UNIVERSITY OF SOUTHAMPTON

Faculty of Natural and Environmental Sciences

Department of Chemistry

Diastereo- and Chemoselective Oxidative Monocyclisations of Trienes; Application of Permanganate Mediated Oxidative Cyclisation to the Synthesis of Eurylene.

by

Azzam Ahmed Mohammed Al-Hadedi

Thesis for the degree of Doctor of Philosophy

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(يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ ۚ وَاللَّهُ بِمَا تَعْمَلُونَ خَبِيرٌ) المجادلة: 11

Allah will raise those who have believed among you and those who were given knowledge, by degrees. And Allah is Acquainted with what you do. Almujaadila: 11

(يَا أَيُّهَا النَّاسُ إِنَّا خَلَقْنَاكُمْ مِنْ ذَكَرٍ وَأُنْثَىٰ وَجَعَلْنَاكُمْ شُعُوبًا وَقَبَائِلَ لِتَعَارَفُوا ۚ إِنَّ أَكْرَمَكُمْ عِنْدَ اللَّهِ أَتْقَاكُمْ ۚ إِنَّ اللَّهَ عَلِيمٌ خَبِيرٌ) الحجرات: 13

O mankind, indeed We have created you from male and female and made you peoples and tribes that you may know one another. Indeed, the most noble of you in the sight of Allah is the most righteous of you. Indeed, Allah is Knowing and Acquainted. Al-Hujurat: 13

To this whom is well missed in my life and whom I wish he was still with us to share another happy moment of achievement I dedicate this work: **my dad** 15/9/2011.

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ABSTRACT

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A formal synthesis of eurylene (**1.1**) has been achieved where both *trans*- and *cis*-THF fragments were synthesised using diastereo- and chemoselective oxidative monocyclisations of triene systems. Synthesis of the *trans*-THF aldehyde fragment **1.50** of eurylene was accomplished starting from nerol, using (+)-*trans*-tritylcyclohexanol (TTC) as a chiral auxiliary to direct the stereosfacial selectivity during the oxidative cyclisation of 1,5,9-triene **1.185** by sodium permanganate. The oxidative cyclisation used the new chiral auxiliary (TTC) as a highly effective chiral controller for the formation of the 2,5-substituted THF diol product with high diastereoselectivity (dr ~13:1).

Synthesis of *cis*-THF right hand fragment **1.189** was also achieved using permanganate mediated oxidative cyclisation of a 1,5,9-triene **1.60**. The diastereoselectivity of the oxidation was controlled by using (2*S*)-10,2-camphorsultam as a chiral auxiliary. Consequently, seven, out of eight, stereogenic centres of eurylene were established by stereoselective permanganate oxidative cyclisations of 1,5,9-trienes.

Towards the completion of the total synthesis of eurylene a chiral sulfoxide strategy was investigated to establish the eighth stereogenic centre and couple the two fragments. In addition a hydroxylsulfone dianion coupling strategy was also investigated.

The stereochemical correlation for oxidative cyclisation products from *trans*-cumylcyclohexanol (TCC) and *trans*-tritylcyclohexanol (TTC) diene and triene esters was achieved. The oxidative cyclisation products were converted to a common intermediate and analysed by chiral HPLC to confirm absolute configuration. NOESY and NOE NMR studies were applied to some of 2-substituted cyclohexyl dienoates and an oxidative cyclisation product to study their conformation in solution.

CONTENTS

Academic Thesis: Declaration Of Authorship

I, Azzam Ahmed Mohammed Al-Hadedi

declare that the thesis entitled

Diastereo- and Chemoselective Oxidative Monocyclisations of Trienes; Application of Permanganate Mediated Oxidative Cyclisation to the Synthesis of Eurylene

and the work presented in it are my own and has been generated by me as the result of my own original research.

I confirm that:

- This work was done wholly or mainly while in candidature for a research degree at this University;
- Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
- Where I have consulted the published work of others, this is always clearly attributed;
- Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
- I have acknowledged all main sources of help;
- Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
- Parts of this work have been published as: *Org. Lett.*, **2014,** 16, 5104.

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Acknowledgements

First of all, I have to thanks ALLAH, my god who is making me on the right path, supporting me all the time and gave me the good people who I am going to thank, thanks my god.

Richard Brown, I wonder how to thank you, you were more than a supervisor, it is great to know you as a man of good moral values and social conducts. I am truly grateful for the opportunity to study within your group. Thanks for your supervision, support and the assistance during the time in Southampton. Thanks Richard; I owe a debt of gratitude.

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Finally I have to end with thanking my good and nice mum: thanks for your love, care, kindness and support. Your presence by my side is a daily bliss. I don't know how to thank you; I owe a debt of gratitude.

Abbreviations

δ	chemical shift
Ac	acetyl
AIBN	2,2´-azobisisobutyronitrile
aq.	aqueous
Ar	aromatic
br	broad
CSA	10-camphorsulfonic acid
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBALH	di-iso-butylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMP	2,2-Dimethoxypropoane
DMF	*N*,*N*-dimethylformamide
de	diastereoisomeric excess
dr	diastereoisomeric ratio
ee	enantiomeric excess
equiv.	equivalent(s)
er	enantiomeric ratio
Et_2O	diethyl ether
EtOAc	ethyl acetate
ES	electrospray
h	hour(s)
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Imid	imidazole
^{i}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
min	minute(s)
MOM	methoxymethyl
mmol	millimole(s)
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	mass spectrometry
MW	micro wave
NaHMDS	sodium hexamethyldisilazide
^{n}BuLi	*n*-butyl lithium
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
NOESY	nuclear overhauser effect spectroscopy
PCC	pyridinium chlorochromate
PFP	pentaflourophenyl
Ph	phenyl
PMP	*p*-methoxyphenyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
PTC	phase transfer catalyst
p-TSA	*p*-toluenesulfonic acid
pyr	pyridine
q	quartet (NMR)
rt	room temperature
s	singlet (NMR) or strong (IR)
sol.	solution
t	triplet (NMR)
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
^{t}Bu	*tert*-butyl

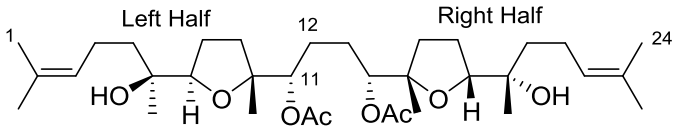
TEMPO	2,2,6,6-Tetramethylpiperidinyloxy
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMS	trimethylsilyl
TCC	*trans*-2-cumylcyclohexanol
Ts	*p*-toluenesulfonyl (tosyl)
TTC	*trans*-2-tritylcyclohexanol
TTMSS	*tris*-trimethylsilylsilane
UV	ultraviolet
w	weak (IR)

Chapter One: Introduction

1.1. Eurylene

1.1.1. Background

Eurylene (**1.1**) is a bioactive bicyclic squalenoid natural product isolated from *Eurycoma longifolia*, a simaroubaceous slender shrub commonly found in Burma, Indochina, Thailand and Southeast Asia. It is commonly present as an understory in the lowland forests at up to 500 m above sea level. The tree is known by different names depending on the regions in which it is found. It is known locally as "Tongkat Ali" in Malaysia, "Pasakbumi" in Indonesia, "Cay Ba Binh" in Vietnam and "Ian-Don" in Thailand. The crude extract of this shrub is popularly used in herbal remedies as a traditional folk medicine.[1,2] Spectroscopic analysis and X-ray data showed that the eurylene structure contains two nonadjacent connected tetrahydrofuran rings with eight chiral centres (figure 1.1). The left (C_1-C_{11}) segment contains a 2,5-*trans*-tetrahydrofuran ring, whilst the right (C_{13}-C_{14}) segment has a 2,5-*cis*-tetrahydrofuran.[1]

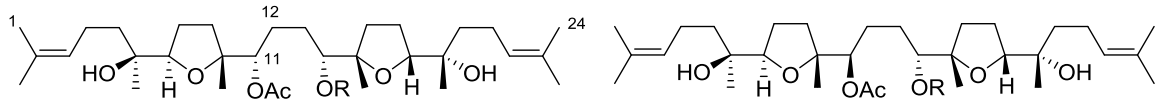


Eurylene **1.1**

Figure 1.1: Structures of eurylene.

The cytotoxic activities of eurylene (**1.1**) and its derivatives were found to have an interesting relationship depending on the conformations of these polyethers (figure 1.2).[3,4] It was found that eurylene (**1.1**) with extended conformation has no cytotoxic activity on KB cells, whereas 14-deacetyl eurylene (**1.2**) having folded conformation showed signivigant activity (table 1.1). The relationships between ion transport for K^+, Na^+ and Ca^{+2} and cytotoxic activity on KB cells of eurylene (**1.1**) and the derivatives **1.2-1.4** were studied by Kodama *et al.*[5] The study showed eurylene (**1.1**) had no ability to transfer any of these ions, while **1.2** and **1.4** to transported K^+ ion quite effectively (table 1.1). The cytotoxic activity study in KB cells showed a higher cytotoxicity of (**1.3**) in contrast to eurylene. This result indicated an important relationship between the stereochemistry at C_{11} and the cytotoxicity. However, the activity of **1.2** was comparable to that of its epimer **1.4**. The authors concluded the cytotoxic activity

resulted from the complexation with a metal ion, in particular with K^+, which supported the hypothesis that the ionophoric nature of **1.2** led to its cytotoxic activity.[3]



1.1 R=Ac Eurylene
1.2 R=H 14-Deacetyl eurylene

1.3 R=Ac11-*epi*-Eurylene
1.4 R=H 11-*epi*-14-Deacetyl eurylene

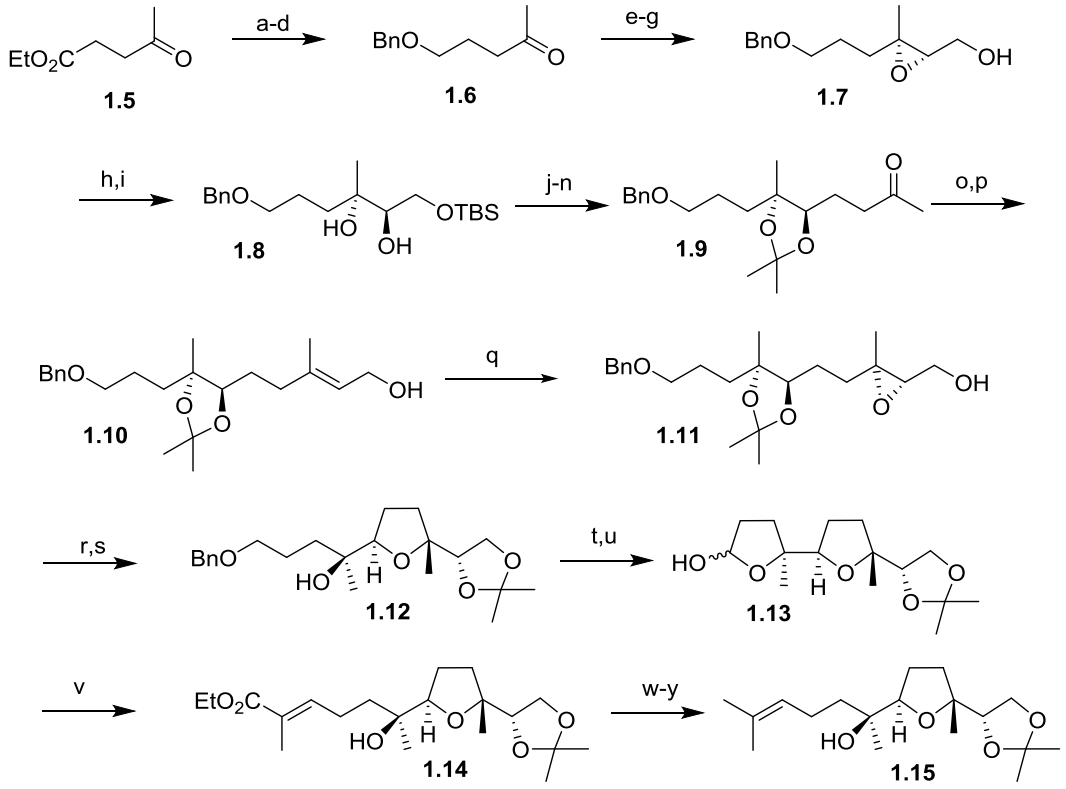
Figure 1.2: Structures of eurylene derivatives.

Compound	Ionic transport[a] K^+	Na^+	Ca^{+2}	Cytotoxic activity on KB cells IC_{50}[b](µg/ml)
1.1	1	0	0	>100
1.2	14	2	1	13.6±1.7, (0.52)[c]
1.3	7	1	0	8.9±2.3
1.4	23	2	2	14.1±2.1

Table 1.1: Cytotoxic activity and ion transport ability of eurylene derivatives reported by Kodama *et al*.[5] [a]Percentage transported of the ions in liposomes composed of egg phosphatidylcholine in 3 min. [b]IC_{50} (Inhibitory concentration 50) values are the drug concentration (±SD) required to reduce cell growth by 50%. [c]The reported value by Itokawa *et al*.[3]

1.1.2. Previous Synthetic Routes to Eurylene

The first stereoselective synthesis of a *trans*-THF containing left hand fragment **1.15** of eurylene was reported in 1993 starting from ethyl 2-oxo-pentanoate (**1.5**) in 25 linear steps (scheme 1.1)[6]. The synthesis involved two Sharpless asymmetric epoxidation reactions. The second epoxidation was applied to the 5-hydroxyalkene **1.10**, followed by acid-catalysed 5-*exo-tet* cyclisation to give hydroxyl THF **1.12**. Then the synthesis was continued to form the required **1.15**.

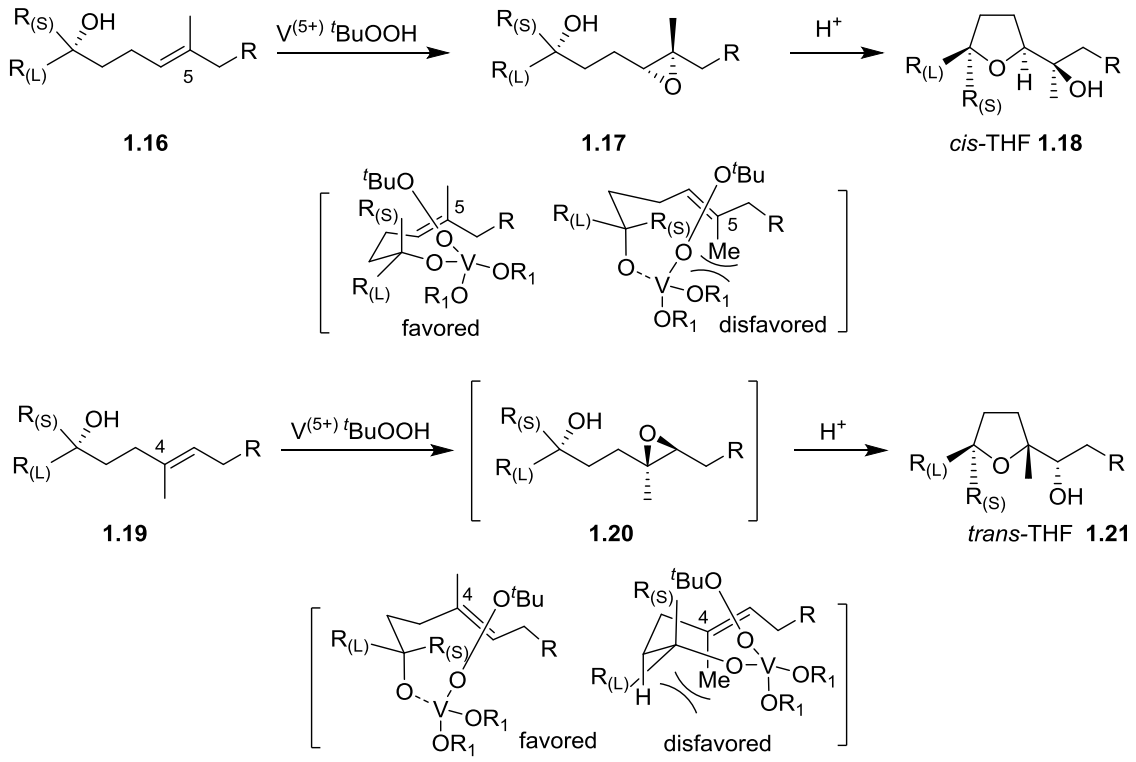


Scheme 1.1: The first synthesis of the left fragment **1.15** of eurylene. **Reagents and conditions**: a) $HOCH_2CH_2OH$, PTSA, PhH, heating, 12 h. b) $LiAlH_4$, THF, heating, 6 h. c) NaH, BnBr, THF, 3 h. d) MeOH, PTSA, 3 h. e) $(EtO)_2P(O)CH_2COOEt$, NaH, PhH, 60 °C, 6 h. f) DIBALH, CH_2Cl_2, –15 °C, 1 h. g) (+)-DIPT, TBHP, $Ti(O^iPr)_4$, CH_2Cl_2, –20 °C, 6 h. h) KOH (0.3N), DMSO:H_2O (4:1), 12 h, 50%. i) TBSCl, imid., CH_2Cl_2, 3 h. j) $Me_2C(OMe)_2$, PTSA, CH_2Cl_2, 10 min. k) Bu_4NF, THF, 3 h. l) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 1 h. m) $CH_3COCH{=}PPh_3$, CH_2Cl_2, 3 h. n) Pd-C, H_2, $NaHCO_3$, MeOH, 3 h. o) $(EtO)_2P(O)CH_2COOEt$, NaH, PhH, 60 °C, 6 h, 79%. p) DIBALH, CH_2Cl_2, –15 °C, 1 h. q) (+)-DIPT, TBHP, $Ti(^iOPr)_4$, CH_2Cl_2, –20 °C, 3 h, 54%. r) Amberlyst 15 A, MeOH, 1 h. s) $Me_2C(OMe)_2$, PTSA, CH_2Cl_2, 10 min, 41%. t) Pd-C, H_2, MeOH, 1 h. u) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 1 h. v) $Ph_3P{=}C(Me)COOEt$, CH_2Cl_2, 12 h, 89%. w) DIBALH, CH_2Cl_2, –15 °C, 1 h. x) Ac_2O, pyr., DMAP, CH_2Cl_2, 1 h. y) Pyr-SO_3 complex, THF, 1 h; then $LiAlH_4$, 3 h, 82%.

1.1.1. Vanadium Catalysed Epoxidation-Cyclisation Protocol

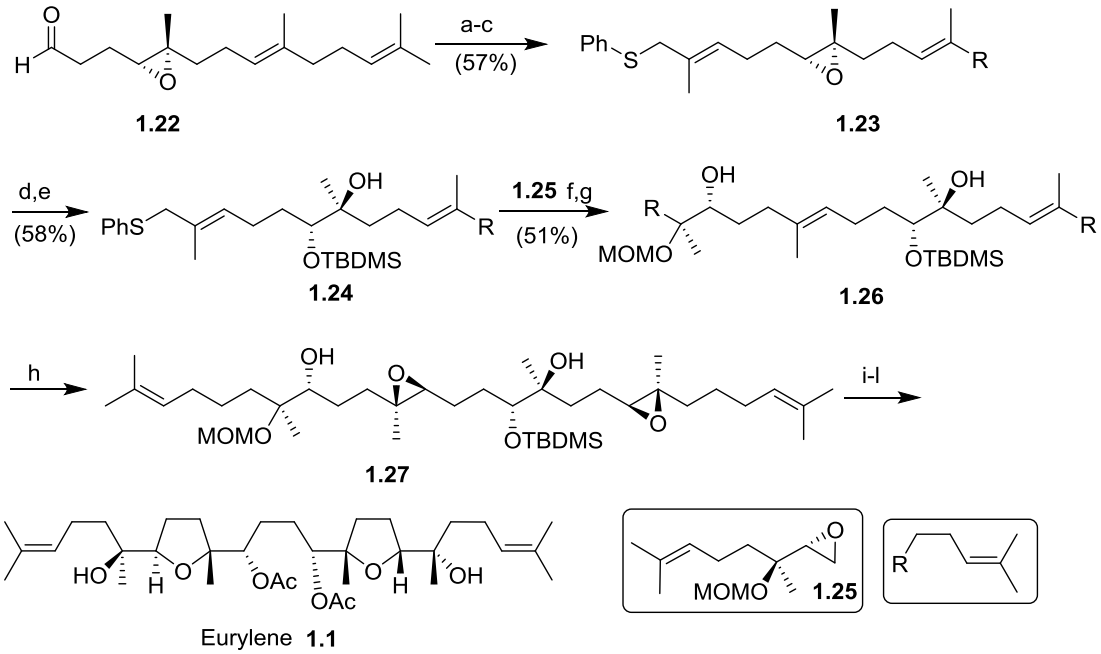
It was not until 1996, that Ujihara *et al*.[7] achieved the first total synthesis of eurylene (**1.1**) using vanadium$^{(v)}$ promoted epoxidation followed by cyclisation under acidic conditions to afford both THF ring systems **1.18** and **1.21** (scheme 1.2).[4] The *cis*-THF intermediate **1.18** was synthesised from 5-substituted-4-alken-1-ol **1.16** via the *syn*-

epoxy alcohol, while the *trans*-THF **1.21** was prepared by using the same approach applied to 4-substituted-4-alken-1-ol **1.19** via the *anti*-epoxide **1.20**.



Scheme 1.2: Strategy for synthesis of *cis*-THF **1.18** and *trans*-THF **1.21** using vanadium oxidative cyclisation reported by Ujihars *et al*.[7]

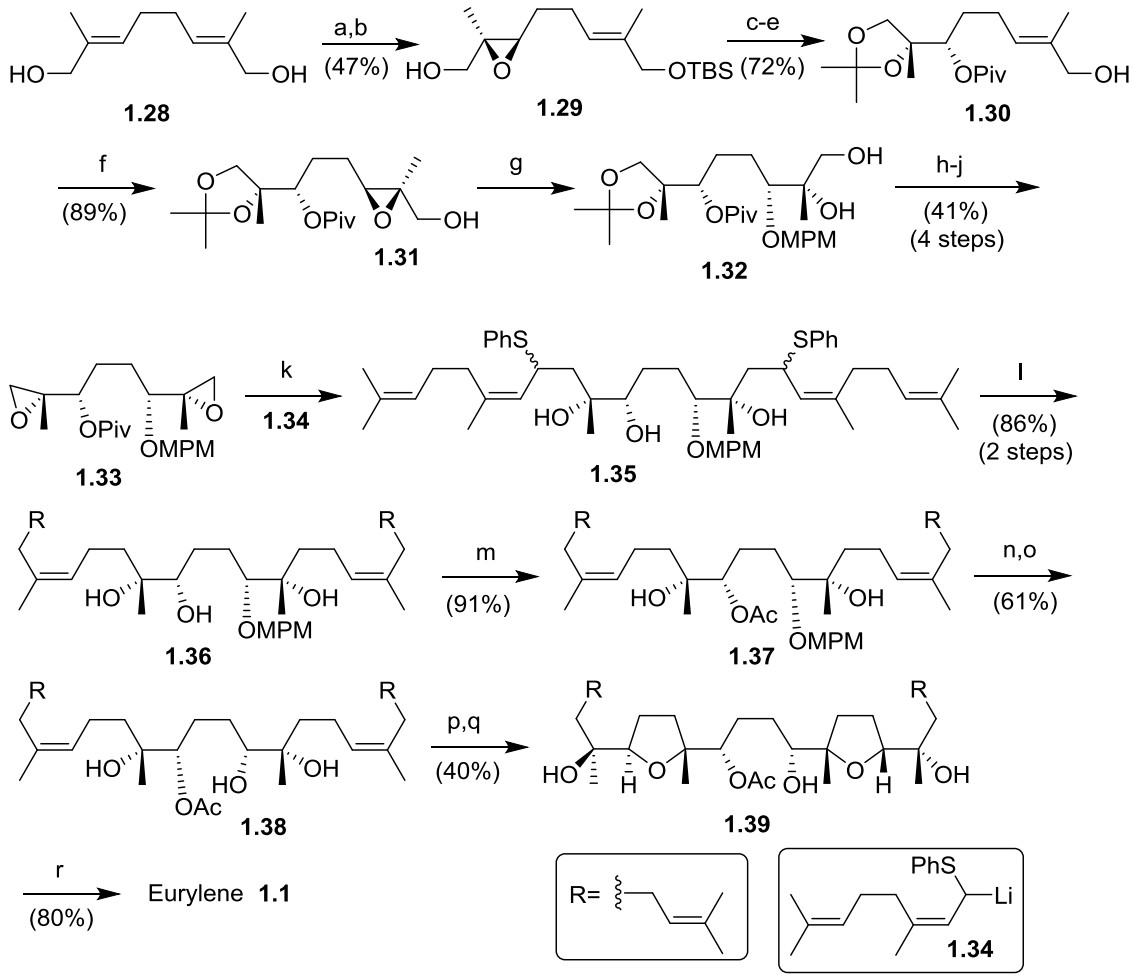
The total synthesis of eurylene (**1.1**) was achieved in 12 steps starting from enantiomerically pure aldehyde **1.22** which was previously reported by Kigoshi *et al.* (scheme 1.3).[7,8] The aldehyde **1.22** underwent Horner-Wardsworth-Emmons olefination to give the ethyl ester, followed by a reduction with DIBALH to afford an alcohol which was converted to thioether **1.23**. Epoxide cleavage of thioether **1.24** and protection of resultant secondary alcohol gave the silyl ether **1.24**. The silyl ether **1.24** was coupled with oxirane **1.25** to afford the *bis*-homoallylic alcohol which was desulphurised using Birch conditions to give the diol **1.26**, followed by epoxidation to afford *bis*-epoxide **1.27**. It is worth noting that the diastereomeric purity of bis-epoxide **1.27** could not be confirmed because of the side reactions including deprotection and/or oxidation of terminal double bonds. Acid catalysed cyclisation of left hand epoxide, deprotection of silyl group and acid catalysed cyclisation of right hand epoxide with simultaneous cleavage of the methoxymethyl group the tetra hydroxyl THF, which was subsequently acetylated to complete the first total synthesis of eurylene (**1.1**).



Scheme 1.3: Total synthesis of eurylene (**1.1**) by Ujihara *et al*.[7] **Reagents and conditions**: a) $(EtO)_2P(O)CH(CH_3)CO_2Et$, NaH, THF, 0 ^oC, 15 min. b) DIBALH, toluene, –78 ^oC, 15 min. c) PhSSPh, $^nBu_3P$, CH_2Cl_2, rt, 30 min. d) cat. $HClO_4$, THF:H_2O (6:1), reflux, 1 h. e) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, –20 ^oC, 20 min. f) Epoxide **1.25**, ^{n}BuLi, TMEDA, HMPA, THF, –20 ^oC, 30 min. g) Li, NH_3:EtOH (1:1), –78 ^oC, 2 h. h) TBHP, cat. $VO(acac)_2$, MS 3Å, benzene, rt, 3 h; Me_2S, rt, 30 min. h) TBHP, cat. $VO(acac)_2$, MS 3Å, benzene, rt, 3 h; Me_2S, rt, 30 min. i) cat. CSA, rt, 2 h. j) TBAF, THF, refux 2 h. k) cat. HCl, THF:H_2O (10:1), reflux, 15 min. l) Ac_2O, pyr., rt, 50 h, 28% over 5 steps from **1.26**.

1.1.2. Rhenium and Chromium Oxidative Cyclisation Protocol

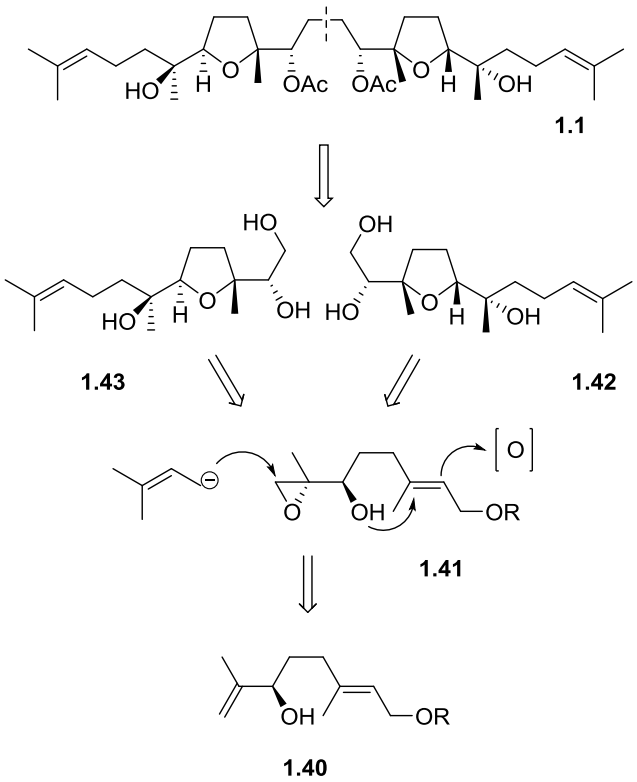
The second total synthesis of eurylene (**1.1**) was achieved in 2000 by Morimoto *et al*.[9] They made use of a rhenium$^{(VII)}$ oxidative cyclisation process for the synthesis of *trans*-THF ring while the construction of *cis*-THF system was achieved by applying chromium$^{(VI)}$ oxide as an oxidant (**1.39**, scheme 1.4). The synthesis started from a known diol **1.28**, which was previously prepared in 4 steps.[10] The synthesis included a smart trick when two neryl units **1.34** were introduced to perform regioselective ring opening of the bis-epoxide **1.33** in a bidirectional manner, to establish the side chains on either side (**1.35**, scheme 1.4).



Scheme 1.4: Total synthesis of eurylene (**1.1**) by Morimoto *et al.*[9] **A) Reagents and conditions**: a) TBSCl, imid., CH_2Cl_2, rt., 1 h. b) TBHP, Ti(^{i}OPr)$_4$, D-(–)-DET, MS 4Å, CH_2Cl_2, –20 °C, 2 h (98% *ee*). c) Ti(^{i}OPr)$_4$, PivOH, PhH, 0 °C, 2 h. d) 2,2-dimethoxypropane, CSA, CH_2Cl_2, 0 °C, 2 h. e) Bu_4NF, THF. rt, 3 h. f) TBHP, Ti(^{i}OPr)$_4$, L-(+)-DET, MS 4 Å, CH_2Cl_2, –20 °C, 3 h. g) Ti(OMPM)$_4$, MPMOH, PhH, 60 °C, 12 h. h) AcOH:H_2O (4:1), rt, 5 h. i) MsCl, pyr., CH_2Cl_2, 0 °C to rt, 5 h. j) K_2CO_3, MeOH, rt, 1 h (4 steps). k) Compound **1.34**, TMEDA, THF, –78 °C, 30 min, then 0 °C, 2 h. l) Na, THF:^{i}PrOH, (2:1), reflux, 15 h. m) Ac_2O, pyr., rt, 12 h. n) DDQ, MS 4Å, CH_2Cl_2, 0 °C, 2 h. o) AcOH:H_2O (4:1), rt, 16 h. p) [$(CF_3CO_2)ReO_3.2CH_3CN$], TFAA, CH_2Cl_2:CH_3CN (9:1), –40 °C, 1.5 h. q) PCC, CH_2Cl_2, rt, 30 min. r) Ac_2O, pyr., rt, 40 h.

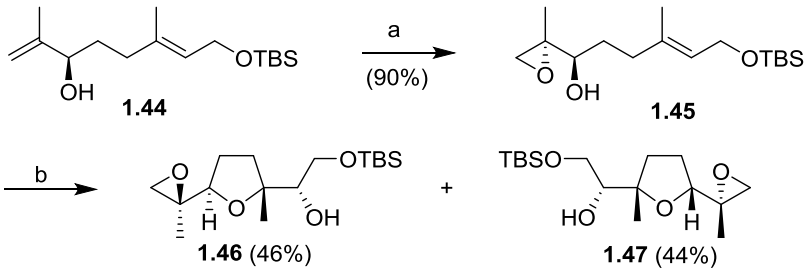
1.1.3. *m*-CPBA Epoxidation – Cyclisation Protocol

Eurylene (**1.1**) was also been synthesised by Kodama *et al.* (scheme 1.5).[5] The two halves of eurylene **1.42** and **1.43** were prepared from a common diene precursor **1.40** as a described in the retrosynthetic analysis below (scheme 1.5).



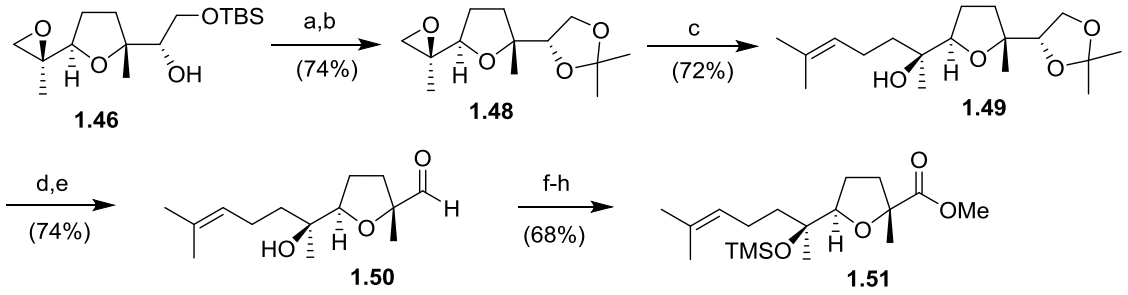
Scheme 1.5: Kodama's Retrosynthetic analysis of eurylene (**1.1**).[5]

In Kodama's synthesis *m*-CPBA was used an oxidant to prepare the THF rings **1.46** and **1.47** in a non-stereoselective fasion (scheme 1.6). The synthesis started from (*R*)-allylic alcohol **1.44**, which was prepared using baker's yeast reduction affording more than 99% *ee*.[11] Epoxidation of the alcohol **1.44** afforded the epoxide **1.45** in an excellent yield (90%) with 98% dr, then reaction with *m*-CPBA gave *trans*-THF **1.46** and *cis*-THF **1.47** in almost equal amounts (scheme 1.6).

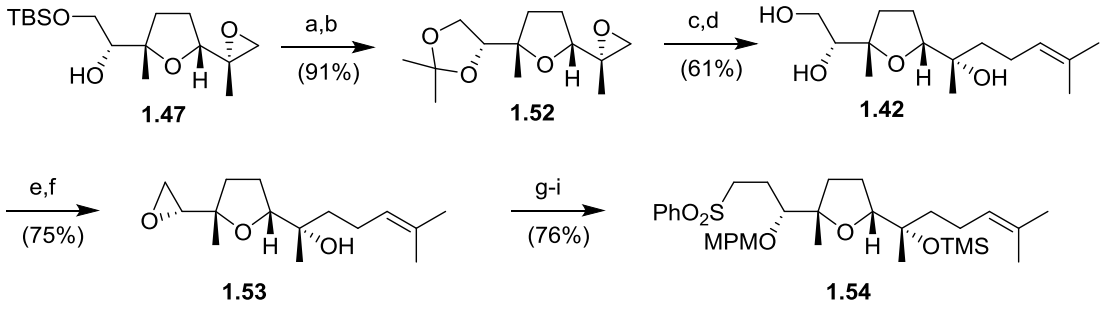


Scheme 1.6: Preparation of the *cis* and *trans*-THF ring using *m*-CPBA by Kodama *et al*. **Reagents and conditions**: a) $VO(acac)_2$, ^tBuOOH, PhH, rt, 20 min. b) *m*-CPBA, CH_2Cl_2, 0 °C, 3 h.

The *trans*-THF **1.46** and *cis*-THF **1.47** were separated by column chromatography, and the stereochemistry was determined by NOE experiments. The two compounds were then used to accomplish the synthesis of the two halves **1.51** and **1.54** of eurylene (schemes 1.7, 1.8).

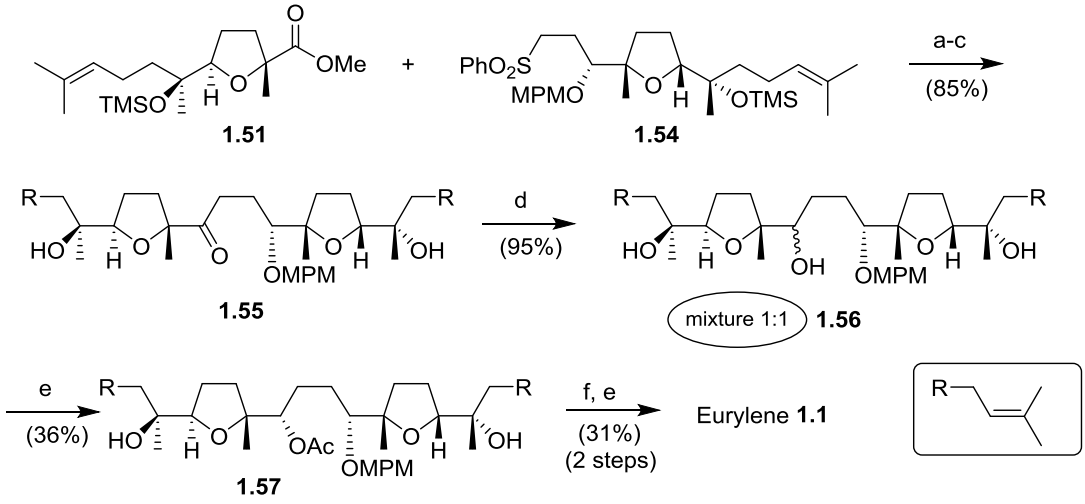


Scheme 1.7: Synthesis of left hand fragment **1.51** of eurylene by Kodama *et al*. **Reagents and conditions**: a) TBAF, THF, rt, 30 min. b) DMP, PPTS, CH_2Cl_2, rt, 7 h. c) $Me_2C{=}CHCH_2MgCl$, CuI, THF, –15 °C, 30 min. d) PPTS, EtOH, H_2O, 50 °C, 2 h. e) $NaIO_4$, THF, H_2O, rt, 30 min. f) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, ^tBuOH, H_2O, rt, 10 min. g) MeI, K_2CO_3, DMF, rt, 10 min. h) TMSCl, imid., DMF, 0 °C, 10 min.



Scheme 1.8: Synthesis of right hand fragment **1.54** of eurylene by Kodama *et al*. **Reagents and conditions**: a) TBAF, THF, rt, 30 min. b) DMP, PPTS, CH_2Cl_2, rt, 7 h. c) $Me_2C{=}CHCH_2MgCl$, CuI, THF, –15 °C, 30 min. d) PPTS, EtOH, H_2O, 50 °C, 2 h. e) MsCl, pyr., 0 °C, 1 h. f) K_2CO_3, MeOH, 0 °C, 20 min. g) $MeSO_2Ph$, ^nBuLi, DMPU, THF, –78 to –25 °C, 5 h. h) MPMCl, NaH, DMF, 0 °C. i) TMSCl, imid., DMF, 0 °C, 10 min.

Coupling of the two halves (**1.51** and **1.54**) of eurylene using LiHMDS in DMPU and THF, then desulfonylation and deprotection of TMS group afforded the ketone **1.55** (scheme 1.9). Reduction of the ketone using $NaBH_4$ (95%) or DIBALH (91%) gave an inseparable mixture (1:1) of epimeric alcohols **1.56**. The mixture was acylated and then chromatographic separation was achieved to give compound **1.57** which was converted to eurylene (**1.1**) over two steps. Following the same process, the second epimeric alcohol was converted to the corresponding acylated epimer.

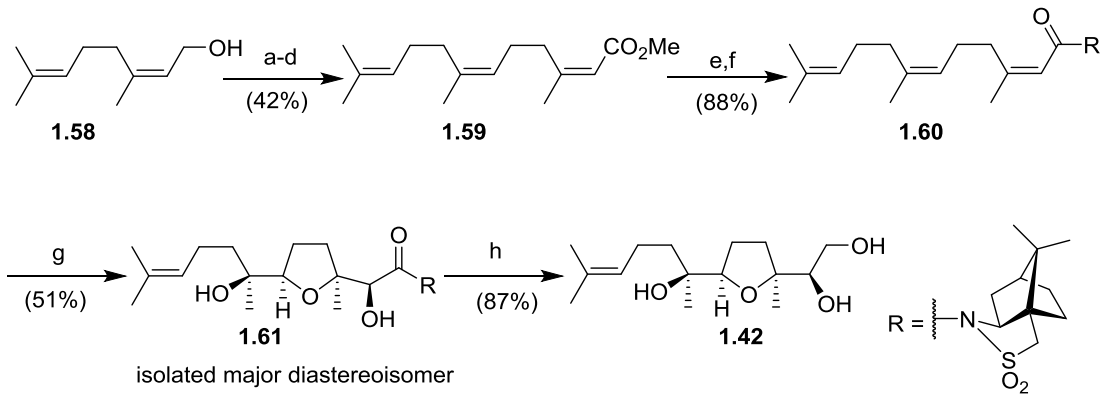


Scheme 1.9: Total synthesis of eurylene by Kodama *et al*.[5] **Reagents and conditions**: a) LiHMDS, DMPU, THF, –78 °C, 2 h, then –25 °C, 3 h. b) SmI_2, THF:MeOH (5:1), –78 °C, 10 min. c) 1.0M HCl, MeOH, rt, 10 min. d) $NaBH_4$, MeOH, 0 °C, 10 min. e) Ac_2O, pyr., 50 °C, 17 h. f) DDQ, CH_2Cl_2:$NaHCO_3$ (10:1), rt, 2 h.

1.1.4. Southampton Formal synthesis of Eurylene

In 2010 the Brown group reported the synthesis of the *trans*-THF and *cis*-THF fragments used by Kodama *et al.* using stereoselective permanganate mediated oxidative cyclisation.[5,12]

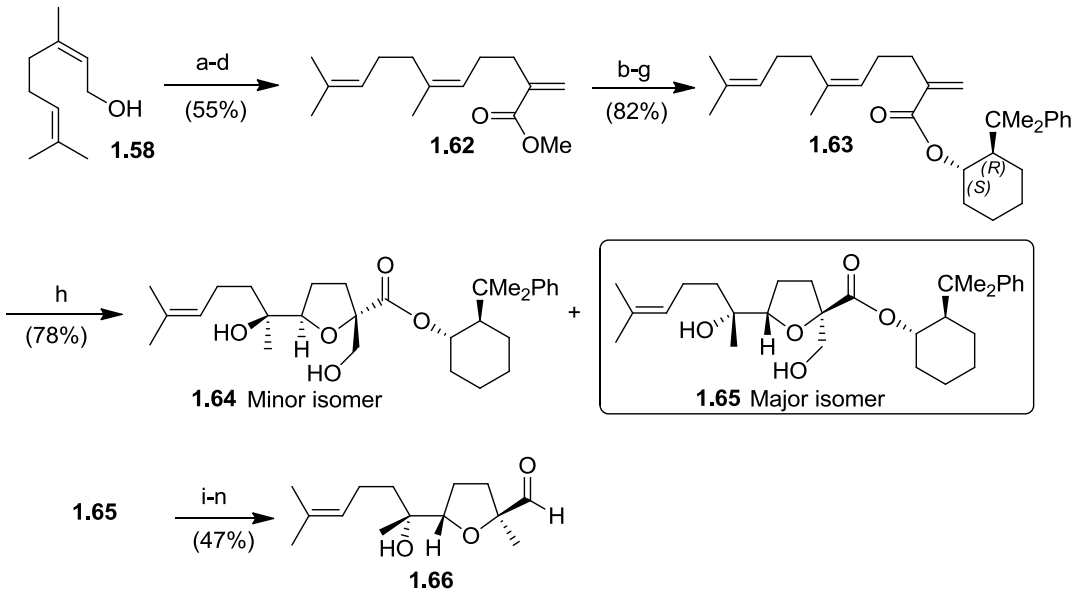
The *cis*-THF fragment **1.61** of eurylene was synthesised using an expeditious synthetic route starting from nerol (**1.58**) in 9 steps with (16%) overall yield (scheme 1.10). The key step in this route was the oxidative cyclisation of trienoate **1.60** bearing (+)-(*2S*)-10, 2-camphorsultam to afford the desired *cis*-THF diol **1.61** as an 8:1 diastereomeric mixture, which was separable by flash column chromatography. The monocyclisation was achieved in regio- and stereoselective fashion. The *cis*-THF diol **1.61** underwent reductive cleavage of the chiral auxiliary to achieve the formal synthesis of Kodama's *cis*-THF fragment **1.42**.[5]



Scheme 1.10: Brown's permanganate oxidative monocyclisation strategy to the *cis*-THF fragment of eurylene. **Reagents and conditions**: a) MsCl, LiCl, 2,6-lutidine, DMF, 0 °C to rt, 4 h. b) methyl acetate, NaH, ^{n}BuLi, THF, 0 °C to rt, 55 min. c) $(EtO)_2POCl$, Et_3N, DMPU, DMAP, –20 °C to rt, 17 h (2*E*:2*Z* 49:1 by ^{1}H NMR). d) CuI, MeLi, MeMgCl, THF, –35 to 5 °C, 2.25 h (2*Z*:2*E* 11:1 by GC). e) NaOH, MeOH:H_2O (1:1.7), reflux, 6 h. f) $(COCl)_2$, DMF, ^{n}hexane, rt, 2 h then (2*S*)-camphorsultam, NaH, toluene, 0 °C to rt, 9 h. g) $NaMnO_4$ (0.4M), AcOH, acetone, phosphate buffer (KH_2PO_4:NaH_2PO_4 8:2), acetone, –21 to –7 °C, 70 min. h) $NaBH_4$, THF:H_2O (25:1), –5 °C, 4 h.

For the synthesis of *trans*-THF fragment **1.65** the approach also commenced from nerol (**1.58**) to afford the methyl trienoate **1.59** in 4 steps, which was converted to its PFP-ester before coupling with a variety of chiral auxiliaries including (+)-(1*S*,2*R*)-*trans*-2-cumylcyclohexanol ((+)-TCC, scheme 1.11). Permanganate oxidative cyclisation of the trienoate was undertaken using the different chiral auxiliaries; the best result was for

TCC-trienoate in (78%) to give an inseparable mixture of monocyclised diols **1.64** and **1.65** in a diastereomeric ratio of 6.7:1. Recently, we have corrected the assignment of the major and minor isomers, showing that the major isomer obtained from (+)-TCC was infact **1.65** (for details see chapter two, section four).[13] The two diastereomers were separated after protection of the alcohols with TMSCl; then the major oxidative cyclisation product **1.65** underwent a sequence of reactions to afford the *trans*-THF aldehyde **1.66** (scheme 1.11).



Scheme 1.11: Brown's synthetic strategy for the *trans*-THF system; permanganate oxidative monocyclisation. **Reagents and conditions**: a) MsCl, LiCl, 2,6-lutidine, DMF, 0 °C to rt, 4 h. b) CH_2=CHMeCH_2OH, ^{n}BuLi, TMEDA, Et_2O, –78 °C to rt, 24 h. c) MnO_2, ^{n}hexane, 0 °C to rt, 1.5 h. d) NaCN, AcOH, MnO_2, MeOH, rt, 18 h. e) NaOH, MeOH:H_2O, reflux, 9 h. f) C_6H_5OH, DCC, EtOAc, rt, 21 h. g) (+)-TCC, NaHMDS, THF, –20 to 5 °C, 1.5 h. h) $NaMnO_4$ (0.4M), AcOH, acetone, phosphate buffer, –20 to –8 °C, 40 min. i) TMSCl, imid., DMF, –5 to 0 °C, 30 min. j) K_2CO_3, MeOH, –10 to 10 °C, 2.5 h. k) thiocarbonyl diimidazole, imid. CH_2Cl_2, rt, 8 h. l) TTMSS, AIBN, toluene, 85 °C, 1.5 h. m) DIBALH, CH_2Cl_2, –78 °C, 2 h. n) 1N HCl, THF, rt, 30 min.

1.2. 1,5-Diene Cyclisation Towards 2,5-Disubstituted Tetrahydrofurans

Many natural products which are biologically active contain 2,5-disubstituted tetrahydrofuran (THF) rings as a structural feature.[14-18] Therefore, in the field of synthetic chemistry there is considerable interest in routes to prepare these heterocyclic compounds, particularly in a stereoselective fashion. Oxidative cyclisation involving

metal-oxo-promoted processes are among the most attractive. Synthesis of 2,5-disubstituted THF systems has been reported using a number of metal based oxidants involving oxidative cyclisation of 1,5-dienes (figure 1.3a),[19,20] 5,6-dihydroxyalkenes (figure 1.3b),[21-23] 5-hydroxyalkenes (figure 1.3c),[24,25] and sequential epoxidation–5-exo-tet cyclisation applied to 5-hydroxyalkenes (figure 1.3d).[26] The focus here will be to summarise the main synthetic approaches to *cis*-2,5-disubstituted THFs from 1,5-diene precursors using metal mediated oxidative cyclisation.

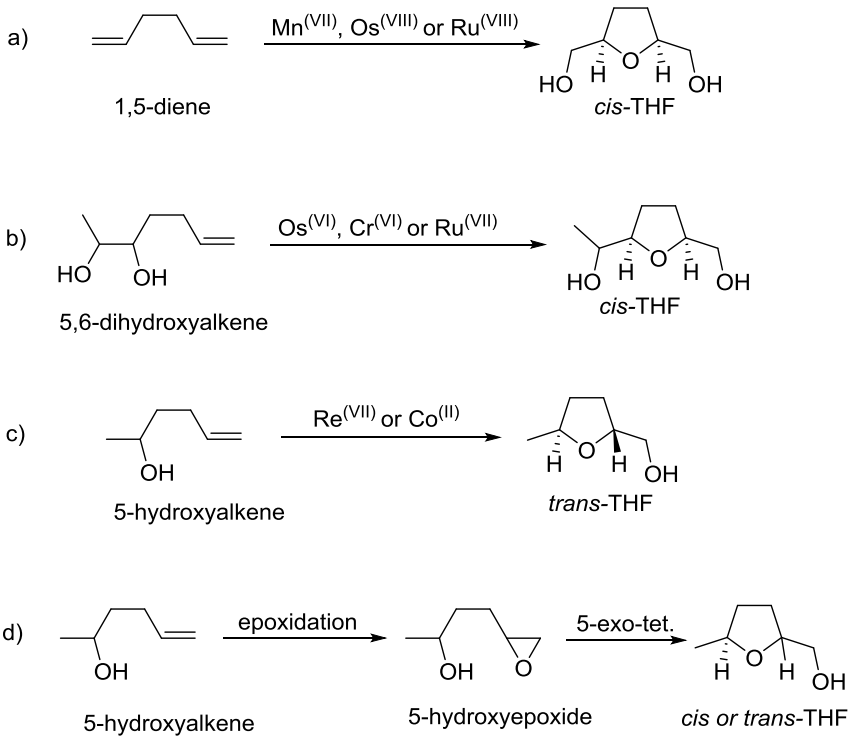
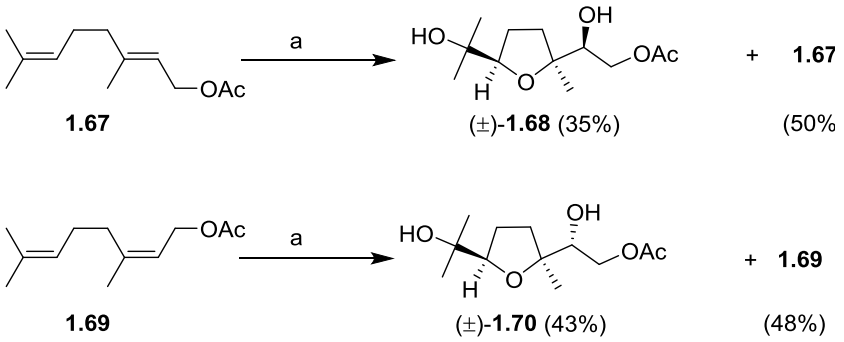


Figure 1.3: Oxidative cyclisation by metal-oxo species: a) 1,5-diene; b) 5,6-dihydroxyalkenes; c) 5-hydroxyalkenes; d) epoxidation-cyclisation tandem sequence.

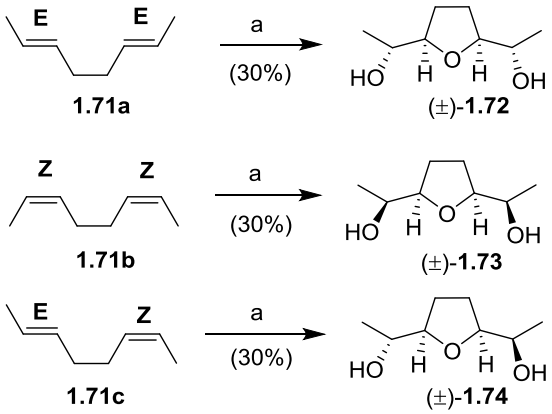
1.2.1. Permanganate Mediated Oxidative Cyclisation of 1,5-Dienes

Permanganate has been shown to be a mediator of oxidative cyclisation of 1,5-dienes. In 1924, Kotz and Steche could not identify a product which resulted from reaction of geranyl acetate (**1.63**) with potassium permanganate, and the product was described as "oxidodioxygeraniolmonoacetate".[27] However, in 1965 this product was identified as a *cis*-2,5-disubstituted THF diol **1.68** by Klein *et al.*, who obtained it in 35%, along with 50% recovered starting material (scheme 1.12).[28] Neryl acetate (**1.69**) was also subjected to the permanganate oxidative cyclisation, affording *cis*-THF diol **1.70** in a stereospecific fashion in 43% yield (scheme 1.12).



Scheme 1.12: Oxidative cyclisation of 1,5-dienes by $KMnO_4$. **Reagents and conditions**: a) $KMnO_4$, acetone: H_2O (5:1), CO_2, pH = 7.5, 0 °C, 30 min.

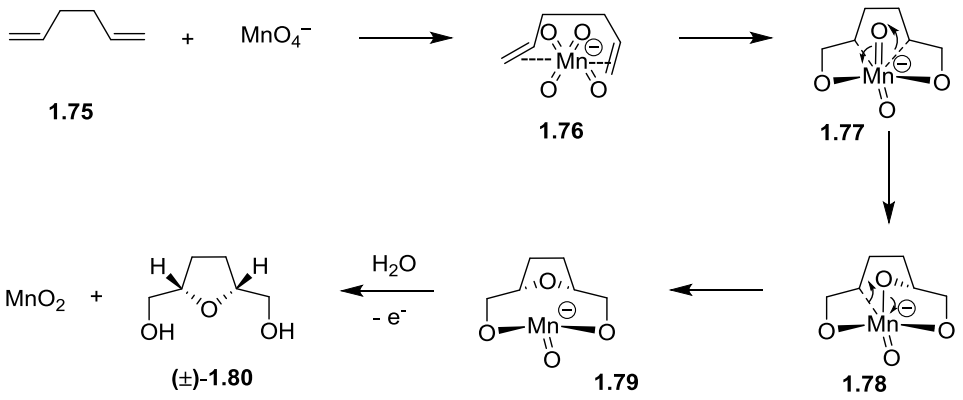
Oxidative cyclisation of 1,5-dienes using potassium permanganate was investigated by Walba *et al.*[29] Different dienes **1.71a-c** were oxidised to form the corresponding diols **1.72-1.74** with excellent *cis*-stereoselectivity (~ 97%, scheme 1.13). It was confirmed that the geometry of the diene precursor determined the stereochemistry of the resultant THF.



Scheme 1.13: The relationship between alkene geometry and the stereochemistry of permanganate oxidative cyclisation product. **Reagents and conditions**: a) $KMnO_4$, acetone:H_2O (5:1), CO_2 bubbling, pH = 7.5, –20 °C, 30 min.

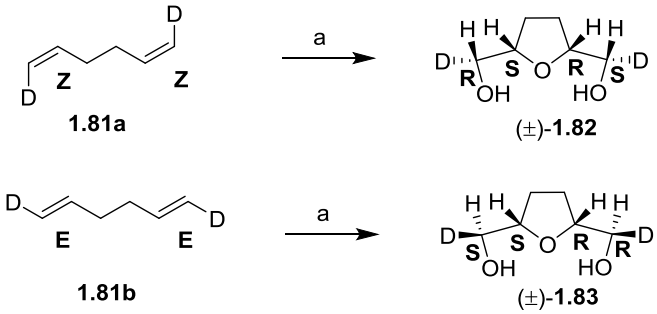
A mechanism of the permanganate oxidative cyclisation was proposed by Walba *et al.* based on the Sharpless mechanistic proposal for the oxidation of olefins by oxo-transition metal species (scheme 1.14).[29,30] It was proposed that after the initial formation of a *bis*-π-complex **1.76** between diene **1.75** and MnO_4^-, an octahedral $Mn^{(VII)}$ intermediate **1.77** is produced *via* two Sharpless-type [2+2] cycloadditions. Migration of alkyl from $Mn^{(VII)}$ to an oxygen atom with reaction of configuration produces a $Mn^{(V)}$ intermediate **1.78**, which affords $Mn^{(III)}$ diester **1.79** after reductive elimination.

Oxidation of $Mn^{(III)}$ ester **1.79**, then hydrolysis process affords the desired *cis*-THF **1.80** with the observed relative stereochemistry, and MnO_2 as a co-product.



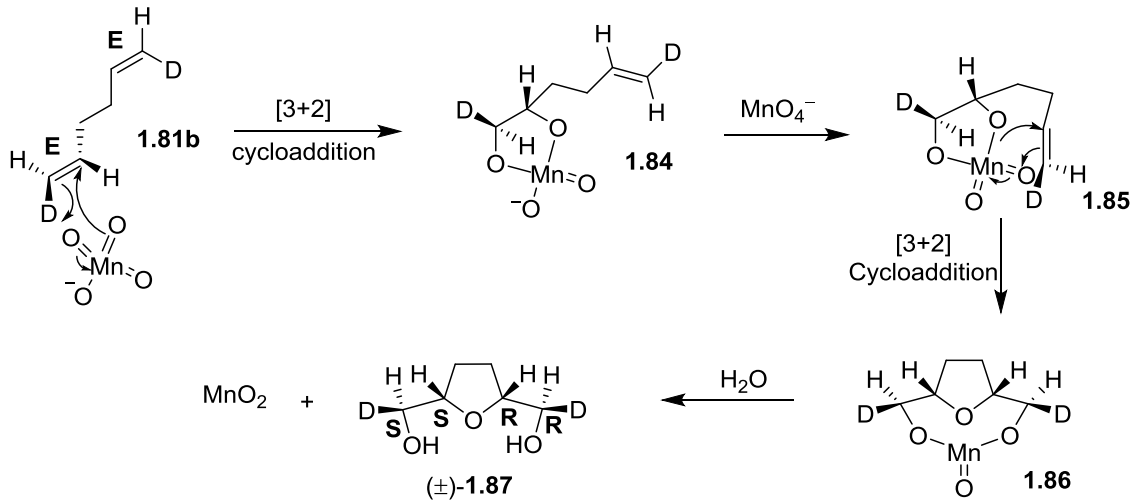
Scheme 1.14: Walba's proposed mechanism for $KMnO_4$ mediated oxidative cyclisation of 1,5-dienes.

Baldwin *et al.* also investigated the permanganate oxidative cyclisation using deuterated dienes **1.81a,b** to produce the corresponding racemic THF systems **1.82** and **1.83** (scheme 1.15).[31] The *cis*-stereoselectivity of diols **1.82** and **1.83** was confirmed by NMR analysis of the THF-diol product.



Scheme 1.15: Baldwin's stereochemical study of the permanganate oxidative cyclisation. **Reagents and conditions**: a) $KMnO_4$, acetone:H_2O (5:1), CO_2 bubbling, pH = 7.5, –20 °C, 30 min.

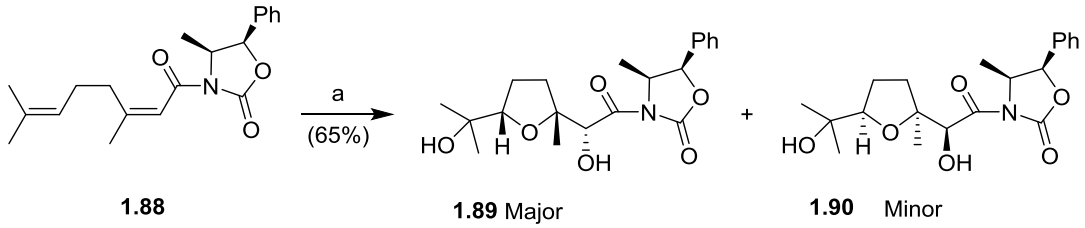
Baldwin *et al*. suggested an alternative mechanism for the permanganate oxidative cyclisation involving two sequential [3+2] cycloadditions (scheme 1.16).[31] The mechanism involved initial [3+2] cycloaddition of permanganate ion to one of the diene double bonds affording the intermediate $Mn^{(V)}$ ester **1.84**. After rapid oxidation with permanganate ion, a second [3+2] cycloaddition with the second double bond occurs to form the intermediate ester **1.86**. Finally basic hydrolysis of the diester **1.86** gives the *cis*-THF **1.87**. The mechanism was also supported by evidence of the intermediacy of a cyclic $Mn^{(V)}$ ester in the reaction of alkenes with permanganate.[32]



Scheme 1.16: Baldwin's proposed mechanism for the $KMnO_4$ promoted oxidative cyclisation of 1,5-dienes.

