Diastereoselective Synthesis of α-Tocopherol

INAUGURALDISSERTATION

zur

Erlangung der Würde eines Doktors der Philosophie

vorgelegt der

Philosophisch-Naturwissenschaftlichen Fakultät

der Universität Basel

von

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Deutschland

Basel, 2008

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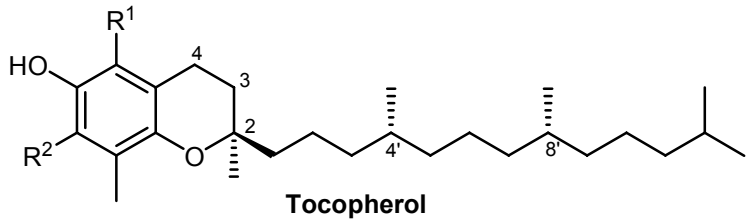
1 Introduction

1.1 Vitamin E

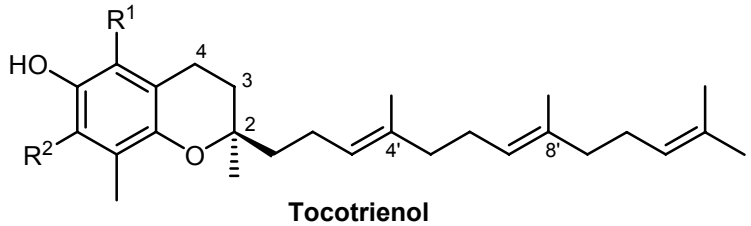
1.1.1 History and Discovery of Vitamin E

Vitamin E is the collective name given to a family of biologically active molecules called tocopherols and tocotrienols. In 1922, the discovery of vitamin E by Evans and Bishop resulted from a rat feeding study in which a diet of purified foods (casein 18%, cornstarch 54%, lard 15%, butterfat 9%) with essential salts (4%) and known vitamins (vitamin A (as cod liver oil), vitamin B (as yeast) and vitamin C (as orange juice)) was shown to produce adverse effects to pregnant females leading to fetus resorption.[1] However, when fed with fresh lettuce such symptoms were no longer observed and therefore upon the addition of certain vegetable products the reproductive ability of the rats could be restored. Consequently, an unknown nutrient was shown to be essential for fetal development. They concluded: “natural foods, as opposed to purified diets contained a substance not needed for normal growth, but essential for reproduction.” In 1924, Sure observed independently of Evans that a missing nutrient in the diet was responsible for making rats sterile and he termed this missing nutrient, Vitamin E because vitamins A, B, C and D were at this time already known.[2] Intense investigations were undertaken by Evans et al., however, little progress was observed until 1936 when a fat soluble molecule possessing the properties ascribed to the unknown molecule Vitamin E was extracted from wheat germ oil.[3] They called the substance tocopherol. The name is derived from the ancient Greek word *phero,* “to bring” and the word *tocos*, meaning “childbirth”. The structure of this molecule was elucidated in 1936 and today this molecule is called α-tocopherol (**1**) (*figure 1*). In the following years the three remaining tocopherols, β-, γ-, and δ-tocopherol (**2 - 4**) were isolated.[4, 5] In 1963 the (*R*)-configuration could be assigned to the three stereo centers of α-tocopherol for the first time, by Isler and coworkers.[6] About at that time the four remaining members of the vitamin E family, the tocotrienols **5 - 8**, were isolated,[7] which also showed vitamin E activity. Consequently, there are in total four tocopherols and four tocotrienols known today, which belong to the vitamin E family and occur in nature.



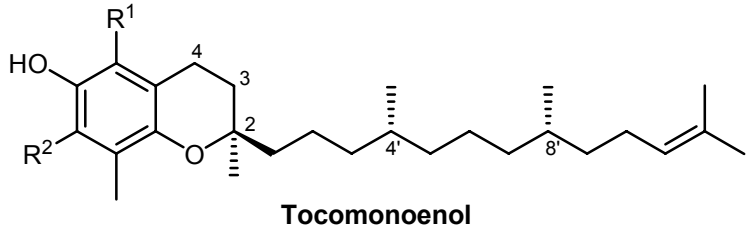
Tocopherol

	R^1	R^2	prefix:
1	Me	Me	α–
2	Me	H	β–
3	H	Me	γ–
4	H	H	δ–

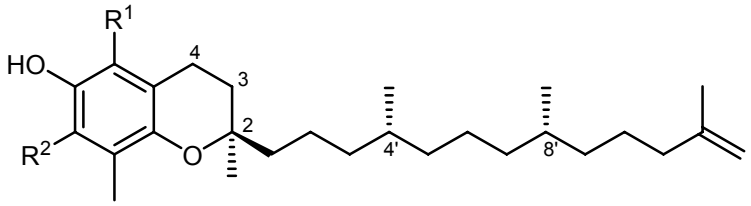


Tocotrienol

	R^1	R^2	prefix:
5	Me	Me	α–
6	Me	H	β–
7	H	Me	γ–
8	H	H	δ–

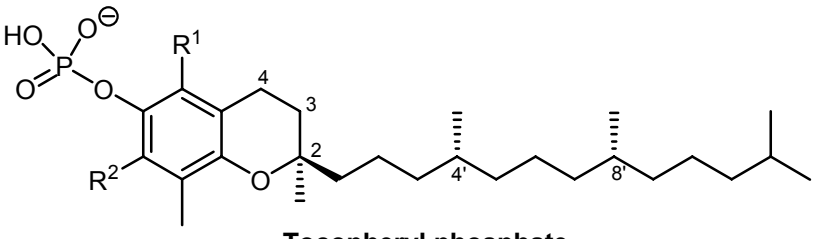


Tocomonoenol



Marine Derived Tocopherol (MDT)

R^1	R^2	prefix:
Me	Me	α–
Me	H	β–
H	Me	γ–
H	H	δ–



Tocopheryl phosphate

Figure 1: *Natural vitamin E analogues*

1.1.2 Structure and Occurrence of Vitamin E

Natural vitamin E comprises eight different forms which are all derived from 6-chromanol, the α-, β-, γ-, and δ-tocopherols and the α-, β-, γ-, and δ-tocotrienols.

The tocotrienols have an unsaturated isoprenoid side chain with three *trans* double bonds at the 3', 7' and 11' positions and possess one stereo centre with *R* configuration at C(2). In contrast the tocopherols also contain a trimethyltridecyl tail and possess three chiral centres at the 2, 4', 8' positions which naturally occur in the *R,R,R* configuration (*figure 1*). These compounds are only synthesised by plants and other oxygenic, photosynthetic organisms, but they are essential components of the diet of animals. Plants produce a range of tocochromanols which vary in their abundance and compositions and in general, photosynthetic plant tissues contain from 10 to 50 µg of tocochromanols per g fresh weight. Despite these variations, α-tocopherol is often the principle tocochromanol in leaves.

Seed oils are a major source of vitamin E for the human diet and the compositions of tocopherols in some unrefined oils are listed in ***table 1***. Sunflower and olive oils are good sources of α-tocopherol and palm oil of the tocotrienols. In general, tocotrienols tend to be more abundant in seeds of monocots, such as wheat, rice and barley.[8]

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
palm	89	-	18	-	128	-	323	72
soybean	100	8	1021	421	-	-	-	-
maize	282	54	1034	54	49	8	161	6
sunflower	670	27	11	1	-	-	-	-
rapeseed	202	65	490	9	-	-	-	-

Table 1: *Tocopherol and tocotrienol contents (mg/Kg) in some seed oils.*[9]

In human plasma of unsupplemented individuals, α-tocopherol is found on average at concentrations of 22–28 µM, which is 10 and 100 times higher than the concentrations of γ-tocopherol (2.5 µM) and of δ-tocopherol (0.3 µM), respectively.[10, 11] The highest content of α-tocopherol is found in adipose tissue (150 µg/g tissue) and the adrenal glands (132 µg/g tissue). Other organs such as the kidneys, heart or liver contain between 7 and 40 µg/g tissues. In contrast erythrocytes have a relatively low content of 2 µg/g tissue.[12, 13] Of the eight vitamin E family members only α-

tocopherol (and to a much lesser extent γ-tocopherol) appears to be retained in significant amounts by a living organism.[14]

Relatively recently, novel natural vitamin E analogues have been discovered. For example, palm oil also contains small amounts of α-tocomonoenol, and some marine organisms also contain marine derived tocopherol (MDT), with a single unsaturated bond at the end of the side chain, which is assumed to be the result of cold-water adaptation.[15, 16] α-Tocopheryl phosphate has recently been detected at low levels in liver and adipose tissue, and it is possible that it may be an ubiquitous constituent of animal and plant tissues (*figure 1*).[17, 18]

1.1.3 Biological Activity of Vitamin E

As already mentioned Vitamin E was discovered in 1922 by Evans and Bishop as a necessary dietary factor for reproduction in rats.[1] Many other disorders and diseases are thought to be in connection with a Vitamin E deficiency.[19, 20] Among them are:

- Many types of cancer
- Atherosclerosis and other circulatory diseases
- Arthritis
- Cataract formation
- Senile dementia (Alzheimer type)
- Respiratory diseases induced by pollution

Some foods become rancid when they are stored, which is a sign that the lipid material, i.e., the fats, in the food have undergone a chemical reaction with atmospheric oxygen. Such oxidations that occur under mild conditions are called *autoxidations*[21], or, in biological circles, *lipid peroxidations* (*figure 2*).

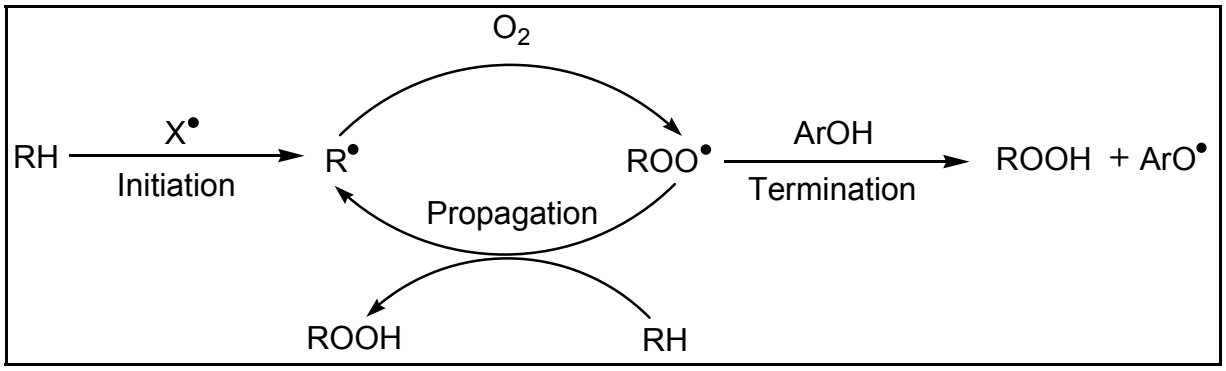


Figure 2: *Autoxidation of lipids (RH).*

The first step for each chain involves the production of a lipid-radical (R$^{\bullet}$). Such chain initiation may occur by the reaction of a lipid (RH) with a reactive oxygen-species. In general, the oxidation of lipids is known to proceed by a chain process mediated by a free radical, in which the lipid peroxyl radical (ROO$^{\bullet}$) serves as a chain carrier. These peroxyl radicals are trapped in the presence of tocopherols (ArOH) because the tocopheroxyl radicals (ArO$^{\bullet}$) formed are more stable (*figure 2*) due to resonance stabilization. Consequently they do not continue the chain, but are eventually destroyed by reaction with a second peroxyl radical or with two electron oxidants (such as peroxynitrite, ONOO^{-}). This yields 8α-substituted tocopherones, which are readily hydrolysed to 8α-hydroxy tocopherones. These then rearrange spontaneously to form α-tocopheryl quinones (*figure 3*).[22] In an alternative pathway, epoxy-α-tocopheryl quinones are also formed.[23]

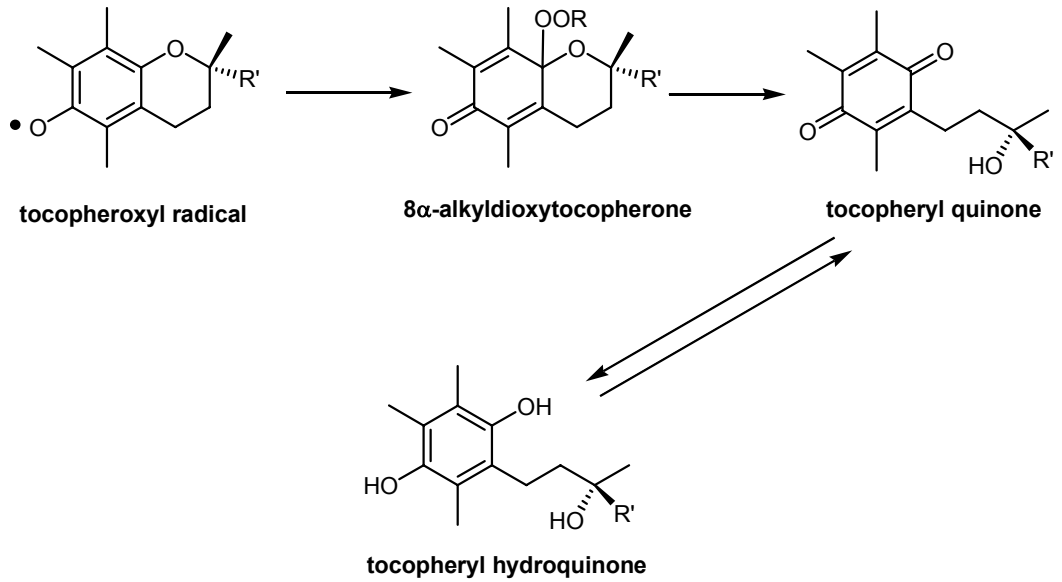


Figure 3: *Oxidation products of* α-tocopherol*.*

In comparison to simple phenols, α-tocopherol (**1**) is the more effective antioxidant. It could be shown that stabilization of the phenoxyl radical in α-tocopherol is maximized due to the optimized interaction of the orbital of the ring-oxygen with the half-occupied molecular orbital (SOMO) of the phenoxyl radical (*figure 4*).[24] Additionally, the completely substituted phenol-ring with three methyl-groups also has a stabilizing effect on the radical.

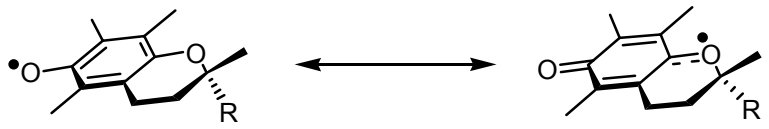


Figure 4: *Resonance stabilization of the tocopheroxyl radical.*

In plant and animal tissues, tocopherols can be regenerated from the tocopheroxyl radicals in a redox cycle mediated by a number of antioxidants, including vitamins A and C and coenzyme Q, this greatly extends their biological potency.[25] Vitamin C (ascorbate) may be especially important in aqueous systems, although it may also act at the surface of membranes.[26]

The materials that are most readily autoxidised in living organisms and hence in most need of protection are the polyunsaturated fatty acids. Like other fatty acids, these form part of various lipid materials within the organism including, particularly, biomembranes. The protection of organic material, including living organisms, against oxidative degradation is provided by fairly small quantities of certain specific compounds called antioxidants.[27] Such compounds can be divided into two broad classes, referred to as *preventive* antioxidants, which reduce the rate of chain initiation, and *chain-breaking* antioxidants (ArOH in *figure 2*).

It has been proposed by Traber and Atkinson that all of the observations concerning the *in vivo* mechanism of action of α-tocopherol result from its role as a lipid-soluble chain-breaking antioxidant, a so-called peroxyl radical scavenger. The importance of this function is to maintain the integrity of long-chain polyunsaturated fatty acids and thus maintain their bioactivity. These bioactive lipids are important signalling molecules. Changes in their amounts, loss due to oxidation, or their oxidation products are the key cellular events that are responded to by cells.[28] This hypothesis

is supported by studies in plants where the genes for vitamin E synthesis are missing.[29]

In animals, all tocopherols are absorbed to a similar extent in the intestines and are transported to the liver mainly in chylomicrons. Despite the fact that all members of the vitamin E family have similar antioxidant functions *in vitro* (rate constants for H-atom donation are within an order of magnitude), α-tocopherol is preferentially utilized and re-exported by the hepatic α-tocopherol transfer protein (α-TTP).[30] Moreover defects in the human α-TTP[31] lead to severe vitamin E deficiency.[32]

α-TTP is responsible for maintaining plasma α-tocopherol concentrations.[33] The important structural features of the ligand for recognition by α-TTP include:

(1) A fully methylated chroman ring.

(2) A phytyl pyrophosphate-derived tail[34] (trimethyltridecyl-residue).

(3) The *R*-configuration at C(2) where the tail attaches to the chromanol ring.[35]

This third requirement makes α-TTP selective for the 2*R*-isomers of synthetic all-*rac*-α-tocopherol. Thus only natural α-tocopherol (*RRR*-α-tocopherol) and 2*R*-α-tocopherols in synthetic α-tocopherol, are maintained in human plasma and tissues by α-TTP unlike the remaining forms of vitamin E.[36]

1.1.4 The Biosynthesis of Vitamin E

Enzymes required for the biosynthesis of vitamin E are found specifically in chloroplasts[37, 38, 39] and chromoplasts.[40] Two substrates are required for vitamin E biosynthesis: Homogentisate (**11**) and a C_{20} prenyldiphosphate (either geranylgeranyldiphosphate for tocotrienols or phytyldiphosphate (**12**) for tocopherols). Homogentisate (**11**) supplies the aromatic ring of the chromanol head group and is derived from tyrosine (**9**), which itself is biosynthesised via the shikimate pathway. Tyrosine is deaminated to *p*-hydroxy-phenylpyruvate (**10**), which in turn is oxygenated to homogentisate (**11**). The prenyl groups, which are also required, are supplied by the 1-deoxy-D-xylulose-5-phosphate pathway.[41]

The first step of vitamin E biosynthesis is the transfer of a prenyl group to homogentisate (**11**). This transfer involves a condensation and a decarboxylation[42] and occurs via either homogentisate phytyltransferase or homogentisate geranylgeranyl-transferase. The substrate specificity of the prenyltransferase determines whether the final tocochromanol will be a tocopherol or a tocotrienol. In order to have γ- or α-tocochromanols, the number 3 position on the benzoquinol ring must be methylated. This methylation step is omitted when β- and δ-tocochromanols are produced. The enzyme that catalyses this reaction is called 2-methyl-6-prenylbenzoquinol methyltransferase. Recent work shows that this enzyme shows no activity towards β- and δ-tocopherols.[43, 44] Consequently, if the 3 position is methylated, it appears that this methylation must happen prior to the cyclization step.

Ring closure to the chromanol head group is performed by tocopherol/tocotrienol cyclase[45] from a benzoquinol intermediate. The product is either γ- or δ-tocochromanol. The activity shows little, if any, preference for phytylated substrates over geranylgeranylated substrates.[46, 47] Thus, tocopherol/tocotrienol cyclase produces both γ- and δ-tocopherols as well as γ- and δ-tocotrienols.

The final step of the synthesis of α- or β-tocochromanols is the methylation of carbon 5 on the chromanol ring. This is catalyzed by tocopherol/tocotrienol methyl-transferase (*figure 5)*.[48]

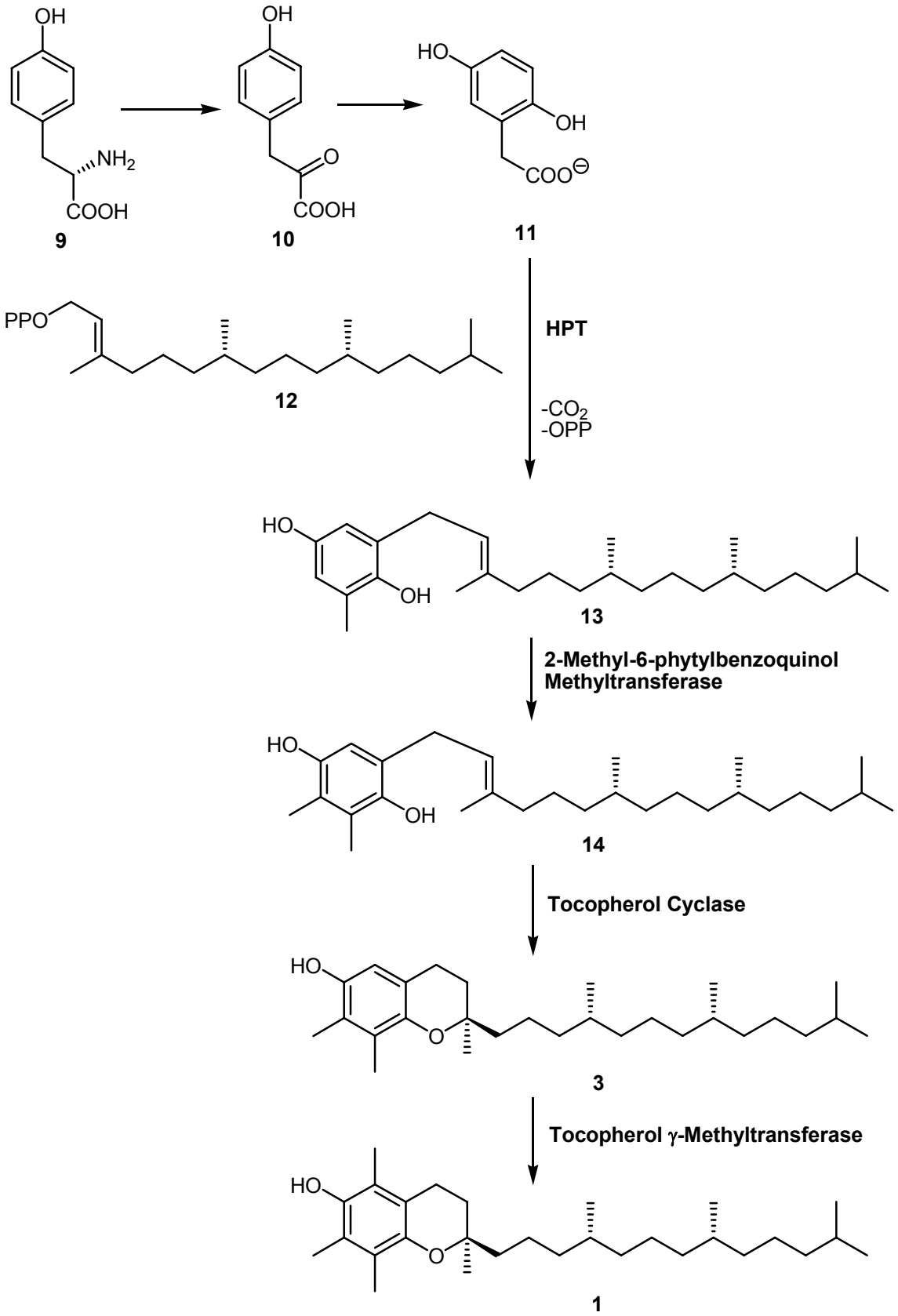


Figure 5: *Biosynthesis of γ- (**3**) and α-tocopherol (**1**).*

1.1.5 The Tocopherol Cyclase

The tocopherol cyclase was isolated in the *Woggon* group from cultures of the blue-green algae *Anabaena variabilis* KUETZING (Cyanobacteria).[49] The rationale for this enzyme isolation was the hope to find a replacement for the difficult synthetic cyclisation step in the preparation of *R,R,R*-tocopherols by an enzymatic process. It could be shown that the isolated tocopherol cyclase was able to cyclize 2,3-dimethyl-5-phytylhydroquinone (**14)** to γ-tocopherol (**3**) (*figure* 5) with nearly quantitative substrate turnover under precisely defined conditions.[49]

In order to fully understand the mechanism of the enzymatic cyclisation, three independent possible routes were considered (*figure 6*):[50]

Route A involves the stereospecific hydration of the (*E*)-double bond of (O^4-^{18}O)-**14** followed by cyclisation to give (3*S*)-(3-^{2}H)-**3** via the intermediate (O^4-^{18}O, 2'-^{2}H)-**15**. This cyclisation would proceed under retention of configuration at the tertiary alcohol in (O^4-^{18}O, 2'-^{2}H)-**15**. This last step had already been exploited in the stereospecific acid catalyzed, non-enzymatic ring-closure in the total synthesis of α-tocopherols (*figure 6*).[51]

The second possible pathway is illustrated as *Route B* in ***Figure 6***. This pathway involves the reverse addition of H_2O (or any other species like HS-enzyme) to the double bond of (O^4-^{18}O)-**14** which would yield **16** as an alcohol (or thio adduct). This could in turn cyclise under inversion of configuration by attack of the phenolic O-atom to give (3*R*)-(1-^{18}O,3-^{2}H)-**3**.

The third possibility, *Route C*, simply involves the stereospecific addition to the protonated double bond of (O^4-^{18}O)-**14**.

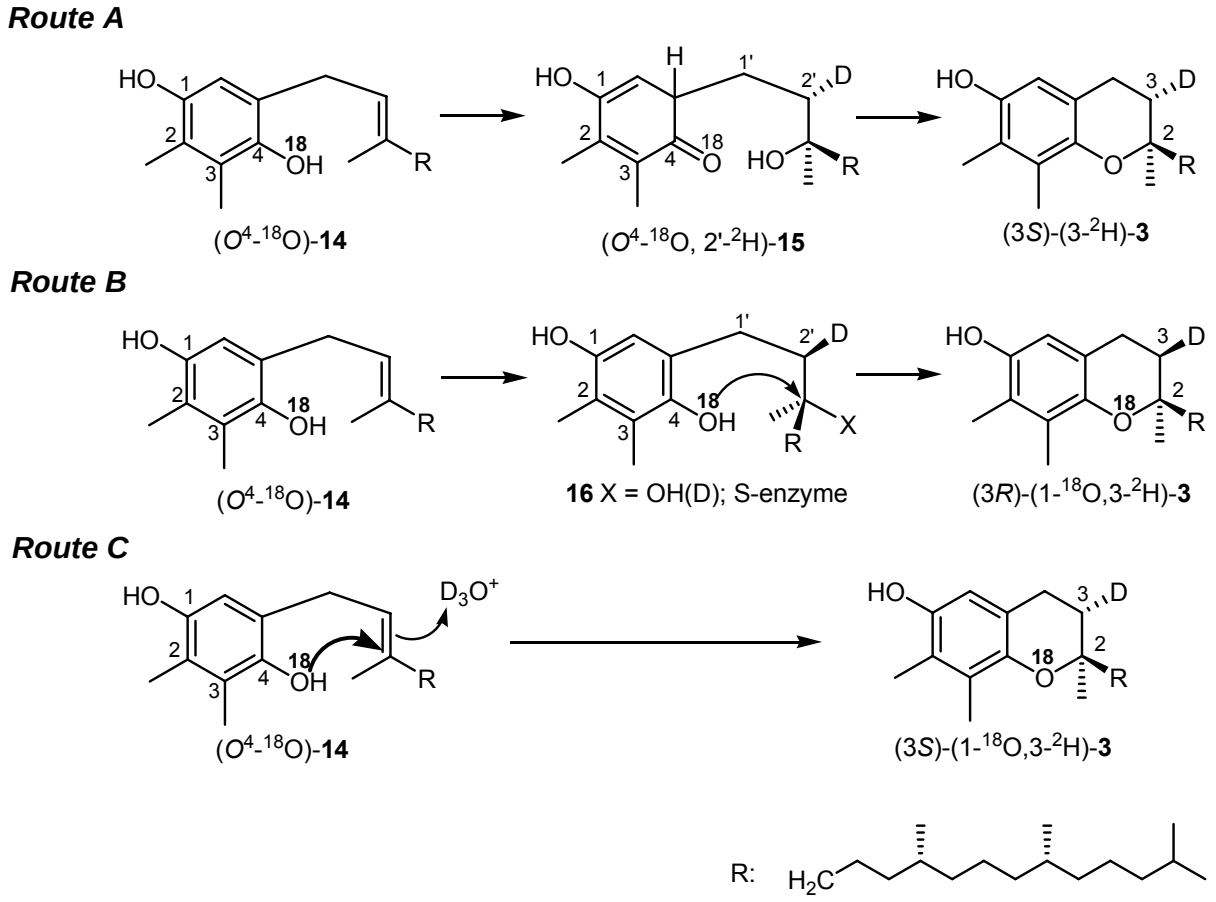


Figure 6: *Three possible mechanisms of the tocopherol cyclase catalyzed ring-closure.*

Route A is distinguished from *Routes B* and *C* by the elimination of the phenolic 0-atom and *Routes B* and *C* are distinct with respect to the configuration at C(3) of **1,** if the incubation of (O^4-^{18}O)-**14** is done in deuterated buffer. To analyse the incubation product, it was necessary to synthesise derivatives of the two cyclisation products (3*R*)-(3-^{2}H)-**3** and (3*S*)-(3-^{2}H)-**3**. Spectroscopic comparison of the two synthetic products with the corresponding compound of enzymatic origin revealed that tocopherol cyclase operates by *si*-protonation of the double bond of **14** followed by *re*-attack of the phenolic O-atom to yield γ-tocopherol (**3**) (Route C in *figure 6*). This means that the reaction mechanism clearly requires an acidic residue for catalysis.

This hypothesis involving a concerted, nonsynchronous cyclisation, during which positive charge develops at the carbon atom that is trapped by the phenol, is supported by the following two observations (*figure 7)*:

(1) The transition-state analogue tetrahydroisoquinolinium terpenoid **17** (*figure 7)* was designed so that the positive charge is placed near to the position which

corresponds to the double bond in the natural substrate **14**. Binding studies showed that compound **17** is an excellent inhibitor (IC_{50} = 1.4 nM) of tocopherol cyclase.[52]

(2) It could be shown, that the epoxide of **14** cyclises under acidic conditions affording two compounds, the five-membered ring "Baldwin" product and the favored six-membered ring analogue of the enzymatic product.[53]

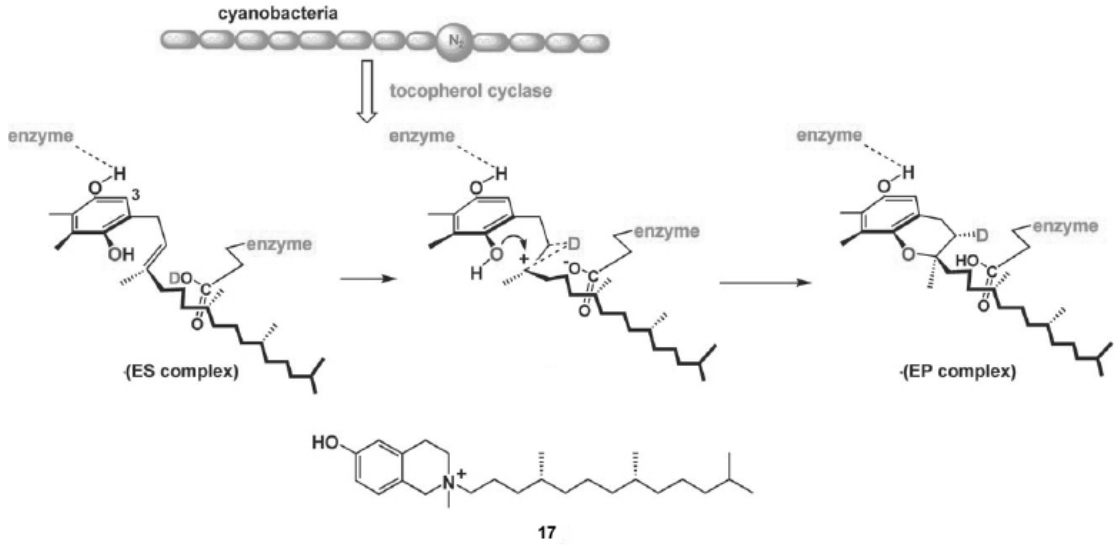


Figure 7: *The reaction mechanism of ring closure catalyzed by tocopherol cyclase. ES = enzyme-substrate; EP = enzyme product.*[54]

1.1.6 A Biomimetic Chromanol Cyclisation

The first biomimetic chromanol cyclisation has been investigated in the group of *Woggon*[54] and this concept involves:

(1) The modification of **14** by attaching a chiral acid at the unsubstituted aromatic position (C(6)) and by introducing a bulky substituent through derivatization of the phenolic OH group at C(1) in order to restrict conformational freedom of this acid.

(2) The choice of a suitable chiral acid.

(3) The removal as well as the recovery of the chiral unit after cyclisation and determination of the product on an α-tocopherol derivative.

First biomimetic cyclisation studies were performed with prolinyl phytylhydroquinone derivatives **18** and **19** in the presence of either Lewis or BrØnsted acids. Cyclisation products **20** and **21**, could be isolated, and subsequently converted into α-tocopheryl camphanate **22** (*figure 8*). The diastereomeric excess (*de*) was determined by HPLC, and a maximum value of 35 – 40% *de* was obtained in favour of the *S*-configuration at C(2). It seemed that the acidity of the chiral unit had no big influence on the reaction rate, yield, and *de* value. Therefore it was concluded that systems **18** and **19** were too flexible and the distances between the acids and the double bonds were too large.

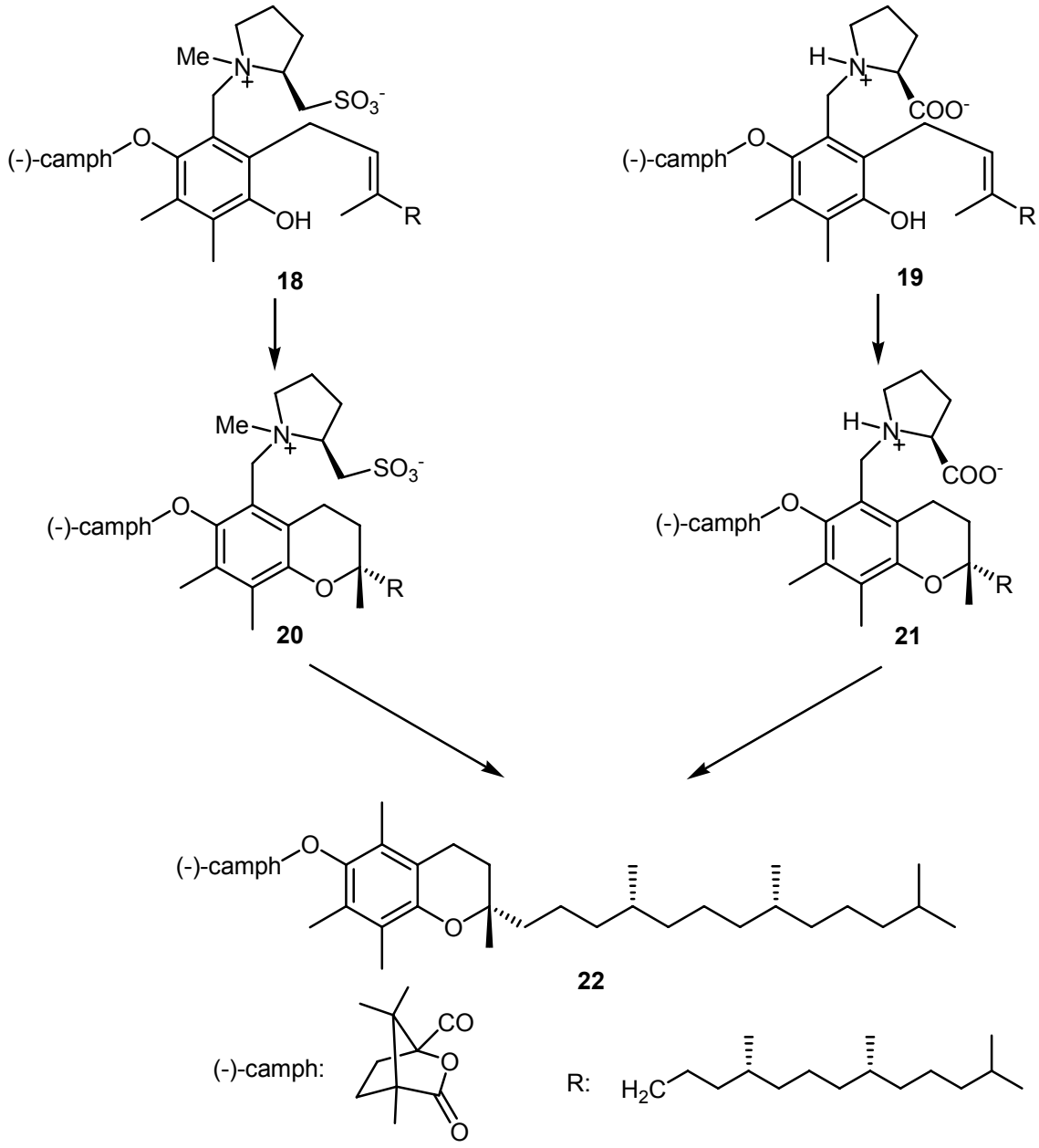


Figure 8: *Biomimetic chromanol cyclisation of **18** and **19**.*

Consequently, cyclisation precursor (-)-(*S*,*S*)-**23**, possessing a more-rigid proline-aspartate acidic spacer, was synthesised. Cyclisation in the presence of *p*TsOH yielded (-)-(2*S*,4'*R*,8'*R*)-**22** with an improved *de* value of 80% (*figure 9*).

In order to obtain the *R*-configuration at C(2), the *S*-configured amino acids and the (-)-camphanate in **23** were replaced by their enantiomers to give (+)-(*R*,*R*)-**24**. Cyclisation of the latter occurred in the presence of *p*TsOH to yield the natural (2*R*,4'*R*,8'*R*)-α-tocopherol (**1**) as the dominant diastereomer with 70% *de* (*figure 9*).

These results imply that the attachment of a proline-aspartate unit to a phytyl-hydroquinone creates an enzyme-like conformation of the cyclisation precursor allowing diastereoface-selective preferential protonation of the double bond and concomitant attack of the phenolic oxygen atom.

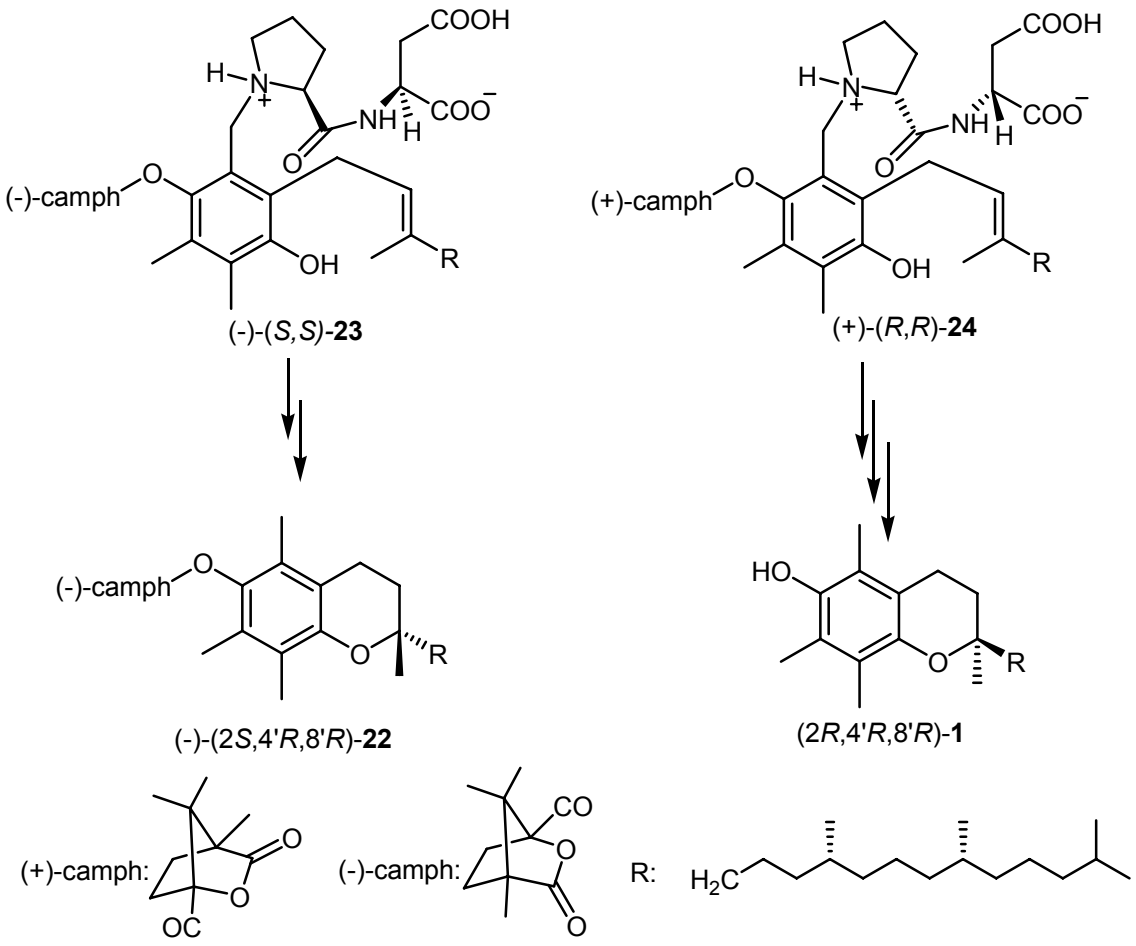


Figure 9: *Cyclisation of (-)-(S,S)-**23** and (+)-(R,R)-**24**.*

1.1.7 Industrial Synthesis of "Vitamin E"

The industrial importance of this group of compounds is based on their biological and antioxidant activity.[55] The determination of the vitamin E activity by the fetal resorption-gestation test in rats shows that (2*R*,4'*R*,8'*R*)-α-tocopherol (**1**) has the highest value of the eight naturally occurring compounds **1 – 8** (*Figure 1*) and also of its eight stereoisomers.[57, 58] Due to its prominent biological activity most efforts have been directed to (2*R*,4'*R*,8'*R*)-α-tocopherol (**1**). But despite the rapid advances in stereoselective synthesis and the considerable efforts in approaches to this product, no economic commercial total synthesis of naturally identical (*RRR*)-α-tocopherol (**1**) could be realized until today.[56]

Although biologically less active than natural (*RRR*)-α-tocopherol (**1**),[57, 58] all-racemic-α-tocopherol [(all-*rac*)-**1**], an equimolar mixture of all eight stereoisomers, is industrially the most important product, manufactured in about 35,000 tons per year worldwide, mainly applied as its acetate derivative.[59]

The first synthesis of (all-*rac*)-**1** ("synthetic vitamin E") was carried out as an acid catalyzed condensation reaction of all-racemic isophytol (**25**) with trimethyl-hydroquinone (**26**)[60, 61] which resulted in the first Vitamin E production at F. Hoffmann-La Roche in the early 1950s (*figure 10*).

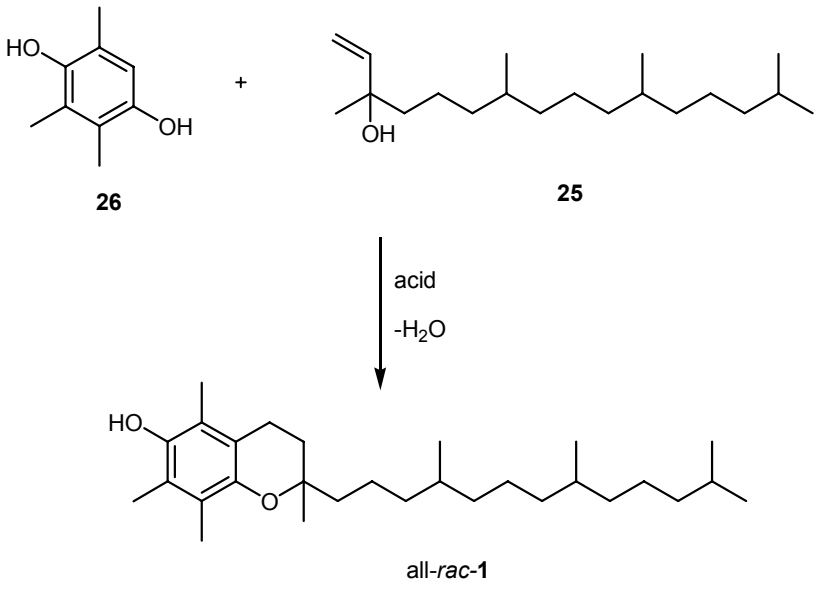


Figure 10: *Industrial synthesis of all-racemic-α-tocopherol (all-rac-**1**).*

Several classical Lewis and BrØnsted acids, or combinations thereof, work well in this reaction. Typical examples are $ZnCl_2$/HCl, BF_3, or $AlCl_3$, applied in various organic solvents. Until today a large number of new catalysts and new reaction conditions have been developed in order to find environmental friendly and more efficient procedures. Examples of novel catalysts are clays, ion exchange resins, rare earth and indium metal halides and triflates, heteropolytungsten acids, various polyfluorinated compounds (imides, methides), and boron and phosphorous compounds.[59]

The second form of industrially produced "vitamin E", about 10% of the total amount, is isomerically pure (2*R*,4'*R*,8'*R*)-α-tocopherol (**1**), which is obtained by enrichment and purification of mixtures of tocopherol homologues **1 – 4** from soybean deodorizer distillates. To increase the value of the vitamin E concentrate, the lower β-, γ-, δ-homologues **2 – 4** have to be converted to the biologically more active α-tocopherol (**1**) (only ca. 5% in the original mixture) by permethylation with subsequent reduction.[59] As permethylation methods, the halo-,[62] the amino-,[63] or the hydroxymethylation[64] reaction are employed. An example of an aminomethylation of δ-tocopherol (**4**) with subsequent hydrogenation is shown in ***figure 11***.[65]

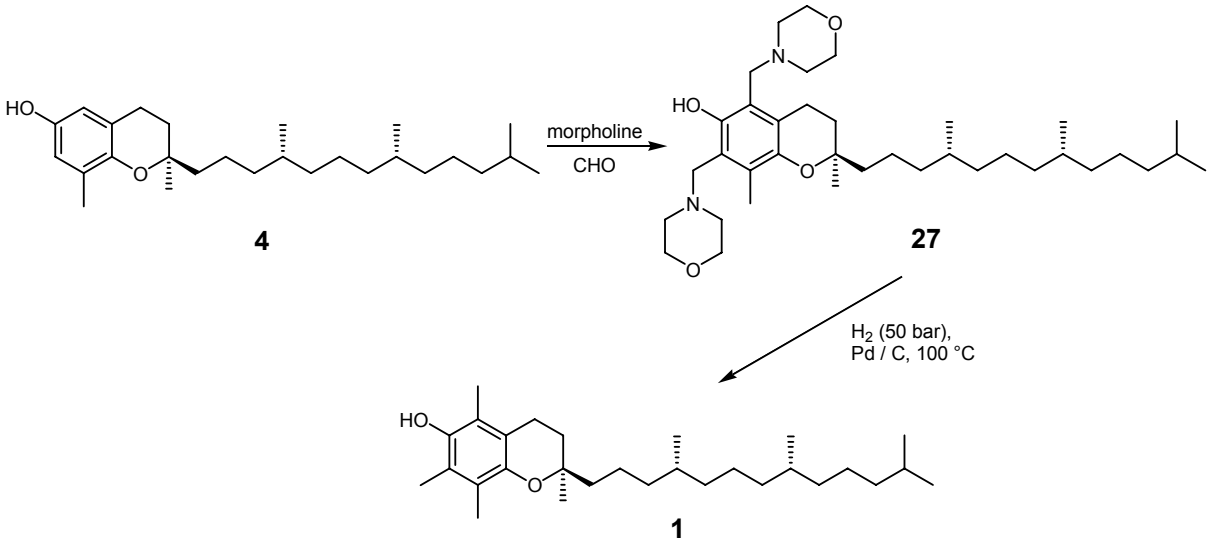


Figure 11: *Aminomethylation of δ-tocopherol (**4**) to α-tocopherol (**1**).*[66]

The unsubstituted aromatic positions are aminomethylated via a *Mannich*-reaction with morpholine and formaldehyde to yield *Mannich*-product **27**. Removal of the morpholine-groups by hydrogenation gives the desired α-tocopherol (**1**). The two

forms of α-tocopherol (**1**) (or their acetate derivatives) are produced for applications in animal feed, food or the pharma and cosmetic industries.

