 31.4, 37.8, 39.6, 54.3, 54.9, 75.3, 91.1, 117.9, 123.9, 124.0, 124.3, 127.4, 131.2, 134.9, 135.3, 150.0, 166.0, 177.9 ppm;

MS (ESI - MeOH): 661.5$^+$ (M + Na)$^+$, 675.3$^+$ (M + [HCl])$^+$.



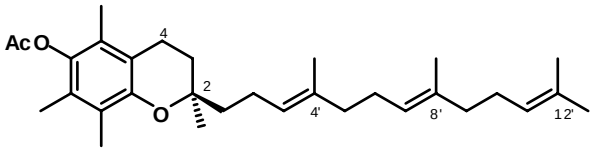
all-E-(*R*)-19



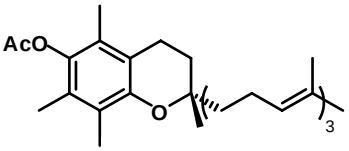
all-E-(*S*)-19

Reductive cleavage with $LiAlH_4$ - α-Tocotrienols all-*E*-(*R*)-19 and all-*E*-(*S*)-19. To a solution of benzyl chloride **82** (59.8 μmol) in THF (2.5 mL) was added $LiAlH_4$ (1 M in THF, 0.150 mmol) and the mixture was refluxed 18 h. The reaction was quenched with H_2O / 1 N HCl, and extracted with Et_2O (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and purified by column chromatography on SiO_2 (CH_2Cl_2) to afford α-tocotrienol **19** as a colourless oil (92% yield). Spectral data were identical to those of an original sample – Selected data; Analytics were identical for both enantiomers.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ= 1.26 (s, 3H, C_2-C$\underline{H}_3$), 1.57-1.70 (m, 14H, $H_{1'}$, $C_{4'/8'/12'}$-C$\underline{H}_3$), 1.75-1.87 (m, 2H, H_3), 1.90-2.20 (m, 19H, $C_{5/7/8}$-C$\underline{H}_3$, $H_{2'/5'/6'/9'/10'}$), 2.61 (t, 2H, J = 6.8 Hz, H_4), 4.20 (s, 1H, OH), 5.05-5.18 (m, 3H, $H_{3'/7'/11'}$) ppm.



all-E-(*R*)-83

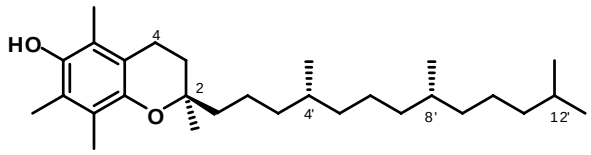


all-E-(*S*)-83

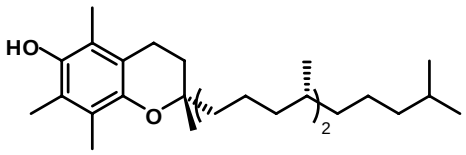
Acetate-protection - α-Tocotrienyl acetates all-E-(*R*)-83 and all-E-(*S*)-83. To a solution of α-tocotrienol **19** (55.0 μmol) in pyridine (2 mL) was added acetic anhydride (400 μL) and the mixture was stirred at room temperature for 4 h. The reaction was quenched with 1 N HCl, and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and purified by column chromatography on SiO_2 (CH_2Cl_2) to afford α-tocotrienyl acetate **83** as a colourless oil (>99% yield). Analytics were identical for both enantiomers.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 1.26 (s, 3H, C_2-C$\underline{H}_3$), 1.57-1.70 (m, 14H, $H_{1'}$, $C_{4'/8'/12'}$-C$\underline{H}_3$), 1.75-1.87 (m, 2H, H_3), 1.92-2.18 (m, 19H, $C_{5/7/8}$-C$\underline{H}_3$, $H_{2'/5'/6'/9'/10'}$), 2.33 (s, 3H, C$\underline{H}_3$(CO)O), 2.60 (t, 2H, J = 6.6 Hz, H_4), 5.05-5.22 (m, 3H, $H_{3'/7'/11'}$) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 11.7, 12.0, 12.8, 15.8, 15.9, 17.6, 20.5, 22.1, 25.6, 26.5, 26.7, 39.6, 74.7, 91.1, 117.2, 123.0, 124.1, 124.3, 126.6, 131.2, 134.9, 135.0, 140.4, 149.3, 169.6 ppm;
MS (ESI - MeOH): 489.6$^+$ $(M + Na)^+$, 505.4$^+$ $(M + K)^+$.



(*R*,*R*,*R*)-15

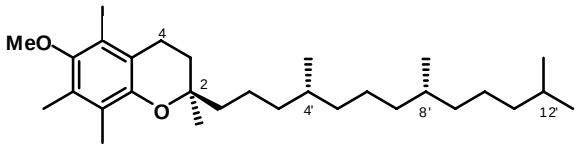


(*S*,*R*,*R*)-15

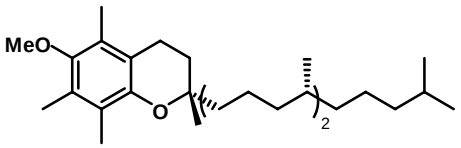
Asymmetric hydrogenation - α-Tocopherols (*R*,*R*,*R*)-15 and (*S*,*R*,*R*)-15. To a solution of α-tocotrienyl acetate **83** (55.0 μmol) in CH_2Cl_2 (0.5 mL) was added Iridium catalyst **61** (0.55 μmol) and the mixture was stirred at room temperature, under 50 bar H_2 for 3 h. The solvent was removed in vacuum and hexane (1 mL) was added. Solids were filtered off (0.45 μm filter), and washed with hexane. The solvent was removed in vacuum, and the crude colourless oil directly used for next step.

The crude oil was solved in THF (1 mL) and $LiAlH_4$ (1 M in THF, 0.38 mmol) was added. The mixture was stirred at room temperature for 2 h. The reaction was quenched with H_2O, and extracted with Et_2O (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness to afford α-tocopherol **15** as a colourless oil (90% yield). The crude material was used without further purification. Spectral data were identical to those of an original sample – Selected data. Analytics were identical for both diastereoisomers.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 0.80-0.91 (m, 12H, $C_{4'/8'/12'}$-C$\underline{H}_3$), 0.97-1.57 (m, 24H, C_2-C$\underline{H}_3$, $H_{1'/2'/3'/4'/5'/6'/7'/8'/9'/10'/11'/12'}$), 1.78 (m, 2H, H_3), 2.11 (s, 6H, $C_{5/7/8}$-C$\underline{H}_3$), 2.16 (s, 3H, $C_{5/7/8}$-C$\underline{H}_3$), 2.60 (t, 2H, J = 6.9 Hz, H_4), 4.19 (s, 1H, OH) ppm;
HPLC (Chiracel OD-H, 0.5% EtOH in n-hexane, 1 mL/min, 25°C, 220 nm): $t_{(2R,4'RS,8'RS)}$ = 7.9 min, $t_{(2S,4'RS,8'RS)}$ = 9.0 min;
Diastereoisomeric excess at C-2 = 65% (2*R*) from D-Pro-D-Asp; 73% (2*S*) from L-Pro-L-Asp.



(*R*,*R*,*R*)-84



(*S*,*R*,*R*)-84

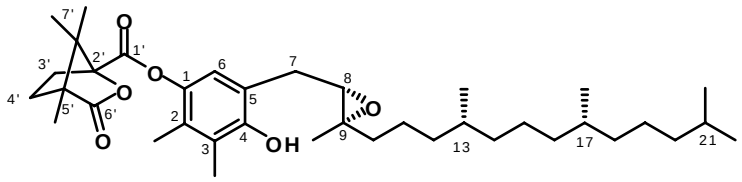
Methylether protection - α-Tocopheryl methylethers (*R*,*R*,*R*)-84 and (*S*,*R*,*R*)-15. To a suspension of NaH (60% on mineral oil, 74.0 μmol) in DMF (0.5 mL) at 0 °C was added a solution of α-tocopherol **15** (49.5 μmol) in DMF (1 mL). The mixture was stirred 30 min at 0 °C and MeI (59.0 μmol) was added. The solution was allowed to warm up to room temperature and stirred for 3 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue purified by column chromatography on SiO_2 (hexane – EtOAc, 9:1) to afford α-tocopheryl methylether **84** as a colourless oil (86% yield). Spectral data were identical to those already reported[52] – Selected data. Analytics were identical for both diastereoisomers.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.85 (d, 3H, *J* = 6.6 Hz, $C_{4'/8'}$-C$\underline{H}_3$), 0.86 (d, 3H, *J* = 6.6 Hz, $C_{4'/8'}$-C$\underline{H}_3$), 0.87 (d, 6H, *J* = 6.6 Hz, $C_{12'}$-C$\underline{H}_3$); 0.90-1.19 (m, 7H, $H_{2'/3'/5'/6'/7'/9'/10'}$), 1.23 (s, 3H, C_2-C$\underline{H}_3$), 1.19-1.47 (m, 13H, $H_{1'/2'/3'/4'/5'/6'/7'/8'/9'/10'/11'}$), 1.53 (m, 1H, $H_{12'}$), 1.78 (m, 2H, H_3), 2.09 (s, 3H, C_5-C$\underline{H}_3$), 2.14 (s, 3H, C_8-C$\underline{H}_3$), 2.18 (s, 3H, C_7-C$\underline{H}_3$), 2.58 (t, 2H, *J* = 6.8 Hz, H_4), 3.63 (s, 3H, C$\underline{H}_3$O) ppm;

GC (CP-Sil-88 column, 50m x 0.25 mm, 0.25 μm; split injector (1:30), injector temp. 280 °C; FID detector, detector temp. 250 °C, carrier gas: H_2, 90 kPa; 170 °C, 140 min): $t_{(2R,4'R,8'S\ /\ 2S,4'S,8'R)}$ = 136.9 min, $t_{(2R,'4R,8'R\ /\ 2S,4'S,8'S)}$ = 138.9 min, $t_{(2R,4'S,8'R\ /\ 2S,4'R,8'S)}$ = 140.7 min, $t_{(2R,4'S,8'S\ /\ 2S,4'R,8'R)}$ = 144.9 min;

Diastereoisomeric excess at C-4' = >98% (*R*);

Diastereoisomeric excess at C-8' = >98% (*R*).



100

(-)-CamphanoylO-/OH epoxide – Sharpless epoxidation. In a two-neck round bottom flask filled with molecular sieves (6 mg), was added CH_2Cl_2 (0.7 mL) followed by $Ti(OiPr)_4$ (15 µL, 0.048 mmol) and (-)-diethyltartrate (9 µL, 0.050 mmol) and the solution cooled to -20 °C and stirred for 20 min. Then a solution of **99** (21.6 mg, 0.044 mmol) in CH_2Cl_2 (1 mL) was added and the mixture was stirred at -20 °C for 20 min. Finally, TBHP (5.5M in decane, 20 µL, 0.109 mmol) was added dropwise and stirring was continued at -20 °C for 16 h. The reaction was quenched with 40% $NaOH_{aq}$ and brine, and Et_2O was added followed by celite. Filtration of the slurry over a pad of celite, concentration of the residue in vacuuo and purification on SiO_2 (hexane - EtOAc, 75:25) afforded **100** (5.0 mg, 20%) as a colourless oil.

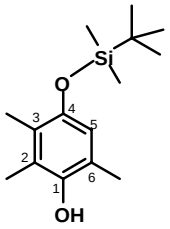
^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 0.82-0.88 (m, 12H, $C_{13/17/21}$-C<u>H</u>$_3$), 0.97-1.18 (m, 6H, $H_{12/14/16/18/20}$), 1.13 (s, 3H, $C_{7'}$-C<u>H</u>$_3$), 1.17 (s, 6H, $C_{5'/7'}$-C<u>H</u>$_3$), 1.17-1.47 (m, 13H, $H_{10/11/12/13/14/15/16/17/18/19}$), 1.48 (s, 3H, C_9-C<u>H</u>$_3$), 1.51 (sept, 1H, J=6.7 Hz, H_{21}), 1.61 (m, 1H, H_{10}), 1.78 (m, 1H, $H_{4'}$), 2.00 (m, 1H, $H_{4'}$), 2.07 (s, 3H, C_2-C<u>H</u>$_3$), 2.20 (s, 3H, C_3-C<u>H</u>$_3$), 2.22 (m, 1H, $H_{3'}$), 2.58 (m, 1H, $H_{3'}$), 2.78-2.87 (m, 2H, H_7), 3.04 (dt, 1H, J=9.8 and 2.60 Hz, H_8) 6.66 (s, 1H, H_6), 7.37 (s, 1H, OH) ppm;

^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 9.8, 12.5, 13.1, 16.8, 16.9, 22.3, 22.5, 22.6, 24.7, 27.9, 28.9, 31.1, 31.8, 32.8, 37.2, 37.7, 37.8, 38.7, 39.0, 54.9, 64.7, 90.8, 120.0, 126.2, 128.3, 128.5, 141.4, 151.8, 177.6 ppm;

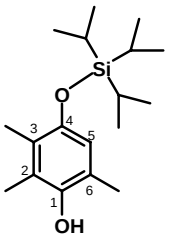
MS (ESI - MeOH): 635.7^+ $(M + Na)^+$, 1248.2^+ $(2M + Na)^+$;

HPLC (Protonsil® 120-5-CN, 3% iPrOH in n-heptane, 1 mL/min, 280 nm): t_{minor} = 15.1 min, t_{major} = 15.9 min;

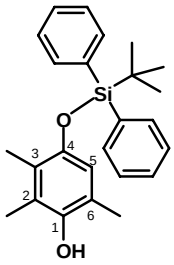
UV (n-heptane) λ_{max}: 204 nm, 280 nm.



102a



102b



102c

Monosylilation of **50** – General procedure. To a solution of **50** (14.44 mmol) and imidazole (57.8 mmol) in DMF (20 mL) at -30 °C, was added dropwise a solution of silyl chloride (17.3 mmol) in DMF (14 mL). The mixture was allowed to warm up to room temperature and stirred for 4 h. The reaction was quenched with water and extracted with CH_2Cl_2 (3 ×). Combined organic phases were washed with water, brine, dried over Na_2SO_4, and evaporated to dryness. The crude oil was purified by column chromatography on SiO_2 using hexane – CH_2Cl_2 mixtures.

Mono TBSO-hydroquinone 102a. 12.85 g (88% yield) as a slight yellow solid. Compound has already been described,[125] selected data.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 0.17 (s, 6H, C$\underline{H}_3$Si), 1.01 (s, 9H, (C$\underline{H}_3$)$_3$CSi), 2.11 (s, 3H, C_{Ar}-C$\underline{H}_3$), 2.16 (s, 3H, C_{Ar}-C$\underline{H}_3$), 2.18 (s, 3H, C_{Ar}-C$\underline{H}_3$), 4.24 (br, 1H, OH), 6.45 (s, 1H, H_6) ppm.

Mono TIPSO-hydroquinone 102b. 800.9 mg (47% yield) as a slight yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 1.10 (d, 18H, J=7.2 Hz, CH(C$\underline{H}_3$)$_3$), 1.30 (m, 3H, C$\underline{H}$(CH$_3$)$_3$), 2.13 (s, 3H, C_{Ar}-C$\underline{H}_3$), 2.15 (s, 3H, C_{Ar}-C$\underline{H}_3$), 2.17 (s, 3H, C_{Ar}-C$\underline{H}_3$), 6.45 (s, 1H, H_5) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ= 12.8, 13.3, 13.4, 16.5, 18.1, 18.5, 117.6, 120.4, 123.6, 125.7, 146.1, 147.8 ppm.

Mono DPSO-hydroquinone 102c. 5.29 g (94% yield) as a colourless oil.

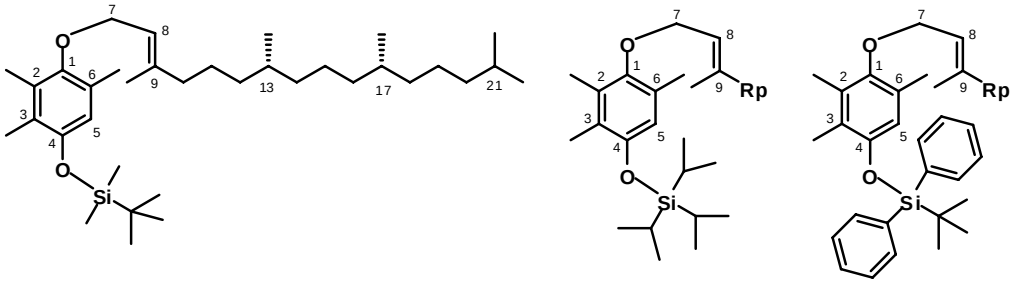
^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.10 (s, 9H, tBu), 1.86 (s, 3H, C_6-C$\underline{H}_3$), 2.19 (s, 3H, C_2-C$\underline{H}_3$), 2.30 (s, 3H, C_3-C$\underline{H}_3$), 4.16 (s, 1H, OH), 6.08 (s, 1H, H_5), 7.38 (m, 6H, H_m/H_p TBDPS-), 7.73 (dd, 4H, J = 7.9 and 1.3 Hz, H_o TBDPS-) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ= 12.8, 13.4, 16.2, 20.0, 27.1, 118.0, 120.1, 123.6, 125.5, 128.1, 130.1, 133.8, 135.9, 146.2, 147.3 ppm;

MS (EI): 390.2;

IR (neat) υ_{max} 3576, 2930, 2856, 1472, 1427, 1326, 1233, 1189, 1107, 1082, 876, 822, 698 cm^{-1};

anal. calcd. for $C_{25}H_{30}O_2Si$: C 76.88, H 7.74; found: C 76.92, H 7.79.



104a **104b** **104c**

Phytyl ether formation – General procedure. To a suspension of NaH (60% on mineral oil, 8.75 mmol) in DMF (20 mL) at 0 °C was added a solution of **102** (7.36 mmol) in DMF (20 mL). The mixture was stirred 30 min. at 0 °C and phytylbromide[76] (8.18 mmol) was added dropwise in DMF (20 mL). The solution was allowed to warm up to room temperature and stirred for 5 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue purified by column chromatography on SiO_2 with hexane – EtOAc mixtures.

TBSO-/phytylO- hydroquinone 104a. 4.29 g (87% yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.19 (s, 6H, C$\underline{H}_3$Si), 0.82-0.89 (m, 12H, $C_{13/17/21}$-C$\underline{H}_3$), 0.95-1.17 (m, 6H, $H_{12/14/16/18/20}$), 1.01 (s, 9H, (C$\underline{H}_3$)$_3$CSi), 1.17-1.48 (m, 12H, $H_{11/12/13/14/15/16/17/18/19}$), 1.53 (sept, 1H, J=6.6 Hz, H_{21}), 1.67 (s, 3H, C_9-C$\underline{H}_3$), 2.03 (m, 2H, H_{10}), 2.09 (s, 3H, C_6-C$\underline{H}_3$), 2.18 (s, 3H, C_2-C$\underline{H}_3$), 2.22 (s, 3H, C_3-C$\underline{H}_3$), 4.22 (d, 2H, J=6.8 Hz, H_7), 5.57 (t, 1H, J=6.8 Hz, H_8), 6.45 (s, 1H, H_5) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ= -3.8, 13.3, 13.6, 16.8, 16.9, 18.7, 20.1, 20.2, 23.0, 23.1, 24.9, 25.2, 25.5, 26.2, 28.4, 33.1, 33.2, 37.1, 37.7, 37.8, 37.9, 39.8, 40.4, 69.8, 118.1, 118.4, 120.6, 126.1, 128.4, 131.2, 141.3, 149.6, 150.3 ppm.

TIPSO-/phytylO- hydroquinone 104b. 1.47 g (97% yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.80-0.90 (m, 12H, $C_{13/17/21}$-C$\underline{H}_3$), 0.99-1.17 (m, 6H, $H_{12/14/16/18/20}$), 1.10 (d, 18H, CH(C$\underline{H}_3$)$_3$), 1.17-1.48 (m, 15H, $H_{11/12/13/14/15/16/17/18/19}$, C$\underline{H}$(CH$_3$)$_3$),

1.52 (sept, 1H, J=6.7 Hz, H_{21}), 1.65 (s, 3H, C_9-C$\underline{H}_3$), 2.02 (m, 2H, H_{10}), 2.12 (s, 3H, C_6-C$\underline{H}_3$), 2.18 (s, 3H, C_2-C$\underline{H}_3$), 2.21 (s, 3H, C_3-C$\underline{H}_3$), 4.23 (d, 2H, J=7.3 Hz, H_7), 5.56 (t, 1H, J=6.9 Hz, H_8), 6.46 (s, 1H, H_5) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ= 13.3, 13.5, 13.7, 16.8, 16.9, 18.5, 20.1, 20.2, 23.0, 23.1, 24.9, 25.2, 25.5, 28.4, 33.1, 33.2, 37.1, 37.7, 37.8, 39.8, 40.4, 69.8, 117.8, 120.6, 125.7, 128.2, 131.0, 141.3, 150.1 ppm;

MS (ESI - MeOH): 610.0$^+$ $(M+Na)^+$.

DPSO-/phytylO- hydroquinone 104c. 4.29 g (87% yield) as a colourless oil.

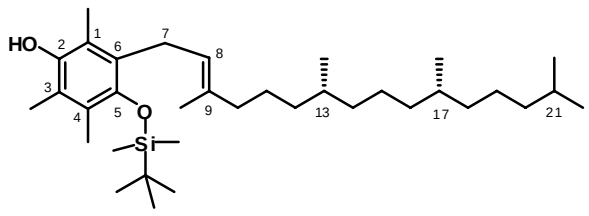
^{1}H NMR (500 MHz, $CDCl_3$): δ= 0.83 (d, 3H, *J* = 4.1 Hz, $C_{13/17}$-C$\underline{H}_3$), 0.85 (d, 3H, *J* = 4.1 Hz, $C_{13/17}$-C$\underline{H}_3$), 0.87 (d, 6H, *J* = 6.9 Hz, C_{21}-C$\underline{H}_3$), 0.99-1.07 (m, 5H, $H_{12/14/16/18}$), 1.10 (s, 9H, tBu), 1.14 (m, 2H, H_{20}), 1.17-1.48 (m, 9H, $H_{11/12/14/15/16/18/19}$), 1.38 (m, 2H, $H_{13/17}$), 1.53 (sept, 1H, *J* = 6.6 Hz, H_{21}), 1.62 (s, 3H, C_9-C$\underline{H}_3$), 1.89 (s, 3H, C_6-C$\underline{H}_3$), 2.02 (m, 2H, H_{10}), 2.21 (s, 3H, C_2-C$\underline{H}_3$), 2.27 (s, 3H, C_3-C$\underline{H}_3$), 4.17 (d, 2H, *J* = 6.9 Hz, H_7), 5.52 (t, 1H, *J* = 6.9 Hz, H_8), 6.10 (s, 1H, H_5), 7.35 (m, 4H, H_m TBDPS-), 7.41 (m, 2H, H_p TBDPS-), 7.70 (d, 4H, *J* = 6.9 Hz, H_o TBDPS-) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ= 13.0, 13.3, 16.2, 16.4, 19.7, 19.8, 22.7, 24.5, 24.8, 25.1, 26.7, 28.0, 32.7, 32.8, 36.7, 37.3, 37.4, 39.4, 40.0, 69.3, 118.0, 120.2, 125.0, 127.6, 127.8, 129.7, 130.5, 133.3, 135.5, 140.8, 149.2, 149.7 ppm;

MS (EI): 668.4;

IR (neat) υ_{max} 2926, 2857, 1473, 1428, 1377, 1322, 1220, 1113, 1086, 981, 886, 700 cm^{-1};

anal. calcd. for $C_{45}H_{68}O_2Si$: C 80.78, H 10.24; found: C 80.64, H 10.22.