Wolfe *et al.*[33] investigated the permanganate oxidative cyclisation of 1,5-hexadiene (**1.181b**, scheme 1.16) using H_2O (92% ^{18}O enrichment) as a reaction solvent. The THF system was analysed by Mass spectrometry, and oxygen labelling was identified in the oxidation product. That means that the oxygen label was derived from the solvent. This investigation was incompatible with the mechanism proposed by Walba *et al*. which showed that all three oxygen atoms were derived from a single permanganate molecule. 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 **1.84** (scheme 1.16). The finding of the wolfe study is more consistent with the Baldwin mechanism; but still requires ^{18}O exchange at the Mn center. As $KMnO_4$ only exchanges $H_2{}^{18}O$ slowly under the reaction conditions, it is likely that the occurs in an intermediate such as **1.84.**

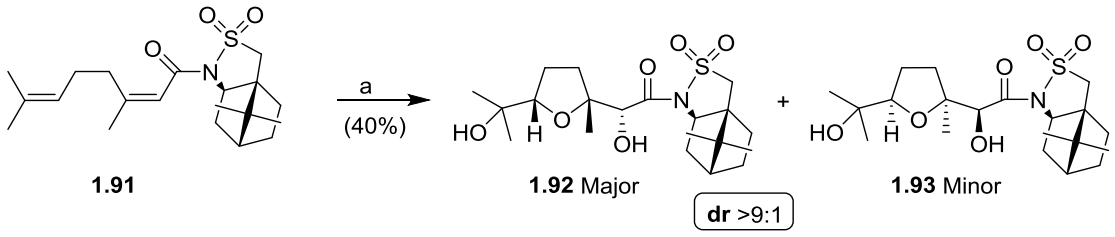
Permanganate oxidative cyclisation was successfully achieved asymmetrically using the Evans' oxazolidinone as a chiral auxiliary by Walba *et al.*[34,35] The oxidative cyclisation of oxazolidinone functionalized dienoate **1.88** gave non racemic THF diols **1.89** and **1.90** with moderate diastereoselectivity (dr 3:1) and in a good yield (65%, scheme 1.17). The major isomer **1.89** resulted from attack of the MnO_4^- from the *Re* face of the dienoate alkene.



1.88 **1.89** Major **1.90** Minor

Scheme 1.17: Auxiliary controlled oxidative cyclisation of dienoate **1.88**. **Reagents and conditions:** a) $KMnO_4$, acetone:H_2O (10:1), CO_2 bubbling, pH = 7.5, –30 °C, 30 min.

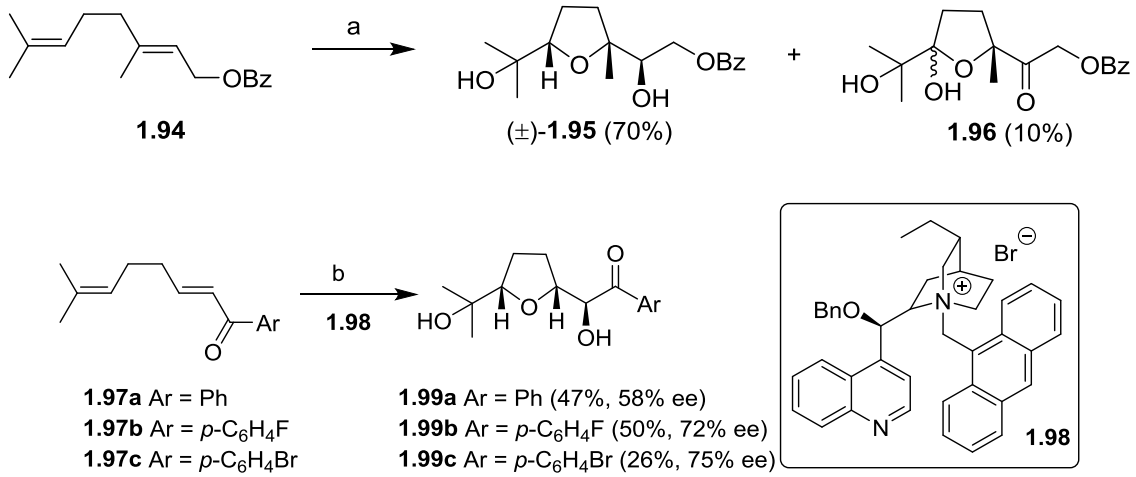
The diastereoselectivity was improved by using Oppolzer's sultam instead Evans' oxazolidinone auxiliary (scheme 1.18).[36,37] Permanganate oxidative cyclisation of the 1,5-dienoate **1.91** bearing (2*R*)-camphorsultum was achieved in an improved diastereoselectivity (dr >9:1) and in a moderate yield (40%, scheme 1.18). The oxidant attack from *Re* face of the conjugated double bond afforded the major diastereoisomer **1.92** with the improved diastereoselectivity. The same facial preference was observed previously by Oppolzer *et al.* in dihydroxylation reactions of enoyl sultams.[36]



1.91 **1.92** Major **1.93** Minor

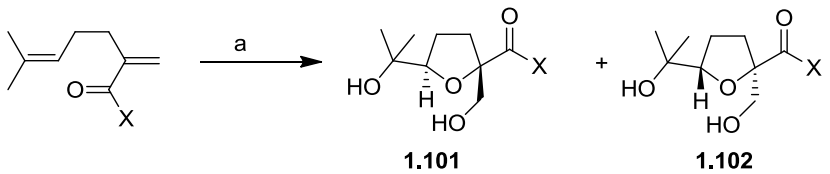
Scheme 1.18: Oxidative cyclisation of dienoate **1.91** bearing Oppolzer's auxiliary. **Reagents and conditions**: a) $KMnO_4$, acetone:H_2O (10:1), CO_2 bubbling, pH = 7.5, –30 °C, 30 min.

More examples were reported during previous studies in the Brown group,[38,39] and selected oxidative cyclisation reactions that were achieved within the group will reviewed here. In 2001, Brown and co-workers achieved an asymmetric oxidative cyclisation using a chiral phase-transfer catalyst (PTC). Geranyl benzoate (**1.94**) was successfully oxidized to *cis*-THF compounds **1.95** in a good yield (70%) in presence of adogen 446 as a PTC (scheme 1.19). In different attempts, asymmetric oxidative cyclisation of dienes **1.97a-c** was achieved using a chiral phase-transfer catalyst **1.98** to afford the corresponding THF diols **1.99a-c** in promising enantiomeric excesses and moderate yields.[40]



Scheme 1.19: Oxidative cyclisations of 1,5-dienes by $KMnO_4$ using phase-transfer catalysis. **Reagents and conditions**: a) $KMnO_4$ (2.0 equiv. of 0.4M aq. sol.), AcOH (4.0 equiv.), Adogen 464 (0.4 equiv.), Et_2O. b) $KMnO_4$ (1.6 equiv. powder), AcOH (6.5 equiv.), PTC **1.98** (0.1 equiv.), CH_2Cl_2.

A study of permanganate oxidative cyclisation of dienoates using a variety of different auxiliaries was reported recently by the Brown group.[13] (2*R*)-10,2-Camphorsultam and a selection of cyclohexyl chiral auxiliaries (entry 1-6, table 1.2) were used in the study (scheme 1.20). Oxidative cyclisation of dienoate **1.100a** bearing the (2*R*)-10,2-camphorsultam afforded the THF system **1.101** as a single isomer, although moderate yield (38%) was obtained (entry 1, table 1.2). While the dienoates **1.100b-e** bearing different auxiliaries afforded diastereoisomeric THF diols **1.101b-e** and **1.102b-e** with optimized yields in the range 57−99%, but with markedly different levels of diastereoinduction (entry 2-5). Oxidative cyclisation of tolylcyclohexyl dienoate **1.100f** gave no diastereoselectivity (dr 1:1) with 57% yield (entry 6), while oxidation of methyl dienoate **1.100g** gave excellent yield of the racemic product (92%, entry 7, scheme 1.20).



Reaction 1.20: Stereocontrolled permanganate oxidative cyclisation of 1,5-diene systems by Brown and co-workers.[13] **Reagents and conditions**: a) MnO_4^-, AcOH, acetone.

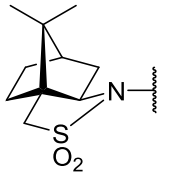
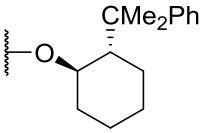
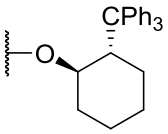
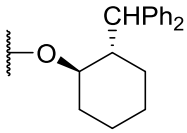
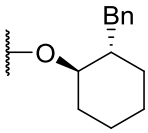
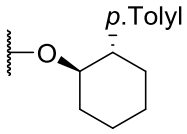
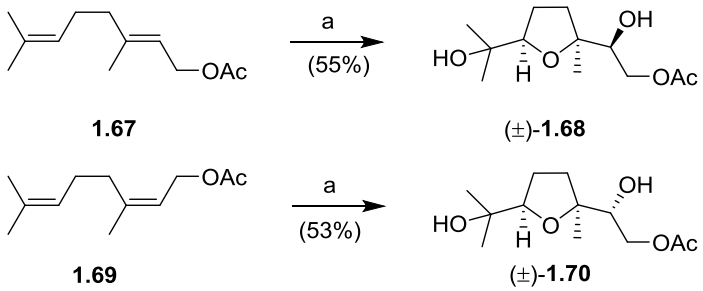
Entry	X	Diene	Reaction Yield (%)	dr (1.101:1.102)
1		**(–)-1.100a**	38	Only **1.101**
2		**(–)-1.100b**	94	4.2:1[b]
3		**(±)-1.100c**	62[a]	32.3:1[c]
4		**(±)-1.100d**	99[a]	1.8:1[c]
5		**(±)-1.100e**	82[a]	1.3:1[c]
6		**(±)-1.100f**	57[a]	1:1[b]
7		**1.100g**	92	1:1

Table 1.2: Investigation of permanganate oxidative cyclisation of 1,5-dienes by Brown and co-workers.[13] [a]Racemic products were obtained. [b]Ratio of diastereoisomers estimated from the ^{1}H NMR spectrum. [c]Ratio of diastereoisomers determined using HPLC.

The Brown group have also applied the auxiliary mediated oxidative cyclisation to the total synthesis of acetogenins,[41] and linalool oxide.[13]

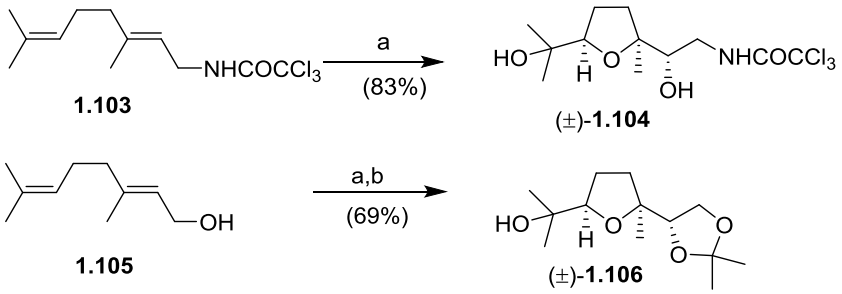
1.2.2. Osmium Tetroxide Mediated Oxidative Cyclisation of 1,5-Dienes

In 1998, osmium tetroxide catalysed oxidative cyclisation was first reported by Piccacialli *et al.* using sodium periodate as a co-oxidant.[20] The *cis*-THF systems **1.68** and **1.70** were prepared using geranyl acetate (**1.67**) and neryl acetate (**1.69**) as starting materials respectively (scheme 1.21). Interestingly, using *n*-methylmorpholine-*n*-oxide (NMO) as a co-oxidant instead of sodium periodate did not afford the desired cyclised products.



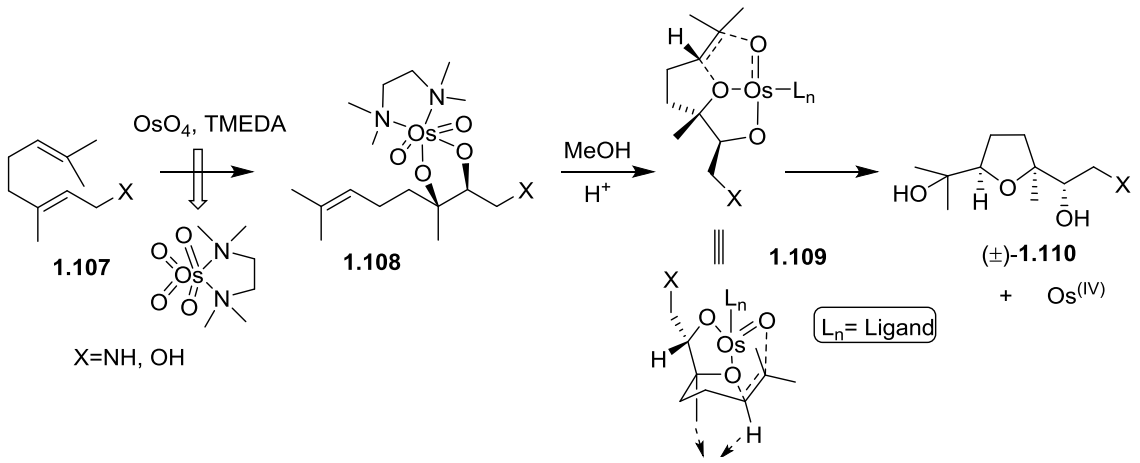
Scheme 1.21: Osmium-catalysed oxidative cyclisations of geranyl acetate (**1.67**) and neryl acetate (**1.69**) by OsO_4. **Reagents and conditions**: a) OsO_4 (5.0 mol %), $NaIO_4$ (4.0 equiv.), DMF, 16 h.

Donohoe *et al.* reported the synthetic application of an OsO_4/TMEDA combination for the oxidative cyclisation of 1,5-functionalised dienes (scheme 1.22).[42] The original expectation was to obtain the corresponding dihydroxylated products by reacting dienes **1.103** and geraniol (**1.105**), however *cis*-THF diols **1.104** and **1.106** were obtained in good yields. It was thought that OsO_4/TMEDA combination provides a hydrogen bond acceptor which can direct the regeoselectivity of the initial osmylation.[43] Exposure of the intermediate osmate ester to the acidic conditions promoted the cyclisation.



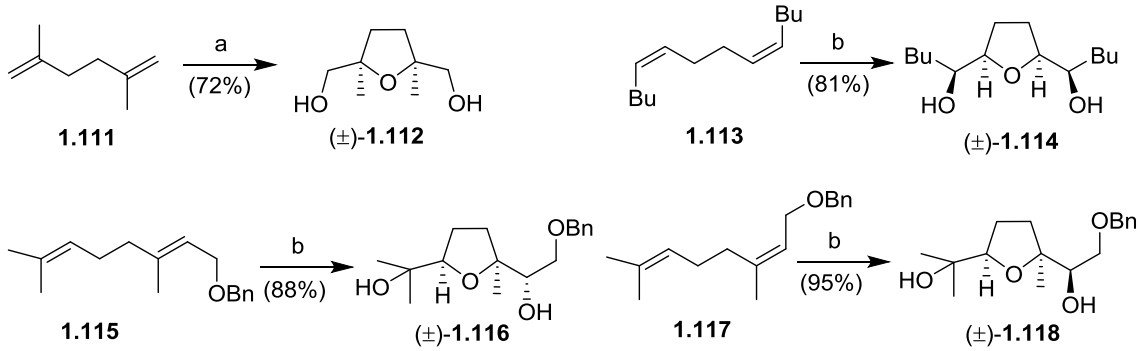
Scheme 1.22: Synthesis of THF ring system using OsO_4/TMEDA complex. **Reagents and conditions**: a) OsO_4 (1.0 equiv.), TMEDA (1.0 equiv.), CH_2Cl_2, –78 °C then MeOH, HCl, rt. b) $(MeO)_2CMe_2$, TFA.

Donohoe *et al.* proposed a mechanism for OsO_4/TMEDA cyclisation based on the sequential [3+2] cycloadditions pathway proposed by Baldwin *et al.* for permanganate oxidative cyclisation (scheme 1.23).[31] Initially, regioselective osmylation of one of the double bonds of the 1,5-diene **1.107** proceeded under hydrogen bonding control to form an osmate$^{(VI)}$ ester **1.108**. Then intramolecular cyclisation with the remaining double bond afforded osmate$^{(IV)}$ ester **1.109**. Hydrolysis of the ester **1.109** gives the observed *cis*-THF system **1.110**. It was thought that the acid either serves to promote the rapid ligand exchange to allow the cyclisation or protonate the oxo-ligand species. In the case of protonation of the oxo-ligand species the acid will make the osmium-oxo species a better electrophile and more reactive toward the cyclisation. The *cis*-stereoselectivity of the THF ring was explained by the transition structure **1.109**, in which the intact glycol osmium bonds provide the *cis*-stereochemistry across the incipient THF ring.[42]



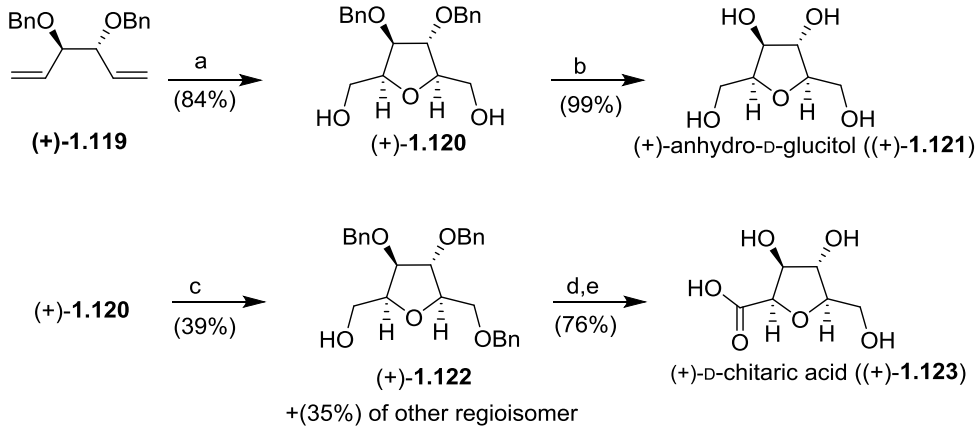
Scheme 1.23: Donohoe's proposed mechanism of OsO_4/TMEDA oxidation cyclisation.

In order to avoid the unattractive use of stoichiometric OsO_4, Donohoe *et al.*[44] developed catalytic method using Me_3NO as a co-oxidant under acidic conditions. Various 1,5-dienes were cyclised by OsO_4 to afford racemic *cis*-THF diols in good to excellent yields (scheme 1.24).



Scheme 1.24: Catalytic use of OsO_4 as oxidising agent under acidic conditions. **Reagents and conditions**: a) OsO_4 (5.0 mol %), Me_3NO (4.0 equiv.), CSA (6.0 equiv.), CH_2Cl_2; b) OsO_4 (5.0 mol %), Me_3NO (4.0 equiv.), TFA (excess), acetone:H_2O (9:1).

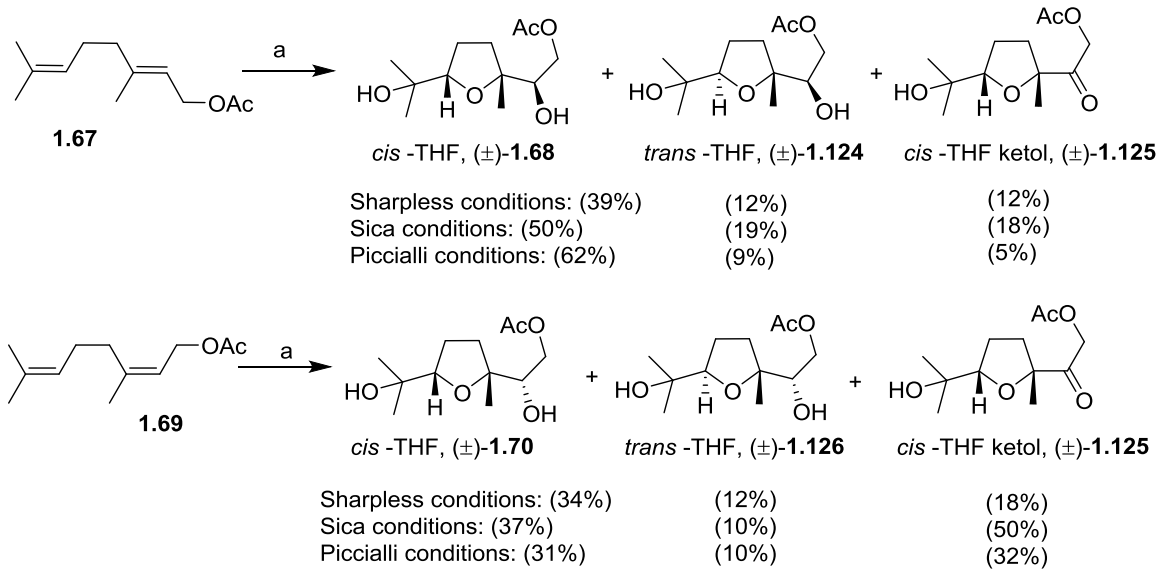
OsO_4 promoted oxidative cyclisation was used to afford a stereocontrolled synthesis of (+)-anhydro-D-glucitol ((+)-**1.121**) and ((+)-D-chitaric acid (+)-**1.123**, scheme 1.25).[44] Enantiomerically enriched 1,5-diene (+)-**1.119** was oxidised by OsO_4 and yielded a single stereomeric *cis*-THF diol (+)-**1.120** in good yield (84%). The synthesis of (+)-anhydro-D-glucitol ((+)-**1.121**) was completed by deprotection of benzyl ethers. In addition, *cis*-THF diol (+)-**1.120** was selectively momo protected, followed by alcohol oxidation and finally deprotection process achieved the synthesis of (+)-D-chitaric acid ((+)-**1.123**, scheme 1.25).



Scheme 1.25: Stereocontrolled synthesis of (+)-anhydro-D-glucitol (**1.121**) and (+)-D-chitaric acid (**1.123**). **Reagents and conditions**: a) OsO_4 (5.0 mol %), Me_3NO (4.0 equiv.), CSA (6.0 equiv.), CH_2Cl_2; b) H_2, Pd/C, EtOH; c) BnBr, Ag_2O, toluene; d) TEMPO (catalytic), $NaClO_2$, NaClO, MeCN; e) H_2, Pd/C, MeOH.

1.2.3. Ruthenium Mediated Oxidative Cyclisation of 1,5-Dienes

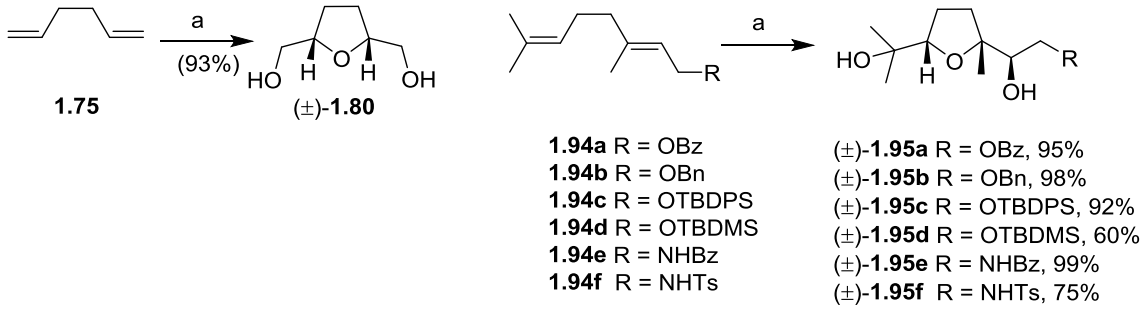
Sharpless *et al.* were the first group to report the oxidative cyclisation of 1,5-dienes using ruthenium tetroxide (scheme 1.26).[45] In fact, oxidative cyclisation of geranyl acetate (**1.67**) and neryl acetate (**1.69**) to THF-diols isomers was discovered during attempts to optimize the preparation of carboxylic acids from a primary alcohols, using catalytic RuO_4. The 2,5-disubstituted THF compounds were obtained as a mixture of *cis* and *trans* isomers along with *cis*-THF ketol **1.125** as a byproduct (scheme 1.26). The same transformation was investigated by Sica *et al.,* although attempts to improve the *cis* selectivity of the reaction did not lead to a signifigant improvment.[46] Piccialli *et al*. investigated a range of different conditions for the Ru-catalysed oxidative cyclisation to afford the THF rings.[47] Some success with geranyl acetate (**1.67**) was achieved and the over-oxidised product **1.25** was reduced.



Scheme 1.26: Oxidative cyclisation using RuO_4. **Reagents and conditions**: a) *Sharpless conditions*: $RuCl_3.(H_2O)_n$, (2.2 mol %), $NaIO_4$ (3.1 equiv.), CCl_4:CH_3CN:H_2O (2:2:3), 0 °C, 15 min; *Sica conditions*: $RuO_2.2H_2O$, (5.0 mol %), $NaIO_4$ (2.5 equiv.), EtOAc:$(CH_3)_2CO$:H_2O (2:1:1), 0 °C, 4 min; *Piccialli conditions*: $RuO_2.2H_2O$, (4.0 mol %), $NaIO_4$ (4.0 equiv.), EtOAc:CH_3CN:H_2O (3:3:1), 0 °C, 4 min.

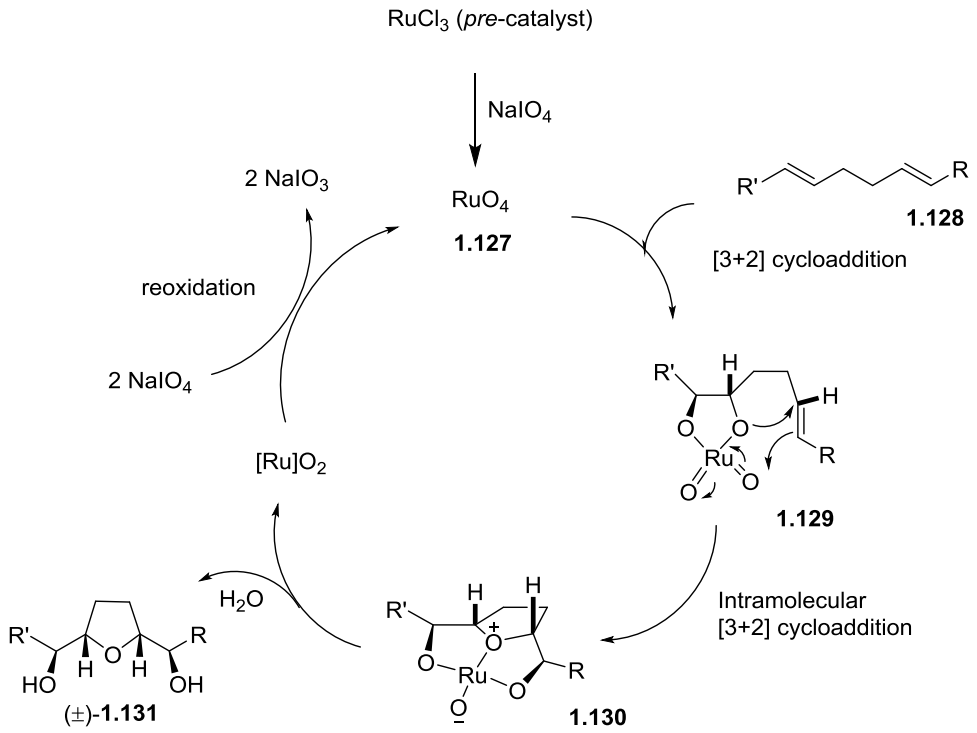
Stark *et al.* reported a highly efficient procedure to prepare THF diols with high *cis*-stereoselectevity (dr >95:5) using RuO_4 as an oxidant, applying the conditions to a range of different 1,5-dienes (scheme 1.27).[48,49] In this method $NaIO_4$ on wet silica was used as a co-oxidant in a solvent mixture of THF and CH_2Cl_2 (9:1). The conditions did

not afford any of the corresponding *trans*-THF diols except in the case of **1.95b,c**. Various functional and protecting groups showed compatibility with the reaction conditions, and the oxidative cyclisation proceeded in a good yield for a range of different substituted alkenes.



Scheme 1.27: Catalytic RuO_4 mediated cyclisation of 1,5-dienes. **Reagents and conditions**: a) $RuCl_3$ (0.2 mol %), $NaIO_4$ on wet silica (3.0 equiv.), THF:CH_2Cl_2 (9:1).

Stark *et al.* proposed a mechanism for the ruthenium oxidative cyclisation of 1,5-diene, which is analogous to the $KMnO_4$ and OsO_4 mediated oxidative cyclisation (scheme 1.28).[31,42] It was proposed that after oxidation of the pre-catalyst, an initial [3+2] cycloaddition occurs between RuO_4 and one of the double bonds of diene **1.128** to afford $Ru^{(VI)}$ intermediate **1.129**. A second [3+2] interamolecular cycloaddition to the intermediate **1.130** is followed by hydrolysis to afford *cis*-THF diol **1.131** and RuO_2, which is oxidised back to RuO_4.



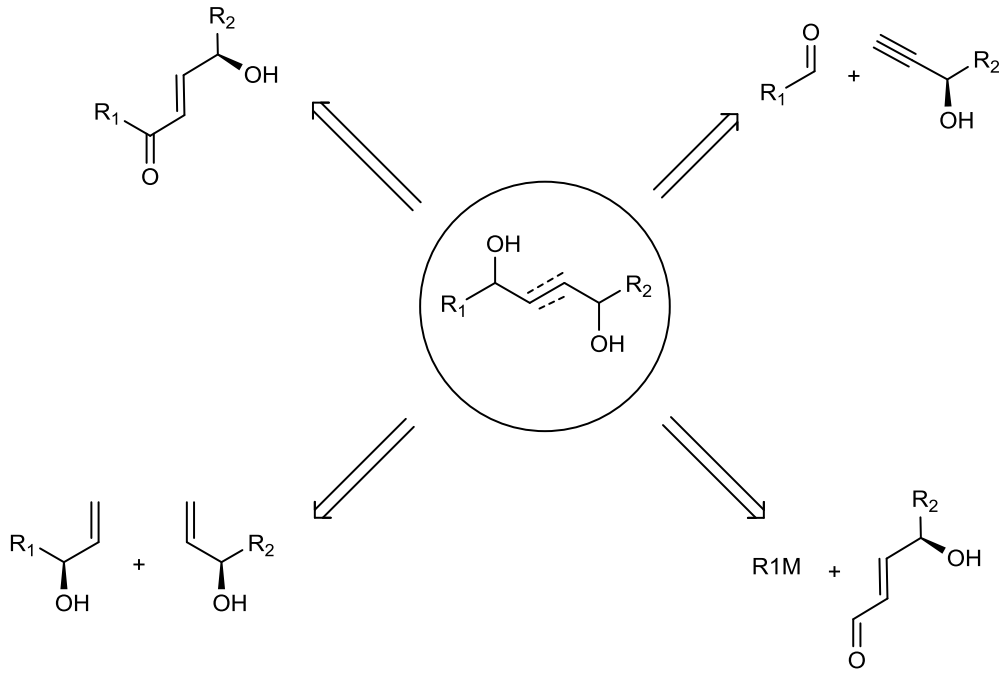
Scheme 1.28: Stark's proposed mechanism for ruthenium-catalysed oxidative cyclisation of 1,5-dienes.

1.2.4. Conclusions

The oxidative cyclisation of 1,5-dienes has been applied in synthesis of natural products in racemic and asymmetric versions. A number of metal-oxo agents have been employed in the oxidative cyclisation of 1,5-dienes such as $KMnO_4$, $NaMnO_4$, OsO_4 and RuO_4 to afford THF rings. Generally permanganate ions affords moderate to good yields, is environmental friendly and cheaper compared to other metal-oxo reagents. However, permanganate ions 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. One of the major advantages of permanganate oxidative cyclisation is that when used with chiral phase transfer catalysts and chiral auxiliaries the stereoselectivity of the oxidation can be controlled. Osmium tetroxide provides an efficient oxidation, however it does not allow direct asymmetric oxidative cyclisation of 1,5-dienes.

1.3. Synthetic Approaches Toward 1,4-Diols

In this section, the stereoselective synthesis of 1,4-diols is reviewed with a focus on application to our proposed synthesis of eurylene. The most widely used strategies to achieve the synthesis of nonsymmetrical, enantiomerically pure 1,4-diols involve the addition of alkylmetallic reagent,[50] or terminal alkynes,[51,552] to carbonyl derivatives (scheme 1.29). Alternatively, stereoselective reduction of γ-hydroxy ketones was successfully used to afford chiral 1,4-diols.[53-55] In addition, a combination of temporary silicon or phosphate tethering methodology with ring-closing metathesis has been used to achieve the synthesis of 1,4-diols[56-60] In most cases, two different chiral sources are needed to install the two stereocentres in the 1,4-diols.[61] The method will be described below and evaluated for potential application in our proposed synthesis of eurylene.

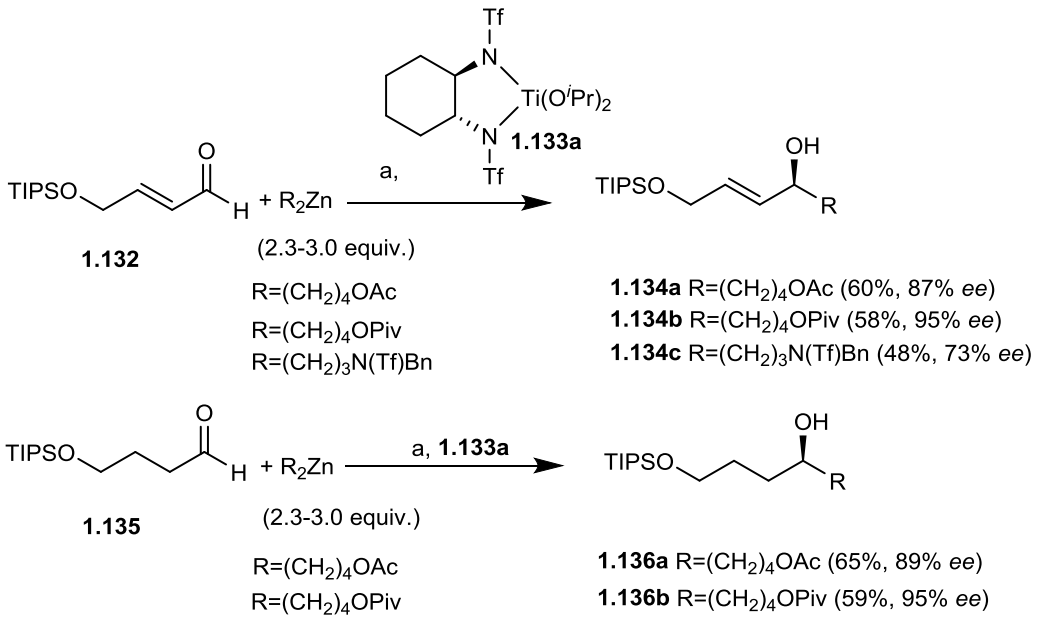


Scheme 1.29: Synthetic approaches to chiral non-racemic 1,4-diols.

1.3.1. Addition of Organometallic Reagents to Carbonyl Compounds

Synthesis of 1,4-diols was achieved by addition of organometallic reagents to carbonyl compounds (schemes 1.30 and 1.31). Dialkylzinc reagents have been used with saturated or unsaturated γ-alkoxyaldehydes in the presence of chiral titanium catalyst **1.133a,b**.[50] The addition of diorganozinc (R_2Zn) to saturated or unsaturated γ-alkoxyaldehydes **1.132** and **1.135** catalysed by the chiral catalyst **1.133** afforded the required mono-protected 1,4-diols **1.134a-c** and **1.136a,b** with moderate to high enantioselectivity (73-95%) and acceptable yields (48-65%). Preparation of the chiral

catalyst was achieved by reaction of, $Ti(O^iPr)_4$ with the corresponding diamine.[62] The substrate aldehydes **1.132** and **1.135** were prepared in 2 steps from (*Z*)-2-butene-1,4-dials and 1,4-butanediol in 56-73% overall yield. The organometallic reagent (R_2Zn) was prepared by reacting the corresponding alkyl iodide (RI) with Et_2Zn (1.3 equiv., 55 °C, 3-18 h) in the presence of CuI or CuCN (0.3 mol %).[63,64]

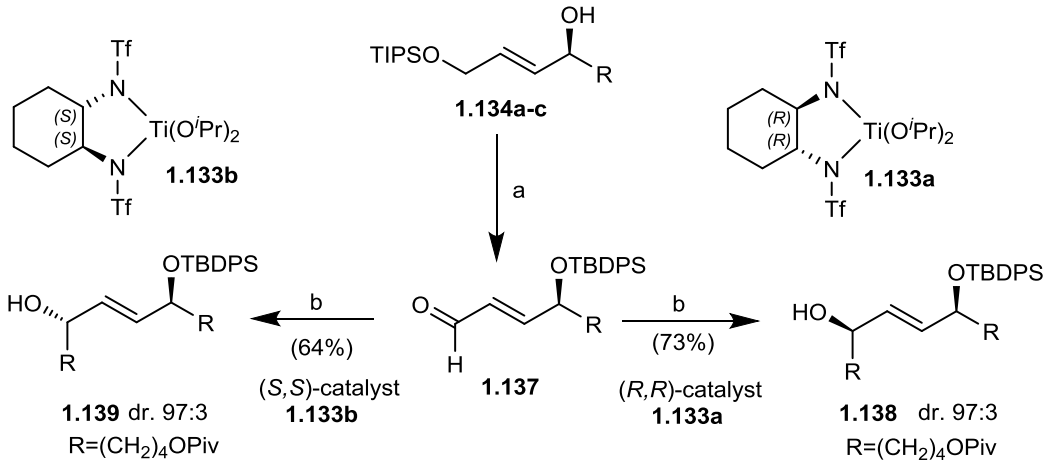


Scheme 1.30: Stereocontrol addition of organozinc reagent to the aldehydes **1.132** and **1.135**. **Reagents and conditions**: a) Titanium catalyst **1.133a** (8 mol %), $Ti(O^iPr)_4$ (2.0 equiv.), toluene, –75 to –15 °C.

It was found the addition of bis(4-acetoxybutyl)zinc to the aldehyde **1.132** gave alcohol **1.134a** (87% *ee*, scheme 1.30). The saturated aldehyde **1.135** afforded **1.136a** with slightly higher yield and enantioselectivity. The best result where obtained from the sterically hindered bis(4-pivaloxybutyl)zinc reagent with the same aldehydes affording alcohols **1.134b** and **1.136b** (95% *ee*, scheme 1.30). The results were attributed to the poorer chelating ability of the pivaloxy group with the zinc centre compared to that of the acetoxy group. The chelating functionality deactivated the zinc reagent and made alkoxy ligand exchange processes at the chiral titanium centre slow down. In the case of using zinc reagent containing nitrogen ($Zn((CH_2)_3N(Tf)Bn)_2$), a deactivation of the zinc reagent by the basic nitrogen atom occurred and an enantioselectivity of only 73% *ee* was obtained.

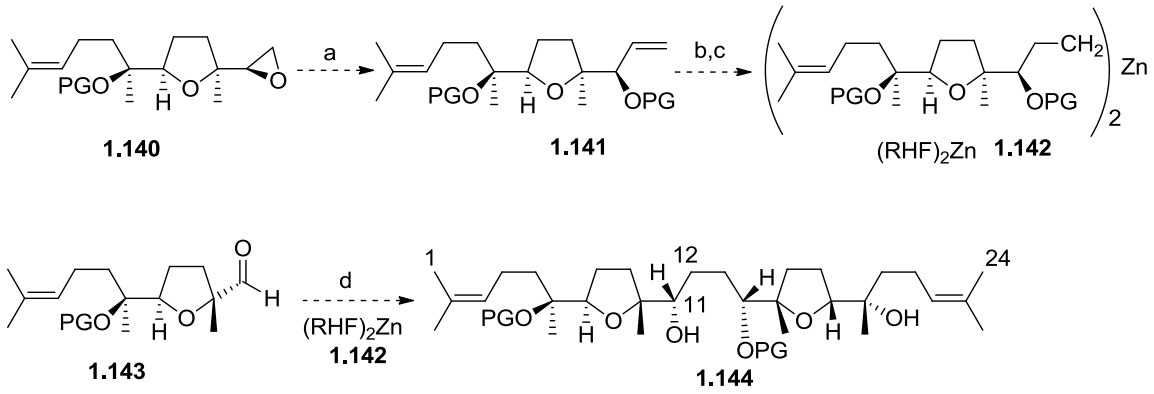
The alcohol products **1.134a-c** were converted by simple reactions into γ-alkoxyaldehydes **1.137** and reacted again with the organozinc reagent $(FG\text{-}R)_2Zn$ to

afford precursors to 1,4-diols (scheme 1.31). It was found that the configuration of the newly formed chiral centre depended only on the configuration of the titanium catalyst and not on the configuration of the chiral centre already present in the molecule. Thus, the use of (*R,R*)-catalyst **1.133a** with **1.137** afforded 1,4-diol **1.138** in good yield (73%) and high dr 97:3 (scheme 1.31). Whereas reaction of **1.137** using (*S,S*)-catalyst **1.133b** provided *meso*-diastereoisomer **1.139** in satisfactory yield (64%) with dr 97:3.



Scheme 1.31: Stereocontrolled addition of organozinc compounds using chiral titanium catalysts **1.133a,b**. **Reagents and conditions**: a) i) TBDPSCl, ii) TFA, H_2O, iii) NMO, Pr_4NRuO_4. b) $((CH_2)_3OPiv)_2Zn$, titanium catalyst **1.133a** or **b** (8 mol %), Ti(O^{i}Pr)$_4$, toluene.

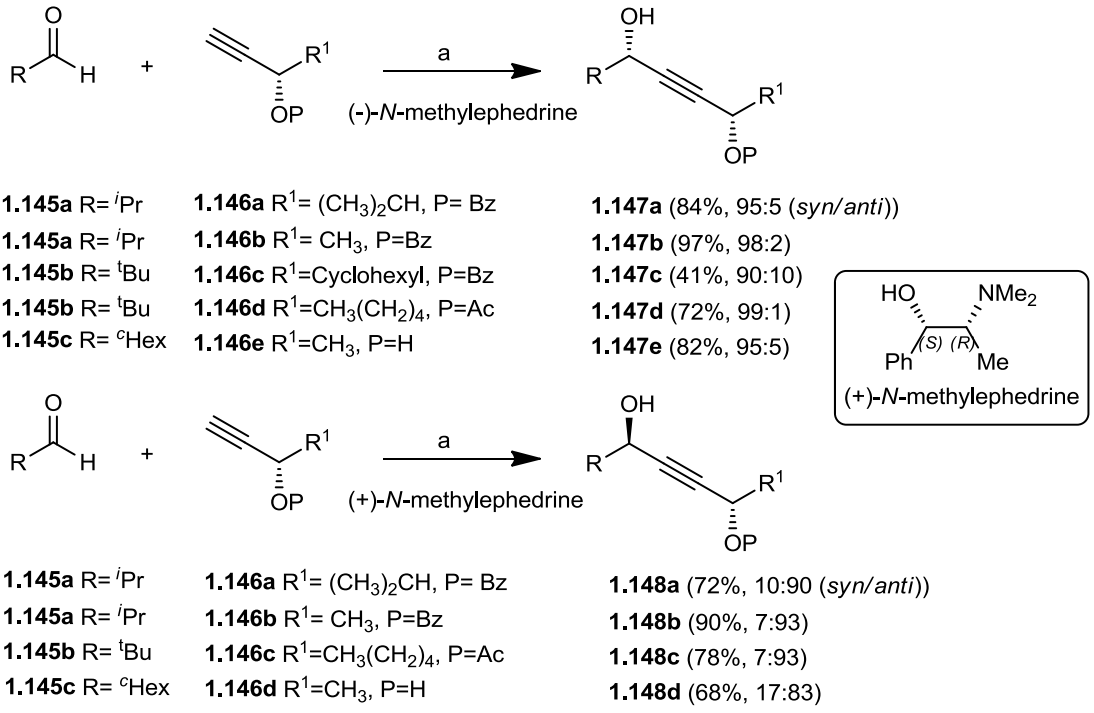
In principle, this organozinc methodology could be applied in our approach to establish the new chiral centre at C_{11} and couple the left (C_1-C_{11}) and right (C_{12}-C_{24}) fragments of eurylene (scheme 1.32). A significant challenge would be preparation of a highly fuctionalised RHF-zinc reagent. Furthermore, our substrates contain multiple Lewis-basic groups that could affect the stereoselectivity.



Scheme 1.32: Proposed route to achieve coupling of the two fragments **1.410** and **1.143**. **Reagents and conditions**: a) Me_3S^+I, ^nBuLi. b) Selective iodination. c) Et_2Zn, CuI. d) Chiral titanium catalyst **1.133a**, $Ti(O^iPr)_4$, toluene.

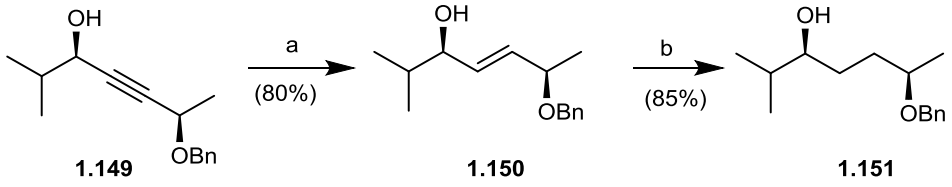
1.3.2. Addition of Terminal Alkynes to Carbonyl Compounds

A well-established method for the stereoselective addition of alkynes to aldehydes is based on the addition of alk-1-yn-3-ols **1.146a-e** (or their protected derivatives) to aldehydes **1.145a-c** mediated by zinc triflate, Et_3N, and (+)- or (–)-*N*-methylephedrine (scheme 1.33).[51,52] This method has been applied to the preparation of alk-2-yne-1,4-diols. In general, the configuration observed at the emergent stereocenter depends on the enantiomer of *N*-methylephedrine employed resulting in good to excellent diastereoselectivities. The process was tolerant with a range of protective groups (benzyl, benzoyl, acetyl and *tert*-butyldimethylsilyl groups). In general, better stereoselectivity was obtained for 1-alkyn-3-ols where the hydroxyl protected as benzoate or acetate than for protected as silyl ethers or benzyl ethers.[51]



Scheme 1.33: Stereocontrolled addition of 1-alkyn-3-ols to aldehydes.[51,52] **Reagents and conditions**: a) $Zn(OTf)_2$ (1.1 equiv.), *N*-methylephedrine (1.2 equiv.), Et_3N (1.2 equiv.), toluene, rt to 65 °C.

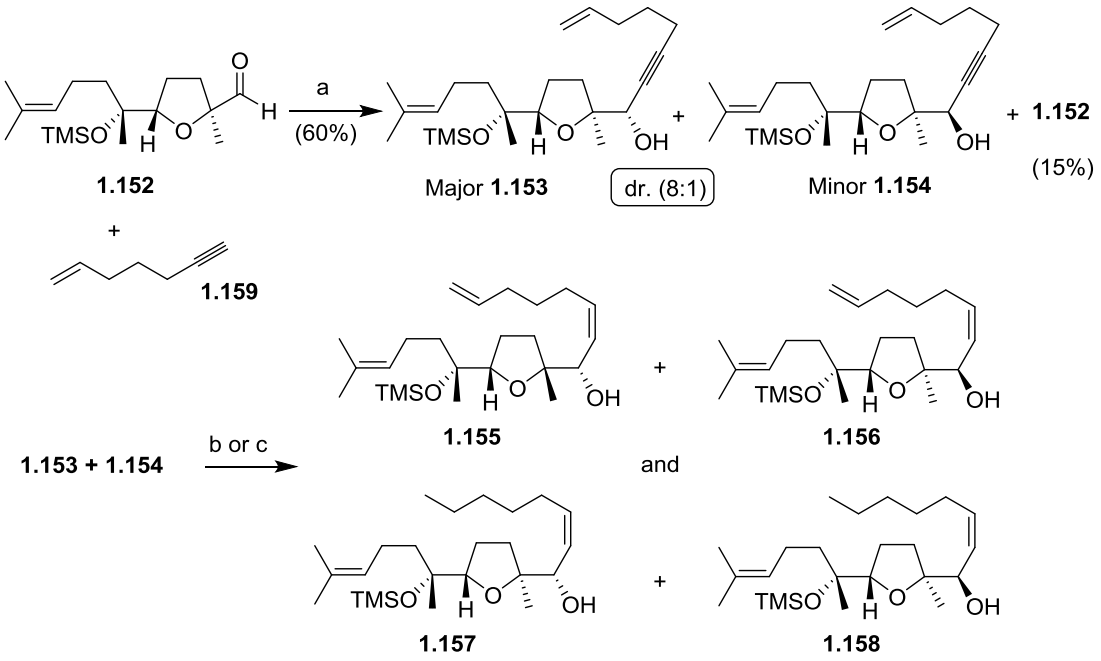
Reduction of the unsaturated bond was achieved over two steps during the application of the methodology in synthesis of natural products (scheme 1.34).[51,65]



Scheme 1.34: Reduction of alkyne **1.19** and **1.150**. **Reagents and conditions**: a) $LiAlH_4$, THF, rt, 1 h. b) H_2 (1 atm.), Pt cat., EtOAc, rt, 1 h.

In an attempt to apply this methodology in the synthesis of eurylene within the Brown group, a terminal alkyne was reacted with *trans*-THF in a previous study (scheme 1.35).[38] The reaction of *trans*-THF **1.152** with synthesised hept-1-en-6-yne (**1.159**) afforded inseparable mixture of epimeric propargylic alcohols **1.153** and **1.154** (dr. 8:1) in 60% yield, along with recovered starting aldehyde **1.152** in 15% yield. The mixture of propargylic alcohols **1.153** and **1.154** was reduced by Lindlar reduction. Unfortunately, the reaction was unselective and resulted in partial reduction of the terminal double bond in the model substrate.

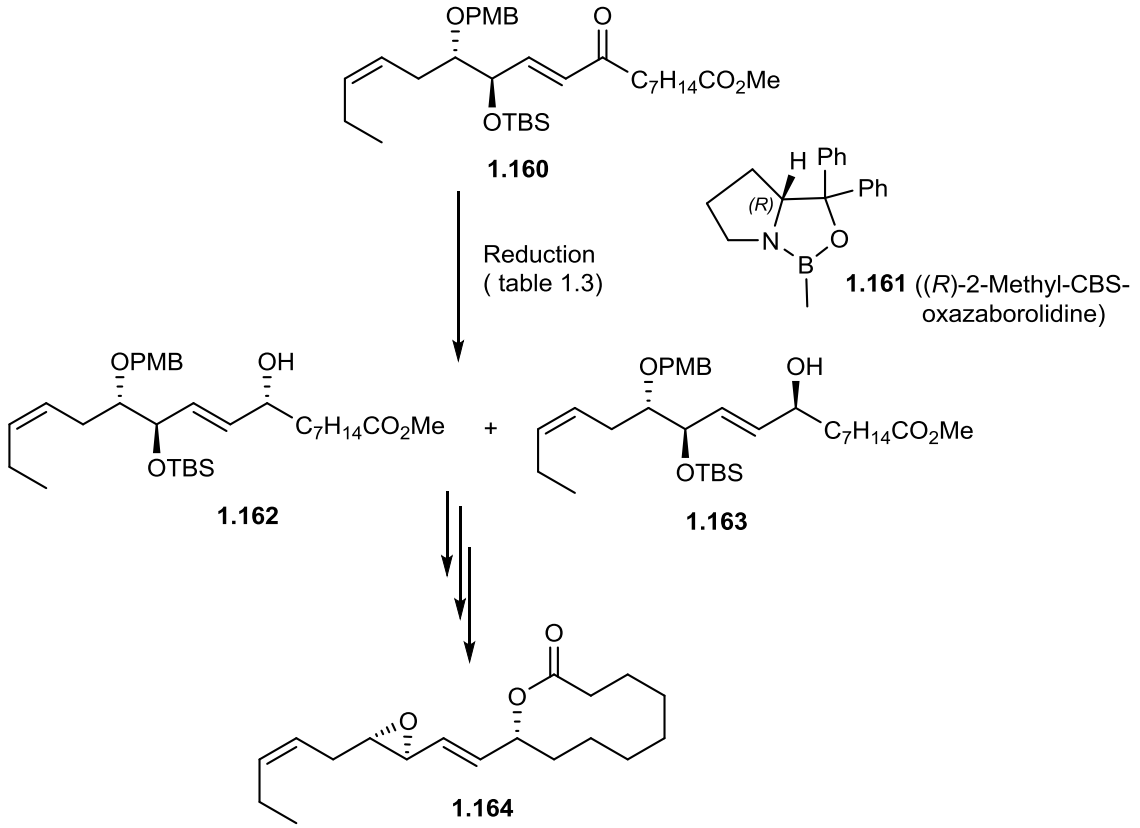
The requested allylic alcohols **1.155** and **1.156** could not be separated from the over reduced compounds **1.157** and **1.158** by flash chromatography. There were no more attempts to investigate the methodology to achieve selective reduction.



Scheme 1.35: Synthesis and reduction of propargylic alcohols **1.153** and **1.154**. **Reagents and conditions**: a) $Zn(Otf)_2$, Et_3N, (+)-*N*-methylephedrine, toluene, 60 °C, 20 h. b) Lindlar catalyst, quinoline, hexane, $H_{2(g)}$, rt, 30 min. c) $MnCl_2$-Pd-$CaCO_3$, quinoline, hexane, $H_{2(g)}$, rt, 15 min.

1.3.3. Stereoselective Ketone Reduction Approaches to 1,4-Diols

Non racemic chiral 1,4-diols have been synthesised using stereoselective reduction of carbonyl group by different organometallic reagents such as boron and aluminium reagents.[53-55,5] Kitahara *et al.* investigated the reduction of γ-protected hydroxyl ketone during the first total synthesis of mueggelone (**1.164**, scheme 1.36, table 1.3), a compound isolated from a bloom-foaming strain of *Aphanizomenon flos-aquae* in 1995.[55,66] Several conditions were investigated for the stereoselective reduction of γ-protected hydroxyl ketone **1.160**, and the highest stereoselectivity (9:1) was found with (*R*) and (*S*) CBS-catalysts and borane THF complex (scheme 1.36).[55,67,68]

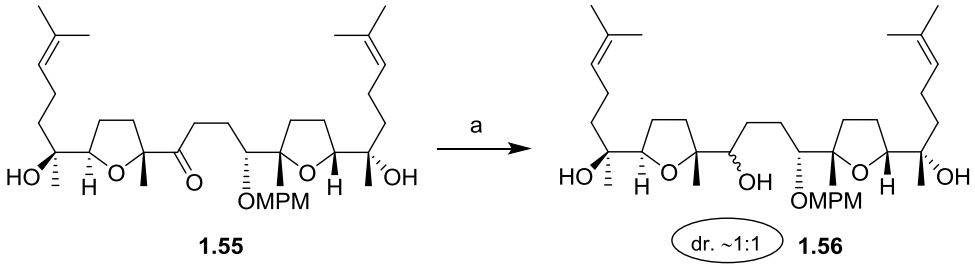


Scheme 1.36: Stereoselective reduction of ketone **1.160** using CBS catalyst.

Entry	Conditions reduction	Yield (%)	Ratio (1.162:1.163)
1	$NaBH_4$, $CeCl_3$, MeOH,	80	1:2
2	L- Selectride, THF	80	1:2
3	(*S*)-CBS reagent, $BH_3.SMe_2$, THF	80	3:1
4	(*R*)-CBS reagent, $BH_3.SMe_2$, THF	58	1:2
5	(*S*)-CBS reagent, BH_3.THF, THF	66	9:1
6	(*R*)-CBS reagent, BH_3.THF, THF	65	1:9

Table 1.3: Investigation of reduction of ketone **1.160**.[55]

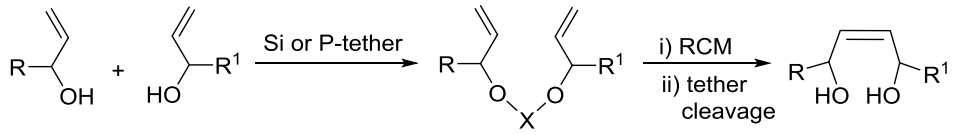
In the total synthesis of eurylene (**1.1**, section **1.1.3**), Kodama *et al.*[5] reduced γ-protected hydroxyl ketone **1.55** with DIBALH (91%) or $NaBH_4$ (95%) to obtain an inseparable mixture of epimeric alcohols **1.56** (scheme 1.37). In principle, a chiral reducing agent or catalyst could be applied to control the diastereoselectivity of the reduction of Kodama's intermediate.



Scheme 1.37: Reduction of ketone **1.55**. **Reagents and conditions**: a) $NaBH_4$, MeOH, 95% or DIBALH, 91%.

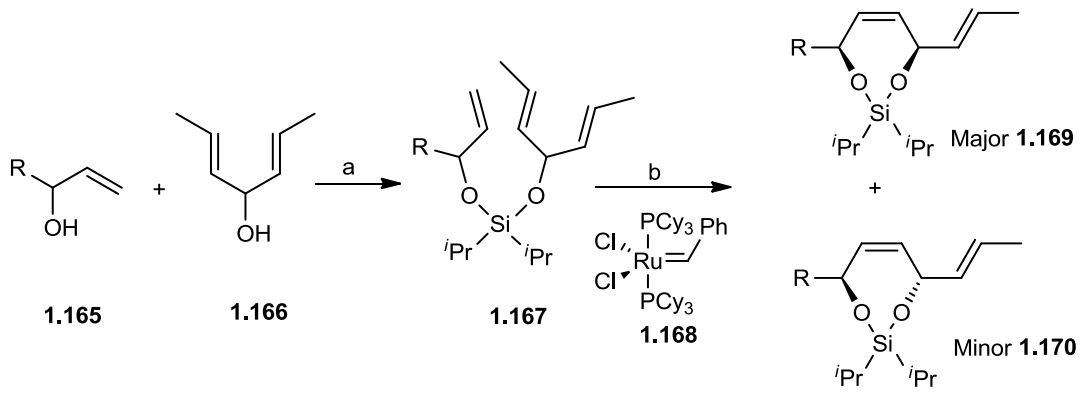
1.3.4. Ring Closing Metathesis Towards 1,4-Diols

The combination of temporary silicon or phosphate tethering methodology with ring-closing metathesis has been demonstrated, to be a useful method for the preparation of simple 1,4-diols (scheme 1.38).[56-60]



Scheme 1.38: Silicon or phosphate-tethered RCM approach to 1,4-diols.

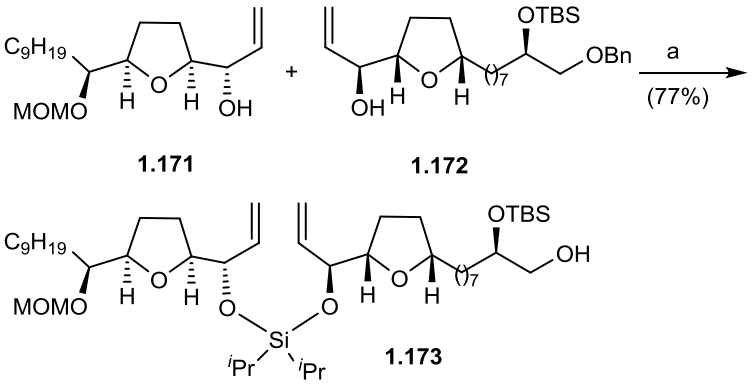
Evans *et al*.[56] described diastereoselective silicon-tethered ring closing metathesis providing suitable way to obtain 1,4-diols (scheme 1.39). Different allylic alcohols **1.65a-e** and **1.66a-e** were reacted with diisopropyldichlorosilane to afford a mixed bisalkoxy silane. Ring closing metathesis of bisalkoxysilanes **1.167a-e** was achieved using 10-15 mmol % of Grubbs' catalyst **1.168** in CH_2Cl_2. The diastereoselective TST-RCM was tolerant of several substituents, the best diastereomeric ratio (99:1) was obtained when R= 2-naphthyl (75% yield). A lower diastereomeric ratio (~40:1) resulted from using allylic alcohol with benzyloxymethyl and carboalkoxy substituents (scheme 1.39). The silyl tether was removed by 5% aqueous HF at rt to afford the required 1,4-diols. It is worth noting that the steric nature of the substituents on the silicon tether was indeed crucial in terms of silaketal formation, overall efficiency and the level of diastereoselection achieved. Diisopropylsilane was superior to methyl and phenyl silane linkers.



1.165a R= Np	**1.166a** (88%)	**1.169a:1.170a** d.r: 99:1 (75%)
1.165b R= *c*-Hex	**1.166b** (85%)	**1.169b:1.170b** d.r: 22:1 (54%)
1.165c R= ^{i}Bu	**1.166c** (77%)	**1.169c:1.170c** d.r: 34:1 (73%)
1.165d R= $BnOCH_2$	**1.166d** (72%)	**1.169d:1.170d** d.r: 41:1 (61%)
1.165e R= BnO_2CCH_2	**1.166e** (72%)	**1.169e:1.170e** d.r: 40:1 (73%)

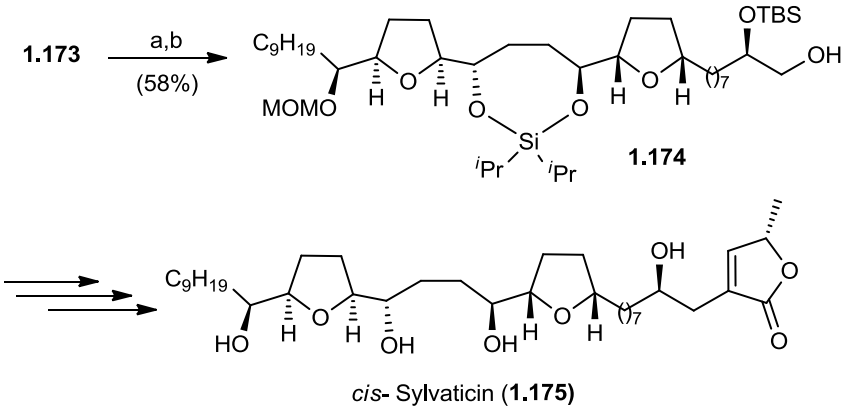
Scheme 1.39: Diastereoselective TST-RCM reaction. **Reagents and conditions**: a) (^{i}Pr)$_2$SiCl$_2$, imid., CH_2Cl_2, 0 °C to rt, overnight. b) Grubbs' catalyst **1.168** (Cy= Cyclohexyl), CH_2Cl_2, 40 °C, 6 h.

