UNIVERSITY OF SOUTHAMPTON

FACULTY OF ENGINEERING, SCIENCE AND MATHEMATICS

SCHOOL OF CHEMISTRY

A New Cyclohexyl-based Chiral Auxiliary: Application In The Total Synthesis of (+)-Linalool Oxide

Ali Mohsen Al Hazmi

A Thesis Submitted for the Degree of Doctor of Philosophy

May 2010

Declaration

This thesis was submitted for the examination in May 2010. The research described in this thesis was carried out by myself at the School of Chemistry, University of Southampton between June 2006 and September 2009, unless otherwise acknowledged. No part of this thesis has been submitted in any previous application for a higher degree.

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ABSTRACT

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by

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Seven different racemic cyclohexyl-based chiral auxiliaries (**2.4-2.10**) were synthesised in moderate to good yields (38-85%) by nucleophilic opening of cyclohexene oxide using carbanions. The racemic cyclohexyl-based chiral auxiliaries were coupled with the 6-methyl-2-methylenehept-5-enoyl chloride (**2.20**) to form the dienes esters **2.38-2.44**. The chiral auxiliary-diene ester adducts **2.38-2.44** were subjected to a comparative study in the permanganate mediated oxidative cyclisation. The best result was obtained by using (±)-*trans*-2-trityl-1-cyclohexanol ((±)-**2.10** (±)-TTC)), resulting in high diastereoselectivity (dr = 97:3) in the resulting THF diols **2.51a/b**. The other auxiliaries synthesised gave only moderate to no diastereoinduction.

Different methods were used to resolve the racemic auxiliary (±)-TTC including enzymatic resolution and classical resolution. A successful classical resolution was achieved and the enantiomer (–)-TTC was obtained in excellent yield and enantiopurity (99 % ee). The stereochemistry of the obtained enantiomer was defined as (1*S*,2*R*) from the X-ray structure of its Mosher ester derivative **2.76**.

(–)-TTC was used in the total synthesis of (+)-linalool oxide (**1.247**) which was achieved in 9 steps and 13% overall yield. Finally, nucleophilic additions to α-keto esters containing (±)-TTC were investigated and the preliminary results are described.

CONTENTS

Acknowledgements

I would like to thank God for giving me this work and giving me the ability to do it. I'd also like to thank God for giving us a beautiful and amazing universe for us to explore and the ability to apply the discoveries we make toward improving our life.

I would like to thank my supervisor, Dr. Richard Brown, for welcoming me into his research group and fostering his love and enthusiasm for organic chemistry into me. Under his supervision, I have been able to take a general project outline and truly make it my own. I am grateful to him for helping me during the writing up time. Special thanks to my advisor, Prof. David Harrowven, for his timely and constructive feedback on my quarterly reports.

Great thanks to the Saudi Cultural Bureau in London and Al-Qunfudah university college in Saudi Arabia for the financial support and the scholarship to study for the PhD degree.

I'd also like to thank the old and new members of the Brown group specially Dr. Lynda Brown for her help in the HPLC and GC analyses. Also, I thank the project student, Mathew Roberts who worked under my supervision and provided us with the X-ray structure for the racemic auxiliary (±)-TTC. Special thanks to Nadeem Sheikh and Sherif Abdel Gani who I enjoyed their great friendship and discussions.

Many thanks to my close friends in Southampton, Mohammed Al Shadoki, Mohammed Al Dosari, Faisal Al Odail and Mohammed Geesi for their support and help.

Last not least, great thanks to my parents, my brother, my sisters, my wife and my children for their prayers and encouragement.

Abbreviations

Ac	acety1
AIBN	2,2’-azobisisobutyronitrile
aq.	aqueous
Ar	aromatic
br	broad (NMR) or (IR)
cat.	catalytic
CI	chemical ionisation
CSA	camphorsulfonic acid
d	doublet (NMR)
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	di-*iso*-butylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMPU	*N,N’*-dimethyl-*N,N’*-propylene urea
DMSO	dimethylsulfoxide
d.r.	diastereoisomeric ratio
ee	enantiomeric excess
EI	electron impact ionisation
equiv.	equivalent(s)
er	enantiomeric excess
ES	electrospray
Et	ethyl
FT	Fourier transform
GC	gas chromatography
h	hour(s)
HF	hydrofluoric acid

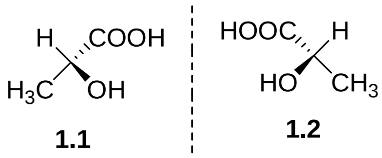
HMDS	potassium hexamethyldisilazide
HMPA	hexamethylphosphoric triamide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
imid	imidazole
Pr	*iso*-propyl
IR	infrared
J	coupling constant (NMR)
LDA	lithium diisopropylamide
LRMS	low resolution mass spectrometry
m	multiplet (NMR) or medium (IR)
m/z	mass to charge ratio
m-CPBA	3-chloroperoxybenzoic acid
MeCN	acetonitrile
MEM	methoxyethoxymethyl
min	minute(s)
mmol	millimole(s)
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	mass spectrometry
NBSH	nitrobenzesulfonylhydrazide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PFP	pentaflourophenyl
Ph	phenyl
PMBM	*p*-methoxybenzylmethoxy
PMP	*p*-methoxyphenyl
ppm	parts per million

ppt.	precipitate(s)
psi	pound per square inch
PTC	phase-transfer catalyst
p-TSA	*p*-toluenesulfonic acid
py	pyridine
q	quartet (NMR)
quin	quintet (NMR)
RCM	ring closing metathesis
RRCM	relay ring closing metathesis
rt	room temperature
s	singlet (NMR) or strong (IR)
sol.	solution
t	tertiary
t	triplet (NMR)
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBAPI	tetrabutylammonium periodate
TBDMS	*t*-butyldimethylsilyl
TBDPS	*t*-butyldiphenylsilyl
TEMPO	2,2,6,6-Tetramethylpiperidinyloxy
TFA	triflouroacetic acid
TFAA	triflouroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*- tetramethylethylenediamine
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammonium perruthenate
Ts	*p*-toluenesulfonyl (tosyl)
TTMSS	*tris*-trimethylsilylsilane
UV	ultraviolet

W	watt
w	weak (IR)

Chapter 1: Introduction

Chirality is a fundamental property of three dimentional structures that can found in both microscopic and macroscopic environments. It has a dramatic impact on the world around us and plays a key role in biological systems, technology and almost every aspect of science.[1] A molecule is chiral if it cannot be superimposed upon its mirror image, as in lactic acid. The two mirror images of lactic acid are refered to as enantiomers, and have identical chemical and physical properties but different optical rotations when in an achiral environment (**Figure 1.1**).[2, 3]



1.1 **1.2**

Figure 1.1. The two enantiomeric forms of lactic acid.

Although enantiomers have the same chemical and physical properties when in an achiral environment, under the influence of an external source of chirality their chemical and physical properties are not the same. These differences become important, especially when considering the biological properties of potential pharmaceuticals. Since biological systems are chiral, different enantiomers of chiral drugs often have different biological effects.[3] For example, consider a drug whose activity is the result of an interaction with a specific receptor in the human body. If the receptor is chiral, one enantiomer of the drug will interact correctly with it, while the other may have a mismatched arrangement of atoms (**Figure 1.2**).[4]

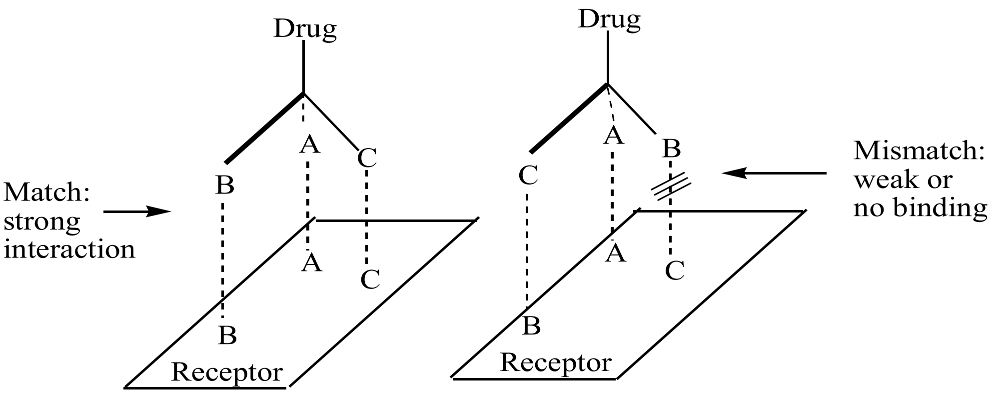
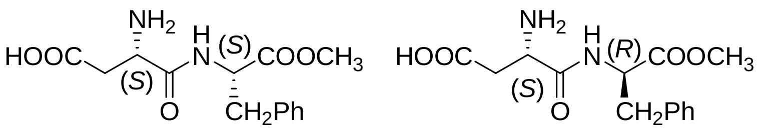


Figure 1.2. Cartoon representation of enantiomeric drugs interacting with a chiral receptor.

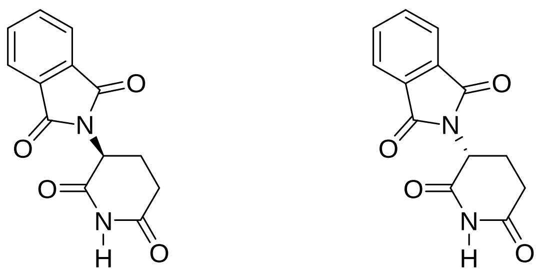
Since the discovery of chirality in the last century, [5, 6] much effort has been made by chemists to develop methods to obtain enantioenriched substances. The importance of obtaining compounds as single enantiomers is underscored by the fact that nearly all natural products contain chiral centres and their physiological or pharmacological properties depend upon their recognition by chiral receptors and/or enzymes. Receptors will typically interact only with molecules of the proper absolute configuration (as discussed above). For example, aspartame (**1.3**) contains two proteinogenetic α-aminoacids which belong to the L-series. This dipeptide is a potent sweetener that has the (*S,S*) configuration, while the (*S,R*) diastereoisomer **1.4** has a bitter taste (**Figure 1.3**). Thus, taste receptors in the mouth are able to differentiate the two diastereoisomers.



Aspartame (**1.3**) **1.4**

Figure 1.3. Structure of aspartame and its diastereoisomer.

The important relationship of pharmacological activity and the absolute chirality was underlined in the 1960s following the tragedy that occurred after racemic thalidomide was administrated to pregnant women. The (*R*)-enantiomer of thalidomide does exhibit the desired analgetic properties; however the (*S*)-enantiomer does not. Furthermore, the (*S*)-enantiomer was teratogenic leading to birth defects in the unborn foetus (**Figure 1.4**).[7]



1.5 **1.6**

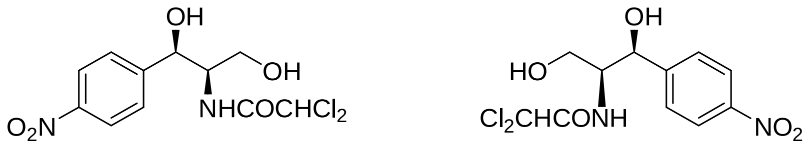
(*S*)-thalidomide
teratogenetic

(*R*)-thalidomide
analgetic

Figure 1.4. Enantiomers of thalidomide.

The marketing regulations for synthetic drugs have become more stringent since the thalidomide tragedy. These days the activity of each enantiomer must be carefully evaluated before a racemic drug can come to the market. Commercialisation of the racemate is only authorized if both enantiomers have similar potencies or that the non potent enantiomer is devoid of any side effects. As a result the marketing of drugs as single enantiomers is becoming more and more popular.[8] The reasons for producing drug substances in optically pure form include the following:[9]

- Bioactivity may be associated with only one enantiomer or diastereoisomer. For example, the (*R*,*R*)-enantiomer of chloramphenicol is antibacterial whereas (*S*,*S*)-enantiomer is inactive (**Figure 1.5**).[10]



(*R*,*R*)-Chloramphenicol (**1.7**)
(*R*,*R*) antibacterial

(*S*,*S*)-Chloramphenicol (**1.8**)
(*S*,*S*) inactive

Figure 1.5. Stereoisomers of chloramphenicol.

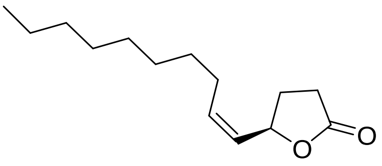
- In some cases enantiomers may display very different types of activity, both of which may be the desired activity or one may be beneficial and the other undesirable (as observed for thalidomide). The enantiomers of ethambutol, the (*S*,*S*) enantiomer is tuberculostatic whereas the (*R*,*R*) enantiomer causes blindness (**Figure 1.6**).[10] Production of only one enantiomer allows separation of the effects.

(*S*,*S*)-Ethambutol (**1.9**)
(*S*,*S*) tuberculostatic

(*R*,*R*)-Ethambutol (**1.10**)
(*R*,*R*) causes blindness

Figure 1.6. Enantiomers of ethambutol.

- The optically pure compound may be more than twice as active as the racemate because of antagonism. An example of this is the pheromone of the Japanese beetle **1.11**, where as little as 1% of the (*S*,*Z*)-isomer inhibits the (*R*,*Z*)-isomer.[11]



(*R*,*Z*) **1.11**

Figure 1.7. (*R*,Z)-Isomer of the Japenese beetle pheromone.

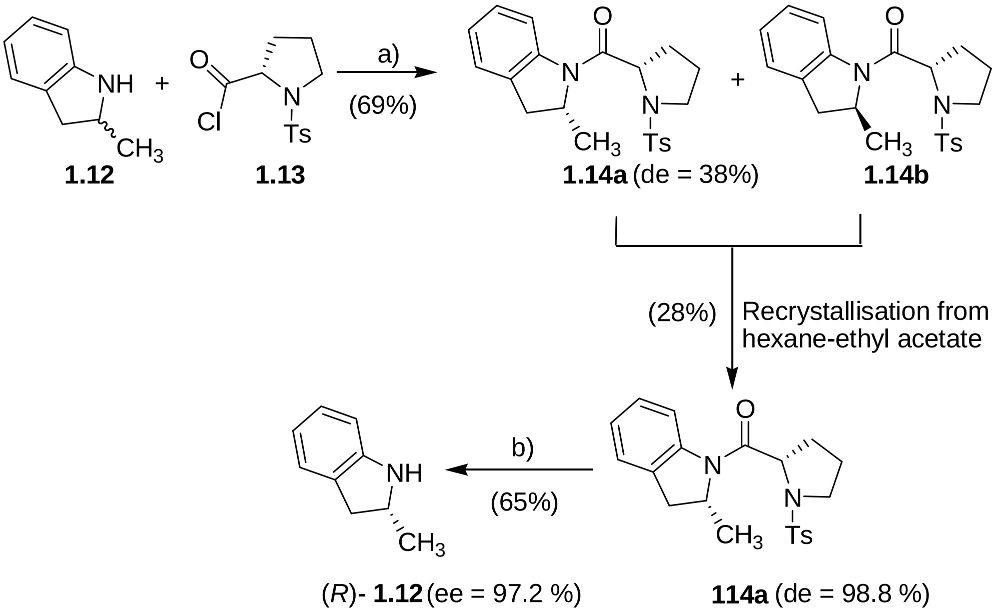
- In some countries, production of materials as the required enantiomer is now a question of law and the unwanted enantiomer is considered as an impurity.
- Cost-efficiency may be improved: There is the opportunity to effectively double the capacity of an industrial process by producing the drug as a single enantiomer. Where the optically active component of the synthesis is not the most costly, it may allow significant savings to be made in some other achiral but very expensive process intermediate.
- Less obvious benefits are that the physical characteristics of single enantiomers versus racemates may confer processing or formulation advantages.[9]

The desire to have drugs as single enantiomers has led chemists to explore different strategies to obtain optically pure substances. This has to a large extent driven advances in methods to obtain compounds as single enantiomers. A summary of the main techniques for obtaining chiral molecules in enantioenriched form are discussed below.

A- Resolution

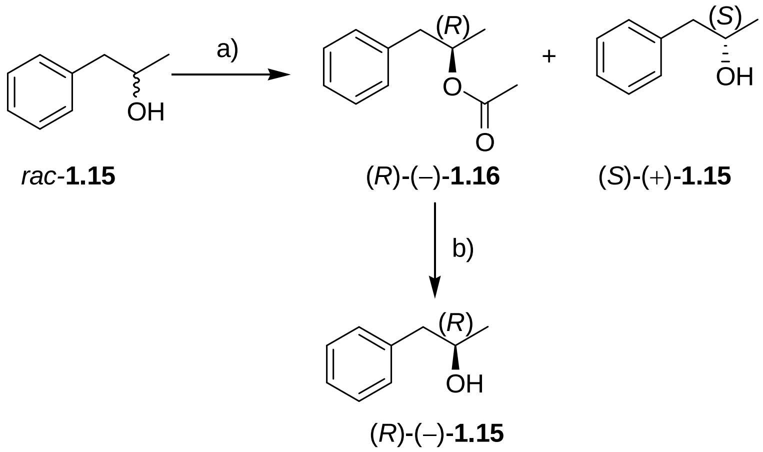
Resolution of racemic material can be achieved in a variety of different ways. Classically, crystallisation has been used widely. This may be achieved by spontaneous resolution (the way Pasteur resolved a tartaric acid salt) or with aid of an enantiopure reagent.[8] In classical resolution, two diastereoisomers are formed, which posses different properties. Therefore, they can be separated by conventional methods such as chromatography or fractional crystallisation. The desired enantiomer is then obtained from one of the purified diastereoisomers, while the other one can be recycled or discarded. These classical methods are frequently applied on a large scale, particulary crystallisation.

Krasnov *et al.* reported the resolution of 2-methylindoline **1.12** using the resolving agent *N*-tosyl-(*S*)-prolyl chloride (**1.13**) (**Scheme 1.1**). Reaction of the racemic amine **1.12** with the resolving agent **1.13** in a molar ratio of 2:1 afforded the (*R*,*S*)-diastereoisomer **1.14a** in 38% de. Repeated recrystallisation of the diastereoisomeric mixture **1.14a** and **1.14b** gave the (*R*,*S*)-diastereoisomer **1.14a** in de = 98.8 %. (*R*,*S*)-Diastereoisomer **1.14a** was hydrolysed to give the (*R*)-enantiomer **1.12** in 97.2 ee.[12]



Scheme 1.1. Classical resolution of racemic 2-methylindoline. **Reagents & conditions:** a) triethyl amine, benzene, rt; b) CH_3COOH, HCl, reflux.

Methods based on kinetic resolution are also frequently used. For example, enzymes can recognize and transform a single enantiomer of a racemate, leaving the other one unchanged. For example, Fogassy *et al.* reported the kinetic resolution of 1-phenyl-2-propanol by using different enzymes (**Scheme 1.2 & Table 1.1**).[13]



Scheme 1.2. Enzymatic kinetic resolution of racemic 1-phenyl-2-propanol. **Reagents & conditions:** a) enzyme (**Table 1.1**), vinyl acetate, rt; b) NaOH, H_2O, CH_3OH.

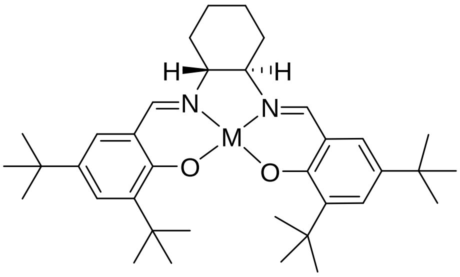
Table 1.1. Enzymatic acetylation of racemic 1-phenyl-2-propanol with six commercially available enzymes.

Enzymes	Time (h)	(*R*)-Alcohol obtained from hydrolysis of resolved acetate (*R*)-(–)-**1.15**		(*S*)-Alcohol recovered from resolution (*S*)-(+)-**1.15**	
		Yield (%)[a]	ee (%)	Yield (%)[a]	ee (%)
Lipase Amano AK	68	85	97	104	81
Lipase Amano PS	191	92	82	97	77
Lipase Amano PS-C	48	97	93	92	> 99
Lipase PfL	68	81	> 99	108	44
Lipase Novozym 435	3	79	> 99	110	85
Lipase CrL	191	46	64	142	19

a: yield reported based on theortical maximium yield of a single enantiomer from the racemate.

The ester (*R*)-(−)-**1.16** was hydrolyzed to afford the enantiomerically enriched alcohol (*R*)-(−)-**1.15** in high ee when lipase Amano AK, lipase PfL and lipase Novozym 435 were used for the esterfication. The enantiomeric excess of the remaing alcohol (*S*)-(+)-**1.15** was >99 % by using lipase Amano PS-C.[13]

A chiral enantiopure reagent can also be used for a kinetic resolution provided that the rates of reaction with each enantiomer of racemate are considerably different. This type of kinetic resolution can be carried out using catalysts. Jacobsen *et al.* reported a hydrolytic kinetic resolution of terminal epoxides using the catalyst **1.17** (**Figure 1.8 & Table 1.2**).[14]

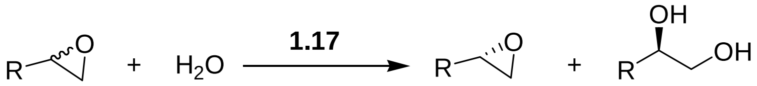


M = $Co(O_2CCH_3)(H_2O)$

1.17

Figure 1.8. Structure of Jacobsen catalyst.

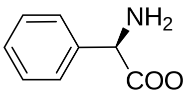
Table 1.2. Hydrolytic kinetic resolution of terminal epoxide using catalyst **1.17**



Entry	R	Concentration		Time (h)	Epoxide		Diol	
		1.17 (mol %)	H_2O (equiv.)		ee (%)	Yield (%)	ee (%)	Yield (%)
1	CH_3	0.2	0.55	12	> 98	44	98	50
2	CH_2Cl	0.3	0.55	8	98	44	86	38
3	$(CH_2)_3CH_3$	0.42	0.55	5	98	46	98	48
4	$(CH_2)_5CH_3$	0.42	0.55	6	99	45	97	47
5	Ph	0.8	0.70	44	98	38	98	39

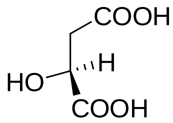
It can be concluded from the high ee values for the epoxide and diol products that the hydrolytic kinetic resolution of terminal epoxides using catalyst **1.17** is one of the most efficient methods for the kinetic resolution of epoxides.

B- Chiral pool: Chiral pool refers to inexpensive single enantiomer chiral substrates, mainly of natural origin, which may undergo highly stereoselective transformations leading to the desired enantiomeric target. Many types of compounds are commonly used as chiral pool starting materials, including amino acids, hydroxy acids, carbohydrates, terpenes and alkaloids (**Figure 1.9**).



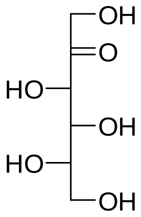
1.18

D-Phenylglycine (Amino acid)



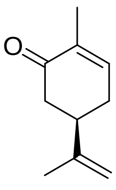
1.19

(*S*)-(-)-Malic acid(Hydroxy acid)



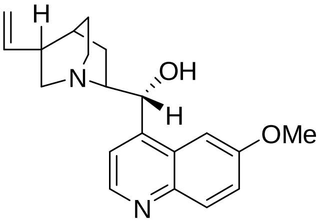
1.20

L-Sorbase (Carbohydrate)



1.21

(–)-Carvone (Terpene)

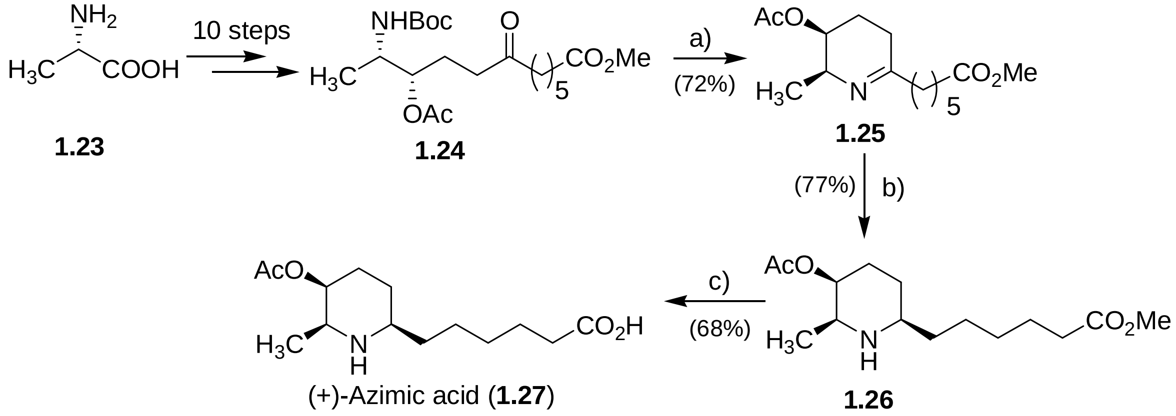


1.22

Quinine (Alkaloid)

Figure 1.9. Some examples of starting materials from the chiral pool.

Kumar *et al.* reported a stereoselective synthesis of (+)-azimic acid starting from L-alanine **1.23** as a chiral pool starting material (**Scheme 1.3**).[15]



Scheme 1.3. Synthesis of (+)-azimic acid. **Reagents & conditions:** a) HCO_2H, CH_2Cl_2; b) Pd-C, H_2; c) $N_2H_4.H_2O$, MeOH.

C- Asymmetric synthesis: Asymmetric synthesis involves the conversion of prochiral precursors into chiral products. This topic will be discussed in greater detail in the following section.[8]

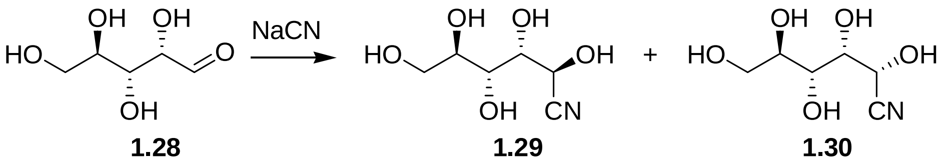
1.1-Strategies for achieving asymmetric synthesis.

Demand for enantiomerically pure compounds has led to the development of many methods and strategies for asymmetric synthesis. There are a number of stoichiometric strategies that can be utilised to generate new asymmetric centres in molecules and these can be divided into three main groups: (1) substrate based control, (2) auxiliary based control, and (3) reagent based control.[16]

1.1.1-Substrate based control

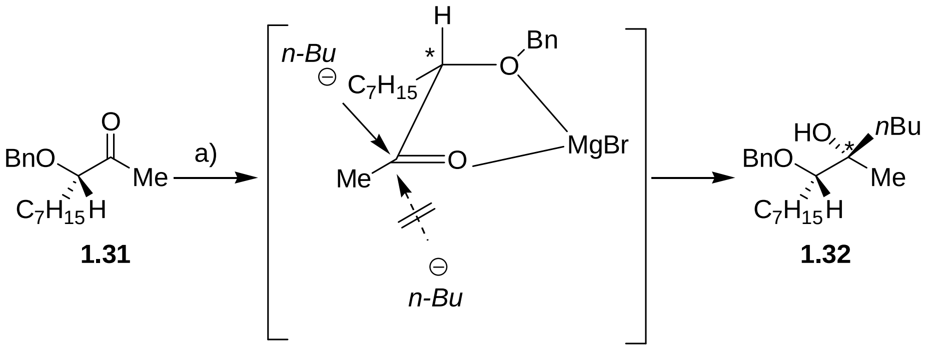
This approach involves the transformation of a substrate (S) containing a stereogenic centre (A) where the reaction of a prochiral group is influenced by the pre-existing stereogenic centre. The chiral group is close enough so that a subsequent reaction with an achiral reagent (R) is effectively controlled by (A) which induces asymmetry in the substrate portion (S) of the molecule to provide the product (P) with the new stereogenic centre(s) present. One of the earliest examples of substrate controlled diastereoselective nucleophilic addition to a carbonyl group was reported by Fischer at the end of the 19th century (**Scheme 1.4**).[17] He observed that when hydrogen cyanide added to D-arabinose (**1.28**) to form D-guconitrile, the diastereoselectivity was 66:34 (**1.29**:**1.30**).

$$\boxed{\text{S-}\mathbf{A} \xrightarrow{\text{R}} \text{P-}\mathbf{A}}$$



Scheme 1.4. Diastereoselective addition of HCN to D-arabinose reported by Fisher 1894.

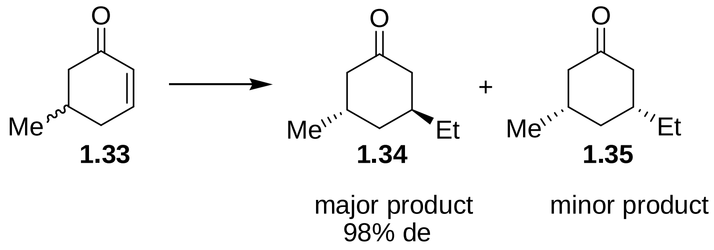
Another example is the substrate controlled addition of reagents to ketones containing chiral centers α to the carbonyl group (**Scheme 1.5**).



Scheme 1.5. Substrate control strategy. **Reagents & conditions:** *n-Bu*MgBr, THF, – 78 °C.

In the example shown in **Scheme 1.5** the chiral ketone **1.31** is converted into the alcohol **1.32** by nucleophilic addition of the Grignard reagent to a carbonyl group. In this reaction, the stereogenic centre marked is introduced with good control (de > 98%) under chelation control.[16, 18, 19]

Another example of substrate based control is the addition of $(CH_3CH_2)_2Zn$ to a 5-substituted 2-cyclohexenone (**Scheme 1.6**).[20] In this system the *trans* product is favoured over the *cis* because of steric interactions between the reacting nucleophile, $(CH_3CH_2)_2Zn$ and the methyl substituent of 2-cyclohexenone in the transition state.



Scheme 1.6. Addition of $(CH_3CH_2)_2Zn$ to a 5-methyl-2-cyclohexenone.

1.1.2-Auxiliary based control

Chiral auxiliary control is achieved by using a group (chiral auxiliary: **Aux**) as a temporary chiral influence by attaching it to the substrate (S), usually by a C-O or C-N covalent bond which can later be cleaved.[8] When the substrate–auxiliary (S-**Aux**) molecule is treated with an achiral reagent, an asymmetric reaction occurs, to give the product (P) which now contains asymmetry and is still attached to the auxiliary. The chiral auxiliary (**Aux**) is then removed in a subsequent step to give the desired product and the auxiliary, which can be recycled. A well known example is the asymmetric alkylation of carboxylic acid derivatives using Evans oxazolidinone auxiliaries (**Scheme 1.7**).

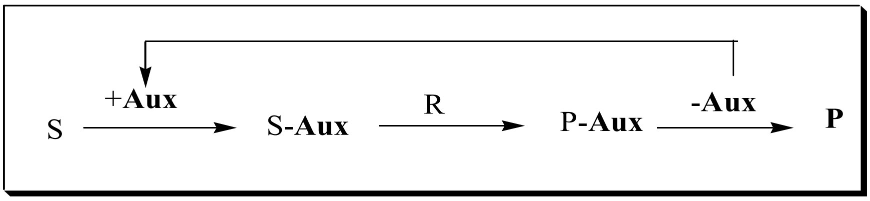
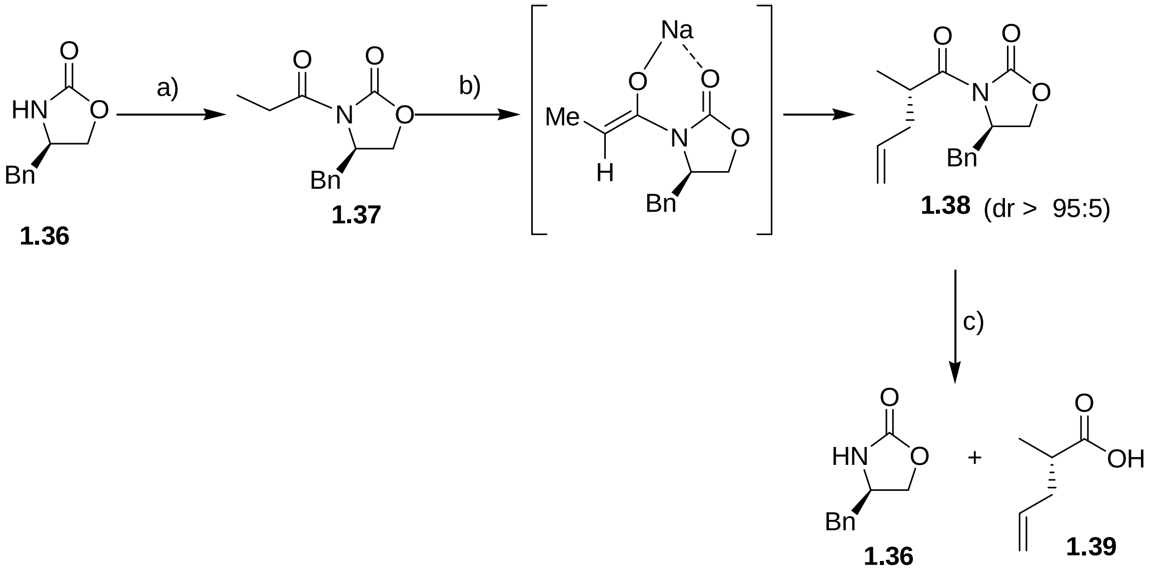


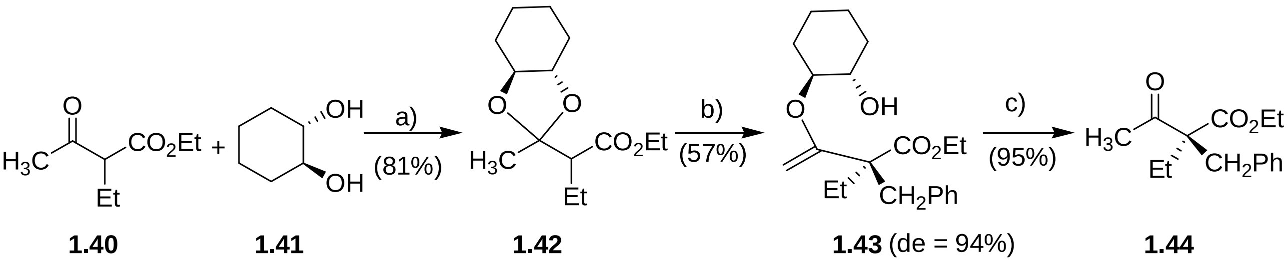
Figure 1.10. Auxiliary-based control.



Scheme 1.7. Asymmetric alkylation controlled by an Evans oxazilidinone chiral auxiliary. **Reagents & conditions:** a) (i) *n*-BuLi, (ii) CH_3CH_2COCl; b) NaHMDS, allyl bromide; c) LiOH, H_2O_2.

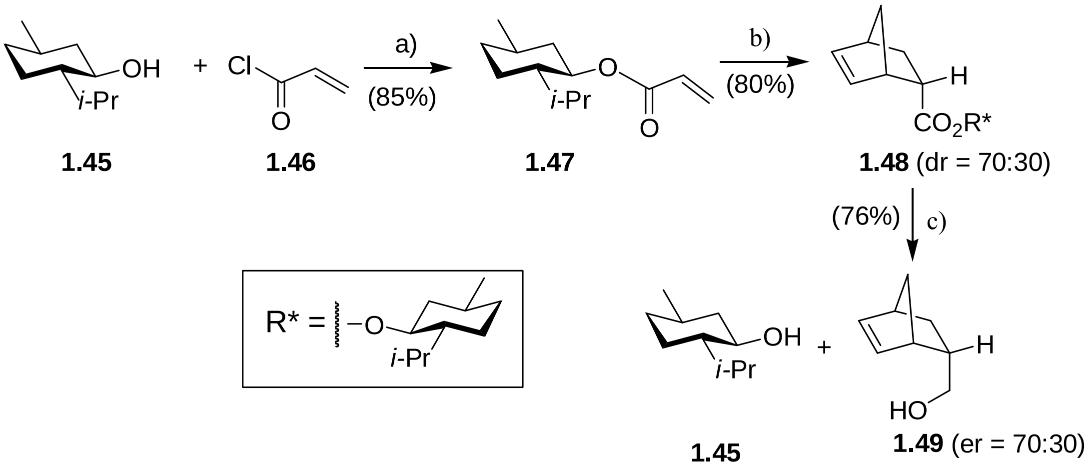
The oxazolidinone **1.36** is derived from the amino acid phenyl alanine, which is a cheap chiral pool starting material. The achiral substrate is attached to give the substrate-auxiliary intermediate **1.37** which undergoes an asymmetric alkylation to provide product **1.38** (dr > 95:5). The auxiliary is then removed by hydrolysis to give the acid **1.39** and auxiliary **1.36** ready to recycle.[16, 21, 22]

Another example of an auxiliary-contolled asymmetric alkylation involves the chiral β-keto ester derivative **1.42** (**Scheme 1.8**).[23] In this synthesis the auxiliary, (*S*,*S*)-cyclohexane-1,2-diol, is reacted with the substrate, 2-ethylacetoacetate, to form a ketal. The ester is deprotonated with LDA to form an enolate and then alkylated. The chirality of the newly formed centre is controlled by the auxiliary, which shields one face of the enolate while leaving the other face open to electrophilic attack. Once the reaction is complete the auxiliary is removed under Lewis-acid conditions.



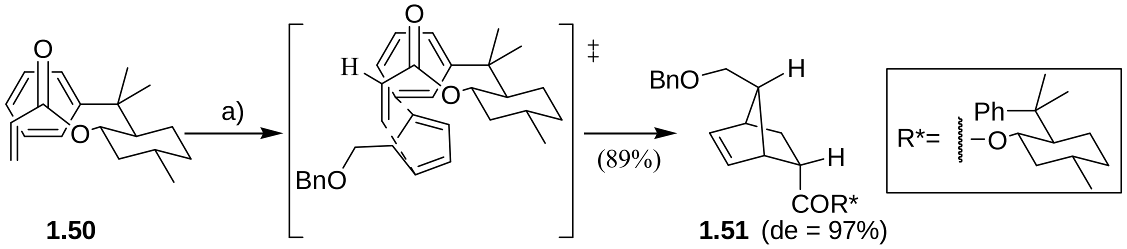
Scheme 1.8. Auxiliary-contolled asymmetric alkylation of a β-keto ester. **Reagents & conditions:** a) *p*-toluenesulfonic acid, benzene; b) (i) LDA, BnBr, (ii) THF, HMPA; c) $BF_3.OEt_2$.

L-Menthol **1.45** has been used extensively in asymmetric synthesis. In an early study it was employed as a chiral auxiliary in the asymmetric Lewis acid-promoted Diels-Alder reaction.[24] L-Menthol was reacted with acryloyl chloride (**1.46**) to afford the acrylate **1.47** that was then reacted with cyclopentadiene in the presence of $SnCl_4$, to form the cycloadduct **1.48** diastereoselectively. The product was reduced with lithium aluminiumhydride to afford the major *endo*-adduct **1.49** as a mixture of enantiomers (70:30) and the L-menthol auxiliary (**Scheme 1.9**).



Scheme 1.9. Application of L-menthol as a chiral auxiliary in an asymmetric Diels-Alder reaction. **Reagents & conditions:** a) Et_3N, ether, reflux; b) $SnCl_4$ (1 equiv.), toluene, cyclopentadiene, 3 to 8 °C; c) $LiAlH_4$, ether, 10 h (*endo*:*exo* = 95:5).

Subsequently, a number of other auxiliaries have been applied in asymmetric Diels-Alder reactions, providing enhanced srereoselectivities. For example, the menthol analogue (+)-8-phenylmenthol was applied in a Diels-Alder reaction by treating the acrylate **1.50** with 5-benzyloxymethylcyclopentadiene to give Diels-Alder adduct **1.51** in 89% yield and 97% diastereoselectivity (**Scheme 1.10**).[25] Some additional examples of auxiliary based control in cycloadditions are provided in the following sections.

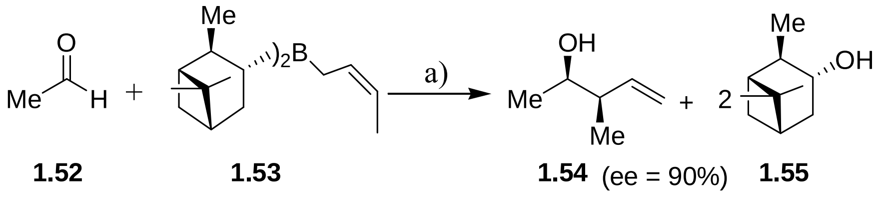


Scheme 1.10. Asymmetric Diels-Alder reaction using (+)-8-phenylmenthol. **Reagents & conditions:** 5-Benzyloxymethylcyclopentadiene, $AlCl_3$.

1.1.3- Reagent control

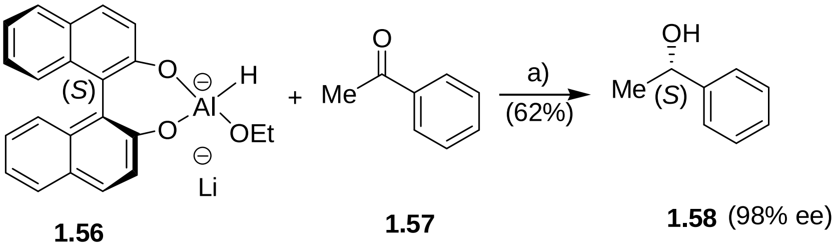
In this strategy a chiral reagent (**R**) is allowed to react with an achiral substrate (**S**) to produce a chiral product (**P**). One example is the asymmetric crotylation of aldehydes using chiral crotylborane **1.53** (**Scheme 1.11**).[16]

$$\boxed{\mathrm{S} \xrightarrow{\mathbf{R}} \mathbf{P}}$$



Scheme 1.11. Reagent based control in the asymmetric crotylation of ethanal. **Reagents & conditions:** a) **1.52** + **1.53**, then H_2O_2, OH^-.

The chiral crotyl borane reagent **1.53** attacks acetaldehyde carbonyl group exclusively from the *Si* face while the double bond geometry controls the relative stereochemistry. This results in the production of the *syn*-adduct **1.54** with high stereoselectivity (90% ee). The crotylation products are useful intermediates in synthesis because the alkene can undergo oxidative cleavage to deliver aldehydes. Another example is the asymmetric reduction of aromatic ketones using chiral binaphthol hydride reagent (*S*)-BINAL-H (**1.56**). Acetophenone (**1.57**) was reduced to the (*S*)-alcohol **1.58** with high enatioselectivity (ee = 98%) (**Scheme 1.12**).[26]



Scheme 1.12. Reagent based control: asymmetric reduction of acetophenone using (*S*)-BINAL-H. **Reagents & conditions:** THF, –78 °C.

1.2- Conclusions

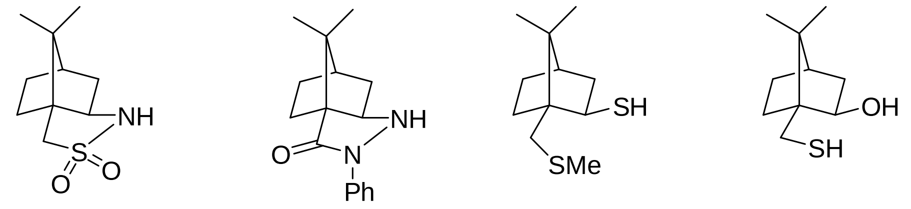
The discovery of chirality of organic compounds has led scientists to understand the important relationship between pharmacological activity and structure. Different methods were applied by chemists to obtain drugs and organic compounds as single enantiomers such as resolution, chiral pool and asymmetric synthesis. Three main strategies are applied in asymmetric synthesis to obtain compound in enriched form. These strategies are substrate controlled, chiral auxiliary controlled and reagent controlled asymmetric synthesis.

1.3- Chiral auxiliaries in organic synthesis

Chiral auxiliaries are used extensively in asymmetric synthesis.[27-33] This thesis concerns the development of a new cyclohexanol chiral auxiliary. Therefore, the following sections describe the synthesis and some applications of chiral auxiliaries in organic synthesis, but with an emphasis on cyclohexyl auxiliaries.

1.3.1- Camphor-derived auxiliaries

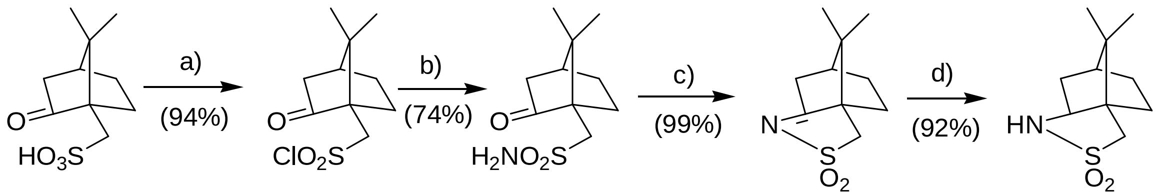
Both enantiomeric forms of camphor are commericially available, and its rigid structure is attractive for chiral auxiliaries (**Figure 1.11**). As a consequence, many different camphor-derived auxiliaries have been prepared in few steps and have been successfully employed in a variety of different reactions.[34]



(−)-D-(2*R*)-10,2-camphorsultam (**1.59**) **1.60** **1.61** **1.62**

Figure 1.11. Selected examples of camphor derived auxiliaries.

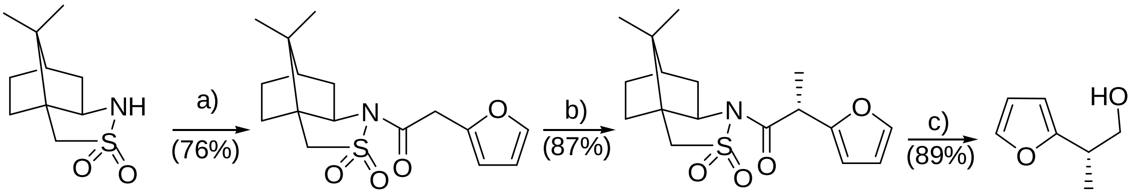
The most prominent camphor-derived auxiliary is Oppolzer's sultam (**1.59**) which can be prepared from (*1R*) or (*1S*)-camphorsulfonic acid (**Scheme 1.13**).[35]



1.63 **1.64** **1.65** **1.66** **1.59**

Scheme 1.13. Synthesis of camphor sultam. **Reagents & conditions:** a) PCl_5; b) NH_3; c) NaOMe, MeOH, rt; d) $LiAlH_4$, THF, 0 °C.

Camphor sultam has been used for many applications in asymmetric synthesis including the diastereoselctive alkylation of acylsultams. Bierstedt *et al.*[36] have described the use of Oppolzer's camphor sultam in developing an alternative route to hydroxylalkyl furan **1.69** by diastereoselective alkylation (**Scheme 1.14**). After acylation of the sodium salt of (2*R*)-sultam **1.59** with furan-2-yl-acetyl chloride, the resultant sulfonamide **1.68** was methylated with high diastereoselectivity (de = 97% by GC). A single recrystallisation improved the purity of compound **1.68** to > 99% de.

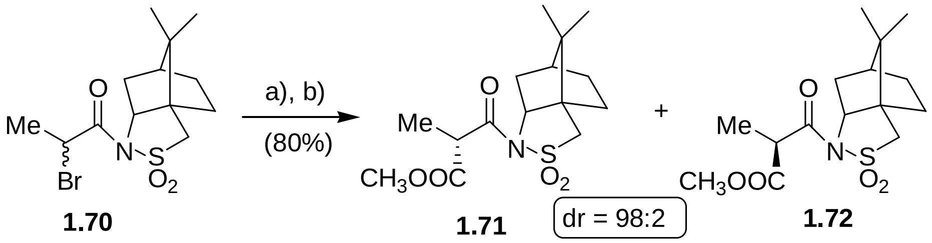


1.59 **1.67** **1.68** **1.69**

.

Scheme 1.14. Asymmetric alkylation of acylsultam. **Reagents & conditions:** a) (i) NaH, toluene, rt, (ii) furan-2-yl-acetyl chloride, rt; b) (i) $NaN(SiMe_3)_2$, THF, –78 °C, (ii) MeI, HMPA, –78 °C to rt, (iii) recrysallisation, (>99 % de); c) $LiAlH_4$, THF, rt.

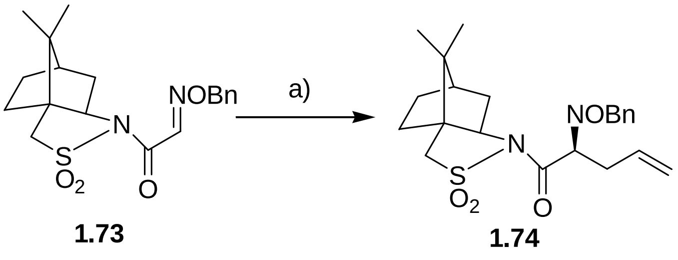
Feroci *et al.* described the use of camphor sultam in the electrochemical carboxylation of chiral α-bromocarboxylic acid derivatives (**Scheme 1.15**).[37]



1.70 **1.71** **1.72**

Scheme 1.15. Electrochemical carboxylation of chiral α-bromocarboxylic acid derivatives. **Reagents & conditions:** a) e⁻ (Al anode, Pt cathode), CO_2, THF/Bu_4NBF_4; (b) CH_2N_2.

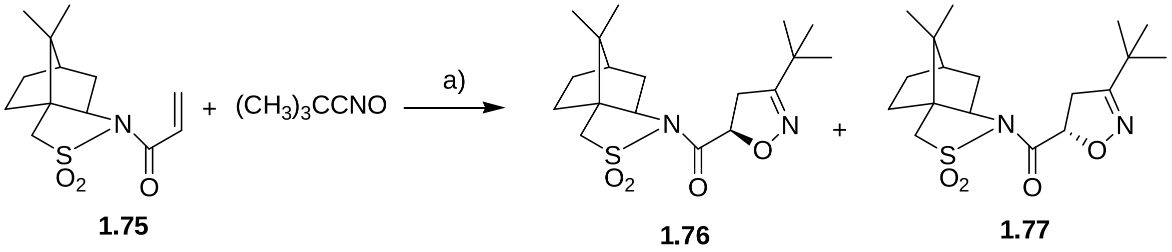
Another application of camphor sultam was reported by Kulkarni *et al.* in the allylation of glyoxylic oxime ethers (**Scheme 1.16**).[38]



Scheme: 1.16. Diastereselective allylation of glyoxylic oxime ethers. **Reagents & conditions:** Allyltributyltin, $Sn(OTf)_2$, CH_3CN.

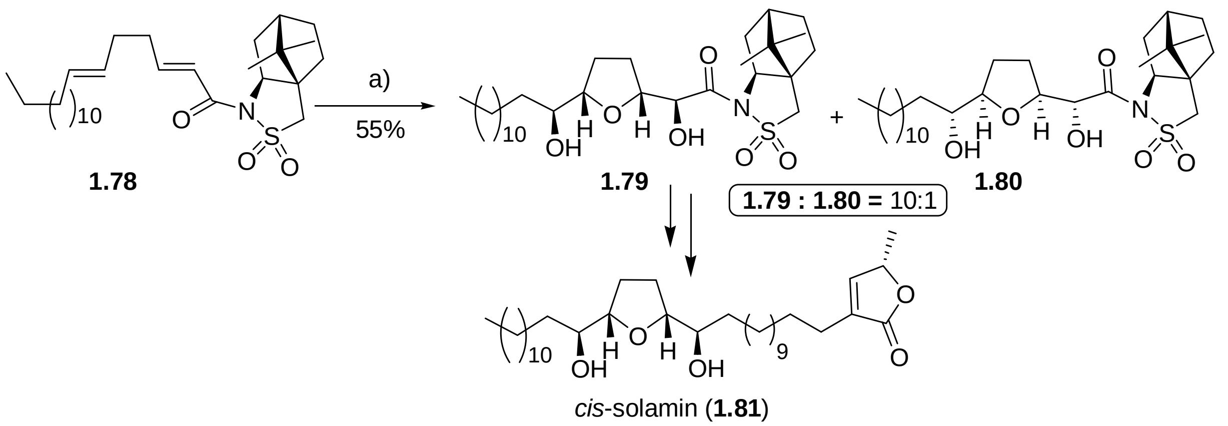
It was found that the diastereoselectivity was highly dependent on the reaction temperature. The de was 56% when the reaction was carried at room temperature, while reducing the temperature to –40 °C led to dramatically improved de of 91%.

Curran *et al.* described the cycloaddition reaction of a nitrile oxide with the acrylate ester of camphor sultam chiral auxiliary. They studied the effect of the solvent on the diastereoselectivity (**Scheme 1.17**).[39] When the reaction was carried out in hexane the diastereoismers **1.76** and **1.77** were formed in a ratio of 95:5, but was found to decrease with solvent polarity (CH_2Cl_2 dr = 81:19, THF/MeOH 85:15).



Scheme 1.17. Cycloaddition reaction of a nitrile oxide with with camphor sultam acrylate ester.

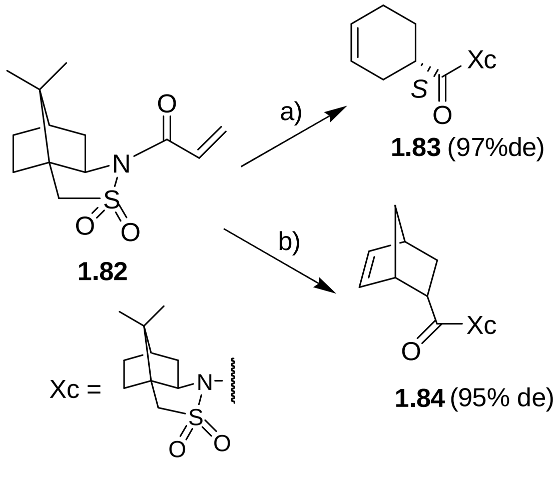
Brown *et al.* have described the use of camphor sultam in the oxidative cyclisation of 1,5-dienes in the synthesis of *cis*-solamin (**Scheme 1.18**).[40]



Scheme 1.18. Oxidative cyclisation of 1,5-dienes. **Reagents & conditions:** a) $KMnO_4$ (1.4 equiv), AcOH (8 equiv), Adogen 464 (0.1 equiv), EtOAc, from –30 to 0 °C.

They reported that the two diastereoisomers **1.79** and **1.80** were formed in a ratio of 10:1 (estimated from the ^{1}H-NMR analysis). The major diastereoisomer **1.79** was converted to the natural product *cis*-solamin (**1.81**).

Oppolzer *et al.* reported the use of camphor sultam in Diels-Alder reactions. The *N*-acyl sultam **1.82** was reacted with various dienes in the presence of Lewis acids. Both butadiene and cyclopentadiene react with it to provide the corresponding adducts **1.83** and **1.84** with (*S*)-stereochemistry at the newly created asymmetric centre (**Scheme 1.19**).[16, 41]



Scheme 1.19. Asymmetric Diels-Alder reaction of enoyl sultam. **Regents & conditions:** a) 1,3-butadiene, $EtAlCl_2$, CH_2Cl_2, −78 °C; b) $EtAlCl_2$, cyclopentadiene, EtCl.

1.3.2- Oxazolidinone chiral auxiliaries

One of the most widely applied classes of chiral auxiliaries in asymmetric synthesis are the oxazilidinones (**Figure 1.12**).[42] These compounds were first introduced by Evans in 1981,[43] and since that time have been used for many applications in asymmetric synthesis.[44]

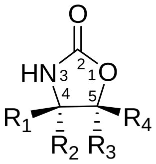
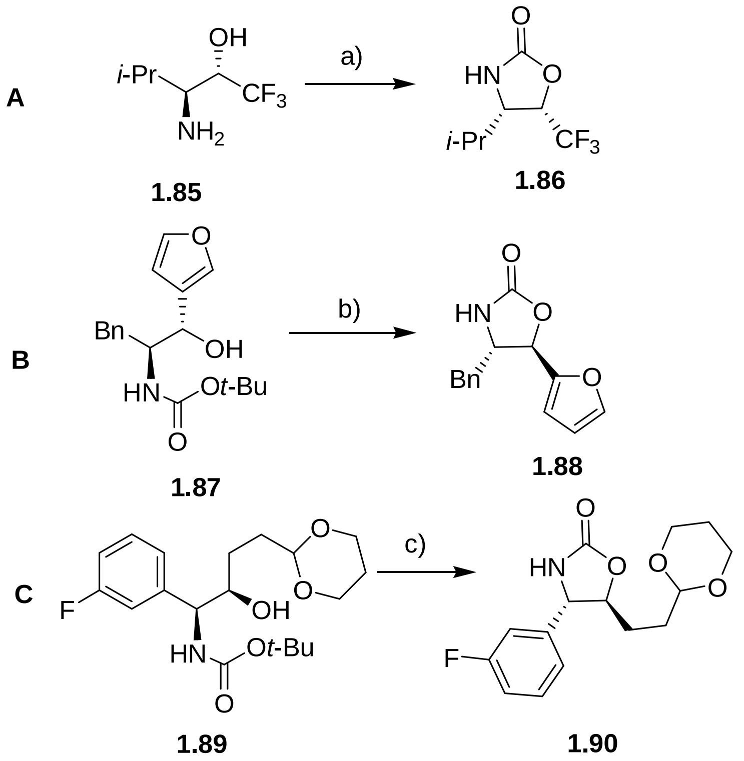


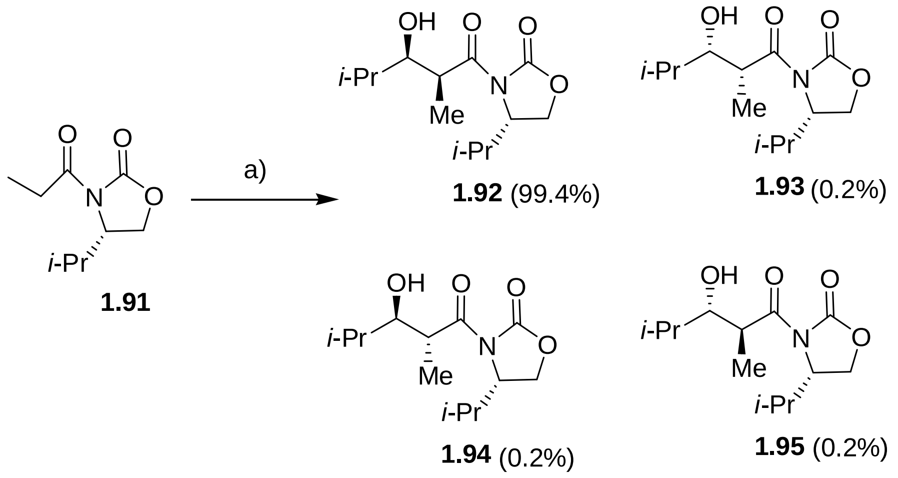
Figure 1.12: General structure of oxazilidinones.

A wide variety of chiral oxazilidinones have been developed.[42, 45] Functionlised oxazilidinones are synthesised from chiral α-amino alcohols which are most conveniently obtained from α-amino acids.[46] While numerous techniques exist to convert amino alcohols to the corresponding oxazilidinones,[44] several general strategies are most frequently employed. The necessary carbonyl functionality can be added to unprotected amino alcohol **1.85** by using phosgene (**Scheme 1.20 A**).[47] Alternately, the corresponding *N*-carbamoyl derivatives **1.87** can be cyclised, either by using a strong base to promote addition to the carbamate carbonyl (**Scheme 1.20 B**),[48] or by converting the alcohol to a leaving group leading to S_N2 attack at the hydroxyl centre in **1.89** (**Scheme 1.20 C**).[49] These last two variations are particulary useful in generating different diastereomers of the target oxazilidinone, as the former methods proceed with retention of stereochemistry at the 5 position, while the later results in inversion.



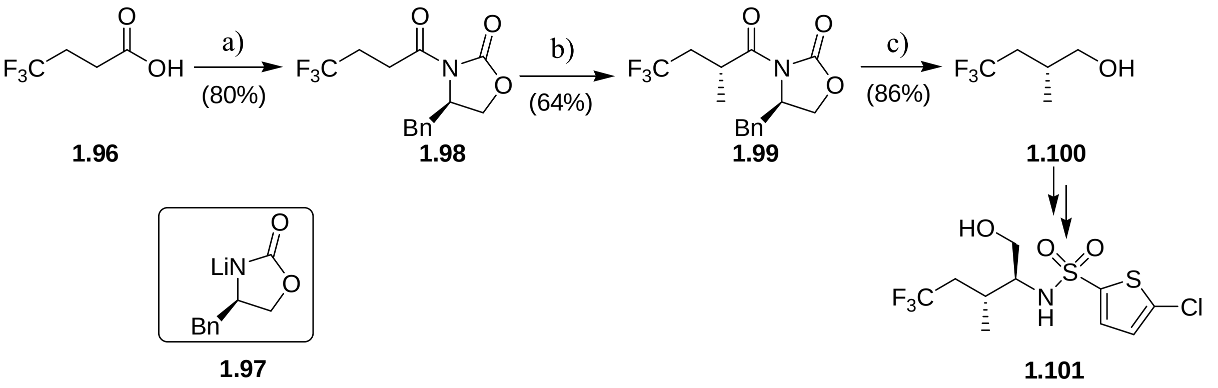
Scheme 1.20. Methods for the synthesis of oxazilidinones from amino alcohols. **Reagents & conditions:** a) $(CCl_3O)_2CO$, DIPEA, CH_2Cl_2, 0 °C to rt; b) NaH, DMF, THF, reflux; c) (i) MsCl, pyridine, rt; (ii) pyridine, 80 °C.

Oxazilidinone chiral auxiliaries have been extensively employed in asymmetric chemistry.[44, 50, 51] Initially these auxiliaries were introduced by Evans *et al.*[43] for asymmetric alkylation and aldol reactions using boron enolates derived from oxazilidinone **1.91**. Aldol reactions of borane enolates of imide **1.91** with a variety of aldehydes are highly selective for *syn*-aldol products **1.92** (**Scheme 1.21**).



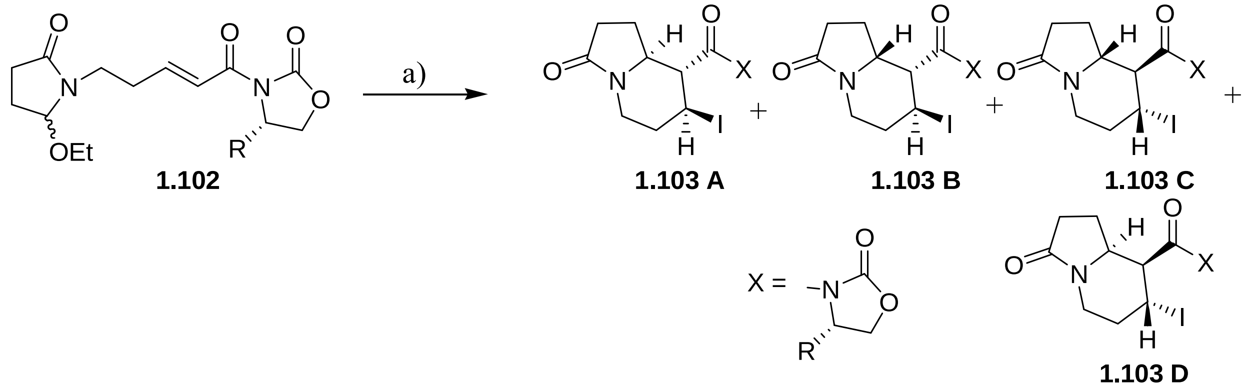
Scheme 1.21. Asymmetric aldol reactions of *N*-acyloxazilidinones. **Reagents & conditions:** a) Bu_2BOTf, DIPEA, *i*-PrCHO, CH_2Cl_2, 0 °C.

Zheng Wang *et al.* applied the asymmetric alkylation of acyl oxazolidinones in the synthesis of a γ-secretase inhibitor.[52] The key steps in the synthesis include formation of chiral oxazolidinone ester **1.98** followed by diastereoselctive methylation and reduction (**Scheme 1.22**). It was found that one diastereoisomer **1.99** was obtained from the asymmetric methylation reaction.



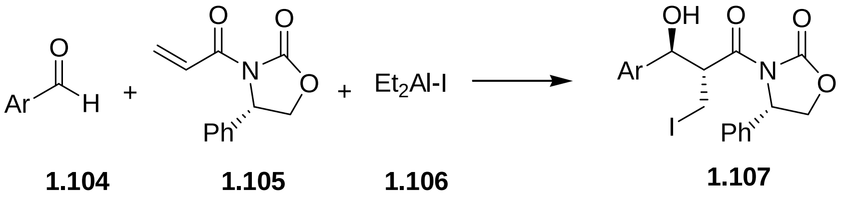
Scheme 1.22. Asymmetric alkylation of Evans *N*-acyl oxazolidinone applied in the synthesis of a γ-secretase inhibitor. **Reagents & conditions:** a) (i) t-BuCOCl, Et_3N, THF, (ii) **1.97**; b) NaHMDS, MeI, THF, – 40 to – 30 °C; c) $LiBH_4$, Et_2O.

An interesting example of the use of the oxazilidinone chiral auxiliaries was provided by Koseki *et al.* who reported intramolecular tandem Michael/Mannich type reactions using a combination of $TiCl_4$/*n*-Bu_4NI (**Scheme 1.23**).[53]



Scheme 1.23. Cyclisation of compound **1.102** to indolizidine **1.103** via an *N*-acyliminium ion intermediate by $TiCl_4/n\text{-}Bu_4NI$. **Reagents & conditions:** a) $TiCl_4/n\text{-}Bu_4NI$, solvent.

No reaction was observed in CH_2Cl_2 (R=Ph). When the solvent was changed to AcOEt/CH_2Cl_2, the product was obtained in 60% yield as a mixture of diastereoisomers (**1.103A:1.103B:1.103C** = 65:28:7). When (R=Bn), the diastereoselectivity was improved. Two diastereomers (**1.103A:1.103B**) were formed in a ratio of 90:10 and in 58% combined yield. Another similar application of Evans oxazolidinones was reported by Guigen Li *et al.*[54] They investigated the asymmetric halo aldol reaction (AHA) using Evans oxazolidinones to control the stereochemistry (**Scheme 1.24**).



Scheme 1.24. Asymmetric halo aldol reaction using Evans oxazolidinone.

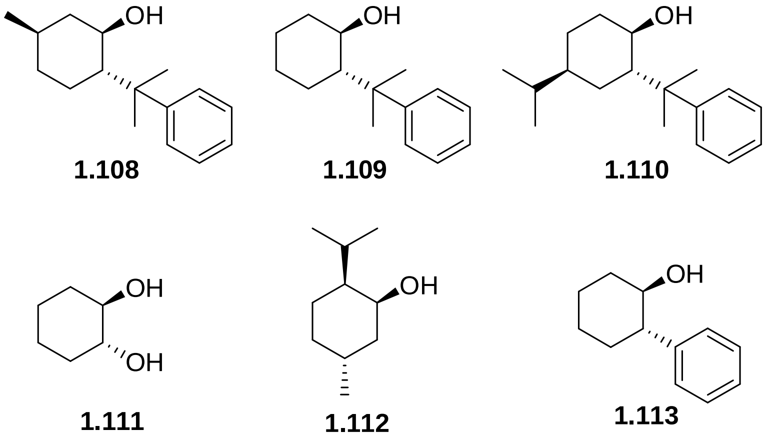
The AHA reaction was achieved by performing the slow addition of the solution of diethylaluminium iodide (1.3 equiv) into the mixture of α,β-unsaturated *N*-acyl-4-phenyl-oxazolidinone and aldehyde (2.0 equiv) in CH_2Cl_2 at –20 °C. Depending on the aromatic aldehyde used yields ranged of 82-93% and the de was > 95 %.