Double-Claisen rearrangement – General procedure. To a solution of **104** (6.41 mmol) in CH_2Cl_2 (150 mL) at -35 °C, was added $BF_3{\cdot}Et_2O$ (BF_3 content: 48%, 9.62 mmol) dropwise. The yellow solution was stirred 10 min at -30 °C and quenched by the addition of water. The

mixture was warmed up to room temperature and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue purified three times by column chromatography on SiO_2 using hexane – CH_2Cl_2 mixtures.

TBSO- phytylhydroquinone 105a. 167.3 mg (66% yield) as a slight yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.12 (s, 6H, C$\underline{H}_3$Si), 0.80-0.90 (m, 12H, $C_{13/17/21}$-C$\underline{H}_3$), 0.95-1.17 (m, 6H, $H_{12/14/16/18/20}$), 1.02 (s, 9H, (C$\underline{H}_3$)$_3$CSi), 1.17-1.45 (m, 12H, $H_{11/12/13/14/15/16/17/18/19}$), 1.52 (sept, 1H, J=6.7 Hz, H_{21}), 1.63 (s, 0.06H, C(*Z*)$_9$-C$\underline{H}_3$), 1.69 (s, 2.98H, C(*E*)$_9$-C$\underline{H}_3$), 1.91 (m, 2H, H_{10}), 2.11 (s, 3H, C_3-C$\underline{H}_3$), 2.12 (s, 3H, C_2-C$\underline{H}_3$), 2.13 (s, 3H, C_6-C$\underline{H}_3$), 3.32 (d, 2H, J=6.1 Hz, H_7), 4.28 (s, 1H, OH), 4.96 (t, 1H, J=5.6 Hz, H_8) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ= -2.9, 12.8, 12.9, 15.1, 16.6, 19.1, 20.1, 23.0, 23.1, 24.9, 25.2, 25.8, 26.6, 28.4, 33.1, 33.2, 37.1, 37.7, 37.8, 37.9, 39.8, 40.2, 120.4, 120.8, 124.0, 129.6, 135.3, 145.1, 146.7 ppm;

MS (EI): 544.4;

***E*/*Z* ratio**: 98:2.

TIPSO- phytylhydroquinone 105b. 873.8 mg (59% yield) as a slight yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.80-0.90 (m, 12H, $C_{13/17/21}$-C$\underline{H}_3$), 0.95-1.17 (m, 6H, $H_{12/14/16/18/20}$), 1.10 (d, 18H, CH(C$\underline{H}_3$)$_3$), 1.17-1.45 (m, 15H, $H_{11/12/13/14/15/16/17/18/19}$, C$\underline{H}$(CH$_3$)$_3$), 1.52 (sept, 1H, J=6.9 Hz, H_{21}), 1.64 (s, 0.04H, C(Z)$_9$-C$\underline{H}_3$), 1.70 (s, 2.98H, C(E)$_9$-C$\underline{H}_3$), 1.92 (m, 2H, H_{10}), 2.10 (s, 3H, C_3-C$\underline{H}_3$), 2.14 (s, 3H, C_2-C$\underline{H}_3$), 2.16 (s, 3H, C_6-C$\underline{H}_3$), 3.32 (d, 2H, J=5.3 Hz, H_7), 4.26 (s, 1H, OH), 4.98 (t, 1H, J=5.7 Hz, H_8) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ= 12.7, 12.9, 14.6, 14.8, 16.6, 18.3, 18.6, 20.1, 23.0, 23.1, 24.9, 25.2, 25.8, 27.2, 28.4, 33.1, 33.2, 37.0, 37.7, 37.8, 37.9, 39.8, 40.2, 120.3, 120.6, 124.2, 125.0, 129.0, 135.4, 146.4, 147.0 ppm;

MS (EI): 586.5;

***E*/*Z* ratio**: 98.7:1.3.

DPSO- phytylhydroquinone 105c. 2.57 g (60% yield) as a slight yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ= 0.82 (d, 3H, *J* = 6.6 Hz, $C_{13/17}$-C$\underline{H}_3$), 0.84 (d, 3H, *J* = 6.6 Hz, $C_{13/17}$-C$\underline{H}_3$), 0.86 (d, 6H, *J* = 6.6 Hz, C_{21}-C$\underline{H}_3$), 0.99-1.03 (m, 4H, $H_{12/14/16/18}$), 1.10 (s, 9H, tBu), 1.13 (m, 2H, H_{20}), 1.17-1.31 (m, 10H, $H_{11/12/14/15/16/18/19}$), 1.31-1.43 (m, 2H, $H_{13/17}$), 1.48 (s, 3H, C_9-C$\underline{H}_3$, *E*-isomer), 1.52 (sept, 1H, *J* = 6.6 Hz, H_{21}), 1.81 (s, 3H, C_3-C$\underline{H}_3$), 1.83 (m,

2H, H_{10}), 2.03 (s, 3H, C_2-C<u>H</u>$_3$), 2.06 (s, 3H, C_6-C<u>H</u>$_3$), 3.26 (d, 2H, J = 5.4 Hz, H_7), 4.29 (s, 1H, OH), 4.84 (t, 1H, J = 5.7 Hz, H_8), 7.31 (m, 4H, H_m TBDPS-), 7.39 (m, 2H, H_p TBDPS-), 7.67 (d, 4H, J = 6.6 Hz, H_o TBDPS-) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ= 12.3, 12.6, 16.0, 16.3, 19.8, 20.4, 22.7, 22.8, 24.6, 24.9, 25.4, 27.2, 27.4, 28.1, 32.8, 32.9, 36.8, 37.4, 37.5, 37.6, 39.5, 39.9, 120.2, 120.4, 123.5, 124.6, 127.5, 128.8, 129.5, 134.8, 135.0, 135.3, 146.0, 146.3 ppm;

MS (EI): 668.5;

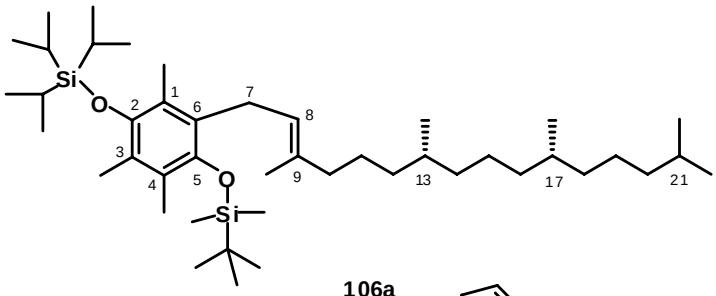
IR (neat) υ_{max} 3465, 2926, 2856, 1462, 1428, 1376, 1251, 1190, 1112, 1086, 840, 821, 701 cm^{-1};

HPLC (Protonsil® 120-5-CN, 0.3% iPrOH in n-heptane, 0.4 mL/min, 220 nm): $t_{E\text{-isomer}}$ = 17.4 min, $t_{Z\text{-isomer}}$ = 18.4 min;

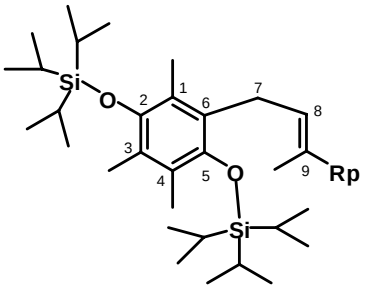
***E*:*Z* ratio** = 98.3:1.7;

UV (n-heptane) λ_{max} : 206 nm, 287 nm;

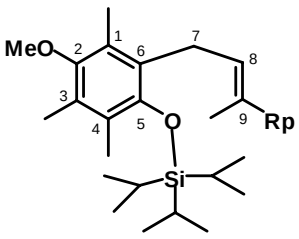
anal. calcd. for $C_{45}H_{68}O_2Si$: C 80.78, H 10.24; found: C 80.38, H 10.15.



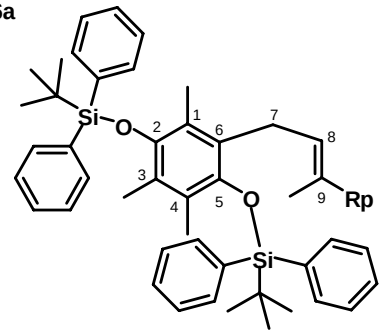
106a



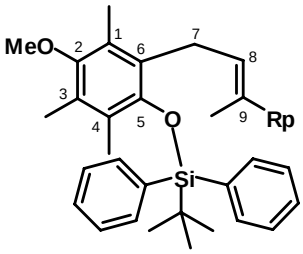
106c



106d



106e



106f

<u>Synthesis of **106a**, **106c-f** – General procedure</u>. To a suspension of NaH (60% on mineral oil, 5.76 mmol) in DMF (20 mL) at 0 °C was added a solution of **105** (3.84 mmol) in DMF (20 mL). The mixture was stirred 30 min at 0 °C and TIPSCl, DPSCl or MeI (7.68 mmol) was added dropwise. The solution was allowed to warm up to room temperature and stirred for 4

h. The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue purified by column chromatography on SiO_2 using hexane – CH_2Cl_2 mixtures.

TIPSO-/TBSO- phytylhydroquinone 106a. 43.1 mg (60% yield) as a colourless oil.
^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.11 (s, 6H, C$\underline{H}_3$Si), 0.80-0.88 (m, 12H, $C_{13/17/21}$-C$\underline{H}_3$), 0.95-1.17 (m, 6H, $H_{12/14/16/18/20}$), 1.00 (s, 9H, (C$\underline{H}_3$)$_3$CSi), 1.07 (d, 18H, CH(C$\underline{H}_3$)$_3$), 1.17-1.43 (m, 15H, $H_{11/12/13/14/15/16/17/18/19}$, C$\underline{H}$(CH$_3$)$_3$), 1.52 (sept, 1H, J=6.6 Hz, H_{21}), 1.61 (s, 0.03H, C(Z)$_9$-C$\underline{H}_3$), 1.68 (s, 2.98H, C(E)$_9$-C$\underline{H}_3$), 1.89 (m, 2H, H_{10}), 2.09 (s, 3H, C_3-C$\underline{H}_3$), 2.11 (s, 3H, C_2-C$\underline{H}_3$), 2.12 (s, 3H, C_6-C$\underline{H}_3$), 3.29 (d, 2H, J=5.9 Hz, H_7), 4.92 (t, 1H, J=5.9 Hz, H_8) ppm;
^{13}C NMR (100 MHz, $CDCl_3$): δ= -2.9, 14.5, 14.6, 14.8, 15.4, 16.7, 18.4, 19.1, 20.1, 23.0, 23.1, 24.9, 25.2, 25.8, 26.6, 27.4, 28.4, 33.1, 33.2, 37.1, 37.7, 37.8, 37.9, 39.8, 40.2, 124.0, 125.4, 125.5, 129.5, 135.1, 145.5, 148.2 ppm;
***E*:*Z* ratio** = 98.5:1.5.

TIPSO-/TIPSO- phytylhydroquinone 106c. Characterization made by A. Buss and reported in his Ph-D thesis.

MeO-/TIPSO- phytylhydroquinone 106d. 15.1 mg (85% yield) as a colourless oil.
^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.80-0.90 (m, 12H, $C_{13/17/21}$-C$\underline{H}_3$), 0.99-1.17 (m, 6H, $H_{12/14/16/18/20}$), 1.09 (d, 18H, CH(C$\underline{H}_3$)$_3$), 1.17-1.45 (m, 15H, $H_{11/12/13/14/15/16/17/18/19}$, C$\underline{H}$(CH$_3$)$_3$), 1.52 (sept, 1H, J=6.6 Hz, H_{21}), 1.64 (s, 0.04H, C(Z)$_9$-C$\underline{H}_3$), 1.70 (s, 2.96H, C(E)$_9$-C$\underline{H}_3$), 1.92 (m, 2H, H_{10}), 2.13 (s, 3H, C_6-C$\underline{H}_3$), 2.14 (s, 3H, C_2-C$\underline{H}_3$), 2.16 (s, 3H, C_3-C$\underline{H}_3$), 3.30 (d, 2H, J=5.6 Hz, H_7), 3.61 (s, 1H, C$\underline{H}_3$O), 4.99 (t, 1H, J=4.8 Hz, H_8) ppm;
^{13}C NMR (100 MHz, $CDCl_3$): δ= 12.8, 13.4, 14.7, 14.8, 16.6, 18.5, 20.1, 23.0, 23.1, 24.9, 25.2, 25.8, 27.3, 28.4, 33.1, 33.2, 37.1, 37.7, 37.8, 37.9, 39.8, 40.2, 60.6, 124.0, 125.3, 127.7, 127.8, 129.3, 135.4, 149.3, 151.4 ppm;
***E*:*Z* ratio** = 98.5:1.5.

DPSO-/DPSO- phytylhydroquinone 106e. Characterization made by A. Buss and reported in his Ph-D thesis.

MeO-/DPSO- phytylhydroquinone 106f. 31.1 mg (81% yield) as a colourless oil.

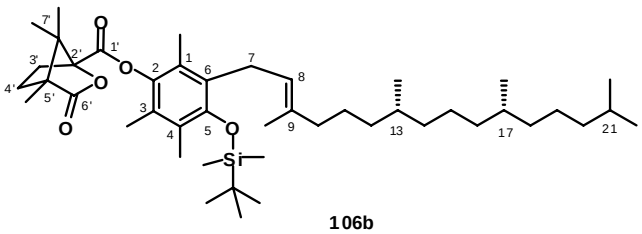
^{1}H NMR (500 MHz, $CDCl_3$): δ= 0.81 (d, 3H, *J* = 6.8 Hz, $C_{13/17}$-C<u>H</u>$_3$), 0.83 (d, 3H, *J* = 6.7 Hz, $C_{13/17}$-C<u>H</u>$_3$), 0.86 (d, 6H, *J* = 6.6 Hz, C_{21}-C<u>H</u>$_3$), 0.94-1.09 (m, 4H, $H_{12/14/16/18}$), 1.12 (s, 9H, tBu), 1.13 (m, 2H, H_{20}), 1.16-1.41 (m, 14H, $H_{10/11/12/13/14/15/16/17/18/19}$), 1.17 (s, 3H, C_9-C<u>H</u>$_3$), 1.52 (sept, 1H, *J* = 6.1 Hz, H_{21}), 1.76 (s, 3H, C_3-C<u>H</u>$_3$), 2.04 (s, 3H, C_2-C<u>H</u>$_3$), 2.23 (s, 3H, C_6-C<u>H</u>$_3$), 2.49 (m, 1H, H_7), 2.76 (d, 1H, 5.7 Hz, H_8), 3.22 (m, 1H, H_7), 3.62 (s, 3H, C<u>H</u>$_3$O), 7.32 (m, 4H, H_m TBDPS-), 7.40 (m, 2H, H_p TBDPS-), 7.66 (d, 4H, *J* = 6.9 Hz, H_o TBDPS-) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ= 12.9, 13.2, 15.8, 16.1, 19.6, 19.7, 20.3, 22.2, 22.6, 22.7, 24.5, 24.8, 27.1, 27.9, 28.0, 32.8, 37.1, 37.3, 37.4, 38.6, 39.4, 60.2, 60.7, 63.9, 125.0, 126.4, 127.5, 127.6, 128.5, 129.6, 134.3, 135.1, 148.5, 151.3 ppm;

MS (EI): 698.5;

IR (neat) υ_{max} 2926, 2858, 1461, 1404, 1246, 1111, 1086, 880, 701 cm^{-1};

anal. calcd. for $C_{46}H_{70}O_3Si$: C 79.03, H 10.09; found: C 78.88, H 9.79.



106b

CamphO-/TBSO- phytylhydroquinone 106b. To a solution of **105a** (51.6 mg, 94.8 μmol) in CH_2Cl_2 (3 mL) at room temperature, was added DMAP (35.0 mg, 0.28 mmol), followed by (-)-camphanoyl chloride (62.0 mg, 0.28 mmol). The mixture was stirred at room temperature for 5 h, quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue purified by column chromatography on SiO_2 (hexane – EtOAc, 95:5) to afford **106b** (383.8 g, 99%) as a colourless oil.

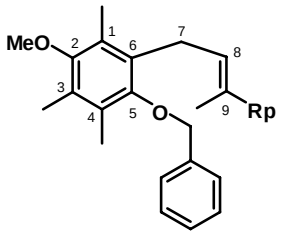
^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.14 (s, 6H, C<u>H</u>$_3$Si), 0.79-0.89 (m, 12H, $C_{13/17/21}$-C<u>H</u>$_3$), 0.97-1.18 (m, 6H, $H_{12/14/16/18/20}$), 1.02 (s, 9H, (C<u>H</u>$_3$)$_3$CSi), 1.15 (s, 3H, $C_{5'}$-C<u>H</u>$_3$), 1.17 (s, 3H, $C_{7'}$-C<u>H</u>$_3$), 1.18-1.44 (m, 12H, $H_{11/12/13/14/15/16/17/18/19}$), 1.19 (s, 3H, $C_{7'}$-C<u>H</u>$_3$), 1.52 (sept, 1H, J=6.6 Hz, H_{21}), 1.63 (s, 0.05H, C(Z)$_9$-C<u>H</u>$_3$), 1.67 (s, 2.97H, C(E)$_9$-C<u>H</u>$_3$), 1.78 (m, 1H, $H_{4'}$), 1.81 (m, 2H, H_{10}), 1.99 (m, 1H, $H_{4'}$), 2.00 (s, 3H, C_3-C<u>H</u>$_3$), 2.02 (s, 3H, C_2-C<u>H</u>$_3$), 2.12 (s, 3H, C_6-C<u>H</u>$_3$), 2.24 (m, 1H, $H_{3'}$), 2.58 (m, 1H, $H_{3'}$), 3.32 (m, 2H, H_7), 4.95 (t, 1H, J=5.7 Hz, H_8) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ= -2.7, 10.1, 13.7, 14.0, 15.1, 16.6, 19.1, 20.1, 20.2, 23.0, 23.1, 24.9, 25.2, 26.6, 28.4, 29.4, 31.8, 33.1, 33.2, 37.1, 37.7, 37.8, 39.8, 40.2, 54.6, 55.3, 70.3, 70.9, 91.2, 91.6, 123.4, 126.7, 130.2, 135.7, 142.4, 149.6, 166.4, 178.4, 201.7 ppm;

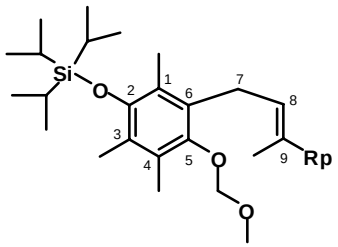
HPLC (Protonsil® 120-5-CN, 0.5% iPrOH in n-heptane, 0.6 mL/min, 220 nm): $t_{E\text{-isomer}}$ = 14.2 min (96.0%), $t_{Z\text{-isomer}}$ = 14.7 min (2.3%);

E:Z ratio = 98:2;

UV (n-heptane) λ_{max} : 211 nm, 280 nm.



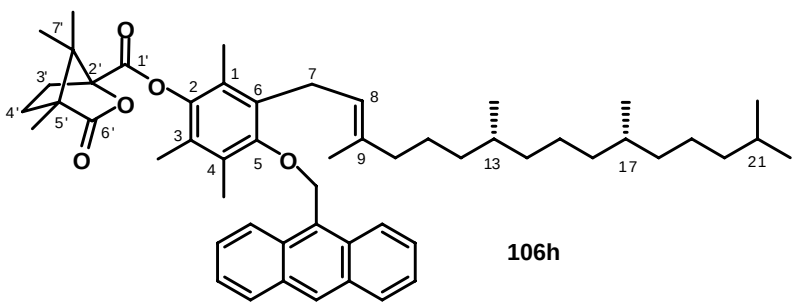
106g



106i

MeO-/BnO- phytylhydroquinone 106g. Synthesis and characterization made by A. Buss and reported in his Ph-D thesis.

TIPSO-/MOMO- phytylhydroquinone 106i. Synthesis and characterization made by A. Buss and reported in his Ph-D thesis.



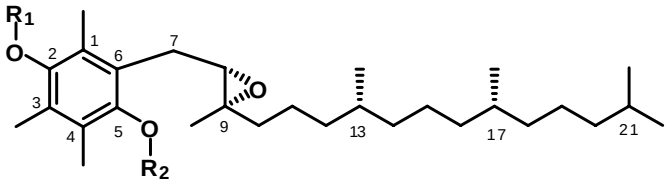
106h

CamphO-/AnthrO- phytylhydroquinone 106h. To a solution of **106d** (98.4 mg, 0.126 mol) in THF (10 mL) at room temperature, was added TBAF (1M in THF, 150 µL, 0.15 mmol). The mixture was stirred at room temperature for 1 h, quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried

over Na_2SO_4, evaporated to dryness and the residue purified by column chromatography on SiO_2 (hexane – EtOAc, 9:1) to afford the free phenol (72.9 mg, 95%) as a colourless oil.

To a suspension of NaH (60% on mineral oil, 6.0 mg, 0.143 mmol) in DMF (2 mL) at 0°C was added a solution of freshly prepared phenol (72.9 mg, 0.12 mmol) in DMF (2.5 mL). The mixture was stirred 30 min at 0 °C and 9-(chloromethyl)-anthracene (35.2 mg, 0.155 mmol) was added. The solution was allowed to warm up to room temperature and stirred for 3 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 ×). Combined organic phases are dried over Na_2SO_4, evaporated to dryness and the residue purified by column chromatography on SiO_2 (hexane – EtOAc, 85:15) to afford **106h** (84.0 mg, 87%) as a yellow oil/solid.

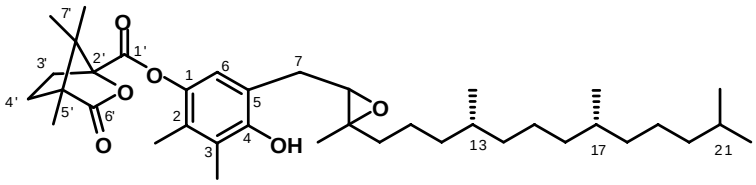
^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.74 (m, 3H, J=6.5 Hz, $C_{13/17}C\underline{H}_3$), 0.79 (m, 3H, J=6.5 Hz, $C_{13/17}C\underline{H}_3$), 0.85 (m, 6H, J=6.6 Hz, C_{21}-$C\underline{H}_3$), 0.88-1.38 (m, 18H, $H_{11/12/13/14/15/16/17/18/19/20}$), 1.17 (s, 3H, $C_{5'}$-$C\underline{H}_3$), 1.18 (s, 3H, $C_{7'}$-$C\underline{H}_3$), 1.21 (s, 3H, $C_{7'}$-$C\underline{H}_3$), 1.51 (sept, 1H, J=6.7 Hz, H_{21}), 1.53 (s, 3H, C_9-$C\underline{H}_3$), 1.76-1.90 (m, 3H, $H_{10/4'}$), 1.98-2.02 (m, 4H, C_6-$C\underline{H}_3$, $H_{4'}$), 2.05 (s, 3H, C_2-$C\underline{H}_3$), 2.06 (s, 3H, C_3-$C\underline{H}_3$), 2.27 (m, 1H, $H_{3'}$), 2.60 (m, 1H, $H_{3'}$), 3.41 (m, 2H, H_7), 4.96 (t, 1H, J=5.6 Hz, H_8), 5.83 (s, 2H, $OC\underline{H}_2$Anth), 7.49 (m, 4H, $H_{Ar\text{-}Anth}$), 8.02 (d, 2H, J=7.9 Hz, $H_{Ar\text{-}Anth}$), 8.36 (d, 2H, J=9.2 Hz, $H_{Ar\text{-}Anth}$), 8.49 (s, 1H, $H_{Ar\text{-}Anth}$) ppm;
^{13}C NMR (100 MHz, $CDCl_3$): δ= 10.1, 13.5, 13.8, 14.4, 16.5, 17.4, 20.0, 20.1, 23.0, 23.1, 24.8, 25.2, 25.8, 27.2, 28.4, 29.4, 31.9, 33.1, 33.2, 37.2, 37.7, 37.8, 39.8, 40.2, 54.7, 55.4, 69.1, 91.5, 122.9, 124.9, 125.4, 126.6, 129.0, 129.4, 131.3, 132.9, 136.6, 144.3, 155.2, 166.3, 178.4 ppm;
MS (ESI - MeOH): 840.0$^+$ $(M+Na)^+$.