Temporary silicon tethered RCM (TST-RCM) has been applied to the total synthesis of *cis*-sylvaticin (**1.175**) by Brown *et al*. (schemes 1.40 and 1.41).[59] The stoichiometric sequential reaction of diisopropyldichlorosilane with allylic alcohol **1.171** and then allylic alcohol **1.172** successfully afforded the required bisalkoxysilane **1.173** (scheme 1.40).



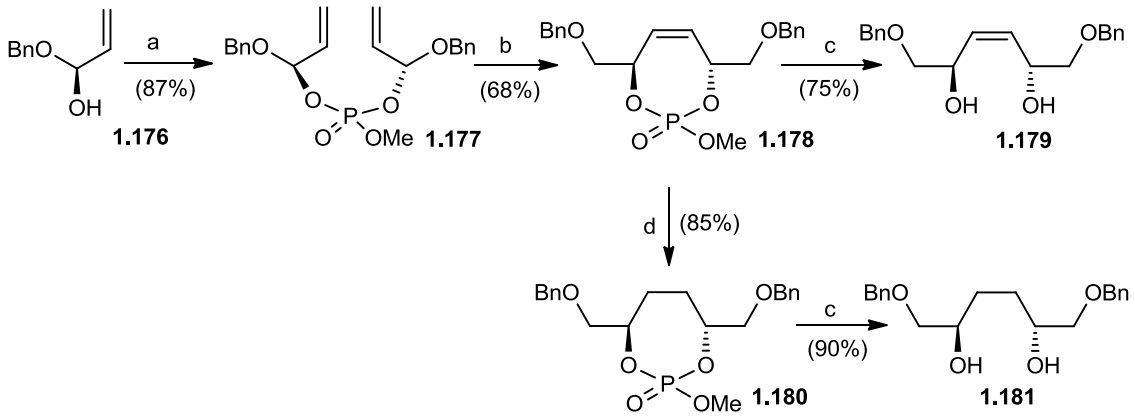
Scheme 1.40: TST-RCM reaction applied to the total synthesis of *cis*-sylvaticin (**1.173**).[59] **Reagents and conditions**: a) (^{i}Pr)$_2$SiCl$_2$, imid., CH_2Cl_2, rt, 3 h.

The siloxane **1.173** was treated with Grubb's 2nd generation catalyst, followed by hydrogenation in the presence of Pd/C to afford the saturated bisalkoxysilane **1.174** (scheme 1.41). The silyl tether was later removed by 5% solution of AcOH in MeOH at rt to afford the required 1,4-diol. In this case there were no other double bonds present in the target, so selective reduction was not an issue.



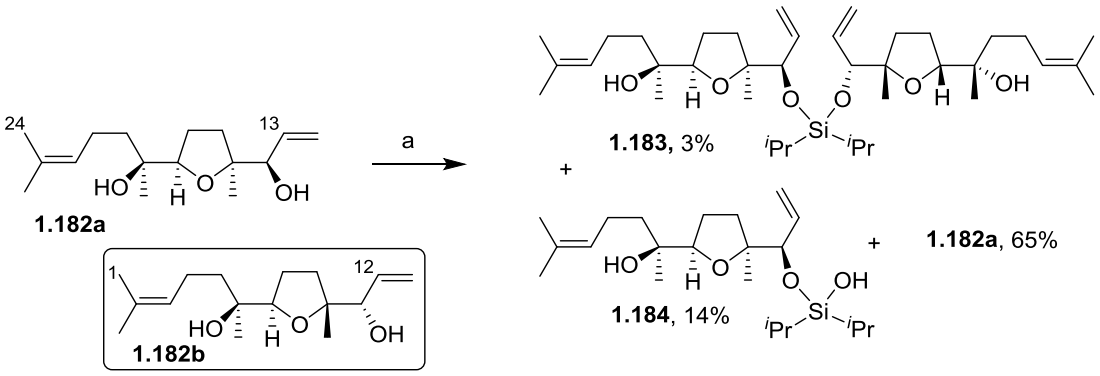
Scheme 1.41: TST-RCM reaction applied to the total synthesis of *cis*-sylvaticin (**1.175**).[59] **Reagents and conditions**: a) Grubb's 2nd generation catalyst, toluene, 75 °C, 40 min. b) $H_{2(g)}$, Pd/C, EtOAc, rt, 2.5 h.

Hanson *et al.*[60] reported using a temperary phosphate tether-RCM approach to synthesise 1,4-diols (scheme 1.42). Condensation of allylic alcohol **1.176** with dichloromethoxy phosphate ($(MeO)POCl_2$) using ^{n}BuLi as a base afforded phosphate triester **1.177** in a good yield (87%). Ring closing metathesis was then applied to the phosphate triester tether **1.177** to couple the two olefins and provide a monocyclic phosphate triester **1.178**. High pressure hydrogenation of the monocyclic phosphate triester **1.178** gave saturated monocyclic phosphate triester **1.180**, which was cleaved with $LiAlH_4$ to remove the phoaphate tether and afforded 1,4-diol **1.181**. The unsaturated phosphate triester **1.178** was reacted with $LiAlH_4$ to afford the corresponding unsaturated 1,4-diol **1.179** in good yield (75%).



Scheme 1.42: Hanson's TPT-RCM approach to 1,4-diols.[60] **Reagents and conditions**: a) $(MeO)POCl_2$ (0.45 equiv.), ^{n}BuLi, THF, –30 °C to rt, 2.5 h. b) $(IMesH_2)(Pcy_3)$-$(Cl_2)Ru$=CHPh (Grubbs II), toluene, reflux, 30 min. c) $LiALH_4$, THF, 0 °C to rt, 2 h. d) $H_{2(g)}$ (300 psi), CH_2Cl_2, 80 °C, 2 h.

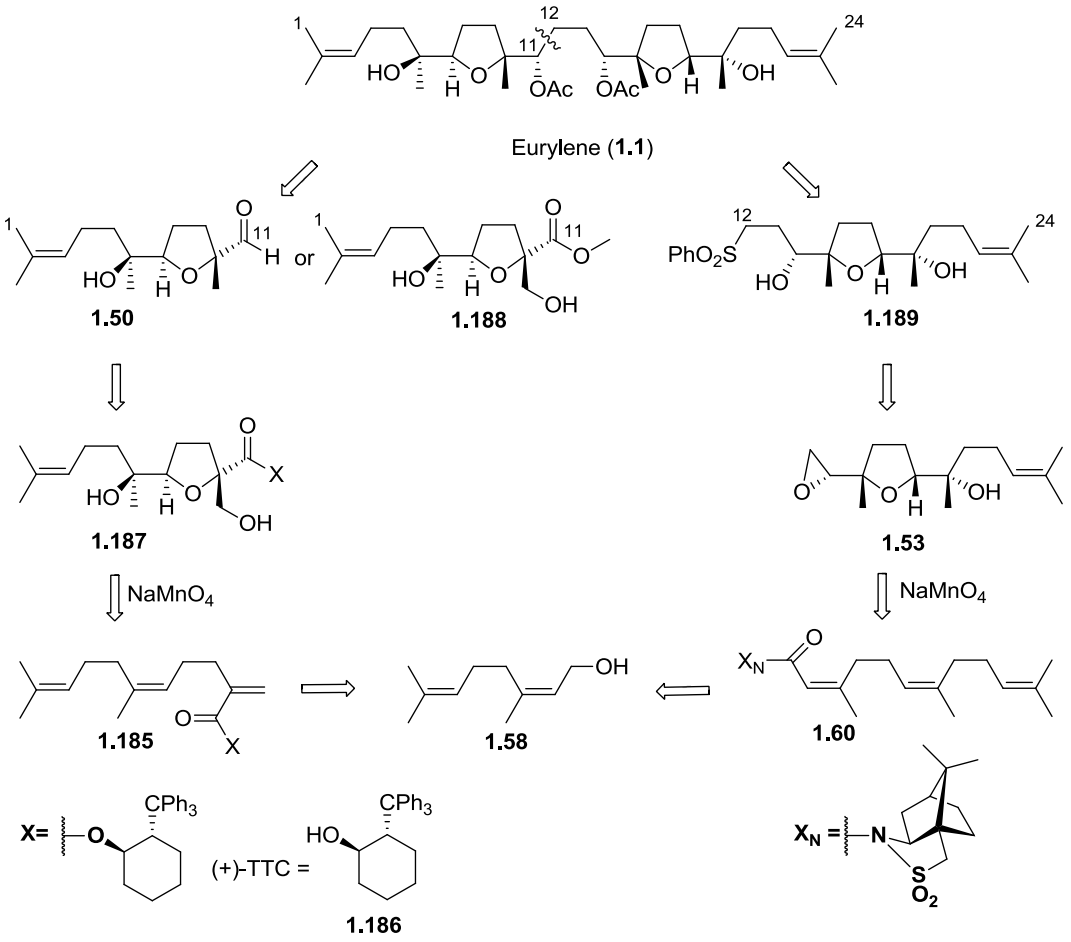
Silicon-tethered RCM has been investigated in a previous study toward eurylene within the group (scheme1.43).[38] Self tethering of right hand allylic alcohol **1.182a** afforded bisalkoxysilane **1.183** in a disappointing yield (3%). The silane **1.183** was not isolated in pure form from unidentified byproduct. A hydrolysed product **1.184** was isolated in (14%) yield along with recovered starting allylic alcohol **1.182a** (65%). The disappointing result may be due to purity of chlorosilicone reagent or the effect moisture on a small scale reaction. However, due to the failure in synthesis of left (C_1-C_{12}) allylic alcohol **1.182b** fragment, there were no more attempts to investigate this approach.



Scheme 1.43: Synthesis of silicon tethered diol **1.184**. **Reagents and conditions:** a) (^{i}Pr)$_2$SiCl$_2$ (0.5 equiv.), imid. (5.0 equiv.), CH_2Cl_2, rt, 15 h.

1.4. Aims and Objectives of the project

The main aim of this project is to achieve the total synthesis of eurylene by using chemo and stereoselective permanganate oxidative mono cyclisation of 1,5,9-trienes **1.185** and **1.60** (scheme 1.44). In this work (+)-(1*R*,2*S*)-*trans*-2-trityl cyclohexanol (**1.186**, (+)-TTC), a new sterically hindered chiral auxiliary will be used to improve the stereoselectivity of the oxidative cyclisation towards the *trans*-THF fragment of eurylene.[10,11] By the permanganate methodology, synthesis of both *trans*-THF and *cis*-THF rings of eurylene (**1.1**) along with fixing seven out of eight chiral centres will be achieved. Our retrosynthetic analysis shows the approach to eurylene, the disconnection between C_{11} and C_{12} will lead to the left (C_1-C_{11}) fragment **1.50** or **1.188** (*trans*-THF) and right (C_{12}-C_{24}) fragment **2.38** (*cis*-THF). Synthesis of 1,5,9-trienes **1.185** and **1.60** will start from a cheap commercially available starting material nerol (**1.58**). Stereoselectivity of the oxidative cyclisations of 1,5,9-triene **1.60** to afford the *cis*-THF ring will be controlled by using (+)-(*2S*)-10, 2-camphorsultam as a chiral auxiliary.



Scheme 1.44: Suggested retrosynthetic analysis of eurylene (**1.1**).

In order to achieve the synthesis of eurylene, the work could be summarised into three parts:

1) Stereocontrolled synthesis of the left (C_1-C_{11}) fragment of eurylene via selective oxidative cyclisation of a 1,5,9-triene using (+)-(1*R*,2*S*)-*trans*-2-trityl cyclohexanol (**1.186**, (+)-TTC) chiral auxiliary .

2) Synthesis of the right (C_{12}-C_{24}) fragment via the selective oxidative cyclisation using (+)-(*2S*)-10, 2-camphorsultam chiral auxiliary.

3) Coupling of the two fragments of eurylene, and establish a suitable way to fix the last seterocentre at C_{11} of the molecule. The new chiral centre could be established by using a chiral reducing agent after coupling of the left (C_1-C_{11}) aldehyde **1.50** and right (C_{12}-C_{24}) fragment **1.189** and re-oxidise the resulted alcohol (scheme 1.44). Alternatively, the primary alcohol on C_{10} could be used to control the reduction of carbonyl on C_{11} after coupling the left (C_1-C_{11}) methyl ester **1.188** with right (C_{12}-C_{24}) fragment **1.189**.

Chapter Two: Results and discussion

Our proposed synthesis of eurylene (**1.1**) required the stereoselective synthesis of the *trans*- and *cis*-THF ring of eurylene, which was to be carried out by selective oxidative cyclisation of a 1,5,9-trienes **1.185** and **1.60** (scheme 1.44). The following sections will detail the synthesis of the left (C_1-C_{11}) and right (C_{12}-C_{24}) fragments of eurylene (**1.1**) using permanganate oxidative cyclisation, and efforts to develop coupling methodology to combine the fragments. In addition, the stereochemical correlation of the oxidative cyclisation products using TTC and TCC auxiliaries will be described. Conformation analysis of 1,5-dienes bearing some of the cyclohexyl auxiliaries by ^{1}H NMR will be explained. The description of the research will be divided into five sections:

1) Stereocontrolled synthesis of the left (C_1-C_{11}) fragment of eurylene (**1.1**).
2) Stereocontrolled synthesis of the right (C_{12}-C_{24}) fragment of eurylene.
3) Coupling of the fragments towards the total Synthesis of eurylene.
4) Stereochemical correlation for oxidative cyclisation products from TTC and TCC esters.
5) NMR studies of cyclohexyl dienoates and THF diol product.

2.1. Stereocontrolled Synthesis of the Left (C_1-C_{11}) Fragment of Eurylene

In this section, the stereoselective synthesis of the *trans*-THF ring of eurylene will be described. The synthesis proceeded via selective oxidative cyclisation of a 1,5,9-triene bearing (+)-(1*R*,2*S*)-*trans*-2-trityl cyclohexanol ((+)-TTC, **1.186**), a new chiral auxiliary.[13] The work toward the synthesis of the left (C_1-C_{11}) fragment will be divided into four parts:

2.1.1. Synthesis of 1,5,9-trienoic acid.

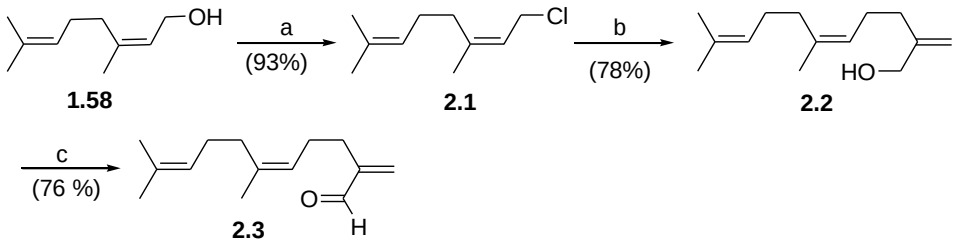
2.1.2. Synthesis and resolution of (+)-TTC, and synthesis of TTC trienoate.

2.1.3. Permanganate oxidative cyclisation of TTC trienoate.

2.1.4. Toward the synthesis of left (C_1-C_{11}) fragment of Eurylene

2.1.1. Synthesis of 1,5,9-Trienoic Acid

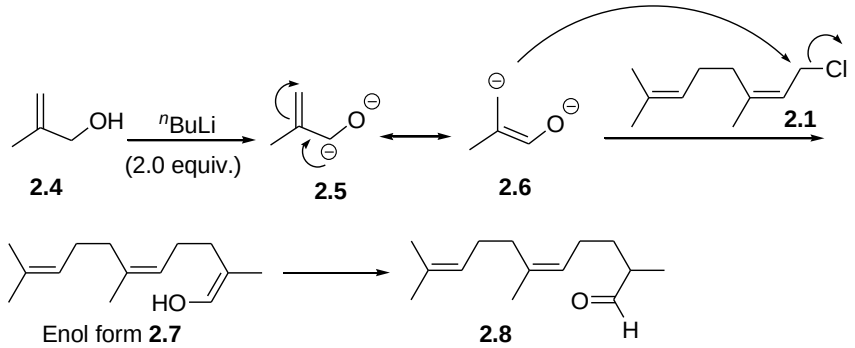
A new modified method to prepare 1,5,9-trienoic acid **2.9** starting from nerol (**1.58**) will be explained. The triene aldehyde **2.3**, a precursor of the trienoic acid was successfully synthesised over 3 steps from nerol (**1.58**, scheme 2.1).



Scheme 2.1: Synthesis of triene aldehyde **2.3** from nerol (**1.58**) as a starting material. **Reagent and conditions**: a) 2,6-lutidine, DMF, LiCl, MsCl, 0 ^{o}C to rt, 6 h. b) Methallyl alcohol (1.0 equiv.), ^{n}BuLi (3.0 equiv.), TMEDA, Et_2O, THF, 0 ^{o}C to rt, 23 h, **2.1**, –78 ^{o}C to rt, 9 h. c) activated MnO_2, distilled hexane, 0 ^{o}C, 30 min.

Reaction of nerol (**1.58**) with MsCl and LiCl provided neryl chloride (**2.1**), without any significant allylic rearrangement (scheme 2.1).[69] It was previously reported that in the absence of LiCl rearrangement via an S_N1 pathway can occur. Neryl chloride (**2.1**) was produced in an excellent yield (93%) on a 29 g scale. Neryl chloride was found to decompose on column chromatography and short path distillation, so it was purified by Kugelrohr distillation which afforded neryl chloride as a colourless oil. The synthesis of the trienol **2.2** was carried out by reaction of the dianion of methallyl alcohol with neryl

chloride after making some modifications to the previously reported procedure, giving the desired trienol **2.2** in 78% yield (scheme 2.1).[12,70] The modifications included concentration of ^{n}BuLi solution by removing hexane at a reduced pressure whilest stirring in a warm water bath. Then, alternatively Et_2O and THF were used as solvent. If the reaction conditions are not carefully controlled an aldehyde byproduct **2.8** is formed (scheme 2.2).[70]

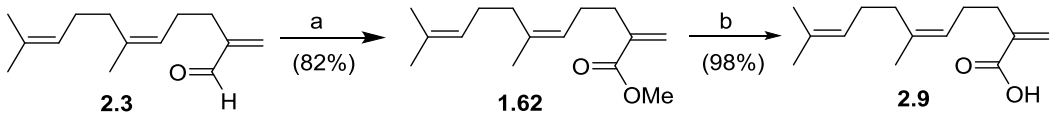


Scheme 2.2: Proposed mechanism for formation of aldehyde byproduct **2.8**.

Formation of the dianion of methalyl alcohol was also investigated using ultrasound to reduce the time required for its formation.[71] This method afforded a reasonable yield of the triene alcohol (42%) but proved to be inferior to the method described above. It is important to note that the trienol **2.2** is volatile and care is needed during the process of removing the solvent.

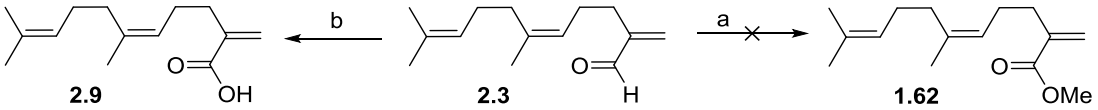
The trienol **2.2** was oxidised to the aldehyde **2.3** in 76% yield; the reaction was clean and the aldehyde was used in the next step without further purification (scheme 2.1).[72] As often observed with MnO_2 oxidation, activation of MnO_2 by heating at 160 ^{o}C was required for efficient reaction.[73] Activation of commercial MnO_2 by an isotropic distillation with toluene gave the aldehyde with a moderate to good yield (61-78%) over 30 h. Oxidation of the alcohol was also investigated in a novel electrochemical microflow reactor, developed by the Brown group, using TEMPO as a catalyst which was recycled electrochemically.[74] Unfortunately, this method afforded a lower yield than MnO_2 reaction (42%, along with 22% of recovered SM.) It is important to note that the aldehyde was also volatile and it decomposed on prolonged storage at rt; therefore it should be stored in a freezer.

In order to avoid the undesired NaCN oxidative esterification of aldehyde **2.3**, during the synthesis of trienoic acid **2.9** (scheme 2.3),[12,72] alternative routes were investigated to prepare the acid **2.4** in a safe and/or shorter method.



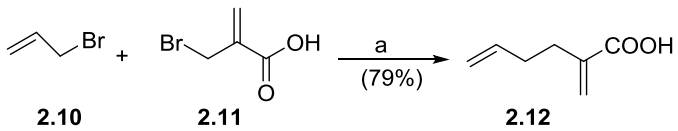
Scheme 2.3: Synthesis of trienoic acid **2.9** from triene aldehyde **2.3**.[12] **Reagents and conditions**: a) NaCN, AcOH, MnO_2, MeOH, rt, 18 h. b) NaOH, $NaHCO_3$, MeOH/H_2O, reflux, 9 h.

Oxidative esterification of aldehyde **2.3** using 1,3-dimethyltriazolium iodide with DBU was applied as a first attempt to obtain the methyl trienoate **1.62** (scheme 2.4).[75] Unfortunately, the reaction did not afford the desired methyl trienoate **1.62**; the starting material was consumed, evident by ^{1}H NMR of the reaction mixture. Pinnick oxidation was also investigated to prepare the acid **2.4**.[76-78] This method afforded the desired acid, but difficulties were found during purification of the crude product (scheme 2.4).



Scheme 2.4: Synthetic approaches to trienoic acid **2.9**. **Reagents and conditions**: a) DBU; 1,3-dimethyltriazolium iodide; 3,3′,5,5′-tetra-*tert* butyldiphenoquinone, THF, MeOH, rt, 6 h. b) 2-Methyl-2-butene, ^{t}BuOH, $NaClO_2$, NaH_2PO_4, H_2O, rt, 17 h.

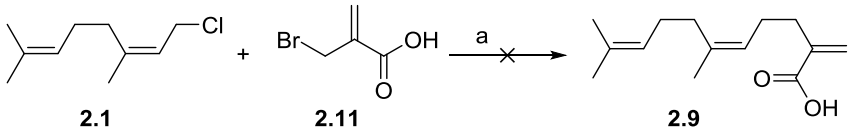
In 1998, Ma J. and Chan T. H. reported a synthesis of 1,5-dienes using a cross coupling of two allylic halides in the presence of manganese/cupric chloride, giving a good yield (79%) of the 1,5-diene **2.12** (scheme 2.5).[79]



Scheme 2.5: Approach to 1,5-diene **2.12** reported by Ma *et al.*[79] **Reagents and conditions**: a) Mn/$CuCl_2$, H_2O, THF, rt, 16 h.

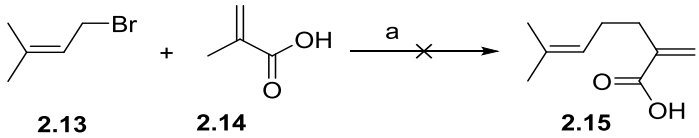
Their results encouraged us to investigate coupling of 2-(bromomethyl)acrylic acid with neryl choride (**2.1**) to prepare the required trienoic acid **2.9** (scheme 2.6). Unfortunately,

the reaction failed to give the desired product, although ^{1}H NMR showed that the starting material had been consumed.



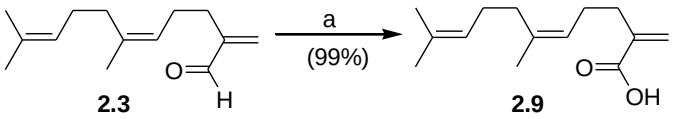
Scheme 2.6: Attempt to prepare the trienoic acid **2.9**. **Reagents and conditions**: a) Mn/$CuCl_2$, H_2O, THF, rt, 20 h.

The alkylation of the dianion of methacrylic acid **2.14** was investigated as well, using prenyl bromide (**2.13**) as a model for neryl chloride (**2.1**, scheme 2.7). LDA and ^{n}BuLi were used as bases under sonication.[71] Unfortunately these reactions were not successful, and the desired product **2.15** was not obtained.



Scheme 2.7: Suggested reaction to prepare dienoic acid **2.15**. **Reagents and conditions**: a) ^{n}BuLi, TMEDA, Et_2O, THF, –78 ^{o}C to rt, 13 h.

The synthesis of trienoic acid **2.9** was successfully completed using a simple, mild method with an excellent conversion using silver oxide as oxidant (99 %, scheme 2.8).[80] Silver oxide was freshly prepared from silver nitrate and sodium hydroxide in water, and then reacted with the aldehyde **2.3** at rt. The acid was used in the next step without further purification. The silver oxide method helped to shorten synthesis of the acid **2.9** from triene aldehyde directly and avoided the use of cyanide used previously.[12,72]



Scheme 2.8: Modified method to synthesise trienoic acid **2.9** from triene aldehyde **2.3**.

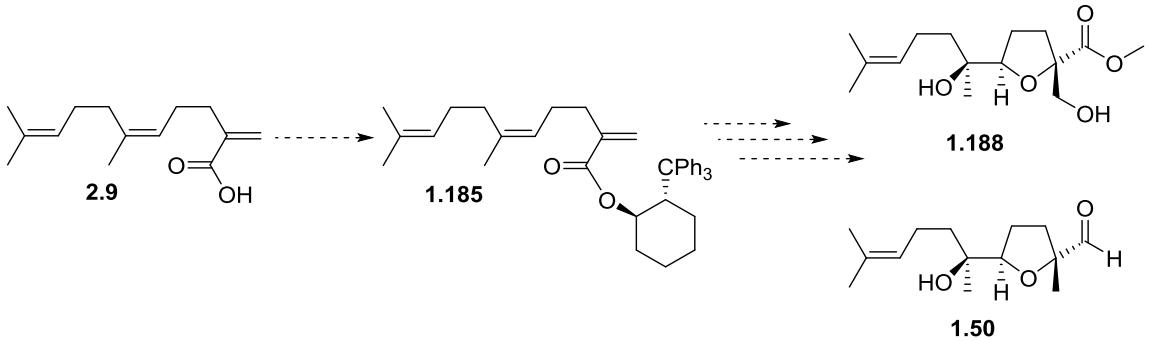
Reagents and conditions: a) $AgNO_3$, NaOH, H_2O, rt, 23 h,

2.1.1.2. Conclusions

The synthesis of trienoic acid **2.9** was successfully completed over 4 steps starting from nerol (**1.58**) in 55% overall yield. The method helped to shorten the route to the left (C_1-C_{11}) fragment of eurylene, whilst avoiding the use of NaCN in the oxidative esterification.

2.1.2. Synthesis and Resolution of (+)-TTC, and Synthesis of TTC Trienoate

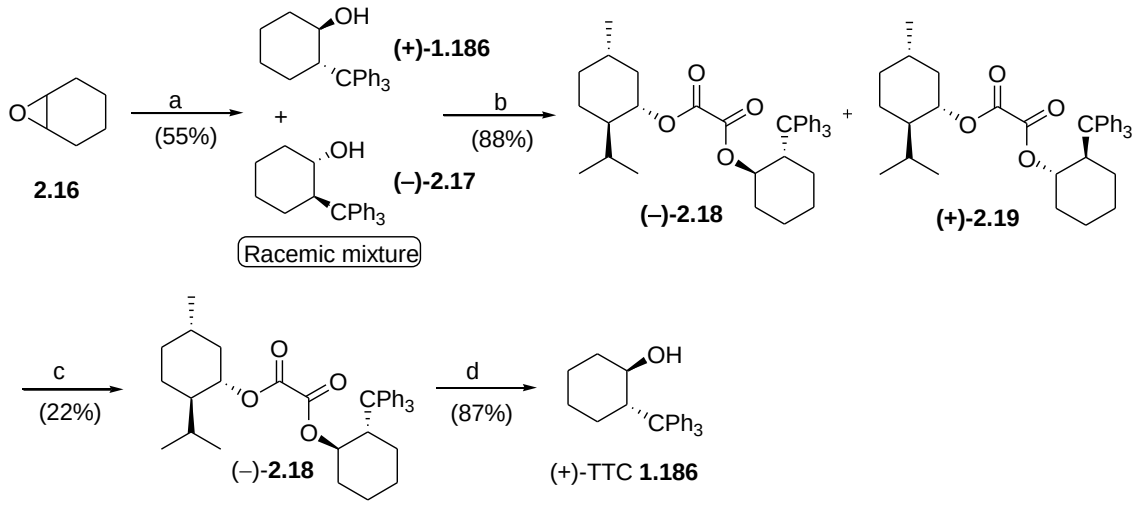
After developing a practical route to trienoic acid **2.9**, TTC trienoate **1.185** was required as a key intermediate in the synthetic route towards the left (C_1-C_{11}) fragment of eurylene (scheme 2.9).



Scheme 2.9: Approach towards the left (C_1-C_{11}) fragment from the acid **2.9**.

The preparation of TTC trienoate **1.185** required enantiopure (+)-(1*R*,2*S*)-*trans*-2-trityl cyclohexanol (**1.186**, (+)-TTC) which would be coupled with trienoic acid **2.9** (scheme 2.10). The enantiopure (+)-TTC was successful prepared on a 10 g scale with excellent enantiopurity (99.6% *ee*). Synthesis of (±)-racemic TTC was achieved in one step using a procedure that was modified by the Brown group.[13] A method reported by Corey *et al.* for the resolution of (±)–2-triphenylsilyl-4-cyclohexen-1-ol was applied to the resolution of (±)-TTC, giving (–)-TTC with excellent enantiopurity (>99% *ee*).[13,81] Therefore, to obtain (+)-TTC, the same procedure was carried out using (1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexanol ((+)-menthol) which afforded diastereomers **2.18** and **2.19** in 88% yield. Refluxing the oxalate diester mixture in MeOH followed by a hot filtration and repeated washing with a warm MeOH afforded the (–)-oxalate diester **2.18** as a single diastereomer in moderate yield (22%) with an excellent diastereomeric excess (100% *de*). Isolation of (+)-TTC **1.186** was achieved in a very good yield (87%, 99.6% *ee*) by saponification of **2.18** with KOH in refluxing aqueous MeOH.

Recrystallization of (+)-TTC from EtOH gave the enantiomerically enriched product (99.6% *ee*).



Scheme 2.10: Synthesis and resolution of (+)-TTC **1.186**. **Reagent and conditions**: a) Ph_3CH, $^{n}BuLi$, THF, –78 ^{o}C, 14 h. b) Oxalyl chloride, (+)- menthol, pyr, CH_2Cl_2, 0 ^{o}C. c) Hot filtration from MeOH. d) KOH, $MeOH/H_2O$, reflux, 20 h.

The enantiomeric purity was confirmed by analytical HPLC using an ODH column, eluenting with 5% IPA in hexane. HPLC traces for the racemic (±)-TTC and the enantiopure isomer (+)-TTC are shown in figures 2.1 and 2.2.

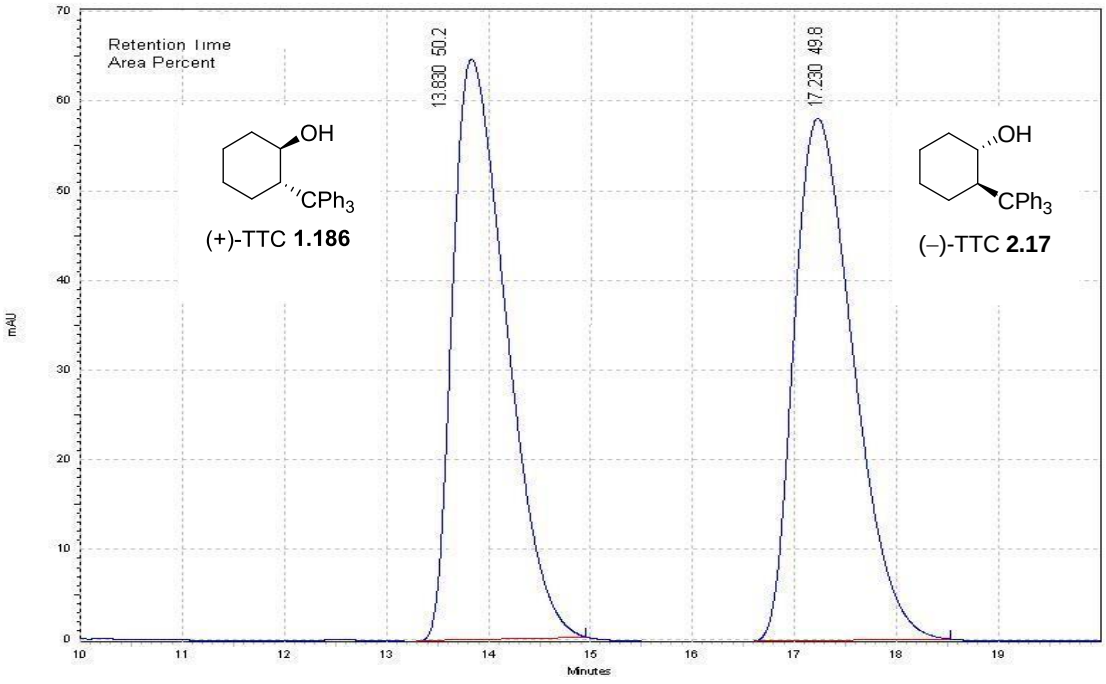


Figure 2.1: HPLC trace for the (±)-TTC, 0.5 mL/min flow rate, 30 min, 254 nm.

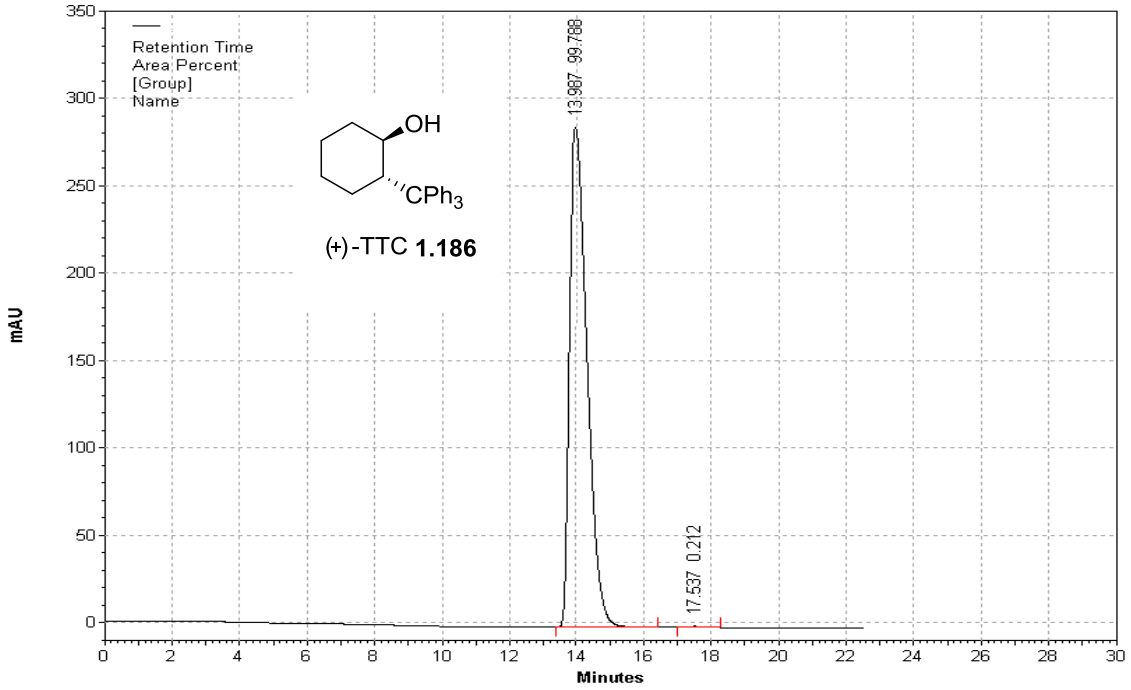
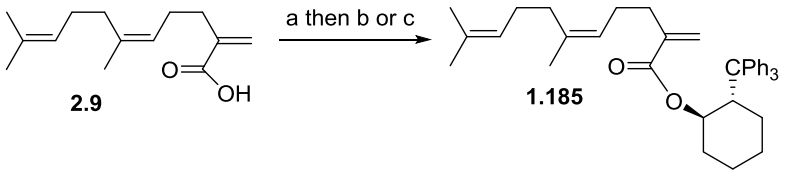


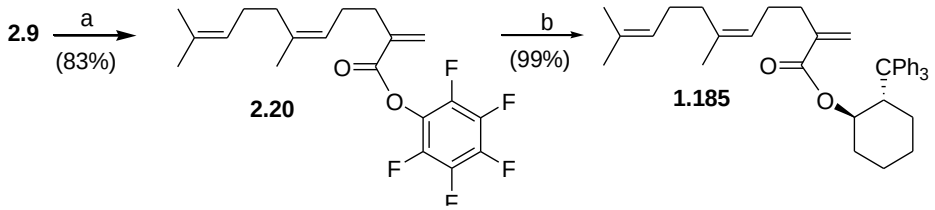
Figure 2.2: HPLC trace for (+)-TTC **1.186**, 0.5 mL/min flow rate, 30 min, 254 nm.

TTC is very sterically hindered in comparsion to the other cyclohexanol auxiliaries such as TCC, which made the coupling reaction with the trienoic acid **2.9** fairly challenging. A number of attempts were carried out to access the TTC trienoate **1.185** (scheme 2.11). The first approach involved conversion of trienoic acid **2.9** to its acid chloride, then a coupling reaction with TTC. The acid chloride was prepared by reaction with $(COCl)_2$, then used directly in the reaction with (+)-TTC in CH_2Cl_2 in the presence of Et_3N.[82] The best yield from this method was less than 21%, and reaction rate was slow, even under heating at reflux. The results suggested that we needed to increase the nucleophilicity of (+)-TTC by deprotonation then coupling with the acid chloride. Various bases such as ^{n}BuLi and NaH were examined. Use of ^{n}BuLi gave a low yield of the desired product (<10%), with a difficult separation from starting materials.[83] Reaction of (+)-TTC with NaH and then with the acid chloride led only to recovered starting materials.



Scheme 2.11: Attempted synthesis of TTC trienoate **1.185** from the acid **2.9**. **Reagents and conditions**: a) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C to rt, 3 h. b) TTC, Et_3N, DMAP, CH_2Cl_2, reflux, 15 h, < 21%. c) TTC **1.186**, ^{n}BuLi, 1,10-phenanthroline, THF, 0 °C to rt, 72 h, < 10%; or TTC **1.186**, NaH, 0 °C to rt, 14 h, 0%.

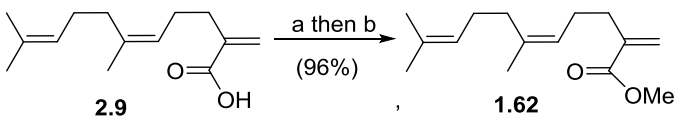
Whilst attempting to improve the yield of the coupling reaction, we discovered that the PFP trienoate **2.19** was a superior to the acid chloride, using a transesterfication reaction of the TTC alkoxide, formed with NaHMDS, which gave TTC trienoate **1.185** in quantitative yield (scheme 2.12).[12,84] This avoided problems with the acid chloride in terms of stability and purification.



Scheme 2.12: Preparation of TTC trienoate **1.185** using PFP trienoate. **Reagents and conditions**: a) PFPOH, DCC, EtOAc, rt, 22 h. b) TTC **1.186**, NaHMDS, THF, –20 °C to reflux, 22 h.

2.1.3. Permanganate Oxidative Cyclisation of TTC Trienoate

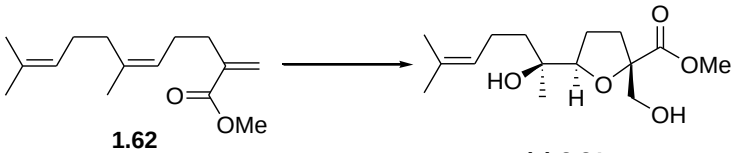
Permanganate oxidative cyclisation of TTC trienoate **1.185** was a key challenge on our way towards the 2,5-*trans*-THF system. Initial attempts at the oxidative cyclisation were unsuccessful. To gain experience in the oxidation and find the optimised conditions, oxidative cyclisation of methyl trienoate **1.62** was studied as a model reaction. The methyl trienoate **1.62** was obtained in two steps, via the acid chloride with subsequent treatment with methanol in an excellent yield (96%, scheme 2.13).[85,86]



Scheme 2.13: Preparation of methyl trienoate **3.6**. **Reagents and conditions**: a) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C to rt, 3 h. b) MeOH, 0 °C to rt, 1.5 h.

Permanganate oxidative cyclisation of methyl trienoate **1.62** under a variety of different reaction conditions afforded the racemic THF diol **2.22** in varied yields (scheme 2.14, tables 2.1; 2.2).[84]

Initially, the oxidative cyclisation was carried out using $KMnO_4$ in aqueous acetone containing AcOH. There was no oxidation when more than 3.5 equiv. of AcOH was used with no recovered starting material. The analysis by ^{1}H NMR of the crude product showed a complex mixture of products (entry 1, table 2.1). In another attempt using 3.0 equiv. of AcOH, ^{1}H NMR on the crude NMR showed very small peaks of the desired product (entry 2, table 2.1). Therefore, the investigation included varying the oxidising reagent along with the amount of AcOH and the reaction time. $NaMnO_4$ with 3.5 equiv. of AcOH was used in the oxidation reaction in the presence of KH_2PO_4/NaOH as a buffer solution; this change improved the reaction and afforded the THF **2.21** in yield (45%). The reaction was clean and there was no further purification (entry 3, table 2.1). For further optimisation the solvent of the reaction was changed to EtOAc with no buffer solution; as a result, the ratios of the desired product to SM from two reactions were 1.4:1 and 1.1:1 based on the crude ^{1}H NMR spectra (entries 4 and 5, table 2.1). TLC of the crude crude showed only two spots.



1.62 **(±) 2.21**

Scheme 2.14: Permanganate oxidative cyclisation of **1.62** (see table 2.1)

Entry	**Oxidant** (0.4M aq. /equiv.)	**AcOH** (equiv.)	**Solvent**	**Buffer solution**	**Temp.** (^{o}C)	**Time** (min)	**Yield of 2.21**, (%)
1	$KMnO_4$ /1.37	> 3.5[a]	Acetone	H_2O	–40 to –5	120	No reaction
2	$KMnO_4$ /1.37	3	Acetone	H_2O	–40 to –5	120	Trace
3	$NaMnO_4$ /1.5	3.5	Acetone	KH_2PO_4/ NaOH[b]	–20 to –10	30	45
4	$NaMnO_4$ /1.5	3.5	EtOAc	No	–20 to –10	30	1.4:1[c]
5	$NaMnO_4$ /1.5	3.5	EtOAc	No	–20 to –10	120	1.1:1[c]

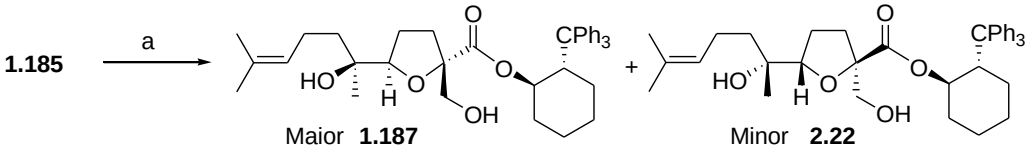
Table 2.1: Optimization of oxidation of methyl trienoate **1.62**. [a]Drops were added. [b]pH 6.3. [c]The ratios of the THF diol **2.21** to SM based on crude ^{1}H NMR spectra.

Phase-transfer catalysis (PTC) were also investigated in an effort to improve the yield of the oxidative cyclisation.[40] Using TBAB as a PTC in the oxidation of methyl trienoate **1.62** led to cyclisation in an improved yield (62%) of the THF diol **2.21** and only 9% of recovered SM; entry 1, table 2.2). Whereas, Adogen 464 gave a lower yield (44%) along with recovered SM (22%, entry 2, table 2.2). Based upon the successful application of PTC in the oxidative cyclisation of the methyl trienoate **1.62**, these conditions were applied in the studies on TTC trienoate **1.185**.

Entry	**Oxidant** (0.4M aq. /equiv.)	**AcOH** (equiv.)	**Solvent**	**PTC**	**Temp.** (^{o}C)	**Time** (min)	**Yield of 2.21**, (%)
1	$NaMnO_4$ /1.37	3.5	EtOAc	TBAB	–20 to –10	60	62
2	$NaMnO_4$ /1.37	3	EtOAc	Adogen 464	–20 to –10	30	44

Table 2.2: Permanganate oxidative cyclisation of methyl trienoate **3.6** using TBAB or adogen 464 as a PTC.

Initially, the oxidative cyclisation of TTC trienoate **1.185** using $KMnO_4$ (0.4M aq., 1.37 equiv.) in aqueous acetone containing AcOH led to recovered starting material (scheme 2.15, entries 1, 2; table 2.3). Changing the oxidant and amount of AcOH in the presence of KH_2PO_4/NaOH (pH 6.3) as a buffer solution yielded 13% of the desired product **1.187**, along with 21% of the over oxidised product (all the double bonds were oxidized) and 28% of recovered SM. The diastereoisomer **2.22** was not observed (entry 3, table 2.3).



Scheme 2.15: Optimization of selective oxidative cyclisation of TTC trienoate **1.185**.

Entry	**Oxidant** (0.4M aq. /equiv.)	**AcOH** (equiv.)	**Solvent**	**Buffer solution**	**Temp.** (^{o}C)	**Time** (min)	**Yield of 1.187**, (%
1	$KMnO_4$ /1.37	> 3.5[a]	Acetone	H_2O	–40 to –5	120	No reaction
2	$KMnO_4$ /1.37	2.96	Acetone	H_2O	–40 to –5	120	No reaction
3	$NaMnO_4$ /1.5	3.5	Acetone	KH_2PO_4/ NaOH[b]	–20 to –5	90	13

Table 2.3: Optimization of selective oxidative cyclisation of TTC trienoate **1.185**. [a]Two drops were added. [b]pH 6.3

Phase-transfer catalysis was used in the investigation with different solvents. The oxidative cyclisation using $KMnO_4$ (0.4M aq.) in Et_2O in the presence of Adogen 464 as PTC improved the yield to 17% of the major diastereoisomer **1.187**, with trace amounts of the minor diastereoisomer **2.22** observed. Starting material was also recovered in 66% (entry 1, table 2.4). With this small improvement in hand, attempts to use the oxidant as a solid, instead of a solution, were tried, but unfortunately with no success. ^{1}H NMR of crude product showed small peaks for THF **1.187**, with SM being the major product (entry 2, table 2.4). Using of $NaMnO_4$ (0.4M aq.) in EtOAc with TBAB as a PTC improved the oxidation, and afforded a better result than before. The oxidation yielded 27% of the major diastereoisomer **1.187**, 4.5% of the minor diastereoisomer **2.22**, and 8% of recovered SM (entry 3, table 2.4). Therefore, this encouraged us to use this oxidant with TBAB but in acetone as a more polar solvent. Fortunately, there was a respectable improvement in the oxidation reaction. The oxidation gave the desired product **1.187** in 40% yield along with the minor diastereoisomer **3.22** in 4% and trace of recovered SM (entry 4, table 2.4).

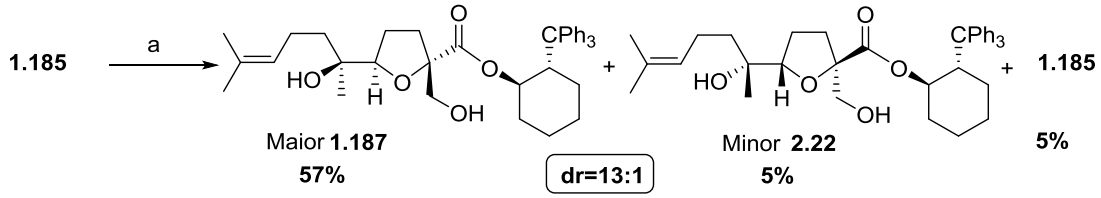
Entry	**Oxidant** (0.4M aq. /equiv.)	**AcOH** (equiv.)	**Solvent**	**PTC**	**Temp.** (^{o}C)	**Time** (min)	**Yield of 1.187**, (%)
1	$KMnO_4$ /1.5	3.5	Ether	Adogen 464	–40 to –5	120	17
2	$KMnO_4$ /1.5[a]	3.5	Ether	Adogen 464	–35 to 0	60	Trace
3	$NaMnO_4$ /1.5	3.5	EtOAc	TBAB	–35 to –13	75	27
4	$NaMnO_4$ /1.5	3.5	Acetone	TBAB	–35 to 0	75	40

Table 2.4: Permanganate oxidative cyclisation of TTC trienoate **1.185** using TBAB or adogen 464 as a PTC. [a]Powdered $KMnO_4$.

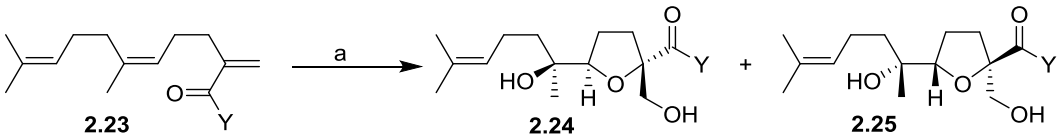
Interestingly, reducing the amount of the oxidant to (1.37 equiv.) with less acidic conditions (2.45 equiv.) with a longer reaction time gave a good yield of the desired diastereoisomer **1.187** in 57% yield, and the minor diastereoisomer **2.22** in 5% yield. Some of TTC trienoate **1.187** starting material was recovered (5%, scheme 2.16, entry 1, table 2.5). Fortunately, crude ^{1}H NMR analysis of the oxidative cyclisation product showed a superior diastereomeric ratio (dr = 13:1) compared to those trienes bearing a range of different auxiliaries, reported in a previous study within the group (table 2.6, scheme 2.17).[12] Pleasingly the resultant diastereoisomers were separable by column chromatography. Use of the buffer solution (KH_2PO_4/NaOH, pH 6.3) with our optimised conditions led to decrease yield of **1.187** to 43% along with 3% of the minor diastereoisomer **2.22** and 14% of recovered SM (entry 2, table 2.5). Overall, the results from the investigation into the oxidative cyclisation conditions led to an improved route to the left (C_1-C_{11}) fragment of eurylene compared to the previous work in term of diastereoselectivity and with the ability to separate the diastereoisomers.

Entry	**Oxidant** (0.4M aq. /equiv.)	**AcOH** (equiv.)	**Solvent**	**PTC**	**Temp.** (^{o}C)	**Time** (min)	**Yield of 1.187**, (%)
1	$NaMnO_4$ /1.37	2.45	Acetone	TBAB	–35 to –5	90	57
2	$NaMnO_4$ /1.37	2.45	Acetone	TBAB	–35 to –5	90	43

Table 2.5: Optimised conditions of permanganate oxidative cyclisation of TTC trienoate **1.187**.



Scheme 2.16: Optimised permanganate oxidative cyclisation of TTC trienoate **1.185**. **Reagents and conditions**: a) $NaMnO_4$ (1.37 equiv.), AcOH (2.45 equiv.), TBAB, acetone, –35 to –5 ^{o}C, 1.5 h.



Scheme 2.17: Permanganate oxidative cyclisation of trienoates **2.23** bearing different auxiliaries.[12,38] **Reagents and conditions**: a) $NaMnO_4$, AcOH, acetone, phosphate buffer (KH_2PO_4:NaH_2PO_4 8:2), –35 to 0 ^oC, 40 min to 1.5 h.

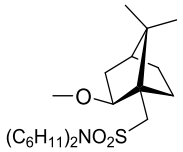
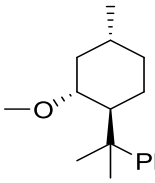
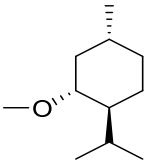
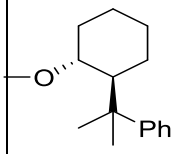
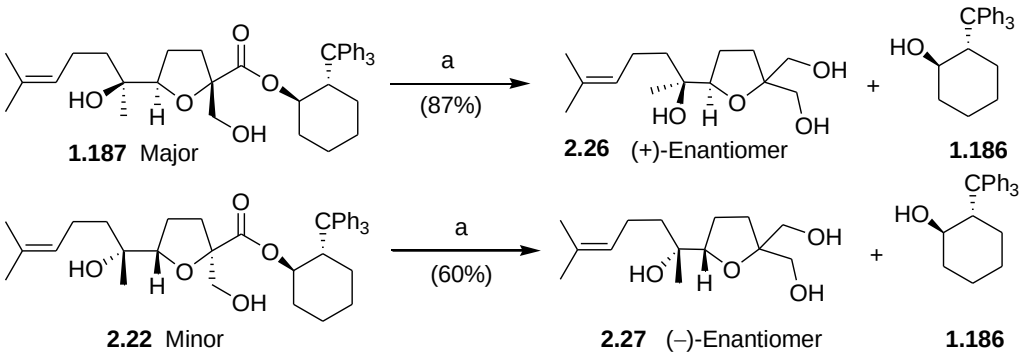
Y				
dr (2.24:2.25)	4:1	1:5.5	1:2	6.7:1

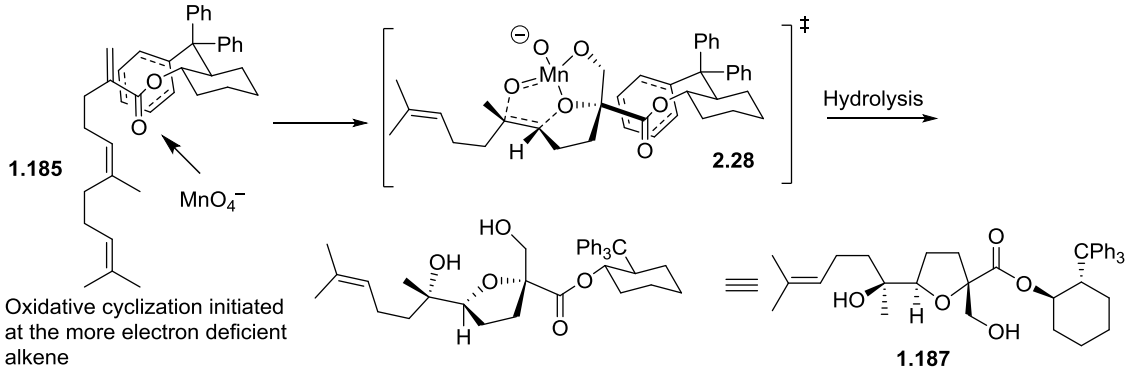
Table 2.6: Diastereoselectivity of permanganate oxidative cyclisation of trienoate **2.23** bearing different auxiliaries.[12,38]

Reduction of each of the diastereoisomers **1.187** and **2.22** using DIBALH whilst heating under reflux afforded the corresponding enantiomeric triols **2.26** and **2.27** (scheme 2.18). Physical and spectroscopic data of the two triols were identical. The major diastereoisomer gave the (+)-enantiomer **2.26** ($[\alpha]^{27}_D$: +4.0 (*c* 1.75, $CHCl_3$)), whilst the minor diastereoisomer gave the (–)-enantiomer **2.27** ($[\alpha]^{25.5}_D$: –2.6 (*c* 0.60, $CHCl_3$)). The difference in magnitude of the values of the specific rotation can be attributed to experimental error due to the low rotatory power of the compounds. The determination of absolute stereochemistry of the major product **1.187** will be described in section four.



Scheme 2.18: DIBALH reductive reaction of oxidative cyclisation products **1.187** and **2.22**. **Reagents and conditions**: a) DIBALH, CH_2Cl_2, reflux, 23 h.

The origin of the improved diastereofacial selectivity compared to TCC trienoate is due to the increase size of the C_2 substituent. The outcome of the reaction may be accounted for by preferential reaction of permanganate ion with the front *Re*-face of the enoate alkene (scheme 2.19). The trityl derivative functions as a comparatively superior chiral controller compared to the TCC.[12,13]



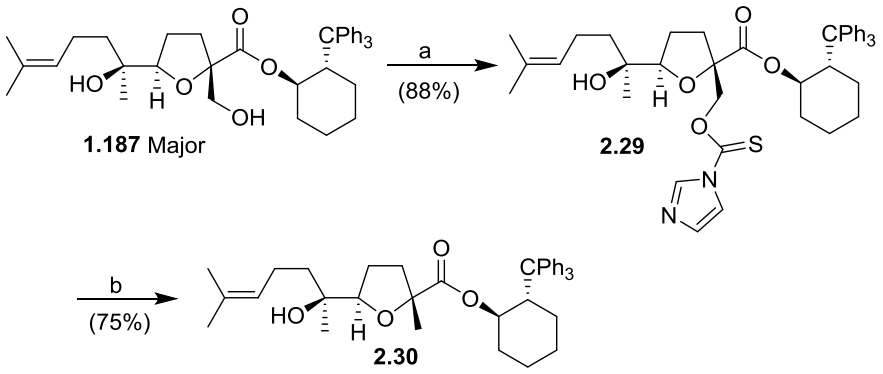
Scheme 2.19: Rationalisation of the diastereoselectivity obtained using (+)-TTC **1.187**.

2.1.3.2. Conclusions

The addition of the TTC auxiliary led to a significant improvement for the permanganate mediated oxidative cyclisation of 1,5,9-trienoate to form the 2,5-*trans*-THF system, in terms of stereoselectivity (dr = 13:1). In addition, obtaining separable diastereoisomers from this oxidation was an important achievement to improve the route towards the key intermediate left (C_1-C_{11}) fragment of eurylene.[12,13]

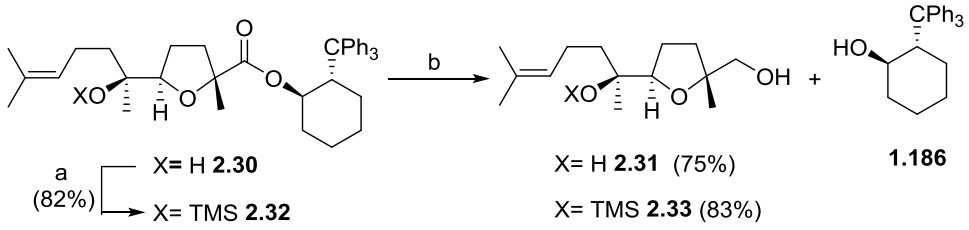
2.1.4. Toward the Synthesis of Left (C_1-C_{11}) Fragment of Eurylene

After the successful preparation of 2,5-*trans*-THF **1.187**, the next step was the deoxygenation of the methyl group at C_{10} of eurylene (**1.1**, scheme 2.20). It was found that thiocarbonyl derivative was a suitable intermediate for radical deoxygenation of the primary alcohol.[12,13,87,88] The process required reaction of **1.187** with thiocarbonyldiimidazole in CH_2Cl_2 in the presence of DMAP. Due to the higher reactivity of the primary hydroxyl group compared to the tertiary alcohol on C_6 of eurylene, there was no need to protect this group,[1,14] and the thiocarbonyl derivative **2.29** was obtained in 88% yield (scheme 2.20). Radical deoxygenation using AIBN with TTMSS in toluene afforded the required *trans*–THF **2.30** in 75% yield (scheme 2.20).



Scheme 2.20: Preparation of *trans*-THF **2.30** by radical deoxygenation of **2.29**. **Reagents and conditions**: a) Thiocarbonyldiimidazol, DMAP, CH_2Cl_2, rt, 8 h. b) TTMSS, AIBN, toluene, 85 °C, 70 min.

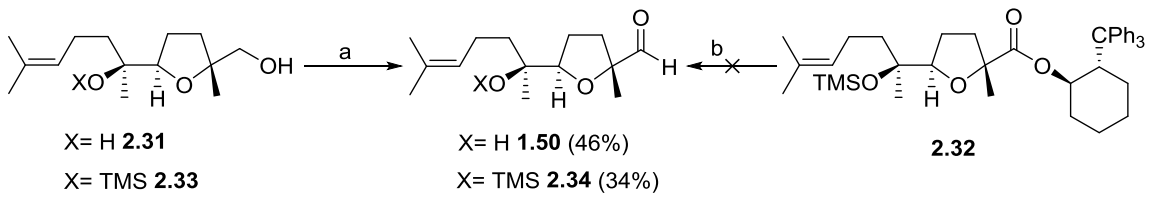
The *trans*-THF **2.30** was then subject to a cleavage reaction to remove the TTC auxiliary **1.186**, generating the THF diol **2.31**, which could be later oxidised as a starting material to the left (C_1-C_{11}) fragment aldehyde **1.50** (scheme 2.21). The *trans*-THF **2.30** was reduced with DIBALH in CH_2Cl_2 with heating under reflux, the THF diol was obtained in a good yield (75%) along with (+)-TTC (74%). The protected *trans*-THF **2.32** was also reduced using DIBALH (scheme 2.21). The TMS protected tertiary alcohol **2.33** gave a slightly improved the yield to 83%, with 88% of the TTC recovered, when supjected to the same reduction conditions. Purification of the protected alcohol **2.33** from the cleaved TTC auxiliary was difficult because of their close polarity.



Scheme 2.21: DIBALH reductive reaction of *trans*-THF **2.31** and **2.33**. **Reagents and conditions**: a) TMSCl, Imid., DMF, –5 to 5 °C, 2 h. b) DIBALH, CH_2Cl_2, reflux, 23 h.