1.1.8 First Total Synthesis of *SRR- and RRR*-α-Tocopherol

The first synthesis of *RRR*-**1** and *SRR*-**1** was published by *Mayer et al.* in 1963.[67] All other approaches, which had been described in the literature until then, had given the C(2)-racemic product with trimethylhydroquinone and natural phytol as starting materials. The problem of generating the right configuration at C(2) was solved by optical resolution. The synthetic pathway for the chroman building block is depicted in ***figure 12***.

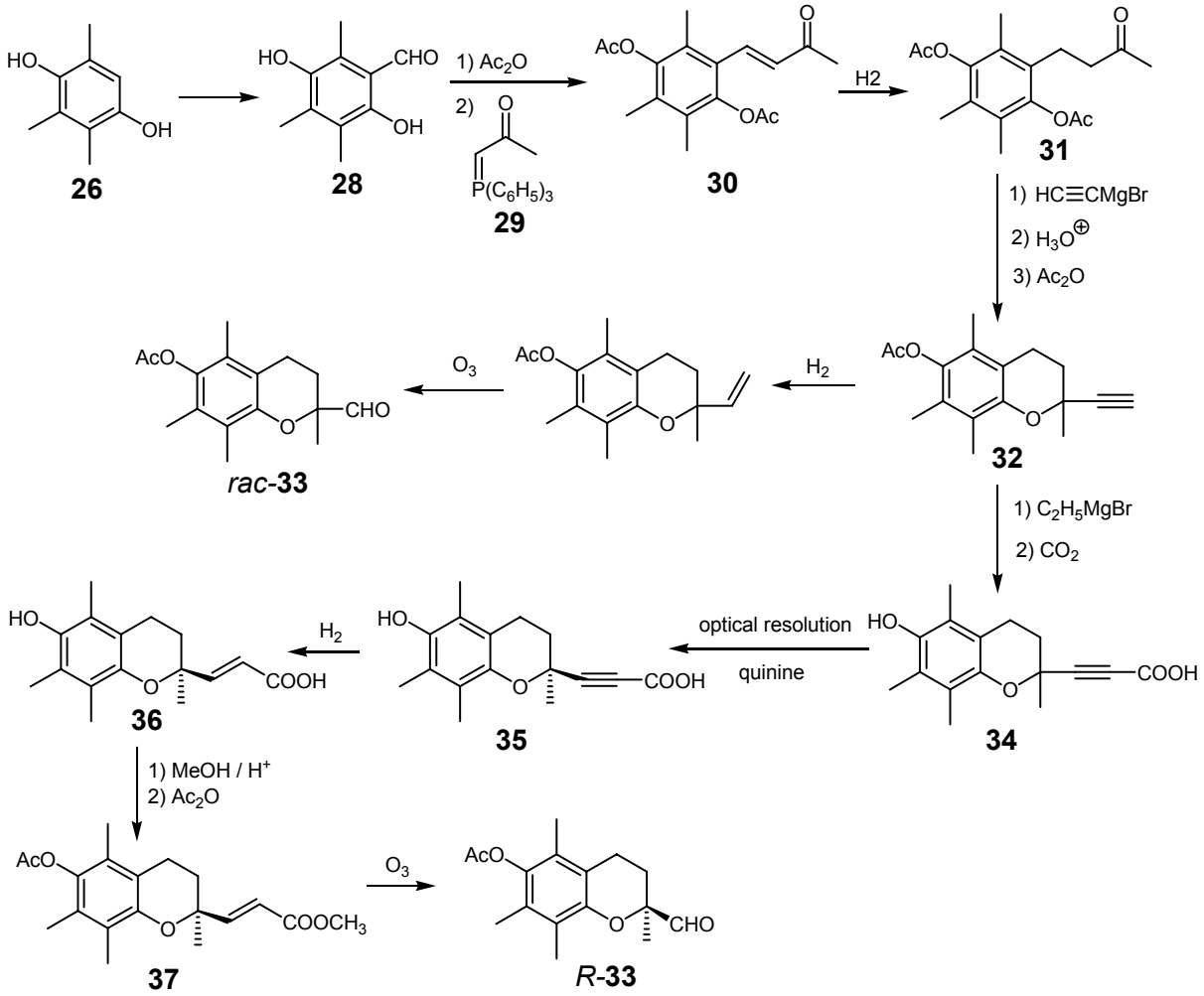


Figure 12: *Synthetic pathway of chroman building block R-**33**.*

Trimethylhydroquinone (**26**) was converted to the benzaldehyde **28** via a *Duff*-reaction.[68, 69] Acetylation and reaction with compound **29** gave the α,β-unsaturated

ketone **30**, which was hydrogenated to the saturated ketone **31**. A *Grignard*-Reaction with ethynylmagnesium bromide gave the corresponding alcohol which could cyclise to the chroman-ring after acidic removal of the acetate protecting groups. The free phenol was reprotected with acetic anhydride to yield compound **32**. A carboxyl-group was introduced through reaction of deprotonated **32** with CO_2 to afford **34**. The key step of the synthesis is the separation of the enantiomers of acid **34**, which was achieved via optical resolution of the corresponding quinine salts to give optically pure **35** as well as the *S*-enantiomer. Partial catalytic hydrogenation employing the *Lindlar*-catalyst yielded compound **36**. Esterification with MeOH followed by acetylation gave compound **37**, which was converted to the isomerically pure building block *R*-**33** by ozonolysis.

The second building block, the C_{15}-component **43**, was obtained by degradation of natural (2*E*,7*R*,11*R*)-phytol **38** as shown in ***figure 13***.

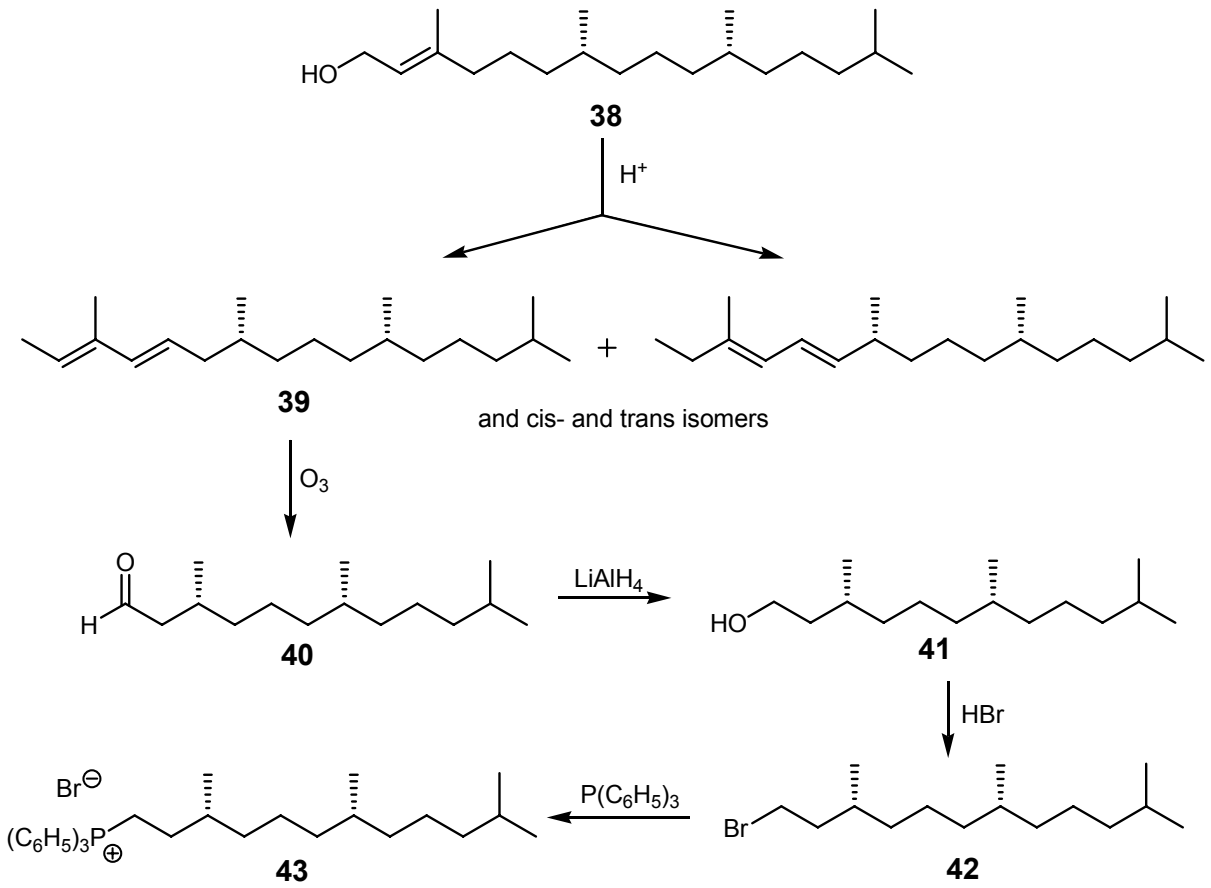


Figure 13: *Synthesis of the building block **43**.*

The aldehyde *R*-**33** was coupled with the phosphonium salt **43** by a *Wittig* reaction. This was followed by the reduction of the coupling product **44** to give *RRR*-α-tocopherol (*figure 14*).

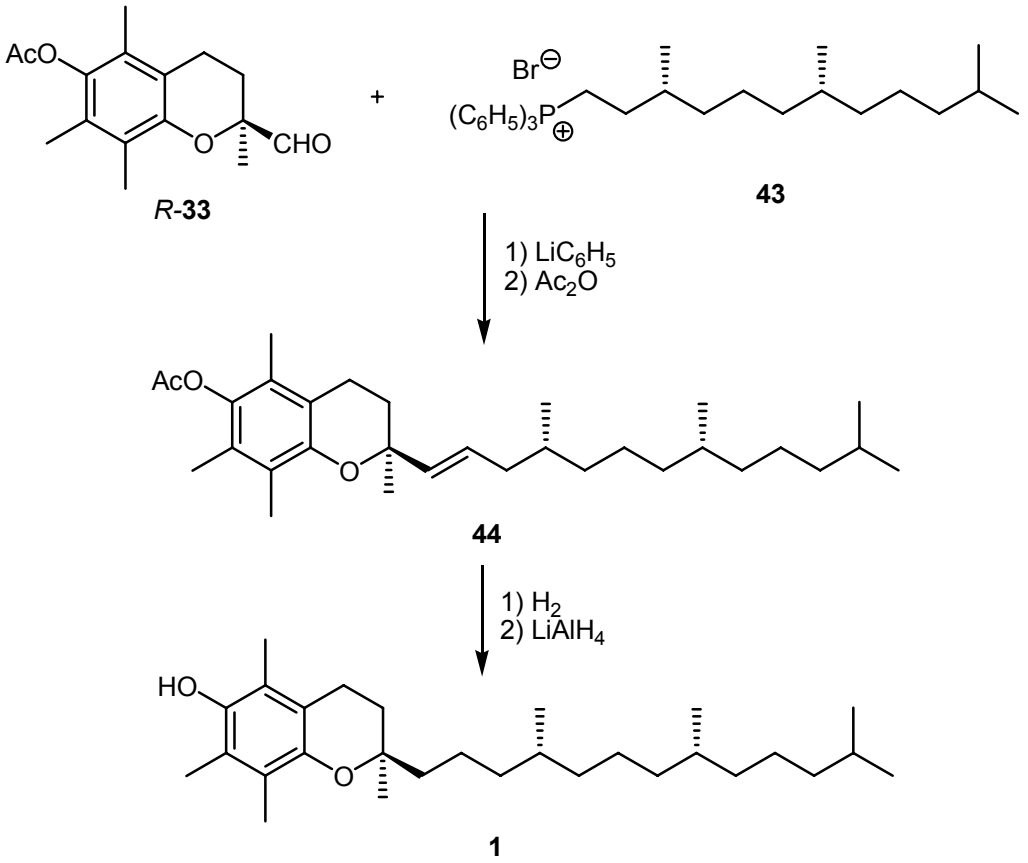


Figure 14: *Final steps of the synthesis of RRR*-α-tocopherol.

In the proceeding years, many of synthetic schemes have been employed for the stereoselective synthesis of isomers of α-tocopherol (**1**), in particular *RRR*-**1**.[59] Four general strategies have been followed:

(1) *Classical optical resolution* delivers mainly chroman building blocks.

(2) *Biocatalysis (by microorganisms and isolated enzymes)* gives access to chiral intermediates.

(3) *Asymmetric catalysis* opens the way to a variety of products.

(4) *Chiral pool starting materials and chiral auxiliaries in stoichiometric amounts* are also applied.

For large scale applications, many of those methods suffer from complexity, limited space-time yield, and formation of excessive amounts of waste material, which is the reason why an economic industrial synthesis of *RRR*-**1** hasn't been found until today.

1.1.9 A Short Route to α-Tocopherol

Recently *Woggon et al.* reported a synthesis of α-tocopherol (**1**) in which an organocatalyst was applied for the first time to the construction of chromanols (*figure 15*).[70]

Phytenal (**46**) was reacted with *ortho*-hydroxy aldehyde **45**[71] by using proline-derived organocatalyst **47** to yield hemiacetal **48**, which was subsequently oxidised to lactone **49** with a *de* value of 97%. Hydrogenation of **49** afforded acid **50**, which could be converted to the α-tocopherol ether **51** by using a *Barton* decarboxylation procedure.[72] Ether **51** was cleaved by treatment with $BF_3 \cdot Me_2S/AlCl_3$ to yield *RRR*-α-tocopherol (**1**) in an overall yield of 29% and with a 93% diastereomeric excess.

The proposed reaction mechanism of the formation of **48** is depicted in ***figure 16***. The iminium salt **52** produced initially leads to dieneamine **53**, which reacts with salicylaldehyde (**45**) to yield the intermediate **54** via an aldol reaction. Compound **54** then cyclises diastereoselectively in an intramolecular oxa-Michael addition to give lactol **48**. The aldol reaction is the key step that controls the stereoselectivity of the formation of the *syn* arrangement of the six-membered lactol.

This synthetic strategy can potentially be applied to the synthesis of other members of the vitamin E family, as well as to other natural products containing highly substituted, chiral compounds.

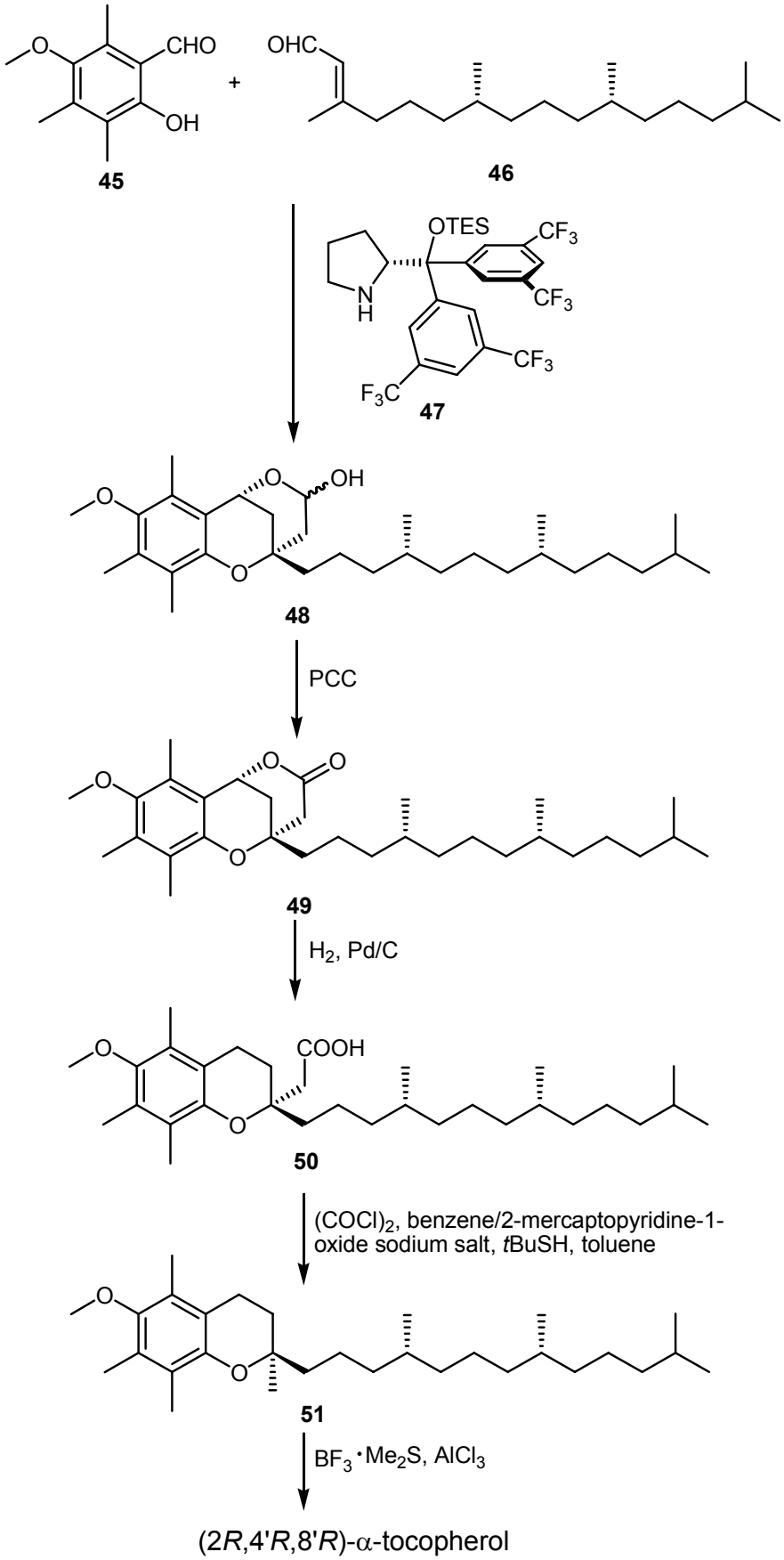


Figure 15: *Synthesis of (RRR)-α-tocopherol via a domino aldol/oxa-Michael reaction.*

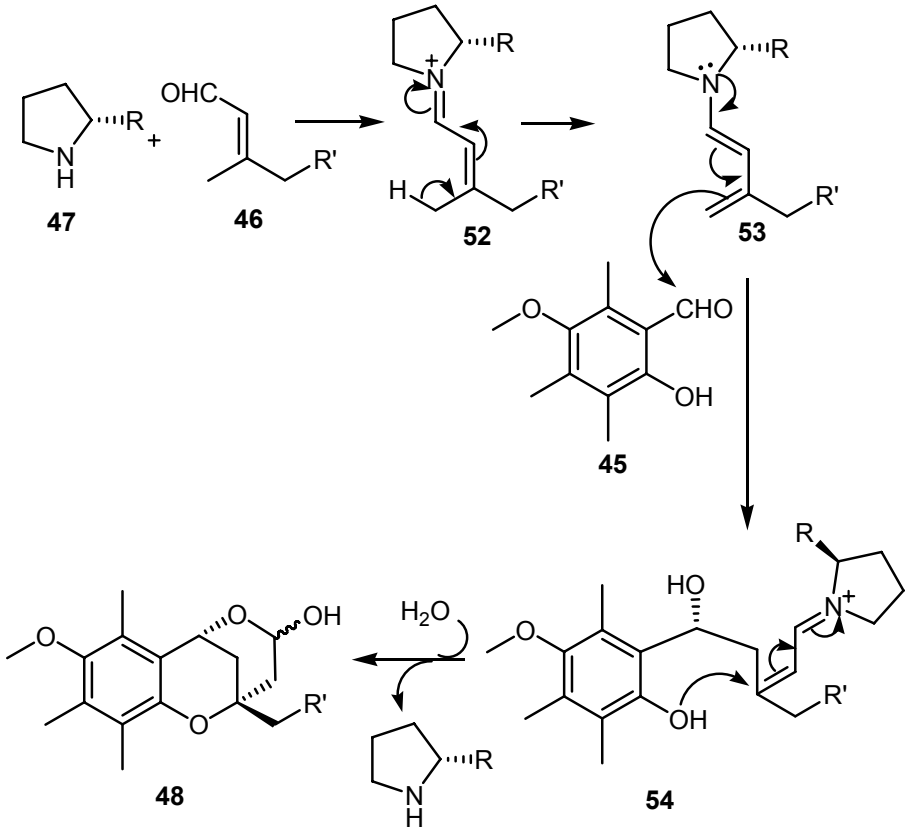


Figure 16: *Proposed mechanism for domino aldol/oxa-Michael reaction leading to lactol* ***48****.*

1.2 Supramolecular Chemistry and Enzyme Mimetics

1.2.1 What is supramolecular chemistry?

Jean-Marie Lehn, one of the protagonists in the field of supramolecular chemistry gave the following definition:[73]

> *"Supramolecular Chemistry can be defined as chemistry beyond the molecule, referring to the organised entities of higher complexity that result from the association of two or more chemical species held together by intermolecular forces."*

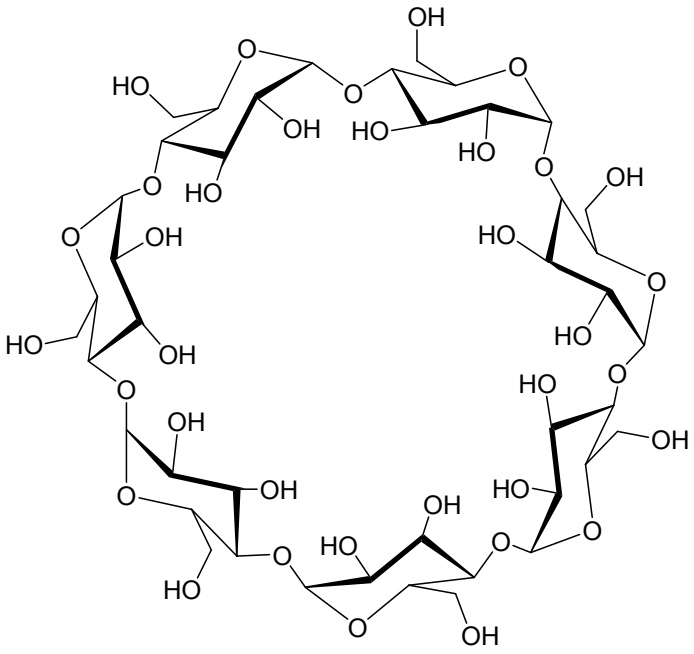
The area of supramolecular chemistry has grown exponentially in the last few decades and therefore this broad, loose description is indeed rather accurate to encompass all subjects related to this area. It is a highly interdisciplinary field, extending over organic chemistry, coordination chemistry, physical chemistry and the experimental/theoretical studies of interactions. Thus, supramolecular chemistry provides the link between physics, chemistry and biology and enables the study and understanding of very large molecular assemblies.

Both intermolecular and intramolcular forces play a crucial role in the organization of large molecular assemblies. In particular, noncovalent interactions, such as *Coulomb* forces, hydrogen bonding, *Van Der Waals*- and hydrophobic interactions are of great importance. These noncovalent interactions are regarded as the basis of many biological processes such as receptor-ligand binding, enzyme-substrate complex formation, antibody-hapten binding, and cell surface recognition. Therefore supramolecular chemistry has provided, and will continue to provide an insight into the process of self-organisation of artificial synthesizable molecular assemblies.

1.2.2 Cyclodextrins

1.2.2.1 Molecular Structure and Chemical Properties

Cyclodextrins (CD's) are a family of natural and synthetic cyclic oligosaccharides containing α-1,4-linked glucopyranose units (*figure 15*). They were first discovered in 1891 by A. Villars,[74] and later the naturally occurring CD's were identified.[75] The α-, β- and γ- CD's are all of industrial importance containing six, seven and eight glucose units respectively. However, it is the β-CD which is produced on the largest scale.[76, 77, 78]



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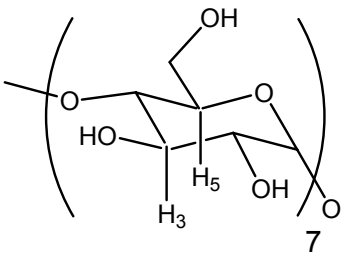

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Figure 15: *Left: The structure of β-CD; right: $^4C_1$-conformation of glucose unit in β-CD.*

The glucopyranose units of β-CD (**55**) are in a $^4C_1$-conformation resulting in all primary hydroxyl groups oriented to the outside of the ring. The diameters of the upper and lower faces of the CD differ in size and the structure is more accurately described as a conical cylinder or more commonly referred to as doughnut-shaped or a bottom-less bowl (*figure 16*).

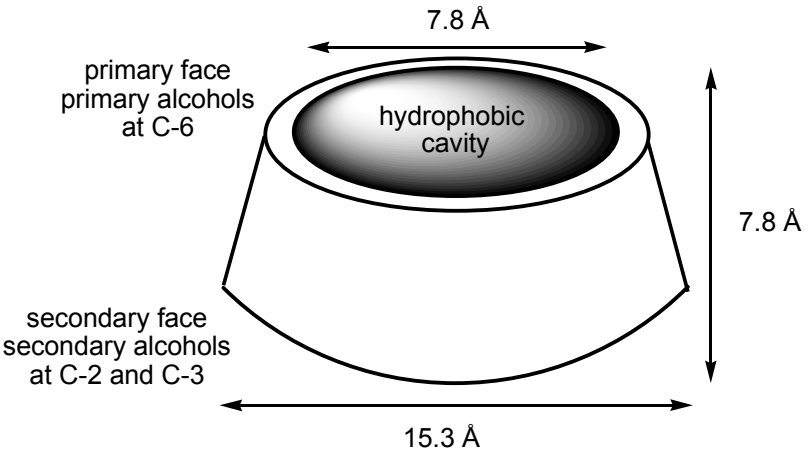


Figure 16: *Doughnut shape icon of CD illustrating the size and dimensions of β-CD (**55**)*

The molecular orientation of the conical-cylinder leads to a polar outer-surface and the potential to form hydrophilic interactions. Contrastingly, the cavity is considerably less hydrophilic due to the axial-hydrogen atoms and glycosidic oxygen atoms pointing to the interior of the molecule. This solubility gradient provides a water soluble exterior with a hydrophobic cavity enabling inclusion of a range on guest molecules. α-, β- and γ-CD molecules have a different number of glucose subunits and therefore differ in size and the cavity diameter. The diameter of β-CD's hydrophobic cavity is 7.8 Å and allows inclusion complex formation with various guest molecules. The diameters of α- and γ-CD will enable selective inclusion of guests of different sizes (*Table 2*).

Cyclodextrin	Mass	Outer diameter (nm)	Inner diameter (nm)	Solubility H_2O (g/kg)
α	972	1.37	0.57	129.5
β	1134	1.53	0.78	18.4
γ	1296	1.69	0.95	249.2

Table 2: *The properties of α-, β- and γ– cyclodextrin.*[79]

The binding constants of inclusion complexes of aromatic (**56**, **57**, **58**, **60**) and aliphatic (**59**) compounds with CD's are shown in ***table 3***.[80] Structures containing a *tert*-butyl- or adamantyl-rest show especially good binding affinities. Non-covalent

interactions, such as hydrogen bonds, dipole-dipole, *Van Der Waals*- and hydrophobic interactions, are of paramount importance and are considered as the driving-force of complex formation. The large variety of guest molecules available for complex formation makes CD's attractive subjects for *supramolecular chemistry*. It's noteworthy that intermolecular interactions (~0.5-5 kcal/mol) are about an order of magnitude weaker than covalent chemical bonds (~40-250 kcal/mol). Consequently, many non-covalent interactions are required in CD-inclusion-complex formation.

Compound	α-CD	β-CD	γ-CD
benzoic acid (**56**)	16 M^{-1}	23 M^{-1}	3 M^{-1}
4-methylbenzoic acid (**57**)	36 M^{-1}	66 M^{-1}	8 M^{-1}
4-*tert*-butylbenzoic acid (**58**)	51 M^{-1}	457 M^{-1}	59 M^{-1}
1-adamantanecarboxylic acid (**59**)	114 M^{-1}	501 M^{-1}	42 M^{-1}
Ibuprofen (**60**)	55 M^{-1}	2600 M^{-1}	59 M^{-1}

Table 3: *Inclusion complex formation constants of CD's with various guest molecules*

Unmodified CD's have fairly rigid structures, due to intramolecular hydrogen bonds between C(2)-OH and C(3)-OH of adjacent glucose units.[81]

To summarise, the following chemical and physical properties make CD's attractive components for substrate-recognition moieties in enzyme models and catalysis:[82]

(1) High water solubilities.
(2) The hydrophobic cavities can accommodate a wide variety of guest molecules.
(3) Their structures are well defined due to intramolecular H-bonds.
(4) "Facile" functionalisation of the hydroxyl groups provides a variety of catalytic residues.
(5) CD's are chiral and can therefore be used in asymmetric catalysis.

CD's are industrially produced from starch by an enzymatic reaction with *cyclodextrin glucosyl transferase* (CTG), which can be isolated from several bacteria like *Bacillus macerans, Klebsiella oxytoca or Bacillus circulans*.[80] In this process a complicated mixture of several cyclic and linear oligosaccharides is produced. This mixture can be

purified by addition of an appropriate complex forming agent (e.g. toluene for the isolation of β-CD), filtration and crystallization. Several 1000 tons of CD's are produced per year. They are widely used as additives in pharmaceuticals, food and cosmetics, as well as in analytical chemistry (e.g. separation of enantiomers by chiral HPLC).[80] Since β-CD is the cheapest of the cyclodextrins, and its cavity has an ideal size to host a broad range of substrates, it has been used most extensively and the following chapters will focus solely on β-CD-examples.

1.2.2.2 Cyclodextrin Based Enzyme Mimics

It has been shown that modification of CD's may not be necessary for the development of enzyme mimics. It should be noted that not all CD-based enzyme mimics have prosthetic groups attached to the CD moiety. *Breslow* showed in 1983 that unmodified β-CD accelerates the hydrolysis of various esters at pH 10.[83] This is a result of the proximity effects existing in intramolecular processes and enzyme-substrate species. Ester **62** hydrolyzes 3.2 x 10^6 times faster in the presence of β-CD *(figure 17).* Interestingly, one of the two enantiomers reacts 20-fold faster than the other one. The stereoselection may be explained by the fact that β-CD forms a stronger inclusion complex with one of the two enantiomers. β-CD-oxyanion **61** attacks the carbonyl group of the ester producing acylated β-CD **63** and *p*-nitrophenolate **64**. It is noteworthy, that this reaction is not catalytic, but can be considered as a first imitation of an enzymatic reaction (*esterase*) due to the attractive properties of β-CD.

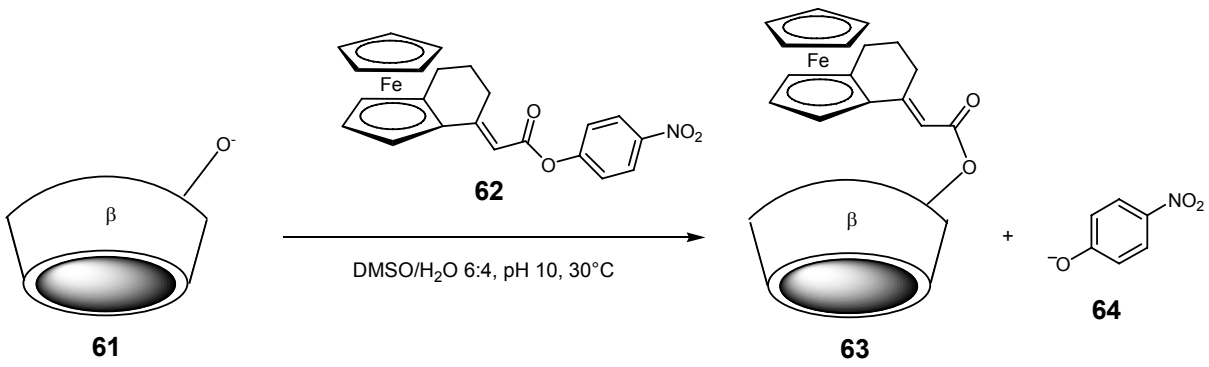


Figure 17: *Hydrolysis of esters with CD-oxyanion* ***61***

Highly sophisticated enzyme mimics can be obtained by attaching catalytic groups to CD. *Breslow* was also the first to report the synthesis of multi-component systems by attaching known catalysts for oxidations, namely metallosalens and metallo-porphyrins, to CD's.[84] In order to mimic the selectivity of enzymes, artificial receptors **65 – 68** (*figure 18*) were prepared.

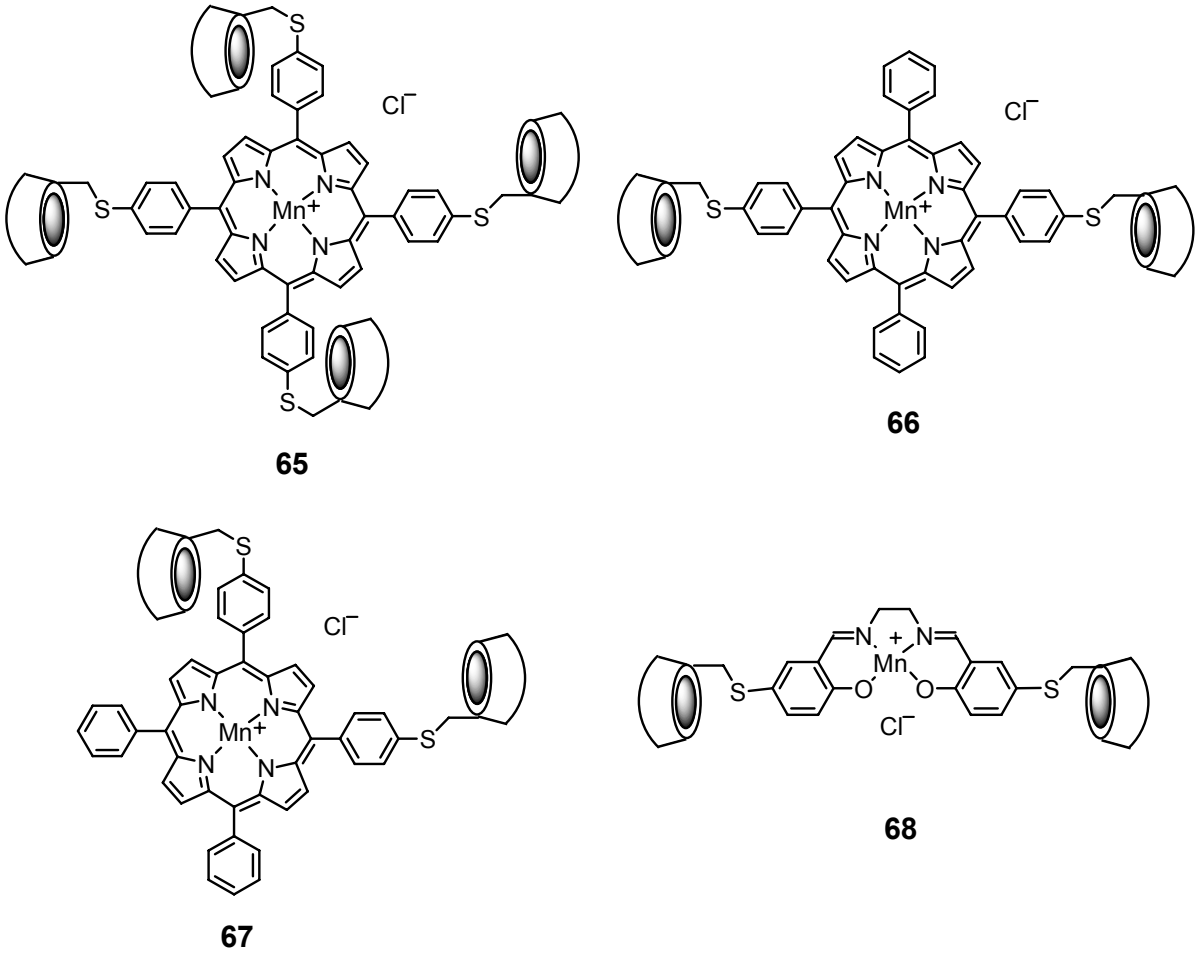
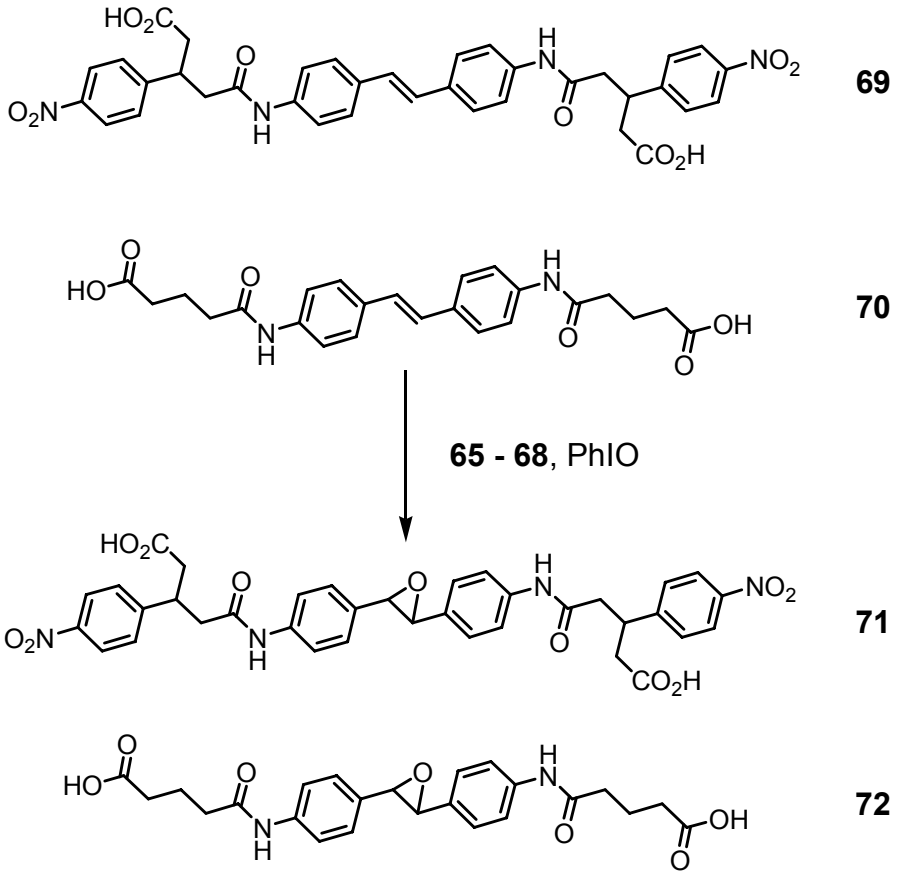


Figure 18: *Structures of CD- receptors **65 – 68***.

Artificial CD-receptors were developed and designed to optimise the binding affinity enabling binding into two CD-moieties of the same receptor (**65**, **66**, **68**). This was accomplished by carefully choosing substrates with the ideal size and geometry. The stilbene derivate **69** was employed in order to test metal complexes **65 – 68** in the selective, competitive epoxidation. In contrast, stilbene derivative **70** was chosen as a "worse fitting" substrate after initial binding studies (*figure 19*). Iodosylbenzene was employed in the formation of the manganese oxo group of catalysts. The selectivity of the epoxidation could be improved upon the addition of adamantanecarboxylate up

to a certain concentration when porphyrin catalysts **65** and **66** were employed. The role of adamantanecarboxylate can be regarded as a face protection agent. The substrate (**69** or **70**) binds to the catalyst (**65** or **66**) on one face of the porphyrin, leaving the possibility that the oxo group goes to the second face to perform nonselective oxidation of substrates. However, adamantanecarboxylate coordinates and blocks the second face thereby preventing nonselective oxidation. Interestingly, substitution of adamantanecarboxylate with a smaller group, such as acetate, resulted in no such face selectivity and consequently the selectivity of the reaction was reduced (*figure 20*).



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72

Figure 19: *The reactions of ideal and 'worst case' stilbene residues with catalysts* ***65 – 68****.*

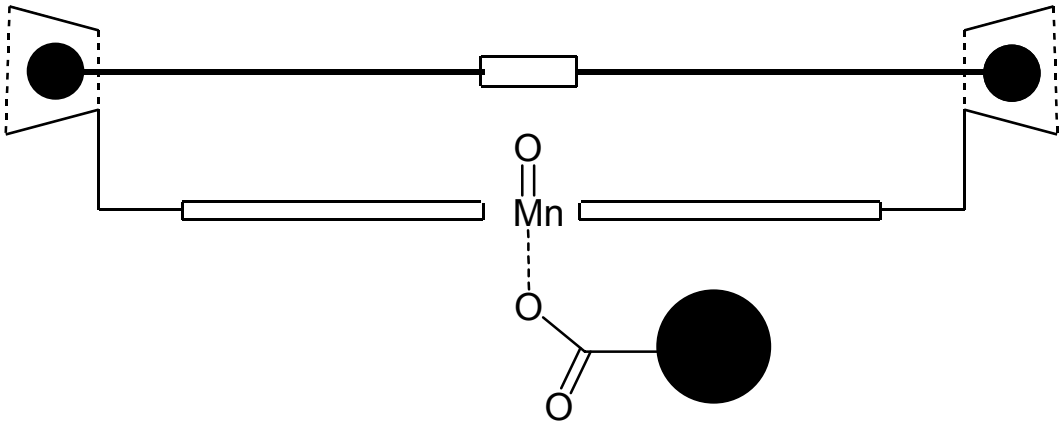
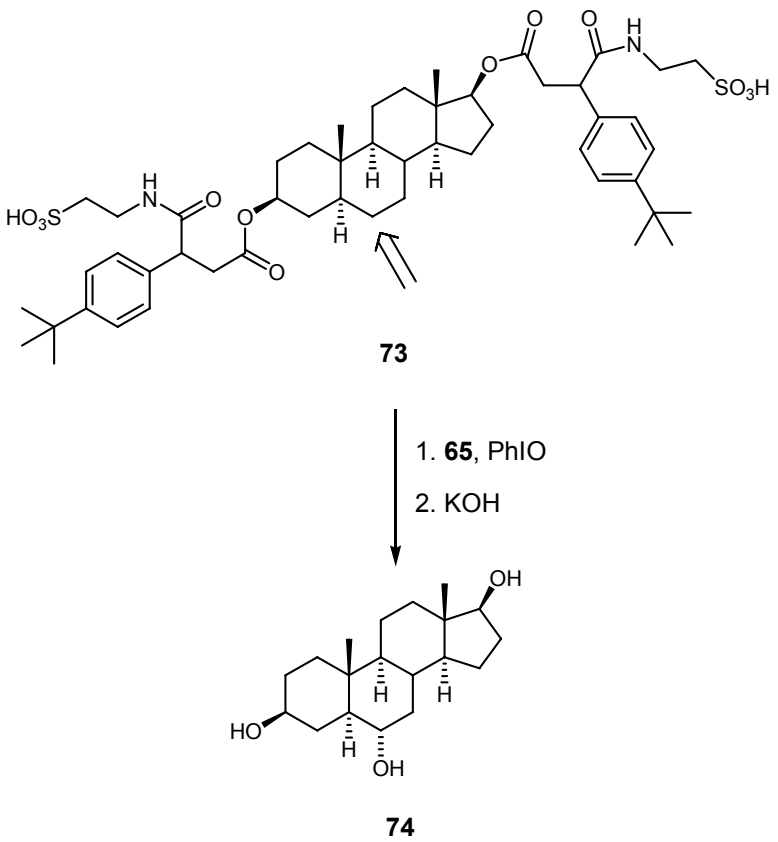


Figure 20: *A schematic representation of a substrate binding into two CD receptors of a Mn(V)porphyrin. The Mn carries an oxygen that will add to the substrate double bond, and the opposite face is shielded by adamantanecarboxylate.*[84]

Previously salen complexes have been employed as selective epoxidation catalysts.[85] However, bis cyclodextrin catalyst **68** incorporating the salen moiety showed almost no selectivity between different substrates. In contrast, catalysts **65** and **66** displayed an oxidation selectivity of up to 50-fold for the epoxidation of **69** relative to **70**. As was predicted, catalyst **67** showed poor selectivity. This evidence supported the proposed binding geometry in the epoxidation reactions with catalysts **65** and **66** in which the substrate spans over the porphyrin ring.

The catalytic capabilities of porphyrin linked CD systems were further improved through the selective catalytic hydroxylation of a steroid derivative by a cytochrome P-450 enzyme mimic.[86, 87, 88] Thus, CD-tetramer **65** (10 mol%) was incubated with derivatised steroid **73** in water for 2h with PhIO as the oxygen source (*figure 21*). 40% conversion of **73** was observed after ester hydrolysis and quantification of the triol **74**. The regioselectivity of the reaction was shown to be complete. The reaction was also stereospecific, yielding only the equatorial C(6)-alcohol. The catalyst was capable of only 4 turnovers before being oxidatively destroyed.



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74

Figure 21: *Regioselective hydroxylation of steroid* ***73*** *by a cytochrome P-450 mimic.*[86]

The system was further improved by increasing the stability and reactivity of the catalyst through the introduction of fluorine to the free aromatic positions of the porphyrin linker (β-CD-tetramer **75** in *figure 22*).[88] In contrast to 4 turnovers from catalyst **65**, **75** was used in 1 mol% and gave 95% conversion of **73** to **74** (95 turnovers). Unfortunately, the attempts to reduce the amount of catalyst employed were unsuccessful. Reaction with 0.1 mol% gave only 18.7% of product thereby indicating that at low catalyst loadings, product inhibition factors come into play.

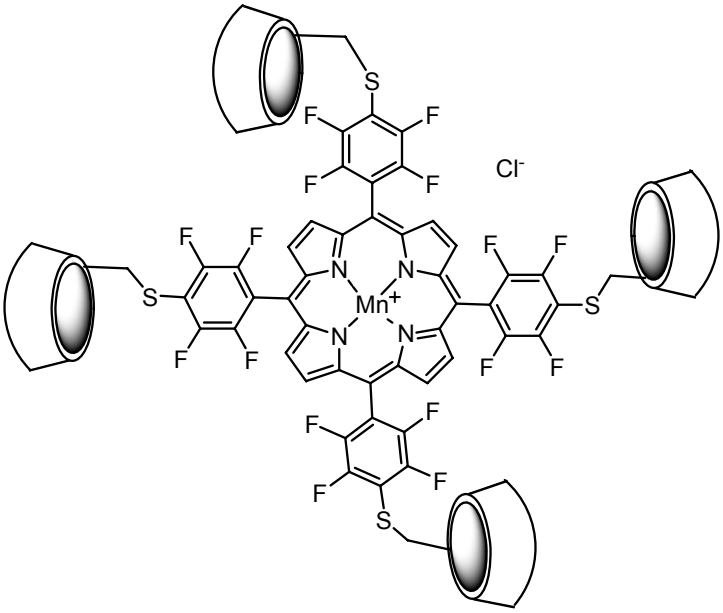

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Figure 22: *Improved cytochrome P-450 enzyme mimic.*

1.2.3 β-CD based enzyme mimic of β,β-carotene-15,15'-moooxygenase: the essential contributions from "Woggon group"[89, 90, 91, 92, 93, 94, 95, 96]

Many organic reactions have shown improved reactivity and selectivity with multi-component, enzyme mimics based on CD. Primarily, this is a consequence of the hydrophobic cavity of CD enabling it to behave as an "artificial receptor". Additionally, dimer/tetramer systems of CD have been shown to be desirable in the cooperative binding and subsequent geometric control of specific substrates. Much of the focus has been on the catalysis of simple organic transformations and few of the complicated enzyme mimics have been devoted to the conversion of natural substrates to biologically important metabolites.