108a-i

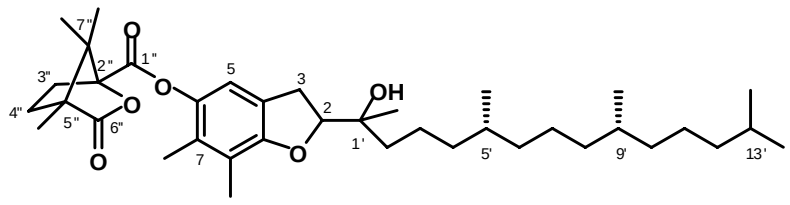
<u>Shi asymmetric epoxidation – General procedure to **108a-i**</u>. To a solution of **106** (54.9 μmol) and catalyst **ent-101** (22.0 μmol) in MeCN:EtOH:CH_2Cl_2 (1:1:2, 200 μL) was added a buffer solution of 2 M K_2CO_3/4.10^{-4} M EDTA (140 μL). The mixture was cooled down to 0 °C and H_2O_2 (30% aq, 0.3 mmol) was added in one portion. The reaction was stirred at 0 °C for 10 h,

and diluted with CH_2Cl_2 and H_2O. The organic phase was extracted and the water phase further extracted with CH_2Cl_2 (2 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue was purified by column chromatography on SiO_2 using hexane – EtOAc mixtures, to afford corresponding epoxides **108** as colourless oils. Characterization of compounds was made by A. Buss and reported in his Ph-D thesis.

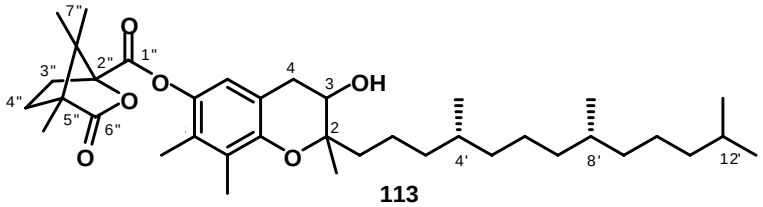


111

CamphO-/OH phytylhydroquinone epoxide 111. To a solution of **99** (208.0 mg, 0.35 mmol) in CH_2Cl_2 (35 mL) at 0 °C was added mCPBA (93.6 mg, 0.56 mmol) at once. The solution was allowed to warm up to rt and stirred for 3 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 ×). Combined organic phases are dried over Na_2SO_4, evaporated to dryness and the residue was purified by column chromatography on SiO_2 (hexane – EtOAc, 8:2) to afford **111** (170.8 mg, 80%) as a colourless oil. Analytics were identical to those of chiral epoxide **100** already described.



112



113

'Anti-Baldwin' cyclisation screening – General procedure. To a solution of **111** (10.5 μmol) in the corresponding solvent (3 mL, *table 4*) was added the Brönsted or Lewis acid, and the mixture stirred at room temperature for 24 h. The conversion and ratio between 5- and 6-membered ring products were determined by HPLC and by ^{1}H NMR on a quenched sample.

Furan ring 112.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.81-0.89 (m, 12H, $C_{5'/9'/13'}$-C<u>H</u>$_3$), 0.99-1.18 (m, 6H, $H_{4'/6'/8'/10'/12'}$), 1.12 (s, 3H, $C_{7''}$-C<u>H</u>$_3$), 1.16 (s, 3H, $C_{5''/7''}$-C<u>H</u>$_3$), 1.17 (s, 3H, $C_{5''/7''}$-C<u>H</u>$_3$), 1.18-1.47 (m, 14H, $H_{2'/3'/4'/5'/6'/7'/8'/9'/10'/11'}$), 1.31 (d, 3H, C_1-C<u>H</u>$_3$), 1.48-1.56 (m, 1H, $H_{13'}$), 1.72 (m, 1H, OH), 1.77 (m, 1H, $H_{4''}$), 1.99 (m, 1H, $H_{4''}$), 2.03 (s, 3H, C_8-C<u>H</u>$_3$), 2.14 (s, 3H, C_7-C<u>H</u>$_3$), 2.21 (m, 1H, $H_{3''}$), 2.56 (m, 1H, $H_{3''}$), 3.06 (dd, 1H, J=15.8 and 9.3 Hz, H_3), 3.22 (dd, 1H, J=15.4 and 9.3 Hz, H_3), 4.61 (t, 1H, J=9.3 Hz, H_2), 6.68 (s, 1H, H_5) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ= 9.9, 12.5, 12.8, 17.1, 19.9, 22.8, 23.5, 24.4, 28.4, 29.3, 30.5, 30.7, 31.2, 31.3, 31.7, 33.2, 37.7, 38.0, 39.5, 55.0, 73.8, 89.1, 91.4, 115.4, 119.5, 127.8, 127.9, 142.3, 156.5, 178.3 ppm;

MS (ESI - MeOH): 635.7$^+$ $(M+Na)^+$, 651.5$^+$ $(M+K)^+$, 1248.0$^+$ $(2M+Na)^+$;

HPLC (Protonsil® 120-5-CN, 3% iPrOH in n-heptane, 1 mL/min, 280 nm): t_1 = 19.0 min, t_2 = 20.0 min;

UV (n-heptane) λ_{max} : 204 nm, 284 nm.

Pyran ring 113.

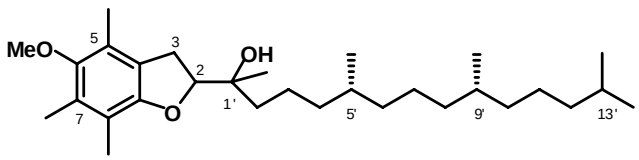
^{1}H NMR (600 MHz, $CDCl_3$): δ= 0.81-0.90 (m, 12H, $C_{4'/8'/12'}$-C<u>H</u>$_3$), 0.97-1.19 (m, 6H, $H_{3'/5'/7'/9'/11'}$), 1.12 (s, 3H, $C_{7''}$-C<u>H</u>$_3$), 1.16 (s, 3H, $C_{5''/7''}$-C<u>H</u>$_3$), 1.17 (s, 3H, $C_{5''/7''}$-C<u>H</u>$_3$), 1.19-1.47 (m, 14H, $H_{1'/2'/3'/4'/5'/6'/7'/8'/9'/10'}$), 1.31 (d, 3H, C_1-C<u>H</u>$_3$), 1.48-1.56 (m, 1H, $H_{12'}$), 1.77 (m, 1H, $H_{4''}$), 1.99 (m, 1H, $H_{4''}$), 2.05 (s, 3H, C_7-C<u>H</u>$_3$), 2.14 (s, 3H, C_8-C<u>H</u>$_3$), 2.21 (m, 1H, $H_{3''}$), 2.56 (m, 1H, $H_{3''}$), 2.74 (dd, 1H, J=16.6 and 5.7 Hz, H_4), 3.01 (dd, 1H, J=16.9 and 3.9 Hz, H_4), 3.83 (m, 1H, H_3), 6.59 (s, 1H, H_6) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ= 9.6, 12.7, 16.9, 19.5, 19.6, 19.9, 22.7, 24.7, 28.0, 28.9, 29.4, 31.3, 31.7, 37.3, 37.4, 39.4, 55.0, 68.3, 78.8, 91.0, 119.3, 126.6, 127.5, 135.4, 141.8, 148.7, 178.2 ppm;

MS (ESI - MeOH): 635.7$^+$ $(M+Na)^+$, 651.5$^+$ $(M+K)^+$, 1248.0$^+$ $(2M+Na)^+$;

HPLC (Protonsil® 120-5-CN, 3% iPrOH in n-heptane, 1 mL/min, 280 nm): $t_{(3R,4R,4'R,8'R\ /\ 3S,4S,4'R,8'R)}$ = 24.7 min and 26.1 min, $t_{(3R,4S,4'R,8'R\ /\ 3S,4R,4'R,8'R)}$ = 23.2 and 23.8 min;

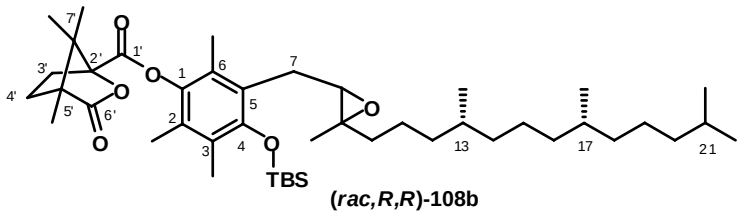
UV (n-heptane) λ_{max} : 204 nm, 287 nm.



115

Furan ring 115 from TBAF deprotection of 108f. To a solution of **108f** (24.2 mg, 0.034 mmol) in THF (1.5 mL) at room temperature, was added TBAF (1 M in THF, 40 μL, 0.039 mmol). The mixture was stirred at room temperature for 1 h, quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue was purified by column chromatography on SiO_2 (hexane – EtOAc, 8:2) to afford **115** (15.9 mg, 99%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ= 0.85 (d, 3H, J=6.6 Hz, $C_{5'/9'}$-C$\underline{H}_3$), 0.87 (d, 9H, J=6.6 Hz, $C_{5'/9'/13'}$-C$\underline{H}_3$), 0.96-1.10 (m, 3H, $H_{4'/6'/8'/10'}$), 1.10-1.17 (m, 2H, $H_{12'}$), 1.17-1.36 (m, 9H, $H_{3'/4'/6'/7'/8'/10'/11'}$), 1.30 (m, 2H, $H_{2'}$), 1.32 (s, 3H, C_1-C$\underline{H}_3$), 1.32-1.46 (m, 2H, $H_{5'/9'}$), 1.46-1.63 (m, 2H, $H_{4'/6'/8'/10'}$), 1.51 (sept, 1H, J=6.6 Hz, $H_{13'}$), 1.80 (m, 1H, OH), 2.10 (s, 3H, C_8-C$\underline{H}_3$), 2.16 (s, 6H, $C_{5/7}$-C$\underline{H}_3$), 2.98 (dd, 1H, J=15.5 and 9.1 Hz, H_3), 3.11 (dd, 1H, J=15.1 and 9.1 Hz, H_3), 3.63 (s, 3H, C$\underline{H}_3$O), 4.57 (t, J=9.5 Hz, 1H, H_2) ppm;
^{13}C NMR (125 MHz, $CDCl_3$): δ= 12.2, 12.3, 13.0, 20.0, 22.7, 22.6, 23.4, 24.5, 24.8, 28.0, 30.0, 32.8, 37.3, 37.4, 37.5, 37.7, 39.4, 60.4, 73.6, 88.3, 115.9, 123.6, 124.1, 128.7, 150.5, 153.5 ppm;
MS (EI): 460.4;
anal. calcd. for $C_{30}H_{52}O_3$: C 78.21, H 11.38, O 10.42; found: C 78.01, H 11.13, O 10.86.



(*rac,R,R*)-108b

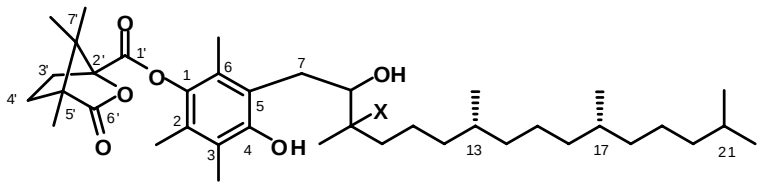
CamphO-/TBSO-phytylhydroquinone epoxide (*rac,R,R*)-108b. To a solution of **106b** (120.1 mg, 0.166 mmol) in CH_2Cl_2 (5 mL) at 0 °C, was added mCPBA (46.0 mg, 0.265 mmol) at once. The solution was allowed to warm up to room temperature and stirred for 2 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue was purified by column chromatography on SiO_2 (hexane – EtOAc, 9:1) to afford **(*rac,R,R*)-108b** (111.5 mg, 91%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.15 (s, 6H, C<u>H</u>$_3$Si), 0.80-0.89 (m, 12H, $C_{13/17/21}$-C<u>H</u>$_3$), 0.95-1.17 (m, 6H, $H_{12/14/16/18/20}$), 1.04 (s, 9H, (C<u>H</u>$_3$)$_3$CSi), 1.15 (s, 3H, $C_{5'}$-C<u>H</u>$_3$), 1.17 (s, 3H, $C_{7'}$-C<u>H</u>$_3$), 1.19 (s, 3H, $C_{7'}$-C<u>H</u>$_3$), 1.20-1.46 (m, 14H, $H_{10/11/12/13/14/15/16/17/18/19}$), 1.52 (sept, 1H, J=6.8 Hz, H_{21}), 1.57 (s, 3H, C_9-C<u>H</u>$_3$), 1.78 (m, 1H, $H_{4'}$), 1.99 (m, 1H, $H_{4'}$), 2.02 (s, 3H, C_3-C<u>H</u>$_3$), 2.03 (s, 3H, C_2-C<u>H</u>$_3$), 2.12 (s, 3H, C_6-C<u>H</u>$_3$), 2.24 (m, 1H, $H_{3'}$), 2.58 (m, 1H, $H_{3'}$), 2.65 (m, 1H, H_7), 2.76 (m, 1H, H_8), 3.18 (m, 1H, H_7) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ= -2.9, 10.1, 12.8, 13.6, 13.8, 17.2, 17.4, 20.1, 20.2, 22.7, 23.0, 23.1, 24.9, 25.2, 27.6, 27.9, 28.4, 29.4, 31.9, 33.1, 33.2, 37.3, 37.7, 37.8, 39.0, 39.8, 54.7, 55.3, 91.5, 121.9, 125.3, 128.1, 152.2, 166.6, 178.4 ppm;

MS (ESI - MeOH): 764.0$^+$ $(M+Na)^+$;

HPLC (Chiracel AD-H, 2% iPrOH in n-heptane, 0.5 mL/min, 280 nm): mixture of 2 stereoisomers, t_1 = 10.8 min (49.8 %), t_2 = 11.8 min (47.5 %).



X = OH, **118**
X = Cl, **119**

<u>TBS cleavage using aqeous HCl – General procedure</u>.(*scheme 55*) To a solution of **(*rac,R,R*)-108b** (14.8 μmol) in the corresponding solvent (MeCN or MeCN:TFA, 0.5 mL) was added aqueous HCl (1N or 6N, 1 mmol) and the reaction was stirred at rt for 18 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue was purified by column chromatography on SiO_2 (hexane – EtOAc, 7:3). Reactions produced several unidentified side-products and yields of **118** and **119** were <10-15% in each cases.

Diol 118.

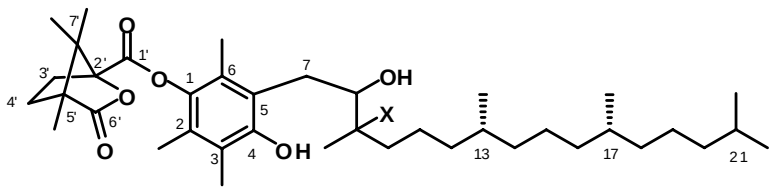
^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.82-0.89 (m, 12H, $C_{13/17/21}$-C<u>H</u>$_3$), 0.95-1.20 (m, 6H, $H_{12/14/16/18/20}$), 1.15 (s, 3H, $C_{5'}$-C<u>H</u>$_3$), 1.17 (s, 3H, $C_{7'}$-C<u>H</u>$_3$), 1.19 (s, 3H, $C_{7'}$-C<u>H</u>$_3$), 1.20-1.46 (m, 14H, $H_{10/11/12/13/14/15/16/17/18/19}$), 1.52 (sept, 1H, J=6.8 Hz, H_{21}), 1.56 (s, 3H, C_9-C<u>H</u>$_3$), 1.78 (m, 1H, $H_{4'}$), 2.00 (m, 1H, $H_{4'}$), 2.05 (s, 6H, $C_{2/3}$-C<u>H</u>$_3$), 2.19 (s, 3H, C_6-C<u>H</u>$_3$), 2.25 (m, 1H, $H_{3'}$), 2.58 (m, 1H, $H_{3'}$), 2.77 (m, 2H, H_8), 3.04 (br, 1H, OH), 3.62 (m, 1H, H_7), 7.61 (br, 1H, OH) ppm;

MS (ESI - MeOH): 667.8$^+$ $(M+Na)^+$, 1312.2$^+$ $(2M+Na)^+$.

Chlorhydrine 119.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.84-0.91 (m, 12H, $C_{13/17/21}$-C<u>H</u>$_3$), 0.95-1.21 (m, 6H, $H_{12/14/16/18/20}$), 1.15 (s, 3H, $C_{5'}$-C<u>H</u>$_3$), 1.17 (s, 3H, $C_{7'}$-C<u>H</u>$_3$), 1.19 (s, 3H, $C_{7'}$-C<u>H</u>$_3$), 1.20-1.46 (m, 14H, $H_{10/11/12/13/14/15/16/17/18/19}$), 1.52 (sept, 1H, J=6.8 Hz, H_{21}), 1.56 (s, 3H, C_9-C<u>H</u>$_3$), 1.78 (m, 1H, $H_{4'}$), 1.98 (m, 1H, $H_{4'}$), 2.06 (s, 3H, C_3-C<u>H</u>$_3$), 2.08 (s, 3H, C_2-C<u>H</u>$_3$), 2.19 (s, 3H, C_6-C<u>H</u>$_3$), 2.26 (m, 1H, $H_{3'}$), 2.58 (m, 1H, $H_{3'}$), 2.78-2.88 (m, 1H, H_8), 2.90-3.04 (m, 2H, OH, H_8), 3.86 (m, 1H, H_7), 7.44 (br, 1H, OH) ppm;

MS (ESI - MeOH): 686.0$^+$ $(M+Na)^+$, 701.6$^+$ $(M+K)^+$.



X = Cl, **119**
X = OMe, **120**

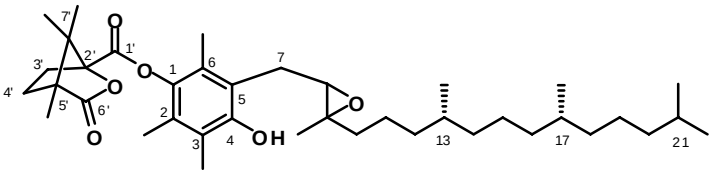
<u>TBS cleavage using anhydrous HCl – General procedure</u>. (*scheme 56*) To a solution of **(*rac,R,R*)-108b** (13.5 μmol) in MeCN (0.5 mL) was added anhydrous HCl (in MeOH, Et_2O or dioxane, 1 mmol) and the reaction was stirred at rt between 7 h and 24 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue was purified by column chromatography on SiO_2 (hexane – EtOAc, 7:3). Yields are reported on scheme 56.

Chlorhydrine 119. <u>Analytics identical to those already described before</u>.

Methoxy ether 120.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.83-0.90 (m, 12H, $C_{13/17/21}$-C<u>H</u>$_3$), 0.95-1.21 (m, 6H, $H_{12/14/16/18/20}$), 1.15 (s, 3H, $C_{5'}$-C<u>H</u>$_3$), 1.17 (s, 3H, $C_{7'}$-C<u>H</u>$_3$), 1.19 (s, 3H, $C_{7'}$-C<u>H</u>$_3$), 1.20-1.46 (m, 14H, $H_{10/11/12/13/14/15/16/17/18/19}$), 1.52 (sept, 1H, J=6.8 Hz, H_{21}), 1.55 (s, 3H, C_9-C<u>H</u>$_3$), 1.78 (m, 1H, $H_{4'}$), 2.00 (m, 1H, $H_{4'}$), 2.05 (s, 6H, $C_{2/3}$-C<u>H</u>$_3$), 2.20 (s, 3H, C_6-C<u>H</u>$_3$), 2.25 (m, 1H, $H_{3'}$), 2.57 (m, 1H, $H_{3'}$), 2.78-2.88 (m, 2H, H_8), 2.90-3.04 (m, 1H, OH), 3.22 (s, 3H, C<u>H</u>$_3$O-) 3.75 (m, 1H, H_7), 7.82 (br, 1H, OH) ppm;

MS (ESI - MeOH): 681.9$^+$ $(M+Na)^+$, 697.6$^+$ $(M+K)^+$.



116

CamphO-/OH phytylhydroquinone epoxide 116 – TBS cleavage. To a solution of **(*rac*,*R*,*R*)-108b** (9.8 mg, 0.013 mmol) in THF (0.5 mL) was added glacial AcOH (28 μL, 0.53 mmol) followed by TBAF (1 M in THF, 53 μL, 0.053mmol). The solution was stirred a room temperature for 36 h quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue was purified by column chromatography on SiO_2 (hexane – EtOAc, 8:2) to afford **116** (6.2 mg, 79%) as a colourless oil.

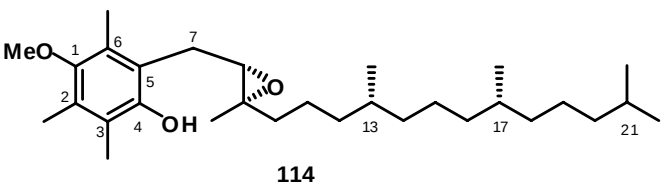
^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.82-0.89 (m, 12H, $C_{13/17/21}$-C<u>H</u>$_3$), 0.99-1.20 (m, 6H, $H_{12/14/16/18/20}$), 1.15 (s, 3H, $C_{5'}$-C<u>H</u>$_3$), 1.17 (s, 3H, $C_{7'}$-C<u>H</u>$_3$), 1.19 (s, 3H, $C_{7'}$-C<u>H</u>$_3$), 1.20-1.46 (m, 14H, $H_{10/11/12/13/14/15/16/17/18/19}$), 1.51 (s, 3H, C_9-C<u>H</u>$_3$), 1.52 (sept, 1H, J=6.8 Hz, H_{21}), 1.79 (m, 1H, $H_{4'}$), 1.99 (m, 1H, $H_{4'}$), 2.06 (s, 3H, C_3-C<u>H</u>$_3$), 2.11 (s, 3H, C_2-C<u>H</u>$_3$), 2.18 (s, 3H, C_6-C<u>H</u>$_3$), 2.26 (m, 1H, $H_{3'}$), 2.58 (m, 1H, $H_{3'}$), 2.67 (dd, 1H, J=14.9 and 10.6 Hz, H_7), 2.94 (m, 1H, H_8), 3.15 (dd, 1H, J=14.9 and 1.5 Hz, H_7), 7.17 (s, 1H, OH) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ= 10.1, 12.8, 13.6, 13.8, 17.2, 17.4, 20.1, 20.2, 22.7, 23.0, 23.1, 24.9, 25.2, 27.6, 27.9, 28.4, 29.4, 31.9, 33.1, 33.2, 37.3, 37.7, 37.8, 39.0, 39.8, 54.7, 55.3, 91.5, 121.9, 125.3, 128.1, 152.2, 166.6, 178.4 ppm;

MS (ESI - MeOH): 649.7$^+$ $(M+Na)^+$, 1276.0$^+$ $(2M+Na)^+$;

HPLC (Protonsil® 120-5-CN, 7% iPrOH in n-heptane, 1 mL/min, 280 nm, 25 °C): $t_{\mathbf{116}}$ = 7.6 min;

UV (n-heptane) λ_{max} : 205 nm, 282 nm.