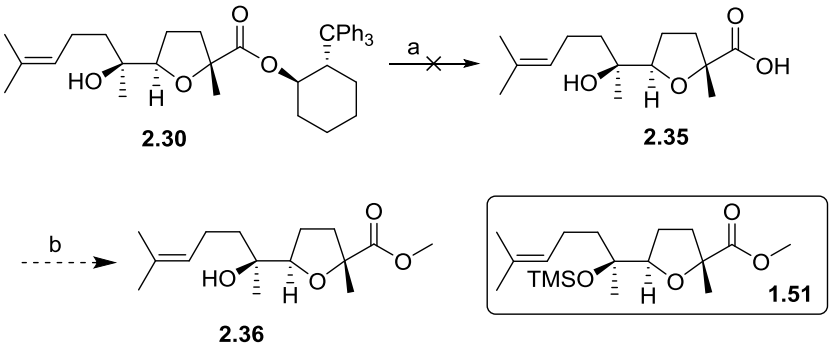
The formal synthesis of left (C_1-C_{11}) fragment aldehyde **1.50** was completed by oxidation of the *trans*-THF alcohol **2.31** using Dess- Martin periodinane (scheme 2.22). The TMS protected aldehyde **2.34** was also synthesised, as it was believed that the volatility of the aldehyde was behind the moderate yields obtained. Unfortunately both the TMS protected alcohol **2.33** and free alcohol **2.31** both gave disappointing yields. To shorten the route to the aldehyde **2.34**, direct reduction of the protected *trans*-THF

2.32 to the aldehyde, was attempted with DIBALH at –78 °C (scheme 2.22). Unfortunately, the reduction was unsuccessful and the starting material was recovered.



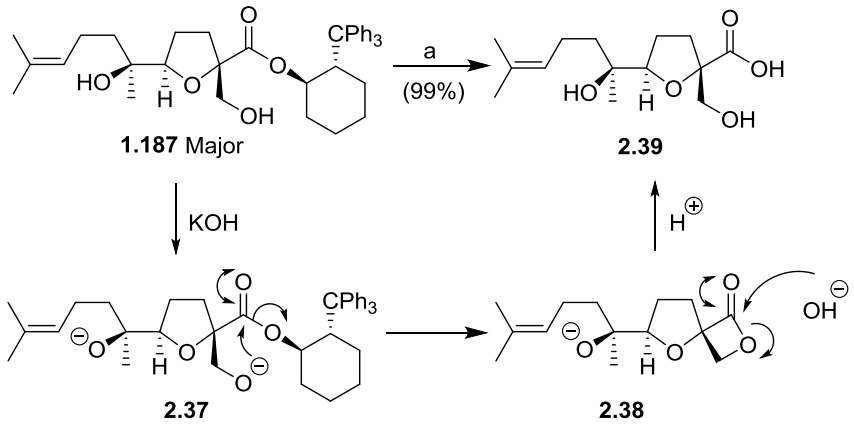
Scheme 2.22: Preparation of the aldehydes **1.50** and **2.34**. **Reagents and conditions**: a) DMP, CH_2Cl_2, rt, 4.5 h. d) DIBALH, CH_2Cl_2, –78 ^oC, 4 h.

In order to synthesise of Kodama's ester intermediate **1.51** (the left (C_1-C_{11}) fragment) in a reduced route, we attempted to hydrolyze the *trans*-THF **2.30** to afford the acid **2.35**, subsequently followed esterification of the acid. Unfortunately this approach was not successful and the starting material was recovered (scheme 2.23). We believe the reason for the resistance to hydrolysis was the low solubility of *trans*-THF **2.30** in the solvent reaction combined with the bulky nature of the system.[5]



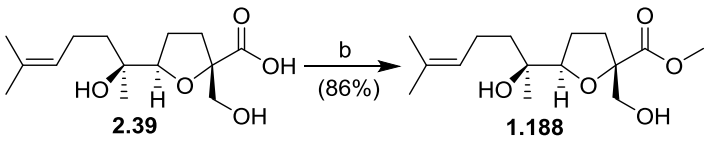
Scheme 2.23: Proposed route to prepare Kodama's intermediate **1.51** from *trans*-THF **2.30**. **Reagents and conditions**: a) KOH, MeOH, H_2O, reflux, >24 h. b) K_2CO_3, MeI, DMF.

An alternative left (C_1-C_{11}) fragment methyl ester **1.188** was successfully synthesised from the oxidative cyclisation product **1.187** over two steps (schemes 2.24 and 2.25). Interestingly, the THF TTC **1.187** hydrolysed in quantitative yield using KOH in mixture of MeOH/H_2O with heating under reflux. It is believed that the presence of the primary alcohol assists the hydrolysis, possibly by formation of intermediate *β*-lacone **2.38** (scheme 2.24).



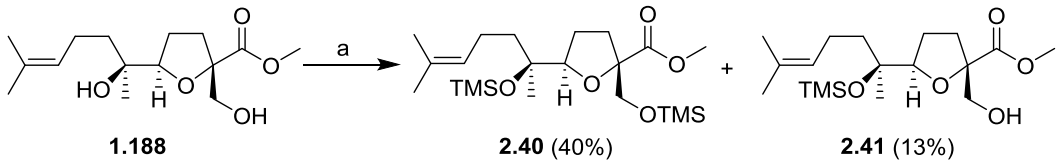
Scheme 2.24: Preparation of the acid **2.39**. **Reagents and conditions**: a) KOH, MeOH/H_2O, reflux, 23 h.

The resulting carboxylic acid **2.39** was reacted with MeI in DMF to afford the required methyl ester **1.188** in good yield (86%, scheme 2.25). Transesterification using MeONa was also attempted on the TTC ester **1.187** using microwave irradiation at 100 °C for 3 h. ^{1}H NMR of the crude product showed mainly starting TTC ester with very small peaks of the desired methyl ester.



Scheme 2.25: Preparation of the left (C_1-C_{11}) fragment methyl ester **1.188**. **Reagents and conditions**: a) K_2CO_3, MeI, DMF, rt, 5 h.

In an attempt to protect the two hydroxyl groups present in the methyl ester **1.188**, the methyl ester **1.188** was treated with TMSCl and imidazole in DMF (scheme 2.26). The reaction yielded a mixture of mon- and di-protected desired products in a moderate yields, with 9% of the starting material also recovered. The lability of the TMS ether of the primary alcohol meant that it was not suitable for this application. An alternative protecting group such as PMB may be more useful for protection of the primary hydroxyl in this substrate.



1.188 **2.40** (40%) **2.41** (13%)

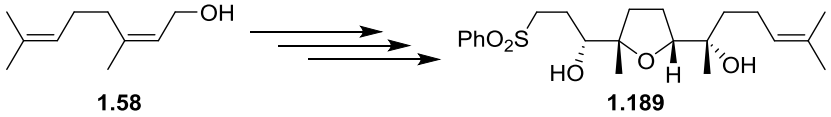
Scheme 2.26: Protection of methyl ester **1.188** with TMSCl. **Reagents and conditions**: a) TMSCl, Imidazole, DMF, –5 to 0 °C, 2 h.

2.1.4.2. Conclusions

The stereocontrolled synthesis of *trans*-THF fragment containing three of the chiral centres of eurylene was achieved using diastereo- and chemoselective oxidative monocyclisations of 1,5,9-trienene bearing the novel (1*R*,2*S*)-TTC auxiliary. Permanganate oxidative cyclisation afforded the left (C_1-C_{11}) fragment aldehyde **1.50** of eurylene (**1.1**) in 11 linear steps (4.2% overall yield). The TTC auxiliary was cleaved from *trans*-THF **2.30** and the protected *trans*-THF **2.32** using DIBALH with heating under reflux to afford THF diols **2.31** and **2.33** respectively. The DIBALH reduction of the protected *trans*-THF **2.32** directly to aldehyde **2.34** was unsuccessful. Hydrolysis of THF TTC required the presence of the primary alcohol to afford the corresponding acid, possibly aiding the cleavage by formation of an intermediate β-lactone. Methylation of the acid gave the alternative left (C_1-C_{11}) fragment methyl ester **1.188** over two steps from the oxidative cyclisation product **1.187** (THF TTC ester). The protected aldehyde **2.34** and protected methyl ester **2.40** are ready to couple with the right (C_{12}-C_{24}) fragment towards the total synthesis of eurylene.

2.2. Stereocontrolled Synthesis of the Right (C_{12}-C_{24}) Fragment of Eurylene

In order to attempt to couple the left (C_1-C_{11}) and right (C_{12}-C_{24}) hand fragments and complete the total synthesis of eurylene, the synthesis of right hand fragment **1.189** was required (scheme 2.27). The following section will detail the synthesis of the fragment **1.189** starting from nerol (**1.58**).

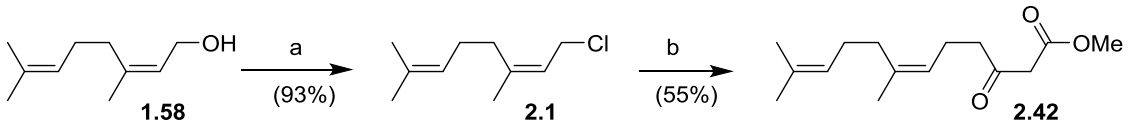


1.58 **1.189**

Scheme 2.27: structures of right (C_{12}-C_{24}) hand fragment **1.189** of eurylene and nerol (**1.58**).

2.2.1. Synthesis of the (+)-(2*S*)-10,2-Camphorsultam Trienoate

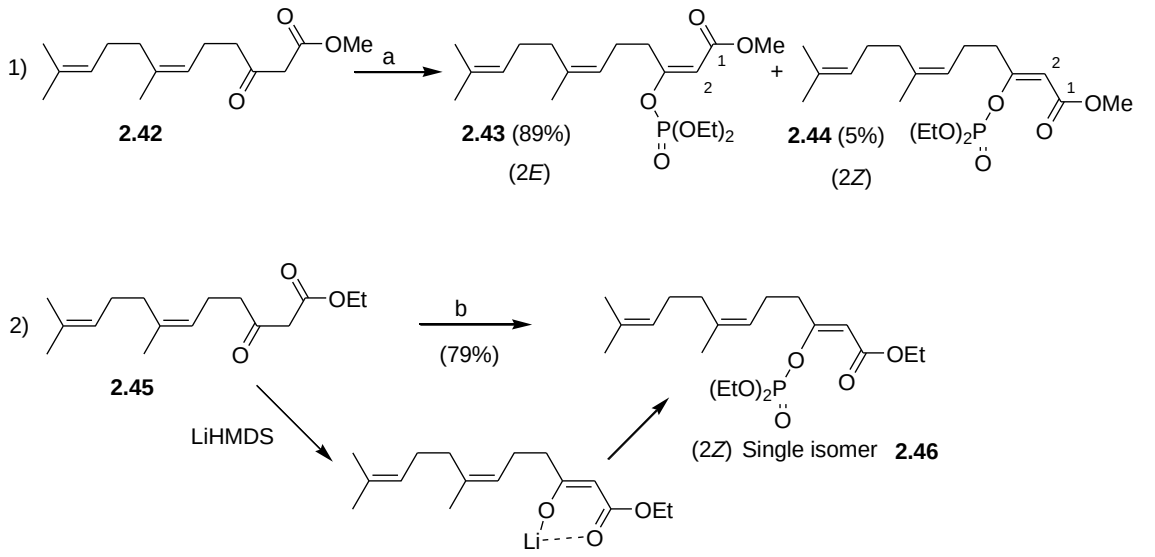
The synthesis had previously developed by the Brown group, starting from neryl chloride (**2.1**).[12] Neryl chloride (**2.1**) was prepared by chlorination of nerol (**1.58**, scheme 2.28). Alkylation of the dianion of methyl acetoacetate afforded the corresponding *β*-ketoester in a moderate yield (scheme 2.28).[12,69,89,90]



1.58 **2.1** **2.42**

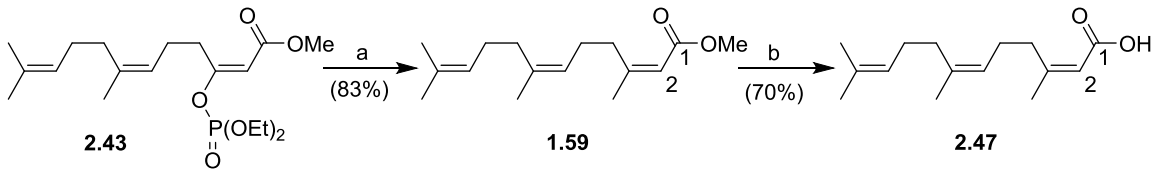
Scheme 2.28: Synthesis of *β*-ketoester **2.42** starting from nerol (**1.58**). **Reagents and conditions**: a) MsCl , LiCl, 2,6-lutidine, DMF, 0 °C to rt, 6 h. b) methyl acetoacetate NaH, ^{n}BuLi, THF, 0 °C to rt, 30 min.

The *β*-ketoester **2.42** was treated with $(EtO)_2POCl/Et_3N$ in DMPU and a catalytic amount of DMAP to provide the 2*E* enol phosphate **2.43** in good yield and selectivity (scheme 2.29).[91] The stereocontrol was due to the use of Et_3N as a non-coordinating base. The 2*Z* enol phosphate can be obtained when NaH or LiHMDS are used as bases (scheme 2.29, 2).[84] Column chromatography was used to separate the two isomers **2.42**, **2.43** and afforded the desired *E*-enol phosphate **2.42** as a pure isomer.



Scheme 2.29: Stereoselective enol phosphate formation from *β*-ketoester. **Reagents and conditions**: a $(EtO)_2POCl$, DMAP, Et_3N, DMPU, –20 °C to rt, 22 h. b) $(EtO)_2POCl$, LiHMDS, Et_2O, 0 °C, 3.5 h.

Stereoselective alkylation of the enol phosphate **2.43** was required to afford 2*Z* methyl trienoate **1.59** (scheme 2.30). Interestingly, use of MeLi.LiBr complex solution in Et_2O was found to improve the stereoselectivity of the alkylation reaction. The complex was treated with CuI and MeMgCl to afford a reagent with a stoichiometry ($Me_2CuMgCl$) which reacted with 2*E* enol phosphate **2.43** and gave the required 2*Z* triene methyl ester **1.59** as a single isomer in a good yield (83%, scheme 2.30).[91,92] The stereoselective alkylation of the enol phosphate **2.43** using MeLi (1.6 M in Et_2O) was reported previously by our group to afford a separable mixture of two isomers with isomeric ratio 2*Z*:2*E* = 11:1.[12]

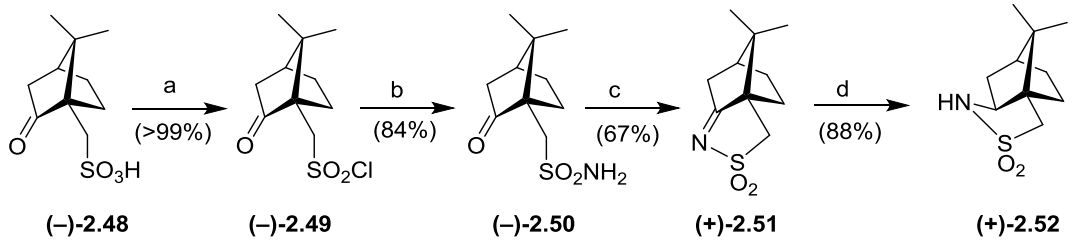


Scheme 2.30: Stereoselective alkylation of enol phosphates **2.43** and hydrolysis of methyl trienoate **1.59**. **Reagents and conditions**: a) CuI (3.0 equiv.), MeLi.LiBr (3.0 equiv.), MeMgCl (5.0 equiv.), THF, –35 °C, 1.5 h. b) NaOH, $NaHCO_3$, $MeOH:H_2O$, reflux. 6 h.

This interesting result was achieved on a 188 mg-scale (enol phosphate **2.43)**. When the alkylation reaction was scaled up, the desired isomer was obtained along with an

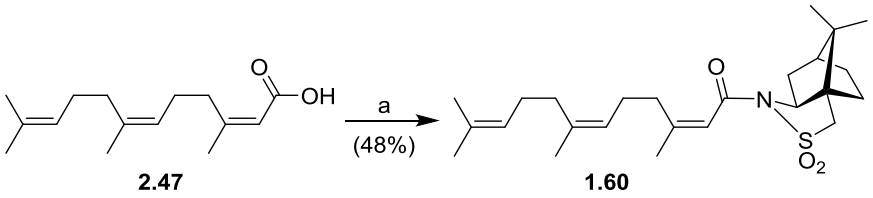
inseparable byproduct which was not identified. Therefore, the mixture was hydrolyzed to the desired carboxylic acid **2.47** which was separated from the byproduct by column chromatography (scheme 2.30). It was not possible to identify the byproduct using NMR.

For the permanganate mediated oxidative cyclisation of the 1,5,9-triene system, the camporsultam chiral auxiliary was used to control the facial selectivity of initial reaction at the enoyl alkene. It was previously established that the use of (2*S*)-10,2-camphorsultam ((+)-**2.52**) would provide the desired stereochemistry required in the right (C_{12}-C_{24}) fragment **1.189** of eurylene.[12,93] Therefore synthesis of (2*S*)-10,2-camphorsultam (+)-**2.52** was undertaken on a multi-gram scale, starting with commercially available (1*R*)-camphorsulfonic acid ((–)-**2.48**, scheme 2.31). Chlorination of sulfonic acid (–)-**2.48** with PCl_5 afforded the sulfonyl chloride (–)-**2.49**, which was then treated with NH_4OH to afford the sulfonamide (–)-**2.50**. Then heating under acidic conditions using a Dean-Stark apparatus gave the sulfonyl imine (+)-**2.51**. The imine **2.51** was reduced with $NaBH_4$ to afford the camphorsultam ((+)-**2.52**).[94-97] The product was recrystallized from absolute ethanol giving the required (+)-(*2S*)-10, 2-camphorsultam ((+)-**2.52**) as white crystals.



Scheme 2.31: Synthesis of (2*S*)-10,2-camphorsultam ((+)-**2.52**). **Reagents and conditions**: a) PCl_5 (3.0 equiv.), CH_2Cl_2, –10 °C to rt, 6 h. b) NH_4OH, CH_2Cl_2, 0 °C to rt, 5 h. c) Amberlyst 15 resin, toluene, reflux, 4 h. d) $NaBH_4$, MeOH, –5 °C, 1 h.

After obtaining (2*S*)-10,2-camphorsultams ((+)-**2.52**), the trienoic acid **2.47** was coupled with the auxiliary using the method reported by Liddle *et al* (scheme 2.32).[98] The acid **2.47** was treated with a slight excess of $(COCl)_2$ and a catalytic amount of DMF in ^{n}hexane. The resultant acid chloride was then immediately treated with the pre-formed sodium salt of (2*S*)-10,2-camphorsultam ((+)-**2.52**) in toluene to afford the trienoate **1.60** in a moderate yield (48%).[12]

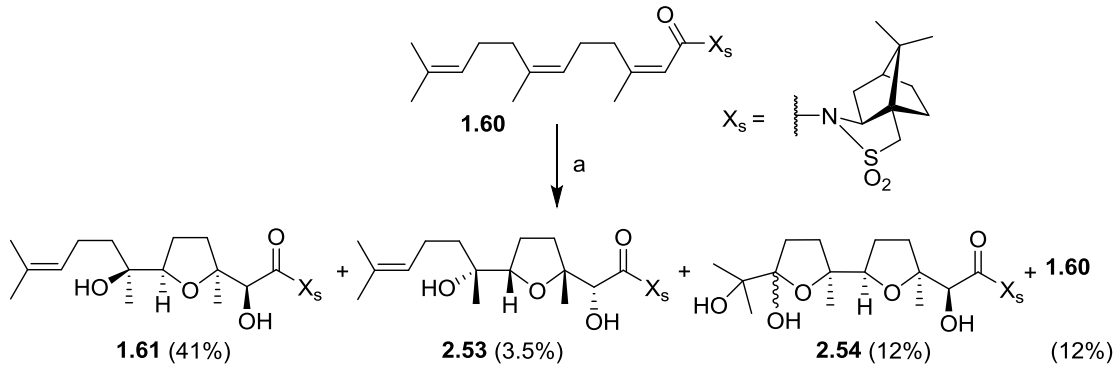


2.47 **1.60**

Scheme 2.32: Preparation of trienoate **2.60**, bearing (2*S*)-10,2-camphorsultam ((+)-**2.52**). **Reagents and conditions**: a) $(COCl)_2$, DMF, ^{n}hexane, rt 2 h then (2*S*)-10,2-camphorsultam ((+)-**2.52**, NaH (1.15 equiv.), toluene, 0 °C to rt, 6 h.

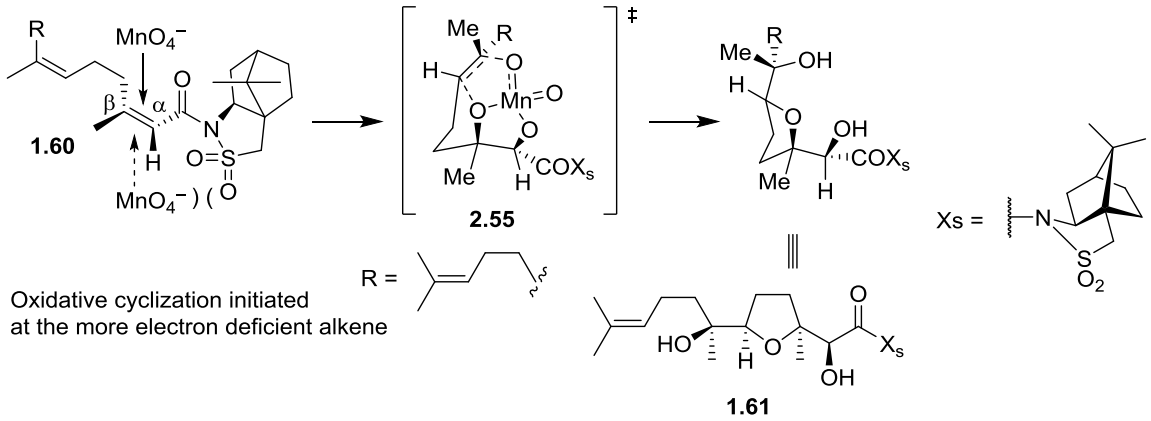
2.2.2. Oxidative Cyclisation of 1,5,9-Trienoate

After preparation of trienoate **1.60** bearing of camphor auxiliary, a permanganate mediated oxidative cyclisation was carried out (scheme 2.33). The trienoate **1.60** was oxidised using $NaMnO_4$ (1.5 equiv. of 0.4M aq. sol.) with AcOH (3.5 equiv.) and buffer solution (KH_2PO_4/ Na_2HPO_4). The oxidation afforded the desired 2,5-*cis* THF system **1.61** in an acceptable yield 41% along with 4% of the minor diastereoisomer **2.53** with 8:1 diastereoselectivity from ^{1}H NMR of the crude product.[12,99] An over-oxidised by-product **2.54** was also obtained from this oxidation (12%) and some of the trienoate **1.60** was recovered (12%). In attempts to optimize the yield, the oxidative cyclisation was conducted without the buffer solution and TBAB was used as a phase-transfer catalyst with $NaMnO_4$ (1.37 equiv.) and AcOH (2.45 equiv.) at a lower temperature (–35 ^{o}C to 2 ^{o}C) for 2.5 h. These conditions gave a same yield of the 2,5-*cis* THF system (41%). The diastereoisomerically pure *cis*-THF diol **1.61** was used to complete the synthesis of right (C_{12}-C_{24}) fragment **1.189** after separation by flash column chromatography.



Scheme 2.33: Stereocontrolled oxidative cyclisation of the 1,5,9-trienoate **1.60**. **Reagents and conditions**: a) $NaMnO_4$ (1.5 equiv. of 0.4M aq. sol.), AcOH (3.5 equiv.), phosphate buffer (KH_2PO_4:Na_2HPO_4, pH 7), acetone, –21 to –7 °C, 90 min.

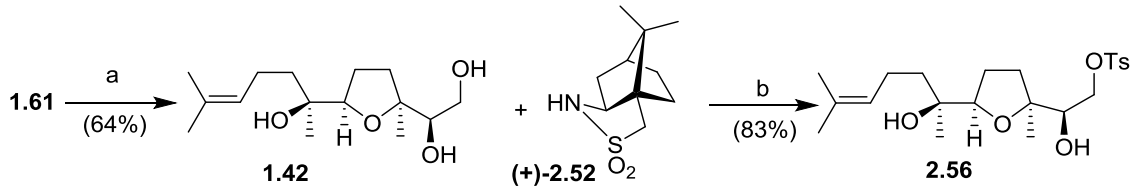
An explanation for the origin of the stereoselectivity was previously given by Reiser,[100] by the orientation of enoyl olefin of triene **1.60** and relevant arrangement of C=O and NSO_2 moieties (Scheme 2.34). Based on steric reasons, it was believed that the s-*cis* orientation of C=O/C(*α*)=C(*β*) and anti-arrangment of C=O and NSO_2 groups are favored. Attack of the MnO_4^- ion from the C(*β*) rear *Re*-face would take place preferentially. Cyclisation then goes through the transition state **2.55** and on hydrolysis gives the required *cis*-THF **2.52** as the major product.



Scheme 2.34: Rationalisation of the diastereoselectivity obtained using (2*S*)-10,2-camphorsultam ((+)-**2.52**).

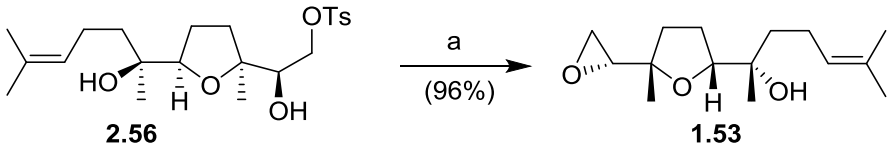
After obtaining the required *cis*-THF adduct **2.52**, The chiral auxiliary **2.52** was cleaved using $NaBH_4$ to afford a triol **1.42** with satisfactory yield (64%, scheme 2.35).[101] The coordination between the excess boron species and triol **1.42**, and loss on the column during purification, may be the reason for the low yield. Some losses may have also

occurred during extraction of the polar triol **1.42** during the work-up. The triol **1.42** was selectively mono-tosylated giving **2.56** in a good yield (83%).



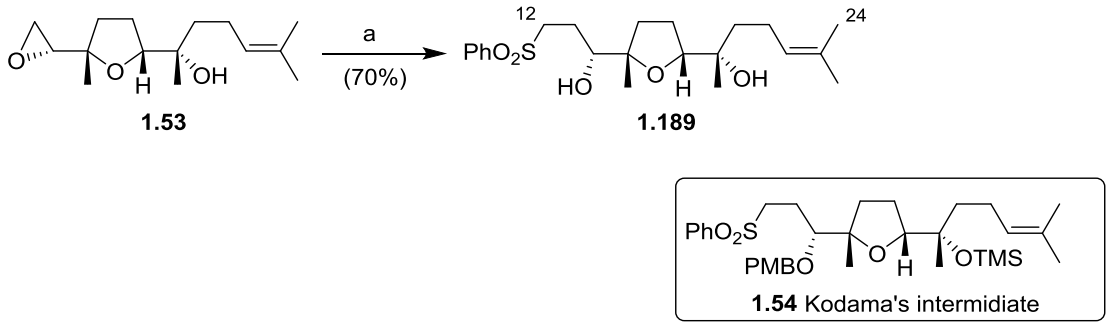
Scheme 2.35: Reductive cleavage of **1.61** and selective mono-tosylation to afford **2.56**. **Reagents and conditions**: a) $NaBH_4$, THF:H_2O (25:1), –10 °C to rt, 4 h. b) Bu_2SnO, TsCl, TBAB, PhH, 95 °C to rt, 23 h.

The tosylation reaction was followed by ring closure under basic conditions to afford epoxide **1.53** in 96% yield (scheme 2.36). In an attempt to protect the hydroxyl group of epoxide **1.53** using TMSCl, the procedure for protection of the LHF (C_1-C_{11}) route was followed. The reaction only afforded partial protection; therefore it was decided to use the unprotected epoxide in the next step. It is worth noting that the epoxide was not stable for long term storage (several weeks) even under storage at –20 °C in the freezer.



Scheme 2.36: Epoxidation of diol **2.56**. **Reagents and conditions**: a) K_2CO_3, MeOH, rt, 40 min.

Following Kodamma's work, methyl phenyl sulphone was employed as a source for the carbon C_{12} of eurylene (**1.1**) and to establish a functional group to facilitate the coupling between the two fragments C_1-C_{11} and C_{12}-C_{24}.[5] The epoxide ring was opened using the anion of methyl phenyl sulphone (scheme 2.37). The anion was generated by reaction of the sulphone with ^{n}BuLi in the presence of DMPU. An excess was required due to the presence of tertiary alcohol in **1.53** to afford the sulphone **1.189**, the right (C_{12}-C_{24}) fragment of eurylene in our approach.



Scheme 2.37: Synthesis of right (C_{12}-C_{24}) hand fragment **1.3**. **Reagents and conditions**: a) $MeSO_2Ph$, ^nBuLi, DMPU, THF, –30 to –25 °C, 6 h.

2.2.3. Conclusions

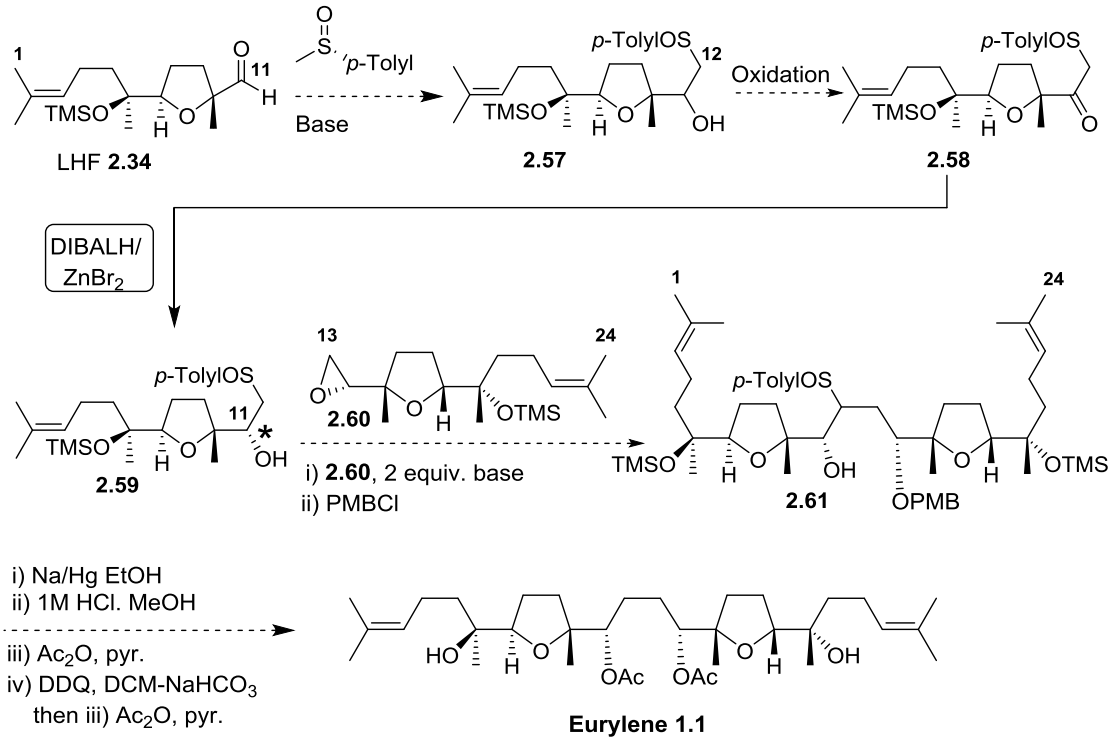
The stereoselectivity of the alkylation of 2*E* enol phosphate **2.43** was improved by using MeLi.LiBr complex solution in Et_2O. The alkylation afforded the required 2*Z* methyl trienoate **1.59** as a single isomer in a good yield (83%). The previous reported selectivity of the alkylation was 2*Z*:2*E* 11:1.0 using MeLi (1.6 M in Et_2O).[12] The synthesis of 2,5-*cis* THF system was achieved using the efficient permanganate mediated oxidative cyclisation. The use of (2*S*)-10,2-camphorsultam ((+)-**2.52**) proved successful and provided a good level of stereoselectivity in the oxidation. Methyl phenyl sulphone was employed as a source for the C_{12} carbon of eurylene and to establish a functional group to facilitate the coupling between the two fragments (C_1-C_{11}) and (C_{12}-C_{24}).

2.3. Coupling Approaches Towards the Total Synthesis of Eurylene

After the successful synthesis of the two eurylene fragments, our attention turned to the coupling of these fragments. A major challenge in the coupling will be to correctly establish the configuration at the C_{11} stereocentre. In this chapter two plans towards the total synthesis of eurylene will be described.

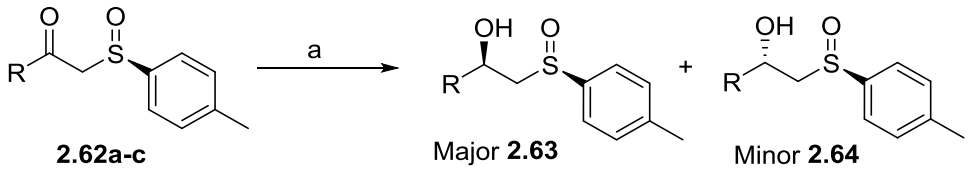
2.3.1. Chiral Methyl Sulfoxide Approach Towards the Total Synthesis

We planned to investigate the use of a chiral sulfoxide to control the C_{11} stereocentre and finish the total synthesis. The plan would commence with coupling the sulfoxide with the left (C_1-C_{11}) fragment aldehyde **2.34**, then oxidation of the resulting *β*-hydroxy sulfoxide **2.57** which could then undergo stereoselective reduction to give the *β*-hydroxy sulfoxide **2.59** (scheme 2.38).[102-105] The next step will be to couple the dianion of the required *β*-hydroxy sulfoxide **2.59** with the *cis*-THF epoxide (C_{12}-C_{24}) **2.60**,[102,106,107] and finally desulfurisation to afford the desired eurylene (**1.1**).[108]



Scheme 2.38: Proposed sulfoxide coupling towards the total synthesis of eurylene.

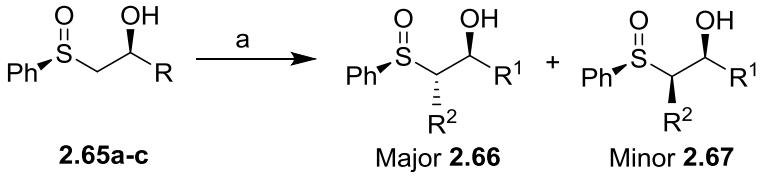
The use of a chiral sulfoxide with DIBALH in the presence of $ZnCl_2$ was reported in the literature to be an efficient way to control the stereoselectivity of the reduction of a *β*-keto sulfoxide (scheme 2.39).[103,105]



Compound	R	dr **2.63:2.64**	Yield (%)
2.62a	Et	>99:1	80
2.62b	Ph	>99:1	80
2.62c	^{t}Bu	10:1	80

Scheme 2.39: Stereocontrolled reduction of *β*-keto sulfoxide **2.62a-c**. **Reagents and conditions**: a) DIBALH, $ZnCl_2$, THF.

Formation of the dianion of *β*-hydroxysulfoxides and sulfones has been reported using ^{n}BuLi as a base. Coupling with an electrophile such as alkyl iodide provided a successful way to alkylate the *β*-hydroxy compound (schemes 2.40). [102,106,107]

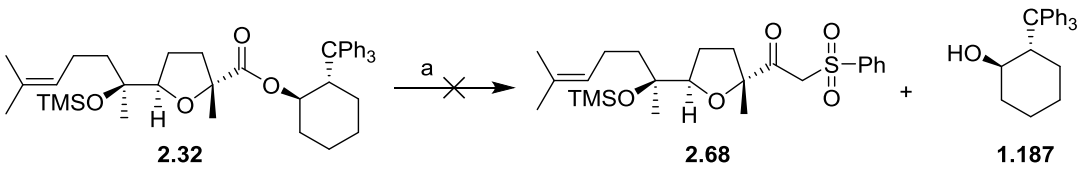


Compound	R	R^1-I	Ratio **2.66:2.67**	Yield (%)
2.65a	CH_3	CH_3	89:11	86
2.65b	$(CH3)_2CHCH_2$	CH_3	96:4	96
2.65c	$^{n}C_6H_{19}$	$^{n}C_8H_{17}$	99:1	59

Scheme 2.40: Dianion formation and allkylation of *β*-hydroxyl sulfoxide **2.65a-c**. **Reagents and conditions**: a) R^1-I, ^{n}BuLi (2.2 equiv.), –78 °C, THF.

We planned to adopt this methodologies initially on the methyl phenyl sulfone in place of the enantiopure chiral sulfoxide, to investigate the dianion coupling. Methyl phenyl sulfone was deprotonated with ^{n}BuLi, then reacted with **2.32** in the presence of ^{n}BuLi to afford *β*-ketosulfone **2.68** (scheme 2.41).[103] Unfortunately, the coupling reaction was unsuccessful, with the majority of the starting material recovered along with an

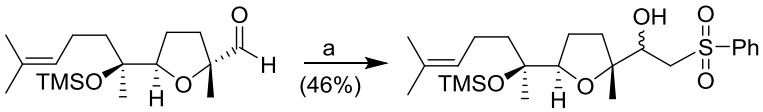
unidentified byproduct. It was believed that the large steric bulk of the TTC auxiliary inhibited the coupling.



2.32 **2.68** **1.187**

Scheme 2.41: Attempted coupling of methyl phenyl sulfone with TTC easter **2.32**. **Reagents and conditions**: a) $MePhSO_2$, ^{n}BuLi, THF, 0 to 10 ^{o}C, 1.5 h.

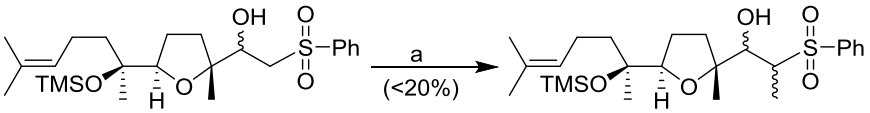
In an alternative approach, reaction of the anion of methyl phenyl sulfone with the protected aldehyde fragment **2.34** afforded alcohol **2.68** as a mixture of inseparable epimers (~1:1, ^{1}H NMR, scheme 2.42).[102]



2.34 **2.69**

Scheme 2.42: Coupling of methyl phenyl sulfone with aldehyde **2.34**. **Reagents and conditions**: a) $PhSO_2Me$, ^{n}BuLi, THF, –78 ^{o}C to –25 ^{o}C, 2 h.

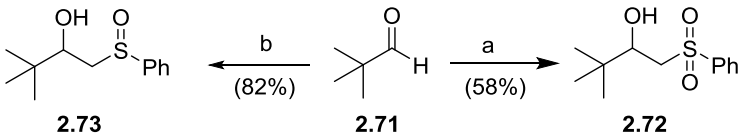
The epimeric alcohols **2.69** were reacted with ^{n}BuLi (2.0 equiv.) Then alkylated with methyl iodide as a model alkylation agent to afford a compound tentatively assigned as **2.70** based on MS data in a low yield (<20%, scheme 2.43).[102-107]



2.69 **2.70**

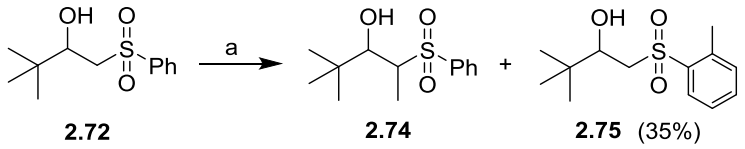
Scheme 2.43: Coupling of the dianion of **2.69** with MeI. **Reagents and conditions**: a) MeI, ^{n}BuLi (2.0 equiv.), THF, –78 ^{o}C to rt, 2 h.

To conserve supplies of the left C_1-C_{11} aldehyde fragment **2.34**, pivaldehyde (**2.71**) was used as a model aldehyde in the investigation of the coupling methodology. *β*-Hydroxyl sulfone **2.72** and *β*-hydroxyl sulfoxide **2.73** were prepared after coupling of pivaldehyde with methyl phenyl sulfone and methyl phenyl sulfoxide (a racemic mixture) respectively using LDA as a base (scheme 2.44).



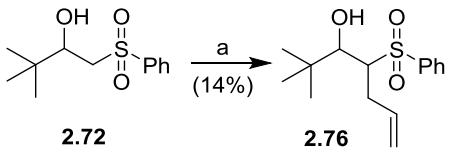
Scheme 2.44: Coupling of pivaldehyde (**2.71**) with $PhSO_2Me$ and PhSOMe. **Reagents and conditions**: a) $PhSO_2Me$, LDA, THF, –10 to 0 °C, 30 min, –78 °C, 1 h. b) PhSOMe, LDA, THF, –10 to 0 °C, 30 min, –78 °C, 1 h.

To establish the optimum conditions for successful dianion formation for the *β*-hydroxy sulfones and sulfoxides, their treatment with the powerful electrophiles methyl iodide and allyl bromide and allyl iodide were invistigated.[102,106,107] Preparation of the dianion of the hydroxyl sulfone **2.72** was a challenge and required identification of suitable conditions. Using ^{n}BuLi as the base to afford the dianion, and reaction with MeI led to an ortho-lithiation byproduct **2.75** (35% yield, δ 2.70 ppm for CH_3, Ar) as well as a mixture of S.M and small quantity of the α-methyl product **2.74** (scheme 2.45).



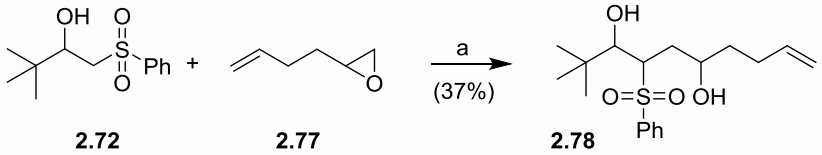
Scheme 2.45: Alkylation of *β*-hydroxy sulfone **2.72** with MeI using ^{n}BuLi as a base. **Reagents and conditions**: a) ^{n}BuLi (2.0 equiv.), MeI, THF,–78 °C to rt, 20 h.

Kaji, *et al,*[107] reported that ^{n}BuLi could be used to afford dianions of hydroxy sulfone derivatives. However, they reported that addition of ^{n}BuLi at –78 °C followed by warming the mixture to –20 °C and then re-cooling to –78 °C was required before the addition of the electrophile. Under these reported conditions formation of the ortho lithiation byproduct was avoided, but unfortunately the coupling with allyl bromide proceed in a disappointing yield, even when using TMEDA as an additive (ca. 14%, scheme 2.46).



Scheme 2.46: Alkylation of *β*-hydroxy sulfone **2.72** with allyl bromide using ^{n}BuLi as a base. **Reagents and conditions**: a) ^{n}BuLi (2.2 equiv.), allyl bromide, TMEDA, THF, –78 °C to –20 °C, 4 h.

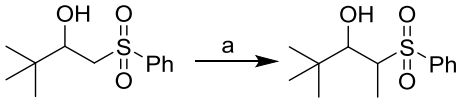
Coupling of the *β*-hydroxy sulfone dianion with an epoxide electrophile was also investigated (scheme 2.47). The best result for coupling the dianion with 1,2-epoxy-5-hexene (**2.78**) was 37% yield along with 35% of recovered hydroxy sulfone **2.72**. The reaction did not improve with using DMPU as additive.



2.72 **2.77** **2.78**

Scheme 2.47: Coupling of *β*-hydroxy sulfone **2.72** with 1,2-epoxy-5-hexene (**2.77**) using ^{n}BuLi as a base. **Reagents and conditions**: a) ^{n}BuLi (2.0 equiv.), THF,–78 ^{o}C to rt, 15 h.

As poor results were achieved when using ^{n}BuLi as a base, LDA was investigated as an alternative to afford the dianion of *β*-hydroxy sulfone **2.72** (scheme 2.48). Alkylation with MeI was carried out and afforded an inseparable mixture of the desired product **2.74** with the starting hydroxyl sulfone **2.72**. As a result, the alkylating agent was changed to allyl bromide or allyl iodide with the hope of improving separation of the products.

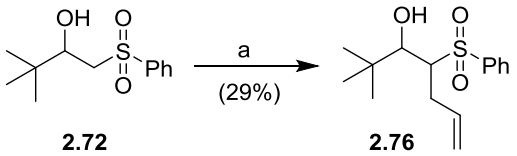


2.72 **2.74**

Scheme 2.48: Alkylation of *β*-hydroxy sulfone **2.72** with MeI using LDA (1.0M solution in THF/ hexane or 2.0M solution in THF/^{n}heptane/ethyl benzene) as a base. **Reagents and conditions**: a) LDA (2.0 equiv.), –78 ^{o}C to 0 ^{o}C, 10 min, then re-cooling at –78 ^{o}C), MeI, THF, –78 ^{o}C to rt, 4 h.

Surprisingly, the alkylation of *β*-hydroxy sulfone **2.72** with allyl bromide was successful using LDA as a solution in THF/^{n}heptane/ethyl benzene, whereas there was no reaction using LDA in THF/hexane (scheme 2.49). The dianion of *β*-hydroxy sulfone was formed using the typical condition (LDA (2.0 equiv.), –78 ^{o}C, to 0 ^{o}C, 10 min, then re-cooling at –78 ^{o}C). These conditions gave the desired product but in an unsatisfactory yield (29%) along with 40% of the starting hydroxyl sulfone **2.72**, the reaction required stirring at rt for 6 h (entry 1, table 2.6). Many attempts to improve the yield were made,

but they did not provide any significant increase in product yield, and elimination of the hydroxyl group was observed as a side reaction (table 2.6)



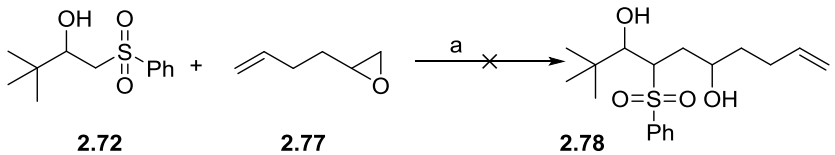
2.72 **2.76**

Scheme 2.49: Investigation of alkylation of *β*-hydroxy sulfone **2.72** with allyl bromide using LDA as a base.

Entry	**LDA** (equiv.)	**Conc.** (M)	**Additive**	**Ratio 2.72:2.76**[a]
1	2.0	0.11	No	1.3:1 (29%)[b]
2	3.0	0.11	No	2:1
3	2.2	0.15	No	1.4:1
4	2.2	0.11	TMEDA	2.2:1
5	2.2	0.11	DMPU	28%[b,c]

Table 2.6: Investigation of alkylation of *β*-hydroxy sulfone **2.72** with allyl bromide using LDA as a base (–78 °C to 0 °C, then –78 °C, allyl bromide, THF,–78 °C to rt, 6 h). [a]The ratio was estimated by ^{1}H NMR for the crude reaction. [b]Isolated yield of **2.76**. [c]Crude ^{1}H NMR showed a complex mixture of product.

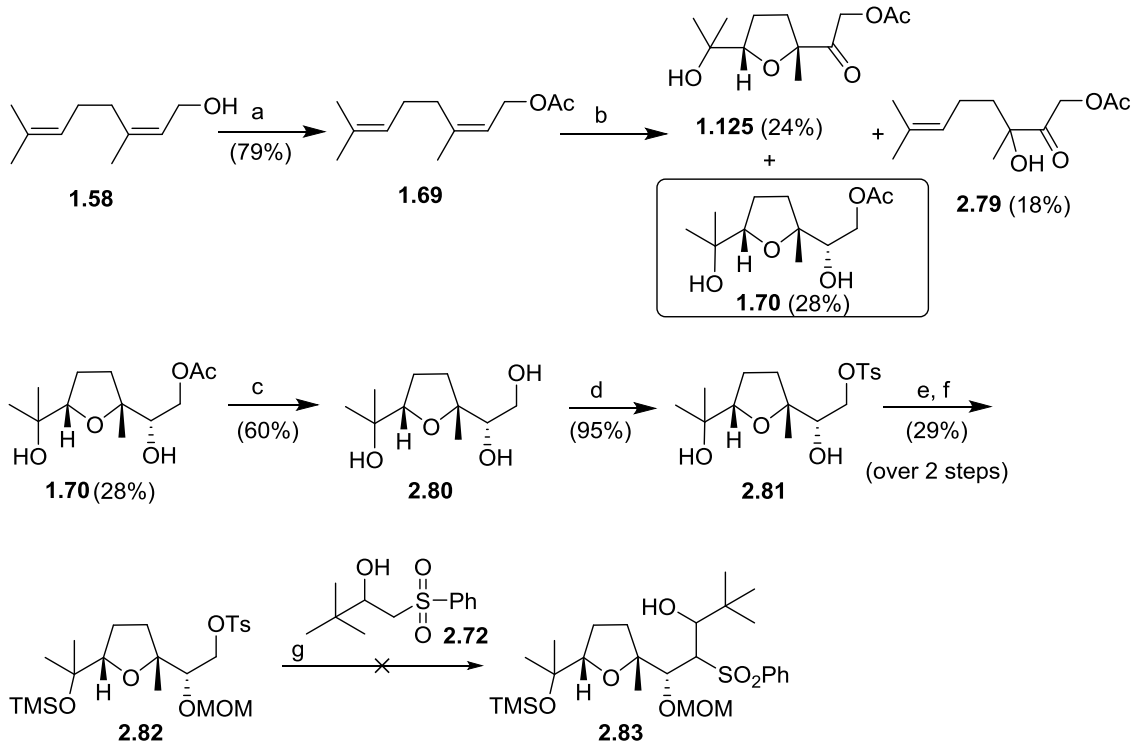
Attempts were carried out to couple the hydroxyl sulfone **2.72** with 1,2-epoxy-5-hexene (**2.77**) to afford the diol **2.78** using LDA as a base (scheme 2.50). Unfortunately, the desired product **2.78** was not formed under the previously successful conditions (entry 1, table 2.6), ^{1}H NMR showed starting materials.



2.72 **2.77** **2.78**

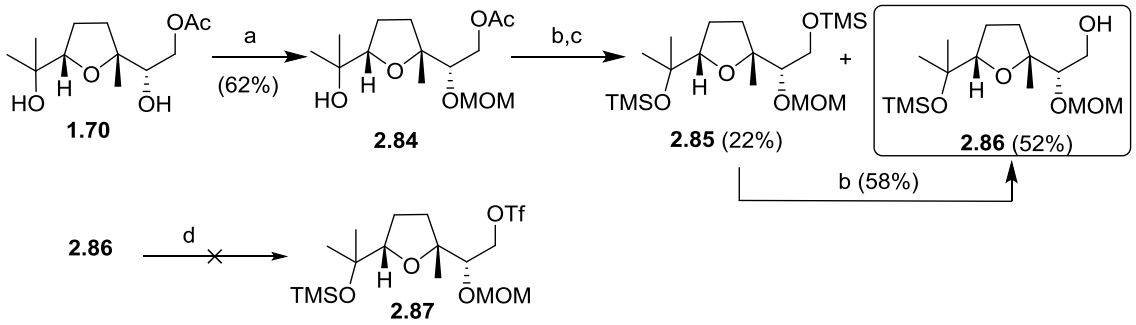
Scheme 2.50: Coupling of *β*-hydroxy sulfone **2.77** with 1,2-epoxy-5-hexene (**2.77**) using LDA as a base. **Reagents and conditions**: a) ^{n}BuLi (2.0 equiv.), THF, –78 °C to rt, 15 h.

To investigate whether the hydroxyl sulfone **2.72** could be coupled with tosylate and triflate derivatives of the right (C_{12}-C_{24}) hand fragment, a closely related model system **2.82** was investigated (scheme 2.51). In this plan, neryl acetate (**1.69**) was subjected to permanganate oxidative cyclisation to afford THF **1.70** in low yield (28%) along with two byproducts **1.125** and **2.79** (24% and 18% respectively). Hydrolysis of THF-acetate **1.70** to triol **2.80** and then selective tosylation at the primary alcohol gave tosylate **2.81**. Protection of the secondary alcohol with a MOM group and the tertiary hydroxyl as its TMS ether led to a protected THF-tosylate **2.82**, which was ready to use in the coupling reaction with the dianion of *β*-hydroxy sulfone **2.72**. Unfortunately, the coupling reaction under the previously described dianion formation conditions was unsuccessful. ^{1}H NMR of the crude reaction showed only starting materials.



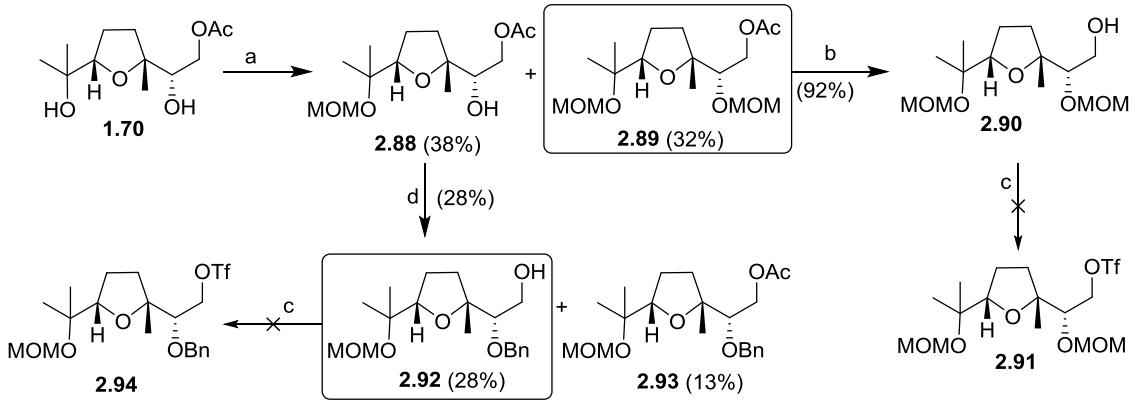
Scheme 2.51: Synthesis of THF-tosylate **2.81** and attempted coupling with the dianion *β*-hydroxy sulfone **2.72**. **Reagents and conditions**: a) Ac_2O, pyr., 50 °C, 23 h. b) $NaMnO_4$ (1.5 equiv.), AcOH (3.0 equiv.), KH_2PO_4/Na_2HPO_4 (pH 7.0, 0.5 equiv.), acetone, –35 °C, 1 h. c) K_2CO_3, MeOH, rt, 1 h. d) Bu_2SnO, TsCl, TBAB, PhH, 95 °C to rt, 3 h. e) MOMCl (1.1 equiv.), DIPEA, CH_2Cl_2, 0 °C to rt, 33%. f) TMSCl, Imid., CH_2Cl_2, –5 °C, 1 h, 89%. g) LDA (2.5 equiv.), THF, –78 °C to rt, 23 h.

It was believed an even better leaving group would be required to facilitate coupling. Therefore attempts were made to synthesise the THF-triflate **2.87** (scheme 2.52). THF-acetate **1.70** was protected as its MOM ether, then hydrolysed to the diol and finally protected with TMS group to give **2.85**. Partial TMS deprotection was observed during the silyl protection reaction work-up. The protected compound **2.85** was hydrolyzed to the required primary alcohol **2.86** and followed by reaction with Tf_2O in the presence of 2,6-lutidine resulted in decomposition products and the desired triflate **2.87** was not observed.



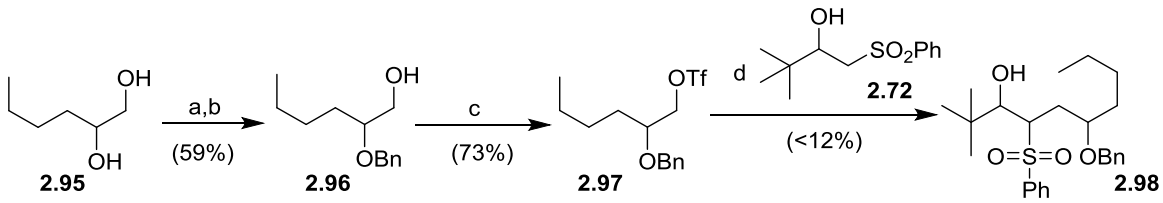
Scheme 2.52: Synthesis of THF-triflate compounds **2.87**. **Reagents and conditions:** a) MOMCl (2.0 equiv.), NaH, DMF, 0 °C, 1.5 h. b) K_2CO_3, MeOH, rt, 1 h, 100%. c) TMSCl, Imid. CH_2Cl_2, –5 to 5 °C , 2 h. d) Tf_2O, 2,6-lutidine, CH_2Cl_2, –78 °C, 30 min.

Attempted formation of the triflate from MOM or Benzyl protected alcohol **2.90** and **2.92** respectively was also unsuccessful (scheme 2.53).



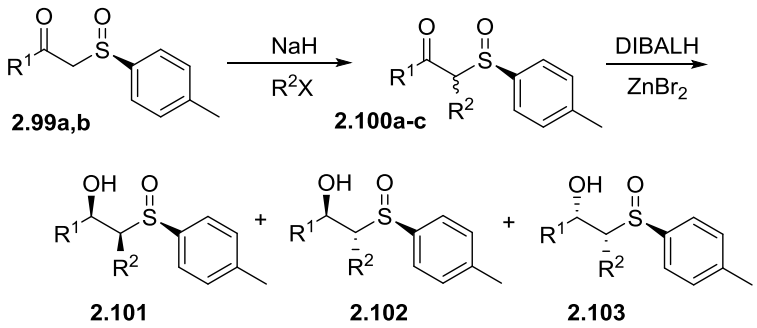
Scheme 2.53: Attempted ynthesis of THF-triflate derivatives **2.91** and **2.94**. **Reagents and conditions:** a) MOMCl (2.0 equiv.), NaH, DMF, 0 °C, 5 h. b) K_2CO_3, MeOH, rt, 1 h. c) Tf_2O, 2,6-lutidine, CH_2Cl_2, –78 °C, 30 min. d) BnBr, NaH, THF, 0 °C to rt, 26 h.

To investigate whether a simplified triflate derivative **2.97** could be coupled with the dianion of *β*-hydroxyl sulfone **2.72**, the triflate **2.97** was synthesised and reacted with *β*-hydroxyl sulfone **2.72** (scheme 2.54). Unfortunately, the reaction afforded low yield of the required product **2.98** (<12%), mixed with hydroxyl elimination byproduct, indicated by ^{1}H NMR (δ 6.22 ppm).



Scheme 2.54: Coupling of *β*-hydroxyl sulfone **2.72** with model triflate **2.97**. **Reagents and conditions**: a) $PhCH(OCH_3)_2$, CSA, CH_2Cl_2, rt, 19 h. b) DIBALH, CH_2Cl_2, 0 ^oC, 30 min. c) Tf_2O, 2,6-lutididne, CH_2Cl_2, –78 ^oC, 1 h. d) **2.72**, LDA (2.4 equiv.), –78 ^oC to 0 ^oC, 10 min, then –78 ^oC, THF, –78 ^oC to rt, 5 h.

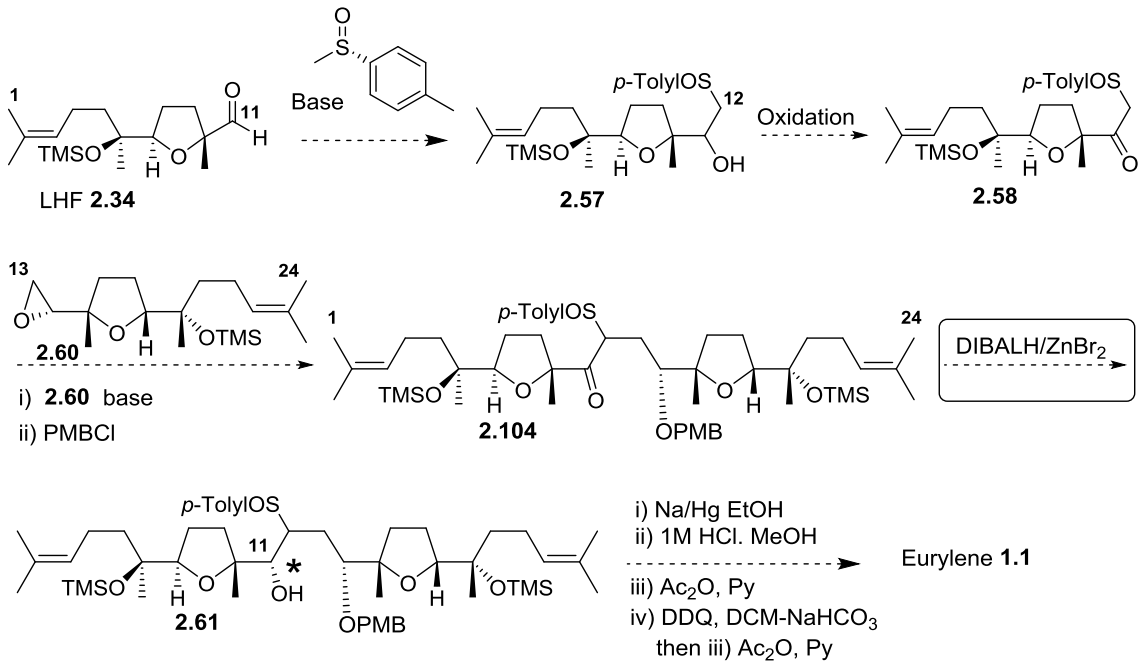
Due to the above unsatisfactory results, it was decided to modify the plan and adopt the strategy reported by Maestro *et al.*[109] (schemes 2.55 and 2.56). Maestro *et al*. reported a reduction of α-alkyl *β*-ketosulfoxides **2.100a-c** with DIBALH in the presence of $ZnBr_2$ which afforded high stereoselectivity at the hydroxyl group. The stereochemistry at the C-S bond was poor, but would be later cleaved in our route (scheme 2.55).