Woggon et al. have succeeded in purifying an important enzyme from chicken's intestinal mucosa. This enzyme has the ability to centrally cleave β,β-carotene. In contrast to earlier belief, further investigation has shown that this enzyme is not a dioxygenase but operates by a monooxygenase mechanism in which the first step is an epoxidation of the central C(15)-C(15') double bond.

An artificial supramolecular system, **76**, was developed in parallel to the efforts to purify and investigate the native protein. The multi-component system **76**, can mimic the enzymatic cleavage of carotenoids (*figure 23*).[89, 90, 91, 92, 93, 95, 96] The structure of the enzyme mimic consists of two β-CD moieties linked via a ruthenium porphyrin on the primary face. Both of the terminal β-CD's units are capable of binding one cyclohexenoid endgroup, either end of the β,β-carotene, leaving the porphyrin to span the polyene chain. It was estimated, based on computational calculations, that approximately half of β,β-carotene would be included in the β-CD cavities and that the critical C(15)-C(15') double bond would be perfectly placed under the catalytic ruthenium centre.

A biphasic system was required in order to apply this multi-component catalyst to the cleavage of β,β-carotene. β,β-Carotene was extracted into the water phase containing the catalyst **76** and cooxidant *tert*-butyl hydroperoxide (TBHP) from a 9:1 mixture of hexane/chloroform. The products of the reaction were then released from the catalyst in the aqueous phase to the organic phase. Aliquots of the organic phase

were subjected to HPLC measure without workup. It was reasonable to conclude that this kind of biphasic system could efficiently avoid the product-inhibition effect.

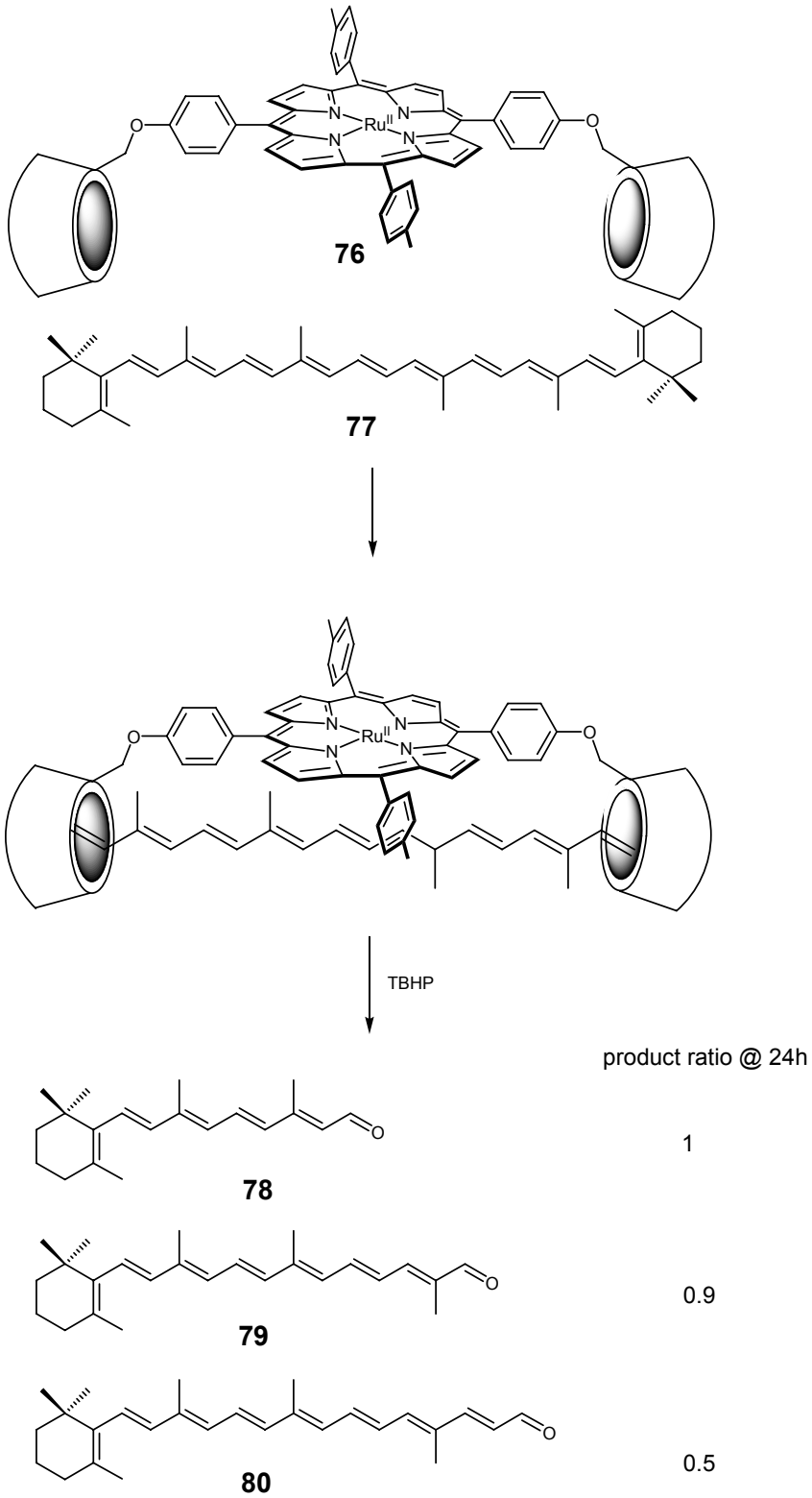


Figure 23: *Proposed binding mode of **76** and **77**, and the cleavage result with TBHP as cooxidant.*

The results indicate that **76**/TBHP catalysed the cleavage of β,β-carotene at not only the central double bond (~40%) but also the excentric double bonds to yield 12'-apo-β-carotenal **14** and 10'-apo-β-carotenal **10**. It may be considered that the lateral sliding of β,β-carotene within the hydrophobic cavity of β-CD would result in the unselective cleavage. This hypothesis was proven by employing 17-nor-ϕ,β-carotene **81** as substrate. The resulting cleavage was in fact very regiospecific as only retinal (**78**) and the corresponding fragment **82** were detected (*figure 24*). This suggested that the stronger hydrophobic interaction between the aromatic endgroup of **81** and β-CD decreased the mobility of the 1:1 inclusion complex thereby increasing the stability. The central double bond is therefore positioned centrally under the reactive ruthenium centre in contrast to the same system with β,β-carotene.

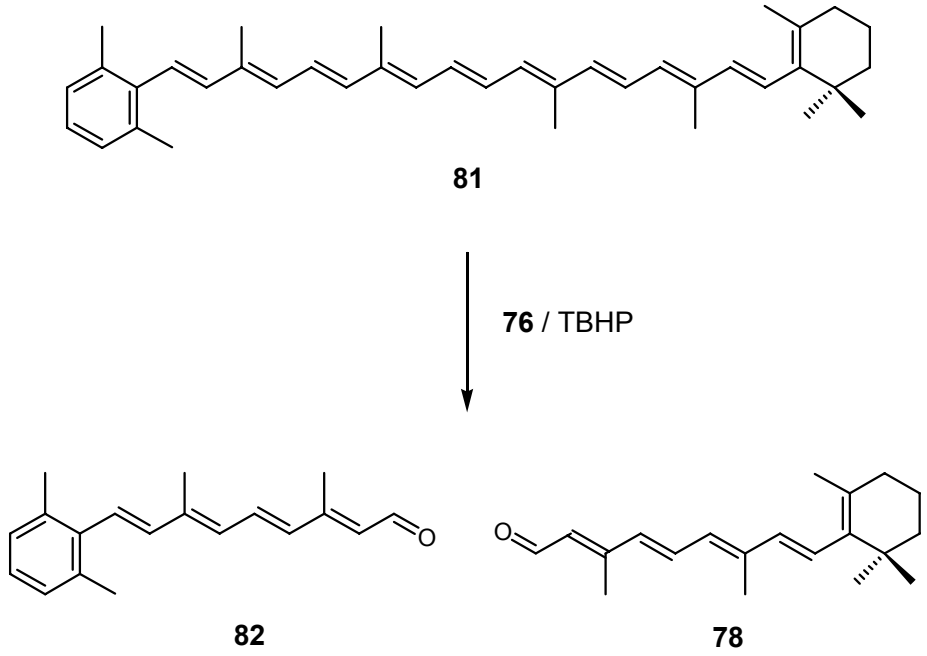


Figure 24: *Selective central cleavage of 17-nor-ϕ,β-carotene* ***81****.*

The initial step in the cleavage of the double bond is epoxide formation catalyzed by the active ruthenium-oxo porphyrin species. This is subsequently followed by ruthenium porphyrin/TBHP mediated fragmentation yielding the aldehydes as shown in ***figure 25***.[94, 96]

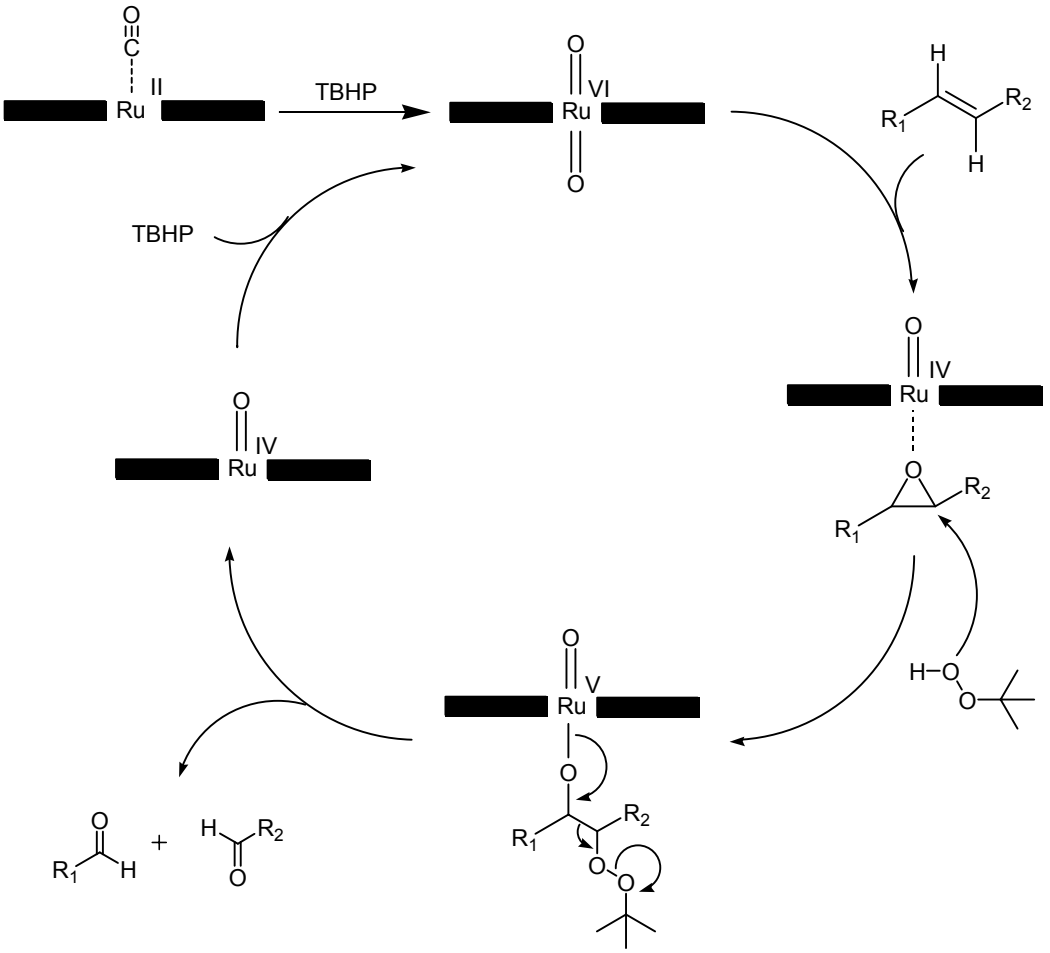


Figure 25: *Proposed catalytic cycle with TBHP as cooxidant.*[94, 96]

2 Aims of this Work

As already mentioned, nature has evolved an enzyme (tocopherol cyclase) which catalyses the stereospecific ring closure of certain phytylhydroquinone derivatives to tocopherols (*figure 5*). Mechanistic studies revealed that the chromanol ring formation involves a *si* protonation of the double bond followed by concomitant attack by the phenolic O-atom to give diastereomerically pure tocopherol (*figure 26*).

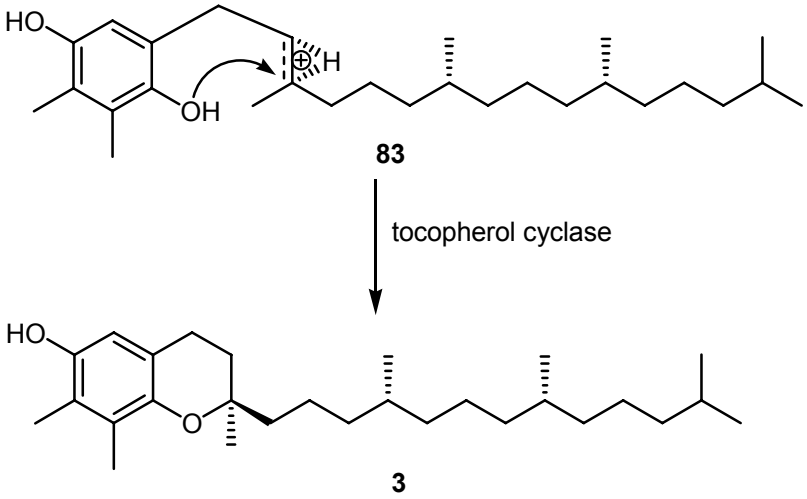


Figure 26: *Enzymatic chromanol formation.*

Based on the mechanistic steps involved in this enzymatic chromanol formation, a novel short and efficient synthetic pathway for natural α-tocopherol (**1**) should be found. One way to imitate the transition state **83** would be by stereoselective epoxidation followed by cyclisation under acidic conditions (*figure 27*).

The main problem to be solved within this work would be to find a catalyst that is capable of epoxidising alkene **84** with high diastereoselectivity and the correct configuration. It would therefore be of critical importance to find suitable protecting groups R and R'.

Among others, novel cyclodextrin based catalysts should be synthesised and their catalytic properties investigated.

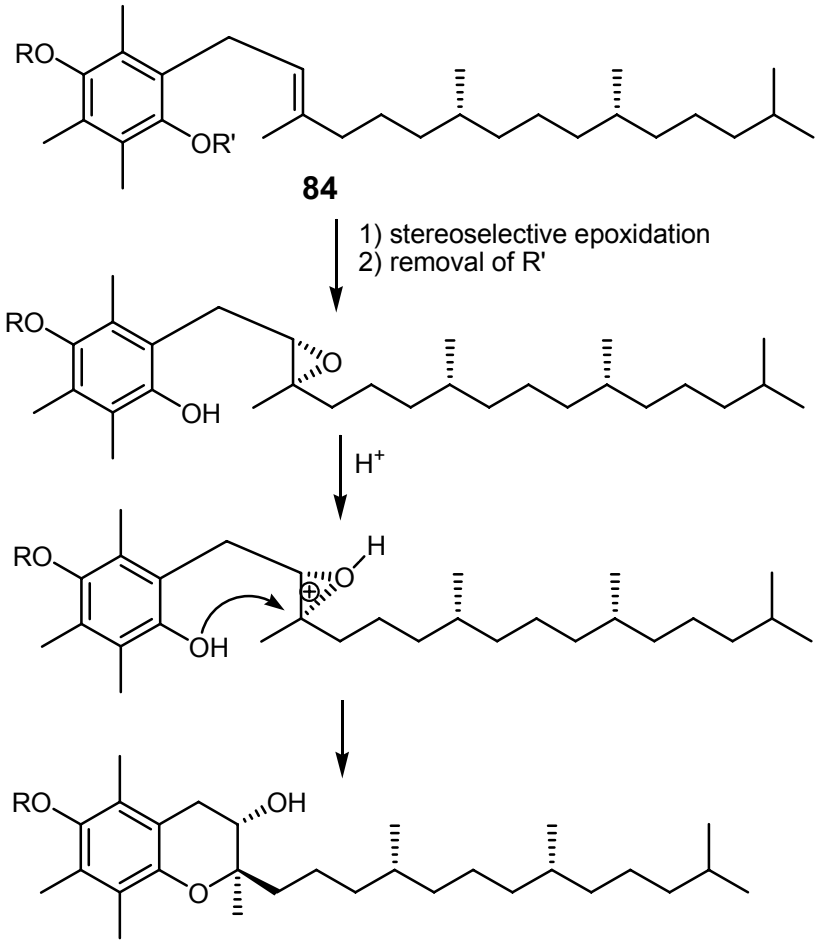


Figure 27: *Possible pathway for the formation of the chromanol moiety.*

3 Results and Discussion

3.1 Cyclodextrin Modified on Primary Face

3.1.1 Attachment of a Tris(2-pyridylmethyl)amine (TPA) Derived Ligand to β-Cyclodextrin

It has been shown by Que *et al.* that iron complexes of tris(2-pyridylmethylamine) (TPA) and related ligands can be utilized as models of nonheme iron oxygenases and as catalysts for selective oxidative transformations of organic substrates (*figure 28*).[97, 98, 99, 100] Evidence has accumulated suggesting that this chemistry is mediated by high-valent iron-oxo species,[101] as well as the ability to induce asymmetry in certain products using chiral ligand derivatives.[102] However, the mechanisms of these reactions vary depending on the added oxidant.[101] In the particular case of *tert*-butyl hydroperoxide (TBHP), O – O bond homolysis was proposed, leading to *tert*-butoxy radical ($^{t}BuO^{\bullet}$) and oxoiron(IV).[101] Aliphatic C – H bond hydroxylation then occurs through sequential H-atom abstraction by $^{t}BuO^{\bullet}$ and recombination of the alkyl radical at oxoiron-(IV), so the metal-centred oxidant is utilized only indirectly.

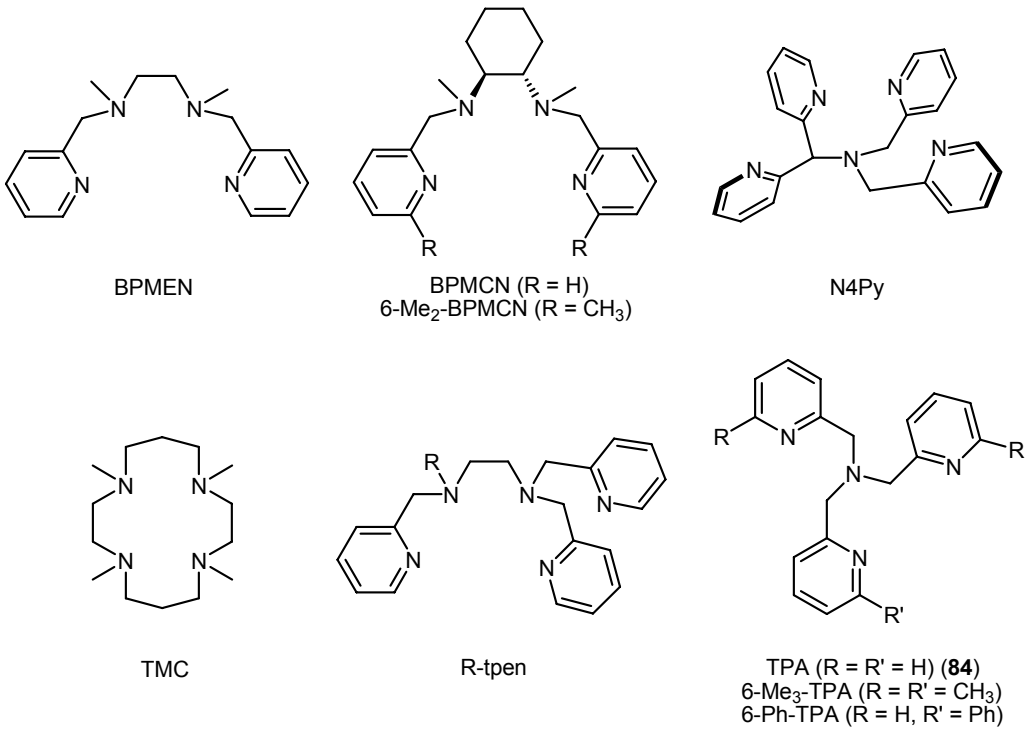


Figure 28: *Selected ligands used for the modelling of nonheme iron centres.*[103]

Since iron complexes of TPA (**84**) type ligands have shown good reactivity in catalytic oxidations of various organic substrates, it was selected as a suitable complexing agent for the attachment to β-CD. For the functionalization of β-CD, monotosylated β-CD **85**, which is commercially available, was chosen as the CD source. In order to be able to displace the tosylate of monotosylated β-CD **85**, a suitable nucleophilic group would have to be incorporated into the TPA ligand. For this purpose an amino-function was introduced in TPA (**84**) to give amine **90**, which then could be attached to β-CD via a nucleophilic substitution reaction with **85** to afford precatalyst **91**. The synthesis of the CD-based ligand **91** is depicted in ***figure 29***.

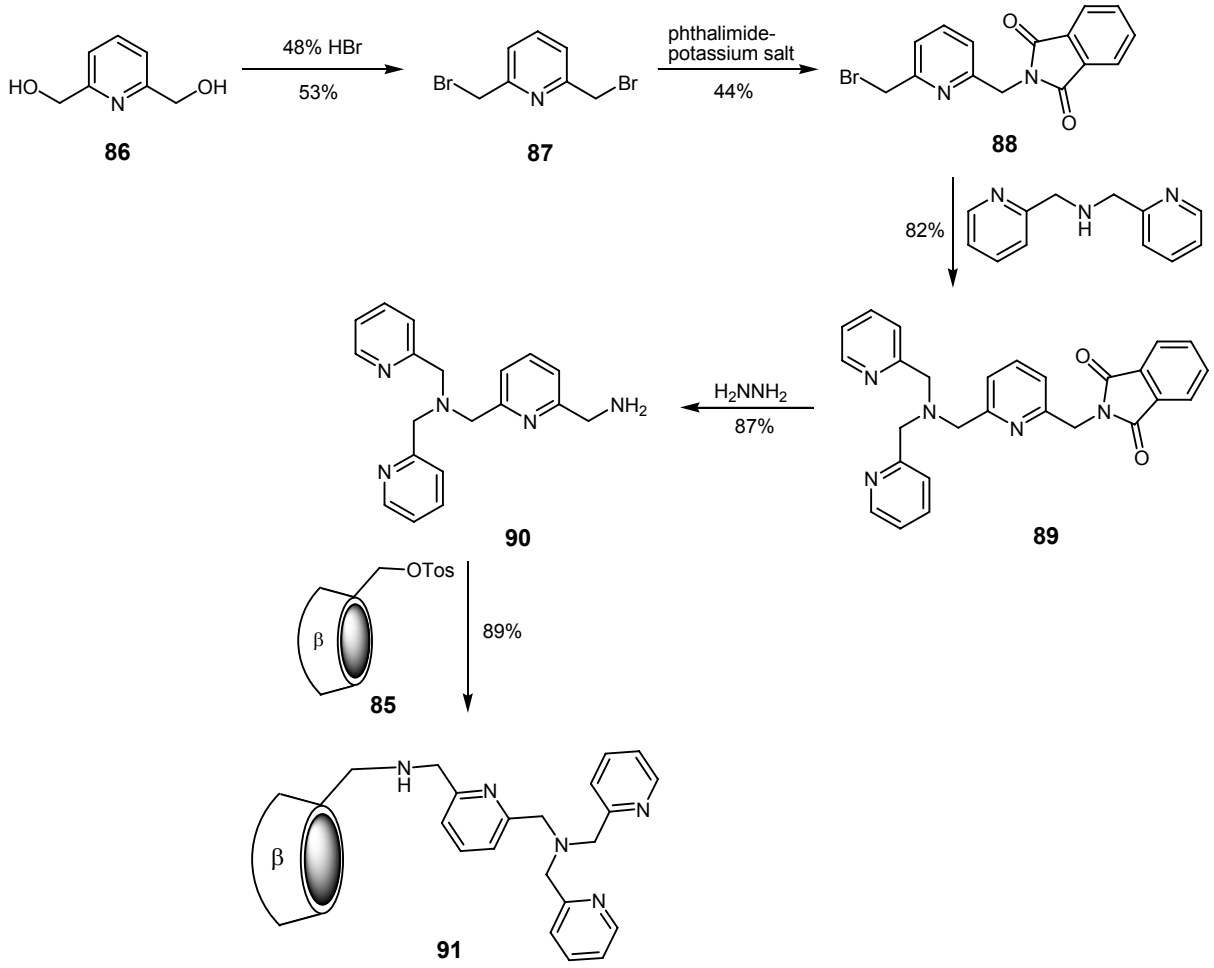


Figure 29: *Synthesis of CD-ligand **91**.*

The commercially available starting material 2,6-bis(hydroxymethyl)pyridine (**86**), was first subjected to a substitution reaction with HBr to brominate the hydroxyl groups to afford 2,6-bis(bromomethyl)pyridine in 53% yield. This was then reacted with 1.1 equivalents of phthalimide potassium salt to give the monosubstituted product **88** in

44% yield. The low yield can be accounted for by the formation of doubly substituted sideproduct. Transformation of **88** by nucleophilic substitution of the remaining bromine atom with di-(2-picolyl)amine afforded the protected primary amine in 82% yield. Deprotection of **89** was performed by hydrazinolysis and gave the desired nucleophilic building block **90**. The TPA linked β-CD **91**, was produced by treatment of monotosylated β-CD **85** with a 25 fold excess of amine **90**. The large excess of amine **90** was used in order to obtain full conversion to **91**, which made the isolation process much easier. The reaction could be monitored by ESI-MS analysis. The exact mass of the modified β-CD **91** is 1435.5. Apart from the molecule ion m/z = 1436.1 $[M+H]^+$, the mass spectrum also shows the peak for the sodium ion adduct $[M+Na]^+$ at 1458.0 (*figure 30*).

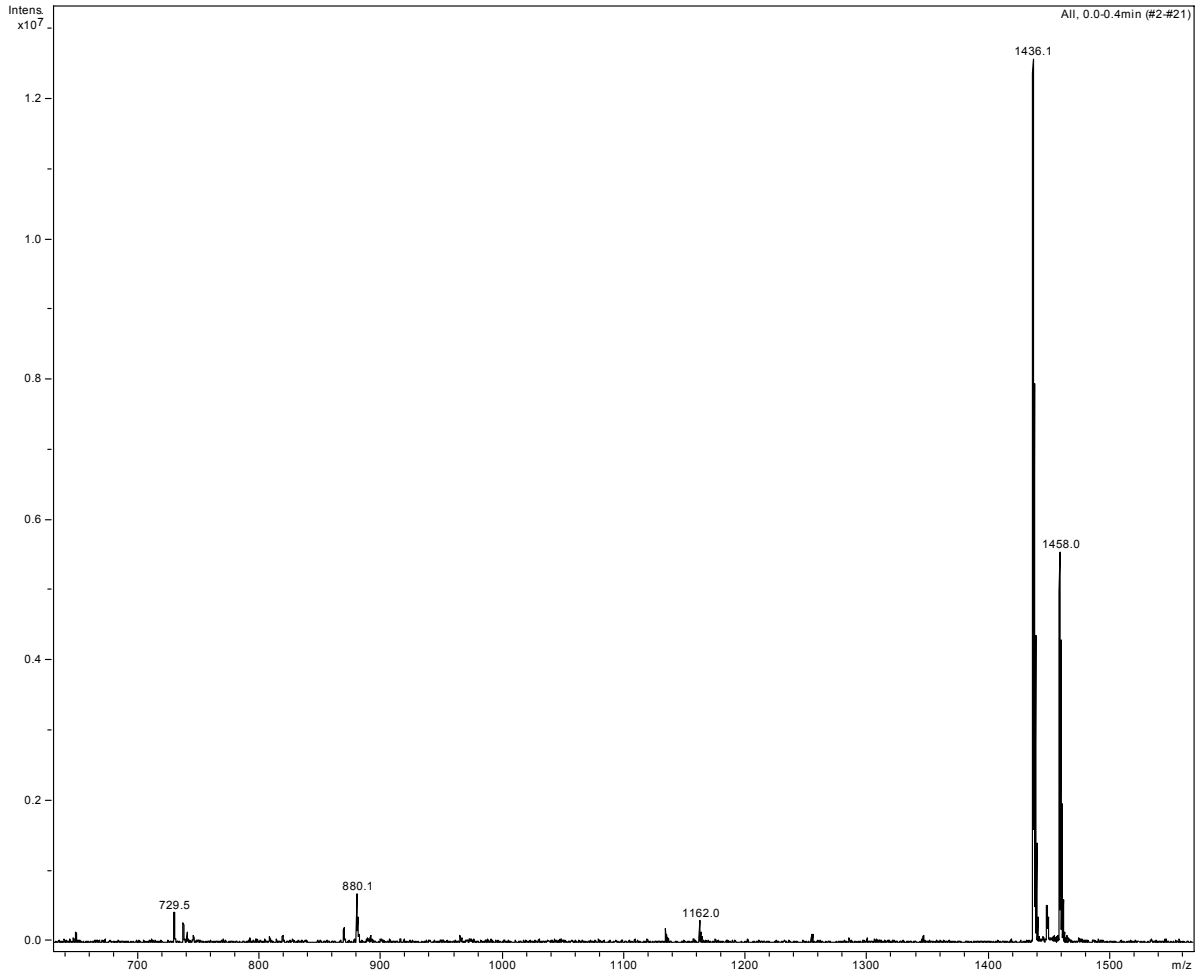


Figure 30: *Positive ion mode ESI-MS spectrum of* ***91****.*

3.1.2 Application of the β-CD Linked Pentadentate Nitrogen Ligand 91 in Catalytic Oxidation Reactions

Selective and catalytic oxidations of organic molecules are amongst the most important technological processes in chemical industry. Chemical raw materials are principally hydrocarbons, alkanes in particular. Due to their intrinsically inert nature, it is difficult to oxidize alkanes in a controlled and selective manner.[104]

High-valent metal-oxo species have been proposed as one of the active intermediates not only in biological metalloenzymes such as oxidases and oxygenases, but also in the oxidative transformation of organic compounds catalyzed by transition metal complexes.[105, 106, 107]

In order to be able to use β-CD-modified pentadentate nitrogen ligand **91** as an oxidation catalyst, suitable metal complexes have to be formed first before they can be oxidized to the corresponding metal-oxo species by treatment with a suitable oxygen atom transfer oxidant.

For the first experiments $MnCl_2$ was chosen as the metal source, because manganese is widely used in catalytic oxidations. For example, it is the metal of choice in the asymmetric *Jacobsen* epoxidation with salen-catalysts.[108]

This catalytic system was then initially tested in epoxidation reactions. 3-(4-*tert*-Butylphenyl)-1-propene (**92**) was chosen as a substrate and synthesized following a published procedure.[109] NMR studies with similar substrates have shown that *tert*-butylphenyl-groups enter the cavity of β-CD.[110] The manganese complex of **91** was formed in situ by stirring a solution of **91** together with 1 eq. $MnCl_2$ in a 1:1 mixture of MeCN and H_2O at room temperature. The complex formation could be monitored by ESI-MS analysis. After substrate **92** was added and the mixture was stirred for 15 min at room temperature in order to preform the substrate-CD-complex. Iodosyl-benzene was slowly added as a methanolic solution, probably resulting in the formation of a manganese-oxo species, which then in turn could epoxidize the double bond in **92** (*figure 31*). The epoxide **93** was obtained in 48% yield, however, chiral HPLC analysis revealed that the racemic product was obtained.

In a first control experiment, the catalytic reaction was run without CD-ligand **91** and in a second control experiment without $MnCl_2$. In both cases no product **93** was formed.

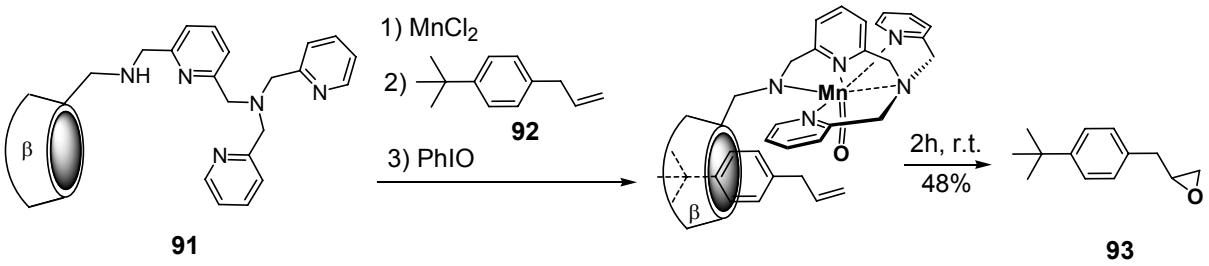


Figure 31: *Catalytic epoxidation of alkene **92**.*

The low yield and the lack of chiral induction through the CD-moiety means this system is not useful for the diastereoselective epoxidation of protected phytyl-hydroquinone substrates (**84** in *figure 27*).

In the next step the oxidation of alkanes was examined. In a first experiment 1-*tert*-butyl-4-propylbenzene (**94**) was employed as a substrate. Attempts to oxidize **94** with iodosyl-benzene as an oxygen atom donor were unsuccessful. However if 20 eq. *tert*-butyl hydroperoxide (TBHP) were used instead, the expected in benzylic position oxidised products could be obtained in 68% and 2% yield for the corresponding ketone (**95**) and alcohol (**96**) respectively (*figure 32*).

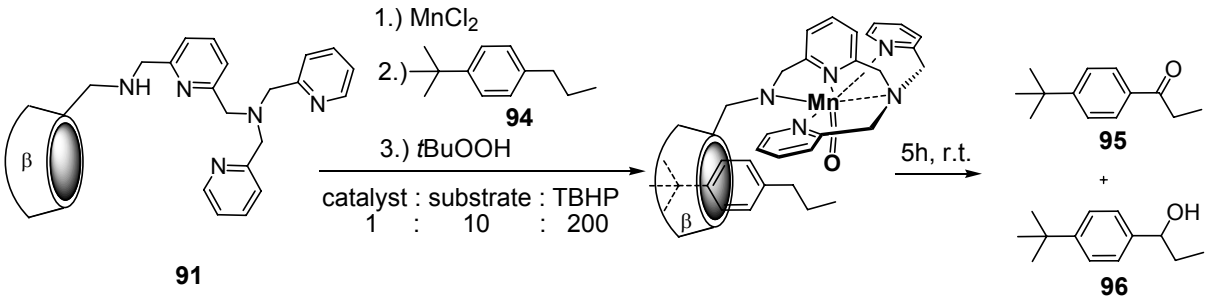


Figure 32: *Catalytic oxidations of benzylic positions.*

Control experiments without **91** and then without $MnCl_2$ again showed no conversion of the starting material **94**.

The oxidation of non-activated C-H bonds was then investigated. *tert*-Butylcyclohexane (**97**) was employed as a substrate for this most challenging type of oxidations (*figure 33*).

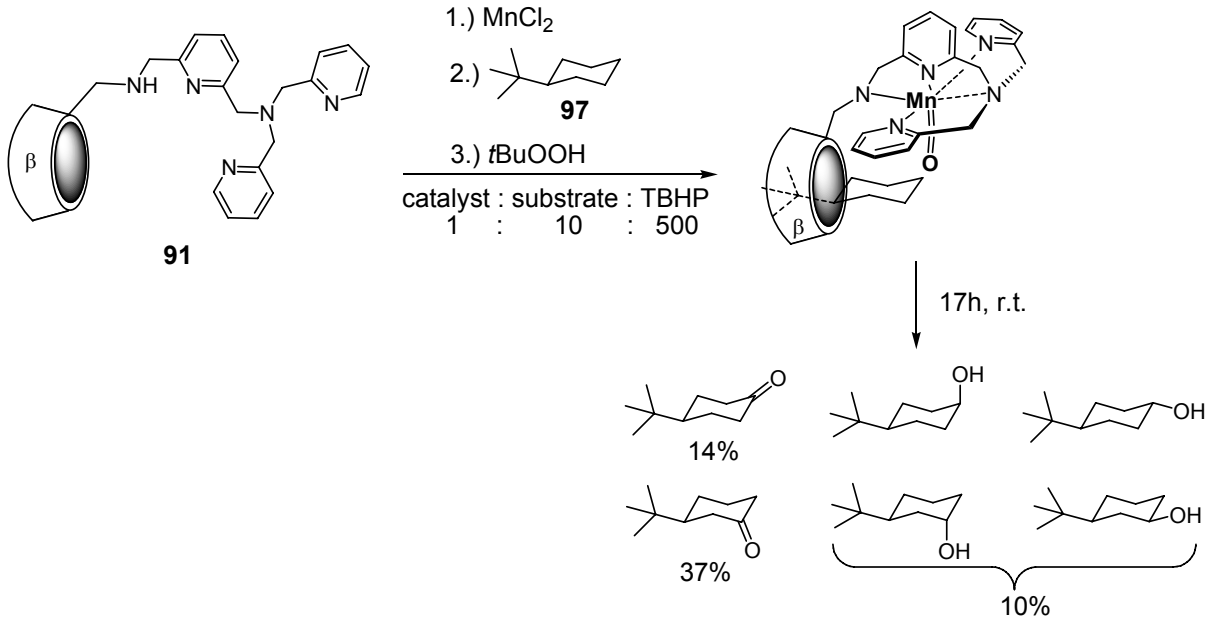


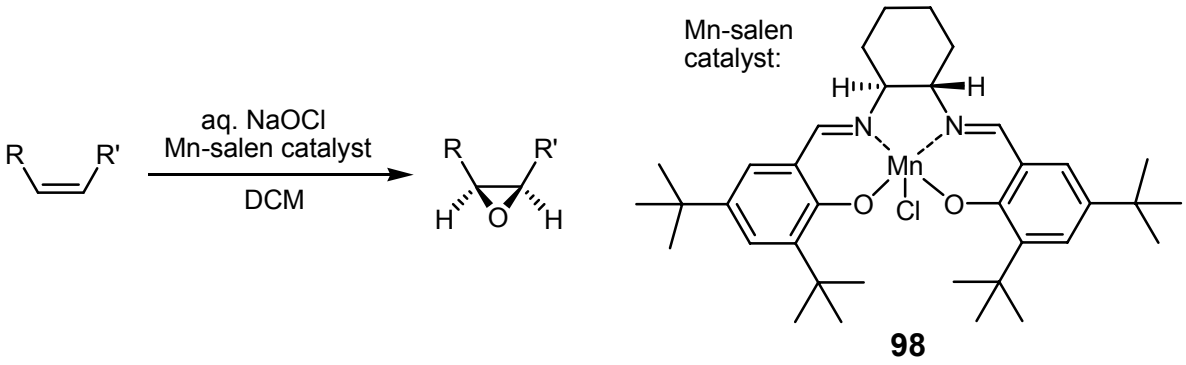
Figure 33: *Catalytic oxidation of non-activated C-H bonds.*

The substrate **97** was oxidised in the 4- and 3-position relative to the *tert*-butyl group, whereas the 2- and 1-position remained untouched. A large excess of TBHP (50 eq.) and a rather high catalyst loading (10 mol%) was necessary in order to obtain a total yield of 61% of oxidised products. Analysis of the products by chiral GC showed that ketone **98** was obtained as a racemate.

These results show that the CD moiety itself is not enough to induce stereoselectivity in these catalytic reactions. In order to get stereoselectivity, a chiral ligand would have to be designed such that an attachment to CD would be feasible.

3.1.3 Design of a Novel CD-linked Salen Ligand

The *Jacobsen* epoxidation allows enantioselective synthesis of epoxides from alkenes. In contrast to other asymmetric catalytic epoxidation methods, such as the *Sharpless* epoxidation[111] (used for epoxidation of allylic alcohols), there are no additional functional groups required, which allows a broader substrate scope for the transformation. By using *Jacobsen* Mn-salen catalysts, epoxides with high stereoselectivity can be obtained from prochiral disubstituted *cis*-olefins, whereas other olefins, with a few exceptions, enable epoxide formation only with moderate stereoselectivities (*figure 34*). This fact is well explained by a side-on perpendicular approach of olefin to the manganese-oxo bond of the Mn(V) intermediate.[112, 113] Consequently this would mean that salen catalysts would be unlikely to give good diastereoselectivities in the epoxidations of protected phytyl-hydroquinone substrates (**84** in *figure 27*).



98

Figure 34: *Jacobsen epoxidation of olefins.*

There was the hope that attaching such salen ligands to β-CD might have a beneficial effect on the stereoslectivity of epoxidation reactions of challenging substrates. In order to be able to attach a salen moiety to β-CD, salen catalyst **98** had to be modified by introducing a nucleophilic group without destroying the C_2-symmetry of the ligand. The replacement of the cyclohexane ring in **98** by pyrrolidine would give the previously synthesised salen ligand **99**.[114] The chiral salen ligand **99** with a pyrrolidine backbone has the advantage that different groups and fragments can be readily tethered to the backbone of the ligand through the N atom of pyrrolidine.[115] Therefore it was assumed that salen ligand **99** potentially could be attached to β-CD (*figure 35*).

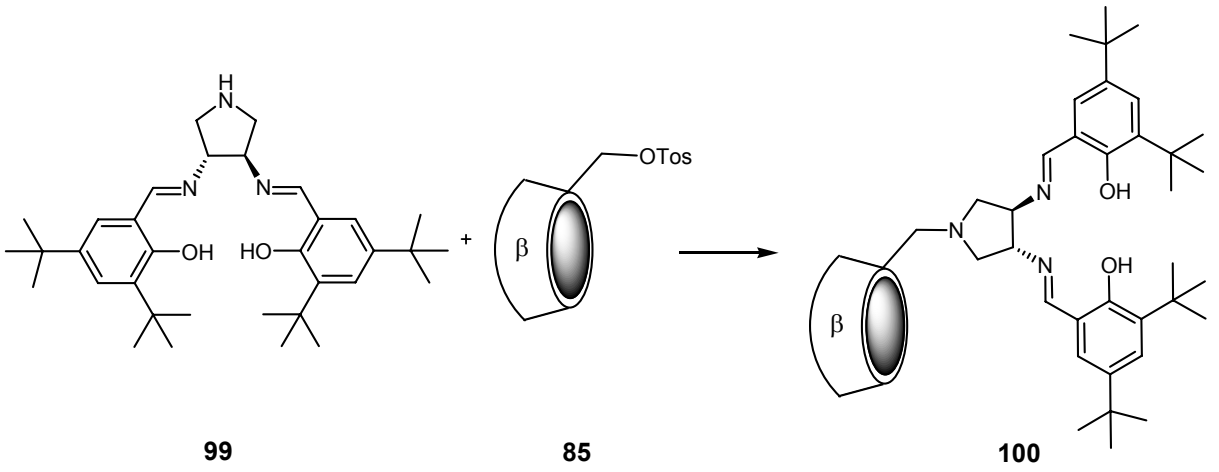


Figure 35: *Attachment of salen ligand **99** to CD.*

The synthesis of salen ligand **99** was carried out following published procedures (*figure 36*).[116, 117, 118]

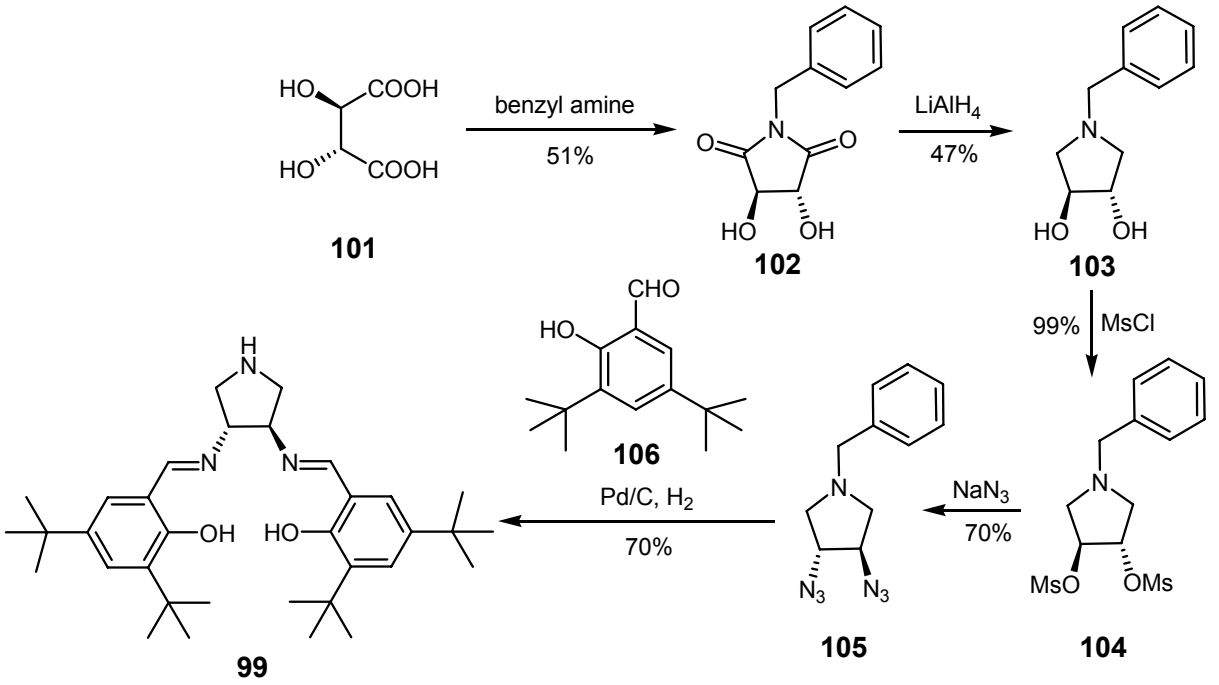
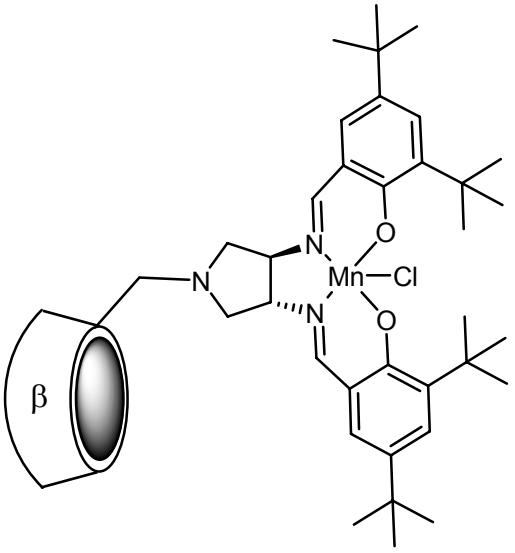


Figure 36: *Synthesis of salen ligand **99**.*

Natural L-(*R,R*)-(+)-tartaric acid (**101**) was reacted with benzylamine to give imide **102**. The condensation reaction was complete when the appropriate amount of water was collected with a Dean-Stark apparatus. Reduction of the imide **102** gave the diol **103**, which then could be mesylated in nearly quantitative yield. Nucleophilic substitution of the mesylate groups by azide proceeded under complete inversion of configuration. The diazide **105** was first reduced to the corresponding diamine, which

subsequently reacted with aldehyde **106** to form the desired Schiff-base ligand **99**. The attachment of **99** to β-CD was performed as shown in ***figure 35*** and gave the CD-modified salen ligand **100** in 49% yield after reversed phase column chromatography. Refluxing of **100** together with $Mn(OAc)_2$ in EtOH followed by the addition of LiCl and air oxidation afforded the corresponding Mn(III)-complex **107** in 82% yield (*figure 37*). The mass spectrum of **107** shows only one peak at m/z = 1703, which corresponds to $[M - Cl^-]^+$ (*figure 38*). To the best of my knowledge, compound **107** is the first example of a chiral salen complex, which is covalently attached to β-CD.