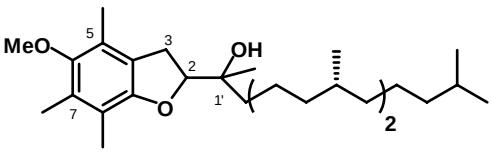


114

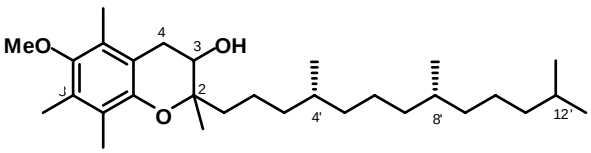
Monoprotected epoxide 114. To a solution of **108f** (63.8 mg, 91.3 μmol) in THF (4.5 mL) at room temperature, was added glacial AcOH (210 μL, 3.65 mmol) followed by TBAF (1 M in THF, 370 μL, 0.365 mmol). The mixture was stirred at room temperature for 36 h, quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3

×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue was purified by column chromatography on SiO_2 (hexane – EtOAc, 95:5) to afford **114** (34.5 mg, 82%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ= 0.84 (d, 3H, J = 4.4 Hz, $C_{13/17}$-C$\underline{H}_3$), 0.85 (d, 3H, J = 5.0 Hz, $C_{13/17}$-C$\underline{H}_3$), 0.86 (d, 6H, J = 6.9 Hz, C_{22}-C$\underline{H}_3$), 0.97-1.10 (m, 4H, $H_{12/14/16/18}$), 1.13 (m, 2H, H_{20}), 1.13-1.32 (m, 8H, $H_{12/14/15/16/18/19}$), 1.32-1.46 (m, 6H, $H_{10/11/13/17}$), 1.50 (s, 3H, C_9-C$\underline{H}_3$), 1.51(sept, 1H, J = 6.9 Hz, H_{21}), 2.17(s, 3H, C_3-C$\underline{H}_3$), 2.20 (s, 3H, C_2-C$\underline{H}_3$), 2.26 (s, 3H, C_6-C$\underline{H}_3$), 2.66 (dd, 1H, J = 14.8 and 10.7 Hz, H_7), 2.95 (dd, 1H, J = 10.7 and 1.6 Hz, H_8), 3.14 (dd, 1H, J = 10.7 and 1.6 Hz, H_7), 3.63 (s, 3H, C$\underline{H}_3$O), 6.92 (s, 1H, OH) ppm;
^{13}C NMR (125 MHz, $CDCl_3$): δ= 12.4, 12.6, 12.7, 16.8, 19.6, 19.7, 22.3, 22.6, 22.7, 24.5, 24.8, 27.1, 28.0, 32.7, 32.8, 36.9, 37.3, 37.4, 38.6, 39.4, 60.4, 63.8, 64.7, 121.3, 123.6, 126.2, 129.2, 149.7, 150.5 ppm;
MS (EI): 460.4;
MS (ESI – MeOH): 944.4$^+$ $(2M+Na)^+$, 484.3$^+$ $(M+Na)^+$;
IR (neat) υ_{max} 3355, 2925, 2847, 1458, 1408, 1379, 1251, 1085, 856, 811, 665 cm^{-1};
anal. calcd. for $C_{30}H_{52}O_3$: C 78.21, H 11.38, O 10.42; found: C 78.24, H 11.19, O 10.57.



115



121

Cyclisation of 108f with aqueous HCl – Formation of furan 115 and pyran 121. To a solution of **108f** (10.3 mg, 22.3 μmol) in MeCN (4.5 mL) at room temperature, was added 1 N HCl (1.5 mL) and the mixture was stirred at room temperature for 36 h. The mixture was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue was purified by column chromatography on SiO_2 (hexane – EtOAc, 85:15) to afford **115** (5.4 mg, 52%) and **121** (4.9 mg, 48%) as colourless oils.

Furan 115. Analytics identical to those already described before.

Pyran 121.

^{1}H NMR (500 MHz, $CDCl_3$): δ= 0.83 (d, 3H, J = 6.3 Hz, $C_{4'/8'}$-C$\underline{H}_3$), 0.86 (d, 9H, J = 6.6 Hz, $C_{4'/8'/13'}$-C$\underline{H}_3$), 0.94-1.09 (m, 4H, $H_{3'/5'/7'/9'}$), 1.09-1.19 (m, 3H, $H_{2'/6'/10'/11'}$), 1.19-1.32 (m, 9H, $H_{2'/3'/5'/6'/7'/9'/10'}$), 1.29 (s, 3H, C_2-C$\underline{H}_3$), 1.32-1.43 (m, 2H, $H_{4'/8'}$), 1.48-1.60 (m, 2H, $H_{1'}$), 1.51 (sept, 1H, J = 6.9 Hz, $H_{12'}$), 1.73 (m, 1H, OH), 2.10 (s, 3H, C_8-C$\underline{H}_3$), 2.13 (s, 3H, C_5-C$\underline{H}_3$), 2.18 (s, 3H, C_7-C$\underline{H}_3$), 2.62 (dd, 1H, J = 16.7 and 5.7 Hz, H_4), 2.86 (dd, 1H, J = 17.0 and 5.4 Hz, H_4), 3.63 (s, 3H, C$\underline{H}_3$O), 3.85 (m, 1H, H_3) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ= 11.6, 11.7, 12.4, 18.9, 19.5, 19.6, 22.5, 22.6, 24.3, 24.6, 24.8, 27.8, 29.8, 32.5, 32.6, 37.0, 37.1, 37.2, 37.3, 39.2, 60.2, 68.6, 77.4, 115.6, 123.0, 126.1, 128.2, 146.3, 149.9 ppm;

MS (EI): 460.4;

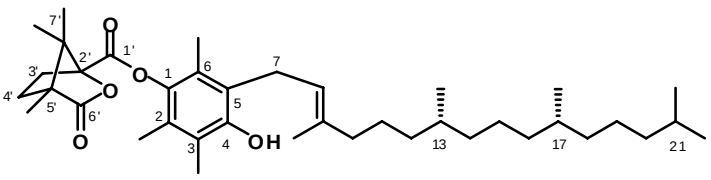
IR (neat) υ_{max} 3405, 2923, 2846, 1458, 1405, 1377, 1249, 1089, 1003 cm^{-1};

HPLC (Chiracel AD-H, 3% iPrOH in n-heptane, 0.5 mL/min, 290 nm): $t_{(2S,3R,4'R,8'R)}$ = 10.1 min, $t_{(2R,3S,4'R,8'R)}$ = 14.3 min, $t_{(2R,3R,4'R,8'R)\ and\ (2S,3S,4'R,8'R)}$ = 10.6 and 12.3 min;

UV (n-heptane) λ_{max} : 206 nm, 287 nm;

anal. calcd. for $C_{30}H_{52}O_3$: C 78.21, H 11.38, O 10.42; found: C 78.24, H 11.19, O 10.57.

(-)-CamphanoylO- / HO- phytylhydroquinone 122. To a solution of **106b** (153.3 mg, 0.212 mmol) in THF (6 mL) at room temperature, was added TBAF (1 M in THF, 240 µL, 0.240 mmol). The mixture was stirred at room temperature for 1 h, quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue was purified by column chromatography on SiO_2 (hexane – EtOAc, 9:1) to afford **122** (120.6 mg, 94%) as a colourless oil.



122

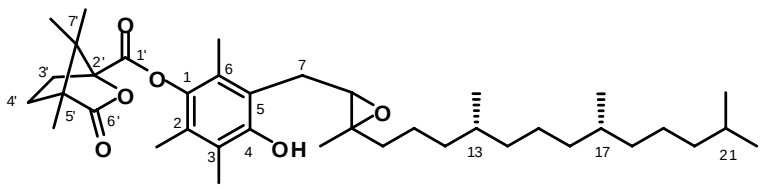
^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.82-0.88 (m, 12H, $C_{13/17/21}$-C$\underline{H}_3$), 0.99-1.20 (m, 6H, $H_{12/14/16/18/20}$), 1.15 (s, 3H, $C_{5'}$-C$\underline{H}_3$), 1.17 (s, 3H, $C_{7'}$-C$\underline{H}_3$), 1.19 (s, 3H, $C_{7'}$-C$\underline{H}_3$), 1.20-1.46 (m, 12H, $H_{11/12/13/14/15/16/17/18/19}$), 1.52 (sept, 1H, J=6.6 Hz, H_{21}), 1.79 (m, 1H, $H_{4'}$), 1.81 (s, 3H, C_9-C$\underline{H}_3$), 1.99 (m, 3H, $H_{10/4'}$), 2.05 (s, 3H, C_3-C$\underline{H}_3$), 2.08 (s, 3H, C_2-C$\underline{H}_3$), 2.15 (s, 3H, C_6-

$C\underline{H}_3$), 2.25 (m, 1H, $H_{3'}$), 2.58 (m, 1H, $H_{3'}$), 3.37 (d, 2H, J=6.6 Hz, H_7), 5.12 (t, 1H, J=6.8 Hz, H_8), 5.13 (s, 1H, OH) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ= 10.1, 12.5, 13.5, 13.7, 16.7, 17.3, 17.4, 20.1, 20.2, 23.0, 23.1, 24.9, 25.2, 26.7, 28.4, 29.4, 31.9, 33.1, 33.2, 37.1, 37.7, 37.8, 39.8, 40.4, 54.7, 55.3, 91.5, 121.3, 122.1, 123.9, 125.6, 127.2, 139.6, 141.4, 151.1, 166.4, 178.4 ppm;

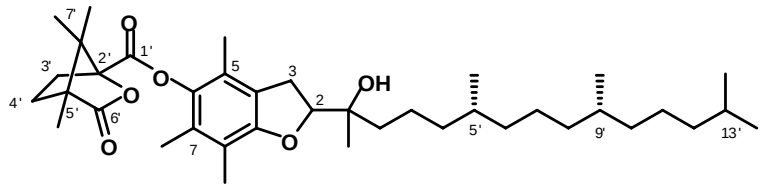
MS (ESI - MeOH): 635.7$^+$ $(M+Na)^+$, 1245.0$^+$ $(2M+Na)^+$, 1854.8$^+$ $(3M+Na)^+$.

CamphO-/OH phytylhydroquinone epoxide 116 – mCPBA epoxidation. To a solution of

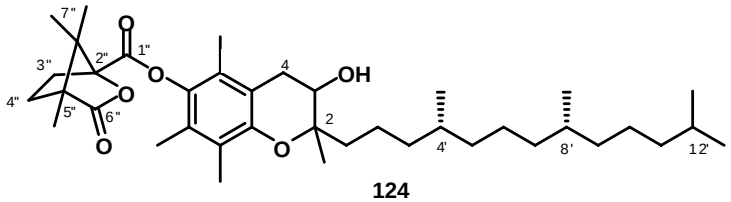


116

122 (101.1 mg, 0.165 mmol) in CH_2Cl_2 (15 mL) at 0 °C, was added mCPBA (45.7 mg, 0.26 mmol) at once. The solution was allowed to warm up to room temperature and stirred for 3 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue was purified by column chromatography on SiO_2 (hexane – EtOAc, 8:2) to afford **116** (95.2 mg, 92%) as a colourless oil. Analytics identical to those already described before.



123



124

'Anti-Baldwin' cyclisation screening – General procedure. To a solution of **116** (5.42 μmol) in the corresponding solvent (1 mL, *table 6*) was added the Brönsted acid, and the mixture stirred at room temperature for 15 h. The conversion and ratio between 5- and 6-membered ring products were determined by HPLC and by ^{1}H NMR on a quenched sample.

Furan ring 123.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.81-0.90 (m, 12H, $C_{5'/9'/13'}$-C<u>H</u>$_3$), 0.97-1.20 (m, 6H, $H_{4'/6'/8'/10'/12'}$), 1.15 (s, 3H, $C_{5''}$-C<u>H</u>$_3$), 1.17 (s, 3H, $C_{7''}$-C<u>H</u>$_3$), 1.19 (s, 3H, $C_{7''}$-C<u>H</u>$_3$), 1.20-1.47 (m, 17H, $H_{2'/3'/4'/5'/6'/7'/8'/9'/10'/11'}$, $C_{1'}$-C<u>H</u>$_3$), 1.47-1.59 (m, 1H, $H_{13'}$), 1.79 (m, 1H, $H_{4''}$), 1.96-2.07 (m, 7H, C_7-C<u>H</u>$_3$, C_8-C<u>H</u>$_3$, $H_{4''}$), 2.12 (s, 3H, C_5-C<u>H</u>$_3$), 2.25 (m, 1H, $H_{3''}$), 2.58 (m, 1H, $H_{3''}$), 3.00 (dd, 1H, J=16.4 and 9.5 Hz, H_3), 3.14 (dd, 1H, J=15.4 and 8.9 Hz, H_3), 4.61 (t, 1H, J=9.1 Hz, H_2) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ= 10.1, 12.5, 13.5, 17.1, 19.9, 22.8, 23.5, 24.4, 28.4, 29.3, 30.5, 30.7, 31.2, 31.3, 31.7, 33.2, 37.7, 38.0, 39.5, 55.0, 73.8, 89.1, 91.4, 115.4, 119.5, 127.8, 127.9, 142.3, 156.5, 178.3 ppm;

HPLC (Protonsil® 120-5-CN, 7% iPrOH in n-heptane, 1 mL/min, 220 nm): $t_{\mathbf{123}}$ = 8.6 min;

UV (n-heptane) λ_{max} : 204 nm, 287 nm.

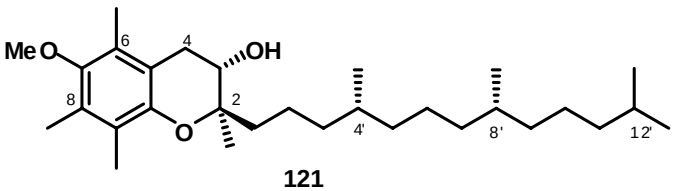
Pyran ring 124.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.81-0.90 (m, 12H, $C_{4'/8'/12'}$-C<u>H</u>$_3$), 0.97-1.20 (m, 6H, $H_{3'/5'/7'/9'/11'}$), 1.15 (s, 3H, $C_{5''}$-C<u>H</u>$_3$), 1.17 (s, 3H, $C_{7''}$-C<u>H</u>$_3$), 1.19 (s, 3H, $C_{7''}$-C<u>H</u>$_3$), 1.20-1.47 (m, 17H, $H_{1'/2'/3'/4'/5'/6'/7'/8'/9'/10'}$, C_2-C<u>H</u>$_3$), 1.47-1.59 (m, 1H, $H_{12'}$), 1.79 (m, 1H, $H_{4''}$), 1.96-2.07 (m, 7H, C_7-C<u>H</u>$_3$, C_8-C<u>H</u>$_3$, $H_{4''}$), 2.12 (s, 3H, C_5-C<u>H</u>$_3$), 2.25 (m, 1H, $H_{3''}$), 2.58 (m, 1H, $H_{3''}$), 2.63 (dd, 1H, J=18.5 and 5.3 Hz, H_4), 2.88 (dd, 1H, J=16.4 and 5.2 Hz, H_4), 3.86 (m, 1H, H_3) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ= 10.1, 12.5, 13.5, 16.9, 19.5, 19.6, 19.9, 22.7, 24.7, 28.0, 28.9, 29.4, 31.3, 31.7, 37.3, 37.4, 39.4, 55.0, 68.3, 78.8, 91.0, 119.3, 126.6, 127.5, 135.4, 141.8, 148.7, 178.2 ppm;

HPLC (Protonsil® 120-5-CN, 7% iPrOH in n-heptane, 1 mL/min, 220 nm): $t_{\mathbf{124}}$ = 10.1 min;

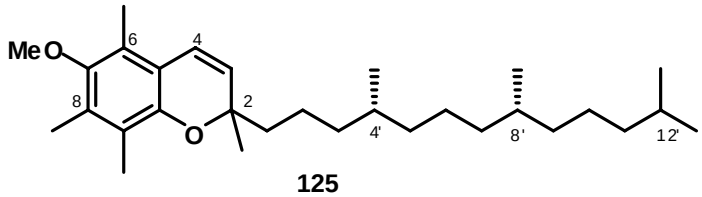
UV (n-heptane) λ_{max} : 204 nm, 284 nm.



121

Cyclisation of 114 using optimized conditions – Pyran 121. To a solution of **114** (28.3 mg, 61.3 μmol) in MeCN (12.5 mL) at 0 °C, was added HCl (2 M in Et_2O, 4.2mL). The solution was allowed to warm up to room temperature and stirred for 6 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 ×).

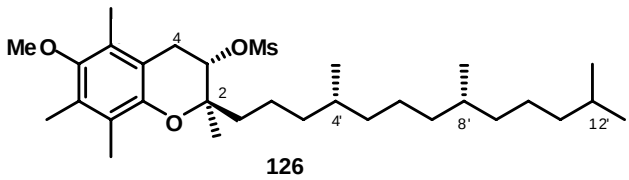
Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue was purified by column chromatography on SiO_2 (hexane – EtOAc, 85:15) to afford **121** (22.3 mg, 79%) as a colourless oil. Analytics identical to those already described before.



125

Chromene 125. During chlorination/iodination attempts on **121**, using PPh_3, I_2 or CCl_4 in refluxing toluene, chromene **125** was isolated as main side-product, by elimination of Ph_3PO, up to 70% yield. Analytics were identical to those already reported[126] – Selected data.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.81-0.90 (m, 12H, $C_{4'/8'/12'}$-C<u>H</u>$_3$), 0.97-1.20 (m, 6H, $H_{3'/5'/7'/9'/11'}$), 1.20-1.47 (m, 17H, $H_{1'/2'/3'/4'/5'/6'/7'/8'/9'/10'}$, C_2-C<u>H</u>$_3$), 1.47-1.59 (m, 1H, $H_{12'}$), 1.79 (m, 1H, $H_{4''}$), 2.09 (s, 3H, $C_{7/8}$-C<u>H</u>$_3$), 2.17 (s, 3H, $C_{7/8}$-C<u>H</u>$_3$), 2.21 (s, 3H, C_5-C<u>H</u>$_3$), 3.62 (s, 3H, C<u>H</u>$_3$O), 5.58 (d, 1H, J=10.1 Hz, $H_{3/4}$), 6.50 (d, 1H, J=10.1 Hz, $H_{3/4}$) ppm.



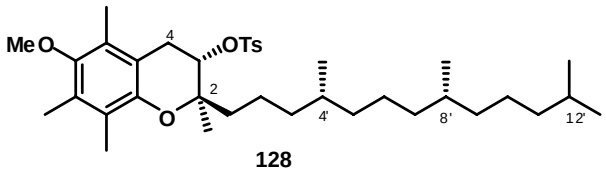
126

Mesylate 126. To a solution of **121** (4.4 mg, 0.010 mmol) in CH_2Cl_2 (1 mL) at 0 °C, was added Et_3N (3 μL, 0.020 mmol) followed by MsCl (2 μL, 0.020 mmol) and the mixture was stirred at room temperature for 5 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with Et_2O (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue was purified by column chromatography on SiO_2 (hexane – EtOAc, 8:2) to afford **126** (4.7 mg, 91%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.83 (d, 3H, J = 6.3 Hz, $C_{4'/8'}$-C<u>H</u>$_3$), 0.86 (d, 9H, J = 6.6 Hz, $C_{4'/8'/13'}$-C<u>H</u>$_3$), 0.94-1.09 (m, 4H, $H_{3'/5'/7'/9'}$), 1.09-1.19 (m, 3H, $H_{2'/6'/10'/11'}$), 1.19-1.32 (m, 9H, $H_{2'/3'/5'/6'/7'/9'/10'}$), 1.29 (s, 3H, C_2-C<u>H</u>$_3$), 1.32-1.43 (m, 2H, $H_{4'/8'}$), 1.48-1.60 (m, 2H, $H_{1'}$), 1.51 (sept, 1H, J = 6.9 Hz, $H_{12'}$), 1.73 (m, 1H, OH), 2.10 (s, 3H, C_8-C<u>H</u>$_3$), 2.13 (s, 3H, C_5-C<u>H</u>$_3$), 2.18 (s, 3H, C_7-C<u>H</u>$_3$), 2.66 (m, 1H, H_4), 2.88 (m, 1H, H_4), 3.07 (s, 3H, SO_2C<u>H</u>$_3$), 3.63 (s, 3H, C<u>H</u>$_3$O), 4.89 (m, 1H, H_3) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ= 11.5, 11.9, 12.5, 18.6, 19.6, 19.7, 22.6, 22.6, 22.7, 24.5, 24.8, 27.7, 27.9, 32.4, 32.5, 37.1, 37.2, 37.5, 39.3, 60.3, 75.5, 79.3, 115.5, 123.2, 126.5, 128.8, 146.4, 150.5 ppm;

MS (ESI - MeOH): 561.7$^+$ $(M+Na)^+$, 577.5$^+$ $(M+K)^+$.



128

Tosylate 128. To a solution of **121** (15.3 mg, 33.2 μmol) in dry pyridine (250 μL) at 0 °C, was added tosyl chloride (19.1 mg, 99.6 μmol) at once. The solution was allowed to warm up to room temperature and stirred for 36 h. The reaction was quenched with 1 N HCl and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue was purified by column chromatography on SiO_2 (hexane – EtOAc, 85:15) to afford **128** (19.1 mg, 94%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ= 0.81 (d, 3H, J = 6.6 Hz, $C_{4'/8'}$-C$\underline{H}_3$), 0.84 (d, 3H, J = 6.9 Hz, $C_{4'/8'}$-C$\underline{H}_3$), 0.86 (d, 6H, J = 6.6 Hz, $C_{13'}$-C$\underline{H}_3$); 0.90-1.09 (m, 4H, $H_{3'/5'/7'/9'}$), 1.09-1.20 (m, 4H, $H_{2'/6'/10'/11'}$), 1.15 (s, 3H, C_2-C$\underline{H}_3$), 1.19-1.39 (m, 10H, $H_{2'/3'/4'/5'/6'/7'/8'/9'/10'/11'}$), 1.40-1.47 (m, 2H, $H_{1'}$), 1.52 (sept, 1H, J = 6.6 Hz, $H_{12'}$), 2.01 (s, 3H, C_5-C$\underline{H}_3$), 2.04 (s, 3H, C_8-C$\underline{H}_3$), 2.15 (s, 3H, C_7-C$\underline{H}_3$), 2.45 (s, 3H, C$\underline{H}_3$-Tos), 2.70 (dd, 1H, J = 16.7 and 7.9 Hz, H_4), 2.92 (dd, 1H, J = 17.0 and 6.0 Hz, H_4), 3.60 (s, 3H, C$\underline{H}_3$O), 4.65 (t, J = 5.8 Hz, 1H, H_3), 7.34 (d, 2H, J = 7.9 Hz, H_m-Tos), 7.81 (d, 2H, J = 8.2 Hz, H_o-Tos) ppm;

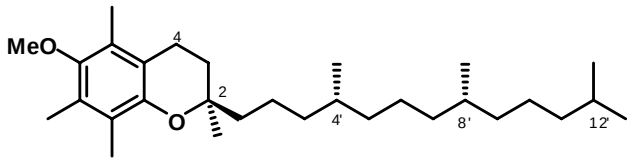
^{13}C NMR (125 MHz, $CDCl_3$): δ= 11.6, 11.8, 12.5, 18.6, 19.6, 19.7, 21.6, 22.6, 22.7, 24.4, 24.8, 27.8, 27.9, 32.6, 32.8, 37.2, 37.3, 37.4, 39.3, 60.3, 75.5, 79.2, 115.2, 123.2, 126.2, 128.0, 128.8, 129.9, 134.2, 146.3, 144.9, 150.2 ppm;

MS (EI): 614.4;

IR (neat) υ_{max} 2924, 2847, 1451, 1369, 1250, 1175, 1090, 976, 887, 814, 667 cm^{-1};

anal. calcd. for $C_{37}H_{58}O_5S$: C 72.27, H 9.51; found: C 72.29, H 9.32;

$[\alpha]_D^{20}$ = + 37.4 ± 0.2 (c = 0.89 in $CHCl_3$).