In, conclusion, the Evans oxazolidinone auxiliaries have been used for many years in a wide range of asymmetric reactions. Well known examples include asymmetric alkylation, aldol and

Diels-Alder reactions. However, oxazolidinones continue to find applications in new reactions and in the synthesis of important synthetic intermediates.

1.3.3- Cyclohexyl-based chiral auxiliaries

Cyclohexyl-based chiral auxiliaries are one of the most commonly used chiral auxiliaries in asymmetric synthesis.[55] Cyclohexyl-based chiral auxiliaries **1.108-1.113** are commercially available in enantiopure form (**Figure 1.13**).

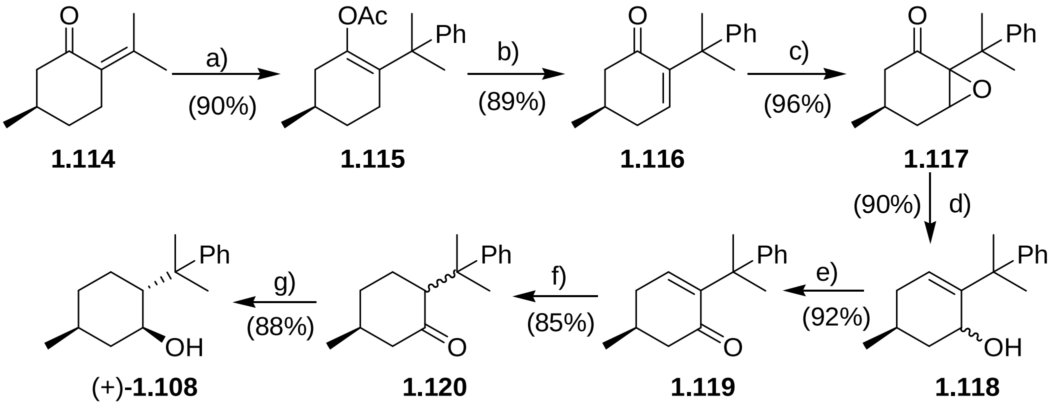


1.108 **1.109** **1.110**

1.111 **1.112** **1.113**

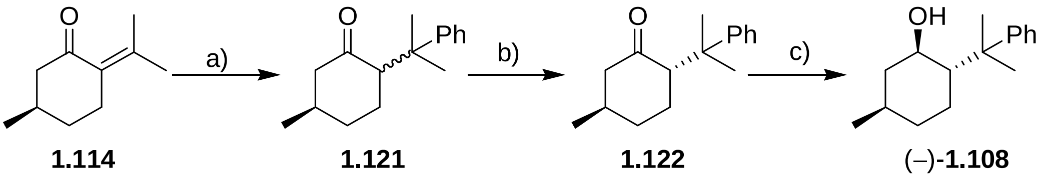
Figure 1.13. Examples of commercially available cyclohexanol-based chiral auxiliaries.

8-Phenylmenthol is probably the best known cyclohexyl-based chiral auxiliary. While (–)-8-phenylmenthol is prepared fairly easily, the enatiomer (+)-8-phenylmenthol requires a more tedious synthetic route. (+)-8-Phenylmenthol was introduced by Corey *et al.*[56] The synthesis of (+)-8-phenylmenthol includes seven steps starting from (*R*)-(+)-pulegone (**1.114**, **Scheme 1.25**).



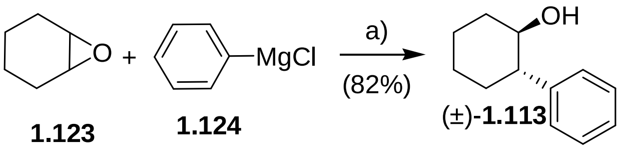
Scheme 1.25. Synthesis of (+)-8-phenylmenthol from (*R*)-(+)-pulegone (**1.114**). **Reagents & conditions:** a) (i) PhMgBr, CuI, Et_2O, (ii) AcCl; b) (i) Br_2, CH_2Cl_2, (ii) LiBr, DMF; c) NaOH, H_2O_2; d) NH_2-NH_2, AcOH, MeOH; e) CrO_3, pyridine, CH_2Cl_2; f) (i) NH_3, Li, *t*-BuOH; (ii) chromic acid; g) Na, Toluene, *i*-PrOH.

(–)-8-Phenylmenthol was synthesised in three steps starting from *R*)-(+)-pulegone (**1.114**, **Scheme 1.26**).[25]



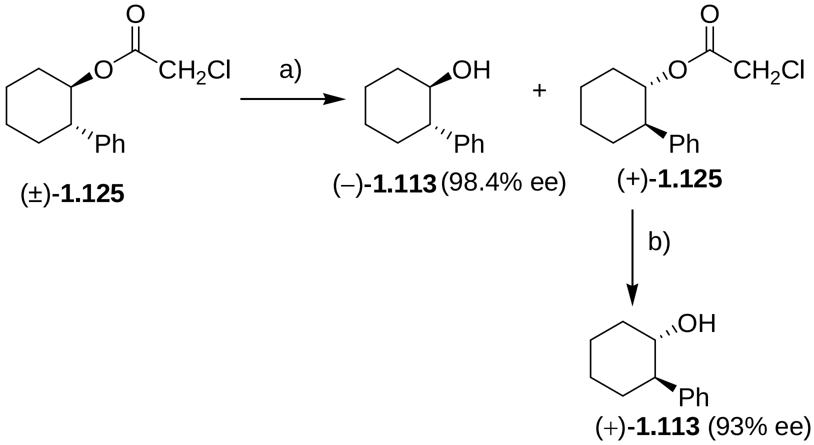
Scheme 1.26. Synthesis of (–)-8-phenylmenthol. **Reagents & conditions:** a) PhMgBr, CuCl, Et_2O, b) KOH, EtOH, c) Na, Toluene, *i*-PrOH, reflux.

Due to the difficulty in accessing both enantiomers of 8-phenylmenthol (specifically (+)-8-phenylmenthol), others have investigated alternative cyclohexyl auxiliaries. Most of the known cyclohexyl-based chiral auxiliaries are synthesised by reacting Grignard reagents or organolithium reagents with cyclohexene oxide. For example, (±)-*trans*-2-phenyl-1-cyclohexanol was prepared by Linstrumelle *et al.* by reacting phenylmagnesium chloride with cyclohexene oxide in the presence of copper iodide (**Scheme 1.27**).[57]



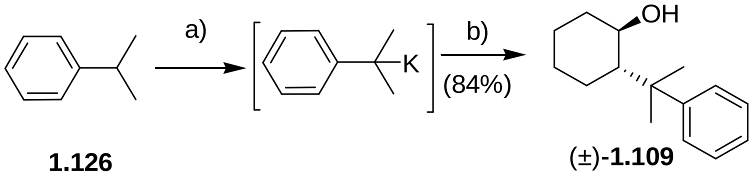
Scheme 1.27. Synthesis of (±)-*trans*-2-phenyl-1-cyclohexanol. **Reagents & conditions:** CuI, THF, – 30 °C.

Shwarts *et al.* reported an enzymatic resolution of (±)-*trans*-2-phenyl-1-cyclohexanol (**Scheme 1.28**).[58]



Scheme 1.28. Enzymatic resolution of (±)-*trans*-2-phenyl-1-cyclohexanol. **Reagents & conditions:** a) lipase (p. fluorescens), H_2O, pH buffer; b) NaOH, MeOH.

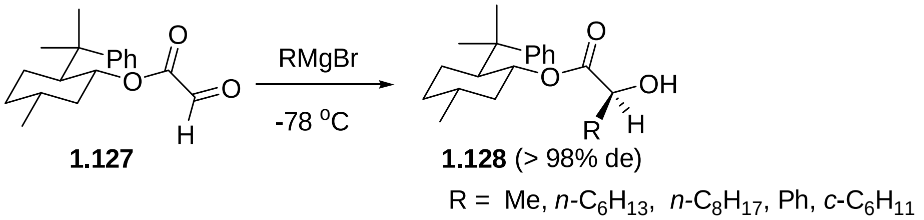
Trans-2-(α-cumyl)-1-cyclohexanol ((±)-TCC, (**1.109**)) was first introduced by Comins *et al.* as an alternative to 8-phenyl menthol. Reaction of α-cumyl anion with cyclohexene oxide afforded the (±)-*trans*-2-(α-cumyl)-1-cyclohexanol in 84% yield (**Scheme 1.29**).[59]



Scheme 1.29. Synthesis of (±)-TCC. **Reagents & conditions:** a) *n*-BuLi, *t*-BuOK, cyclohexane, rt; b) cyclohexene oxide.

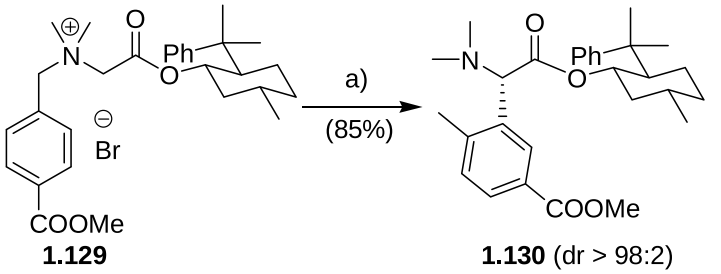
Comins *et al.* also described an enzyme catalysed method for the resolution of (±)-TCC **1.109** which is discussed later (see **Section 2.4**).[59]

(–)-8-Phenylmenthol ((–)-**1.108**) was used extensively in asymmetric synthesis. For example, a variety of nucleophiles have been added to 8-phenylmenthyl glyoxylates with high levels of absolute stereochemical control. For example a variety of organomagnesium reagents, both alkyl and aryl, have been added to 8-phenylmenthyl glyoxylates with more than 98% de (**Scheme 1.30**).[55]



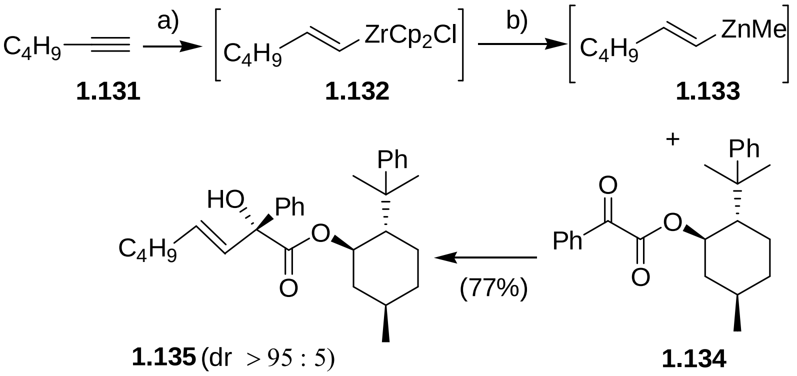
Scheme 1.30. Diastereoselctive addition of organomagnesium reagents to glyoxalate ester **3.69**.

Tayama *et al.* reported the use of (+)-8-phenylmenthol (+)-**1.108** in the Sommelet-Hauser rearrangement of *para*-substituted *N*-benzylic ammonium salt **1.129** (**Scheme 1.31**).[60] The reaction proceeded with a variety of electron-withdrawing aromatic substituents.



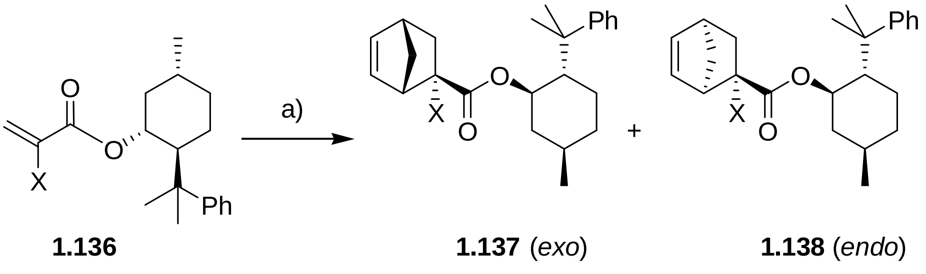
Scheme 1.31. Sommelet-Hauser rearrangement of *para*-substituted *N*-benzylic ammonium salt **1.130**. **Reagents & conditions:** *t*-BuOK, THF, – 40 or – 60 °C.

Wipf *et al.* reported the use of (–)-8-phenylmenthol in the formation of allylic tertiary alcohol **1.135** (**Scheme 1.32**). The alkyne **1.131** was treated with Cp_2ZrHCl to form (*E*)-alkenylzirconocene **1.132** which was treated with $ZnMe_2$ to form the more nucleophilic alkenylzinc species **1.133**. Reaction of **1.133** with α-keto ester **1.134** afforded the allylic tertiary alcohol **1.135** with excellent diastereoselectivity (dr > 95 : 5) and 77% yield.[61]



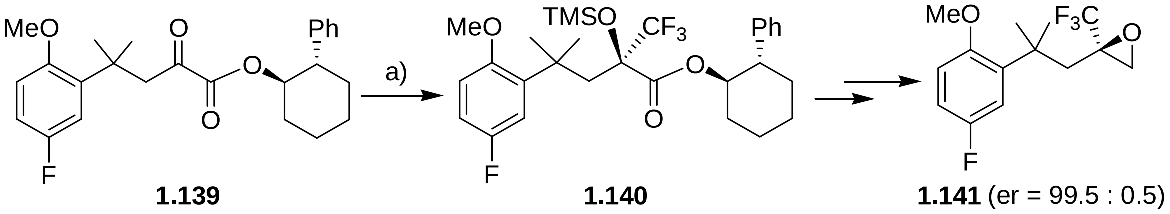
Scheme 1.32. Synthesis of tertiary alcohol **1.135**. **Reagents & conditions:** a) Cp_2ZrHCl, CH_2Cl_2, rt; b) $ZnMe_2$, toluene, – 78 to – 20 °C.

Ito *et al.* described the asymmetric Diels-Alder reactions of 2-substituted acrylic acid derivatives **1.136** with cyclopentadiene in the presence of different Lewis acids (**Scheme 1.33**).[62] When X= F (Lewis acid = Et_2AlCl or $TiCl_4$ or Me_3Al), the diastereoselectivity was excellent and only the *exo* adduct **1.137** was observed from analysis of the ^{1}H-NMR spectrum. When X= Cl, the best result was obtained when $TiCl_4$ was used (*exo*:*endo*=10:1). When X=Me, (Lewis acid = $TiCl_4$), the ratio of *exo*:*endo* was 6.9:1. Lower diastereoselectivity (*exo*:*endo* = 1:8.1) was obtained when X = H, (Lewis acid=$TiCl_4$ or Me_2AlCl).



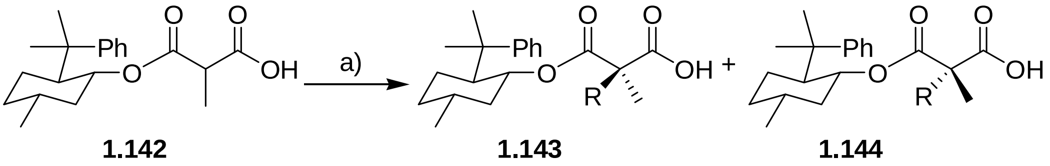
Scheme 1.33. Diels-Alder reactions of 2-substituted acrylic acid derivatives **1.136** with cyclopentadiene. **Reagents & conditions:** Lewis acid, cyclopentadiene, CH_2Cl_2.

(−)-*trans*-2-Phenyl-1-cyclohexanol was used by Song *et al.* in the trifluoromethylation of α-keto esters. The reaction was carried out in different solvents (THF, DMF, CH_2Cl_2, MTBE, hexane and toluene) at −20 °C in the presence of TBAF or TBAT as initiator. High diastereoselectivity was obtained when the reaction was carried out in toluene using TBAT (dr = 86:14). The dr was improved to 99.5 : 0.5 after recrystallisation from methanol. The ester **1.140** was used in the subsequent steps to synthesise α-trifluoromethyl-α-alkyl epoxide **1.141** (**Scheme 3.22**).[63]



Scheme 1.34. Asymmetric trifluoromethylation of α-keto esters. **Reagents & conditions:** a) $TMSCF_3$, TBAT, toluene, – 20 °C.

Ihara *et al.* studied the alkylation of 2-methylmalonic acid ester with (−)-8-phenylmenthol. The reaction was carried out in THF using LDA (**Scheme 1.35**).[64]



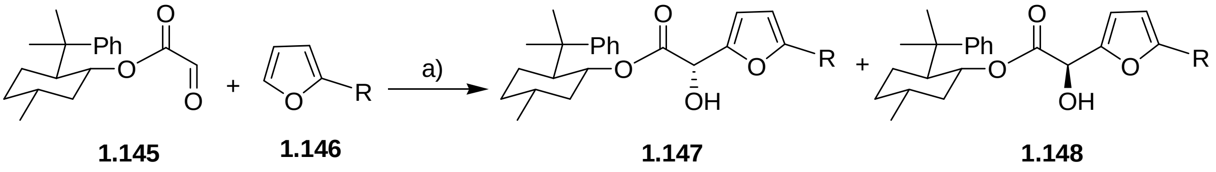
Scheme 1.35. Alkylation of 2-methylmalonic acid ester with (−)-8-phenylmenthol. **Reagents & conditions:** a) LDA (2 equiv.), R-X, THF, – 78 °C.

Different alkyl halides were used. When R-X = Et-I or Pr-I, the ratio of the diastereoisomers **1.143**:**1.144** was 4:1. The diastereoselectivity was improved to 16:1 when R-X = 2-methoxybenzyl bromide (**Table 1.3**).

Table 1.3. Alkylation of 2-methylmalonic acid ester of (−)-8-phenylmenthol.

Entry	R-X	Yield (%)	1.143 : 1.144
1	EtI	83	4:1
2	PrI	72	4:1
3	Benzyl bromide	72	12:1
4	2-Nitrobenzyl bromide	94	10:1
5	2-Methoxybenzyl bromide	73	16:1

Kwiatkowski *et al.* reported the Friedel-Crafts reaction of (1*R*)-8-phenylmenthyl glyoxylate with variously substituted furans (**Scheme 1.36**). The reaction was found to be efficiently promoted by $SnCl_4$. Different substituents were used (R = CH_2OBn, H, Me, Et, *i*-Pr, *t*-Bu, Bn, $C(Me)_2Ph$, Ph, TMS and CH_2OH). In all cases, excellent diastereoselectivity was obtained (de > 99%) and with moderate to good yields (41- 87%).[65]



Scheme 1.36. Friedel-Crafts reaction of (1*R*)-8-phenylmenthyl glyoxylate with variously substituted furans. **Reagents & conditions:** a) $SnCl_4$, CH_2Cl_2, – 78 °C.

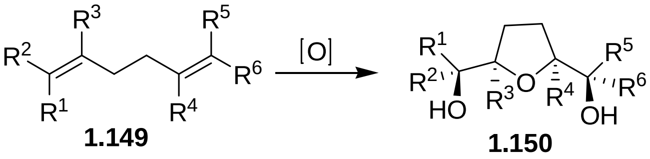
1.4- Conclusions

Camphor derived chiral auxiliaries and Evans oxazolidinone auxiliaries have been used for many years in a wide range of asymmetric reactions. Well known examples include asymmetric alkylation, aldol and Diels-Alder reactions. However, these chiral auxiliaries continue to find applications in new reactions and in the synthesis of important synthetic intermediates. Also, cyclohexyl based auxiliaries have been applied extensively in asymmetric synthesis with varying levels of success. Highest selectivities are often observed for the more sterically bulky derivatives such as 8-phenylmenthol and TCC. However we believe that in some reactions, even bulkier derivatives may offer further improvements in stereocontrol.

1.5-The oxidative cyclisation of 1,5-dienes

This thesis concerns the oxidative cyclisation 1,5-dienes. Therefore, the following section gives a brief overview of the oxidative cyclisation 1,5-dienes.

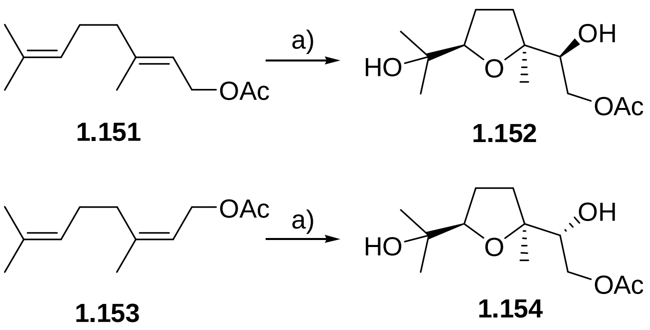
The oxidative cyclisation of 1,5-dienes provides a unique method for producing tetrahydrofurans which has been known for some time.[66-70] The reaction is particularly powerful because it involves the stereospecific suprafacial addition of two oxygen atoms across each of the two alkenes, combined with the stereoselective formation of a *cis*-2,5-disubstituted tetrahydrofuran ring (**Scheme 1.37**).[71]



Scheme 1.37. Stereoselective formation of 2,5-*cis*-disubstituted tetrahydrofurans by oxidative cyclisation of 1,5-dienes. **Reagents & conditions:** [O] = $KMnO_4$, OsO_4, RuO_4.

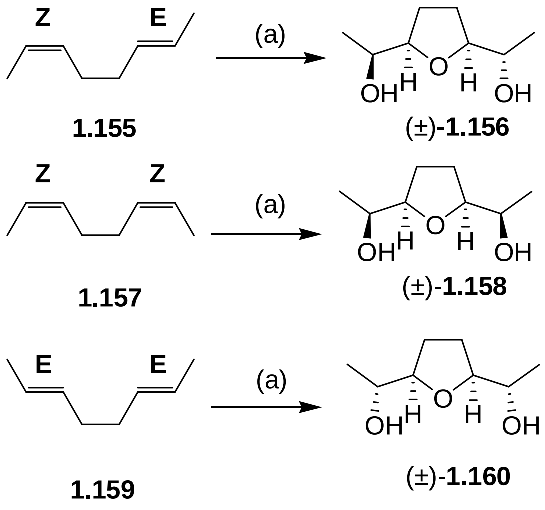
1.5.1- Permanganate mediated oxidative cyclisation

In 1965 Klein and Rojahn studied the oxidation of neryl acetate and geranyl acetate with potassium permanganate under slightly alkaline conditions (**Scheme 1.38**).[72] They showed that this oxidation reaction proceeded stereospecifically and yielded only 2,5-*cis*-disubstituted THFs.



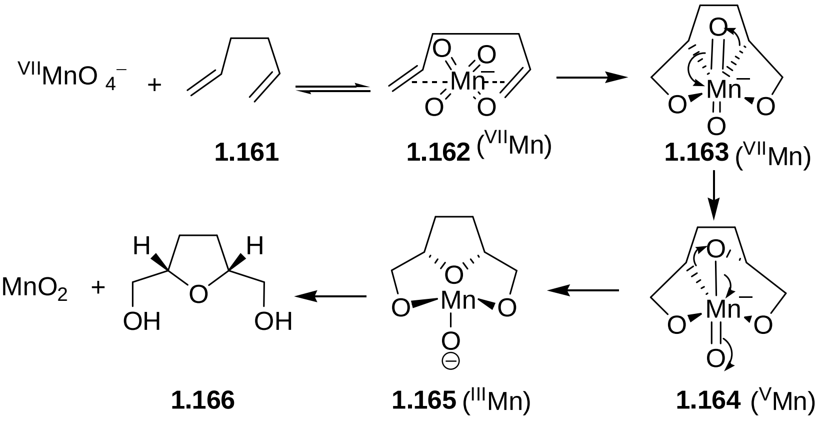
Scheme 1.38. $KMnO_4$ mediated oxidative cyclisation of neryl acetate and geranyl acetate. **Reagents & conditions:** (a) $KMnO_4$, acetone/water (5:1), pH = 7.5, CO_2 bubbling, 0 °C, 30 min.

Walba *et al.* subsequently went on to study the oxidative cyclisation of 1,5-dienes using potassium permanganate.[73] After the reaction of several 1,5-dienes **1.155**, **1.157** and **1.159**, gas chromatography analysis showed that the products **1.156**, **1.158** and **1.160** were obtained in at least 97% stereoselectivity (**Scheme 1.39**). This study also illustrated the stereospecificity of the reaction, highlighting the influence of diene geometry on diastereoselectivity.



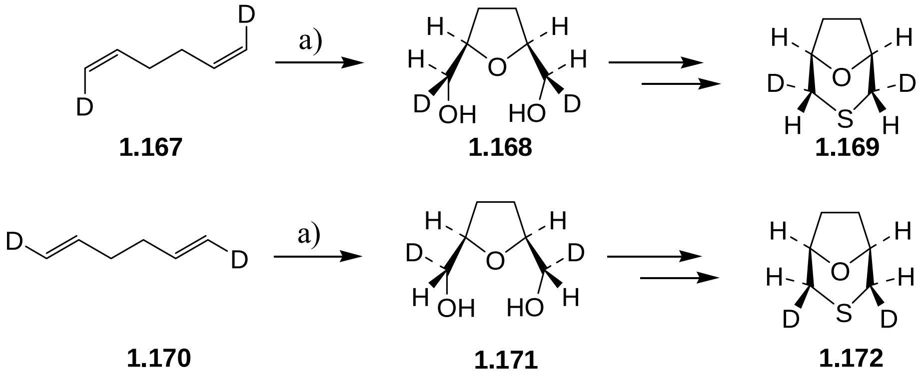
Scheme 1.39. $KMnO_4$ oxidation of dienes. **Reagents & conditions:** (a) $KMnO_4$, acetone/water (5:1), pH = 7.5, CO_2 bubbling, –20 °C, 30 min.

Walba *et al.*[73] proposed a mechanism based on the Sharpless proposals concerning the mechanism of oxidations of olefins by oxo transition metal species (**Scheme 1.40**).[74] It was proposed that after the initial formation of a *bis*-π-complex **1.162** between diene **1.161** and MnO_4^-, an octahedral Mn(VII) intermediate **1.163** is produced *via* two Sharpless-type [2+2] cycloadditions. Alkyl migration from the Mn to one of the oxygen atoms with retention of stereochemistry affords **1.164** and after a reductive elimination, Mn(III) diester **1.165** undergoes oxidation and hydrolysis to yield MnO_2 and the desired *cis*-THF **1.166** with the correct relative stereochemistry.



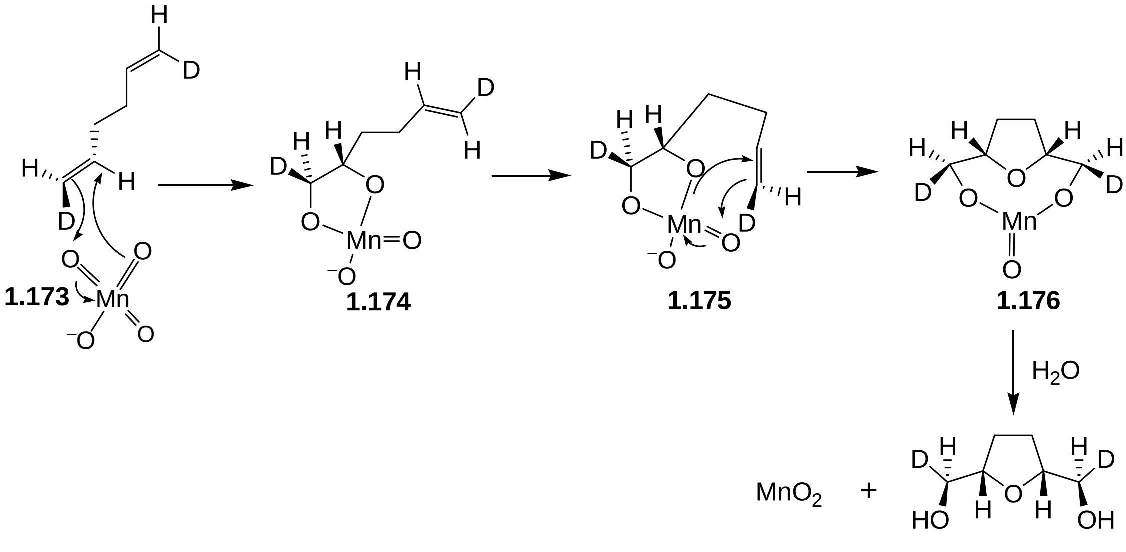
Scheme 1.40. Walba's proposed mechanism for the $KMnO_4$ oxidative cyclisation of 1,5-dienes.

Baldwin *et al.* investigated the oxidative cyclization reaction of the deuterated dienes **1.167** and **1.170** which yielded the corresponding racemic THFs **1.168** and **1.171** (**Scheme 1.41**). NMR analysis of THFs **1.169** and **1.172** confirmed the *cis* stereoselectivity of the reaction.



Scheme 1.41. $KMnO_4$ oxidation of deutrated dienes; **Reagents & conditions:** (a) $KMnO_4$, acetone/water (5:1), pH = 7.5, CO_2 bubbling, –20 °C.

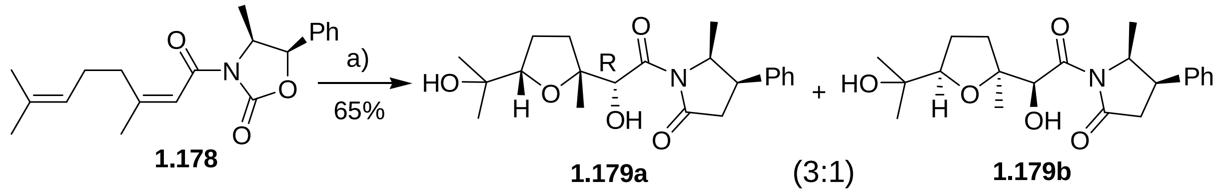
An alternative mechanism was put forward by Baldwin *et al.*[75] (**Scheme 1.42**), which involved initial [3+2] cycloaddition of MnO_4^- to one of the diene double bonds forming the intermediate Mn(V) ester **1.174**. After rapid oxidation with permanganate, a second [3+2] cycloaddition occurs on the remaining double bond and finally the basic hydrolysis of the diester **1.176** affords the *cis*-THF **1.177**.



Scheme 1.42. Baldwin's proposal for the $KMnO_4$ promoted oxidative cyclization of 1,5-dienes.[75]

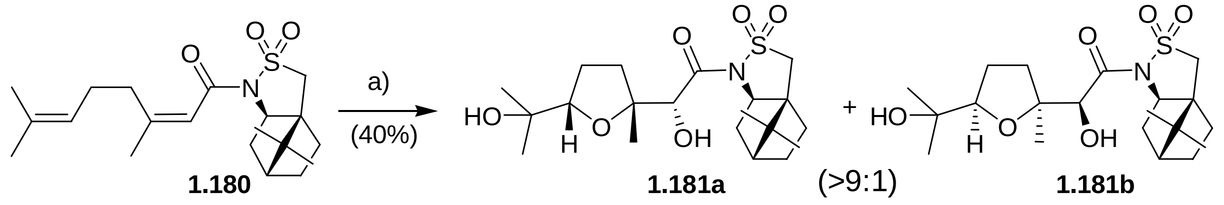
The permanganate oxidative cyclization of 1,5-hexadiene **1.167** was also investigated by Wolfe *et al.*[76] in the presence of 92% $H_2{}^{18}O$ as a solvent. Mass spectrometry analysis showed the presence of only one labelled oxygen in the THF adduct. That means that one of the oxygen atoms was derived from the solvent. This result is incompatible with the mechanism described by Walba *et al.* in which all three oxygen atoms are derived from a single molecule of permanganate. The fact that a symmetrical substrate is converted into a symmetrical product in an unsymmetrical manner confirms a sequential oxidation of the two double bonds *via* the intermediate Mn^V ester **1.174** and that is in agreement with the mechanism proposed by Baldwin *et al.*

Chiral auxiliaries were used to control the diastereofacial selectivity of permanganate oxidative cyclization of 1,5-dienoates. Walba *et al.* investigated asymmetric induction in the oxidative cyclisation using 1,5-dienes bearing Evans oxazilidinone chiral auxiliary.[77] Oxazolidinone-functionalized dienoate **1.178** was prepared by addition of the lithiated oxazolidinone to the corresponding acid chloride. Oxidative cyclisation of dienoate **1.178** afforded non racemic THFs **1.179a,b** in a 3:1 ratio and in a good yield, with the major diastereoisomer **1.179a** resulting from an attack on the *Re* face of the conjugated double bond (**Scheme 1.43**).



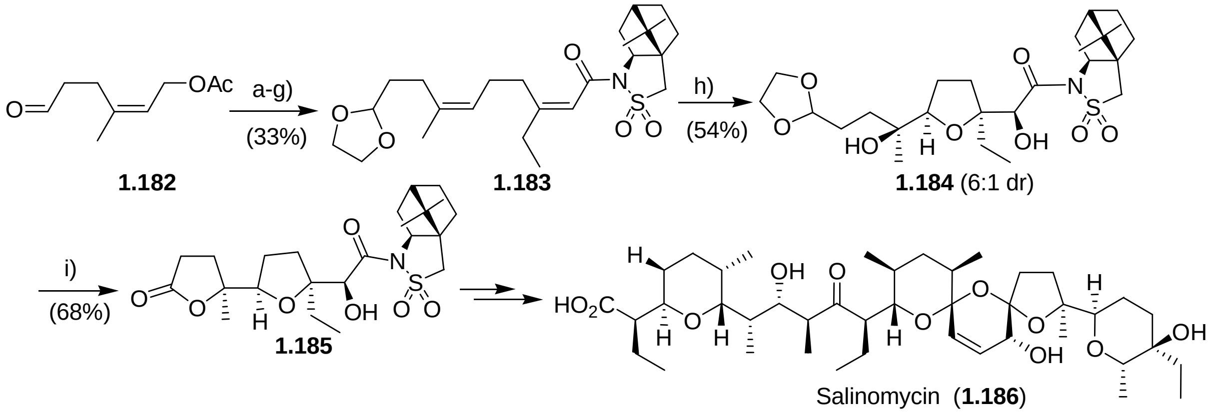
Scheme 1.43. Oxidative cyclisation of dienoate **1.178**. **Reagents & conditions:** a) $KMnO_4$, acetone/water (10:1), pH = 7.5, CO_2 bubbling, –30 °C.

The stereoselectivity was improved by changing the auxiliary from the Evans' oxazolidinone to Oppolzer's camphorsultam auxiliary.[78, 79] Diene **1.180** was prepared by addition of the sodium salt of (2*R*)-camphorsultam to the corresponding acid chloride. Oxidative cyclisation of diene **1.180** yielded the corresponding THF adducts **1.181a,b** in an improved 9:1 ratio and moderate yield (**Scheme 1.44**). The major diastereoisomer **1.181a** resulted from the attack on the *Re* face of the conjugated double bond, the same facial preference was observed previously by Oppolzer *et al.* in dihydroxylation reactions of enoyl sultams.[78]



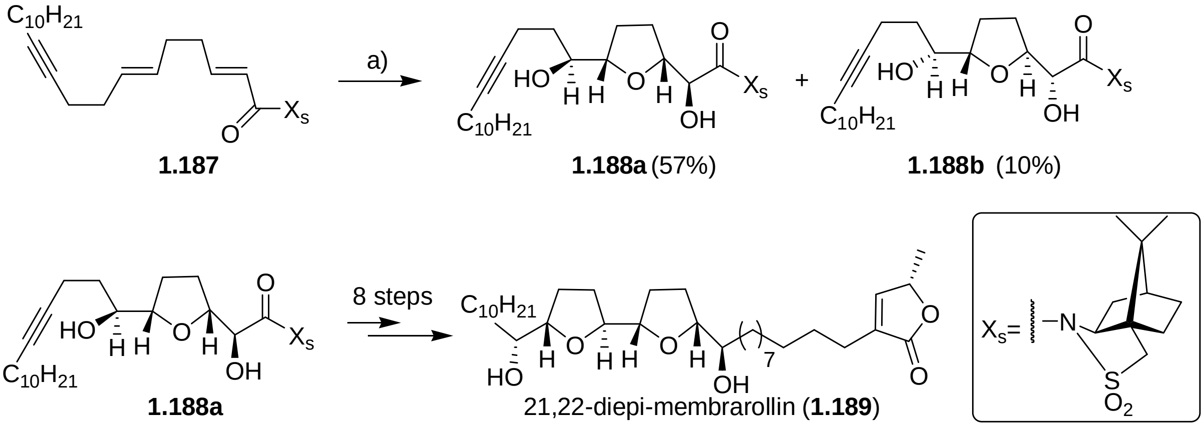
Scheme 1.44. Oxidative cyclisation of dienoate **1.180**. **Reagents & conditions:** a) $KMnO_4$, acetone/water (10:1), pH = 7.5, CO_2 bubbling, –30 °C, 30 min.

Permanganate oxidative cyclisation has been employed in natural product synthesis in racemic and asymmetric versions.[80-82] Kocienski *et al.* reported the first application of permanganate oxidative cyclisation of a diene bearing the Oppolzer sultam in total synthesis.[83] Aldehyde **1.182** was converted in seven steps to the requisite 1,5-diene precursor **1.183** in high overall yield (**Scheme 1.45**). The oxidative cyclisation of dienoate **1.183** using modified conditions yielded the THF adduct **1.184** in a good yield and diastereoselectivity (dr 6:1). It is interesting to notice that if the reaction was run in the absence of added acetic acid, inferior results were obtained. Treatment of THF adduct **1.184** with excess ozone gave intermediate hydroxy esters which cyclised using PTSA to afford the corresponding lactone **1.185** in good yield. The minor diastereoisomer obtained during the oxidative cyclisation step was successfully separated from lactone **1.185** at this stage and optically enriched lactone **1.185** was used in the subsequent steps to accomplish the total synthesis of salinomycin (**1.186**).



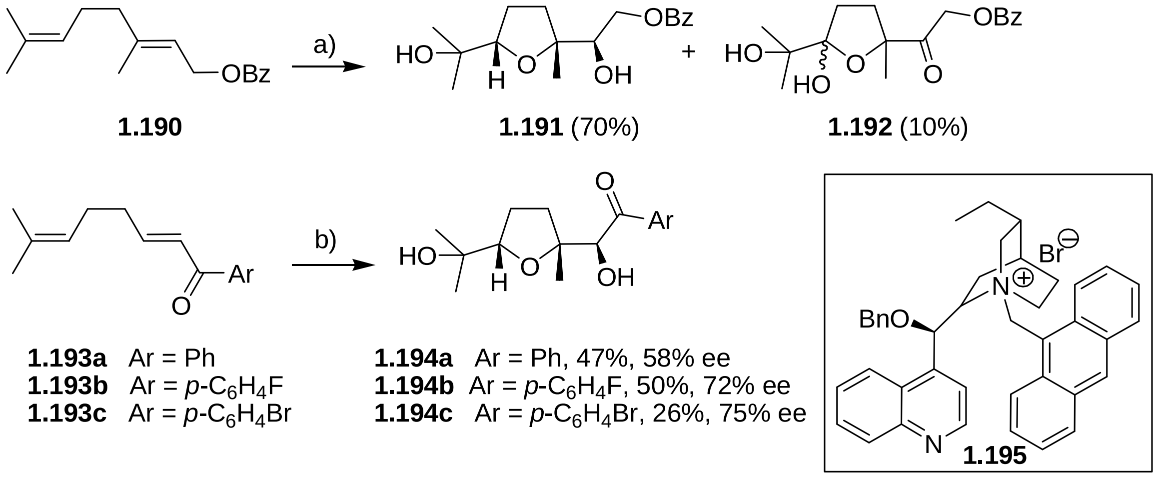
Scheme 1.45. $KMnO_4$ oxidative cyclisation of dienoate **1.183**. **Reagents & conditions:** (a) $HOCH_2CH_2OH$, PTSA, PhH, reflux ($-H_2O$), 3 h; (b) K_2CO_3, MeOH, rt, 6.5 h; (c) MsCl, LiCl, 2, 6-lutidine, DMF, 0 to 15 °C, 3.5 h; (d) $LiC{\equiv}CCH_2Li$, THF, –65 to –10 °C, 2.25 h; (e) (i) BuLi, THF, –78°C; (ii) $ClCO_2Me$, –90 to –10 °C, 3.5 h; (f) Et_2CuLi, THF, –85 °C, 3 h; (g) (i) NaOH, MeOH; (ii) $(COCl)_2$; (iii) (2*S*)-bornane-10,2-sultam, BuLi; (h) $KMnO_4$, pH 6 acetate buffer, acetone-AcOH-water, –35 °C, 5 h; (i) (I) O_3, EtOAc, –80 °C, 70 min; (ii) PTSA, CH_2Cl_2, rt, 8 h.

The Brown group have applied the permanganate mediated oxidative cyclisation to the synthesis of a number of biologically active annonaceous acetogenins such as *cis*-uvariamicin, *cis*-reticulatacin and *cis*-sylvaticin.[84, 85] Brown *et al.* also reported the synthesis of an unknown acetogenin analogue 21,22-di*epi*-membrarollin by permanganate mediated oxidative cyclisation of dienyne **1.187**.[86] The key oxidative cyclisation afforded the THF diols **1.188a,b** in good yield and diastereoselectivity (dr 6:1). The diastereoisomers were separable and the synthesis was subsequently completed in 8 steps with diastereomerically pure *cis*-THF diol **1.188a** (**Scheme 1.46**).



Scheme 1.46. Synthesis of 21,22-di*epi*-membrarollin. **Reagents & conditions:** a) $KMnO_4$, acetone:AcOH(1:1).

Brown *et al.* have reported the use of phase-transfer catalysis (PTC) for the permanganate promoted oxidative cyclisation of 1,5-dienes.[87] The oxidation of geranyl benzoate (**1.190**) with stoichiometric $KMnO_4$ in presence of AcOH and phase-transfer catalyst Adogen 464 afforded *cis*-THF **1.191** in good yield (**Scheme 1.47**). An asymmetric oxidation was also attempted on dienes **1.193a-c** using a chiral phase-transfer catalyst **1.195** affording the corresponding THF **1.194 a-c** in moderate yield and good ee.



1.190

1.191 (70%)

1.192 (10%)

1.193a Ar = Ph
1.193b Ar = *p*-C_6H_4F
1.193c Ar = *p*-C_6H_4Br

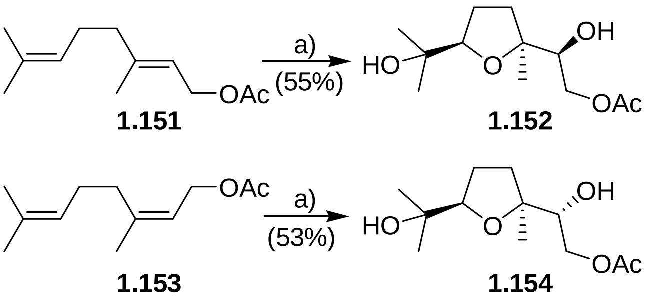
1.194a Ar = Ph, 47%, 58% ee
1.194b Ar = *p*-C_6H_4F, 50%, 72% ee
1.194c Ar = *p*-C_6H_4Br, 26%, 75% ee

1.195

Scheme 1.47. $KMnO_4$ oxidative cyclisation under phase transfer conditions. **Reagents & conditions:** a) $KMnO_4$ (2 equiv. of a 0.4 M aq. sol.), AcOH (4 equiv.), Adogen 464 (0.4 equiv.)/Et_2O; b) $KMnO_4$ (powdered, 1.6 equiv.), AcOH (6.5 equiv.), **1.195** (0.1 equiv.)/CH_2Cl_2, –30 °C.

1.5.2- Osmium tetroxide oxidative cyclisation

Piccialli *et al.* were the first to report the catalytic osmium tetroxide mediated oxidative cyclisation of 1,5-dienes using sodium periodate as a co-oxidant.[88] Geranyl acetate (**1.151**) and neryl acetate (**1.153**) were oxidised using catalytic OsO_4 in the presence of sodium periodate as co-oxidant and the corresponding 2,5-*cis*-disubstituted THFs **1.152** and **1.154** were obtained in moderate yields (**Scheme 1.48**).



1.151

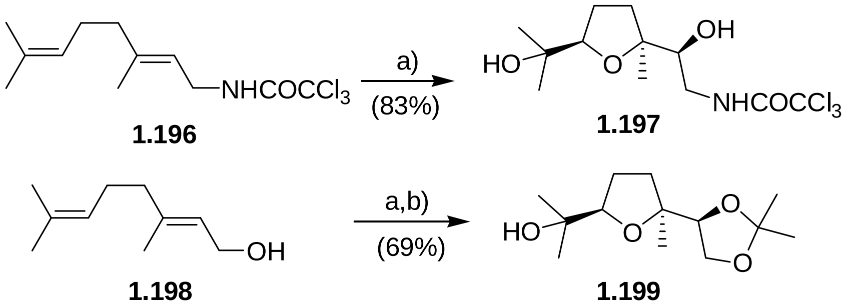
1.152

1.153

1.154

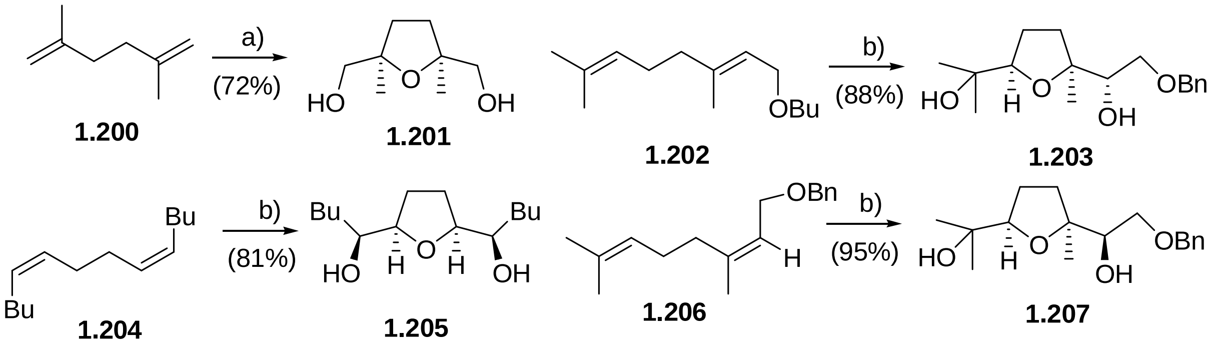
Scheme 1.48. First example of OsO_4 mediated oxidative cyclisation. **Reagents & conditions:** a) OsO_4 (5 mol %), $NaIO_4$ (4 eq.), DMF, –10 ºC, 16 h.

Donohoe *et al.* subsequently reported the osmium tetroxide mediated oxidative cyclisation of 1,5-functionalised dienes, using an OsO_4/TMEDA combination.[89] Dienes **1.196** and geraniol (**1.198**) were oxidised in a regeoselective fashion, expecting the corresponding dihydroxylated products. However *cis*-THF diols **1.197** and **1.199** were obtained in good yields during the attempted acidic decomplexation of the intermediate osmate ester (**Scheme 1.49**). It is thought that the OsO_4/TMEDA combination affords a complex that is directed by carbamate or allylic alcohol groups under hydrogen-bonding control, directing the regeoselectivity of the initial osmylation.[90] The acidic conditions then promote cyclisation of the intermediate osmate ester.



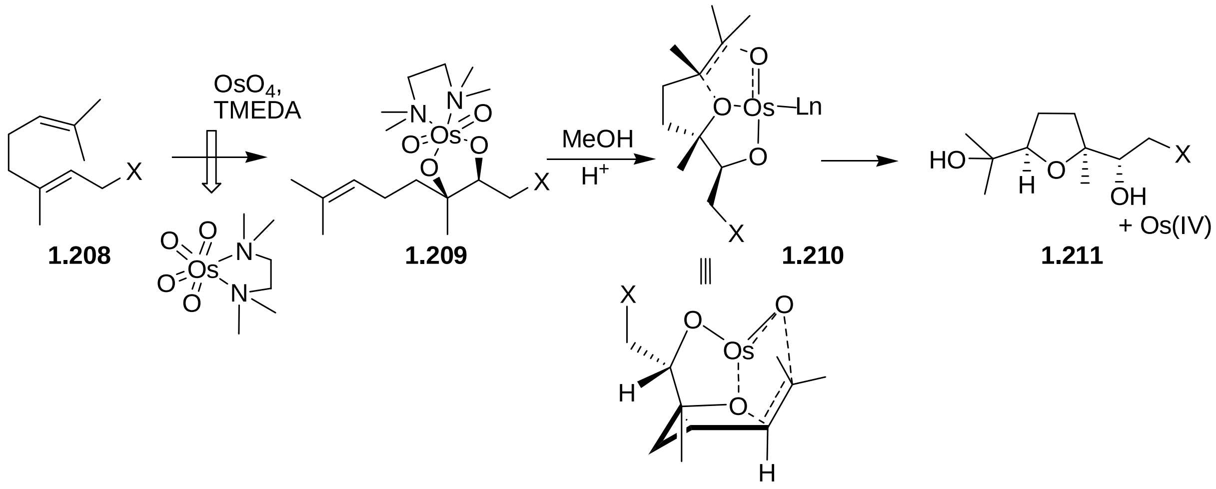
Scheme 1.49. Oxidative cyclisation of dienes **1.196** and **1.198** using OsO_4/TMEDA complex. **Reagents & conditions:** a) OsO_4 (1.0 eq.), TMEDA (1.0 eq.), CH_2Cl_2, – 78 °C then MeOH, HCl, rt; b) $(MeO)_2CMe_2$, TFA.

Donohoe's group subsequently investigated the use of catalytic osmium tetroxide with Me_3NO as a co-oxidant under acidic conditions.[71] A wide range of dienes were subjected to catalytic OsO_4 promoted oxidative cyclisation to yield racemic *cis*-THF diols in good to excellent yields (**Scheme 1.50**).



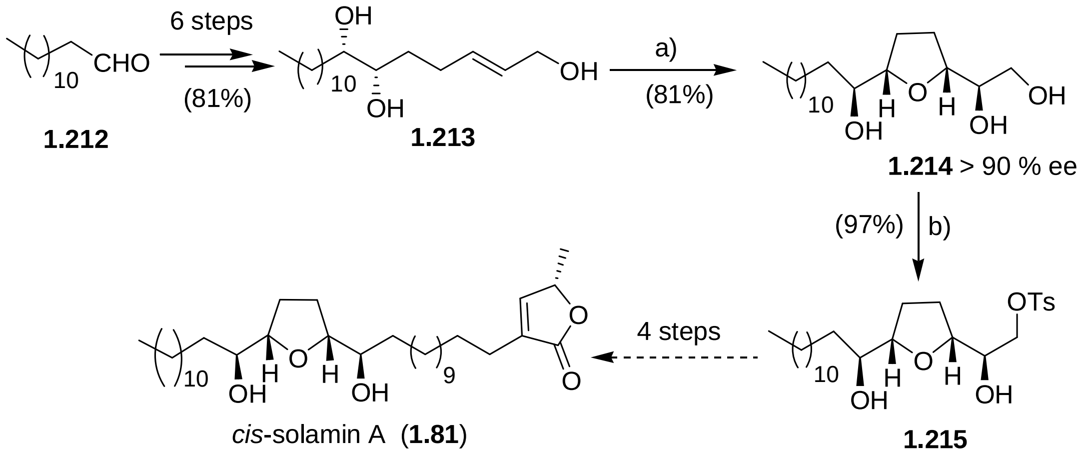
Scheme 1.50. Osmium-catalysed cyclisation under acidic conditions. **Reagents & conditions:** a) OsO_4 (5 mol %), Me_3NO (4.0 eq.), CSA (6.0 eq.), CH_2Cl_2, b) OsO_4 (5 mol %), Me_3NO (4.0 eq.), TFA (excess), acetone: H_2O (9:1).

Donohoe *et al.* proposed a mechanism for the OsO_4 catalysed cyclisation, which is believed to follow the same principles of cyclisation reported by Bladwin *et al.* for the permanganate mediated oxidative cyclisation of 1,5-dienes.[75] The sequence begins with a regioselective dihydroxylation of the diene under hydrogen bonding control (**Scheme 1.51**). The Os atom then undergoes a second pericyclic reaction with the remaining double bond. It is thought that the acid serves to activate the osmate ester intermediate by protonation of the oxo ligands to make the metal a better electrophile and more reactive during the cyclisation. The *cis* stereoselectivity of this reaction is explained by the transition structure **1.210** where the osmium is coordinated to two oxygen atoms.[89]



Scheme 1.51. Proposed mechanism for osmium-mediated oxidative cyclisation

Donohoe applied a two-step OsO_4/Me_3NO catalysed variant of the reaction in the formal synthesis of *cis*-solamin. The key step is the formation of triol **1.213** which was synthesised in six steps starting from the aldehyde **1.212**. The triol **1.213** was cyclised to the THF compound **1.214** using catalytic OsO_4 in the presence of Me_3NO. A formal synthesis of *cis*-solamin was achieved by converting THF compound **1.214** to the tosylate **1.215** in > 90% ee (**Scheme 1.52**), [91] which is an intermediate in the Brown group's synthesis of *cis*-solamin.[40]

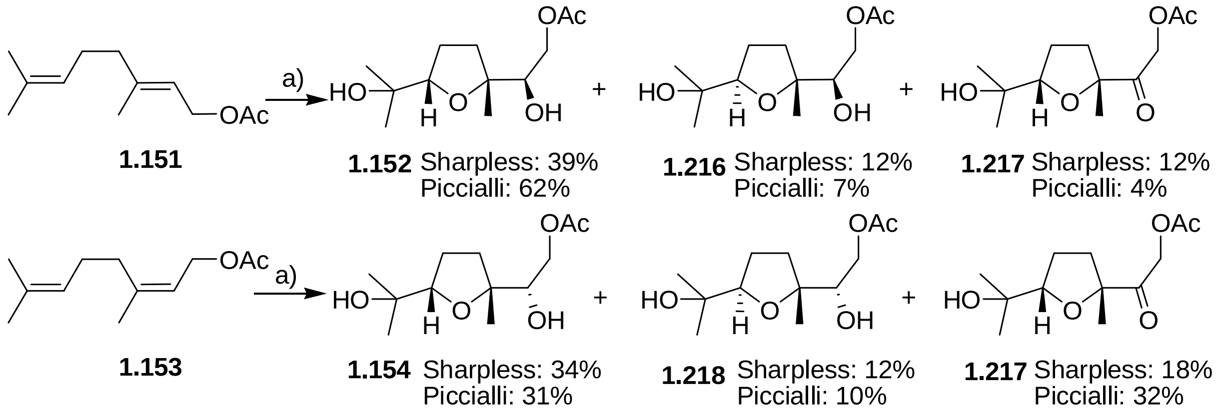


Scheme 1.52. Formal synthesis of *cis*-solamin. **Reagents & conditions:** a) OsO_4 (5 mol %), Me_3NO (4.0 eq.), TFA (6.0 eq.), isoprene (5 equiv.), acetone, H_2O, rt; b) Bu_2SnO, TsCl, benzene, $(DHQ)_2PHAL$.

Subsequent research in the Donohoe lab has focused on the two-step oxidative cyclisation, which involves Sharpless asymmetric dihydroxylation followed by osmium (VI/VIII) catalysed oxidative cyclisation of the resulting dihydroxy alkenes.[92, 93]

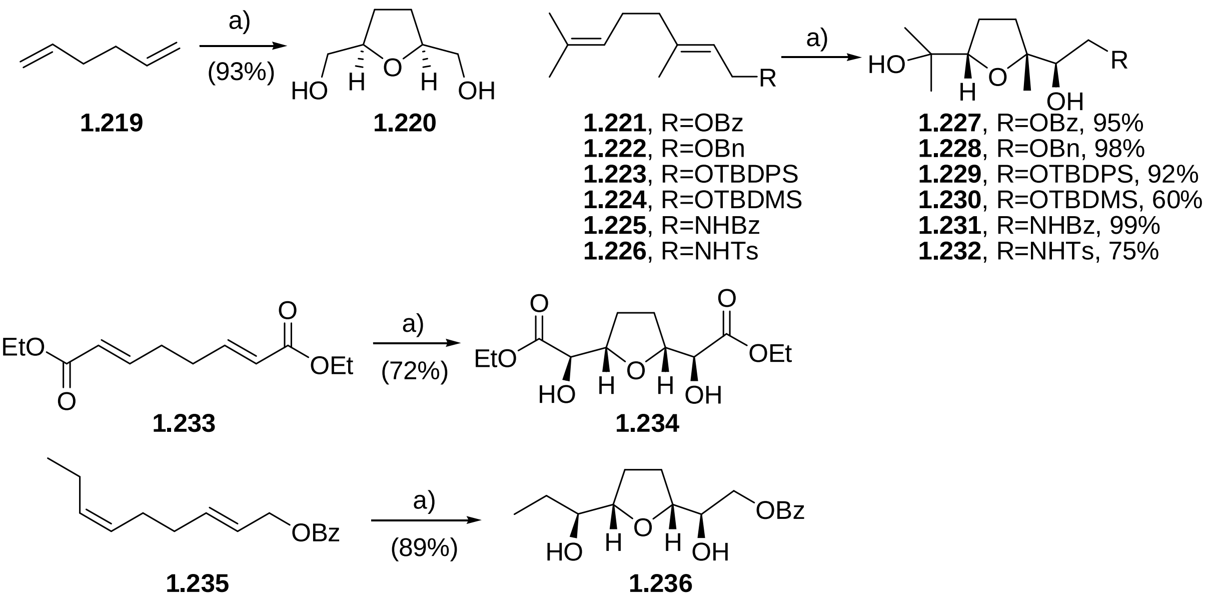
1.5.3-Ruthenium tetroxide oxidative cyclisation

The use of ruthenium tetroxide in the oxidative cyclisation of 1,5-dienes was first reported by Sharpless *et al.*, [94] and was discovered during a study to improve the catalytic conversion of primary alcohols to carboxylic acids using ruthenium. They discovered that the oxidation of geranyl and neryl acetates (**1.151** and **1.153**) led to the formation of THF diols **1.152**, **1.216**, **1.154** and **1.218** (**Scheme 1.53**). The 2,5-disubstituted THFs were obtained as mixtures of *cis* and *trans* isomers (3:1 ratio) and along side the *cis*-THF-ketone **1.217**. Piccialli *et al.* later investigated this reaction and reported a method improving the *cis* stereoselectivity for the process.[95]



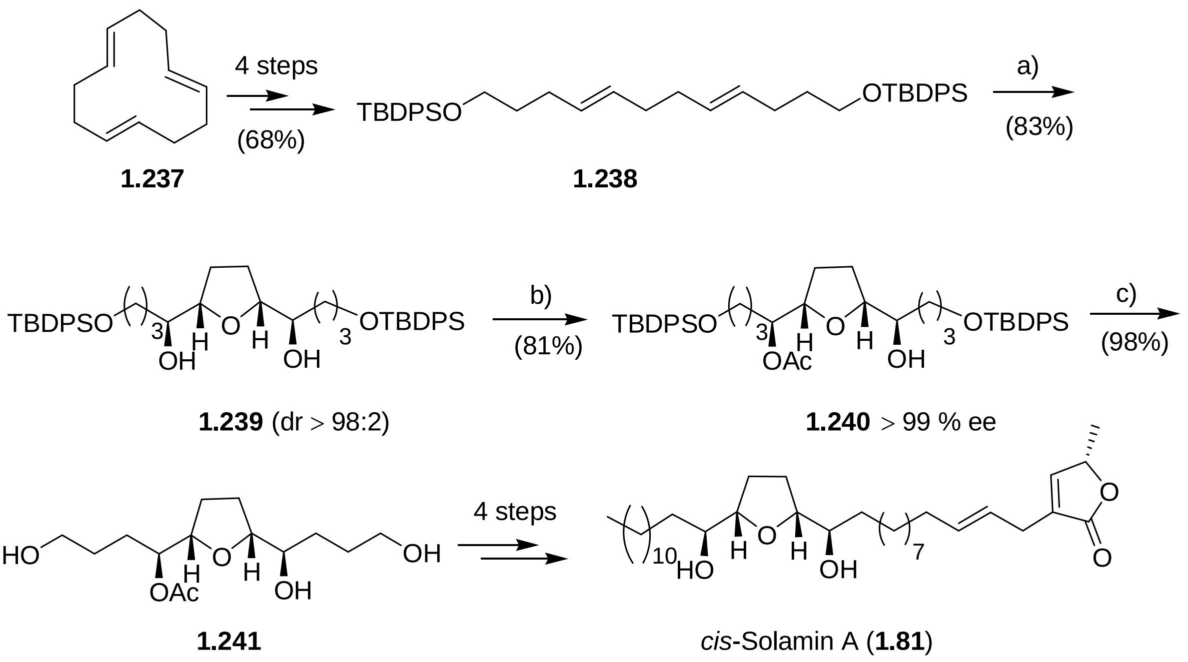
Scheme 1.53. Oxidative cyclisation of neryl and geranyl acetates **1.151** and **1.153** with RuO_4. **Reagents & conditions:** a) **Sharpless**: $RuCl_3.(H_2O)_n$ (2.2 mol %), $NaIO_4$ (3.1 equiv.), CCl_4/ H_2O/ MeCN, 25 °C, 15 min; **Picialli**: $RuO_2.2\ H_2O$ (4 mol %), $NaIO_4$ (4 equiv.), $EtOAc/CH_3CN/H_2O$ (3:3:1), 0 °C, 4 min.

Stark *et al.* reported further improvements on the RuO_4 mediated oxidative cyclisation of 1,5-dienes to afford THF diols in good to excellent yield and with high *cis*-stereoselectivity (d.r. > 95:5, **Scheme 1.54**).[96, 97] The corresponding *trans*-THF diols were not detected except in the case of diols **1.228** and **1.229**. $NaIO_4$ on wet silica was used as co-oxidant in a solvent mixture of THF and CH_2Cl_2 (9:1). A wide range of functional and protecting groups showed compatibility with the reaction conditions, and the cyclisation proceeded in a good yield for a variety of differently substituted alkenes.



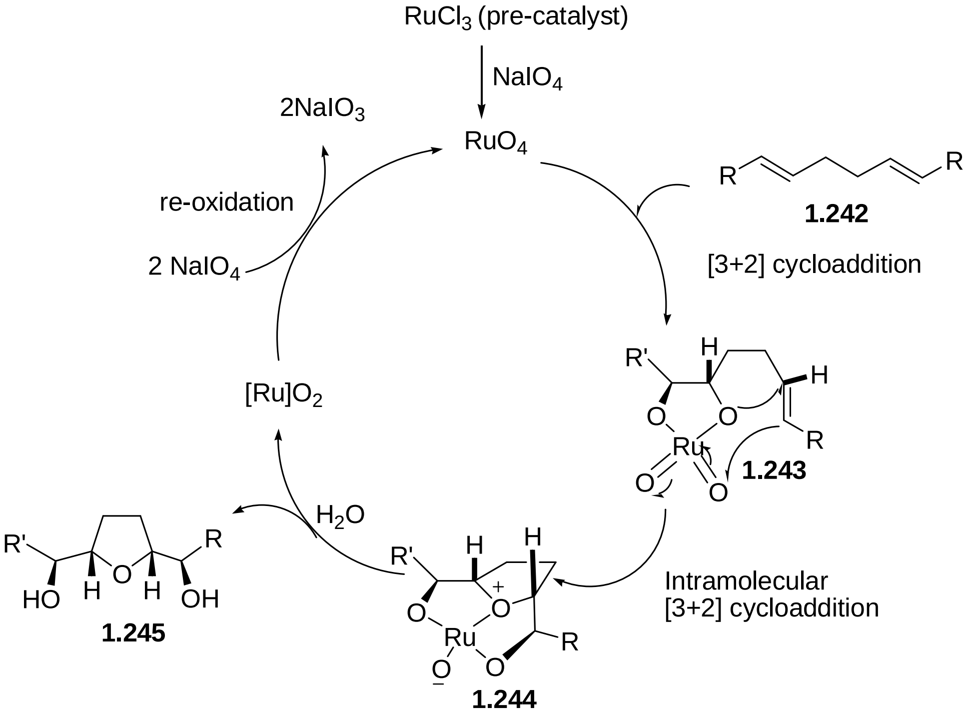
Scheme 1.54. Catalytic RuO_4 mediated cyclisation of 1,5-dienes. **Reagents & conditions:** a) $RuCl_3$ (0.2 mol %), $NaIO_4$ on wet silica (3.0 equiv.), THF:CH_2Cl_2 (9:1).

Stark *et al.* published a synthesis of *cis*-solamin A (**1.81**) using catalytic RuO_4 mediated oxidative cyclisation in 11 steps with an overall yield of 7.5%.[98] Diene **1.238** was synthesised from commercially available (*E,E,E*)-1-5-9-cyclododecatriene **1.237** in 4 steps (**Scheme 1.55**). The ruthenium-catalysed oxidative cyclisation of diene **1.238** afforded the *meso*-diol **1.239** in an excellent yield and as a single diastereoisomer. *Meso*-diol **1.239** was subjected to enzymatic esterfication to afford enantiomerically pure acetate (+)-**1.240** (> 99 % ee) in good yield. The absolute configuration of acetate (+)-**1.240** was assigned by the Moshers ester method. Silyl deprotection of *cis*-THF afforded the triol **1.241**, which was subsequently converted to *cis*-solamin A (**1.81**) in 4 steps.[99]



Scheme 1.55. Stereoselective synthesis of *cis*-solamin. **Reagents & conditions:** a) $RuCl_3$ (0.2 mol %), $NaIO_4$ on wet silica (3.0 equiv.), THF, 0 °C, 6 h; b) lipase Amano AK, vinyl acetate, hexane, 60 °C, 5-7 days; c) HF/py THF, py, rt, 24 h.

Stark proposed a mechanism for the ruthenium-catalysed cyclisation of 1,5-dienes, which is analogous to the $KMnO_4$ and OsO_4 mediated oxidative cyclisations.[75, 89] It is proposed that after oxidation of the pre-catalyst, an intial [3+2] cycloaddition takes place between RuO_4 and one of the double bonds of diene **1.242** to afford Ru(VI) intermediate **1.243** (**Scheme 1.56**). The intermediate **1.243** undergoes another [3+2] intramolecular cyclisation to give Ru(IV) diester **1.244**, which on subsequent hydrolysis furnishes a *cis*-THF diol **1.245** and RuO_2, which is oxidised back to RuO_4, by the co-oxidant.



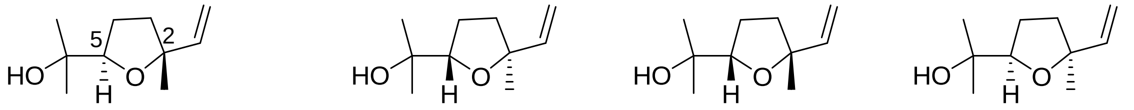
Scheme 1.56. Stark's proposed mechanism for catalytic RuO_4 promoted cyclisation.

1.6-Conclusions

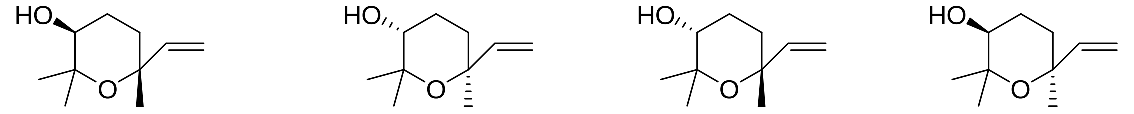
The oxidative cyclisation of 1,5-dienes has been employed in natural products synthesis in racemic and asymmetric versions. Different oxidants were used the oxidative cyclisation of 1,5-dienes such as $KMnO_4$, OsO_4 and RuO_4. Permanganate generally effects cyclisation in good yield, and it is environmental friendly compared to other metal-oxo reagents. However, permanganate based oxidation requires a stiochiometric amount of oxidant while osmium tetroxide and ruthenium tetroxide are catalytic, yet they require excesses of co-oxidants such as Me_3NO, NMO and $NaIO_4$. The advantage of using osmium tetroxide is that it gives high yields while ruthenium tetroxide affects polycyclisation. Permanganate has been used with chiral phase transfer catalysts and chiral auxiliaries to give effective control of absolute stereoselectivity. Currently, we are not aware of any direct oxidative cyclisation of 1,5-dienes using Os or Ru oxo species, although 2-step methods have been reported.