107

Figure 37: *CD-modified salen catalyst **107**.*

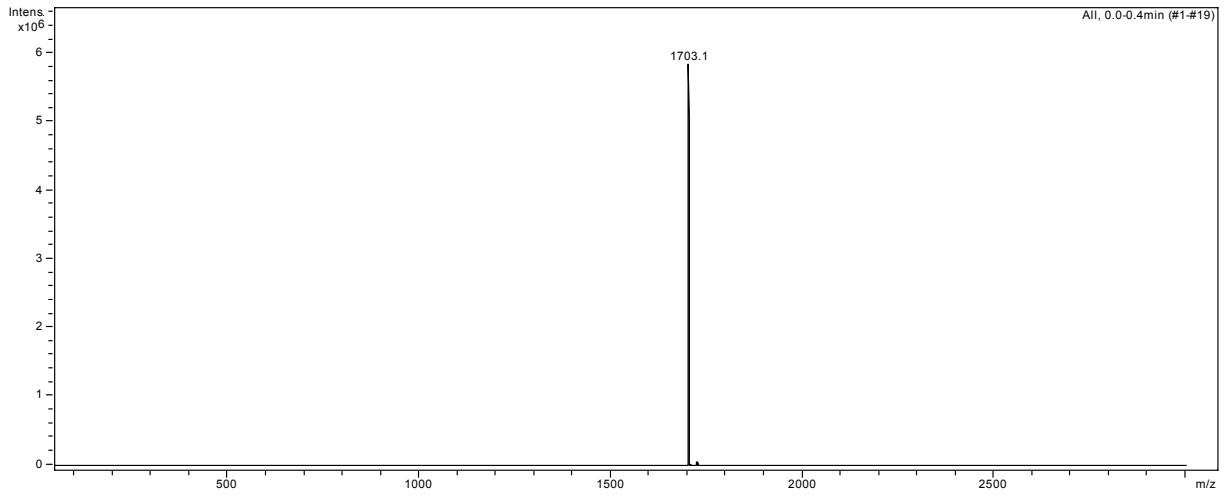


Figure 38: *Positive ion mode ESI-MS spectrum of **107**.*

3.1.4 Catalytic Experiment with CD-catalyst 107

Unfortunately, the solubility of catalyst **107** in H_2O, MeOH, MeCN, DCM or mixtures thereof is very low, which limits its applicability drastically. The reason for this behaviour lies presumably in the different polarity properties within the compound. On the one hand, there is the very polar CD-moiety, which is soluble in polar solvents such as water, on the other hand there are four hydrophobic *tert*-butyl groups on the attached salen moiety. However, eventually one solvent system was found in which catalyst **107** was soluble. When *N*-methylmorpholine-*N*-oxide (NMO) was added to a suspension of **107** in DCM, a solution could be obtained. This system had previously been employed for the epoxidation of unfunctionalized alkenes with chiral (salen)Mn(III) catalysts and *m*CPBA as an oxidant.[115] The combination of NMO and *m*CPBA leads to an unreactive adduct, which is capable of oxygen atom transfer mediated by (salen)Mn(III) complexes.[119, 120]

The use of DCM as a solvent is generally not desirable for reactions with CD-catalysts as the driving force for inclusion complex formation with a hydrophobic substrate is much lower than in aqueous solvents. However, the *m*CPBA/NMO oxidant system with CD-catalyst **107** was tested in the epoxidation of 4-*tert*-butylstyrene (**108**) (*figure 39*).

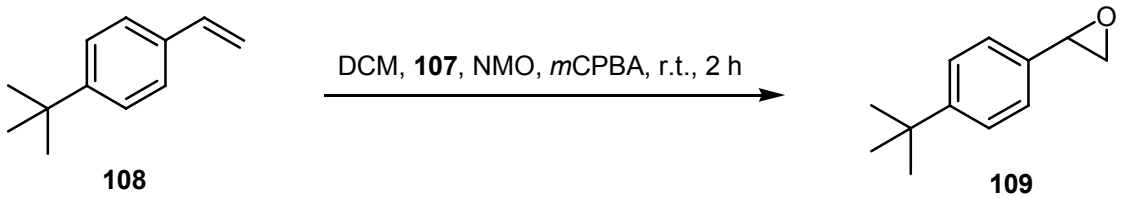


Figure 39: *Catalytic epoxidation of **108*** with CD-catalyst **107**.

The epoxide **109** was obtained in 62% yield and with 9% ee. The stereoselectivity of this epoxidation was even lower than the previous example in which it had been obtained with the corresponding salen complex **110** lacking the CD moiety employing the standard conditions for *Jacobsen*-epoxidations (*figure 40*). When catalyst **110** together with bleach as oxidant and 4-phenylpyridine *N*-oxide as an axial ligand was used, epoxide **109** could be obtained in 50% yield and 30% ee.

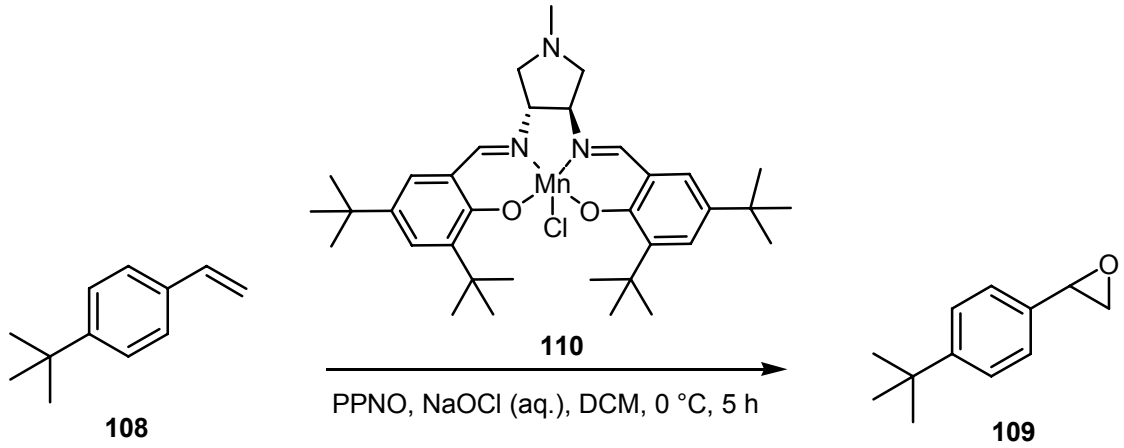


Figure 40: *Catalytic epoxidation of* ***108*** *with salen catalyst* ***110***.

The very low solubility of catalyst **107** in aqueous solvents, its rather difficult synthesis, its high molecular weight, and the low selectivity for the epoxidation of **108** in DCM, limits the usefulness of catalyst **107** drastically.

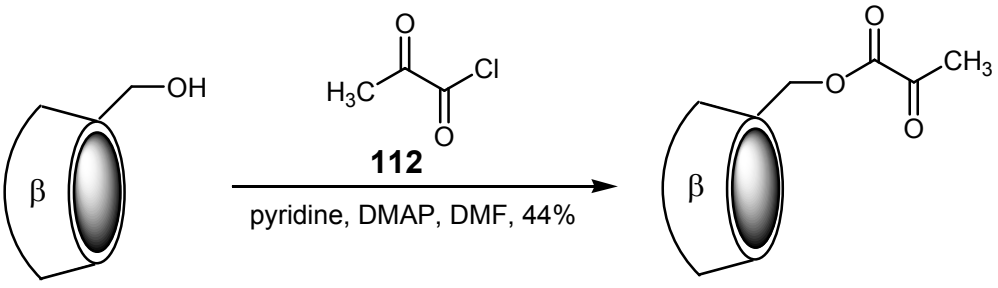
Attempts to synthesise more water soluble derivatives of catalyst **107**, in which the *tert*-butyl groups would be replaced by ionic phosphonium or sulphate groups failed.

For reasons of applicability, catalysts with less complicated structures had to be designed. The attention was drawn to simple organocatalysts, such as ketone catalysts for stereoselective epoxidation of alkenes.

3.1.5 A CD-Modified Ketone Catalyst

Dioxiranes are powerful oxidizing agents that can be generated in situ from the reaction of Oxone ($KHSO_5$) or other oxidants with ketones. Dioxiranes are widely used for epoxidations, C – H bond oxidation, and heteroatom oxidation.[121, 122, 123]

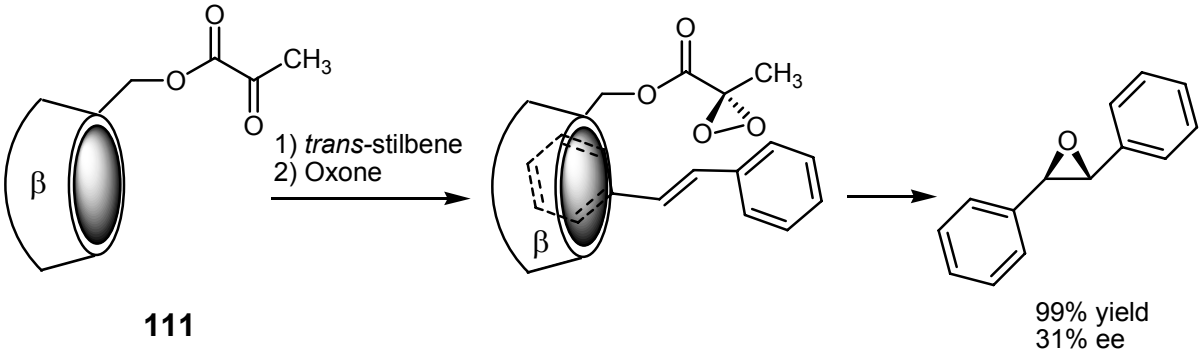
Wong et al. reported in 2003 the use of a CD-modified ketoester as a supramolecular catalyst for stereoselective alkene epoxidation.[124] The CD ketoester **111** was prepared by functionalization of the primary hydroxyl rim of β-CD with pyruvyl chloride (**112**) (*figure 41*).



β–CD **111**

Figure 41: *Synthesis of β-CD ketoester **111**.*

The activity of catalyst **111** was explored by *Wong et al.* for asymmetric epoxidation of styrenes. The epoxidation of *trans*-stilbene with **111** is shown in ***figure 42***. Treatment of *trans*-stilbene with **111** in H_2O/MeCN = 1:1.5 afforded the corresponding CD inclusion complex. Subsequent addition of Oxone then transformed the keto group of **111** into the corresponding dioxirane which is capable of epoxidising the substrate in 99% yield and 31% ee.

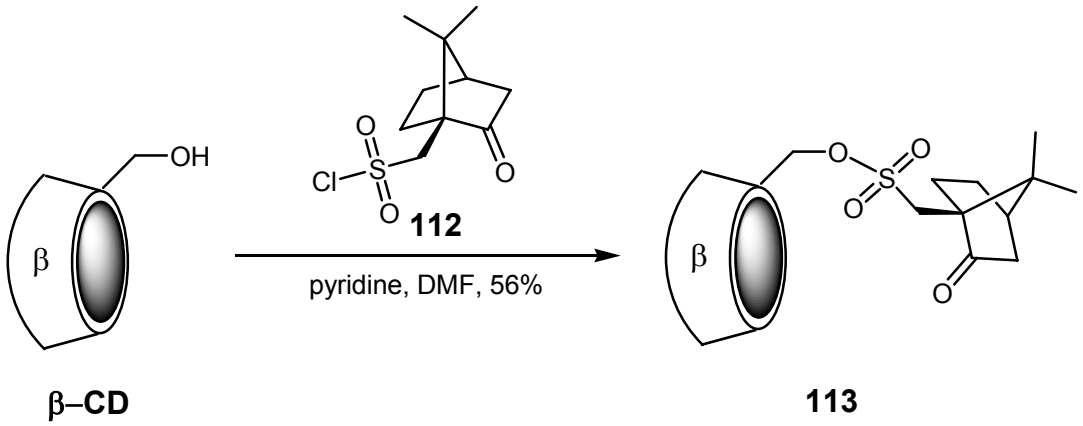


111

Figure 42: *Epoxidation of trans-stilbene with **111**.*

This example shows that CDs can serve as chiral templates to mediate asymmetric epoxidation via inclusion complex formation with moderate enantioselectivity.

In order to obtain higher enantioselectivities for the epoxidation of olefins, a chiral ketone would have to be attached to β-CD. For this purpose a commercially available chiral ketone, which can be readily attached to β-CD, should be found. (1*S*)-(+)-Camphor-10-sulfonic acid chloride (**112**) seemed to be a suitable starting material for the synthesis of a new CD ketone catalyst, because it is chiral and it can be easily attached to β-CD through its sulfonic acid chloride function. The synthesis of the new potential β-CD ketone catalyst **113** is shown in ***figure 43***.



β–CD **113**

Figure 43: *Synthesis of potential β-CD ketone catalyst **113**.*

Reaction of β-CD and **112** gave product **113** in 56% yield. The reaction side product, the doubly substituted β-CD, and unreacted starting material could be removed by C_{18} reversed phase column chromatography.

CD ketone **113** was subsequently tested as a catalyst for the epoxidation of *trans*-stilbene. The reaction conditions were chosen according to *Wong et al.* (*figure 42*).[124] However, no conversion of *trans*-stilbene could be observed by TLC, even after a prolonged reaction time of 12 h instead of 1 h. The lack of reactivity of **113** is most likely due to the fact that the keto function in **113** is not activated, which makes the nucleophilic attack of the oxidant (Oxone), needed for dioxirane formation substantially slower compared to compounds that possess activated keto functionalities, such as **111**.

CD based catalysts appear to be economically unsuitable for stereoselective epoxidation of protected phytyl hydroquinones (**84** in *figure 27*) for the following reasons:

- The molecular weight of CDs is relatively high. Therefore CD-derived catalysts would not be atom economical, unless they are recoverable.[125]
- Since the reaction products may also bind to CD, product inhibition factors come into play, making a high catalyst loading necessary.
- Synthesis and purification of CD-derivatives can be difficult, time consuming and expensive as silica gel column chromatography often isn't possible.

- The choice of solvents is often limited to aqueous solvent systems due to the high polarity of CDs.

The reasons given above made it necessary to find a suitable, *low molecular weight* catalyst that is capable of epoxidising hydroquinones (**84** in *figure 27*) in a highly diastereoselctive fashion and in good yields.

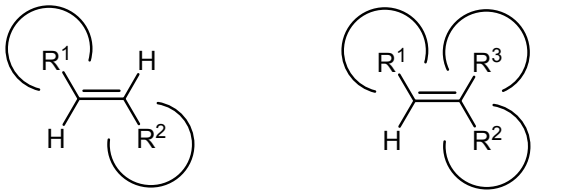
Asymmetric epoxidation has attracted significant attention in the past two decades. The *Sharpless* epoxidation method is a powerful tool for the asymmetric epoxidation of allylic alcohols. As already mentioned, for the enantioselsctive epoxidation of unfunctionalized olefins, the chiral Mn-salen catalysts are effective for a variety of olefin types, particularly conjugated *cis*-olefins.

For our purpose, however, we needed an effective method for asymmetric epoxidation of trisubstituted olefins (*trans*-olefins). We envisaged that chiral ketones could be ideal catalysts for this task.

3.2 Organocatalytic Asymmetric Epoxidation of Protected Phytyl Hydroquinones 84 by Chiral Ketones

3.2.1 Introduction

In recent years, chiral dioxiranes, generated from the corresponding ketones, have been shown to be powerful agents for asymmetric epoxidations of olefins, particularly for unfunctionalized *trans* and trisubstituted olefins, which has been a long-standing problem.[126] When examining the features of trisubstituted and *trans*-disubstituted olefins, it is noticeable that both of them have one large and one small substituent on either one side or one terminus of the C – C double bond (*figure 44*). Under either a spiro or planar transition state (*figure 45*), chiral dioxiranes bearing large and small substituents, respectively, on each face of the dioxirane should have the potential to discriminate between the large and small groups on the C – C double bond. Hence, this could offer a promising solution to the problem of asymmetric epoxidation of hydroquinones **84**.



trans-olefin trisubstituted olefin

Figure 44: *Recognising olefin substitution patterns.*

There is evidence through experimental[127] and computational[128] studies that the spiro transition state is favored, presumably due to the stabilizing interaction of an oxygen lone pair with the π* orbital of the alkene in the spiro transition state (such an orbital interaction is not geometrically feasible in the planar transition state) (*figure 45*).

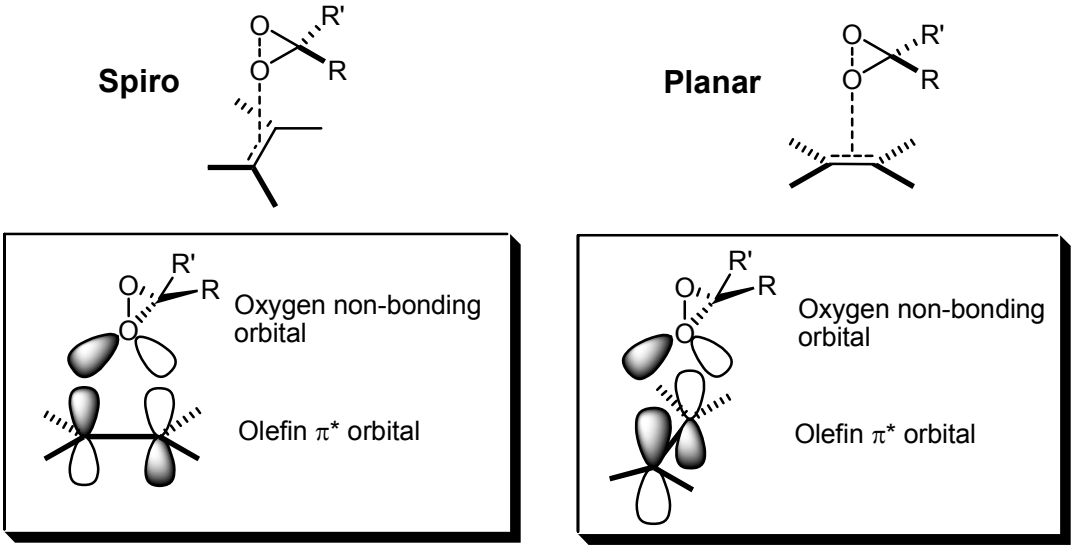
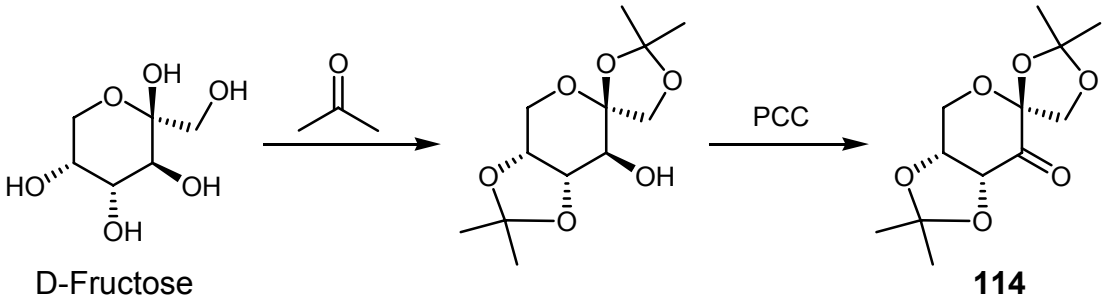


Figure 45: *The spiro and planar transition states for the dioxirane epoxidation of olefins.*[129]

Since the first chiral ketone mediated epoxidation reported by *Curci*[130] in 1984, a variety of chiral ketones have been investigated in a number of laboratories, and significant progress has been made in the field. Among the considerable advances in the search for efficient chiral ketone catalysts, the fructose-derived ketones developed by *Shi* and co-workers have proved to be the best ketone catalysts in chiral dioxirane epoxidation. For example, ketone **114**, which is commercially available, or can be readily prepared from very inexpensive D-fructose by ketalization and oxidation (*figure 46*), gives the highest ee values for a broad range of different olefins.



D-Fructose **114**

Figure 46: *Synthesis of the Shi ketone* ***114****.*

In general, two different oxidants are used for the in situ generation of the corresponding dioxirane from ketone **114**. The oxidant that is almost exclusively used for ketone-mediated epoxidations is Oxone (a commercial mixture of 2:1:1 $KHSO_5$:$KHSO_4$:K_2SO_4) with potassium peroxomonosulfate ($KHSO_5$) being the active component. Generally, the optimum pH for dioxirane epoxidation is 7 – 8. At higher pH, Oxone tends to decompose. However, at pH 7 – 8 the *Shi* catalyst **114** decomposes due to a competing Baeyer-Villiger reaction. By increasing the pH to 10.5 (by addition of K_2CO_3), the amount of Oxone can be reduced to a stoichiometric amount (1.5 eq.), suggesting that the high oxygen content of ketone **114** makes it sufficiently reactive to compete with Oxone decomposition. The proposed catalytic cycle is depicted in ***figure 47****.*

In 1999 *Shi et al.* reported for the first time the use of hydrogen peroxide (H_2O_2) as an oxidant for the generation of dioxiranes from ketones.[131, 132] Hydrogen peroxide (H_2O_2) is a particularly attractive oxidant due to its high active oxygen content with its reduction product being water. Studies have shown that a combination of hydrogen peroxide and a nitrile, used as a solvent, provides an effective system for epoxidation with a catalytic amount of ketone **114**. However, when the reaction was carried out in other solvents, such as DMF, THF, DCM, EtOH, or dioxane without the addition of a nitrile, only trace amounts of epoxide were detected. This result suggests that hydrogen peroxide itself cannot effectively generate the dioxirane and that nitrile plays an important role. Hydrogen peroxide is likely to be activated by the nitrile (**116**) by forming peroxyimidic acid (**117**), which then reacts with ketone **114** to generate the dioxirane (*figure 48*). Out of a number of different nitriles tested, MeCN gave the best results in the asymmetric epoxidation of *trans*-β-methylstyrene with ketone **114** and H_2O_2, in terms of conversion and ee.[132] It was found that the H_2O_2-MeCN system provided similar enantioselectivities to Oxone. The catalyst loading is somewhat

substrate dependent and it can be reduced to as low as 10 mol% in some cases. Further studies showed that a mixed solvent such as MeCN-EtOH-DCM was beneficial for olefins with poor solubility.

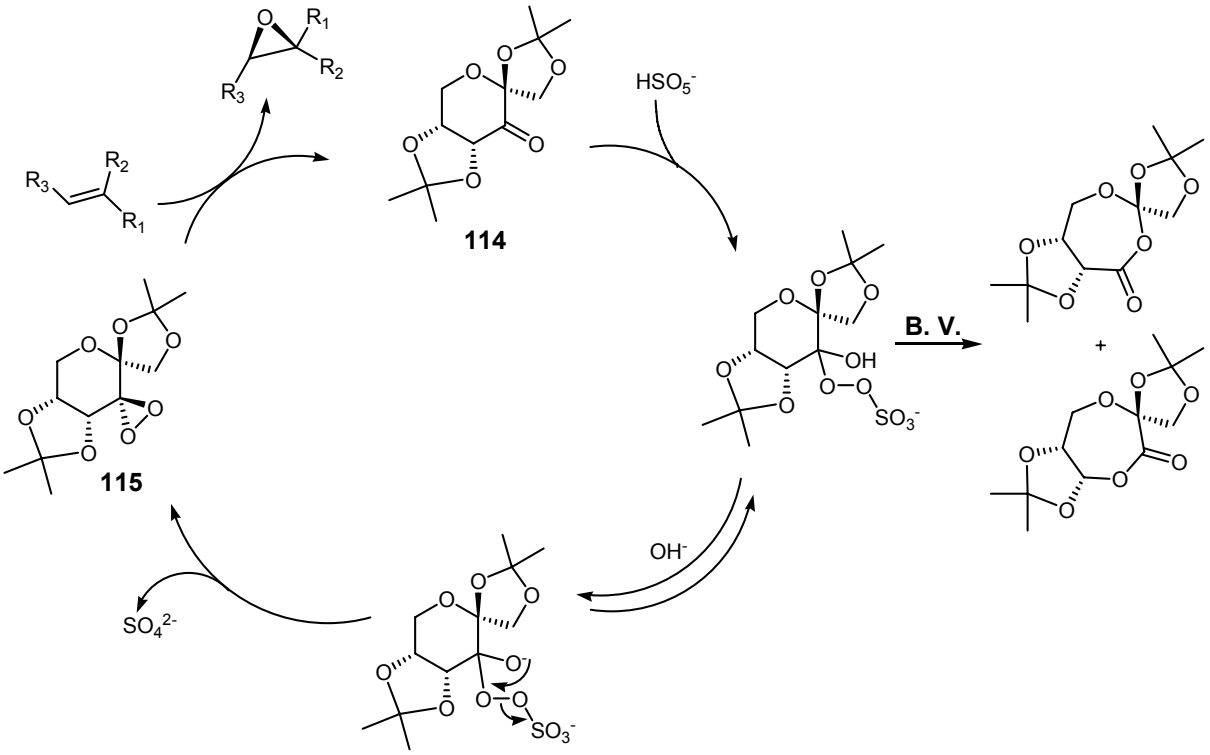


Figure 47: *Proposed catalytic cycle of the epoxidation by ketone **114** using Oxone as the stoichiometric oxidant.*

Analysis of the stereochemistry of the epoxides produced by the chiral dioxirane **115** provided further understanding of the transition state involved in this reaction. The corresponding dioxirane **115** of ketone **114** has two diastereomeric oxygens, and the equatorial oxygen is likely to be sterically more accessible for olefin approach. Among possible spiro and planar transition states for the epoxidation with ketone **114**, spiro **B** – **D** and planar **F** – **H** are disfavoured by destabilizing steric interactions (*figure 49*). Spiro **A** and planar **E** are the two sterically favoured transition states. Experimental data show that spiro **A** is the predominant transition state with planar **E** being the major competing transition state. The extent of the involvement of planar **E** depends on the nature of the substituents on the olefin. ***Figure 50*** shows that epoxidation via spiro **A** and planar **B** result in opposite configuration of the epoxide product, which consequently affects the ee of the product.

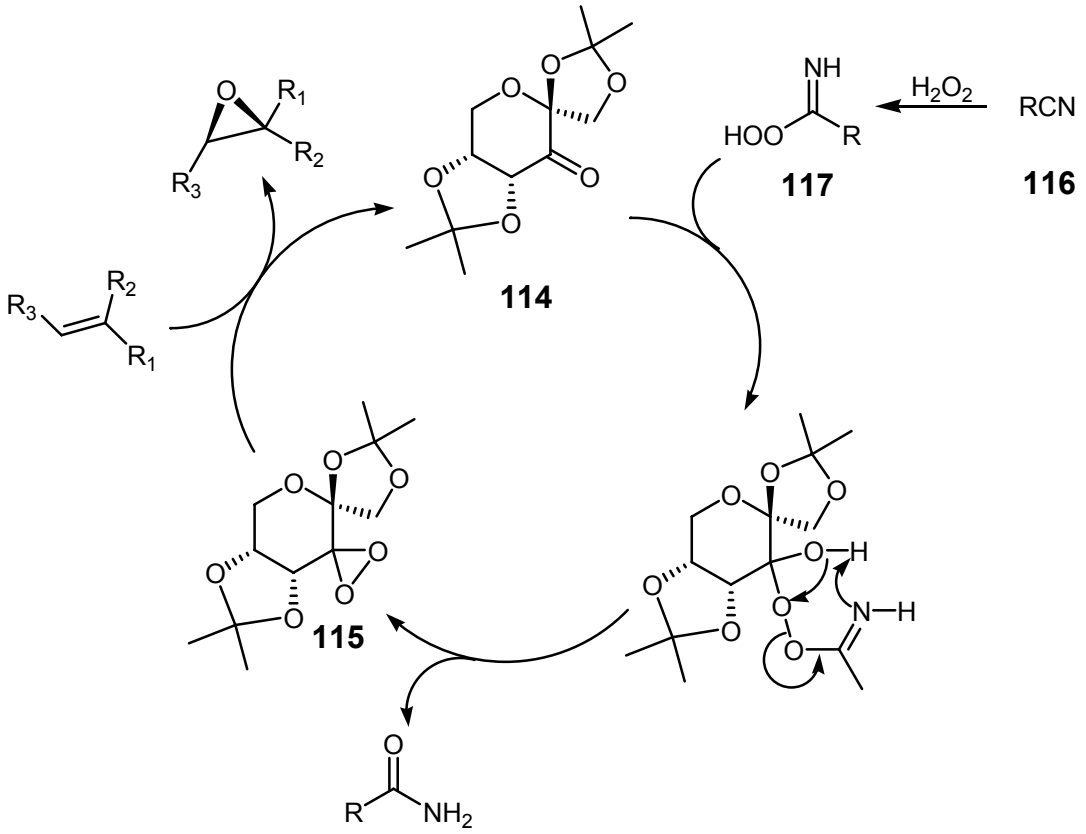


Figure 48: *Proposed catalytic cycle of the epoxidation by ketone* ***114*** *using hydrogen peroxide as the stoichiometric oxidant.*

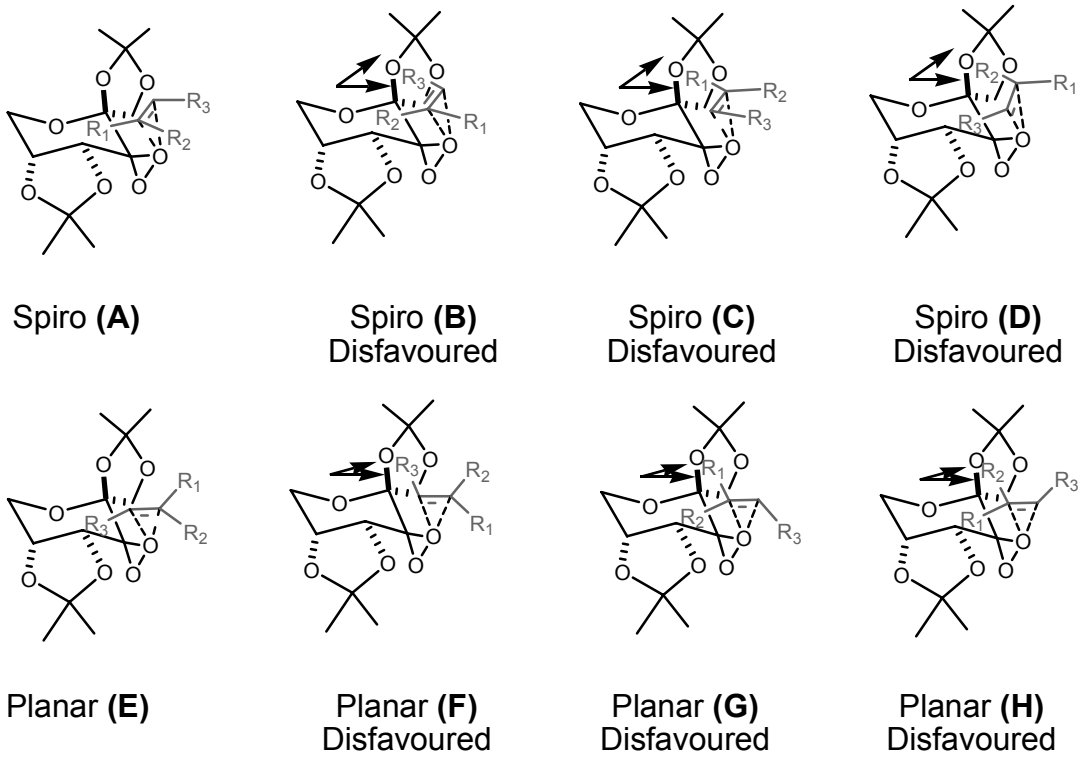


Figure 49: *Possible spiro and planar transition states for the epoxidation for the epoxidation with ketone* ***114****.*

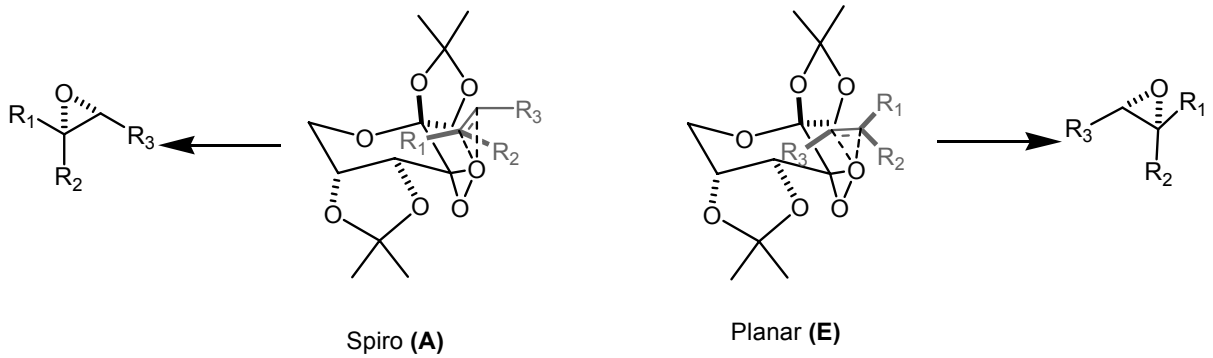
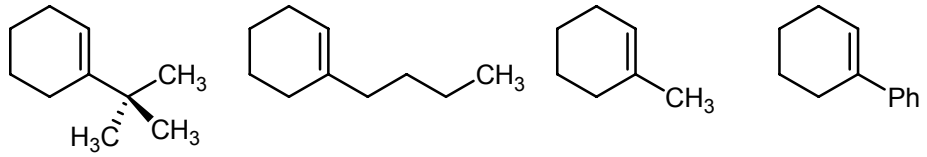


Figure 50: *Competing spiro **A** and planar **E** transition states for the epoxidation with ketone **114**.*

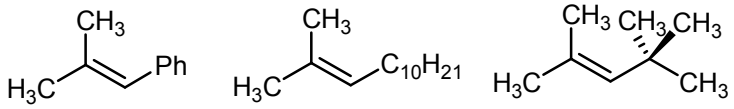
With regard to the steric effect, generally higher ee values can be obtained by decreasing the size of R_1 (favouring spiro **A**), increasing the size of R_3 (disfavouring planar **E**) or both. The experimental data that supports this assumption is given in ***figure 51***.[133]

1. Effect of smaller R_1 (also: "T-branch"; phenyl groups can be considered smaller than methyl).



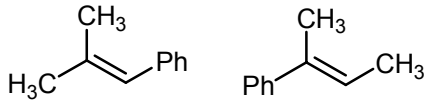
26% *ee* **79% *ee*** **81% *ee*** **98% *ee***

2. Effect of larger R_3



76% *ee* **86% *ee*** **91% *ee***

3. Comparing the size of R_1 and R_3

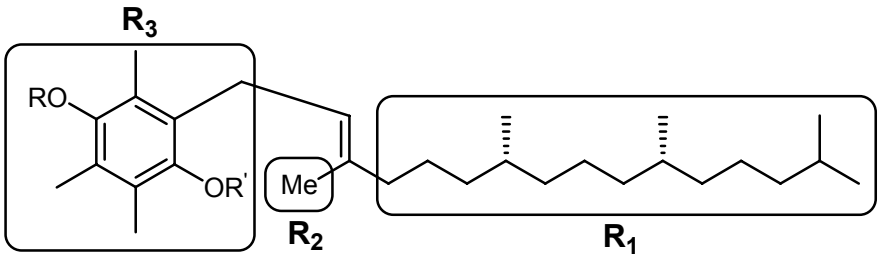


76% *ee* **97% *ee***

Figure 51: *Steric effects that influence the ee of the epoxides obtained by ketone **114** mediated epoxidation.*[133]

3.2.2 Synthetic Strategy for the Synthesis of α-Tocopherol via *Shi* Epoxidation According to *Figure 27*

In our approach for the synthesis of α-tocopherol, the key step is the asymmetric epoxidation of protected phytyl hydroquinone derivatives **84**. The only possibility of influencing the de value of the epoxidation is to change the size of R_3 by choosing different protecting groups R and R', whereas R_1 and R_2 cannot be changed (*figure 52*). However, the fact that the alkyl chain R_1 is rather big, probably makes the task to obtain high de values in the asymmetric *Shi* epoxidation of **84** very challenging (see examples in *figure 51*).



84

Figure 52: *The structural properties of protected phytyl hydroquinone derivatives **84**, which play a role in the asymmetric Shi epoxidation of **84**.*

In order to obtain the chroman moiety in the right configuration by epoxide opening in a S_N2 fashion following the reaction path shown in ***figure 27***, the epoxide of **84** would have to be formed with an (*S,S*)-configuration. By analysing the expected transition state (spiro A in *figure 49*) for the epoxidation of **84** with commercially available D-fructose derived *Shi* catalyst **114**, the undesired (*R,R*)-configuration would have to be expected. This would make the synthesis of the enantiomer of **114** necessary, which can be prepared from readily available L-sorbose in 5 steps.

In a first step some epoxidation precursors **84** would have to be synthesised and tested in the asymmetric *Shi* epoxidation with the commercially available catalyst **114**, in order to see whether good diastereoselectivities can be obtained for the corresponding epoxides and to elucidate their actual configuration.

3.2.3 Asymmetric *Shi* epoxidation of protected phytyl hydroquinone derivatives 84

As a starting point the epoxidation precursor **118**, which was available in our lab and had been synthesised by *Julien Chapelat*, was subjected to the *Shi* asymmetric epoxidation conditions (*figure 53*). It should be noted that **118** differs from **84** by the lack of a methyl group on the aromatic ring, which would give γ-tocopherol (**3**) in the end. Hydrogen peroxide was chosen as the primary oxidant and a mixture of MeCN:EtOH:DCM (1:1:2) was used as a solvent together with 2 M K_2CO_3 in 4 x 10^{-4} M EDTA as a buffer, since this system had proven to be beneficial for olefins with poor solubilities and allowed easy handling, also for small scale reactions.

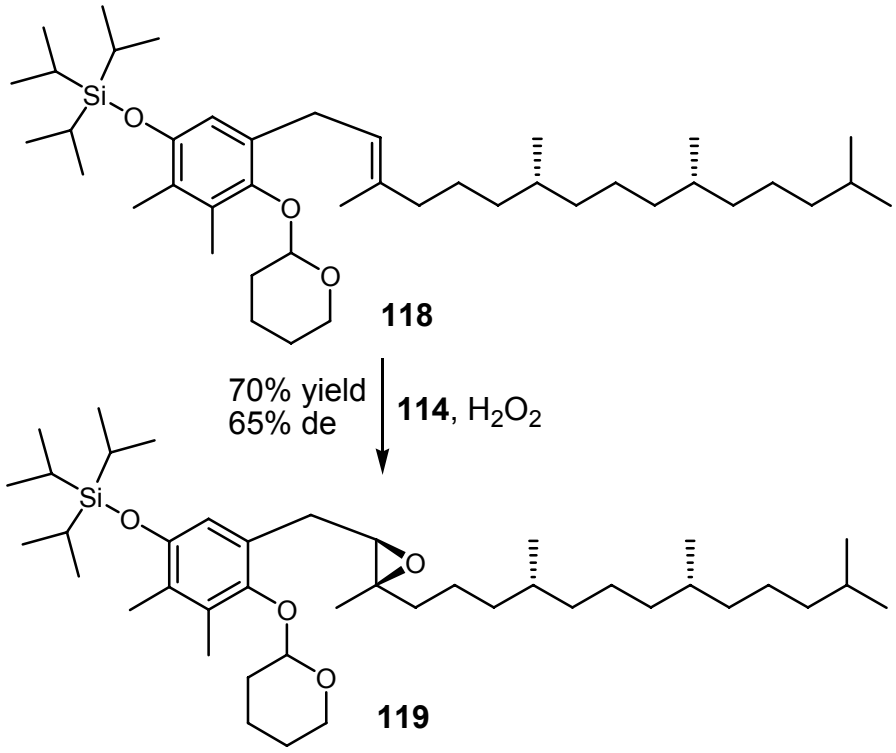


Figure 53: *Shi epoxidation of **118**.*

Analysis of the product by chiral HPLC gave a de value of 65% for epoxide **119**, which is far below the desired >90%. However, there was hope that the stereoselectivity of the reaction could be improved by the right choice of the protecting groups for the hydroquinone moiety. Further investigations done by Julien Chapelat revealed that, it is possible to cyclise **119** under acidic conditions yielding the desired 6-membered ring as the major product. As expected, comparison of the

cyclised product with an authentic sample suggested that the epoxide **119** was obtained in the wrong (*R,R*) configuration.

Accordingly, a number of bis-protected phytyl hydroquinones **84** were prepared in order to optimize the diastereoselectivity of the asymmetric *Shi* epoxidation.

In all syntheses, the phytyl chain was introduced via phytyl bromide (**126**), which was prepared by bromination of phytyl alcohol (**127**) (*figure 54*).

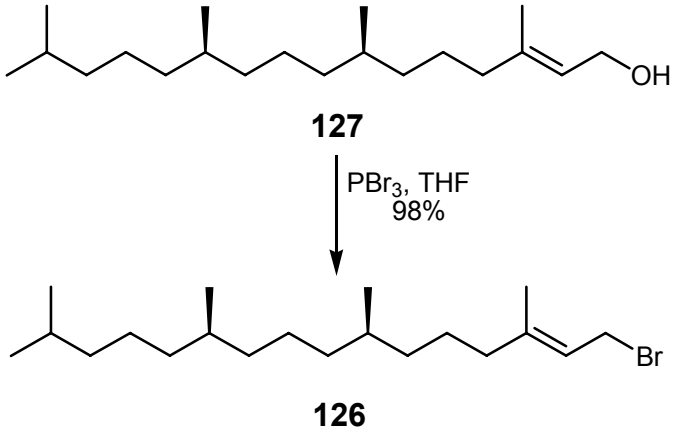


Figure 54: *Synthesis of phytyl bromide (**126**).*

The synthetic pathway for the synthesis of bis-protected phytyl hydroquinones **121**, **124** and **125** is depicted in ***figure 55***. MOM bis-protected hydroquinone **120** was obtained from the reaction of trimethyl hydroquinone **26** and MOMCl using NaH as a base in DMF. The coupling of **120** with **126** involved the directed lithiation of **120** with butyl lithium in ether followed by the addition of a catalytic amount of anhydrous CuBr to form the corresponding cuprate species, and the addition of phytyl bromide (**126**). After stirring for 4 h at r.t. the desired coupled product **121** was obtained in 64% yield. The cleavage of the MOM ethers was achieved by an oxidative cleavage method with cerium ammonium nitrate in a mixture of MeCN and water. The product, quinone **122**, was formed within 1 h in 85% yield. The reduction of quinone **122** to the corresponding hydroquinone **123** was performed using sodium dithionite in a mixture of THF and water. After brief workup, owing to the sensitve nature of the product, hydroquinone **123** was taken directly without further purification for the bis-protection steps using either TIPSCl or DPSCl to obtain the epoxidation precursors **124** and **125**, respectively.

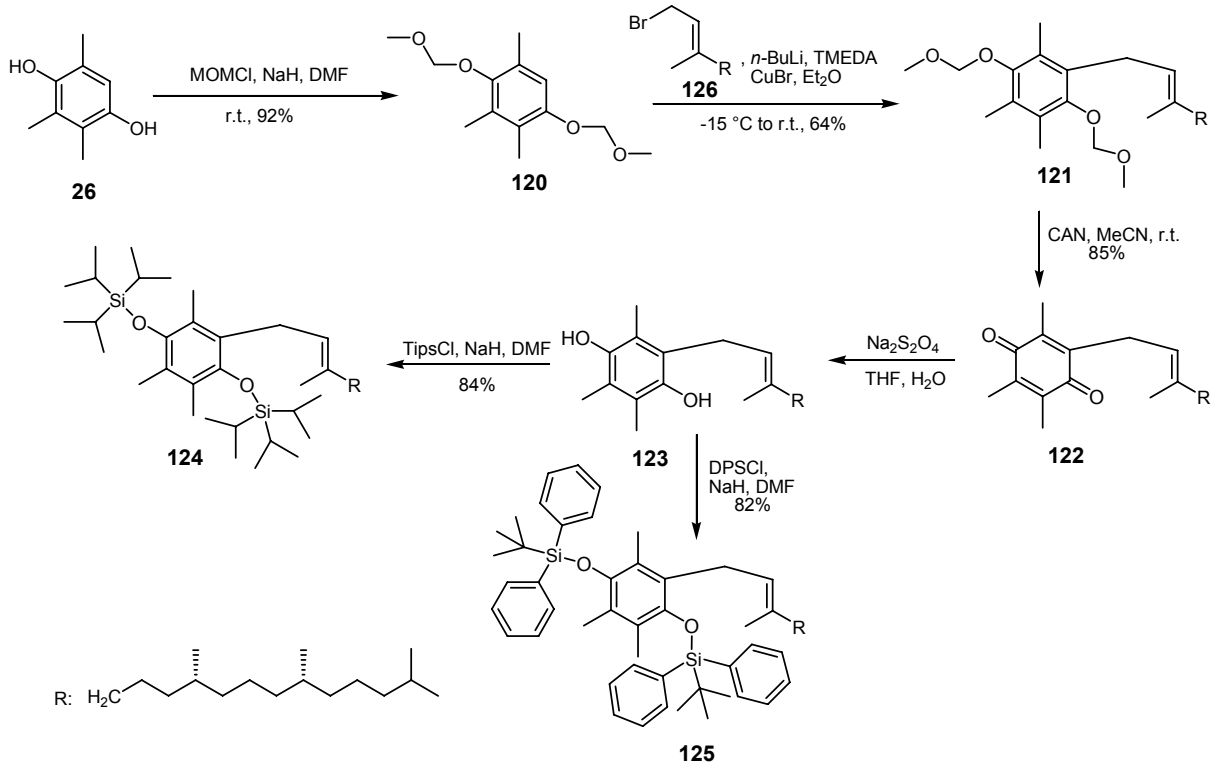


Figure 55: *Synthesis of bis-protected phytyl hydroquinones **124** and **125**.*

In a different approach further substrates for the *Shi* epoxidation were prepared (*figure 56*). Trimethyl hydroquinone was reacted with MeI to afford monomethylated product **128** in 53% yield. It turned out that the remaining free hydroxyl group in **128** is less reactive and therefore only a small amount of its regioisomer apart from the doubly substituted compound was formed. Reaction of phytyl bromide (**126**) with mono-protected hydroquinone **128** gave **129** in 92% yield. A lewis acid mediated Claisen-type rearrangement of **129** in the presence of $BF_3 \cdot Et_2O$ gave rearranged **130** within 10 min at -30 °C in 69% yield.[134, 135] The main product was obtained with an *E*-configured double bond (**130**). As a side product the *Z*-alkene isomer of **130** was also formed in about 15 to 20% which made a separation of the *E* / *Z*-mixture by flash chromatography on silica gel necessary. Since the two isomers could not be separated completely on TLC, the purity of the fractions had to be carefully analysed by ^{1}H-NMR (*figure 57*). The content of the *Z*-isomer was in any case less than 3%, which is about the amount of *Z*-isomer present in phytyl alcohol **127** used as a starting material. The free hydroxyl group could be protected by reaction with either benzyl bromide to give **131**, with *tert*-butyl(diphenyl)silyl chloride (DPSCl) to afford **132** or with chloro(tribenzyl)silane to yield **133**.