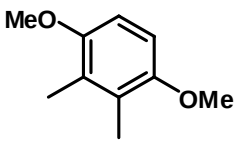


(*R*,*R*,*R*)-84

α-Tocopheryl methylether (*R*,*R*,*R*)-84 – Tosyl elimination / Hydrogenation. To a solution of **128** (9.4 mg, 15.2 μmol) in THF (1 mL) at 0 °C, was added potassium *tert*-butoxide (8.5 mg, 76.0 μmol). The solution was stirred for 1 h at 0 °C, **in the dark**. The reaction was quenched with 1 N HCl and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and used as such for next step without further purification.

The residue was dissolved in EtOAc (1 mL) and Pd/C (Pd content: 10%, 5 mg) was added. The suspension was vigorously stirred under H_2 (1 atm), at room temperature for 3 h. Solids were filtered off through a pad of celite, washed with EtOAc, and solvent was removed in vacuum. The crude oil was purified by column chromatography on SiO_2 (hexane – EtOAc, 9:1) to afford **(*R*,*R*,*R*)-84** (6.6 mg, 96%) as a colourless oil. Analytics were identical to those already described before.

HPLC (Chiracel OD-H, 0.2% iPrOH in n-heptane, 0.8 mL/min, 290 nm): $t_{(2S,4'R,8'R)}$ = 7.1 min, $t_{(2R,4'R,8'R)}$ = 7.96 min;
Diastereoisomeric excess: 93% (2*R*);
UV (n-heptane) λ_{max} : 203 nm, 288 nm;
$[\alpha]_D^{20}$ = + 0.9 ± 0.2 (c = 0.61 in $CHCl_3$).



148

Bis-methoxy hydroquinone 148. To a solution of 2,3-dimethyl-hydroquinone **68** (3.02 g, 21.9 mmol) in acetone (120 mL) was added K_2CO_3 (21.0 g, 152.0 mmol) followed by Me_2SO_4 (3.0 mL, 32.0 mmol). The suspension was vigorously stirred under reflux for 18 h and allowed to cool down to rt. The solids were filtered off through a pad of celite, washed with acetone, and the solvents removed in vacuuo. The residue was purified by column chromatography on SiO_2 (hexane –CH_2Cl_2, 6:4) to afford **148** (3.21 g, 87%) as a white solid.

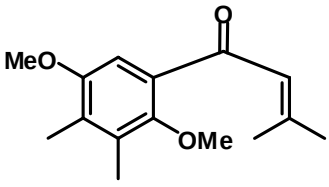
m.p.: 80-81 °C;

^{1}H NMR (400 MHz, DMSO): δ= 2.04 (s, 6H, C_{Ar}-C$\underline{H}_3$), 3.67 (s, 6H, C$\underline{H}_3$O), 6.69 (s, 2H, H_{Ar}) ppm;

^{13}C NMR (100 MHz, DMSO): δ= 12.7, 56.5, 108.8, 126.2, 152.1 ppm;

MS (EI): 166.1;

IR (neat) υ_{max} 2955, 2839, 1466, 1257, 1095, 794 cm^{-1}.



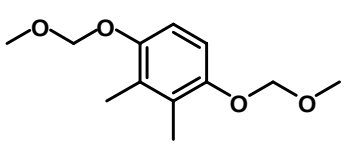
149

Crotonoyl hydroquinone 149. To a solution of **146** (198.2 mg, 2.0 mmol) in CH_2Cl_2 (4 mL) was added DMF (1 drop) followed by $C_2O_2Cl_2$ (170 μL, 2.0 mmol). The mixture was stirred at room temperature till no evolution of gas was observed, and a solution of **148** (200.2 mg, 1.20 mmol) in CH_2Cl_2 (1 mL) was added. The mixture was cooled down to 0 °C, and $TiCl_4$ (130 μL, 1.19 mmol) was added, and stirring was continued at room temperature for 9 h. The reaction was quenched with 1 N HCl and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue was purified by column chromatography on SiO_2 (hexane – EtOAc, 8:2) to afford **149** (125.1 mg, 42%) as a slight yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.98 (s, 3H, C$\underline{H}_3$-C=C), 2.17 (s, 3H, C_{Ar}-C$\underline{H}_3$), 2.22 (s, 3H, C_{Ar}-C$\underline{H}_3$), 2.24 (s, 3H, C$\underline{H}_3$-C=C), 3.62 (s, 6H, C$\underline{H}_3$O), 3.81 (s, 6H, C$\underline{H}_3$O), 6.77 (s, 1H, C$\underline{H}$=C), 6.94 (s, 1H, H_{Ar}) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ= 12.8, 12.9, 22.0, 28.4, 56.2, 63.0, 108.6, 125.5, 131.1, 132.0, 132.4, 151.6, 154.2, 155.6, 193.6 ppm;

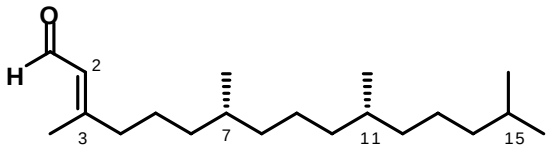
MS (ESI - MeOH): 271.0$^+$ (M+Na)$^+$, 519.0$^+$ (2M+Na)$^+$.



150

Bismethoxymethylether hydroquinone 150. To a solution of 2,3-dimethyl-hydroquinone **68** (1.49 g, 10.9 mmol) in DMF (15 mL) at 0 °C, was added NaH (60% on mineral oil, 1.5 g, 65.2 mmol) followed by MOMCl (3.8 mL, 65.2 mmol). The suspension was allowed to warm up to room temperature and stirred for 4 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with EtOAc (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue was purified by column chromatography on SiO_2 (hexane – EtOAc, 8:2) to afford **150** (2.16 g, 88%) as a colourless oil.

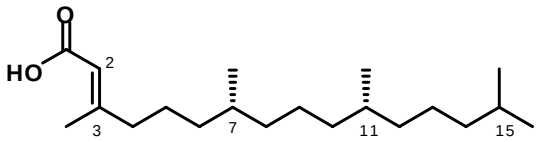
^{1}H NMR (400 MHz, $CDCl_3$): δ= 2.19 (s, 6H, C_{Ar}-C$\underline{H}_3$), 3.48 (s, 6H, C$\underline{H}_3$O), 5.12 (s, 4H, O-C$\underline{H}_2$-O), 6.86 (s, 2H, H_{Ar}) ppm;
^{13}C NMR (100 MHz, $CDCl_3$): δ= 12.8, 56.4, 95.8, 112.8, 128.1, 150.7 ppm.



145

E-(*R*,*R*)-Phytal 145. To a solution of E-(*R*,*R*)-phytol **34** (1.02 g, 3.45 mmol) in CH_2Cl_2 (40 mL) was added MnO_2 (5.9 g, 67.9 mmol) and the suspension was vigorously stirred for 1 h at room temperature. The solids were filtered off through a pad of celite, washed with CH_2Cl_2, and the solvents removed in vacuuo. The residue was purified by column chromatography on SiO_2 (hexane –EtOAc, 10:1) to afford **145** (833.0 g, 82%) as a colourless oil.

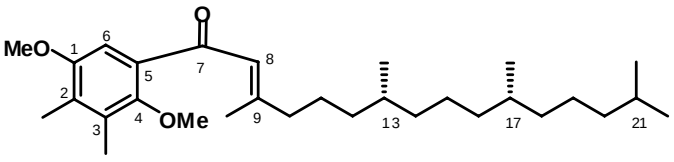
^{1}H NMR (250 MHz, $CDCl_3$): δ= 0.80-0.88 (m, 12H, $C_{7/11/15}$-C$\underline{H}_3$), 0.95-1.90 (m, 19H, $H_{5/6/7/8/9/10/11/12/13/14/15}$), 2.16 (s, 3H, C_3-C$\underline{H}_3$), 2.18 (m, 2H, H_4), 5.87 (d, 1H, *J*=8.2 Hz, H_2), 9.98 (d, 1H, *J*=7.9 Hz, C$\underline{H}$O) ppm;
^{13}C NMR (100 MHz, $CDCl_3$): δ= 17.9, 20.0, 20.1, 23.0, 23.1, 24.8, 25.0, 25.2, 28.4, 33.0, 33.2, 36.9, 37.7, 37.8, 39.7, 41.3, 127.7, 164.9, 191.8 ppm;
MS (ESI - MeOH): 317.3^+ $(M+Na)^+$, 611.4^+ $(2M+Na)^+$;
IR (neat) υ_{max} 2924, 2862, 1674, 1458, 1381, 1196, 833, 648 cm^{-1}.



152

E-(*R*,*R*)-Phytylic acid 152. To a solution of **145** (698.1 mg, 2.37 mmol) in tBuOH (50 mL) was added 2-methyl-2-butene (13 mL, 118.5 mmol) and a solution of $NaClO_2$ (1.28 g, 14.2 mmol) and NaH_2PO_4 (1.0 g, 8.3 mmol) in H_2O (14 mL) was added dropwise at room temperature. The mixture was stirred for 19 h, and the reaction quenched by the addition of 3 M NaOH. The solvents were removed in vacuuo and the residue saturated with NaCl, extracted with n-hexane. The organic layer was extracted with H_2O and the combined aqueous layer were acidified to pH<3 with 1N HCl, and extracted with EtOAc. Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue was purified by column chromatography on SiO_2 (hexane – EtOAc, 7:3) to afford **152** (530.2 mg, 72%) as a colourless oil.

^{1}H NMR (250 MHz, $CDCl_3$): δ= 0.79-0.91 (m, 12H, $C_{7/11/15}$-C<u>H</u>$_3$), 0.96-1.62 (m, 19H, $H_{5/6/7/8/9/10/11/12/13/14/15}$), 2.14 (m, 2H, H_4), 2.16 (s, 3H, C_3-C<u>H</u>$_3$), 5.70 (s, 1H, H_2) ppm;
^{13}C NMR (100 MHz, $CDCl_3$): δ= 19.4, 20.0, 20.2, 23.0, 23.1, 24.8, 25.2, 25.3, 28.4, 33.0, 33.2, 36.9, 37.7, 37.8, 39.8, 41.9, 115.1, 164.1, 171.7 ppm;
MS (EI): 310.2;
IR (neat) υ_{max} 2916, 2862, 1689, 1643, 1458, 1427, 1373, 1259, 594 cm^{-1}.



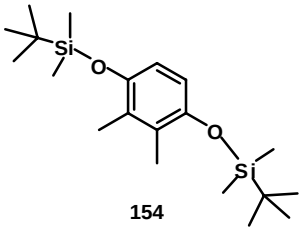
153

Bis-methoxy phytoyl hydroquinone 153 – F-C acylation. To a solution of **152** (152.1 mg, 0.49 mmol) in CH_2Cl_2 (1 mL) was added DMF (1 drop) followed by $C_2O_2Cl_2$ (41 µL, 0.48 mmol). The mixture was stirred at room temperature till no evolution of gas was observed, and a solution of **148** (57.6 mg, 0.35 mmol) in CH_2Cl_2 (1 mL) was added. The mixture was cooled down to -40 °C, and $TiCl_4$ (70 µL, 0.64 mmol) was added, and stirring was continued at room temperature for 2 h. The reaction was quenched with 1 N HCl and extracted with EtOAc (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue was purified by column chromatography on SiO_2 (CH_2Cl_2) to afford ***E*-153** (57.4 mg, 36%) and ***Z*-153** (24.6 mg, 15%) as slight yellow oils.

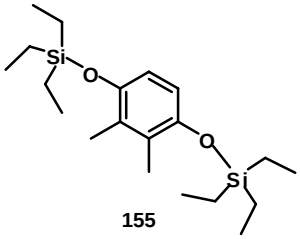
^{1}H NMR (400 MHz, $CDCl_3$): δ= Common signals: 0.81-0.89 (m, 12H, $C_{13/17/21}$-C<u>H</u>$_3$), 0.98-1.59 (m, 19H, $H_{11/12/13/14/15/16/17/18/19/20/21}$), 2.17 (s, 3H, $C_{2/3}$-C<u>H</u>$_3$), 2.22 (s, 3H, $C_{2/3}$-C<u>H</u>$_3$), 3.62 (s, 3H, C<u>H</u>$_3$O), 3.82 (s, 3H, C<u>H</u>$_3$O); Typical signals for ***E*-153**: 2.21 (m, 2H, H_{10}), 2.23 (s, 3H, C_9-C<u>H</u>$_3$), 6.78 (s, 1H, H_8), 6.95 (s, 1H, H_6); Typical signals for ***Z*-153**: 1.96 (s, 3H, C_9-C<u>H</u>$_3$), 2.61-2.66 (m, 2H, H_{10}), 6.74 (s, 1H, H_8), 6.94 (s, 1H, H_6) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ= 12.8, 12.9, 20.0, 20.1, 20.2, 23.0, 23.1, 24.9, 25.2, 25.6, 28.4, 33.1, 33.2, 37.1, 37.7, 37.8, 39.8, 42.3, 56.1, 63.0, 108.7, 124.9, 131.1, 132.0, 132.4, 154.1, 159.8, 193.7 ppm;

MS (ESI - MeOH): 481.3$^+$ $(M+Na)^+$, 939.4$^+$ $(2M+Na)^+$.



154



155

<u>Bis-sylilation of **68** – General procedure</u>. To a solution of **68** (1.93 mmol) and imidazole (9.99 mmol) in DMF (10 mL) at room temperature, was added the silyl chloride (4.9 mmol) and the mixture was stirred for 2 h. The reaction was quenched with water and extracted with EtOAc (3 ×). Combined organic phases were washed with water, brine, dried over Na_2SO_4, and evaporated to dryness. The crude oil was purified by column chromatography on SiO_2 using hexane – EtOAc mixtures.

Bis-TBSO-hydroquinone 154. 543.8 mg (>99% yield) as a slight yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 0.16 (s, 12H, C<u>H</u>$_3$Si), 1.00 (s, 18H, (C<u>H</u>$_3$)$_3$CSi), 2.11 (s, 6H, C_{Ar}-C<u>H</u>$_3$), 6.50 (s, 2H, H_{Ar}) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ= -3.8, 13.7, 18.7, 26.3, 116.2, 128.9, 147.9 ppm;

MS (EI): 366.2;

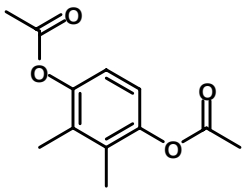
IR (neat) υ_{max} 2955, 2854, 1473, 1242, 1095, 918, 833, 779 cm^{-1}.

Bis-TBSO-hydroquinone 154. 705.1 mg (>99% yield) as a light brown liquid.

^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ= 0.66-0.79 (m, 12H, CH_3C<u>H</u>$_2$Si), 0.90-102 (m, 18H, C<u>H</u>$_3$$CH_2$Si), 2.14 (s, 3H, C_{Ar}-C<u>H</u>$_3$), 6.50 (s, 1H, H_{Ar}) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ= 5.6, 7.1, 13.5, 116.1, 128.7, 148.1 ppm;

IR (neat) υ_{max} 2955, 2877, 1473, 1250, 1095, 1010, 918, 825, 725 cm^{-1}.



156

Bis-AcO-hydroquinone 156. To a solution of **68** (269.2 mg, 1.95 mmol) in pyridine (4 mL) was added acetic anhydride (3 mL). The mixture was stirred at room temperature for 2 h. The reaction was quenched with H_2O and extracted with EtOAc (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue was purified by column chromatography on SiO_2 (hexane – EtOAc, 7:3) to afford **156** (421.0 mg, 97%) as a white solid.

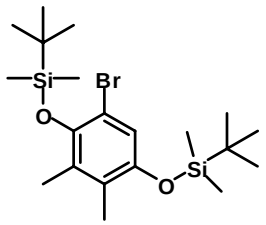
m.p.: 108-109 °C;

^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 2.09 (s, 6H, C_{Ar}-C$\underline{H}_3$), 2.32 (s, 6H, C$\underline{H}_3$CO), 6.88 (s, 2H, H_{Ar}) ppm;

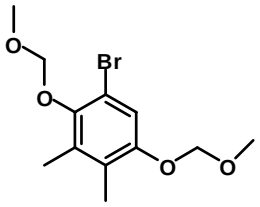
^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.5, 21.2, 120.3, 130.9, 147.2, 169.8 ppm;

IR (neat) υ_{max} 2955, 2854, 1751, 1473, 1365, 1218, 1180, 1080, 1010, 894, 733 cm^{-1};

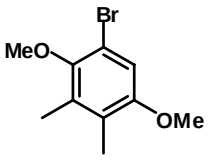
UV (MeOH) λ_{max} : 206 nm, 263 nm.



157



158



159

Bromination of aromatics – General procedure. To a solution of bis-protected aromatic (2.19 mmol) in DMF (25 mL) at room temperature, was added NBS (2.4 mmol) and the mixture was stirred for 15 h. The reaction was quenched with water and extracted with EtOAc (3 ×). Combined organic phases were washed with water, brine, dried over Na_2SO_4, and evaporated to dryness. The crude oil was purified by column chromatography on SiO_2 using hexane – EtOAc mixtures.

Bis-TBSO-bromohydroquinone 157. 866.2 mg (89% yield) as a white solid.

m.p.: 67-68 °C;

^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 0.18 (s, 6H, C$\underline{H}_3$Si), 0.22 (s, 6H, C$\underline{H}_3$Si), 1.00 (s, 9H, (C$\underline{H}_3$)$_3$CSi), 1.04 (s, 9H, (C$\underline{H}_3$)$_3$CSi), 2.06 (s, 3H, C_{Ar}-C$\underline{H}_3$), 2.14 (s, 3H, C_{Ar}-C$\underline{H}_3$), 6.82 (s, 1H, H_{Ar}) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = -3.9, -2.3, 13.7, 15.7, 18.6, 19.2, 26.2, 26.6, 111.6, 120.7, 128.4, 130.4, 145.3, 148.4 ppm;

MS (EI): 444.1, 446.1;

IR (neat) υ_{max} 2955, 2854, 1473, 1242, 1095, 918, 833, 779 cm^{-1}.

Bis-MOMO-bromohydroquinone 158. 297.5 mg (44% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 2.12 (s, 3H, C_{Ar}-C$\underline{H}_3$), 2.27 (s, 3H, C_{Ar}-C$\underline{H}_3$), 3.46 (s, 3H, C$\underline{H}_3$O), 3.65 (s, 3H, C$\underline{H}_3$O), 4.99 (s, 2H, O-C$\underline{H}_2$-O), 5.12 (s, 2H, O-C$\underline{H}_2$-O), 7.15 (s, 1H, H_{Ar}) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ= 12.9, 14.5, 56.5, 58.3, 95.5, 100.2, 114.1, 116.9, 127.4, 133.3, 147.8, 152.5 ppm;

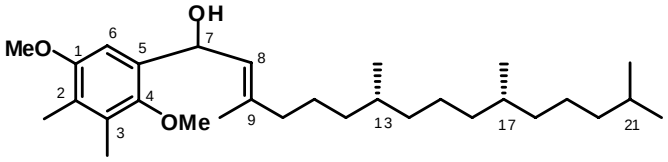
MS (EI): 304.0, 306.0.

Bis-MeO-bromohydroquinone 159. 587.0 mg (90% yield) as a colourless oil.

^{1}H NMR (250 MHz, $CDCl_3$): δ= 2.09 (s, 3H, C_{Ar}-C$\underline{H}_3$), 2.24 (s, 3H, C_{Ar}-C$\underline{H}_3$), 3.73 (s, 3H, C$\underline{H}_3$O), 3.77 (s, 3H, C$\underline{H}_3$O), 6.86 (s, 1H, H_{Ar}) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ= 12.5, 13.7, 56.3, 60.9, 112.7, 113.8, 126.4, 132.8, 149.4, 154.6 ppm;

MS (EI): 243.9, 245.9.



160

Bis-MeO-phytol-hydroquinone 160. To a solution of freshly dried Mg (1.16 g, 48.1 mmol) in dry Et_2O (5 mL), was added a crystal of I_2. A solution of **159** (5.67 g, 23.1 mmol) in THF (8 mL) was added stepwise over 45' and the solution stirred at room temperature for 2 h. Then the mixture was cooled down to 0 °C and a solution of **E-(*R,R*)-145** (2.8 g, 9.6 mmol) in THF (8 mL) was added dropwise. The mixture was allowed to warm up to room temperature and stirred for 12 h. The reaction was quenched with saturated NH_4Cl and extracted with Et_2O (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue was purified by column chromatography on SiO_2 (hexane – EtOAc, 85:15) to afford **160** (4.03 g, 91%) as a colourless oil.

^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ= 0.81-0.89 (m, 12H, $C_{13/17/21}$-C$\underline{H}_3$), 0.98-1.59 (m, 19H, $H_{11/12/13/14/15/16/17/18/19/20/21}$), 1.79 (s, 3H, C_9-C$\underline{H}_3$), 2.00 (m, 2H, H_{10}), 2.12 (s, 3H, $C_{2/3}$-

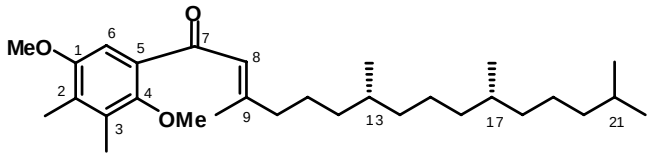
$C\underline{H}_3$), 2.20 (s, 3H, $C_{2/3}$-$C\underline{H}_3$), 2.24 (br, 1H, OH), 3.70 (s, 3H, $C\underline{H}_3O$), 3.81 (s, 3H, $C\underline{H}_3O$), 5.45 (dd, 1H, *J*=8.6 and 1.1 Hz, H_8), 5.77 (dd, 1H, *J*=8.6 and 2.9 Hz, H_7), 6.82 (s, 1H, H_6) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ= 12.4, 13.2, 17.1, 20.1, 23.0, 23.1, 24.9, 25.2, 25.6, 28.4, 33.1, 33.2, 37.2, 37.7, 37.8, 39.8, 40.4, 56.2, 61.6, 66.7, 106.5, 126.1, 127.2, 131.2, 134.5, 139.8, 149.8, 154.4 ppm;

MS (ESI - MeOH): 483.3$^+$ $(M+Na)^+$, 943.5$^+$ $(2M+Na)^+$;

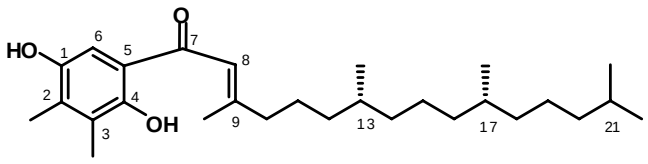
IR (neat) υ_{max} 3394, 2924, 2862, 1466, 1404, 1380, 1218, 1118, 1088, 1018, 849, 640 cm^{-1};

UV (MeOH) λ_{max} : 206 nm, 287 nm.



***E*-153**

Bis-methoxy phytoyl hydroquinone *E*-153 – Oxidation of benzylic alcohol. To a solution of **160** (4.03 g, 8.76 mmol) in CH_2Cl_2 (150 mL) was added MnO_2 (19.0 g, 0.29 mol) and the mixture was stirred for 6 h at room temperature. Solids were filtered through a pad of celite, washed with CH_2Cl_2 and EtOAc, solvents were removed in vacuuo and the residue was purified by column chromatography on SiO_2 (hexane – EtOAc, 9:1) to afford ***E*-153** (2.94 g, 72%) as a slight yellow oil. Analytics were identical to those already described before.