1.7- Synthesis of linalool oxide

Linalool oxides are constituents of oolong (Chinese tea) and black tea. Linalool oxides are also found in many essential oils and are characteristic of fruit aromas; they have an earthy-flowery, slightly bergamot-like odor. Linalool oxide is used in perfumery (e.g. for lavender notes) and for reconstitution of essential oils. It is important to note that linalool oxide is the name commonly given to a number of different structural and stereoisomers, which include four furanoid linalool oxides [5-(1-hydroxy-1-methylethyl)-2-methyl-2-vinyltetrahydrofuran] and four pyranoid linalool oxides [3-hydroxy-2,2,6-trimethyl-6-vinyltetrahydropyran]. The structures of the eight isomers are shown in **Figure 1.14**.[100]



(2*R*,5*R*)-*trans*-furanoid linalool oxide (**1.246**) (2*S*,5*S*)-*trans*-furanoid linalool oxide (**1.247**) (2*R*,5*S*)-*cis*-furanoid linalool oxide (**1.248**) (2*S*,5*R*)-*cis*-furanoid linalool oxide (**1.249**)

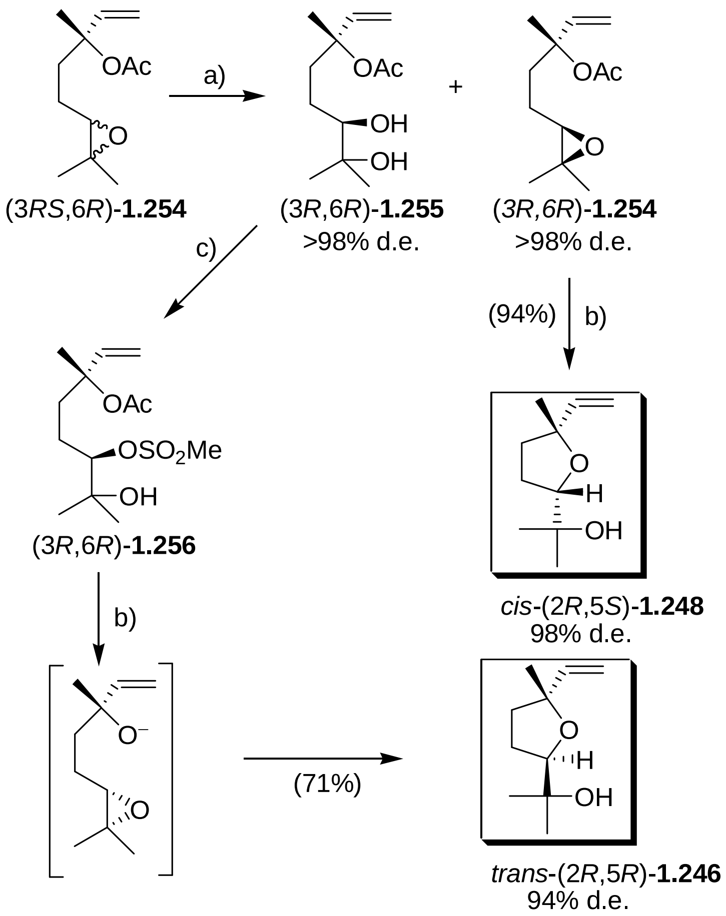


(3*S*,6*R*)-*trans*-pyranoid linalool oxide (**1.250**) (3*R*,6*S*)-*trans*-pyranoid linalool oxide (**1.251**) (3*R*,6*R*)-*cis*-pyranoid linalool oxide (**1.252**) (3*S*,6*S*)-*cis*-pyranoid linalool oxide (**1.253**)

Figure 1.14. Structures of the eight stereoisomers of furanoid and pyranoid linalool oxides.

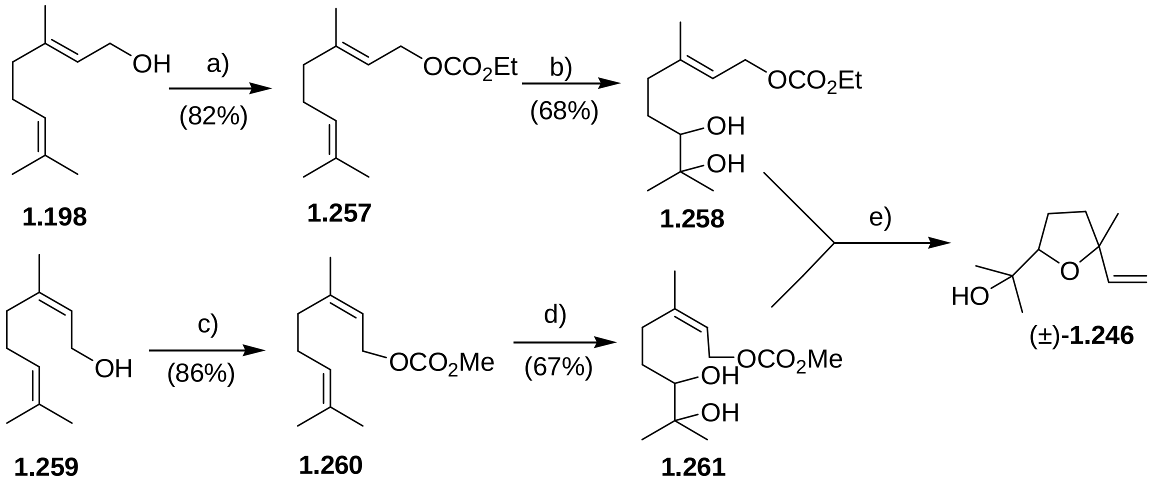
In the work described in this thesis, we are interested in the synthesis of *trans*-furanoid isomers and therefore only the previous syntheses of these compounds will be discussed here.

Faber *et al.* have reported the chemo-enzymatic synthesis of *cis*-(2*R*,5*S*)-(**1.248**) and *trans*-(2*R*,5*R*)-(**1.246**) from (3*RS*,6*R*)-2,3-epoxylinyl acetate **1.254** (**Scheme 1.57**).[101] The key step consists in a kinetic resolution of **1.254** employing an epoxide hydrolase preparation derived from *Rhodocccus sp.* NCIMB 11216, yielding diol (3*R*,6*R*)-**1.255** and epoxide (3*R*,6*R*)-**1.255** in excellent d.e. (≥98%). Chemical transformation of (3*R*,6*R*)-**1.255** and epoxide (3*R*,6*R*)-**1.254** gave two isomers of linalool oxide *cis*-(2*R*,5*S*)-(**1.248**) and *trans*-(2*R*,5*R*)-(**1.246**).



Scheme 1.57. Chemoenzymatic synthesis of *cis*-(2*R*,5*S*) and *trans*-(2*R*,5*R*)-linalool oxide [(2*R*,5*S*)-**1.248** and (2*R*,5*R*)-**1.246**]. **Reagents & conditions:** a) Epoxide hydrolase preparation from *Rhodococcus* sp. NCIMB 11216 in tris-buffer (100 mmol, pH 7.5), rt; b) MeOH, K_2CO_3, reflux; c) MsCl, Et_3N, CH_2Cl_2, 0 °C.

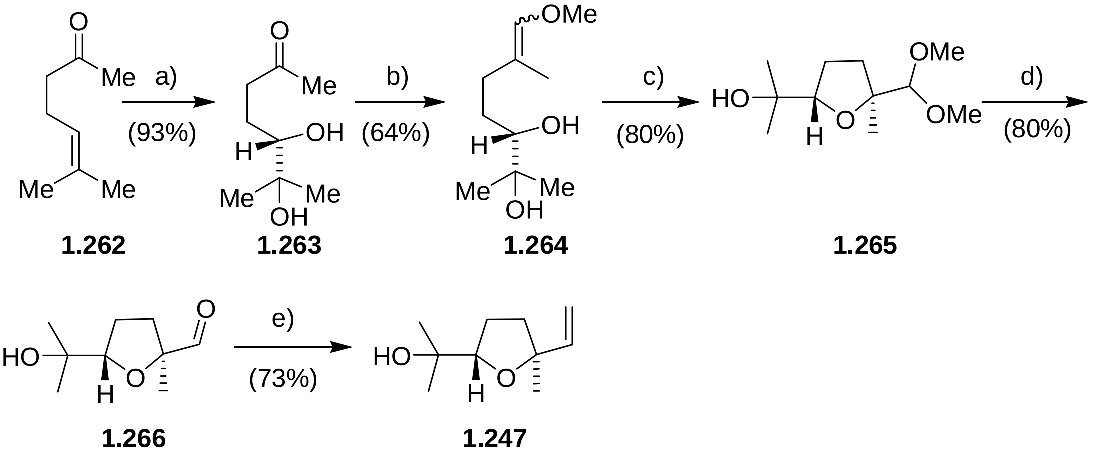
Fournier-Nguefack *et al.* reported a palladium(0)-catalysed synthesis of *cis*- and *trans*-linalool oxide,[102] from geraniol and nerol giving a mixture of *cis*- and *trans*- isomers (**Scheme 1.58**). They investigated the effect of using palladium(0) with different ligands on the ratio of *cis*- to *trans*- isomers of linalool oxide.



Scheme 1.58. Synthesis of *cis*- and *trans*- isomers of linalool oxide. **Reagents & conditions:** a) $ClCO_2Et$, pyridine, CH_2Cl_2; b) 1) *N*-bromosuccinamide, 2) NaOH, 3) H_2SO_4, 25 °C; c) $ClCO_2Me$, pyridine, CH_2Cl_2; d) 1) *N*-bromosuccinamide, 2) NaOH, 3) H_2SO_4, 25 °C; e) Pd(0)/L, THF.

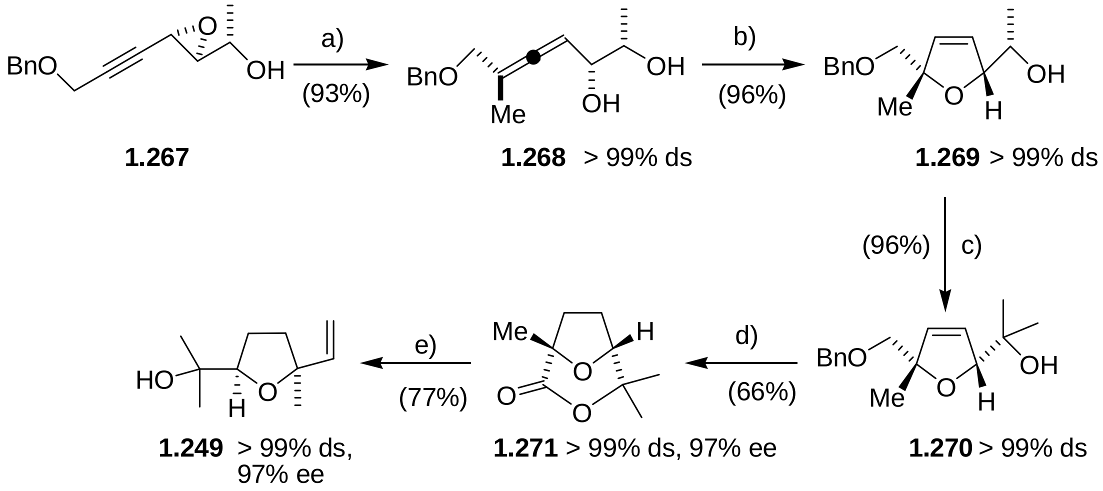
It was found that the *cis-trans* ratio varied little when a wide range of bidentate and monodentate phosphine ligands were used, giving stereoselectivities in the 20/80 range in favour of the *trans* isomer. It was also found that the reaction temperature had no effect on the stereoselectivity. The only difference in stereoselectivity was observed when P(*o*-tolyl)$_3$ was used as giving the *cis*-isomer as the major product (*cis*:*trans* = 65:35).

An asymmetric synthesis of (+)-linalool oxide was also described by Moeller *et al.*[103-104] The synthesis was achieved in 5 steps from the commercially available alkene **1.262** (**Scheme 1.59**). Asymmetric dihydroxylation of **1.262** afforded the keto diol **1.263**, which was then converted into the desired electrolysis substrate **1.264** using a Wittig reaction. The anodic cyclization reaction then afforded the dimethoxy acetal of **1.265** in 80% yield as a 7:1 mixture of *trans*- and *cis*-isomers. Hydrolysis and olefination then completed the synthesis of **1.266** in just five steps. The stereochemistry of the building block was established by conversion of the major isomer into (+)-linalool oxide (2*S*,5*S*)-**1.247**.



Scheme 1.59. Synthesis of (+)-linalool oxide (**1.247**). **Reagents & conditions:** a) (DHQ)-PHAL, $K_3Fe(CN)_6$, K_2CO_3, OsO_4, *t*-BuOH:H_2O (1:1) 0 °C, 6 h; b) $Ph_3P{=}CHOMe$, THF, 0 °C to rt; c) Reticulated Vitreous Carbon anode (RVC), 30% MeOH, THF, Et_4NOTs, 2, 6-lutidine, 2 F/mole, 8 mA; d) 50% TFA/H_2O, $CHCl_3$, rt; e) $Ph_3P{=}CH_2$, THF, 0 °C to rt.

Krause *et al.* reported a stereoselective synthesis of (+)-*cis*-linalool oxide (**Scheme 1.60**).[105] The key steps included the *anti*-selective copper-mediated S_N2'-substitution of propargyl oxarine **1.267** and the gold-catalyzed cycloisomerization of the resulting dihydroxyallene **1.268**



Scheme 1.60. Synthesis of (+)-*cis*-linalool oxide. **Reagents & conditions:** a) MeMgCl, CuCN, $(PhO)_3P$, THF; b) $AuCl_3$ (0.1 mol %), THF; c) 1) DMP, 2) MeMgCl; d) 1) H_2, Pd/C 2) IBX, DMSO; e) 1) DIBAH, Et_2O, –110 °C, 2) Me_3SiCH_2MgCl, $CeCl_3$, 3) KH.

Treatment of **1.267** with a methylmagnesium cyanocuprate in the presence of triphenylphosphite (in order to prevent epimerization of the allene) afforded **1.268** with excellent chemical yield (93%) and diastereoselectivity (de > 99%). The subsequent gold-catalyzed cycloisomerization was achieved in the presence of only 0.1 mol % $AuCl_3$ in THF, which gave the 2,5-dihydrofuran **1.269** in 96% yield as a single diastereoisomer. The secondary alcohol **1.269** was converted into the tertiary alcohol **1.270** by the oxidation and subsequent Grignard addition. The lactone **1.271** was obtained in 66% yield over two steps. (+)-linalool oxide was formed by treating the lactone **1.271** with DIBAL-H to form the lactol which was treated under modified Peterson conditions to afford (+)-linalool oxide with > 99% ds and 97% ee. The absolute configuration (*2*S,5*R*)-(+)-linalool oxide (**1.249**) was confirmed from the optical rotation which was in agreement with literature {$[\alpha]_D$ + 4.0 (c 0.028, $CHCl_3$, 20 °C)}.[106]

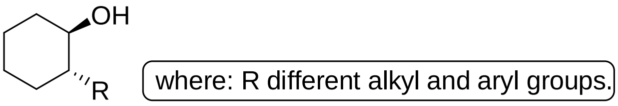
1.8- Conclusions

Linalool oxides are important constituents of many essential oils and are characteristic of fruit aromas. Linalool oxide is the name commonly given to a number of different structural and stereoisomers, which include four furanoid linalool oxides and four pyranoid linalool oxide. Different methodologies were applied in the synthesis of the furanoid linalool oxide as mixture of isomers and as a single enantiomer.

1.9- Aims & objectives of the project

The aims of this thesis are:

1- To synthesise different structures of cyclohexyl-based chiral auxiliaries (**Figure 1.15**).

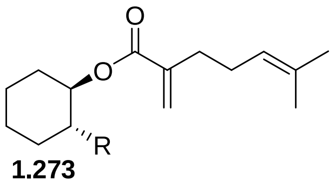


1.272

where: R different alkyl and aryl groups.

Figure 1.15

2- To synthesise 1,5-diene esters bearing different cyclohexyl-based chiral auxiliaries (**Figure 1.16**).

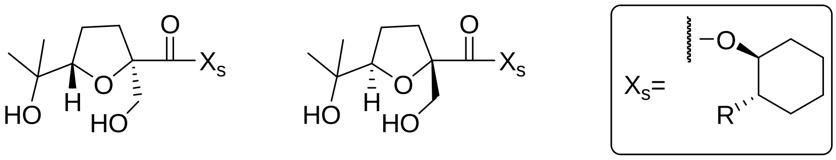


1.273

where: R different alkyl and aryl groups.

Figure 1.16

3- To study the oxidative cyclisation of 1,5-dienes and to determine the ratio of the two diastereoisomers **1.274** and **1.275** (**Figure 1.17**). This will allow us to identify the most effective auxiliaries.

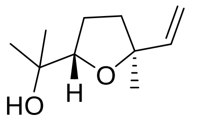


1.274 **1.275**

Figure 1.17

4- To resolve the cyclohexyl-based chiral auxiliary which gives high diastereoselectivity to it's enantiomers.

5- To apply enantiomerically pure chiral auxiliary in the total synthesis of (+)-linalool oxide (**1.247**) (**Figure 1.18**).



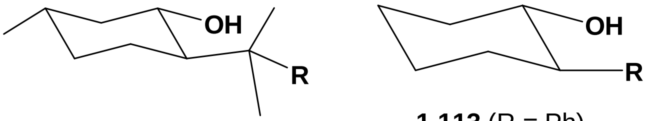
(+)-Linalool oxide (**1.247**)

Figure 1.18

6- To investigate other applications for the cyclohexyl-based chiral auxiliary.

Chapter 2: Results and Discussion

Enantiomerically pure cyclohexanols such as menthol (**1.112**) and 8-phenylmenthol (**1.108**) are some of the most widely used classical chiral reagents in organic chemistry, both for analytical and synthetic applications (**Figure 2.1**). Although (–)-(**1.108**) and (+)-(**1.108**) are powerful auxiliaries in asymmetric synthesis, synthetic routes starting from (+)-pulegone or (–)-pulegone, respectively, are rather laborious. This is also reflected in the high price of these reagents, and so more readily accessible substitutes for (–)-and (+)-(**1.108**) are highly desirable. Closely related structures are *trans*-phenyl- and *trans*-benzyl-cyclohexanols ((**1.113**) and (**2.1**) respectively). It was shown that (1*R*,2*S*)-(**1.113**) is as powerful as (–)-(**1.108**) for efficient absolute stereocontrol in the ene reactions of the *N*-sulfinylcarbamates.[107, 108]



(–)-**1.112** (R = H)
(–)-**1.108** (R = Ph)

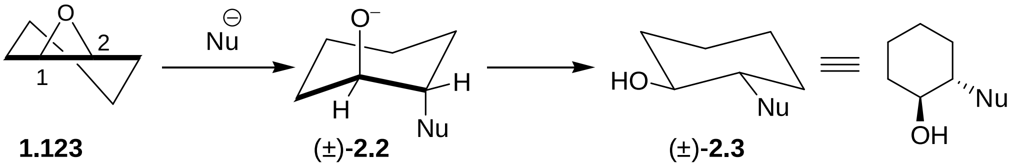
1.113 (R = Ph)
2.1 (R = Bn)

Figure 2.1. Known cyclohexanol-based chiral auxiliaries.

We considered that cyclohexanol-based chiral auxiliaries may be useful in controlling the diastereoselective oxidative cyclisation of 1,5-dienes. The first part of this study aimed to further investigate the synthesis of some cyclohexyl-based chiral auxiliaries and their application in the oxidative cyclization of 1,5-dienes.

2.1-Synthesis of cyclohexanol-based chiral auxiliaries

Racemic *trans*-2-substituted cyclohexanols have been synthesised many times.[109-115] Most conveniently, this class of compounds are prepared by stereospecific opening of epoxides by nucleophilic reagents. *Trans*-diaxial opening of the epoxides ensures that the products have the *trans*-configuration (**Scheme 2.1**)

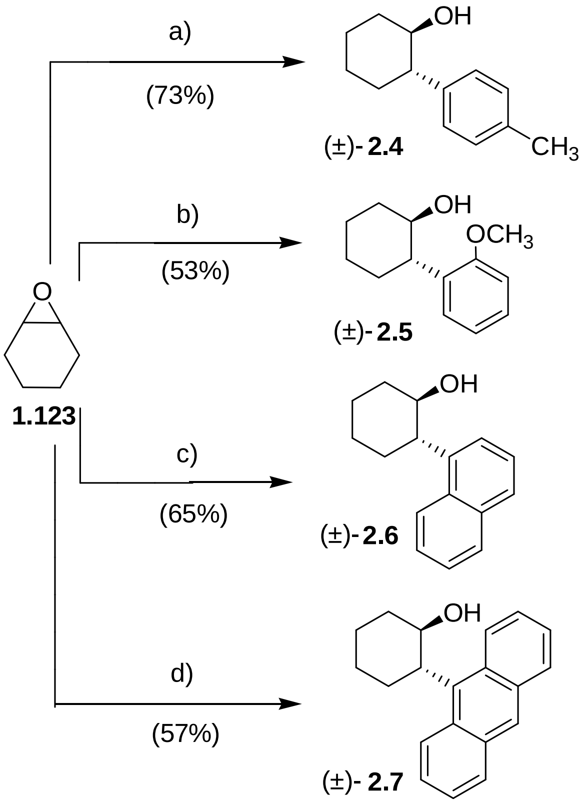


1.123 (±)-**2.2** (±)-**2.3**

Scheme 2.1. *Trans*-diaxial opening of cyclohexene oxide

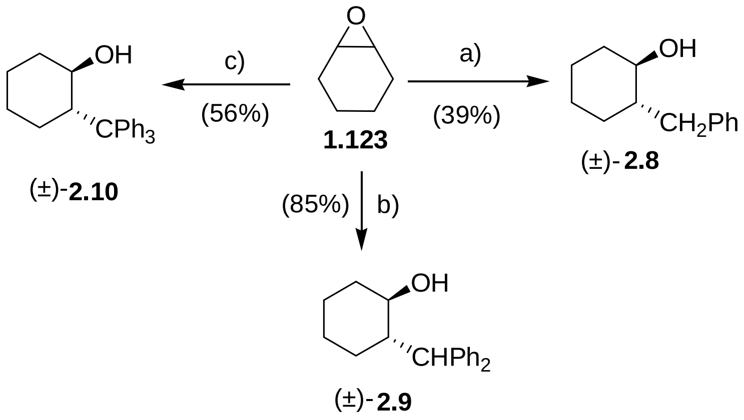
The reaction at C-2 gives the chair intermediate **2.2** and thence **2.3**. The transition state that leads to the chair intermediate is a lower energy process than that leading to the twist-boat. In principle, ring opening of cyclohexene oxides always leads directly to the *trans*-diaxial products,[116, 117] which may then undergo conformational change to their most stable conformation.

Initially, seven racemic cyclohexanol compounds were prepared for our study of the oxidative cyclization of 1,5-dienes. All of these compounds were formed by nucleophilic opening of cyclohexene oxide using carbanions. In most cases, the carbanions were prepared from aryl halides and alkyl halides. The cyclohexanols **2.4-2.10** were prepared by forming the Grignard reagent from the corresponding aryl halide. The cyclohexanols **2.4-2.6** were prepared following the procedures described by Schwartz *et al.*[58] Their synthesis was by formation of Grignard reagents from 4-bromotoluene, bromoanisole and 1-bromonaphthalene. The cyclohexanol **2.7** was prepared by combination of two procedures: first by following the procedure of Vance *et al.*[118] for the preparation of 9-anthracenylmagnesium bromide by reacting 9-bromoanthracene (1.0 equiv.) with magnesium turnings (2.0 equiv.) in dry ether (concentration of reactants = 1.2 M). The preparation was under reflux for 23 hours and the rest of the synthesis was by following the procedure of Schwartz *et al.*[58] The aryl Grignard reagents reacted with cyclohexene oxide in the presence of catalytic copper(I) bromide (**Scheme 2.2**).



Scheme 2.2. Synthesis of *trans*-2-arylcyclohexanols from aryl halides. **Reagents & conditions:** a) Mg, 4-bromotoluene, THF, then CuBr, –30 to rt, 2 h; b) Mg, 2-bromoanisole, THF, then CuBr, –30 to rt, 3 h; c) Mg, 1-bromonaphthalene, THF, then CuBr, –30 to rt, 205 min; d) Mg, 9-bromoanthracene, Et_2O, then CuBr, –30 to rt, 27 h.

It was also decided that a selection of cyclohexanols, contained a carbon spacer between the aromatic ring and the cyclohexane should be included in our study. Indeed, *trans*-2-benzyl cyclohexanols were already known to be excellent chiral auxiliaries (e.g. 8-phenylmenthol etc.) in certain reactions.[55] Therefore, to explore the effect of extending the distance of the aromatic ring(s) from the cyclohexane ring by one carbon, three cyclohexanols **2.8**, **2.9** and **2.10** were synthesised (**Scheme 2.3**).



Scheme 2.3. Synthesis of cyclohexanol-based chiral auxiliaries from alkyl halides. **Reagents & conditions:** a) Mg, BnCl, THF, −78 to rt, 52 h; b) diphenyl methane, *n*-BuLi, THF -78 to rt, 7 h; c) triphenylmethane, *n*-BuLi, THF, −78 to rt, 12 h.

The *trans*-2-benzylcyclohexanol (±)-**2.8** was prepared by following the procedures of Wong *et al.*[119] by reacting benzylmagnesium chloride (1.44 equiv.) with cyclohexene oxide (1.0 equiv.). The benzylmagnesium chloride was formed by reacting benzyl chloride (1.0 equiv.) with magnesium turnings. The *trans*-2-diphenylmethyl and *trans*-2-triphenylmethyl cyclohexanol (±)-**2.9** and (±)-**2.10** were prepared by reacting the diphenylmethyl lithium or triphenylmethyl lithium (1.0 equiv.) respectively with cyclohexene oxide (2.5 equiv.) overnight at room temperature.[120] The alkyl (diphenylmethyl and triphenyl methyl) lithium anions were formed first by direct deprotonation of the parent acids with *n*-BuLi at −78 °C. Pleasingly, all of the chiral auxiliaries formed are solid and stable at room temperature. An X-ray structure of racemic *trans*-2-trityl cyclohexanol **2.10** was obtained showing it to exist in the stable chair conformation (**Figure 2.2**).

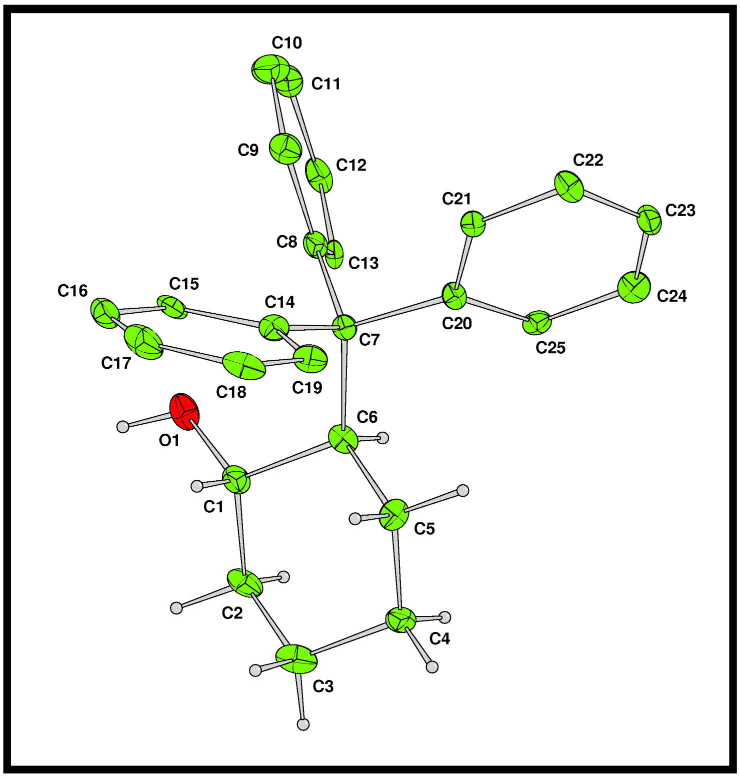
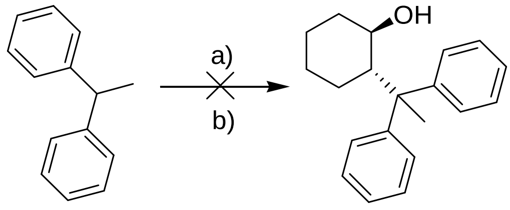


Figure 2.2. X-ray structure for racemic *trans*-2-trityl cyclohexanol **2.10**.

2.1.1 – Attempts toward the synthesis of (±)-*trans*-2-(1,1-diphenylethyl) cyclohexanol:

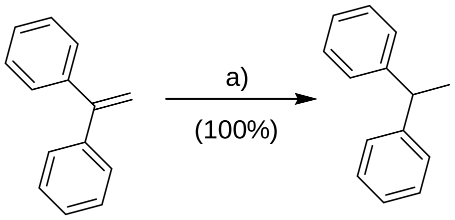
In order to see the effect of replacing one of the methyl groups in TCC with a phenyl group, the synthesis of (±)-*trans*-2-(1,1-diphenylethyl)cyclohexanol was investigated. The anion of 1,1-diphenylethane was formed by using *n*-BuLi (1.0 equiv.) or using *n*-BuLi (2.0 equiv.) with TMEDA (2.0 equiv.) in THF as solvent at – 78 °C (**Scheme 2.4**). The formation of the anion was indicated by the change in the solution colour to blood-red. Cyclohexene oxide (2.5 equiv.) was added dropwise to the anion in the both cases. Unfortunately, the NMR analysis showed no signals corresponding the desired alcohol **2.12**.



2.11 (±)-**2.12**

Scheme 2.4. Attempted synthesis of (±)-*trans*-2-(1,1-diphenylethyl) cyclohexanol. **Reagents & conditions:** a) *n*-BuLi, THF, − 78 °C to rt or *n*-BuLi, TMEDA, − 78 °C to rt, b) cyclohexene oxide, overnight.

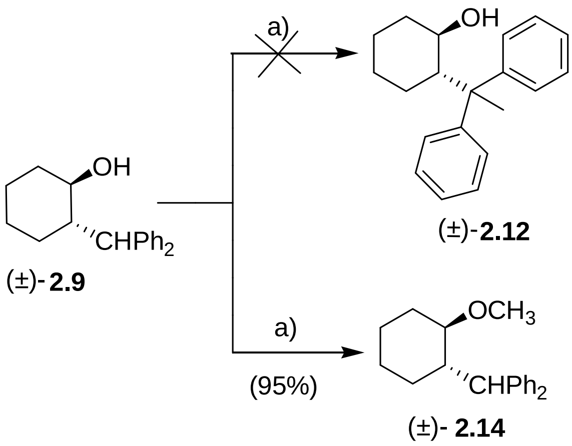
The starting material 1,1-diphenylethane (**2.11**) is not commercially available. Therefore, it was prepared by reducing 1,1-diphenylethylene (**2.13**) following the procedure of Gordon *et al.* (**Scheme 2.5**).[121]



2.13 **2.11**

Scheme 2.5. Synthesis 1,1-diphenylethane. **Reagents & conditions:** a) I_2, H_2PO_3, AcOH, 24 h reflux.

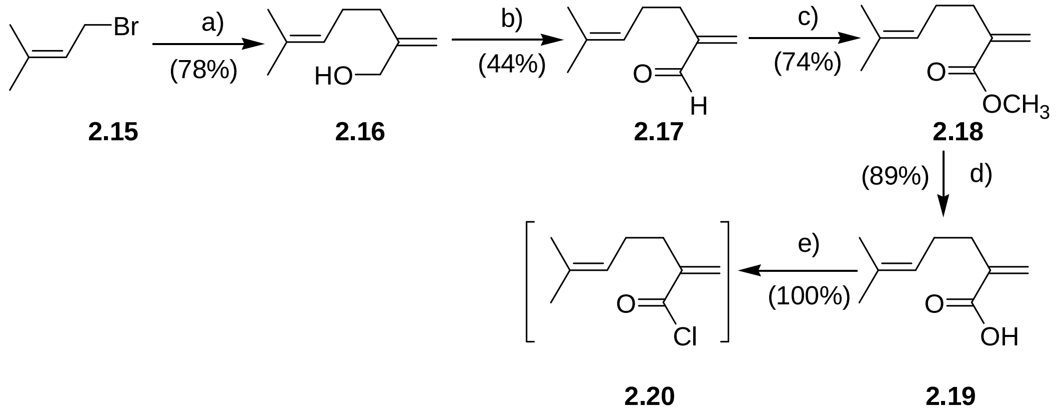
Finally, we attempted to synthesise (±)-*trans*-2-(1,1-diphenylethyl) cyclohexanol ((±)-**2.12**) by forming the dianion from 2-diphenylmethyl-1-cyclohexanol using NaH (1.0 equiv.) and *n*-BuLi (1.0 equiv.) in THF, followed by addition of methyl iodide. The reaction gave (±)-*trans*-2-diphenylmethyl-1-methoxycyclohexane ((±)-**2.14**) in quantitative yield (**Scheme 2.6**). Presumably dianion formation was unsuccessful.



Scheme 2.6. Synthesis of (±)-*trans*-2-diphenylmethyl-1-methoxycyclohexane. **Reagents & conditions:** a) i) NaH, THF, 0 °C, 1 h, ii) *n*-BuLi, THF, – 78 °C, 0.5 h, iii) MeI, – 78 °C to rt, 3 h.

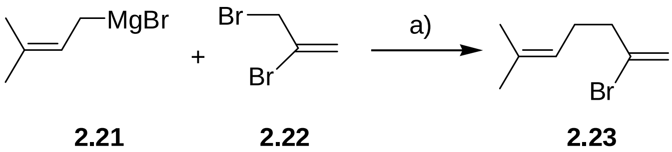
2.2-Synthesis of methyl-2-methylenehept-5-enoyl chloride intermediate

In order to carry out our study in the oxidative cyclisation of 1,5-dienes under the influence of the prepared cyclohexanols **2.4**-**2.10**, the synthesis of the dienoyl chloride **2.20** was achieved in good yield by following a 5 step sequence (**Scheme 2.7**) previously established in our group.[122] The alcohol **2.16** was synthesised in good yield by following the procedure of Taber *et al.,* [123] by reacting the bromide **2.15** with the dianion of methallyl alcohol. The aldehyde **2.17** was prepared by oxidation of alcohol **2.16** using activated manganese dioxide (17 equiv.) in *n*-hexane. The aldehyde **2.17** then was converted to the ester **2.18** following Corey-Gilman-Ganem oxidation.[124] The ester **2.18** was used without further purification in the hydrolysis reaction to give the acid **2.19** in excellent yield.[125] In these preliminary studies, the coupling reaction with cyclohexanol auxiliaries was carried out on a small scale and was not optimised. Preparation of the dienoyl chloride intermediate **2.20** was achieved conveniently by reacting the acid **2.19** with oxalyl chloride (4.75 equiv.) in presence of DMF (1.0 equiv.) as a catalyst in hexane as a solvent.[126] The use of hexane as solvent was an important modification reported by Ward *et al.* because the intermediate *N*-(chloromethylene)-*N*-methylmethanaminium chloride (DMFCI) is solid in hexane and can be removed by filtration. The crude acid chloride **2.20** was used in the subsequent coupling reactions with cyclohexanol auxiliaries (**Scheme 2.7**).



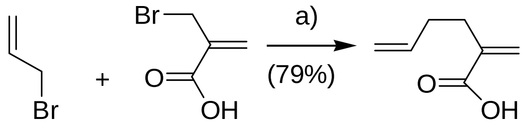
Scheme 2.7. Synthesis of methyl-2-methylenehept-5-enoyl chloride **2.20**. **Reagents & conditions:** a) *n*-BuLi, TMEDA, $CH_3C(=CH_2)CH_2OH$, Et_2O, −78 °C to rt, 22 h; b) MnO_2, *n*-hexane, 0 °C to rt, 1 h; c) NaCN, MnO_2, MeOH, AcOH, rt, 17.5 h; d) NaOH, $NaHCO_3$, H_2O, MeOH, Reflux, 6 h; e) $(COCl)_2$, DMF, hexane, rt, 1 h.

After following the previously established 5 step sequence for the synthesis the acid chloride **2.20**, we decided to investigate alternative methodologies to prepare the acid **2.19**. Corey *et al.* reported the synthesis of the diene **2.23**. Reaction of 3,3-dimethylallylmagnesium bromide with 2,3-dibromoprop-1-ene afforded the diene **2.23** in the presesnce of CuCN in THF as a solvent (**Scheme 2.8**).[127]



Scheme 2.8. Synthesis of diene **2.23**. **Reagents & conditions:** a) CuCN, THF, rt.

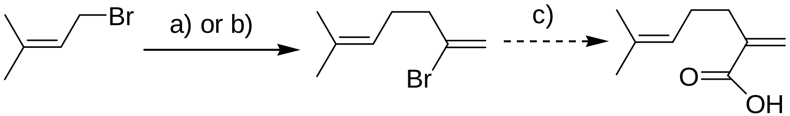
Chan *et al.* reported the synthesis of the acid **2.26** by reacting α-bromomethyl acrylic acid with allyl bromide in the presence of manganese and copper(II) chloride in aqueous medium.[128] This is an interesting reaction in that an organometallic species is generated in water, to produce the unsymmetrical coupling product. Excess allyl bromide is employed, giving the diene **2.26** in good yield (**Scheme 2.9**).



2.24 **2.25** **2.26**

Scheme 2.9. Synthesis of 2-methylenehex-5-enoic acid. **Reagents & conditions:** a) Mn, CuCl(II), THF, H_2O, rt, 16 h.

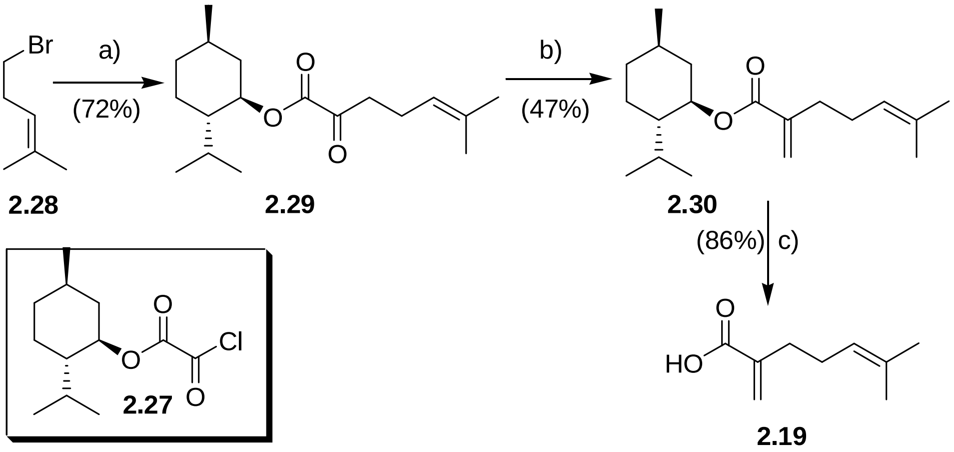
Attempts were made to synthesise the diene **2.23** following these literature procedures. None of the desired products were observed from NMR analysis of the reaction mixtures (**Scheme 2.10**).



2.15 **2.23** **2.19**

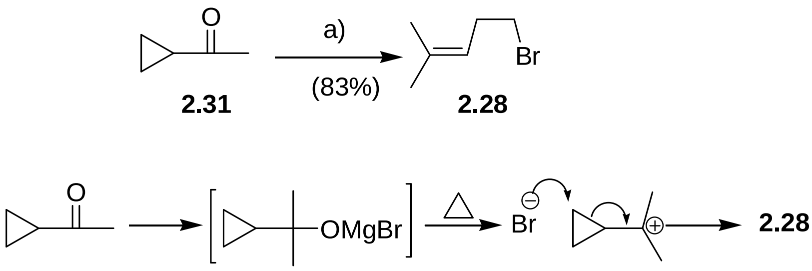
Scheme 2.10. Proposed route to 6-methyl-2-methylenehept-5-enoic acid. **Reagents & conditions:** a) 1) Mg, THF, reflux, 2) 2,3-dibromoprop-1-ene, b) Mn, CuCl(II), THF, H_2O, rt, 48 h, c) *t*-BuLi, CO_2.

After the unsuccessful trials to make the the diene **2.23**, we deciced to investigate the synthesis of α-keto esters which can be converted to α,β-unsaturated esters. Therefore, the synthesis of the acid **2.19** was achieved by following a 3 steps sequence. The first step was carried out by following the procedure of Babudri *et a1.*[129] by reacting the freshly prepared (–)-menthoyl ester **2.27** with the Grignard reagent of bromide **2.28** (1.2 equiv.) in THF at –78 °C to give the ester **2.29** in 72% yield. The dienoyl ester **2.30** was formed in 47 % yield by Wittig reaction.[130] Subsequent hydrolysis of the ester **2.30** afforded the acid **2.19** in good yield (**Scheme 2.11**).



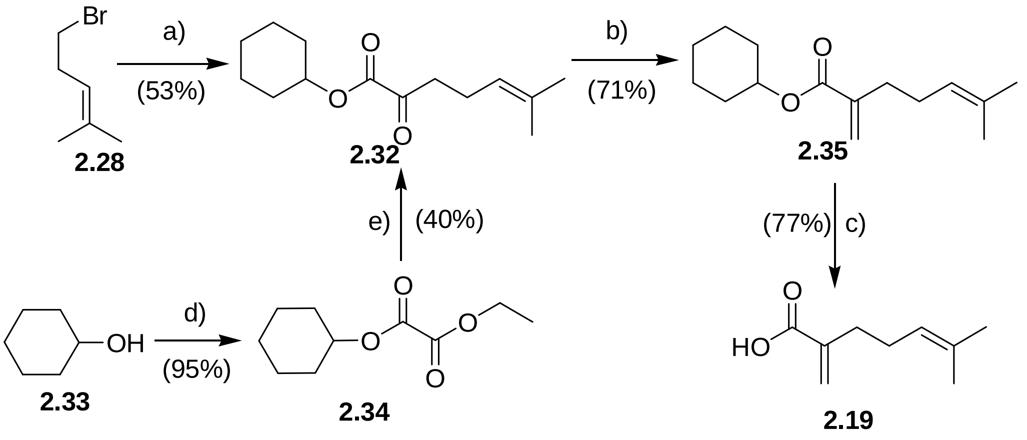
Scheme 2.11. New synthetic route towards 6-methyl-2-oxohept-5-enoic acid. **Reagents & conditions:** a) 1) Mg, THF, rt to reflux, 1 h, 2) CuBr, LiBr, **2.27**, −78 °C, 30 min; b) Ph_3PCH_3Br, LDA, rt, 4 h; c) NaOH, $NaHCO_3$, H_2O, MeOH, Reflux, 6 h.

The bromide **2.28** which was used in the first step was prepared by reacting cyclopropyl methyl ketone with methylmagnesium bromide in THF as a solvent (**Scheme 2.12**). [131]



Scheme 2.12. Synthesis of bromide **2.28**. **Reagents & conditions:** a) Methylmagnesium bromide, THF, rt to reflux, 50 min.

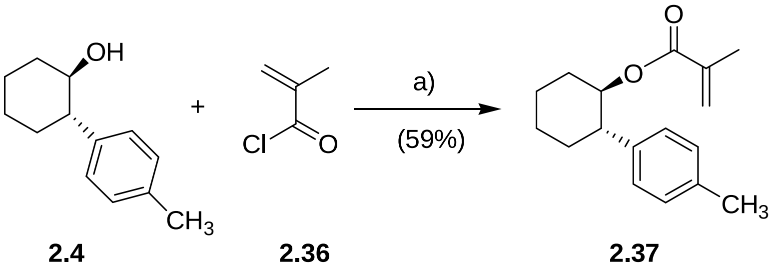
Finally, an alternative synthesis of the acid **2.19** was investigated. Starting from bromide **2.28** in a three step sequence or starting the cyclohexanol **2.33** in 4 steps. The two established routes proceeded in good yields (**Scheme 2.13**).



Scheme 2.13. New synthetic routes towards 6-methyl-2-oxohept-5-enoic acid. **Reagents & conditions:** a) 1) Mg, THF, rt to reflux, 1 h, 2) CuBr, LiBr, cyclohexyl (chlorocarbonyl)formate, −78 °C, 30 min; b) Ph_3PCH_3Br, DBU, reflux, 4 h; c) NaOH, $NaHCO_3$, H_2O, MeOH, Reflux, 6 h; d) 1) Et_3N, CH_2Cl_2, 0°C, 45 min, 2) DMAP, Ethyl chloro oxoacetate, 1.5 h; e) Grignard of bromide **2.28**, THF, −78 °C, 1 h.

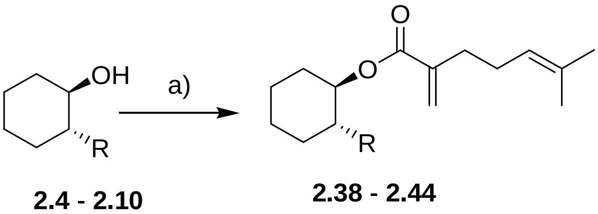
2.3-Synthesis of chiral auxiliary-diene ester adducts

Before attempting to couple the dienoyl chloride **2.20** with the cyclohexanol auxiliaries, a model esterfication was carried out between the cyclohexanol **2.4** and methacryloyl chloride **2.36** (**Scheme 2.14**). The desired ester **2.37** was formed in 59% yield.



Scheme 2.14. Synthesis of a model enoate ester. **Reagents & conditions:** (a) NaHMDS, THF, – 35 to rt, 2 h.

Given the hindered nature of some of the auxiliaries (eg (±)-**2.10**) and the reduced reactivity of α,β-unsaturated acid chlorides we opted to form the alkoxide anion to promote esterfication of the alcohol. After the successful coupling reaction of the chiral auxiliary **2.4** with model acid chloride, the chiral auxiliaries **2.4-2.10** were coupled with the dienoyl chloride **2.20** under the same conditions to form the dienes esters **2.38-2.44** in reasonable yields (30-68%) (**Scheme 2.15 & Table 2.1**). The coupling reactions were carried out in dry THF for esters **2.38-2.42** by reacting chiral auxiliary (1.05 equiv.) with the dienoyl chloride (1.0 equiv.) using NaHMDS (1.2 equiv.). For preparation of esters **2.43** and **2.44** the solvent was changed to dry ether and 2.10 equiv. of the auxiliary and 2.40 equiv. of NaHMDS were used.

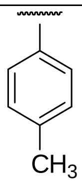
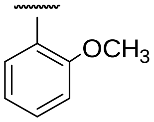
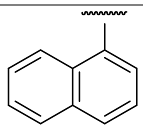
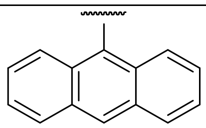


2.4 - 2.10

2.38 - 2.44

Scheme 2.15. Synthesis of dienoates **2.38-2.44**. **Reagents & conditions:** a) 1) NaHMDS, THF or Et_2O, – 35 to –25 °C, 30 min, 2) **2.20**, rt, 2-4 h.

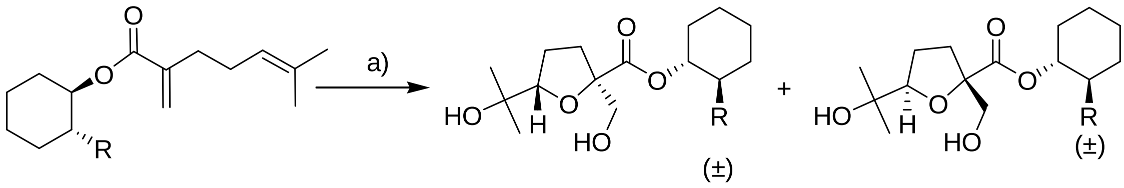
Table 2.1. Synthesis of dionates **2.38-2.44**

Entry	Substituent R	Solvent	Reaction time (h)	Yield[a] %
1	 **2.38**	THF	3.0	57 %
2	 **2.39**	THF	3.0	61 %
3	 **2.40**	THF	2.75	68 %
4	 **2.41**	THF	2.75	64 %
5	$-CH_2Ph$ **2.42**	THF	3.5	56 %
6	$-CHPh_2$ **2.43**	Et_2O	4.0	43 %
7	$-CPh_3$ **2.44**	Et_2O	1.5	30 %

a) Yield given is for purified isolated compounds.

2.4-Oxidative cyclisation reactions

With the required dienoates **2.38-2.44** in hand, we were now in a position to investigate how the structure of the auxiliaries influenced the diastereoselectivities of the permanganate oxidative reaction. Therefore, the esters **2.38-2.44** were subjected to the oxidative cyclization to form THF diols **2.45a-2.51a** and **2.45b-2.51b** using conditions developed in the group (**Scheme 2.16**).[132] The oxidation reaction was carried out by using 1.35 equiv. of sodium permanganate (in the presence of phosphate buffer (1/15M aq. sol. of both KH_2PO_4 and NaH_2PO_4 in volumetric ratio 8:2) and glacial acetic acid (2.95 equiv.) in acetone as a solvent.

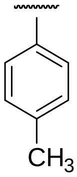
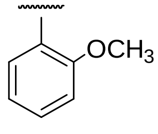
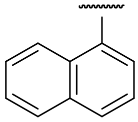
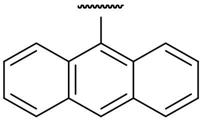


2.38-2.44 **2.45a-2.51a** **2.45b-2.51b**

Scheme 2.16. The oxidative cyclization of 1,5-dienes **2.38-2.44**. **Reagents & conditions:** a) $NaMnO_4$ (0.4 M aq. sol.), Phosphate buffer (KH_2PO_4 : NaH_2PO_4 , 8:2 aq. sol.), AcOH, Acetone, −22 to −5 °C, 1-3 h.

It was found that the diastereoselectivity was low when the chiral auxiliaries were (±)-*trans*-2-*p*-tolylcyclohexanol, (±)-*trans*-2-(2-methoxyphenyl)cyclohexanol and (±)-*trans*-2-(naphthalen-1-yl)cyclohexanol. The ratio of the two diastereoisomers were approximately 1:1. The diastereoselectivity was improved slightly when the chiral auxiliary was (±)-*trans*-2-(anthracen-9-yl)cyclohexanol, (±)-*trans*-2-benzylcyclohexanol and (±)-*trans*-2-benzhydrylcyclohexanol. The diastereoisomeric ratio was 1.75:1, 1.32:1 and 1.79:1 respectively. In the case of (±)-*trans*-2-tritylcyclohexanol, the diastereoselectivity was improved dramatically (dr = 97:3) (**Table 2.2**).

Table 2.2. Diastereoselectivity for oxidative cyclizations reaction.

Entry	Substituent R	Reaction time (h)	Yield %[a]	Diastereoisomeric ratio[b,c] (a:b)
1	 **2.45**	1.0	56%	**1:1**[d]
2	 **2.46**	2.75	89%	**1.03:1**
3	 **2.47**	2.5	95%	**1.08:1**
4	 **2.48**	4.0	69%	**1.75:1**
5	$-CH_2Ph$ **2.49**	2.0	82%	**1.32:1**
6	$-CHPh_2$ **2.50**	3.0	99%	**1.79:1**
7	$-CPh_3$ **2.51**	3.0	61%	**32.3:1**

a) Yield given is for purified isolated compounds. b) Determined by HPLC analysis (column: Agilent Zobax Sil C18 (5 µm, 4.6 × 250 mm), flow rate: 0.5 mL/min, eluent: 5% isopropanol/hexane). c) The stereochemistry of the major diastereoisomer has been tentatively assigned as the 2*R*,5*S*-isomer in all cases. It has been proven for the triphenylmethyl derivative **2.51** (see later), d) estimated from ^{13}C-NMR.

2.5- Conclusions

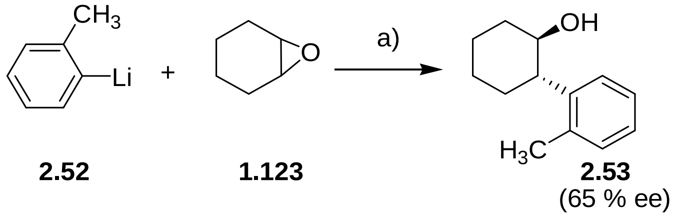
Seven cyclohexanol-based chiral auxiliaries **2.4-2.10** were prepared in moderate to good yields (38-85%) and coupled with the dienoyl chloride **2.20** to afford diene esters **2.38-2.44** in yields between 30 – 68%. Oxidative cyclisation reactions of the diene esters **2.38-2.44** gave the THF diols **2.45-2.51** in high yield (58 to 98%) but with variable diastereoisomeric ratios. *Trans*-2-substituted cyclohexanols containing simple aryl groups gave very low levels of diastereoinduction, the best result being anthracenyl derivative which afforded the THF diol diastereoisomers in a ratio of 1.75:1 (estimated from HPLC chromatogram). The diastereoisomeric ratio was 1.32:1 and 1.79:1 in case of (±)-*trans*-2-benzylcyclohexanol and (±)-*trans*-2-benzhydrylcyclohexanol respectively. In case of (±)-*trans*-2-trityl-1-cyclohexanol, the diastereoselectivity was improved dramatically (dr = 97:3). Improved syntheses of the dienoic acid **2.19** were also developed, resulting in a route requiring 3 steps and 29% overall yield.

2.6- Towards enantiomerically pure (±)-*trans*-2- triphenylmethyl-1-cyclohexanol

During our preliminary oxidative cyclisation studies using different racemic cyclohexanol-based chiral auxiliaries, seven chiral auxiliaries were synthesised. Excellent selectivity was achieved by using (±)-*trans*-2-triphenylmethyl-1-cyclohexanol, and we wanted to explore the use of this auxiliary further.

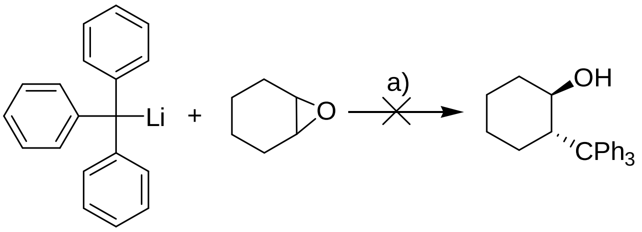
In order for the (±)-*trans*-2-triphenylmethyl-1-cyclohexanol to be useful as a chiral auxiliary, we required a convenient method to obtain it as a single enantiomer. Several options were considered including asymmetric synthesis, enzymatic resolution and classical resolution. Our first studies investigated the option of preparing the auxiliary by asymmetric synthesis.

The concept of the combination of an organolithium reagent and a chiral Lewis base for enantioselective reactions has been widely explored. Similarly, the combination of an organolithium and BF_3 also been extensively studied. Mangeney *et al.*[133] used an organolithium reagent in combination with a strong chiral Lewis base and BF_3 for the enantioselective nucleophilic ring-opening of various *meso*-oxiranes. They carried out their study in different conditions. Among the organolithium species they used was *o*-methylphenyllithium (**Scheme 2.17**).



Scheme 2.17. Enantioselective ring-opening of cyclohexene oxide reported by Mangeney *et al.*[133] **Reagents & conditions:** a) (–) sparteine (2 equiv.), Lewis acid (1.5 equiv.), Et_2O, – 78 °C.

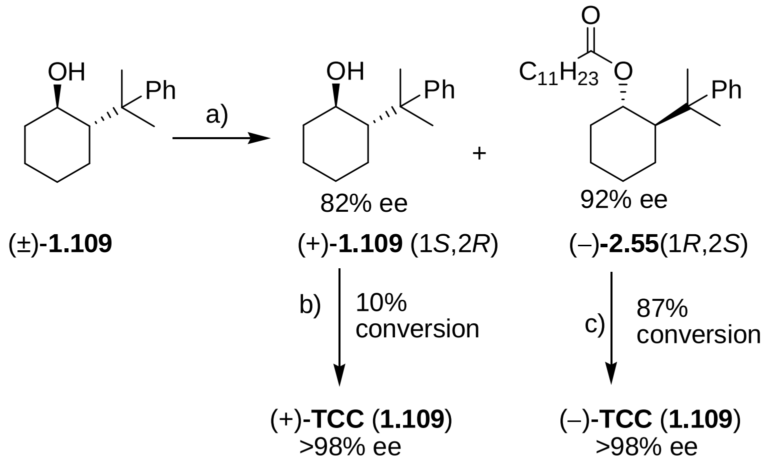
Our intial attempt was to prepare *trans*-2-triphenylmethyl-1-cyclohexanol in enantiomerically enriched form by following the same procedure reported by Mangeney *et al.* In this procedure freshly prepared triphenylmethyllithium was added to a vigriously stirred solution of cyclohexene oxide in the presence of $BF_3.Et_2O$ and (–)-sparteine. Unfortunately, no reaction was observed after 4 hours (**Scheme 2.18**). We did not explore the asymmetric synthesis route any further.



2.54 **1.123** **2.10**

Scheme 2.18. Enantioselective ring-opening of cyclohexene oxide. **Reagents & conditions:** (–) sparteine (1.0 equiv.), $BF_3.Et_2O$ (1.0 equiv.), Et_2O, –78 °C.

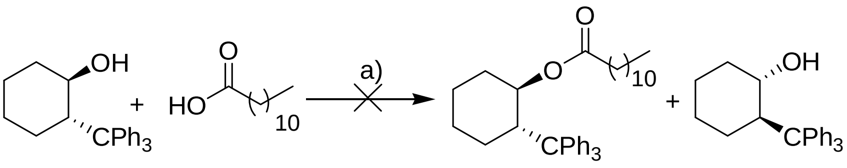
In recent years, biocatalytic methodology has become routinely applied in organic synthesis.[134-141] Kinetic resolution, using an enzyme or crude extract, is often a very efficient method to selectively convert one enantiomer of a racemic mixture to an enantiomerically enriched product, which can be separated. Comins *et al.* reported the enzymatic resolution of (±)-*trans*-2-(α-cumyl)cyclohexanol ((±)-TCC) using Lipase AY 30 (**Scheme 2.19**).[59]



Scheme 2.19. Resolution of (±)-TCC. **Reagents & conditions:** lipase AY 30, lauric acid, cyclohexane, 40 °C; b) i) lipase AY 30, lauric acid, cyclohexane, 40 °C, ii) KOH, EtOH; c) 1) KOH, EtOH, 2) lipase AY 30, lauric acid, cyclohexane, 40 °C, 3) KOH, EtOH.

We decided to apply this strategy to the resolution of (±)-TTC. Our intial attempt at enzymatic esterfication of (±)-TTC was by following the method of Langrand *et al.*[142] This method involved the reaction between the cyclohexanol auxiliary (±)-**2.10** (1.0 equiv.) and lauric acid (1.0 equiv.) in the presence of the Lipase Amano 30 catalyst using cyclohexane as the solvent.

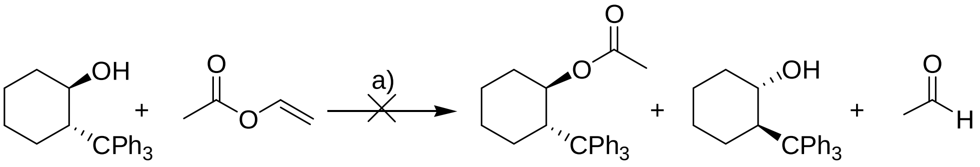
The reaction was followed by thin layer chromatography. After 48 hours there was no sign of any conversion to the product (**Scheme 2.20**).



(±)-**2.10** **2.56** (+)-**2.57** (–)-**2.10**

Scheme 2.20. Attempted enzyme-catalysed esterfication of (±)-*trans*-2-triphenylmethyl-1-cyclohexanol. **Reagents & conditions:** lauric acid (1.0 equiv.), Lipase Amano 30, cyclohexane, 40 °C, 48 h.

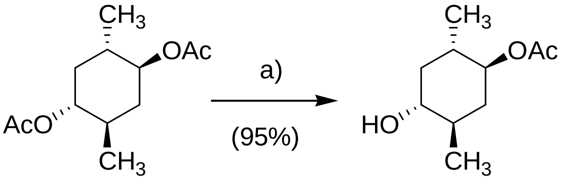
Another attempt to make the ester using the same enzyme was carried out subsequently following the procedure of Soro *et al.*, [143] using vinyl acetate (5.0 equiv.) in diethyl ether as a solvent (**Scheme 2.21**). Unfortunately, this experiment also gave no reaction.



(±)-2.10 **2.58** (+)-**2.59** (–)-**2.10** **2.60**

Scheme 2.21. Attempted enzyme-catalysed acetylation of (±)-*trans*-2-triphenylmethyl-1-cyclohexanol **2.10**. **Reagents & conditions:** a) vinyl acetate (5.0 equiv.), Lipase Amano 30, Et_2O, 40 °C, 48 h.

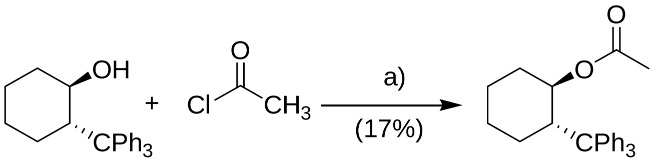
Arguably, estrases such as pig liver estrase (PLE) have proven to be the most widely successful enzymes in asymmetric synthesis. They are cheap, stable, do not require a coenzyme and tolerate a wide variety of substrates. Bohm *et al.*[144] used PLE to catalyse the hydrolysis of cyclohexane diacetate (**Scheme 2.22**). The hydrolysis gave rise to the enantiomerically pure cyclohexanediol monoacetate in 95% yield and more than 99.5 % ee.



2.61 **2.62**

Scheme 2.22. Enzymatic hydrolysis of the cyclohexane diacetate.[144] **Reagents & conditions:** a) PLE, H_2O.

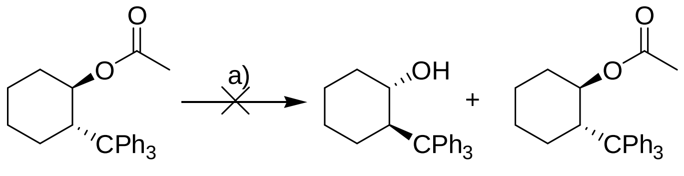
We were attracted by the high selectivity reported for the hydrolysis of the many acetates by PLE. As we had already attempted the enzymatic esterfication reactions to resolve the two enantiomers of the auxiliary, we reinvestigated the use of the esterase for the hydrolysis of the racemic esters (±)-**2.64**. We began by preparing the acetyl ester of the auxiliary by reacting the auxiliary with acetyl chloride following deprotonation of the auxiliary (±)-**2.10** with NaHMDS (**Scheme 2.23**).



(±)-**2.10** **2.63** (±)-**2.64**

Scheme 2.23. Preparation of (±)-cyclohexanol auxiliary acetate. **Reagents & conditions:** a) acetyl chloride (2.0 equiv.), NaHMDS (2.0 equiv.), Et_2O.

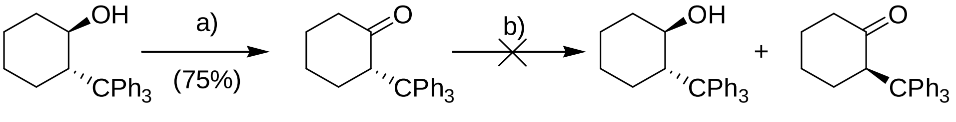
It was found that the yield was low (17%). We concluded this low yield was due to steric hinderence caused by the cyclohexanol auxiliary preventing reaction at the hydroxyl group. Fortunately, a further experiment was performed to prepare the same ester using 4 equivalents of acetyl chloride and using pyridine/ether (3:1 ratio) as the solvent, the concentration of reactants was (0.13M). The yield improved to 87%. The ester (±)-**2.64** was used in the first trial of enzyme-catalysed hydrolysis following the procedure of Bohm *et al.*[144] using 2 units of PLE enzyme in Tris-HCl buffer (pH = 7.5) (**Scheme 2.24**).



Scheme 2.24. Pig liver esterase catalysed hydrolysis of acetyl ester of the cyclohexanol chiral auxiliary. **Reagents & conditions:** a) PLE , H_2O (buffer, pH = 7.5).

Unfortunately, after 48 h the reaction was stopped with no sign of hydrolysis observed by TLC or ^{1}H-NMR. In addition, no reaction was observed in the hydrolysis of the same ester using novozyme 435 in 10% water/*t*-BuOH (Ester concentration = 2.71 x 10^{-3}M)

It has been reported that Baker's yeast reduction of ketones can provide an alternative to alcohol resolution.[145, 146] Therefore, the cyclohexanol chiral auxiliary was converted to the ketone using Dess-Martin periodinine in a yield of 75% (**Scheme 2.25**).

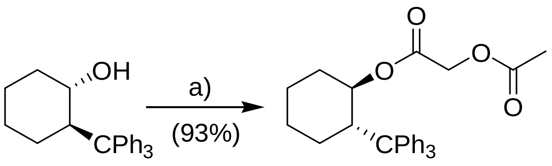


(±)-**2.10** **2.65** (+)-**2.10** **2.65**

Scheme 2.25. Preparation and reduction of (±)-*trans*-2-triphenylmethylcyclohexan-1-one. **Reagents & conditions:** a) DMP, CH_2Cl_2, −10 °C; b) Hovis baker's yeast, sucrose, ether/ethanol/water, rt, 7 days.

Following the method of Zueger *et al.*, [147] the attempted reduction was performed in a mixture of ether/ethanol/water (concentration of the cyclohexanone = 0.03 M) and by using a forcing amount of Hovis baker's yeast (4.1 g) in the presence of sucrose (0.27 g). The reaction was stopped after 7 days. From the crude ^{1}H-NMR, there was no sign of the reaction proceeding (**Scheme 2.25**).

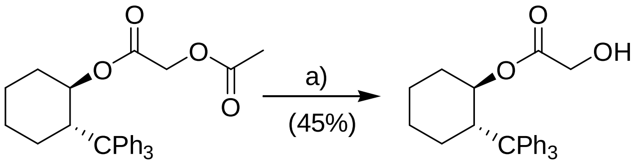
At this point it was conceeded that the trityl group was too sterically demanding to permit reactions at C1 of the cyclohexanol/cyclohexanone. Therefore the reaction site was moved away from trityl group. A new ester derivative was considered as a substrate, which was prepared by reacting acetoxyacetyl chloride with the cyclohexanol chiral auxiliary. This was successful using pyridine/ether solvent 3:1 ratio giving the ester **2.66** in 93% yield (**Scheme 2.26**).



(±)-**2.10** (±)-**2.66**

Scheme 2.26. Preparation of (±)-**2.66** containing a spacer between the cyclohexanol and the reaction site. **Reagents & conditions:** a) acetoxyacetyl chloride (4.0 equiv.), pyridine/ether solvent (3:1), rt, overnight.

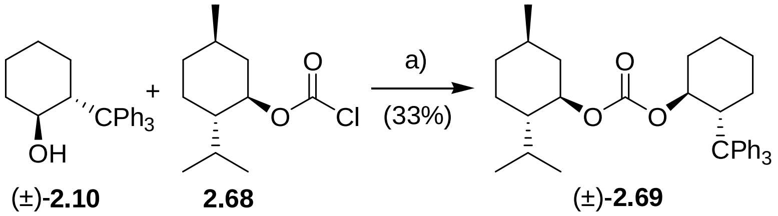
Lipase Novozyme 435 was used to catalyse the hydrolysis of the racemic ester (±)-**2.66**. The hydrolysis reaction was carried out in 10% water/*t*-BuOH (Ester concentration = 2.71x10^{-3} M) at 40 °C (**Scheme 2.27**).