Compound	R^1	**2.100**	R^2	**2.101:2.102:2.103**[a]	Yield (%)
2.99a	^{n}Pr	**2.100a**	Me	60:40:0	98
2.99a	^{n}Pr	**2.100b**	Allyl	60:40:0	77
2.99b	^{t}Bu	**2.100c**	Me	60:35:5	98
2.99b	^{t}Bu	**2.100c**	Me	60:37:3[b]	98

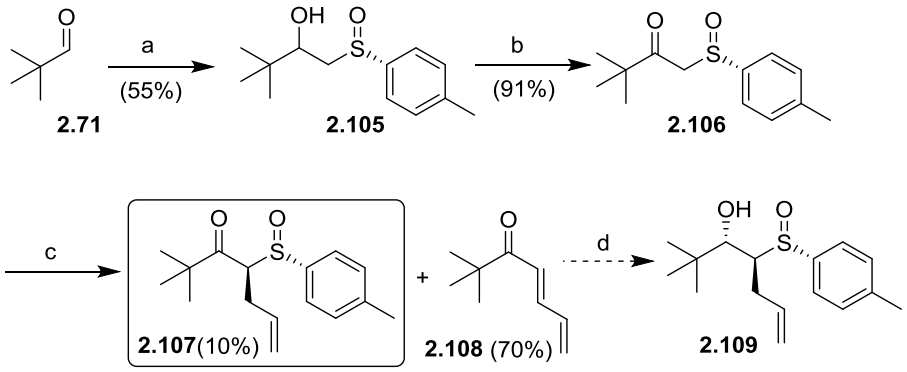
Scheme 2.55: Stereocontrolled reduction of α-alkyl *β*-keto sulfoxide **2.66a-c**.[a]Hydroxy sulfoxide ratio by use 1.4 equiv. of $ZnBr_2$. [b]Use 5 equiv. of $ZnBr_2$.

Maestro's results encouraged us to couple the *β*-keto sulfoxide **2.58** with the right (C_{13}-C_{24}) fragment epoxide **2.60**, followed by DIBALH/$ZnBr_2$ reduction towards the total synthesis of eurylene (scheme 2.56).



Scheme 2.56: Proposed to complete the total synthesis of eurylene (**1.1**).

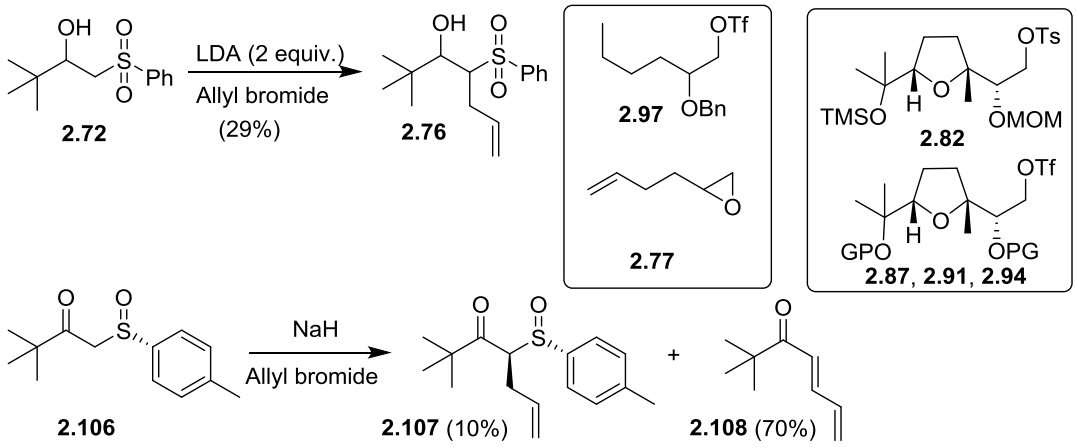
In this attempt the enantiomerically pure sulfoxide was used; (*S*)-(–)-methyl phenyl sulfoxide was coupled with pivaldehyde (**2.71**) to afford *β*- hydroxy sulfoxide **1.105** in a satisfactory yield (55%, dr. 1.2:1, scheme 2.57). *β*-Hydroxy sulfoxide **2.105** was oxidized using Dess-Martin periodinane to afford *β*-ketosulfoxide **2.106** in excellent yield (91%). It was disappointing that coupling of *β*-ketosulfoxide led to diene **2.108** as the main product (~70%) along with 10% yield of the desired product **2.107** as single isomer. The minor stereoisomer was inseparable from unreacted sulfoxide. The side elimination reaction possibly occurred due to the allylic nature of the system. However, the result indicated that the alkylation was possible at the *β*-ketosulfoxide.



Scheme 2.57: Synthesis of *β*-keto sulfoxide **2.106** followed by alkylation with allyl bromide. **Reagents and conditions**: a) (*S*)-(–)-Methyl phenyl sulfoxide, LDA, THF, –10 to 0 ^{o}C, 30 min, –78 ^{o}C, 3 h, 28% recovered S.M. b) Dess-Martin periodinane, CH_2Cl_2, 0 ^{o}C, 2 h. c) Allyl bromide, NaH, TBAI, THF, rt, 19 h. d) DIBAL/$ZnBr_2$, THF.

2.3.1.2. Conclusions

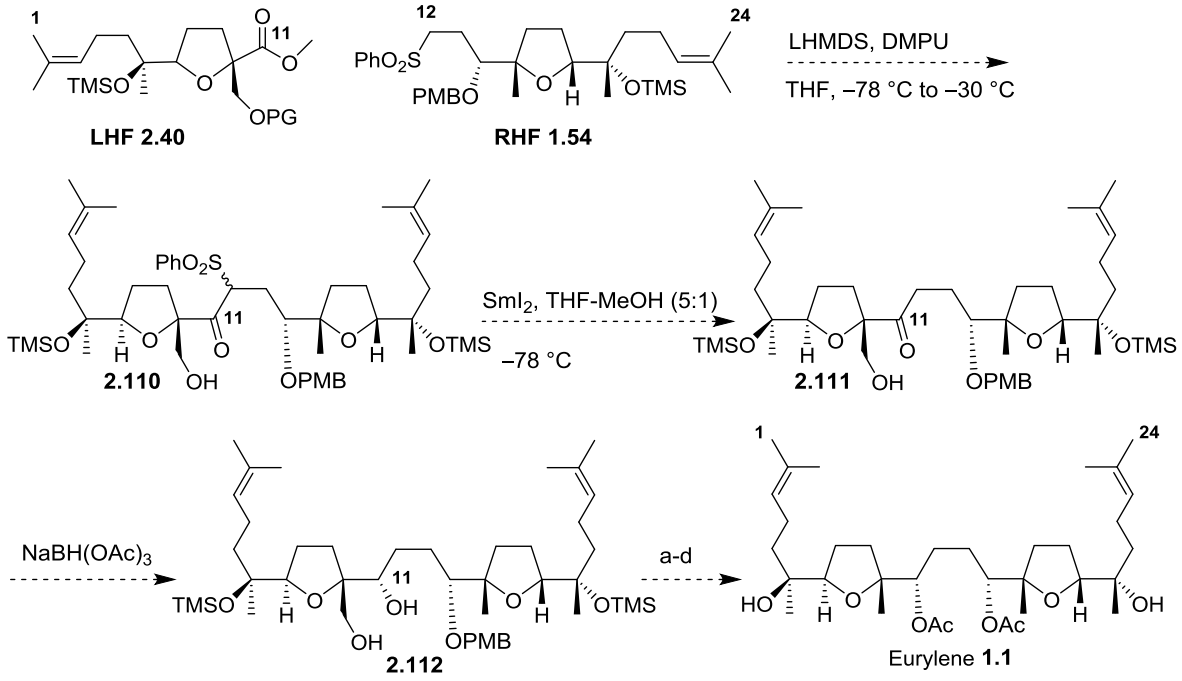
The formation of dianion of *β*-hydroxy sulfone **2.72** was demonstrated using LDA (2.0 equiv.) as a base. However, its coupling with good electrophiles such as allyl bromide, epoxide and simple triflate was only achieved in moderate yields (29%, 37% and <12% respectively, scheme 2.57). Coupling the dianion of the sulfone **2.72** with THF-tosylate **2.82** was unsuccessful and the starting materials were recovered. Attempts to facilitate the coupling by replacing the tosylate with triflate group resulted in decomposition and the desired triflate derivatives **2.87**, **2.91** and **2.94** were not obtained (scheme 2.58). Alkylation of *β*-ketosulfoxide **2.106** synthesised from enantiomerically pure sulfoxide with allyl bromide was successful, but elimination led to the loss of the majority of the desired product, which decomposed to give diene byproduct **2.108**. However, this elimination may not be a problem in the real system.



Scheme 2.57: Alkylation of **2.72** and **2.106**, and some used structures.

2.3.2. Hydroxyl- Directed Reduction Approach Towards the Total Synthesis of Eurylene

In this approach right (C_{12}-$_{24}$) hand fragment **1.54** will react with left (C_1-C_{11}) hand fragment methyl ester **2.40** (scheme 2.58). Then a hydroxyl directed reduction at C_{10} of eurylene will be investigated as a means to control the attack of hydride and afford a stereoselective reduction [5, 110,111] Due to the time constraints, the methodology will be carried out in future work.



a) Thiocarbonyldiimidazole. b) AIBN, TTMSS. c) 1M HCl. MeOH. d) Ac_2O, pyr. d) DDQ, CH_2Cl_2:$NaHCO_3$ (10:1).

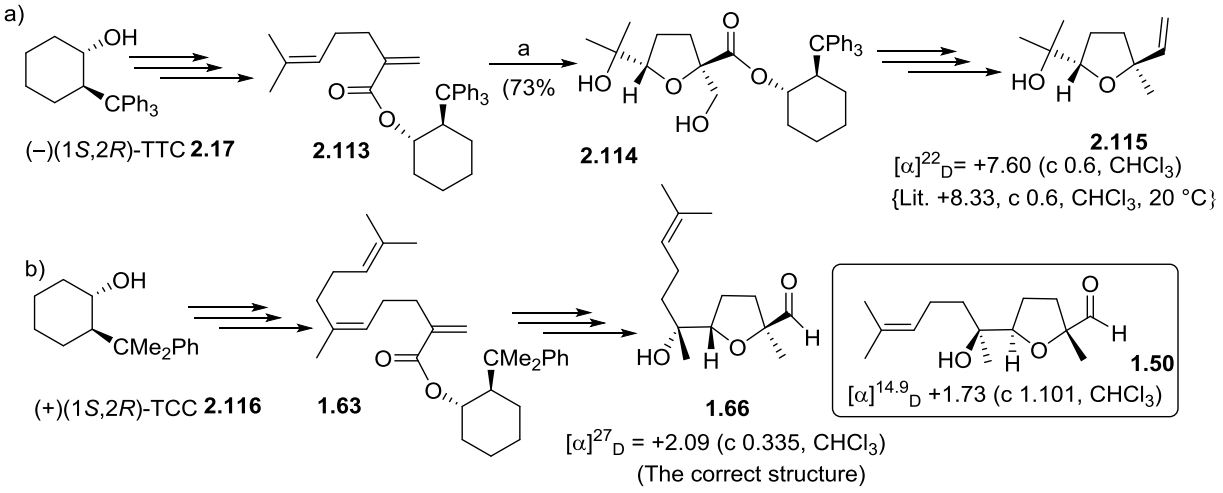
Scheme 2.58: Proposed approach to complete the total synthesis of eurylene (**1.1**) using a directed reduction.

2.4. Stereochemical Correlation for the Oxidative Cyclisation Products from TCC and TTC Esters

This section details some of the work to establish the absolute configurations of the oxidative cyclisation products from TCC and TTC esters.

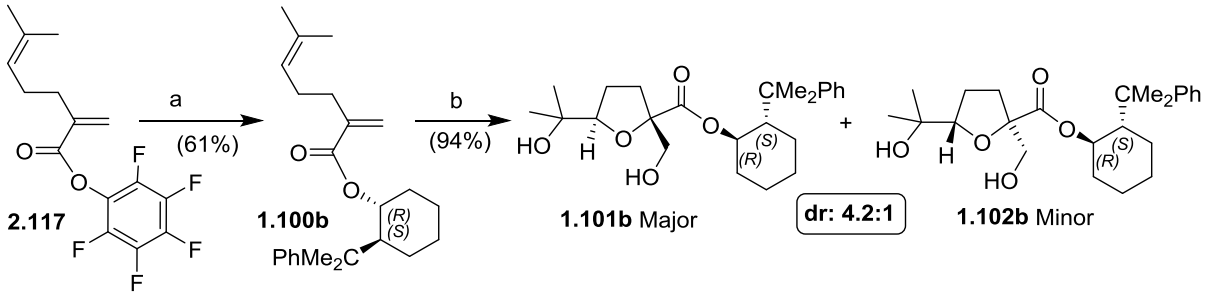
2.4.1. Stereochemical Correlation (1*R*,2*S*)-TCC and (1*S*,2*R*)-TTC Dienoate Esters

The stereochemistry of the major oxidative cyclisation product (–)-**2.114** obtained from diene (–)-**2.113** ((1*S*,2*R*)-*trans*-2-tritylcyclohexanol, TTC) was established through its conversion to (+)-linalool oxide (**2.115**) as described in a previous study within the Brown group (scheme 2.59).[13] The sense of diastereoinduction observed for the trityl-substituted auxiliary ((1*S*,2*R*)-*trans*-2-trityl cyclohexanol, TTC) was inconsistent with an earlier study within the group which reported assignment of the oxidation product of trienoate system **1.63**, bearing the cumyl-substituted auxiliary TCC (scheme 2.59).[12] It transpired that the original assignment of the major stereoisomer **1.66** from triene oxidation was in error ($[\alpha]^{27}_{D}$ = +2.09, *c* 0.335, $CHCl_3$). The original assignment was based on comparison of optical rotation data with a known compound **1.50** that was reported by Kotama *et al.* ($[\alpha]^{14.9}_{D}$ = +1.73, *c* 1.101, $CHCl_3$).[5] In this chapter the stereochemical confirmation for the major oxidative cyclisation diastereoisomers from TCC and TTC dienoates and trienoates will be described.



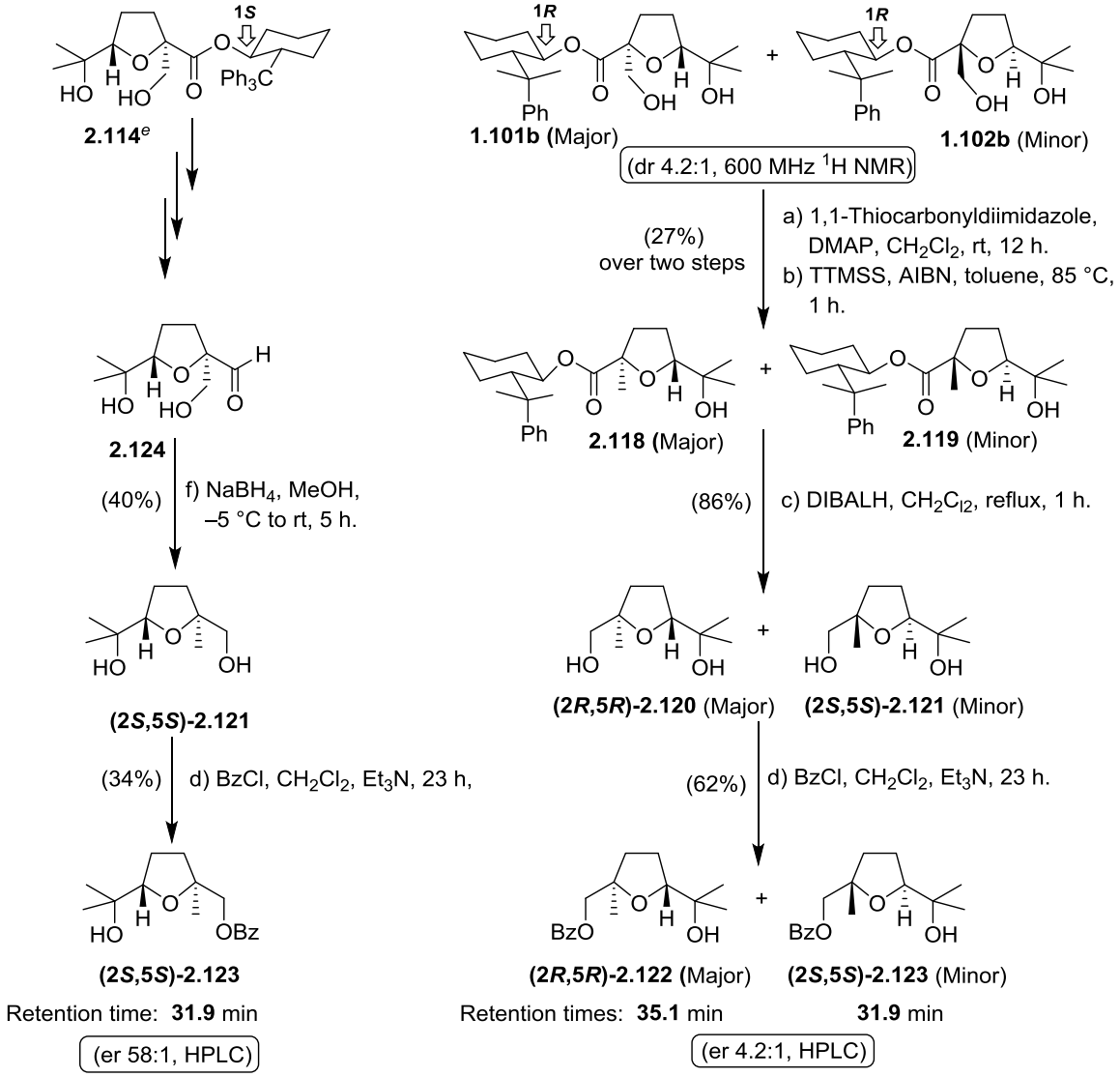
Scheme 2.59: a) The total synthesis of (+)-linalool oxide using (1*S*,2*R*)-TTC (**2.17**). [13] b) Synthesis of *cis*-THF system using (1*S*,2*R*)-TCC (**2.116**).[12] **Reagent and conditions**: a) $NaMnO_4$ (0.4M), AcOH, H_2O, Acetone, –40 to –5 °C, 1 h.

To unambiguously establish the sense of the diastereofacial selectivity for oxidative cyclisation of (1*R*,2*S*)-TCC dienoate **1.100b**, the oxidative cyclisation products of (1*S*,2*R*)-TTC dienoate **2.113** and (1*R*,2*S*)-TCC dienoate **1.100b** were converted to a common intermediate and analysed by chiral HPLC. (1*R*,2*S*)-TCC dienoate **1.100b** was prepared by coupling (–)(1*R*,2*S*)-TCC **2.116** (*ee*:97) with PFP dienoate **2.117**, previously prepared within the group (scheme 2.60).[12] Permanganate oxidative cyclisation of the resulting TCC dienoate **1.100b** gave a mixture of inseparable diastereoisomers **1.101b** and **1.102b** in an excellent yield (94%). The dr. of the two diastereoisomers was 4.2:1 by 600 MHz ^{1}H NMR.

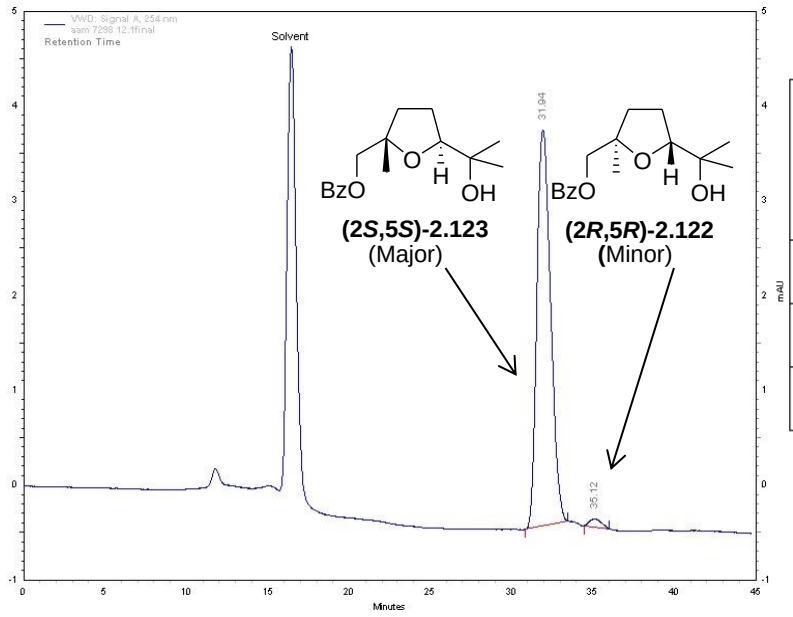


Scheme 2.60: Oxidative cyclisation of (1*R*,2*S*)-TCC dienoate **1.100b**. **Reagents and conditions**: a) (–)(1*R*,2*S*)-TCC **2.116**, NaHMDS, THF, –5 to 5 ^{o}C, 1.5 h. b) $NaMnO_4$ (1.5 equiv.), AcOH (3.0 equiv.), KH_2PO_4/Na_2HPO_4, pH 7.0, acetone, –35 to –2 ^{o}C, 1.5 h.

Following the approach used in the formal synthesis of the eurylene left (C_1-C_{11}) hand aldehyde fragment **1.50**, the mixture of diastereomeric THFs **1.101b**/**1.102b** was taken through the reaction sequence of radical deoxygenation and reductive cleavage of the auxiliary to afford a mixture of two enantiomeric diols **2.120/2.121** (scheme 2.61). The diols were converted to the enantiomeric benzoates **2.122** and **2.123** by reaction with freshly distilled benzoyl chloride. The enantiomeric ratio was analysed by analytical HPLC- Chiralpak® AD-H - (*eluent*: IPA/hexane 7.5:92.5) giving retention times of 35.1 and 31.9 min for the major and minor diastereoisomers respectively. Integration of the peaks showed a diastereomeric ratio of **1.101b**:**1.102b** was 4.2:1. The benzoate derivative **2.123** was synthesised from the (1*S*,2*R*)-TTC-THF **2.114** in the same way. An intermediate aldehyde **2.124** from a previous study was used to afford the required benzoate over two steps (scheme 2.61).[13] The enantiomeric ratio was analysed by analytical HPLC- Chiralpak® AD-H - (*eluent*: IPA/hexane 7.5:92.5), giving retention times of 31.9 and 35.1 min for the major and minor diastereoisomers respectively. Integration of the peaks showed a diastereomeric ratio of the oxidative cyclisation was 59:1. Chiral HPLC analysis indicated that the major product from the (1*S*,2*R*)-TTC dienoate had the same absolute configuration at the THF 2 and 5 positions as the minor product from the (1*R*,2*S*)-TCC dienoate. HPLC traces for the benzoate derivatives are shown in figures 2.3, 2.4.

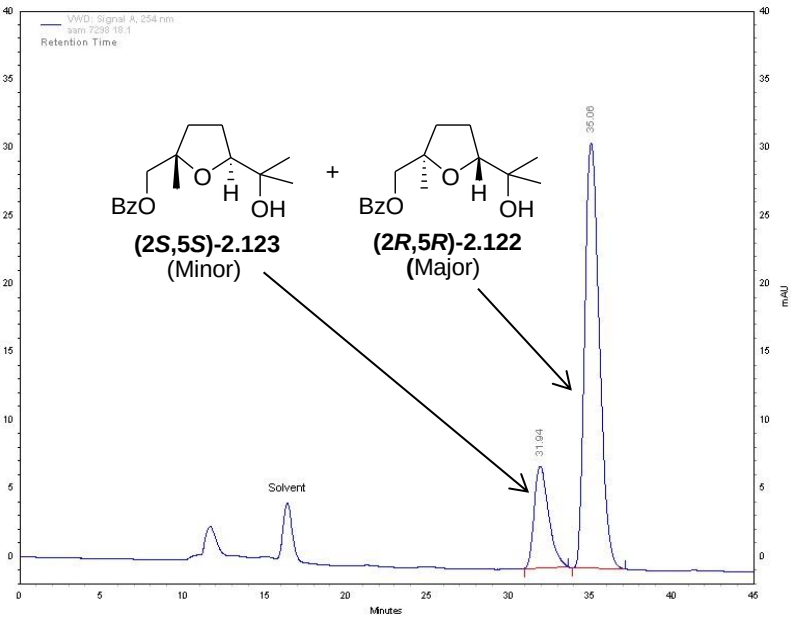


Scheme 2.61: Synthesis of benzoate derivatives **(2*S*,5*S*)-2.123**, and **(2*R*,5*R*)-2.122** for stereochemical correlation using chiral HPLC. [e]The aldehyde was prepared in a previous study within the Broun group.[13]



Retention Time	Area	Area%
31.94	4110581	98.33
35.12	69933	1.67
Total	4180514	100.00

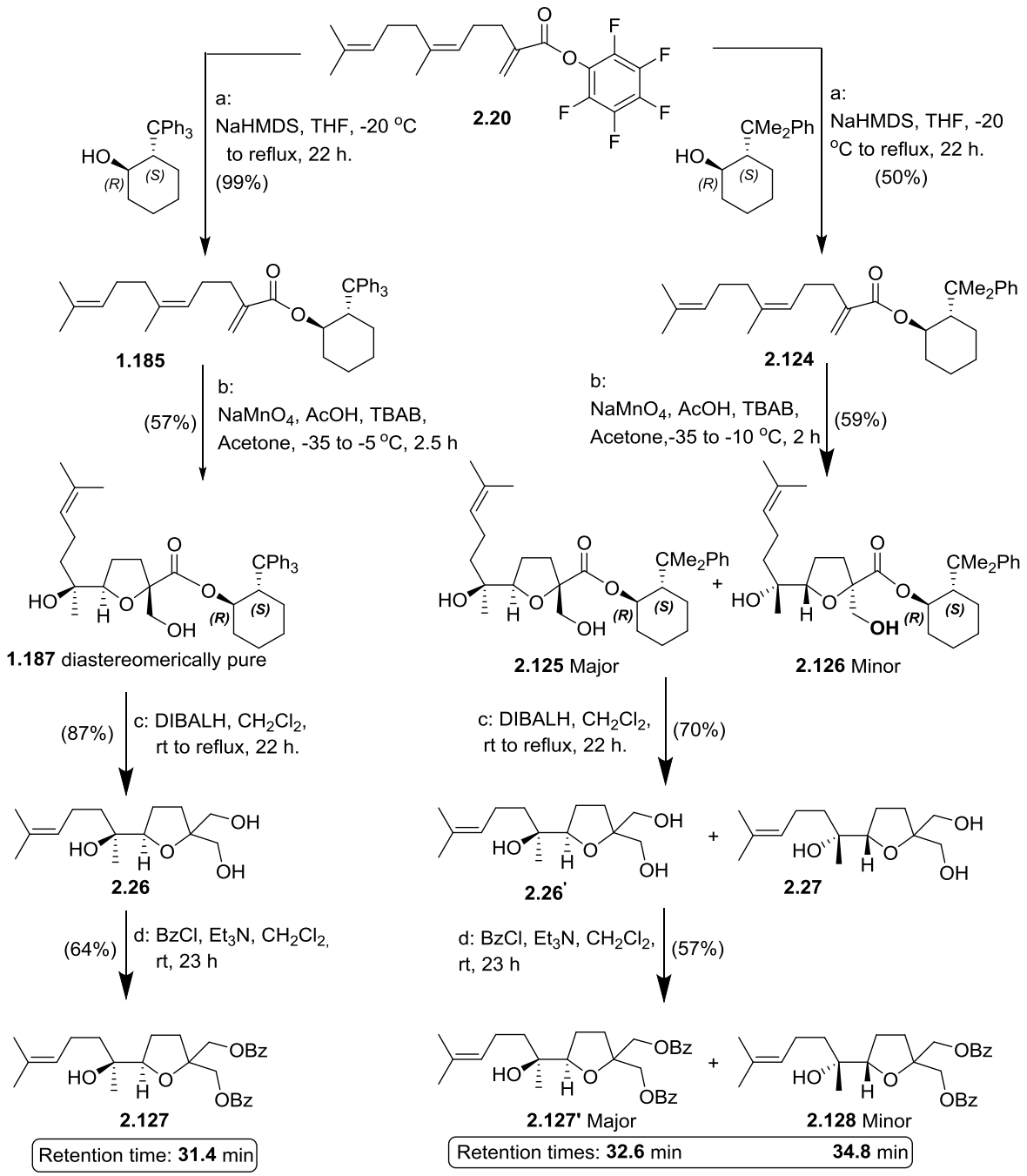
Figure 2.3: HPLC trace for the (1*S*,2*R*)-TTC benzoate **2.123**, 0.3 mL/min, 245 nm.



Retention Time	Area	Area%
31.94	7733851	19.12
35.06	32719419	80.88
Total	40453270	100.00

Figure 2.3: HPLC trace for the (1*R*,2*S*)-TCC benzoate **2.122** and **2.123**, 0.3 mL/min, 245 nm.

2.4.2.Stereochemical Correlation for the Oxidative cyclisation products from (1*R*,2*S*)-TCC and (1*R*,2*S*)-TTC Trienoates



Scheme 2.62: Conversion of the oxidative cyclisation products from (1*R*,2*S*)-TTC and (1*R*,2*S*)-TCC to benzoate esters **2.127** and **2.128** for stereochemical correlation using chiral HPLC.

The stereochemical correlation for oxidative cyclisation products from TCC and TTC trienoates **2.124** and **1.185** respectively followed the same approach described above (scheme 2.62). Dibenzoate esters **2.127** and **2.128** were synthesised from (1*R*,2*S*)-TCC trienoate **2.124** and (1*R*,2*S*)-TTC trienoate **1.185** respectively. The oxidative cyclisation product **1.187** was synthesised from (1*R*,2*S*)-TTC trienoate **1.185** and reduced by DIBALH reduction to afford THF triol **2.26** in a good yield (87%). The triol **2.26** was converted to dibenzoate ester **2.127** by a reaction with BzCl. Synthesis of the dibenzoate **2.127** and **2.128** from (1*R*,2*S*)-TCC required a preparation of (1*R*,2*S*)-TCC trienoate **2.124** (scheme 2.62). The trienoate **2.124** was prepared by coupling PFP trienoate **2.20** with (1*S*,2*R*)-*trans*-2-cumylcyclohexanol (TCC, *ee*: 97%), followed by permanganate oxidative cyclisation to afford the THFs **2.125/2.126** as an inseparable diasteromeric mixture in a reasonable yield (59%). The mixture **2.125/2.126** was reduced to afford the triols **2.26/2.27** that were converted to the required dibenzoates **2.127** and **2.128**.

The enantiomeric ratio of the benzoates **2.127**and **2.128** was analysed by analytical HPLC-IB column - (*eluent*: IPA/hexane 2.0:98). Chiral HPLC analysis indicated that the major product resulted from the (1*R*,2*S*)-TCC trienoate **2.124** had the same absolute configuration as the product from the (1*R*,2*S*)-TTC trienoate **1.185**. HPLC traces for the benzoate derivatives are shown in figures **2.5** and **2.6**. This was also consistent with results from the dienoate oxidative cyclisations; and it was carried out in parallel with the correlation for oxidative cyclisation products from (1*S*,2*R*)-TCC and (1*R*,2*S*)-TTC trienoates by synthesised monobenzoate derivatives described in the next section (2.4.3).

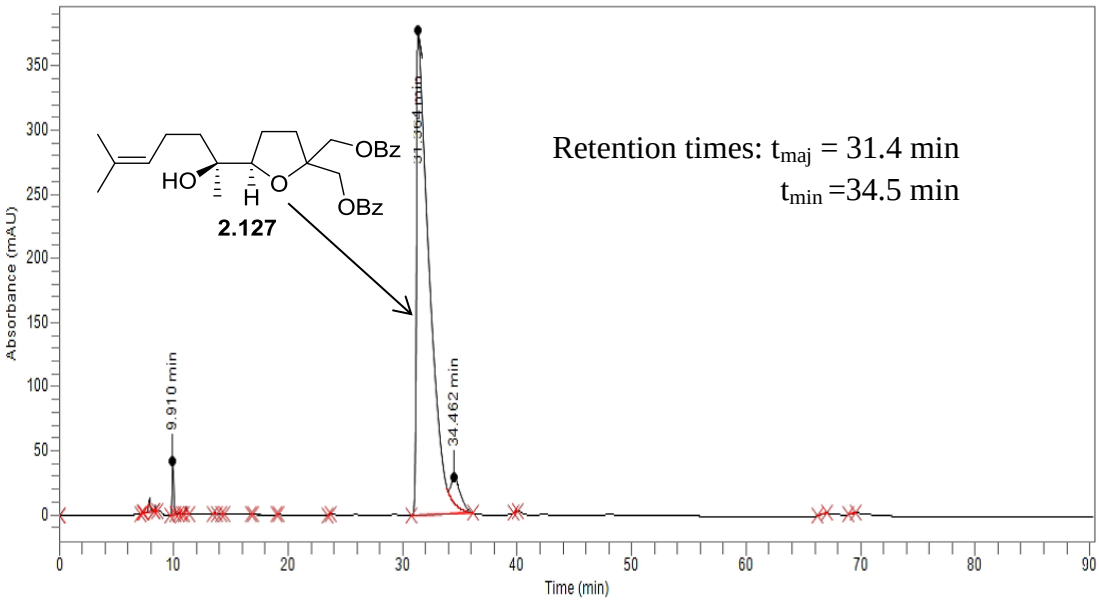


Figure 2.5: HPLC trace for (1R,2S)-TTC benzoate **2.127**, 0.4 mL/min, 245 nm.

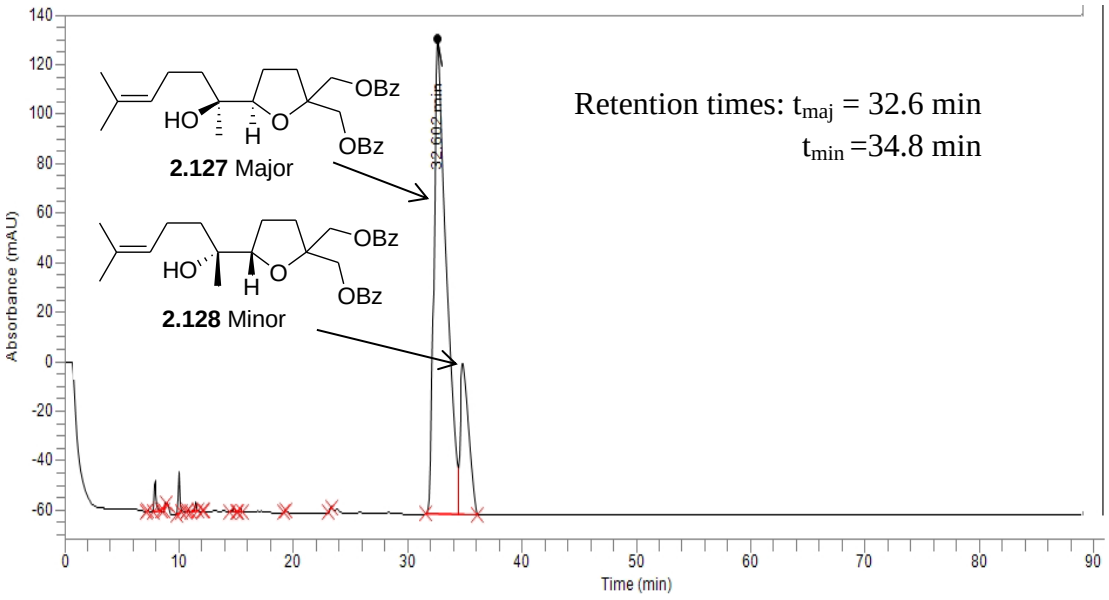
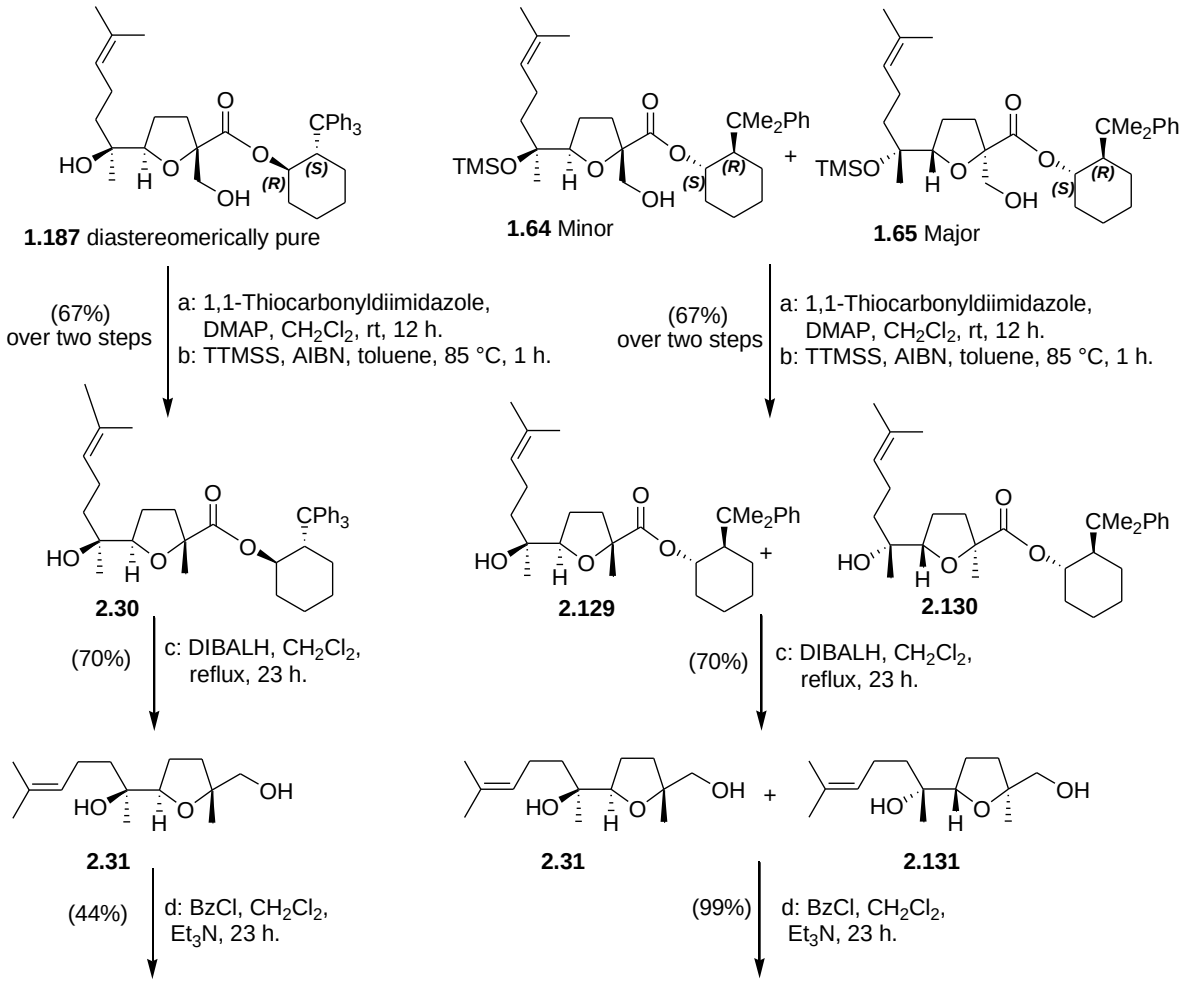
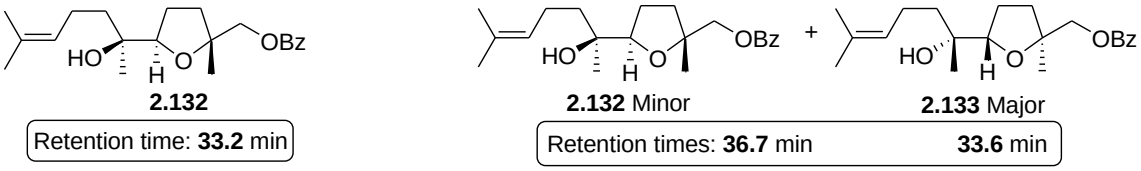


Figure 2.6: HPLC trace for (*1R,2S*)-TCC benzoates **2.127** and **2.128**, 0.4 mL/min, 245nm.

2.4.3. Stereochemical Correlation for the Oxidative Cyclisation Product from (1*S*,2*R*)-TCC and (1*R*,2*S*)-TTC Trienoates

The stereochemical correlation for oxidative cyclisation products **1.64/1.65** and **1.187** obtained from (1*S*,2*R*)-TCC and (1*R*,2*S*)-TTC respectively followed the same approaches described above. The THF-TTC **1.187** was converted to mono benzoate **2.132** (scheme 2.63). The radical deoxygenation product **2.30** was reduced with DIBALH to afford THF diol **2.31** followed by reaction with benzoyl chloride to give the monbenzoate **2.132**. The monbenzoate derivatives **2.132** and **2.133** were synthesised in the same way starting from a mixture of two diastereoisomers **1.64/1.65** (bearing (1*S*,2*R*)-TCC) that were prepared in a previous study within the Brown group (scheme 2.63).[12]





Scheme 2.63: Conversion of the oxidative cyclisation products from (1*R*,2*S*)-TTC and (1*S*,2*R*)-TCC to benzoate esters **2.132** and **2.133** for stereochemical correlation using chiral HPLC.

The enantiomeric ratio of the resulted benzoates were analysed by analytical chiral HPLC-Chiralpak® AD-H - (*eluent*: IPA/hexane 5:95) which indicated that the major benzoate **2.132** from the (1*R*,2*S*)-TTC had the same absolute configuration as the minor benzoate **2.132** from the (1*R*,2*S*)-TCC. HPLC traces for the benzoate derivatives are shown in figures **2.7** and **2.8**.

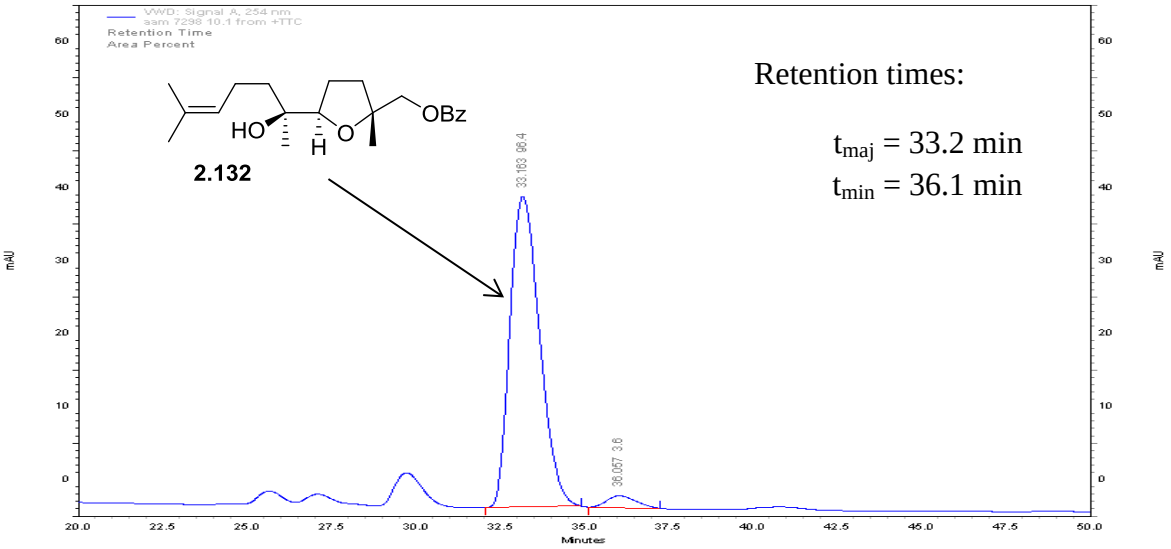


Figure 2.7: HPLC trace for (1*R*,2*S*)-TTC benzoate **2.132** (0.3 mL/min).

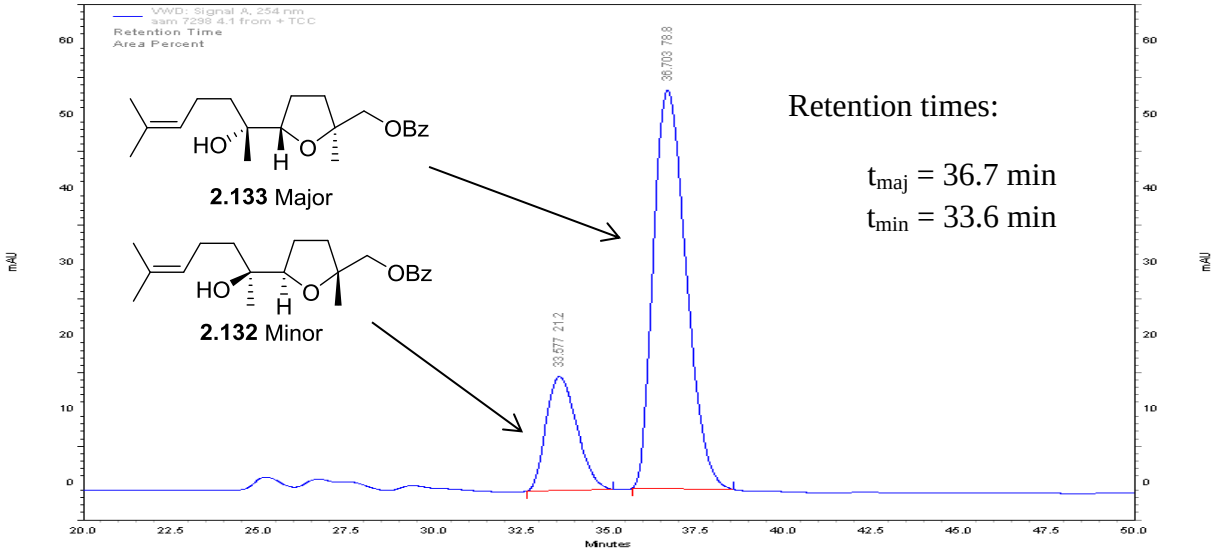


Figure 2.8: HPLC trace for (1*S*,2*R*)-TCC derived benzoate **2.132** and **2.133** (0.3 mL/min).

2.4.4. Conclusions

The unambiguous establishment of the sense of the diastereofacial selectivity for oxidative cyclisation of (1*R*,2*S*)-TCC dienoate and trienoate systems, and (1*S*,2*R*)-TCC trienoate was achieved by the stereochimical correlation with oxidative cyclisation products of (1*S*,2*R*)-TTC dienoate and (1*R*,2*S*)-TTC trienoate. The stereochemistry of the major oxidative cyclisation product obtained from (1*S*,2*R*)-TTC dienoate was established through its conversion to (+)-linalool oxide as described in a previous study within the Brown group.[13] The TTC and TCC compounds were converted to a common intermediate and analysed by chiral HPLC.

2.5. NMR Studies of Cyclohexyl Dienoates and THF Diol product

2.5.1. Conformational Analysis of 2-Substituted Cyclohexyl Dienoates

The TCC dienoate **1.100b** and 2-substituted cyclohexyl dienoate **2.113**, synthesised in a previous study within the group, displayed typical NMR spectroscopic data (figure 2.9 and 2.10). However, the dienoate **2.113** exhibited significant broadening of signals in its ^{1}H and ^{13}C NMR spectra corresponding to the trityl group, highlighting the increased steric congestion of this system (figure 2.9).[13,39] The permanganate oxidative cyclisation of the TCC and benzyl derivatives showed lower diastereoselectivities compared to TTC ester **2.113** that has been attributed to conformational and steric effects due to the substituent at the 2-positions. In order to investigate solution conformational preferences of 2-substituted cyclohexyl dienoates, through space interactions of these systems was investigation. NOESY NMR (Nuclear Overhauser Effect SpectroscopY) was used as a tool to study interactions in (1*S*,2*R*)-2-tritylcyclohexyl-6-methyl-2-methylenehept-5-enoate (**2.113**), (1*R*,2*S*)-2-cumylcyclohexyl-6-methyl-2-methylenehept-5-enoateand (**1.100b**) and (1*R*,2*S*)-2-benzylcyclohexyl-6-methyl-2-methylenehept-5-enoate (**2.134**, figure 2.9).

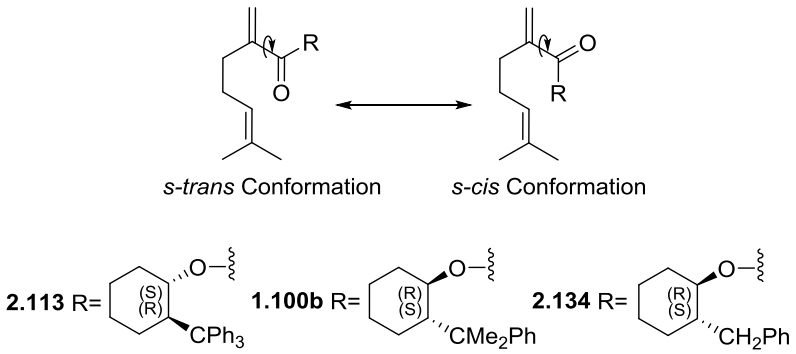
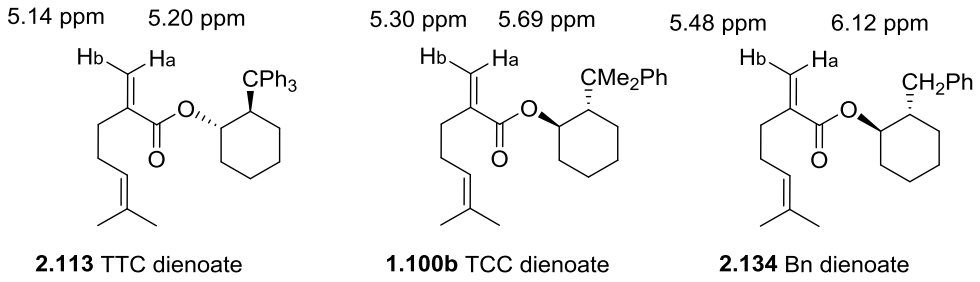


Figure 2.9: Structures and conformations of cyclohexyl dienoates **2.113**, **1.100b** and **2.134**.

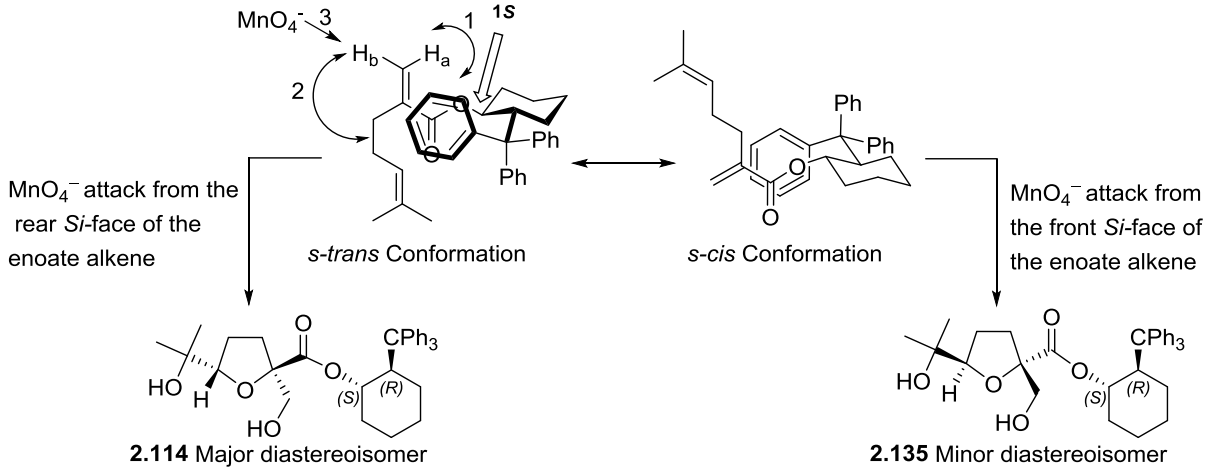
^{1}H NMR data for these dienoates showed that the vinylic β proton signals (H_a, H_b) of the TTC dienoate **2.113** displayed upfield shifts (δ 5.14 and 5.20 ppm) compared to the 2-benzylcyclohexyl dienoate **2.134** (δ 5.48 and 6.12 ppm) while the chemical shifts for TCC dieoate **1.100b** in between (δ 5.30 and 5.69 ppm, figure 2.10).



2.113 TTC dienoate **1.100b** TCC dienoate **2.134** Bn dienoate

Figure 2.10: *S-trans*-enoate conformations and methylene chemical shifts for cyclohexyl dienoates **2.113**, **1.100b** and **2.134**.

NOESY data for TTC dienoate **2.113** showed an interesting cross peak between the β proton H_a signal (δ 5.20 ppm) and the aromatic ring protons (δ 7.21-7.34 ppm, scheme 2.64, figure 2.11). This through space interaction indicated there was a stacked conformation of the phenyl ring and enoate moiety (scheme 2.64).[112] This conformation was consistent with the high diastereoselectivety observed by permanganate oxidative cyclisation of the TTC dienoate **2.113** (dr 32.3:1).[13]



Scheme 2.64: Through space interactions of vinylic β proton signals (H_a, H_b) of the TTC dienoate **2.113** with rationalisation of the diastereoselectivity of permanganate oxidative cyclisation. [1]The through space interaction between H_a (5.20 ppm) and the aromatic ring protons (δ 7.21-7.34). [2]The through space interaction between H_b proton (5.14 ppm) and alkyl chain signal (δ 2.11-1.96 ppm). [3]Preferred approach of permanganate ion.

While the H_b signal for dienoate **2.113** (δ 5.14 ppm) had a cross peak with the alkyl chain signal (δ 2.11-1.96 ppm) with no an aromatic cross peak (figure 2.11).

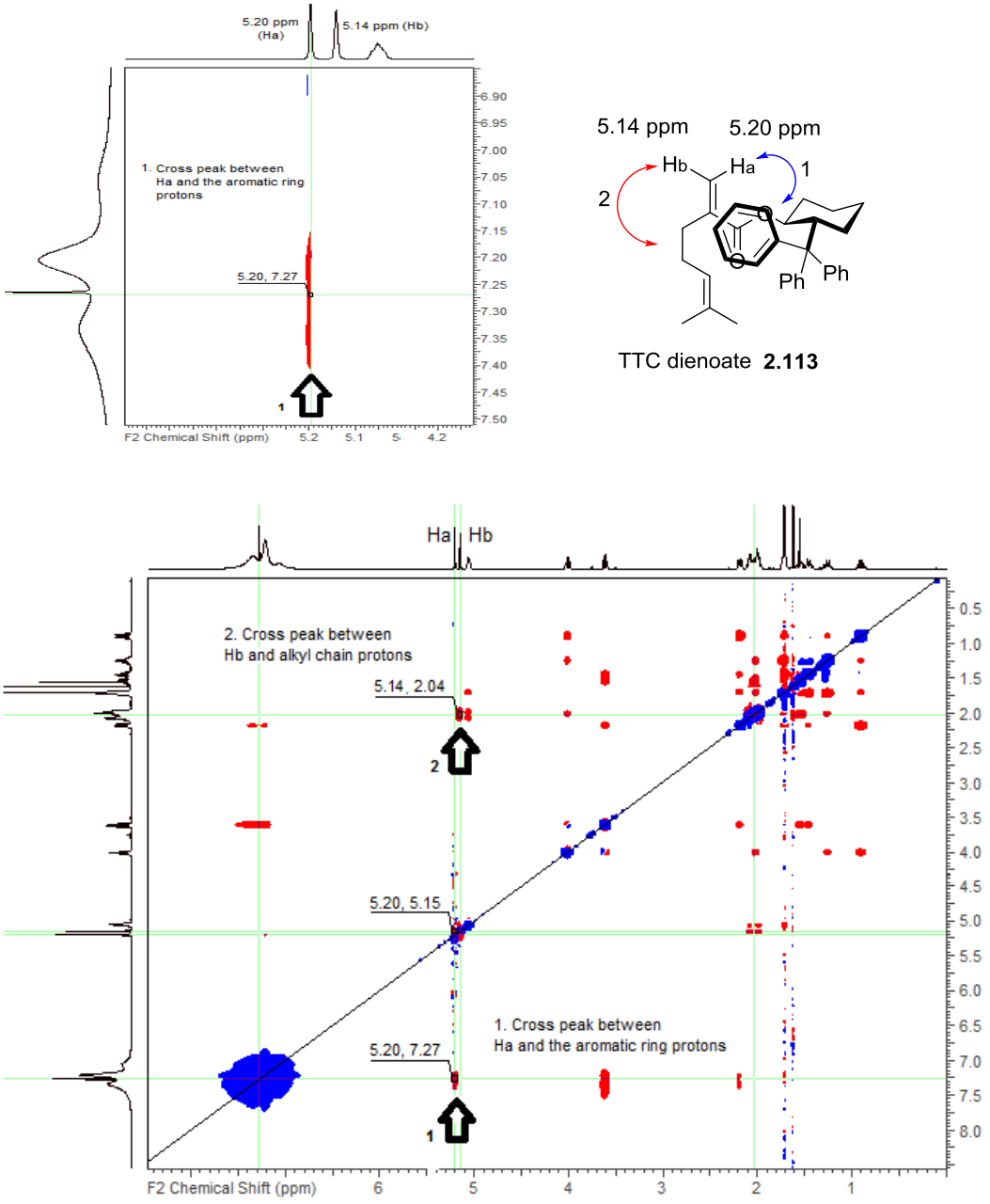


Figure 2.11: Through space interactions (NOESY) spectrum of TTC dienoate **2.113**. [1]The cross peak between H_a (5.20 ppm) and the aromatic ring protons (δ 7.21-7.34 ppm). [2]The cross peak between H_b (5.14 ppm) and alkyl chain (δ 2.11-1.96 ppm).

For the TCC dienoate **1.100b**, through space interactions were indicated by a cross peak between H_a (δ 5.69 ppm) and one of the cumyl methyl groups (δ 1.32 ppm) and there was no cross peak with the aromatic proton (figure 2.12). The through space interaction

between H_a and the methyl protons showed they were on average closer in 3D space (structure **1.100b**, figure 2.12). This fact was consistent with permanganate oxidative cyclisation result; diastereoselectivety of the cyclisation was lower than TTC dienoate **2.113** (dr 4.2:1). There was also an interaction between H_a and the alkyl chain (δ 2.13-1.92 ppm). While *β* H_b for the TCC dienoate (δ 5.30 ppm) had a cross peak with the alkyl chain (δ 2.13-1.92 ppm, figure 2.12).

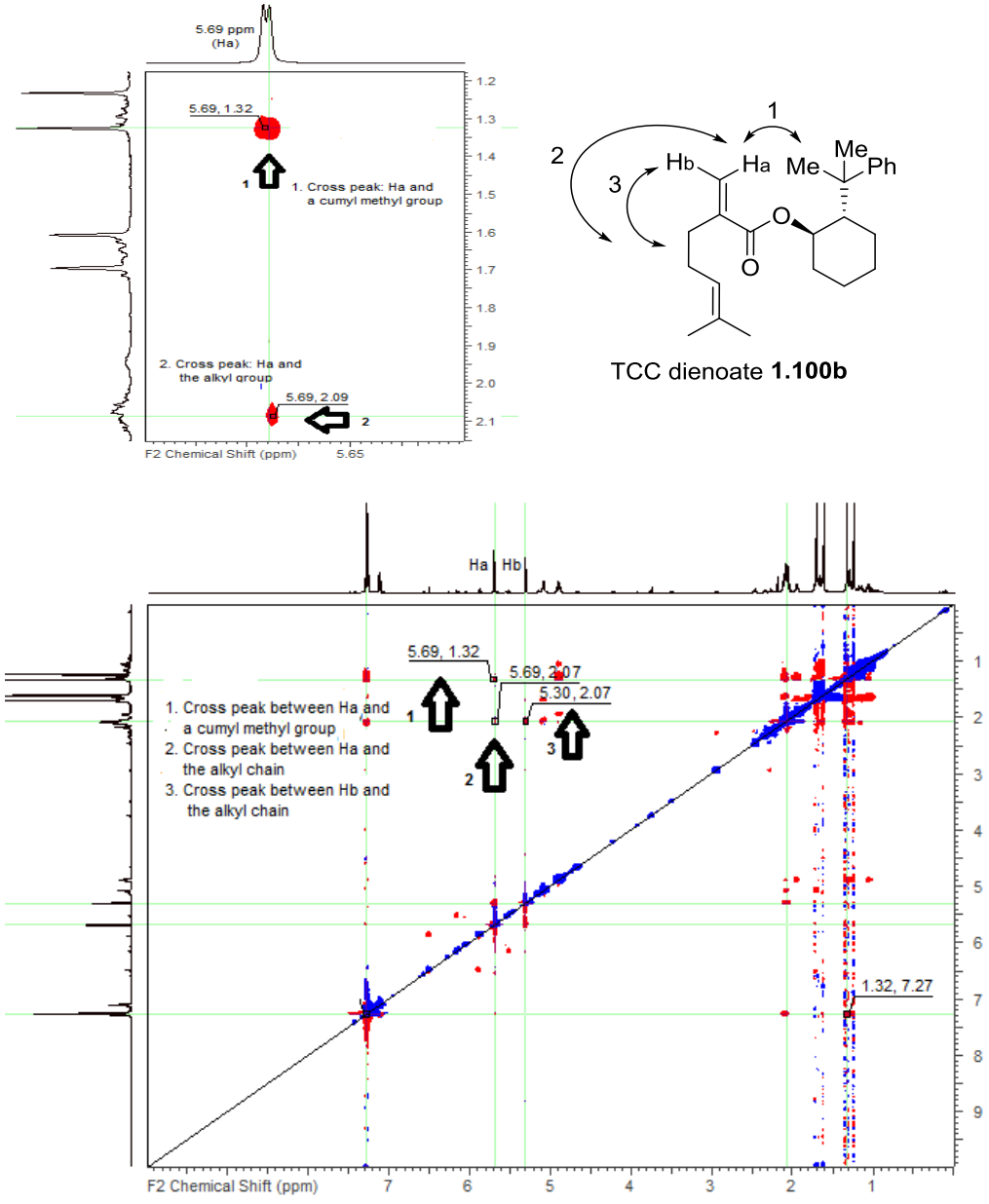


Figure 2.12: Through pace interactions (NOESY) spectrum of TCC dienoate **1.00b**. [1]The cross peak between H_a (5.69 ppm) and one of cumyl methyl groups (δ 1.32 ppm). [2]The cross peak between H_a and the alkyl chain (δ 2.13-1.92 ppm). [3]The cross peak between H_b (δ 5.30 ppm) and the alkyl chain (δ 2.13-1.92 ppm).