161

Phytoyl hydroquinone 161. To a solution of ***E*-153** (2.23 g, 4.86 mmol) in CH_2Cl_2 (100 mL) at -78 °C, was carefully added BBr_3 (1 M in CH_2Cl_2, 10.7 mL, 10.7 mmol) and the mixture was allowed to warm up to room temperature and stirred for 1 h. The reaction was quenched with MeOH, saturated $NaHCO_3$ and extracted with EtOAc (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue was purified by column chromatography on SiO_2 (hexane – EtOAc, 85:15) to afford ***E*-161** (887.1 mg, 43%) and ***Z*-161** (577.7 mg, 28%) as yellow oils.

^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ= Common signals: 0.81-0.89 (m, 12H, $C_{13/17/21}$-$C\underline{H}_3$), 0.98-1.59 (m, 19H, $H_{11/12/13/14/15/16/17/18/19/20/21}$), 2.20 (s, 3H, $C_{2/3}$-$C\underline{H}_3$), 2.22 (s, 3H, $C_{2/3}$-$C\underline{H}_3$),

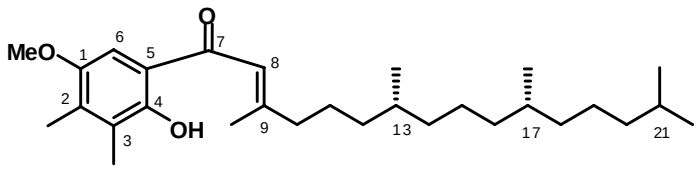
12.8 (s, 1H, OH); Typical signals for ***E*-161**: 2.16 (s, 3H, C_9-C<u>H</u>$_3$), 2.21 (m, 2H, H_{10}), 4.47 (br, 1H, OH), 6.64 (s, 1H, H_8), 7.04 (s, 1H, H_6); Typical signals for ***Z*-161**: 1.99 (s, 3H, C_9-C<u>H</u>$_3$), 2.53 (m, 2H, H_{10}), 4.37 (br, 1H, OH), 6.61 (s, 1H, H_8), 7.05 (s, 1H, H_6) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = Common signals: 12.0, 13.4, 20.1, 20.2, 23.0, 23.1, 24.9, 25.2, 28.4, 33.1, 33.2, 37.7, 37.8, 39.8, 111.9, 117.8, 127.2, 133.7, 145.5, 156.5, 160.9; Typical signals for ***E*-161**: 25.6, 37.1, 42.3, 120.1, 196.4; Typical signals for ***Z*-161**: 26.1, 30.1, 34.9, 37.5, 120.8, 196.1 ppm;

MS (ESI - MeOH): 429.5$^-$ $(M-H)^-$, 859.7$^-$ $(2M-H)^-$;

IR (neat) υ_{max} 3408, 2924, 2866, 1631, 1589, 1462, 1365, 1313, 1211, 1143, 1086, 835 cm^{-1};

HPLC (Protonsil® 120-5-CN, 1% to 2% iPrOH in n-heptane, 1 mL/min, 270 nm): $t_{E\text{-isomer}}$ = 12.2 min, $t_{Z\text{-isomer}}$ = 12.8 min.



162

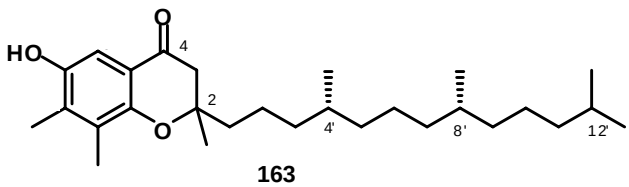
Mono-MeO Phytoyl hydroquinone 162. To a solution of ***E*-153** (497.1 mg, 1.09 mmol) in CH_2Cl_2 (15 mL) at -78 °C, was carefully added BBr_3 (1 M in CH_2Cl_2, 2.73 mL, 2.73 mmol) and the mixture stirred for 1 h at -78 °C. The reaction was quenched with MeOH, saturated $NaHCO_3$ and extracted with EtOAc (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue was purified by column chromatography on SiO_2 (hexane – CH_2Cl_2, 7:3) to afford ***E*-162** (222.2 mg, 46%) and ***Z*-162** (90.1 mg, 19%) as yellow oils.

^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = Common signals: 0.81-0.89 (m, 12H, $C_{13/17/21}$-C<u>H</u>$_3$), 0.98-1.59 (m, 19H, $H_{11/12/13/14/15/16/17/18/19/20/21}$), 2.21 (s, 6H, $C_{2/3}$-C<u>H</u>$_3$), 3.80 (s, 3H, C<u>H</u>$_3$O), 13.0 (s, 1H, OH); Typical signals for ***E*-162**: 2.15 (s, 3H, C_9-C<u>H</u>$_3$), 2.25 (m, 2H, H_{10}), 6.67 (s, 1H, H_8), 7.00 (s, 1H, H_6); Typical signals for ***Z*-162**: 2.02 (s, 3H, C_9-C<u>H</u>$_3$), 2.53 (m, 2H, H_{10}), 6.65 (s, 1H, H_8), 6.99 (s, 1H, H_6) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = Common signals: 11.9, 13.3, 20.0, 20.1, 23.0, 23.1, 24.9, 28.3, 33.0, 33.2, 37.7, 37.8, 39.8, 56.6, 107.7, 117.3, 127.3, 136.3, 149.9, 157.0; Typical signals for ***E*-161**: 25.2, 25.5, 36.1, 37.1, 42.2, 120.4, 160.0, 196.8; Typical signals for ***Z*-161**: 26.1, 34.9, 37.5, 120.9, 160.5, 196.3 ppm;

MS (ESI - MeOH): 445.2^{+} $(M+H)^{+}$, 889.3^{+} $(2M+H)^{+}$;

HPLC (Chiralpak AD-H, 1% to 3% iPrOH in n-heptane, 0.5 mL/min, 270 nm): $t_{Z\text{-isomer}} = 8.6$ min, $t_{E\text{-isomer}} = 9.0$ min.



163

Lewis acid mediated cyclisation of ***E*-161** – General procedure (*table 7*, *table 8*). To a solution of the Lewis acid in the corresponding solvent (MeCN, CH_2Cl_2, THF or CF_3CH_2OH; 0.5 mL) was added the additive is prescripted, followed by a solution of ***E*-161** (0.023 mmol) in the corresponding solvent (MeCN, CH_2Cl_2, THF, CF_3CH_2OH; 0.5 mL). The reaction was stirred between 15 h and 24 h at the temperature described, and quenched samples (H_2O/Hexane) are analysed by HPLC (Protonsil® 120-5-CN, 1% to 2% iPrOH in n-heptane, 1 mL/min, 270 nm). A pure sample was obtained by column chromatography purification on SiO_2 (hexane – EtOAc, 8:2) for analysis.

^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 0.81-0.89 (m, 12H, $C_{4'/8'/12'}$-C$\underline{H}_3$), 0.98-1.59 (m, 21H, $H_{1'/2'/3'/4'/5'/6'/7'/8'/9'/10'/11'/12'}$), 1.37 (s, 3H, C_2-C$\underline{H}_3$), 2.15 (s, 3H, $C_{7/8}$-C$\underline{H}_3$), 2.22 (s, 3H, $_{7/8}$-C$\underline{H}_3$), 2.61 (d, 1H, H_3), 2.74 (d, 1H, H_3), 5.89 (s, 1H, OH), 7.25 (s, 1H, H_6) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 12.3, 13.4, 20.0, 20.1, 21.4, 23.0, 23.1, 24.3, 24.8, 25.2, 28.4, 33.0, 33.2, 37.5, 37.7, 37.8, 39.8, 39.9, 40.0, 48.0, 81.0, 107.6, 118.0, 127.6, 134.5, 148.3, 152.8, 194.4 ppm;

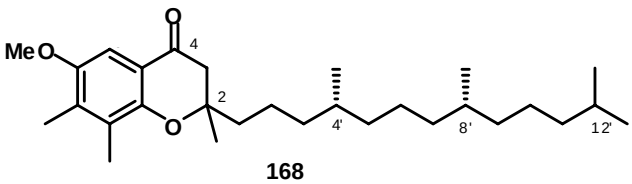
MS (ESI - MeOH): 453.3^{+} $(M+Na)^{+}$, 883.5^{+} $(2M+Na)^{+}$;

IR (neat) υ_{max} 3404, 2924, 2866, 1668, 1608, 1441, 1230, 1089, 804 cm^{-1};

HPLC (Protonsil® 120-5-CN, 1% to 2% iPrOH in n-heptane, 1 mL/min, 270 nm): $t_{\mathbf{163}} = 8.2$ min;

HPLC (Chiralpak AD-H, 1% to 3% iPrOH in n-heptane, 0.5 mL/min, 270 nm): mixture of 2 diastereoisomers, $t_{(2R,4'R,8'R)} = 35.0$ min, $t_{(2S,4'R,8'R)} = 43.2$ min;

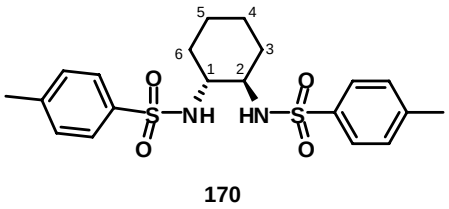
UV (MeOH) λ_{max} : 271 nm, 365 nm.



168

Lewis acid mediated cyclisation of ***E*-162** – General procedure. To a solution of the Lewis acid in CH_2Cl_2 (1 mL) was added the additive is prescripted, followed by a solution of ***E*-162** (0.046 mmol) in CH_2Cl_2 (1 mL). The reaction was stirred between 15 h and 24 h at room temperature, quenched with H_2O and extracted with EtOAc (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue was purified by preparative TLC on SiO_2 (hexane – EtOAc, 85:15) to afford **168** as a slight yellow oil.

^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ= 0.81-0.89 (m, 12H, $C_{4'/8'/12'}$-C<u>H</u>$_3$), 0.98-1.59 (m, 21H, $H_{1'/2'/3'/4'/5'/6'/7'/8'/9'/10'/11'/12'}$), 1.38 (s, 3H, C_2-C<u>H</u>$_3$), 2.15 (s, 3H, $C_{7/8}$-C<u>H</u>$_3$), 2.19 (s, 3H, $_{7/8}$-C<u>H</u>$_3$), 2.61 (d, 1H, H_3), 2.73 (d, 1H, H_3), 3.81 (s, 3H, C<u>H</u>$_3$O), 7.13 (s, 1H, H_6) ppm;
^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ= 12.3, 13.4, 20.0, 20.1, 21.4, 23.0, 23.1, 24.3, 24.8, 25.2, 28.4, 33.0, 33.2, 37.5, 37.7, 37.8, 39.8, 39.9, 40.0, 48.0, 60.2, 81.0, 107.6, 118.0, 127.6, 134.5, 149.9, 156.7, 194.4 ppm;
MS (ESI - MeOH): 467.2$^+$ $(M+Na)^+$, 911.3$^+$ $(2M+Na)^+$;
HPLC (Chiralpak AD-H, 0.5% to 5% iPrOH in n-heptane, 0.5 mL/min, 270 nm): mixture of 2 diastereoisomers, $t_{(2R,4'R,8'R)}$ = 10.2 min, $t_{(2S,4'R,8'R)}$ = 11.1 min.



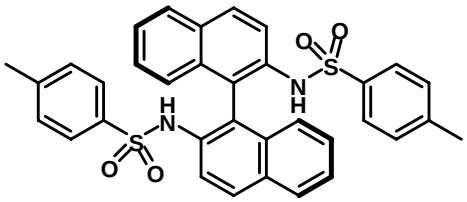
170

Bis-tosylated cyclohexyldiamine 170. To a solution of (1*R,2R*)-1,2-cyclohexanediamine **169** (62.6 mg, 0.55 mmol) in THF (4 mL) was added TsCl (267.3 mg, 1.41 mmol) followed by Et_3N (0.3 mL, 1.64 mmol) and the mixture stirred for 17 h at room temperature. The reaction was quenched with 1 N HCl and extracted with EtOAc (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue was purified by column chromatography on SiO_2 (hexane – EtOAc, 6:4) to afford **170** (234.2 mg, 99%) as a white solid. Analytics were identical to those already reported[127] – Selected data.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 1.03-1.25 (m, 4H, $H_{4/5}$), 1.50-1.60 (m, 2H, $H_{3/6}$), 1.82-1.95 (m, 2H, $H_{3/6}$), 2.46 (s, 6H, C<u>H</u>$_3$-Ts), 2.70-2.80 (m, 2H, $H_{1/2}$), 4.71 (d, 2H, *J*=4.9 Hz, N<u>H</u>), 7.26-7.33 (m, 4H, H_{Ar}), 7.72-7.77 (m, 4H, H_{Ar}) ppm.

Bis-tosylated cyclohexyldiamine – Silver complex [Ag-170-(SbF_6)]. A solution of **170** (9.5 mg, 0.023 mmol) and $AgSbF_6$ (7.7 mg, 0.023 mmol) in CH_2Cl_2 (2 mL) was stirred for 2 h at room temperature and solvents were removed in vacuuo to afford the silver complex (16.6 mg, 96%) as a white solid, highly light sensitive.

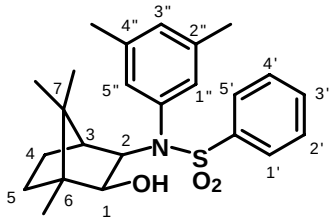
^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 0.80-0.99 (m, 2H, $H_{4/5}$), 1.01-1.18 (m, 2H, $H_{4/5}$), 1.18-1.45 (m, 4H, $H_{3/6}$), 2.40 (s, 6H, C<u>H</u>$_3$-Ts), 2.94 (m, 2H, $H_{1/2}$), 5.82 (d, 2H, *J*=6.5 Hz, N<u>H</u>), 7.26-7.28 (m, 4H, H_{Ar}), 7.77-7.79 (m, 4H, H_{Ar}) ppm;
MS (ESI - MeCN): 528.9$^+$/530.9$^+$ (Ag-**170**)$^+$, 950.8$^+$/952.8$^+$ (Ag-(**170**)$_2$)$^+$.



172

Bis-tosylated DABN 172. To a solution of (R)-DABN **171** (48.3 mg, 0.17 mmol) in pyridine (4 mL) was added TsCl (162.1 mg, 0.85 mmol) followed and the mixture stirred for 17 h at room temperature. The reaction was quenched with 1 N HCl and extracted with EtOAc (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue was purified by column chromatography on SiO_2 (hexane – EtOAc, 5:5) to afford **172** (99.8 mg, 99%) as a white solid. Analytics were identical to those already reported[128] – Selected data.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 1.92 (s, 6H, C<u>H</u>$_3$-Ts), 6.10 (s, 2H, N<u>H</u>), 6.51 (m, 2H, H_{Ar}), 6.59 (m, 2H, H_{Ar}), 6.64 (m, 4H, H_{Ar}), 6.97 (m, 2H, H_{Ar}), 7.41 (m, 2H, H_{Ar}), 7.48 (m, 4H, H_{Ar}), 7.58 (m, 2H, H_{Ar}), 8.37 (m, 2H, H_{Ar}) ppm.



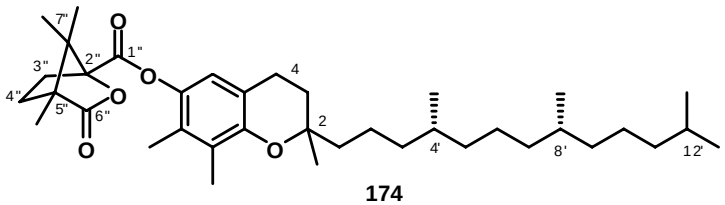
173

'Helmchen Ligand' 173.[121]

^{1}H NMR (250 MHz, CD_2Cl_2, 25 °C): δ= 0.61 (s, 3H, C_6-C<u>H</u>$_3$), 1.00 (s, 6H, C_7-C<u>H</u>$_3$), 1.20 (m, 1H, H_5), 1.50-1.72 (m, 3H, $H_{4/5}$), 2.13 (br, 3H, $C_{2"/4"}$-C<u>H</u>$_3$), 2.34 (br, 3H, $C_{2"/4"}$-C<u>H</u>$_3$), 3.55 (d, 1H, J=6.0 Hz, H_1), 3.67 (d, 1H, J= 2.7 Hz, OH), 3.97 (dd, 1H, J= 6.0 and 2.7 Hz, H_2), 5.85 (br, 1H, $H_{1"/5"}$), 6.98 (br, 1H, $H_{1"/5"}$), 7.44-7.56 (m, 4H, H_{Ar}), 7.62-7.72 (m, 1H, $H_{3'}$) ppm.

'Helmchen Ligand' 173 – Silver complex [Ag-173-(SbF_6)]. A solution of **173** (4.3 mg, 0.010 mmol) and $AgSbF_6$ (3.6 mg, 0.010 mmol) in CH_2Cl_2 (2 mL) was stirred for 1 h at room temperature and solvents were removed in vacuuo to afford the silver complex (7.9 mg, >99%) as a white solid, highly light sensitive.

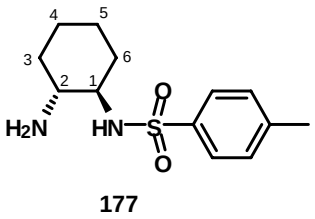
^{1}H NMR (250 MHz, CD_2Cl_2, 25 °C): δ = 0.64 (s, 3H, C_6-C<u>H</u>$_3$), 0.95 (s, 3H, C_7-C<u>H</u>$_3$), 1.06 (s, 3H, C_7-C<u>H</u>$_3$), 1.07 (m, 1H, H_5), 1.26 (m, 1H, H_5), 1.50-1.80 (m, 2H, H_4), 2.15 (br, 3H, $C_{2"/4"}$-C<u>H</u>$_3$), 2.32 (br, 3H, $C_{2"/4"}$-C<u>H</u>$_3$), 2.40-3.40 (br, 1H, OH), 3.79 (d, 1H, J=6.6 Hz, H_1), 4.05 (d, 1H, J= 6.6 Hz, H_2), 5.79 (br, 1H, $H_{1"/5"}$), 7.11 (br, 1H, $H_{1"/5"}$), 7.44-7.56 (m, 4H, H_{Ar}), 7.64-7.75 (m, 1H, $H_{3'}$) ppm;
MS (ESI - MeCN): 519.9$^+$ / 521.9$^+$ (Ag-**173**)$^+$, 560.9$^+$ / 562.9$^+$ (Ag-**173**-(MeCN))$^+$, 592.9$^+$ / 594.9$^+$ (Ag-**173**-(MeCN)(MeOH))$^+$, 932.9$^+$/934.9$^+$ (Ag-(**173**)$_2$)$^+$.



174

γ-Tocopheryl camphanate 174 – Silver mediated cyclisation – General procedure. To a solution of the silver complex **[Ag-170-(SbF_6)]** or **[Ag-173-(SbF_6)]** (0.009 mmol) in CH_2Cl_2 (1 mL) was added a solution of **99** (0.030 mmol) in CH_2Cl_2 (1 mL) and the mixture stirred for 15 h at room temperature. The reaction was quenched with saturated $NaHCO_3$ and extracted with EtOAc (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue was purified by column chromatography on SiO_2 (hexane – CH_2Cl_2, 8:2) to afford **174** as a colourless oil. Analytics were identical to those already reported[31b] – Selected data.

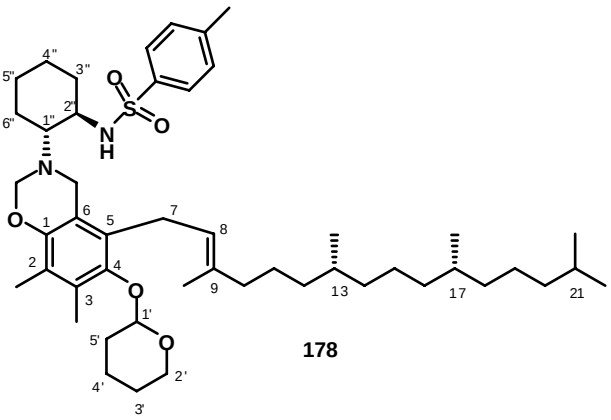
HPLC (Protonsil® 120-5-CN, 0.5% to 3% iPrOH in n-heptane, 0.5 mL/min, 270 nm): mixture of two diastereoisomers, $t_{(R,R,R)}$ = 10.4 min, $t_{(S,R,R)}$ = 11.2 min.



177

Mono-tosylated (*R,R*)-cyclohexanediamine 177. To a solution of **169** (242.2 mg, 2.12 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (0.35 mL, 2.04 mmol) and the solution cooled down to 0 °C. Then a solution of TsCl (331.1 mg, 1.74 mmol) in CH_2Cl_2 (5 mL) was added dropwise and the mixture stirred at room temperature for 4 h. The solvents were removed in vacuuo and the residue flash chromatographied on SiO_2 (CH_2Cl_2 – MeOH – Et_3N, 100:10:1). The product was solved in CH_2Cl_2, and extracted with 1 N HCl (3 ×). Combined aqueous layers were washed with 1 N NaOH and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness to afford **177** (337.2 mg, 72%) as white solid. Analytics were identical to those already described[129] – Selected data.

^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ= 1.03-1.25 (m, 4H, $H_{4/5}$), 1.50-1.60 (m, 2H, $H_{3/6}$), 1.82-1.95 (m, 2H, $H_{3/6}$), 2.31 (m, 1H, $H_{1/2}$), 2.43 (s, 3H, C<u>H</u>$_3$-Ts), 2.60 (m, 1H, $H_{1/2}$), 7.26-7.33 (m, 2H, H_{Ar}), 7.72-7.79 (m, 2H, H_{Ar}) ppm.

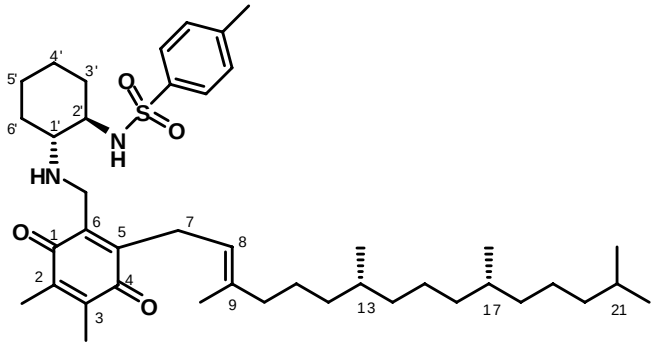


178

Mannich reaction – Formation of 178. To a solution of **177** (130.1 mg, 0.48 mmol) in MeOH (2 mL) was added HCHO (50 µL, 0.48 mmol) followed by glacial AcOH (50 µL, 0.50 mmol) and the solution stirred at 80 °C under a steam of N_2 for 30'. Then a solution of **176** (143.1 mg, 0.29 mmol) and glacial AcOH (50 µL, 0.50 mmol) in MeOH (5 mL) was added and stirring continued at 80 °C for 24 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and purified on SiO_2 (CH_2Cl_2 – MeOH, 10:0 to 9:1) to afford **178** (105.5 mg, 46%) as a yellow oil. <u>Compound was not stable and full characterization was not possible</u>.