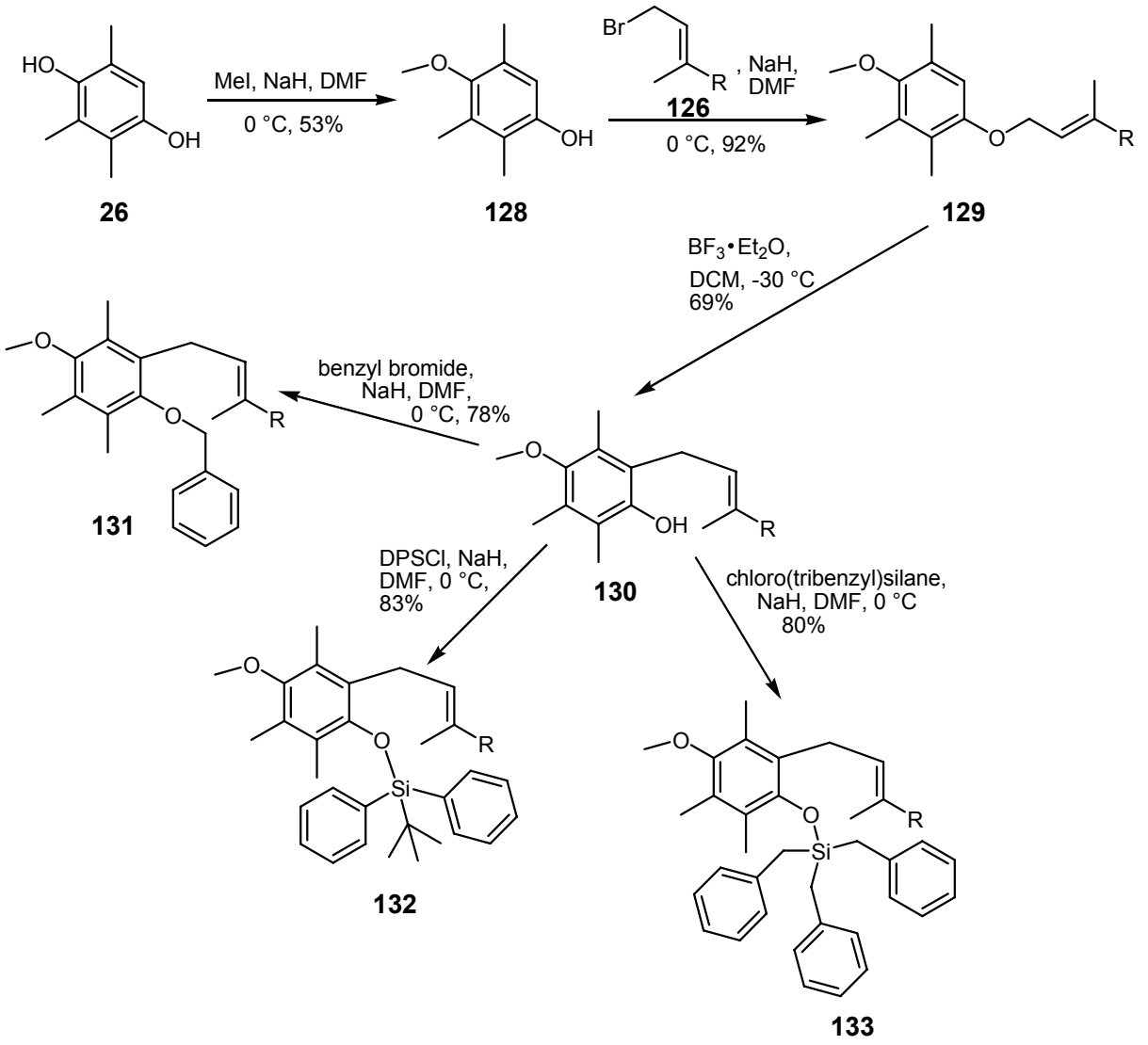


Figure 56: *Synthesis of epoxidation precursors **131**, **132**, **133**.*

Swenton et al. reported that trimethylhydroquinone (**26**) can be monoprotected regioselectvely at the sterically less hindered hydroxyl function by *tert*-butyl-(diphenyl)silyl chloride (DPSCl).[136] This reaction was used for an alternative synthetic pathway for **132** (*figure 58*). The monoprotected intermediate **134** was reacted with **126** to give the coupling product **135**. The Lewis acid mediated Claisen-type rearrangement of **135** in the presence of BF_3•Et_2O, to our surprise, worked also well for this case. However, the separation of the *E / Z* mixture of **136** was a lot more difficult than the one for **130**. On TLC, there was no difference in R_f value. Separation could be achieved by flash chromatography, using a very long column and by analysing each fraction by HPLC. Methylation of the remaining free hydroxyl afforded **132** again.

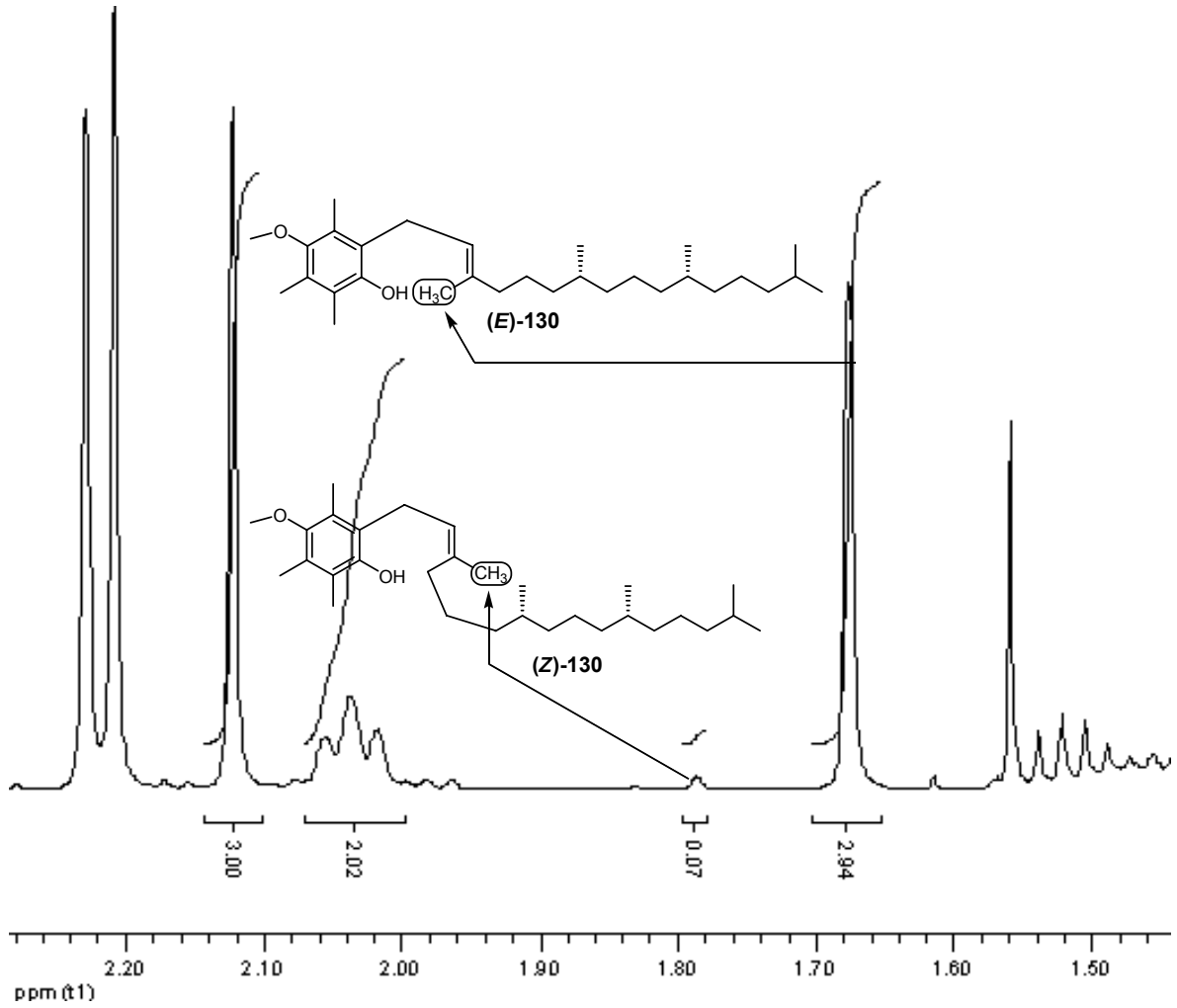


Figure 57: *Section of the ^{1}H-NMR spectrum of* ***130***

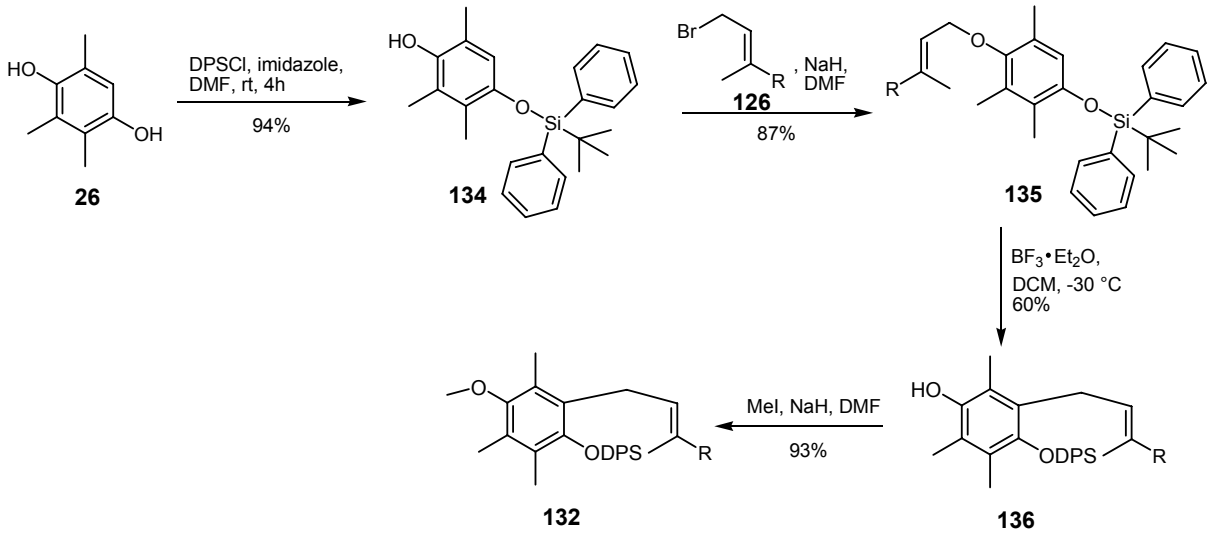


Figure 58: *Alternative synthesis of* ***132****.*

In order to be able to form the chromanol ring with *R*-configuration at C(2) by epoxide opening as shown in ***figure 27***, the enantiomer of the D-fructose derived *Shi* catalyst **114** had to be prepared. In 2006 *Shi et al.* reported a synthesis of the enantiomer of **114**, which involves the preparation of L-fructose from readily available L-sorbose (*figure 59*).[137] Ketalization of pulverized L-sorbose gave katal **137**, which was used directly for mesylation to give mesylate **138** in 37% yield over two steps after recrystallization. The transformation of mesylate **138** to L-fructose could be achieved via deprotection of the 4,6-*O*-isopropylidene group of **138**, which could be easily done using 4.5% H_2SO_4 at room temperature for 3 h to give diol **139**. After the solution became alkaline using 9 M NaOH, the conversion of compound **139** to **141** via epoxide **140** can be efficiently achieved at 90 – 100 °C in 8 h. The 1,2-*O*-isopropylidene group of triol **141** was then easily removed to give a syrup from which L-fructose was obtained by extraction with hot ethanol. The crude L-fructose was directly ketalized with dimethoxypropane and H_2SO_4 in acetone to give alcohol **142** in 38% overall yield from mesylate **138**. The oxidation of alcohol **142** with PDC gave ketone **ent-114** in 82% yield.

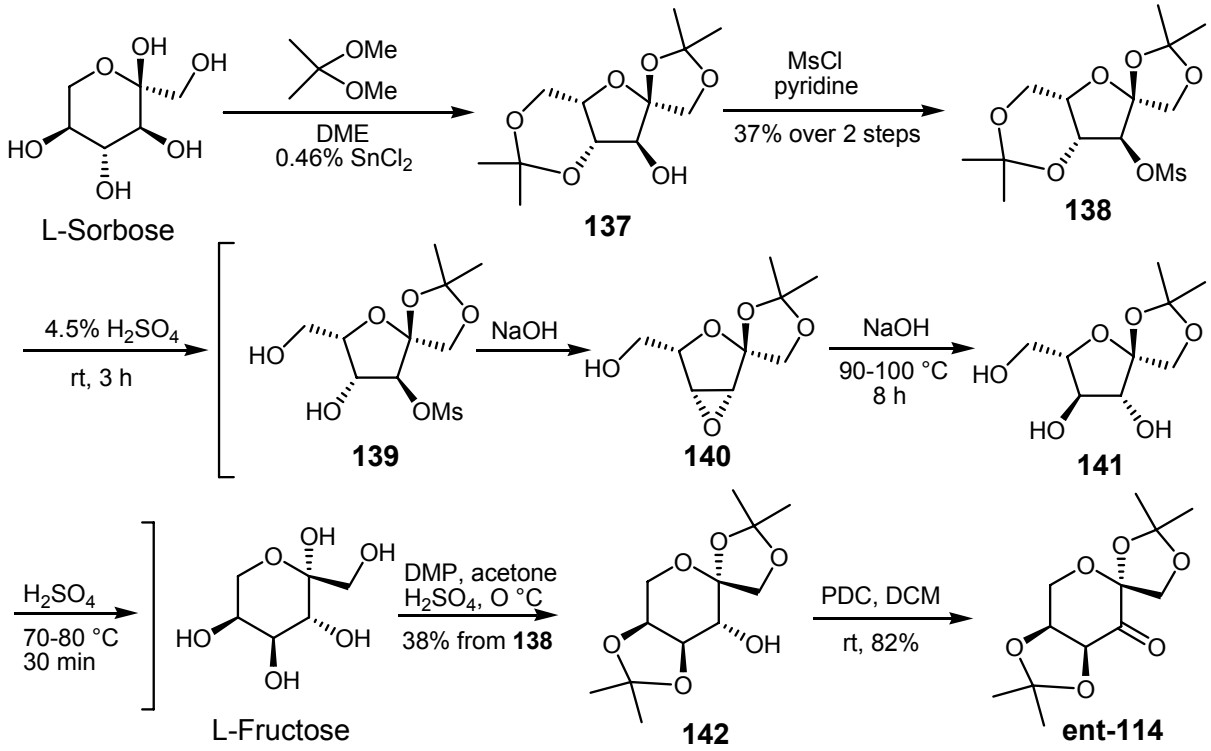
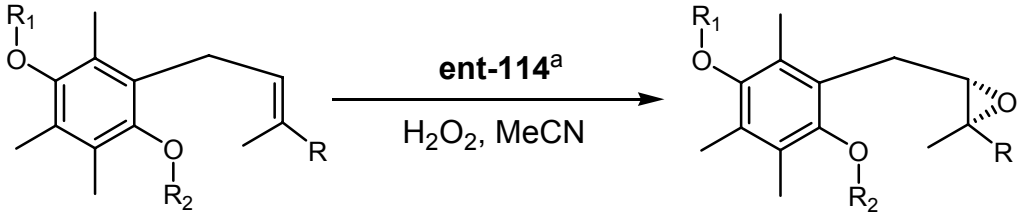


Figure 59: *Synthesis of L-fructose-derived Ketone* ***ent-114****.*

With catalyst **ent-114** in hand the asymmetric *Shi* epoxidations of the synthesised bis-protected phytyl hydroquinones were carried out (*figure 60*). Alkene-substrates **143**, **144**, **145** and **146** for asymmetric *Shi* epoxidation were synthesised and provided by *Julien Chapelat*. The corresponding epoxides were obtained in moderate to good yields.



entry	alkene	R_1	R_2	yield[b] (%)	de[c] (%)
1	**143**	(-)-Camph[d]	TBS	73	79
2	**144**	TIPS	TBS	76	73
3	**124**	TIPS	TIPS	75	82
4	**133**	Me	$(Benzyl)_3Si$[e]	84	89
5	**145**	Me	TIPS	78	85
6	**131**	Me	Benzyl	87	73
7	**146**	(-)-Camph[d]	Anthr[f]	76	74
8	**125**	DPS	DPS	81	91
9	**132**	**Me**	**DPS**	**81**	**97**

[a] General experimental conditions: 1 eq. alkene, 0.4 eq. **ent-114**, 5.4 eq. H_2O_2 (30% aq.) in a buffered (2 M K_2CO_3 / EDTA) mixture of MeCN: EtOH:DCM (1:1:2) at 0 °C, for 10 h. [b] Isolated yields. [c] Determined by chiral HPLC. [d] (-)-camphanoyl. [e] tribenzyl silyl. [f] 9-methylanthracenyl.

Figure 60: *Shi epoxidation of bis-protected hydroquinones.*[138]

Screening of these substrates gave one outstanding result (entry 9) revealing that a small R_1 group and a large R_2 substituent (DPS, *tert*-butyldiphenylsilylether) are required to accomplish high diastereoselectivities in the *Shi* epoxidation. The epoxidation of substrate **132** gave the corresponding epoxide **147** in 81% yield and with a de value of 97%. Its HPLC chromatogram is shown in ***figure 61***. It can be

assumed that background epoxidation for all examples is below 2% in the absence of ketone **ent-114**.[132]

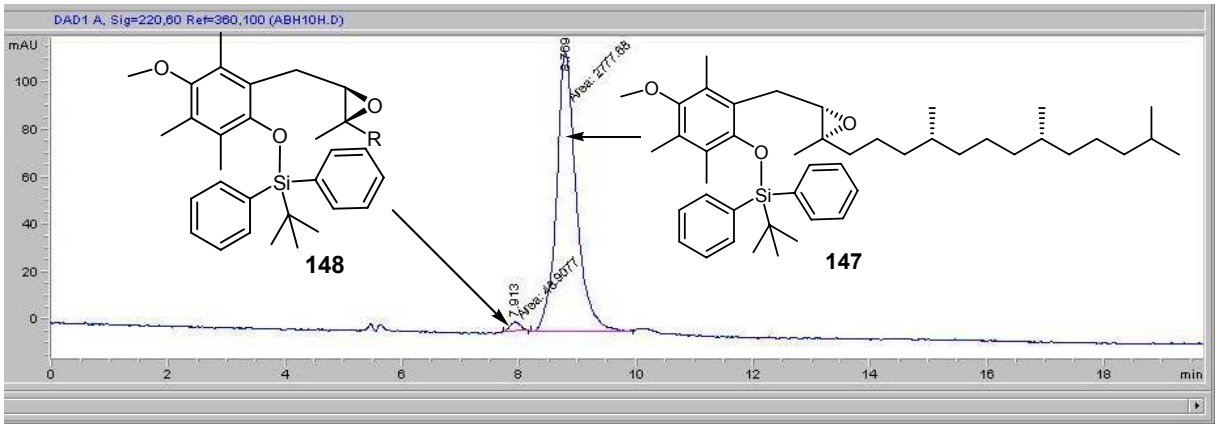


Figure 61: *HPLC chromatogram of the products **147** and **148** of the Shi epoxidation of alkene **132** using ketone **ent-114**.*

3.2.4 Transformation of Chiral Epoxide 147 to α-Tocopherol (1) via Acid Supported Epoxide Ring Opening

Before the 6-membered chromanol ring formation from epoxide **147** could be performed, a suitable method for the removal of the silyl protecting group had to be found. Initial studies on the cleavage of the TIPS ether in **149** under usual conditions (TBAF, THF) had shown that in this basic reaction medium the undesired 5-membered ring product **150** is formed exclusively (*figure 62*).

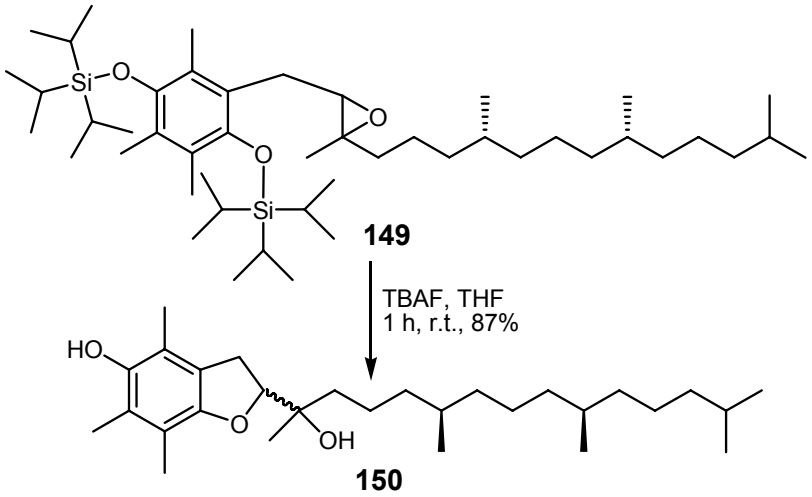


Figure 62: *Cleavage of the TIPS ether, yielding 5-membered ring product **150**.*

In general, γ-epoxy alcohols preferably cyclise to furans obeying rules published by *Baldwin* in 1976 (*figure 63*).[139]

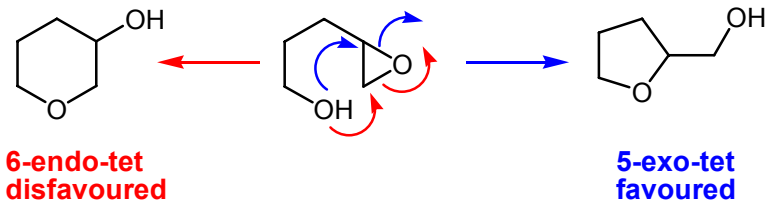


Figure 63: *Baldwin rules for γ-epoxy alcohol cyclisations.*

A method had to be found to circumvent these rules in order to favour the formation of pyrans. In the past two decades, several methods have been published to favour the formation of pyrans.[140, 141, 142, 143] However, none of the published procedures are applicable to the transformation of an epoxide, such as **151**, which can be obtained from **147**, to the chromanol **152** (*figure 64*).

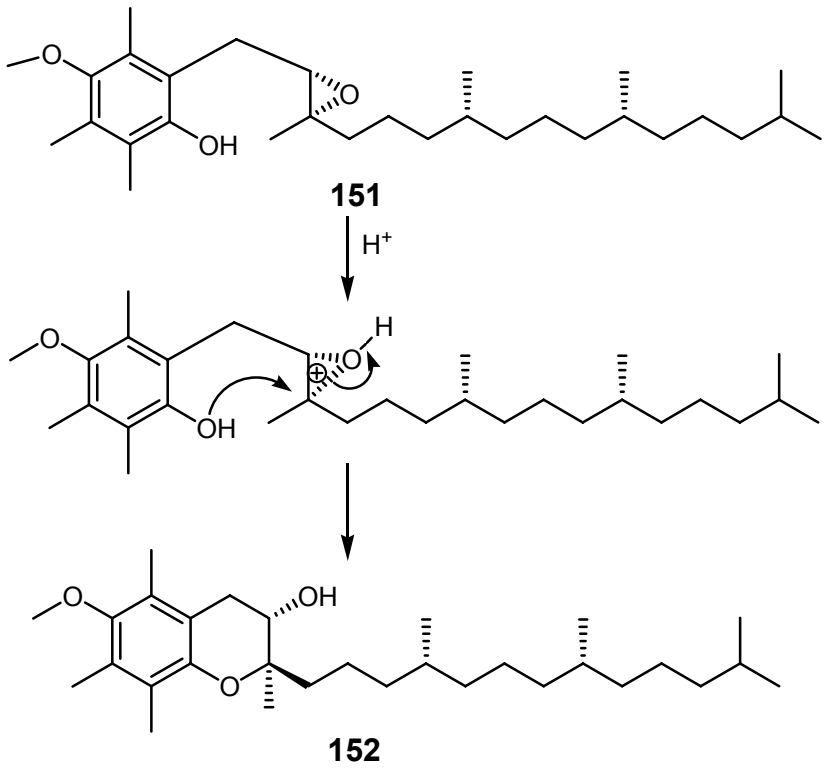


Figure 64: *Proposed chromanol ring construction.*

The following reaction sequence of **147** to α-tocopherol (**1**) was carried out by *Julien Chapelat* (*figure 65*).[138] Under slightly acidic conditions (AcOH, TBAF, THF) the silyl ether in **147** could be cleaved to obtain epoxide **151** without the formation of the

corresponding 5-membered ring product (compare *figure 62*).[144] A number of different reaction conditions had to be tested in order to obtain cyclisation in favour of the pyran product **152**. By performing the cyclisation of **151** in a mixture of MeCN and 2 M HCl in diethylether the desired 6-membered ring product **152** was obtained in 79% yield and with a de value of 93%. The corresponding 5-membered ring was formed as a side product in 19% yield. Finally removal of the hydroxyl group went smoothly through the tosylate **153**, easily eliminated, and directly hydrogenated to afford **154** in almost quantitative yield. Deprotection of the methyl ether could be performed without any loss of chirality, by means of $BF_3 \cdot Me_2S/AlCl_3$, giving α-tocopherol (**1**).[70]

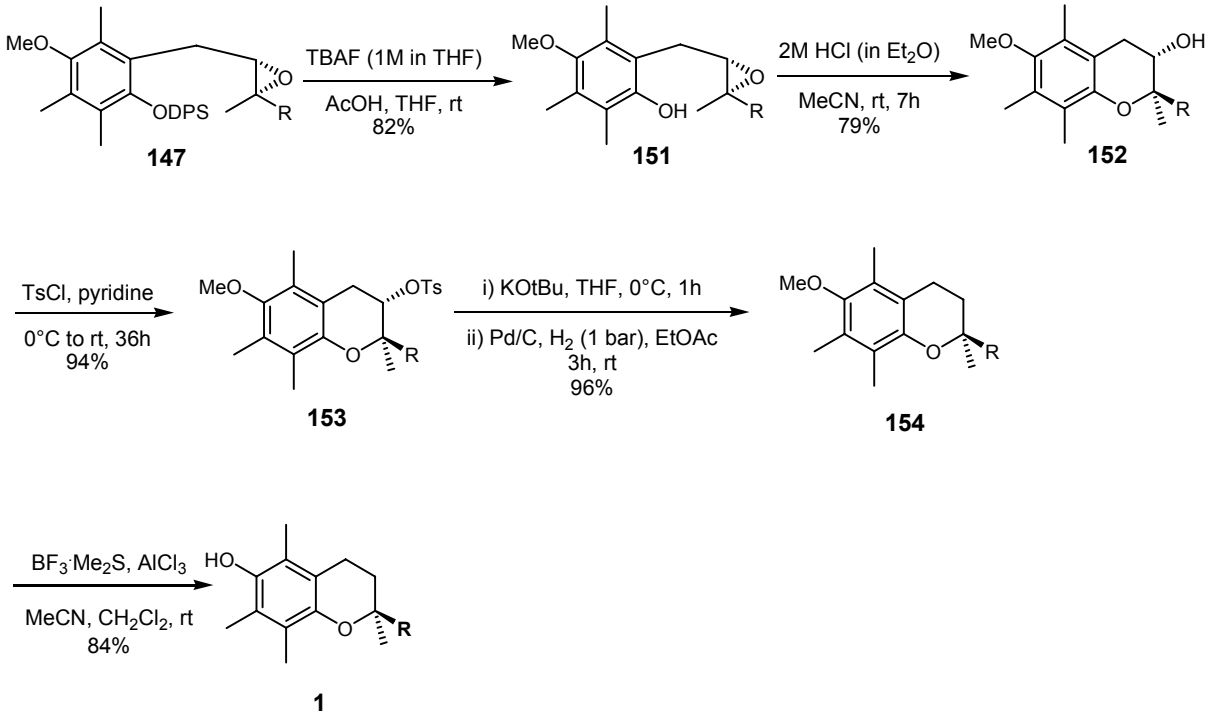


Figure 65: *Synthesis of α-tocopherol (**1**) from epoxide **147**.*

This highly diastereoselective synthesis of α-tocopherol (**1**) involves a *Shi* epoxidation as the key step. However, the enantiomer **ent-114** of the commercially available catalyst **114** had to be synthesised in five steps in order to obtain α-tocopherol (**1**) with *R*-configuration at C(2). It would therefore be desirable to find an alternative synthetic pathway for the transformation of alkene **132** to α-tocopherol (**1**) in which the commercially available catalyst **114** could be employed.

3.2.5 An Alternative Synthetic Pathway for the Transformation of Alkene 132 to α-Tocopherol (1) using Catalyst 114

An alternative strategy for the synthesis of α-tocopherol (**1**) is shown in ***figure 66***. This new route takes into account common knowledge concerning the stereospecific ring closure of the tertiary alcohol **155**.[145] This ring closure occurs under retention of configuration, which means that tertiary alcohol **155** has to be obtained with *R*-configuration. This could be done by opening the epoxide in **148** with hydride, followed by the removal of the protecting groups. It can be assumed that hydride attacks at the less substituted C-atom of the epoxide function, which would yield the corresponding alcohol under retention of configuration.[50] Epoxide **148** can be prepared by asymmetric *Shi* epoxidation using the commercially available ketone catalyst **114**.

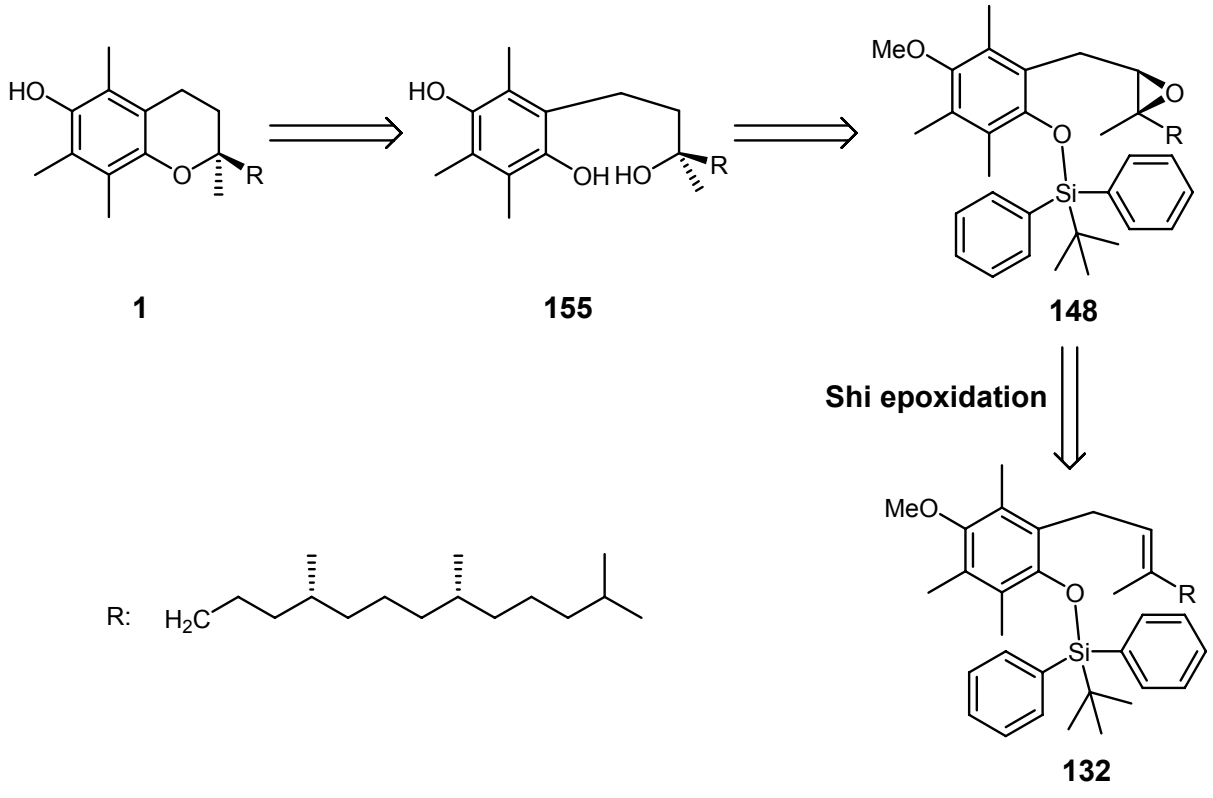


Figure 66: *Retrosynthetic analysis for the transformation of **148** to **1**.*

The mechanism of the proton-catalysed ring closure of hydroquinone **155** to α-tocopherol (**1**) was reported by *Cohen et al.* in 1981 (*figure 67*).[145] This conversion involves the intermediacy of quinone **156** formed in trace quantity by air oxidation of **155**. The derived hemiketal **157** could then undergo reduction by the starting

hydroquinone **155**, yielding α-tocopherol (**1**) and regenerating quinone **156**, thus establishing a catalytic redox cycle.

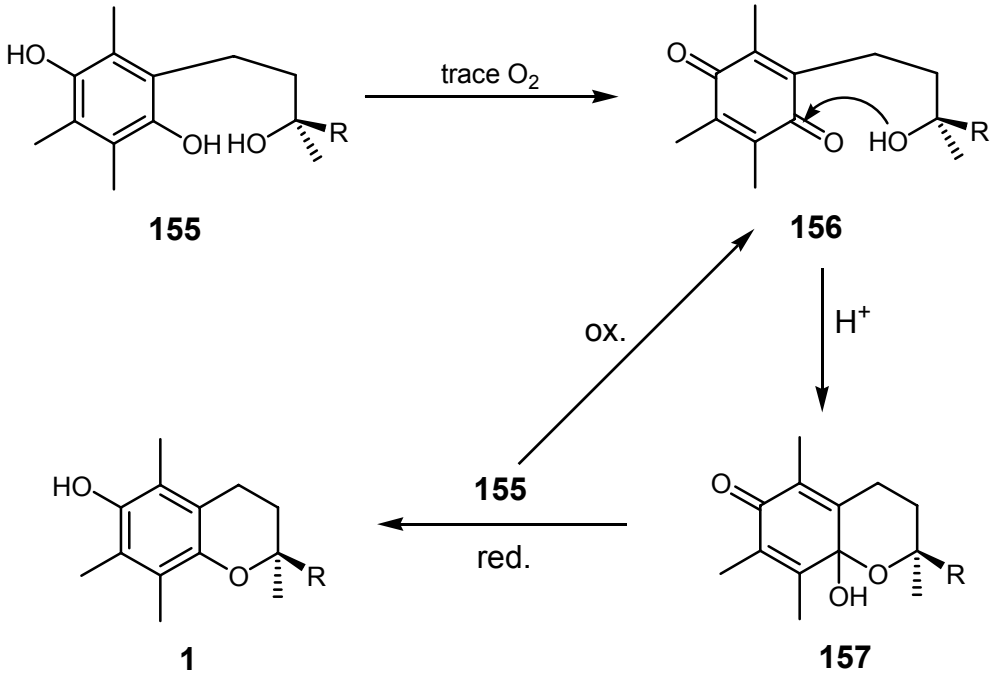


Figure 67: *The mechanism of the proton-catalysed ring closure of **155** to α-tocopherol (**1**).*[145]

The alternative synthetic pathway is depicted in ***figure 68***. Olefin **132** (>98:2, E:Z) was epoxidised employing the commercially available *Shi* ketone **114** to give epoxide **148** (96% de) with *R,R*-configuration. Epoxide ring opening of **148** could be achieved by treatment with $LiEt_3BH$, which yielded the tertiary alcohol **158** in 49% yield. The opening of the epoxide function required the refluxing of the reaction mixture for 4 h. These relatively harsh reaction conditions led to the formation of side products. Attempts to use less reactive $LiAlH_4$ in ether to open the epoxide were unsuccessful. Oxidative removal of the protecting groups using CAN afforded quinone **159**. Subsequent chromanol cyclisation was carried out following a published procedure.[145] Quinone **159** was first hydrogenated to the corresponding hydroquinone **155**, subsequent acid catalysed (*p*TsOH) cyclisation gave α-tocopherol (**1**) in 92% yield and 93% de (*figure 69*). When the cyclisation was performed in MeOH using conc. HCl (aq.) the de value dropped to 82%.[146]

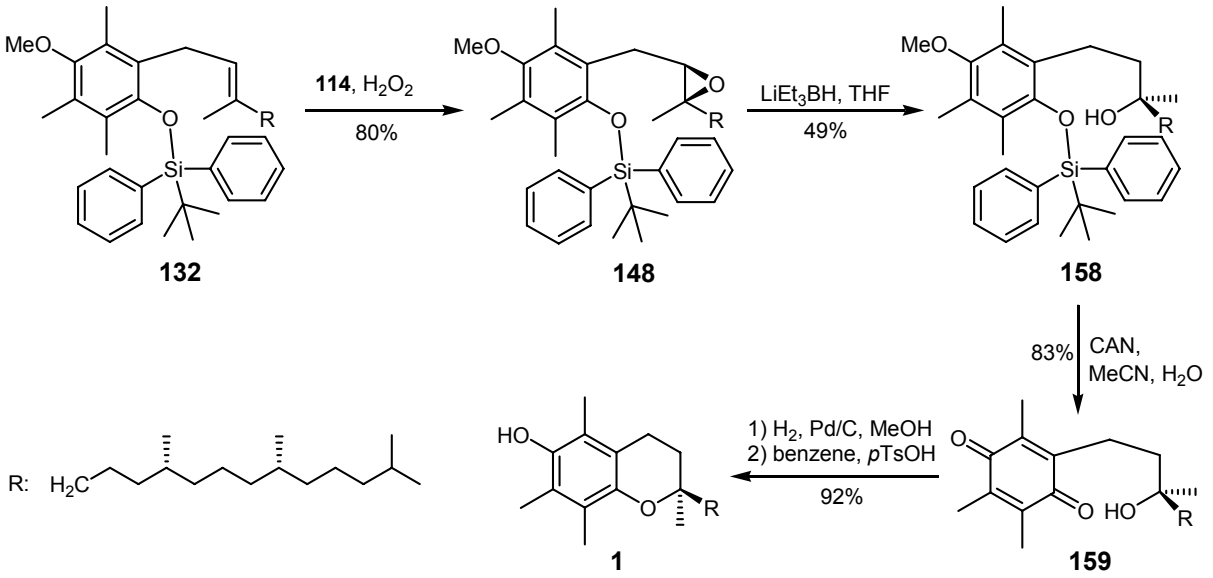


Figure 68: *Alternative synthetic pathway for the transformation of olefin* ***132*** *to* α-tocopherol (**1**).

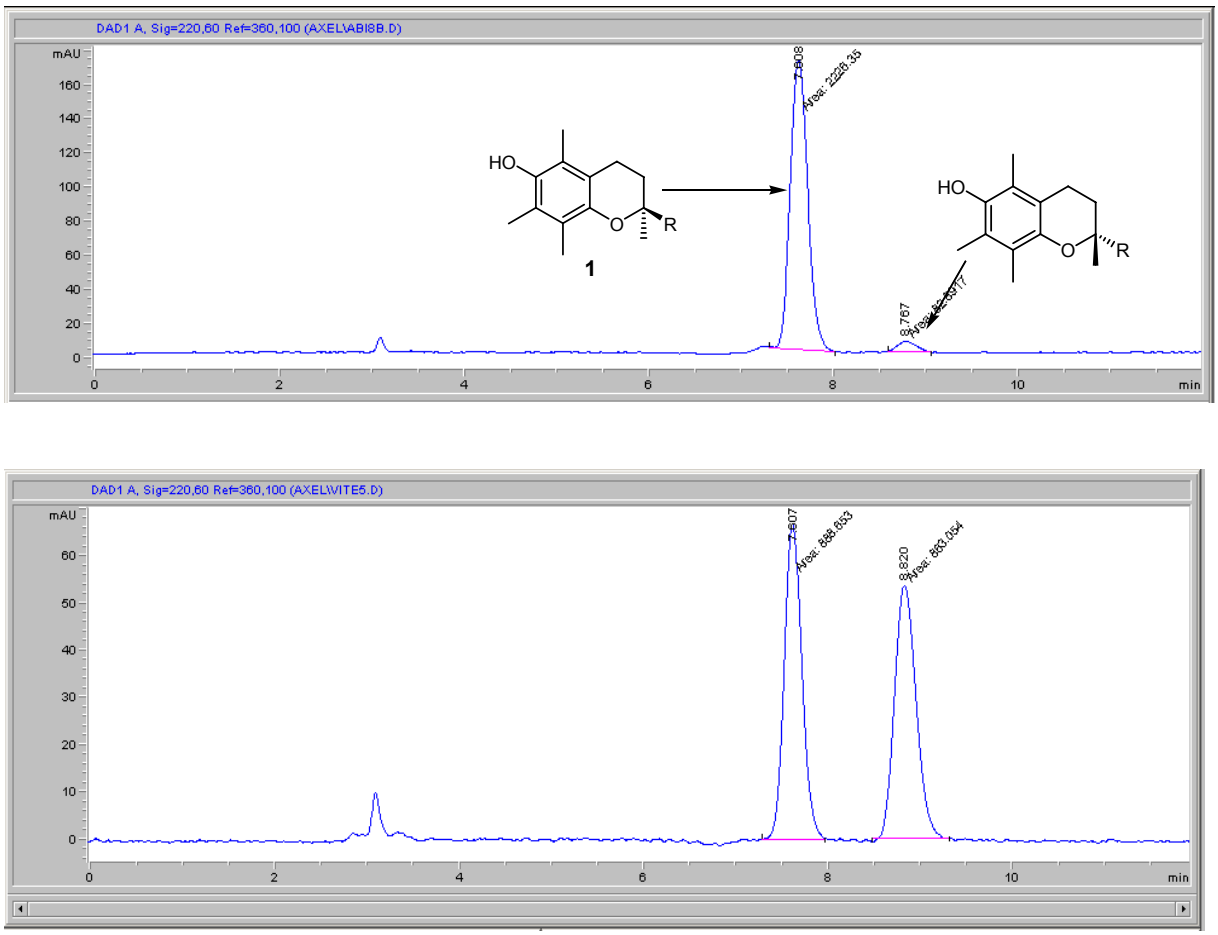


Figure 69: *Top: HPLC chromatogram of the products of the cyclisation of* ***157****. Bottom: HPLC chromatogram of commercial all racemic α-tocopherol.*

This alternative synthetic route has several advantages. Firstly, the commercially available ketone **114** can be employed for the *Shi* epoxidation of olefin **132**, whereas the previously reported route requires the synthesis of **ent-114** (5 steps). Secondly, this route is considerably shorter in terms of number of reaction steps (8 vs. 10) as well as overall reaction time.

4 Summary and Conclusions

Vitamin E exists in eight different forms, four tocopherols and four tocotrienols. All possess a hydrophobic side chain, which allows them to penetrate into biological membranes. Their second common feature is a chromanol moiety with a hydroxyl group that can donate a hydrogen atom. These properties make vitamin E a very important radical chain-breaking antioxidant in living organisms, and therefore also an industrial product.

α-Tocopherol is the member of the vitamin E family that is preferentially absorbed and accumulated in humans. There are three stereocenters in α-tocopherol, whereas *RRR*-α-tocopherol (**1**) is the natural and biologically most active form. The *R*-configuration at C(2) is essential in order to be recognised by the α-tocopherol transport protein and thus maintained in the plasma. The biological activity rendered *RRR*-α-tocopherol (**1**) a synthetic target.

In this work two novel syntheses of *RRR*-α-tocopherol (**1**) are presented. Both syntheses involve a highly diastereoselective epoxidation of the bis-protected phytyl hydroquinone **132** as the key step followed by a cyclisation to form the chromanol ring (*figure 70*).

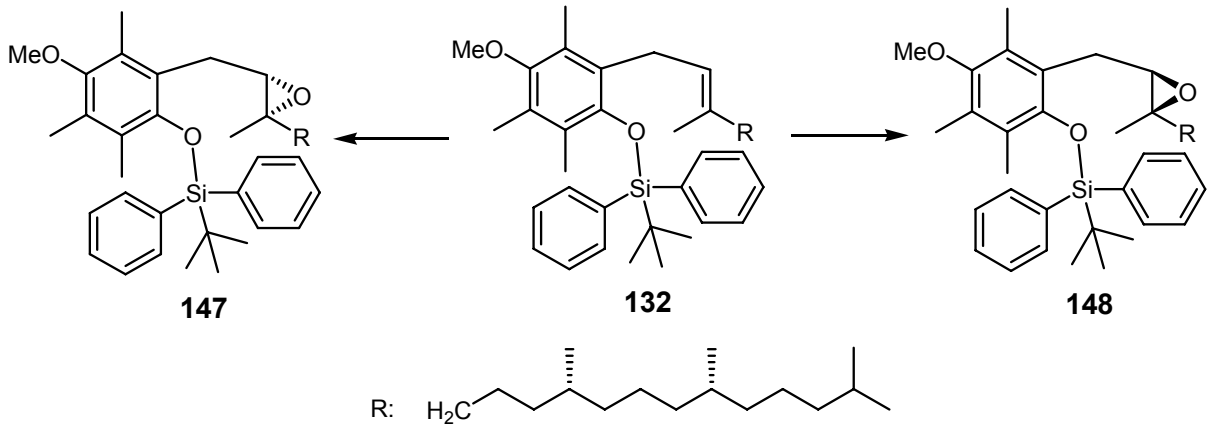


Figure 70: *Asymmetric epoxidation of* ***132*** *giving* ***147*** *or* ***148****.*

In order to find suitable stereoselective epoxidation catalysts, cyclodextrin-based catalysts were prepared and tested (*figure 71*). However, none of these catalysts

were reactive or selective enough to be applicable to the epoxidation of bis-protected phytyl hydroquinones.

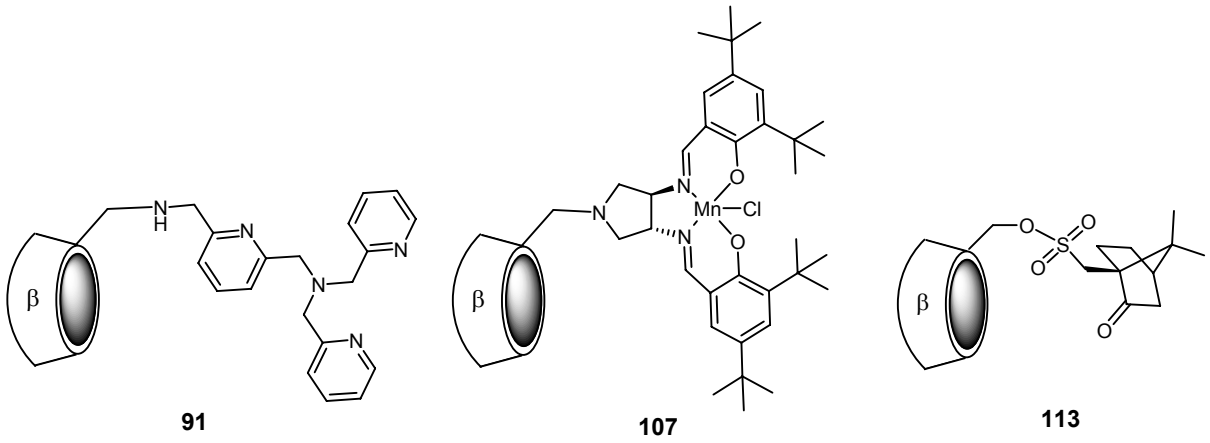
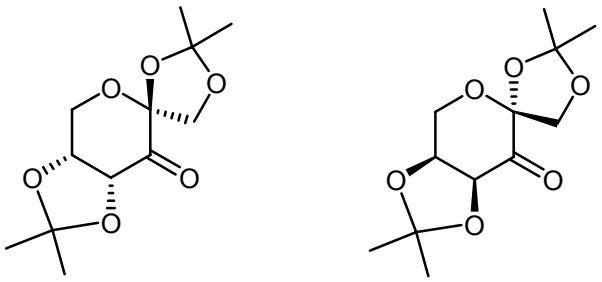


Figure 71: *Cyclodextrin based catalysts*

However, the asymmetric *Shi* epoxidation proved to be a suitable epoxidation method for this purpose. A number of bis-protected phytyl hydroquinones were synthesised and subsequently epoxidised under *Shi* epoxidation conditions. The highest diastereoslectivity could be obtained for substrate **132**. By applying *Shi* ketone **114**, which is derived from D-fructose, epoxide **148** could be obtained with 96% de, whereas if the enantiomer **ent-114** (synthesised in 5 steps from L-sorbose) was used, **147** was formed with 97% de (*figure 71*).