(±)-**2.66** (±)-**2.67** (12.5 ee)

Scheme 2.27. Enzymatic hydrolysis of ester (±)-**2.66**. **Reagents & conditions:** a) Lipase Novozyme 435, 10% water/*t*-BuOH, 24 h.

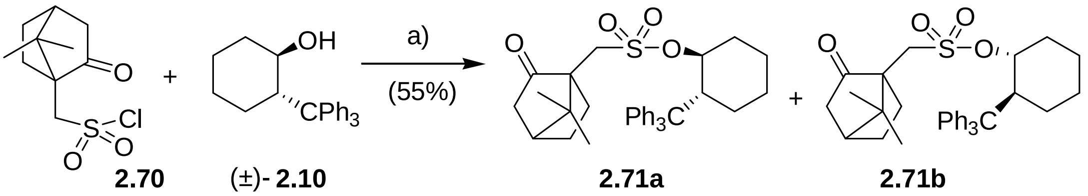
After 24 hours the ester **2.67** was formed in 45 % yield in 12.5 ee. Due to the disappointing results from the asymmetric synthesis and enzymatic resolution for the auxiliary (±)-**2.10**, we decided to look at classical resolution. Several attempts were made to resolve the chiral auxiliary (±)-**2.10** by using commercially available resolving agents. The first was by reacting the chiral auxiliary with (–)-menthoyl chloroformate (2.6 equiv.) in pyridine/ether (2:1) as solvent (**Scheme 2.28**). The reaction was continued for 60 h, although not all of the alcohol (±)-**2.10** was consumed. The product was recrystallised directly from the crude reaction mixture in hexane. ^{1}H-NMR showed that the ratio of the two isomers to be 3.5:1 in the recrystallised material.



Scheme 2.28. Synthesis of ester (±)-**2.69**. **Reagents & conditions:** a) Pyridine, ether, rt, 60 h.

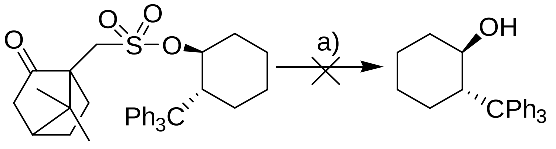
The product was recrystallised a second time from different solvent mixtures (*i*PrOH/hexane (2:1), pentane and ethanol). All the recrystallisation trials gave the same ratio 3.5:1 without improvement in de. The ratio of the isomers was estimated from the ^{1}H-NMR spectrum. The reaction was repeated using 2 equiv. of the chiral alcohol against 1.0 equiv. of menthoyl chloride to give the ester in a yield of 4% after 24 h. Interstingly, the ratio remained the same 3.5:1 from the two isomers. Attempted *trans*-esterfication of the carbonate (±)-**2.69** was unsuccessful at room temperature, underlining the hindered nature of the substrate. In view of the poor results from resolution, this chemistry was not investigated further.

Another trial was carried out with another resolving agent by following the procedure of Hirai.[148] (1*S*)-(+)-10-Camphor sulfonyl chloride was reacted with the cyclohexanol (±)-**2.10** in the presence of NaHMDS and DMAP in THF as solvent to give the sulfonate ester in good yield (**Scheme 2.29**).



Scheme 2.29. Synthesis of sulfonate ester **2.71a** and **2.71b**. **Reagents & conditions:** a) NaHMDS, DMAP, THF, – 78 °C to rt, 2 h.

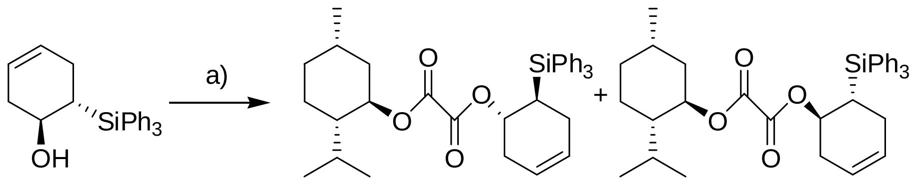
The two diastereoisomers were separated by column chromatography. Interestingly, they were formed in a ratio of 3.6:1. The diastereoisomeric ratio was estimated from the ^{1}H-NMR spectrum. Unfortunately, atempted hydrolysis of the sulfonate ester was unsuccessful (**Scheme 2.30**).



(±)- **2.71** (±)- **2.10**

Scheme 2.30. Hydrolysis of sulfonate derivatives (±)-**2.71**. **Reagents & conditions:** a) K_2CO_3, MeOH, THF, H_2O, rt 48 h or NaOH, $NaHCO_3$, MeOH, H_2O, reflux overnight

Corey *et al.* reported a procedure to resolve (±)-2-triphenylsilyl-4-cyclohexen-1-ol.[149] It involved the reaction of the racemic alcohol with (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-chloro-2-oxoacetate to form the diastereomeric oxalates **2.73a** and **2.73b** followed by recrystallisation of the diastereoisomers (**Scheme 2.31**).



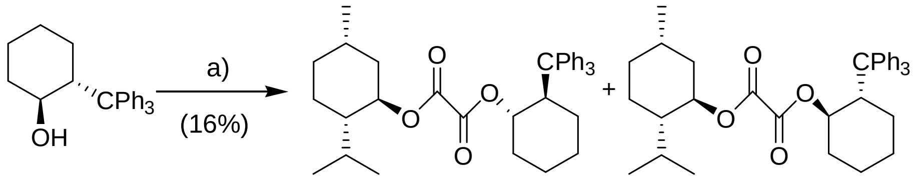
38%, 99% de

17%, 99% de

2.72 **2.73a** **2.73b**

Scheme 2.31. Corey's *et al.* classical resolution of (±)-*trans*-2-triphenylsilyl-4-cyclohexen-1-ol.[149] Reagents **& conditions:** a) (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-chloro-2-oxoacetate (1.05 equiv.), Et_3N (1.2 equiv.), CH_2Cl_2, 23 °C, 1 h.

Recrystallisation to separate the oxalate isomers was achieved using isopropanol giving the ester **2.73a** in 38% yield (99% de) and the ester **2.73b** in 17% yield (99% de). Using the same procedure, (±)-TTC afforded the mixed oxalate diesters **2.74a/b** in low yield (17%) (**Scheme 2.32**).

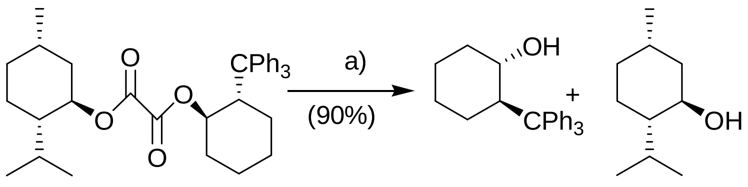


(±)-**2.10** **2.74a** **2.74b**

Scheme 2.32. Resolution of (±)-*trans*-2-triphenylmethyl cyclohexan-1-ol. **Reagents & conditions:** a) (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-chloro-2-oxoacetate (1.05 equiv.), Et_3N (1.2 equiv.), CH_2Cl_2, 23 °C, 1 h.

Separation of the diastereoisomers was then investigated from a variety of different recrystallisation solvents. Recrystallisation from *i*-PrOH and hexanes both gave a mixture of the two isomers. Recrystalisation from ether and *n*-pentane (3:2) provided 0.05 g of one pure isomer representing 10% of the total material (0.5 g). The purity of the isolated isomer was initially confirmed by ^{13}C and ^{1}H-NMR. To improve this procedure, the reaction conditions were changed by using 2.0 equiv. of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-chloro-2-oxoacetate and pyridine/CH_2Cl_2 as solvent. The thin layer chromatography showed completed reaction in two hours. It was also discovered that one of the stereoisomers was poorly soluble in methanol and sequential triturations with hot methanol gave the pure diastereoisomer **2.74b** in 35 % yield.

The pure isomer was hydrolysed under basic conditions to give the enantiomerically pure alcohol (−)-**210** in quantitative yield and > 99 % ee (**Scheme 2.33**).



2.74b (−)-**2.10** (> 99 % ee) (−)-**1.112**

Scheme 2.33. hydrolysis of oxalate ester **2.74b**. **Reagents & conditions:** a) NaOH, $NaHCO_3$, MeOH, H_2O, rt.

The enantiomeric purity was measured by HPLC analysis using Chiralcel-OJ column and 5 % *i*-PrOH/hexane as the eluent. HPLC traces for the racemic auxiliary and the enantiomeric pure auxiliary are shown in **Figure 2.2** & **Figure 2.3**, clearly showing a single peak for (–)-**210**.

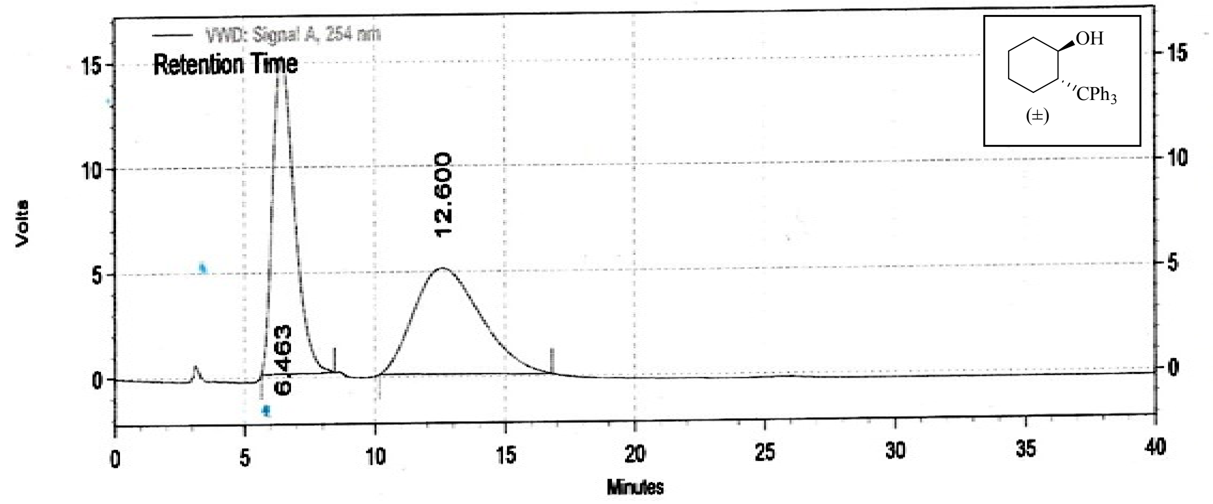


Figure 2.2. HPLC analysis for the racemic alcohol (±)-**2.10**.

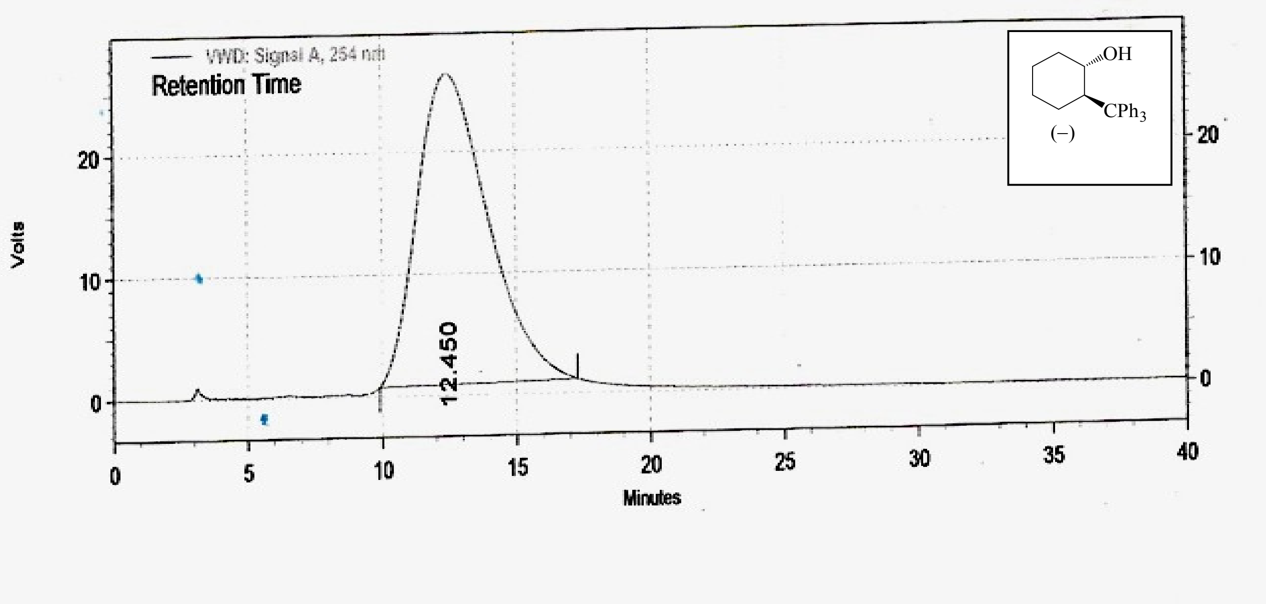
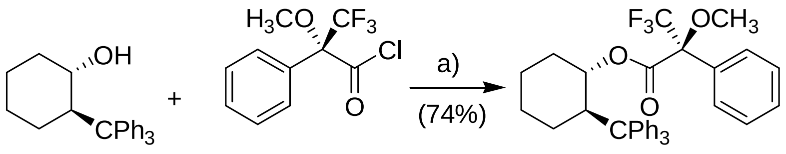


Figure 2.3. HPLC analysis for the enantiomeric pure alcohol (–)-**2.10**.

The obtained enantiomer has a negative value for optical rotation [$[\alpha]_D$ = – 59 (*c* 0.745, $CHCl_3$, 23 °C)]. (*S*)-Mosher ester of the obtained enantiomer was prepared (**Scheme 2.34**). The obtained enantiomer has an (*S*)-configuration at C1 and an (*R*)-configuration at C2 that was confirmed from an X-ray structure of (*S*)-Mosher ester **2.76**.



(−)-**2.10** **2.75** **2.76**

Scheme 2.34. Synthesis of (*S*)-Mosher ester **2.76**. **Reagents & conditions:** a) NaHMDS, THF, −30 °C to rt, 1 h.

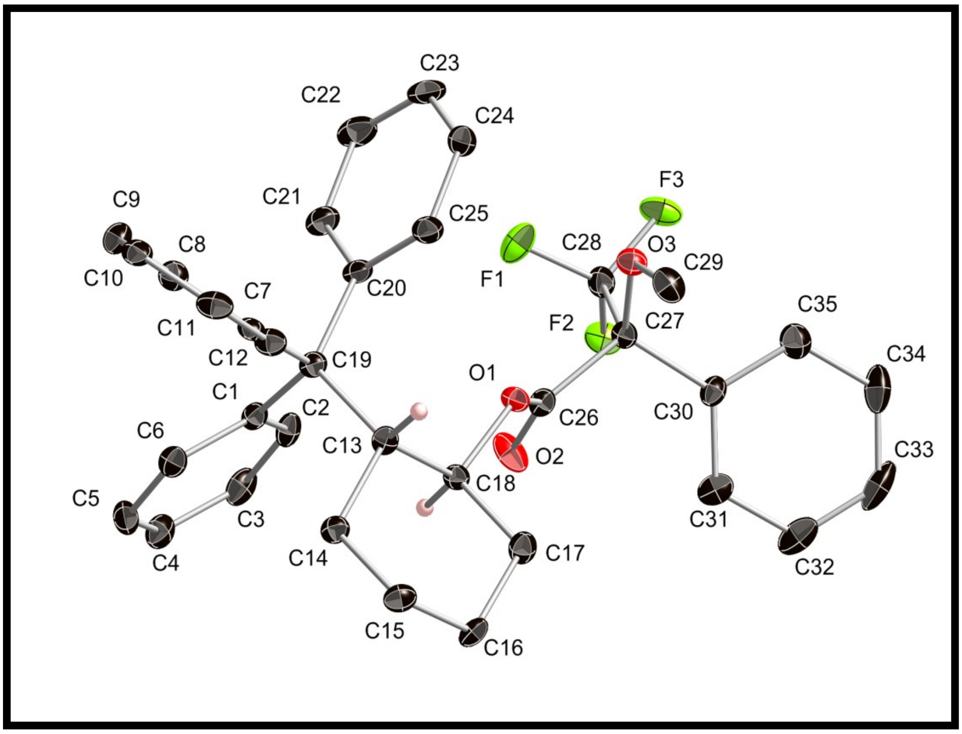


Figure 2.4. X-ray structure of (*S*)-Mosher ester **2.76**.

2.7- Conclusions

The auxiliary (±)-*trans*-2-tritylcyclohexanol (±)-TTC was synthesised using a literature method in one step from cyclohexene oxide. Following successful application of the racemic auxiliary in the oxidative cyclisation chemistry, attention moved on to the resolution of the racemic auxiliary using different methodologies. Enzymes were used in the esterfication reactions for the racemic alcohol (±)-**2.10** and in the hydrolysis reactions for the racemic alcohol (±)-**2.10** but no success was achieved. Different resolving agents were also investigated by forming covalent diastereoisomeric derivatives with camphor and menthol. Finally, a successful resolution was achieved by using (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-chloro-2-oxoacetate as a resolving agent. One isomer of oxalate ester **2.74b** was separated in 30% yield and was hydrolysed to give (–)-**2.10** in excellent yield and in enantipure form (> 99 % ee). The obtained enantiomer (−)-**2.10** has the (*S*)-configuration at C1 and (*R*)-configuration at C2 which was confirmed by an X-ray structure of (*S*)-Mosher ester **2.76**.

2.8- The oxidative cyclization of (*E*)-*trans*-2-tritylcyclohexyl hepta-2, 6-dienoate

One of our aims was to use the *trans*-2-triphenylmethyl-1-cyclohexanol auxiliary in the oxidative cyclization of different 1,5-dienes containing differently substituted enoate systems. Therefore, we decided to investigate oxidative cyclisation of different diene structural types. These studies were performed using racemic TCC.

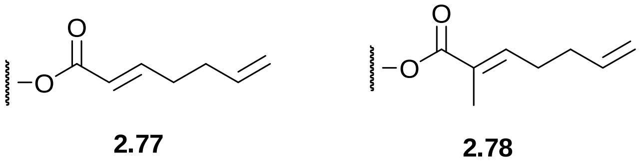
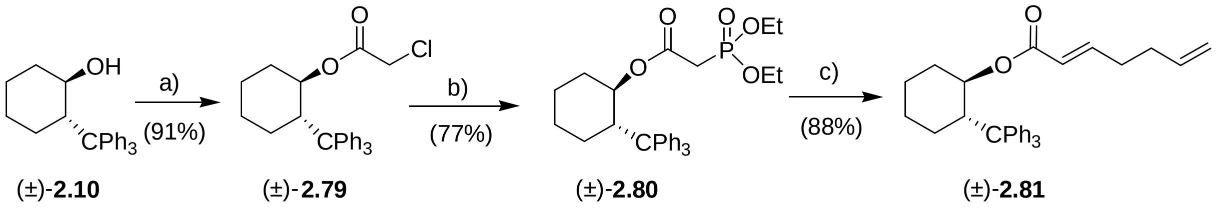


Figure 2.5. Alternative diene structure for oxidative cyclisation.

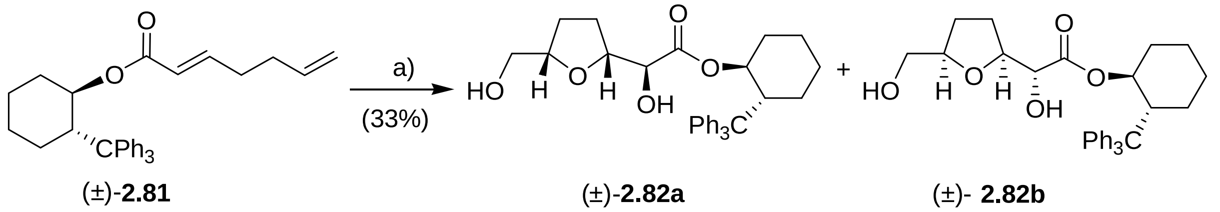
To investigate whether the (±)-TTC auxiliary was effective for other asymmetric oxidative cyclisation reactions, we chose to investigate a simple dienoate containing a *trans*-disubstituted enoate system (**Figure 2.5**). Typically, these oxidative cyclisations are carried out using the camphor sultam auxiliary and give stereoselectivities in the range 6:1-10:1.[40]

The synthesis of the required dienoyl ester (±)-**2.81** was achieved in 3 steps (**Scheme 2.35**). Reaction of 2-chloroacetyl chloride with alcohol (±)-**2.10** in presence of Et_3N and DMAP afforded the chloride (±)-**2.79** in high yield. Triethyl phosphite was heated with chloride (±)-**2.79** to give phosphonate (±)-**2.80** by the Arbuzov reaction. Diethoxyphosphoryl ester (±)-**2.80** was then reacted with 4-pentenal to give the dienoyl ester (±)-**2.81**.[150]



Scheme 2.35. Synthesis of (*E*)-*trans*-2-(1,1-diphenylethyl)cyclohexylhepta-2,6-dienoate. **Reagents & conditions:** a) $ClCOCH_2Cl$, NEt_3, DMAP, DCM, 0 °C to rt, 34 h; b) $(EtO)_3P$, reflux, 4 h; c) 4-pentenal, LiCl, DIPEA, MeCN, rt, 20 h.

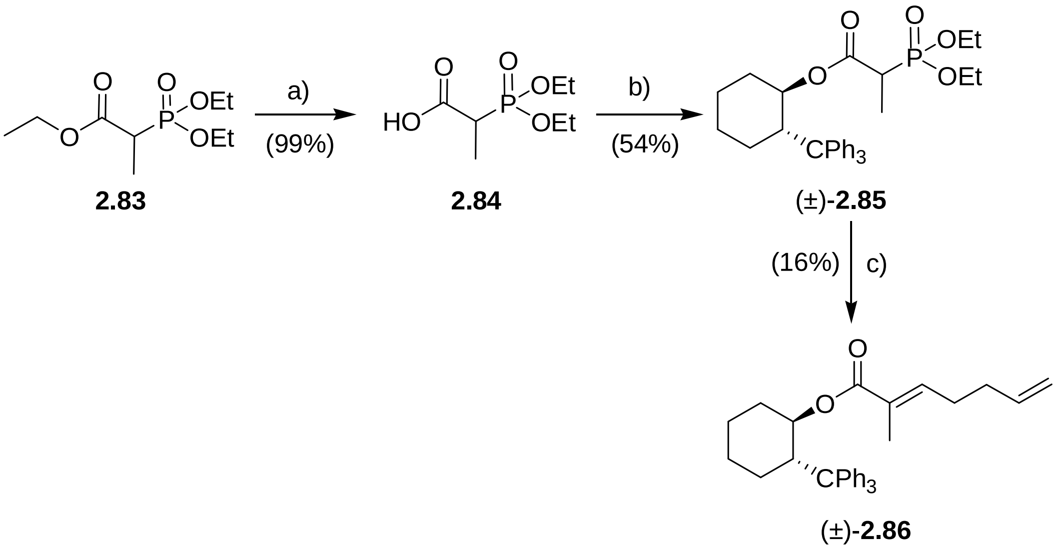
The oxidative cyclization reaction of the dienoyl ester was carried out using 1.3 equiv. of powdered $KMnO_4$ in acetone and acetic acid medium.[151] Analysis of the crude reaction showed complete oxidation of the diene and the ^{1}H-NMR analysis showed 2:1 ratio of the two diastereoisomers. It was difficult to separate the products by column chromatography and the NMR data for the mixture were complex. Recrystallisation of the crude mixture from methanol allowed separation of a reasonable amount of the major diastereoisomer in 33% yield. Unfortunately, we were not able to assign the relative stereochemistry in the major diastereoisomer because the amorphous solid obtained was not suitable for X-ray structure determination.



Scheme 2.36. Oxidative cyclization of diene (±)-**2.81**. **Reagents & conditions:** a) $KMnO_4$, AcOH, acetone, – 40 °C to rt, 6 h.

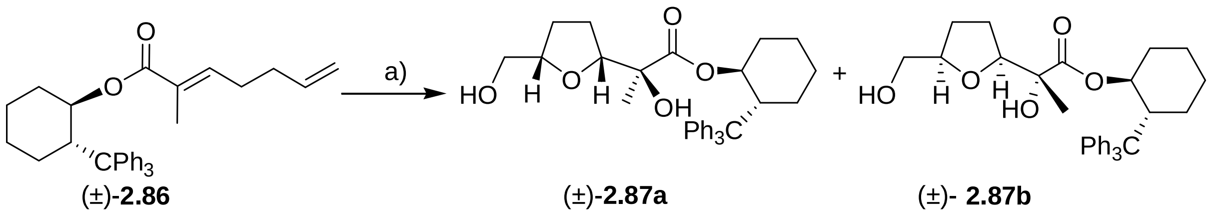
2.9- Synthesis of rac-(*E*)-*trans*-2-tritylcyclohexyl 2-methylhepta-2,6-dienoate

Another diene containing *rac*-TTC auxiliary was prepared to investigate the oxidative cyclisation. In this substrate ((±)-**2.86**) a trisubstituted enoate system was present (**Scheme 2.37**). First commercially available ester **2.83** was hydrolysed to give the acid **2.84**, then the cyclohexyl ester was formed by reacting the freshly prepared acid chloride with sodium alkoxide of (±)-**2.10** in THF. Finally the diene was formed using the Horner-Emmons reaction between the phosphonate ester (±)-**2.85** and 4-pentenal. Unfortunately, this last step proceeded in poor yield, but gave sufficient isomerically pure material to study the oxidative cyclisation.



Scheme 2.37. Synthesis of *rac*-(*E*)-*trans*-2-tritylcyclohexyl 2-methylhepta-2,6-dienoate. **Reagents & conditions:** a) NaOH, THF, rt, 24 h, b) i) $SOCl_2$, CH_2Cl_2, rt, 4 h, ii) (±)-**2.14**, NaHMDS, THF, – 78 °C to rt, 2 h; c) 4-pentenal, LiCl, DIPEA, MeCN, rt, 24 h.

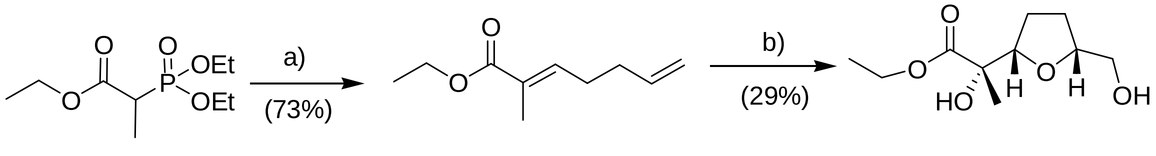
The oxidative cyclization of the diene (±)-**2.86** was carried out using 1.3 equiv. of powdered $KMnO_4$ in acetone and acetic acid. Analysis of the crude reaction showed a complete oxidation and the ^{1}H-NMR analysis for the crude showed a 2:1 ratio of the two diastereoisomers. However, due to an inseparable undefined byproduct the yield could not be obtained and the NMR data for the mixture was complex. Due to the low selectivity and the purification problems this part of the research was discontinued.



Scheme 2.38. Oxidative cyclisation of diene (±)-**2.86**. **Reagents & conditions:** a) $KMnO_4$, AcOH, acetone, – 40 °C to rt, 6 h.

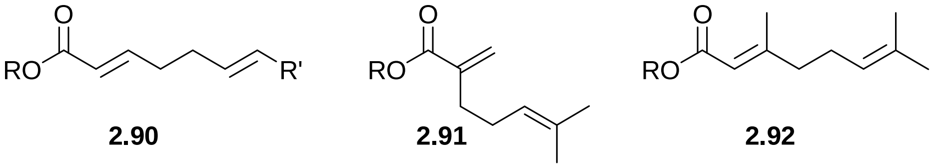
2.10- Synthesis of rac-(*S*)-ethyl 2-((2*S*, 5*R*)-tetrahydro-5-(hydroxymethyl)furan-2-yl)-2-hydroxyacetate

The THF diol (±)-**2.89** containing the trisubstituted enoate system was synthesised to see how different structural classes performed in the oxidative cyclisation and to help us interpret the NMR data for the THF diol (±)-**2.82** containing the chiral auxiliary (**Scheme 2.39**).



2.83 **2.88** **2.89**

Scheme 2.39. The oxidative cyclization of (*E*)-ethyl 2-methylhepta-2,6-dienoate. **Reagents & conditions:** a) 4-pentenal, LiCl, DIPEA, MeCN, rt, 24 h; b) $KMnO_4$, AcOH, Acetone, –30 °C to –10 °C , 1 h.



2.90 **2.91** **2.92**

Figure 2.6. Dienoate systems containing disubstituted and trisubstituted alkenes.

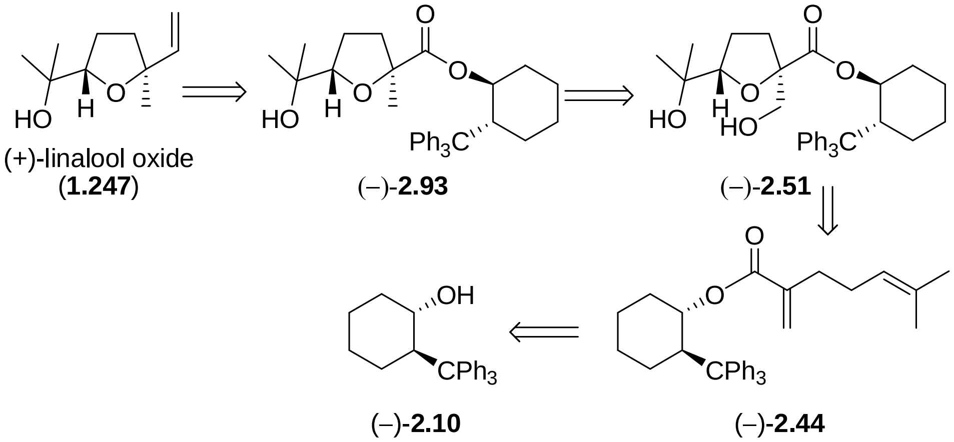
Oxidative cyclisation of dienoate **2.88** proceeded in lower yield than for related dienoate systems containing disubstituted and trisubstituted alkenes (**Figure 2.6**). It is not clear to us why these substrates give inferior results in the oxidative cyclisation.

2.11- Conclusions

Two different structural classes of dienes (±)-**2.81** and (±)-**2.86** were subjected to the oxidative cyclisation reaction. NMR analysis showed poor selectivity and moderate yields. This chemistry was not investigated further due to the difficulties in purification and the modest yields and selectivities obtained.

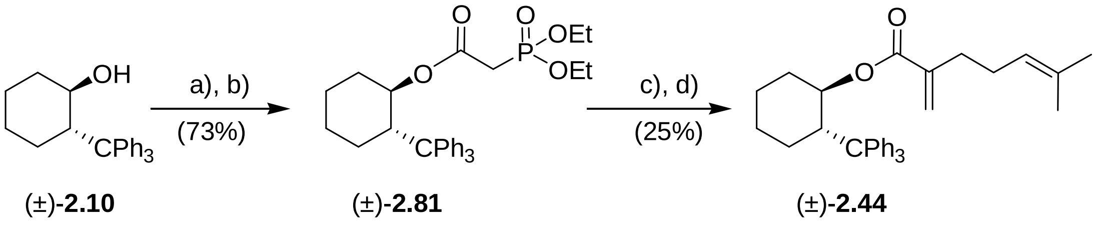
2.12– Towards the total synthesis of (+)-linalool oxide

In order to accomplish the total synthesis of (+)-linalool oxide, we required a shorter route to the diene (–)-**2.44**, which is the key precursor. The synthetic plan for the total synthesis (+)-linalool oxide is summerised in the retrosynthetic analysis (**Scheme 2.39**).



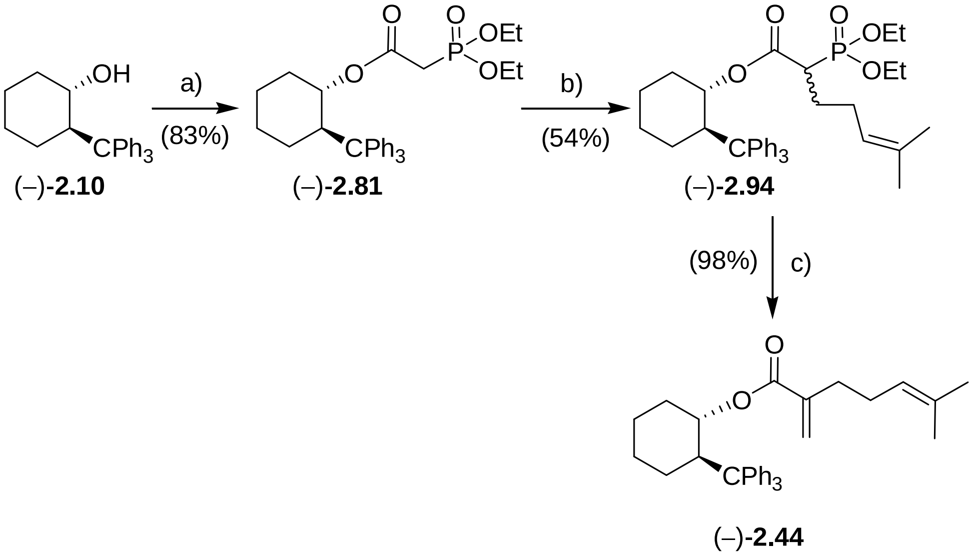
Scheme 2.40. Retrosynthetic analysis of (+)-linalool oxide synthesis.

Firstly, we decided to investigate the synthesis of (±)-**2.44** in a two step sequence starting from the auxiliary (±)-**2.10**. Reaction of freshly prepared (diethoxyphosphoryl)acetyl chloride with the alcohol (±)-**2.10** afforded phosphonate ester (±)-**2.81** in 73% yield. The phosphonate ester (±)-**2.81** was converted in one pot to the dienoyl ester (±)-**2.44** in 25% yield (**Scheme 2.41**).



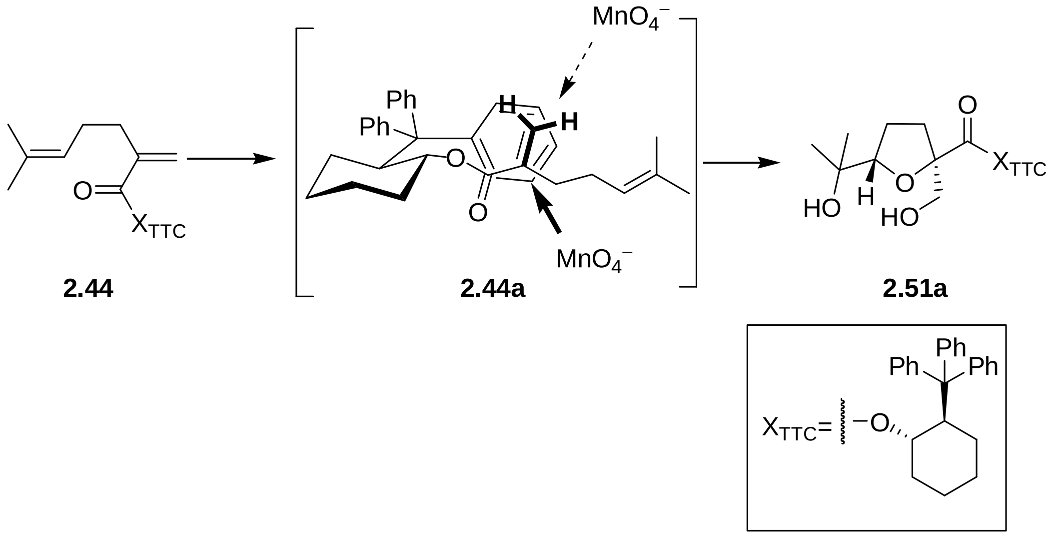
Scheme 2.41. Synthesis of *trans*-2-tritylcyclohexyl 6-methyl-2-methylenehept-5-enoate.
Reagents & conditions: a) (diethoxyphosphoryl)acetic acid, $SOCl_2$, rt, 1 h; b) NaHMDS, DMAP, THF, –78 °C to rt; c) NaH, DMSO, $(CH_3)_2C{=}CHCH_2CH_2Br$, 50 °C, 5 h; d) K_2CO_3, HCHO, rt to 50 °C, overnight.

Due to the realively low yield obtained for the one-pot alkylation-olefination process, we decided to investigate each step on its own. By starting from (–)-TTC ((–)-**2.10**), the phosphonate ester (–)-**2.81** was formed in good yield. However, the best yield obtained for the alkylation step was 54% using *t*-BuOK as the base and 2 equiv. of 5-bromo-2-methylpent-2-ene in DMF. The olefination also proceeded in excellent yield (**Scheme 2.42**).



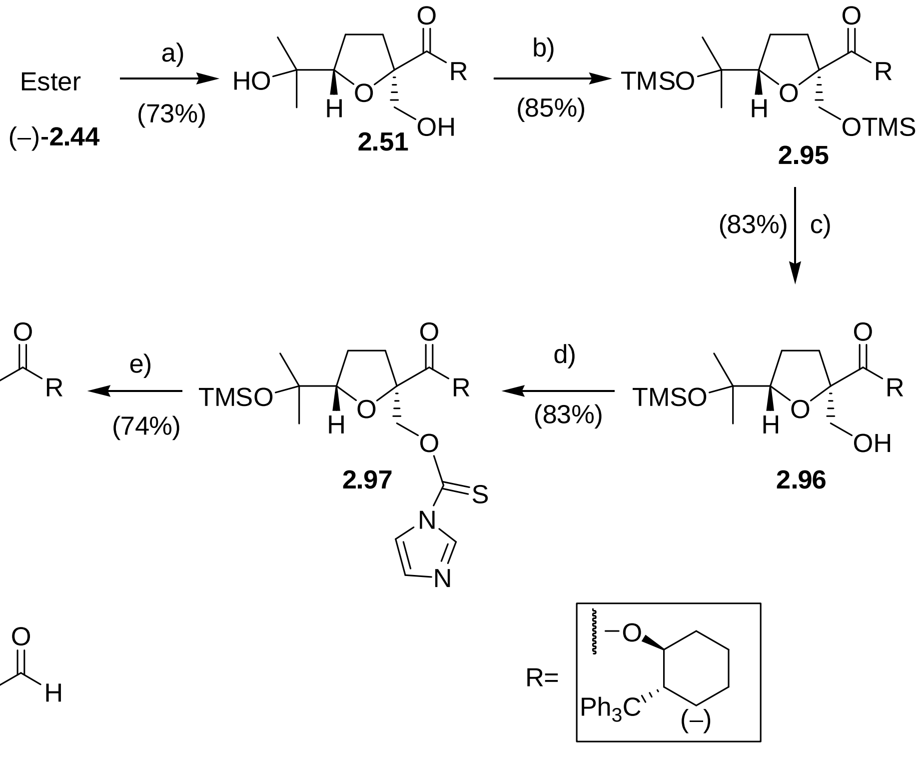
Scheme 2.42. Synthesis of (1*S*,2*R*)-2-tritylcyclohexyl 6-methyl-2-methylenehept-5-enoate. **Reagents & conditions:** a) (i) (diethoxyphosphoryl)acetic acid, $SOCl_2$, rt, 1 h; (ii) NaHMDS, DMAP, THF, –78 °C to rt; b) *t*-BuOK, DMF, $(CH_3)_2C=CHCH_2CH_2Br$, 0 °C to rt, 6 h; c) K_2CO_3, HCHO, rt to 50 °C, overnight.

After the synthesis of multigram quantities of the diene (–)-**2.44** in enantiopure form (**Scheme 2.42**), the oxidative cyclization of dienoate (–)-**2.44** proceeded in 73% giving a single observable diastereoisomer by ^{1}H-NMR analysis. Subsequently, the diastereoselectivity of this reaction was shown to be 97:3 by chiral HPLC and GC of the final product. The oxidation reaction was carried out using 1.35 equiv. of sodium permanganate in the presence of phosphate buffer containing glacial acetic acid in acetone.[132] It is proposed that the origin of the stereoselectivity is due to the blockage of *Re*-face by the tertiary centre bearing the phenyl ring, as indicated in the conformer **2.44a** (**Scheme 2.43**). Due to the shielding of *Re*-face, the attack of the oxidant would take place preferentially from the *Si*-face, affording the desired THF diol diastereoisomer **2.51a** as the major product (dr = 97:3).



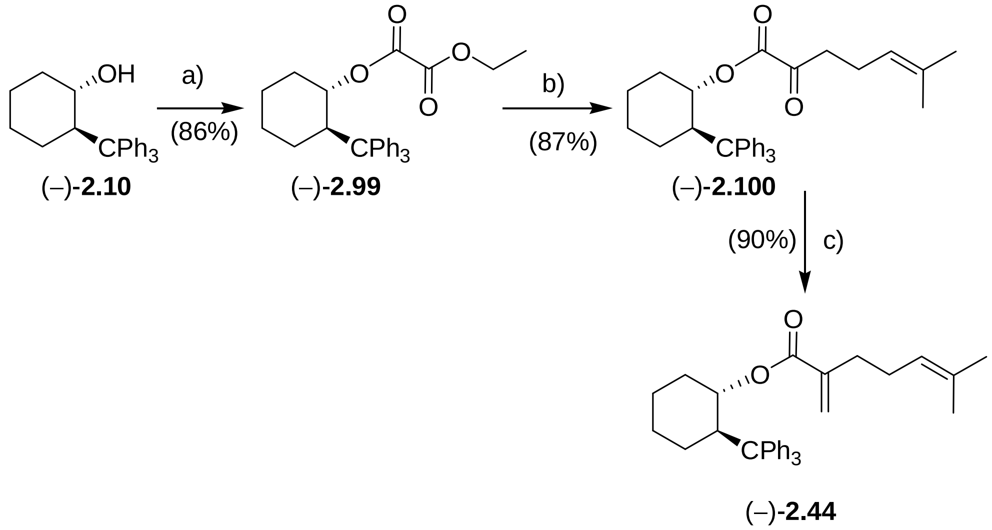
Scheme 2.43. Rationalisation of the diastereoselectivity obtained using (–)-**TTC** (–)-**2.10**.

Initially, the oxidation step was followed by protection of the diol (–)-**2.51** by reaction with excess TMSCl in the presence of imidazole in DMF. The less hindered primary hydroxyl in **2.95** was then selectively deprotected using K_2CO_3 in methanol. Under these conditions, the deprotection could be stopped prior to significant cleavage of the teriary silyl ether. The next step required was to deoxygenate at the primary alcohol, establishing the *trans*-THF system required in the product. The mono-silylated THF **2.96** was reacted with 1,1-thiocarbonyl diimidazole in the presence of DMAP in CH_2Cl_2 to give the THF thiocarbamate **2.97** in 83% yield. The subsequent deoxygenation was carried out using tris-(trimethylsilyl)silane and azobisisobutyronitrile as a radical initiator in toluene affording the reduced product in 74% yield. The aldehyde **2.98** was formed directly by reducing ester **2.94** with DIBAL-H in THF at −78 °C, thus completing a formal synthesis of (+)-linalool oxide in 9 steps and 4% overall yield. (**Scheme 2.44**).



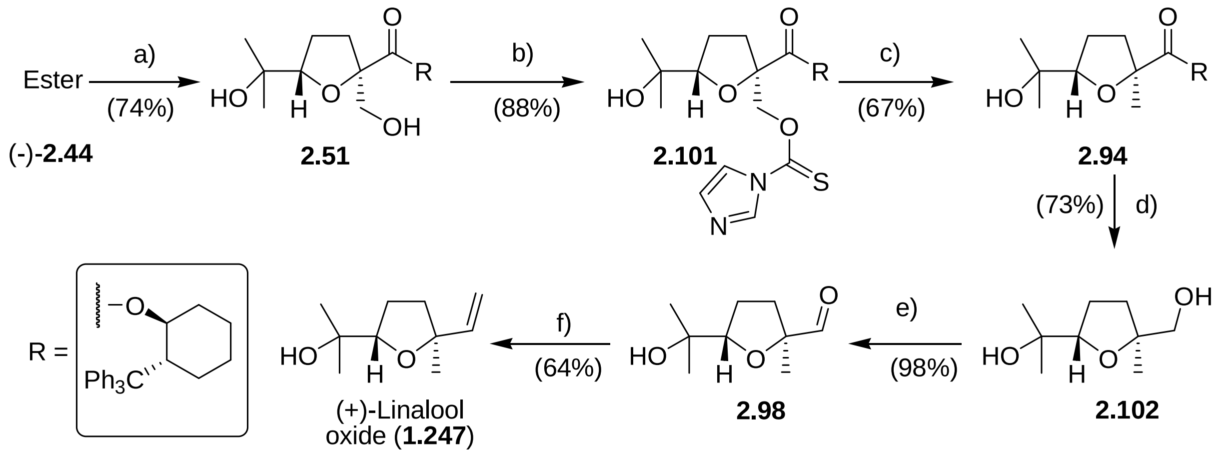
Scheme 2.44. Formal synthesis of (+)-linalool oxide. **Reagents & conditions:** a) $KMnO_4$, AcOH, Phosphate buffer, Acetone, –35 to –5 °C, 1.5 h; b) TMS-Cl, imidazole, DMF, –5 °C, 1 h; c) K_2CO_3, MeOH, – 10 °C, 2 h; d) imid$_2$(C=S), DMAP, CH_2Cl_2, rt, 14 h; e) TTMSS, AIBN, Toluene, 85 °C, 20 min; f) DIBAL-H, THF, –78 °C, 5 h.

Finally, we wanted to optmise the synthesis of (+)-linalool oxide and further shorten the number of steps required. In the final approach investigated, α-keto ester (–)-**2.100** was identified as the key intermediate. Reacting the auxiliary (–)-**2.10** with ethyl chlorooxoacetate in pyridine gave the mixed oxalate ester (–)-**2.99** in 86% yield. The oxalate ester (–)-**2.99** was reacted with the Grignard reagent of bromide **2.28** in THF at –78 °C to form the α-keto ester (–)-**2.100** in 87% yield. The Grignard reaction proceeded by selective reaction at the less hindered ethyl ester. The α-keto ester (–)-**2.100** was converted to the dienoyl ester (–)-**2.44** by Wittig olefination under two different sets of conditions. The first was by using methyltriphenylphosphonium bromide and sodium hydroxide in CH_2Cl_2. Alternatively, a combination of methyltriphenylphosphonium bromide and DBU also provided the desired dienoate (–)-**2.44**, but in improved yield (**Scheme 2.45**).



Scheme 2.45. Synthesis of (1*S*,2*R*)-2-tritylcyclohexyl 6-methyl-2-methylenehept-5-enoate. **Reagents & conditions:** a) Ethyl chlorooxoacetate, pyridine; or Ethyl chlorooxoacetate, DMAP, CH_2Cl_2, rt; b) (i) prenyl bromide, Mg, THF, rt to reflux, (ii) (–)-**2.99**, THF, −78 °C, 45 min; c) Ph_3PCH_3Br, NaOH (50%), CH_2Cl_2, rt or Ph_3PCH_3Br, DBU, CH_2Cl_2 , reflux.

After the synthesis of the dienoate (–)-**2.44** by the optimized route in 3 steps and 67% overall yield, it was felt that the radical deoxygenation could be carried out without the need for protection of the tertiary alcohol. Gratifyingly, when the oxidative cyclisation product was reacted with 1,1-thiocarbonyl diimidazole in the presence of DMAP in CH_2Cl_2. The mono thionocarbamate **2.101** was formed selectively in 88% yield. The deoxygenation step was carried out using tris-(trimethylsilyl)silane and azobisisobutyronitrile as a radical initiator in toluene, affording the deoxygenated product **2.94** in good yield. The diol **2.102** was formed by reduction of ester **2.94** with DIBAL-H at reflux in CH_2Cl_2. The diol **2.102** was converted to the aldehyde **2.98** using Dess-Martin peridinane. Finally, (+)-linalool oxide (**1.247**) was formed in 64% yield by Wittig reaction in CH_2Cl_2 as a solvent. The optical rotation of the synthetic (+)-linalool oxide (**1.247**) ($[\alpha]_D$ = +7.6 (*c* 0.6, $CHCl_3$, 22 °C) was in agreement with literature ($[\alpha]_D$ = +8.33 (*c* 0.6, $CHCl_3$, 20 °C).[103, 104] Thus, it was confirmed that the (+)-enantiomer was produced. The optical purity of the synthetic (+)-linalool oxide (**1.247**) was 97:3 from chiral GC analysis (**Scheme 2.46**).



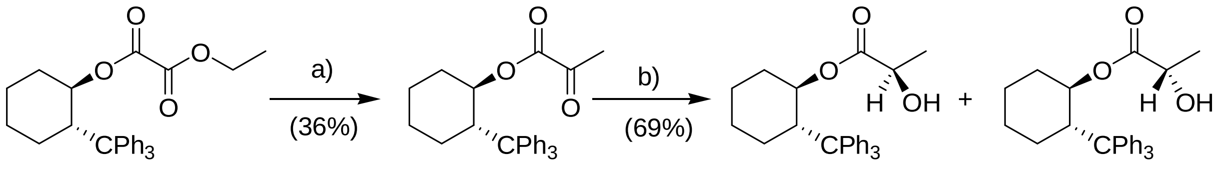
Scheme 2.46. The total synthesis of (+)-linalool oxide. **Reagents & conditions:** a) $KMnO_4$, AcOH, Phosphate buffer, acetone, –35 to –5 °C, 1.5 h; b) imid$_2$(C=S), DMAP, CH_2Cl_2, rt, 14 h; c) TTMSS, AIBN, toluene, 85 °C, 20 min; d) DIBAL-H, THF, –78 °C, 5 h; e) Dess-Martin peridinane, CH_2Cl_2, reflux; f) Ph_3PCH_3Br, DBU, CH_2Cl_2 , reflux, 48 h.

2.13-Conclusions

The synthesis of (+)-linalool oxide (**1.247**) was accomplished in nine steps in 13% overall yield. Key steps in the synthesis included an efficient approach to the diene (–)-**2.44** and the oxidative cyclisation-deoxygenation sequence to the *trans*-THF diol intermediate (–)-**2.102**. This synthesis illustrated the value of the TTC auxiliary in the total synthesis.

2.14- Other applications of *trans*-TTC ((±)-2.10)

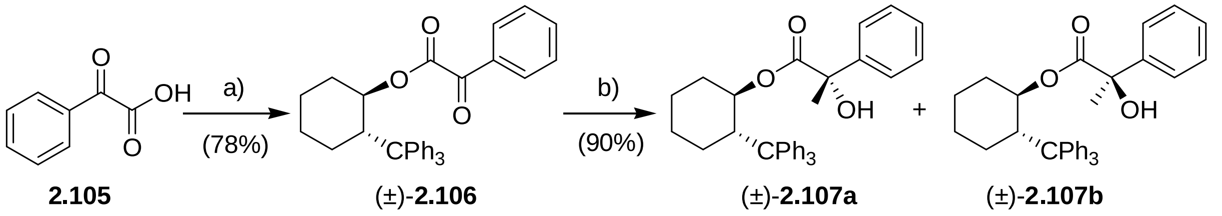
As a part of this research programme we also wished to investigate the use of the cyclohexanol (±)-**2.10** in other types of reactions. The following section includes the use of *trans*-TTC in nucleophilic additions to α-keto esters. Our preliminary results from these studies are summarized below. The α-keto ester (±)-**2.103** was prepared by reaction of ester (±)-**2.99** with methylmagnesium bromide in THF. Reduction of ester **2.103** with $NaBH_4$ in THF at room temperature gave a mixture of two diastereoisomers **2.104a/b** in a ratio 3:1 (50% de) (**Scheme 2.47**). The ratio was estimated from the integrals in the ^{1}H-NMR spectrum. For comparison, the corresponding reaction using (−)-8-phenylmenthol gave the two diastereoisomers in ratio of 2:1 (33% de).[152]



(±)-**2.99** (±)-**2.103** **2.104a** **2.104b**

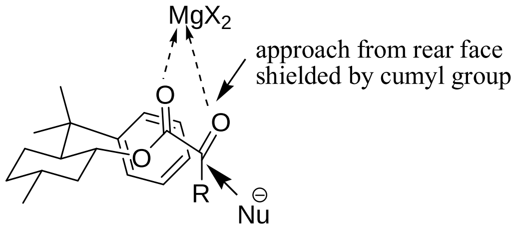
Scheme 2.47. Reduction of ester (±)-**2.103**. **Reagents & conditions:** a) MeMgBr, THF, –78 °C, 2 h; b) $NaBH_4$, THF, rt, 3.5 h.

The phenyl ketone (±)-**2.106** was prepared as a substrate to study Grignard addition reactions. Reaction of the freshly prepared acid chloride of **2.105** with the alcohol (±)-**2.10** in THF at room temperature afforded the keto ester (±)-**2.106** in 78% yield (**Scheme 2.48**). Reaction of keto ester **2.106** with MeMgBr in THF at –78 °C gave the tertiary alcohol (±)-**2.107a/b** in 90% yield. The ratio of the two diastereoisomers was 7:1 (75 % de) which was determined from the integration in the ^{1}H-NMR spectrum. Interestingly, the diastereoselectivity was lower compared to the corresponding reaction using (−)-8-phenylmenthol, which was reported to give the two diastereoisomers in diastereoisomeric excess of at least 90% de.[152]



Scheme 2.48. Synthesis of ester **2.107**. **Reagents & conditions:** a) i) $(COCl)_2$, DMF, hexane, rt, 1 h, ii) (±)-**2.10**, DMAP, THF, rt, overnight; b) MeMgBr, THF, –78 °C, 3 h.

The final result is suprising because we expected the increased steric demand of the trityl group to enhance diastereoselectivity. It has been assumed that the sence of the stereoinduction in these reactions is the same as that observed in Whitesell's studies with 8-phenylmenthol (–)-**1.108**.[152] He explained the formation of the major stereoisomer by reaction of the nucleophilic reagent from the *Si* face of the ketone (**Figure 2.7**).



2.108

Figure 2.7: Whitesell's model to account for the facial selectivity observed in nucleophilic additions to α-keto esters of 8-phenylmenthol.

2.15-Conclusions

The preliminary results of the studies in the nucleophilic additions to α-keto esters showed moderate to good stereoselectivity. The reduction of α-keto ester (±)-**2.103** with $NaBH_4$ gave mixture of two diastereoisomers **2.104a/b** in a ratio 3:1. On the other hand, the nucleophilic addition of MeMgBr to the α-keto ester (±)-**2.106** gave the two diastereoisomers (±)-**2.107a/b** in 90% yield in a ratio of 7:1. The ratio of the two diastereoisomers was determined from the integration in the ^1H-NMR spectrum in both cases. The sense of the asymmetric induction has been tentaviely assigned on the basis of Whitesell's work with 8-phenylmenthol. However, this will need to be confirmed in future studies.

Chapter 3: Experimental

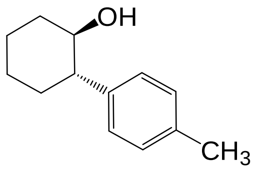
3.1-General Procedures

All air/sensitive reactions were carried out under an inert atmosphere, in oven dried glassware. The solvents THF and Et_2O (from Na/benzophenone) and CH_2Cl_2 from (CaH_2) were distilled before use, and where appropriate, other reagents and solvents were purified by standard techniques.[153] TLC was performed on aluminium-precoated plates coated with silica gel 60 with an F_{254} indicator; visualized under UV light (254 nm) and/or by staining with $KMnO_4$ (10% aq.) Flash column chromatography was performed with Merck Kieselgel 60 silica gel. Fourier-transform infrared (FT-IR) spectra are reported in wavenumbers (cm^{-1}) and were collected on a Nicolet 380 fitted with a diamond platform, as solids or neat liquids. The abbreviations s (strong), m (medium), w (weak) and br (broad) are used when reporting the spectra. ^1H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution using a Bruker AC300 or and AV300 (300 and 75 MHz respectively) or on a Bruker DPX400 (400 and 100 MHz respectively). ^9F and ^{31}P NMR spectra were recoreded in $CDCl_3$ solution on a Bruker AV300 (282 and 121 MHz respectively). Chemical shifts are reported in δ units using $CHCl_3$ as an internal standard (δ 7.27 ppm ^1H and δ 77.00 ppm ^{13}C). Coupling constant (J) were recorded in Hz. The following abbreviations for the multiplicity of the peaks are s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sxt (sextet), br (broad), and m (multiplet).

Melting points were obtained using a Gallenkamp Electrothermal apparatus and are uncorrected. Optical rotations were measured using PolAAr 2001 polarometer with 589 nm light source. Low –resolution mass spectra were obtained on a Fisons VG platform single quadraploe mass spectrometer in either chemical ionization or electron impact ionization mode or a Micromass platform mass analyser with an electrospray ion source. Enantiomeric excesses were determined by chiral HPLC analysis on a Hewlett-Packard 1090 series II HPLC and Agilent Technologies 1120 compact LC using a Chiralcel-OJ column (Diaicell Chemical Industries, Ltd) and Agilent Zobax Sil C18 (5 μm, 4.6 × 250 mm) eluting with IPA/hexane. Enantiomeric excesses for (+)-linalool oxide were determined on Perkin Elmer clarus 400 gas chromatograph using a CP-Cyclodextrin-B-236-M-19 (50 m × 0.25 mm i.d.) column.

3.2- Experimental details

3.2.1 – *rac*- (1*R*,2*S*)-2-*p*-Tolylcyclohexanol ((±)-2.4)



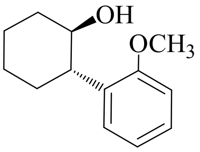
$C_{13}H_{18}O$

Mwt: 190.28 g/mol.

A 100 mL 2-neck round bottom flask equipped with a stirrer, an addition funnel, a reflux condenser and a nitrogen inlet was charged with magnesium turnings (1 g, 0.04 g-atom) and 4-bromotoluene (6.98 g, 40 mmol) in dry THF (7 mL) was added dropwise. After the addition of 4-bromotoluene was completed, dry THF (27 mL) was added. The solution was cooled to – 30 °C (dry ice-acetone bath) and CuBr (0.258 g, 1.8 mmol) was added. The resulting mixture was stirred for 10 min then a solution of cyclohexene oxide (2.8 mL, 27.2 mmol) in dry THF (3 mL) was added dropwise. On completion, the reaction mixture was allowed to warm to 0 °C and stirred for 2 h then quenched by adding sat. aq. sol. of ammonium sulfate (14 mL). The layers were separated and the organic layer was washed with sat. sol. of $(NH_4)_2SO_4$ (5 mL). The combined aqueous layers were extracted with ether (3 x 30 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and the solvent was removed *in vacuo*. The crude was recrystallised from pentane to give the title alcohol (±)-**2.4** as a white powder (3.76 g, 19.7 mmol, 73 %). Spectroscopic data are consistent with reported values.[154]

mp	66-68 °C; (lit. 70-72 °C)[154].
FT-IR (neat) ν_{max}	3450-3100 (br), 2920 (s), 2849 (m), 1513 (m), 1446 (m), 1417 (m) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 7.15 (4H, m, $C\underline{H}_{Ar}$), 3.64 (1H, m, $C\underline{H}OH$), 2.45 (1H, m, $C\underline{H}Ar$), 2.35 (3H, s, $C\underline{H}_3$), 2.13 (1H, m, OH), 1.94-1.72 (3H, m, $C\underline{H}_2$), 1.67-1.26 (5H, m, $C\underline{H}_2$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 140.1 ($\underline{C}_{Ar}$), 136.3 ($\underline{C}_{Ar}$), 129.4 ($2\underline{C}H_{Ar}$), 127.7 ($2\underline{C}H_{Ar}$), 74.0 ($\underline{C}HOH$), 52.8 ($\underline{C}HAr$), 34.4 ($\underline{C}H_2$), 33.4 ($\underline{C}H_2$), 26.1 ($\underline{C}H_2$), 25.1 ($\underline{C}H_2$), 21.0 ($\underline{C}H_3$).
LRMS (ES^+) *m/z*	213 ($[M+Na]^+$).

3.2.2- *rac*- (1*R*,2*S*)-2-(2-Methoxyphenyl)cyclohexanol ((±)-2.5)



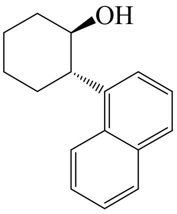
$C_{13}H_{18}O_2$

Mwt: 206.28 g/mol

Following the procedure for the preparation of compound (±)-**2.4**, the cuprate of 2-bromoanisole was prepared from 2-bromoanisole (5.1 mL, 40 mmol), Mg turnings (1 g, 0.04 g-atom) and CuBr (0.258 g, 1.8 mmol). The cuprate was reacted with cyclohexene oxide (2.8 mL, 27.2 mmol) over 3 h. The crude was purified by column chromatography (SiO_2 eluting with ether/hexane (10 → 25%)) to afford the desired product (±)-**2.5** as a white solid (2.97 g, 0.0144 mol, 53%). Spectroscopic data are consistent with reported values.[133]

mp	49-51 °C
FT-IR (neat) ν_{max}	3421 (br), 2928 (m), 2853 (m), 1599 (w), 1585 (w) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 7.26 (1H, dt, *J* = 7.5 and 1.1 Hz, $C\underline{H}_{Ar}$), 7.22 (1H, dd, *J* = 7.5 and 1.1 Hz, $C\underline{H}_{Ar}$), 6.99 (1H, dt, *J* = 7.5 and 1.1 Hz, $C\underline{H}_{Ar}$), 6.92 (1H, dd, *J* = 8.2 and 1.1 Hz, $C\underline{H}_{Ar}$), 3.85 (3H, s, $OC\underline{H}_3$), 3.76 (1H, m, $C\underline{H}OH$), 3.03 (1H, m, $C\underline{H}Ar$), 2.16 (1H, m, $O\underline{H}$), 1.92-1.72 (4H, m, $C\underline{H}_2$), 1.61-1.29 (4H, m, $C\underline{H}_2$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 157.7 ($\underline{C}_{Ar}$), 131.5 ($\underline{C}_{Ar}$), 127.3 ($\underline{C}H_{Ar}$), 127.2 ($\underline{C}H_{Ar}$), 121.0 ($\underline{C}H_{Ar}$), 110.8 ($\underline{C}H_{Ar}$), 73.9 ($\underline{C}HOH$), 55.4 ($\underline{C}H_3$), 45.1 ($\underline{C}H$), 35.2 ($\underline{C}H_2$), 32.3 ($\underline{C}H_2$), 26.1 ($\underline{C}H_2$), 25.1 ($\underline{C}H_2$).
LRMS (ES^+) *m/z*	229 ($[M+Na]^+$).

3.2.3- *rac*- (1*R*,2*S*)-2-(1-Naphthyl)-1-cyclohexanol ((±)-2.6)



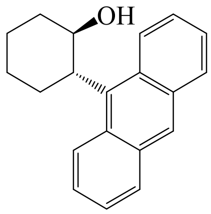
$C_{16}H_{18}O$

Mwt: 226.31 g/mol

Following the procedure for the preparation of compound (±)-**2.4**, the cuprate of 1-bromonaphthalene was prepared from 1-bromonaphthalene (5.73 mL, 40 mmol), Mg turnings (1 g, 0.04 g-atom) and CuBr (0.258 g, 1.8 mmol). The cuprate was reacted with cyclohexene oxide (2.8 mL, 27.2 mmol) over 3.75 h. The crude was purified by recrystalisation from *n*-hexane to afford the product as a white solid (4 g, 17.67 mmol, 65 %). Spectroscopic data are consistent with reported values.[154]

mp	129-130 °C; (lit. 129-130 °C)[154].
FT-IR (neat) ν_{max}	3388 (br), 3045 (w), 2928 (m), 2854 (m), 1596 (w) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 8.22 (1H, d, *J* = 7.7 Hz, $C\underline{H}_{Ar}$), 7.88 (1H, m, $C\underline{H}_{Ar}$), 7.75 (1H, m, $C\underline{H}_{Ar}$), 7.58-7.45 (4H, m, $C\underline{H}_{Ar}$) 4.10 (1H, m, $C\underline{H}OH$), 3.41 (1H, m, $C\underline{H}Ar$), 2.25 (1H, m, $C\underline{H}_2$), 2.10-1.90 (2H, m, $C\underline{H}_2$ and $O\underline{H}$), 1.85 (1H, m, $C\underline{H}_2$), 1.40-1.65 (5H, m, $C\underline{H}_2$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 139.5 ($\underline{C}_{Ar}$), 134.1 ($\underline{C}_{Ar}$), 132.6 ($\underline{C}_{Ar}$), 128.9 ($\underline{C}H_{Ar}$), 127.0 ($\underline{C}H_{Ar}$), 126.0 ($\underline{C}H_{Ar}$), 125.6 ($\underline{C}H_{Ar}$), 125.5 ($\underline{C}H_{Ar}$), 123.2 ($\underline{C}H_{Ar}$), 122.8 ($\underline{C}H_{Ar}$), 34.8 ($\underline{C}HOH$), 46.7 ($\underline{C}HAr$), 35.0 ($\underline{C}H_2$), 33.9 ($\underline{C}H_2$), 26.5 ($\underline{C}H_2$), 25.1 ($\underline{C}H_2$).
LRMS (ES^+) *m/z*	249 ($[M+Na]^+$).

3.2.4- *rac*- (1*R*,2*S*)-2-(Anthracen-9-yl)cyclohexanol ((±)-2.7)



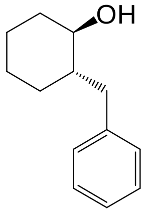
$C_{20}H_{20}O$

Mwt: 276.37g/mol

9-Bromoanthracene (3.2 g, 10 mmol) in dry ether (35 mL) was added dropwise to magnesium turnings (0.486 g, 0.02 g-atom) in dry ether (15 mL). Dibromoethane (5 drops) was added and the mixture was heated to reflux for 23 h. The mixture was cooled to –30 °C, CuBr (62 mg, 0.43 mmol) was added then cyclohexene oxide (0.7 mL, 6.78 mmol) was added dropwise. The mixture was warmed to room temperature and stirred for 4 h. The reaction was worked up and the crude purified as described in the preparation of compound (±)-**2.4**. The product was obtained as a yellow powder (1.07 g, 2.89 mmol, 57 %).

mp	55-60 °C.
FT-IR (neat) ν_{max}	3418 (br), 3049 (w), 2929 (m), 2855 (w), 1671 (w), 1623 (w) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 8.61 (1H, m, $C\underline{H}_{Ar}$), 8.51 (1H, d, *J* = 8.8 Hz, $C\underline{H}_{Ar}$), 8.40 (1H, s, $C\underline{H}_{Ar}$), 8.08-8.95 (2H, m, $C\underline{H}_{Ar}$), 7.60-7.42 (4H, m, $C\underline{H}_{Ar}$), 4.83 (1H, td, *J* = 10.1 and 4.2 Hz, $C\underline{H}OH$), 4.14 (1H, ddd, *J* = 13.5, 10.0 and 4.0 Hz, $C\underline{H}Ar$), 2.58 (1H, m, $C\underline{H}_2$), 2.34 (1H, m, $C\underline{H}_2$), 2.15-1.90 (3H, m, $C\underline{H}_2$ and $O\underline{H}$), 1.80-1.49 (3H, m, $C\underline{H}_2$), 1.35 (1H, m, $C\underline{H}_2$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 134.0 ($\underline{C}_{Ar}$), 132.1 ($\underline{C}_{Ar}$), 131.9 ($\underline{C}_{Ar}$), 131.7 ($\underline{C}_{Ar}$), 129.9 ($\underline{C}H_{Ar}$) 129.6 ($\underline{C}_{Ar}$), 129.3 ($\underline{C}H_{Ar}$), 127.5 ($\underline{C}H_{Ar}$), 126.1 ($\underline{C}H_{Ar}$), 125.6 ($\underline{C}H_{Ar}$), 124.8 ($\underline{C}H_{Ar}$), 124.6 ($\underline{C}H_{Ar}$), 124.5 ($\underline{C}H_{Ar}$), 124.2 ($\underline{C}H_{Ar}$), 72.5 ($\underline{C}HOH$), 48.3 ($\underline{C}HAr$), 35.7 ($\underline{C}H_2$), 31.6 ($\underline{C}H_2$), 26.9 ($\underline{C}H_2$), 25.1 ($\underline{C}H_2$).
LRMS (ES$^+$) *m/z*	277 ([M+H]$^+$).