^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ= 0.81-0.89 (m, 12H, $C_{13/17/21}$-C<u>H</u>$_3$), 0.98-1.70 (m, 28H, $H_{11/12/13/14/15/16/17/18/19/20/21/3'/5'/3''/4''/5''/6''}$), 1.70 (s, 3H, C_9-C<u>H</u>$_3$), 1-85-2.10 (m, 7H,

$H_{10/4'/5'/3''/6''}$), 2.06 (s, 3H, $C_{2/3}$-C$\underline{H}_3$), 2.18 (s, 3H, $C_{2/3}$-C$\underline{H}_3$), 2.43 (m, 1H, $H_{1''/2''}$), 2.48 (s, 3H, C$\underline{H}_3$-Ts), 2.64 (m, 1H, $H_{1''/2''}$), 3.15-3.70 (m, 4H, $H_{7/2'}$, C$\underline{H}_2$-N), 3.74-3.90 (m, 1H, N-C$\underline{H}_2$-O), 4.02 (m, 1H, $H_{2'}$), 4.25-4.35 (m, 1H, N-C$\underline{H}_2$-O), 4.60 (m, 1H, $H_{1'}$), 4.95 (m, 1H, H_8), 7.30-7.36 (m, 2H, H_{Ar}), 7.59-7.65 (m, 2H, H_{Ar}) ppm;
MS (ESI - MeOH): 793.3^+ $(M+H)^+$, 815.2^+ $(M+Na)^+$.

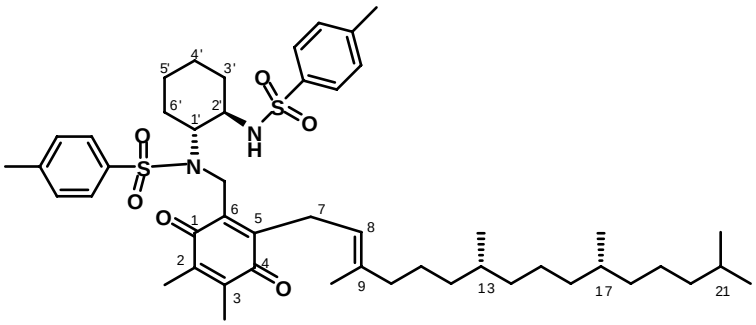


179

Mono-tosylated quinone 179. To a solution of **178** (100.1 mg, 0.126 mmol) in THF (10 mL) was added 1 N HCl (2.5 mL) and the solution was stirred at room temperature for 2 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 ×). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and used as such for the next step.

The residue was solved in CH_2Cl_2 (10 mL) and MnO_2 (220 mg, 2.52 mmol) was added. The suspension was stirred at room temperature for 30', solids were filtered off through a pad of celite and washed with CH_2Cl_2 and EtOAc. Solvents were removed in vacuuo and the residue was purified on SiO_2 (CH_2Cl_2 – MeOH, 96:4) to afford **179** (61.5 mg, 70%) as a strong orange oil. Compound was not stable (highly light sensitive) and full characterization was not possible.

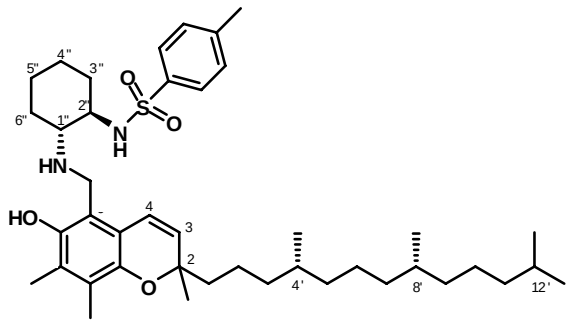
^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ= 0.81-0.89 (m, 12H, $C_{13/17/21}$-C$\underline{H}_3$), 0.98-1.70 (m, 28H, $H_{11/12/13/14/15/16/17/18/19/20/21/3'/4'/5'/6'}$), 1.70 (s, 3H, C_9-C$\underline{H}_3$), 1-85-2.10 (m, 4H, $H_{10/3'/6'}$), 2.04 (s, 6H, $C_{2/3}$-C$\underline{H}_3$), 2.10-2.20 (m, 1H, $H_{1'/2'}$), 2.38 (s, 3H, C$\underline{H}_3$-Ts), 2.56 (m, 1H, $H_{1'/2'}$), 3.17-3.22 (m, 2H, H_7), 3.34 (d, 1H, *J*= 12.0 Hz, C$\underline{H}_2$-NH-), 3.64 (d, 1H, *J*= 12.0 Hz, C$\underline{H}_2$-NH-), 4.87 (m, 1H, H_8), 7.21 (d, 2H, *J*= 8.5 Hz, H_{Ar}), 7.68 (d, 2H, *J*= 8.5 Hz, H_{Ar}) ppm;
MS (ESI - MeOH): 695.3^+ $(M+H)^+$, 717.3^+ $(M+Na)^+$.



180

Bis-tosylated quinone 180. To a solution of **179** (146.1 mg, 0.211 mmol) in CH_2Cl_2 (12 mL) was added DMAP (51.1 mg, 0.42 mmol) followed by TsCl (88.4 mg, 0.46 mmol) and the solution was stirred at room temperature for 15 h. Solvents were removed in vacuuo and the residue was purified on SiO_2 (CH_2Cl_2 – MeOH, 99:1) to afford **180** (133.6 mg, 75%) as a yellow oil. Compound was not stable (highly light sensitive) and full characterization was not possible.

^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ= 0.79-0.87 (m, 12H, $C_{13/17/21}$-C<u>H</u>$_3$), 0.98-1.70 (m, 28H, $H_{11/12/13/14/15/16/17/18/19/20/21/3'/4'/5'/6'}$), 1-71-1.90 (m, 4H, $H_{10/3'/6'}$), 1.75 (s, 3H, C_9-C<u>H</u>$_3$), 1.88 (s, 6H, $C_{2/3}$-C<u>H</u>$_3$), 2.00-2.20 (m, 2H, $H_{1'/2'}$), 2.35 (s, 3H, C<u>H</u>$_3$-Ts), 2.40 (s, 3H, C<u>H</u>$_3$-Ts), 3.43-3.47 (m, 2H, H_7), 4.11 (m, 2H, C<u>H</u>$_2$-NH-), 5.52 (m, 1H, H_8), 7.10-7.17 (m, 2H, H_{Ar}), 7.24-7.32 (m, 2H, H_{Ar}), 7.45-7.53 (m, 2H, H_{Ar}), 7.80-7.87 (m, 2H, H_{Ar}) ppm;
MS (ESI - MeOH): 871.1$^+$ $(M+Na)^+$, 887.1$^+$ $(M+K)^+$.

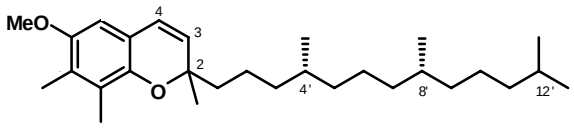


181

Mono-tosylated chromene 181. A solution of **179** (34.8 mg, 0.036 mmol) in pyridine (8 mL) was stirred at room temperature for 8 h. The reaction was quenched with 1 N HCl, extracted with CH_2Cl_2 (3 ×), and combined organic phases were dried over Na_2SO_4, evaporated to dryness and purified on SiO_2 (CH_2Cl_2 – MeOH, 95:5) to afford **181** (10.2 mg, 40%) as a yellow oil.

^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ= 0.82-0.88 (m, 12H, $C_{4'/8'/12'}$-C<u>H</u>$_3$), 0.98-1.70 (m, 33H, C_2-C<u>H</u>$_3$, $H_{1'/2'/3'/4'/5'/6'/7'/8'/9'/10'/11'/12'/3''/4''/5''/6''}$), 1-71-1.80 (m, 2H, $H_{3''/6''}$), 2.11 (s, 3H, $C_{7/8}$-C<u>H</u>$_3$), 2.13 (s, 3H, $C_{7/8}$-C<u>H</u>$_3$), 2.00-2.10 (m, 1H, $H_{1''/2''}$), 2.33 (s, 3H, C<u>H</u>$_3$-Ts), 2.95-3.05 (m, 1H, $H_{1''/2''}$), 3.88 (s, 2H, C<u>H</u>$_2$-NH-), 5.59 (d, 1H, J= 9.9 Hz, $H_{3/4}$), 6.44 (d, 1H, J= 9.8 Hz, $H_{3/4}$), 7.15-7.22 (m, 2H, H_{Ar}), 7.70-7.77 (m, 2H, H_{Ar}) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ= 12.1, 12.4, 20.0, 20.1, 20.2, 21.7, 21.8, 21.9, 23.0, 23.1, 24.4, 24.9, 25.2, 25.4, 28.4, 33.2, 37.7, 37.8, 37.9, 39.8, 40.8, 44.5, 61.1, 76.8, 114.9, 116.8, 119.6, 124.8, 125.1, 127.3, 130.2, 130.9, 138.0, 143.7, 144.1, 149.7 ppm;
MS (ESI – MeOH): 695.3$^+$ $(M+H)^+$.



183

Chromene 183. To a solution of ***E*-162** (22.2 mg, 0.050 mmol) in THF (2 mL) at -78 °C was added (*R*)-Alpine-hydride (0.5 M in THF, 0.25 mL, 0.125 mmol) and the mixture was stirred at -60 °C for 1 h and allowed to warm up to room temperature. Stirring was continued for 12 h and the reaction was quenched with H_2O, extracted with CH_2Cl_2 (3 ×), and combined organic phases were dried over Na_2SO_4, evaporated to dryness and purified on SiO_2 (hexane – EtOAc, 85:15) to afford **183** (26.6 mg, 30%) as a pale yellow oil. Analytics were identical to those already described[31b] – Selected data.

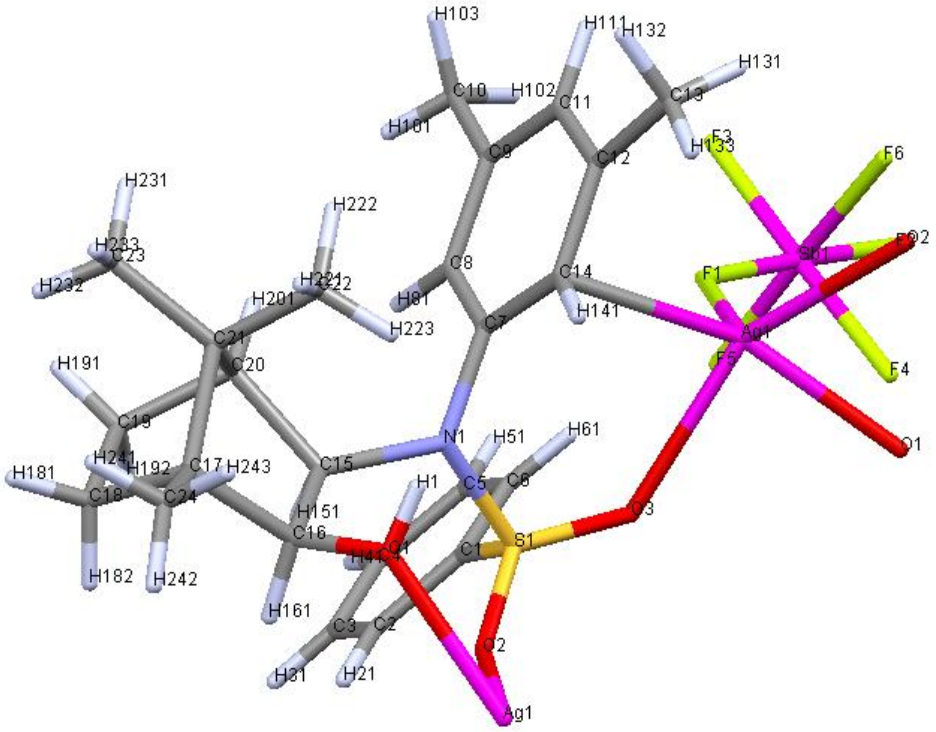
^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ= 0.82-0.88 (m, 12H, $C_{4'/8'/12'}$-C<u>H</u>$_3$), 0.98-1.55(m, 24H, C_2-C<u>H</u>$_3$, $H_{1'/2'/3'/4'/5'/6'/7'/8'/9'/10'/11'/12'}$), 2.12 (s, 6H, $C_{8/9}$-C<u>H</u>$_3$), 3.76 (s, 3H, C<u>H</u>$_3$O), 5.53 (d, 1H, J= 9.7 Hz, $H_{3/4}$), 6.28 (d, 1H, J= 9.6 Hz, $H_{3/4}$), 6.37 (s, 1H, H_6) ppm.

5.3. X-Ray data for [Ag-173-(SbF_6)]

Crystal and Structure Refinement Data for [Ag-**173**-(SbF_6)] complex.

[Ag-**173**-(SbF_6)]	
Formula	$C_{24}H_{31}AgF_6NO_3SSb$
Composition	$C_{24}H_{31}AgNO_3S$, F_6Sb
FW	757.19
Crystal size (mm)	0.04x0.05x0.44
Morphology	plate
Cryst color	colorless
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	$P2_1\ 2_1\ 2_1$
T, K	173
a/Å	11.46540(10)
b/Å	14.0539(2)
c/Å	17.2269(2)
α, deg	90.00
β, deg	90.00
γ, deg	90.00
V, $Å^3$	2775.83(6)
Z	4
θ (min, max)	1.870, 30.011
h, k, l (min, max)	(-16, 16), (-19, 19), (-24, 24)
no. of refln measured	28400
no. of unique reflns	6099
no. of parameters	335
ρ_{calc} (g/cm^3)	1.812
μ, mm^{-1}	0.1820
F(000)	1496
R indexes	R1 = 0.0209
[I>3.00σ(I)]	wR2 = 0.0224
R (all data)	R1 = 0.0324
	wR2 = 0.0303
GoF	1.1055

Structure (mercury view) and atoms coordination for [Ag-**173**-(SbF_6)] complex.



Atoms	X	Y	Z	Atoms	X	Y	Z
Sb1	0.1856	/0.4746/	0.4873	C6	0.5581	/0.5580/	0.4447
Ag1	0.4262	/0.2565/	0.4766	C7	0.5772	/0.3286/	0.3452
S1	0.6919	/0.4004/	0.4641	C8	0.5159	/0.3972/	0.3047
F1	0.3142	/0.4146/	0.4410	C9	0.4070	/0.3762/	0.2725
F2	0.0595	/0.5328/	0.5366	C10	0.3388	/0.4516/	0.2306
F3	0.1317	/0.5151/	0.3905	C11	0.3636	/0.2851/	0.2807
F4	0.2375	/0.4275/	0.5840	C12	0.4228	/0.2142/	0.3207
F5	0.2735	/0.5845/	0.5009	C13	0.3750	/0.1142/	0.3226
F6	0.1001	/0.3625/	0.4767	C14	0.5308	/0.2371/	0.3543
O1	0.8877	/0.2322/	0.3911	C15	0.7930	/0.3762/	0.3282
O2	0.8078	/0.3885/	0.4941	C16	0.9040	/0.3131/	0.3416
O3	0.5946	/0.3648/	0.5072	C17	0.9432	/0.2885/	0.2580
N1	0.6909	/0.3483/	0.3779	C18	0.9906	/0.3846/	0.2263
C1	0.6719	/0.5235/	0.4502	C19	0.8776	/0.4432/	0.2105
C2	0.7678	/0.5838/	0.4434	C20	0.7808	/0.3757/	0.2387
C3	0.7479	/0.6800/	0.4298	C21	0.8278	/0.2780/	0.2127
C4	0.6356	/0.7141/	0.4233	C22	0.7532	/0.1926/	0.2354
C5	0.5411	/0.6545/	0.4305	C23	0.8443	/0.2705/	0.1241

C24	1.0300 /0.2073/ 0.2549	H111	0.2871 /0.2707/ 0.2573
H1	0.8303 /0.2043/ 0.3742	H131	0.2957 /0.1123/ 0.3426
H21	0.8460 /0.5592/ 0.4487	H132	0.3720 /0.0919/ 0.2686
H31	0.8136 /0.7219/ 0.4253	H133	0.4249 /0.0727/ 0.3533
H41	0.6215 /0.7820/ 0.4144	H141	0.5778 /0.1878/ 0.3778
H51	0.4631 /0.6813/ 0.4261	H151	0.8138 /0.4409/ 0.3427
H61	0.4927 /0.5156/ 0.4505	H161	0.9637 /0.3523/ 0.3673
H81	0.5496 /0.4612/ 0.2986	H181	1.0355 /0.3755/ 0.1781
H101	0.3908 /0.5023/ 0.2167	H182	1.0392 /0.4159/ 0.2653
H102	0.2768 /0.4772/ 0.2618	H191	0.8685 /0.4573/ 0.1545
H103	0.3059 /0.4244/ 0.1844		

APPENDIX

6. Appendix

6.1. Abbreviations

Ac	acetyl
Anthr	9-methylanthracenyl
Ar	aromatic
Asp	aspartic acid
BINAP	2,2’-bis(diphenylphosphino)-1,1’-binaphtalene
BINOL	1,1’-binaphtalene-2,2’-diol
Bn	benzyl
Boc	t-butyloxycarbonyl
BOX	bis-oxazoline
Camph	camphanoyl
conv	conversion
CSA	camphorsulfonic acid
d	days
DABN	1,1'-binaphthalene-2,2'-diamine
dba	dibenzylideneacetone
de	diastereoisomeric excess
DIBAL-H	diisobutylaluminium hydride
DIEA	diisopropyl-ethylamine
DMAP	4-dimethylamino-pyridine
DMF	N,N-dimethylformamide
DNBA	dinitro-benzyl alcohol
DPPB	o-diphenylphosphanyl benzoate
dppp	1,3-bis(diphenylphosphino)propane
DPS	t-butyl-diphenylsilyl
e^-	electron
EC_{50}	median effective concentration
EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
ESI	electrospray ionisation

Et	ethyl
FID	flame ionization detector
GC	gas chromatography
HCTU	2-(6-Chloro-1H-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium hexafluorophosphate
HIV	human immunodeficiency virus
HMPA	hexamethylphosphoramide
HPLC	high pressure liquid chromatography
Hz	hertz
iPr	isopropyl
KHMDS	potassium bis(trimethylsilyl)amide
KLH	keyhole limpet hemocyanin
load	loading
mCPBA	m-chloroperbenzoic acid
Me	methyl
MOM	methoxy methyl
Ms	mesyl
MS	mass spectroscopy
NBS	N-bromosuccinimide
nBu	n-butyl
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Nuc	nucleophile
PC	propylene carbonate
PCC	pyridium chlorochromate
Ph	phenyl
PFP	pentafluorophenol
ppm	parts per million
Pro	proline
pTsOH	p-toluene sulfonic acid
PyBOX	pyridyl bis-oxazoline
rt	room temperature
temp	temperature

TADDOL	α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanols
TBAF	tetrabutylammonium fluoride
TBHP	t-butylhydroperoxide
TBS	t-butyl-dimethylsilyl
tBu	t-butyl
TES	triethylsilyl
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TMEDA	N,N,N',N'-tetramethylethylendiamine
TMS	trimethylsilyl
Tf	triflate
TFA	trifuoracetic acid
Ts	tosyl
v	volume
w	weight

6.2. References

[1] Hughes, G. K.; Lahey, F. N.; Price, J. R. *Nature* **1948**, *162*, 223.

[2] Brum-Bousquet, M.; Mitaku, S.; Skaltsounis, A.-L.; Tillequin, F.; Koch, M. *Planta Med.* **1988**, *54*, 470.

[3] Costes, N.; Le Deit, H.; Michel, S. ; Tillequin, F. ; Koch, M. ; Pfeiffer, B. ; Renard, P. ; Léonce, S. ; Guilbaud, N. ; Kraus-Berthier, L. ; Pierré, A.; Atassi, G. *J. Med. Chem.* **2000**, *43*, 2395 and references cited therein.

[4] Burns, T. L.; Ineck, J. R. *The Annals of Pharmacotherapy* **2006**, *40*, 251 and references cited therein.

[5] Ishibashi, K. J. *Antibiot. Ser. A.* **1962**, *15*, 161.

[6] Belloti, M. G.; Riviera, L. *Chemioterapia* **1985**, *4*, 431.

[7] Nozoe, S.; Hirai, K.; Snatzke, F.; Snatzke, G *Tetrahedron* **1974**, *30*, 2773 and references cited therein.

[8] Trost, B. M.; Shen, H. C.; Surivet, J.-P. *J. Am. Chem. Soc.* **2004**, *126*, 12565.

[9] Kashiwada, Y.; Yamazaki, K.; Ikeshiro, Y.; Yamagishi, T.; Fujioka, T.; Mihashi, K.; Mizuki, K.; Cosentino, L. M.; Fowke, K.; Morris-Natschke, S. L.; Lee, K.-H. *Tetrahedron* **2001**, *57*, 1559 and references cited therein.

[10] (a) Kurdyumov, A. V.; Hsung, R. P.; Ihlen, K.; Wang, J. *Org. Lett.* **2003**, *5*, 3935. (b) Kang, Y.; Mei, Y.; Du, Y.; Jin, Z. *Org. Lett.* **2003**, *5*, 4481.

[11] Mondal, M.; Puranik, V. G.; Argade, N. P. *J. Org. Chem.* **2007**, *72*, 2068 and references cited therein.

[12] Evans, H. M.; Bishop, K. S. *Science* **1922**, *56*, 650.

[13] Evans, H. M.; Burr, G. O. *Proc. Natl. Acad. Sci.* **1925**, *11*, 334.

[14] Evans, H. M.; Emerson, O. H.; Emerson, G. A. *Journal of Biological Chemistry* **1936**, *113*, 319.

[15] Fernholz, E. J. Am. Chem. Soc. 1938 *J. Am. Chem. Soc.* **1938**, *60*, 700.

[16] (a) Emerson, O. H.; Emerson, G. A.; Mohammad, A.; Evans, H. M. *Journal of Biological Chemistry* **1937**, *122*, 99. (b) Stern, H. M.; Robeson, C. D.; Weisler, .; Baxter, J. G. *J. Am. Chem. Soc.* **1947**, *69*, 869

[17] Mayer, H.; Schudel, P.; Rüegg, R.; Isler, O. *Helv. Chim. Acta* **1963**, *46*, 963.

[18] (a) Bauernfreind, J. B., ed. (1980) Tocopherols in foods. In *Vitamin E: Comprehensive treatise*, pp. 99-167, Marcel Dekker, New York. (b) Machlin, L. J., *Handbook of Vitamins; Nutritional, Biochemical and Clinical Aspects*, M. Dekker, Inc., New York, **1984**.

[19] Scherf, H.; Machlin, L. J.; Frye, T. M.; Krautmann, B. A.; Williams, S. N. *Animal Feed Sci. Techn.* **1996**, *59*, 115 and references cited therein.

[20] Traber, M. G.; Sies, H. *Annu. Rev. Nutr.* **1996**, *16*, 321 and references cited therein.

[21] (a) Hosomi, A.; Arita, M.; Sato, Y.; Kiyose, C.; Ueda, T.; Igarashi, O.; Arai, H.; Inoue, K. *FEBS Lett.* **1997**, *409*, 105. (b) Brigelius-Flohé, R.; Traber, M. G. *FASEB Journal* **1999**, *13*, 1145. (c) Ricciarelli, R.; Zingg, J.-M.; Azzi, A. *FASEB Journal* **2001**, *15*, 2314.

[22] Birringer, M.; Pfluger, P.; Kluth, D.; Landes, N.; Brigelius-Flohé, R. *Journal of Nutrition* **2002**, 3113 and references cited therein.

[23] Simon, E. J. ; Eisengart, A. ; dheim, L.; Milhorat, A. T. *J. Biol. Chem.* **1956**, *221*, 807.

[24] Tappel, A. L. *Vitam. Horm.* **1962**, *20*, 493.