For the Bn dienoate **2.134**, through space interactions were indicated by a cross peak between H_a signal (δ 6.12 ppm) and H_b signal (δ 5.48 ppm) and there was no cross peak with the aromatic protons (structure 2.134, figure 2.13). While the H_b signal showed more than one cross peak. In addition to the interaction with the H_a signal, the proton had a cross peak with five protons signal (δ 2.37-2.09 ppm). The five protons were related to a one of two benzyl protons, and four protons for the alkyl chain (figure 2.13). This fact was consistent with the low diastereoselectivety of oxidative cyclisation of Bn dienoate **2.134** (dr 1.3:1).

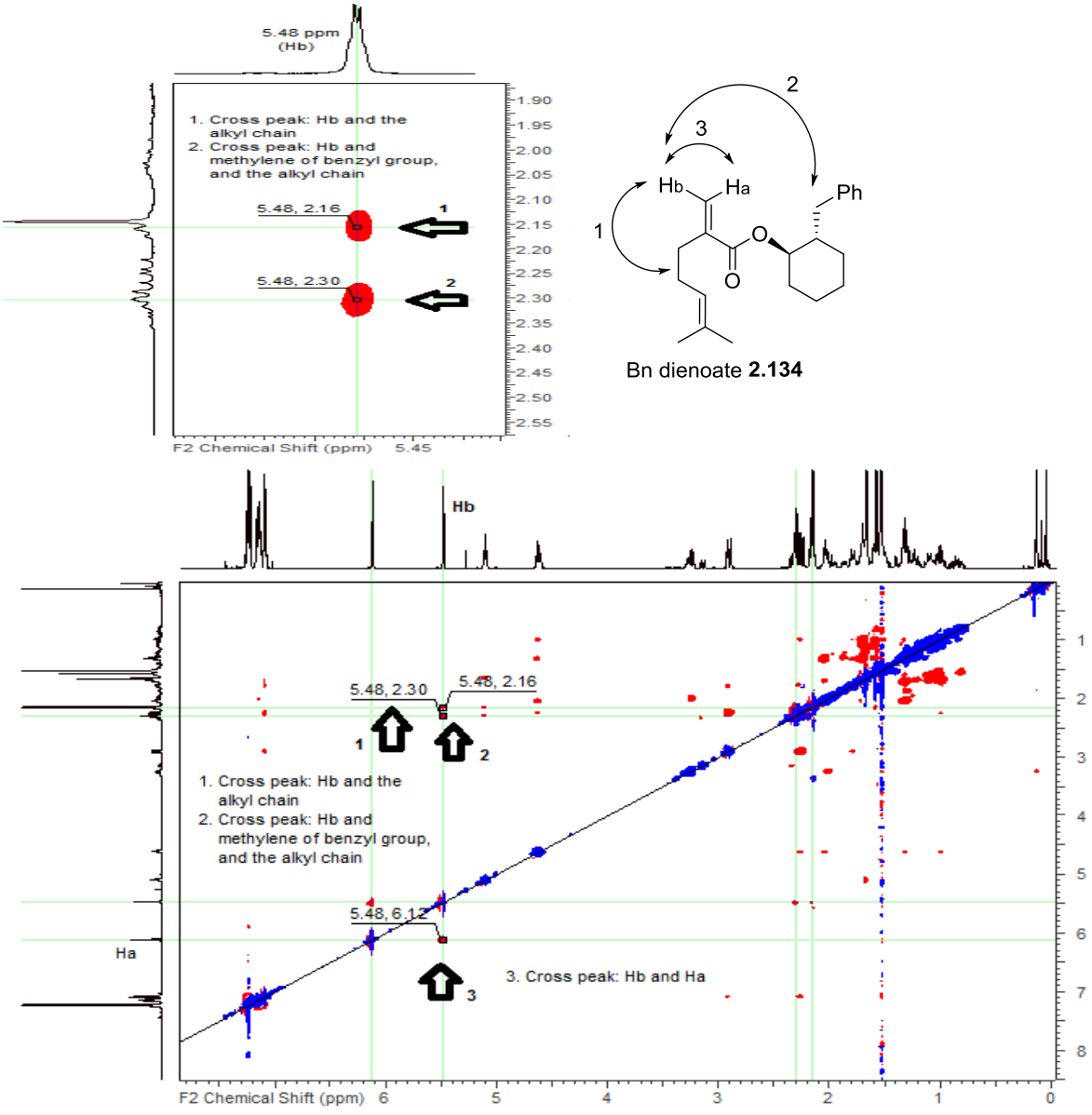
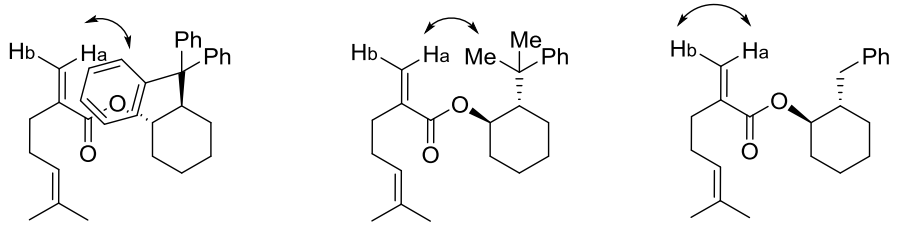


Figure 2.13: Through pace interactions (NOESY) spectrum of Bn dienoate **2.134**.[1]The cross peak between H_b (5.48 ppm) and the alkyl chain (δ 1.32 ppm). [2]The cross peak between H_b and a methylene's proton of the benzyl group and alkyl chain (δ 3.37-2.09 ppm). [3]The cross peak between H_b and H_a (δ 6.12 ppm).

2.5.1.2. Conclusions

The through space interactions of the vinylic β proton signals (H_a, H_b) of the dienoates **2.113**, **1.100b** and **2.134**. were investigated by NOESY NMR (figure 2.14). NOESY data showed H_a with a higher chemical shift than H_b for TTC- and TCC dienoates (**2.113** and **1.100b**) had a cross peak with the 2-substituted cyclohexyl auxiliary, for Bn dienonate **2.134**, there was no cross peak with the auxiliary. This fact gave more information about the conformation of the three dienoates (figure 2,14). The through space interaction of TTC dinoate **2.113** showed the H_a signal (5.20 ppm) had a cross peak with the aromatic ring protons (7.21-7.34 ppm), which was consisted with a stacked conformation of the phenyl ring and enoate moiety (structure **2.113**, figure 2.14). In the case of TCC dienoate **1.100b**, NOESY data showed a cross peak between H_a signal (5.69 ppm) and one of cumyl methyl groups (δ 1.32 ppm, structure **1.100b**, figure 2.14). While the NOESY spectrum for the Bn dienoate **2.134** indicated a cross peak between H_a (6.12 ppm) and H_b (5.48 ppm), which had unexpected a cross peak with a methylene's proton of the benzyl group (structure **2.134**, figure 2.14). The NOESY study was consistent with the diastereoselectivities of permanganate oxidative cyclisation of the dienoates **2.113**, **1.100b** and **2.134**. (dr. 32.3:1, 4.2:1 and 1.3:1 respectively, figure 2.14).



2.113 TTC dienoate dr: 32.3:1 | **1.100b** TCC dienoate dr: 4.2:1 | **2.134** Bn dienoate dr: 1.3:1

Figure 2.14: The space interactions of the vinylic β proton (H_a) of dienoate **2.113**, **1.100b** and **2.134**.

2.5.2. Assignment of THF Ring Protons by NOE and NOESY Techniques

The permanganate oxidative cyclisation products displayed similar NMR spectroscopic data for the four THF ring protons. It was of interest to us to assign the four protons of one of our oxidative cyclisation products, ((2*S*,5*S*)-5-(2-hydroxypropan-2-yl)-2-methyltetrahydrofuran-2-yl)methyl benzoate (**2.123,** figure 2.15). The benzoate **2.123** exhibited a triplet peak (δ 3.88 ppm) for 1H at C_5 and three interesting multiplets integrating as 4H for C_3 and C_4 (δ 1.80 ppm (1H), 1.95-1.90 ppm (2H) and 2.04 ppm (1H, figure 2.15a). The benzoate **2.123** was analysed by NOE experiment. By using ^{1}H homonuclear decoupling, it was easy to identify each of the three multiplet peaks. Firstly, ^{1}H homonuclear irradiation at δ 3.88 ppm (H_5) led to simplification the second multiplet (δ 1.95-1.89 ppm) which showed that it was related to 2H at C_4 (figure 2.15b).

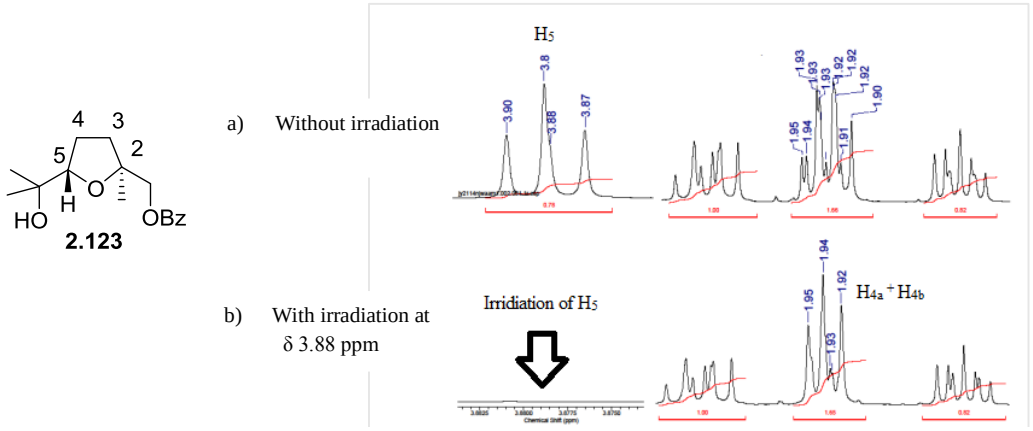


Figure 2.15: Structure of the benzoate **2.123**, ^{1}H NMR of its THF ring protons and ^{1}H homonuclear decoupling of H_5 (δ 3.88 ppm, b).

Irradiation of the assigned protons (H_{4a}+H_{4b}) at δ 1.92 ppm simplified the triplet peak for H_5, as well as the next two multiplets at δ 1.80 and 2.04 ppm (figure 2.16b). Therefore, the two multiplets at δ 1.80 ppm and 2.04 ppm were related to (H_{3a}+H_{3b}).

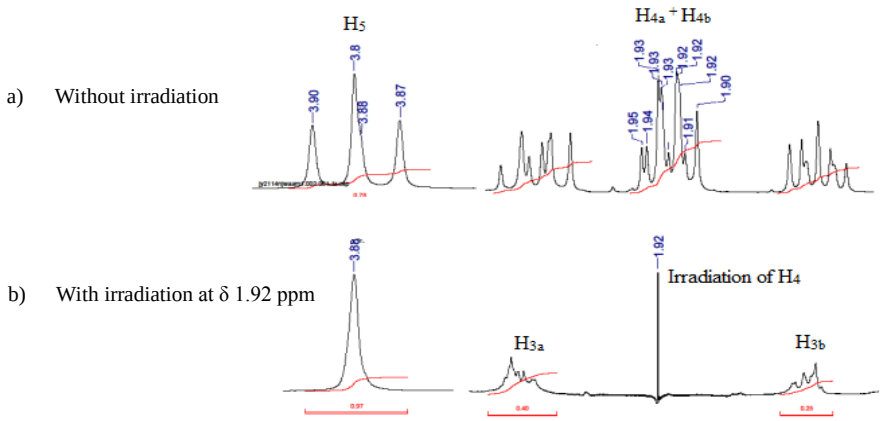


Figure 2.16: ^{1}H Homonuclear decoupling of H_4 (δ 1.92 ppm, b).

Irradiation at δ 2.04 ppm (H_{3a}) ppm made a simplification of the two multiplets at δ 1.80 and 1.92 ppm (H_{3b}, H_{4a}+H_{4b}) with no effect to the triplet peak at 3.88 ppm (figure 2.17b). A similar effect resulted from irradiation at δ 1.80 ppm (figure 2.17c).

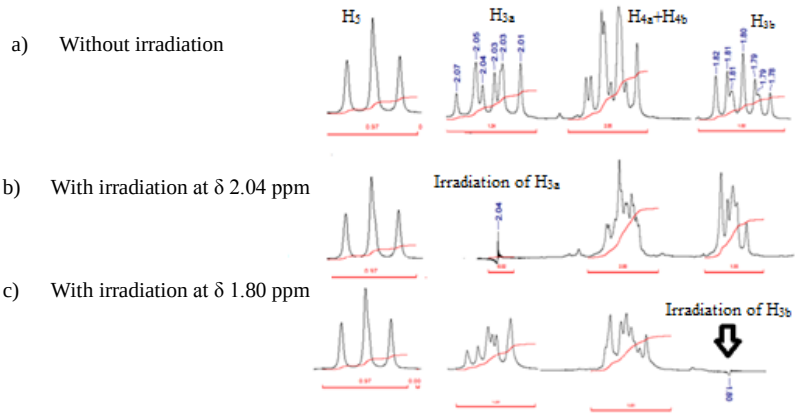


Figure 2.17: ^{1}H Homonuclear decoupling of H_{3a} and H_{3b} (δ 2.04 (b) and 1.80 ppm (c) respectively).

NOESY spectroscopy was used to identify H_{3a} and H_{3b} and a cross peak was found between H_5 at 3.88 ppm and H_{3b} at 1.80 ppm (figure 2.18).

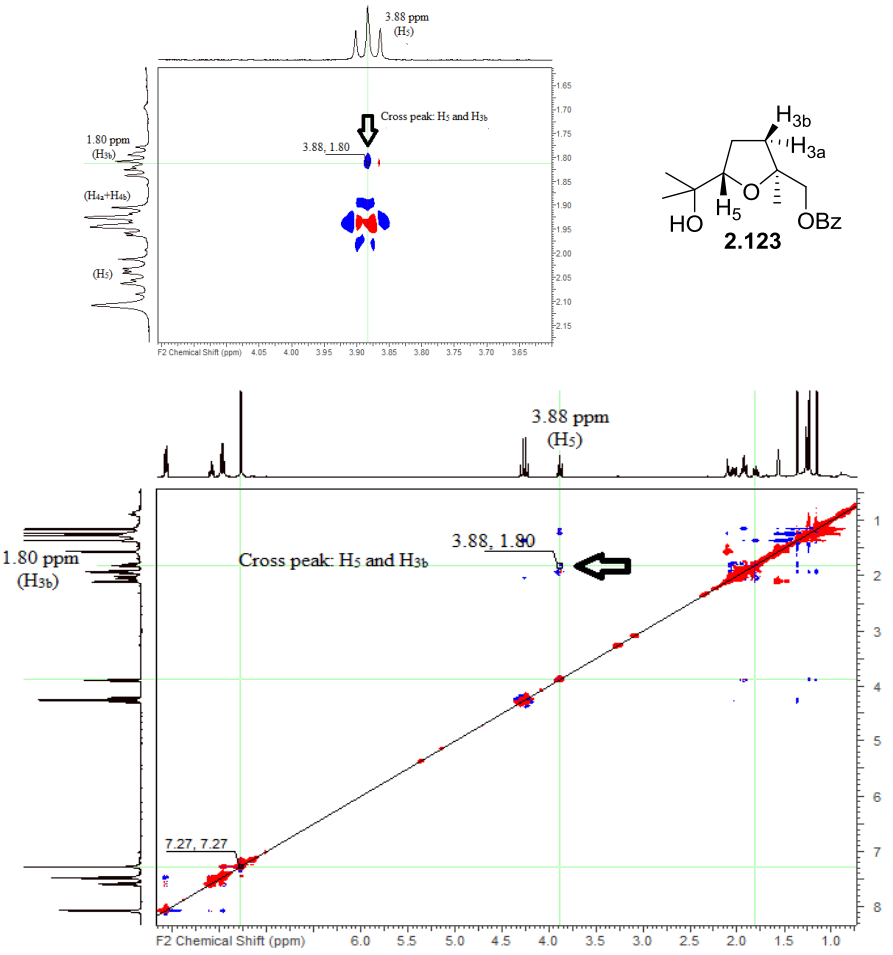


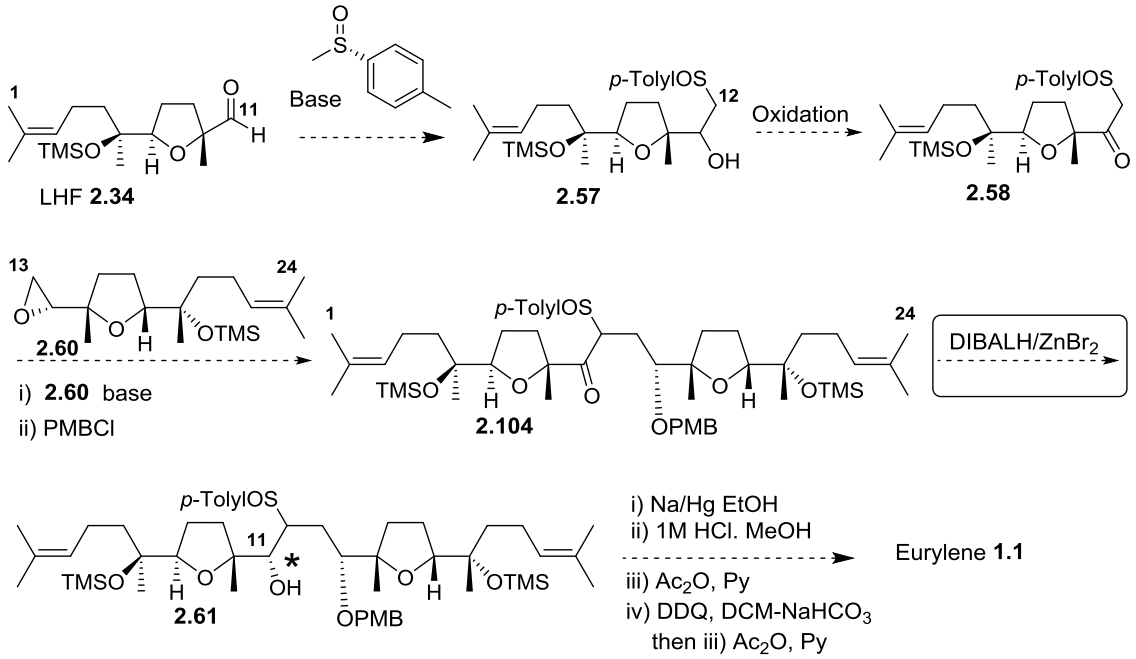
Figure 2.8: Structure of **2.123** and its NOESY.

2.5.2.2. Conclusions

The NOE and NOESY NMR spectroscopy were applied for assignment of protons of the THF ring in THF **2.123**. The two H_{4a}+H_{4b} at δ 1.95-1.89 ppm were related to C_4, while the two protons (H_{3a}+H_{3b}) at δ 2.04 and 1.80 ppm respectively were related to C_3. H_{3b} has space interaction with H_5 which at δ 3.88 ppm.

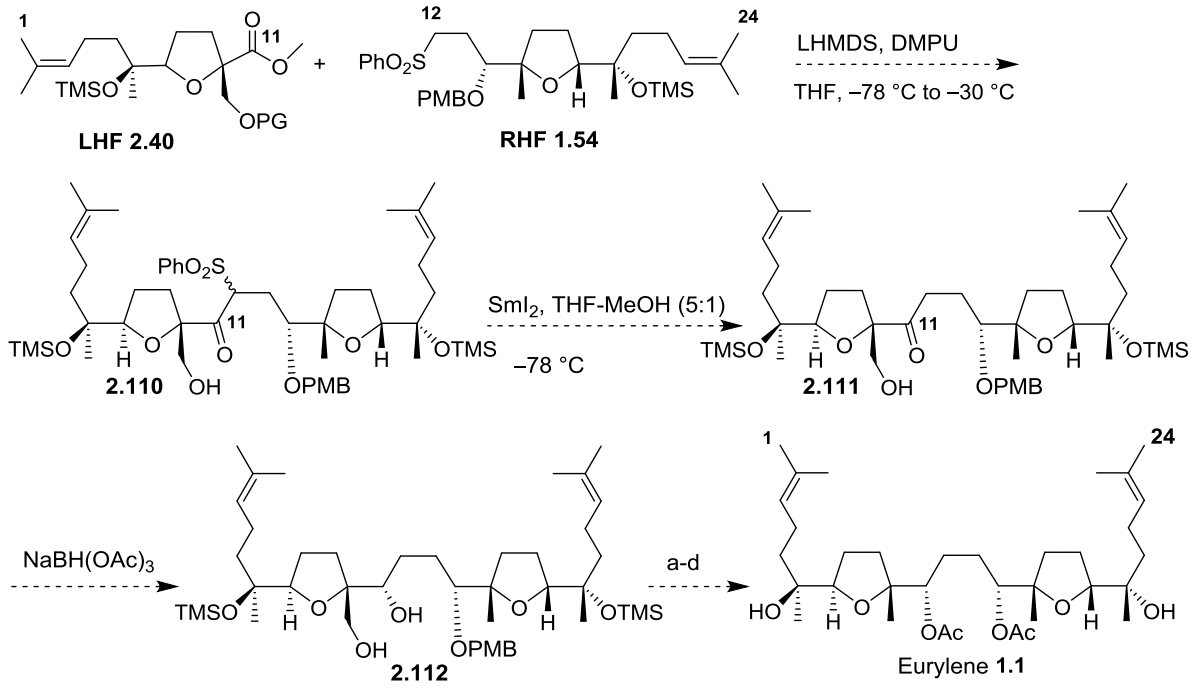
2.6. Future work

Due to the time constraints, the total synthesis of eurylene (**1.1**) was not accomplished and two proposed plans are presented to achieve the synthesis with establish means of the chiral centre at C_{11} of eurylene. In the future work, the *β*-keto sulfoxide **2.58** will synthesise and couple with the right (C_{13}-C_{24}) fragment epoxide **2.60**, followed by DIBALH/$ZnBr_2$ reduction towards the total synthesis of eurylene (scheme 2.65).



Scheme 2.65: Proposed approach to complete the total synthesis of eurylene (**1.1**).

As well as, the future work will include the use of hydroxyl directed reduction to achieve the total synthesis by coupling the two fragments **1.189** and **2.40** (scheme 2.66).



a) Thiocarbonyldiimidazole. b) AIBN, TTMSS. c) 1M HCl. MeOH. d) Ac_2O, pyr. d) DDQ, CH_2Cl_2:$NaHCO_3$ (10:1).

Scheme 2.66: Proposed approach to complete the total synthesis of eurylene (**1.1**) using a directed reduction.

Chapter Three: Experimental

3.1. General Procedure

Chemicals were purchased from Sigma-Aldrich, Fisher Scientific, Alfa Aesar, Fluorochem or Apollo Scientific. All air/moisture sensitive reactions were carried out under an inert atmosphere, in oven-dried or flame dried glassware. The solvents toluene, THF and Et_2O (from Na/benzophenone), MeCN, MeOH and CH_2Cl_2 (from CaH_2) were distilled before use, and where appropriate, other reagents and solvents were purified using standard techniques. TLC was performed on aluminium-precoated plates coated with silica gel 60 containing F_{254} indicator; visualised under UV light (254 nm) and/or by staining with, phosphomolybdic acid, potassium permanganate or 2,4-dinitrophenylhydrazine. Flash column chromatography was performed using; high purity silica gel, Geduran®, pore size 60 Å, 230-400 mesh particle size, purchased from Merck.

Fourier-transform infrared (FT-IR) spectra are reported in wavenumbers (cm^{-1}) and were collected as solids or neat liquids on a Nicolet 380 fitted with a Smart Orbit Goldengate attachment using OMNIC software package. Optical rotations were collected on an Optical Activity PolAAr 2001 machine. The solvent used for the measurement of the optical activity was normal choroform.

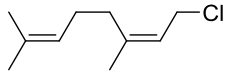
^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ (purchased from Cambridge Isotope Laboratories, Inc.) at 298 K using Bruker AC300, AV300 (300 and 75 MHz respectively) or Bruker DPX400, AVII400, AVIIHD400 (400 and 100 MHz respectively), or Bruker AVIIHD500 (500 and 125 MHz respectively) and at 298 K using Cryoprobe 600 MHz with 5 mm HCN probe (600 and 150 MHz respectively) spectrometers. Chemical shifts values (δ) are reported in ppm relative to residual chloroform (δ 7.27 ppm for ^{1}H, δ 77.00 ppm for ^{13}C). All spectra were reprocessed using ACD/Labs software version: 12.1. Coupling constants (*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), br (broad), and m (multiplet).

Melting points were obtained using a Gallenkamp Electrothermal apparatus and are uncorrected. Analytical HPLC was performed on an Agilent 1220 Infinity LC System utilising the Agilent EZChrom software package eluting either from Daicel Chiralcel®

OD-H, Chiralpak® AD-H or IB columns eluting with IPA/hexane mixtures (details in the experimental). Electrospray low resolution mass spectra were recorded on a Waters ZMD quadrupole spectrometer or Waters (Manchester, UK) TQD triple quadrupole analyser. High resolution mass spectra were obtained using Bruker APEX III FT-ICR mass spectrometer or MaXis (Bruker Daltonics, Bremen, Germany) mass spectrometer equipped with a Time of Flight analyser. HRMS were recorded using positive ion electrospray ionisation (ESI^+). Microwave synthesis was performed in a sealed tube using a CEM discover microwave synthesizer.

3.2. Experimental Details

(2*Z*)-1-Chloro-3,7-dimethylocta-2,6-diene (Neryl chloride, 2.1)



$C_{10}H_{17}Cl$
Mol. wt. 172.69 g/mol
(Brownish yellow oil)

Using a procedure described by Collington and Meyer,[69] to a solution of nerol (**1.58**, 5.00 g, 32.4 mmol) in 2,6-lutidine (5.00 mL, 38.9 mmol) was added a solution of LiCl (1.50 g, 35.7 mmol) in DMF (26 mL). The mixture was cooled to 0 °C and MsCl (3.0 mL, 37.0 mmol) was added dropwise to the reaction mixture. The reaction was allowed to warm to room temperature and the resultant yellow mixture was stirred for 6 h. The reaction mixture was diluted in Et_2O (30 mL) and washed sequentially with water (3 x 50 mL), HCl (2.0N, 2 x 10 mL), brine (10 mL) and sat. aq. $NaHCO_3$ (8 mL). The organic phase dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title compound **2.1** as a brownish yellow oil (5.20 g, 30.1 mmol, 93%). The crude product was used in subsequent reactions without further purification. Spectroscopic data are in agreement with the literature.[12]

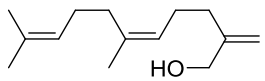
FT-IR ν_{max} (neat): 2968 (s), 2916 (s), 2858 (m), 1661 (s), 1445 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.46 (1H, t, *J* = 8.1 Hz, C=C**H**CH_2Cl), 5.12 (1H, m, C=C**H**CH_2), 4.10 (2H, d, *J* = 8.1 Hz, C**H**$_2$Cl), 2.10-2.16 (4H, br, 2 x C**H**$_2$), 1.79 (3H, s, C**H**$_3$), 1.70 (3H, s, C**H**$_3$), 1.62 (3H, s, C**H**$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 142.7 (CH_3**C**=$CHCH_2$Cl), 132.4 (Me_2**C**=C), 123.5 (C=**C**HCH_2Cl), 121.2 (C=**C**H), 50.0 (**C**H_2Cl), 31.9 (**C**H_2CCH_3), 26.5 (**C**H_2CH_2), 25.7 (**C**H_3), 23.5 (**C**H_3), 17.7 (**C**H_3) ppm.

LRMS (ESI$^+$) m/z: 196 (100%) Da.

(5*Z*)-6,10-Dimethyl-2-methyleneundeca-5,9-dien-1-ol (2.2)



$C_{14}H_{24}O$
Mol. wt. 208.34 g/mol
(Yellow oil)

Procedure 1

A solution of ^{n}BuLi (158 mL, 2.2M in hexane, 347.4 mmol) was added to an Ar purged flask. Using a double manifold the flask was placed under vacuum to remove the

hexane. After 3 h the flask was refilled with Ar. To the concentrated ^{n}BuLi was added Et_2O (139 mL) followed by TMEDA (62.5 mL, 416.9 mmol) at 0 °C. To this was added dropwise methallyl alcohol (9.75 mL, 115.8 mmol) at 0 °C, followed by THF (80 mL). The solution was stirred at 0 °C for 5 min, then the cooling bath was removed and the resultant yellow solution was stirred for 38 h at rt, during which time a dark red gum attributed to the corresponding dianion was observed in the reaction mixture. A solution of neryl chloride (**2.1**, 10.0 g, 57.91 mmol) in Et_2O (20 mL) was added dropwise at −78 °C, and the mixture was stirred for 15 min. The cooling bath was removed and the reaction mixture was stirred for 9 h at rt. At 0 ^{o}C the reaction was carefully quenched with H_2O (60 mL), acidified to pH 3 with HCl (2.0N), and re-extracted with Et_2O (6 x 100 mL). The resulting combined organic phases were washed with sat. $CuSO_4$ sol. (2 x 80 mL), and then with H_2O (3 x 60 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a crude product as a brownish yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/hexane (5 to 25%) gave the title compound **2.0** as a yellow oil (9.50 g, 45.4 mmol, 78%).

Procedure 2

Using a procedure described by Alonso *et al*.[71] ^{n}BuLi (5.0 mL, of 2.0M in hexane, 10.0 mmol) was added to an Ar purged flask. Using a double manifold the flask was placed under vacuum to remove the hexane for 1.5 h. At this, to the concentrated ^{n}BuLi was added Et_2O (4.0 mL) and TMEDA (2.7 ml) at 0 ^{o}C. To the mixture was added methallyl alcohol (280 µL, 3.30 mmol) dropwise over 4 min at 0 ^{o}C, followed by THF (2.7 mL). The solution was stirred at 0 °C for 5 min. The flask content was sonicated for 6 h with formation of a dark red gum attributed to the corresponding dianion. A solution of neryl chloride (**2.1**, 280 mg, 3.30 mmol) in Et_2O (2 mL) was added dropwise at −78 ^{o}C over 11 min, the mixture was allowed to warm slowly to rt, and stirred for 13 h. The reaction was quenched with H_2O (3.3 mL), acidified to pH 3 with HCl (2.0N), and re-extracted with Et_2O (3 x 13 mL). The resulting combined organic phases were washed with sat. aq. $CuSO_4$ (2 x 3 mL), then with H_2O (2 x 3 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a crude product as a pale yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/hexane (5%) gave the title compound **2.2** as a yellow oil (0.29 g, 1.39 mmol, 42%). Spectroscopic data are in agreement with the literature.[12]

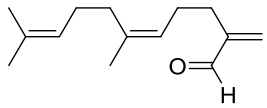
FT-IR ν_{max} (neat): 3314 (br), 2964 (s), 2917 (s), 2856 (s), 1447 (w) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.16-5.12 (2H, m, 2 x C=C**H**), 5.04 (1H, d, *J* = 1.1 Hz, C**H**H), 4.90 (1H, d, *J* = 1.1 Hz, CH**H**), 4.09 (2H, d, *J* = 6.2 Hz, C**H**$_2$OH), 2.19-2.14 (2H, m, C**H**$_2$), 2.11-2.09 (2H, m, C**H**$_2$), 2.06-2.05 (4H, m, 2 x C**H**$_2$), 1.70 (6H, s, 2 x C**H**$_3$), 1.62 (3H, s, C**H**$_3$), 1.35 (1H, t, *J* = 6.2 Hz, O**H**) ppm**.**

^{13}C NMR (75 MHz, $CDCl_3$): δ 148.9 (**C**=CH_2), 135.7 (CH_3**C**), 131.6 (Me_2**C**), 124.5 (C=**C**HCH_2), 124.3 (C=**C**HCH_2), 109.3 (C=**C**H_2), 65.9 (**C**H_2OH), 33.3 (**C**H_2C=CH_2), 32.0 (**C**H_2C=CH), 26.6 (**C**H_2CH_2), 26.2 (**C**H_2CH_2), 25.7 (**C**H_3), 23.3 (**C**H_3), 17.6 (**C**H_3) ppm.

LRMS (ESI$^+$) m/z: 209 ($[M+H]^+$) Da.

(5*Z*)-6,10-Dimethyl-2-methyleneundeca-5,9-dienal (2.3)



$C_{14}H_{22}O$
Mol. wt. 206.32 g/mol
(yellow oil)

Procedure 1

Using a procedure described by Corey *et al.*,[72] a mixture of allylic alcohol **2.2** (73.0 mg, 0.349 mmol) and activated MnO_2 (570 mg, 5.95 mmol) in hexane (6.0 mL) under Ar gas at 0 ^oC, was stirred for 2 h. Then the ice bath was removed and stirring was continued for a further 1 h at rt. Filtration through celite and concentration *in vacuo* afforded the title compound **2.3** as a yellow oil (55.0 mg, 0.265 mmol, 76%). The crude product was used in subsequent reaction without further purification.

Procedure 2

Using a procedure described by the Brown group,[74] a solution of allylic alcohol **2.2** (116 mg, 0.562 mmol) and TEMPO (248 mg, 1.59 mmol) in a solution of *t*-BuOH (2.5 mL) and aqueous buffer solution (2.5 mL of Na_2CO_3 (0.1M):$NaHCO_3$ (0.1M), 8:2, pH 11.5) was passed through the electrolytic cell at a flow rate of 0.1 mL min^{-1}.[74] The electrolysis was carried out under a constant current of ~ 20 mA, and the cell temperature was maintained at 25 °C. The reaction solution was collected, HCl (2.0N, 10 mL) was added and the resulting mixture extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and filtered and concentrated in *vacuo* to afford a crude product. The crude product was purified by column chromatography

(SiO_2) eluting with EtOAc/hexane (5%) to give the title compound **2.3** as a yellow oil (48.0 mg, 0.233 mmol, 41%) and recovered alcohol **2.2** (25.0 mg, 0.120 mmol, 21%). Spectroscopic data are in agreement with the literature.[12]

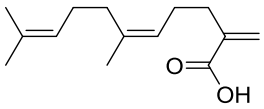
FT-IR ν_{max} (neat): 2965 (m), 2921 (m), 2856 (m), 1694 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.55 (1H, s, C**H**O), 6.25 (1H, d, *J* = 0.9 Hz, C=C**H**H), 6.00 (1H, s, =CH**H**), 5.12-5.08 (2H, m, 2 x C=C**H**CH_2), 2.28 (2H, t, *J* = 7.3 Hz, C$\mathbf{H}_2$), 2.19-2.12 (2H, m, C$\mathbf{H}_2$), 2.09-2.00 (4H, m, 2 x C$\mathbf{H}_2$), 1.69 (6H, s, 2 x C$\mathbf{H}_3$), 1.61 (3H, s, C$\mathbf{H}_3$) ppm**.**

^{13}C NMR (75 MHz, $CDCl_3$): δ 195.1 (**C**=O), 150.3 (**C**=CH_2), 136.7 (CH_3**C**), 134.5 (C=**C**H_2), 132.1 (Me_2**C**=C), 124.6 (C=**C**HCH_2), 124.4 (C=**C**HCH_2), 32.4 (**C**H_2C=CH_2), 28.6 (**C**H_2CH=C), 27.0 (**C**H_2CH_2), 26.4 (**C**H_2CH_2), 26.1 (**C**H_3), 23.8 (**C**H_3), 18.0 (**C**H_3) ppm.

LRMS (ESI$^+$) m/z: 207($[M+H]^+$) Da.

(5*Z*)-6,10-Dimethyl-2-methyleneundeca-5,9-dienoic acid (2.9)



$C_{14}H_{22}O_2$
Mol. wt. 222.32 g/mol
(Yellow oil)

Using a procedure described by Campaign *et al*.,[80] silver oxide was prepared by adding a solution of silver nitrate (13.5 g, 79.5 mmol) in water (42 mL) to a solution of sodium hydroxide (6.30 g, 158.6 mmol) in water (116 mL) with rapid stirring at rt. Stirring was continued for 5 min, a brown semi-solid mixture was resulted. Aldehyde **2.3** (8.00 g, 38.8 mmol) was added at 0 ^oC; after 1.5 h of stirring, the ice bath was removed and the mixture was stirred at rt for 23 h. The silver suspension was removed by filtration and was washed with several portions of hot water. EtOAc (200 mL) was added to the filtrate and washings, then acidified with concentrated HCl to pH 1-2. The organic phase was separated, and the aqueous phase was re-extracted with EtOAc (3 x 150 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentration *in vacuo* to afford the title compound **2.9** as a brownish yellow oil (8.90 g, 40.0 mmol, 99%). The crude product was used in subsequent reactions without further purification. Spectroscopic data are in agreement with the literature.[12]

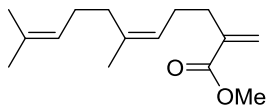
FT-IR ν_{max} (neat): 3342 (br.), 2971 (m), 2928 (s), 2856 (m), 1696 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.31 (1H, d, *J* = 1.1 Hz, C=C**H**H), 5.66 (1H, d, *J* = 1.1 Hz, C=CH**H**), 5.13 (2H, td, *J* = 7.1, 1.3 Hz, 2 x C=C**H**CH_2), 2.36-2.31 (2H, m, C$\mathbf{H}_2$), 2.16-2.23 (2H, m, C$\mathbf{H}_2$), 2.05-2.04 (4H, m, 2 x C$\mathbf{H}_2$), 1.70 (6H, m, 2 x C$\mathbf{H}_3$), 1.61 (3H, s, C$\mathbf{H}_3$) ppm. (OH signal not observed)

^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3 (**C**=O), 139.7 (**C**=CH_2), 136.2 (CH_3**C**), 131.6 (Me_2**C**), 127.3 (C=**C**H_2), 124.2 (C=**C**HCH_2), 123.9 (C=**C**HCH_2), 32.0 (**C**H_2C=CH_2), 31.9 (**C**H_2C=CH), 26.7 (**C**H_2CH_2), 26.6 (**C**H_2CH_2), 25.7 (**C**H_3), 23.6 (**C**H_3), 17.6 (**C**H_3) ppm.

LRMS (ESI$^+$) m/z:223 ($[H+Na]^+$) Da.

(5*Z*)-Methyl 6,10-dimethyl-2-methyleneundeca-5,9-dienoate (1.62)



$C_{15}H_{24}O_2$
Mol. wt. 236.35 g/mol
(Colourless oil)

Procedure 1

Using a procedure described by Price *et al.*,[86] trienoic acid **2.9** (200 mg, 0.90 mmol) was dissolved in CH_2Cl_2 (5.0 mL), and the mixture was cooled to 0 ^oC under Ar gas. Oxalyl chloride (190 µL, 2.25 mmol) was added dropwise, followed by the addition of DMF (2 drops). The cooling bath was removed, and the mixture was stirred for 3 h at rt until gas evolution had stopped. The excess of oxalyl chloride and CH_2Cl_2 were removed *in vacuo*. The acid chloride was cooled at 0 ^oC, and MeOH (5.0 mL) was added dropwise. The solution was stirred at 0 ^oC for 30 min, then the cooling bath was removed and the stirring was continued for 1 h at rt. The resultant solution was concentrated *in vacuo*. EtOAc (5.0 mL) was added to the residue, the solution was washed with sat. aq. $NaHCO_3$ (10 mL), water (10 mL), and brine (10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated in *vacuo* to afford the title compound **2.9** as a brownish yellow oil (204 mg, 0.86 mmol, 96%). The crude product was used in the next reactions without further purification.

Procedure 2

Using a procedure described by Antia *et al*.,[22] to a solution of the carboxylic acid **2.9** (31.5 mg, 0.14 mmol) in DMF (2.8 mL) were added K_2CO_3 (40 mg) and MeI (180 µL, 2.89 mmol) at rt, The mixture was stirred for 21 h at rt. The mixture was concentrated *in vacuo*, dissolved in EtOAc (15 mL), stirred for 15 min, and then was washed with water (5 x 11 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacou* to afford a crude product. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/hexane (5%) to afford the title compound **1.62** as a colourless oil (17.2 mg, 0.073 mmol, 52 %). Spectroscopic data are in agreement with the literature.[12]

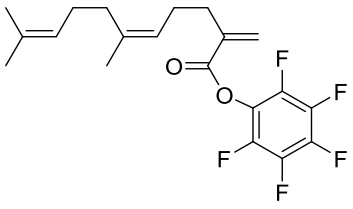
FT-IR ν_{max} (neat): 2954 (m), 2921 (m), 2857 (m), 1722 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.15 (1H, s, C=C**H**H), 5.53 (1H, d, *J* = 1.3 Hz, C=CH**H**), 5.15-5.11 (2H, m, 2 x C=C**H**), 3.76 (3H, s, OC**H**$_3$), 2.33 (2H, t, *J* = 7.2 Hz, C**H**$_2$), 2.17 (2H, q, *J* = 7.2 Hz, C**H**$_2$), 2.04 (4H, s, 2 x C**H**$_2$), 1.69 (6H, s, 2 x C**H**$_3$), 1.61 (3H, s, C**H**$_3$) ppm.

^{13}C NMR (300 MHz, $CDCl_3$): δ 167.3 (**C**=O), 139.9 (**C**=CH_2), 135.6 (CH_3**C**=C), 131.2 (Me_2**C**), 124.4 (C=**C**H_2), 123.8 (C=**C**HCH_2), 123.6 (C=**C**HCH_2), 51.3 (O**C**H_3), 31.8 (**C**H_2C=CH_2), 31.5 (**C**H_2C=CH), 26.3 (**C**H_2CH_2), 26.1 (**C**H_2CH_2), 25.3 (**C**H_3), 22.9 (**C**H_3), 17.2 (**C**H_3) ppm.

LRMS (ESI$^+$) m/z: 275 ([M+K]$^+$) Da.

(5*Z*)-Perflourophenyl 6,10-dimethyl-2-methyleneundeca-5,9-dienoate (2.20)



$C_{20}H_{21}F_5O_2$
Mol. wt. 388.37 g/mol
(yellow oil)

Using a procedure described by the Brown group,[84] to a solution of acid **2.9** (8.90 g, 39.9 mmol) and pentafluorophenol (8.80 g, 47.9 mmol) in EtOAc (65 mL) was added dropwise a solution of DCC (9.90 g, 47.9 mmol) in EtOAc (115 mL) at rt. After stirring for 21 h, the mixture was diluted in hexane (100 mL) and white solids were removed by

filtration. The organic layer was washed with sat. aq. $NaHCO_3$ (3 x 100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a crude product as a brownish yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with Et_2O/hexane (10%) to give the title compound **2.20** as yellow oil (12.9 g, 33.2 mmol, 83%) and recovered acid **2.9** (1.00 g; 4.50 mmol, 11%). Spectroscopic data are in agreement with the literature.[12]

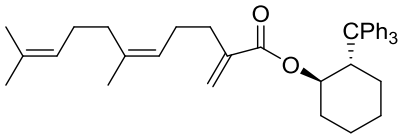
FT-IR ν_{max} (neat): 2993 (w), 2927 (m), 2882 (w), 1762 (s), 1520 (s), 1078 (s), 997 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.49 (1H, s, C=C**H**H), 5.87 (1H, s, C=CH**H**), 5.15 (2H, m, 2 x C=C**H**), 2.46 (2H, t, *J* = 8.1 Hz, C$\mathbf{H}_2$), 2.25 (2H, q, *J* = 7.0 Hz, C$\mathbf{H}_2$), 2.06 (4H, m, 2 x C$\mathbf{H}_2$), 1.72 and 1.69 (6H, s, 2 x C$\mathbf{H}_3$), 1.61 (3H, s, C$\mathbf{H}_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 163.0 (**C**=O), 137.8 (**C**=CH_2), 136.8 (CH_3**C**=C), 131.7 (Me_2**C**=C), 129.3 (C=**C**H_2), 124.1 (C=**C**HCH_2), 123.3 (C=**C**HCH_2), 32.3 (**C**H_2C=CH_2), 32.0 (**C**H_2C=CH), 26.6 (**C**H_2CH_2), 26.5 (**C**H_2CH_2), 25.7 (**C**H_3), 23.3 (**C**H_3), 17.6 (**C**H_3) ppm. (Aromatic carbons were not observed)

LRMS (ESI$^+$) m/z: 427 ($[M+K]^+$) Da.

(*Z*)-(*1R,2S*)-2-(Triphenylmethyl)cyclohexyl 6,10-dimethyl-2-methyleneundeca-5,9-dienoate (1.185) (*ee*: 99.6%)



$C_{39}H_{46}O_2$
Mol. wt. 546.78 g/mol
(Yellow gum)

Using a modified procedure described by the group,[12] to a solution of (+)(*1R, 2S*)-TTC (**1.186**, *ee*: 99.6%, 1.58 g, 4.60 mmol) in THF (29 mL) at −20 ^oC, was added NaHMDS (6.4 mL, of 1.0M in THF, 6.40 mmol). The mixture was allowed to warm to −5 ^oC over 2 h, then a solution of PFP ester **2.20** (1.70 g, 4.38 mmol) in THF (9.0 mL) was added dropwise at –5 ^oC. The cooling bath was removed and the mixture was stirred for 30 min at rt; then the solution was heated at reflux for 22 h. After cooling to rt, Et_2O (30 mL) and then sat. aq. NH_4Cl (17 mL) were added to the mixture. The organic phase was separated, washed with sat. aq. $NaHCO_3$ (2 x 23 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product as a yellow oil. The crude product

was purified by column chromatography (SiO_2) eluting with EtOAc/ Pet. Et_2O (5 to 10%) to give the title TTC trienoate **1.185** as a yellow gum (1.40 g, 2.56 mmol, 99%).

$[\alpha]^{24}_D$ = −16.3 (*c* 1.12, $CHCl_3$).

FT-IR ν_{max} (neat): 3055 (w), 2926 (s), 2857 (m), 1710 (s), 1631 (w) cm^{-1}.

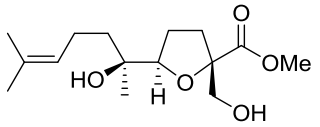
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.07 (15H, br. m, Ar), 5.19 (1H, d, *J* = 1.5 Hz, C=C**H**H), 5.13-5.11 (2H, m, C=CH**H**, Me_2C=C**H**), 5.05 (1H, m, C=C**H**), 3.98 (1H, td, *J* = 10.2 and 3.8 Hz, OC**H**), 3.59 (1H, td, *J* = 10.2 and 2.1 Hz, C**H**CPh_3), 2.15 (1H, m, C**H**H), 2.11-1.94 (9H, br. m, C**H**$_2$), 1.70 (7H, s, 2 x CH_3, C**H**H), 1.62 (3H, m, C**H**$_3$), 1.60-1.42 (3H, s, 2 x C**H**H), 1.26 (1H, s, C**H**H), 0.88 (1H, m, C**H**H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4 (C=O), 140.4 (**C**=CH_2), 135.6 (CH_3**C**=C), 131.5 (Me_2**C**=C), 127.5 (br, C=**C**H_2, 15 x **C**H, Ar), 124.3 (d, 2 x C=**C**HCH_2), 76.3 (O**C**H), 60.8 (**C**Ph_3), 46.6 (**C**HCPh_3), 33.3 (**C**H_2C=C), 32.0 **C**H_2C=C), 31.9 (**C**H_2CO), 29.7 (**C**H_2CCPh_3), 29.1 (**C**H_2C=C), 26.6 (**C**H_2C=C), 26.3 (**C**H_3), 25.7 (**C**H_3), 24.9 (**C**H_2), 23.4 (**C**H_2), 17.7 (**C**H_3)ppm. (Quaternary aromatic carbons were not observed)

LRMS (ESI$^+$) m/z: 569 ([M+Na]$^+$) Da.

HRMS (ESI$^+$) m/z: Calculated: 564.3836; Found: 564.3836 ([M+NH_4]$^+$) Da.

***Rac*-(*2S,5R*)-Methyltetrahydro-5-((*S*)-2-hydro-6-methylhept-5-en-2-yl(hydroxymethyl) furan-2-carboxylate (2.21)**



$C_{15}H_{26}O_5$
Mol. wt. 286.36 g/mol
(Yellow oil)

To a vigorously stirred mixture of methyl ester **1.62** (100 mg, 0.42 mmol) and TBAB (140.0 mg, 0.434 mmol) in EtOAc (17 mL) at −20 °C was added in one portion a solution of $NaMnO_4$ (1.600 mL of 0.4M aq., 0.635 mmol) containing AcOH (85.0 µL, 1.48 mmol). The purple mixture was stirred rapidly for 1 h, during which time the temperature of the acetone cooling bath rose to −10 °C and the reaction mixture turned dark brown. At this stage, the reaction was quenched with sat. aq. $Na_2S_2O_5$ (ice cooling) until all of the precipitated manganese salts were dissolved, and then brine (15 mL) was added. The organic phase was separated and the aqueous layer was extracted

with EtOAc (3 x 20 mL). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a crude product. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/hexane (5 to 70%) to give the title compound **2.21** as a yellow oil (75 mg, 0.26 mmol, 62%) and recovered methyl ester **1.62** (14.0 mg ,0.05 mmol, 12%). The Spectroscopic data are in agreement with the literature.[12]

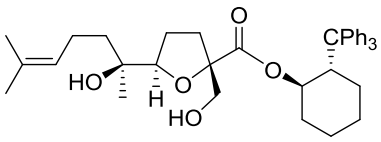
FT-IR ν_{max} (neat): 3414 (br), 2977 (m), 2927 (m), 2878 (w), 1732 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.12 (1H, t, *J* = 7.1 Hz, C=C**H**), 4.1 (1H, t, *J* = 7.3 Hz, C**H**, THF ring), 3.89 (1H, s, C**H**HOH), 3.85 (1H, s, CH**H**OH), 3.77 (3H, s, OC**H$_3$**), 3.73 (1H, s, O**H**), 2.18-1.95 (6H, m, C**H$_2$** and 2 x C**H$_2$**), 1.69 (3H, s, C**H$_3$**), 1.63 (3H, s, C**H$_3$**), 1.48-1.39 (3H, m, O**H** and C**H$_2$**), 1.31 (3H, s, C**H$_3$**) ppm.

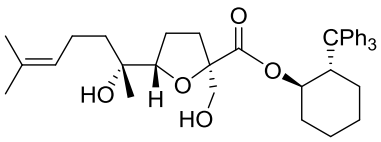
^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0 (**C**=O), 131.6 (Me_2**C**), 123.8 (C=**C**H), 86.6 (**C**H, THF), 86.0 (**C**CH_2OH, THF), 73.1 (**C**OH), 65.9 (**C**H_2OH), 53.5 (O**C**H_3), 51.9 (**C**H_2COH), 37.7 (**C**H_2, THF), 31.6 (**C**H_3), 25.3 (**C**H_2, THF), 23.6 (**C**H_3), 21.7 (**C**H_2CH_2), 17.2 (**C**H_3) ppm.

LRMS (ESI$^+$) m/z: 309 ($[M+Na]^+$) Da.

(2*S*,5*R*)-((1*R*,2*S*)-2-(Triphenylmethyl)cyclohexyl)tetrahydro-5-((*S*)-2-hydroxy-6-methylhepta-5-en-2-yl)-2-(hydroxymethyl)furan-2-carboxylate (1.187) and (*2R,5S*)-((*1R,2S)*-2-(Triphenylmethyl)cyclohexyl)tetrahydro-5-((*R*)-2-hydroxy-6-methylhepta-5-en-2-yl)-2-(hedroxymethyl)furan-2-carboxylate (2.22) (TTC: *ee*: 99.6%)



1.187 Major (white solid)



2.22 Minor (white solid)

$C_{39}H_{48}O_5$

Mol.wt. 596.81 g/mol

Using a procedure described by the Brown group,[18] to a vigorously stirred mixture of TTC ester **1.185** (2.30 g, 4.21 mmol) and TBAB (1.40 g, 4.33 mmol) in acetone (92 mL) at −35 °C was added in a one portion a solution of $NaMnO_4$ (14.4 mL, of 0.4M aq., 5.76 mmol) containing AcOH (590 µL, 10.31 mmol). The purple mixture was stirred rapidly for 1.5 h, during which time the temperature of the acetone cooling bath was

kept under −5 °C and the reaction mixture had turned dark brown. At this stage, the reaction was quenched with sat. aq. $Na_2S_2O_5$ (with ice cooling, 300 mL) to dissolve the precipitated manganese salt, then brine (180 mL), CH_2Cl_2 (300 mL) and H_2O (100 mL) were added. The organic phase was separated and the aqueous phase was re-extracted using CH_2Cl_2 (5 x 20 mL). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude products as chromatographically separable diastereomers (yellow-white gummy oil, dr = 13:1 by ^{1}H NMR). The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/ Pet. Et_2O (30 to 70%) to give the title compounds. The desired product **1.187** was isolated as a white solid (1.43 g, 2.40 mmol, 57%). The minor diastereomer **2.22** was collected as a white solid (114.5 mg, 0.191 mmol, 5%), and starting material **1.185** (120 mg, 0.22 mmol, 5%) was also recovered.

Data for major diastereomer 1.187:

$[\alpha]^{26}_D$: −5.2 (*c* 0.61, $CHCl_3$).

mp: 80-83 °C.

FT-IR ν_{max} (neat): 3427 (br), 2929 (s), 2851 (m), 1727 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.07 (15 H, m, C**H**, Ar), 5.12 (1H, t, *J* = 7.1 Hz, C=C**H**CH_2), 4.11 (1H, td, *J* = 10.1, 4.0 Hz, OC**H**), 3.87 (1H, t, *J* = 7.3 Hz, C**H**, THF), 3.62 (1H, d, *J* = 11.1 Hz, C**H**HOH), 3.58 (1H, br. s, C**H**CPh_3), 3.43 (1H, d, *J* = 11.1 Hz, CH**H**OH), 2.37 (1H, br. s, O**H**), 2.17-1.96 (4H, m, C$\mathbf{H}_2$, THF ring), 1.82-1.71 (5H, m, C$\mathbf{H}_2$, C$\mathbf{H}_3$), 1.64 (3H, br. s, CH_3), 1.55-1.33 (5H, m, 2 x C$\mathbf{H}_2$, O**H**), 1.32-1.28 (2H, m, C$\mathbf{H}_2$), 1.25(3H, br. s, C$\mathbf{H}_3$), 1.19-1.06 (2H, m, C$\mathbf{H}_2$), 0.92-0.80 (2H, m, C$\mathbf{H}_2$) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.2 (**C**=O), 131.9 (**C**=CH), 128.8 (6 x **C**H, Ar), 127.5 (3 x **C**H, Ar), 125.2 (6 x **C**H, Ar), 124.4 (C=**C**H), 86.6 (**C**O, THF ring), 86.3 (**C**HO**,** THF ring), 76.7 (O**C**H), 73.4 (CH_3**C**OH), 66.1 (**C**H_2OH), 61.1 (**C**Ph_3), 45.7 (**C**HCPh_3), 38.0 (**C**H_2CCH_3), 33.0 (**C**H_2, THF ring), 30.4 (**C**H_2CH(O)CH), 28.7 (**C**H_2CHCH(O)), 25.9 (**C**H_2, THF ring), 25.7 (**C**H_3), 25.4 (CH_2**C**H_2CH_2), 24.6 (CH_2**C**H_2CH_2), 23.9 (**C**H_3COH), 22.2 (**C**H_2CH=C), 17.7 (**C**H_3) ppm. (Quaternary aromatic carbons were not observed)

LRMS (ESI$^+$) m/z: 619 ($[M+Na]^+$) Da.

HRMS (ESI$^+$) m/z: Calculated: 614.3840; Found: 614.3828([M+NH_4]$^+$): 619.3394; 619.3383 ([M+Na]$^+$) Da.

Data for minor diastereomer 2.22:

[α]$^{25}_D$: −9.1 (*c* 1.04, $CHCl_3$).

mp: 74-76 °C.

FT-IR ν_{max} (neat): 3431 (br), 2925 (s), 2856 (m), 1724 (s) cm^{-1}.

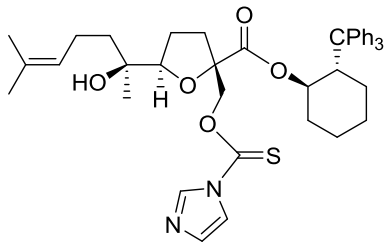
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.54-7.03 (15H, m, Ar), 5.11 (1H, t, *J* = 7.1 Hz, C=C**H**CH_2), 4.04 (1H, td, *J* = 10, 10, 3.2 Hz, OC**H**), 3.91 (1H, t, *J* = 7.0 Hz, C**H**, THF ring), 3.60 (1H, t, *J* = 10.2 Hz, C**H**CPh_3), 2.88 (1H, d, *J* = 11.4 Hz, C**H**HOH), 2.85 (1H, d, *J* = 11.4 Hz, CH**H**OH), 2.18 (1H, d, *J* = 13.5 Hz, O**H**), 2.14-1.97 (4H, m, C**H**$_2$, THF ring), 1.84-1.67 (9H, m, 3 x C**H**$_2$, C**H**$_3$), 1.63 (3H, br. s, C**H**$_3$), 1.52-1.40 (3H, m, C**H**$_2$, O**H**), 1.35-1.21 (2H, m, 2 x C**H**$_2$), 1.26 (3H, s, C**H**$_3$), 0.85-0.79 (2H, m, C**H**$_2$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1 (**C**=O), 131.9 (**C**=CH), 128.8 (6 x **C**H, Ar), 127.5 (3 x **C**H, Ar), 125.2 (6 x **C**H, Ar), 124.3 (C=**C**H), 86.4 (**C**O**,** THF ring), 86.3 (**C**HO, THF), 76.7 (O**C**H), 37.2 (CH_3**C**OH), 65.3 (**C**H_2OH), 61.0 (**C**Ph_3), 45.8 (**C**HCPh_3), 37.9 (**C**H_2CCH_3), 32.9 (**C**H_2, THF), 31.2 (**C**H_2CH(O)CH), 28.8 (**C**H_2CHCH(O)), 26.0 (**C**H_2, THF ring), 25.7 (**C**H_3), 25.5 (**C**$H_2CH_2CH_2$), 24.4 (CH_2**C**H_2CH_2), 24.0 (**C**H_3COH), 22.1 (**C**H_2CH=C), 17.7 (**C**H_3) ppm. (Quarternary aromatic carbons were not observed)

LRMS (ESI$^+$) m/z: 619 ([M+Na]$^+$) Da.

HRMS (ESI$^+$) m/z: Calculated: 619.3394; Found: 619.3400([M+Na]$^+$).

(*2S,5R*)-((*1R,2S*)-2-Tritylcyclohexyl tetrahydro-5-((S)-2-hydroxy-6-methylhept-5-en-2-yl)-2-(*O*-methoxy-1H-imidazol-1-carbothioyl)furan-2-carboxylate (2.29) (TTC: *ee*: 99.6%)



$C_{43}H_{50}N_2O_5S$
Mol. wt.: 706.93 g/mol
(White solid)

To a solution of THF-TTC diol **1.187** (960 mg, 1.61 mmol) in CH_2Cl_2 (24 mL) was added DMAP (118 mg, 0.965 mmol) and thiocarbonyldiimidazole (860 mg, 4.83 mmol) at rt. The resultant yellow solution was stirred at rt for 8 h. Then concentrated *in vacuo* to afford the crude product as a yellow solid. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/hexane (40 to 70%) to give the title xanthate **2.29** as a white solid (1.00 g, 1.42 mmol, 88%).

$[\alpha]^{26}_{D}$: −2.9 (*c* 0.32, $CHCl_3$).

mp: 67-69 °C.

FT-IR ν_{max} (neat): 2924 (m), 2855 (w), 1932 (w), 1743 (s) cm^{-1}.