3.2.5- *rac*- (1*R*,2*S*)-2-Benzylcyclohexanol ((±)-2.8).



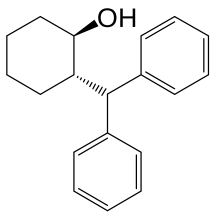
$C_{13}H_{18}O$

Mwt: 190.28 g/mol.

A solution of benzyl chloride (1.16 mL, 10 mmol) in dry THF (8 mL) was added dropwise to stirred magnesium turnings (1.01 g, 0.04 g-atom) in dry THF (12 mL) followed by the addition of 5 drops of dibromoethane. The mixture was stirred at rt for 24 h. The resulting reddish-brown solution of benzylmagnesium chloride was added dropwise to a stirred solution of cyclohexene oxide (0.7 mL, 6.78 mmol) in dry THF (15 mL) at – 78 °C. Subsequently, the mixture was warmed to rt and stirred for 24 h. Water (30 mL) was added and the reaction mixture was neutralized using HCl (2M aq. sol.). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. The crude was recrystallised from *n*-pentane to afford the product as a white powder (0.5 g, 2.62 mmol, 39 %). Spectroscopic data are consistent with reported values.[119]

mp	69-71 °C; (lit. 74-75 °C) [119].
FT-IR (neat) ν_{max}	3349 (br), 3025 (w), 2923 (m), 2854 (m), 1603 (w) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 7.35-7.14 (5H, m, $C\underline{H}_{Ar}$), 3.31 (1H, td, *J* = 9.8 and 4.6 Hz, $C\underline{H}OH$), 3.18 (1H, dd, *J* = 4.0 and 13.4 Hz, $CH\underline{H}Ar$), 2.37 (1H, dd, *J* = 9.2 and 13.4 Hz, $C\underline{H}HAr$), 1.98 (1H, m, $C\underline{H}CH_2Ar$), 1.81-1.45 (5H, m, $C\underline{H}_2$ + $O\underline{H}$), 1.37-1.18 (2H, m, $C\underline{H}_2$), 1.10 (1H, m, $C\underline{H}_2$), 0.92 (1H, m, $C\underline{H}_2$)
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 140.7 ($\underline{C}_{Ar}$), 129.4 ($2\underline{C}H_{Ar}$), 128.1 ($2\underline{C}H_{Ar}$), 125.7 ($\underline{C}H_{Ar}$), 74.5 ($\underline{C}HOH$), 47.0, ($\underline{C}HCH_2Ar$), 39.0 ($\underline{C}H_2Ar$), 35.8 ($\underline{C}H_2$), 30.0 ($\underline{C}H_2$), 25.4 ($\underline{C}H_2$), 24.9 ($\underline{C}H_2$)
LRMS (ES^+) *m/z*	213 ($[M+Na]^+$)

3.2.6- *rac*- (1*R*,2*S*)-2-benzhydrylcyclohexanol ((±)-2.9)



$C_{19}H_{22}O$

Mol. Wt.: 266.38 g/mol.

To a stirred solution of diphenylmethane (4 mL, 23.7 mmol) in dry THF (50 mL) at – 78 °C, was added dropwise a solution of *n*-BuLi (9.7 mL, 23.7 mmol, 2.45 M in hexane) producing an orange solution. The solution was warmed to rt and stirred for 4 h, then the resulting blood-red solution of diphenylmethyl anion was re-cooled to –78 °C. Cyclohexene oxide (6.1 mL, 59.25 mmol) was added dropwise and the reaction mixture was warmed to rt and stirred for 3 h. The reaction was quenched by adding H_2O (60 mL) and the aqueous layer was extracted with Et_2O (3 × 50 mL). The organic layer was washed with brine (100 mL) and dried (Na_2SO_4). The crude was purified by column chromatography (SiO_2 eluting with Et_2O/hexane (5 → 50 %)) to afford the product as a pale yellow viscous oil (5.38 g, 20.2 mmol, 85 %).

FT-IR (neat) ν_{max}	3334 (br), 3025 (w), 2929 (m), 2856 (w), 1599 (w) cm^{-1}.

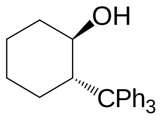
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34-7.13 (10H, m, $C\underline{H}_{Ar}$), 4.21 (1H, d, J = 7.9 Hz, $C\underline{H}Ar_2$), 3.44 (1H, td, J = 8.4 and 4.0 Hz, $C\underline{H}OH$), 2.31 (1H, m, $C\underline{H}CHAr_2$), 1.90 (1H, m, $C\underline{H}_2$), 1.82-1.64 (2H, m, $C\underline{H}_2$), 1.58 (1H, m, $C\underline{H}_2$), 1.42-1.18 (3H, m, $C\underline{H}_2$), 1.39 (1H, d, J = 4.0 Hz, $O\underline{H}$), 0.95 (1H, m, $C\underline{H}_2$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 144.1 ($\underline{C}_{Ar}$), 143.1 ($\underline{C}_{Ar}$), 129.0 ($2\underline{C}H_{Ar}$), 128.6 ($2\underline{C}H_{Ar}$), 128.3 ($2\underline{C}H_{Ar}$), 128.1 ($2\underline{C}H_{Ar}$), 126.3 ($\underline{C}H_{Ar}$), 126.1 ($\underline{C}H_{Ar}$), 72.5 ($\underline{C}HOH$), 53.5 ($\underline{C}HAr_2$), 47.3 ($\underline{C}HCHAr_2$), 34.2 ($\underline{C}H_2$), 27.6 ($\underline{C}H_2$), 24.6 ($\underline{C}H_2$), 23.9 ($\underline{C}H_2$).

LRMS (ES^+) *m/z* 289 ($[M+Na]^+$).

HRMS (ES^+) *m/z* Calculated: 533.3420, found: 533.3414 ($[2M+H]^+$)

3.2.7- *rac*- (1*R*,2*S*)-2-Tritylcyclohexanol ((±)-2.10)



$C_{25}H_{26}O$

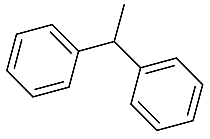
Mol. Wt.: 342.47 g/mol.

To a solution of triphenylmethane (45.18 g, 183.06 mmol) in anhydrous THF (200 mL) at –78 °C under N_2 was added a solution of *n*-BuLi (73.22 mL, 183.06 mmol, 2.5 M in hexane) dropwise producing an orange solution. The solution was stirred at 0 °C for 40 min then the resulting blood-red solution of the trityl anion was re-cooled to –78 °C. Cyclohexene oxide (47.25 mL, 457.7 mmol) was added dropwise and the reaction mixture was warmed to rt and stirred overnight. The reaction was quenched by adding water (100 mL) and the aqueous layer was extracted with ethyl aetate (3 × 80 mL). The organic layer was washed with brine (100 mL), dried (Na_2SO_4) and the solvent was removed *in vacuo*. Hexane (150 mL) was added to the pale yellow crude and was removed *in vacuo* to give a white solid which was filtered and washed with hexane to give the product as a white powder (35.02 g, 102.3 mmol, 56 %). The product was subjected to HPLC analysis (Chiral-cel-OJ column, Daicell Chemical Industries, Ltd., 5% IPA/hexane, 0.5 mL/min). Elution times $t_{(+)\text{-TTC}}$ 6.5 min, $t_{(-)\text{-TTC}}$ 12.6 min. This compound exhibited broadening of some signals in its NMR spectra due to restricted rotation.

mp 162-166 °C.

FT-IR (neat) ν_{max}	3583 (w), 3400 (br), 2933 (m), 1594 (w), 1491(m) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 7.67-7.05 (15H, m, $C\underline{H}_{Ar}$), 3.28 (1H, m, $C\underline{H}OH$), 3.10 (1H, m, $C\underline{H}CPh_3$), 2.05 (1H, m, $C\underline{H}_2$), 1.95 (1H, m, $C\underline{H}_2$), 1.48 (1H, d, J = 4.4 Hz, $O\underline{H}$), 1.80-133 (4H, m, $C\underline{H}_2$), 1.10 (1H, m, $C\underline{H}_2$), 0.50 (1H, m, $C\underline{H}_2$)
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 129.7 (br, 6$\underline{C}H_{Ar}$), 127.6 (6$\underline{C}H_{Ar}$), 125.7 (3$\underline{C}H_{Ar}$), 73.6 ($\underline{C}HOH$), 60.7 ($\underline{C}Ph_3$), 48.8 ($\underline{C}HCPh_3$), 37.0 ($\underline{C}H_2$), 28.9 ($\underline{C}H_2$), 26.2 ($\underline{C}H_2$), 25.2 ($\underline{C}H_2$), (quaternary aromatic carbons signal not observed).
LRMS (ES^+) *m/z*	365 ($[M+Na]^+$).
HRMS (ES^+) *m/z*	Calculated: 685.4046, found: 685.4040 ($[2M+H]^+$).

5.2.8- 1,1-Diphenylethane (2.11)



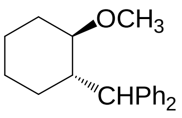
$C_{14}H_{14}$

Mol. Wt.: 182.26 g/mol

Following the method reported by Gordon *et al.,*[121] iodine (1 g, 4 mmol) and 1,1-diphenylethylene (1.0 mL, 5.56 mmol) were added to acetic acid (25 mL) under a nitrogen atmosphere. Phosphonic acid (2 mL, 19.3 mmol, 50% aq. sol.) was added. The mixture was heated to 60 °C and stirred for 24 h. The reaction was quenched with water (50 mL) and extracted with benzene. The organic extracts were washed with $NaHCO_3$ (sat. aq. sol.) and $NaHSO_3$ (sat. aq. sol.), dried ($MgSO_4$), filtered and the solvent was removed *in vacuo* to afford the product as coulerless oil (1.01g, 5.48 mmol, 100%). The product was used without further purification.

FT-IR (neat) ν_{max}	3026 (w), 2966 (w), 1657 (w), 1598 (w), 1580 (w) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 7.35-7.19 (10H, m, $C\underline{H}_{Ar}$), 4.19 (1H, q, J = 7.0 Hz, $C\underline{H}$), 1.68 (3H, d, J = 7.0, $C\underline{H}_3$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 146.4 (2$\underline{C}_{Ar}$), 128.3 (4$\underline{C}H_{Ar}$), 127.6 (4$\underline{C}H_{Ar}$), 126.0 (2$\underline{C}H_{Ar}$), 44.80 ($\underline{C}H$), 21.8 ($\underline{C}H_3$).

3.2.9- *rac*- *Trans*-2-diphenylmethyl-1-methoxycyclohexane ((±)-2.14)



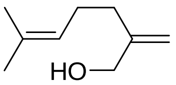
$C_{20}H_{24}O$

Mwt: 280.40 g/mol.

To a stirred solution of *trans*-2-diphenylmethyl-1-cyclohexanol (±)-**2.9** (0.833 g, 3.13 mmol) in dry THF (15 mL) at – 78 °C, was added NaH (125 mg, 3.13 mmol). The mixture was warmed to 0 °C and stirred for 1 h. Then, it was recooled to – 78 °C and *n*-BuLi (1.47 mL, 3.13 mmol, 2.13 M in hexane) was added and stirring was continued for 0.5 h. MeI (0.39 mL, 6.26 mmol) was added dropwise and the mixture was warmed to rt and stirred for 3 h. Subsequently, the mixture was cooled to 0 °C, diluted with hexane (20 mL) and quenched with water (10 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The organic layer was dried (Na_2SO_4), filtered and the solvents were removed *in vacuo* to afford the product as viscous colourless oil (0.83 g, 2.96 mmol, 95 %).

FT-IR (neat) ν_{max}	3025 (w), 2929 (m), 2857 (w), 1599 (w), 1494 (w) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 7.37-7.11 (10H, m, $C\underline{H}_{Ar}$), 4.39 (1H, d, *J* = 8.1 Hz, $C\underline{H}Ph_2$), 3.24 (3H, s, $C\underline{H}_3$), 2.86 (1H, td, *J* = 7.1 and 3.3 Hz, $C\underline{H}OCH_3$), 2.49 (1H, m, $C\underline{H}CHPh_2$), 1.97-1.17 (6H, m, $C\underline{H}_2$), 1.07 (1H, m, $C\underline{H}_2$), 0.87 (1H, m, $C\underline{H}_2$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 144.1 ($\underline{C}_{Ar}$), 143.1 ($\underline{C}_{Ar}$), 129.4 ($2\underline{C}H_{Ar}$), 128.3 ($2\underline{C}H_{Ar}$), 128.1 ($\underline{C}H_{Ar}$), 128.0 ($\underline{C}H_{Ar}$), 126.1 ($\underline{C}H_{Ar}$) 125.8 ($\underline{C}H_{Ar}$), 78.9 ($C\underline{H}OCH_3$), 55.5 ($\underline{C}HPh_2$), 50.8 ($O\underline{C}H_3$), 43.9 ($\underline{C}HCHPh_2$), 29.7 ($\underline{C}H_2$), 27.9 ($\underline{C}H_2$), 25.2 ($\underline{C}H_2$), 23.2 ($\underline{C}H_2$), 23.4 ($\underline{C}H_2$), 22.7 ($\underline{C}H_2$).
LRMS (ES^+) *m/z*	281 ($[M+H]^+$).

3.2.10- 6-Methyl-2-methylenehept-5-en-1-ol (2.16)



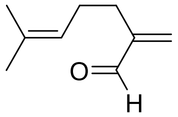
$C_9H_{16}O$

Mwt: 140.22 g/mol.

Following the method reported by Taber *et al.*, [123] TMEDA (45.1 mL, 305.3 mmol) was added dropwise to *n*-BuLi (129.9 mL of 2.35 M in hexane, 305.3 mmol) at –78 °C resulting in a white precipitation. After stirring for 20 min, methallyl alcohol (14.6 mL, 170.4 mmol) was added dropwise and Et_2O (120 mL) was added. The cooling bath was removed and stirring was continued for 22 h at room temperature. A dark orange mass was observed in the reaction mixture. Subsequently, the reaction mixture was chilled to –78 °C and 3,3-dimethylallyl bromide (8.5 mL, 71 mmol) in distilled Et_2O (15 mL) was added to the reaction mixture. The cooling bath was removed and the resultant yellow mixture was allowed to warm to rt and stirred for 1 h. The reaction was chilled to 0 °C and quenched with 10% aq. HCl (325 mL). The aqueous layer was extracted with Et_2O (5 × 150 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude as a dark yellow oil (15.34 g). Purification by column chromatography (SiO_2 eluting with ether/hexane (5 → 20 %)) afforded the title alcohol **2.16** as pale yellow oil (7.72 g, 55.06 mmol, 78%).

FT-IR (neat) ν_{max}	3600-3150 (br), 2967 (s), 2915 (s), 2856 (s) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 5.14 (1H, t.septet, *J* = 6.7 and 1.5 Hz, $=C\underline{H}CH_2$), 5.04 (1H, m, $=C\underline{H}H$), 4.90 (1H, sextet, *J* = 1.3 Hz, $=CH\underline{H}$), 4.09 (2H, d, *J* = 6.0 Hz, $C\underline{H_2}OH$), 2.24-2.05 (4H, m, $C\underline{H_2}CH_2$) 1.7 (3H, d, *J* = 1.1 Hz, $C\underline{H_3}$), 1.64 (3H, s, $C\underline{H_3}$), 1.39 (1H, t, *J* = 6.0 Hz, $CH_2O\underline{H}$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 149.0 ($\underline{C}$) 140.0 ($\underline{C}$), 123.9 ($=\underline{C}HCH_2$), 109.3 ($=\underline{C}H_2$), 66.0 ($\underline{C}H_2OH$), 33.1 ($\underline{C}H_2$), 26.5 ($\underline{C}H_2$), 25.6 ($\underline{C}H_3$), 17.7 ($\underline{C}H_3$).
LRMS (EI) *m/z*	139 ($[M–H]^+$).

3.2.11- 6-Methyl-2-methylenehept-5-enal (2.17)



$C_9H_{14}O$

Mwt: 138.21 g/mol.

At 0 °C a mixture of alcohol **216** (2.42 g, 17.26 mmol) and active MnO_2 (29.76 g, 290.95 mmol) in hexane (250 mL) was stirred for 30 min. Then, the ice bath was removed and stirring was continued for a further 30 min. Filtration over celite and concentration *in vacuo* afforded the title aldehyde **2.17** as a colourless oil (1.06 g, 7.67 mmol, 44%) which was used in the next step without further puification.

FT-IR (neat) ν_{max} 2967 (m), 2917 (m), 2856 (m), 1692 (s) cm^{-1}.

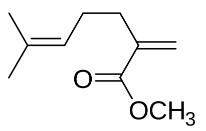
^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.55 (1H, s, $C\underline{H}O$), 6.25 (1H, q, *J* = 1.3 Hz =$C\underline{H}H$), 5.99 (1H, d, *J* = 0.7 Hz, =$CH\underline{H}$), 5.09 (1H, t.septet, *J* = 7.0 and 1.5 Hz, =$C\underline{H}CH_2$), 2.29 (2H, t, *J* = 6.6 Hz, $CH_2C\underline{H}_2$), 2.15 (2H, q, *J* = 7.5 Hz, $C\underline{H}_2CH_2$), 1.69 (3H, d, *J* = 1.1 Hz, $C\underline{H}_3$), 1.61 (3H, s, $C\underline{H}_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 194.7 ($\underline{C}HO$), 149.9 ($\underline{C}CHO$), 134.0 ($\underline{C}HCH_2$), 132.5 ($\underline{C}$=CH), 123.2 (=$\underline{C}H_2$), 28.0 ($CH_2\underline{C}H_2$), 26.19 ($\underline{C}H_2CH_2$), 25.6 ($\underline{C}H_3$), 17.7 ($\underline{C}H_3$).

LRMS (EI) *m*/*z* 138 ($M^{+\cdot}$).

HRMS (EI) *m*/*z* Calculated: 138.1045, found: 138.1042 (M^+).

3.2.12- Methyl 6-methyl-2-methylenehept-5-enoate (2.18)



$C_{10}H_{16}O_2$

Mwt: 168.23 g/mol.

Following the procedure of Yamamoto *et al.*,[124] aldehyde **2.17** (1.55 g, 11.21 mmol) in dry MeOH (60 mL) was added over 30 min to a mixture prepared from powdered NaCN (2.98 g, 59.64 mmol) and absolute AcOH (1.0 mL, 17.82 mmol) in dry MeOH (100 mL). After stirring for 60 min at rt, the mixture was further stirred for 17.5 h after adding MnO_2 (20.94 g, 204.7 mmol, activated powder). The solution was filtered over celite and methanol was removed *in vacuo*. The organic material was extracted into ether (3 x 50 mL), washed with sat. aq. $NaHCO_3$ (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude ester **2.18** as a yellow oil (1.4 g, 8.32 mmol, 74 %) which was used without further purification.

FT-IR (neat) ν_{max} 2950 (w), 2923 (w), 2858 (w), 1721 (s), 1631 (m) cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.14 (1H, s with fine coupling, $C\underline{H}H$), 5.53 (1H, q, *J* = 1.5 Hz, =$C\underline{H}H$), 5.12 (1H, t.septet, *J* = 7.1 and 1.3 Hz, =$C\underline{H}CH_2$), 3.76 (3H, s, $OC\underline{H}_3$), 2.33 (2H, t, *J* = 7.1 Hz, $C\underline{H}_2CH_2$), 2.16 (2H, q, *J* = 7.1 Hz, $C\underline{H}_2CH_2$), 1.69 (3H, d, *J* = 1.1 Hz, $C\underline{H}_3$), 1.60 (3H, s, $C\underline{H}_3$).

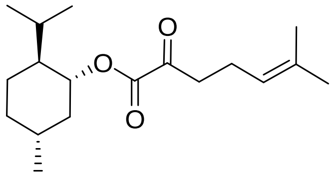
^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.8 ($\underline{C}$=O), 140.4 ($\underline{C}COCH_3$), 132.3 ($\underline{C}CHCH_2$), 124.8 (=$\underline{C}H_2$), 123.3 ($\underline{C}HCH_2$), 51.7 ($\underline{C}H_3$), 32.1 ($\underline{C}H_2C$), 26.9 ($\underline{C}H_2CH_2$), 25.6 ($\underline{C}H_3$), 17.7

(<u>C</u>H$_3$).

LRMS (EI) *m/z* 168 ($M^{+\cdot}$).

HRMS (EI) *m/z* Calculated: 168.1150, found: 168.1147 (M^+).

3.2.13 (1*R*,2*S*,5*R*)-2-*iso*-Propyl-5-methylcyclohexyl 6-methyl-2-oxohept-5-enoate (2.29)



$C_{18}H_{30}O_3$

Mol. Wt.: 294.43 g/mol.

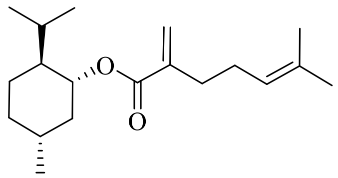
a) Preparation of Grignard solution of bromide **2.28**: To a stirred solution of Mg (0.518 g, 0.021 g-atom) in dry THF (15 mL), was added dropwise bromide **2.28** (1.74 g, 10.67 mmol) and 2 drops of dibromoethane. The mixture was stirred at room temperature for 30 min then heated to reflux for 30 min. Then, the mixture was cooled to rt and the solution was used directly in step (c).

b) Preparation of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl(chlorocarbonyl)formate: To stirred oxalyl chloride (1.60 mL, 17.8 mmol) at −10 °C, was added dropwise a solution of (−)-menthol (1.40 g, 8.89 mmol) in dry CH_2Cl_2 (10 mL). The mixture was warmed to rt and stirred for 1 h then the excess of oxalyl chloride and the solvent was removed *in vacuo* to afford the formate intermediate which was used directly in step (c).

c) Grignard solution of bromide **2.28** (15 mL, 0.7 M in THF, prepared in step (a)) was added to stirred solution of LiBr (1.87 g, 21.34 mmol) and CuBr (1.53 g, 10.67 mmol) in dry THF (15 mL) at room temperature then the mixture was cooled to − 78 °C. The solution of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl(chlorocarbonyl)formate (2.19 g, 8.85 mmol, prepared in step (b)) in dry THF (10 mL) was added and the mixture was stirred for 30 min at − 78 °C. Then, the reaction was quenched with sat. aq. NH_4Cl (40 mL) and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. The crude was purified by column chromatography (SiO_2 eluting with Et_2O/hexane (1 → 5%)) to afford the product as a pale yellow oil (1.89 g, 6.42 mmol, 72%).

[α]$_D$	– 24.7 (*c* 1.05, $CHCl_3$, 23 °C).
FT-IR (neat) ν_{max}	2956 (m), 2926 (m), 2871 (m), 1720 (s), 1729 (s), 1455 (m) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 5.10 (1H, m, C$\underline{H}$=), 4.81 (1H, td, *J* = 11.0 and 4.6 Hz, C$\underline{H}$OR), 2.84 (2H, t, *J* = 7.7 Hz, C$\underline{H}_2$), 2.31 (2H, q, *J* = 7.3 Hz, C$\underline{H}_2$), 2.03 (1H, m, C$\underline{H}_2$), 1.86 (1H, m, C$\underline{H}_2$), 1.77-1.42 (3H, m, C$\underline{H}_2$), 1.69 (3H, s, C$\underline{H}_3$), 1.63 (3H, s, C$\underline{H}_3$), 1.18-0.97 (4H, m, C$\underline{H}_2$), 0.95-0.87 (6H, m, C$\underline{H}_3$), 0.77 (3H, d, *J* = 7.0 Hz, C$\underline{H}_3$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 194.7 (C=O), 160.9 (C=O), 133.4 ($\underline{C}$), 121.9 ($\underline{C}$H=), 76.8 ($\underline{C}$HOR), 46.8 ($\underline{C}$H), 40.4 ($\underline{C}H_2$), 39.6 ($\underline{C}H_2$), 34.0 ($\underline{C}H_2$), 31.4 ($\underline{C}$H), 26.2 ($\underline{C}H_3$), 25.6 ($\underline{C}H_2$), 23.3 ($\underline{C}H_2$), 21.9 ($\underline{C}H_2$), 21.8 ($\underline{C}H_3$), 20.7 ($\underline{C}H_3$), 17.6 ($\underline{C}H_3$), 16.1 ($\underline{C}H_3$).
LRMS (ES^+) *m/z*	312 ($[M+NH_4]^+$).

3.2.14 (1*R*,2*S*,5*R*)-2-*iso*-Propyl-5-methylcyclohexyl 6-methyl-2-methylenehept-5-enoate (2.30)



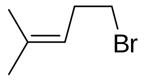
$C_{19}H_{32}O_2$

Mol. Wt.: 292.46 g/mol.

A solution of lithium diisopropylamide [generated by adding *n*-BuLi (0.38 mL of 2.41 M solution in hexanes, 0.91 mmol) to diisopropylamine (0.15 mL, 1.06 mmol) at 0 °C and the mixture was stirred for 1 h] in dry THF (2.0 mL) was added to a solution of Ph_3PMeBr (361 mg, 0.99 mmol) in THF (5.0 mL) at − 10 ° C. After 30 min of stirring at − 10 ° C, a solution of ester **2.29** (215 mg, 0.73 mmol) in dry THF (5.0 mL) was added. The reaction mixture was subsequently allowed to warm to room temperature and stirred for 4 h. The reaction was quenched with sat. aq. NH_4Cl (10 mL). The reaction mixture was diluted with CH_2Cl_2 (20 mL) and H_2O (20 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and the solvents were removed *in vacuo*. The crude was purified by column chromatography (SiO_2 eluting with CH_2Cl_2/hexane (2→ 5%)) to afford the product as a colourless oil (0.1 g, 0.34 mmol, 47 %).

$[\alpha]_D$	–22.7 (*c* 1.1, $CHCl_3$, 26 °C).
FT-IR (neat) ν_{max}	2955 (m), 2925 (m), 2869 (m), 1712 (s), 1630 (m) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 6.12 (1H, d, *J* = 1.5 Hz, $=C\underline{H}H$), 5.49 (1H, q, *J* = 1.1 Hz, $=CH\underline{H}$), 5.12 (1H, m, $C\underline{H}=$), 4.76 (1H, td, *J* = 10.8 and 4.4 Hz, $C\underline{H}OR$), 2.38-2.25 (2H, m, $C\underline{H}_2$), 2.16 (2H, q, *J* = 7.1 Hz $C\underline{H}_2$), 2.04 (1H, m, $C\underline{H}_2$), 1.89 (1H, m, $C\underline{H}_2$), 1.70-1.30 (5H, m, $C\underline{H}_2$), 1.60 (3H, s, $C\underline{H}_3$), 1.59-1.37 (2H, m, $C\underline{H}_2$), 1.16-0.84 (3H, m, $C\underline{H}_2$), 0.91 (6H, dd, *J* = 3.7 and 7.0 Hz, $C\underline{H}_3$), 0.77 (3H, d, *J* = 7.0 Hz, $C\underline{H}_3$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 166.8 (C=O), 141.0 ($\underline{C}$), 132.2 ($\underline{C}$), 124.3 ($=\underline{C}H$), 123.4 ($=\underline{C}H_2$), 74.3 ($\underline{C}HOCOR$), 47.1 ($\underline{C}H$), 40.7 ($\underline{C}H_2$), 34.3 ($\underline{C}H_2$), 32.1 ($\underline{C}H_2$), 31.4 ($\underline{C}H_3$), 27.1 ($\underline{C}H_2$), 26.4 ($\underline{C}H_3$), 25.7 ($\underline{C}H$), 23.5 ($\underline{C}H_2$), 22.0 ($\underline{C}H_3$), 20.8 ($\underline{C}H_3$), 17.7 ($\underline{C}H_3$), 16.4 ($\underline{C}H_3$).
LRMS (ES^+) *m/z*	315 ($[M+Na]^+$).
HRMS (ES^+) *m/z*	Calculated: 315.2300, found: 315.2295 ($[M+Na]^+$).

3.2.15- 5-Bromo-2-methylpent-2-ene (2.28)



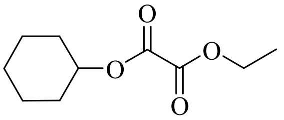
$C_6H_{11}Br$

Mol. Wt.: 163.06 g/mol.

Following the procedure reported by Williams,[131] to a stirred solution of methylmagnesium bromide (40 mL, 120 mmol, 3 M in diethyl ether) in dry THF (40 mL), was added dropwise a solution of cyclopropyl methyl ketone (10 mL, 100 mmol) in THF (15 mL). The mixture was heated to reflux for 20 min. On cooling to room temperature, the reaction mixture was slowly added to a cooled solution of conc. sulfuric acid in water (1:2, 75 mL) at a rate that ensured that the temperature did not rise above 10 °C. Stirring was continued for 30 min. The organic layer was then separated, the aqueous solution was extracted with Et_2O (3 × 50 mL) and the combined organic phases were washed with sat. aq. $NaHCO_3$ (50 mL) and brine (30 mL). The organic layer was dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The crude was distilled under reduced pressure (60-65 °C/water aspirator) to afford the product as a colourless oil (13.5 g, 82.8 mmol, 83%). Physical and spectroscopic data were consistent with reported values.[133]

FT-IR (neat) ν_{max}	2966 (w), 2857 (w), 1643 (w) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 5.12 (1H, t with fine coupling *J* = 7.1 Hz, $C\underline{H}CH_2$), 3.36 (2H, t, *J* = 7.3 Hz, $C\underline{H}_2$), 2.57 (2H, q, *J* = 7.3 Hz, $C\underline{H}_2$), 1.72 (3H, s, $C\underline{H}_3$), 1.64 (3H, s, $C\underline{H}_3$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 134.9 ($\underline{C}$), 120.9 ($\underline{C}H$), 32.9 ($\underline{C}H_2$), 31.7 ($\underline{C}H_2$), 25.7 ($\underline{C}H_3$), 17.9 ($\underline{C}H_3$).

3.2.16- Cyclohexyl ethyl oxalate (2.34)



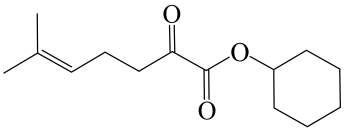
$C_{10}H_{16}O_4$

Mol. Wt.: 200.23 g/mol

To a stirred solution of cyclohexanol (2.6 mL, 37.0 mmol) in dry CH_2Cl_2 (55 mL) at 0 °C, was added triethyl amine (5.3 mL, 37.0 mmol). The mixture was stirred for 45 min then, ethyl chloro oxoacetate (5.4 mL, 48 mmol) and DMAP (0.23 g, 18.5 mmol) were added. The mixture was warmed to room temperature and stirred for 2.5 h. The mixture was quenched with H_2O (20 mL) and 2N HCl (20 mL). The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. The crude was purified by column chromatography (SiO_2 eluting with EtOAc/hexane (hexane → 15% EtOAc/hexane) to afford the product as a viscous colourless oil (6.0 g, 14.98 mmol, 95%).

FT-IR (neat) ν_{max}	2939 (w), 2861 (w), 1763 (s), 1736 (s) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 4.92 (1H, m, $C\underline{H}OR$), 4.34 (2H, q, *J* = 7.3 Hz $C\underline{H}_2O$), 1.98-1.88 (2H, m, $C\underline{H}_2$), 1.84-1.72 (2H, m, $C\underline{H}_2$), 1.63-1.49 (3H, m, $C\underline{H}_2$), 1.45-1.22 (3H, m, $C\underline{H}_2$), 1.37 (3H, t, *J* = 7.0 Hz, $C\underline{H}_3$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 158.2 ($\underline{C}$=O), 157.5 ($\underline{C}$=O), 76.2 ($\underline{C}HOR$), 62.9 ($\underline{C}H_2O$), 31.2 ($2\underline{C}H_2$), 25.1 ($\underline{C}H_2$), 23.6 ($2\underline{C}H_2$), 13.9 ($\underline{C}H_3$).
HRMS (ES^+) *m/z*	Calculated: 223.0946 found: 223.0941 ($[M+Na]^+$).

3.2.17- Cyclohexyl 6-methyl-2-oxohept-5-enoate (2.32)



$C_{14}H_{22}O_3$

Mol. Wt.: 238.32 g/mol

Procedure 1:

a) Prepation of a Grignard solution from bromide **2.28**: To a stirred solution of Mg (0.25 g, 0.01 g-atom) in dry THF (10 mL), was added dropwise bromide **2.28** (0.83 g, 5.1 mmol) and 2 drops of dibromoethane. The mixture was stirred at room temperature for 30 min then heated to reflux for 30 min. The mixture was cooled to rt and the solution was used directly in step (c).

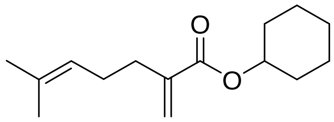
b) Preparation of cyclohexyl(chlorocarbonyl)formate: to stirred oxalyl chloride (0.9 mL, 10.2 mmol) at −10 °C, was added dropwise cyclohexanol (0.3 mL, 4.25 mmol) in dry CH_2Cl_2 (10 mL). The mixture was warmed to rt and stirred for 1 h then, the excess of oxalyl chloride and the solvent were removed *in vacuo* to afford the formate intermediate which was used directly in step (c).

c) To a stirred solution of LiBr (0.89 g, 10.2 mmol) and CuBr (0.73 g, 5.1 mmol) in dry THF (10 mL) at rt, was added Grignard solution of bromide **2.28** (10 mL, 0.51 M in THF, prepared in step (a)). Then, the mixture was cooled to − 78 °C and cyclohexyl(chlorocarbonyl)formate (0.81 g, 4.25 mmol, prepared in step (b)) was added. The mixture was stirred at − 78 °C for 30 min. Then, the reaction was quenched with sat. aq. NH_4Cl (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layer was dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. The crude was purified by column chromatography (SiO_2 eluting with CH_2Cl_2/hexane (10 → 30%)) to afford the product as pale yellow oil (0.54 g, 2.26 mmol, 53%).

Procedure 2: To a stirred solution of ester **2.34** (5.88 g, 29.37 mmol) in dry THF (20 mL) at − 78 °C, was added dropwise the Grignard solution from bromide **2.28** (60 mL, 0.59 M in THF, prepared by following the method in step (a) in procdure 1). The mixture was stirred at − 78 °C for 1 h. Then, the reaction was quenched with sat. aq. NH_4Cl (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layer was dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. The crude was purified by column chromatography (SiO_2 eluting CH_2Cl_2/hexane (10 → 30%)) to afford the product as pale yellow oil (2.8 g, 11.7 mmol, 40%).

FT-IR (neat) ν_{max}	2963 (m), 2866 (w), 1721(s), 1451 (w) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 5.09 (1H, m, =CH), 4.89 (1H, m, $C\underline{H}OR$), 2.84 (2H, t, J = 7.3 Hz, $C\underline{H}_2$), 2.33 (2H, q, J = 7.3 Hz, $C\underline{H}_2$), 1.99-1.83 (2H, m, $C\underline{H}_2$), 1.83-1.73 (2H, m, $C\underline{H}_2$), 1.68 (3H, s, $C\underline{H}_3$), 1.62 (3H, s, $C\underline{H}_3$), 1.62-1.21 (6H, m, $C\underline{H}_2$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 194.7 ($\underline{C}$=O), 160.6 ($\underline{C}$=O), 133.4 ($\underline{C}$=), 121.9 (=$\underline{C}$H), 75.3 ($\underline{C}$HOR), 39.6 ($\underline{C}H_2$), 31.3 ($2\underline{C}H_2$), 25.6 ($\underline{C}H_3$) 25.1 ($\underline{C}H_2$), 23.6 ($2\underline{C}H_2$), 21.8 ($\underline{C}H_2$), 17.6 ($\underline{C}H_3$).
LRMS (ES$^+$) *m/z*	261 ([M+Na]$^+$).
HRMS (ES$^+$) *m/z*	Calculated: 261.1467 found: 261.1461 ([M+Na]$^+$).

3.2.17- Cyclohexyl 6-methyl-2-methylenehept-5-enoate (2.35)



$C_{15}H_{24}O_2$

Mol. Wt.: 236.35 g/mol

To a stirred solution of Ph_3PMeBr (0.61 g, 1.68 mmol) in dry CH_2Cl_2 (8 mL) at rt, was added DBU (0.28 mL, 1.85 mmol) in dry CH_2Cl_2 (8 mL) then the mixture was heated to reflux for 30 min. Then, a solution of ester **2.32** (0.2 g, 0.84 mmol) in dry CH_2Cl_2 (5 mL), was added dropwise to the mixture. The reaction was continued under reflux for 7 h. Then, the mixture was cooled to rt and quenched with H_2O (15 mL). The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. The crude was purified by column chromatography (SiO_2 eluting with CH_2Cl_2/hexane (hexane → 10% CH_2Cl_2/hexane)) to give the product as a courless oil (0.14 g, 0.6 mmol, 71%).

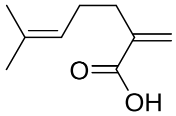
FT-IR (neat) ν_{max}	2933 (m), 2859 (w), 1711 (s) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 6.13 (1H, d, J = 1.3 Hz, $=C\underline{H}H$), 5.49 (1H, q, J = 1.3 Hz, $=CH\underline{H}$), 5.12 (1H, m, $C\underline{H}$=), 4.85 (1H, m, $C\underline{H}OR$), 2.32 (2H, m, $C\underline{H}_2$), 2.16 (2H, q, J

= 7.4 Hz, $C\underline{H}_2$), 1.92-1.83 (2H, m, $C\underline{H}_2$), 1.72 (2H, m, $C\underline{H}_2$), 1.69 (3H, s, $C\underline{H}_3$), 1.61 (3H, s, $C\underline{H}_3$), 1.58-1.23 (6H, m, $C\underline{H}_2$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.7 ($\underline{C}$=O), 141.0 ($\underline{C}$=), 132.2 ($\underline{C}$=), 124.3 (=$C\underline{H}_2$), 123.5 (=$C\underline{H}_2$), 72.6 ($\underline{C}$HOR), 32.1 ($\underline{C}H_2$), 31.5 (2$\underline{C}H_2$), 27.1 ($\underline{C}H_2$), 25.7 ($\underline{C}H_3$) 25.4 ($\underline{C}H_2$), 23.6 (2$\underline{C}H_2$), 17.7 ($\underline{C}H_3$).

LRMS (ES^+) *m*/*z* 275 ($[M+K]^+$).

3.2.19- 6-Methyl-2-methylenehept-5-enoic acid (2.19)



$C_9H_{14}O_2$

Mwt: 154.21 g/mol.

Procedure 1: According to the method of Kulkarni *et al.* [125] at rt, a solution of NaOH (1.60 g, 39.21 mmol) and $NaHCO_3$ (0.27 g, 3.19 mmol) in water (11 mL) was added to a solution of ester **2.18** (1.00 g, 5.94 mmol) in MeOH (14 mL). The resulting solution was heated to reflux for 6 h. Then, the mixture was cooled, washed with hexane (2 × 50 mL) and carefully acidified (pH = 4.0) with 2 M HCl while maintaining the temperature at 0 °C. Methanol was removed *in vacuo* and the aqueous layer was extracted with ethyl acetate (3 × 70 mL). The organic layer was dried (Na_2SO_4), filtered and the solvent was removed *in vacuo* to afford the acid **2.19** as dark yellow oil (0.82 g, 5.32 mmol, 89%) which was used without further purification.

Procedure 2: Following procedure 1 for the hydrolysis of ester **2.18**, the ester **2.30** (73 mg, 0.25 mmol) was hydrolysed to afford the acid **2.19** as dark yellow oil (29.6 mg, 0.19 mmol, 86%) which was used without further purification.

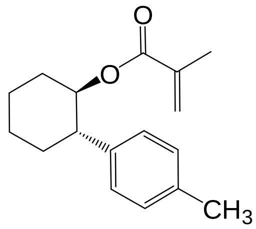
Procedure 3: Following procedure 1 for the hydrolysis of ester **2.18**, the ester **2.35** (40 mg, 0.17 mmol) was hydrolysed to afford the acid **2.19** as dark yellow oil (20 mg, 0.13 mmol, 77%) which was used without further purification.

FT-IR (neat) ν_{max} 3300 (br), 2968 (m), 2916 (m), 2857 (m), 1690 (s), 1627 (m) cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.30 (1H, d, *J* = 1.3 Hz, =$C\underline{H}H$), 5.65 (1H, q, *J* = 1.3 Hz, =$CH\underline{H}$), 5.12 (1H, t with fine coupling, *J* = 7.2 Hz, =$C\underline{H}CH_2$), 2.34 (2H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_2$), 2.20 (2H, q, *J* = 7.2 Hz, $CH_2C\underline{H}_2$), 1.70 (3H, d, *J* = 0.9 Hz,

	$C\underline{H}_3$), 1.61 (3H, s, $C\underline{H}_3$), (OH signal was not observed).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ = 172.4 ($\underline{C}OOH$), 139.8 ($\underline{C}COOH$), 132.5 ($\underline{C}(CH_3)_2$), 127.1 (=$\underline{C}H_2$), 123.2 ($\underline{C}HCH_2$), 31.7 ($\underline{C}H_2C$), 26.9 ($\underline{C}H_2CH_2$), 25.6 ($\underline{C}H_3$), 17.7 ($\underline{C}H_3$).
LRMS (ES$^-$) *m/z*	153 ([M–H]$^+$].
HRMS (ES$^-$) *m/z*	Calculated 153.0921, found 153.0918 ([M–H]$^+$).

3.2.20- *rac*- (1*R*,2*S*)-2-*p*-Tolylcyclohexyl methacrylate ((±)-2.37)



$C_{17}H_{22}O_2$

Mwt: 258.36 g/mol.

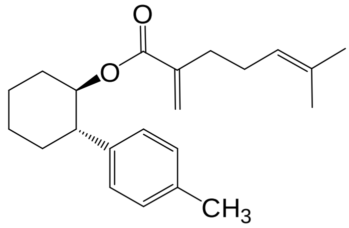
To a stirred solution of the cyclohexanol (±)-**2.4** (248 mg, 1.3 mmol) in dry THF (19 mL) at – 35 °C, was added dropwise NaHMDS (1.42 mL of 1.0 M solution in THF, 1.42 mmol). The solution was allowed to warm to – 25 °C over 30 minutes whereupon a solution of methacryloyl chloride (124 μL, 1.24 mmol) in dry THF (5 mL) was added dropwise. The reaction mixture was allowed to warm to rt and stirred for 2 h. Then, it was diluted with Et_2O (30 mL) and quenched with sat. aq. NH_4Cl (90 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (3 × 30 mL), dried (Na_2SO_4) and the solvent was removed *in vacuo*. The crude was purified by column chromatography (SiO_2 eluting with 5% ether/ hexane) to afford the title ester (±)-**2.37** (191 mg, 0.74 mmol, 59%) as white solid.

mp	51-54 °C
FT-IR (neat) ν_{max}	3931 (m), 2858 (w), 1712 (s), 1638 (m), 1164 (s) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 7.12-7.04 (4H, m, $C\underline{H}_{Ar}$), 5.84 (1H, dq, *J* = 2.0 and 1.0 Hz, =$C\underline{H}H$), 5.37 (1H, quintet, *J* = 1.6 Hz, =$CH\underline{H}$), 4.96 (1H, ddd, *J* = 14.6, 10.7 and 3.8 Hz, $C\underline{H}OH$), 2.71 (1H, ddd, *J* = 14.6, 10.7 and 3.8 Hz, $C\underline{H}Ar$), 2.3 (3H, s, $C\underline{H}_3$), 2.20 (1H, m, $C\underline{H}_2$), 2.00-1.75 (3H, m, $C\underline{H}_2$), 1.75 (3H, dd, *J* = 1.7 and 1.1 Hz, $C\underline{H}_3$), 1.70-1.28 (4H, m, $C\underline{H}_2$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 166.7 (C=O), 140.1 ($\underline{C}_{Ar}$), 136.6 ($\underline{C}_{Ar}$), 135.7 ($\underline{C}$=CH_2), 128.9 ($2CH_{Ar}$), 127.4 ($2CH_{Ar}$), 124.6 (=$\underline{C}H_2$), 77.2 ($\underline{C}HOH$), 49.4 ($\underline{C}HAr$), 33.8 ($\underline{C}H_2$),

32.3 ($\underline{C}H_2$), 25.9 ($\underline{C}H_2$), 24.8 ($\underline{C}H_2$), 21.0 ($\underline{C}H_3$), 18.2 ($\underline{C}H_3$)

LRMS (ES$^+$) *m/z* 281 ([M+Na]$^+$).

3.2.21- *rac*- (1*R*,2*S*)-2-*p*-Tolylcyclohexyl 6-methyl-2-methylenehept-5-enoate ((±)-2.38)



$C_{22}H_{30}O_2$

Mwt: 326.47 g/mol.

a) Preparation of 6-methyl-2-methylenehept-5-enoyl chloride **2.20**: To a stirred solution of acid **2.19** (0.16 g, 1.04 mmol) and DMF (80.6 μL, 1.04 mmol) in *n*-hexane (30 mL) at rt, was added dropwise oxalyl chloride (440 μL, 4.94 mmol). A white precipitate formed immediately and the mixture was stirred at rt for 1 h. Then, the mixture was filtered and the solvent and the excess of oxalyl chloride were removed *in vacuo* to give the acid chloride as a yellow oil (179 mg g, 1.04 mmol, 100%).

b) To a stirred solution of the cyclohexanol (±)- **2.4** (0.21, 1.1 mmol) in dry THF (16 mL) was added NaHMDS (1.2 mL, 1.0 M solution in THF, 1.2 mmol) at – 35 °C. The solution was allowed to warm to – 25 °C over 30 min whereupon a solution of the acid chloride **2.20** (179 mg, 1.1 mmol) in dry THF (11 mL) was added dropwise. The mixture was stirred for 3 h at rt then, the reaction was diluted with Et_2O (33 mL) and quenched with sat. aq. NH_4Cl (75 mL). The organic layer was separated and washed with sat. aq. $NaHCO_3$ (3 × 25 mL). The organic layer was dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The crude was purified by column chromatography (SiO_2 eluting with Et_2O/hexane (5 →10%)) to afford the product as a colourless oil (0.194 g, 0.59 mmol, 57%).

FT-IR (neat) ν_{max} 2929 (m), 2857 (w), 1710 (s), 1631 (w) cm^{-1}.

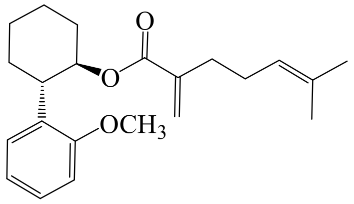
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.13-7.06 (4H, m, $\underline{C}H_{Ar}$), 5.86 (1H, d, *J* = 1.5 Hz, =C$\underline{H}$H), 5.30 (1H, q, *J* = 1.5 Hz, =CH$\underline{H}$), 4.99 (2H, m, =C$\underline{H}$CH$_2$ and C$\underline{H}$OR), 2.70 (1H, ddd, *J* = 14.5, 10.8 and 3.7 Hz, C$\underline{H}$Ar), 2.29 (3H, s, C$\underline{H_3}$), 2.21 (1H, m, C$\underline{H_2}$), 2.13 (2H, t, *J* = 7.5 Hz, C$\underline{H_2}$CH$_2$), 1.99 -1.73 (4H, m, C$\underline{H_2}$), 1.67 (3H, d,

J = 1.1 Hz, $C\underline{H}_3$), 1.69-1.28 (5H, m, $C\underline{H}_2$), 1.51 (3H, s, $C\underline{H}_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.6 (C=O), 140.7 (=$\underline{C}$COOR), 140.2 ($\underline{C}_{Ar}$), 135.7 ($\underline{C}_{Ar}$), 132.0 ($\underline{C}CHCH_2$), 129.0 ($2\underline{C}H_{Ar}$), 127.3 ($2\underline{C}H_{Ar}$), 124.0 (=$\underline{C}H_2$), 123.5 ($\underline{C}HCH_2$), 76.5 ($\underline{C}$HOH), 49.4 ($\underline{C}$HAr), 34.0 ($\underline{C}H_2$), 32.3 ($\underline{C}H_2$), 32.0 ($\underline{C}H_2$), 26.8 ($\underline{C}H_2$), 25.9 ($\underline{C}H_2$), 25.6 ($\underline{C}H_3$), 24.8 ($\underline{C}H_2$), 21.0 ($\underline{C}H_3$), 17.6 ($\underline{C}H_3$).

LRMS (ES^+) *m/z* 349 ($[M+Na]^+$).

3.2.22- *rac*- (1*R*,2*S*)-2-(2-Methoxyphenyl)cyclohexyl 6-methyl-2-methylenehept-5-enoate ((±)-2.39)



$C_{22}H_{30}O_3$

Mol. Wt.: 342.47 g/mol.

Following the procedure for the preparation of diene (±)-**2.38**, reaction of the freshly prepared acid chloride **2.20** (224 mg, 1.3 mmol) with the cyclohexanol (±)-**2.6** (0.28 g, 1.37 mmol) in dry THF (25 mL) for 3 h afforded the title diene (±)-**2.39** as a colourless oil (0.27 g, 0.79 mmol, 61%).

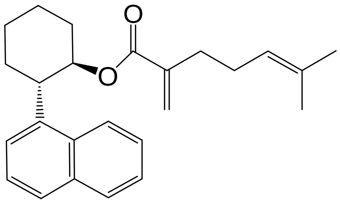
FT-IR (neat) ν_{max} 2930 (m), 2857 (w), 1710 (s), 1630 (w), 1601 (w) cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.18-7.09 (2H, m, $\underline{C}H_{Ar}$), 6.90-6.78 (2H, m, $\underline{C}H_{Ar}$), 5.82 (1H, d, J = 1.8 Hz, =C$\underline{H}$CH), 5.27 (1H, q, J= 1.8 Hz, =CHC$\underline{H}$), 5.13 (1H, td, J = 11.0 and 4.0 Hz, C$\underline{H}$OR), 4.97 (1H, t.septet, J = 7.1 and 1.5 Hz, =C$\underline{H}CH_2$), 3.80 (3H, s, $OC\underline{H}_3$), 3.27 (1H, td, J = 11.0 and 3.7 Hz, C$\underline{H}$Ar), 2.24 (1H, m, $C\underline{H}_2$), 2.09 (2H, t, J = 7.7 Hz, $C\underline{H}_2$), 1.90 (2H, q, J = 7.7 Hz, $C\underline{H}_2$), 1.64 (3H, s, $C\underline{H}_3$), 1.49 (3H, s, $C\underline{H}_3$), 1.85-1.28 (7H, m, $C\underline{H}_2$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 166.7 ($\underline{C}$OOCH), 157.3 ($\underline{C}_{Ar}$), 140.8 ($\underline{C}$COCH), 131.9 ($\underline{C}CHCH_2$), 131.4 ($\underline{C}_{Ar}$), 127.4, ($\underline{C}H_{Ar}$), 127.0 ($\underline{C}H_{Ar}$), 123.9 (=$\underline{C}H_2$), 123.5 ($\underline{C}HCH_2$), 120.6 ($\underline{C}H_{Ar}$), 110.5 ($\underline{C}H_{Ar}$), 75.8 (CHOR), 55.4 ($O\underline{C}H_3$), 42.2 ($\underline{C}$H), 32.7 ($\underline{C}H_2$), 32.0 ($\underline{C}H_2$), 31.4 ($\underline{C}H_2$), 26.7 ($\underline{C}H_2$), 26.0 ($\underline{C}H_2$), 25.6 ($\underline{C}H_3$), 24.8 ($\underline{C}H_2$), 17.6 ($\underline{C}H_3$).

LRMS (ES$^+$) *m/z* 365 ([M+Na]$^+$).

3.2.23- *rac*- (1*R*,2*S*)-2-(Naphthalen-1-yl)cyclohexyl 6-methyl-2-methylenehept-5-enoate ((±)-2.40)



$C_{25}H_{30}O_2$

Mol. Wt.: 362.5 g/mol.

Following the procedure for the preparation of diene (±)-**2.38**, reaction of the freshly prepared acid chloride **2.20** (112 mg, 0.65 mmol) with the cyclohexanol (±)-**2.6** (154 mg, 0.68 mmol) in dry THF (15 mL) for 2.75 h afforded the title diene (±)-**2.40** as a colourless oil (160 mg, 0.4 mmol, 68%).

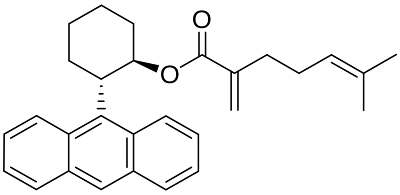
FT-IR (neat) ν_{max} 3388 (br), 3045 (w), 2928 (m), 2854 (m), 1596 (w) cm^{-1}.

^{1}H-NMR (300 MHz, CDCl$_3$) δ 8.20 (1H, d, *J* = 8.4 Hz, C$\underline{H}_{Ar}$), 7.83 (1H, m, C$\underline{H}_{Ar}$), 7.68 (1H, m, C$\underline{H}_{Ar}$), 7.55-7.39 (4H, m, C$\underline{H}_{Ar}$), 5.62 (1H, d, *J* = 1.7 Hz, =C$\underline{H}$H), 5.27 (1H, td, *J* = 10.3 and 4.8 Hz, C$\underline{H}$OR), 5.13 (1H, q, *J* = 1.7 Hz, =CH$\underline{H}$), 4.79 (1H, t.septet, *J* = 7.1 and 1.5 Hz, =C$\underline{H}$CH$_2$), 3.70 (1H, td, *J* = 11.4 and 3.5 Hz, C$\underline{H}$Ar), 2.33 (1H, m), 2.10 (1H, m, C$\underline{H}_2$), 2.03-1.82 (4H, m, C$\underline{H}_2$C$\underline{H}_2$), 1.80-1.32 (6H, m, C$\underline{H}_2$), 1.59 (3H, d, *J* = 1.3 Hz, C$\underline{H}_3$) 1.39 (3H, s, C$\underline{H}_3$).

^{13}C-NMR (75 MHz, CDCl$_3$) δ 166.7 ($\underline{C}$OOR), 140.4 ($\underline{C}$), 139.4 ($\underline{C}_{Ar}$), 134.0 ($\underline{C}_{Ar}$), 132.1 ($\underline{C}_{Ar}$), 131.8 ($\underline{C}$), 128.9 ($\underline{C}H_{Ar}$), 126.6 ($\underline{C}H_{Ar}$), 125.6 ($\underline{C}H_{Ar}$), 125.1 (2$\underline{C}H_{Ar}$), 124.2 (=$\underline{C}H_2$), 123.3 ($\underline{C}H_{Ar}$), 123.1 ($\underline{C}$H=), 122.9 ($\underline{C}H_{Ar}$), 76.5 ($\underline{C}$HOR), 43.5 ($\underline{C}$HAr), 34.1 ($\underline{C}H_2$), 32.7 ($\underline{C}H_2$), 31.8 ($\underline{C}H_2$), 26.5 ($\underline{C}H_2$), 26.2 ($\underline{C}H_2$), 25.5 ($\underline{C}H_3$), 24.9 ($\underline{C}H_2$), 17.5 ($\underline{C}H_3$).

LRMS (ES$^+$) *m/z* 385 ([M+Na]$^+$).

3.2.24- *rac*- (1*R*,2*S*)-2-(Anthracen-9-yl)cyclohexyl 6-methyl-2-methylenehept-5-enoate ((±)-2.41)



$C_{29}H_{32}O_2$

Mol. Wt.: 412.56 g/mol.

Following the procedure for the preparation of diene (±)-**2.38**, reaction of the freshly prepared acid chloride **2.20** (112 mg, 0.65 mmol) with the cyclohexanol (±)-**2.7** (188 mg, 0.68 mmol) in dry THF (15 mL) for 2.75 h afforded the title diene (±)-**2.41** as a colourless oil (170 mg, 0.4 mmol, 64%).

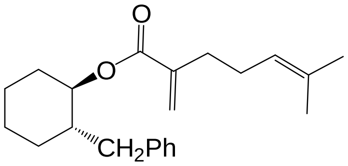
FT-IR (neat) ν_{max} 3050 (w), 2927 (m), 2856 (m), 1711 (s), 1674 (w), 1625 (m) cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.60 (1H, d, *J* = 8.8 Hz, $C\underline{H}_{Ar}$), 8.5 (1H, d, *J* = 8.8 Hz, $C\underline{H}_{Ar}$), 8.32 (1H, s, $C\underline{H}_{Ar}$), 8.0-7.93 (2H, m, $C\underline{H}_{Ar}$), 7.65-7.35 (4H, m, $C\underline{H}_{Ar}$), 6.04 (1H, td, *J* = 10.6 and 4.6 Hz, $C\underline{H}OCOR$), 5.44 (1H, d, *J* = 1.6 Hz, $=C\underline{H}H$), 4.97 (1H, q, *J* = 1.6 Hz, $=CH\underline{H}$), 4.63 (1H, t.septet, *J* = 7.1 and 1.5 Hz, $-C\underline{H}=C$), 4.42 (1H, td, *J* = 12.8 and 4.2 Hz, $C\underline{H}Ar$), 2.69 (1H, ddd, 26.7, 12.8 and 4.0 Hz, $C\underline{H}$), 2.55 (1H, m, $C\underline{H}_2$), 2.11-1.92 (4H, m, $C\underline{H}_2$), 1.55 (3H, s, $C\underline{H}_3$), 1.90-1.33 (6H, m, $C\underline{H}_2$), 1.29 (3H, s, $C\underline{H}_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.3 ($\underline{C}=O$), 140.2 ($\underline{C}$), 134.2 ($\underline{C}$), 132.0 ($\underline{C}_{Ar}$), 131.6 ($\underline{C}_{Ar}$), 131.2 ($\underline{C}_{Ar}$), 129.7 ($\underline{C}H_{Ar}$), 129.4 ($\underline{C}_{Ar}$), 129.3 ($\underline{C}_{Ar}$), 127.2 ($2\underline{C}H_{Ar}$), 125.6 ($\underline{C}H_{Ar}$) 125.5 ($\underline{C}H_{Ar}$), 124.6 ($\underline{C}H_{Ar}$), 124.4 ($2\underline{C}H_{Ar}$), 124.2 ($\underline{C}H_{Ar}$), 124.0 ($=\underline{C}H_2$), 123.2 ($\underline{C}H=C$), 75.4 ($\underline{C}HOR$), 44.4 ($\underline{C}HAr$), 33.4 ($\underline{C}H_2$), 31.8 ($\underline{C}H_2$), 31.5 ($\underline{C}H_2$), 26.8 ($\underline{C}H_2$), 26.2 ($\underline{C}H_2$), 25.5 ($\underline{C}H_3$), 24.8 ($\underline{C}H_2$), 17.4 ($\underline{C}H_3$).

LRMS (ES^+) *m*/*z* 435 ($[M+Na]^+$).

3.2.25- *rac*- (1*R*,2*S*)-2-Benzylcyclohexyl 6-methyl-2-methylenehept-5-enoate (2.42)



$C_{22}H_{30}O_2$

Mwt: 326.47 g/mol.

Following the procedure for the preparation of diene (±)-**2.38**, reaction of the freshly prepared acid chloride **2.20** (112 mg, 0.65 mmol) with the cyclohexanol (±)-**2.8** (129 mg, 0.68 mmol) in dry THF (15 mL) for 3.5 h afforded the title diene (±)-**2.42** as a colourless oil (119 mg, 0.36 mmol, 56%).

FT-IR (neat) ν_{max} 3930 (m), 2857 (m), 1711 (s), 1630 (w) cm^{-1}.

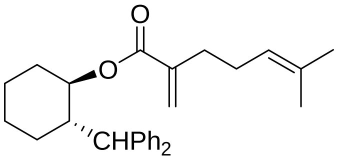
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.28-7.05 (5H, m, $C\underline{H}_{Ar}$), 6.12 (1H, d, *J* = 1.5 Hz, $=C\underline{H}CH$), 5.48 (1H, q, *J* = 1.5 Hz, $=CHC\underline{H}$), 5.11 (1H, t.septet, *J* = 7.0 and 1.5 Hz, $=C\underline{H}CH_2$), 4.62 (1H, td, *J* = 10.0 and 4.4 Hz, $C\underline{H}OR$), 2.91 (1H, dd, *J* = 3.9 and 13.5 Hz, $CH\underline{H}Ar$), 2.37- 2.09 (5H, m, $C\underline{H}_2$), 2.05 (1H, m, $C\underline{H}_2$), 1.87-1.59 (5H, m, $C\underline{H}_2$), 1.67 (3H, s, $C\underline{H}_3$), 1.58 (3H, s, $C\underline{H}_3$), 1.43-1.25 (2H, m, $C\underline{H}_2$), 1.10 (1H, m, $C\underline{H}_2$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 166.9 ($\underline{C}=O$), 140.8 ($\underline{C}COCH$), 140.3 ($\underline{C}_{Ar}$), 132.3 ($\underline{C}CHCH_2$), 129.2 ($2\underline{C}H_{Ar}$), 128.2 ($2\underline{C}H_{Ar}$), 125.8 ($\underline{C}H_{Ar}$), 124.5 ($=\underline{C}H_2$), 123.4 ($\underline{C}HCH_2$), 76.9 ($\underline{C}HOH$), 43.9 ($\underline{C}HCH_2Ar$), 38.8 ($\underline{C}H_2$), 32.1 ($\underline{C}H_2$), 31.7 ($\underline{C}H_2$), 29.9 ($\underline{C}H_2$), 27.1 ($\underline{C}H_2$), 25.6 ($\underline{C}H_3$), 25.0 ($\underline{C}H_2$), 24.5 ($\underline{C}H_2$), 17.7 ($\underline{C}H_3$).

LRMS (ES^+) *m*/*z* 349 ($[M+Na]^+$).

HRMS (ES^+) *m*/*z* Calculated: 349.2143, found: 349.2138 ($[M+Na]^+$).

3.2.26- *rac*- (1*R*,2*S*)-2-Benzhydrylcyclohexyl 6-methyl-2-methylenehept-5-enoate ((±)-2.43)



$C_{28}H_{34}O_2$

Mwt: 402.57 g/mol.

Following the procedure for the preparation of diene (±)-**2.38**, reaction of the freshly prepared acid chloride **2.20** (143 mg, 0.83 mmol) with the cyclohexanol (±)-**2.9** (0.46 g, 1.7 mmol) in dry

Et_2O (27 mL) for 4 h afforded the title diene (±)-**2.43** as a colourless highly viscous oil (0.144 g, 0.36 mmol, 43%).

FT-IR (neat) ν_{max} 3026 (w), 2933 (m), 2860 (w), 1710 (s), 1630 (w) cm^{-1}.

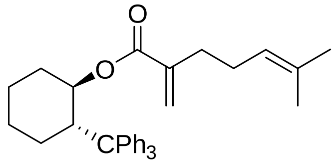
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.38-7.15 (10H, m, C<u>H</u>$_{Ar}$), 6.0 (1H, d, *J* = 0.9 Hz, =C<u>H</u>H), 5.43 (1H, d, *J* = 0.9 Hz, =CH<u>H</u>), 5.10 (1H, t, *J* = 6.8 Hz, =C<u>H</u>CH$_2$), 4.75 (1H, td, *J* = 7.1 and 3.3 Hz, C<u>H</u>OR), 4.15 (1H, d, *J* = 9.0 Hz, C<u>H</u>Ar$_2$), 2.78 (1H, m, C<u>H</u>CHAr$_2$), 2.25 (2H, t, *J* = 7.7 Hz, C<u>H</u>$_2$CH$_2$), 2.20-2.07 (2H, m, C<u>H</u>$_2$CH=), 1.95 (1H, m, C<u>H</u>$_2$), 1.83-1.25 (6H, m, C<u>H</u>$_2$), 1.70 (3H, s, C<u>H</u>$_3$), 1.61 (3H, s, C<u>H</u>$_3$), 1.12 (1H, m, C<u>H</u>$_2$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 166.4 (<u>C</u>=O), 143.5 (<u>C</u>$_{Ar}$), 143.1 (<u>C</u>$_{Ar}$), 140.7 (<u>C</u>=), 132.1 (<u>C</u>=), 128.7 (2<u>C</u>H$_{Ar}$), 128.5 (2<u>C</u>H$_{Ar}$), 128.4 (2<u>C</u>H$_{Ar}$), 128.0 (2<u>C</u>H$_{Ar}$), 126.2 (<u>C</u>H$_{Ar}$), 126.1 (<u>C</u>H$_{Ar}$), 124.4 (=<u>C</u>H$_2$), 123.0 (<u>C</u>HCH$_2$), 74.3 (<u>C</u>HOCOR), 52.2 (<u>C</u>HAr$_2$), 42.8 (<u>C</u>HCHAr$_2$), 31.9 (<u>C</u>H$_2$), 29.3 (<u>C</u>H$_2$), 27.0 (<u>C</u>H$_2$), 26.3 (<u>C</u>H$_2$), 25.7 (<u>C</u>H$_3$), 23.0 (<u>C</u>H$_2$), 22.9 (<u>C</u>H$_2$), 17.7 (<u>C</u>H$_3$).

LRMS (ES^+) *m/z* 425 ($[M+Na]^+$).

HRMS (ES^+) *m/z* Calculated: 403.2637, found: 403.2632 ($[M+H]^+$).

3.2.27- *rac*- (1*R*,2*S*)-2-Tritylcyclohexyl 6-methyl-2-methylenehept-5-enoate ((±)-2.44)



$C_{34}H_{38}O_2$

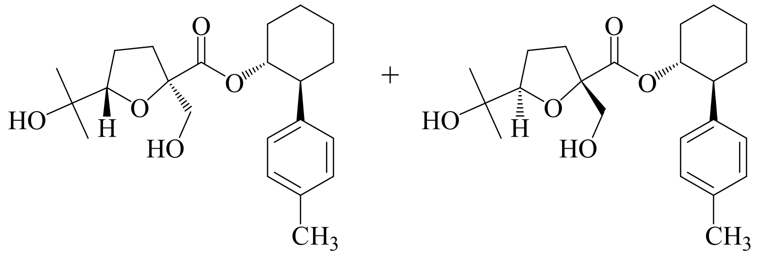
Mol. Wt.: 478.66 g/mol.

Procedure 1: Following the procedure for the preparation of diene (±)-**2.38**, reaction of the freshly prepared acid chloride **2.20** (112 mg, 0.65 mmol) with the cyclohexanol (±)-**2.10** (0.467 g, 1.36 mmol) in dry Et_2O (27 mL) for 1.5 h afforded the title diene (±)-**2.44** as a colourless highly viscous oil (93 mg, 0.19 mmol, 30%).

Procedure 2: To a stirred suspension of NaH (70 mg, 1.75 mmol) in dry DMSO (1 mL), was added the phosphonate ester (±)-**2.82** (0.76 g, 1.46 mmol) in dry DMSO (2 mL). The mixture was stirred for 45 min then, 5-bromo-2-methylpent-2-ene (0.18 g, 1.1 mmol) was added dropwise. On completion, the mixture was heated to 50 °C and sirred for 5.0 h. Then, the mixture was cooled to rt and K_2CO_3 (0.3 g, 2.14 mmol) followed by the addition of HCHO (7.6 mL, 93.6 mmol, 37% in H_2O). The mixture was heated to 50 °C and stirred overnight. The mixture was cooled to rt, diluted with 10 mL of water and extracted with Et_2O (4 × 50 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo*. The crude was purified by column chromatography ((SiO_2 eluting with ether/hexane (hexane → 5 %)) to afford the title diene (±)-**2.44** as a colourless highly viscous oil (0.173 g, 0.36 mmol, 25%). This compound exhibited broadening of some signals in its NMR spectra due to restricted rotation.