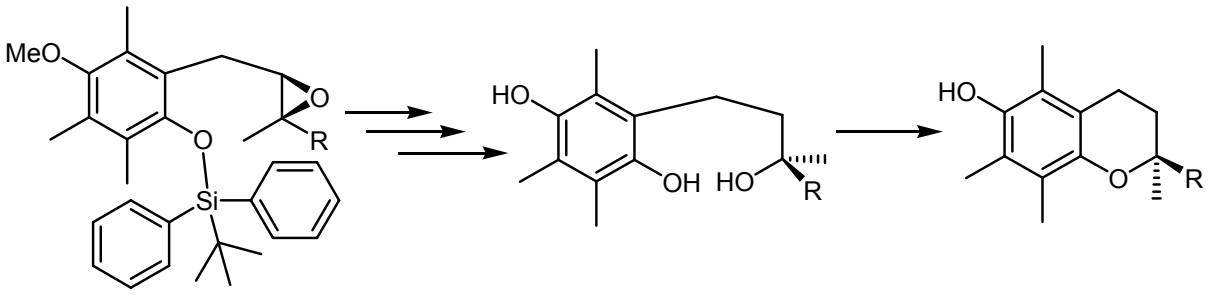


114 **ent-114**

Figure 71: *D-fructose derived Shi ketone **114** and its enantiomer **ent-114**.*

The epoxide function in **148** could be selectively opened with hydride. Further transformations led to the hydroquinone **155**, which could be cyclised under acidic conditions to form the chromanol ring of **1** with the desired *R*-configuration at C(2) (*figure 72*). α-Tocopherol could be synthesised in 8 steps with 93% de via this route. To the best of my knowledge, this highly diasteroselective synthesis of α-tocopherol

(**1**) is one of the shortest in terms of numbers of steps, employing a commercially available organocatalyst.



148 **155** **1**

Figure 72: *Transformation of epoxide **148** to α-tocopherol (**1**).*

In a different approach an acid supported, “anti-Baldwin” epoxide ring opening of desilylated **147** under inversion of configuration led to the 6-membered chromanol ring. α-Tocopherol could be synthesised in 10 steps and with 93% de. This synthesis was carried out in collaboration with *Julien Chapelat*.

To the best of our knowledge this is the second application of an organocatalyst to the construction of chromanols, having a tetrasubstituted chiral carbon centre, in high diastereoselectivity.[70]

5 Experimental Part

5.1 General Remarks

5.1.1 Solvents and Reagents

Reagents were used as received from Fluka AG, Acros Organics and Aldrich unless otherwise stated. Chemicals of the quality purum, purum p.a. or > 98% were used without further purification. 6-*O*-monotosyl-β-CD (**85**) was purchased from *CycloLab Ltd* (Budapest, Hungary).
Solvents for chromatography and extractions were distilled prior to use. 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 HPLC on chiral phase (Chiralcel OD-H and Chiralcel AD-H).
For an inert atmosphere Argon 56 (< 4 ppm other gases) from Carbagas AG (Lenzburg, Switzerland) or Argon 6.0 (<1.5 ppm other gases) from PanGas AG (Dagmersellen, Switzerland) were used.

5.1.2 Materials and Instruments

Solvents were removed with a Büchi (Switzerland) rotary evaporator (Waterbath 461, Rotavapor RE 111 and Vauum Controller 168) and a MZ 2C membrane pump (Vacuubrand). For cooling a mixture of EtOH and water was kept at 2 °C with a UKW 300 thermostat (Vacuubrand).
For weighing compounds and reagents Mettler (Switzerland) balances P1200 (>1g), AE 163 (<1g), and AX205 (<100mg) were used.
A high-vacuum pump D5E from Trivac (Köln, Germany) was used for drying compounds.
For all non-aqueous reactions glassware was dried with a heat gun for several minutes under vacuum, and the atmosphere was exchanged by three cycles of evacuating and flushing with argon.

Melting points (mp) were determined on a büchi 510 apparatus and are uncorrected.

Elemental Analysis (EA) was performed with a Perkin-Elmer 240 Analyser by Mr. W. Kirsch at the Department of Chemistry, University of Basel. Description: EA (chemical formula, molecular weight): calculated (calc.) abundance of C, H in %; found abundance of C, H in %.

Chromatographic Methods

Analytical thin layer chromatography (TLC) was performed on 0.25 mm precoated glass plates (5×10 cm, silica gel 60 F254, Merck AG, Germany), 0.25 mm precoated glass plates (5×10 cm, aluminium oxide 60 F254, Merck AG, Germany), or on 0.25 mm precoated glass plates (5×10 cm, RP-18 F254s, Merck AG, Germany). Compounds were detected at 254 nm (UV) or at 366 nm (fluorescence). For carbohydrates, compounds were visualized by p-anisaldehyde dip (6 g p-anisaldehyde and 3 ml concentrated sulphuric acid in 250 ml ethanol). Description: (solvent): Rf.

For **normal phase column chromatography** silica gel 60 from Merck (0.040-0.063 mm, 230-400 mesh) or aluminum oxide 90 from Merck (standardized (activity II-III), 0.063-0.2 mm, 70-230 mesh) were used. For **reversed phase column chromatography**, RP-18 silica gel (fully endcapped) from Fluka (0.040-0.063mm, 230-400 mesh) was used. Flash chromatography was performed under pressure with an aquarium pump.

Analytical chiral phase HPLC (ee determination) was performed with a *Chiralcel* OD-H or a *Chiralcel* AD-H column using HPLC-grade solvents on a Agilent 1100 Series HPLC system with Solvent degasser G1322A, BinPump G1312A, Autosampler G1313A, Thermostatic column housing G1316A, Diode array UV detector G1315B. All samples were filtrated prior to injection.

Spectroscopic Methods

Infrared spectras (IR) were measured on a Perkin-Elmer 1600 series FTIR spectrometer in KBr or on a FTIR-8400S from SHIMADZU. Description: IR (medium): wavenumbers of transmission maxima in cm-1.

Electron spray ionization mass spectra (ESI-MS) were recorded on a *Bruker* Esquire 3000^{plus}. Description: ESI-MS (solvent): mass peaks in m/z.

Electron impact mass spectra (EI-MS) were measured by Dr. H. Nadig on a Varian double focussing VG-70-250 spectrometer at the Department of Chemistry, University of Basel. Description: MS(EI): mass peaks in m/z (relative intensity in %).

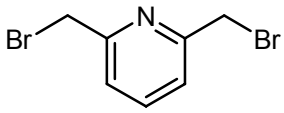
^{1}H-Nuclear magnetic resonance spectroscopy (^{1}H-NMR) was performed using either a Bruker av250 (250MHz), Bruker DPX-NMR (400MHz), Bruker DRX-500 (500MHz) or Bruker DRX-600 (600MHz) spectrometer. Solvents for NMR were obtained from Cambridge Isotope Laboratories (Andover, MA, USA). $CDCl_3$ was filtered through basic alumina prior to use. All spectra were recorded at 298 K. Description: ^{1}H-NMR (frequency, solvent): δ_H in ppm relative to TMS or residual solvent peaks (CDCl3: 7.26, D2O: 4.79). Peak multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; 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 (100MHz) or Bruker DRX-500 (125 MHz) spectrometer. For the assignment of carbons ATP, DEPT, HETCOR, HMQC and HMBC experiments were carried out. Description: ^{13}C-NMR (frequency, solvent): δ_C in ppm relative to residual solvent peaks.

5.2 Syntheses

5.2.1 Syntheses of Cyclodextrin Catalysts and Catalytic Reactions

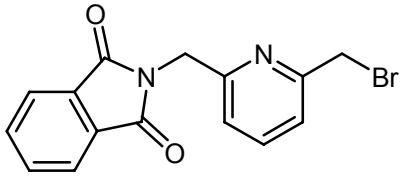
2,6-bis(bromomethyl)pyridine (87)



A solution of 4.00 g diol (**86**) (28.7 mmol, 1.0 eq.) in 60 mL 48% HBr was heated to reflux for 17 h. After being cooled to 0 °C, the reaction mixture was neutralised with 40% NaOH. The mixture was extracted with DCM (3x) and the combined organic phases were dried over Na_2SO_4. Chromatography (SiO_2, DCM) yielded 4.02 g (15.2 mmol, 53%) of a white solid.

TLC (SiO_2, DCM): R_f = 0.41.
^{1}H-NMR (400 MHz, $CDCl_3$): 4.55 (s, 4H, C$\underline{H}_2$), 7.39 (d, J = 7.8 Hz, 2H, H_{ar}), 7.73 (t, J = 7.8 Hz, 1H, H_{ar}).
^{13}C-NMR (100 MHz, $CDCl_3$): 33.3, 123.1, 138.5, 156.8.
MS (EI): *m/z* (%) = 266.9 (8), 264.9 (17), 262.9 ([M^+], 9), 186.0 (97), 184.0 (100).
EA: calculated for $C_7H_7N_1Br_2$: C 31.73, H 2.66, N 5.29; found: C 31.68, H 2.55, N 5.32.

2-((6-(bromomethyl)pyridin-2-yl)methyl)isoindoline-1,3-dione (88)



A suspension of 3.75 g dibromide (**87**) (14.2 mmol, 1.0 eq.), 5.89 g K_2CO_3 (42.6 mmol, 3.0 eq.), 2.88 g phthalimide potassium salt (15.6 mmol, 1.1 eq.) and 150 mL abs. MeCN was refluxed for 3 h. The solvent was removed in vacuo and the residue was dissolved in a DCM/H_2O mixture. The phases were separated and the aqueous phase was extracted with DCM (2x). The combined organic phases were dried over Na_2SO_4. Chromatography (SiO_2, hexane/EtOAc = 6:4) yielded 2.07 g (6.25 mmol, 44%) of a white solid.

TLC (SiO_2, hexane/EtOAc = 1:1): R_f = 0.41.

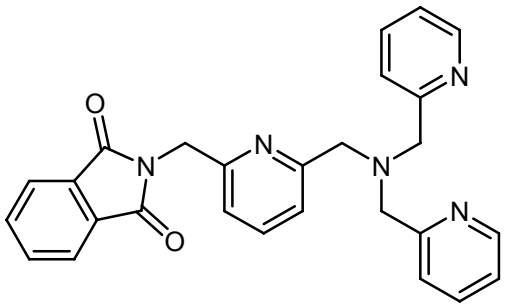
^{1}H-NMR (400 MHz, $CDCl_3$): 4.51 (s, 2H, Br-C$\underline{H}_2$), 5.05 (s, 2H, N-C$\underline{H}_2$), 7.16 (d, *J* = 7.8 Hz, 1H, Br-CH_2CC$\underline{H}$), 7.37 (d, *J* = 7.7 Hz, 1H, N-CH_2CC$\underline{H}$), 7.67 (t, *J* = 7.8 Hz, 1H, NCCHC$\underline{H}$), 7.75 (dd, *J* = 3.0, 5.4 Hz, 2H, C$\underline{H}$ phthalimide), 7.90 (dd, *J* = 3.0, 5.4 Hz, 2H, C$\underline{H}$ phthalimide).

^{13}C-NMR (100 MHz, $CDCl_3$): 33.2, 42.7, 120.7, 122.7, 123.7, 132.3, 134.3, 138.4, 155.2, 156.7, 168.2.

ESI-MS (MeOH): Positive ion mode: 331.0 ($[M+H]^+$), 333.0, 352.9 ($[M+Na]^+$), 354.9.

EA: calculated for $C_{15}H_{11}N_2O_2Br$: C 54.40, H 3.35, N 8.46; found: C 54.36, H 3.23, N 8.49.

2-((6-((bis(pyridin-2-ylmethyl)amino)methyl)pyridin-2-yl)methyl)isoindoline-1,3-dione (89)



To a suspension of 1.23 mL di-(2-picolyl)amine (6.84 mmol, 1.1 eq.) and 1.29 g K_2CO_3 (9.33 mmol, 1.5 eq.) in 50 mL abs. MeCN was added a solution of 2.06 g bromide (**88**) (6.22 mmol, 1.0 eq.) in 20 mL abs. DMF over a period of 10 min at 88 °C. The reaction mixture was refluxed for 3 h and the solvent was then removed in vacuo. Chromatography (Al_2O_3, EtOAc) yielded 2.30 g (5.11 mmol, 82%) of a white solid.

TLC (Al_2O_3, EtOAc): R_f = 0.45.

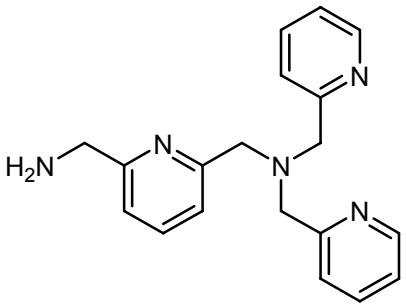
^{1}H-NMR (400 MHz, $CDCl_3$): 4.22 (br s, 6H, N(C$\underline{H}_2$)$_3$), 5.00 (s, 2H, N-C$\underline{H}_2$), 7.15-7.22 (m, 3H, H_{ar}), 7.44 (d, *J* = 7.7 Hz, 1H, H_{ar}), 7.58-7.76 (m, 7H, H_{ar}), 7.87 (dd, *J* = 3.0, 5.5 Hz, 2H, H_{ar}), 8.49 (d, *J* = 5.0 Hz, 2H, H_{ar}).

^{13}C-NMR (100 MHz, $CDCl_3$): 43.3, 60.2, 60.6, 119.7, 122.1, 122.3, 123.4, 123.8, 132.6, 134.4, 136.8, 137.5, 149.4, 155.0, 159.7, 159.8, 168.6.

ESI-MS (MeOH): Positive ion mode: 472.1 ($[M+Na]^+$);
Negative ion mode: 448.2 ($[M^-]$).

EA: calculated for $C_{27}H_{23}N_5O_2$: C 72.14, H 5.16, N 15.58; found: C 71.29, H 5.18, N 15.29.

(6-(aminomethyl)pyridin-2-yl)-N,N-bis(pyridin-2-ylmethyl)methanamine (90)



To a solution of 2.25 g of phthalimide (**89**) (5.01 mmol, 1.0 eq.) in 110 mL MeOH was added 0.56 mL hydrazine monohydrate (11.5 mmol, 2.3 eq.). The reaction mixture was refluxed for 7 h and the solvent was removed in vacuo. The residue was then dissolved in $CHCl_3$ and washed with 1 M NaOH and brine. The organic phase was dried over Na_2SO_4. Chromatography (Al_2O_3, DCM/MeOH = 20:1 to 5:1) yielded 1.40 g (4.38 mmol, 87%) of a light yellow oil.

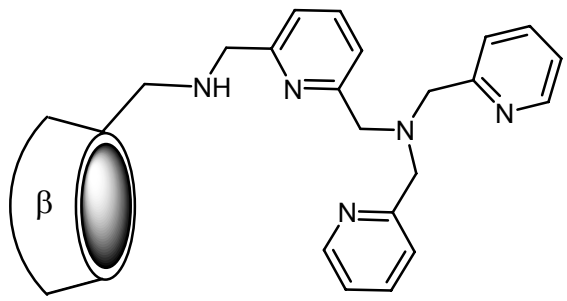
TLC (Al_2O_3, DCM/MeOH = 20:1): R_f = 0.23.

^{1}H-NMR (400 MHz, $CDCl_3$): 2.00 (br s, 2H, N$\underline{H}_2$), 3.87 (s, 2H, N-C$\underline{H}_2$), 3.88 (s, 4H, N-C$\underline{H}_2$), 3.94 (s, 2H, NH_2-C$\underline{H}_2$), 7.10-7.15 (m, 3H, H_{ar}), 7.42 (d, J = 7.7 Hz, 1H, H_{ar}), 7.57-7.67 (m, 5H, H_{ar}), 8.52 (d, J = 4.9 Hz, 2H, N-C$\underline{H}$).

^{13}C-NMR (100 MHz, $CDCl_3$): 48.1, 60.5, 60.6, 119.8, 121.3, 122.4, 123.3, 136.8, 137.4, 149.5, 159.3, 159.9, 161.5.

ESI-MS (MeOH): Positive ion mode: 320.1 ($[M+H]^+$), 324.1 ($[M+Na]^+$).

mono-6-deoxy-6-(N-6-methylpyridin-2-yl)-N,N-bis(pyridin-2-ylmethyl)-methanamine (91)

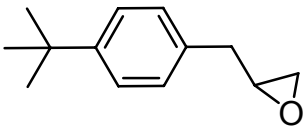


A mixture of 1.40 g amine (4.38 mmol, 25 eq.) and 229 mg monotosylated cyclodextrin (**85**) was heated to 70 °C for 3 h. Then 0.4 mL abs. DMF was added and the reaction mixture was stirred at 70 °C for 17 h. The mixture was added dropwise to 150 mL acetone, the precipitate was filtered off and washed with acetone. The precipitate was then redissolved in 0.4 mL DMF and added again to 150 mL acetone, filtered off and washed again with acetone. This procedure was repeated once more. One obtained 227 mg (0.158 mmol, 89%) of a white solid.

^{1}H-NMR (500 MHz, MeOH-d4): 2.80-4.50 (m, 50H,7x$H_{2/3/4/5/6}$ and 4xCH_{1}-4.90-5.04 (m, 6H, 6xH_1),5.12 (d, *J* = 3.4 Hz, 1H, 1xH_1), 7.11 (d, *J* = 7.8 Hz, 1H, N-CC<u>H</u>), 7.30-7.33 (m, 3H, N-CC<u>H</u> and NCHC<u>H</u>), 7.57 (d, *J* = 8.2 Hz, 2H, N-CHCHCHC<u>H</u>), 7.60 (t, *J* = 7.8 Hz, 1H, N-CCHC<u>H</u>), 7.84 (m, 2H, N-CHCHC<u>H</u>), 8.49 (d, *J* = 4.4 Hz, 2H, N-C<u>H</u>).

ESI-MS (MeOH): Positive ion mode: 1436.1 ($[M+H]^+$), 1458.0 ($[M+Na]^+$).

Catalytic epoxidation of 1-allyl-4-*tert*-butylbenzene (92) using catalyst 91 to give 2-(4-*tert*-butylbenzyl)oxirane (93)



A solution of 14.8 mg of **91** (10.3 µmol, 0.06 eq.) and 2.0 mg of $MnCl_2 \cdot 4H_2O$ (10.3 µmol, 0.06 eq.) in 6 mL H_2O/MeCN (1:1) was stirred for 1 h at r.t. before a solution of 30 mg 1-allyl-4-*tert*-butylbenzene (**92**) (172 µmol, 1.0 eq.) in 3 mL MeCN was added. To the resulting solution a solution of 189 mg iodosylbenzene (861 µmol, 5.0 eq.) was added over a period of 20 min. The reaction mixture was stirred for 2 h at r.t.. The reaction was quenched by the addition of $Na_2S_2O_3$ and H_2O. The mixture was extracted with hexane (3x). The combined organic phases were dried over Na_2SO_4 and the crude product was purified by column chromatography (SiO_2, hexane/EtOAc = 10:1) to give 15.7 mg (82.6 µmol, 48%) of a colourless oil.

TLC (SiO_2, hexane/EtOAc = 10:1): R_f = 0.32.

^{1}H-NMR (250 MHz, $CDCl_3$): 1.35 (s, 9H, C<u>H</u>$_3$), 2.59 (dd, *J* = 2.7 Hz, 5.0 Hz, 1H, OC<u>H</u>$_2$), 2.75-2.86 (m, 2H, OC<u>H</u>$_2$ + CC<u>H</u>$_2$), 2.95 (dd, *J* = 5.5 Hz, 14.5 Hz, 1H, CC<u>H</u>$_2$), 3.18 (m, 1H, OC<u>H</u>), 7.22 (d, *J* = 8.2 Hz, 2H, H_{ar}), 7.37 (d, *J* = 8.2 Hz, 2H, H_{ar}).

^{13}C-NMR (100 MHz, $CDCl_3$): 31.7, 34.8, 38.7, 47.4, 52.9, 125.9, 129.1, 134.5, 149.9.

Catalytic Oxidation of 1-*tert*-Butyl-4-propylbenzene (94) Using Catalyst 91

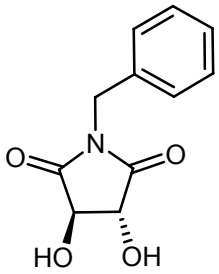
A solution of 9.0 mg of **94** (51 µmol, 1.0 eq.), 7.3 mg of **91** (5.1 µmol, 0.1 eq.) and 1.0 mg of $MnCl_2 \cdot 4H_2O$ (5.1 µmol, 0.1 eq.) in 3 mL MeCN/H_2O (2:1) was stirred at r.t. for 30 min. Then 140 µL TBHP (70% in H_2O) (1.0 mmol, 20 eq.) was added and the resulting mixture was stirred for 5 h at r.t. The mixture was then analysed by gas

chromatography using a *Finnigan Focus GC-FID* with a 15 m Supelcowax column, after being extracted with hexane.
GC: t_{ret} = 2.22 min (30%) **94**, 6.68 min (68%) ketone **95**, 7.61 min (2%) alcohol **96**.

Catalytic Oxidation of *tert*-Butyl-cyclohexane (97) Using Catalyst 91

A solution of 3.0 mg of **91** (2.1 µmol, 0.1 eq.), 0.41 mg of $MnCl_2 \cdot 4H_2O$ (5.1 µmol, 0.1 eq.) and 2.9 mg *tert*-butyl-cyclohexane (**97**) (21 µmol, 1.0 eq.) was stirred at r.t. for 30 min. Then 143 µL TBHP (70% in H_2O) (1.0 mmol, 500 eq.) were added and the resulting solution was stirred at r.t. for 17 h. The mixture was then analysed by gas chromatography using a *Finnigan Focus GC-FID* with a 15 m Supelcowax column, after being extracted with hexane.
GC: t_{ret} = 5.98 min (37%), 6.07 (14%), 6.07, 6.34, 6.54.

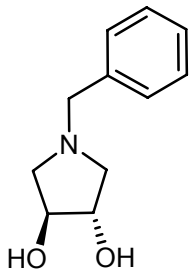
(3*R*,4*R*)-*N*-benzyl-3,4-dihydroxy-2,5-dioxopyrrolidine (102)[116]



To a suspension of 45.0 g (300 mmol, 1.0 eq.) L-(*R,*R)-(+)-tartaric acid (**101**) in 200 mL of *o*-xylene was added 32.1 g (300 mmol, 1.0 eq.) of benzylamine and the mixture was refluxed with stirring in a round-bottomed flask equipped with a Dean-Stark apparatus. The reaction was complete when the appropriate amount of water was collected (10.8 mL, 600 mmol, 4 h). After cooling the reaction mixture to r.t., the product was filtered off and recrystallised from ethanol to give 34.0 g (153 mmol, 51%) of a white solid.

^{1}H-NMR (400 MHz, $(CD_3)_2SO$): 4.36 (d, *J* = 6.6 Hz, 2H, NC*H*$_2$C$_{ar}$), 4.53 (m, 2H, HOC*H*CO), 6.27 (d, *J* = 7.1 Hz, 2H, O*H*), 7.23 (m, 3H, *H*$_{ar}$), 7.31 (m, 2H, *H*$_{ar}$).
^{13}C-NMR (100 MHz, $CDCl_3$): 42.0, 75.3, 128.3, 128.4, 129.4, 136.8, 175.4.

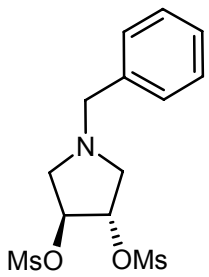
(3*S*,4*S*)-*N*-benzyl-3,4-dihydroxypyrrolidine (103)[116]



5.13 g (135 mmol, 2.3 eq.) Lithium aluminium hydride was slowly added to a 0 °C cooled solution of 13.0 g (58.8 mmol, 1.0 eq.) of **102** in 235 mL abs. diethyl ether. The reaction mixture was refluxed for 48 h. At 0 °C, 15 mL EtOAc were slowly added, followed sequentially by 5.1 mL water, 5.1 mL 15% NaOH and 15.3 mL water. The resulting mixture was stirred for 1 h, filtered over celite and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the resulting oil was crystallised. The crude product was recrystallised form EtOAc to give 5.34 g (27.6 mmol, 47%) of a white solid.

TLC (SiO_2, DCM/MeOH + 1% Et_3N = 10:1): R_f =0.21.
^{1}H-NMR (400 MHz, $CDCl_3$): 2.41 (dd, *J* = 4.3 Hz, 10.3 Hz, 2H, NCH_2CH), 2.88 (dd, *J* = 5.8 Hz, 10.1 Hz, 2H, NCH_2CH), 3.52 (d, *J* = 12.6 Hz, 1H, HOC*H*CH_2), 3.61 (d, *J* = 12.6 Hz, 1H, HOC*H*CH_2), 4.03 (m, 2H, NCH_2C_{ar}), 4.41 (br s, 2H, O*H*), 7.27 (m, 5H, H_{ar}).
^{13}C-NMR (100 MHz, $CDCl_3$): 60.2, 60.4, 78.2, 127.7, 128.5, 129.4, 137.1.

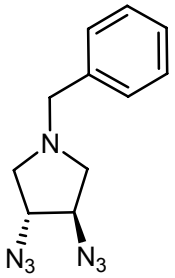
(3S,4S)-1-benzylpyrrolidine-3,4-diyl dimethanesulfonate (104)[117]



To a 0 °C cooled solution of 2.50 g (12.9 mmol, 1.0 eq.) of **103** and 3.6 mL (25.9 mmol, 2.0 eq.) Et_3N in 20 mL abs. DCM, was added 2.00 mL (25.9 mmol, 2.0 eq.) methanesulfonyl chloride over a period of 15 min. The mixture was stirred for 30 min at r.t. and subsequently washed with water (2x). The DCM phase was then extracted with 1 M HCl. The aqueous phase was made basic with 20% NaOH and extracted with DCM (2x). The combined organic phases were washed with brine and dried over Na_2SO_4. One obtained 4.45 g (12.7 mmol, 99%) of a colourless oil.

TLC (SiO_2, hexane/EtOAc = 1:1): R_f =0.21.
^{1}H-NMR (400 MHz, $CDCl_3$): 2.81 (m, 2H, NCH_2CH), 3.09 (s, 6H, CH_3), 3.14 (m, 2H, NCH_2CH), 3.68 (m, 2H, NCH_2C_{ar}), 5.15 (m, 2H, OC*H*), 7.27-7.36 (m, 5H, H_{ar}).
^{13}C-NMR (100 MHz, $CDCl_3$): 38.8, 58.1, 59.7, 82.5,128.3, 129.0, 129.3, 137.5.

(3*R*,4*R*)-(-)-3,4-Diazido-1-(phenylmethyl)pyrrolidine (105)[147]



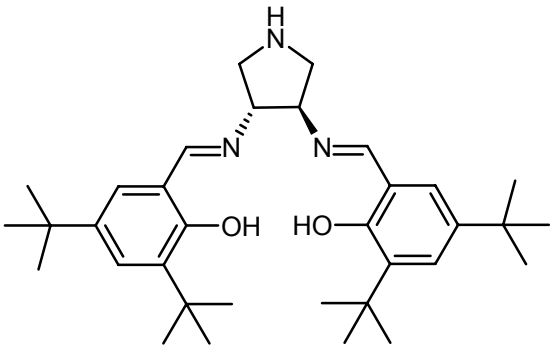
A stirred mixture of 2.50 g (12.9 mmol, 1.0 eq.) of **104** and 2.40 g (36.9 mmol, 3.0 eq.) of NaN_3 in 19 mL dry DMF was heated to 100 °C for 4 h. The solvent was removed *in vacuo*. The residue was dissolved in DCM and washed with saturated $NaHCO_3$ and brine and was dried over Na_2SO_4. Chromatography (SiO_2, hexane/EtOAc = 5:1) afforded 2.08 g (8.57 mmol, 70%) of a colourless oil.

TLC (SiO_2, hexane/EtOAc = 2:1): R_f =0.66.

^{1}H-NMR (400 MHz, $CDCl_3$): 2.60 (dd, *J* = 4.8 Hz, 9.8 Hz, 2H, NCH_2CH), 2.99 (dd, *J* = 4.8 Hz, 9.8 Hz, 2H, NCH_2CH), 3.62 (d, *J* = 13.0 Hz, 2H, NCH_2C_{ar}), 3.67 (d, *J* = 13.0 Hz, 2H, NCH_2C_{ar}), 3.87 (m, 2H, NC*H*), 7.29-7.35 (m, 5H, H_{ar}).

^{13}C-NMR (100 MHz, $CDCl_3$): 58.1, 59.8, 66.2, 127.4, 127.8, 128.9, 129.0,129.1, 138.1.

6,6'-(1E,1'E)-(3R,4R)-pyrrolidine-3,4-diylbis(azan-1-yl-1-ylidene)bis(methan-1-yl-1-ylidene)bis(2,4-di-tert-butylphenol) (99)[118]



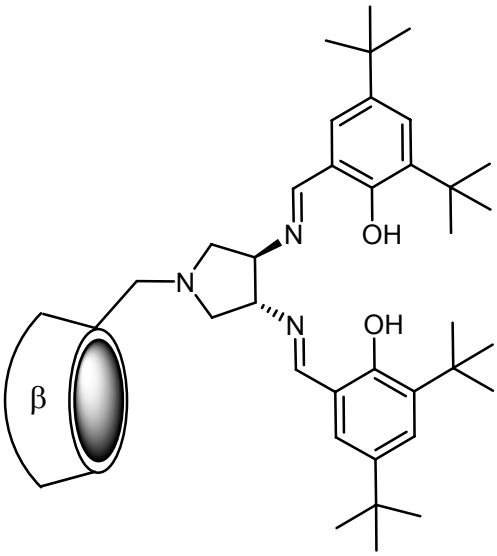
197 mg Palladium on carbon (10% w/w) was added to a solution of 536 mg (2.20 mmol, 1.0 eq.) of **105** in a mixture of 5.7 mL EtOH and 1.43 mL TFA. The suspension was stirred under 1 atm hydrogen for 46 h, filtered through Celite, and concentrated under vacuum. The crude residue was dissolved in 18 mL EtOH/H_2O (9:1) and neutralized with 1.06 g (7.70 mmol, 3.5 eq.) potassium carbonate. 1.13 g (4.84 mmol, 2.2 eq.) of neat 3,5-di-*tert*-butyl-salicylaldehyde (**106**) was added at once and the reaction was heated to reflux for 2 h. The reaction mixture was then poured into 40 mL brine and extracted with DCM (3x). The organic phases were combined and washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by chromatography (SiO_2, TBME:hexane = 2:1) to give 818 mg (1.53 mmol, 70%) of a foamy yellow solid.

TLC (SiO_2, hexane/TBME = 1:2): R_f =0.11.

^{1}H-NMR (400 MHz, $CDCl_3$): 1.27 (s, 18 H, C(CH_3)$_3$), 1.45 (s, 18 H, C(CH_3)$_3$), 3.17 (dd, *J* = 11.9 Hz, 4.8 Hz, 2H, NHCH_2CH), 3.50 (dd, *J* = 11.9 Hz, 4.8 Hz, 2H, NHCH_2CH), 3.89 (m, 2H, NHCH$_2$C*H*), 7.05 (d, *J* = 2.0, 2H, H_{ar}), 7.38 (d, *J* = 2.0, 2H, H_{ar}), 8.34 (s, 2H, NC*H*C), 13.37 (s, 2H, O*H*).

^{13}C-NMR (100 MHz, $CDCl_3$): 29.6, 31.6, 34.3, 35.2, 54.9, 117.7, 126.4, 127.4, 136.8, 140.5, 157.9, 166.5.

CD-Modified Salen Ligand 100

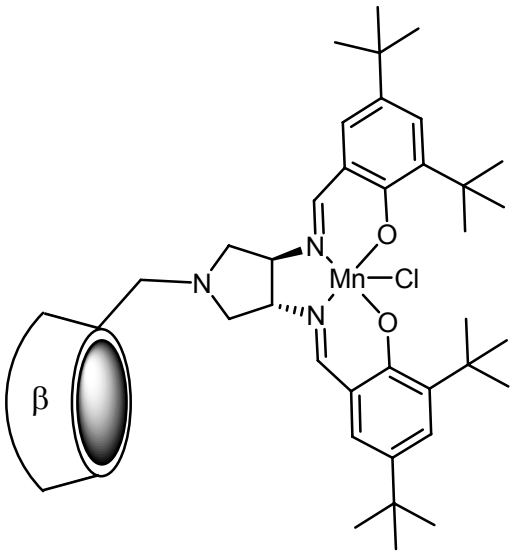


A mixture of 50 mg **99** (94 µmol, 1.0 eq.), 241 mg **85** (187 µmol, 2.0 eq.) and 48 µL Hünig's base (281 µmol, 3.0 eq.) and 0.4 mL dry DMF was stirred at 100 °C for 24 h. The solvent was removed under reduced pressure. The crude product was purified by column chromatography (RP-18, MeOH/H_2O = 2:1 to MeOH) to give 76 mg (46 µmol, 49%) of a yellow solid.

TLC (RP-18, MeOH): R_f =0.11.

ESI-MS (MeOH): Positive ion mode: 1673.4 ([M+Na]$^+$).

CD-Modified Mn Salen Complex 107



A suspension of 30 mg of **100** (18 µmol, 1.0 eq.) in 0.5 mL EtOH was heated to reflux. 13 mg $Mn(OAc)_4 \cdot 4H_2O$ (55 µmol, 3.0 eq.) was added and the mixture was refluxed for 2 h. Then 2.3 mg LiCl (55 µmol, 3.0 eq.) was added and the mixture was refluxed for another hour under air. The mixture was allowed to cool to r.t. and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (RP-18, MeOH/H_2O = 1:1 to MeOH) to give 26 mg (15 µmol, 82%) of a brown solid.

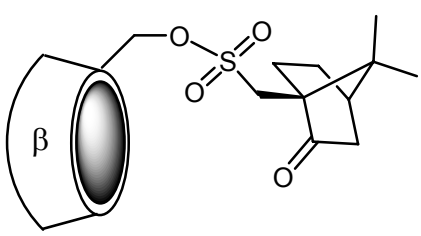
ESI-MS (MeOH): Positive ion mode: 1703.1 ($[M+Na]^+$).

Catalaytic Epoxidation of 4-*tert*-Butylstyrene (108) Using Catalyst 107

To a suspension of 7.3 mg of **108** (45 µmol, 1.0 eq.) and 3.9 mg of **107** (2.3 µmol, 0.05 eq.) in 0.3 mL DCM was added 27.0 mg of NMO (227 µmol, 5.0 eq.). To the resulting solution was added 23.5 mg of *m*CPBA (136 µmol, 3.0 eq.) and the reaction mixture was stirred at r.t. for 2 h. DCM was added and the mixture was washed with saturated NaOH and brine. The organic phase was dried over Na_2SO_4. The crude product was filtered over silica gel (hexane/EtOAc = 20:3) and analysed by gas chromatography using a *Finnigan Focus GC-FID* with a 15 m Supelcowax column.

GC: t_{ret} = 2.43 min (38%) **108**, 4.45 min (62%) epoxide **109**.
HPLC (Chiralcel OD-H, n-heptane, 0.5 mL/min, 220 nm): t = 21.14 min (54.5%) **109**, t = 22.75 min (45.5%) **109**.

CD-Modified (1*S*)-(+)-10-Camphorsulfonyl (113)

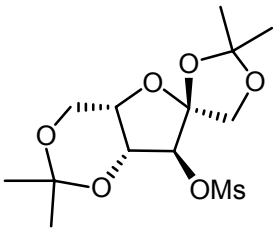


To a mixture of 1.00 g β-CD (881 µmol, 3.0 eq.), 0.9 mL abs. Pyridine and 5.5 mL abs. DMF was added at 0 °C 74 mg of (1S)-(+)-10-camphorsulfonyl chloride (294 µmol, 1.0 eq.). The reaction mixture was stirred for 4 h at r.t. and then added dropwise to 150 mL acetone. The precipitate was filtered off and purified by columnn chromatography (RP-18, gradient H_2O to MeOH) to give 222 mg (165 µmol, 56%) of a white solid.

TLC (SiO_2, EtOAc/isopropanol/NH_3 (30%)/H_2O = 7:7:5:4): 0.34.
ESI-MS (MeOH): Positive ion mode: 1371.7 ($[M+Na]^+$).
^{1}H-NMR (400 MHz, DMSO): 0.79 (s, 3H, C$\underline{H}_3$), 0.99 (s, 3H, C$\underline{H}_3$), 1.40 (m,1H), 1.54 (m, 1H), 1.90 (m, 2H), 2.04 (m, 1H), 2.22 (m, 2H), 3.20-3.75 (m, overlapped with water), 3.92 (m, 1H), 4.47 (m, 7H), 4.85 (m, 6H), 5.78 (m, 13H).

5.2.2 Synthesis of L-fructose-derived Shi-ketone catalyst ent-114

Mesylate 138



A solution of 10 mL dry 1,2-dimethoxyethane containing 250 mg $SnCl_2$ (1.32 mmol) was added to a suspension of 50.0 g L-sorbose (pulverized) (278 mmol, 1.0 eq.) in 150 mL 2,2-dimethoxypropane with vigorous stirring. The mixture was refluxed gently with stirring under argon at 70 °C for 2.3 h. At this point, there is still a substantial amount of solid (L-sorbose) remaining in the reaction mixture. The reaction was quenched immediately with 1.25 mL Et_3N, filtered to remove the unreacted L-sorbose, and the solid was washed with 15 mL EtOAc. The filtrate was concentrated to give a syrup.

The syrup was dissolved in 121 mL pyridine. After cooling with an ice bath, 26.6 mL methanesulfonyl chloride (343 mmol, 1.2 eq.) was added dropwise over 2 h. After stirring at 0 °C for an additional 3 h, the reaction mixture was poured into 750 mL ice-water, stirred for 30 min, and filtered. The filter cake was washed with water several times and recrystallized from ethanol (ca. 85 mL) to give 34.9 g mesylate (103 mmol, 37% yield over two steps based on L-sorbose) as a white crystal.

TLC (SiO_2, EtOAc): R_f = 0.32.

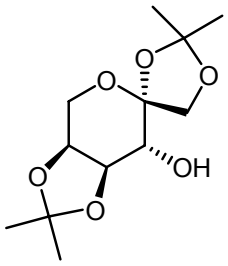
mp: 121 – 122 °C.

$[\alpha]_D^{20}$ = -28.1 (c = 1.06 in $CHCl_3$).

^{1}H-NMR (500 MHz, $CDCl_3$): 1.35 (s, 3H, C-C$\underline{H}_3$), 1.39 (s, 3H, C-C$\underline{H}_3$), 1.44 (s, 3H, C-C$\underline{H}_3$), 1.51 (s, 3H, C-C$\underline{H}_3$), 3.13 (s, 3H, S-C$\underline{H}_3$), 3.89 (dd, *J* = 13.0, 3.0 Hz, 1H, O-CH-C$\underline{H}_2$), 3.98 (dd, *J* = 13.0, 3.1 Hz, 1H, O-CH-C$\underline{H}_2$), 4.18 (d, *J* = 9.8 Hz, 1H, C-C$\underline{H}_2$-O), 4.20 (m, 1H, CH-C$\underline{H}$-CH), 4.22 (d, *J* = 9.8 Hz, 1H, C-C$\underline{H}_2$-O), 4.43 (m, 1H, O-C$\underline{H}$-CH_2), 4.85 (d, *J* = 1.7 Hz, 1H, S-C$\underline{H}$).

^{13}C-NMR (125 MHz, $CDCl_3$): 20.0, 25.8, 26.0, 28.2, 38.9, 60.4, 72.2, 73.3, 73.4, 84.3, 98.3, 109.9, 111.6.

Alcohol 142



A suspension of 33.7 g mesylate **138** (pulverised) (99.6 mmol, 1.0 eq.) in 337 mL 4.5% (w) H_2SO_4 was stirred at r.t. until all the starting material had been consumed as monitored by TLC (3 h). After it was made alkaline with 67 mL 9 M NaOH (600 mmol), the reaction mixture was heated at 90 – 100 °C until the reaction was completed as monitored by TLC (8 h). After being acidified to pH ~ 1 with 9 M H_2SO_4 (~17 mL), the reaction mixture was heated at 70 – 80 °C for 30 min, neutralized (pH 7.0) with 9 M NaOH (~15 mL), and concentrated to give a residue. The resulting residue was extracted by refluxing with ethanol (4 x 170 mL). The ethanol solution was concentrated to give L-fructose as a yellow syrup.

To a suspension of the above L-fructose syrup in 169 mL acetone was added 36.7 mL 2,2-dimethoxypropane (300 mmol, 3.0 eq.). After cooling to 0 °C, 1.4 mL concentrated H_2SO_4 (25 mmol) was added dropwise under argon. The resulting reaction mixture was stirred at 0 °C for 6 h. After addition of 8.5 mL concentrated NH_4OH, the reaction mixture was concentrated to a solid which was then dissolved in 135 mL DCM. The resulting solution was washed H_2O (2 x 70 mL), brine (70 mL), dried over Na_2SO_4, filtered, concentrated, and purified by silica gel chromatography (EtOAc/hexane = 1:5 to 1:3) to give 9.89 g (38.0 mmol, 38%) of a white solid.

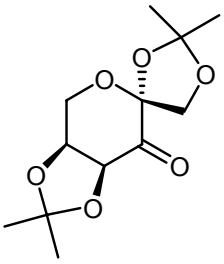
TLC (SiO_2, hexane/EtOAc = 2:1): R_f = 0.17.

mp: 114-116 °C.

$[\alpha]_D^{20}$ = +143.0 (c = 1.05 in $CHCl_3$).

^{1}H-NMR (250 MHz, $CDCl_3$): 1.36 (s, 3H, C$\underline{H}_3$), 1.43 (s, 3H, C$\underline{H}_3$), 1.50 (s, 3H, C$\underline{H}_3$), 1.52 (s, 3H, C$\underline{H}_3$), 2.08 (d, *J* = 8.3 Hz, 1H), 3.65 (dd, *J* = 8.2, 6.9 Hz, 1H), 3.99 (d, *J* = 9.0 Hz, 1H), 4.02 (d, *J* = 13.2 Hz, 1H), 4.13 (dd, *J* = 13.2, 2.7 Hz, 1H), 4.14 (dd, *J* = 6.9, 5.7 Hz, 1H), 4.19 (d, *J* = 9.0 Hz, 1H), 4.21 (ddd, *J* = 5.7, 2.7, 0.6 Hz, 1H).

Ketone ent-114



To a solution of 1.00 g alcohol **142** (3.84 mmol, 1.0 eq.) in 10 mL DCM was added 2.26 g PDC (6.01 mmol, 1.6 eq.), followed by 3.8 g freshly powdered 3 Å molecular sieves and 1 drop of acetic acid. After stirring at r.t. under argon overnight, the reaction mixture was filtered through a pad of silica gel and washed (EtOAc/hexane = 1:1, 50 mL) until no product came out. The filtrate was concentrated and recrystallized from hot hexane (ca. 4.5 mL) to give 810 mg (3.14 mmol, 82%) white crystals.

TLC (SiO_2, hexane/EtOAc = 2:1): R_f = 0.38.

mp: 98 – 100 °C.

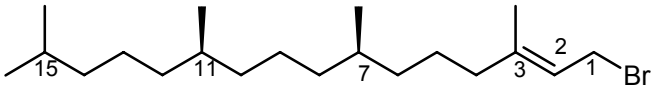
$[\alpha]_D^{20}$ = +120.2 (c = 1.00 in $CHCl_3$).

^{1}H-NMR (500 MHz, $CDCl_3$): 1.39 (s, 6H, C$\underline{H}_3$), 1.45 (s, 3H, C$\underline{H}_3$), 1.54 (s, 3H, C$\underline{H}_3$), 3.99 (d, *J* = 9.5 Hz, 1H, C-C$\underline{H}_2$-O), 4.11 (d, *J* = 13.5 Hz, 1H, CH-C$\underline{H}_2$-O), 4.38 (dd, *J* = 13.5, 2.1 Hz, 1H, CH-C$\underline{H}_2$-O), 4.54 (dd, *J* = 5.5, 2.1 Hz, 1H, C$\underline{H}$-CH$_2$-O), 4.60 (d, *J* = 9.5 Hz, 1H, C-C$\underline{H}_2$-O), 4.72 (d, *J* = 5.5 Hz, 1H, C-C$\underline{H}$-CH).

^{13}C-NMR (125 MHz, $CDCl_3$): 26.1, 26.2, 26.7, 27.3, 60.2, 70.1, 76.0, 78.1, 104.2, 110.8, 114.0, 197.1.

5.2.3 Synthesis of bis-protected phytyl hydroquinones

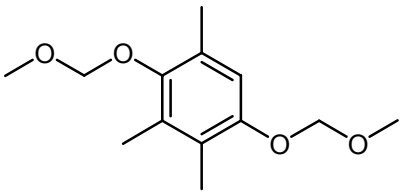
(7R,11R,E)-1-bromo-3,7,11,15-tetramethylhexadec-2-ene (126)



To a 0 °C cooled solution of 6.00 g natural E-phytol (**127**) (20.2 mmol, 1.0 eq.) in 150 ml dry THF was slowly added 2.10 mL PBr_3 (22.3 mmol, 1.1 eq.). The reaction mixture was stirred for 15 min at 0 °C. The reaction was quenched with saturated $NaHCO_3$ and the mixture was extracted with ether (3x). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was filtered through a pad of silica gel (ether) to yield 7.10 g (19.7 mmol, 98%) of a light yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): 0.84 (d, *J* = 6.7 Hz, 3H, $C_{7/11}$-C$\underline{H}_3$), 0.85 (d, *J* = 6.7 Hz, 3H, $C_{7/11}$-C$\underline{H}_3$), 0.86 (d, *J* = 6.7 Hz, 6H, C_{15}-C$\underline{H}_3$), 1.00-1.45 (m, 18H, $H_{5\text{-}14}$), 1.54 (sept, *J* = 6.7 Hz, 1H, H_{15}), 1.71 (d, *J* = 1.2 Hz, 3H, C_3-C$\underline{H}_3$), 2.02 (t, *J* = 7.6 Hz, 2H, H_4), 4.03 (d, *J* = 8.5 Hz, 2H, H_1), 5.52 (m, 1H, H_2).
^{13}C-NMR (100 MHz, $CDCl_3$): 16.3, 20.1, 20.2, 23.0, 23.1, 24.9, 25.2, 25.4, 28.4, 30.2, 33.1, 33.2, 36.9, 37.7, 37.75, 37.83, 39.8, 40.2, 120.7, 144.6.

1,4-bis(methoxymethoxy)-2,3,5-trimethylbenzene (120)



5.00 g trimethylhydroquinone (**26**) (32.9 mmol, 1.0) was dissolved in 100 mL dry DMF. The solution was cooled to 0 °C and 3.42 g NaH (60% in mineral oil) (85.4 mmol, 2.6 eq.) were carefully added. The mixture was stirred for 15 min at 0 °C. Then a solution of 6.88 g Chloromethyl methyl ether (85.4 mmol, 2.6 eq.) were added dropwise. The mixture was stirred for 3 h at r.t. The reaction was quenched with H_2O, and the mixture was extracted with ether (3x). The combined organic phases were washed with brine and dried over Na_2SO_4. Chromatography (SiO_2, hexane/EtOAc = 5:1) afforded 7.28 g (30.3 mmol, 92%) of a colourless oil.

TLC (SiO_2, hexane/EtOAc = 5:1): R_f = 0.35.