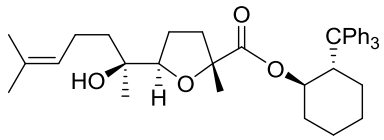
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (1H, s, NC**H**N), 7.66 (1H, s, C**H**NC=S), 7.36-7.09 (16H, br. m, 15 x C**H**, Ar, NC**H**CH), 5.15 (1H, t, *J* = 7.3 Hz, =C**H**CH_2), 4.85 (1H, d, *J* = 11.1 Hz, C**H**HO), 4.43 (1H, d, *J* = 11.1 Hz, CH**H**O), 4.21-4.10 (2H, m, OC**H,** C**H**, THF ring), 3.61 (1H, t, *J* = 10.2, C**H**CPh_3), 2.21-1.98 (6H, m, 2 x C$\mathbf{H}_2$, C**H**, O**H**), 1.74 (3H, s, C$\mathbf{H}_3$), 1.90-1.78 (4H, m, 2 x C$\mathbf{H}_2$), 1.67 (3H, s, C$\mathbf{H}_3$), 1.26 (3H, s, C$\mathbf{H}_3$), 1.54-1.14 (4H, m, 2 x C$\mathbf{H}_2$), 1.12-0.75 (3H, 2 x C$\mathbf{H}_2$, C**H**,) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 184.3 (**C**=S), 170.6 (**C**=O), 137.5 (N**C**HN), 132.2 (Me_2**C**), 131.3 (N**C**H=C), 129.0 (6 x **C**H, Ar), 128.0 (3 x **C**H, Ar $_r$), 125.6 (6 x **C**H, Ar), 124.6 (C=**C**H), 118.1 (CN**C**H=C), 87.5 (**C**CH_2O, THF ring), 84.4 (**C**H, THF ring), 77.8 (COO**C**H), 75.8 (**C**H_2OC=S), 73.2 (**C**OH), 61.3 (**C**Ph_3), 45.9 (**C**HCPh_3), 38.2 (**C**H_2COH), 33.3 (**C**H_2C(CH_2), THF ring), 31.6 (**C**H_2CH(O)CH), 30.0 (**C**H_2CHCH(O)), 29.1 (**C**H_3), 26.1 (**C**H_2, THF ring), 26.0 (**C**$H_2CH_2CH_2$), 25.1 (CH_2**C**H_2CH_2), 24.0 (**C**H_3COH), 22.4 (**C**H_2CH=C), 18.0 (**C**H_3) ppm. (Quaternary aromatic carbons were not observed)

LRMS (ESI$^+$) m/z: 770 ($[M+CH_3CN+Na]^+$) Da.

HRMS (ESI$^+$) m/z: Calculated: 707.3513; Found: 707.3525 ($[M+H]^+$) Da.

(2*S*,5*R*)-((1*R*,2*S*)-2-(Triphenylmethyl)cyclohexyl)tetrahydro-5-((*S*)-2-hydroxy-6-methylhepta-5-en-2-yl)-2-methyl furan-2-carboxylate (2.30)



$C_{39}H_{48}O_4$
Mol. wt.: 580.8 g/mol
(Yellow oil)

To a solution of xanthate **2.29** (2.50 g, 3.54 mmol) in toluene (48 mL) was added AIBN (290 mg, 1.77 mmol), followed by dropwise addition of TTMSS (10.9 mL, 23.0 mmol). The resultant solution was stirred at 85 °C for 70 min, and the reaction mixture was diluted with EtOAc (50 mL) and washed with HCl (2.0N, 25 mL). The organic phase was separated and dried ($MgSO_4$) concentrated *in vacuo* to afford the crude product as a pale yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/ hexane (30 to 40%) to give the title THF **2.30** as a yellow oil (1.50 g, 2.65 mmol, 75%).

$[\alpha]^{24}_D$: −16.1 (*c* 2.38 , $CHCl_3$).

FT-IR ν_{max} (neat): 3538 (br.), 2936 (m), 2859 (m), 1731 (s) cm^{-1}.

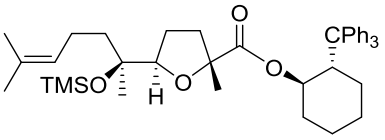
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.06 (15 H, m, Ar), 5.14 (1H, t, *J* = 7.2 Hz, =C**H**CH_2), 4.04 (1H, td, *J* = 9.8 and 3.8 Hz, OC**H**), 3.87 (1H, t, *J* = 7.2 Hz, C**H**, THF ring), 3.64-3.56 (1H, m, C**H**CPh_3), 2.18-87 (5H, m, 2 x C$\mathbf{H}_2$, C**H**), 1.71 (6H, s, 2 x C$\mathbf{H}_3$), 1.64 (4H, s, 2 x C$\mathbf{H}_2$), 1.60-1.27 (5H, m, 2 x C$\mathbf{H}_2$, O**H**), 1.22 (3H, s, C$\mathbf{H}_3$), 1.18 (3H, s, C$\mathbf{H}_3$), 1.18-1.13 (2H, m, C$\mathbf{H}_2$), 0.81 (1H, m, C**H**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5 (**C**=O), 131.6 (**C**=CH), 128.7 (**C**H, Ar), 127.5 (**C**H, Ar), 125.1 (**C**H, A_r), 124.5 (C=**C**H), 85.6 (**C**HO, THF ring), 83.4 (**C**O, THF ring), 76.4 (**C**HO), 72.8 (CH_3**C**OH), 61.0 (**C**Ph_3), 45.6 (**C**HCPh_3), 37.4 (**C**$H_2C(CH_3)OH$), 35.1 (**C**H_2, THF ring), 32.8 (**C**$H_2CH(O)CH$), 28.6 (**C**$H_2CHCH(O)$), 25.9 (**C**H_2, THF ring), 25.9 (**C**H_3), 25.7 (**C**$H_2CH_2CH_2$), 25.1(**C**H_3), 24.5 (CH_2**C**H_2CH_2), 23.7 (**C**H_3COH), 22.1 (**C**H_2CH=C), 17.7 (**C**H_3) ppm. (Quaternary aromatic carbons were not observed)

LRMS (ESI$^+$) m/z: 603 ($[M+Na]^+$).

HRMS (ESI$^+$) m/z: Calculated: 603.3445; Found: 603.3443 ($[M+Na]^+$).

(2*S*,5*R*)-((1*R*,2*S*)-2-(Triphenylmethyl)cyclohexyl)tetrahydro-5-((*S*)-2trimethylsiloxy-6-methylhepta-5-en-2-yl)-2-methyl furan-2-carboxylate (2.32)



$C_{42}H_{56}O_4Si$
Mol. wt.: 652.98 g/mol
(White solid)

To a solution of the THF **2.30** (1.48 g, 2.55 mmol) in DMF (25 mL) was added imidazole (1.70 g, 28.48 mmol), followed by the addition of TMSCl (3.20 mL, 21.9 mmol) at −5 °C. The reaction mixture was stirred for 2 h, during which time the temperature rose to 5 ^{o}C. At this stage, the reaction was quenched with sat. aq. NH_4Cl (15 mL) and H_2O (30 mL). The organic phase was separated, and the aqueous phase was re-extracted with Et_2O (8 x 60 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product as a yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/hexane (20%) to give the title protected THF **2.32** as a white solid (1.40 g, 2.10 mmol, 82%).

$[\alpha]^{24}_{D}$: −17.9 (*c* 0.49 $CHCl_3$).

FT-IR ν_{max} (neat): 3057 (w), 2949 (s), 2936 (s), 2858 (m), 1738 (s) cm^{-1}.

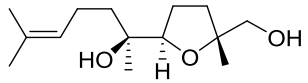
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.00 (15H, m, Ar), 5.13 (1H, t, *J* = 7.0 Hz, C=C**H**CH_2), 4.06 (1H, td, *J* = 10.0, 3.8 Hz, OC**H**), 3.93 (1H, dd, *J* = 8.2, 5.5 Hz, C**H**, THF), 3.63-3.57 (1H, m, C**H**CPh_3), 2.16-1.93 (4H, m, 2 x C**H**$_2$, THF ring), 1.77 (1H, m, C**H**) 1.71 (3H, s, C**H**$_3$), 1.65 (3H,s, C**H**$_3$), 1.62-1.33 (8H, m, 2 x C**H**$_2$, 4 x C**H**), 1.2 (3H, s, C**H**$_3$), 1.17 (4H, m, C**H**, C**H**$_3$), 1.12-1.08 (2H, m, 2 x C**H**), 0.13 (9H, s, COSi(C**H**$_3$)$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.0 (**C**=O), 131.1 (**C**=CH), 128.7 (2 x **C**H, Ar), 127.6 (2 x **C**H, Ar), 125.5 (**C**H, Ar), 124.8 (C=**C**H), 84.6 (**C**H, THF ring), 83.7, (**C**HO), 76.2 (**C**O$SiMe_3$), 61.1 (**C**Ph_3), 45.6 (**C**HCPh_3), 40.6 (**C**H_2CO$SiMe_3$), 35.0 (**C**H_2, THF ring), 32.7 (**C**H_2CH(O)CH), 28.6 (**C**H_2CHCH(O)), 25.9 (**C**H_2, THF), 25.7 (**C**H_3), 25.5 (**C**$H_2CH_2CH_2$), 24.5 (**C**H_3), 23.5 (CH_2**C**H_2CH_2), 22.6 (**C**H_3COH), 22.4 (**C**H_2CH=C), 17.7 (**C**H_3), 2.7 (3C, COSi**Me**$_3$) ppm. (Quaternary carbons were not observed)

LRMS (ESI^{+}) m/z: 675.3 ($[M+Na]^{+}$)Da.

HRMS (ESI^{+}) m/z: Calculated: 675.3840; Found: 675.3832 ($[M+Na]^{+}$) Da.

(2*S*,5*R*)-2-((Hydroxymethyl)methyl)-5-((*S*)-2-hydroxyl-6-methylhepta-5-en-2-yl tetrahydrofuran (2.31)



$C_{14}H_{26}O_3$
Mol. wt.: 242.35 g/mol
(Yellow oil)

To a solution of TTC ester **2.30** (389 mg, 0.67 mmol) in CH_2Cl_2 (12 mL) was added dropwise a solution of DIBALH (2.70 mL, 1.0M, 2.68 mmol) at rt. The reaction mixture was heated at reflux for 23 h. After that the reaction was cooled at rt, then quenched by adding sat. aq. NH_4Cl (21 mL) and Rochelle's salt (sat. aq. 25 mL) and the solution was stirred for 1.5 h at rt. CH_2Cl_2 (35 mL) was added, the aqueous layer was re-extracted with CH_2Cl_2 (2 x 50 mL) then with Et_2O (3 x 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product as a yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/ hexane (40 to 60%) to provide the title diol **2.31** as a yellow oil (121 mg, 0.499 mmol, 75%) and (+)-TTC as a white solid (170 mg, 0.496 mmol, 74%).

$[\alpha]^{24.5}_{D}$: +8.9 (*c* 1.14, $CHCl_3$).

FT-IR ν_{max} (neat): 3422 (br.), 2968 (s), 2927 (s), 2870 (m) cm^{-1}.

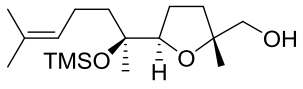
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.12 (1H, m, C=C**H**CH_2), 3.80 (1H, m, C**H**, THF ring), 3.46 (2H, d, *J* = 4.8 Hz, C**H**$_2$OH), 2.12-1.82 (8H, m, 3 x C**H**$_2$, 2 x O**H**), 1.69 (3H, s, C**H**$_3$), 1.63 (3H, s, C**H**$_3$), 1.52 (1H, ddd, *J* = 13.7, 11.4 and 5.4 Hz, C**H**), 1.36 (1H, ddd, *J* = 13.7, 11.4 and 5.4 Hz, C**H**),), 1.22 (3H, s, C**H**$_3$), 1.21 (3H, s, C**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 131.7 (**C**=CH), 124.5 (C=**C**H), 86.5 (**C**H, THF ring), 83.2 (**C**O, THF ring), 72.3 (**C**(CH_3)OH), 68.5 (**C**H_2OH), 37.2 (**C**H_2COH), 33.5 (**C**H_2, THF), 26.0 (**C**H_2, THF ring), 25.7 (**C**H_3C=CH), 24.3 (**C**H_3, **C**-THF), 23.9 (**C**H_3C(OH)), 22.1 (**C**H_2CH=C), 17.6 (**C**H_3) ppm.

LRMS (ESI$^+$) m/z: 306 ([M+Na+CH_3CN]$^+$) Da.

HRMS (ESI$^+$) m/z: Calculated: 265.1774; Found: 265.1775 ([M+Na]$^+$) Da.

(2*S*,5*R*)-2-((Hydroxymethyl)methyl)-5-((*S*)-2-trimethylsiloxy-6-methylhepta-5-en-2-yl tetrahydrofuran (2.33)



$C_{17}H_{34}O_3Si$
Mol. wt.: 314.54 g/mol
(Yellow oil)

Following the DIBALH reduction procedure for the preparation of THF-diol **2.31**, protected THF **2.32** (600 mg, 0.919 mmol) gave the title alcohol **2.33** as a yellow oil (239 mg, 0.760 mmol, 83%) and (*1R,2S*)-TTC (277mg, 0.81, 88%). Purification was carried out by column chromatography (SiO_2) eluting with EtOAc/hexane (4 to 10%).

$[\alpha]^{24.5}_{D}$: + 4.8 (*c* 0.57 $CHCl_3$).

FT-IR ν_{max} (neat): 3422 (br), 2964 (m), 2924 (m), 2884 (w) cm^{-1}.

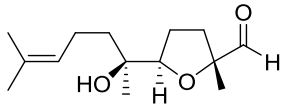
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.10 (1H, t, *J* = 7.0 Hz, C=C**H**CH_2), 3.82-3.78 (1H, m, C**H**, THF ring), 3.42 (2H, s, C**H_2**OH), 2.03-1.83 (5H, m, O**H**, and 2 x C**H_2**, THF ring), 1.69 (3H, s, C**H_3**), 1.64-1.36 (4H, m, 2 x C**H_2**), 1.62 (3H, s, C**H_3**), 1.22 (3H, s, C**H_3**), 1.19 (3H, s, C**H_3**), 0.13 (9H, s, COSi**Me_3**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 131.2 (Me_2**C**=C), 124.8 (C=**C**H), 85.4 (**C**H, THF ring), 83.2 (**C**HO, THF ring), 76.5 (**C**OSiMe_3), 68.4 (**C**H_2OH), 40.3(**C**H_2COSiMe_3), 33.6 (**C**H_2, THF), 26.5 (**C**H_2, THF), 25.7 (**C**H_3), 23.9 (**C**H_3), 33.0 (**C**H_3), 22.5 (**C**H_2CH_2), 17.6 (**C**H_3), 2.7 (3C, COSi**Me_3**) ppm.

LRMS (ESI^+) m/z: 337 ($[M+Na]^+$) Da.

HRMS (ESI^+) m/z: Calculated: 337.2169; Found: 337.2175 ($[M+Na]^+$) Da.

(2*R*,5*R*)-Tetrahydro-5-((*S*)-2-hydroxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-carbaldehyde (1.50)



$C_{14}H_{24}O_3$
Mol. wt.: 240.34 g/mol
(Yellow oil)

To a solution of diol **2.31** (41 mg, 0.169 mmol) in CH_2Cl_2 was added Dess-Martin periodinane (113 mg, 0.27 mmol) at room temperature and the reaction mixture was stirred for 2 hours. The reaction mixture was diluted with CH_2Cl_2 (5 mL), washed with H_2O followed by brine (5.0 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product as a yellow oil. The product was purified by column chromatography (SiO_2) eluting with EtOAc/hexane (30%) to afford

the title compound **1.50** as a yellow oil (18.80 mg, 0.078 mmol, 46%). Spectroscopic data are in agreement with the literature.[12]

[α]$^{27}_{D}$: +0.7 (*c* 0.94, $CHCl_3$) {lit. [α]$^{14.9}_{D}$ +1.73 (*c* 1.101, $CHCl_3$)}.[5]

FT-IR ν_{max} (neat): 3469 (br), 2969 (m), 2925 (m), 2856 (w), 1737 (s) cm^{-1}.

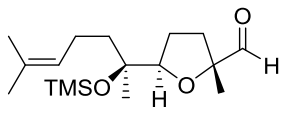
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.58 (1H, s, C**H**O), 5.13 (1H, m,C=C**H**), 3.87 (1H, dd, *J* = 8.8, 6.3 Hz, C**H**, THF ring), 2.17-1.92 (5H, m, O**H** and 2 x C**H$_2$**, THF ring), 1.69 (3H, s, C**H$_3$**), 1.63 (3H, s, C**H$_3$**), 1.58-1.37 (4H, m, 2 x C**H$_2$**), 1.32 (3H, s, C**H$_3$**), 1.26 (3H, s, C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.8 (**C**HO), 131.9 (Me_2**C**), 124.3 (C=**C**H), 87.1 (**C**H, THF ring), 86.3 (**C**CH_3, THF ring), 72.5 (**C**OH), 37.5 (**C**H_2COH), 32.7 (**C**H_2, THF), 25.7 (**C**H_2, THF ring), 25.4 (**C**H_3), 24.0 (**C**H_3), 22.1 (**C**H_2CH_2), 21.1 (**C**H_3), 17.7 (**C**H_3) ppm.

LRMS (ESI$^+$) m/z: 503 ([2M+Na]$^+$) Da.

HRMS (ESI$^+$) m/z: Calculated: 263.1618; Found: 263.1617 ([M+Na]$^+$) Da.

(2*R*,5*R*)-Tetrahydro-5-((*S*)-2-trimethylsiloxy-6-methylhept-5-en-2-yl)-2-methylfuran-2- carbaldehyde (2.34)



$C_{17}H_{32}O_3Si$
Mol. wt.: 312.52 g/mol
(Yellow oil)

To a solution of the alcohol **2.33** (83 mg, 0.264 mmol) in CH_2Cl_2 (2.3 mL) was added Dess-Martin periodinane (180 mg, 0.42 mmol) at room temperature and the reaction mixture was stirred for 4.5 h. At this stage, the reaction mixture was filtered through a short silica pad and concentrated *in vacuo* to afford the crude product as a pale yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/ hexane (5%) to give the title aldehyde **2.34** as a yellow oil (28.0 mg, 0.09 mmol, 34%).

[α]$^{22}_{D}$: –2.8 (*c* 1.81, $CHCl_3$).

FT-IR ν_{max} (neat): 2960 (m), 2935 (w), 2848 (w), 1737 (m), 1451 (w), 1374 (w), 1250 (m) cm^{-1}.

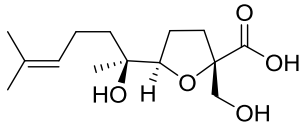
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.57 (1H, s, C**H**O), 5.10 (1H, m, C=C**H**), 3.87 (1H, t, *J* = 7.3 Hz, C**H**, THF ring), 2.15-1.77 (4H, m, 2 x C**H**$_2$, THF ring), 1.69 (3H, s, C**H**$_3$), 1.67-1.39 (4H, m, 2 x C**H**$_2$), 1.62 (3H, s, C**H**$_3$), 1.29 (3H, s, C**H**$_3$), 1.27 (3H, s, C**H**$_3$), 0.13 (9H, s, COSi**Me**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 203.7 (**C**HO), 131.3 (**C**=CH), 124.6 (C=**C**H), 86.6 (**C**H, THF ring), 86.1 (**C**CH_3, THF ring), 76.4 (**C**O$SiMe_3$), 40.5 (**C**H_2O$SiMe_3$), 32.6 (**C**H_2, THF), 25.8 (**C**H_2, THF ring), 25.6 (**C**H_3), 23.0 (**C**H_3), 22.4 (**C**H_2CH_2), 20.9 (**C**H_3), 17.6 (**C**H_3), 2.7 (3C, COSi**Me**$_3$) ppm.

LRMS (ESI$^+$) m/z: 647 ($[2M+Na]^+$) Da.

HRMS (ESI$^+$) m/z: Calculated: 335.2013; Found: 335..2017 ($[M+Na]^+$) Da.

(2*S*,5R)-5-((*S*)-2-Hydroxy-6-methylhept-5-en-2-yl)-2-(hydroxymethyl)tetrahydrofuran-2-carboxylic acid (2.39)



$C_{14}H_{24}O_5$
Mol. wt.: 272.34 g/mol
(Yellow gum)

To a solution of the TTC ester **1.187** (100.0 mg, 0.168 mmol) in MeOH (1.3 mL) and H_2O (250 µL) was added KOH (14.0 mg, 0.25 mmol) at rt. The mixture was heated under reflux for 23 h. The mixture was cooled to rt, then CH_2Cl_2 (3.0 mL) was added. The organic phase was separated and the aqueous phase was re-extracted with CH_2Cl_2 (5 x 2 mL) to collect the auxiliary TTC. The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford the (+)-TTC as a white solid (54.0 mg, 0.16 mmol, 94%). To the aqueous layer was added CH_2Cl_2 (5.0 mL) and the mixture was acidified with conc. HCl (pH 2-3). The organic phase was separated and the aqueous phase was re-extracted with CH_2Cl_2 (6 x 3 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title acid **2.39** as yellow gum (45.0 mg, 0.165 mmol, 99%).

$[\alpha]^{25}_D$: +21 (*c* 1.17, $CHCl_3$).

FT-IR ν_{max} (neat): 3362 (br), 2968 (m), 2919 (m), 2878 (w), 1717(s), 1376 (m) cm^{-1}.

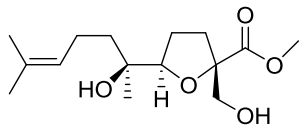
^{1}H NMR (300 MHz, $CDCl_3$): δ 5.12 (1H, br. t, *J* = 6.6 Hz, C=C**H**CH_2), 4.09 (1H, t, *J* = 8.4 Hz, C**H**, THF ring), 3.90 (1H, d, *J* = 11.5 Hz, C**H**HOH), 3.76 (1H, d, *J* = 11.5 Hz, CH**H**OH), 2.31-1.91 (6H, m, O**H**, C**H**, and 2 x C**H_2**, THF ring), 1.70 (3H, s, C**H_3**), 1.64 (3H, s, C**H_3**), 1.55-1.35 (2H, m, C**H_2**), 1.33 (3H, s, C**H_3**), 1.29 (1H, m, C**H**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 175.2 (**C**=O), 132.5 (Me_2**C**), 123.9 (C=**C**HCH_2), 87.8 (**C**H, THF), 87.1 (**C**CH_2OH, THF), 73.6 (**C**OH), 66.4 (**C**H_2OH), 37.7 (**C**H_2COH), 32.1 (**C**H_2, THF ring), 26.0 (**C**H_3), 25.6 (**C**H_2, THF ring), 24.1 (**C**H_3), 22.1 (**C**H_2CH=C), 17.7 (**C**H_3) ppm.

LRMS (ESI$^+$) m/z: 567 ([2M+Na]$^+$) Da.

HRMS (ESI$^+$) m/z: Calculated: 295.1516; Found: 295.1514 ([M+Na]$^+$) Da.

Methyl (2*S*,5*R*)-5-((*S*)-2-hydroxy-6-methylhept-5-en-2-yl)-2-(hydroxymethyl)tetrahydrofuran-2-carboxylate (1.188)

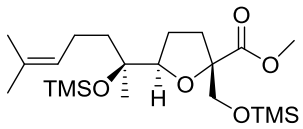


$C_{15}H_{26}O_5$
Mol.wt.: 286.37 g/mol
(Brownish yellow oil)

To a solution of enantiomerically pure acid **2.39** (35.6 mg, 0.131 mmol) in DMF (1.0 mL) was added anhydrous K_2CO_3 (20.0 mg, 0.14 mmol) at rt. The mixture was stirred for 15 min. MeI (16.30 µL, 0.262 mmol) was added at rt and the reaction mixture was stirred for 13 h. The reaction was quenched with sat. aq NH_4Cl (1.0 mL) and H_2O (1.0 mL). Et_2O (10.0) was added, the mixture was stirred for 5 min, then the organic phase was separated and the aqueous phase was re-extracted with Et_2O (10 mL). The combined organic phases were washed with H_2O (3 x 25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title methyl ester **1.188** as a brownish yellow oil (32.3 mg, 0.113 mmol, 86%). The compound was used in the next reactions without any further purification. Physical and Spectroscopic data are consistent with that reported earlier for the racemic methyl ester **2.21**.

$[\alpha]^{23}_D$: +4.6 (*c* 0.52, CH_3Cl_3).

Methyl (2*S*,5*R*)-5-((*S*)-6-Methyl-2-((trimethylsilyl)oxy)hept-5-en-2-yl)-2-(((trimethylsilyl)oxy)methyl)tetrahydrofuran-2-carboxylate (2.40)



$C_{21}H_{42}O_5Si_2$
Mol. wt. 430.73 g/mol
(Yellow oil)

To a solution of methyl ester **1.188** (36.9 g, 0.223 mmol) in DMF (2.0 mL) was added imidazole (185 mg, 27.23 mmol), followed by the addition of TMSCl (286 µL, 2.25 mmol) at −5 °C. The reaction mixture was stirred for 2 h, during which the temperature rose to 0 ^{o}C. At this stage, the reaction was quenched with sat. aq. NH_4Cl (286 µL) and H_2O (1.0 mL). The mixture was extracted with Et_2O (2 x 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude product as a yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/hexane (10 to 50%) to give the title protected methyl ester **2.40** as a yellow oil (38.5 mg, 0.089 mmol, 40%) along with mono protected ester (10.50 mg, 0.029 mmol, 13%) and recovered methyl ester **18** (6.0 mg, 0.021 mmol, 9%).

$[\alpha]^{24}_{D}$: +5.8 (*c* 0.22 $CHCl_3$).

FT-IR ν_{max} (neat): 2955 (m), 2925 (m), 2872 (w), 1736 (m) cm^{-1}.

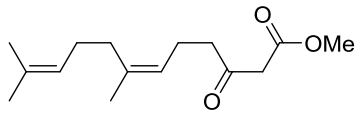
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.11 (1H, m, C=C**H**), 4.04 (1H, m, C**H**, THF), 3.84 (1H, d, *J* = 10.3 Hz, C**H**HOH), 3.73 (3H, s, OC**H$_3$**), 3.71 (1H, d, *J* = 10.3 Hz, CH**H**OH), 2.17-1.78 (6H, m, C**H$_2$** and 2 x C**H$_2$**, THF), 1.69 (3H, s, C**H$_3$**), 1.62 (3H, s, C**H$_3$**), 1.47-1.36 (3H, m, O**H** and C**H$_2$**), 1.24 (3H, s, C**H$_3$**) 0.12 (9H, s, COSi**Me$_3$**), 0.10 (9H, s, COSi**Me$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4 (**C**OO), 131.2 ($(CH_3)_2$**C**), 124.7 (=**C**HCH_2), 87.7 (**C**H, THF), 85.6 (**C**CH_2OH, THF), 76.8 (**C**OSiMe_3), 66.6 (**C**H_2OSiMe_3), 52.0 (O**C**H_3), 40.5 (**C**H_2COH), 31.8 (**C**H_2, THF), 25.7 (**C**H_3), 25.4 (**C**H_2, THF), 22.9 (**C**H_3), 22.4 (**C**H_2CH=C), 17.6 (**C**H_3), 2.63 (3C, COSi**Me$_3$**), –0.52 (3C, CH_2OSi**Me$_3$**)

LRMS (ESI$^+$) m/z: 453 ([M+Na]$^+$) Da.

HRMS (ESI$^+$) m/z: Calculated: 453.2463; Found: 453.2459 ([M+Na]$^+$) Da.

Methyl (6*Z*)-7,11-dimethyl-3-oxo-6, 10-dodecadienoate (2.42).



$C_{15}H_{24}O_3$
Mol. wt. 252.35 g/mol
(Pale yellow oil)

To an ice-cooled suspension of NaH (71.7 mg, 60% in mineral oil, 1.82 mmol) in dry THF (1.8 mL) was added dropwise methyl acetoacetate (197 µL, 1.82 mmol). After 10 min, ^{n}BuLi (1.02 mL, 1.78M in hexanes, 1.82 mmol) was added and the mixture was stirred for a further 15 min. A solution of neryl chloride (**2.1**, 300 mg, 1.74 mmol) in dry THF (300 µL) was added to the reaction and the orange mixture was allowed to warm to room temperature. After 30 min a solution of aqueous HCl (2.0N, 2.5 mL) and Et_2O (3.0 mL) was added. The aqueous phase was re-extracted with Et_2O (3 x 3 mL). The organic layers were combined, washed with brine (25 mL), sat. $KHCO_3$ aq. (8 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo* to afford the crude product as a yellow oil. The crude product was purified by column chromatography (SiO_2) eluting (15 to 20%) gave the title *β*-ketoester **2.42** as a yellow oil (243 mg, 0.963 mmol, 55%). Spectroscopic data are in agreement with the literature.[12]

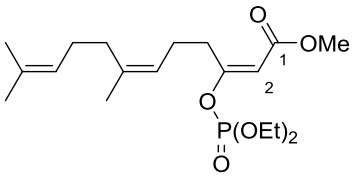
FT-IR ν_{max}: 2964 (m), 2918 (m), 2857 (w), 1747 (s), 1717 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.10-5.05 (2H, m, 2 x C=C**H**), 3.73 (3H, s, OC**H$_3$**), 3.44 (2H, s, C**H$_2$**$COOCH_3$), 2.55 (2H, t, *J* = 7.6 Hz, C**H$_2$**CO), 2.28 (2H, q, *J* = 7.6 Hz, C**H$_2$**CH_2CO), 2.05-2.04 (4H, m, 2 x C**H$_2$**), 1.68 (6H, s, 2 x C**H$_3$**), 1.61 (3H, s, C**H$_3$**) ppm.

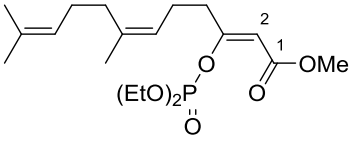
^{13}C NMR (100 MHz, $CDCl_3$): δ 202.31 (**C**OCH_2), 167.57 (**C**$OOCH_3$), 136.85 (CH_3**C**), 131.68 (Me_2**C**), 124.08 (Me_2C=**C**H), 122.82, ((CH_3)CH_2C=**C**H), 52.27 (COO**C**H_3), 49.05 (**C**H_2COOCH_3), 43.28 (**C**H_2COCH_2), 31.84 (**C**H_2CCH_3), 26.43 (**C**H_2CH_2CO), 25.66 (**C**H_2CH_2), 23.30 (**C**H_3), 21.94 (**C**H_3), 17.60 (**C**H_3) ppm.

LRMS (ESI^{+}) m/z: 253 ($[M+Na]^{+}$)Da.

Methyl (2*E*,6*Z*)-3-[(diethoxyphosphoryl)oxy]-7,11-dimethyl-2,6,10-dodecatrienoate (2.43) and Methyl (2*Z*, 6*Z*)-3-[(diethoxyphosphoryl)oxy]-7,11-dimethyl-2,6,10-dodecatrienoate (2.44)



2.43 Major **(**Golden yellow oil)



2.44 Minor (Yellow oil)

$C_{19}H_{33}O_6P$
Mol. wt. 388.44 g/mol

To an ice-cooled solution of DMAP (314 mg, 2.57 mmol) and Et_3N (6.50 mL, 46.8 mmol) in DMPU (46 mL) was added a solution of *β*-keto ester **2.42** (5.90 g, 23.38 mmol) in DMPU (6.6 mL). After 40 min, the mixture was cooled to –20 °C and $(EtO)_2POCl$ (5.20 mL, 35.07 mmol) was added dropwise (**Note**: A strong magnetic stirring was required as the reaction mixture became viscous after the addition of $(EtO)_2POCl$). The reaction mixture was allowed to warm to rt and stirred for 22 h. The mixture was diluted with Et_2O (130 mL) and acidified with aqueous HCl (2.0N, 50 mL). The aqueous layer was re-extracted with Et_2O (2 x 130 mL) and the combined organic layers were washed with sat. aq. $CuSO_4$ solution (2 x 35 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a crude product as an orange oil. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/hexane (10 to 30%) to give the title 2*E* isomer **2.43** as a bright yellow oil (8.1 g, 20.85 mmol, 89%) along with 2*Z*-isomer **2.44** as a yellow oil (421 mg, 1.09 mmol, 5%). Spectroscopic data are in agreement with the literature.[12]

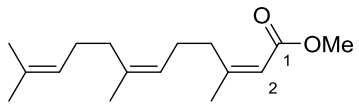
FT-IR ν_{max} (neat): 2985 (m), 2915 (m), 2860 (w), 1720 (s), 1645 (s), 1438 (w), 1028 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.86 (1H, s, C=C**H**COO), 5.17-5.10 (2H, m, 2 x C=C**H**CH_2), 4.20 (4H, quin, *J* = 7.4 Hz, POC**H$_2$**), 3.70 (3H, s, OC**H$_3$**), 2.82 (2H, t, *J* = 7.8 Hz, C**H$_2$**), 2.28 (2H, q, *J* = 7.4 Hz, C**H$_2$**), 2.05 (4H, br. s, 2 x C**H$_2$**), 1.68 (6H, s, 2 x C**H$_3$**), 1.61 (3H, s, C**H$_3$**), 1.35 (6H, t, *J* = 7.4, $POCH_2C$**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.54 (**C**$OOCH_3$), 166.47 (**C**OP), 136.63 (CH_3**C**), 131.57 (Me_2**C**), 124.22 (Me_2C=**C**H), 123.20 (CH_3)C=**C**H), 104.95 (**C**HCOO), 64.79 (d, *J* = 5.9 Hz, PO**C**H_2), 64.72 (PO**C**H_2), 51.24 (O**C**H_3), 32.10 (**C**$H_2C(CH_3)$, 32.02 (**C**H_2COP), 26.57 (**C**H_2CH_2), 25.66 (**C**H_3), 25.21 (**C**H_3), 23.35 (**C**H_2CH_2COP), 17.60 (**C**H_3), 16.07 (d, *J* = 5.9 Hz, $POCH_2$**C**H_3), 16.02 (OCH_2**C**H_3) ppm.

LRMS (ESI$^+$) m/z: 777 ($[2M+H]^+$)Da.

Methyl (2Z, 6Z)-3,7,11-trimethyl-2,6,10-dodecatrienoate (**1.59)**



$C_{16}H_{26}O_2$
Mol. wt. 250.38 g/mol
(Yellow oil)

To a suspension of CuI (277 mg, 1.45 mmol) in THF (2.7 mL) was added dropwise MeLi.LiBr complex (1.10 mL, 1.3M in Et_2O, 1.45 mmol) at 0 °C. The resultant orange mixture was stirred at 0 ˚C for 15 min, before cooling to –35 °C. MeMgCl (970 µL, 2.5M in THF, 2.420 mmol) was added dropwise while keeping the temperature at –35 °C. After 30 min, the resulting light brown suspension was treated with a solution of enol phosphate **2.43** (188 mg, 0.484 mmol) in THF (400 µL), and the mixture stirred at –35 °C for 1.5 h, then quenched by pouring rapidly onto ice-cold sat. NH_4Cl aq. (2.5 mL). The mixture was diluted with Et_2O (20 mL) and the organic layer was separated, washed with sat. NH_4Cl aq. (5.0 mL), brine (2 x 4 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a crude product as a yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with (100% hexane and then 3% EtOAc/hexane) to give the title trienoate **1.59** as a yellow oil with 100% stereoselectivity (101 mg, 0.403 mmol, 83%). Spectroscopic data are in agreement with that reported in the literature.[12]

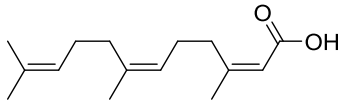
FT-IR ν_{max} (neat): 2986 (m), 2916 (m), 2856 (w), 1720 (s), 1647 (m), 1437(m), 1161 (s), 1149 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.66 (1H, s, C=C**H**COO), 5.19-5.09 (2H, m, 2 x =C**H**CH_2), 3.67 (3H, s, OC**H$_3$**), 2.64 (2H, t, *J* = 7.7 Hz, C**H$_2$**), 2.20-2.13 (2H, m, C**H$_2$**), 2.05-2.04 (4H, m, 2 x C**H$_2$**), 1.89 (3H, d, *J* = 1.5 Hz, C**H$_3$**C=CHCOO), 1.69 (6H, s, 2 x C**H$_3$**), 1.61 (3H, s, C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7 (**C**=O), 160.4 (**C**=CHCOO), 135.8 (CH_3**C**), 131.5 ((CH_3)$_2$**C**), 124.4 (Me_2C=**C**H), 124.3 (CH_3)CH_2C=**C**H), 115.8 (**C**HCOO), 50.7 (O**C**H_3), 33.7 (**C**H_2C(CH_3), 31.9 (**C**H_2C(CH_3), 26.6 (2 x **C**H_2CH_2), 25.7 (**C**H_3), 25.4(**C**H_3), 23.3 (**C**H_3), 17.6 (**C**H_3) ppm.

LRMS (ESI$^+$) m/z: 251 ($[M+H]^+$) Da.

(2*Z*, 6*Z*)-3,7,11-Trimetryl-2,6,10-dodecatrienoic acid (2.47)



$C_{15}H_{24}O_2$
Mol. wt. 236.35 g/mol
(Yellow oil)

At room temperature, a solution of NaOH (3.00 g, 75.3 mmol) and $NaHCO_3$ (3.20 g, 38.2 mmol) in water (68 mL) was added to a solution of trienoate **2.47** (2.90 g, 11.5 mmol) in MeOH (47 mL). The resulting solution was heated to reflux and stirred for 7 h. The reaction was cooled at 0 ºC, washed with hexane (20 mL) and acidified with HCl (6.2M, pH 2) while keeping the temperature at 0 ºC. The methanol was evaporated and the resultant residue was dissolved in ether (100 mL) and water (40 mL). The organic layer was separated; the aqueous layer was re-extracted with ether (3 × 50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product as a brownish yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/ hexane (5 to 30%) to give the title trienoic acid **2.47** as a yellow oil (1.9 g, 7.87 mmol, 70%). Spectroscopic data are in agreement with that reported in the literature.[12]

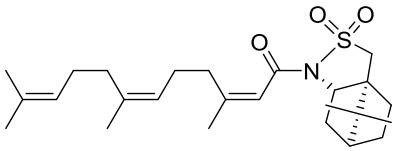
FT-IR ν_{max} (neat): 2964 (m), 2917 (m), 2856 (m), 1688 (s), 1640 (s), 1440 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.69 (1H, s, C=C**H**COO), 5.19-5.14 (2H, m 2 x C=C**H**CH_2), 2.66 (2H, t, *J* = 7.8 Hz, C**H$_2$**), 2.22-2.14 (2H, m, C**H$_2$**), 2.05 (4H, s, 2 x C**H$_2$**), 1.93 (3H, d, *J* = 1.5 Hz C**H$_3$**C=CHCOO), 1.70-1.69 (6H, s, 2 x C**H$_3$**), 1.62 (3H, s, C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4 (**C**OOH), 163.4 (**C=**CHCOO), 136.0 (CH_3**C**), 131.5 (Me_2**C**), 124.9 (Me_2C=**C**H), 124.2 (CH_3)CH_2C=**C**H), 115.7 (**C**HCOO), 33.9 (**C**H_2C(CH_3), 31.9 (**C**H_2C(CH_3), 26.6 (2 x **C**H_2CH_2), 25.7 (2 x **C**H_3), 23.4 (**C**H_3), 17.6 (**C**H_3) ppm.

LRMS (ESI$^+$) m/z: 237 ($[M+H]^+$) Da.

***N*-((*2Z,6Z*)-3,7,11-Trimethyl- 2,6,10- dodecatrienoyl)-(2*S*)-camphor-10,2-sultam (1.60)**



$C_{25}H_{39}NO_3S$
Mol. wt. 433.65 g/mol
(Yellow oil)

According to the method of Liddle *et al.*,[98] to a dispersion of NaH (372 mg, 60% in meniral oil, 9.31 mmol), in dry toluene (15 mL) at 0 °C, a solution of (2*S*)-10,2-camphorsultam ((+)-**2.52**), 1.15 g, 5.35 mmol) in dry toluene (13.2 mL) was added dropwise and the resulting mixture was stirred at rt for 1 h.

To a solution of acid **2.47** (1.10 g, 4.65 mmol) in CH_2Cl_2 (26 mL) was added DMF (200 µL), followed by the dropwise addition of oxalyl chloride (2.00 mL, 23.3 mmol). Evolution of gas was observed, the reaction was stirred for 2 h at rt, evaporated to dryness and the resulting residue was dissolved in dry toluene (3.2 mL). This solution was added dropwise to the pre-formed sodium salt of (2*S*)-10,2-camphorsultam ((+)-**2.52)** in toluene at 0 °C. The resulting mixture was allowed to warm to rt and was stirred for 6 h. The reaction was quenched by pouring in sat. aq. NH_4Cl (15 mL) and diluted with EtOAc (15 mL). The organic pase was separated and aqueous phase was re-extracted with EtOAc (5 × 20 mL). The combined organic phases were washed with brine (2 x 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product as a yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/ hexane (5 to 10%) to give the title trienamide **1.60** as a yellow oil (970 mg, 2.70 mmol, 48%). Spectroscopic data are in agreement with the literature.[12]

FT-IR ν_{max} (neat): 2959 (m), 2915 (m), 2857 (w), 1677 (s), 1630 (m), 1534 (w), 1449 (m), 1327 (s), 1266 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.32 (1H, s, =C**H**CON), 5.16-5.09 (2H, m, 2 x =C**H**), 3.91 (1H, t, *J* = 6.2 Hz, C**H**N), 3.46 (1H, d, *J* = 13.9 Hz, C**H**HSO$_2$), 3.43 (1H, d, *J* = 13.9 Hz, CH**H**SO$_2$), 2.66-2.51 (2H, m, C**H$_2$**), 2.22-2.03 (8H, m, 4 x C**H$_2$**), 1.95 (3H, s, C**H$_3$**C=CHCON), 1.94-1.86 (3H, m, C**H$_3$**), 1.68 (6H, s, 2 × C**H$_3$**), 1.60 (3H, s, C**H$_3$**), 1.44-1.37 (2H, m, C**H$_2$**CH$_2$S), 1.18 (3H, s, C**H$_3$**), 0.97 (3H, s, C**H$_3$**) ppm.

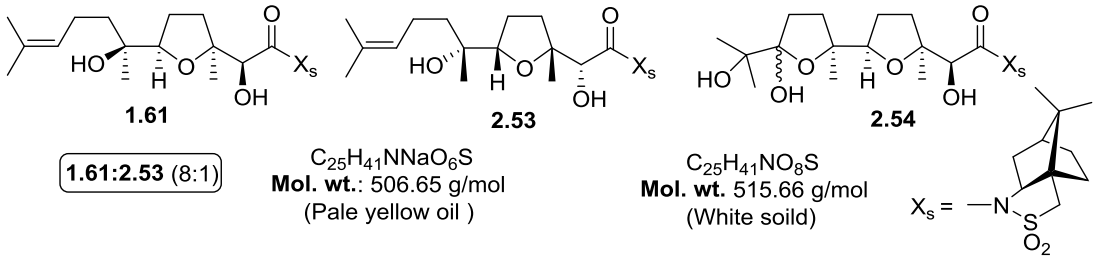
^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9 (**C**ON), 162.8 (**C**=CHCON), 135.8 (CH$_3$**C**), 131.4 (Me$_2$**C**), 124.4 (Me$_2$C=**C**H) and (CH$_3$)CH$_2$C=**C**H), 116.1 (**C**HCON), 65.1

(**C**HN), 53.2 (**C**CH_2SO_2), 48.1 (**C**H_2SO_2), 47.7 (**C**Me_2), 44.7 (**C**HCMe_2), 38.7 (**C**H_2CHN), 34.8 (**C**$H_2CH_2CCH_2S$), 32.9 (**C**H_2CCH_2S), 31.9 (**C**$H_2C(CH_3)$, 26.6 (**C**$H_2C(CH_3)$, 26.6 (**C**H_2CH_2), 26.5 (**C**H_2CH_2), 25.9 (**C**H_3), 25.7 (**C**H_3), 23.3 (**C**H_3), 20.9 (**C**H_3), 19.9 (**C**H_3), 17.6 (**C**H_3) ppm.

LRMS (ESI$^+$) m/z:456 ($[M+Na]^+$) Da.

***N*-[(*S*)-2-((2*S*,5*R*)-Tetrahydro-5-((*S*)-2-hydroxy-6-methylhept-5en-2-yl)-2-methylfuran-2-yl)]-2-hydroxy-(2*S*)-10,2-camphorsultam (1.61) and**

***N*-[(*R*)-2-((2*R*,5*S*)-Tetrahydro-5-((*R*)-2-hydroxy-6-methylhept-5en-2-yl)-2-methylfuran-2-yl)]-2-hydroxy-(2*S*)-10,2-camphorsultam (2.53)**



To a vigorously stirred mixture of trienamide **1.60** (1.52 g, 3.51 mmol) and phosphate buffer (15.3 mL) in acetone (111 mL) at –21 °C was added a solution of $NaMnO_4$ (13.1 mL, 0.4M aq., 5.26 mmol) containing AcOH (705 µL, 12.27 mmol). The purple mixture was stirred rapidly for 1.5 h during which time the temperature in acetone bath was raised to –7 °C and the reaction mixture had turned to dark brown. At this, the reaction was quenched with sat. aq. $Na_2S_2O_5$ (200 mL) to dissolve all of the precipitated manganese salt. The mixture was diluted with brine (50 mL) and EtOAc (150 mL) and the organic phase was separated. The aqueous phase was re-extracted using EtOAc (4 x 150 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product as a yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/hexane (5 to 20%) to afford the major diastereoisomer, THF diol **1.61** as a pale yellow oil (695 mg, 1.44 mmol, 41%) and minor diastereoisomer, THF diol **2.53** as a pale yellow oil (65 mg, 0.13 mmol, 4%). Lactol **2.54** was isolated as a white solid (208 mg, 0.40 mmol, 12%). The starting material **1.60** was also recovered as a pale yellow oil (184 mg, 0.42 mmol, 12%). Spectroscopic and analytic data were in agreement with the literature.[12]

Spectroscopic data for **1.61**:

FT-IR ν_{max} (neat): 3514 (br), 2965 (m), 2920 (w), 2877(w), 1697 (m), 1453 (m), 1330 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.10 (1H, t, *J* = 7.0 Hz, C=C**H**), 4.63 (1H, s, C**H**OH), 3.92 (1H, dd, *J* = 7.3 and 5.1 Hz, C**H**N), 3.85 (1H, t, *J* = 7.1 Hz, C**H**, THF ring), 3.79 (1H, br, O**H**), 3.55 (1H, d, *J* = 13.7 Hz, C**H**HSO_2), 3.46 (1H, d, *J* = 13.7 Hz, CH**H**SO_2), 3.15 (1H, br, O**H**), 2.30-2.00 (6H, m, C$\mathbf{H_2}$), 1.96-1.74 (5H, m, C$\mathbf{H_2}$), 1.68 (3H, s, C$\mathbf{H_3}$), 1.61 (3H, s, C$\mathbf{H_3}$), 1.50-1.32 (4H, m, C$\mathbf{H_2}$), 1.29 (6H, s, C$\mathbf{H_3}$), 1.26 (3H, s, C$\mathbf{H_3}$), 1.18 (3H, s, C$\mathbf{H_3}$), 0.96 (3H, s, C$\mathbf{H_3}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1 (**C**ON), 131.6 (Me_2**C**), 124.5 (C=**C**H), 83.87 (**C**H, THF), 83.8 (**C**OH), 75.5 (**C**HOH), 73.4 (**C**CH_3, THF ring), 65.2 (**C**HN), 53.0 (**C**H_2SO_2), 48.7 (**C**CH_2SO_2), 47.8 (**C**$HCMe_2$), 44.5 (**C**Me_2), 38.3 (**C**H_2CHN), 38.1 (**C**$H_2CH_2CCH_2S$), 33.2 (**C**H_2, THF ring), 32.8 (**C**H_2CCH_2S), 26.4 (**C**H_2. THF ring), 26.0 (**C**H_2), 25.7(**C**H_3), 24.4 (**C**H_3), 24.1 (**C**H_3), 22.2 (**C**H_2CH=C), 20.8 (**C**H_3), 19.8 (**C**H_3), 17.6 (**C**H_3) ppm.

LRMS (ESI$^+$) m/z: 538 $[M+Na]^+$) Da.

Spectroscopic data for **2.53**:

FT-IR ν_{max} (neat): 3523 (br), 2964 (m), 2937(w), 2883 (w), 1698 (m), 1456 (m), 1329 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.09 (1H, m, C=C**H**), 4.65 (1H, s, C**H**OH), 3.96 (1H, dd, *J* = 7.8 and 4.8 Hz, C**H**N), 3.80 (1H, dd, *J* = 8.2, 6.6 Hz, C**H**, THF ring), 3.54 (1H, m, C**H**HSO_2), 3.49 (1H, m, CH**H**SO_2), 3.46 (1H, m, O**H**), 2.33-1.84 (11H, m, C$\mathbf{H_2}$), 1.68 (3H, s, C$\mathbf{H_3}$), 1.61 (3H, s, C$\mathbf{H_3}$), 1.53-1.29 (4H, m, C$\mathbf{H_2}$**),** 1.25 (3H, s, C$\mathbf{H_3}$), 1.24 (3H, s, C$\mathbf{H_3}$), 1.22 (3H, s, C$\mathbf{H_3}$), 0.97 (3H, s, C$\mathbf{H_3}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9 (**C**ON), 131.5 (Me_2**C**), 124.5(C=C**H**), 84.7 (**C**H, THF ring), 84.4 (**C**OH), 75.6 (**C**CH_3, THF ring), 72.4 (**C**HOH), 65.4 (**C**HN), 53.1 (**C**H_2SO_2), 48.3 (**C**CH_2SO_2), 47.7 (**C**$HCMe_2$), 44.7 (**C**Me_2), 38.4 (**C**H_2CHN), 38.3 (**C**$H_2CH_2CCH_2S$), 34.5 (**C**H_2, THF ring), 32.9 (**C**H_2CCH_2S), 26.4 (**C**H_2, THF ring), 25.6 (**C**H_2), 25.3 (**C**H_3), 24.4 (**C**H_3), 22.9 (**C**H_3), 22.2 (**C**H_2CH=C), 21.0 (**C**H_3), 19.8 (**C**H_3), 17.6 (**C**H_3) ppm.

Spectroscopic data for **2.54**:

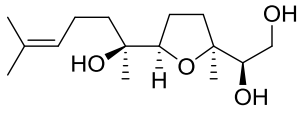
FT-IR ν_{max} (neat): 3509 (br), 2964 (m), 2937 (w), 2883 (w), 1692 (m), 1455 (w), 1332 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.55 (1H, d, *J* = 4.4 Hz C**H**OH), 4.23(1H, s, O**H**), 4.01 (1H, t, *J* = 7.3 Hz, C**H**N), 3.93 (1H, m, C**H**, THF), 3.57-3.41 (2H, m, 2 x O**H**), 3.53 (1H, d, *J* = 13.7 Hz, CH**H**SO_2), 3.45 (1H, d, *J* = 13.7 Hz, CH**H**SO_2), 2.44-2.03 (8H, m, C$\mathbf{H_2}$), 1.96-1.30 (4H, m, C$\mathbf{H_2}$), 1.34 (3H, s, C$\mathbf{H_3}$), 1.27 (3H, s, C$\mathbf{H_3}$), 1.26-1.16 (3H, m, C**H** and C$\mathbf{H_2}$), 1.26 (3H, s, C$\mathbf{H_3}$), 1.20 (3H, s, C$\mathbf{H_3}$), 1.17 (3H, s, C$\mathbf{H_3}$), 0.98 (3H, s, C$\mathbf{H_3}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6 (**C**ON), 109.3 (**C**OH, THF ring), 86.7 (**C**OH, THF ring), 84.1 (**C**H, THF ring), 82.95 (**C**HOH), 75.4 (**C**CH_3, THF ring), 73.6 (**C**CH_3, THF ring), (**C**OH, THF ring), 65.3(**C**HN), 53.2 (**C**H_2SO_2), 48.7 (**C**CH_2SO_2), 47.8 (**C**$HC(CH_3)_2$, 44.6 (**C**Me_2), 38.2 (**C**H_2CHN), 33.6 (**C**$H_2CH_2CCH_2S$), 32.9 (**C**H_2), 30.0 (**C**H_2CCH_2S), 29.7 (**C**H_2), 27.8 (**C**H_2), 26.4 (**C**H_2), 24.8 (**C**H_3), 24.6 (**C**H_3), 24.0 (**C**H_3), 23.8 (**C**H_3), 20.8 (**C**H_3), 19.6 (**C**H_3) ppm.

LRMS (ESI$^+$) m/z: 989 $[2M+Na]^+$), 484 $[M+H]^+$) Da.

(*R*)-1-((2*S*,5*R*)-Tetrahydro-5-((*S*)-2-hydroxy-6-methylhept-5en-2-yl)-2-methylfuran-2-yl)ethane-1,2-diol (1.42)



$C_{15}H_{28}O_4$
Mol. wt.: 272.38 g/mol
(Yello oil)

To a stirrerd solution of *cis*-THF diol **1.60** (597 mg, 1.23 mmol) in THF:H_2O (25:1, 4.9 mL) was added $NaBH_4$ (94.0 mg, 2.48 mmol) at –10 °C and the mixture was allowed to warm to rt and was stirred for 5 h whereupon the reaction mixture was quenched by adding HCl (2.0N, 1.8 mL) and diluted with EtOAc (20 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product as a pale yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/hexane (50 to 100%) to give the title THF triol **1.42** as a yellow oil (215 mg, 0.789 mmol, 64%) and (2*S*)-10,2-camphorsultam

((+)-**2.52**) as a white solid (119 mg, 0.924 mmol, 75%). Spectroscopic and analytic data were in agreement with the literature.[12]

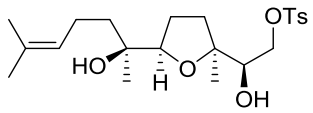
FT-IR ν_{max} (neat): 3364 (br), 2972 (w), 2937 (w), 2870 (w), 1452 (w), 1376 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.11 (1H, t, *J* = 7.0 Hz, C=C**H**), 3.83 (1H, t, *J* = 7.3 Hz, C**H**O, THF), 3.71 (2H, m, C$\mathbf{H_2}$OH), 3.54 (1H, m, C**H**OH), 2.48 (2H, br, 2 x O**H**), 2.17-1.89 (6H, m, O**H**, C$\mathbf{H_2}$), 1.69 (3H, s, C$\mathbf{H_3}$), 1.62 (3H, s, C$\mathbf{H_3}$), 1.59-1.34 (4H, m, C$\mathbf{H_2}$), 1.28 (3H, s, C$\mathbf{H_3}$), 1.19 (3H, s, C$\mathbf{H_3}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 132.0 (Me_2**C**), 124.2 (C=**C**H), 84.6 (**C**H, THF), 83.8 (**C**HOH), 76.7(**C**OH), 74.0 (**C**CH_3, THF), 63.3 (**C**H_2OH), 38.5 (**C**H_2COH), 32.6 (**C**H_2, THF), 26.3 (**C**H_2CH=C), 25.7 (**C**H_3), 24.2 (**C**H_3), 23.7 (**C**H_3), 22.3 (**C**H_2CH=C), 17.6 (**C**H_3) ppm.

LRMS (ESI^+) m/z: 295 ($[M+Na]^+$) Da.

(2*R*)-2-hydroxy-2-{(2*S*,5*R*)-5-[(1*S*)-1-hydroxy-1,5-dimethyl-4-hexenyl]-tetrahydro-2-furanyl}-ethyl-4-methyl-1-benzenesulfonate (2.56)



$C_{22}H_{34}O_6S$
Mol. wt. 426.57 g/mol
(Yellow oil)

To the solution of THF triol **1.42** (215 mg, 0.79 mmol) in anhydrous benzene (18 mL) was added Bu_2SnO (236 mg, 0.95 mmol) and the mixture was heated to reflux (oil bath temperature 95 °C) for 3 h. The reaction was cooled to room temperature using a water bath, then TsCl (196 mg, 1.03 mmol) and TBAB (127 mg, 0.39 mmol) were added and the reaction was stirred for 23 h. The reaction mixture was concentrated *in vacuo* to afford the crude product as yellow oil. The crude was purified by column chromatography (SiO_2) eluting with EtOAc/hexane (20 to 50%) to give the title tosylate **2.56** as a yellow oil (278 mg, 0.652 mmol, 83%). Spectroscopic and analytic data were in agreement with the literature.[12]

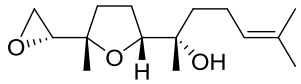
FT-IR ν_{max} (neat): 3404 (br, w), 2973 (m), 2931 (m), 2882 (w), 1454 (w), 1176 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (2H, d, *J* = 7.8 Hz, 2 x SCC**H**, Ar), 7.34 (2H, d, *J* = 7.8 Hz, 2 x SCCHC**H**, Ar), 5.10 (1H, t, *J* = 7.0 Hz, C=C**H**), 4.24 (1H, dd, *J* = 10.5 and 2.7 Hz, C**H**OH), 3.99 (2H, dd, *J* = 10.5 and 7.4 Hz, C**H$_2$**OS), 3.81 (1H, m, C**H**O, THF ring), 3.34 (1H, s, O**H**), 2.45 (3H, s, C**H$_3$**, Ar), 2.17-1.83 (7H, m, C**H$_2$**, O**H** and 2 x C**H$_2$**, THF), 1.69 (3H, s, C**H$_3$**), 1.62 (3H, s, C**H$_3$**), 1.48-1.26 (2H, m, C**H$_2$**), 1.21 (3H, s, C**H$_3$**), 1.15 (3H, s, C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.9 (**C**CH_3, Ar), 132.8 (Me_2**C**), 132.0 (**C**S, Ar), 129.9 (2 x **C**HCS, Ar), 127.9 (2 x **C**HCHCS, Ar), 124.2 (C=**C**H), 84.4 (**C**OH), 83.8 (**C**HOH), 75.0 (**C**HO, THF ring), 73.6 (**C**CH_3, THF ring), 71.6 (**C**H_2OS), 38.2 (**C**H_2COH), 33.4 (**C**H_2, THF ring), 26.1 (**C**H_2, THF ring), 25.7 (**C**H_3), 24.0 (**C**H_3), 23.0 (**C**H_3), 22.2 (**C**H_2CH=C), 21.6 (**C**H_3), 17.6 (**C**H_3) ppm.

LRMS (ESI$^+$) m/z: 427 ($[M+H]^+$) Da.

(*S*)-2-((2*R*,5*S*)-Tetrahydro-5-methyl-5-((*R*)-oxiran-2-yl)-furan-2-yl)-6-methylhept-5-en-2-ol (1.53)



$C_{15}H_{26}O_3$
Mol. wt. 254.37 g/mol
(Pale yellow oil)

At room temperature, a solution of tosylate **2.56** (309 mg, 0.72 mmol) in dry MeOH (7.4 mL) was stirred with anhydrous K_2CO_3 (113 mg, 0.82 mmol) at room temperature for 2 h, during which time, the reaction mixture was turned milky in appearance. The methanol was removed *in vacuo* and the resultant residue was dissolved in water (5.0 mL) and Et_2O (10 mL). The organic phase was separated and the aqueous phase was re-extracted with Et_2O (3 x 15 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a crude product as a yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/hexane (30%) to give the title epoxide **1.53** as a pale yellow oil (176 mg, 0.692 mmol, 96%). Spectroscopic and analytic data were in agreement with the literature.[12,5]

$[\alpha]^{19.5}_D$: +8.0 (*c* 1.03, $CHCl_3$), {lit. $[\alpha]^{19.8}_D$ = +8.4 (*c* 0.61, $CHCl_3$), +9.98 (*c* 1.15, $CHCl_3$)}.[12,5]

FT-IR ν_{max} (neat): 3477 (br), 2970 (s), 2927 (m), 2873(w), 1451 (m), 1372 (s) cm^{-1}.

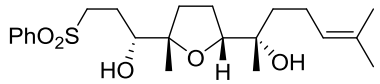
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.11 (1H, t, *J* = 7.0 Hz, =C**H**CH_2), 3.85 (1H, t, *J* = 7.1 Hz, C**H**O, THF ring), 3.07 (1H, dd, *J* = 4.3 and 2.7 Hz, C**H**HO), 2.76 (1H, t, *J* = 4.5 Hz, C**H**CH_2), 2.60 (1H, dd, *J* = 4.8 and 2.7 Hz, C**H**HO), 2.13-1.77 (5H, m, 2 x C**H_2**, THF ring and O**H**), 1.67 (3H, s, C**H_3**), 1.61 (3H, s, C**H_3**), 1.58-1.31 (4H, m, 2 x C**H_2**), 1.23 (3H, s, C**H_3**), 1.21 (3H, s, C**H_3**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 131.5 (Me_2**C**), 124.6 (Me_2C=**C**), 84.9 (**C**HO, THF ring), 81.7 (**C**OH), 73.1 (**C**CH_3, THF ring), 56.4 (**C**HCH_2), 44.6 (**C**H_2O), 37.5 (**C**H_2COH), 32.6 (**C**H_2, THF ring), 26.0 (**C**H_2, THF ring), 25.7 (**C**H_3), 23.9 (**C**H_3), 23.4 (**C**H_3), 22.1 (**C**H_2CH=C), 17.6 (**C**H_3) ppm.

LRMS (ESI^+) m/z: 277 ($[M+Na]^+$) Da.

HRMS (ESI^+) m/z: Calculated: 277.1774; Found: 277.1776 ($[M+Na]^+$) Da.

(*S*)-2-((2*R*,5*S*)-5-((*R*)-1-Hydroxy-3-(phenylsulfonyl)propyl)-5-methyltetrahydrofuran-2-yl)-6-methylhept-5-en-2-ol (1.189)



$C_{22}H_{34}O_5S$
Mol. wt: 410.57 g/mol
(Yellow oil)

To a solution of $MeSO_2Ph$ (276 mg, 1.73 mmol) and DMPU (84 µL) in THF at –78 °C was added dropwise ^{n}BuLi (726 µL, 2.38M in hexane, 1.73 mmol). The mixture was stirred at this temperature for 30 min, then a solution of the epoxide **1.53** (176 mg, 0.692 mmol) in THF (700 µL) was added dropwise at –78 °C. The mixture was stirred at (–30 to –25 °C) for 6 h. The reaction was quenched with sat. aq. NH_4Cl (1.5 mL) and the mixture was diluted with EtOAc (7.0 mL). The organic phase was separated and the aqueous phase was re-extracted with EtOAc (2 x 20 mL), and the combined organic phases were dried ($MgSO_4$), filtered and concentrated in *vacuo* to afford the crude product as a yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with toluene/EtOAc (5/1) to give the title sulfone **1.189** as a yellow oil (200 mg, 0.49 mmol, 70%). Spectroscopic and analytic data were in agreement with the literature.[5]

$[\alpha]^{24}_{D}$: + 19.0 (*c* 1.33, $CHCl_3$), {lit. $[\alpha]^{19.7}_{D}$ = +17.95 (*c* 1.70, $CHCl_3$)}.[5]

FT-IR ν_{max} (neat): 3505 (br), 2967 (m), 2930 (w), 2873(w), 1445 (m), 1303 (m) cm^{-1}.