FT-IR (neat) ν_{max}	3032 (w), 2925 (m), 2857 (w), 1708 (s), 1630 (w) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 7.70- 6.90 (15H, m, $C\underline{H}_{Ar}$), 5.20 (1H, d, J = 1.3 Hz, $=C\underline{H}H$), 5.14 (1H, q, J = 1.3 Hz, $=CH\underline{H}$), 5.05 (1H, m, $C\underline{H}CH_2$), 4.00 (1H, td, J = 10.0 and 3.8 Hz, $C\underline{H}OR$), 3.60 (1H, td, J = 10.0 and 2.3 Hz, $C\underline{H}CPh_3$), 2.25-2.11 (2H, m, $C\underline{H_2}$), 2.10-1.90 (5H, m, $\underline{C}H_2$), 1.73 (3H, s, $C\underline{H_3}$), 1.85-1.34 (4H, m $C\underline{H_2}$), 1.61 (3H, s, $C\underline{H_3}$), 0.88 (1H, m, $C\underline{H_2}$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 166.4 (C=O), 148.5 (3 x $\underline{C}_{Ar}$), 140.4 ($\underline{C}$), 131.9 ($\underline{C}$), 128.9 ($6\underline{C}H_{Ar}$), 127.4 ($6\underline{C}H_{Ar}$), 125.1 ($3\underline{C}H_{Ar}$), 124.3 ($=\underline{C}H_2$), 123.6 ($C\underline{H}CH_2$), 76.3 ($C\underline{H}OH$), 60.7 ($\underline{C}Ph_3$), 46.5 ($\underline{C}HCPh_3$), 33.3 ($\underline{C}H_2$), 31.9 ($\underline{C}H_2$), 29.0 ($\underline{C}H_2$), 26.9 ($\underline{C}H_2$), 26.3 ($\underline{C}H_2$), 25.7 ($\underline{C}H_2$), 24.9 ($\underline{C}H_2$), 17.7 ($\underline{C}H_3$)
LRMS (ES^+) *m*/*z*	501 ($[M+Na]^+$).

3.2.28- *rac*- (2*S*,5*R*)-(1*S*,2*R*)- 2-*p*-Tolylcyclohexyl tetrahydro-2-(hydroxymethyl)-5-(2-hydroxypropan-2-yl)furan-2-carboxylate and *rac*- (2*R*,5*S*)-(1*S*,2*R*)- 2-*p*-Tolylcyclohexyl tetrahydro-2-(hydroxymethyl)-5-(2-hydroxypropan-2-yl)furan-2-carboxylate ((±)-2.45a/b)



$C_{22}H_{32}O_5$

Mol. Wt.: 376.49 gmol

To vigorously stirred mixture of diene (±)-**2.38** (100 mg, 0.306 mmol) and phosphate buffer (1/15M aq. sol. of both KH_2PO_4 and NaH_2PO_4 in volumetric ratio 8:2, 0.6 mL) in acetone (6.6 mL) at – 35 °C was added a solution of $NaMnO_4$ (1.1 mL of 0.4 M (aq. sol.), 0.42 mmol) containing AcOH (43.5 μL, 0.75 mmol). The purple mixture was stirred rapidly for 1 h during which the temperature of acetone bath raised to –5 °C and the reaction mixture turned to dark brown. The reaction was quenched with sat. aq. $Na_2S_2O_5$ (20 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL), dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The crude was purified by column chromatography (SiO_2 eluting with EtOAc/hexane (10 → 60 %)) to afford the title THF (±)-**2.45a/b** as a colourless foam (0.0647 g, 0.1719 mmol, 56 %). Spectroscopic data are reported for a mixture of two diastereoisomers (1:1) estimated from ^{13}C-NMR.

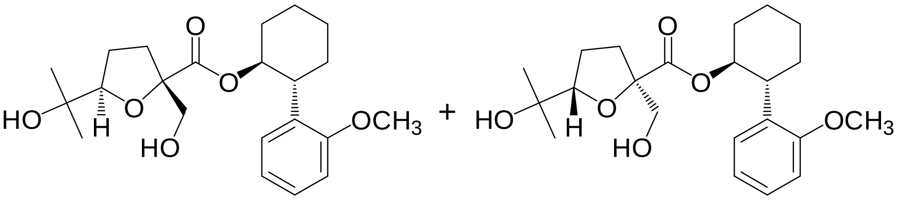
FT-IR (neat) ν_{max} 3394 (br), 3933 (m), 2859 (w), 1721 (m) cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.08 (4H, d, *J* = 1.3 Hz, $\mathrm{C\underline{H}_{Ar}}$), 5.00 (1H, td, *J* = 10.6 and 4.6 Hz, $\mathrm{C\underline{H}OCOR}$), 3.77 and 3.66 (1H, t, *J* = 7.1 Hz, $\mathrm{OC\underline{H}}$), 3.65 and 3.52 (1H, d, *J* = 11.6 Hz, $\mathrm{C\underline{H}HOH}$), 3.53 and 3.45 (1H, d, *J* = 11.6 Hz, $\mathrm{CH\underline{H}OH}$), 2.65 (1H, m, $\mathrm{C\underline{H}Ar}$), 2.38 (1H, br, $\mathrm{O\underline{H}}$), 2.29 (3H, s, $\mathrm{ArC\underline{H}_3}$), 2.14 (1H, m, $\mathrm{C\underline{H}_2}$), 1.97-1.30 (12H, m, $\mathrm{C\underline{H}_2 + O\underline{H}}$), 1.21 and 1.20 (3H, s, $\mathrm{C\underline{H}_3}$), 1.06 and 1.05 (3H, s, $\mathrm{C\underline{H}_3}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 173.4 and 172.7 (C=O), 140.1 and 139.9 ($\mathrm{\underline{C}_{Ar}}$), 136.1 and 136.0 ($\mathrm{\underline{C}_{Ar}}$), 129.1 and 128.9 ($\mathrm{2\underline{C}H_{Ar}}$), 127.4 and 127.2 ($\mathrm{2\underline{C}H_{Ar}}$), 87.1 and 86.9 ($\mathrm{\underline{C}HO}$), 86.6 ($\mathrm{\underline{C}}$), 77.7 and 77.0 ($\mathrm{\underline{C}H}$), 71.3 ($\mathrm{\underline{C}}$), 65.8 and 65.7 ($\mathrm{\underline{C}H_2}$), 49.6 and 49.5 ($\mathrm{\underline{C}HAr}$), 34.3 and 33.9 ($\mathrm{\underline{C}H_2}$), 32.2 and 32.1 ($\mathrm{\underline{C}H_2}$), 31.8 and 31.1 ($\mathrm{\underline{C}H_2}$), 27.3 ($\mathrm{\underline{C}H_3}$), 25.8 and 25.7 ($\mathrm{\underline{C}H_2}$), 25.5 and 25.4 ($\mathrm{\underline{C}H_2}$), 24.8 and 24.7 ($\mathrm{\underline{C}H_3}$), 24.6 ($\mathrm{\underline{C}H_2}$), 20.9 ($\mathrm{\underline{C}H_3}$).

LRMS (ES^+) *m/z* 399 ($[M+Na]^+$).

3.2.29- *rac*- (2*S*,5*R*)-(1*S*,2*R*)-2-(2-Methoxyphenyl)cyclohexyl tetrahydro-2-(hydroxymethyl)-5-(2-hydroxypropan-2-yl)furan-2-carboxylate and *rac*- (2*R*,5*S*)-(1*S*,2*R*)-2-(2-Methoxy phenyl)cyclohexyl tetrahydro-2-(hydroxymethyl)-5-(2-hydroxypropan-2-yl)furan-2-carboxylate ((±)-2.46a/b)



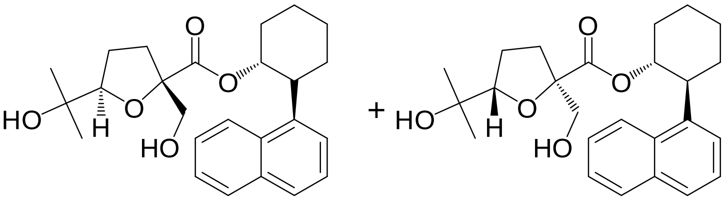
$C_{22}H_{32}O_6$

Mol. Wt.: 392.49 g/mol.

Following the procedure for the preparation of THF diol (±)-**2.45a/b**, the oxidative cyclisation of diene (±)-**2.39** (50 mg, 0.146 mmol) over 2 h and 45 min afforded the title THF (±)-**2.46a/b** as a pale yellow foam (51 mg, 0.13 mmol, 89%). Spectroscopic data are reported for a mixture of two diastereoisomers (1.03:1) determined by HPLC analysis (column: Agilent Zobax Sil C18 (5μm, 4.6 × 250 mm), flow rate: 0.5 mL/min, eluent: 5% isopropanol/hexane, elution times: t_{maj} = 48.36 min, t_{min} = 50.60 min).

FT-IR (neat) ν_{max}	3388 (br), 3045 (w), 2928 (s), 2854 (m), 1596 (w) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 7.20-7.11 (2H, m, $C\underline{H}_{Ar}$), 6.92-6.81 (2H, m, $C\underline{H}_{Ar}$), 5.15 (1H, m, $C\underline{H}OCOR$), 3.82 (3H, s, $OC\underline{H}_3$), 3.62 and 3.54 (1H, d, *J* = 11.5 Hz, $C\underline{H}HOH$), 3.49 and 3.42 (1H, d, *J* = 11.5 Hz, $CH\underline{H}OH$), 3.25 (1H, m, $C\underline{H}Ar$), 2.50-2.25 (2H, br, $O\underline{H}$), 2.15 (1H, m), 2.0-1.30 (12H, m, $C\underline{H}_2$), 1.19 (3H, s, $C\underline{H}_3$), 1.05 and 1.04 (3H, s, $C\underline{H}_3$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ = 173.4 and 172.7 (C=O), 157.3 and 157.2 ($\underline{C}_{Ar}$-OCH_3), 131.1 and 131.0 ($\underline{C}_{Ar}$), 127.4 and 127.3 (2$\underline{C}H_{Ar}$), 120.7 and 120.6 ($\underline{C}H_{Ar}$), 110.7 ($\underline{C}H_{Ar}$), 87.1 and 86.9 ($\underline{C}HO$), 86.5 and 86.4 ($\underline{C}$), 76.3 ($C\underline{H}OCOR$), 71.4 and 71.3 ($\underline{C}$), 65.7 and 65.3 ($\underline{C}H_2OH$), 55.5 and 55.3 ($\underline{C}HAr$), 32.3 and 32.2 ($\underline{C}H_2$), 31.9 ($\underline{C}H_2$), 31.1 ($\underline{C}H_2$), 27.2 ($\underline{C}H_3$), 25.9 ($\underline{C}H_2$), 25.5 ($\underline{C}H_2$), 25.4 ($\underline{C}H_2$), 24.9 and 24.8 ($\underline{C}H_2$), 24.7 ($\underline{C}H_3$).
LRMS (ES^+) *m/z*	432 ($[M+K+H]^+$).

3.2.30- *rac-* (2*S*,5*R*)-(1*R*,2*S*)-2-(Naphthalen-1-yl)cyclohexyl tetrahydro-2-(hydroxymethyl)-5-(2-hydroxypropan-2-yl)furan-2-carboxylate and *rac-* (2*R*,5*S*)-(1*R*,2*S*)-2-(Naphthalen-1-yl)cyclohexyl tetrahydro-2-(hydroxymethyl)-5-(2-hydroxypropan-2-yl)furan-2-carboxylate ((±)-2.47a/b)



$C_{25}H_{32}O_5$

Mol. Wt.: 412.52 g/mol.

Following the procedure for the preparation of THF diol (±)-**2.45a/b**, the oxidative cyclisation of diene (±)-**2.40** (52.9 mg, 0.146 mmol) over 2 h and 35 min afforded the title THF (±)-**2.47a/b** as a yellow foam (57 mg, 0.14 mmol, 95%). Spectroscopic data are reported for a mixture of two diastereoisomers (1.75:1) determined by HPLC analysis (column: Agilent Zobax Sil C18 (5µm, 4.6 × 250 mm), flow rate: 0.5 mL/min, eluent: 5% isopropanol/hexane, elution times: t_{maj} = 49.09 min, t_{min} = 55.55 min).

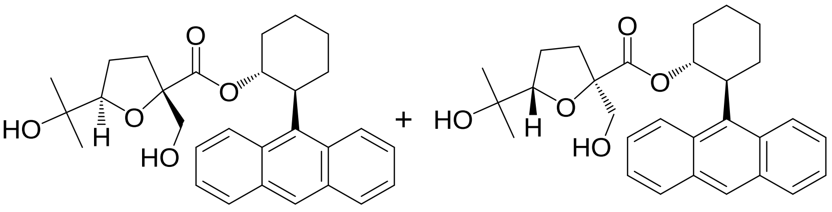
FT-IR (neat) ν_{max} 3395(br), 3047 (w), 2934 (s), 1721 (m), 1597 (w) cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 8.18 (1H, t, *J* = 8.3 Hz, $C\underline{H}_{Ar}$), 7.87-7.80 (1H, m, $C\underline{H}_{Ar}$), 7.73 -7.65 (1H, m, $C\underline{H}_{Ar}$), 7.56-7.38 (4H, m, $C\underline{H}_{Ar}$), 5.21 (1H, m, C$\underline{H}$COR), 3.66 (1H, m, C$\underline{H}$Ar), 3.55 and 2.95 (1H, d, *J* = 7.1 Hz, C$\underline{H}$O), 3.51 and 3.33 (1H, d, *J* = 11.3 Hz, C$\underline{H}$HOH), 3.36 and 3.27 (1H, d, *J* = 11.3 Hz, CH$\underline{H}$OH), 2.70-1.77 (6H, m, $C\underline{H}_2$ + 2O$\underline{H}$), 1.75-1.12 (7H, m, $C\underline{H}_2$), 1.05 and 0.93 (3H, s, $C\underline{H}_3$), 0.82 (1H, m, $C\underline{H}_2$), 0.92 and 0.75 (3H, s, $C\underline{H}_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 173.8 and 172.7 (C=O), 139.3 and 139.1 ($\underline{C}_{Ar}$), 133.9 and 133.8 ($\underline{C}_{Ar}$), 132.1 and 131.9 ($\underline{C}_{Ar}$), 128.9 and 128.8 ($\underline{C}H_{Ar}$), 126.8 and 126.7 ($\underline{C}H_{Ar}$), 125.9 and 125.8 ($\underline{C}H_{Ar}$), 125.6 ($\underline{C}H_{Ar}$), 125.5 and 125.4 ($\underline{C}H_{Ar}$), 125.3 ($\underline{C}H_{Ar}$), 122.9 and 122.8 ($\underline{C}H_{Ar}$), 86.8 and 86.7 ($\underline{C}$HO), 86.4 and 86.3 ($\underline{C}$), 77.5 and 77.4 ($\underline{C}$HOCOR) 71.1 and 70.9 ($\underline{C}$), 65.6 and 65.5 ($\underline{C}H_2OH$), 43.2 ($\underline{C}$HAr), 34.1 and 33.8 ($\underline{C}H_2$), 32.6 and 32.5 ($\underline{C}H_2$), 31.8 ($\underline{C}H_2$), 30.6 ($\underline{C}H_2$), 27.1 and 26.9 ($\underline{C}H_3$), 26.0 and 25.4 ($\underline{C}H_2$), 24.9 and 24.8 ($\underline{C}H_2$), 24.7 and 24.5 ($\underline{C}H_3$).

LRMS (ES^+) *m/z* 847 ($[2M+Na]^+$).

3.2.31- *rac*- (2*S*,5*R*)-(1*R*,2*S*)-2-(Anthracen-9-yl)cyclohexyl tetrahydro-2-(hydroxymethyl)-5-(2-hydroxypropan-2-yl)furan-2-carboxylate and *rac*- (2*R*,5*S*)-(1*R*,2*S*)-2-(Anthracen-9-yl) cyclohexyl tetrahydro-2-(hydroxymethyl)-5-(2-hydroxypropan-2-yl)furan-2-carboxylate ((±)-2.48a/b)



$C_{29}H_{34}O_5$

Mol. Wt.: 462.58 g/mol.

Following the procedure for the preparation of THF diol (±)-**2.45a/b**, the oxidative cyclisation of diene (±)-**2.41** (58.8 mg, 0.158 mmol) over 3 h afforded the title THF (±)-**2.48a/b** as a yellow foam (51 mg, 0.11 mmol, 69%). Spectroscopic data are reported for a mixture of two diastereoisomers (1.75:1) determined by HPLC analysis (column: Agilent Zobax Sil C18 (5μm, 4.6 × 250 mm), flow rate: 0.5 mL/min, eluent: 5% isopropanol/hexane, elution times: t_{maj} = 61.86 min, t_{min} = 56.59 min). Isomers are identified as maj and min where possible.

FT-IR (neat) ν_{max} 3393 (br), 2935 (w), 2862 (w), 1720 (m), 1624 (w) cm^{-1}.

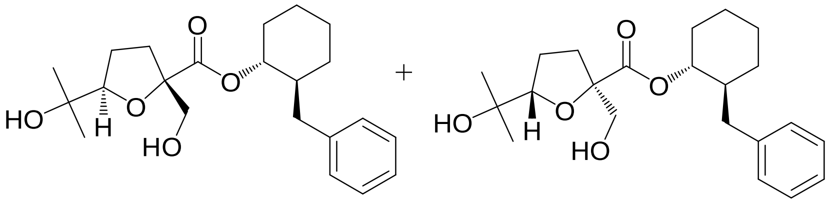
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.57 (1H, d, *J* = 8.8, $C\underline{H}_{Ar}$), 8.50 (1H, m, $C\underline{H}_{Ar}$), 8.35 (1H, d, *J* = 5.0 Hz, $C\underline{H}_{Ar}$), 8.04-7.95 (2H, m, $C\underline{H}_{Ar}$), 7.57-7.39 (4H, m, $C\underline{H}_{Ar}$), 6.04 (1H, m, $C\underline{H}OR$), 4.40 (1H, m, $C\underline{H}Ar$), 3.34$_{maj}$ and 3.18$_{min}$ (1H, d, *J* = 11.3 Hz, $C\underline{H}HOH$), 3.20$_{min}$ and 2.61$_{maj}$ (1H, t, *J* = 7.3 Hz, $C\underline{H}O$), 3.23$_{maj}$ and 3.15$_{min}$ (1H, d, *J* = 11.6 Hz, $C\underline{H}HOH$), 2.73-2.56 (1H, m, $C\underline{H}_2$), 2.41 (1H, m, $C\underline{H}_2$), 2.30-0.30 (12H, m, $C\underline{H}_2$ + OH), 0.93$_{min}$ and 0.89$_{maj}$ (3H, s, $C\underline{H}_3$), 0.84$_{min}$ and 0.74$_{maj}$ (3H, s, $C\underline{H}_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 173.6$_{maj}$ and 172.3$_{min}$ (C=O), 133.9$_{maj}$ and 133.7$_{min}$ ($\underline{C}_{Ar}$), 131.9 (2$\underline{C}_{Ar}$), 131.5 ($\underline{C}_{Ar}$), 131.1$_{min}$ and 131.0$_{maj}$ ($\underline{C}_{Ar}$), 129.6$_{min}$ and 129.4$_{maj}$ ($\underline{C}H_{Ar}$), 129.3$_{maj}$ and 129.2$_{min}$ ($\underline{C}H_{Ar}$), 127.2$_{min}$ and 127.1$_{maj}$ ($\underline{C}H_{Ar}$), 126.0$_{maj}$ and 125.8$_{min}$ ($\underline{C}H_{Ar}$), 125.4$_{min}$ and 125.2$_{maj}$ ($\underline{C}H_{Ar}$), 125.0$_{maj}$ and 124.8$_{min}$ ($\underline{C}H_{Ar}$), 125.7$_{min}$ and 124.6$_{maj}$ ($\underline{C}H_{Ar}$), 124.6 ($\underline{C}H_{Ar}$), 123.9$_{maj}$ and 123.8$_{min}$ ($\underline{C}H_{Ar}$), 86.7$_{maj}$ and 86.6$_{min}$ ($C\underline{H}O$), 86.0$_{min}$ and 85.8$_{maj}$ ($\underline{C}$), 76.0$_{maj}$ and 75.7$_{min}$ ($\underline{C}HOCOR$), 71.0$_{min}$ and 70.9$_{maj}$ ($\underline{C}$), 65.4 ($\underline{C}H_2OH$), 44.5$_{maj}$ and 44.4$_{min}$ ($\underline{C}HAr$), 33.4$_{maj}$ and 33.3$_{min}$ ($\underline{C}H_2$), 31.6$_{maj\ and\ min}$

($\underline{C}H_2$), 30.6$_{\text{maj and min}}$ ($\underline{C}H_2$), 27.0$_{\text{min}}$ and 26.9$_{\text{maj}}$ ($\underline{C}H_3$), 26.6 $_{\text{maj and min}}$ ($\underline{C}H_2$), 25.1$_{\text{min}}$ and 24.8$_{\text{maj}}$ ($\underline{C}H_2$), 24.7 $_{\text{maj and min}}$ ($\underline{C}H_2$), 24.6$_{\text{min}}$ and 24.5$_{\text{maj}}$ ($\underline{C}H_3$).

LRMS (ES$^+$) *m/z* 485 ([M+Na]$^+$).

3.2.32- *rac-* (2*S*,5*R*)-(1*R*,2*S*)-2-Benzylcyclohexyl tetrahydro-2-(hydroxymethyl)-5-(2-hydroxy propan-2-yl)furan-2-carboxylate and *rac-* (2*R*,5*S*)-(1*R*,2*S*)-2-Benzylcyclohexyl tetrahydro-2-(hydroxymethyl)-5-(2-hydroxypropan-2-yl)furan-2-carboxylate ((±)-2.49a/b)



$C_{22}H_{32}O_5$

Mol. Wt.: 376.49 g/mol

Following the procedure for the preparation of THF diol (±)-**2.45a/b**, the oxidative cyclisation of diene (±)-**2.42** (58.8 mg, 0.18 mmol) over 2 h afforded the title THF (±)-**2.49a/b** as a colourless foam (55.6 mg, 0.15 mmol, 82%). Spectroscopic data are reported for a mixture of two diastereoisomers (1.32:1) determined by HPLC analysis (column: Agilent Zobax Sil C18 (5µm, 4.6 × 250 mm), flow rate: 0.5 mL/min, eluent: 5% isopropanol/hexane, elution times: t_{maj} = 40.49 min, t_{min} = 35.97 min). Isomers are identified as maj and min where possible.

FT-IR (neat) ν_{max} 3403 (br), 2934 (m), 2859 (w), 1725 (s), 1604 (w) cm^{-1}.

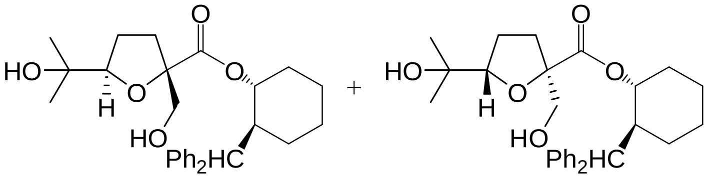
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.30-7.08 (5H, m, $C\underline{H}_{\text{Ar}}$), 4.61 (1H, m, $C\underline{H}OR$), 4.08$_{\text{maj}}$ and 4.06 $_{\text{min}}$ (1H, t, *J* = 7.1 Hz, $C\underline{H}OC$), 3.90$_{\text{min}}$ and 3.87$_{\text{maj}}$ (1H, d, *J* = 11.4 Hz, $C\underline{H}HOH$), 3.77$_{\text{min}}$ and 3.75$_{\text{maj}}$ (1H, d, *J* = 11.4 Hz, $CH\underline{H}OH$), 3.10 (1H, br, $O\underline{H}$), 2.91 (1H, dt, *J* = 13.0 and 3.1 Hz, $CH\underline{H}Ar$), 2.68 (1H, br, $O\underline{H}$), 2.30-1.52 (11H, m), 1.37-0.90 (3H, m, $C\underline{H}_2$), 1.30 (3H, s, $C\underline{H}_3$), 1.14 (3H, s, $C\underline{H}_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 173.7$_{\text{maj}}$ and 173.6$_{\text{min}}$ ($\underline{C}$=O), 140.0$_{\text{maj and min}}$ ($\underline{C}_{\text{Ar}}$) 129.20$_{\text{maj and min}}$ (2 × $\underline{C}H_{\text{Ar}}$), 128.20$_{\text{maj and min}}$ (2 × $\underline{C}H_{\text{Ar}}$), 125.90$_{\text{maj and min}}$ ($\underline{C}H_{\text{Ar}}$), 87.6$_{\text{maj}}$ and 87.5$_{\text{min}}$ ($\underline{C}H$), 86.8$_{\text{min}}$ and 86.6$_{\text{maj}}$ ($\underline{C}$), 77.6$_{\text{min}}$ and 77.4$_{\text{maj}}$ ($\underline{C}H$), 71.5$_{\text{min}}$ and 71.4$_{\text{maj}}$ ($\underline{C}$), 66.2$_{\text{maj}}$ and 66.1$_{\text{min}}$ ($\underline{C}H_2$), 43.8$_{\text{maj}}$ and 43.7$_{\text{min}}$ ($\underline{C}HCH_2Ar$), 38.5$_{\text{maj}}$ and 38.4$_{\text{min}}$ ($\underline{C}H_2Ar$), 32.0$_{\text{maj}}$ and 31.9$_{\text{min}}$ ($\underline{C}H_2$), 31.5$_{\text{maj and min}}$ ($\underline{C}H_2$), 29.60$_{\text{maj and min}}$ ($\underline{C}H_2$), 27.5 ($\underline{C}H_3$), 26.1$_{\text{maj}}$ and 26.0$_{\text{min}}$ ($\underline{C}H_2$), 25.1$_{\text{maj}}$ and 25.0$_{\text{min}}$ ($\underline{C}H_3$), 24.9$_{\text{maj}}$ and 24.8$_{\text{min}}$ ($\underline{C}H_2$), 24.30$_{\text{maj and min}}$ ($\underline{C}H_2$).

LRMS (ES$^+$) *m*/*z* 399 ([M+Na]$^+$).

HRMS (ES$^+$) *m*/*z* Calculated: 399.2147, found: 399.2142 ([M+Na]$^+$).

3.2.33- *rac*- (2*S*,5*R*)-(1*R*,2*S*)-2-Benzhydrylcyclohexyl tetrahydro-2-(hydroxymethyl)-5-(2-hydroxypropan-2-yl)furan-2-carboxylate and *rac*- (2*R*,5*S*)-(1*R*,2*S*)-2-Benz hydryl cyclo hexyl tetrahydro-2-(hydroxymethyl)-5-(2-hydroxypropan-2-yl)furan-2-carboxylate ((±)-2.50a/b)



$C_{28}H_{36}O_5$

Mol. Wt.: 452.58 g/mol.

Following the procedure for the preparation of THF diol (±)-**2.45a/b**, the oxidative cyclisation of diene (±)-**2.43** (0.1 g, 0.25 mmol) over 3 h afforded the title THF (±)-**2.50a/b** as a highly viscous oil (111 mg, 0.245 mmol, 99%). Spectroscopic data are reported for a mixture of two diastereoisomers (1.79:1) determined by HPLC analysis (column: Agilent Zobax Sil C18 (5μm, 4.6 × 250 mm), flow rate: 0.5 mL/min, eluent: 5% isopropanol/hexane, elution times: t_{maj} = 36.18 min, t_{min} = 42.82 min). Isomers are identified as maj and min where possible.

FT-IR (neat) ν_{max} 3402 (br), 3036 (w), 2936 (m), 2863 (m), 1724 (s), 1598 (w) cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.39-7.13 (10H, m, $C\underline{H}_{Ar}$), 4.73 (1H, m, $C\underline{H}OCOR$), 4.15 (1H, d, *J* = 8.6 Hz, $C\underline{H}Ar_2$), 4.06$_{\text{maj}}$ and 4.05$_{\text{min}}$ (1H, t, *J* = 7.1 Hz, $C\underline{H}OC$), 3.83$_{\text{min}}$ and 3.82$_{\text{maj}}$ (1H, d, *J* = 11.3 Hz, $C\underline{H}HOH$), 3.72$_{\text{min}}$ and 3.71$_{\text{maj}}$ (1H, d, *J* = 11.3 Hz, $CH\underline{H}OH$), 3.05 (1H, br, OH), 2.72-2.53 (2H, br, OH and $C\underline{H}CHAr_2$), 2.21-1.22 (11H, m, $C\underline{H}_2$), 1.31$_{\text{min}}$ and 1.30$_{\text{maj}}$ (3H, s, $C\underline{H}_3$), 1.15 (3H, s, $C\underline{H}_3$), 1.15 (1H, m, $CH\underline{H}$).

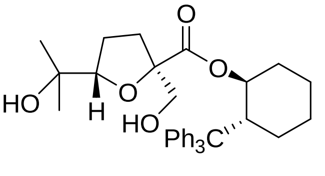
^{13}C-NMR (75 MHz, $CDCl_3$) δ = 173.3 $_{\text{maj}}$ and 173.1$_{\text{min}}$ (C=O) 143.1$_{\text{maj}}$ and 143.0$_{\text{min}}$ ($\underline{C}_{Ar}$) 142.7$_{\text{min}}$ and 142.6$_{\text{maj}}$ ($\underline{C}_{Ar}$), 128.8$_{\text{maj}}$ and 128.7$_{\text{min}}$ ($\underline{C}H_{Ar}$), 128.6$_{\text{min}}$ and 128.5$_{\text{maj}}$ ($\underline{C}H_{Ar}$), 128.4 $_{\text{maj and min}}$ ($\underline{C}H_{Ar}$), 128.0 $_{\text{maj and min}}$ ($\underline{C}H_{Ar}$), 126.4$_{\text{maj and min}}$

($\underline{C}H_{Ar}$), 126.3$_{min}$ and 126.2$_{maj}$ ($\underline{C}H_{Ar}$), 87.6$_{maj}$ and 87.5$_{min}$ ($\underline{C}$HOC), 86.7$_{min}$ and 86.4$_{maj}$ ($\underline{C}$OCH), 74.8$_{maj}$ and 74.3$_{min}$ ($\underline{C}$HOH), 71.5$_{min}$ and 71.4$_{maj}$ ($\underline{C}H_2OH$), 66.2 $_{maj\ and\ min}$ ($\underline{C}H_2OH$), 51.5$_{maj}$ and 51.2$_{min}$ ($\underline{C}Ph_2$), 42.3$_{maj}$ and 41.9$_{min}$ ($\underline{C}HCPh_2$), 31.9 $_{maj\ and\ min}$ ($\underline{C}H_2$), 28.5$_{maj}$ and 28.1$_{min}$ ($\underline{C}H_2$), 27.5 $_{maj}$ and 27.4$_{min}$ ($\underline{C}H_2$), 26.1$_{maj}$ and 26.0$_{min}$ ($\underline{C}H_2$), 25.4 $_{maj\ and\ min}$ ($\underline{C}H_3$), 25.1$_{maj}$ and 25.0$_{min}$ ($\underline{C}H_2$), 22.5 $_{maj\ and\ min}$ ($\underline{C}H_3$), 22.2$_{maj}$ and 22.1$_{min}$ ($\underline{C}H_2$)

LRMS (ES^+) *m/z* 475 ($[M+Na]^+$).

HRMS (ES^+) *m/z* Calculated: 475.2460, found: 475.2455 ($[M+Na]^+$).

3.2.34- *rac.* (2*R*,5*S*)-(1*R*,2*S*)-2-Tritylcyclohexyl tetrahydro-2-(hydroxymethyl)-5-(2-hydroxy propan-2-yl)furan-2-carboxylate (±)-(2.51a/b)



$C_{34}H_{40}O_5$

Mol. Wt.: 528.68 g/mol.

Following the procedure for the preparation of THF diol (±)-**2.45**, the oxidative cyclisation reaction of diene (±)-**2.44** (58.9 mg, 0.12 mmol) over 3 h afforded the title THF (±)-**2.51** as a white foamy material (40 mg, 0.076 mmol, 61%). Spectroscopic data are reported for a mixture of diastereoisomers (32.33:1) determined by HPLC analysis (column: Agilent Zobax Sil C18 (5µm, 4.6 × 250 mm), flow rate: 0.5 mL/min, eluent: 5% isopropanol/hexane, elution times: t_{maj} = 43.85 min, t_{min} = 34.90 min, dr = 97: 3). This compound exhibited broadening of some signals in its NMR spectra due to restricted rotation.

mp 61-65 °C

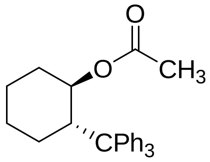
FT-IR (neat) ν_{max} 3423 (br), 3056 (w), 2939 (m), 2860 (w), 1729 (s), 1595 (w) cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.50-6.95 (15H, m, $C\underline{H}_{Ar}$), 4.08 (1H, td, *J* = 13.8 and 3.8 Hz, C$\underline{H}$OCOR), 3.81 (1H, t, *J* = 7.2 Hz, C$\underline{H}$O), 3.62 (1H, d, *J* = 11.3 Hz, C$\underline{H}$HOH) 3.59 (1H, td, *J* = 12.1 and 2.0 Hz, $C\underline{H}CPh_3$), 3.43 (1H d, *J* = 11.3 Hz, CH$\underline{H}$OH), 2.35 (1H, br, O$\underline{H}$), 2.15 (1H, m, $C\underline{H}_2$), 1.97 (1H, m, $C\underline{H}_2$), 1.79-1.60 (5H, m, $C\underline{H}_2$ + O$\underline{H}$), 1.52-1.30 (3H, m, $C\underline{H}_2$), 1.25 (3H, s, $\mathrm{C\underline{H}_3}$), 1.14 (2H, m, $\mathrm{C\underline{H}_2}$), 1.09 (3H, s, $\mathrm{C\underline{H}_3}$), 0.8 (1H, m, $\mathrm{C\underline{H}_2}$).

^{13}C-NMR (75 MHz, $\mathrm{CDCl_3}$) δ = 172.1 (C=O), 128.7 ($\mathrm{6\underline{C}H_{Ar}}$), 127.5 ($\mathrm{6\underline{C}H_{Ar}}$), 125.0 ($\mathrm{3\underline{C}H_{Ar}}$), 86.8 ($\mathrm{\underline{C}}$), 86.7 ($\mathrm{\underline{C}HO}$), 77.2 ($\mathrm{\underline{C}HOCOR}$), 71.5 ($\mathrm{\underline{C}}$), 66.1 ($\mathrm{\underline{C}H_2OH}$), 61.0 ($\mathrm{\underline{C}}$), 45.6 ($\mathrm{\underline{C}HCPh_3}$), 33.0 ($\mathrm{\underline{C}H_2}$), 30.3 ($\mathrm{\underline{C}H_2}$), 28.7 ($\mathrm{\underline{C}H_2}$), 27.3 ($\mathrm{\underline{C}H_3}$), 25.9 ($\mathrm{\underline{C}H_2}$), 25.7 ($\mathrm{\underline{C}H_2}$), 25.0 ($\mathrm{\underline{C}H_3}$), 24.6 ($\mathrm{\underline{C}H_2}$), (quaternary aromatic carbons signal not observed).

LRMS (ES$^+$) *m/z* 546 ([M+Na]$^+$).

3.2.35- *rac*- (1*R*,2*S*)-2-Tritylcyclohexyl acetate (2.64)



$\mathrm{C_{27}H_{28}O_2}$

Mol. Wt.: 384.51 g/mol.

To a stirred solution of (±)-2-triphenylmethyl cyclohexanol (0.332 g, 0.97 mmol) in a mixture of dry pyridine (20 mL) and dry $\mathrm{Et_2O}$ (10 mL) at rt, was added dropwise acetyl chloride (0.2 mL, 2.91 mmol). The reaction mixture was stirred at rt overnight then washed with 10% aq. $\mathrm{NaHCO_3}$ (15 mL) and water (15 mL). The organic layer was separated and the aqueous layer was extracted with $\mathrm{Et_2O}$ (3 × 15 mL). The organic layer was dried ($\mathrm{Na_2SO_4}$), filtered and the solvent was removed *in vacuo*. The crude was purified by column chromatography (($\mathrm{SiO_2}$) eluting with $\mathrm{Et_2O}$/hexane (2% → 8%)) to afford the product as a white solid (0.324 g, 0.8 mmol, 87 %). This compound exhibited broadening of some signals in its NMR spectra due to restricted rotation.

mp 153-156 ^{o}C.

FT-IR (neat) ν_{max} 3055 (w), 2939 (m), 1731 (s), 1595 (w) cm^{-1}

^{1}H-NMR (300 MHz, $\mathrm{CDCl_3}$) δ 7.50-7.00 (15H, m, $\mathrm{C\underline{H}_{Ar}}$), 4.20 (1H, td, *J* = 10.4 and 4.0 Hz, $\mathrm{C\underline{H}COR}$), 3.50 (1H, td , *J* = 11.2 and 2.0 Hz, $\mathrm{C\underline{H}CPh_3}$), 2.14 (1H, m, $\mathrm{C\underline{H}H}$), 2.03 (1H, m, $\mathrm{CH\underline{H}}$), 1.79-1.42 (4H, m, $\mathrm{C\underline{H}_2}$), 1.4 (3H, s, $\mathrm{C\underline{H}_3}$), 1.19 (1H, m, $\mathrm{C\underline{H}H}$), 0.64 (1H, m, $\mathrm{CH\underline{H}}$).

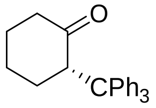
^{13}C-NMR (75 MHz, $\mathrm{CDCl_3}$) δ = 169.9 (C=O), 148.3 ($\mathrm{3\underline{C}_{Ar}}$), 129.0 ($\mathrm{6\underline{C}H_{Ar}}$), 127.1 ($\mathrm{6C\underline{H}_{Ar}}$), 125.2 ($\mathrm{3C\underline{H}_{Ar}}$), 75.0 ($\mathrm{C\underline{H}COR}$), 60.7 ($\mathrm{\underline{C}Ph_3}$), 46.2 ($\mathrm{C\underline{H}CPh_3}$), 33.3 ($\mathrm{\underline{C}H_2}$), 29.0

($\underline{C}H_2$), 25.9 ($\underline{C}H_2$), 24.7 ($\underline{C}H_2$), 20.6 ($\underline{C}H_3$).

LRMS (ES^+) *m/z* 407 ($[M+Na]^+$).

HRMS (ES^+) *m/z* Calculated: 402.2433, found: 402.2428 ($[M+NH_4]^+$).

3.2.36- *rac*- (*S*)-2-Tritylcyclohexanone (2.65)



$C_{25}H_{24}O$

Mol. Wt.: 340.46 g/mol.

To a stirred solution of (±)-2-triphenylmethyl cyclohexanol (0.24 g, 0.7 mmol) in dry CH_2Cl_2 (5 mL) at – 10 ºC, was added dropwise a solution of Dess–Martin periodinane (0.47 g, 1.071 mmol) in dry CH_2Cl_2 (3.5 mL) over 1 h. After stirring for an additional 10 min, the reaction mixture was quenched with 10% aq. sol. of $NaHCO_3$ (2.5 mL), and extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were combined, filtered, dried (Na_2SO_4) and concentrated to about 2.5 mL. The crude was purified by column chromatography ((SiO_2) eluting with Et_2O/hexane (2% → 10 %)) to afford the product as a white solid (0.18 g, 0.53 mmol, 75%). This compound exhibited broadening of some signals in its NMR spectra due to restricted rotation.

mp 162-164 °C.

FT-IR (neat) ν_{max} 3055 (w), 2940 (m), 2862 (w), 1714 (s), 1595 (m) cm^{-1}.

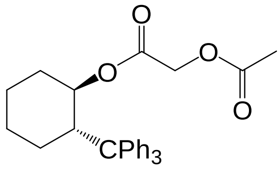
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.10 (15H, m, $C\underline{H}_{Ar}$), 4.33 (1H, td, *J* = 12.8 and 3.5 Hz, $C\underline{H}CPh_3$), 2.54 (1H, m, $C\underline{H}_2$), 2.46-2.21 (2H, m, $C\underline{H}_2$), 2.09 (1H, m, $C\underline{H}_2$), 1.95-1.85 (2H, m, $C\underline{H}_2$), 1.57 (1H, m, $C\underline{H}_2$), 1.07 (1H, m, $C\underline{H}_2$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 208.9 (C=O), 130.0 ($6\underline{C}H_{Ar}$), 127.4 ($6C\underline{H}_{Ar}$), 125.7 ($3C\underline{H}_{Ar}$), 58.4 ($\underline{C}Ph_3$), 56.5 ($C\underline{C}Ph_3$), 44.4 ($\underline{C}H_2$), 32.5 ($\underline{C}H_2$), 28.0 ($\underline{C}H_2$), 26.1 ($\underline{C}H_2$), (quaternary aromatic carbons signal not observed).

LRMS (ES^+) *m/z* 363 ($[M+Na]^+$).

HRMS (ES^+) *m/z* Calculated: 358.2171, found: 358.2165 $[M+NH_4]^+$.

3.2.37- *rac*- (1*R*, 2*S*)-2-Tritylcyclohexyl acetoxy acetate (2.65)



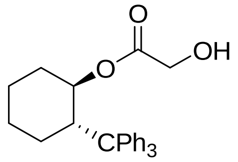
$C_{29}H_{30}O_4$

Mol. Wt.: 442.55 g/mol.

To a stirred solution of (±)-2-triphenylmethyl cyclohexanol (0.45 g, 1.31 mmol) in a mixture of dry pyridine (20 mL) and dry Et_2O (10 mL) at rt, was added dropwise acetoxyacetyl chloride (0.6 mL, 5.24 mmol). The reaction mixture was stirred at rt overnight then washed with 10% aq. sol. of $NaHCO_3$ (15 mL) and water (15 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The organic layer was dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The crude was purified by column chromatography ((SiO_2) eluting with Et_2O/hexane (2% → 8%)) to afford the product as a white solid (0.543 g, 1.23 mmol, 93 %). This compound exhibited broadening of some signals in its NMR spectra due to restricted rotation.

mp	59-64 °C.
FT-IR (neat) ν_{max}	3056(w), 2940 (m), 1744 (s), 1594 (w) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 7.45-7.00 (15H, m, $C\underline{H}_{Ar}$), 4.27 (1H, td, *J* = 10.4 and 4.0 Hz, $C\underline{H}OCOR$), 4.05 (1H, d, *J* = 10.4 Hz, $OC\underline{H}H$), 3.52 (1H, td, *J* = 12.1 and 2.1 Hz, $C\underline{H}CPh_3$), 3.36 (1H, d, *J* = 10.4 Hz, $OCH\underline{H}$), 2.20-2.0 (2H, m, $C\underline{H}_2$), 2.10 (3H, s, $C\underline{H}_3$) 1.78-1.35 (4H, m, $C\underline{H}_2$), 1.15 (1H, qt, *J* = 13.0 and 4.2 Hz, $C\underline{H}H$), 0.56 (1H, m, $C\underline{H}H$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ = 170.0 (C=O), 166.6 (C=O), 130.9 ($6\underline{C}H_{Ar}$), 128.9 ($6\underline{C}H_{Ar}$), 125.3 ($3\underline{C}H_{Ar}$), 76.3 ($C\underline{H}OR$), 60.7 ($\underline{C}Ph_3$), 60.1 ($\underline{C}H_2$), 46.2 ($\underline{C}HCPh_3$), 33.3 ($\underline{C}H_2$), 28.9 ($\underline{C}H_2$), 25.8 ($\underline{C}H_2$), 24.7 ($\underline{C}H_2$), 20.4 ($\underline{C}H_3$), (quaternary aromatic carbons signal not observed).
LRMS (ES^+) *m/z*	465 ($[M+Na]^+$).
HRMS (ES^+) *m/z*	Calculated: 465.2042, found: 465.2036 ($[M+Na]^+$).

3.2.38- *rac*- (1*R*,2*S*)-2-Tritylcyclohexyl 2-hydroxyacetate (2.67)



$C_{27}H_{28}O_3$

Mol. Wt.: 400.51 g/mol.

To a stirred solution of ester (±)-**2.66** (0.1 g, 0.226 mmol) in a mixture of *t*-BuOH (7.5 mL) and H_2O (0.83 mL) at 50 ºC, was added novozyme 435 (50 mg). The mixture was stirred at 50 ºC for 24 h. The reaction was stopped by filtration through celite using ether. The mixture was dried (Na_2SO_4) and the solvent was removed *in vacuo*. The crude was purified by column chromatography (SiO_2 eluting with EtOAc/hexane (5 → 10 %)) to afford the product as colourless oily material (0.041 g, 45 %). The product was subjected to HPLC analysis (column: Chiralcel-OJ, flow rate: 0.5 mL/min, eluent: 5% isopropanol/hexane, elution times: 21.88 min and 29.75 min, ee = 12.5 %.). This compound exhibited broadening of some signals in its NMR spectra due to restricted rotation.

FT-IR (neat) ν_{max} 3465 (br), 3055 (w), 2938 (m), 1731 (s), 1594 (w) cm^{-1}.

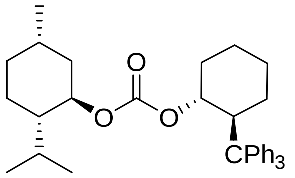
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.45-7.0 (15H, m, C$\underline{H}_{Ar}$), 4.27 (1H, td, *J* = 10.4 and 4.2 Hz, C$\underline{H}$OR), 3.63 (1H, dd, *J* = 17.0 and 4.9 Hz, C$\underline{H}$HOH), 3.53 (1H, td, *J* = 10.3 and 2.0 Hz, C$\underline{H}$CPh$_3$), 3.13 (1H, dd, *J* = 17.0 and 5.7 Hz, CH$\underline{H}$OH), 2.15 (1H, m, C$\underline{H}_2$), 2.05 (1H, m, C$\underline{H}_2$), 1.90 (1H, t, *J* = 5.7, CH$_2$O$\underline{H}$), 1.80-1.34 (4H, m, C$\underline{H}_2$), 1.19 (1H, m, C$\underline{H}_2$), 0.63 (1H, m, C$\underline{H}_2$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 171.8 (C=O), 129.4 (6$\underline{C}$H$_{Ar}$), 127.3 (6C$\underline{H}_{Ar}$), 125.5 (3C$\underline{H}_{Ar}$), 76.7 ($\underline{C}$HOCOR), 60.7 ($\underline{C}$Ph$_3$), 60.4 ($\underline{C}$H$_2$OH), 46.3 ($\underline{C}$HCPh$_3$), 33.4 ($\underline{C}$H$_2$), 29.0 ($\underline{C}$H$_2$), 25.9 ($\underline{C}$H$_2$), 24.8 ($\underline{C}$H$_2$), (quaternary aromatic carbons signal not observed).

LRMS (ES^+) *m*/*z* 423 ($[M+Na]^+$).

HRMS (ES^+) *m*/*z* Calculated: 423.1936 found: 423.1931 ($[M+Na]^+$).

3.2.39- *rac-* (1*R*,2*S*,5S)-2-*iso*-Propyl-5-methylcyclohexyl (1*R*,2*S*)-2-tritylcyclohexyl carbonate (2.69)



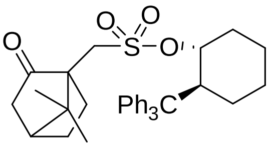
$C_{36}H_{44}O_3$

Mol. Wt.: 524.73 g/mol

To a stirred solution of (±)-2-triphenylmethyl cyclohexanol (2.00 g, 5.84 mmol) in dry pyridine (20 mL) at rt, was added dropwise a solution of (−)-menthoyl chloroformate (2.5 mL, 11.68 mmol) in dry ether (10 mL). The mixture was stirred at rt for 60 h then, the solvents were removed *in vacuo*. The crude was recrystallised from hexane to afford the product as a white solid (1.00 g, 1.9 mmol, 33 %). Spectroscopic data are reported for the mixture of isomers (3.5:1) identified from ^{1}H NMR as major and minor where possible. This compound exhibited broadening of some signals in its NMR spectra due to restricted rotation.

mp	138-141 °C.
FT-IR (neat) ν_{max}	3058 (w), 2925 (w), 1728 (m) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 7.50-7.00 (15H, m, $C\underline{H}_{Ar}$), $4.28_{maj\ and\ min}$ (1H, td, *J* = 10.4 and 4.4 Hz, $C\underline{H}OR$), 4.22_{maj} and 3.92_{min} (1H, td, *J* = 10.1 and 3.8 Hz, $C\underline{H}OR$), $3.58_{maj\ and\ min}$ (1H, m, $C\underline{H}CPh_3$), 2.20-0.60 (17H, m, $C\underline{H}_2$), 0.94_{maj} and 0.89_{min} (3H, d, *J* = 13.4 Hz, $C\underline{H}_3$), 0.88_{maj} and 0.8_{min} (3H, d, *J* = 7.0 Hz, $C\underline{H}_3$), 0.72_{maj} and 0.68_{min} (3H, d, *J* = 7.0 Hz, $C\underline{H}_3$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 153.7_{maj} and 153.5_{min} ($\underline{C}OOR$), 129.5 ($6\underline{C}H_{Ar}$), 127.2 ($6\underline{C}H_{Ar}$), 125.3 ($3\underline{C}H_{Ar}$), 78.3_{min} and 77.9_{maj} ($\underline{C}HOR$), 77.2_{maj} and 76.8_{min} ($\underline{C}HOR$), 61.0_{min} and 60.8_{maj} ($\underline{C}Ph_3$), 46.8_{maj} and 46.7_{min} ($\underline{C}HCPh_3$), 46.1_{maj} and 45.9_{min} ($\underline{C}H$), 40.7_{maj} and 40.5_{min} ($\underline{C}H_2$), 34.1_{maj} and 34.0_{min} ($\underline{C}H_2$), 33.1_{min} and 32.8_{maj} ($\underline{C}H_2$), $31.6_{maj\ and\ min}$ ($\underline{C}H$), 31.3_{maj} and 31.2_{min} ($\underline{C}H$), 28.6_{maj} and 28.5_{min} ($\underline{C}H_2$), 26.0_{maj} and 24.9_{min} ($\underline{C}H_3$), 25.8_{min} and 25.4_{maj} ($\underline{C}H_2$), 24.6_{min} and 24.0_{maj} ($\underline{C}H_2$), 23.3_{maj} and 22.7_{min} ($\underline{C}H_2$), 22.0_{maj} and 21.9_{min} ($\underline{C}H(CH_3)_2$), 20.9_{min} and 20.7_{maj} ($\underline{C}H_3$), 16.3_{maj} and 15.6_{min} ($\underline{C}H_3$), (quaternary aromatic carbons signal not observed).
LRMS (ES$^+$) *m/z*	547 ([M + Na]$^+$).

3.2.40- *rac*- (1*R*,2*S*)-2-Tritylcyclohexyl (7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl) methanesulfonate (2.71)



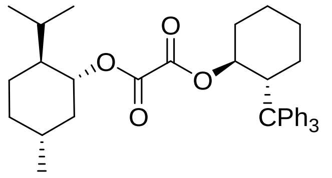
$C_{35}H_{40}O_4S$

Mol. Wt.: 556.75 g/mol

To a stirred solution of (±)-2-triphenylmethyl cyclohexanol (1.0 g, 2.92 mmol) in dry THF (18 mL) at –78 °C, was added dropwise NaHMDS (3.8 mL, 3.8 mmol, 1.0 M in THF). The mixture was stirred at –78 °C for 45 min then DMAP (90 mg, 0.73 mmol) and (1*S*)-(+)-10-camphor sulfonyl chloride (1.5 g, 5.84 mmol) were added. The mixture was warmed to rt and stirred for 2 h. The solvent was removed *in vacuo* and the dark brown crude was purified by column chromatography (SiO_2 eluting with EtOAc/hexane (10 → 50 %)) to afford the compound **2.71** (0.926 g, 1.66 mmol, 57 %) as a white powder. Spectroscopic data are reported for mixture of isomers (3.6:1) identified from ^{1}H NMR as major and minor where possible. This compound exhibited broadening of some signals in it's NMR spectra due to restricted rotation.

mp	152-157 °C.
FT-IR (neat) ν_{max}	2951 (w), 1744 (m), 1643 (m) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 7.70-6.90 (15H, m, $C\underline{H}_{Ar}$), 4.40 (1H, td, *J* = 10.4 and 3.8 Hz, $C\underline{H}COR$), 3.60 (1H, m, $C\underline{H}CPh_3$), 2.90-0.90 (17H, m, $C\underline{H_2}$), 1.05_{min} and 0.97_{maj} (3H, s, $C\underline{H}_3$), 0.77_{min} and 0.74_{maj} (3H, s, $C\underline{H}_3$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 213.6 ($\underline{C}$=O), 148.8 ($3\underline{C}_{Ar}$, br), 128.7 ($6\underline{C}H_{Ar}$), 127.3 ($6\underline{C}H_{Ar}$), 125.0 ($3\underline{C}H_{Ar}$), 82.8 ($\underline{C}HOR$), 60.7 ($\underline{C}Ph_3$), 57.3 ($\underline{C}$), 47.9 ($\underline{C}$), 47.4 ($\underline{C}H_2$), 46.2_{maj} and 46.1_{min} ($\underline{C}HCPh_3$), 42.6 ($\underline{C}H$), 42.4 ($\underline{C}H_2$), 35.1 ($\underline{C}H_2$), 29.0 ($\underline{C}H_2$), 26.9 ($\underline{C}H_2$), 25.3 ($\underline{C}H_2$), 24.7 ($\underline{C}H_2$), 24.6 ($\underline{C}H_2$), 19.9_{min} and 19.8_{maj} ($\underline{C}H_3$), 19.7_{min} and 19.6_{maj} ($\underline{C}H_3$).
LRMS (ES^+) *m*/*z*	579 ($[M + Na]^+$).

3.2.40 (1*R*, 2*S*, 5*R*)-2-*iso*-Propyl-5-methylcyclohexyl (1*S*,2*R*)-2-tritylcyclohexyl oxalate (2.74b)



$C_{37}H_{44}O_4$

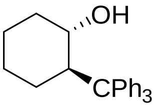
Mol. Wt.: 552.74 g/mol.

(–)-Menthol (32.28 g, 204.5 mmol) was dissolved in dry CH_2Cl_2 (80 mL) and added dropwise to a stirred oxalyl chloride (36.40 mL, 409 mmol) at 0 °C over 0.5 h. The mixture was warmed to room temperature and stirred for 2 h. Then, the solvent and the excess of oxalyl chloride was removed *in vacuo*. The resulting oily acid chloride was dissolved in dry CH_2Cl_2 (80 mL) and it was added dropwise to a stirred solution of (±)-triphenylmethyl cyclohexanol (35.02 g, 102.26 mmol) in dry pyridine (100 mL). The mixture's colour changed to yellowish white and the reaction was stirred at room temperature for 3 h. CH_2Cl_2 was removed *in vacuo* and the residue was dissolved in ethyl acetate (100 mL) and it was washed with 2 N HCl (60 mL). The crude was transferred to a round bottom flask (1000 mL) equipped with condenser. Methanol (450 mL) was added and the mixture was heated to reflux for 0.5 h. The remaining undissolved white solid powder was filtered and washed with hot methanol (150 mL) to give desired isomer as a white powder (20 g, 36.18 mmol, 35%). This compound exhibited broadening of some signals in its NMR spectra due to restricted rotation.

$[\alpha]_D$	+12.2 (*c* 1.065, $CHCl_3$, 24 °C).
mp	190-193 °C.
FT-IR (neat) ν_{max}	3056 (w), 2954 (w), 2668 (w), 1756 (s) 1729 (s) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 7.52-7.00 (15H, m, $C\underline{H}_{Ar}$), 4.65 (1H, td, *J* = 11.0 and 4.4 Hz, $C\underline{H}OR$), 4.15 (1H, td, *J* = 10.3 and 3.7 Hz, $C\underline{H}OR'$), 3.60 (1H, m, $C\underline{H}CPh_3$), 2.13 (1H, m, $C\underline{H}_2$), 1.99 (1H, m, $C\underline{H}_2$), 1.90-1.55 (7H, m, $C\underline{H}_2$), 1.52-0.80 (8H, m, $C\underline{H}_2$), 0.95 (3H, d, *J* = 6.2 Hz, $C\underline{H}_3$), 0.88 (3H, d, *J* = 7.0 Hz, $C\underline{H}_3$), 0.75 (3H, d, *J* = 7.0 Hz, $C\underline{H}_3$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 157.8 (COOR), 157.7 (COOR'), 129.8 (6$\underline{C}H_{Ar}$), 127.4 (6$\underline{C}H_{Ar}$), 125.6 (3$\underline{C}H_{Ar}$), 78.5 ($\underline{C}HOR$), 76.9 ($\underline{C}HOR$), 60.8 ($\underline{C}Ph_3$), 46.3 ($\underline{C}HCPh_3$), 46.2 ($\underline{C}HCH(CH_3)$), 40.0 ($\underline{C}H_2$), 34.0 ($\underline{C}H_2$), 32.7 ($\underline{C}H_2$), 31.4 ($\underline{C}HCH_3$), 28.9

	(<u>C</u>H$_2$), 26.0 (<u>C</u>H$_3$), 25.9 (<u>C</u>H$_2$), 24.6 (<u>C</u>H$_2$), 23.2 (<u>C</u>H$_2$), 22.0 (<u>C</u>H(CH$_3$)$_2$), 20.6 (<u>C</u>H$_3$), 16.2 (<u>C</u>H$_3$), (quaternary aromatic carbons signal not observed).
LRMS (ES$^+$) *m*/*z*	1127 [(2M+Na)$^+$].
HRMS (ES$^+$) *m*/*z*	Calculated: 570.3583, found: 570.3578 [(M+NH$_4$)$^+$].

3.2.41 (−)-(1*S*,2*R*)-Triphenylmethyl cyclohexanol ((−)-2.10)



$C_{25}H_{26}O$

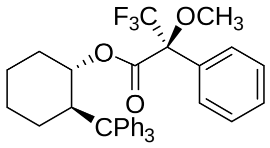
Mol. Wt.: 342.47 g/mol.

To a stirred solution of oxalate ester **2.74b** (17.5 g, 31.66 mmol) in MeOH (150 mL) was added a solution of NaOH (31.5 g, 771.9 mmol) and NaHCO$_3$ (2.87 g, 33.99 mmol) in H$_2$O (110 mL). The mixture was heated to reflux for 3 h. Then, it was concentrated by removing MeOH *in vacuo*. EtOAc (200 mL) and H$_2$O (200 mL) were added and the mixture was stirred vigorously to form two clear layers which were separated. The aqoueous layer was exracted with ethyl acetate (3x 100 mL). The organic layer was dried (MgSO$_4$), filtered and the solvent was removed *in vacuo*. Hexane (2 × 100 mL) was added and removed *in vacuo* to give a white solid which was washed with hexane to give enantiomeric pure alcohol (−)-**2.10** (9.77 g, 28.53 mmol, 90%, > 99% *ee*). The product was subjected to HPLC analysis (Chiral-cel-OJ column, Daicell Chemical Industries, Ltd., 5% IPA/hexane, 0.5 mL/min). Elution times: $t_{(-)\text{-TTC}\ (-)\text{-}\mathbf{2.10}}$ 12.5 min. This compound exhibited broadening of some signals in its NMR spectra due to restricted rotation.

[α]$_D$	−59 (*c* 0.745, CHCl$_3$, 23 °C).
Mpt	190-192 °C.
FT-IR (neat) ν_{max}	3585 (w), 3055 (w), 2933 (m), 2853(w), 1594 (w) cm^{-1}.
^{1}H-NMR (300 MHz, CDCl$_3$)	δ 7.65-7.05 (15H, m, C<u>H</u>$_{Ar}$), 3.28 (1H, m, C<u>H</u>OH), 3.11 (1H, m, C<u>H</u>CPh$_3$), 2.08 (1H, m, C<u>H$_2$</u>), 2.06 (1H, m, <u>OH</u>), 1.94 (1H, m, C<u>H$_2$</u>), 1.80-1.30 (3H, m, C<u>H</u>$_2$), 1.48 (1H, m, C<u>H$_2$</u>) 1.09 (1H, m, C<u>H$_2$</u>), 0.50 (1H, m, C<u>H$_2$</u>).
^{13}C-NMR (75 MHz, CDCl$_3$)	δ 129.3 (6<u>C</u>H$_{Ar}$), 127.6 (6C<u>H</u>$_{Ar}$), 125.7 (3<u>C</u>H$_{Ar}$), 73.6 (<u>C</u>HOH), 60.7 (<u>C</u>Ph$_3$), 48.8 (<u>C</u>HCPh$_3$), 37.1 (<u>C</u>H$_2$), 28.9 (<u>C</u>H$_2$), 26.2 (<u>C</u>H$_2$), 25.2 (<u>C</u>H$_2$),

	(quaternary aromatic carbons signal not observed).
LRMS (ES$^+$) *m*/*z*	365 [(M+Na)$^+$].
HRMS (ES$^+$) *m*/*z*	Calculated: 685.4046, found: 685.4040 [(2M+H)$^+$].

3.2.42- (2*S*)-(1*S*,2*R*)-2-Tritylcyclohexyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (2.76)



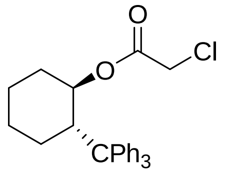
$C_{35}H_{33}F_3O_3$

Mol. Wt.: 558.63 g/mol.

To a stirred solution of (1*S*,2*R*)-2-tritylcyclohexanol (–)-**2.10** (27.3 mg, 0.08 mmol) in dry THF (2 mL), was added NaHMDS (0.12 mL of 1.0 M solution in THF, 0.12 mmol) at – 35 °C. The solution was allowed to warm to –10 °C over 30 min whereupon (*R*)-α-methoxy-α-triflourophenyl acetic acid chloride (30 µL, 0.16 mmol) was added dropwise. The reaction mixture was allowed to warm to rt and stirred for 1 h. The crude was purified by column chromatography (SiO_2 eluting with ether/ hexane (5% → 20 %)) to give the title ester **2.76** as a colourless solid which was recrystalised from ethanol to give the product as a colourless crystalline solid (33 mg, 0.059 mmol, 74%).

$[\alpha]_D$	+16.4 (*c* 0.24, $CHCl_3$, 27 °C).
mp	169-171 °C
FT-IR (neat) ν_{max}	3057 (m), 2944 (w), 2862 (w), 1737 (s), 1595 (w) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 7.52-7.00 (20H, m, $\mathrm{Ar\underline{H}}$), 4.70 (1H, td, *J* = 7.0 and 3.0 Hz, $\mathrm{C\underline{H}OR}$), 3.61 (1H, m, $\mathrm{C\underline{H}CPh_3}$), 3.32 (3H, s, $\mathrm{C\underline{H}_3}$), 2.05 (1H, m, $\mathrm{C\underline{H}_2}$), 1.55-1.25 (5H, m, $\mathrm{C\underline{H}_2}$), 1.20-1.01 (2H, m, $\mathrm{C\underline{H}_2}$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 165.6 (C=O), 132.0 ($\mathrm{4\underline{C}_{Ar}}$), 129.3 ($\mathrm{2\underline{C}H_{Ar}}$), 128.3 ($\mathrm{8\underline{C}H_{Ar}}$, br), 127.5 ($\mathrm{6\underline{C}H_{Ar}}$), 125.5 ($\mathrm{3\underline{C}H_{Ar}}$), 78.6 ($\mathrm{\underline{C}F_3}$), 76.7 ($\mathrm{\underline{C}HOR}$), 61.2 ($\mathrm{\underline{C}Ph_3}$), 55.0 ($\mathrm{\underline{C}HCPh_3}$), 44.2 ($\mathrm{O\underline{C}H_3}$), 29.5 ($\mathrm{\underline{C}H_2}$), 26.5 ($\mathrm{\underline{C}H_2}$), 23.7 ($\mathrm{\underline{C}H_2}$), 21.9 ($\mathrm{\underline{C}H_2}$).
LRMS (ES$^+$) *m*/*z*	581 ([M+Na]$^+$).
HRMS (ES$^+$) *m*/*z*	Calculated: 581.2279, found: 581.2274 ([M+Na]$^+$).

3.2.43- *rac*- (1*R*,2*S*)-2-Tritylcyclohexyl 2-chloroacetate (2.79)



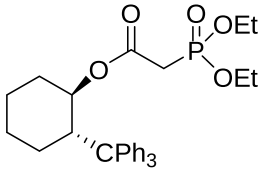
$C_{27}H_{27}ClO_2$

Mol. Wt.: 418.96 g/mol.

To a stirred solution of (±)-triphenylmethyl cyclohexanol (±)-**2.10** (0.2 g, 0.584 mmol) in dry CH_2Cl_2 (10 mL) was added triethylamine (0.16 mL, 1.168 mmol) at 0 °C. The mixture was stirred at 0 °C for 0.5 h then DMAP (10 mg, 0.082 mmol) and chloroacetyl chloride (94.9 µL, 1.168 mmol) were added. On completion, the mixture was warmed to rt and stirred for 34 h. The reaction was quenched with H_2O (10 mL). The organic layer was separated and the aqueous layer was extracted using ether (3 × 20 mL). The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude was purified using column chromatography (SiO_2 eluting with ether/hexane (hexane → 5 %)) to afford the title chloride **2.79** as a creamy powder (0.223 g, 0.533 mmol, 91 %). This compound exhibited broadening of some signals in its NMR spectra due to restricted rotation.

mp	159-162 °C.
FT-IR (neat) ν_{max}	3055 (w), 2938 (w), 1748 (m), 1712 (m), 1652 (w) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 7.60-7.0 (15H, m, Ar$\underline{H}$), 4.35 (1H, td, *J* = 10.4 and 4.2 Hz, $C\underline{H}OR$), 3.51 (1H, td, *J* = 11.5 and 2.0 Hz, $C\underline{H}CPh_3$), 3.40 (1H, d, *J* = 15.0 Hz, $C\underline{H}_2$), 3.00 (1H, d, *J* = 15.0 Hz, $C\underline{H}_2$), 2.14 (1H, m, $C\underline{H}_2$), 2.02 (1H, m, $C\underline{H}_2$), 1.78-1.30 (4H, m, $C\underline{H}_2$), 1.19 (1H, tq, *J* = 4.0 and 13.0 Hz, $C\underline{H}_2$), 0.55 (1H, m, $C\underline{H}_2$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 166.1 (C=O), 148.0 (3$\underline{C}_{Ar}$, br), 129.0 (6$\underline{C}H_{Ar}$), 127.3 (6$\underline{C}H_{Ar}$), 125.3 (3$\underline{C}H_{Ar}$), 76.9 ($C\underline{H}OR$), 60.6 ($\underline{C}Ph_3$), 46.2 ($\underline{C}HCPh_3$), 40.5 ($\underline{C}H_2$) 33.2 ($\underline{C}H_2$), 29.0 ($\underline{C}H_2$), 25.8 ($\underline{C}H_2$), 24.7 ($\underline{C}H_2$).
LRMS (ES^+) *m/z*	441 ($[M+Na]^+$).

3.2.44- *rac*- (1*R*,2*S*)-2-Tritylcyclohexyl 2-diethyl phosphorylacetate (±)-(2.80)



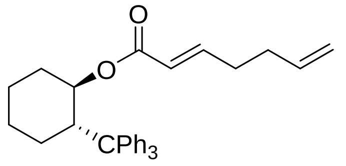
$C_{31}H_{37}O_5P$

Mol. Wt.: 520.6 g/mol.