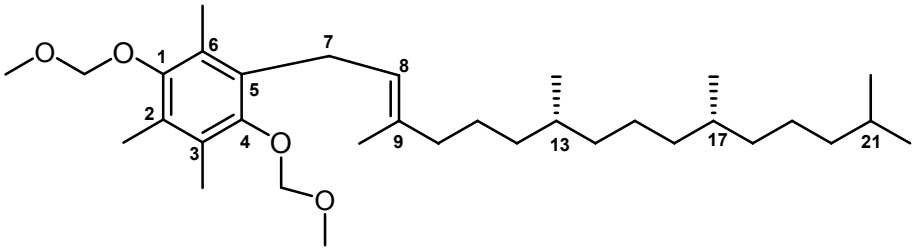
^{1}H-NMR (500 MHz, $CDCl_3$): 2.12 (s, 3H, C-C$\underline{H}_3$), 2.19 (s, 3H, C-C$\underline{H}_3$), 2.25 (s, 3H, C-C$\underline{H}_3$), 3.47 (s, 3H, O-C$\underline{H}_3$), 3.59 (s, 3H, O-C$\underline{H}_3$), 4.87 (s, 2H, C$\underline{H}_2$), 5.11 (s, 2H, C$\underline{H}_2$), 6.74 (s, 1H, C$\underline{H}$).

^{13}C-NMR (125 MHz, $CDCl_3$): 12.5, 13.7, 17.3, 56.2, 57.7, 95.4, 99.6, 114.6, 114.6, 125.0, 128.7, 131.1, 149.3, 151.7.

Ms (EI): *m/z* (%) = 240.1 ([M^+], 27), 195.1 (15), 45.0 (100).

EA: calculated for $C_{13}H_{20}O_4$: C 64.98, H 8.39; found: C 64.89, H 8.31.

1,4-bis(methoxymethoxy)-2,3,5-trimethyl-6-((7R,11R,E)-3,7,11,15-tetramethylhexadec-2-enyl)benzene (121)



To a solution of 15.7 mL *n*-BuLi (1.6 M in hexane) (25.2 mmol, 1.1 eq.) in 74 mL dry Et_2O was added at 0 °C 3.78 mL TMEDA (25.2 mmol, 1.1 eq.) together with 5.50 g protected hydroquinone **120** (22.9 mmol, 1.0 eq.). The mixture was stirred for 2.5 h at 0 °C and then cooled to -20 °C. 328 mg CuBr (2.29 mmol, 0.1 eq.) followed by a solution of 6.40 g phytylbromide (**126**) (17.8 mmol, 0.8 eq.) in 5 mL dry Et_2O were added. The reaction mixture was stirred for 4 h at r.t. The reaction was quenched with saturated $NaHCO_3$ and the mixture was extracted with ether and the combined organic phases were dried over Na_2SO_4. Chromatography (SiO_2, hexane/EtOAc = 20:1) afforded 5.89 g (11.4 mmol, 64%) of a colourless oil.

TLC (SiO_2, hexane/EtOAc = 20:1) R_f = 0.22.

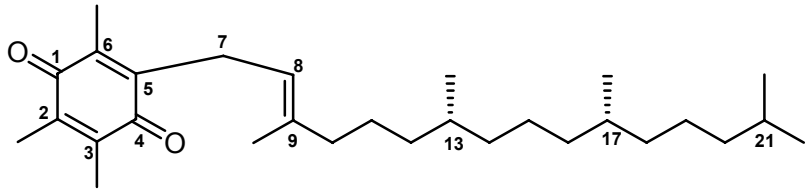
^{1}H-NMR (400 MHz, $CDCl_3$): 0.82 (d, *J* = 6.6 Hz, 3H, $C_{13/17}$-C$\underline{H}_3$), 0.83 (d, *J* = 6.6 Hz, 3H, $C_{13/17}$-C$\underline{H}_3$), 0.86 (d, *J* = 6.6 Hz, 6H, C_{21}-C$\underline{H}_3$), 0.94-1.43 (m, 18H, $H_{11/12/13/14/15/16/17/18/19/20}$), 1.51 (sept, *J* = 6.6 Hz, 1H, H_{21}), 1.73 (s, 3H, C_9-C$\underline{H}_3$), 1.93 (t, *J* = 7 Hz, 2H, H_{10}), 2.18 (s, 3H, $C_{2/3/6}$-C$\underline{H}_3$), 2.19 (s, 3H, $C_{2/3/6}$-C$\underline{H}_3$), 2.20 (s, 3H, $C_{2/3/6}$-C$\underline{H}_3$), 3.37 (d, *J* = 6.1 Hz, 2H, H_7), 3.59 (s, 3H, O-C$\underline{H}_3$), 3.61 (s, 3H, O-C$\underline{H}_3$), 4.86 (s, 2H, O-C$\underline{H}_2$-O), 4.88 (s, 2H, O-C$\underline{H}_2$-O), 5.02 (t, *J* = 6.1 Hz, 1H, H_8).

^{13}C-NMR (100 MHz, $CDCl_3$): 13.5, 14.0, 14.1, 16.7, 20.1, 23.0, 23.1, 24.9, 25.2, 25.8, 27.0, 28.4, 33.1, 33.2, 37.2, 37.7, 37.8, 37.9, 39.8, 40.4, 57.9, 58.0, 99.8, 100.2, 123.2, 128.5, 128.6, 128.9, 132.4, 136.0, 150.7, 151.3.

Ms (EI): *m/z* (%) = 518.4 ([M^+], 34), 486.4 (20), 441.4 (100).

EA: calculated for $C_{33}H_{58}O_4$: C 76.40, H 11.27; found: C 76.26, H 11.08.

2,3,5-trimethyl-6-((7R,11R,E)-3,7,11,15-tetramethylhexadec-2-enyl)cyclohexa-2,5-diene-1,4-dione (122)



To a solution of 500 mg alkene **121** (964 µmol, 1.0 eq.) in 30 mL MeCN was added a solution of 1.04 g CAN (1.90 mmol, 2.0 eq.) in 3 mL H_2O. The reaction mixture was stirred for 1 h at r.t. H_2O was added and the mixture was extracted with DCM (3x). The combined organic phases were dried over Na_2SO_4. Chromatography (SiO_2, hexane/EtOAc = 15:1) afforded 351 mg (819 µmol, 85%) of a yellow oil.

TLC (SiO_2, hexane/EtOAc = 10:1): R_f = 0.46.

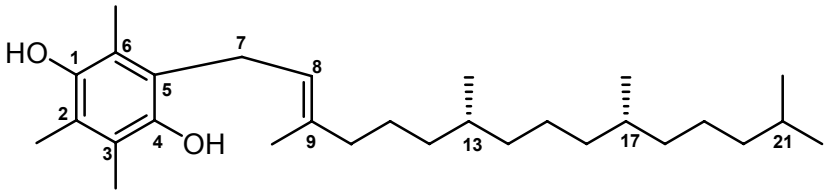
^{1}H-NMR (500 MHz, $CDCl_3$): 0.82 (d, *J* = 6.3 Hz, 3H, $C_{13/17}$-C$\underline{H}_3$), 0.83 (d, *J* = 6.6 Hz, 3H, $C_{13/17}$-C$\underline{H}_3$), 0.86 (d, *J* = 6.6 Hz, 6H, C_{21}-C$\underline{H}_3$), 0.95-1.43 (m, 18H, $H_{11/12/13/14/15/16/17/18/19/20}$), 1.51 (sept, *J* = 6.6 Hz, 1H, H_{21}), 1.72 (s, 3H, C_9-C$\underline{H}_3$), 1.92 (m, 2H, H_{10}), 2.01 (s, 6H, $C_{2/3}$-C$\underline{H}_3$), 2.02 (s, 3H, C_6-C$\underline{H}_3$), 3.19 (d, *J* = 7.0 Hz, 2H, H_7), 5.02 (t, *J* = 7.0 Hz, 1H, H_8).

^{13}C-NMR (125 MHz, $CDCl_3$): 12.4, 12.59, 12.61, 16.4, 19.94, 19.96, 22.8, 22.9, 24.7, 25.0, 25.5, 25.8, 28.2, 32.9, 33.0, 36.9, 37.51, 37.59, 37.64, 39.6, 40.2, 119.4, 137.7, 140.47, 140.54, 140.58, 143.5, 187.3, 188.2.

Ms (EI): *m/z* (%) = 428.4 ([M^+], 100), 203.1 (52), 176.1 (39), 165.1 (45).

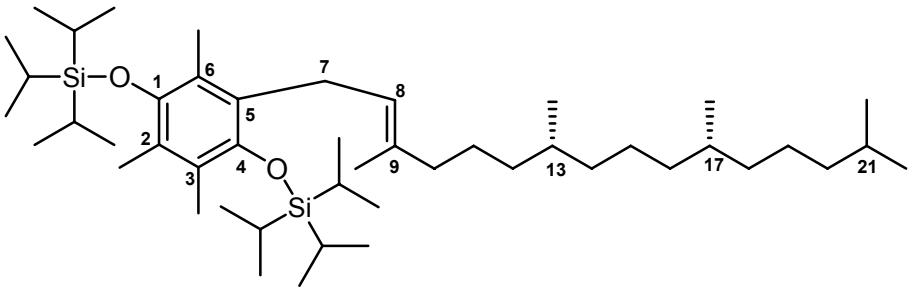
EA: calculated for $C_{29}H_{48}O_2$: C 81.25, H 11.29; found: C 81.22, H 11.13.

2,3,5-trimethyl-6-((7R,11R,E)-3,7,11,15-tetramethylhexadec-2-enyl)benzene-1,4-diol (123)



To 1.50 g of quinone **122** (3.50 mmol, 1.0 eq.) in 100 mL of THF was added a large excess of $Na_2S_2O_4$. H_2O (ca. 70 mL) was added until all $Na_2S_2O_4$ was dissolved. The characteristic yellow colour of the quinone disappeared immediately and the reaction was stirred at r.t. for 15 min to ensure completion. The mixture was then poured into a 1:1 mixture of DCM and H_2O and extracted with three portions of DCM. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under vacuo to give 1.42 g of the crude title compound as a white waxy solid. The crude hydroquinone was used directly used for subsequent reactions to prevent the facile oxidation to the starting quinone **122**.

(2,3,5-trimethyl-6-((7R,11R,E)-3,7,11,15-tetramethylhexadec-2-enyl)-1,4-phenylene)bis(oxy)bis(triisopropylsilane) (124)



To a solution of 425 mg hydroquinone **123** (987 µmol, 1.0 eq.) in 10 mL dry DMF was slowly added 89 mg of NaH (60% in mineral oil) (2.23 mmol, 2.3 eq.) at 0 °C. The mixture was stirred for 20 min at 0 °C. To the resultant dark solution was then added dropwise 472 µL of chlorotriisopropylsilane (2.23 mmol, 2.3 eq.). The mixture was stirred for 2 h at 0 °C. The reaction was quenched with H_2O and the mixture was extracted with ether (3x). The combined organic phases were dried over Na_2SO_4. Chromatography (SiO_2, hexane/EtOAc = 60:1) afforded 619 mg (832 µmol, 84%) of a colourless oil.

TLC (SiO_2, hexane/EtOAc = 40:1): R_f = 0.62.

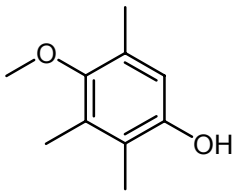
^{1}H-NMR (400 MHz, $CDCl_3$): 0.82 (d, *J* = 6.5 Hz, 3H, $C_{13/17}$-C<u>H</u>$_3$), 0.84 (d, *J* = 6.5 Hz, 3H, $C_{13/17}$-C<u>H</u>$_3$), 0.86 (d, *J* = 6.6 Hz, 6H, C_{21}-C<u>H</u>$_3$), 0.95-1.43 (m, 24H, $H_{11/12/13/14/15/16/17/18/19/20}$ +C<u>H</u>$_{Tips}$), 1.07 (d, *J* = 7.4 Hz, 36H, C<u>H</u>$_3$ Tips), 1.51 (sept, *J* = 6.6 Hz, 1H, H_{21}), 1.68 (s, 3H, C_9-C<u>H</u>$_3$), 1.90 (t, *J* = 7.3 Hz, 2H, H_{10}), 2.10 (s, 3H, $C_{2/3/6}$-C<u>H</u>$_3$), 2.13 (s, 6H, $C_{2/3/6}$-C<u>H</u>$_3$), 3.29 (d, *J* = 5.5 Hz, 2H, H_7), 4.95 (t, *J* = 5.5 Hz, 1H, H_8).

^{13}C-NMR (100 MHz, $CDCl_3$): 14.29, 14.35, 14.40, 14.7, 14.8, 16.5, 18.2, 18.3, 19.95, 19.97, 22.9, 23.0, 24.7, 25.0, 25.6, 27.3, 28.2, 32.98, 33.03, 36.9, 37.5, 37.6, 37.7, 39.6, 40.0, 124.0, 124.8, 125.1, 125.2, 128.9, 135.0, 147.1, 147.7.

Ms (EI): *m/z* (%) = 742.6 ([M^+], 100), 433.4 (29).

EA: calculated for $C_{47}H_{90}O_2Si_2$: C 75.94, H 12.20; found: C 75.95, H 12.04.

4-methoxy-2,3,5-trimethylphenol (128)



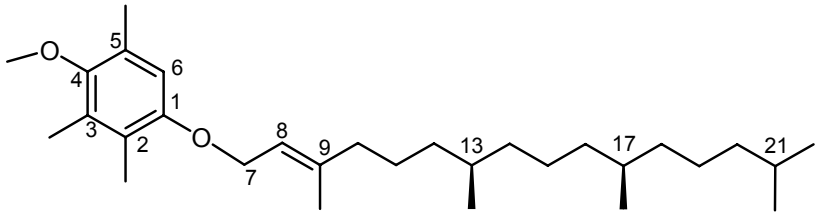
To a 0°C cooled solution of 5.00 g trimethylhydroquinone (**26**) (32.9 mmol, 1.3 eq.) in 70 mL abs. DMF 3.42 g of NaH (60% in mineral oil) (85.4 mmol, 3.2 eq.) were carefully added. The mixture was stirred for 30 min at 0 °C. 1.63 mL MeI (26.3 mmol, 1.0 eq.) was added dropwise. The mixture was stirred for 1h at 0 °C. The reaction was quenched with H_2O followed by saturated NH_4Cl. The mixture was extracted with ether (3x) and the combined organic phases were washed with brine and dried over Na_2SO_4. Chromatography (SiO_2, hexane/EtOAc = 4 : 1) afforded 2.33 g (14.0 mmol, 53%) of an orange oil.

TLC (SiO_2, hexane/EtOAc = 4 : 1): R_f = 0.27.

^{1}H-NMR (500 MHz, $CDCl_3$): 2.13 (s, 3H, C_{ar}-C<u>H</u>$_3$), 2.20 (s, 3H, C_{ar}-C<u>H</u>$_3$), 2.22 (s, 3H, C_{ar}-C<u>H</u>$_3$), 3.65 (s, 3H, O-C<u>H</u>$_3$), 4.60 (br s, 1H, O<u>H</u>), 6.46 (s, 1H, C_{ar}-<u>H</u>).

^{13}C-NMR (125 MHz, $CDCl_3$): 12.0(C_{ar}-<u>C</u>H$_3$), 12.8 (C_{ar}-<u>C</u>H$_3$), 16.1 (C_{ar}-<u>C</u>H$_3$), 60.3 (O-<u>C</u>H$_3$), 114.6 (<u>C</u>$_{ar}$-H), 121.1 (<u>C</u>$_{ar}$-CH$_3$), 128.5 (<u>C</u>$_{ar}$-CH$_3$), 130.8 (<u>C</u>$_{ar}$-CH$_3$), 149.5 (<u>C</u>$_{ar}$-O), 150.7 (<u>C</u>$_{ar}$-O).

2-methoxy-1,3,4-trimethyl-5-((7R,11R,E)-3,7,11,15-tetramethylhexadec-2-enyloxy)benzene (129)



330 mg of 4-methoxy-2,3,5-trimethylphenol (**128**) (1.96 mmol,1.0 eq.) were dissolved in 50 mL abs. DMF. The solution was cooled to 0°C and 111 mg NaH (60% in mineral oil) (2.78 mmol, 1.4 eq.) were carefully added. The suspension was stirred for 25 min. at 0°C. Then a solution of 845 mg of phytylbromide (2.35 mmol, 1.2 eq.) in 10 ml abs. DMF was added dropwise. The mixture was stirred for 2h at 0°C. The reaction was quenched with water and extracted with ether (3x). The combined organic phases were dried over Na_2SO_4. Chromatography (SiO_2, hexane/EtOAc = 40:1) gave 801 mg (1.80 mmol, 92%) of a light yellow oil.

TLC (SiO_2, hexane/EtOAc = 20 : 1): R_f = 0.40.

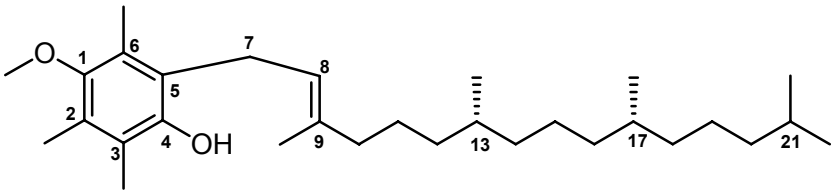
^{1}H-NMR (400 MHz, $CDCl_3$): 0.84 (d, 3H, *J* = 3.7 Hz, $C_{13/17}$-C$\underline{H}_3$), 0.86 (d, 3H, *J* = 3.7 Hz, $C_{13/17}$-C$\underline{H}_3$), 0.87 (d, 6H, *J* = 6.6 Hz, C_{21}-C$\underline{H}_3$), 1.00-1.47 (m, 18H, $H_{11/12/13/14/15/16/17/18/19/20}$), 1.51 (sept, 1H, *J* = 6.6 Hz, H_{21}), 1.70 (s, 3H, C_9-C$\underline{H}_3$), 2.03 (t, 2H, *J* = 7.4 Hz, H_{10}), 2.12 (s, 3H, $C_{2/3/5}$-C$\underline{H}_3$), 2.19 (s, 3H, $C_{2/3/5}$-C$\underline{H}_3$), 2.26 (s, 3H, $C_{2/3/5}$-C$\underline{H}_3$), 3.65 (s, 3H, O-C$\underline{H}_3$), 4.47 (d, 2H, *J* = 6.4 Hz, H_7), 5.48 (t, 1H, *J* = 6.4 Hz, H_8), 6.54 (s, 1H, H_5).

^{13}C-NMR (100 MHz, $CDCl_3$): 12.46, 13.09, 16.69, 16.92, 20.14, 20.16, 23.04, 23.13, 24.88, 25.21, 25.49, 28.39, 33.09, 33.20, 37.03, 37.70, 37.78, 37.84, 39.78, 40.27, 60.54, 66.23, 112.50, 120.55, 124.71, 127.98, 130.94,140.97, 150.97, 153.28.

MS (EI): *m/z* (%) = 444.4 ([M^+], 1), 166.1 (100), 151.1 (15).

EA: calculated for $C_{30}H_{52}O_2$: C 81.02, H 11.78; found: C 80.77, H 11.50.

4-methoxy-2,3,5-trimethyl-6-((7R,11R,E)-3,7,11,15-tetramethylhexadec-2-enyl)phenol (130)



100 mg of ether **129** (225 µmol, 1.0 eq.) were dissolved in 3 mL abs. DCM. At -30 °C 85 µL of boron trifluoride ethyl etherate (675 µmol, 3.0 eq.) were added to the solution. The mixture was stirred for 10 min at -30 °C. The cooling bath was removed and wet DCM followed by water was added. The phases were separated and the aqueous phase was further extracted with DCM. Chromatography (SiO_2, hexane/EtOAc = 20:1) gave 69 mg (155 µmol, 69%) of a colourless oil.

TLC (SiO_2, hexane/EtOAc = 20:1): R_f = 0.40.

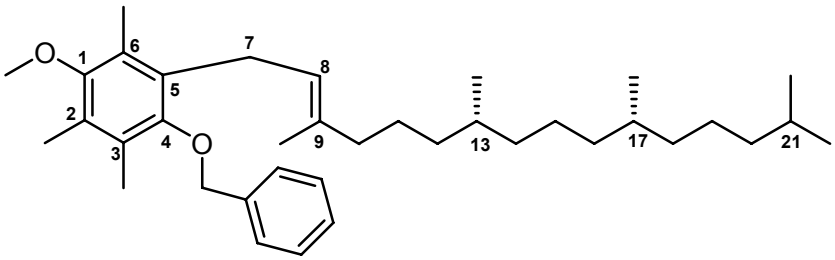
^{1}H-NMR (400 MHz, $CDCl_3$): 0.83 (d, 3H, J = 6.6 Hz, $C_{13/17}$-C$\underline{H}_3$), 0.84 (d, 3H, J = 6.6 Hz, $C_{13/17}$-C$\underline{H}_3$), 0.86 (d, 6H, J = 6.6 Hz, C_{21}-C$\underline{H}_3$), 1.00-1.47 (m, 18H, $H_{11/12/13/14/15/16/17/18/19/20}$), 1.51 (sept, 1H, J = 6.6 Hz, H_{21}), 1.81 (s, 3H, C_9-C$\underline{H}_3$), 1.99 (t, 2H, J = 7.3 Hz, H_{10}), 2.14 (s, 3H, $C_{2/3/6}$-C$\underline{H}_3$), 2.20 (s, 3H, $C_{2/3/6}$-C$\underline{H}_3$), 2.23 (s, 3H, $C_{2/3/6}$-C$\underline{H}_3$), 3.36 (d, 2H, J = 6.8 Hz, H_7), 3.63 (s, 3H, O-C$\underline{H}_3$), 4.96 (s, 1H, O$\underline{H}$), 5.13 (m, 1H, H_8).

^{13}C-NMR (100 MHz, $CDCl_3$): 12.45, 12.82, 13.06, 14.53, 16.61, 23.03, 23.07, 23.13, 24.87, 25.21, 25.71, 26.79, 28.39, 32.00, 33.08, 33.19, 37.09, 37.70, 37.78, 37.84, 39.78, 40.43, 60.78, 121.76, 121.84, 123.82, 126.88, 128.52, 139.08, 149.19, 150.84.

MS (EI): *m/z* (%) = 445.4 (25), 444.4 ([M^+], 77), 179.1 (100).

EA: calculated for $C_{30}H_{52}O_2$: C 81.02, H 11.78; found: C 81.05, H 11.51.

1-(benzyloxy)-4-methoxy-2,3,5-trimethyl-6-((7R,11R,E)-3,7,11,15-tetramethylhexadec-2-enyl)benzene (131)



162 mg of phenol **130** (365 µmol, 1.0 eq.) were dissolved in 2 mL abs. DMF. At 0 °C 16 mg NaH (60% in mineral oil) (400 µmol, 1.1 eq.) were added. The mixture was stirred for 15 min at 0 °C. After 52 µL benzyl bromide (440 µmol, 1.2 eq.) were added. The mixture was stirred for 2 h at 0 °C. The reaction was quenched with H_2O and the mixture was extracted with ether (3x). The combined organic phases were dried over Na_2SO_4. Chromatography (SiO_2, hexane/EtOAc = 40 : 1) afforded 153 mg (286 µmol, 78%) of a light yellow oil.

TLC (SiO_2, hexane/EtOAc = 20 : 1): R_f = 0.34.

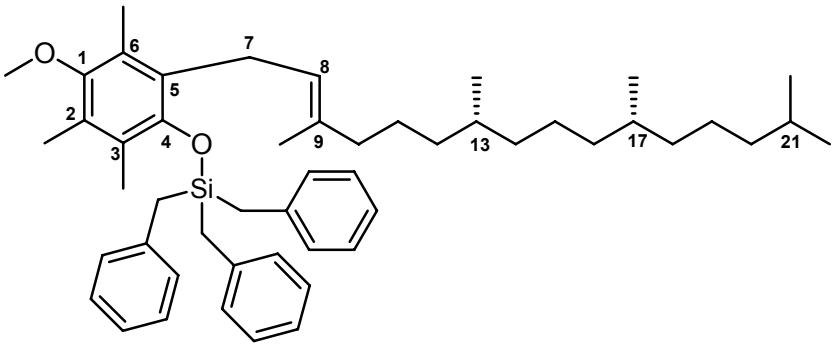
^{1}H-NMR (400 MHz, $CDCl_3$): 0.81 (d, 3H, J = 6.8 Hz, $C_{13/17}$-C$\underline{H}_3$), 0.83 (d, 3H, J = 6.8 Hz, $C_{13/17}$-C$\underline{H}_3$), 0.86 (d, 6H, J = 6.6 Hz, C_{21}-C$\underline{H}_3$), 0.95-1.45 (m, 18H, $H_{11/12/13/14/15/16/17/18/19/20}$), 1.52 (sept, 1H, J = 6.6 Hz, H_{21}), 1.68 (s, 3H, C_9-C$\underline{H}_3$), 1.93 (m, 2H, H_{10}), 2.20 (s, 6H, $C_{2/3/6}$-C$\underline{H}_3$), 2.22 (s, 3H, $C_{2/3/6}$-C$\underline{H}_3$), 3.41 (d, 2H, J = 5.5 Hz, H_7), 3.66 (s, 3H, O-C$\underline{H}_3$), 4.72 (s, 2H, $C_{benzyl}\underline{H}_2$), 5.08 (m, 1H, H_8), 7.33 (m, 1H, $\underline{H}_{p,\ benzyl}$), 7.39 (t, 2H, J = 7.2 Hz, $\underline{H}_{m,\ benzyl}$), 7.48 (d, 2H, J = 7.2 Hz, $\underline{H}_{o,\ benzyl}$).

^{13}C-NMR (100 MHz, $CDCl_3$): 12.65, 13.17, 13.48, 16.68, 20.12, 20.14, 23.04, 23.13, 24.88, 25.20, 25.81, 26.69, 28.38, 33.11, 33.19, 37.14, 37.70, 37.80, 37.84, 39.78, 40.37, 60.55, 75.57, 123.50, 127.95, 128.17, 128.28, 128.52, 128.66, 128.85, 132.41, 136.09, 138.31, 151.82, 153.61.

MS (EI): *m/z* (%) = 534.4 ([M^+], 36), 256.1 (17), 217 (20), 191.1 (30), 179.1 (100).

EA: calculated for $C_{37}H_{58}O_2$: C 83.09, H 10.93; found: C 82.90, H 10.81.

tribenzyl(4-methoxy-2,3,5-trimethyl-6-((7R,11R,E)-3,7,11,15-tetramethylhexadec-2-enyl)phenoxy)silane (133)



390 mg of phenol **130** (877 µmol, 1.0 eq.) were dissolved in 8 mL abs. DMF. At 0 °C 45 mg NaH (60% in mineral oil) (1.14 mmol, 1.3 eq.) were added. The mixture was stirred for 30 min at 0 °C. Then 384 mg chlorotribenzylsilane (1.14 mmol, 1.3 eq.) were added. The mixture was stirred for 2 h at 0 °C. The reaction was quenched with H_2O and the mixture was extracted with ether (3x). The combined organic phases were dried over Na_2SO_4. Chromatography (SiO_2, hexane/TBME = 20:1) afforded 521 mg (699 µmol, 80%) of a colourless oil.

TLC (SiO_2, hexane/TBME = 20:1): R_f = 0.32.

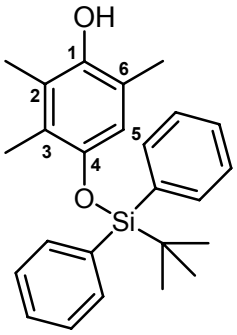
^{1}H-NMR (500 MHz, $CDCl_3$): 0.82 (d, J = 6.6 Hz, 3H, $C_{13/17}$-C$\underline{H}_3$), 0.83 (d, J = 6.6 Hz, 3H, $C_{13/17}$-C$\underline{H}_3$), 0.87 (d, J = 6.7 Hz, 6H, C_{21}-C$\underline{H}_3$), 0.96-1.45 (m, 18H, $H_{11/12/13/14/15/16/17/18/19/20}$), 1.52 (sept, J = 6.6 Hz, 1H, H_{21}), 1.64 (s, 3H, C_9-C$\underline{H}_3$),1.89 (s, 3H, $C_{2/3/6}$-C$\underline{H}_3$), 1.91-1.98 (m, 2H, H_{10}), 2.15 (s, 3H, $C_{2/3/6}$-C$\underline{H}_3$), 2.16 (s, 3H, $C_{2/3/6}$-C$\underline{H}_3$), 2.34 (s, 6H, C$\underline{H}_{2,\ benzyl}$), 3.24 (d, J = 5.5 Hz, 2H, H_7), 3.68 (s, 3H, O-C$\underline{H}_3$), 4.91 (m, 1H, H_8), 6.83 (d, J = 7.2 Hz, 6H, $\underline{H}_{o,\ benzyl}$), 7.07 (t, J = 7.3 Hz, 3H, $\underline{H}_{p,\ benzyl}$), 7.12 (t, J = 7.3 Hz, 6H, $\underline{H}_{m,\ benzyl}$).

^{13}C-NMR (125 MHz, $CDCl_3$): 12.50, 13.09, 14.65, 16.44, 19.86, 19.89, 22.78, 22.88, 23.86, 24.64, 24.95, 25.68, 27.12, 28.13, 32.88, 32.95, 37.01, 37.44, 37.56, 37.60, 39.52, 40.07, 60.50, 123.06, 124.71, 125.87, 127.72, 127.86, 128.33, 129.28, 129.55, 136.32, 137.81, 148.06, 151.98.

Ms (EI): *m/z* (%) = 744.5 ([M^+], 43), 388.2 (33), 387.2 (100).

EA: calculated for $C_{51}H_{72}O_2Si$: C 82.20, H 9.74; found: C 82.25, H 9.73.

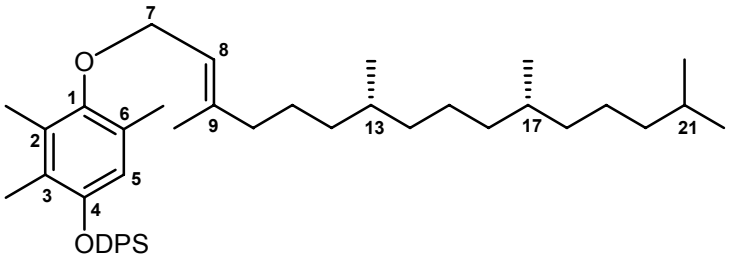
4-(*tert*-butyldiphenylsilyloxy)-2,3,6-trimethylphenol (134)



To a solution of 2.20 g 2,3,5-trimethylbenzene-1,4-diol (**26**) (14.4 mmol, 1.0 eq.) and 3.90 g imidazole (57.8 mmol, 4.0 eq.) in 20 mL DMF at -30°C, was added dropwise a solution of 4.5 mL DPSCl (17.3 mmol, 1.2 eq.) in 14 mL DMF. The mixture was allowed to warm up to room temperature and stirred for 4 h. The reaction was quenched with H_2O and extracted with DCM (3x). The combined organic phases were washed with H_2O, brine, dried over Na_2SO_4, and evaporated to dryness. The crude oil was purified by column chromatography (SiO_2, hexane/DCM = 7:3) to afford 5.29 g (13.5 mmol, 94%) of a colourless oil.

TLC (SiO_2, hexane/EtOAc = 10:1): R_f = 0.19.
^{1}H-NMR (400 MHz, $CDCl_3$): 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 DPS-), 7.73 (dd, 4H, J = 7.9, 1.3 Hz, H_o DPS-).
^{13}C-NMR (100 MHz, $CDCl_3$): 12.8 (C_3-$\underline{C}H_3$), 13.4 (C_2-$\underline{C}H_3$), 16.2 (C_6-$\underline{C}H_3$), 20.0 ($\underline{C}$-$(CH_3)_3$), 27.1 (C-($\underline{C}H_3$)$_3$), 118.0 (C_5), 120.1 (C_3), 123.6 (C_2), 125.5 (C_6), 128.1 (C_m, DPS-), 130.1 (C_p, DPS-), 133.8 (C_{Si}, DPS-), 135.9 (C_o, DPS), 146.2 (C_4), 147.3 (C_1).
MS (EI): *m/z* (%) = 390.2 ([M^+]).
EA: calculated for $C_{25}H_{30}O_2Si$: C 76.88, H 7.74; found: C 76.92, H 7.79.
IR(neat) ν_{max} 3576, 2930, 2856, 1472, 1427, 1326, 1233, 1189, 1107, 1082, 876, 822, 698 cm^{-1}.

***tert*-butyldiphenyl(2,3,5-trimethyl-4-((7R,11R,E)-3,7,11,15-tetramethylhexadec-2-enyloxy)phenoxy)silane (135)**[138]

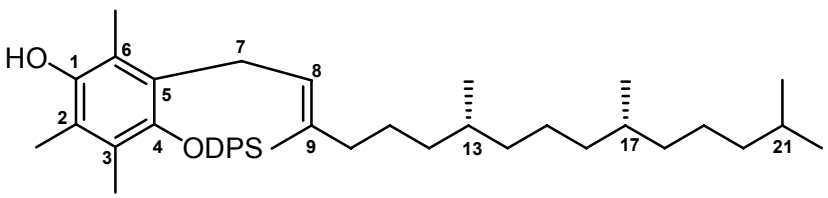


To a 0 °C cooled suspension of 350 mg NaH (60% in mineral oil) (8.75 mmol, 1.2 eq.) in 20 mL dry DMF was added a solution of 2.88 g mono-protected hydroquinone **134** (7.36 mmol, 1.0 eq.) in 20 mL DMF. The mixture was stirred for 30 min at 0 °C and then a solution of 2.94 g phytylbromide (**126**)

(8.18 mmol, 1.1 eq.) in 20 mL DMF was added dropwise. The solution was allowed to warm up to r.t. and stirred for 5 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with DCM (3x). The combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue purified by column chromatography (SiO_2, hexane/EtOAc = 97:3) to afford 4.29 g (6.40 mmol, 87%) of a colourless oil.

TLC (SiO_2, hexane/EtOAc = 20:1): R_f = 0.52.
^{1}H-NMR (500 MHz, $CDCl_3$): 0.83 (d, *J* = 4.1 Hz, 3H, $C_{13/17}$-C$\underline{H}_3$), 0.85 (d, *J* = 4.1 Hz, 3H, $C_{13/17}$-C$\underline{H}_3$), 0.87 (d, *J* = 6.9 Hz, 6H, 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, *J* = 6.6 Hz, 1H, 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, *J* = 6.9 Hz, 2H, H_7), 5.52 (t, *J* = 6.9 Hz, 1H, H_8), 6.10 (s, 1H, H_5), 7.35 (m, 4H, H_m DPS-), 7.41 (m, 2H, H_p DPS-), 7.70 (d, *J* = 6.9 Hz, 4H, H_o DPS-).
^{13}C-NMR (125 MHz, $CDCl_3$): 13.0 (C_3-$\underline{C}H_3$), 13.3 (C_2-$\underline{C}H_3$), 16.2 (C_6-$\underline{C}H_3$), 16.4 (C_9-$\underline{C}H_3$), 19.7 ($\underline{C}$-$(CH_3)_3$), 19.8 ($C_{13/17}$-$\underline{C}H_3$), 22.7 (C_{22}), 24.5 ($C_{15/19}$), 24.8 ($C_{15/19}$), 25.1 (C_{11}), 26.7 (C-($\underline{C}H_3$)$_3$), 28.0 (C_{21}), 32.7 ($C_{13/17}$), 32.8 ($C_{13/17}$), 36.7 (C_{12}), 37.3 ($C_{14/16/18}$), 37.4 ($C_{14/16/18}$), 39.4 (C_{20}), 40.0 (C_{10}), 69.3 (C_7), 118.0 (C_5), 120.2 (C_8), 125.0 (C_3), 127.6 (C_6), 127.8 (C_m, DPS-), 129.7 (C_p, DPS-), 130.5 (C_2), 133.3 (C_{Si}, DPS-), 135.5 (C_o, DPS), 140.8 (C_9), 149.2 (C_4), 149.7 (C_1).
MS (EI): *m/z* (%) = 668.5 ([M^+], 0.16), 390.2 (100), 333.1 (63), 255.1 (13).
EA: calculated for $C_{45}H_{68}O_2Si$: C 80.78, H 10.24; found: C 80.64, H 10.22.
IR(neat) ν_{max} 2926, 2857, 1473, 1428, 1377, 1322, 1220, 1113, 1086, 981, 886, 822, 700 cm^{-1}.

4-(tert-butyldiphenylsilyloxy)-2,3,6-trimethyl-5-((7R,11R,E)-3,7,11,15-tetramethylhexadec-2-enyl)phenol (136)[138]



To a -30 °C cooled solution of 4.29 g alkene **135** (6.41 mmol, 1.0 eq.) in 150 mL DCM, was added dropwise 2.5 mL of $BF_3 \cdot Et_2O$ (9.62 mmol, 1.5 eq.). The yellow solution was

stirred for 10 min at -30 °C and then quenched by the addition of H_2O. The mixture was warmed up to room temperature and extracted with DCM (3x).The combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue was purified by column chromatography (SiO_2, hexan/CH_2Cl_2 = 75:25) to afford 2.57 g (3.85 mmol, 60%) of a slight yellow oil.

TLC (SiO_2, hexane/DCM = 7:3): R_f = 0.23.

^{1}H-NMR (500 MHz, $CDCl_3$): 0.82 (d, *J* = 6.6 Hz, 3H, $C_{13/17}$-C<u>H</u>$_3$), 0.84 (d, *J* = 6.6 Hz, 3H, $C_{13/17}$-C<u>H</u>$_3$), 0.86 (d, *J* = 6.6 Hz, 6H, C_{21}-C<u>H</u>$_3$), 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<u>H</u>$_3$, E-isomer), 1.52 (sept, *J* = 6.6 Hz, 1H, H_{21}), 1.81 (s, 3H, C_3-C<u>H</u>$_3$), 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, *J* = 5.4 Hz, 2H, H_7), 4.29 (s, 1H, OH), 4.84 (t, *J* = 5.7 Hz, 1H, H_8), 7.31 (m, 4H, H_m DPS-), 7.39 (m, 2H, H_p DPS-), 7.67 (d, *J* = 6.6 Hz, 4H, H_o DPS-).

^{13}C-NMR (125 MHz, $CDCl_3$): 12.3 (C_6-<u>C</u>H$_3$), 12.6 (C_2-<u>C</u>H$_3$), 16.0 (C_3-<u>C</u>H$_3$), 16.3 (C_9-<u>C</u>H$_3$), 19.8 ($C_{13/17}$-<u>C</u>H$_3$), 20.4 (<u>C</u>-(CH$_3$)$_3$), 22.7 (C_{22}), 22.8 (C_{22}), 24.6 ($C_{11/15/19}$), 24.9 ($C_{11/15/19}$), 25.4 ($C_{11/15/19}$), 27.2 (C-(<u>C</u>H$_3$)$_3$), 27.4 (C_7), 28.1 (C_{21}), 32.8 ($C_{13/17}$), 32.9 ($C_{13/17}$), 36.8 ($C_{12/14/16/18}$), 37.4 ($C_{12/14/16/18}$), 37.5 ($C_{12/14/16/18}$), 37.6 ($C_{12/14/16/18}$), 39.5 (C_{20}), 39.9 (C_{10}), 120.2 (C_6), 120.4 (C_2), 123.5 (C_8), 124.6 (C_3), 127.5 (C_m, DPS-), 128.8 (C_5), 129.5 (C_p, DPS-), 134.8 (C_{Si}, DPS-), 135.0 (C_9), 135.3 (C_o, DPS), 146.0 (C_4), 146.3 (C_1).

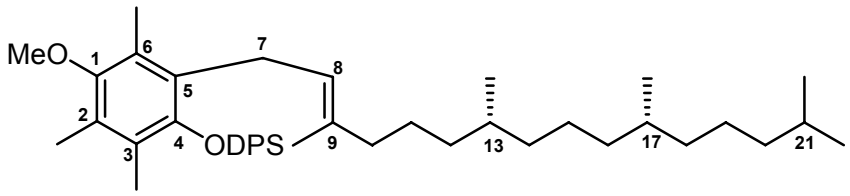
MS (EI): *m/z* (%) = 668.5 ([M^+]).

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

HPLC (Protonsil® 120-5-CN, heptane/isopropanol = 99.7:0.3, 0.4 mL/min, 220 nm): $t_{E\text{-isomer}}$ = 17.4 min (94.4%), $t_{Z\text{-isomer}}$ = 18.4 min (1.6%), **E:Z ratio** = 98.3:1.7.

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

tert-butyl(4-methoxy-2,3,5-trimethyl-6-((7R,11R,E)-3,7,11,15-tetramethylhexadec-2-enyl)phenoxy)diphenylsilane (132)[138]



To a 0 °C cooled suspension of 230 mg NaH (60% in mineral oil) (5.76 mmol, 1.5 eq.) in 20 mL DMF was added a solution of 2.57 g phenol **136** (3.84 mmol, 1.0 eq.) in 20 mL DMF. The mixture was stirred for 30 min at 0 °C and 500 µL MeI (7.68 mmol, 2 eq.) were 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 DCM (3x). The combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue purified by column chromatography (SiO_2, hexan/CH_2Cl_2 = 75:25) to afford 2.44 g (3.57 mmol, 93%) of a colourless oil.

TLC (SiO_2, hexane/EtOAc = 20:1): R_f = 0.51.

^{1}H-NMR (500 MHz, $CDCl_3$): 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$\underline{H}_3$), 0.87 (d, 6H, *J* = 6.6 Hz, C_{21}-C$\underline{H}_3$), 0.94-1.09 (m, 4H, $H_{12/14/16/18}$), 1.10 (s, 9H, tBu), 1.13 (m, 2H, H_{20}), 1.17-1.35 (m, 10H, $H_{11/12/14/15/16/18/19}$), 1.35-1.40 (m, 2H, $H_{13/17}$), 1.50 (s, 3H, C_9-C$\underline{H}_3$, E-isomer), 1.51 (sept, 1H, *J* = 6.6 Hz, H_{21}), 1.78 (s, 3H, C_3-C$\underline{H}_3$), 1.83 (m, 2H, H_{10}), 2.05 (s, 3H, C_2-C$\underline{H}_3$), 2.11 (s, 3H, C_6-C$\underline{H}_3$), 3.25 (d, 2H, *J* = 5.7 Hz, H_7), 3.61 (s, 3H, C$\underline{H}_3$O), 4.86 (t, 1H, *J* = 5.4 Hz, H_8), 7.31 (m, 4H, H_m TBDPS-), 7.38 (m, 2H, H_p DPS-), 7.66 (d, 4H, *J* = 6.9 Hz, H_o DPS-).

^{13}C-NMR (125 MHz, $CDCl_3$): 12.4 (C_6-$\underline{C}H_3$), 12.9 (C_2-$\underline{C}H_3$), 15.8 (C_3-$\underline{C}H_3$), 16.1 (C_9-$\underline{C}H_3$), 19.8 ($C_{13/17}$-$\underline{C}H_3$), 20.3 ($\underline{C}$-$(CH_3)_3$), 22.6 (C_{22}), 22.7 (C_{22}), 24.5 ($C_{11/15/19}$), 24.8 ($C_{11/15/19}$), 25.3 ($C_{11/15/19}$), 27.1 (C-($\underline{C}H_3$)$_3$), 27.4 (C_7), 28.0 (C_{21}), 32.7 ($C_{13/17}$), 32.8 ($C_{13/17}$), 36.7 ($C_{12/14/16/18}$), 37.3 ($C_{12/14/16/18}$), 37.4 ($C_{12/14/16/18}$), 37.5 ($C_{12/14/16/18}$), 39.4 (C_{20}), 39.8 (C_{10}), 60.3 ($\underline{C}H_3O$), 123.2 (C_8), 124.9 (C_3), 127.4 (C_6), 127.5 (C_2), 127.6 (C_m, TBDPS-), 129.1 (C_5), 129.4 (C_p, DPS-), 134.6 (C_{Si}, DPS-), 134.9 (C_9), 135.2 (C_o, TBDPS), 148.2 (C_4), 151.1 (C_1).

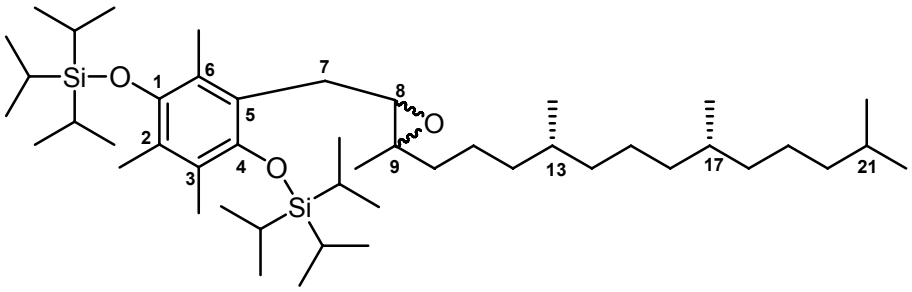
MS (EI): *m/z* (%) = 682.5 ([M^+], 9), 359.1 (100).

EA: calculated for $C_{46}H_{70}O_2Si$: C 80.88, H 10.33; found: C 80.93, H 10.27.

IR (neat): ν_{max} 2926, 2857, 1461, 1405, 1246, 1112, 1087, 886, 701 cm^{-1}.

5.2.4 Epoxidation of bis-protected phytyl hydroquinone substrates

(2,3,5-trimethyl-6-((3-methyl-3-((4R,8R)-4,8,12-trimethyltridecyl)oxiran-2-yl)methyl)-1,4-phenylene)bis(oxy)bis(triisopropylsilane) (149)



50 mg alkene **124** (67.3 µmol, 1.0 eq.) was dissolved in 1 mL of dry ether. At 0 °C 14 mg of *m*CPBA (80.7 µmol, 1.2 eq.) were added. The mixture was stirred over night at r.t. The reaction was quenched with 1 M NaOH, and the mixture was extracted with ether (3x). The combined organic phases were washed with H_2O and dried over Na_2SO_4. Chromatography (SiO_2, hexane/EtOAc = 40:1) afforded 40 mg (53 µmol, 78%) of a colourless oil.

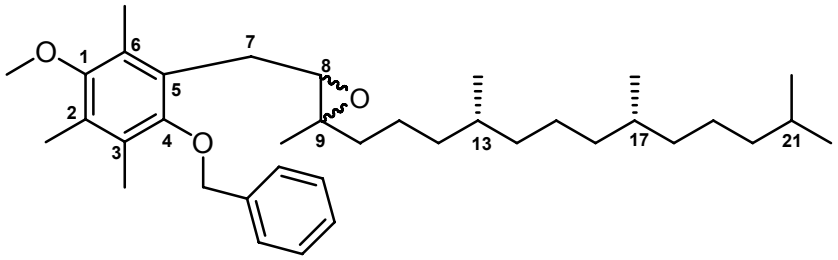
TLC (SiO_2, hexane/EtOAc = 40:1): R_f = 0.22.

^{1}H-NMR (500 MHz, $CDCl_3$): 0.81 (d, *J* = 6.6 Hz, 3H, $C_{13/17}$-C$\underline{H}_3$), 0.83 (d, *J* = 6.6 Hz, 3H, $C_{13/17}$-C$\underline{H}_3$), 0.86 (d, *J* = 6.6 Hz, 6H, C_{21}-C$\underline{H}_3$), 0.95-1.43 (m, 24H, $H_{11/12/13/14/15/16/17/18/19/20}$ +C$\underline{H}_{Tips}$), 1.06-1.10 (m, 36H, C$\underline{H}_3$ Tips), 1.36 (s, 3H, C_9-C$\underline{H}_3$),1.52 (sept, *J* = 6.6 Hz, 1H, H_{21}), 2.13 (s, 6H, $C_{2/3}$-C$\underline{H}_3$), 2.21 (s, 3H, C_6-C$\underline{H}_3$), 2.70-2.76 (m, 1H, H_7), 2.73-2.76 (m, 1H, H_8), 3.05 (dd, *J* = 13.9, 3.4 Hz, 1H, H_7).