[25] (a) Burton, G. W.; Doba, T.; Gabe, E. J. ; Hughes, L.; Lee, F. L.; Prasad, L.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 7053 and references cited therein. (b) Burton, G. W.; Ingold, K. U. *Acc. Chem. Res.* **1986**, *19*, 194.

[26] Ingold, K. U. *Spec. Publ.-Chem. Soc.* **1971,** *24*, 285.

[27] (a) Garcia, I.; Rodgers, M.; Lenne, C. ; Rolland, A. ; Sailland, A. ; Matringe M. *Biochem. J.* **1997**, *325*, 761. (b) Garcia, I.; Rodgers, M.; Pepin, R.; Hssich, T.; Matringe, M. *Plant. Physiol.* **1999**, *119*, 1507. (c) Norris, S. R.; Shen, X.; DellaPenna, D. *Plant. Physiol.* **1998**, *117*, 1317.

[28] Savidge, B. ; Weiss, J. D.; Wong, Y.-H. H.; Lassner, M. W.; Mitsky, T. A.; Shewmaker, C. K.; Post-Beittenmiller, D.; Valentin, H. E. *Plant Physiol.* **2002**, *129*, 321 and references cited therein.

[29] Soll, J. *Methods Enzymol.* **1987**, *148*, 383.

[30] (a) Marshall, P. S.; Morris, S. R.; Threlfall, D. R. *Phytochemistry* **1985**, *24*, 1701. (b) Shintani, D. K.; Cheng, Z.; DellaPenna, D. *FEBS Lett.* **2002**, *511*, 1.

[31] (a) Stocker, A.; Rüttimann, A.; Woggon, W.-D. *Helv. Chim. Acta* **1993**, *76*, 62. (b) Stocker, A.; Netscher, T.; Rüttimann, A.; Müller, R. K.; Schneider, H.; Todaro, L. J.; Derungs, G.; Woggon, W.-D. *Helv. Chim. Acta* **1994**, *77*, 1721. (c) Porfirova, S.; Bergmuller, E.; Tropf, S.; Lemke, R.; Dormann, P. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 12495 and references cited therein.

[32] Shintani, D.; DellaPenna, D. *Science* **1998**, *282*, 2098.

[33] Cahoon, E. B.; Hall, S. E.; Ripp, K. G.; Ganzke, T. S.; Hitz, W. D.; Coughlan, S. J. *Nature Biotechnology* **2003**, *21*, 1082 and references cited therein.

[34] Grütter, C. ; Alonso, E. ; Chougnet, A. ; Woggon, W.-D. *Angew. Chem. Int. Ed.* **2006**, *45*, 1126.

[35] Netscher, T. *Vitam. Horm.* **2007**, *76*, 155.

[36] (a) Cohen, N.; Banner, B. L.; Neukom, C. *Synth. Commun.* **1982**, *12*, 57. (b) Netscher, T.; Gautschi, I. *Liebigs Ann. Chem.* **1992**, 543. (c) Mayer, H.; Schudel, P.; Rüegg, R.; Isler, O. *Helv. Chim. Acta* **1963**, *46*, 650.

[37] (a) Barner, R.; Schmid, M. *Helv. Chim. Acta* **1979**, *62*, 2384. (b) Mizuguchi, E.; Suzuki, T.; Achiwa, K. *Synlett* **1994**, 929.

[38] Chênevert, R.; Courchesne, G. *Tetrahedron Lett.* **2002**, *43*, 7971.

[39] (a) Imfeld, M. (1986) 'Verfahren zur herstellung von hydrochinonderivativen' EP 0 183 042 A2. (b) Takabe, K. ; Okisaka, K. ; Uchiyama, Y. ; Katagiri, T. ; Yoda, H. *Chem. Lett.* **1985**, 561.

[40] (a) Tietze, L. F. ; Görlitzer, J. *Synthesis* **1998**, 873. (b) Tietze, L. F. ; Görlitzer, J. ; Schuffenhauer, A. ; Hübner, M. *Eur. J. Org. Chem.* **1999**, 1075.

[41] Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813 and references cited therein.

[42] Tietze, L. F. ; Stecker, F. ; Zinngrebe, J. ; Sommer, K. M. *Chem. Eur. J.* **2006**, *12*, 8770.

[43] Netscher, T. *Recent. Res. Dev. Org. Chem.* **2003**, *7*, 71 and references cited therein.

[44] Outten, R. A. ; Bohrer, P. ; Müller, R. K. ; Schneider, H. ; Rüttimann, A. ; Netscher, T. *Chem. Listy. Symposia* **1999**, *93*, S49.

[45] (a) Breit, B. ; Demel, P. *Adv. Synth. Cat.* **2001**, *343*, 429. (b) Rein, C. ; Demel, P. ; Outten, R. A. ; Netscher, T. ; Breit, B. *Angew. Chem. Int. Ed.* **2007**, *46*, 8670.

[46] Liu, K. ; Chougnet, A. ; Woggon, W.-D. *Angew. Chem. Int. Ed.* **2008**, *47*, 5827.

[47] Scott, J. W.; Bizzarro, F. T.; Parrish, D. R.; Saucy, G. *Helv. Chim Acta* **1976**, *59*, 290.

[48] Chenevert, R. ; Courchesne, G. ; Pelchat, N. *Bioorg. Med. Chem.* **2006**, *14*, 5389.

[49] Roseblade, S. J. ; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402 and references cited therein.

[50] (a) Nakamura, S.; Ishihara, K. ; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8131; (b) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2002**, *124*, 3647.

[51] Yamamoto, H.; Futatsugi, K. *Angew. Chem.* **2005**, *117*, 1958; *Angew. Chem. Int. Ed.* **2005**, *44*, 1924.

[52] Bell, S. ; Wüstenberg, B.; Kaiser, S.; Menges, T.; Pfaltz, A. *Science* **2006**, *311*, 642.

[53] (a) Birch, A. J. *J. Chem. Soc.* **1944**, 430; (b) Birch, A. J. *J. Chem. Soc.* **1945**, 809; (c) Birch, A. J. *J. Chem. Soc.* **1946**, 593; (d) Birch, A. J. *J. Chem. Soc.* **1947**, 102; (e) Birch, A. J. *J. Chem. Soc.* **1949**, 2531; (f) Birch, A. J.; Smith, H. *Quart. Rev.* **1958**, *12*, 17.

[54] Von Braun, J. *Chem. Ber.* **1900,** *33*, 1438.

[55] Hageman, H. A. *Org. React.* **1953**, *7*, 198.

[56] For an excellent review, see : Cooley, J.H. ; Evain, E. J. *Synthesis* **1989**, 1.

[57] Walther, W. ; Netscher, T. *Chirality* **1996**, *8*, 397.

[58] Baldwin, J. E. *J. Chem. Soc. Chem. Comm.* **1976**, *18*, 734.

[59] Walden, P. *Ber* . **1896**, *29*, 133.

[60] Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563.

[61] (a) Nicolaou, K. C. ; Duggan, M. E. ; Hwang, C. K.; Somers, P. K. *J. Chem. Soc. Chem. Comm.* **1985**, *19*, 1359. (b) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C. K. *J. Am. Chem. Soc.* **1989**, *111*, 5330.

[62] Selected examples : (a) Gonzalez, I. C.; Forsyth, C. J. *J. Am. Chem. Soc.* **2000,** *122*, 9099. (b) Morimoto, Y.; Nishikawa, Y.; Takaishi, M. *J. Am. Chem. Soc.* **2005**, *127*, 5806. (c) Simpson, G. L.; Heffron, T. P.; Merino, E.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 1056. (d) Morimoto, Y.; Nishikawa, Y.; Ueba, C.; Tanaka, T. *Angew. Chem.* **2005**, *118*, 824; *Angew. Chem. Int. Ed.* **2006**, *45*, 810

[63] Mukai, C. ; Ikeda, Y. ; Sugimoto, Y.-I. ; Hanaoka, M. *Tet. Lett.* **1994**, *35*, 2179.

[64] Fujiwara, K. ; Tokiwano, T. ; Murai, A. *Tet. Lett.* **1995**, *36*, 8063.

[65] Wu, M. H.; Hansen, K. B.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **1999**, 38, 2012.

[66] Janda, K. D. ; Shevlin, C. G. ; Lerner, R. A. *Science* **1993**, *259*, 490.

[67] Gruber, K.; Zhou, B.; Houk, K. N.; Lerner, R. A.; Shevlin, C. G.; Wilson, I. A. *Biochemistry* **1999**, *38*, 7062.

[68] (a) Heffron, T. P. ; Jamison, T. F. *Synlett* **2006**, 2329. (b) Vilotijevic, I. ; Jamison, T. F. *Science* **2007**, *317*, 1189.

[69] For a review, see: (a) Besse, P.; Veschambre, H. *Tetrahedron* **1994**, *50*, 8885. (b) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341.

[70] For a review, see: (a) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; 103. (b) Katsuki, T.; Martin, V.S.; *Org. React.* **1996**, *48*, 1. (c) Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; 159. (d) Katsuki, T. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 2000; 287. (e) Porte, M. J.; Skidmore, J. *Chem. Commun.* **2000**, 1215. (f) Nemoto, T; Ohshima, T.; Shibasaki, M. *J. Synth. Org. Chem. Jpn.* **2002**, *60*, 94.

[71] Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R. ; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224.

[72] (a) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488. (b) Shu, L.; Shi, Y. *Tetrahedron* **2001**, *57*, 5213.

[73] Zhao, M.-X.; Shi, Y. *J. Org. Chem*. **2006**, *71*, 5377.

[74] Hussain, H. H.; Babic, G.; Durst, T.; Wright, J. S.; Flueraru, M.; Chichirau, A.; Chepelev, L. L. *J. Org. Chem.* **2003**, *68*, 7023.

[75] For a review, see: (a) Maruyama, K.; Nagai, N.; Naruta, Y. *J. Org. Chem.* **1986**, *51*, 5083. (b) Zsindley, J.; Schmid, H. *Helv. Chim. Acta* **1968**, *51*, 1510. (c) Netcher, T.; Malaisé, G.; Bonrath, W.; Breuninger, M. *Catalysis Today* **2007**, *121*, 71.

[76] Grütter, C., *Diastereoselektive Synthese von a-Tocopherol durch eine neue, enzym-änlich Chromanol-Zyklisierung*, Ph-D Thesis, University of Basel, **2005**.

[77] Smith, L. I. ; Boyack, G. A. *J. Am. Chem Soc.* **1948**, *70*, 2690.

[78] Nicolaou, K. C. ; Li, H. ; Nold, A. L. ; Pappo, D. ; Lenzen, A. *J. Am. Chem. Soc.* **2007**, *129*, 10356.

[79] Ye, Y. Q. ; Koshino, H. ; Onose, J.-I. ; Yoshikawa, K. ; Abe, N.; Takahashi, S. *Org. Lett.* **2007**, *9*, 4131.

[80] Barrett, E. S. ; Dale, T. J. ; Rebek, J. *J. Am. Chem. Soc.* **2007**, *129*, 3818.

[81] Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969.

[82] (a) Krause, N.; Gerold, A. *Angew Chem Int. Ed.* **1997**, *36*, 186; (b) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771; (c) Krause, N. *Kontakte (Darmstadt)* **1993**, *1*, 3.

[83] For a review, see : Krause, N. ; Hoffmann-Röder, A. *Synthesis* **2001**, *2*, 171.

[84] For recent examples: (a) Yin, Y. ; Li, X. ; Lee, D.-S. ; Yang, T.-K. *Tetrahedron Asymmetry* **2000**, *11*, 3329; (b) Christoffers, J.; Rösler, U.; Werner, T. *Eur. J. Org. Chem*. **2000**, 701.

[85] For recent examples: (a) Spieler, J. ; Huttenloch, O. ; Waldmann, H. Eur. *J. Org. Chem.* **2000**, 391; (b) End, N.; Macko, L.; Zehnder, M.; Pfaltz, A. *Chem. Eur. J.* **1998**, *4*, 818.

[86] For recent examples : (a) Sawamura, M. ; Hamashima, H. ; Shinoto, H.; Ito, Y. *Tetrahedron Lett.* **1995**, *36,* 6479; (b) Inagaki, K.; Nozaki, K.; Takaya, H. *Synlett* **1997**, 119; (c) Takaya, Y.; Ogasawara, M.; Hayashi, T. *Chirality* **2000**, 12, 469; (d) Wand, H.; Watanabe, M.; Ikariya, T. *Tetrahedron Lett.* **2005**, *46*, 963.

[87] Jha, S. C.; Joshi, N. N. *Tetrahedron Asymmetry* **2001**, *12*, 2463.

[88] Kim, Y. S. ; Matsunaga, S. ; Das, J. ; Sekine, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6506 and references cited therein.

[89] (a) De Vries, A. H. M. ; Meetsma, A. ; Feringa, B. L. *Angew Chem. Int. Ed. Engl.* **1996**, *35*, 2374; (b) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; De Vries, A. H. M. *Angew Chem. Int. Ed. Engl.* **1997**, *36*, 2620.

[90] Helmchen, G. ; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336 and references cited therein.

[91] Huttenloch, O. ; Spieler, J. Waldmann, H. *Chem. Eur. J.* **2001**, *7*, 671.

[92] Seebach, D. ; Jaeschke, G. ; Pichota, A. ; Audergon, L. *Helv. Chim. Acta.* **1997**, *80*, 2515.

[93] (a) Alexakis, A. ; Vastra, J. ; Burton, J. ; Benhaim, C. ; Mangeney, P. *Tetrahedron Lett.* **1998**, *39*, 7869 ; (b) Alexakis, A.; Benhaim, C. *Org. Lett.* **2000**, *2*, 2579.

[94] Zhou, Q.-L. ; Pfaltz, A. *Tetrahedron Lett.* **1993**, *34*, 7725.

[95] Bernardi, A. ; Colombo, G. ; Scolastico, C. *Tetrahedron Lett.* **1996**, *37*, 8921.

[96] (a) Evans, D. A. ; Rovis, T. ; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 1994; (b) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325 and references cited therein.

[97] Nising, C. F.; Bräse, S. *Chem. Soc. Rev.* **2008**, *37*, 1218.

[98] Vicario, J. L. ; Badia, D. ; Carrillo, L. *Synthesis* **2007**, 2065.

[99] Enders, D. ; Lüttgen, K. ; Narine, A. A. *Synthesis* **2007**, 959.

[100] Enders, D. ; Saint-Dizier, A. ; Lannou, M. I. ; Lenzen, A. *Eur. J. Org. Chem.* **2006**, 29.

[101] Loydl, F. *Justus Liebigs Ann. Chem.* **1878**, *192*, 80.

[102] Enders, D. ; Haertwig, A. ; Raabe, G.; Runsink, J. *Eur. J. Org. Chem.* **1998**, 1771 and references cited therein.

[103] Xong, X. ; Ovens, C. ; Pilling, A. W.; Ward, J. W.; Dixon, D. J. *Org. Lett.* **2008**, *10*, 565.

[104] For recent examples : (a) Bertelsen, S. ; Diner, P.; Johansen, R. L.; Joergensen, K. A. *J. Am. Chem. Soc.* **2007**, *129*,1536; (b) Kano, T.; Tanaka, Y.; Maruoka, K. *Tetrahedron* **2007**, *63*, 8658; (c) Li, D. R.; Murugan, A.; Falck, J. R. *J. Am. Chem. Soc.* **2008**, *130*, 46.

[105] For recent examples : (a) Biddle, M. M.; Lin, M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 3830; (b) Dittmer, C.; Raabe, G.; Hintermann, L. *Eur. J. Org. Chem.* **2007**, 5886; (c) Sekino, E.; Kumamoto, T.; Tanaka, T.; Ikeda, T.; Ishikawa, T. *J. Org. Chem.* **2004**, *69*, 2760; (d) de Figueiredo, R. M.; Fröhlich, R.; Christmann, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 2883.

[106] Vanderwal, C. D. ; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 14724.

[107] Van Lingen, H. L. ; Zhuang, W. ; Hansen, T.; Rutjes, F. P. J. T.; Joergensen, K. A. *Org. Biomol. Chem.* **2003**, *1*, 1953.

[108] Wang, L. ; Liu, X. ; Dong, Z. ; Fu, X.; Feng, X. *Angew. Chem. Int. Ed.* **2008**, *47*, 8670.

[109] Friedel, C.; Crafts, J. M. *Compt. Rend.* **1877**, *84*, 1450.

[110] Drutu, I. ; Krygowski, S. E. ; Wood, J. L. *J. Org. Chem.* **2001**, *66*, 7025.

[111] Timar, T. J. *Heterocycl. Chem.* **1988**, *25*, 871.

[112] Sowmithran, D. ; Rajendra Prasad, K. J. *Synthesis* **1985**, 545.

[113] Piccolo, O. ; Filippini, L. ; Tinucci, L. ; Valoti, E.; Citterio, A. *Tetrahedron* **1986**, *42*, 885.

[114] Moher, E. D.; Grieco, P. A.; Collins, J. L. *J. Org. Chem.* **1993**, *58*, 3789.

[115] Grignard, V. *Compt. Rend.* **1900**, *130*, 1322

[116] Vickery, E. H. ; Pahler, L. F. ; Eisenbraun, E. J. *J. Org. Chem.* **1979**, *44*, 4444.

[117] Evans, D. A. ; Murry, J. A. ; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 798.

[118] Kitajima, H. ; Katsuki, T. *Synlett* **1997**, 568.

[119] Lavanant, H. ; Virelizier, H. ; Hoppilliard, Y. *J. Am. Soc. Mass. Spectrom.* **1998**, *9*, 1217 and references cited therein.

[120] Momiyama, N. ; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5360 and references cited therein.

[121] Helmchen, G. ; Wegner, G. *Tetrahedron Lett.* **1985**, *26*, 6051.

[122] Linn, B. O. ; Shunk, C. H. ; Wong, E. L.; Folkers, K. *J. Am. Chem. Soc.* **1963**, *85*, 239.

[123] a) Ryu, D. H. ; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388; b) Corey, E. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 1650 and references cited therein.

[124] R. M. Coates, D. A. Ley, P. L. Cavender, *J. Org. Chem* **1978**, *43*, 4915.

[125] Hussain, H. H. ; Babic, G. ; Durst, T. ; Wright, J. S.; Flueraru, M.; Chichirau, A.; Chepelev, L. L. *J. Org. Chem.* **2003**, *68*, 7023.

[126] Ishar, M. P. S. ; Kaur, R. ; Kaur, G. R. P. *Indian Journal of Chemistry, Section B* **1996**, *35B*, 641.

[127] Boyd, E. ; Coumbarides, G. S. ; Eames, J. ; Hay, A. ; Jones, R. V. H. ; Stenson, R. A. ; Suggate, M. J. *Tetrahedron Lett.* **2004**, *45*, 9465.

[128] Jamieson, J. Y. ; Schrock, R. R.; Davis, W. M.; Bonitatebus, P. J.; Zhu, S. S.; Hoveyda, A. H. *Organometallics* **2000**, *19*, 925.

[129] Somanathan, R. ; Walsh, P. J. *Tetrahedron: Asymmetry* **2001**, *12*, 1719.

7. Curriculum Vitae

Date of birth : 12.09.1980 (Paris – FR)
Address : 6, rue Théo Bachmann, F-68300 St-Louis
Phone/Mail : +33(0)662 03 15 16, julien.chapelat@unibas.ch
Nationality : French, Swiss permit G.
Civil status : Married, 1 child

Education

1995 – 1998 : Lycée Pravaz – Pont de Beauvoisin (F)

French Baccalaureat – Mention AB

1998 – 2000 : Lycée Champollion – Grenoble (F)

Preparation for admission to French graduate engineering schools.

2000 – 2004 : National Graduate School of Chemistry and Chemical Engineering – Clermont Ferrand (F)

ENGINEER DEGREE

General Chemistry during 2 years.
Specialization in Fine Organic Chemistry
Ranked 11 out of 61

2003 – 2004 : Blaise Pascal University – Clermont Ferrand (F)

MASTER DEGREE

"Chemical and Biochemical Transformations"
Mention Bien (n>14/20)

Since 2004 : Basel University – Department of Organic Chemistry – Basel (CH)

PH-D THESIS - Under the supervision of Pr. Dr. Wolf-D. Woggon
Final examination scheduled by end of 2008.

"Synthesis of Vitamin E compounds"

Design of asymmetric synthesis of new tocopherol derivatives
Development and application of various analytical methods
LC, LC-MS, GC, GC-MS, MS, NMR, UV, IR
'Praktikum' assistant for 4 semesters (Biology/Pharmacy students)

Professional Experience

2001 : Le Clos D'Aguzon – St Auban sur Ouvèze (F)

2 months trainee: "Extraction of Essential Oils"

Production of Sage concrete in 5000L-extractor units
Extraction of lavender essential oil

2002 : Institute of Chemical Technology – Department of Environmental Chemistry – Praha (Cz)

3 months trainee: "Adsorption of heavy metals in water"

Adsorption of Cd and Pb in water using an ecologically friendly bio-polymer.
Influence of the concentration and the temperature
Selectivity of the biopolymer

2002 - 2003 : Novartis Pharma AG – Basel (CH)

1 year trainee: "*In silico* methods of drug discovery"

Registration of compounds in the Novartis database, according to their chemical and physical properties.
Literature search
Formation of new trainees

2004 : Novartis Pharma AG – Basel (CH)

6 months trainee: "Combinatorial synthesis on solid support"

Solid phase synthesis of a 4,6-diaminopyridine library – over 10000 compound synthesised
Optimisation of reaction conditions
Screening for suitable reagents
Use of analytics (LC, LC-MS, NMR)

Publications & Contributions

2007 J. Chapelat, A. Chougnet, W.-D. Woggon, "Biomimetic syntheses of tocotrienols and tocopherols" Oral presentation at the Fall Spring Meeting of the Swiss Chemical Society, September 12. **2007**, Lausanne, Switzerland.

2008 J. Chapelat, A. Buss, A. Chougnet, W.-D. Woggon, "Diastereoselective Synhtesis of α-Tocopherol – a New Concept for the Formation of Chromanols", *Org. Lett.* **2008**, *10*, 5123.

J. Chapelat, A. Chougnet, W.-D. Woggon, "Biomimetic Chromanol Cyclisation: a Common Route to α-Tocotrienol and α-Tocopherol.", *Eur. J. Org. Chem.*, **2008**, in preparation.

Languages & Computer

French : Mother tongue
English : Fluent – TOEIC 2004: 900/990
German : Basic level

Computer : Windows XP, Vista, Microsoft Office 2003/2007

WinNMR, MestreC, MestReNova, IconNMR, IsisDraw, ChemDraw, Belstein, SciFindrer, HPLC (Agilent, Shimadzu), IR (Shimadzu), MS (Bruker), UV (Agilent).

Hobbies

Sports : Tennis, Basket-Ball
Music : Musical Studies in Saxophone Alto & Baryton (Superior Degree, 2nd place at the European Contest for Young Solists – Gap, 1996)
Culture : Music, Books, Movies, Travel, Computer

References

Dr. Ulrich Schopfer (2002-2003)
Novartis Institutes for BioMedical Research
CH-4002 Basel
+41 61 324 49 51
Ulrich.Schopfer@novartis.com

Dr. Philipp Grosche (2004)
Novartis Institutes for BioMedical Research
CH-4002 Basel
+41 61 324 68 87
Philipp.Grosche@novartis.com

Pr. Wolf-D. Woggon (2004-)
University of Basel – Department of Organic Chemistry
St. Johanns-Ring 19
CH-4056 Basel
+41 61 267 11 04
Wolf-D.Woggon@unibas.ch

Pr. Antoinette Chougnet (2004-)
University of Basel – Department of Organic Chemistry
St. Johanns-Ring 19
CH-4056 Basel
+41 61 267 11 09
Antoinette.Chougnet@unibas.ch