Under a nitrogen atmosphere, triethyl phosphite (4 mL, 22.86 mmol) was added to the chloride **2.79** (177 mg, 0.422 mmol) and the mixture was heated to reflux for 5 h. Then the excess of triethyl phosphite was removed by distillation under reduced pressure. The remaining crude was purified by column chromatography (SiO_2 eluting with EtOAc/hexane (2.5 → 50 %)) to afford the title ester **2.80** as a yellow viscous oil (0.169 g, 0.325 mmol, 77%). This compound exhibited broadening of some signals in its NMR spectra due to restricted rotation.

FT-IR (neat) ν_{max}	2938 (w), 2861 (w), 1727 (m), 1680 (m), 1581 (w) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 7.50 -7.00 (15H, m, C$\underline{H}_{Ar}$), 4.29 (1H, td, *J* = 10.4 and 4.0 Hz, C$\underline{H}$OR), 4.19- 4.06 (4H, m, OC$\underline{H}_2$), 3.50 (1H, td, *J* = 12.2 and 2.0 Hz, C$\underline{H}$CPh$_3$), 2.32-1.98 (4H, m, C$\underline{H}_2$), 1.75-1.25 (4H, m, C$\underline{H}_2$), 1.37 (3H, t, *J* = 7.1 Hz, C$\underline{H}_3$), 1.33 (3H, t, *J* = 7.1 Hz, C$\underline{H}_3$), 1.15 (1H, m, C$\underline{H}_2$), 0.55 (1H, m, C$\underline{H}_2$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 164.5 (d, *J* = 6.0 Hz, C=O), 129.2 (6$\underline{C}H_{Ar}$), 127.2 (6$\underline{C}H_{Ar}$), 125.2 (3$\underline{C}H_{Ar}$), 76.0 (C$\underline{H}$OH), 62.5 (d, *J* = 2.7 Hz, $\underline{C}H_2$), 62.4 (O$\underline{C}H_2$) 62.3 (O$\underline{C}H_2$), 60.6 ($\underline{C}Ph_3$), 46.0 ($\underline{C}HCPh_3$), 34.4 ($\underline{C}H_2$), 33.0 ($\underline{C}H_2$), 32.6 ($\underline{C}H_2$), 28.9 ($\underline{C}H_2$), 25.7 ($\underline{C}H_2$), 24.6 ($\underline{C}H_2$), 16.4 ($\underline{C}H_3$), 16.3 ($\underline{C}H_3$), (quaternary aromatic carbons signal not observed).
LRMS (ES^+) *m/z*	543 ($[M+Na]^+$).

3.2.45- *rac*- (1*R*,2*S*)-(*E*)-2-Tritylcyclohexyl hepta-2,6-dienoate (2.81)



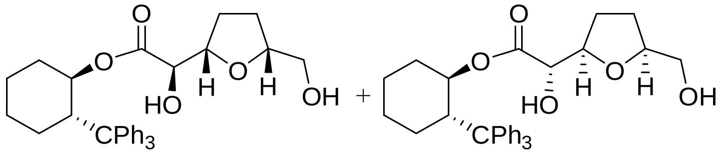
$C_{32}H_{34}O_2$

Mol. Wt.: 450.61 g/mol

To a stirred suspension of dry LiCl (9.4 mg, 0.22 mmol) in dry acetonitrile (2.3 mL) under a nitrogen atmosphere, were added DIPEA (31.7 µL, 0.18 mmol), ester (±)-**2.80** (112 mg, 0.22 mmol) and 4-pentanal (16.9 µL, 0.18 mmol). The reaction mixture was stirred for 20 h then it was diluted with ethyl acetate (20 mL) and washed with brine (10 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo*. The crude was purified using column chromatography (SiO_2 eluting with ether/hexane (hexane → 4 % ether/hexane)) to afford the title ester **2.81** as a white powder (85 mg, 0.19 mmol, 88 %). This compound exhibited broadening of some signals in its NMR spectra due to restricted rotation.

mp	149-151 °C.
FT-IR (neat) ν_{max}	3055 (w), 2944 (w), 1728 (m), 1657 (w), 1580 (w) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 7.70-6.90 (15H, m, $C\underline{H}_{Ar}$), 6.28 (1H, m, $C\underline{H}$=CH), 5.75 (1H, m, $C\underline{H}$=CH), 5.15-4.96 (3H, m, $C\underline{H}$=$C\underline{H}_2$), 4.01 (1H, td, *J* = 10.4 and 3.7 Hz, $C\underline{H}OR$), 3.55 (1H, td, *J* = 10 and 1.8 Hz, $C\underline{H}CPh_3$), 2.20-2.0 (6H, m, $C\underline{H}_2$), 1.77-132 (4H, m, $C\underline{H}_2$), 1.20 (1H, m, $C\underline{H}_2$), 0.75 (1H, m, $C\underline{H}_2$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 165.5 (C=O), 147.6 ($\underline{C}H$), 137.3 ($\underline{C}H$), 131.0 (3$\underline{C}_{Ar,}$, br), 128.7 (6$\underline{C}H_{Ar,}$) 127.1 (6$\underline{C}H_{Ar}$), 124.8 (3$\underline{C}H_{Ar}$), 121.8 ($\underline{C}H$), 115.2 ($\underline{C}H_2$), 75.6 ($C\underline{H}OR$), 60.7 ($\underline{C}Ph_3$), 46.5 ($\underline{C}HCPh_3$), 33.4 ($\underline{C}H_2$), 31.7 ($\underline{C}H_2$), 31.2 ($\underline{C}H_2$), 28.9 ($\underline{C}H_2$), 26.2 ($\underline{C}H_2$), 24.8 ($\underline{C}H_2$).
LRMS (ES^+) *m/z*	473 ($[M+Na]^+$).

3.2.46- *rac*- (2*R*)-(1*R*,2*S*)-2-Tritylcyclohexyl 2-((2*S*,5*R*)-tetrahydro-5-(hydroxymethyl) furan-2-yl)-2-hydroxyacetate (2.82)



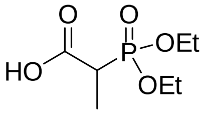
$C_{32}H_{36}O_5$

Mol. Wt.: 500.63 g/mol.

To a stirred solution of ester **2.81** (0.54 g, 1.2 mmol) in acetone (47 mL) and acetic acid (15 mL) at – 30 °C, was added powdered $KMnO_4$ (0.249 g, 1.56 mmol) portionwise. The purple mixture was stirred rapidly for 1.5 h, during which time the temperature of the acetone bath rose to –10 °C and the reaction mixture turned dark brown. At this stage, the reaction mixture was diluted with ethyl acetate (10 mL) and quenched with sat. aq. $Na_2S_2O_5$ (20 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The organic layer was washed with sat. aq. $NaHCO_3$ and dried ($MgSO_4$). The solvent was removed *in vacuo*. The crude was recrystallised from MeOH to afford the product as a single diastereoisomer (0.2 g, 0.4 mmol, 33%). This compound exhibited broadening of some signals in its NMR spectra due to restricted rotation.

mp	126-128 °C.
FT-IR (neat) ν_{max}	3469 (br), 3055 (w), 2942 (m), 1728 (m) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ = 7.80-6.90 (15H, m, $C\underline{H}_{Ar}$), 4.01 (1H, td, *J* = 10.2 and 3.7 Hz, $C\underline{H}OR$), 3.91 (1H, m, $C\underline{H}OH$), 3.76 (1H, dd, *J* = 11.5 and 2.7 Hz, $C\underline{H}HOH$), 3.68 (1H, m, $C\underline{H}O$), 3.63 (1H, td, *J* = 10.1 and 1.8 Hz, $C\underline{H}CPh_3$), 3.46 (1H, dd, *J* = 11.5 and 4.3 Hz, $CH\underline{H}OH$), 3.53-2.50 (2H, br, $O\underline{H}$), 2.58 (1H, dt, *J* = 1.5 and 7.3 Hz, $C\underline{H}$), 2.15 (2H, m, $C\underline{H}_2$), 1.95-1.63 (5H, m, $C\underline{H}_2$), 1.62-1.34 (3H, m, $C\underline{H}_2$), 1.98 (1H, m, $C\underline{H}_2$), 0.8 (1H, m, $C\underline{H}_2$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ = 172.2 ($\underline{C}$=O), 139.9 ($3\underline{C}_{Ar}$), 128.0 ($6\underline{C}H_{Ar}$), 127.1 ($6\underline{C}H_{Ar}$), 125.0 ($3\underline{C}H_{Ar}$), 79.5 ($\underline{C}HO$), 78.0 ($\underline{C}HO$), 77.9 ($\underline{C}HOR$), 72.0 ($\underline{C}HOH$), 65.1 ($\underline{C}H_2OH$), 61.0 ($\underline{C}Ph_3$), 45.6 ($\underline{C}HCPh_3$), 33.0 ($\underline{C}H_2$), 28.7 ($\underline{C}H_2$), 27.2 ($\underline{C}H_2$), 27.1 ($\underline{C}H_2$), 26.0 ($\underline{C}H_2$), 24.9 ($\underline{C}H_2$).
LRMS (ES^+) *m/z*	523 ($[M+Na]^+$).

3.2.47- 2-Diethylphosphoryl propanoic acid (2.84)



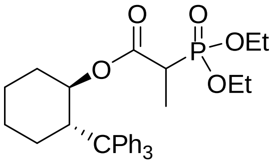
$C_7H_{15}O_5P$

Mol. Wt.: 210.16 g/mol.

To a stirred solution of the ester **2.83** (4.0 g, 16.79 mmol) in THF (40 mL) was added NaOH (4.6 mL, 1.0 M aq.). The mixture was stirred at room temperature for 24 h then the mixture was acidified to pH = 1.0 using HCl (40 mL, 10% aq.) and saturated with NaCl. The organic layer was separated and the aqueous layer was extracted using EtOAc (3 × 20 mL). The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo* to give the title acid **2.84** as a viscous colourless oil (3.5 g, 16.65 mmol, 99%). The product was used without further purification.

FT-IR (neat) ν_{max}	2985 (w), 1731 (m), 1014 (s) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 10.72 (1H, br. s, COO$\underline{H}$), 4.27-4.10 (4H, m, OC$\underline{H}_2$), 3.06 (1H, dq, *J* = 23.8 and 7.3 Hz, C$\underline{H}$), 1.47-1.38 (3H, m, C$\underline{H}_3$), 1.33 (6H, t, *J* = 7.1 Hz, C$\underline{H}_3$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 171.4 ($\underline{C}$=O), 63.2 (2O$\underline{C}H_2$), 39.0 (d, *J* = 135 Hz, $\underline{C}$H), 15.9 (2$\underline{C}H_3$), 8.1 ($\underline{C}H_3$).
LRMS (ES$^+$) *m/z*	233 ($[M+Na]^+$).

3.2.48- *rac*- (1*R*,2*S*)-2-Tritylcyclohexyl 2-diethyl phosphoryl propanonate (2.85)



$C_{32}H_{39}O_5P$

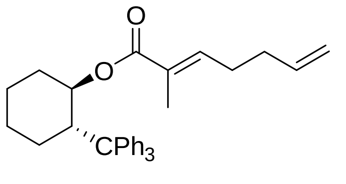
Mol. Wt.: 534.62 g/mol.

a) Preparation of 2-(diethylphosphoryl)propanoyl chloride: To a stirred $SOCl_2$ (3.5 mL, 46.5 mmol) was added the acid **2.84** (3.26 g, 15.5 mmol) dropwise at room temperature. The mixture was stirred for 4 h, then the excess $SOCl_2$ was removed *in vacuo* to give the acid chloride (3.54 g, 15.5 mmol, 100%).

b) NaHMDS (8.6 mL, 8.6 mmol of 1.0 M solution in THF) was added dropwise to a stirred solution of (±)-2-tritylcyclohexanol (±)-**2.10** (2.25 g, 6.6 mmol) in dry THF (40 mL) at –78 °C and the mixture was stirred at –78 °C for 0.5 h. Then, the freshly prepared acid chloride (3.54 g, 15.5 mmol) was dissolved in dry THF (10 mL) and added dropwise to the mixture. On completion the mixture was stirred at rt for 2 h. Then, the solvent was removed *in vacuo*. The crude was purified by column chromatography (SiO_2 eluting with ethyl acetate/hexane (10 → 50 %)) to afford the title ester **2.85** as a yellow viscous oil (1.90 g, 3.55 mmol, 54 %). This compound exhibited broadening of some signals in its NMR spectra due to restricted rotation.

FT-IR (neat) ν_{max}	2938 (w), 2986 (w), 1727 (m), 1680 (m), 1581 (w) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ = 7.75-6.85 (15H, m, $C\underline{H}_{Ar}$), 4.36 (1H, td, *J* = 10.3 and 4.0 Hz, $C\underline{H}OR$), 4.19-4.06 (4H, m, $OC\underline{H}_2$), 3.50 (1H, td, *J* = 12.0 and 2.2 Hz, $C\underline{H}CPh_3$), 2.32-1.82 (3H, m, $C\underline{H}_2$), 1.79-1.25 (4H, m, $C\underline{H}_2$), 1.43-1.23 (6H, m, $C\underline{H}_3$), 1.15 (1H, m, $C\underline{H}_2$), 1.00-0.89 (3H, m, CH_3), 0.54 (1H, m, $C\underline{H}_2$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ = 168.65 and 168.58 (C=O), 130.0 ($6\underline{C}H_{Ar}$), 127.5 ($6\underline{C}H_{Ar}$), 125.2 ($3\underline{C}H_{Ar}$), 75.6 ($C\underline{H}OR$), 62.5 ($O\underline{C}H_2$) 62.4 ($O\underline{C}H_2$), 60.7 ($\underline{C}Ph_3$), 46.2 ($\underline{C}HCPh_3$), 39.4 and 37.7 ($\underline{C}H$, d), 33.1 ($\underline{C}H_2$), 29.1 ($\underline{C}H_2$), 25.8 ($\underline{C}H_2$), 24.7 ($\underline{C}H_2$), 16.4 ($2\underline{C}H_3$), 11.4 ($\underline{C}H_3$), (quaternary aromatic carbons signal not observed).
LRMS (ES^+) *m/z*	557 ($[M+Na]^+$).

3.2.49- *rac*- (*E*)-(1*R*,2*S*)-2-Tritylcyclohexyl 2-methylhepta-2,6-dienoate (2.86)



$C_{33}H_{36}O_2$

Mol. Wt.: 464.64 g/mol

To a stirred suspension of dry LiCl (30 mg, 0.696 mmol) in dry acetonitrile (7.0 mL) under a nitrogen atmosphere, were added DIPEA (0.1 mL, 0.58 mmol), ester **2.85** (0.37 g, 0.696 mmol), and 4-pentanal (65.2 μL, 0.696 mmol). The reaction mixture was stirred for 24 h then diluted with ethyl acetate (30 mL) and washed with brine (15 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo*. The crude was purified using column chromatography (SiO_2 eluting with ether/hexane (hexane → 4 % ether/hexane)) to afford the title ester **2.86** as a viscous oil (0.05 g, 0.1 mmol, 16 %). This compound exhibited broadening of some signals in its NMR spectra due to restricted rotation.

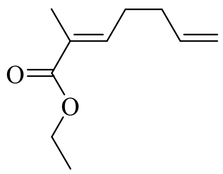
FT-IR (neat) ν_{max} 3056 (w), 2938 (w), 1712 (m), 1655 (w), 1595 (w) cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.60-6.95 (15H, m, $C\underline{H}_{Ar}$), 5.87-5.68 (2H, m, $C\underline{H}$=), 5.07-4.95 (2H, m, =$C\underline{H}_2$), 3.95 (1H, td, J = 10.3 and 3.7 Hz, $C\underline{H}OR$), 3.59 (1H, td, J = 10.6 and 1.8 Hz, $C\underline{H}CPh_3$), 2.17 (1H, m, $C\underline{H}_2$), 2.07-1.93 (5H, m, $C\underline{H}_2$), 1.77-1.35 (4H, m, $C\underline{H}_2$), 1.54 (3H, s, $C\underline{H}_3$), 1.30 (1H, m, $C\underline{H}_2$), 0.9 (1H, m, $C\underline{H}_2$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.3 (C=O), 140.6 (=$\underline{C}H$), 148.5 ($3\underline{C}_{Ar}$), 137.8 (=$\underline{C}H$), 129.0 ($6\underline{C}H_{Ar}$), 128.3 ($\underline{C}$=), 127.4 ($6\underline{C}H_{Ar}$), 125.1 ($3\underline{C}H_{Ar}$), 114.9 (=$\underline{C}H_2$), 76.3 ($C\underline{H}OR$), 60.7 ($\underline{C}Ph_3$), 46.7 ($\underline{C}HCPh_3$), 33.4 ($\underline{C}H_2$), 32.4 ($\underline{C}H_2$), 29.2 ($\underline{C}H_2$), 28.0 ($\underline{C}H_2$), 26.4 ($\underline{C}H_2$), 24.9 ($\underline{C}H_2$), 12.3 ($\underline{C}H_3$), (quaternary aromatic carbons signal not observed).

LRMS (ES^+) *m/z* 952 ($[2M+Na]^+$).

3.2.50- (*E*)-Ethyl 2-methylhepta-2, 6-dienoate (2.88)



$C_{10}H_{16}O_2$

Mol. Wt.: 168.23 g/mol

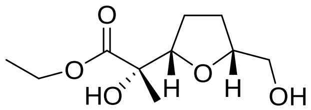
To a stirred suspension of dry LiCl (88 mg, 2.064 mmol) in dry acetonitrile (21 mL) under a nitrogen atmosphere, were added triethyl 2-phosphonopropionate (0.5 g, 2.064 mmol), DIPEA (0.3 mL, 1.72 mmol) and 4-pentanal (0.22 mL, 2.37 mmol). The reaction mixture was stirred for 24 h then, it was diluted with ether (30 mL) and washed with brine (15 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo*. The crude was purified using column chromatography (SiO_2 eluting with ether/hexane (hexane → 4 % ether/hexane)) to afford the title ester **2.88** as a colourless liquid (0.257 g, 1.53 mmol, 73 %).

FT-IR (neat) ν_{max} 2980 (w), 2931 (w), 1708 (s), 1650 (w) cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$)	δ = 6.75 (1H, qt, *J* = 1.5 and 7.1 Hz, C$\underline{H}$=), 5.85 (1H, m, C$\underline{H}$=), 5.12-4.95 (2H, m, =C$\underline{H}_2$), 4.18 (2H, q, *J* = 7.1 Hz, OC$\underline{H}_2$), 2.34-2.15 (4H, m, C$\underline{H}_2$), 1.83 (3H, s, C$\underline{H}_3$), 1.29 (3H, t, *J* = 7.1 Hz, C$\underline{H}_3$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ = 168.0 ($\underline{C}$=O), 141.2 ($\underline{C}$H=), 137.5 ($\underline{C}$H=), 128.2 ($\underline{C}$), 115.3 (=CH_2), 60.4 ($\underline{C}H_2$), 32.5 ($\underline{C}H_2$), 28.0 ($\underline{C}H_2$), 14.3 ($\underline{C}H_3$), 12.4 ($\underline{C}H_3$).
LRMS (ES^+) *m/z*	191 ($[M+Na]^+$).

3.2.51-(*S*)-Ethyl 2-((2*S*,5*R*)-tetrahydro-5-(hydroxymethyl)furan-2-yl)-2-hydroxypropanoate

(2.89)



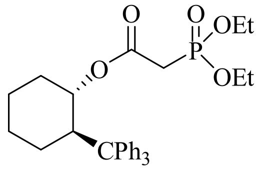
$C_{10}H_{18}O_5$

Mol. Wt.: 218.25 g/mol

To a stirred solution of ester **2.88** (176.8 mg, 1.05 mmol) in acetone (40 mL) and acetic acid (13 mL) at −30 °C was added powdered $KMnO_4$ (0.216 g, 1.365 mmol) portionwise. The purple mixture was stirred rapidly for 1 h, during which time the temperature of the acetone bath rose to −10 °C and the reaction mixture turned dark brown. At this stage, the reaction was quenched with sat. aq. $Na_2S_2O_5$ (8 mL) and H_2O (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The organic layer was washed with sat. aq. $NaHCO_3$ and dried ($MgSO_4$). The solvent was removed *in vacuo*. The crude was purified by column chromatography (SiO_2 eluting with EtOAc/hexane (20 → 80%)) to afford the title compound **2.89** as a colourless liquid (0.067 g, 0.3 mmol, 29 %).

FT-IR (neat) ν_{max}	3408 (br), 2982 (w), 2941 (w), 1727 (s) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ = 4.36-4.18 (3H, m, OC$\underline{H}_2$ and C$\underline{H}$O), 4.10 (1H, m, C$\underline{H}$O), 3.77 (1H, dd, *J* = 2.7 and 11.7 Hz C$\underline{H}$HOH), 3.47 (1H, dd, *J* = 4.0 and 11.7 Hz CH$\underline{H}$OH), 2.82 (1H, br s, O$\underline{H}$), 2.17 (1H, s, O$\underline{H}$), 2.13-1.27 (4H, m, C$\underline{H}_2$), 1.32 (3H, s, CH_3), 1.31 (3H, t, *J* = 7.3 Hz, C$\underline{H}_3$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ = 175.9 ($\underline{C}$=O), 83.6 ($\underline{C}$HO), 80.2 ($\underline{C}$HO), 75.9 ($\underline{C}$), 65.1 ($\underline{C}H_2OH$), 62.0 (O$\underline{C}H_2$), 27.3 ($\underline{C}H_2$), 25.7 ($\underline{C}H_2$), 22.1 ($\underline{C}H_3$), 14.1 ($\underline{C}H_3$).
LRMS (ES^+) *m/z*	241 ($[M+Na]^+$).

3.2.52- (1*S*,2*R*)-2-Tritylcyclohexyl 2-diethyl phosphorylacetate (2.81)



$C_{31}H_{37}O_5P$

Mol. Wt.: 520.6 g/mol.

a) Preparation of 2-diethyl phosphoryl acetyl chloride: To stirred $SOCl_2$ (5.5 mL, 72.99 mmol) was added 2-diethyl phosphoryl acetic acid (4.0 mL, 24.33 mmol) dropwise at room temperature. The mixture was stirred for 2 h then the excess of $SOCl_2$ was removed *in vacuo* to give the acid chloride (5.22 g, 100%).

b) NaHMDS (10.53 mL, 10.53 mmol of 1.0 M solution in THF) was added dropwise to a stirred solution of (–)-(1*S*,2*R*)-2-tritylcyclohexanol (2.77 g, 8.1 mmol) in dry THF (50 mL) at –78 °C and the mixture was stirred at –78 °C for 0.5 h. Then, the freshly prepared acid chloride (5.22 g, 24.33 mmol) was dissolved in dry THF (10 mL) and added dropwise to the mixture. On completion the mixture was stirred at rt for 2 h. The solvent was removed *in vacuo*. The crude was purified by column chromatography (SiO_2 eluting with ethyl acetate/hexane (10 → 40%)) to afford the title ester (–)-**2.81** as a yellow viscous oil (3.51 g, 6.74 mmol, 83 %). This compound exhibited broadening of some signals in its NMR spectra due to restricted rotation.

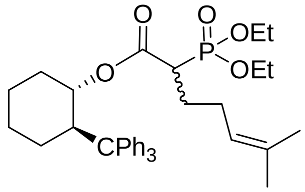
$[\alpha]_D$	– 44.0 (*c* 1.12, $CHCl_3$, 24 °C).
FT-IR (neat) ν_{max}	2937 (w), 2860 (w), 1727 (m), 1595 (w) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 7.50-7.0 (15H, m, $C\underline{H}_{Ar}$), 4.29 (1H, td, *J* = 10.2 and 4.0 Hz, $C\underline{H}OR$), 4.19- 4.06 (4H, m, $OC\underline{H}_2$), 3.50 (1H, td, *J* = 12.4 and 2.2 Hz, $C\underline{H}CPh_3$), 2.32-1.98 (4H, m, $C\underline{H}_2$), 1.75-1.25 (4H, m, $C\underline{H}_2$), 1.37 (3H, t, *J* = 7.3 Hz, $C\underline{H}_3$), 1.33 (3H, t, *J* = 7.0 Hz, $C\underline{H}_3$), 1.13 (1H, m, $C\underline{H}_2$), 0.55 (1H, m, $C\underline{H}_2$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 164.5 (C=O), 129.2 ($6\underline{C}H_{Ar}$), 127.2 ($6\underline{C}H_{Ar}$), 125.2 ($3\underline{C}H_{Ar}$), 76.0 ($C\underline{H}OH$), 62.4 ($O\underline{C}H_2$, d), 62.3 ($O\underline{C}H_2$, d), 60.6 ($\underline{C}Ph_3$), 46.0 ($\underline{C}HCPh_3$), 34.4 ($\underline{C}H_2$), 32.8 (d, *J* = 30 Hz, $\underline{C}H_2$), 28.9 ($\underline{C}H_2$), 25.7 ($\underline{C}H_2$), 24.6

(<u>C</u>H$_2$), 16.4 (<u>C</u>H$_3$), 16.3 (<u>C</u>H$_3$), (quaternary aromatic carbons signal not observed).

LRMS (ES$^+$) *m*/*z* 543 ([M+Na]$^+$).

HRMS (ES$^+$) *m*/*z* Calculated: 521.2457, found: 521.2451 ([M+H]$^+$).

3.2.53- (1*S*,2*R*)-2-Tritylcyclohexyl 2-diethyl phosphoryl-6-methylhept-5-enoate (2.95)



$C_{37}H_{47}O_5P$

Mol. Wt.: 602.74 g/mol

Procedures: Solid *t*-BuOK (0.11 g, 0.96 mmol) was added to a stirred solution of ester (–)-**2.81** (0.25 g, 0.48 mmol) in dry DMF (4.0 mL) at 0 °C. The mixture was stirred until the evolution of gas ceased, then 5-bromo-2-methylpent-2-ene (0.16 g, 0.96 mmol) was added dropwise and the mixture was warmed to room temperature and stirred for 4 h. The mixture was cooled to 0 °C and HCl (1 mL, 3.3 M) was added. The organic layer was extracted with EtOAc, dried ($MgSO_4$) and the solvent was removed *in vacuo*. The crude was purified by column chromatography (SiO_2 eluting with ethyl acetate/hexane (hexane → 40%)) to give the product as a yellow oil (157 mg, 0.26 mmol, 54%). This compound exhibited broadening of some signals in its NMR spectra due to restricted rotation.

[α]D – 9.0 (*c* 0.5, $CHCl_3$, 25 °C).

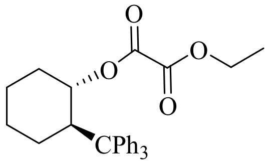
FT-IR (neat) ν_{max} 2938 (w), 2986 (w), 1727 (m), 1680 (m), 1581 (w) cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.60-6.89 (15H, m, Ar<u>H</u>), 5.01 (1H, t, *J* = 7.0 Hz, C<u>H</u>=), 4.26 (1H, td, *J* = 10.2 and 3.8 Hz, C<u>H</u>OR), 4.12 (4H, m, OC<u>H</u>$_2$), 3.56 (1H, m, C<u>H</u>CPh$_3$), 2.50-1.21 (11 H, m, C<u>H</u>$_2$), 1.70 (3H, s, C<u>H</u>$_3$), 1.64 (3H, s, C<u>H</u>$_3$), 1.40 (3H, t, *J* = 7.1 Hz, C<u>H</u>$_3$), 1.31 (3H, t, *J* = 7.1 Hz, C<u>H</u>$_3$), 1.10 (1H, m, C<u>H</u>$_2$), 0.58 (1H, m, C<u>H</u>$_2$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 167.8 (d, *J* = 7.5 Hz, C=O), 132.5 ((CH$_3$)$_2$<u>C</u>=), 131.8 (3<u>C</u>$_{Ar}$, br), 128.7 (6<u>C</u>H$_{Ar}$) 127.0 (6<u>C</u>H$_{Ar}$), 125.0 (3<u>C</u>H$_{Ar}$), 123.0 (=<u>C</u>H$_2$), 76.1 (C<u>H</u>OR), 62.4 (O<u>C</u>H$_2$), 62.3 (O<u>C</u>H$_2$), 60.9 (<u>C</u>Ph$_3$), 45.7 (d, *J* = 15 Hz,

	$\underline{C}H$), 44.2 ($\underline{C}HCPh_3$), 32.6 ($\underline{C}H_2$), 28.7 ($\underline{C}H_2$), 28.9 ($\underline{C}H_2$), 26.9 ($\underline{C}H_2$), 26.4 ($\underline{C}H_2$), 25.8 ($\underline{C}H_2$), 25.6 ($\underline{C}H_3$), 24.6 ($\underline{C}H_2$), 17.7 ($\underline{C}H_3$), 16.5 ($\underline{C}H_3$), 16.3 ($\underline{C}H_3$).
LRMS (ES^+) *m/z*	625 ($[M+Na]^+$).
HRMS (ES^+) *m/z*	Calculated: 603.3239, found: 603.3234 ($[M+H]^+$).

3.2.54- Ethyl (1*S*,2*R*)-2-tritylcyclohexyl oxalate (2.99)



$C_{29}H_{30}O_4$

Mol. Wt.: 442.55 g/mol

Ethyl chloro oxoacetate (4.7 mL, 41.25 mmol) was added dropwise over 20 minutes to a stirred mixture of DMAP (6.79 g, 55 mmol) and (−)-(1*S*,2*R*)-triphenylmethylcyclohexanol (9.42 g, 27.5 mmol) in dry CH_2Cl_2 (80 mL). The mixture was stirred at rt for 1 h then, CH_2Cl_2 was removed *in vacuo*. The mixture was dissolved in EtOAc (60 mL) and washed with 2N HCl (60 mL). The organic layer was separated, dried ($MgSO_4$), and EtOAc was removed *in vacuo*. Hexane (60 mL) was added to the crude and removed *in vacuo* to give the crude as a white solid which was washed with hexane to give the product as a white powder (10.5 g, 23.6 mmol, 86%). This compound exhibited broadening of some signals in its NMR spectra due to restricted rotation.

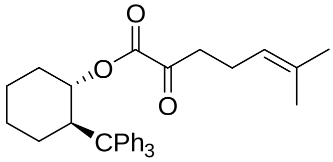
$[\alpha]_D$	+23.1 (*c*, 0.915, $CHCl_3$, 23 °C).
Mpt	124-127 °C.
FT-IR (neat) ν_{max}	3056 (w), 2939 (w), 2861 (w), 1760 (s) 1733 (s) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 7.60-6.85 (15H, m, Ar$\underline{H}$), 4.30 (1H, td, *J* = 10.3 and 4.0 Hz, $C\underline{H}OR$), 4.09 (2H, q, *J* = 7.0 Hz, $OC\underline{H}_2$), 3.60 (1H, m, $C\underline{H}CPh_3$), 2.14 (1H, m, $C\underline{H}_2$), 1.99 (1H, m, $C\underline{H}_2$), 1.80-1.60 (3H, m, $C\underline{H}_2$), 1.55-1.10 (2H, m, $C\underline{H}_2$), 1.24 (3H, t, *J* = 7.1 Hz, $C\underline{H}_3$), 0.78 (1H, m, $C\underline{H}_2$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 157.8 ($\underline{C}$=O), 157.1 ($\underline{C}$=O), 129.6 ($6\underline{C}H_{Ar}$), 127.3 ($6\underline{C}H_{Ar}$), 125.3 ($3\underline{C}H_{Ar}$), 78.3 ($\underline{C}HOR$), 62.4 ($O\underline{C}H_2$), 60.7 ($\underline{C}Ph_3$), 46.2 ($\underline{C}HCPh_3$), 32.7 ($\underline{C}H_2$), 28.9 ($\underline{C}H_2$), 25.8 ($\underline{C}H_2$), 24.6 ($\underline{C}H_2$), 13.8 ($\underline{C}H_3$), (quaternary

aromatic carbons signal not observed).

LRMS (ES$^+$) *m/z* 907 ([2M+Na]$^+$).

HRMS (ES$^+$) *m/z* Calculated: 460.5846, found: 460.2496 ([M+NH$_4$]$^+$).

3.2.55- (1*S*,2*R*)-2-Tritylcyclohexyl 6-methyl-2-oxohept-5-enoate (2.100)



$C_{33}H_{36}O_3$

Mol. Wt.: 480.64 g/mol

A solution of 5-bromo-2-methylpent-2-ene (5.69 g, 34.91 mmol) in dry THF (10 mL) was added to stirred Mg (2.55 g, 0.105 g-atom) in dry THF (50 mL). A few crystals of iodine were added, and the mixture was heated to reflux for 45 minutes. The resulting Grignard solution was added dropwise through canula to a stirred solution of ester **2.99** (10.3 g, 23.27 mmol) in dry THF (60 mL) at –78 °C. The mixture was stirred at the same temperature for 2 h. The reaction was quenched with water (80 mL) and sat. aq. NH_4Cl (40 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 100 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo*. The crude mixture was purified by column chromatography (SiO_2 eluting with CH_2Cl_2/hexane (2 → 60%)) to give the product as a white powder (9.69 g, 20.16 mmol, 87 %). This compound exhibited broadening of some signals in its NMR spectra due to restricted rotation.

[α]$_D$ +2.1 (*c* 0.8, $CHCl_3$, 25 °C).

mp 162-165 °C.

FT-IR (neat) ν_{max} 3056 (w), 2935 (w), 2859 (w), 1719 (s) cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.50-7.00 (15H, m, Ar$\underline{H}$), 4.97 (1H, t with fine coupling, *J* = 7.0 Hz, CH=), 4.32 (1H, td, *J* = 10.2 and 4.0 Hz, C$\underline{H}$OR), 3.60 (1H, m, C$\underline{H}$CPh$_3$), 2.48-1.58 (6H, m, C$\underline{H}_2$), 1.80-1.10 (5H, m, C$\underline{H}_2$), 1.70 (3H, s, C$\underline{H}_3$), 1.62 (3H, s, C$\underline{H}_3$), 0.75 (1H, m, C$\underline{H}_2$).

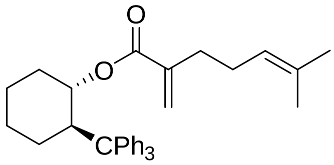
^{13}C-NMR (75 MHz, $CDCl_3$) δ 194.2 (C=O), 160.5 (COOR), 132.9 ($\underline{C}$=), 129.6 (6$\underline{C}$H$_{Ar}$), 127.5 (6$\underline{C}$H$_{Ar}$), 125.6 (3$\underline{C}$H$_{Ar}$), 122.0 (CH=), 77.6 ($\underline{C}$HOR), 60.8 ($\underline{C}$Ph$_3$), 46.2

$(\underline{C}HCPh_3)$, 39.1 $(\underline{C}H_2)$, 33.0 $(\underline{C}H_2)$, 29.1 $(\underline{C}H_2)$, 25.8 $(\underline{C}H_2)$, 25.7 $(\underline{C}H_3)$, 24.7 $(\underline{C}H_2)$, 21.3 $(\underline{C}H_2)$, 17.6 $(\underline{C}H_3)$, (quaternary aromatic carbons signal not observed)..

LRMS (ES^+) *m/z* 983 ($[2M+Na]^+$).

HRMS (ES^+) *m/z* Calculated: 498.3008, found: 498.3003 ($[M+NH_4]^+$).

3.2.56- (1*S*,2*R*)-2-Tritylcyclohexyl 6-methyl-2-methylenehept-5-enoate (2.44)



$C_{34}H_{38}O_2$

Mol. Wt.: 478.66 g/mol

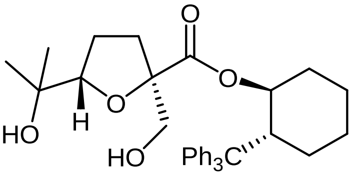
Procedure 1: To a stirred solution of ester (−)-**2.95** (0.1571 g, 0.26 mmol) in dry DMF (2 mL) was added anhydrous K_2CO_3 (72.6 mg, 0.52 mmol) then HCHO (3.0 mL, 37% in H_2O) and the mixture was stirred overnight at room temperature then at 60 °C for 3.5 h. The mixture was diluted with water (10 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (4 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvents were removed *in vacuo*. The crude was purified by column chromatography (SiO_2 eluting with ether/hexane (hexan → 5 %)) to afford the title ester **2.44** as a colourless highly viscous oil (0.122 g, 0.255 mmol, 98%).

Procedure 2: DBU (3.49 mL, 22.86 mmol) was added dropwise at room temperature to a stirred solution of CH_3Ph_3PBr (5.56 g, 15.24 mmol) in dry CH_2Cl_2 (40 mL). The mixture was heated to reflux for 1 h. Then, the ester **2.100** (2.45 g, 5.08 mmol) was added in dry CH_2Cl_2 (30 mL) and the reaction was continued under reflux for 21 h. The solvent was removed *in vacuo* and the mixture was dissolved in ethyl acetate (40 mL) and washed with 2N HCl (60 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo*. The crude mixture was purified by column chromatography (SiO_2 eluting with CH_2Cl_2/hexane (2 → 20%)) to give the product as a colourless viscous oil (2.19 g, 4.58 mmol, 90%). This compound exhibited broadening of some signals in its NMR spectra due to restricted rotation.

$[\alpha]_D$ +50.5 (*c* 0.86, $CHCl_3$, 25 °C).

FT-IR (neat) ν_{max}	3056 (w), 2924 (w), 2857 (w), 1705 (s) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 7.60-6.85 (15H, m, Ar$\underline{H}$), 5.20 (1H, d, *J* = 1.5 Hz, =C$\underline{H}$H), 5.14 (1H, m, =CH$\underline{H}$), 5.05 (1H, m, C$\underline{H}$CH$_2$), 4.00 (1H, td, *J* = 10.3 and 3.7 Hz, C$\underline{H}$OR), 3.60 (1H, m, C$\underline{H}$CPh$_3$), 2.16 (1H, m, C$\underline{H_2}$), 2.10-1.89 (5H, m, C$\underline{H_2}$), 1.78-1.35 (4H, m, C$\underline{H_2}$), 1.71 (3H, s, C$\underline{H_3}$), 1.61 (3H, s, C$\underline{H_3}$), 1.25 (1H, m, C$\underline{H_2}$), 0.88 (1H, m, C$\underline{H_2}$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 166.4 (C=O), 148.5 (3$\underline{C}_{Ar}$), 140.4 ($\underline{C}$), 131.9 ($\underline{C}$), 128.8 (6$\underline{C}$H$_{Ar}$), 127.4 (6$\underline{C}$H$_{Ar}$), 125.3 (3$\underline{C}$H$_{Ar}$), 124.3 (=$\underline{C}$H$_2$), 123.6 (=C$\underline{H}$), 76.3 (C$\underline{H}$OH), 60.8 ($\underline{C}$Ph$_3$), 46.6 ($\underline{C}$HCPh$_3$), 33.3 ($\underline{C}$H$_2$), 31.9 ($\underline{C}$H$_2$), 29.1 ($\underline{C}$H$_2$), 26.9 ($\underline{C}$H$_2$), 26.3 ($\underline{C}$H$_2$), 25.7 ($\underline{C}$H$_3$), 24.9 ($\underline{C}$H$_2$), 17.7 ($\underline{C}$H$_3$).
LRMS (ES^+) *m/z*	501 ($[M+Na]^+$).
HRMS (ES^+) *m/z*	Calculated: 479.2950, found: 479.2945 ($[M+H]^+$).

3.2.57- (2*R*,5*S*)-(1*S*,2*R*)-2-Tritylcyclohexyl tetrahydro-2-(hydroxymethyl)-5-(2-hydroxypropan-2-yl)furan-2-carboxylate (2.51)



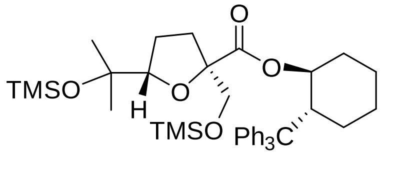
$C_{34}H_{40}O_5$

Mol. Wt.: 528.68 g/mol

To a stirred solution of the diene (–)-**2.44** (6.66 g, 13.9 mmol) in acetone (250 mL) and H_2O (40 mL) at – 40 °C was added a solution of $NaMnO_4$ (52.1 mL, 20.85 mmol, 0.4 M aq.) and AcOH (2.76 mL, 48.1 mmol). The colour changed to dark brown and the mixture stirred for 1 h during which the temperature rose to – 5 °C. Then, the reaction was quenched by adding $Na_2S_2O_5$ (120 mL, sat. aq.). The crude was concentrated *in vacuo* then the residue was extracted with ethyl acetate (4 x 100 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. The crude was purified by column chromatography (SiO_2 eluting with EtOAc/hexane (2.5 → 50 %)) to give the product as a white foam (5.35 g, 10.12 mmol, 73%). This compound exhibited broadening of some signals in its NMR spectra due to restricted rotation.

[α]$_D$	– 3.8 (c 0.52, CHCl$_3$, 24 ^{o}C).
FT-IR (neat) ν$_{max}$	3410 (br), 2939 (m), 2860 (w), 1728 (m) cm^{-1}.
^{1}H-NMR (300 MHz, CDCl$_3$)	δ 7.55-6.90 (15H, m, Ar$\underline{\text{H}}$), 4.09 (1H, td, *J* = 10.2 and 3.8 Hz, C$\underline{\text{H}}$OR), 3.82 (1H, t, *J* = 7.3 Hz, C$\underline{\text{H}}$O), 3.65 (1H, d, *J* = 11.2 Hz, C$\underline{\text{H}}$HOH), 3.60 (1H, m, C$\underline{\text{H}}$CPh$_3$), 3.44 (1H, d, *J* = 11.2 Hz, CH$\underline{\text{H}}$OH), 2.45 (1H, br, O$\underline{\text{H}}$), 2.35 (1H, s, O$\underline{\text{H}}$), 2.15 (1H, m, C$\underline{\text{H}}_2$), 198 (1H, m, C$\underline{\text{H}}_2$), 1.82-1.60 (4H, m, C$\underline{\text{H}}_2$), 1.58-0.95 (5H, m,C$\underline{\text{H}}_2$), 1.26 (3H, s, C$\underline{\text{H}}_3$), 1.10 (3H, s, C$\underline{\text{H}}_3$), 0.8 (1H, m, C$\underline{\text{H}}_2$).
^{13}C-NMR (75 MHz, CDCl$_3$)	δ 172.1 (C=O), 131.4 (3$\underline{\text{C}}_{\text{Ar}}$), 128.7 (6$\underline{\text{C}}H_{\text{Ar}}$), 127.5 (6$\underline{\text{C}}H_{\text{Ar}}$), 125.0 (3$\underline{\text{C}}H_{\text{Ar}}$), 86.8 ($\underline{\text{C}}$), 86.7 ($\underline{\text{C}}$HO), 77.2 ($\underline{\text{C}}$HOCOR), 71.5 ($\underline{\text{C}}$), 66.1 ($\underline{\text{C}}H_2$OH), 61.0 ($\underline{\text{C}}$), 45.6 ($\underline{\text{C}}$HCPh$_3$), 33.0 ($\underline{\text{C}}H_2$), 30.3 ($\underline{\text{C}}H_2$), 28.7 ($\underline{\text{C}}H_2$), 27.3 ($\underline{\text{C}}H_3$), 25.9 ($\underline{\text{C}}H_2$), 25.7 ($\underline{\text{C}}H_2$), 25.0 ($\underline{\text{C}}H_3$), 24.6 ($\underline{\text{C}}H_2$).
LRMS (ES$^+$) *m*/*z*	551 ([M+Na]$^+$).
HRMS (ES$^+$) *m*/*z*	Calculated: 546.3219, found: 546.3214 ([M+NH$_4$]$^+$).

3.2.58- (2*R*,5*S*)-(1*S*,2*R*)-2-Tritylcyclohexyl tetrahydro-2-(methoxytrimethylsilyl)-5-(2-trimethylsiloxyoxypropan-2-yl)furan-2-carboxylate (2.95)



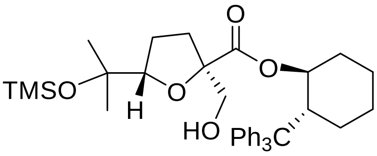
$C_{40}H_{56}O_5Si_2$

Mol. Wt.: 673.04 g/mol.

To a stirred solution of THF diol **2.51** (134.7 mg, 0.2547 mmol) in dry DMF (3.0 mL) was added imidazole (0.214 g, 3.11 mmol), followed by TMS-Cl (0.33 mL, 2.57 mmol) at – 5 ^{o}C. The reaction mixture was stirred for 1 h, during which the temperature rose to 0 ^{o}C. At this stage, the reaction was quenched with NH$_4$Cl (1.0 mL, sat. aq. sol.) and H$_2$O (2.0 mL). The organic phase was extracted with Et$_2$O (2 × 25 mL), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give the crude as a yellow oil. Purification by column chromatography (SiO$_2$ eluting with EtOAc/hexane 5 → 20%) afforded the title THF **2.95** (0.146 g, 0.216 mmol, 85%). This compound exhibited broadening of some signals in its NMR spectra due to restricted rotation.

$[\alpha]_D$	+31.5 (*c* 0.745, $CHCl_3$, 23 °C).
FT-IR (neat) ν_{max}	2952 (w), 1738 (m), 1595 (w), 1492 (w) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 7.55-6.85 (15H, m, Ar$\underline{H}$), 4.05 (1H, td, *J* = 10.1 and 3.7 Hz, C$\underline{H}$OR), 3.89 (1H, dd, *J* = 4.0 and 8.4 Hz, C$\underline{H}$O), 3.74 (1H, d, *J* = 10.0 Hz, C$\underline{H}$HO-Si), 3.59 (1H, t, *J* = 9.5 Hz, C$\underline{H}$CPh$_3$), 3.33 (1H, d, *J* = 10.0 Hz, C$\underline{H}$HO-Si), 2.11 (2H, m, C$\underline{H}_2$), 1.83-0.67 (9H, m, C$\underline{H}_2$), 1.19 (3H, s, C$\underline{H}_3$), 1.17 (3H, s, C$\underline{H}_3$), 0.58 (1H, ddd, *J* = 12.8, 8.2 and 2.7 Hz, C$\underline{H}_2$), 0.14 (9H, s, (C$\underline{H}_3$)$_3$Si), 0.10 (9H, s, (C$\underline{H}_3$)$_3$Si).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 172.0 (C=O), 131.5 (3$\underline{C}_{Ar}$, br), 128.7 (6$\underline{C}H_{Ar}$), 127.3 (6$\underline{C}H_{Ar}$), 124.8 (3$\underline{C}H_{Ar}$), 88.0 ($\underline{C}$), 87.1 ($\underline{C}$HO), 76.5 ($\underline{C}$HOCOR), 75.1 ($\underline{C}$), 67.3 ($\underline{C}H_2$), 61.0 ($\underline{C}$), 45.6 ($\underline{C}$HCPh$_3$), 32.9 ($\underline{C}H_2$), 29.8 ($\underline{C}H_2$), 28.7 ($\underline{C}H_2$), 27.9 ($\underline{C}H_3$), 26.1 ($\underline{C}H_2$), 25.2 ($\underline{C}H_3$), 25.0 ($\underline{C}H_2$), 24.7 ($\underline{C}H_2$), 2.6 (3×$\underline{C}H_3$), 0.5 (3×$\underline{C}H_3$).
LRMS (ES^+) *m/z*	695 ($[M+Na]^+$).
HRMS (ES^+) *m/z*	Calculated: 695.3564, found: 695.3558 ($[M+Na]^+$).

3.2.59- (2*R*,5*S*)-(1*S*,2*R*)-2-Tritylcyclohexyl tetrahydro-2-(hydroxymethyl)-5-(2-trimethylsiloxyoxypropan-2-yl)furan-2-carboxylate (2.96)



$C_{37}H_{48}O_5Si$

Mol. Wt.: 600.86 g/mol.

To a stirred solution of compound **2.95** (73 mg, 0.1 mmol) in dry MeOH (2 mL) was added dried powdered K_2CO_3 (6.4 mg, 0.046 mmol) at – 10 °C, and the resultant milky mixture was stirred for 2 h, while maintaining the temperature at – 10 °C. H_2O (3.0 mL) was added and MeOH was evaporated *in vacuo*. The residue was diluted with Et_2O (10 mL) and H_2O (5.0 mL). The organic phase was separated. The aqueous phase was extracted with Et_2O (2 × 10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product as a yellow oil. Purification by column chromatography (SiO_2) eluting with EtOAc/hexane (5.0 → 40%) afforded the title THF

2.96 as a pale yellow oil (0.054 g, 0.09 mmol, 83%). This compound exhibited broadening of some signals in its NMR spectra due to restricted rotation.

[α]$_D$ +11.6 (*c* 0.715, $CHCl_3$, 25 °C).

FT-IR (neat) ν_{max} 3467 (br), 3056 (w), 2948 (w), 2861 (w), 1736 (m), 1595 (s) cm^{-1}

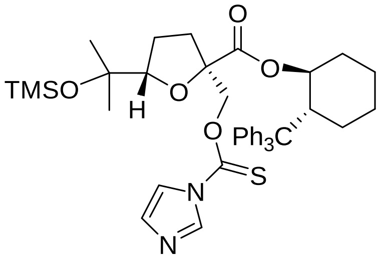
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.50-6.95 (15H, m, Ar$\underline{H}$), 4.09 (1H, td, *J* = 10.1 and 4.0 Hz, C$\underline{H}$OR), 3.73 (1H, t, *J* = 7.1 Hz, C$\underline{H}$O), 3.59 (1H, dd, *J* = 8.0 and 11.0 Hz, C$\underline{H}$HOH), 3.59 (1H, m, C$\underline{H}$CPh$_3$), 3.40 (1H dd, *J* = 8.0 and 11.0 Hz, CH$\underline{H}$OH), 2.59 (1H, m, O$\underline{H}$), 2.14 (1H, m, C$\underline{H}_2$), 2.03-1.77 (2H, m, C$\underline{H}_2$), 1.75-1.57 (4H, m, C$\underline{H}_2$), 1.54-1.05 (4H, m, C$\underline{H}_2$), 1.30 (3H, s, C$\underline{H}_3$), 1.15 (3H, s, C$\underline{H}_3$), 0.80 (1H, m, C$\underline{H}_2$), 0.14 (9H, s, (C$\underline{H}_3$)$_3$Si-).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.3 (C=O), 131.9 (3$\underline{C}_{Ar}$), 128.6 (6$\underline{C}H_{Ar}$), 127.5 (6$\underline{C}H_{Ar}$), 125.2 (3$\underline{C}H_{Ar}$), 87.7 ($\underline{C}$HO), 86.7 ($\underline{C}$), 76.7 ($\underline{C}$HOCOR), 75.1 ($\underline{C}$), 65.8 ($\underline{C}H_2$OH), 61.0 ($\underline{C}$), 45.6 ($\underline{C}$HCPh$_3$), 33.0 ($\underline{C}H_2$), 30.5 ($\underline{C}H_2$), 28.7 ($\underline{C}H_2$), 27.1 ($\underline{C}H_3$), 27.1 ($\underline{C}H_3$), 26.1 ($\underline{C}H_2$), 26.0 ($\underline{C}H_2$), 24.6 ($\underline{C}H_2$), 2.3 (3×$\underline{C}H_3$).

LRMS (ES^+) *m/z* 623 ([M+Na]$^+$).

HRMS (ES^+) *m/z* Calculated: 623.3169, found: 623.3163 ([M+Na]$^+$).

3.2.60- (2*R*,5*S*)-(1*S*,2*R*)-2-Tritylcyclohexyl tetrahydro-2-(*O*-methyl1*H*-imidazole-1-carbothioyl)-5-(2-trimethylsiloxyoxypropan-2-yl)furan-2-carboxylate (2.97)



$C_{41}H_{50}N_2O_5SSi$

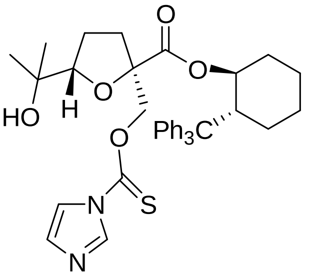
Mol. Wt.: 711 g/mol.

To a stirred solution of THF **2.96** (0.461 g, 0.767 mmol) in dry CH_2Cl_2 (15 mL) was added DMAP (28.4 mg, 0.23 mmol) and thiocarbonyl diimidazole (0.43 g, 2.30 mmol). The reaction mixture was stirred at room temperature for 14 h then concentrated *in vacuo* to give the crude as a yellow oil. Purification by column chromatography (SiO_2) eluting with EtOAc /hexane (5.0 →

40%) afforded the title THF **2.97** as a yellow oil (0.455 g, 0.64 mmol, 83%). This compound exhibited broadening of some signals in its NMR spectra due to restricted rotation.

[α]$_D$	−11.8 (*c* 0.885, $CHCl_3$, 24 °C).
FT-IR (neat) ν_{max}	2950 (w), 1742 (m), 1594 (w), 1531 (w) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 8.36 (1H, s, CH=), 7.62 (1H, s, CH=), 7.55-7.11 (15H, m, ArH), 7.02 (1H, s, CH=), 4.93 (1H, d, *J* = 10.6 Hz, CHHOC), 4.27 (1H, d, *J* = 10.6 Hz, CHHOC), 4.07 (1H, td, *J* = 10.0 and 3.5 Hz, CHOR), 3.97 (1H dd, *J* = 4.8 and 8.1 Hz, CHO), 3.55 (1H, m, $CHCPh_3$), 2.12 (1H, m, CH_2), 2.0-0.68 (11H, m, CH_2), 1.20 (3H, s, CH_3), 1.15 (3H, s, CH_3), 0.1 (9H, s, 3 × CH_3).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 184.0 (C=S), 170.6 (C=O), 137.1 (CH=), 131.7 ($3C_{Ar}$), 130.8 (CH=), 128.6 ($6CH_{Ar}$), 127.7 ($6CH_{Ar}$), 125.1 ($3CH_{Ar}$), 117.7 (CH=), 88.6 (CHO), 84.6 (C), 77.2 (CHOCOR), 76.4 (CH_2), 74.9 (C), 61.0 (C), 45.4 ($CHCPh_3$), 32.9 (CH_2), 31.1 (CH_2), 28.7 (CH_2), 27.3 (CH_3), 26.0 (CH_3), 25.8 (CH_2), 25.1 (CH_2), 24.7 (CH_2), 2.5 (3 × CH_3).
LRMS (ES^+) *m/z*	711 ($[M+H]^+$).
HRMS (ES^+) *m/z*	Calculated: 711.3210, found: 711.3289 ($[M+H]^+$).

3.2.61- (2*R*, 5*S*)-(1*S*,2*R*)-2-Tritylcyclohexyl tetrahydro-2-(*O*-methoxy-1*H*-imidazole-1-carbothioyl)-5-(2-hydroxypropan-2-yl)furan-2-carboxylate (2.101)



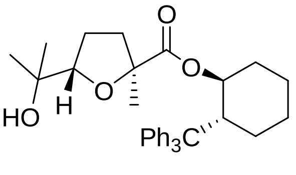
$C_{38}H_{42}N_2O_5S$

Mol. Wt.: 638.82 g/mol.

To a stirred solution of THF-diol (−)-**2.51** (3.53 g, 6.68 mmol) in dry CH_2Cl_2 (100 mL) was added DMAP (0.49 g, 4.01 mmol) and 1,1’-thiocabonyldiimidazole (3.76 g, 20.0 mmol). The mixture was stirred overnight at room temperature. Following removal of the solvent under reduced pressure, the crude product was purified directly by column chromatography (EtOAc/hexane, 0:1→1:1) to give the product as a yellow foam (3.74 g, 5.58 mmol, 88%). This compound exhibited broadening of some signals in its NMR spectra due to restricted rotation.

$[\alpha]_D$	+10.0 (*c* 0.5, $CHCl_3$, 24 °C).
FT-IR (neat) ν_{max}	3400 (br), 2941 (m), 2859 (w), 1740 (s) cm^{-1}.
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.36 (1H, s, C$\underline{H}$=), 7.61 (1H, s, C$\underline{H}$=), 7.55-7.00 (15H, m, Ar$\underline{H}$), 7.04 (1H, s, C$\underline{H}$=), 4.82 (1H, d, *J* = 11.0 Hz, OC$\underline{H}$H), 4.38 (1H, d, *J* = 11.0 Hz, OCH$\underline{H}$), 4.13 (1H, td, *J* = 10.2 and 3.8 Hz, $CO_2C\underline{H}$), 4.07 (1H, t, *J* = 7.3 Hz, OC$\underline{H}$), 3.56 (1H, m, $C\underline{H}CPh_3$), 2.14 (1H, m, $C\underline{H}_2$), 2.04-1.00 (11H, m, $C\underline{H}_2$), 1.24 (3H, s, $C\underline{H}_3$), 1.11 (3H, s, $C\underline{H}_3$), 0.72 (1H, m, $C\underline{H}_2$).
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 184.0 ($\underline{C}$=S), 170.2 ($\underline{C}$=O), 137.1 ($\underline{C}$H=), 131.5 ($3\underline{C}_{Ar}$), 131.0 ($\underline{C}$H=), 128.6 ($6\underline{C}H_{Ar}$), 127.7 ($6\underline{C}H_{Ar}$), 125.2 ($3\underline{C}H_{Ar}$), 117.8 ($\underline{C}$H=), 87.7 (O$\underline{C}$H), 84.3 (O$\underline{C}$), 77.5 ($CO_2\underline{C}H$), 75.5 (C(S)O$\underline{C}H_2$), 71.0 ($\underline{C}$), 61.0 ($\underline{C}$), 45.6 ($\underline{C}HCPh_3$), 33.0 ($\underline{C}H_2$), 31.2 ($\underline{C}H_2$), 28.8 ($\underline{C}H_2$), 27.1 ($\underline{C}H_3$), 25.8 ($\underline{C}H_2$), 25.1 ($\underline{C}H_2$), 24.9 ($\underline{C}H_2$), 24.7 ($\underline{C}H_3$).
LRMS (ES^+) *m/z*	661 ($[M+Na]^+$).
HRMS (ES^+) *m/z*	Calculated: 639.2893, found: 639.2887 ($[M+H]^+$).

3.2.62-(2*S*,5*S*)-(1*S*,2*R*)-2-Tritylcyclohexyl tetrahydro-5-(2-hydroxypropan-2-yl)-2-methyl furan-2-carboxylate (2.94)



$C_{34}H_{40}O_4$

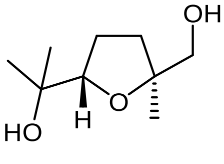
Mol. Wt.: 512.68 g/mol.

Procedure 1: To a stirred solution of THF compound **2.97** (0.243 g, 0.34 mmol) in dry toluene (19 mL) was added AIBN (28 mg, 0.17 mmol), followed by dropwise addition of TTMSS (0.7 mL, 2.21 mmol). The resultant solution was stirred at 85 °C for 20 min then diluted by EtOAc (20 mL). The mixture was washed with sat. aq. $NaHCO_3$ (20 mL), dried ($MgSO_4$) and the solvent was removed *in vacuo* to afford the crude as a pale yellow oil. Purification by column chromatography (SiO_2) eluting with EtOAc/hexane (20→ 40%) afforded the title THF **2.94** as a pale yellow foam (0.1297 g, 0.253 mmol, 74%).

Procedure 2: To a degassed stirred solution of the thiocarbonyl derivative **2.101** (3.74 g, 5.85 mmol) in dry toluene (80 mL) at 85 °C was added AIBN (0.49 g, 2.93 mmol) and TTMSS (5.58 mL, 17.55 mmol). The flask was wrapped in aluminium foil and heated at 85 °C for 1 h. EtOAc (100 mL) was added and the mixture was washed with 2 N HCl (60 mL). The organic layer was dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (EtOAc/hexane, 0:1→1:9) to afford the title compound as pale yellow foam (2.00 g, 3.90 mmol, 67%). This compound exhibited broadening of some signals in its NMR spectra due to restricted rotation.

$[\alpha]_D$	+1.6 (*c* 0.59, $CHCl_3$, 26 °C).
FT-IR (neat) ν_{max}	3468 (br), 2937 (m), 2860 (w), 1728 (s), 1595(w) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 7.62-6.92 (15H, m, Ar$\underline{H}$), 4.06 (1H, td, *J* = 10.1 and 3.7 Hz, C$\underline{H}$OR), 3.82 (1H, t, *J* = 7.1 Hz, C$\underline{H}$O), 3.61 (1H, m, C$\underline{H}$CPh$_3$), 2.15 (1H, m, C$\underline{H}_2$), 2.04-1.90 (2H, m, C$\underline{H}_2$ and OH), 1.77-1.57 (4H, m, C$\underline{H}_2$), 1,55-1.35 (2H, m, C$\underline{H}_2$), 1.30-1.02 (3H, m, C$\underline{H}_2$), 1.23 (3H, s, C$\underline{H}_3$), 1.19 (3H, s, C$\underline{H}_3$), 1.10 (3H, s, C$\underline{H}_3$), 0.83 (1H, m, C$\underline{H}_2$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 173.5 (C=O), 131.4 (3$\underline{C}_{Ar}$, br), 128.8 (6$\underline{C}H_{Ar}$), 127.4 (6$\underline{C}H_{Ar}$), 125.4 (3$\underline{C}H_{Ar}$), 86.1 ($\underline{C}$HO), 83.6 ($\underline{C}$), 76.4 ($\underline{C}$HOCOR), 71.1 ($\underline{C}$), 61.0 ($\underline{C}$Ph$_3$), 45.6 ($\underline{C}$HCPh$_3$), 35.1 ($\underline{C}H_2$), 32.8 ($\underline{C}H_2$), 28.6 ($\underline{C}H_2$), 27.0 ($\underline{C}H_3$), 25.9 ($\underline{C}H_2$), 25.6 ($\underline{C}H_2$), 24.6 ($\underline{C}H_2$), 24.3 ($\underline{C}H_3$), 23.7 ($\underline{C}H_3$).
LRMS (ES^+) *m/z*	535 ($[M+Na]^+$).
HRMS (ES^+) *m/z*	Calculated: 530.3270, found: 530.3265 ($[M+NH_4]^+$).

3.2.63- 2-((2*S*,5*S*)-Tetrahydro-5-(hydroxymethyl)-5-methylfuran-2-yl)propan-2-ol (2.102)



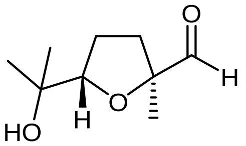
$C_9H_{18}O_3$

Mol. Wt.: 174.24 g/mol.

To a stirred solution of ester **2.94** (0.8 g, 1.56 mmol) in dry CH_2Cl_2 (28 mL) at rt was added dropwise a solution of DIBAL-H (6.24 mL of 1.0 M in hexanes, 6.24 mmol). The mixture was heated under reflux for 1 h, before cooling to rt and quenching by successive addition of sat. aq. NH_4Cl (24 mL) and a solution of Rochelle's salt (24 mL, sat. aq.). After vigorous stirring for 30 min, the mixture was extracted with CH_2Cl_2 (4 x 30 mL) and Et_2O (2 x 30 mL) (monitored by TLC to ensure complete extraction of the diol). The combined organic phases were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure to give the crude diol as a yellow liquid. Purification by column chromatography (Et_2O/hexane, 1:1→1:0) afforded the title alcohol **2.102** as a pale yellow oil (0.197 g, 1.14 mmol, 73%) and (–)-TTC (0.448 g, 1.31 mmol, 85%).

$[\alpha]_D$	–19.8 (*c* 0.69, $CHCl_3$, 23 °C).
FT-IR (neat) ν_{max}	3396 (br), 2970 (m), 2931 (m), 1052 (s) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 3.79 (1H, t, *J* = 7.7 Hz, OC$\underline{H}$), 3.45 (2H, d, *J* = 5.9 Hz, C$\underline{H}_2$OH), 2.33 (1H, t, *J* = 6.4 Hz, CH_2O$\underline{H}$), 2.28 (1H, s, O$\underline{H}$), 2.02-1.81 (3H, m, C$\underline{H}_2$), 1.65 (1H, m, C$\underline{H}_2$), 1.20 (3H, s, C$\underline{H}_3$), 1.19 (3H, s, C$\underline{H}_3$), 1.13 (3H, s, C$\underline{H}_3$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 86.9 (O$\underline{C}$H), 83.6 ($\underline{C}$), 70.8 ($\underline{C}$), 68.4 ($\underline{C}H_2$OH), 33.6 ($\underline{C}H_2$), 27.4 ($\underline{C}H_3$), 26.6 ($\underline{C}H_2$), 23.9 ($\underline{C}H_3$), 23.8 ($\underline{C}H_3$).
LRMS (ES^+) *m/z*	197 ($[M+Na]^+$).
HRMS (ES^+) *m/z*	Calculated: 197.1154, found: 197.1152 ($[M+Na]^+$).

3.2.64-(2S,5*S*)-Tetrahydro-5-(2-hydroxypropan-2-yl)-2-methylfuran-2-carbaldehyde (2.98)



$C_9H_{16}O_3$

Mol. Wt.: 172.22 g/mol.

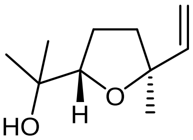
Procedure 1: To a stirred solution of THF **2.94** (105 mg, 0.2 mmol) in dry CH_2Cl_2 (4.0 mL) was added DIBAL-H (2.0 mL of 1.0 M in hexanes, 2.0 mmol) at – 78 °C and the resultant solution was stirred for 5 h, while keeping the temperature at – 78 °C. The reaction was quenched at the same temperature by adding NH_4Cl (5.0 mL, sat. aq.) and the reaction was warmed to rt.

Rochelle's salt (6.0 mL, sat. aq.) was added to the mixture and it was stirred for 30 min at room temperature. The mixture was diluted with CH_2Cl_2 (10 mL) and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude as a pale yellow oil. Purification by column chromatography (SiO_2 eluting with Et_2O/pentane 20 →50 %)) gave the pure product **2.98** as a pale yellow oil (10.2 mg, 0.059 mmol, 29%).

Procedure 2: To a stirred solution of primary alcohol **2.102** (0.199 g, 1.14 mmol) in dry CH_2Cl_2 (10 mL) at rt was added Dess–Martin periodinane (0.62 g, 1.42 mmol). After 1 h and the reaction mixture was diluted with Et_2O (35 mL) and sat. aq. $NaHCO_3$ (35 mL) and sat. aq. $Na_2S_2O_5$ (14 mL) were added. The mixture was stirred vigorously for 1 h, then the organic layer was separated and the aqueous layer was re-extracted with CH_2Cl_2 (20 mL) followed by Et_2O (5 x 20 mL). The combined organic phases were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure to give the title aldehyde as a colourless oil (198 mg, 1.15 mmol, 98%). The aldehyde **2.98** was used in the subsequent reaction without further purification.

$[\alpha]_D$	+19.0 (*c* 0.46, $CHCl_3$, 24 °C).
FT-IR (neat) ν_{max}	3435 (br), 2976 (m), 2873 (m), 1732 (s) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 9.58 (1H, s, -$C\underline{H}O$), 3.86 (1H, dd, *J* = 6.6 and 8.4 Hz, $OC\underline{H}$), 2.15 (1H, m, $C\underline{H}_2$), 1.97-1.82 (2H, m, $C\underline{H}_2$), 1.71 (1H, m, $C\underline{H}_2$), 1.32 (3H, s, $C\underline{H}_3$), 1.28 (3H, s, $C\underline{H}_3$), 1.16 (3H, s, $C\underline{H}_3$), (OH signal was not observed).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 202.7 ($\underline{C}HO$), 87.5 ($\underline{C}H$), 86.5 ($\underline{C}$), 70.7 ($\underline{C}H$), 32.7 ($\underline{C}H_2$), 27.3 ($\underline{C}H_3$), 25.9 ($\underline{C}H_2$) 24.3 ($\underline{C}H_3$), 21.0 ($\underline{C}H_3$).
LRMS (ES^+) *m*/*z*	195 ($[M+Na]^+$).
HRMS (ES^+) *m*/*z*	Calculated, 195.0997 found 195.0995 ($[M+Na]^+$).