^{13}C-NMR (125 MHz, $CDCl_3$): 14.2, 14.4, 14.7, 14.8, 15.0, 17.3, 18.1, 18.17, 18.20, 19.8, 19.9, 22.6, 22.8, 22.9, 24.6, 24.9, 28.0, 28.1, 32.90, 32.94, 37.3, 37.4, 37.6, 39.0, 39.5, 61.1, 64.1, 125.0, 125.3, 126.0, 126.1, 147.4, 147.8.

HPLC (Chiralcel AD-H, n-heptane, 0.6 mL/min, 220 nm): $t_{(2R)}$ = 7.27 min (50%), $t_{(2S)}$ = 8.31 min (50%).

3-(2-(benzyloxy)-5-methoxy-3,4,6-trimethylbenzyl)-2-methyl-2-((4R,8R)-4,8,12-trimethyltridecyl)oxirane



73 mg alkene **131** (136 µmol, 1.0 eq.) was dissolved in 1 mL of dry ether. At 0 °C 35 mg *m*CPBA (205 µmol, 1.5 eq.) were added. The mixture was stirred for 5 h at 0 °C. The reaction was quenched with 1 M NaOH, and the mixture was extracted with ether (3x). The combined organic phases were washed with H_2O and dried over Na_2SO_4. Chromatography (SiO_2, hexane/EtOAc = 20:1) afforded 64 mg (116 µmol, 85%) of a colourless oil.

TLC (SiO_2, hexane/EtOAc = 20:1): R_f = 0.17.

^{1}H-NMR (500 MHz, $CDCl_3$): 0.80 (d, *J* = 6.6 Hz, 3H, $C_{13/17}$-C$\underline{H}_3$), 0.83 (d, *J* = 6.6 Hz, 3H, $C_{13/17}$-C$\underline{H}_3$), 0.86 (d, *J* = 6.6 Hz, 6H, C_{21}-C$\underline{H}_3$), 0.96-1.08 (m, 4H, $H_{12/14/16/18}$), 1.10-1.38 (m, 16H, $H_{10/11/12/13/14/15/16/17/18/19/20}$), 1.32 (s, 3H, C_9-C$\underline{H}_3$), 1.52 (sept, 1H, J=6.1 Hz, H_{21}), 2.21 (s, 3H, $C_{2/3/6}$-C$\underline{H}_3$), 2.23 (s, 3H, $C_{2/3/6}$-C$\underline{H}_3$), 2.29 (s, 3H, $C_{2/3/6}$-C$\underline{H}_3$), 2.80-2.87 (m, 2H, $H_{7/8}$), 2.99-3.06 (m, 1H, H_7), 3.67 (s, 3H, C$\underline{H}_3$O), 4.73 (d, *J* = 11.3 Hz, 1H, C$\underline{H}_2$ benzyl), 4.80 (d, *J* = 11.3 Hz, 1H, C$\underline{H}_2$ benzyl), 7.34 (t, *J* = 7.3 Hz, 1H, H_p benzyl), 7.40 (t, *J* = 7.3 Hz, 2H, H_m benzyl), 7.49 (d, 4H, *J* = 7.3 Hz, H_o benzyl).

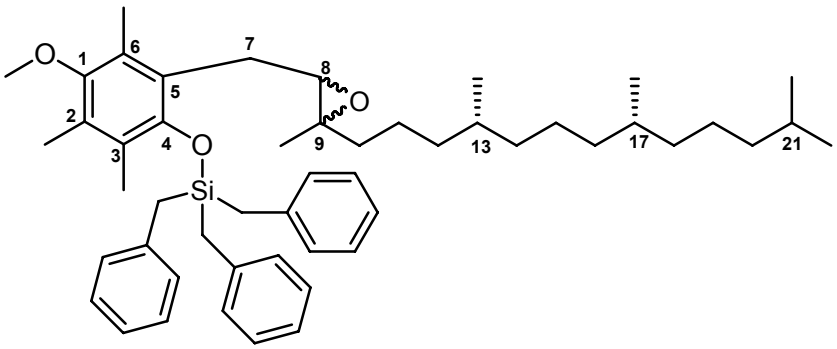
^{13}C-NMR (125 MHz, $CDCl_3$): 12.97, 13.04, 13.35, 17.13, 19.73, 19.88, 22.77, 22.87, 24.62, 24.94, 27.11, 28.12, 32.89, 32.92, 32.94, 37.11, 37.13, 37.43, 37.46, 37.56, 39.04, 39.51, 60.29, 61.52, 63.88, 75.23, 127.71, 128.01, 128.23, 128.44, 128.64, 129.06, 129.33, 137.83, 152.03, 153.46.

HPLC (Chiralcel OD-H, heptane/isopropanol = 98:2, 0.6 mL/min, 220 nm): $t_{(2R)}$ = 7.61 min (50%), $t_{(2S)}$ = 13.07 min (50%).

MS (EI): *m/z* (%) = 550.4 ([M^+], 29), 191.1 (33), 179.1 (100).

EA: calculated for $C_{37}H_{58}O_3$: C 80.67, H 10.61; found: C 80.60, H 10.50.

tribenzyl(4-methoxy-2,3,5-trimethyl-6-((3-methyl-3-((4R,8R)-4,8,12-trimethyltridecyl)oxiran-2-yl)methyl)phenoxy)silane



150 mg alkene **133** (201 µmol, 1.0 eq.) was dissolved in 1 mL of dry ether. At 0 °C 45 mg *m*CPBA (262 µmol, 1.3 eq.) were added. The mixture was stirred for 5 h at 0 °C. The reaction was quenched with 1 M NaOH, and the mixture was extracted with ether (3x). The combined organic phases were washed with H_2O and dried over Na_2SO_4. Chromatography (SiO_2, hexane/TBME = 20:1) afforded 139 mg (183 µmol, 91%) of a colourless oil.

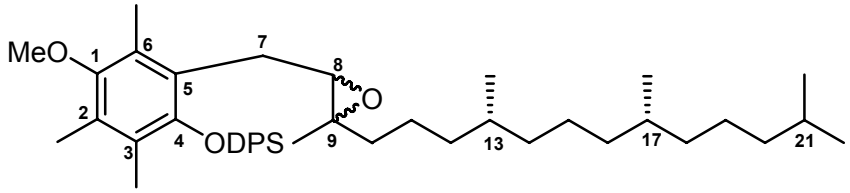
TLC (SiO_2, hexane/TBME = 20:1): R_f = 0.32.

^{1}H-NMR (500 MHz, $CDCl_3$): 0.79 (d, *J* = 6.6 Hz, 3H, $C_{13/17}$-C$\underline{H}_3$), 0.83 (d, *J* = 6.6 Hz, 3H, $C_{13/17}$-C$\underline{H}_3$), 0.86 (d, *J* = 6.6 Hz, 6H, C_{21}-C$\underline{H}_3$), 0.94-1.40 (m, 18H, $H_{11/12/13/14/15/16/17/18/19/20}$), 1.26 (s, 3H, C_3-C$\underline{H}_3$),1.52 (sept, *J* = 6.6 Hz, 1H, H_{21}), 1.96 (s, 3H, C_9-C$\underline{H}_3$), 2.16 (s, 3H, $C_{2/6}$-C$\underline{H}_3$), 2.24 (s, 3H, $C_{2/6}$-C$\underline{H}_3$), 2.36 (m, 6H, C$\underline{H}_2$ benzyl), 2.56 (m, 1H, H_7), 2.66 (m, 1H, H_8), 2.87-2.94 (m, 1H, H_7), 3.24 (d, *J* = 5.5 Hz, 2H, H_7), 3.68 (s, 3H, O-C$\underline{H}_3$), 6.83 (d, *J* = 7.2 Hz, 6H, $\underline{H}_{o,\ benzyl}$), 7.06 (t, *J* = 7.3 Hz, 3H, $\underline{H}_{p,\ benzyl}$), 7.12 (t, *J* = 7.3 Hz, 6H, $\underline{H}_{m,\ benzyl}$).

^{13}C-NMR (125 MHz, $CDCl_3$): 13.17, 13.24, 14.81, 17.04, 17.07, 19.72, 19.73, 19.88, 22.61, 22.65, 22.78, 22.87, 24.63, 24.65, 24.94, 27.87, 28.12, 32.89, 32.92, 32.95, 37.25, 37.43, 37.49, 37.56, 28.89, 39.51, 60.49, 61.17, 63.49, 124.84, 125.86, 126.85, 128.07, 128.38, 128.73, 129.26, 137.56, 148.50, 152.09.

HPLC (Chiralcel AD-H, heptane/isopropanol = 99.8:0.2, 0.6 mL/min, 220 nm): $t_{(2R)}$ = 13.00 min (50%), $t_{(2S)}$ = 15.27 min (50%).

tert-butyl(4-methoxy-2,3,5-trimethyl-6-((3-methyl-3-((4R,8R)-4,8,12-trimethyltridecyl)oxiran-2-yl)methyl)phenoxy)diphenylsilane



72 mg alkene **132** (105 µmol, 1.0 eq.) was dissolved in 1 mL of dry ether. At 0 °C 27 mg *m*CPBA (173 µmol, 1.5 eq.) were added. The mixture was stirred for 5 h at 0 °C. The reaction was quenched with 1 M NaOH, and the mixture was extracted with ether (3x). The combined organic phases were washed with H_2O and dried over Na_2SO_4. Chromatography (SiO_2, hexane/EtOAc = 20:1) afforded 63 mg (90 µmol, 86%) of a colourless oil.

TLC (SiO_2, hexane/EtOAc = 20:1): R_f = 0.12.

^{1}H-NMR (500 MHz, $CDCl_3$): 0.81 (d, *J* = 6.8 Hz, 3H, $C_{13/17}$-C$\underline{H}_3$), 0.83 (d, *J* = 6.7 Hz, 3H, $C_{13/17}$-C$\underline{H}_3$), 0.86 (d, *J* = 6.6 Hz, 6H, C_{21}-C$\underline{H}_3$), 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$\underline{H}_3$), 1.52 (sept, *J* = 6.1 Hz, 1H, H_{21}), 1.76 (s, 3H, C_3-C$\underline{H}_3$), 2.04 (s, 3H, C_2-C$\underline{H}_3$), 2.23 (s, 3H, C_6-C$\underline{H}_3$), 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$\underline{H}_3$O), 7.32 (m, 4H, H_m DPS-), 7.40 (m, 2H, H_p DPS-), 7.66 (d, *J* = 6.9 Hz, 4H, H_o DPS-).

^{13}C-NMR (125 MHz, $CDCl_3$): 12.9 (C_6-$\underline{C}H_3$), 13.2 (C_2-$\underline{C}H_3$), 15.8 (C_3-$\underline{C}H_3$), 16.1 (C_9-$\underline{C}H_3$), 19.6 ($C_{13/17}$-$\underline{C}H_3$), 19.7 ($C_{13/17}$-$\underline{C}H_3$), 20.3 ($\underline{C}$-$(CH_3)_3$), 22.2 (C_{11}), 22.6 (C_{22}), 22.7 (C_{22}), 24.5 ($C_{15/19}$), 24.8 ($C_{15/19}$), 27.1 (C-($\underline{C}H_3$)$_3$), 27.9 (C_7), 28.0 (C_{21}), 32.8 ($C_{13/17}$), 37.1 ($C_{12/14/16/18}$), 37.3 ($C_{12/14/16/18}$), 37.4 ($C_{12/14/16/18}$), 38.6 (C_{10}), 39.4 (C_{20}), 60.2 ($\underline{C}H_3$O), 60.7 (C_9), 63.9 (C_8), 125.0 (C_3), 126.4 (C_6), 127.5 (C_2), 127.6 (C_m, DPS-), 128.5 (C_5), 129.6 (C_p, DPS-), 134.3 (C_{Si}, DPS-), 135.1 (C_o, DPS), 148.5 (C_4), 151.3 (C_1).

MS (EI): *m/z* (%) = 698.5, 641.4.

EA: calculated for $C_{46}H_{70}O_3Si$: C 79.03, H 10.09; found: C 78.84, H 9.82.

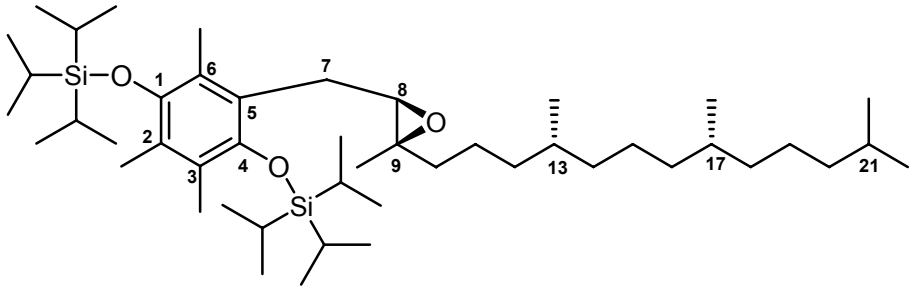
HPLC (Chiralcel AD-H, 0.1% iPrOH in n-heptane, 0.6 mL/min, 220 nm): $t_{(2R,3R)}$ = 7.9 min (50 %), $t_{(2S,3S)}$ = 8.7 min (50 %).

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

Asymmetric Shi Epoxidation, General Procedure:

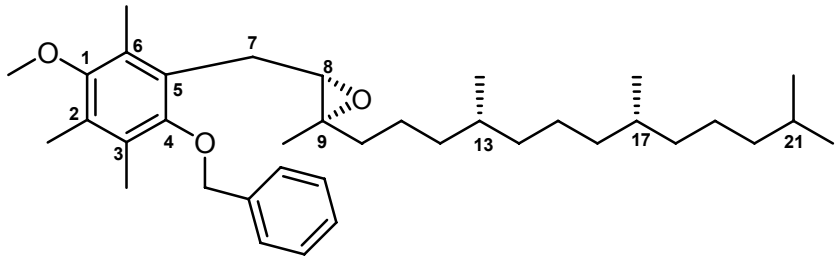
To a solution of alkene (55 µmol, 1.0 eq) and catalyst **ent-114** (or **114**) (22 µmol, 0.4 eq) in ACN:EtOH:CH_2Cl_2 (1:1:2, 200 µL) was added a buffer solution of 2M K_2CO_3/4.10^{-4} M EDTA (140 µL). The mixture was cooled down to 0°C and H_2O_2 (30% aq., 30 µL, 5.4 eq.) was added in one portion. The reaction was stirred at 0 °C for 10h, and diluted with CH_2Cl_2 and H_2O. The organic phase was extracted and the water phase further extracted with CH_2Cl_2 (2x). Combined organic phases were dried over Na_2SO_4, evaporated to dryness and the residue was purified by column chromatography on SiO_2.

(2,3,5-trimethyl-6-(((2*R*,3*R*)-3-methyl-3-((4*R*,8*R*)-4,8,12-trimethyltridecyl)oxiran-2-yl)methyl)-1,4-phenylene)bis(oxy)bis(triisopropylsilane)



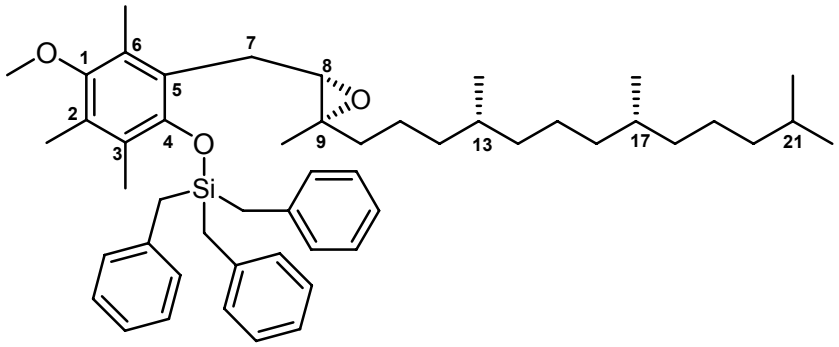
Was obtained in 75% yield and with 82% de by following the general procedure employing ketone catalyst **114**.

(2S,3S)-3-(2-(benzyloxy)-5-methoxy-3,4,6-trimethylbenzyl)-2-methyl-2-((4R,8R)-4,8,12-trimethyltridecyl)oxirane



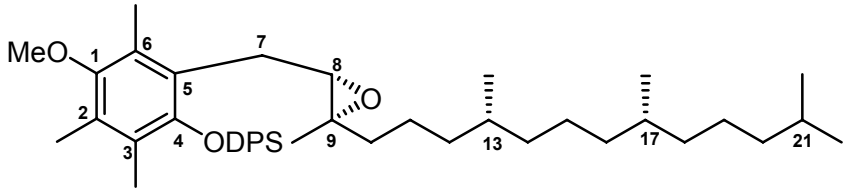
Was obtained in 75% yield and with 82% de by following the general procedure employing ketone catalyst **ent-114**.

tribenzyl(4-methoxy-2,3,5-trimethyl-6-(((2S,3S)-3-methyl-3-((4R,8R)-4,8,12-trimethyltridecyl)oxiran-2-yl)methyl)phenoxy)silane



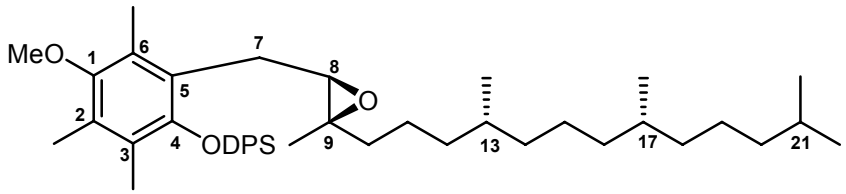
Was obtained in 84% yield and with 89% de by following the general procedure employing ketone catalyst **ent-114**.

tert-butyl(4-methoxy-2,3,5-trimethyl-6-(((2S,3S)-3-methyl-3-((4R,8R)-4,8,12-trimethyltridecyl)oxiran-2-yl)methyl)phenoxy)diphenylsilane (147)



Was obtained in 81% yield and with 97% de by following the general procedure employing ketone catalyst **ent-114**.

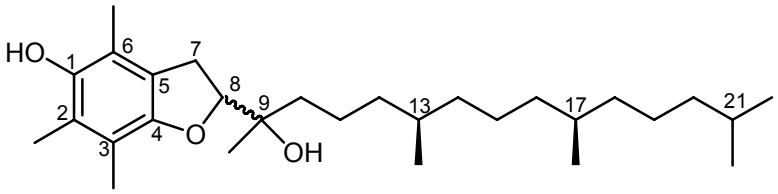
tert-butyl(4-methoxy-2,3,5-trimethyl-6-(((2R,3R)-3-methyl-3-((4R,8R)-4,8,12-trimethyltridecyl)oxiran-2-yl)methyl)phenoxy)diphenylsilane (148)



Was obtained in 80% yield and with 96% de by following the general procedure employing ketone catalyst **114**.

5.2.5 Cyclisation of 149 to furan 150

2-((6R,10R)-2-hydroxy-6,10,14-trimethylpentadecan-2-yl)-4,6,7-trimethyl-2,3-dihydrobenzofuran-5-ol (150)



To a solution of 35 mg epoxide **149** (46 µmol, 1.0 eq.) in 1 mL THF was added at r.t. 100 µL of TBAF (1 M in THF) (100 µmol, 2.2 eq.). The reaction mixture was stirred for 1 h at r.t. The reaction was then quenched with saturated $NaHCO_3$ and the mixture was extracted with ether. The combined organic phases were dried over Na_2SO_4. Chromatography (SiO_2, hexane/EtOAc = 4:1) afforded 18 mg (40 µmol, 87%) of a colourless oil.

TLC (SiO_2, hexane/EtOAc = 4:1): R_f = 0.22.

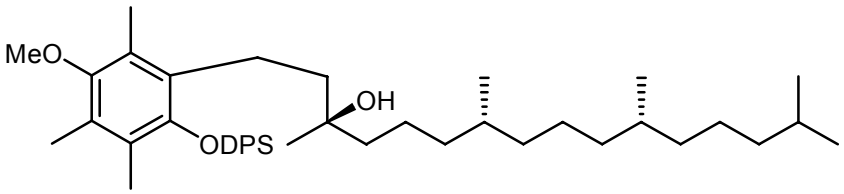
^{1}H-NMR (500 MHz, $CDCl_3$): 0.83-0.88 (m, 12H, $C_{13/17/21}$-C<u>H</u>$_3$), 1.00-1.58 (m, 21H, $H_{10/11/12/13/14/15/16/17/18/19/20/21}$), 1.32 (s, 3H, C_9-C<u>H</u>$_3$), 1.79 (s, 1H, O<u>H</u>) 2.12 (s, 3H, $C_{2/3/6}$-C<u>H</u>$_3$), 2.13 (s, 6H, $C_{2/3/6}$-C<u>H</u>$_3$), 2.99 (dd, J = 9.2, 15.4 Hz, 1H, H_7), 3.12 (dd, J = 9.2, 15.4 Hz, 1H, H_7), 4.15 (s, 1H, O<u>H</u>), 4.55 (t, J = 9.2 Hz, 1H, H_8).

^{13}C-NMR (125 MHz, $CDCl_3$): 12.1, 12.3, 13.0, 19.8, 19.9, 20.9, 22.8, 22.9, 23.5, 24.6, 25.0, 28.1, 30.3, 33.0, 37.4, 37.51, 37.58, 37.61, 37.9, 39.5, 73.7, 88.2, 115.7, 117.3, 121.4, 123.4, 145.8, 151.5.

HPLC (Chiralcel OD-H, heptane/isopropanol = 90:10, 0.5 mL/min, 220 nm): t = 11.3 min (51%), t = 12.1 min (49%).

5.2.6 Synthesis of α-Tocopherol (1) via Epoxide 148

(3R,7R,11R)-1-(2-(tert-butyldiphenylsilyloxy)-5-methoxy-3,4,6-trimethylphenyl)-3,7,11,15-tetramethylhexadecan-3-ol



To 172 mg of epoxide **148** (247 µmol, 1.0 eq.) were added 7.4 mL of Super-Hydride®-Solution (1.0 M in THF, 7.4 mmol, 30 eq.). The mixture was heated at reflux for 4 h. The solution was cooled to 0 °C and 70 mL wet DCM was carefully added followed by 70 mL of H_2O. Two spatulas of solid NH_4Cl were added so that both phases became clear. The phases were separated and the aqueous phase was further extracted with DCM. The combined organic phases were dried over Na_2SO_4. Chromatography (SiO_2, hexane/EtOAc = 10:1) afforded 85 mg (121 µmol, 49%) of a colourless oil.

TLC (SiO_2, hexane/EtOAc = 20:3): R_f = 0.28.

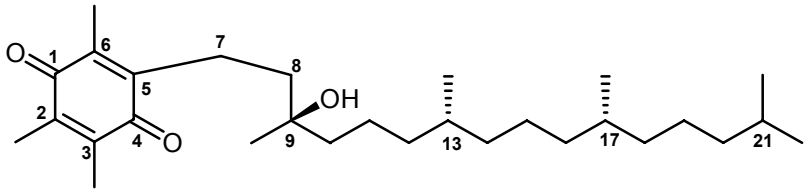
^{1}H-NMR (500 MHz, $CDCl_3$): 0.65 (s, 1H, O<u>H</u>), 0.86-0.93 (m, 12H, $C_{13/17/21}$-C<u>H</u>$_3$), 0.95 (s, 3H, C_9-C<u>H</u>$_3$), 1.05-1.45 (m, 20H, $H_{10/11/12/13/14/15/16/17/18/19/20}$), 1.41-1.44 (m, 2H, H_8), 1.52 (sept, 1H, J=6.6 Hz, H_{21}), 1.89 (s, 3H, C_3-C<u>H</u>$_3$), 2.06 (s, 3H, C_2-C<u>H</u>$_3$), 2.15 (s, 3H, C_6-C<u>H</u>$_3$), 2.49-2.52 (m, 2H, H_7), 3.62 (s, 3H, C<u>H</u>$_3$O), 7.31-7.35 (m, 4H, H_m DPS-), 7.38-7.43 (m, 2H, H_p DPS-), 7.70 (t, 4H, J=6.6 Hz, H_o DPS-);

^{13}C-NMR (125 MHz, $CDCl_3$): 12.4 (C_6-<u>C</u>H$_3$), 13.1 (C_2-<u>C</u>H$_3$), 15.9 (C_3-<u>C</u>H$_3$), 19.86, 19.90, 20.47, 21.48, 22.77, 22.87, 22.91, 24.66, 24.94, 25.74, 27.15, 28.12, 32.96, 37.43, 37.59, 37.77, 39.51, 41.63, 41.66, 43.06, 60.35 (<u>C</u>H$_3$O), 72.72 (C_9), 125.32 (C_3), 126.99 (C_6), 127.68 (C_m, DPS-), 127.75 (C_2), 127.96 (C_5), 129.75 (C_p, DPS-), 134.45 and 134.59 ($C_{Si,diastereotopic}$, DPS-), 135.38 (C_o, DPS), 148.31 (C_4), 151.59 (C_1);

MS (EI): *m/z* (%) = 700.5 ([M^+], 16), 377.2 (100), 359.2 (85), 299.1 (76).

EA: calculated for $C_{46}H_{72}O_3Si$: C 78.80, H 10.35; found: C 78.49, H 10.22.

2-((3R,7R,11R)-3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (159)

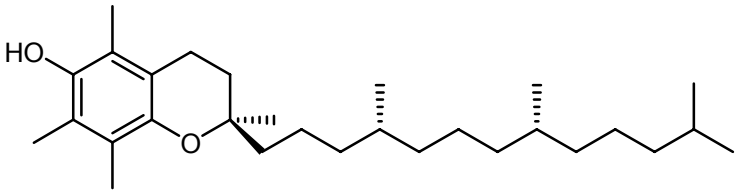


79 mg of protected hydroquinone **158** (113 µmol, 1.0 eq.) was dissolved in 5 ml MeCN. A solution of 139 mg of CAN (252 µmol, 2.2 eq.) in 520 µL H_2O was added dropwise at r.t. The mixture was stirred for 1h at r.t. DCM and H_2O were added and the phases were separated. The aqueous phase was further extracted with DCM. The combined organic phases were dried over Na_2SO_4. Chromatography (SiO_2, hexane/EtOAc = 4:1) afforded 42 mg (94 µmol, 83%) of a yellow oil.

TLC (SiO_2, hexane/EtOAc = 4:1): R_f = 0.28.

^{1}H-NMR (500 MHz, $CDCl_3$): 0.82-0.88 (m, 12H, $C_{13/17/21}$-C<u>H</u>$_3$), 1.0-1.55 (m, 24H, $H_{8/10/11/12/13/14/15/16/17/18/19/20/21/OH}$), 1.23 (s, 3H, C_9-C<u>H</u>$_3$), 2.01 (s, 6H, $C_{3/2}$-C<u>H</u>$_3$), 2.03 (s, 3H, C_6-C<u>H</u>$_3$), 2.50-2.58 (m, 2H, H_7).

(2*R*,4'*R*,8'*R*)-α-Tocopherol (1)



A mixture of 42 mg of quinone **159** (94 µmol, 1.0 eq.), 8 mg Pd/C (10%) and 7 ml MeOH were stirred at r.t. under an atmosphere of hydrogen for 12 h. The catalyst was filtered, and the filtrate was concentrated *in vacuo*. Because of the tendency to air oxidise, the hydroquinone so obtained was immediately dissolved in 4.2 mL benzene and 4.1 mg pTsOH·H_2O (22 µmol, 0.23 eq.) were added. The solution was heated to 80°C for 1.25 h. The mixture was cooled down to r.t. and treated with saturated $NaHCO_3$. The mixture was extracted with ether (3x) and the combined organic phases were dried over Na_2SO_4. Chromatography (SiO_2, hexane/EtOAc = 10 : 1) afforded 37 mg (86 µmol, 92%) of a colourless oil.

TLC (SiO_2, hexane/EtOAc = 20:3): R_f = 0.40.

HPLC (Chiralcel OD-H, 0.5% EtOH in hexane, 1.0 mL/min, 220 nm): $t_{(2R)}$ = 7.6 min (96.5%); $t_{(2S)}$ = 8.8 min (3.5%).

6 Appendix

6.1 List of Abbreviations

µL	microliters
µmol	micromole
AcOH	acetic acid
aq.	aqueous
atm	atmosphere
calc.	calculated
CAN	ceric ammonium nitrate
CTG	cyclodextrin glucosyl transferase
CD	cyclodextrin
d	doublet
DCM	dichloromethane
de	diastereomeric excess
DME	dimethoxyethane
DMF	*N*,*N*'-dimethylformamide
DMP	2,2-dimethoxypropane
DMSO	dimethylsulfoxide
DPS	*tert*-butyldiphenylsilyl
EA	elemental analysis
EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
EI-MS	electron impact mass spectra
Ent	enantiomer
EP	Enzyme Product
ESI-MS	Electron Spray Ionization Mass Spectra
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
eq.	equivalents
ES	Enzyme Substrate
FTIR	Fourier Transform Infrared Spectroscopy

GC	Gas Chromatography
h	hours
HPLC	High Performance Liquid Chromatography
IR	infrared spectrum
J	coupling constant in Hertz.
m	multiplet
*m*CPBA	*meta*-chloroperoxybenzoic acid
MDT	Marine Derived Tocopherol
Me	methyl
MeCN	acetonitrile
MeOH	methanol
min	minutes
mL	milliliters
mmol	millimole
M	molar
MOM	methoxymethyl
mp	melting point
m/z	mass/charge
Ms	methanesulfonoyl
MS	mass spectroscopy
NMO	*N*-methylmorpholine-*N*-oxide
NMR	Nuclear Magnetic Resonance
ox.	oxidation
p	*para*
PCC	Pyridinium Chlorochromate
ppm	parts per million
PPNO	4-phenylpyridine N-oxide
PDC	pyridinium dichromate
q	quartet
r.t.	room temperature
rac	racemic
red.	reduction
R_f	Retention Factor (chromatography)
s	singlet

SiO_2	silica gel
S_N2	bimolecular nucleophilic substitution
SOMO	single-occupied molecular orbital
t	triplet
TBAF	tetra-*N*-butylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
TBME	*tert*-butyl-methyl ether
TBS	*tert*-butyldimethylsilyl
^tBu	*tert*-butyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPSCl	triisopropylsilylchloride
TLC	analytical thin layer chromatography
TMC	transition Metal catalysis
TMEDA	tetramethylethylenediamine
TMS	tetramethylsilane
TPA	tris(2-pyridylmethylamine)
Ts	tosyl/*p*-toluenesulfonyl
α-TTP	α-Tocopherol Transfer Protein
UV	Ultra-Violet

6.2 References

1. H. M. Evans, K. S. Bishop, *Science* **1922**, *56*, 650.
2. B. Sure, *Science* **1924**, *59*, 19.
3. H. M. Evans, O. H. Emerson, G. A. Emerson, *Journal of Biological Chemistry* **1936**, *113*, 319.
4. O. H. Emerson, G. A. Emerson, A. Mohammed, H. M. Evans, *Journal of Biological Chemistry* **1937**, *122*, 99.
5. M. H. Stern, C. D. Robeson, L. Weisler, J. G. Baxter, *J. Am. Chem. Soc.* **1947**, *69*, 869.
6. H. Mayer, P. Schudel, R. Rüegg, O. Isler, *Helv. Chim. Acta* **1963**, *46*, 963.
7. J. F. Pennock, F. W. Hemming, J. D. Kerr, *Biochemical and Biophysical Research Communications* **1964**, *17*, 542.
8. H. Crawley, *The Technology of Vitamins in Food*, Blackie Academic & Professional, Chapman & Hall Inc., Glasgow, **1993**.
9. F. D. Gunstone, J. L. Harwood, F. B. Padley, *The Lipid Handbook*, Second Edition, Chapman & Hall, London, **1994**.
10. G. W. Burton, M. G. Traber, R. V. Acuff, D. N. Walters, H. Kayden, L. Hughes, et al., *Am. J. Clin. Nutr.* **1998**, *67 (4)*, 669.
11. K. Hensley et al., *Free Radic. Biol. Med.* **2004**, *36 (1)*, 1.
12. J. C. Bauernfeind et al., *Int. Z. Vitaminforsch.* **1970**, *40 (3)*, 391.
13. M. G. Traber, H. J. Kayden, *Am. J. Clin. Nutr.* **1984**, *40*, 747.
14. M. G. Traber, H. J. Kayden, *Am. J. Clin. Nutr.* **1989**, *49*, 517.
15. M. H. Ng, Y. M. Choo, A. N. Ma, C. H. Chuah, M. A. Hashim, *Lipids* **2004**, *39 (10)*, 1031.
16. Y. Yamamoto, A. Fujisawa, A. Hara, W.C. Dunlap, *Proc. Natl. Acad. Sci. USA 98* **2001**, *23*, 13144.
17. S. West, et al., *Biochem. Biophys. Res. Commun.* **2004**, *318 (1)*, 311.
18. Y. Negis, J. M. Zingg, E. Ogru, R. Gianello, R. Libinaki, A. Azzi, *IUBMB Life* **2005**, *57 (1)*, 23.
19. B. N. Arnes, *Science* **1983**, *221*, 1256.
20. C. E. Cross et al., *Ann. Intern. Med.* **1987**, *107*, 526.
21. J. A. Howard, *Free Radicals*, Wiley, New York, **1973**, Vol. 2, 3-62.
22. D. C. Liebler et al., *Anal. Biochem.* **1996**, *236*, 27.
23. A. C. Terentis et al., *Circ. Res.* **2002**, *90*, 333.
24. G. W. Burton et al., *J. Am. Chem. Soc.* **1985**, *107*, 7053.
25. J. E. Packer, *Nature* **1979**, *278*, 737.

26. D. D. M. Wayner, *FEBS Lett.* **1985**, *187*, 33.
27. K. U. Ingold, *Chem. Rev.* **1961**, *61*, 563.
28. M. G. Traber, J. Atkinson, *Free Radic. Biol. Med.* **2007**, *43*, 4.
29. S. E. Sattler et al., *Plant Cell.* **2006**, *18*, 3706.
30. A. Hosomi et al., *FEBS Lett.* **1997**, *409*, 105.
31. M. Arita et al., *Biochem. J.* **1995**, *306*, 437.
32. K. Ouahchi et al., *Nat. Genet.* **1995**, *9*, 141.
33. M. G. Traber et al., *J. Clin. Invest.* **1990**, *85*, 397.
34. D. DellaPenna et al., *Annu. Rev. Plant Biol.* **2006**, *57*, 711.
35. C. Panagabko et al., *Biochemistry* **2003**, *42*, 6467.
36. M. G Traber, G. W Burton, R. L. Hamilton, *Ann. N. Y. Acad. Sci.* **2005**, *1031*, 1.
37. J. R. Austin II et al., *Plant. Cell.* **2006**, *18*, 1693.
38. D. Hofius et al., *Plant Physiol.* **2004**, *135*, 1256.
39. J. Soll, *Meth. Enzymol.* **1987**, *184*, 383.
40. Y. Arango, K. Heise, *J. Exp. Bot.* **1998**, *49*, 1259.
41. H. K. Lichtenthaler, *Annu. Rev. Plant. Physiol. Plant. Mol. Biol.* **1999**, *50*, 47.
42. J. Soll, *Meth. Enzymol.* **1987**, *184*, 383.
43. Z. Cheng et al., *Plant Cell* **2003**, *15*, 2343.
44. D. K. Shintani et al., *FEBS Lett.* **2002**, *511*, 1.
45. W. D. Woogon et al., *Bioorg. Med. Chem.* **1996**, *4*, 1129.
46. D. Hofius et al., *Plant Physiol.* **2004**, *135 (3)*, 1256.
47. S. Porfirova et al., *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 12495.
48. J. Soll, G. Schultz, *Phytochemistry*, **1980**, *19*, 215.
49. A. Stocker, A. Ruettimann, W.-D. Woggon, *Helv. Chim. Acta* **1993**, *76*, 1729.
50. W.-D. Woggon et al., *Helv. Chim. Acta* **1994**, *77*, 1721.
51. N. Cohen et al., *J. Org. Chem.* **1981**, *46*, 2445.
52. W.-D. Woggon et al., *Chem. Eur. J.* **2004**, *10*, 2487.
53. M. Christen, A. Chougnet, R. Manetsch, J. Chapelat, B. Christen, U. Jenal, W.-D. Woggon, unpublished results.
54. C. Grütter, E. Alonso, A. Chougnet, W.-D. Woggon, *Angew. Chem. Int. Ed.* **2006**, *45*, 1126.
55. G. Pongracz, H. Weiser, D. Matzinger, *Fat Sci. Technol.* **1995**, *97*, 90.
56. S. Akutagawa, *Appl. Catal. A: General* **1995**, *128*, 171.
57. B. J. Weimann, H. Weiser, *Am. J. Clin. Nutr.* **1991**, *53*, 1056.
58. H. Weiser, M. Vecchi, *Int. J. Vit. Nutr. Res.* **1982**, *52*, 351.
59. T. Netscher, *Vitamines and Hormones* **2007**, *76*, 155.
60. P. Karrer et al., *Helv. Chim. Acta* **1938**, *21*, 820.

61. P. Karrer, O. Isler, US 2,411,968, **1946**.
62. L. Weisler, US 2 486 539, **1949**.
63. W. S. Baldwin, S. M. Willging, B. M. Siegel, US 4 977 282, **1990**.
64. P. Lechtken, U. Hoercher, B. Jessel, BASF, EP 338 429, **1989**.
65. R. K. Müller, H. Schneider, EP 0 735 033, **1996**.
66. R. K. Müller, F. Hoffmann-La Roche AG, EP 0735033, **1999**.
67. H. Mayer, P. Schudel, R. Rüegg, O. Isler, *Helv. Chim. Acta* **1963**, *46*, 650.
68. J. C. Duff, E. J. Bills, *J. Chem. Soc.* **1945**, 276.
69. L. N. Ferguson, *Chem. Rev.* **1946**, *38*, 227.
70. K. Liu, A. Chougnet, W.-D. Woggon, *Angew. Chem. Int. Ed.* **2008**, *47*, 5827.
71. H. H. Hussain et al., *J. Org. Chem.* **2003**, *68*, 7023.
72. D. H. R. Barton, D. Crich, W. B. Motherwell, *Tetrahedron* **1985**, *41*, 3901.
73. J. L. Atwood, J. E. D. Davies, D. D. MacNicol, F. Vögtle, J. -M. Lehn, Eds., Comprehensive Supramolecular Chemistry 1996, Pergamon.
74. A. Villars, *Compt. Rend.* **1891**, *112*, 536.
75. F. Z. Schardinger, *Unters. Nahr. u. Genussm.* **1903**, *6*, 865
76. J. Szejtli, *Cyclodextrins and their Inclusion Complexes*, **1982**, Wiley.
77. J. L. Atwood, J. E. D. Davies, D. D. MacNicol and F. Vögtle, *Comprehensive Supramolecular Chemistry Eds.* **1996**, Pergamon, Oxford.
78. J.-M. Lehn, *Supramolecular Chemistry*, **1995**, VCH, Weinheim.
79. E. Sabadini, T. Cosgrovea F. do Carmo Egídio, *Carbohydr. Res.* **2006**, *341*, 270.
80. J. Szejtli, *Chem. Rev.* **1998**, *98*, 1743.
81. K. Harata, *Chem. Rev.* **1998**, *98*, 1803.
82. K. Takahashi, *Chem. Rev.* **1998**, *98*, 2013.
83. R. Breslow, G. Trainor, A. Ueno, *J. Am. Soc.* **1983**, *105*, 2739.
84. R. Breslow et al., *J. Am. Chem. Soc.* **1996**, *118*, 11678.
85. E. N. Jacobsen et al., *J. Am. Chem. Soc.* **1991**, *113*, 7063.
86. R. Breslow, X. Zhang, Y. Huang, *J. Am. Chem. Soc.* **1997**, *119*, 4535.
87. R. Breslow et al., *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 11156.
88. R. Breslow, *J. Org. Chem.* **2002**, *67*, 5057.
89. H. Wang, Ph. D. Thesis, *Ruthenium Porphyrin-β-Cyclodextrin Complexes as Supramolecular Enzyme Models for Regioselective Cleavage of Carotenoids*, University of Basel (CH), **2006**.
90. R. R. French, P. Holzer, M. Leuenberger, M. C. Nold, W. -D. Woggon, *J. Inorg. Biochem*. **2002**, *88*, 295.
91. R. R. French, P. Holzer, M. G. Leuenberger, W. -D. Woggon, *Angew. Chem. Int. Ed.* **2000**, *39*, 1267.

92. R. R. French, J. Wirz, W.-D. Woggon, *Helv. Chim. Acta* **1998**, *81*, 1521.
93. W.-D. Woggon, *Acc. Chem. Res.* **2005**, *38*, 127.
94. P. Holzer, Ph. D. Thesis, *Ruthenium-porphyrin-bis-cyclodextrin-komplexe als supramolekulare enzym-modelle zur regioselektiven spaltung von carotinoiden*, University of Basel (CH) **2002**.
95. W. -D. Woggon, *Chimia* **2000**, *54*, 564.
96. W. -D. Woggon, M. K. Kundu, *Oxidative Stress and Disease* **2004**, 13(Carotenoids in Health and Disease), 357-371.
97. L. Que Jr. et al., *Chem. Commun.* **2002**, 1288.
98. L. Que Jr. et al., *J. Am. Chem. Soc.* **2002**, *124*, 3026.
99. K. Chen, L. Que Jr., *J. Am. Chem. Soc.* **2001**, *123*, 6327.
100. L. Que Jr. et al., *Inorg. Chem.* **2001**, *40*, 3534.
101. L. Que Jr. et al., *J. Am. Chem. Soc.* **1997**, *119*, 10594.
102. L. Que Jr. et al., *J. Am. Chem. Soc.* **2001**, *123*, 6722.
103. L. Que Jr. et al., *Current Opinion in Chemical Biology* **2003**, *7*, 674.
104. M. Costas, K. Chen, L. Que Jr., *Coord. Chem. Rev.* 2000, *200-202*, 517.
105. R. H. Holm, *Chem. Rev.* **1987**, *87*, 314.
106. J. M. Mayer, *Acc. Chem. Res.* **1992**, *25*, 441.
107. T. J. Collins, S. W. Gordon-Wylie, *J. Am. Chem. Soc.* **1989**, *111*, 4511.
108. E. N. Jacobsen et al., *J. Am. Chem. Soc.*, **1991**, *113*, 7063.
109. T. Frejd et al., *J. Org. Chem.* **2002**, *67*, 6376.
110. A. Schlatter, *Asymmetric Transfer Hydrogenation to Aromatic and Aliphatic Ketones Catalyzed by Ruthenium Complexes Linked to both Faces of β-Cyclodextrin*, PhD thesis, University of Basel, **2007**.
111. T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974.
112. E. N. Jacobsen et al., *J. Am. Chem. Soc.* **1990**, *112*, 2801.
113. E. N. Jacobsen et al., *J. Am. Chem. Soc.* **1991**, *113*, 7063.
114. R. G. Konsler, J. Karl, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 10780.
115. L. Sun et al., *Journal of Catalysis* **2006**, *237*, 248.
116. A. M. d'. A. R. Gonsalves et al., *J. Mol. Cat. A : Chemical* **2003**, *195*, 1.
117. U. Nagel et al., *Chem. Ber.* **1986**, *119*, 3326.
118. R. G. Konsler, J. Karl, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 10780.
119. E. N. Jacobsen et al., *J. Am. Chem. Soc.* **1994**, *116*, 9333.
120. M. Palucki, G. J. McGormick, E. N. Jacobsen, *Tetrahedron Lett.* **1995**, *36*, 5457.
121. W. Adam, R. Curci, J. O. Edwards, *Acc. Chem. Res.* **1989**, *22*, 205.
122. R. W. Murray, *Chem. Rev.* **1989**, *89*, 1187.
123. R. Curci, A. Dinoi, M. F. Rubino, *Pure Appl. Chem.* **1995**, *67*, 811.

124. W.-K. Chan, W.-Y. Yu, C.-M. Che, M.-K. Wong, *J. Org. Chem.* **2003**, *68*, 6576.
125. B. M. Trost, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259.
126. M. Frohn, Y. Shi, *Synthesis* **2000**, *14*, 1979.
127. A. L. Baumstark, C. J. McCloskey, *Tetrahedron Lett.* **1987**, *28*, 3311.
128. C. Jenson et al., *J. Am. Chem. Soc.* **1997**, *119*, 12982.
129. Y. Shi, *Acc. Chem. Res.* **2004**, *37*, 488.
130. R. Curci, M. Fiorentino, M. R. Serio, *J. Chem. Soc., Chem Commun.* **1984**, 155.
131. L. Shu, Y. Shi, *Tetrahedron Lett.* **1999**, *40*, 8721.
132. L. Shu, Y. Shi, *Tetrahedron* **2001**, *57*, 5213.
133. Y. Shi et al., *J. Am. Chem. Soc.* **1997**, *119*, 11224.
134. K. Maruyama, N. Nagai, Y. Naruta, *J. Org. Chem.* **1986**, *51*, 5083.
135. F. Ito, K. Fusegi, T.Kumamoto, T. Ishikawa, *Synthesis* **2007**, *12*, 1785.
136. A. Stern, J. S. Swenton, *J. Org. Chem.* **1987**, *52*, 2763.
137. M.-X. Zhao, Y. Shi, *J. Org. Chem.* **2006**, *71*, 5377.
138. J. Chapelat, A. Buss, A. Chougnet, W.-D. Woggon, *Org. Lett.* **2008**, *10*, 5123.
139. J. Baldwin, *J. Chem. Soc. Chem. Commun.* **1976**, *18*, 734.
140. K. C. Nicolaou et al., *J. Am. Chem. Soc.* **1989**, *111*, 5330.
141. E. N. Jacobsen et al., *Sience* **1997**, *277*, 936.
142. K. D. Janda, C. G. Shevlin, R. A. Lerner, *Sience* **1993**, *259*, 490.
143. I. Vilotijevic, T. F. Jamison, Sience **2007**, *317*, 1189.
144. E. S. Barrett, T. J. Dale, J. Rebek Jr., *J. Am. Chem. Soc.* **2007**, *129*, 3818.
145. N. Cohen, R. J. Lopresti, C. Neukom, *J. Org. Chem.* **1981**, *46*, 2445.
146. J. Hübscher, R. Barner, *Helv. Chim. Acta* **1990**, *73*,1068.
147. K. Hegetschweiler et al., *Eur. J. Inorg. Chem.* **2001**, 2525.

6.3 Curriculum Vitae

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6.4 Publications and Presentations

1 J. Chapelat, A. Buss, A. Chougnet, W.-D. Woggon, “Diastereoselective Synthesis of α-Tocopherol: A New Concept for the Formation of Chromanols”, *Org. Lett.* **2008**, *10*, 5123.

2 A. Buss, W.-D. Woggon, “Enzyme Mimics of mononuclear Iron Oxygenases”, Freiburg-Basel International Research Training Group, May **2006** (talk).

3 A. Buss, W.-D.Woggon, “Oxidations Catalysed by a Manganese Complex containing a Pentadentate Nitrogen Ligand Attached to β–Cyclodextrin“, Herbstversammlung der Schweizerischen Chemischen Gesellschaft, October **2005** (poster and talk).

4 A. Buss, W.-D.Woggon, “Oxidations Catalysed by a Manganese Complex containing a Pentadentate Nitrogen Ligand Attached to β–Cyclodextrin”, 25. Regiosymposiums über Organische und Bioorganische Chemie, Sornetan, September 2005 (poster).

6.5 Eidesstattliche Erklärung

Ich erkläre, dass ich die Dissertation “Diastereoselective Synthesis of α-Tocopherol” nur mit der darin angegebenen Hilfe verfasst und bei keiner anderen Universität und keiner anderen Fakultät der Universität Basel eingereicht habe.

Basel, den 26.10.2008

Axel Buss