3.2.65- 2-((2S,5S)-Tetrahydro-5-methyl-5-vinylfuran-2-yl)propan-2-ol (1.247):- (2*S*,5*S*)-linalool oxide



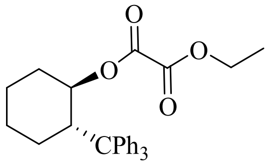
$C_{10}H_{18}O_2$

Mol. Wt.: 170.25 g/mol.

DBU (0.54 mL, 3.58 mmol) was added dropwise at rt to a stirred solution of Ph_3PCH_3Br (0.70 g, 1.92 mmol) in dry CH_2Cl_2 (10 mL). The mixture was heated to reflux for 45 min. A solution of aldehyde **2.98** (189 mg, 1.1 mmol) in dry CH_2Cl_2 (15 mL) was added and the reaction heated under reflux for 48 h. The solvent was removed under reduced pressure and the crude product partitioned between Et_2O (30 mL) and water (30 mL). The organic layer was separated, re-extracting the aqueous layer with Et_2O (3 x 30 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (20 mL) then dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (Et_2O/pentane, 0:1→3:7) to give linalool oxide as a colourless oil (0.12 g, 0.7 mmol, 64%, 94 *ee*). The product was subjected to GC analysis (column: CP-Cyclodextrin-B-236-M-19 (50 m × 0.25 mm i.d., column temp., 100 °C (40-min hold) → 1 °C/min → 130 °C). Elution times: $t_{(2R,5R)\text{-enantiomer}}$ 38.55, $t_{(2S,5S)\text{-enantiomer}}$ 40.39 min. Physical and spectroscopic data were consistent with reported values.[103, 104]

$[\alpha]_D$	$[\alpha]_D = +7.6$ (*c* 0.6, $CHCl_3$, 22 °C) [Lit. +8.33 c 0.6, $CHCl_3$, 20 °C].[103, 104]
FT-IR (neat) ν_{max}	3448 (br), 2973 (s), 2873 (m), 1641 (w) cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 5.88 (1H, dd, *J* = 17.2 and 10.6 Hz, CH=), 5.19 (1H, dd, *J* = 17.2 and 1.7 Hz, =C$\underline{H}$H), 4.99 (1H, dd, *J* = 10.6 and 1.7 Hz, =CH$\underline{H}$), 3.80 (1H, t, *J* = 6.9 Hz, C$\underline{H}$O), 2.16 (1H, s, O$\underline{H}$), 1.95-1.68 (4H, m, C$\underline{H}_2$C$\underline{H}_2$), 1.32 (3H, s, C$\underline{H}_3$), 1.23 (3H, s, C$\underline{H}_3$), 1.14 (3H, s, C$\underline{H}_3$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 143.7 ($\underline{C}H_2$=), 111.3 ($\underline{C}$H=), 85.5 ($\underline{C}$HO), 83.0 ($\underline{C}$), 71.1 ($\underline{C}$), 37.5 ($\underline{C}H_2$), 27.2 ($\underline{C}H_2$), 26.8 ($\underline{C}H_3$), 26.3 ($\underline{C}H_3$), 24.2 ($\underline{C}H_3$).
LRMS (ES^+) *m/z*	193 ($[M+Na]^+$).
HRMS (ES^+) *m/z*	Calculated: 193.1204 found: 193.1199 ($[M+Na]^+$).

3.2.66- *rac*- Ethyl (1*R*,2*S*)-2-tritylcyclohexyl oxalate ((±)-2.99)

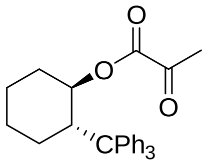


$C_{29}H_{30}O_4$

Mol. Wt.: 442.55 g/mol

Ethyl chloro oxoacetate (2.0 mL, 17.52 mmol) was added dropwise over 20 minutes to a stirred solution of (±)-triphenylmethylcyclohexanol (4.0 g, 11.68 mmol) in dry pyridine (35 mL). The mixture was stirred at rt overnight, then it was diluted with EtOAc (60 mL) and washed with 2M HCl (60 mL). The organic layer was separated, dried ($MgSO_4$) and EtOAc was removed *in vacuo*. Hexane (2 x 20 mL) was added to the crude and removed *in vacuo* to give the product as a white solid which was washed with hexane to give the pure product as a white powder (4.73 g, 10.69 mmol, 91%). **mp:** 155-157 °C; Spectroscopic data were consistent with reported values for **3.2.54**.

3.2.67- *rac*- (1*R*,2*S*)-2-Tritylcyclohexyl 2-oxopropanoate ((±)-2.103)



$C_{28}H_{28}O_3$

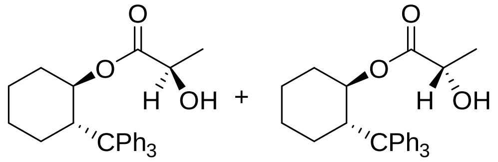
Mol. Wt.: 412.52 g/mol.

To a stirred solution of ester (±)-**2.99** (0.5 g, 1.1 mmol) in dry THF (10 mL) at –78 °C was added dropwise MeMgBr (0.37 mL, 3.0 M in Et_2O, 1.2 mmol). The mixture was stirred at –78 °C for 2 h, then it was quenched by addition of H_2O (10 mL) and NH_4Cl (10 mL, sat. aq.). Et_2O (20 mL) was added and the organic layer was separated. The aqueous layer was extracted with Et_2O (2 × 20 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent was removed *in vacuo* to give the crude ketone. Hexane (2 x 30 mL) was added and removed *in vacuo* to give the solid cude which was recrystalised from hexane/EtOAc to give the product as a white solid (0.17 g, 0.412 mmol, 36%). This compound exhibited broadening of some signals in its NMR spectra due to restricted rotation.

mp	130-133 °C.
FT-IR (neat) ν_{max}	3056 (w), 2936 (w), 1720 (s), 1595 (w) cm^{-1}.

^{1}H-NMR (300 MHz, CDCl$_3$)	δ 7.60-7.00 (15H, m, Ar<u>H</u>), 4.36 (1H, td, *J* = 10.3 and 4.0 Hz, C<u>H</u>OR), 3.61 (1H, m, C<u>H</u>CPh$_3$), 2.16 (1H, m, C<u>H</u>$_2$), 2.05-1.05 (5H, m, C<u>H</u>$_2$), 1.95 (3H, s, C<u>H</u>$_3$), 1.21 (1H, m, C<u>H</u>$_2$), 0.73 (1H, m, C<u>H</u>$_2$).
^{13}C-NMR (75 MHz, CDCl$_3$)	δ 192.0 (<u>C</u>=O), 160.1 (<u>C</u>=O), 129.6 (6<u>C</u>H$_{Ar}$, br), 127.5 (6<u>C</u>H$_{Ar}$), 125.7 (3<u>C</u>H$_{Ar}$), 77.8 (<u>C</u>HOR), 60.7 (<u>C</u>Ph$_3$), 46.3 (<u>C</u>HCPh$_3$), 33.0 (<u>C</u>H$_2$), 29.1 (<u>C</u>H$_2$), 26.4 (<u>C</u>H$_3$), 25.8 (<u>C</u>H$_3$), 24.7 (<u>C</u>H$_2$), (quaternary aromatic carbons signal not observed).
LRMS (ES$^+$) *m/z*	847 ([2M+Na]$^+$).

3.2.68- *rac*- (2*R*)-(1*R*,2*S*)-2-Tritylcyclohexyl 2-hydroxypropanoate and *rac*- (2*S*)-(1*R*,2*S*)-2-tritylcyclohexyl 2-hydroxypropanoate ((±)-2.104a/b)



$C_{28}H_{30}O_3$

Mol. Wt.: 414.54 g/mol.

To a stirred solution of ester (±)-**2.103** (0.1 g, 0.24 mmol) in dry THF (8 mL) at room temperature was added NaBH$_4$ (10.2 mg, 0.27 mmol). The mixture was stirred for 3.5 h then quenched with H$_2$O (5 mL). The organic layer was separated and the aqueous layer was extracted with Et$_2$O (2 × 20 mL). The combined organic phases were dried (MgSO$_4$), filtered and the solvent was removed *in vacuo* to give the crude. The crude was purified by column chromatography eluting with Et$_2$O/hexane from (hexane → 20 % Et$_2$O/hexane) to give the product as a white solid (69 mg, 0.166 mmol, 69%). This compound exhibited broadening of some signals in its NMR spectra due to restricted rotation. Spectroscopic data are reported for a mixture of diastereoisomers (3:1) estimated from ^{1}H-NMR data. Isomers are identified as maj and min where possible.

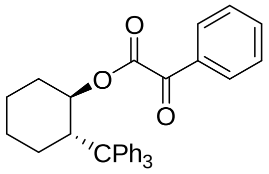
mp	120-123 °C.
FT-IR (neat) ν_{max}	3056 (w), 2936 (w), 1720 (s), 1595 (w) cm^{-1}.
^{1}H-NMR (300 MHz, CDCl$_3$)	δ 7.60-6.90 (15H, m, Ar<u>H</u>), 4.17$_{min}$ and 4.03$_{maj}$ (1H, td, *J* = 10.3 and 3.8 Hz, C<u>H</u>OR), 3.80$_{maj}$ and 3.33$_{min}$ (1H, m, C<u>H</u>OH), 3.60 (1H, m, C<u>H</u>CPh$_3$),

2.25_{min} and 1.92_{maj} (1H, d, J = 5.9 Hz, $\text{O}\underline{\text{H}}$), 2.16 (1H, m, $\text{C}\underline{\text{H}}_2$), 2.05 (1H, m, $\text{C}\underline{\text{H}}_2$), 1.78-1.63 (2H, m, $\text{C}\underline{\text{H}}_2$), 1.62-1.35 (2H, m, $\text{C}\underline{\text{H}}_2$), 1.22 (1H, m, $\text{C}\underline{\text{H}}_2$), 1.13_{min} and 0.88_{maj} (3H, d, J = 6.9 Hz, $\text{C}\underline{\text{H}}_3$), 0.75 (1H, m, $\text{C}\underline{\text{H}}_2$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.9_{min} and 173.5_{maj} ($\underline{\text{C}}$=O), 128.9 ($6\underline{\text{C}}\text{H}_{\text{Ar}}$), 127.3 ($6\underline{\text{C}}\text{H}_{\text{Ar}}$), 125.5 ($3\underline{\text{C}}\text{H}_{\text{Ar}}$), 77.2_{maj} and 76.8_{min} ($\underline{\text{C}}$HOR), 67.6 ($\underline{\text{C}}$HOH), 60.8 ($\underline{\text{C}}\text{Ph}_3$), 46.2_{min} and 46.0_{maj} ($\underline{\text{C}}\text{HCPh}_3$), 33.2_{min} and 33.0_{maj} ($\underline{\text{C}}\text{H}_2$), 28.9 ($\underline{\text{C}}\text{H}_2$), 26.0_{maj} and 25.9_{min} ($\underline{\text{C}}\text{H}_2$), 24.8_{maj} and 24.7_{min} ($\underline{\text{C}}\text{H}_2$), 20.0_{min} and 19.3_{maj} ($\underline{\text{C}}\text{H}_3$), (quaternary aromatic carbons signal not observed).

LRMS (ES$^+$) *m/z* 437 ([M+Na]$^+$).

3.2.69- *rac*- (1*R*,2*S*)-2-Tritylcyclohexyl 2-oxo-2-phenylacetate ((±)-2.106)



$C_{33}H_{30}O_3$

Mol. Wt.: 474.59 g/mol.

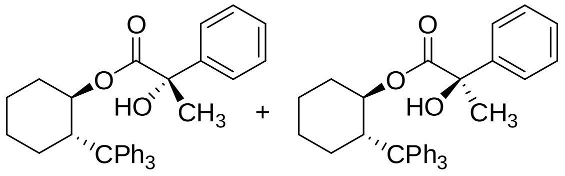
To a stirred solution of phenylglyoxalic acid (0.895 g, 5.84 mmol) in hexane (40 mL) was added DMF (0.45 mL, 5.84 mmol) and oxalyl chloride (2.47 mL, 27.74 mmol). The mixture was stirred for 1.5 h then it was filtered and the solvent and excess oxalyl chloride was removed *in vacuo* to give the acid chloride (0.984 g, 5.84 mmol).

To a stirred solution of (±)-triphenylmethylcyclohexanol (1.0 g, 2.92 mmol) in dry CH_2Cl_2 (40 mL) was added Et_3N (0.83 mL, 5.84 mmol) at – 40 °C. The mixure was stirred for 30 min then, DMAP (0.36 g, 2.92 mmol) was added followed by the acid chloride (0.984 g, 5.84 mmol). The mixture was stirred at room temperature overnight. The reaction was quenched with NH_4Cl (20 mL, sat. aq.) and the solvent was removed *in vacuo*. The crude was dissolved in Et_2O (40 mL), washed with 2 M HCl (30 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give the crude which was purified by column chromatography (SiO_2 eluting with Et_2O/hexane (hexane → 30%)) to give the product as a white powder (1.08 g, 2.28 mmol, 78%).

mp 80-84 °C.

FT-IR (neat) ν_{max}	3056 (w), 2939 (w), 1724 (s), 1688 (s), 1596 (w) cm^{-1}.
^{1}H-NMR (300 MHz, CDCl$_3$)	δ 7.80-7.72 (2H, m, Ar$\underline{\mathrm{H}}$), 7.64 (1H, m, Ar$\underline{\mathrm{H}}$), 7.52-7.44 (2H, m, Ar$\underline{\mathrm{H}}$), 7.44-6.60 (15H, m, Ar$\underline{\mathrm{H}}$), 4.41 (1H, td, J = 10.0 and 4.0 Hz, C$\underline{\mathrm{H}}$OR), 3.63 (1H, m, C$\underline{\mathrm{H}}$CPh$_3$), 2.24-2.10 (2H, m, C$\underline{\mathrm{H}}_2$), 1.83-1.65 (2H, m, C$\underline{\mathrm{H}}_2$), 1.45 (1H, m, C$\underline{\mathrm{H}}_2$), 1.33-1.18 (2H, m, C$\underline{\mathrm{H}}_2$), 0.78 (1H, m, C$\underline{\mathrm{H}}_2$).
^{13}C-NMR (75 MHz, CDCl$_3$)	δ 185.8 ($\underline{\mathrm{C}}$=O), 162.7 ($\underline{\mathrm{C}}$=O), 134.3 ($\underline{\mathrm{C}}$H$_{\mathrm{Ar}}$), 132.4 ($\underline{\mathrm{C}}_{\mathrm{Ar}}$), 129.8 (2$\underline{\mathrm{C}}H_{\mathrm{Ar}}$), 128.6 (8$\underline{\mathrm{C}}H_{\mathrm{Ar}}$, br), 127.1 (6$\underline{\mathrm{C}}H_{\mathrm{Ar}}$, br), 125.3 (3$\underline{\mathrm{C}}H_{\mathrm{Ar}}$), 77.9 ($\underline{\mathrm{C}}$HOR), 60.8 ($\underline{\mathrm{C}}Ph_3$), 45.9 ($\underline{\mathrm{C}}$HCPh$_3$), 32.9 ($\underline{\mathrm{C}}H_2$), 28.7 ($\underline{\mathrm{C}}H_2$), 25.7 ($\underline{\mathrm{C}}H_2$), 24.5 ($\underline{\mathrm{C}}H_2$), (the signal of quaternary aromatic carbons of trityl group was not observed).
LRMS (ES$^+$) *m/z*	497 ([M+Na]$^+$).

3.2.70- *rac*- (2*S*)-(1*R*,2*S*)-2-Tritylcyclohexyl 2-hydroxy-2-phenylpropanoate and *rac*- (2*R*)-(1*R*,2*S*)-2-tritylcyclohexyl 2-hydroxy-2-phenylpropanoate ((±)-2.107a/b)



$C_{34}H_{34}O_3$

Mol. Wt.: 490.63 g/mol.

To a stirred solution of ester (±)-**2.106** (0.365 g, 0.769 mmol) in dry THF (10 mL) at –78 °C was added MeMgBr (0.26 mL, 0.769 mmol). The mixture was stirred at –78 °C for 3 h then quenched with NH_4Cl (sat. aq., 10 mL) and H_2O (10 mL). The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was removed *in vacuo* to give the crude which was purified by column chromatography eluting with Et_2O/hexane (hexane → 40% Et_2O/hexane) to give the product as a viscous oil (0.34 g, 0.69 mmol, 90%). Spectroscopic data are reported for a mixture of diastereoisomers (7:1) estimated from ^{1}H-NMR data.

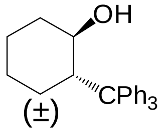
FT-IR (neat) ν_{max}	3527 (br), 2940 (w), 1732 (s), 1594 (w), 1492 (w) cm^{-1}.
^{1}H-NMR (300 MHz, CDCl$_3$)	δ 7.55-6.90 (20H, m, Ar$\underline{\mathrm{H}}$), 3.84 (1H, td, J = 10.2 and 3.8 Hz, C$\underline{\mathrm{H}}$OR), 3.50 (1H, m, C$\underline{\mathrm{H}}$CPh$_3$), 2.13 (1H, m, C$\underline{\mathrm{H}}_2$), 1.95 (1H, m, C$\underline{\mathrm{H}}_2$), 1.90 (1H, s, CO$\underline{\mathrm{H}}$), 1.71-1.61 (2H, m, C$\underline{\mathrm{H}}_2$), 1.55$_{\mathrm{min}}$ and 1.51$_{\mathrm{maj}}$ (3H, s, C$\underline{\mathrm{H}}_3$), 1.42-

	1.13 (4H, m, $C\underline{H}_2$), 0.89 (1H, m, $C\underline{H}_2$).
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 172.1 ($\underline{C}$=O), 143.6 ($\underline{C}_{Ar}$), 131.4 (6$\underline{C}H_{Ar}$), 128.2 (2$\underline{C}H_{Ar}$), 127.9 (6$\underline{C}H_{Ar}$), 127.4 (2$\underline{C}H_{Ar}$), 125.5 (3$\underline{C}H_{Ar}$, br), 124.2 ($\underline{C}H_{Ar}$), 77.8 ($\underline{C}$HOR), 77.2 (C), 60.8 ($\underline{C}Ph_3$), 45.9 ($\underline{C}HCPh_3$), 32.1 ($\underline{C}H_2$), 28.7 ($\underline{C}H_2$), 26.6 ($\underline{C}H_3$), 26.1 ($\underline{C}H_2$), 24.7 ($\underline{C}H_2$), (the signal of quaternary aromatic carbons of trityl group was not observed).
LRMS (ES^+) *m/z*	513 ($[M+Na]^+$).

CHAPTER 4: Appendix: X-ray structure data

X-ray: Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 S**tructure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). S**tructure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

(±)-2-*trans*-tritylcyclohexanol (2.10)



Empirical formula	$C_{25}H_{26}O$	
Formula weight	342.46	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 15.0277(2) Å	
	b = 14.2349(2) Å	β = 95.9030(10)°
	c = 17.7826(3) Å	
Volume	3783.84(10) Å^3	
Z	8 (4 molecules)	
Density (calculated)	1.202 Mg / m^3	
Absorption coefficient	0.071 mm^{-1}	
F(000)	1472	
Crystal	Fragment; Colourless	
Crystal size	0.14 × 0.1 × 0.04 mm^3	
θ range for data collection	2.93 – 27.48°	
Index ranges	$-19 \le h \le 19$, $-18 \le k \le 18$, $-23 \le l \le 23$	
Reflections collected	50004	
Independent reflections	8995 [R_{int} = 0.0800]	
Completeness to θ = 27.48°	99.5 %	
Absorption correction	Semi–empirical from equivalents	

Max. and min. transmission	0.9972 and 0.9801
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8995 / 1 / 943
Goodness-of-fit on F^2	1.093
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0978$, $wR2 = 0.2067$
R indices (all data)	$R1 = 0.1456$, $wR2 = 0.2337$
Largest diff. peak and hole	0.473 and –0.325 e Å^{-3}

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
O1	11637(3)	10971(4)	–299(3)	32(1)	1
C1	10777(5)	11337(6)	–553(4)	26(2)	1
C2	10670(6)	11437(6)	–1403(4)	30(2)	1
C3	9781(6)	11847(6)	–1700(5)	33(2)	1
C4	9031(6)	11244(6)	–1445(5)	32(2)	1
C5	9140(5)	11116(6)	–591(4)	24(2)	1
C6	10035(5)	10685(5)	–306(4)	21(2)	1
C7	10112(5)	10472(5)	576(4)	19(1)	1
C8	10917(4)	9840(6)	857(4)	22(2)	1
C9	11214(6)	9820(6)	1634(5)	30(2)	1
C10	11854(6)	9187(7)	1921(5)	37(2)	1
C11	12206(5)	8532(6)	1456(5)	33(2)	1
C12	11908(5)	8542(6)	688(5)	29(2)	1
C13	11264(4)	9172(5)	404(4)	19(1)	1
C14	10137(5)	11435(6)	984(4)	23(2)	1
C15	10933(6)	11894(6)	1187(4)	28(2)	1
C16	10973(7)	12792(6)	1513(5)	35(2)	1
C17	10171(7)	13239(7)	1630(5)	43(2)	1
C18	9370(6)	12812(6)	1414(4)	32(2)	1
C19	9344(6)	11905(6)	1090(4)	28(2)	1
C20	9314(4)	9859(5)	771(4)	19(1)	1
C21	9015(5)	9889(6)	1490(4)	23(2)	1
C22	8357(5)	9293(6)	1711(5)	33(2)	1
C23	8010(5)	8614(6)	1200(5)	28(2)	1
C24	8304(5)	8532(6)	501(5)	29(2)	1
C25	8951(5)	9155(5)	308(4)	21(2)	1
O2	3315(3)	12041(4)	–343(3)	31(1)	1
C26	5813(4)	11855(5)	–431(4)	21(2)	1
C27	5794(5)	11759(6)	–1286(4)	25(2)	1
C28	4996(6)	11231(6)	–1621(5)	35(2)	1
C29	4137(6)	11656(6)	–1370(4)	31(2)	1
C30	4170(5)	11723(6)	–521(4)	26(2)	1
C31	4965(5)	12334(5)	–196(4)	20(2)	1
C32	5025(4)	12533(5)	684(4)	18(1)	1

C33	5861(4)	13120(5)	949(4)	18(1)	1
C34	6233(5)	13098(6)	1716(4)	28(2)	1
C35	6929(6)	13663(6)	1972(5)	37(2)	1
C36	7282(5)	14327(6)	1491(5)	34(2)	1
C37	6905(6)	14374(6)	754(5)	35(2)	1
C38	6225(5)	13800(6)	493(4)	26(2)	1
C39	5045(5)	11560(5)	1068(4)	23(2)	1
C40	5850(6)	11074(6)	1246(4)	33(2)	1
C41	5856(9)	10149(7)	1534(5)	50(3)	1
C42	5044(9)	9717(7)	1639(5)	51(3)	1
C43	4282(8)	10170(8)	1457(5)	50(3)	1
C44	4240(6)	11100(6)	1181(5)	34(2)	1
C45	4266(4)	13169(5)	889(4)	18(1)	1
C46	3956(5)	13118(7)	1612(4)	29(2)	1
C47	3303(5)	13734(7)	1830(5)	37(2)	1
C48	2939(5)	14406(7)	1330(5)	33(2)	1
C49	3271(5)	14507(6)	630(5)	31(2)	1
C50	3909(5)	13900(5)	431(4)	21(2)	1
O3	1721(3)	7926(4)	4882(3)	31(1)	1
C51	873(5)	8262(5)	4575(4)	22(2)	1
C52	839(5)	8303(7)	3704(5)	31(2)	1
C53	−70(5)	8691(7)	3350(4)	30(2)	1
C54	−840(5)	8119(6)	3606(4)	29(2)	1
C55	−766(5)	8057(6)	4474(4)	28(2)	1
C56	119(5)	7638(5)	4807(4)	22(2)	1
C57	155(5)	7443(5)	5695(4)	24(2)	1
C58	961(5)	6833(6)	6019(4)	24(2)	1
C59	1270(5)	6113(6)	5587(5)	31(2)	1
C60	1939(5)	5495(6)	5896(5)	28(2)	1
C61	2290(5)	5616(6)	6648(5)	32(2)	1
C62	1973(5)	6304(7)	7080(4)	34(2)	1
C63	1306(5)	6910(6)	6767(5)	32(2)	1
C64	132(5)	8425(6)	6069(4)	26(2)	1
C65	915(6)	8930(7)	6270(5)	33(2)	1
C66	894(7)	9827(7)	6551(5)	39(2)	1
C67	117(8)	10266(7)	6625(5)	47(3)	1
C68	−714(7)	9791(7)	6434(5)	41(2)	1
C69	−664(6)	8896(6)	6132(4)	29(2)	1
C70	−635(5)	6837(6)	5888(4)	25(2)	1
C71	−970(5)	6900(6)	6582(5)	30(2)	1
C72	−1648(5)	6311(7)	6767(4)	31(2)	1
C73	−2016(5)	5634(6)	6265(4)	28(2)	1
C74	−1676(5)	5558(5)	5577(4)	24(2)	1
C75	−991(5)	6142(5)	5372(4)	24(2)	1
O4	−3255(3)	3991(4)	5442(3)	32(1)	1
C76	−4107(5)	3647(5)	5600(4)	25(2)	1
C77	−4079(6)	3524(6)	6465(4)	33(2)	1
C78	−4908(6)	3053(7)	6683(5)	36(2)	1

C79	–5738(6)	3625(6)	6385(5)	33(2)	1
C80	–5740(6)	3764(6)	5524(4)	27(2)	1
C81	–4915(5)	4255(6)	5294(4)	24(2)	1
C82	–4981(5)	4473(5)	4426(4)	23(2)	1
C83	–4221(5)	5118(5)	4189(4)	23(2)	1
C84	–3898(5)	5049(6)	3479(4)	28(2)	1
C85	–3289(5)	5695(7)	3288(4)	30(2)	1
C86	–2951(6)	6399(6)	3751(5)	33(2)	1
C87	–3275(5)	6467(6)	4464(5)	29(2)	1
C88	–3910(5)	5854(6)	4684(5)	28(2)	1
C89	–5038(5)	3514(5)	4008(4)	24(2)	1
C90	–4250(6)	3010(6)	3896(4)	30(2)	1
C91	–4277(7)	2125(7)	3584(5)	37(2)	1
C92	–5110(7)	1704(6)	3366(4)	39(2)	1
C93	–5877(6)	2180(6)	3490(5)	34(2)	1
C94	–5850(6)	3070(6)	3799(4)	30(2)	1
C95	–5807(5)	5097(5)	4168(4)	22(2)	1
C96	–6114(5)	5163(6)	3392(4)	26(2)	1
C97	–6792(5)	5785(6)	3136(5)	29(2)	1
C98	–7193(5)	6336(6)	3654(5)	34(2)	1
C99	–6903(5)	6300(6)	4406(5)	31(2)	1
C100	–6206(5)	5684(6)	4673(5)	32(2)	1

Table 3. Bond lengths [Å] and angles [°].

O1–C1	1.423(9)	C16–C17	1.397(14)
C1–C2	1.511(10)	C17–C18	1.367(13)
C1–C6	1.548(10)	C18–C19	1.413(12)
C2–C3	1.503(12)	C20–C25	1.373(10)
C3–C4	1.523(12)	C20–C21	1.398(10)
C4–C5	1.522(10)	C21–C22	1.390(11)
C5–C6	1.518(10)	C22–C23	1.391(12)
C6–C7	1.591(9)	C23–C24	1.366(11)
C7–C8	1.548(10)	C24–C25	1.385(11)
C7–C14	1.550(10)	O2–C30	1.429(9)
C7–C20	1.552(10)	C26–C27	1.523(9)
C8–C13	1.383(10)	C26–C31	1.540(9)
C8–C9	1.407(11)	C27–C28	1.487(12)
C9–C10	1.378(12)	C28–C29	1.532(12)
C10–C11	1.387(12)	C29–C30	1.509(10)
C11–C12	1.393(12)	C30–C31	1.542(10)
C12–C13	1.376(11)	C31–C32	1.582(9)
C14–C15	1.378(11)	C32–C45	1.530(10)
C14–C19	1.396(11)	C32–C39	1.542(10)
C15–C16	1.404(12)	C32–C33	1.542(9)

C33–C38	1.410(10)
C33–C34	1.420(10)
C34–C35	1.359(11)
C35–C36	1.415(13)
C36–C37	1.375(13)
C37–C38	1.353(11)
C39–C40	1.402(12)
C39–C44	1.409(11)
C40–C41	1.413(13)
C41–C42	1.397(16)
C42–C43	1.325(16)
C43–C44	1.411(14)
C45–C50	1.395(10)
C45–C46	1.413(10)
C46–C47	1.399(12)
C47–C48	1.381(13)
C48–C49	1.395(12)
C49–C50	1.364(11)
O3–C51	1.417(9)
C51–C56	1.530(10)
C51–C52	1.545(10)
C52–C53	1.546(11)
C53–C54	1.521(11)
C54–C55	1.540(11)
C55–C56	1.521(10)
C56–C57	1.598(10)
C57–C70	1.536(10)
C57–C58	1.552(10)
C57–C64	1.551(11)
C58–C63	1.381(11)
C58–C59	1.389(11)
C59–C60	1.404(11)
C60–C61	1.396(12)
C61–C62	1.361(13)
C62–C63	1.395(12)
C64–C69	1.386(12)
C64–C65	1.393(11)
C65–C66	1.372(13)
C66–C67	1.343(15)
C67–C68	1.430(14)
C68–C69	1.388(12)
C70–C71	1.382(11)
C70–C75	1.417(11)
C71–C72	1.385(11)
C72–C73	1.390(11)
C73–C74	1.378(11)
C74–C75	1.400(10)
O4–C76	1.426(9)
C76–C77	1.543(10)
C76–C81	1.544(10)
C77–C78	1.500(12)
C78–C79	1.537(13)
C79–C80	1.544(10)
C80–C81	1.516(11)
C81–C82	1.567(10)
C82–C89	1.552(11)
C82–C95	1.556(10)
C82–C83	1.557(10)
C83–C84	1.403(11)
C83–C88	1.416(11)
C84–C85	1.364(12)
C85–C86	1.361(12)
C86–C87	1.407(11)
C87–C88	1.379(11)
C89–C94	1.392(11)
C89–C90	1.416(11)
C90–C91	1.376(13)
C91–C92	1.405(14)
C92–C93	1.374(13)
C93–C94	1.379(12)
C95–C100	1.405(11)
C95–C96	1.412(10)
C96–C97	1.392(11)
C97–C98	1.392(12)
C98–C99	1.365(12)
C99–C100	1.410(11)

O1–C1–C2	110.6(6)
O1–C1–C6	110.4(6)
C2–C1–C6	109.5(7)
C3–C2–C1	112.8(6)
C2–C3–C4	109.6(7)
C5–C4–C3	111.0(7)
C6–C5–C4	112.5(6)
C5–C6–C1	107.6(6)
C5–C6–C1	107.6(6)
C5–C6–C7	112.2(5)
C1–C6–C7	114.3(6)
C8–C7–C14	112.5(6)
C8–C7–C20	101.4(6)
C14–C7–C20	112.1(6)
C8–C7–C6	113.8(5)

C14–C7–C6	106.8(6)	C34–C35–C36	121.1(8)
C20–C7–C6	110.3(6)	C37–C36–C35	117.7(8)
C13–C8–C9	117.2(7)	C38–C37–C36	121.4(8)
C13–C8–C7	122.7(7)	C37–C38–C33	122.8(8)
C9–C8–C7	119.2(7)	C40–C39–C44	118.2(8)
C10–C9–C8	121.1(8)	C40–C39–C32	121.3(7)
C9–C10–C11	120.9(8)	C44–C39–C32	120.2(7)
C10–C11–C12	118.3(8)	C39–C40–C41	121.0(9)
C13–C12–C11	120.6(8)	C42–C41–C40	119.1(10)
C12–C13–C8	121.9(7)	C43–C42–C41	119.9(10)
C15–C14–C19	117.9(8)	C42–C43–C44	123.3(10)
C15–C14–C7	121.3(7)	C39–C44–C43	118.5(9)
C19–C14–C7	120.5(7)	C50–C45–C46	115.3(7)
C14–C15–C16	122.6(9)	C50–C45–C32	123.6(6)
C17–C16–C15	118.4(9)	C46–C45–C32	120.7(7)
C18–C17–C16	120.3(9)	C47–C46–C45	121.8(8)
C17–C18–C19	120.5(8)	C48–C47–C46	119.9(8)
C14–C19–C18	120.3(8)	C47–C48–C49	119.5(8)
C25–C20–C21	115.2(7)	C50–C49–C48	119.5(8)
C25–C20–C7	123.1(6)	C49–C50–C45	124.0(7)
C21–C20–C7	120.9(6)	O3–C51–C56	111.2(6)
C22–C21–C20	123.0(7)	O3–C51–C52	109.6(6)
C21–C22–C23	118.0(7)	C56–C51–C52	110.1(6)
C24–C23–C22	121.2(7)	C51–C52–C53	111.0(6)
C23–C24–C25	118.2(7)	C54–C53–C52	110.7(7)
C20–C25–C24	124.3(7)	C53–C54–C55	110.6(7)
C27–C26–C31	112.4(6)	C56–C55–C54	112.5(6)
C28–C27–C26	112.1(6)	C55–C56–C51	108.0(6)
C27–C28–C29	110.7(7)	C55–C56–C57	113.1(6)
C30–C29–C28	112.0(6)	C51–C56–C57	114.7(6)
O2–C30–C29	107.7(6)	C70–C57–C58	101.2(6)
O2–C30–C31	114.7(6)	C70–C57–C64	111.0(6)
C29–C30–C31	110.9(6)	C58–C57–C64	113.3(6)
C26–C31–C30	106.1(6)	C70–C57–C56	111.7(6)
C26–C31–C32	112.6(6)	C58–C57–C56	114.2(6)
C30–C31–C32	115.7(6)	C64–C57–C56	105.5(6)
C45–C32–C39	114.0(6)	C63–C58–C59	118.5(7)
C45–C32–C33	102.1(5)	C63–C58–C57	121.0(7)
C39–C32–C33	111.9(6)	C59–C58–C57	120.0(7)
C45–C32–C31	112.0(6)	C58–C59–C60	120.8(8)
C39–C32–C31	105.9(6)	C61–C60–C59	118.9(8)
C33–C32–C31	111.1(6)	C62–C61–C60	120.6(8)
C38–C33–C34	115.5(7)	C61–C62–C63	120.0(8)
C38–C33–C32	123.3(6)	C58–C63–C62	121.2(8)
C34–C33–C32	120.7(6)	C69–C64–C65	116.3(8)
C35–C34–C33	121.4(8)	C69–C64–C57	121.9(7)

C65–C64–C57	121.3(7)
C66–C65–C64	121.6(9)
C67–C66–C65	121.4(10)
C66–C67–C68	120.3(9)
C69–C68–C67	116.5(9)
C64–C69–C68	123.8(9)
C71–C70–C75	118.5(7)
C71–C70–C57	121.6(7)
C75–C70–C57	119.7(7)
C70–C71–C72	121.1(8)
C71–C72–C73	121.4(7)
C74–C73–C72	117.7(7)
C73–C74–C75	122.4(7)
C74–C75–C70	118.9(7)
O4–C76–C77	107.6(6)
O4–C76–C81	115.3(6)
C77–C76–C81	110.8(6)
C78–C77–C76	111.7(7)
C77–C78–C79	109.9(7)
C78–C79–C80	109.2(7)
C81–C80–C79	114.1(7)
C80–C81–C76	106.4(6)
C80–C81–C82	112.7(6)
C76–C81–C82	115.3(6)
C89–C82–C95	111.0(6)
C89–C82–C83	113.2(6)
C95–C82–C83	99.7(6)
C89–C82–C81	107.0(6)
C95–C82–C81	111.8(6)
C83–C82–C81	114.1(6)
C84–C83–C88	119.2(7)
C84–C83–C82	122.3(7)
C88–C83–C82	118.2(7)
C85–C84–C83	118.7(8)
C86–C85–C84	124.3(7)
C85–C86–C87	117.0(8)
C88–C87–C86	121.6(8)
C87–C88–C83	119.1(7)
C94–C89–C90	117.1(8)
C94–C89–C82	122.1(7)
C90–C89–C82	120.6(7)
C91–C90–C89	122.1(9)
C90–C91–C92	119.3(9)
C93–C92–C91	118.9(8)
C92–C93–C94	121.8(9)
C93–C94–C89	120.8(8)
C100–C95–C96	117.8(7)
C100–C95–C82	122.1(7)
C96–C95–C82	119.8(6)
C97–C96–C95	121.1(7)
C98–C97–C96	119.6(8)
C99–C98–C97	120.7(8)
C98–C99–C100	120.3(8)
C95–C100–C99	120.4(8)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O1	28(3)	25(3)	45(3)	1(2)	12(2)	0(2)
C1	22(4)	28(4)	29(4)	6(3)	6(3)	−1(3)
C2	45(5)	27(4)	20(4)	2(3)	16(3)	0(4)
C3	54(5)	19(4)	26(4)	−1(3)	8(4)	14(4)
C4	41(5)	22(4)	29(4)	6(3)	−8(3)	−4(3)
C5	16(3)	29(4)	28(4)	−4(3)	5(3)	6(3)
C6	28(4)	16(3)	19(3)	−5(3)	11(3)	4(3)
C7	20(3)	16(3)	20(3)	−1(3)	3(3)	1(3)
C8	13(3)	24(4)	28(4)	6(3)	5(3)	0(3)
C9	35(4)	23(4)	31(4)	0(3)	5(3)	3(3)
C10	36(5)	42(5)	33(4)	7(4)	0(4)	6(4)
C11	23(4)	26(4)	49(5)	10(4)	−1(3)	2(3)
C12	25(4)	19(4)	45(5)	3(3)	11(3)	−1(3)

C13	15(3)	16(3)	26(4)	−2(3)	2(3)	−5(3)
C14	33(4)	23(4)	13(3)	−5(3)	5(3)	0(3)
C15	45(5)	21(4)	19(4)	7(3)	4(3)	−8(4)
C16	53(5)	28(4)	25(4)	1(3)	2(4)	−17(4)
C17	72(7)	20(4)	38(5)	1(4)	10(5)	−4(4)
C18	53(5)	23(4)	23(4)	3(3)	16(4)	16(4)
C19	32(4)	26(4)	26(4)	2(3)	5(3)	6(3)
C20	15(3)	18(3)	25(4)	1(3)	6(3)	2(3)
C21	24(3)	24(4)	21(3)	1(3)	0(3)	−6(3)
C22	33(4)	34(5)	32(4)	6(4)	8(3)	−8(4)
C23	20(4)	25(4)	38(4)	9(3)	1(3)	−4(3)
C24	33(4)	17(4)	36(4)	−4(3)	−1(3)	8(3)
C25	23(3)	18(3)	22(4)	0(3)	−2(3)	6(3)
O2	27(3)	27(3)	40(3)	−4(2)	6(2)	−1(2)
C26	15(3)	23(4)	25(4)	7(3)	6(3)	1(3)
C27	39(4)	21(4)	14(3)	−9(3)	8(3)	8(3)
C28	57(6)	24(4)	24(4)	−3(3)	7(4)	−1(4)
C29	37(4)	27(4)	25(4)	3(3)	−10(3)	3(3)
C30	23(4)	30(4)	23(3)	−3(3)	−3(3)	4(3)
C31	26(3)	21(4)	15(3)	−1(3)	6(3)	4(3)
C32	20(3)	17(3)	15(3)	−1(3)	−2(3)	−7(3)
C33	17(3)	22(4)	15(3)	−3(3)	2(2)	7(3)
C34	28(4)	31(4)	24(4)	−1(3)	2(3)	2(3)
C35	35(4)	38(5)	35(4)	−12(4)	−12(3)	−6(4)
C36	22(4)	26(4)	54(5)	−14(4)	7(4)	−3(3)
C37	35(4)	21(4)	51(5)	−3(4)	18(4)	−7(3)
C38	28(4)	25(4)	26(4)	−2(3)	12(3)	−4(3)
C39	33(4)	21(4)	14(3)	−1(3)	−1(3)	−7(3)
C40	55(5)	22(4)	22(4)	−2(3)	0(4)	−1(4)
C41	95(9)	29(5)	25(4)	1(4)	2(5)	19(6)
C42	93(9)	29(5)	31(5)	6(4)	5(5)	0(6)
C43	81(8)	43(6)	26(5)	1(4)	8(5)	−28(6)
C44	45(5)	30(5)	26(4)	2(3)	6(3)	−8(4)
C45	16(3)	17(3)	22(3)	−6(3)	3(3)	−7(3)
C46	30(4)	43(5)	14(3)	−2(3)	1(3)	4(4)
C47	26(4)	52(6)	34(4)	−13(4)	2(3)	2(4)
C48	18(4)	45(5)	34(4)	−21(4)	−2(3)	4(4)
C49	27(4)	18(4)	45(5)	−5(3)	−7(3)	2(3)
C50	21(3)	20(3)	23(3)	−3(3)	4(3)	−1(3)
O3	29(3)	30(3)	36(3)	5(2)	6(2)	−3(2)
C51	30(4)	14(3)	22(3)	−3(3)	1(3)	0(3)
C52	26(4)	38(5)	31(4)	−9(4)	10(3)	0(4)
C53	29(4)	40(5)	22(4)	0(3)	3(3)	−3(4)
C54	26(4)	37(5)	24(4)	−4(3)	7(3)	3(3)
C55	28(4)	25(4)	30(4)	4(3)	2(3)	2(3)
C56	20(3)	22(4)	23(4)	−2(3)	−6(3)	7(3)

C57	25(4)	22(4)	27(4)	−4(3)	8(3)	−3(3)
C58	25(4)	22(4)	25(4)	5(3)	−2(3)	4(3)
C59	31(4)	26(4)	36(4)	−1(3)	0(3)	−1(3)
C60	25(4)	26(4)	34(4)	10(3)	7(3)	2(3)
C61	19(3)	39(5)	39(4)	12(4)	2(3)	6(3)
C62	30(4)	51(5)	21(4)	11(4)	−1(3)	−4(4)
C63	34(4)	32(4)	29(4)	2(4)	4(3)	3(4)
C64	36(4)	21(4)	21(4)	0(3)	5(3)	−8(3)
C65	35(4)	39(5)	25(4)	−4(4)	4(3)	−9(4)
C66	59(6)	29(5)	29(4)	−3(4)	8(4)	−5(5)
C67	94(8)	23(4)	21(4)	1(3)	−4(5)	−8(5)
C68	61(6)	25(5)	35(5)	−1(4)	−1(4)	13(5)
C69	41(4)	24(4)	22(4)	−4(3)	6(3)	4(4)
C70	25(4)	24(4)	25(4)	−3(3)	−4(3)	−1(3)
C71	22(4)	28(4)	38(4)	−3(4)	−3(3)	1(3)
C72	28(4)	46(5)	20(4)	2(3)	9(3)	−2(4)
C73	27(4)	25(4)	31(4)	−1(3)	−1(3)	−4(3)
C74	26(4)	20(4)	24(4)	−1(3)	−2(3)	3(3)
C75	23(4)	19(4)	29(4)	4(3)	4(3)	1(3)
O4	31(3)	31(3)	32(3)	−1(2)	−4(2)	1(2)
C76	33(4)	20(4)	21(3)	−2(3)	−1(3)	4(3)
C77	46(5)	34(4)	17(4)	1(3)	4(3)	13(4)
C78	54(5)	34(5)	21(4)	4(4)	5(4)	−6(4)
C79	41(5)	27(4)	32(4)	−4(3)	8(4)	−4(4)
C80	39(4)	26(4)	15(3)	−2(3)	5(3)	2(3)
C81	28(4)	22(4)	22(4)	2(3)	−7(3)	−2(3)
C82	20(3)	23(4)	26(4)	1(3)	5(3)	−1(3)
C83	26(4)	22(4)	21(4)	7(3)	1(3)	−1(3)
C84	33(4)	24(4)	28(4)	−2(3)	3(3)	3(3)
C85	27(4)	45(5)	20(4)	9(3)	6(3)	4(4)
C86	32(4)	27(4)	40(5)	7(4)	8(4)	−2(4)
C87	18(3)	35(5)	33(4)	2(4)	−5(3)	1(3)
C88	29(4)	24(4)	31(4)	1(3)	1(3)	2(3)
C89	36(4)	13(3)	24(4)	2(3)	1(3)	1(3)
C90	42(5)	33(4)	15(3)	3(3)	2(3)	5(4)
C91	50(5)	33(5)	28(4)	5(4)	3(4)	13(4)
C92	79(7)	23(4)	13(4)	−1(3)	−1(4)	7(4)
C93	48(5)	28(4)	24(4)	3(3)	−3(4)	−13(4)
C94	37(4)	29(4)	24(4)	−8(3)	5(3)	−4(4)
C95	25(4)	13(3)	27(4)	−4(3)	5(3)	−3(3)
C96	26(4)	30(4)	22(4)	1(3)	5(3)	5(3)
C97	22(4)	34(4)	32(4)	7(3)	2(3)	−2(3)
C98	27(4)	29(4)	46(5)	8(4)	10(3)	4(3)
C99	27(4)	26(4)	41(5)	−6(3)	11(3)	1(3)
C100	32(4)	32(4)	31(4)	0(3)	4(3)	8(4)

Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1	12027	11385	–342	48	1
H1A	10713	11971	–321	31	1
H2A	11153	11844	–1557	36	1
H2B	10735	10811	–1634	36	1
H3A	9733	11870	–2260	39	1
H3B	9731	12495	–1509	39	1
H4A	8448	11546	–1601	38	1
H4B	9034	10621	–1693	38	1
H5A	9082	11734	–346	29	1
H5B	8654	10707	–444	29	1
H6	10084	10071	–573	25	1
H9	10968	10249	1965	35	1
H10	12057	9199	2445	45	1
H11	12640	8088	1655	40	1
H12	12151	8109	357	35	1
H13	11051	9147	–117	23	1
H15	11477	11589	1102	34	1
H16	11532	13090	1651	42	1
H17	10182	13841	1861	52	1
H18	8827	13128	1483	39	1
H19	8784	11614	943	33	1
H21	9274	10337	1843	28	1
H22	8151	9347	2197	39	1
H23	7559	8199	1339	34	1
H24	8071	8061	157	35	1
H25	9158	9091	–177	25	1
H2	3375	12549	–102	47	1
H26A	6344	12226	–237	25	1
H26B	5870	11223	–198	25	1
H27A	5794	12392	–1515	30	1
H27B	6342	11430	–1407	30	1
H28A	5045	10566	–1460	42	1
H28B	4970	11250	–2179	42	1
H29A	4048	12291	–1592	37	1
H29B	3620	11263	–1565	37	1
H30	4265	11075	–311	31	1
H31	4909	12955	–459	24	1
H34	5991	12679	2058	33	1
H35	7181	13611	2482	45	1
H36	7764	14727	1671	41	1
H37	7127	14819	421	42	1
H38	5982	13859	–20	31	1
H40	6401	11372	1173	40	1

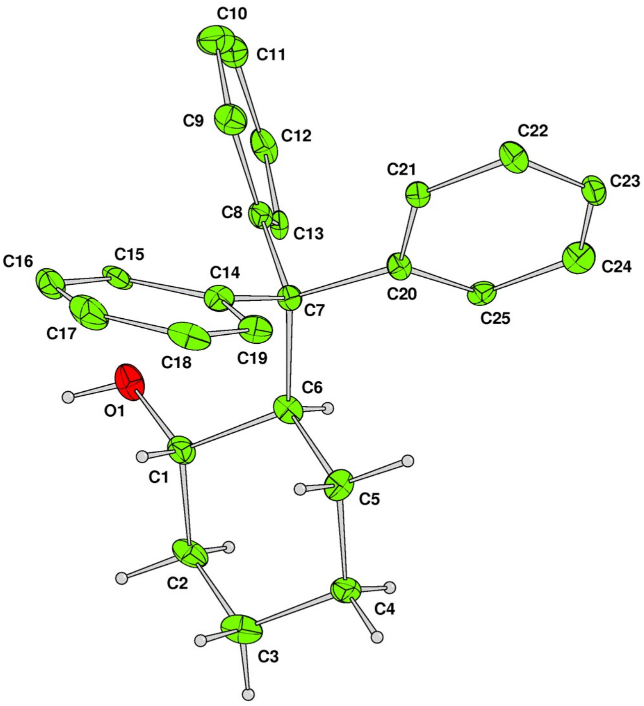
H41	6405	9825	1653	60	1
H42	5038	9099	1841	61	1
H43	3737	9852	1514	60	1
H44	3680	11409	1075	40	1
H46	4196	12654	1959	35	1
H47	3112	13689	2322	45	1
H48	2467	14797	1462	39	1
H49	3054	14995	295	37	1
H50	4122	13980	−50	26	1
H3	2124	8265	4731	47	1
H51	788	8911	4769	27	1
H52A	931	7665	3504	37	1
H52B	1327	8711	3560	37	1
H53A	−132	9355	3502	37	1
H53B	−93	8669	2792	37	1
H54A	−829	7479	3389	34	1
H54B	−1415	8417	3417	34	1
H55A	−830	8694	4685	33	1
H55B	−1262	7666	4626	33	1
H56	180	7015	4557	26	1
H59	1026	6038	5076	37	1
H60	2148	5004	5599	34	1
H61	2755	5214	6859	39	1
H62	2207	6371	7594	41	1
H63	1084	7385	7074	38	1
H65	1476	8647	6212	40	1
H66	1442	10144	6696	47	1
H67	120	10894	6805	56	1
H68	−1270	10074	6509	49	1
H69	−1207	8587	5959	34	1
H71	−731	7355	6938	35	1
H72	−1866	6372	7248	37	1
H73	−2486	5237	6392	34	1
H74	−1914	5093	5230	29	1
H75	−769	6074	4893	28	1
H4	−3325	4464	5160	48	1
H76	−4188	3010	5366	30	1
H77A	−3550	3143	6649	39	1
H77B	−4016	4147	6711	39	1
H78A	−4877	3002	7240	44	1
H78B	−4952	2411	6469	44	1
H79A	−5728	4244	6640	40	1
H79B	−6287	3289	6494	40	1
H80A	−5792	3142	5275	32	1
H80B	−6274	4135	5336	32	1
H81	−4862	4870	5567	29	1
H84	−4099	4563	3137	34	1

H85	−3087	5650	2801	36	1
H86	−2517	6824	3600	39	1
H87	−3050	6948	4803	35	1
H88	−4136	5925	5160	34	1
H90	−3685	3292	4040	36	1
H91	−3738	1801	3516	44	1
H92	−5142	1101	3137	47	1
H93	−6440	1889	3360	41	1
H94	−6394	3383	3869	36	1
H96	−5853	4776	3039	31	1
H97	−6981	5834	2611	35	1
H98	−7674	6741	3481	40	1
H99	−7171	6693	4751	37	1
H100	−6005	5666	5197	38	1

Table 6. Hydrogen bonds [Å and °].

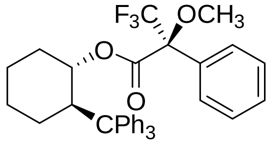
D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*D*H*A*)
O1–H1···O2^{i}	0.84	2.15	2.953(7)	160.3
O3–H3···O4^{ii}	0.84	2.04	2.866(7)	168.3

Symmetry transformations used to generate equivalent atoms:
(i) x+1,y,z (ii) −x,y+1/2,−z+1



Thermal ellipsoids drawn at the 35% probability level, aromatic hydrogen atoms omitted for clarity, other molecules in the asymmetric unit labelled in a similar fashion.

(2S)-(1S,2R)-2-tritylcyclohexyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 2.76



Empirical formula	$C_{35}H_{33}F_3O_3$
Formula weight	558.61
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 9.3223(2) Å
	b = 15.4012(3) Å
	c = 19.5439(3) Å
Volume	2806.01(9) Å^3
Z	4
Density (calculated)	1.322 Mg / m^3

Absorption coefficient	0.096 mm^{-1}
F(000)	1176
Crystal	Block; Colourless
Crystal size	0.12 × 0.08 × 0.03 mm^3
θ range for data collection	3.02 – 26.36°
Index ranges	$-11 \le h \le 11$, $-19 \le k \le 19$, $-24 \le l \le 21$
Reflections collected	20657
Independent reflections	3230 [$R_{int} = 0.0694$]
Completeness to $\theta = 26.36°$	99.8 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9971 and 0.9885
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3230 / 0 / 371
Goodness-of-fit on F^2	1.133
Final *R* indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0581$, $wR2 = 0.1102$
R indices (all data)	$R1 = 0.0735$, $wR2 = 0.1190$
Absolute structure parameter	Referenced to unchanging chiral centre in the synthetic procedure (C27-S)
Largest diff. peak and hole	0.306 and –0.258 e Å^{-3}

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

Chirality: C13 = R, C18 = S, C27 = S

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
F1	−1083(3)	−642(2)	530(2)	39(1)	1
F2	407(3)	−1642(1)	834(1)	30(1)	1
F3	336(3)	−1210(2)	−211(1)	34(1)	1
O1	1027(3)	1003(2)	1322(1)	18(1)	1
O2	746(4)	−324(2)	1789(1)	32(1)	1
O3	1155(3)	372(2)	62(1)	21(1)	1
C1	−2093(4)	1666(2)	2465(2)	19(1)	1
C2	−1968(4)	754(2)	2491(2)	22(1)	1
C3	−2360(4)	306(3)	3077(2)	28(1)	1
C4	−2886(5)	734(3)	3648(2)	27(1)	1
C5	−3027(5)	1627(3)	3624(2)	26(1)	1
C6	−2626(4)	2083(3)	3045(2)	23(1)	1
C7	−2156(4)	3102(2)	1819(2)	18(1)	1
C8	−3654(5)	3160(3)	1822(2)	25(1)	1
C9	−4350(5)	3948(3)	1759(2)	28(1)	1
C10	−3575(5)	4708(3)	1689(2)	26(1)	1
C11	−2080(5)	4667(3)	1679(2)	26(1)	1
C12	−1397(4)	3871(3)	1741(2)	23(1)	1
C13	212(4)	2261(2)	2000(2)	18(1)	1

C14	490(4)	2683(3)	2708(2)	21(1)	1
C15	2071(5)	2895(3)	2824(2)	25(1)	1
C16	2955(4)	2062(3)	2798(2)	22(1)	1
C17	2681(4)	1591(3)	2127(2)	24(1)	1
C18	1086(4)	1423(2)	1999(2)	17(1)	1
C19	−1464(4)	2184(2)	1857(2)	19(1)	1
C20	−1828(4)	1802(2)	1146(2)	20(1)	1
C21	−3009(5)	1266(3)	1042(2)	29(1)	1
C22	−3414(5)	1014(3)	384(2)	37(1)	1
C23	−2650(5)	1304(3)	−178(2)	38(1)	1
C24	−1479(5)	1836(3)	−84(2)	31(1)	1
C25	−1071(5)	2090(3)	571(2)	24(1)	1
C26	992(4)	137(2)	1310(2)	19(1)	1
C27	1368(4)	−228(2)	590(2)	17(1)	1
C28	248(4)	−941(3)	439(2)	24(1)	1
C29	2201(5)	1051(3)	−19(2)	27(1)	1
C30	2868(4)	−635(3)	591(2)	20(1)	1
C31	3669(5)	−761(3)	1184(2)	29(1)	1
C32	5009(5)	−1141(3)	1151(3)	38(1)	1
C33	5559(5)	−1415(3)	536(3)	45(1)	1
C34	4784(5)	−1298(3)	−55(3)	39(1)	1
C35	3446(5)	−904(3)	−32(2)	32(1)	1

Table 3. Bond lengths [Å] and angles [°].

F1–C28	1.335(5)	C13–C14	1.551(5)
F2–C28	1.335(5)	C13–C19	1.591(5)
F3–C28	1.339(4)	C14–C15	1.527(6)
O1–C26	1.334(4)	C15–C16	1.525(6)
O1–C18	1.474(4)	C16–C17	1.520(5)
O2–C26	1.198(5)	C17–C18	1.530(5)
O3–C27	1.401(4)	C19–C20	1.547(5)
O3–C29	1.438(5)	C20–C21	1.392(6)
C1–C6	1.394(5)	C20–C25	1.399(6)
C1–C2	1.410(5)	C21–C22	1.393(6)
C1–C19	1.546(5)	C22–C23	1.383(7)
C2–C3	1.386(6)	C23–C24	1.378(7)
C3–C4	1.386(6)	C24–C25	1.393(6)
C4–C5	1.382(6)	C26–C27	1.554(5)
C5–C6	1.383(6)	C27–C30	1.531(5)
C7–C12	1.388(6)	C27–C28	1.544(5)
C7–C8	1.399(6)	C30–C31	1.393(6)
C7–C19	1.555(5)	C30–C35	1.394(6)
C8–C9	1.382(6)	C31–C32	1.382(6)
C9–C10	1.382(6)	C32–C33	1.373(7)
C10–C11	1.395(6)	C33–C34	1.374(7)
C11–C12	1.387(6)	C34–C35	1.388(6)

C26–O1–C18	117.1(3)	C7–C19–C13	110.4(3)
C27–O3–C29	117.7(3)	C21–C20–C25	118.0(4)
C6–C1–C2	117.4(4)	C21–C20–C19	122.1(4)
C6–C1–C19	121.4(3)	C25–C20–C19	119.4(3)
C2–C1–C19	120.7(4)	C22–C21–C20	121.0(4)
C3–C2–C1	120.2(4)	C23–C22–C21	120.2(4)
C2–C3–C4	121.5(4)	C24–C23–C22	119.7(4)
C5–C4–C3	118.6(4)	C23–C24–C25	120.3(4)
C4–C5–C6	120.5(4)	C24–C25–C20	120.8(4)
C5–C6–C1	121.8(4)	O2–C26–O1	125.6(4)
C12–C7–C8	117.0(4)	O2–C26–C27	122.5(3)
C12–C7–C19	124.7(3)	O1–C26–C27	111.9(3)
C8–C7–C19	118.2(4)	O3–C27–C30	113.5(3)
C9–C8–C7	121.7(4)	O3–C27–C28	103.4(3)
C10–C9–C8	120.4(4)	C30–C27–C28	109.1(3)
C9–C10–C11	119.1(4)	O3–C27–C26	113.3(3)
C10–C11–C12	119.8(4)	C30–C27–C26	110.7(3)
C7–C12–C11	122.0(4)	C28–C27–C26	106.1(3)
C18–C13–C14	105.4(3)	F1–C28–F2	107.8(3)
C18–C13–C19	117.5(3)	F1–C28–F3	106.8(3)
C14–C13–C19	110.6(3)	F2–C28–F3	106.9(3)
C15–C14–C13	112.5(3)	F1–C28–C27	111.0(3)
C16–C15–C14	109.7(3)	F2–C28–C27	112.9(3)
C17–C16–C15	109.8(3)	F3–C28–C27	111.1(3)
C16–C17–C18	112.7(3)	C31–C30–C35	118.5(4)
O1–C18–C17	104.9(3)	C31–C30–C27	123.1(4)
O1–C18–C13	110.6(3)	C35–C30–C27	118.3(4)
C17–C18–C13	112.0(3)	C32–C31–C30	120.3(4)
C1–C19–C20	114.2(3)	C33–C32–C31	120.7(5)
C1–C19–C7	110.4(3)	C34–C33–C32	119.9(4)
C20–C19–C7	102.2(3)	C33–C34–C35	120.2(5)
C1–C19–C13	106.0(3)	C34–C35–C30	120.4(4)
C20–C19–C13	113.6(3)		

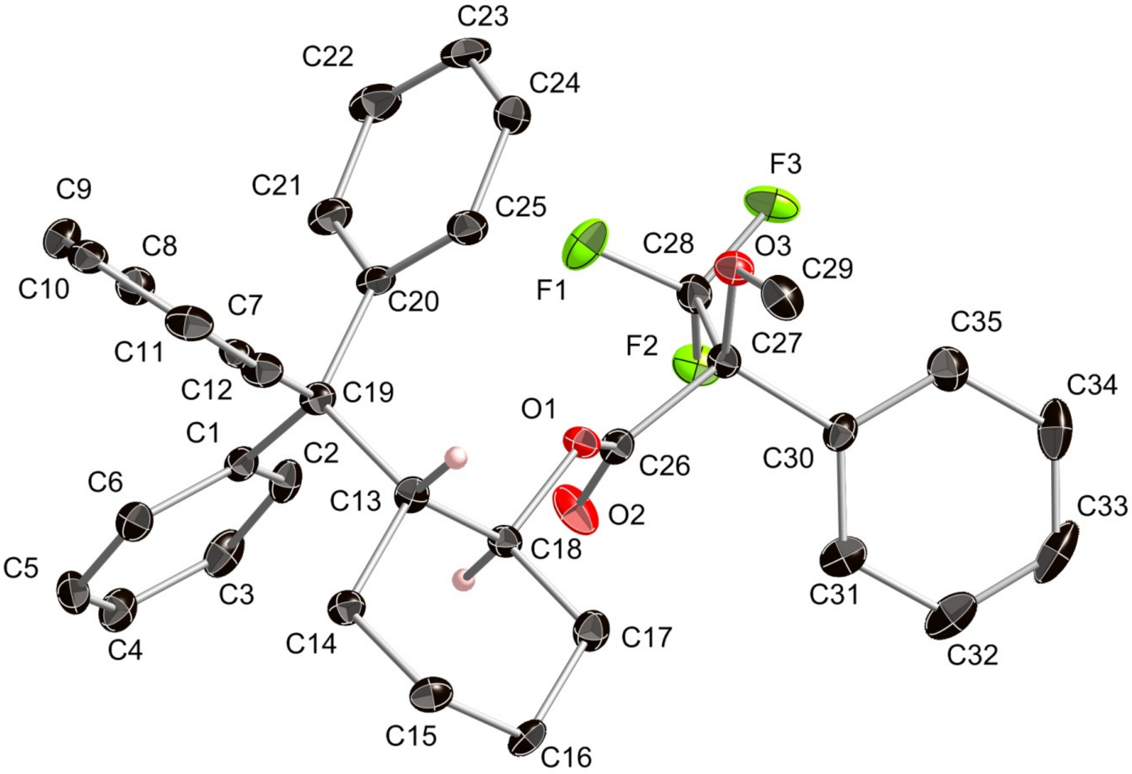
Table 4. Anisotropic displacement parameters [Å^2× 10^3]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F1	20(1)	40(2)	57(2)	2(1)	−2(1)	−2(1)
F2	40(2)	20(1)	29(1)	3(1)	−3(1)	−7(1)
F3	46(2)	31(1)	26(1)	−6(1)	−11(1)	−9(1)
O1	23(1)	16(1)	15(1)	0(1)	−2(1)	2(1)

O2	53(2)	19(1)	22(2)	4(1)	10(2)	1(2)
O3	24(1)	22(1)	19(1)	4(1)	−1(1)	−1(1)
C1	16(2)	19(2)	22(2)	−3(2)	−2(2)	0(2)
C2	14(2)	19(2)	32(2)	−5(2)	2(2)	−3(2)
C3	18(2)	22(2)	43(3)	8(2)	3(2)	−6(2)
C4	22(2)	27(2)	31(2)	9(2)	4(2)	−3(2)
C5	24(2)	30(2)	24(2)	−6(2)	5(2)	2(2)
C6	22(2)	20(2)	26(2)	0(2)	0(2)	1(2)
C7	21(2)	19(2)	13(2)	−3(2)	−3(2)	3(2)
C8	26(2)	26(2)	23(2)	1(2)	0(2)	2(2)
C9	23(2)	32(2)	29(2)	−1(2)	−2(2)	8(2)
C10	33(2)	26(2)	19(2)	−3(2)	−6(2)	14(2)
C11	36(2)	19(2)	23(2)	1(2)	−7(2)	−1(2)
C12	26(2)	22(2)	22(2)	−2(2)	−4(2)	0(2)
C13	18(2)	14(2)	22(2)	−2(2)	0(2)	−2(2)
C14	21(2)	19(2)	22(2)	−1(2)	−3(2)	1(2)
C15	22(2)	26(2)	26(2)	−1(2)	−6(2)	−3(2)
C16	14(2)	23(2)	29(2)	1(2)	−4(2)	1(2)
C17	20(2)	24(2)	28(2)	−3(2)	1(2)	−2(2)
C18	19(2)	16(2)	16(2)	−1(2)	−1(2)	1(2)
C19	19(2)	18(2)	19(2)	−2(2)	−3(2)	0(2)
C20	21(2)	18(2)	20(2)	−2(2)	−7(2)	3(2)
C21	24(2)	31(2)	31(2)	−3(2)	−7(2)	0(2)
C22	35(3)	32(2)	42(3)	−11(2)	−17(2)	5(2)
C23	42(3)	41(3)	30(2)	−14(2)	−21(2)	22(2)
C24	34(2)	36(3)	24(2)	−5(2)	−2(2)	18(2)
C25	28(2)	24(2)	22(2)	−2(2)	−5(2)	7(2)
C26	16(2)	19(2)	22(2)	−1(2)	−1(2)	0(2)
C27	19(2)	15(2)	18(2)	−1(2)	0(2)	1(2)
C28	20(2)	28(2)	23(2)	−4(2)	2(2)	0(2)
C29	35(2)	21(2)	26(2)	1(2)	5(2)	−4(2)
C30	18(2)	18(2)	24(2)	5(2)	2(2)	0(2)
C31	28(2)	24(2)	35(2)	3(2)	−6(2)	−1(2)
C32	28(2)	30(2)	56(3)	3(2)	−11(2)	3(2)
C33	19(2)	36(3)	81(4)	6(3)	3(3)	8(2)
C34	32(3)	33(3)	52(3)	−3(2)	18(2)	8(2)
C35	33(2)	32(2)	30(2)	−3(2)	2(2)	4(2)

Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [Å^2 × 10^3].

Atom	x	y	z	U_{eq}	$S.o.f.$
H2	−1613	446	2105	26	1
H3	−2267	−308	3087	33	1
H4	−3144	420	4048	32	1
H5	−3403	1930	4007	31	1
H6	−2715	2697	3042	27	1
H8	−4206	2645	1868	30	1
H9	−5369	3968	1763	33	1
H10	−4053	5250	1649	31	1
H11	−1532	5183	1629	31	1
H12	−379	3851	1729	28	1
H13	628	2653	1644	22	1
H14A	−79	3224	2745	25	1
H14B	159	2282	3072	25	1
H15A	2409	3302	2467	30	1
H15B	2194	3178	3275	30	1
H16A	3987	2204	2838	26	1
H16B	2690	1682	3187	26	1
H17A	3198	1030	2132	29	1
H17B	3071	1943	1746	29	1
H18	705	1017	2355	20	1
H21	−3548	1068	1424	34	1
H22	−4216	642	322	44	1
H23	−2933	1137	−626	45	1
H24	−946	2030	−470	38	1
H25	−269	2464	629	29	1
H29A	2315	1361	415	41	1
H29B	1879	1457	−373	41	1
H29C	3122	796	−154	41	1
H31	3292	−584	1614	35	1
H32	5555	−1214	1557	46	1
H33	6475	−1685	519	55	1
H34	5165	−1488	−480	47	1
H35	2921	−818	−443	38	1



Thermal ellipsoids drawn at the 35% probability level, only hydrogen atoms at chiral centres shown for clarity.

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