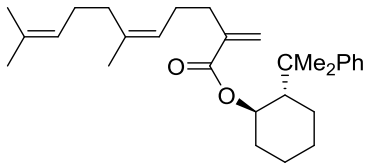
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (2H, d, *J* = 7.6 Hz, 2 x C**H**, Ar), 7.67 (1H, m, C**H**, Ar), 7.58 (2H, t, *J* = 7.7 Hz, 2 x C**H**, Ar), 5.10 (1H, br t, *J* = 7.0 Hz, C=C**H**), 3.83 (1H, t, *J* = 7.5 Hz, C**H**, THF ring), 3.69 (1H, br s, O**H**), 3.60 (1H, dd, *J* = 11.0 and 2.3 Hz, C**H**OH), 3.44 (1H, ddd, 14.1, 10.7 and 5.1 Hz, C**H**HSO$_2$), 3.16 (1H, ddd, 14.1, 10.7 and 5.1 Hz, CH**H**SO$_2$), 2.15-1.87 (7H, m, OH, 3 x C**H$_2$**), 1.68 (3H, s, C**H$_3$**), 1.62 (3H, s, C**H**$_3$), 1.55-1.34 (4H, m, 2 x C**H**$_2$), 1.26 (3H, s, C**H$_3$**), 1.16 (3H, s, C**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 139. (C**H**, Ar), 133.6 (C**H**, Ar), 132.4 (Me$_2$**C**), 129.3 (2 x C**H**, Ar), 127.9 (2 x C**H**, Ar), 124.1 (C=**C**H), 85.9 (**C**OH), 83.9 (**C**HO, THF ring), 75.7 (CHOH), 74.3 (**C**CH$_3$, THF), 53.9 (**C**H$_2$SO$_2$), 38.4 (**C**H$_2$COH), 31.4 (**C**H$_2$, THF ring), 26.6 (**C**H$_2$CH$_2$SO$_2$), 25.7 (**C**H$_2$, THF ring), 25.1 (**C**H$_3$), 24.1 (**C**H$_3$), 23.8 (**C**H$_3$), 22.2 (**C**H$_2$CH=C), 17.7 (**C**H$_3$) ppm.

LRMS (ESI$^+$) m/z: 433 [M+Na]$^+$) Da.

HRMS (ESI$^+$) m/z: Calculated: 433.2019; Found: 433.2020 ([M+Na]$^+$) Da.

(*Z*)-(1*R*,2*S*)-2-(2-Phenylpropan-2-yl)cyclohexyl-6,10-dimethyl-2-methyleneundeca-5,9-dienoate (2.124)



$C_{29}H_{42}O_2$
Mol. wt. 422.64 g/mol
(Yellow oil)

Using a procedure described by the Brown group,[12] to a solution of (–)(1*R*,2*S*)-TCC (*ee*: 97%) (500 mg, 2.29 mmol) in THF (14 mL) at –20 ^{o}C, was added NaHMDS (2.40 mL, 1.0M in THF, 2.40 mmol). The mixture was allowed to warm to –5 ^{o}C over 2 h, then a solution of PFP ester **2.20** (850 mg, 2.19 mmol) in dry THF (2.8 mL) was added dropwise at –5 ^{o}C. The cooling bath was removed and the mixture was stirred for 30 min at rt; then the solution was heated at reflux for 15 h. Et_2O (15 mL) and then sat. aq. NH_4Cl (8 mL) were added to the mixture. The organic phase was separated, washed with $NaHCO_3$ (2 x 12 mL), dried ($MgSO_4$), filtrated and concentrated *in vacuo* to afford the crude product as a brown oil. The crude product was purified by column chromatography (SiO_2) eluting with CH_2Cl_2/ hexane (0% to 25%) to give the title trienoate TCC **2.124** as a yellow oil (460 mg, 1.09 mmol, 50%).

$[\alpha]^{27}_{D}$: –1.2 (*c* 1.78, $CHCl_3$).

FT-IR ν_{max} (neat): 2962 (w), 2928 (m), 2858(w), 1707(s) cm^{-1}.

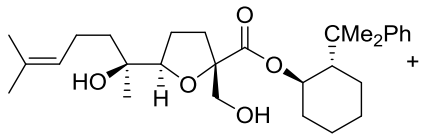
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.09 (5H, m, Ar), 5.71 (1H, s, C=C**H**H), 5.30 (1H, s, C=CH**H**), 5.14-5.10 (2H, m, 2 x =C**H**CH_2), 4.90 (1H, td, *J* = 10.4, 4.5 Hz, OC**H**), 2.14-1.94 (10H, m, 5 x C**H_2**), 1.70 (6H, s, 2 x C**H_3**), 1.70-1.61 (5H, m, C**H_2**), 1.33-1.30 (6H, m, 2 x C**H_3**), 1.24 (3H, s, C**H_3**), 1.18-1.03 (2H, m, C**H_2**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.21 (**C**=O), 151.41 (**C**CH, Ar), 140.54 (**C**=CH_2), 135.68 (CH_3**C**), 131.50 (Me_2**C**), 127.96 (2 x **C**H, Ar), 125.41 (**C**H, Ar), 125.01 (2 x **C**H, Ar), 124.34 (C=**C**H_2), 124.31 (CH_3C=**C**H), 124.27 ((CH_3)$_2$C=**C**H), 74.96 (O**C**H), 50.96 (**C**HCPh), 39.98 (**C**Ph), 33.33 (**C**H_2CHCH), 31.98 (**C**H_2C=CH_2), 31.84 (**C**H_2CH_2), 27.25 (**C**$H_2CH_2CH_2CH$), 26.84 (**C**H_2CH_2), 26.65 (**C**H_2CH_2), 26.58 (**C**H_3), 26.37 (**C**H_3), 25.95 (**C**H_3), 25.69 (**C**H_2CH_2), 24.72 (**C**H_3), 23.35 (**C**H_2), 17.62 (**C**H_3) ppm.

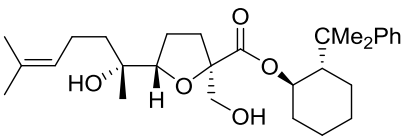
LRMS (ESI$^+$) m/z: 445 [M+Na]$^+$) Da.

HRMS (ESI$^+$) m/z: Calculated: 445.3077; Found: 445.3078 ([M+Na]$^+$) Da.

(2*S*,5*R*)-((1*R*,2*S*)-2-(2-Phenylpropan-2-yl)cyclohexyl)tetrahydro-5-((*S*)-2-hydroxy-6-methylhept-5-en-2-yl)-2-(hydroxymethyl)furan-2-carboxylate (2.125) and (2*R*,5*S*)-((1*R*, 2*S*)-2-(2-Phenylpropan-2-yl)cyclohexyl) tetrahydro-5-((*R*)-2-hydroxy-6-methylhept-5-en-2-yl)-2-(hydroxymethyl)furan-2-carboxylate (2.126)



1.125 Major +



1.126 Minor

$C_{29}H_{44}O_5$
Mol. wt. 472.66 g/mol
(Yellow gum)

Using a procedure described by our group,[12,84] to a vigorously stirred mixture of trienoate TCC **2.124** (380 mg, 0.899 mmol) and TBAB (299 mg, 0.93 mmol) in acetone (19.5 mL) at –35 °C was added a solution of $NaMnO_4$ (3.10 mL, 0.4M aq., 1.23 mmol) containing AcOH (127 µL, 2.20 mmol). The purple mixture was stirred rapidly for 2 h, during which time the temperature of the acetone cooling bath was kept under –10 °C and the reaction mixture had turned dark brown. At this stage, the reaction was quenched with sat. aq. $Na_2S_2O_5$ (with ice-cooling) (60 mL) to dissolve the precipitated manganese salt, then brine (20 mL) and CH_2Cl_2 (30 mL) were added. The organic phase was separated and the aqueous layer was extracted using CH_2Cl_2 (4 x 40 mL). The

organic phases were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/ hexane (10 to 30%) to give the title THF-TCC **2.125/2.126** as an inseparable diasteromeric mixture (250 mg, 0.53 mmol, 59%, dr = 5.5:1 by ^{1}H NMR). ^{1}H NMR and ^{13}C NMR and FT-IR data were in agreement with the literature.[12]

$[\alpha]^{29}_D$: +0.004 (*c* 1.1, $CHCl_3$).

FT-IR ν_{max} (neat): 3403 (br), 2964 (w), 2930 (m), 2860 (w), 1720 (s) cm^{-1}.

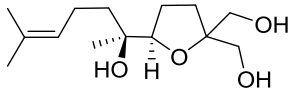
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.14 (5H, m, 5 x C**H**, Ar), 5.09 (1H, t, *J* = 7.1 Hz, C=C**H**CH_2), 4.86_{min} and 4.75_{maj} (1H, td, *J* = 10.1, 4.5 Hz, OC**H**), 4.03_{maj} and 3.94_{min} (1H, m, C**H**, THF ring), 3.68_{maj} and 3.60_{min} (1H, d, *J* = 11.6 Hz, C**H**HOH), 3.52_{maj} and 3.48_{min} (1H, d, *J* = 11.1 Hz, CH**H**OH), 3.15 (1H, br, O**H**), 2.63 (1H, br, O**H)**, 2.14-1.85 (9H, m, C**H**, 2 x C$\mathbf{H_2}$, 2 x C$\mathbf{H_2}$, THF ring), 1.67 (3H, s, C$\mathbf{H_3}$), 1.61 (3H, s, C$\mathbf{H_3}$), 1.67-1.42 (2H, m, C$\mathbf{H_2}$), 1.34 (3H, s, C$\mathbf{H_3}$), 1.38-1.29 (2H, m, C$\mathbf{H_2}$) 1.26-1.23 (6H, s, 2 x C$\mathbf{H_3}$), 1.09-0.89 (2H, m, C$\mathbf{H_2}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6_{maj} and 173.2_{min} (**C**=O), 150.6_{min} and 150.4_{maj} (**C**CH, Ar), 131.8 (Me_2**C**), 128.2_{min} and 128.0_{maj} (2 x **C**H, Ar), 125.6_{maj} and 125.6_{min} (2 x **C**H, Ar), 125.3 (**C**H, Ar), 124.3_{maj} and 124.3_{min} (C=**C**HCH_2), 87.0_{maj} and 86.8_{min} (**C**H, THF), 86.3_{min} and 85.9_{maj} (**C**CH_2OH, THF ring), 77.3_{maj} and 77.2_{min} (O**C**H), 76.5_{maj} and 76.4_{min} (**C**OH), 73.4_{min} and 73.2_{min} (**C**H_2OH), 56.9_{maj} and 65.5_{min} (**C**HCPh), 50.7_{maj} and 50.4_{min} (**C**Ph), 40.3_{min} (**C**H_2COH), 38.2 (**C**H_2CHCH), 33.1_{min} and 31.0_{maj} (**C**H_2, THF ring), 32.0_{maj} and 31.3_{min} (**C**$H_2CH_2CH_2$CH), 28.8_{maj} and 28.5_{min} (**C**H_2), 27.5_{maj} and 27.4_{min} (**C**H_2CH_2), 25.8 (**C**H_3), 25.7 (**C**H_3), 25.3 (**C**H_2, THF), 24.5 (**C**H_3), 24.1_{min} and 24.0_{maj} (**C**H_2CH_2), 22.1 (**C**H_3), 17.6 (**C**H_3) ppm.

LRMS (ESI$^+$) m/z:967 $[2M+Na]^+$) Da.

HRMS (ESI$^+$) m/z: Calculated: 495.3081; Found: 495.3067 ($[M+Na]^+$) Da.

((*R*)-5-((*S*)-2-Hydroxy-6-methylhept-5-en-2-yl)tetrahydrofuran-2,2-diyl)dimethanol (2.26) (from (+)(1*R*,2*S*)-TTC)



$C_{14}H_{26}O_4$
Mol.wt.: 258.35 g/mol
(Yellow oil)

To a solution of the major isomer THF-TTC **1.187** (107 mg, 0.18 mmol) in CH_2Cl_2 (3.3 mL) was added dropwise a solution of DIBALH (720 µL, 1.0M in THF, 0.72 mmol) at rt. The reaction mixture was heated at reflux for 23 h. After that the reaction was cooled at rt, then quenched by adding sat. aq. NH_4Cl (5.0 mL) and Rochelle's salt (5.0 mL) and the solution was stirred for 30 min at rt. The solution was extracted with CH_2Cl_2 (6 x 10 mL) then with Et_2O (6 x 10 mL), combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product as a yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/ hexane (80%) to give mixture of the title triol **2.26** as a yellow oil (40.0 mg, 0.15 mmol, 87%) along with (1*R*,2*S*)-TTC as a white solid (54.0 mg, 0.16 mmol, 88%).

$[\alpha]^{27}_D$: +4.0 (*c* 1.75, $CHCl_3$).

FT-IR ν_{max}: 3363 (br.), 2968 (m), 2927 (m), 2874 (m) cm^{-1}.

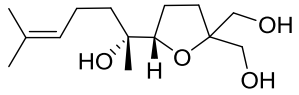
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.09 (1H, m, C=C**H**CH_2), 3.86 (1H, m, C**H**, THF ring), 3.64 (1H, m, C**H**HOH), 3.57-3.49 (3H, m, 3 x C**H**HOH), 3.14 (2H, br, 2 x O**H**), 2.09 - 1.73 (7H, m, O**H**, and 3 x C**H**$_2$), 1.67 (3H, s, C**H**$_3$), 1.60 (3H, s, C**H**$_3$), 1.47 (1H, m, C**H**H), 1.32 (1H, ddd, *J* = 13.6, 11.1 and 5.6 Hz, C**H**H), 1.24 (3H, s, C**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 131.9 (Me_2**C**), 124.3 (C=**C**H), 86.2 (**C**H, THF ring), 85.4 (**C**O, THF), 73.4 (**C**(CH_3)OH), 66.3 (**C**H_2OH), 66.2 (**C**H_2OH), 37.7 (**C**H_2COH), 30.2 (**C**H_2, THF), 26.5 (**C**H_2, THF), 25.7 (**C**H_3), 24.3 (**C**H_3COH), 22.2 (**C**H_2CH=C), 17.6 (**C**H_3) ppm.

LRMS (ESI$^+$) m/z: 281 ([M+Na]$^+$) Da.

HRMS (ESI$^+$) m/z: Calculated: 281.17233; Found: 281.17249 ([M+Na]$^+$) Da.

((*S*)-5-((*R*)-2-Hydroxy-6-methylhept-5-en-2-yl)tetrahydrofuran-2,2-diyl)dimethanol (2.27) (from the minor THF-TTC)



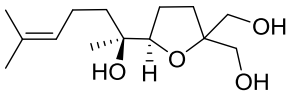
$C_{14}H_{26}O_4$
Mol. Wt.: 258.35 g/mol
(Yellow oil)

Following the procedure for the reduction of the major isomer THF-TTC **1.187** with DIBALH, the minor isomer THF-TTC **2.22** (100 mg, 0.17 mmol) gave the title triol

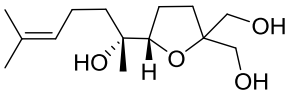
2.27 as a yellow oil (26.0 mg, 0.10 mmol, 60%). Physical and Spectroscopic data are consistent with that reported above (triols **2.26**).

[α]$^{25.5}_{D}$: –2.6 (*c* 0.60, $CHCl_3$).

((*R*)-5-((*S*)-2-hydroxy-6-methylhept-5-en-2-yl)tetrahydrofuran-2,2-diyl)dimethanol (2.26) and ((*S*)-5-((*R*)-2-hydroxy-6-methylhept-5-en-2-yl)tetrahydrofuran-2,2-diyl)dimethanol (2.27) (from (–)(1*R*,2*S*)-TCC)



2.26 Major



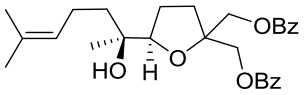
2.27 Minor

$C_{14}H_{26}O_4$
Mol. Wt.: 258.35 g/mol
(Yellow oil)

Following the procedure for the reduction of the THF-TTC **1.187** with DIBALH, the mixture of diastereomeric THF TCC **2.125/2.126** (154 mg, 0.33 mmol) gave a mixture of triols **2.26/2.27** as a yellow oil (155 mg, 0.24 mmol, 70%). Physical and Spectroscopic data are consistent with that reported above (triols **2.26**, from (+)(1*R*,2*S*)-TTC).

[α]$^{27}_{D}$: +6.4 (*c* 0.43, $CHCl_3$).

((*R*)-5-((*S*)-2-Hydroxy-6-methylhept-5-en-2-yl)tetrahydrofuran-2,2-diyl)bis(methylene) dibenzoate (2.127) (from (+)(1*R*,2*S*)-TTC)



$C_{28}H_{34}O_6$
Mol.wt.: 466.57 g/mol
(Yellow oil)

To a solution of the triol **2.26** (from (1*R*,2*S*)-TTC, 40.0 mg, 0.15 mmol) in CH_2Cl_2 (1.7 mL), Et_3N (216 µL) and BzCl (36 µL) were added successively at rt. The mixture was stirred for 21 h. The reaction mixture was diluted with CH_2Cl_2 (3.0 mL) and H_2O (3.0 mL); the organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 3 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was removed in *vacuo* to afford the crude product as a yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/ hexane (5%) to give the title dibenzoate **2.127** as a yellow oil (46.4 mg, 0.10 mmol, 64%), which was analysed by chiral HPLC giving an enantiomeric ratio of ~30:1.

[α]$^{26.5}_{D}$: –2.9 (*c* 1.68, $CHCl_3$).

FT-IR ν_{max}: 3471 (br.), 2957 (w), 2922 (m), 2850 (w), 1717 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09-8.05 (4H, m, 4 x CH, Ar), 7.61-7.56 (2H, 2 x C**H**, Ar), 7.48-7.43 (4H, m, 4 x CH, Ar), 5.1 (1H, t, *J* = 6.6 Hz, =C**H**CH_2), 4.7 (1H, d, *J* = 11.6 Hz, C**H**HOCO), 4.54 (1H, d, *J* = 11.1 Hz, C**H**HOCO), 4.36 (1H, d, *J* = 11.1 Hz, CH**H**OCO), 4.30 (1H, d, *J* = 11.1 Hz, CH**H**OCO), 3.97 (1H, dd, *J* = 8.8, 5.8 Hz, C**H**, THF ring), 2.61 (1H, br. s, O**H**), 2.16-1.95 (6H, m, 3 x C$\mathbf{H}_2$), 1.69 (3H, s, C$\mathbf{H}_3$), 1.62 (3H, s, C$\mathbf{H}_3$), 1.55-1.33 (2H, m, C$\mathbf{H}_2$), 1.21 (3H, s, C$\mathbf{H}_3$) ppm.

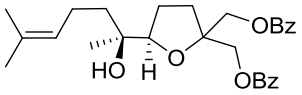
^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7 (**C**=O), 166.3 (**C**=O), 133.2 (d, 2 x **C**H, Ar), 131.7 (**C**=CH), 129.9 (2 x **C**H, Ar), 129.8 (2 x **C**H, Ar), 129.7 (2 x **C**H, Ar), 128.5 (2x **C**H, Ar), 124.4 (C=**C**H), 86.9 (**C**H, THF), 82.5 (**C**O, THF), 72.2 (**C**(CH_3)OH), 66.7 (d, 2 x **C**H_2OCO), 37.7 (**C**H_2COH), 31.4 (**C**H_2, THF ring), 29.7 (**C**H_2, THF ring), 25.7 (**C**H_3), 24.1 (**C**H_3), 22.1 (**C**H_2CH=C), 17.6 (**C**H_3) ppm.

LRMS (ESI$^+$) m/z: 489 ($[M+Na]^+$).

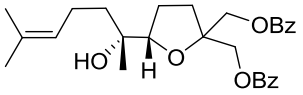
HRMS (ESI$^+$) m/z: Calculated: 489.2245; Found: 489.2257 ($[M+Na]^+$).

HPLC: IB column–(eluent: IPA /*n*-hexane 2.0:98), 0.4 mL/min, 254 nm. Retention times: t_{maj} = 31.2min & t_{min} = 34.5 min.

((*R*)-5-((*S*)-2-Hydroxy-6-methylhept-5-en-2-yl)tetrahydrofuran-2,2-diyl)bis(methylene) dibenzoate (2.127) and ((*S*)-5-((*R*)-2-hydroxy-6-methylhept-5-en-2-yl)tetrahydrofuran-2,2-diyl)bis(methylene) dibenzoate (2.128) (from (–)(1*R*,2*S*)-TCC)



2.127 Major



2.128 Minor

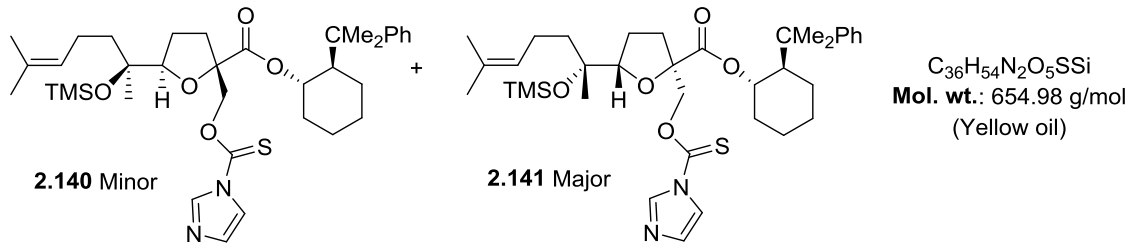
$C_{28}H_{34}O_6$
Mol. Wt.: 466.57 g/mol
(Yellow oil)

Following the procedure for the benzoylation of the triol from (1*R*,2*S*)-TTC **2.127**, the mixture of enantiomeric triol from (1*R*,2*S*)-TCC) **2.26/2.27** (58.5 mg, 0.23 mmol) was converted to the corresponding dibenzoates **2.127/2.128** (60.6 mg, 0.13 mmol, 57%). Physical and Spectroscopic data are consistent with that reported above (dibenzoate **2.127** from (1*R*,2*S*)-TTC). The sample was analysed by chiral HPLC, which showed an enantiomeric ratio of ~4.2:1).

$[\alpha]^{26}_D$: –0.8 (*c* 1.38, $CHCl_3$).

HPLC: IB column – (eluent: IPA /*n*-hexane 2.0:98), 0.4 mL/min, 254 nm. Retention times: t_{maj} = 32.6 min & t_{min} = 34.8 min.

(1*S*,2*R*)-2-(2-Phenylpropan-2-yl)cyclohexyl (2*R*,5*S*)-2-(((1H-imidazole-1-carbonothioyl)oxy)methyl)-5-((*R*)-6-methyl-2-((trimethylsilyl)oxy)hept-5-en-2-yl)tetrahydrofuran-2-carboxylate (2.141) and (1*S*,2*R*)-2-(2-phenylpropan-2-yl)cyclohexyl (2*S*,5*S*)-2-(((1H-imidazole-1-carbonothioyl)oxy)methyl)-5-((*S*)-6-methyl-2-((trimethylsilyl)oxy)hept-5-en-2-yl)tetrahydrofuran-2-carboxylate (2.140) (from (+)(1*S*,2*R*)-TCC)



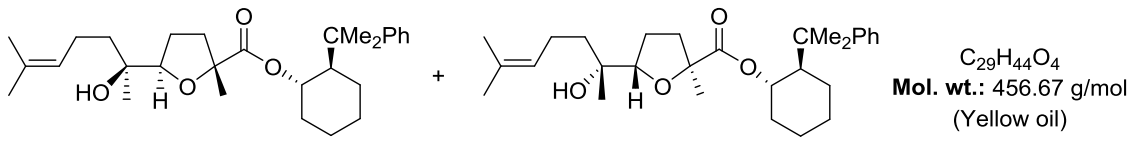
$C_{36}H_{54}N_2O_5SSi$
Mol. wt.: 654.98 g/mol
(Yellow oil)

Following the method for the preparation of xanthate THF-TTC **2.29**, a mixture of distereomeric THF-TCC (which was synthesised from (+)(1*S*,2*R*)-TCC auxiliary in a previous study within the group)[12] (481 mg, 0.88 mmol) gave a mixture of the title xanthates THF-TCC **2.140/2.141** as a yellow oil (553 mg, 0.84 mmol, 96%). ^{1}H NMR data was used to characterize the product and it was found consistent with the one reported.[12]

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31_{maj} and 8.10_{min}(1H, s, NC**H**N), 7.59_{maj} and 7.30_{min}(1H, s, C**H**N), $7.30\text{-}7.16_{maj\ and\ min}$ (5H, m, Ar), 7.06_{min} and 7.02_{maj} (1H, s, 1.7, NC**H**CH), $5.08_{maj\ and\ min}$ (1H, m, C=C**H**CH_2), $4.85_{maj\ and\ min}$ (1H, m, OC**H**), 4.70_{maj} and 4.59_{min} (1H, d, *J* = 10.6 Hz, C**H**HO), 4.38_{maj} and 4.49_{min} (1H, d, *J* = 10.6 Hz, CH**H**O), $4.19_{\ maj\ and\ min}$ (1H, m, C**H**, THF ring), $2.07\text{-}1.90_{maj\ and\ min}$ (7H, m, C**H**, C**H$_2$**, and 2 x C**H$_2$**, THF ring), 1.69_{maj} and 1.61_{min} (3H, s, C**H$_3$**), $1.60\text{-}1.28_{\ maj\ and\ min}$ (8H, m, 4 x C**H$_2$**), $1.56_{\ maj\ and\ min}$ (3H, s, C**H$_3$**), $1.37_{maj\ and\ min}$ (3H, s, C**H$_3$**), $1.20\text{-}0.95_{maj\ and\ min}$ (2H, m, C**H$_2$**), $1.23_{maj\ and\ min}$ (6H, s, 2 x C**H$_3$**), 0.01_{min} and $0.09_{\ maj}$ (9H, s, $COSiMe_3$) ppm.

(1*S*,2*R*)-2-(2-Phenylpropan-2-yl)cyclohexyl (2*S*,5*S*)-5-((*R*)-2-hydroxy-6-methylhept-5-en-2-yl)-2-methyltetrahydrofuran-2-carboxylate (2.129) and (1*S*,2*R*)-

2-(2-phenylpropan-2-yl)cyclohexyl (2*R*,5*S*)-5-((*S*)-2-hydroxy-6-methylhept-5-en-2-yl)-2-methyltetrahydrofuran-2-carboxylate (2.130) (from (+)(1*S*,2*R*)-TCC)



$C_{29}H_{44}O_4$
Mol. wt.: 456.67 g/mol
(Yellow oil)

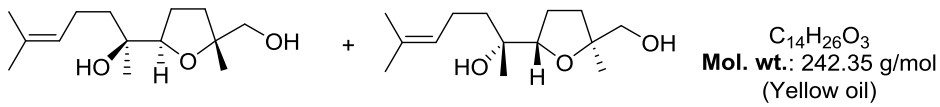
2.129 Minor + **2.130** Major

Following the procedure for the radical deoxygenation of xanthate THF-TTC **2.29**, a mixture of diastereomeric xanthates THF-TCC **2.140/2.141** (553 mg, 0.84 mmol) gave a mixture of the title THF-TCC **2.129/2.130** as a yellow oil (227 mg, 0.49 mmol, 59%). ^{1}H NMR and ^{13}C-NMR data were consistent with the reported data.[12]

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.28-7.12$_{maj\ and\ min}$ (5H, m, Ar), 5.09$_{maj\ and\ min}$ (1H, m, Me_2C=C**H**), 4.88$_{min}$ and 4.77 $_{maj}$ (1H, td, *J* = 10.0, 4.3 Hz, OC**H**), 3.95$_{maj}$ and 3.89$_{min}$ (1H, t, *J* = 7.0 Hz, C**H**, THF ring), 2.15-1.68$_{maj\ and\ min}$ (8H, m, O**H**, C**H**, C**H$_2$**, and 2 x C**H$_2$**, THF ring), 1.67$_{maj\ and\ min}$ (3H, s, C**H$_3$**), 1.67-1.36 (6H, m, 3 x C**H**$_2$), 1.61$_{maj\ and\ min}$ (3H, s, C**H$_3$**), 1.34$_{maj\ and\ min}$ (3H, s, C**H$_3$**), 1.35-0.84$_{maj\ and\ min}$ (4H, m, 2 x C**H**$_2$), 1.31$_{maj\ and\ min}$ (3H, s, C**H$_3$**), 1.25$_{maj\ and\ min}$ (3H, s, C**H$_3$**), 1.20$_{maj\ and\ min}$ (3H, s, C**H$_3$**) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ 174.6$_{maj\ and\ min}$ (**C**=O), 150.6$_{maj\ and\ min}$ (**C**CH, Ar), 131.7$_{maj\ and\ min}$ (Me_2**C**), 128.0$_{maj\ and\ min}$ (2 x **C**H, Ar), 125.7 (2 x **C**H, Ar), 125.3 (**C**H, Ar), 124.5$_{maj\ and\ min}$ (Me_2C=**C**H), 86.5$_{maj\ and\ min}$ (**C**H, THF ring), 83.3$_{maj\ and\ min}$ (**C**CH_3, THF ring), 76.6$_{maj\ and\ min}$ (**C**OH), 75.6$_{maj\ and\ min}$ (O**C**H), 50.1$_{maj\ and\ min}$ (**C**HCPh), 40.4$_{maj\ and\ min}$ (**C**Ph), 37.5$_{maj\ and\ min}$ (**C**H_2COH), 36.6$_{maj\ and\ min}$ (**C**H_2CHCH), 33.1$_{maj\ and\ min}$ (**C**H_2, THF ring), 29.1$_{maj\ and\ min}$ (**C**H_3), 27.6$_{maj\ and\ min}$ (**C**$H_2CH_2CH_2$CH), 25.8$_{maj\ and\ min}$ (**C**H_3), 25.7$_{maj\ and\ min}$ (**C**H_2), 24.4$_{maj\ and\ min}$ (**C**H_2), 25.0$_{maj\ and\ min}$ (**C**H_3), 24.6$_{maj\ and\ min}$ (**C**H_3), 24.2$_{maj\ and\ min}$ (**C**H_2, THF ring), 24.0$_{maj\ and\ min}$ (**C**H_3), 22.1 (**C**H_2C=C), 17.7 (**C**H_3) ppm.

(2*R*,5*S*)-2-((Hydroxymethyl)methyl)-5-((*R*)-2-hydroxyl-6-methylhepta-5-en-2-yl tetrahydrofuran 2.131 (+ minor enantiomer-2.31, from (+)(1*S*,2*R*)-TCC)



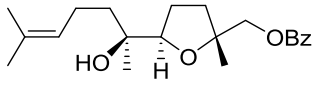
$C_{14}H_{26}O_3$
Mol. wt.: 242.35 g/mol
(Yellow oil)

2.31 Minor + **2.131** Major

Following the procedure for the reduction of the THF-TTC **2.30** with DIBALH, the mixture of diastereomeric THF-TCC **2.129/2.130** (227 mg, 0.43 mmol) gave a mixture of the title diols **2.131/2.31** ((107 mg, 0.44 mmol, 99%). Physical and Spectroscopic data are consistent with that reported above (diol **2.31**, from (1*R*,2*S*)-TTC).

$[\alpha]^{22.5}_{D}$: –5.2 (*c* 1.36, $CHCl_3$).

((2*R*,5*R*)-5-((*S*)-2-Hydroxy-6-methylhept-5-en-2-yl)-2-methyltetrahydrofuran-2-yl)methyl benzoate 2.132 (from (+)(1*R*,2*S*)-TTC)



$C_{21}H_{30}O_4$
Mol. wt.: 346.47 mmol
(Yellow oil)

To a solution of diol **2.31** (from (1*R*,2*S*)-TTC) (98.0 mg, 0.40 mmol) in CH_2Cl_2 (4.5 mL), Et_3N (283 µL, 2.02 mmol) and BzCl (46 µL, 0.37) were added successively at rt. The mixture was stirred for 23 h. The reaction mixture was diluted with CH_2Cl_2 (1.5 mL) and H_2O (1.5 mL); the organic phase was separated, and the aqueous phase was re-extracted with CH_2Cl_2 (2 x 1.5 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/ hexane (0% to 20%) to give the title benzoate **2.132** as a yellow oil (61.7 mg, 0.40 mmol, 44%). The sample was analysed by chiral HPLC, which showed an enantiomeric ratio of 96.4:3.6 (~26.8:1).

FT-IR ν_{max} (neat): 3532 (br.), 2970 (w), 2906 (m), 2877 (w), 1718(s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 8.06 (2H, d, *J* = 7.9 Hz , 2 x C**H**, Ar), 7.58 (1H, t, *J* = 7.3 Hz, C**H**, Ar), 7.47 (2H, t, *J* = 7.6 Hz, 2 x C**H**, Ar), 5.13 (1H, t, *J* = 7.1 Hz, C=C**H**CH_2), 4.28 (1H, d, *J* = 11.0 Hz, C**H**HOCO), 4.23 (1H, d, *J* = 11.0 Hz, CH**H**OCO), 3.90 (1H, dd, *J* = 8.9, 6.1 Hz ,C**H**, THF ring), 2.17-1.77 (7H, m, O**H**, 3 x C$\mathbf{H}_2$), 1.69 (3H, s, C$\mathbf{H}_3$), 1.62 (3H, s, C$\mathbf{H}_3$), 1.57-1.49 (2H, m, C$\mathbf{H}_2$), 1.35 (3H, s, C$\mathbf{H}_3$), 1.21 (3H, s, C$\mathbf{H}_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 166.4 (**C**=O), 133.0 (**C**H, Ar), 131.6 (**C**=CH), 130.2 (**C**H, Ar), 129.6 (2 x **C**H, Ar), 128.4 (2 x **C**H, Ar), 124.5 (C=**C**H), 86.1 (**C**H, THF ring), 81.4 (**C**O, THF), 72.4 (**C**(CH_3)OH), 70.0 (**C**H_2OCO), 37.4 (**C**H_2COH), 34.6

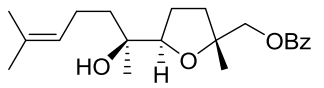
(**C**H_2, THF), 25.8 (**C**H_2, THF ring), 25.7 (**C**H_3C=CH), 24.6 (**C**H_3CO), 24.2 (**C**H_3COH), 22.1 (**C**H_2CH=C), 17.6 (**C**H_3C=CH) ppm.

LRMS (ESI$^+$) m/z: 369 ([M+Na]$^+$) Da.

HRMS (ESI$^+$) m/z: Calculated: 369.2036; Found: 369.2040 ([M+Na]$^+$) Da.

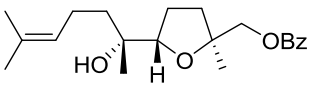
HPLC: Chiralpak® AD-H - (eluent: IPA/n-hexane 5:95) - 0.3 mL/min Retention times: t_{maj} = 33.2 min & t_{min} = 36.1 min.

((2*S*,5*S*)-5-((*R*)-2-Hydroxy-6-methylhept-5-en-2-yl)-2-methyltetrahydrofuran-2-yl)methyl benzoate 2.133 (+ minor enantiomer- 2.132, from (+)(1*S*,2*R*)-TCC)



2.132 Minor

\+



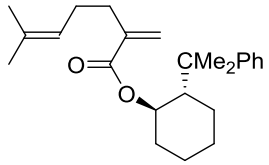
2.133 Major

$C_{14}H_{26}O_3$
Mol. wt.: 242.35 g/mol
(Yellow oil)

Following the procedure for the benzoylation of diol **2.132** (from (1*R*,2*S*)-TTC), the mixture of enantiomeric diols **2.131/2.31** (from (+)(1*S*,2*R*)-TCC)) (30.0 mg, 0.12 mmol) was converted to the corresponding benzoates **2.133/2.132** (43.0 mg, 0.12 mmol, 100%). Physical and Spectroscopic data are consistent with that reported above (benzoate **2.132** from (+)(1*R*,2*S*)-TTC). The sample was analysed by chiral HPLC, which showed an enantiomeric ratio of 78.8:21.2 (~3.7:1).

HPLC: Chiralpak® AD-H-(eluent: IPA/n-hexane 5:95) - 0.3 mL/min Retention times: t_{maj} = 36.7 min & t_{min} = 33.6 min.

(1*R*,2*S*)-2-(2-Phenylpropan-2-yl)cyclohexyl 6-methyl-2-methylenehept-5-enoate (1.100b)



$C_{24}H_{34}O_2$
Mol. wt. 354.53 g/mol
(Yellow oil)

To a solution of (–)-TCC (*ee*: 97 %) (287 mg, 1.31 mmol) in dry THF (19 mL) at –20 ^oC, was added NaHMDS (1.4 mL, 1.0M in THF, 1.40 mmol). The mixture was allowed to warm to –5 ^oC over 40 min, then a solution of PFP dienoate **2.117** (400 mg, 1.25 mmol, was prepared in a previous study within the group)[12] in dry THF (4.0 mL) was

added dropwise at –5 ^{o}C. The mixture was stirred for 1.5h and allowed to warm to 5 ^{o}C. Et_2O (10 mL), sat. aq. NH_4Cl (5.0 mL) and H_2O (5.0 mL) were added to the mixture. The organic phase was separated, washed with sat. aq.$NaHCO_3$ (2 x 25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a crude product as a yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/ hexane (5 to 10%) to give the title dienoate **1.100b** as a yellow oil (269 mg, 0.759 mmol, 61%).

$[\alpha]^{22.5}_{D}$: –17.0 (*c* 1.64, $CHCl_3$)

FT-IR ν_{max} (neat): 2969(w), 2927 (m), 2859 (w), 1707(s) cm^{-1}.

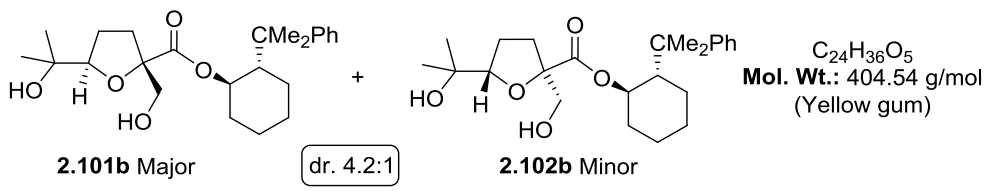
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.22 (4H, m, 4 x C**H**, Ar), 7.11 (1H, tt, *J* = 6.6, 2.2 Hz, C**H**, Ar), 5.69 (1H, d, *J* = 1.6 Hz, C=C**H**H), 5.30 (1H, d, *J* = 1.1 Hz, C=CH**H**), 5.08 (1H, m, =C**H**CH_2), 4.89 (1H, td, *J* = 10.3, 4.4 Hz, OC**H**), 2.13-1.92 (6H, m, C**H**, 3 x C**H$_2$**), 1.70 (3H, s, C**H$_3$**), 1.70-1.62 (4H, m, 2 x C**H$_2$**), 1.61 (3H, s, C**H$_3$**), 1.32 (3H, s, C**H$_3$**), 1.31-1.26 (2H, m, C**H$_2$**), 1.23 (3H, s, C**H$_3$**), 1.17-0.92 (1H, m, C**H**H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3 (**C**=O), 151.4 (**C**CH, Ar), 140.5 (**C**=CH_2), 1312.0 (Me_2**C**), 128.0 (2 x **C**H, Ar), 125.4 (2 x **C**H, Ar), 125.0 (**C**H, Ar), 124.4 (C=**C**H_2), 123.6 (C=**C**HCH_2), 75.0 (O**C**H), 51.0 (**C**HCPh), 40.0 (**C**Ph), 33.3 (**C**H_2CHO), 31.6 (**C**H_2C=CH_2), 27.3 (**C**H_3CPh), 26.9 (**C**H_2CH=C), 26.8 (**C**H_2CH_2), 26.4 (**C**H_3), 26.0 (**C**H_2CH), 25.7 (**C**H_2 CH_2CHO), 24.7 (**C**H_3), 17.7 (**C**H_3) ppm.

LRMS (ESI^{+}) m/z: 377 $[M+Na]^{+}$ Da.

HRMS (ESI^{+}) m/z: Calculated: 377.2451; Found: 377.2457 ($[M+Na]^{+}$) Da.

(1*R*,2*S*)-2-(2-Phenylpropan-2-yl)cyclohexyl(2*S*,5*R*)-tetrahydro-2-(hydroxymethyl)-5-(2-hydroxypropan-2-yl)furan-2-carboxylate (1.101b) and (1*R*,2*S*)-2-(2-Phenylpropan-2-yl)(2*R*,5*S*)-cyclohexyltetrahydro-2-(hydroxymethyl)-5-(2-hydroxypropan-2-yl)furan-2-carboxylate (1.102b)



Following the method from Brown *et al.*,[12] to a vigorously stirred mixture of TCC dieneoate **1.100b** (56.00 mg, 0.158 mmol) and phosphate buffer (KH_2PO_4/Na_2HPO_4, pH 7) (320 µL) in acetone (340 µL) at –35 °C was added a solution of $NaMnO_4$ (590.0 µL, 0.4M aq., 0.237 mmol) containing AcOH (27.00 µL, 0.474 mmol). The purple mixture was stirred rapidly for 1.5 h, during which time the temperature of the acetone cooling bath had raised to –2 °C and the reaction mixture had turned dark brown. At this stage, the reaction was quenched with sat. aq. $Na_2S_2O_5$ (5.0 mL) to dissolve all of the precipitated manganese salt and brine (10 mL) was added. The mixture was then repeatedly extracted using CH_2Cl_2 (6 x 20 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product as a yellow oil. The crude was purified by column chromatography (SiO_2) eluting with EtOAc/hexane (50%) to afford inseparable diastereoisomers **1.101b/1.102b** as a yellow gum (60 mg, 0.148 mmol, 94%). The dr. for **1.101b** and **1.102b** was 4.2:1 by 600 MHz ^{1}H NMR.

$[\alpha]^{25}_D$: +0.3 (*c* 1.12, $CHCl_3$).

FT-IR ν_{max} (neat): 3390 (br), 2911 (w), 2929 (m), 2860 (m), 1721 (s), 1447 (m) cm^{-1}.

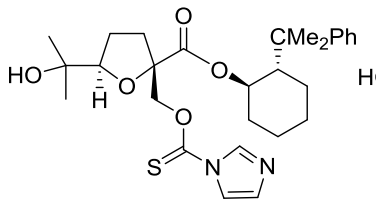
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29-7.23 (4H, m, 4 x C**H**, Ar), 7.14 (1H, m, C**H**, Ar), 4.86_{min} and 4.76_{maj} (1H, td, *J* = 10.7, 4.3 Hz, OC**H**), 4.01_{maj} and 3.90_{min} (1H, t, *J* = 7.1 Hz, C**H**, THF), 3.68_{maj} and 3.60_{min} (1H, d, *J* = 11.0 Hz, C**H**HOH), 3.53_{maj} and 3.49_{min} (1H, d, *J* = 11.0 Hz, CH**H**OH), 3.03 (1H, br, O**H**), 2.82 (1H, br, O**H**), 2.05-1.78 (6H, m, 3 x C**H$_2$**, THF), 1.64 (1H, m, C**H**), 1.56 (1H, m, C**H**), 1.44 (1H, m, C**H**), 1.34_{maj} (3H, s, C**H$_3$**), 1.25-1.20 (2H, m, 2 x C**H**), 1.26_{maj} (3H, s, C**H$_3$**), 1.25_{maj} (3H, s, C**H$_3$**), 1.11_{maj} (3H, s, C**H$_3$**), 1.08 (1H, m, C**H**), 0.94 (1H, m, C**H**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5_{maj} and 173.1_{min} (**C**=O), 150.6_{min} and 150.4_{maj} (**C**CH, Ar), 128.2_{min} and 128.0_{maj} (2 x **C**H, Ar), 125.7_{maj} and 125.3_{min} (2 x **C**H, Ar), 125.34 (**C**H, Ar), 87.6_{maj} and 87.3_{min} (**C**H, THF), 86.6_{min} and 86.2_{maj} (**C**CH_2OH, THF), 76.5_{maj} and 76.4_{min} (O**C**H), 71.4_{min} and 71.30_{mij} (**C**OH), 65.9_{maj} and 65.4_{min} (**C**H_2OH), 50.7_{maj} and 50.4_{min} (**C**HCPh), $40.3_{maj\ and\ min}$ (**C**Ph), 31.9_{maj} and 31.3_{min} (**C**H_2CH(CH_3)), 30.3_{min} and 29.7_{maj} (**C**H_2CH_2CH), 28.7_{maj} and 28.4_{min} (**C**H_2, THF), $27.5_{maj\ and\ min}$ (**C**H_2, THF), $27.4_{maj\ and\ min}$, (**C**H_3), $26.1_{maj\ and\ min}$ (**C**H_3), 25.8_{maj} and 25.7_{min}(**C**H_2C), $25.4_{maj\ and\ min}$ (**C**H_3), $25.1_{maj\ and\ min}$ (**C**H_3), $24.5_{maj\ and\ min}$ (**C**H_3) ppm.

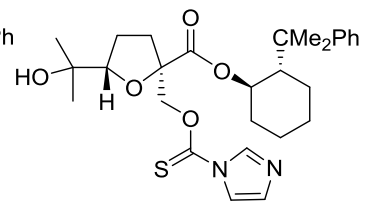
LRMS (ESI$^+$) m/z: 427 $[M+Na]^+$ Da.

HRMS (ESI$^+$) m/z: Calculated: 427.2455; Found: 427.2446 ($[M+Na]^+$) Da.

(2*S*,5*R*)-(1*R*,2*S*)-2-(2-Phenylpropan-2-yl)cyclohexyl 2-(((1H-imidazole-1-carbonothioyl)oxy)methyl)-5-(2-hydroxypropan-2-yl)tetrahydrofuran-2-carboxylate (2.142) (+ minor diastereoisomer- 2.143, dr. 4.2:1)



2.142 Major



2.143 Minor

$C_{28}H_{38}N_2O_5S$
Mol. wt. 514.68 g/mol
(Yellow oil)

Following the method for the preparation of xanthate THF-TTC **2.29**, a mixture of distereomeric diols **1.101b/1.102b** (50.70 mg, 0.125 mmol) gave a mixture of the title xanthates **2.142/2.143** as a yellow oil (35.0 mg, 0.07 mmol, 55%).

$[\alpha]^{27}_D$: –8.5 (*c* 0.6, $CHCl_3$).

FT-IR ν_{max} (neat): 3356 (br.w), 3000(w), 2972 (m), 22937 (w), 1745 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ $8.32_{maj\ and\ min}$ (1H, s, NC**H**N), 7.60 (1H, s, C**H**N), 7.28-7.13 (5H, m, C**H**, Ar), $7.01_{maj\ and\ min}$ (1H, NC**H**CH), 4.90_{min} and $4.84_{maj\ and\ min}$ (1H, m, OC**H**), 4.70_{min} and 4.62_{maj} (1H, d, *J* = 11.3 Hz, C**H**HO), 4.54_{maj} and 4.53_{min} (1H, d, *J* = 11.3 Hz, CH**H**O), 4.12_{maj} and 3.92_{min} (1H, m, C**H**, THF), 2.25-$1.85_{maj\ and\ min}$ (7H, m, 2 x C**H**, O**H** and 2 x C$\mathbf{H_2}$, THF), 1.71-$1.45_{maj\ and\ min}$ (5H, m, C**H** and 2 x C$\mathbf{H_2}$), 1.34_{maj} and 1.31_{min} (3H, s, C$\mathbf{H_3}$), $1.24_{maj\ and\ min}$ (3H, s, C$\mathbf{H_3}$), $1.22_{maj\ and\ min}$ (3H, s, C$\mathbf{H_3}$), $1.12_{maj\ and\ min}$ (3H, s, C$\mathbf{H_3}$), 1.08-$0.90_{\ maj\ and\ min}$ (2H, m, C$\mathbf{H_2}$) ppm.

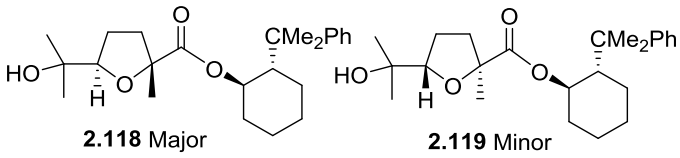
^{13}C NMR (100 MHz, $CDCl_3$): δ 184.0_{maj} and 183.8_{min} (**C**=S), 171.6_{maj} and 171.01_{min} (**C**=O), 150.8_{maj} and 150.5_{min} (**C**CH, Ar), $137.1_{maj\ and\ min}$ (N**C**HN), $131.0_{maj\ and\ min}$, (N**C**HCH), 128.2_{maj} and 128.1_{min} (2 x **C**H, Ar), 125.6_{min} and 125.5_{maj} (2 x **C**H, Ar), $125.38_{maj\ and\ min}$ (**C**H, Ar), $117.8_{maj\ and\ min}$ (**C**HN), 88.4_{maj} and 87.9_{min} (**C**H, THF), 84.09_{maj} and 84.1_{min} (**C**CH_2OH, THF), 77.2_{min} and 77.1_{maj} (O**C**H), 75.0_{maj} and 74.6_{min} (**C**H_2OCS), 70.7_{maj} and 70.6_{min} (**C**OH), 50.4_{maj} and 50.3_{min} (**C**HCPh), 40.3_{min} and 40.2_{maj} (**C**Ph), 33.1_{maj} and 33.0_{min} (**C**H_2CHO), 32.9_{maj} and 32.1_{min} (**C**H_2, THF), 27.9_{maj} and

27.6$_{min}$ (**C**H$_3$CPh), 27.5$_{maj\ and\ min}$ (**C**H$_3$COH), 27.4$_{maj\ and\ min}$ (**C**H$_2$,THF), 26.2$_{maj\ and\ min}$ (**C**H$_2$CHCHO), 25.9$_{min}$ and 25.7$_{maj}$ (**C**H$_2$CH$_2$CH), 25.6$_{maj\ and\ min}$ (**C**H$_3$COH), 24.8$_{maj\ and\ min}$ (**C**H$_3$CPh), 24.5$_{maj\ and\ min}$ (**C**H$_2$CH$_2$CHO) ppm.

LRMS (ESI$^+$) m/z: 515 [M+Na]$^+$ Da.

HRMS (ESI$^+$) m/z: Calculated: 515.2574; Found: 515.2572 ([M+Na]$^+$) Da.

(2*R*,5*R*)-(1*R*,2*S*)-2-(2-Phenylpropan-2-yl)cyclohexyl tetrahydro-5-(2-hydroxypropan-2-yl)-2-methylfuran-2-carboxylate (2.118) (+ minor diastereoisomer- 2.119, dr. 4.2:1)



2.118 Major **2.119** Minor

$C_{24}H_{36}O_4$
Mol. wt. 388.55 g/mol
(Yellow oil)

Following the procedure for the radical deoxygenation of xanthate THF-TTC **2.29**, a mixture of distereomeric xanthates **2.142/2.143** (35 mg, 0.068 mmol) afforded a mixture of the title THF-TCC **2.118/2.119** as a yellow oil (13.0 mg, 0.03 mmol, 49%).

[α]$^{27}_D$: +24.6 (*c* 0.75, $CHCl_3$).

FT-IR ν$_{max}$ (neat): 3458 (br.), 2949 (w), 2927 (s), 2858 (m), 1725 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.28$_{maj\ and\ min}$ (4H, m, 4 x C**H**, Ar), 7.16 (1H, m, x C**H**, Ar), 4.86$_{min}$ and 4.79$_{maj}$ (1H, td, *J* = 10.0, 4.3 Hz, OC**H**), 3.97$_{maj}$ and 3.91$_{min}$ (1H, t, *J* = 7.0 Hz, C**H**, THF), 2.15-1.90$_{maj\ and\ min}$ (4H, m, 2 x C**H$_2$**, THF), 1.87-1.78$_{maj\ and\ min}$ (2H, m, 2 x C**H**), 1.75-1.50 $_{maj\ and\ min}$ (4H, m, 4 x C**H**), 1.48-1.12$_{maj\ and\ min}$ (2H, m, 2 x C**H)**, 1.37$_{maj}$ (3H, s, C**H$_3$**), 1.36$_{maj}$ (3H, s, C**H$_3$**), 1.32$_{min}$ (3H, s, C**H$_3$**), 1.28$_{maj}$ (3H, m, C**H$_3$**), 1.25$_{maj}$ (3H, s, C**H$_3$**), 1.14$_{maj}$ (3H, s, C**H$_3$**), 1.13$_{maj}$ (3H, s, C**H$_3$**), 1.11$_{maj}$ (3H, s, C**H$_3$**) 0.97$_{maj}$ (1H, m, C**H**) ppm.

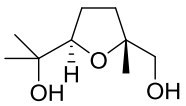
^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6$_{maj}$ and 174.0$_{min}$ (**C**=O), 150.8$_{min}$ and 150.6$_{maj}$ (**C**CH, Ar), 128.3$_{min}$ and 128.0$_{maj}$ (2 x **C**H, Ar), 125.71$_{maj\ and\ min}$ (2 x **C**H, Ar), 125.32 $_{maj\ and\ min}$ (**C**H, Ar), 87.0$_{maj}$ and 86.9$_{min}$ (**C**H, THF), 83.7$_{min}$ and 83.6$_{maj}$ (**C**CH$_2$OH, THF), 76.1$_{maj\ and\ min}$ (O**C**H), 70.9 $_{maj\ and\ min}$ (**C**OH), 50.8$_{maj}$ and 50.6$_{min}$ (**C**HCPh), 40.5$_{min}$ and 40.4 $_{maj}$ (**C**Ph), 36.6$_{maj}$ and 36.0$_{min}$ (**C**H$_2$CHO), 33.13$_{min}$ and 33.08$_{maj}$ (**C**H$_2$, THF), 29.1$_{maj\ and\ min}$ (**C**H$_3$CPh), 27.6$_{maj}$ and 27.5$_{min}$ (**C**H$_3$COH), 27.3$_{min}$ and 27.2$_{maj}$ (**C**H$_2$,THF), 25.9$_{maj}$ and 25.8$_{min}$ (**C**H$_2$CHCHO), 25.84$_{maj}$ and 25.77$_{min}$ (**C**H$_2$CH$_2$CH), 25.0$_{maj}$ and

24.9_{min} (**C**H_3COH), $24.6_{maj\ and\ min}$ (**C**H_3CPh), 24.4_{min} and 24.3_{maj} (**C**H_3CHO), $24.2_{maj\ and}$ 24.0_{min} (**C**H_2CH_2CHO) ppm.

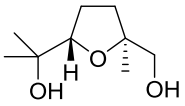
LRMS (ESI$^+$) m/z: 406 $[M+NH_4]^+$ Da.

HRMS (ESI$^+$) m/z: Calculated: 411.2506; Found: 411.2508 ($[M+Na]^+$) Da.

(2*R*,5*R*)-Tetrahydro-5-(2-hydroxypropan-2-yl)-2-methylfuran-2-carbaldehyde ((2*R*,5*R*)-2.120) (+ minor enantiomer-2.121)(from (1*R*,2*S*)-TCC)



2.122 Major



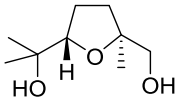
2.123 Minor

$C_9H_{18}O_3$
Mol.Wt.: 174.24 g/mol
(Yellow oil)

Following the procedure for the reduction of the THF-TTC **2.30** with DIBALH, the mixture of distereomeric THF-TCC **2.118/2.119** (13.00 mg, 0.033 mmol) was stirred with DIBALH at rt or 23 h gave a mixture of the title diols **2.120/2.121** (5.00 mg, 0.03 mmol, 86%, er. 4.2:1 by HPLC). ^{1}H NMR data was used to characterize the product which was reported within the group.[13,39]

FT-IR ν_{max} (neat): 3396 (br), 2970 (m), 2931 (m), 1052 (s) cm^{-1}.
^{1}H NMR (300 MHz, CDCl3) δ 3.79 (1H, t, *J* = 7.7 Hz, OC**H**), 3.45 (2H, d, *J* = 5.9 Hz, C**H**$_2$OH), 2.33 (1H, t, *J* = 6.4 Hz, CH_2O**H**), 2.28 (1H, s, O**H**), 2.02-1.81 (3H, m, C**H**$_2$), 1.65 (1H, m, C**H**$_2$), 1.20 (3H, s, C**H**$_3$), 1.19 (3H, s, CH_3), 1.13 (3H, s, C**H**$_3$).
^{13}C NMR (75 MHz, $CDCl_3$) δ 86.9 (O**C**H), 83.6 (**C**), 70.8 (**C**), 68.4 (**C**H_2OH), 33.6 (**C**H_2), 27.4 (**C**H_3), 26.6 (**C**H_2), 23.9 (**C**H_3), 23.8 (**C**H_3).
LRMS (ESI$^+$) m/z: 197 ($[M+Na]^+$).
HRMS (ESI$^+$) m/z: Calculated: 197.1154, found: 197.1152 ($[M+Na]^+$).

(2*S*,5*S*)-Tetrahydro-5-(2-hydroxypropan-2-yl)-2-methylfuran-2-carbaldehyde ((2*S*,5*S*)-2.121) (from (–)(1*S*,2*R*)-TTC)



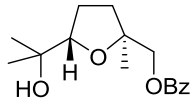
$C_9H_{18}O_3$
Mol.wt.: 174.24 g/mol
(Yellow oil)

To a solution of aldehyde **2.124** (30 mg, 0.174 mmol, the compound was prepared in a previous study within the group using (–)(1*S*, 2*R*)-TTC auxilarary[39]) in MeOH (700 µL)

was added $NaBH_4$ (39.0 mg, 1.03 mmol) at –5 °C. The mixture was stirred at this temperature and allowed to warm to rt. After 5 h, citric acid (10% aq., 500 µL) was added dropwise. MeOH was removed *in vacuo*, CH_2Cl_2 (3.0 mL) and H_2O (3.0 mL) were added. The organic phase was separated and the aqueous phase was re-extracted with CH_2Cl_2 (3 x 3.0 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product as a yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/hexane (10%) to give the title alcohol **2.121** as a yellow oil (12.0 mg, 0.069 mmol, 40%).[1]H NMR was consistent with that reported before.[39]

$[\alpha]^{24}_D$: –4.5 (*c* 0.60, $CHCl_3$).

((2*S*,5*S*)-5-(2-Hydroxypropan-2-yl)-2-methyltetrahydrofuran-2-yl)methyl benzoate ((2.123, er. 59:1) (from (1*S*,2*R*)-TTC)



$C_{16}H_{22}O_4$
Mol.wt.: 278.34 g/mol
(Yellow oil)

To a solution of diol (2*S*,5*S*)-**2.121** (12 mg, 0.069 mmol) in CH_2Cl_2 (300 µL) and Et_3N (48.0 µL, 0.34 mmol) was added BzCl (8.00 µL, 0.07 mmol) at rt. After 23 h at rt, the solvent was removed under reduced pressure and Et_2O (2.0 mL) was added. The mixture was washed with (aq. sol. 10%) K_2CO_3 (2 x 1 mL), then with brine (1.0 mL) and H_2O (3.0 mL). The organic phase was dried ($MgSO_4$), and the solvent was removed *in vacuo* to afford a crude product as a yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/ hexane, (10% to 30%) to afford the title benzoate (2*S*,5*S*)-**2.123** as a yellow oil (6.50 mg, 0.02 mmol, 34%), which was analysed by chiral HPLC giving an enantiomeric ratio of 98.3:1.7 (~59:1).

$[\alpha]^{21}_D$: +10.0 (*c* 0.11, $CHCl_3$).

FT-IR ν_{max} (neat): 6490 (br.), 2974 (m), 2917 (w), 2875 (w), 1720 (s), 1275 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (2H, d, *J* = 7.5 Hz, 2 x C**H**, Ar), 7.59 (1H, t, *J* = 7.5 Hz, 2 x C**H**, Ar), 7.47 (2H, t, *J* = 7.5 Hz, C**H**, Ar), 4.29 (1H, d, *J* = 10.9 Hz, C**H**HOH), 4.24 (1H, d, *J* = 10.9 Hz, CH**H**OH), 3.88 (1H, t, *J* = 7.5 Hz, OC**H**), 2.10 (1H, br, O**H**), 2.10 (1H, br, O**H**), 2.05 (1H, m, C**H**H), 1.96-

1.89 (2H, m, C**H**$_2$), 1.80 (1H, m, CH**H**), 1.36 (3H, s, C**H**$_3$), 1.23 (3H, s, C**H**$_3$), 1.15 (3H, s, C**H**$_3$) ppm.

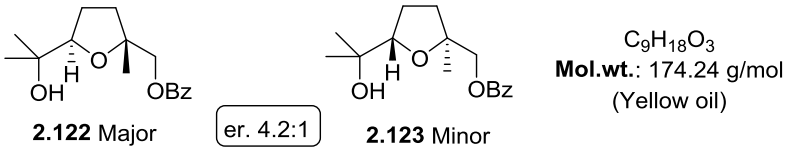
^{13}C NMR (100 MHz, CDCl$_3$): δ 166.4 (**C**=O), 133.0 (2 x **C**H, Ar), 130.2 (**C**, Ar), 129.6 (2 x **C**H, Ar), 128.42 (2 x **C**H, Ar), 86.6 (O**C**H), 81.7 (**C**CH$_3$, THF), 70.7 (**C**OH), 69.9 (**C**H$_2$O), 34.7 (**C**H$_2$, THF), 27.5 (**C**H$_2$, THF), 26.3 (**C**H$_3$COH), 24.6 (**C**H$_3$COH), 24.1 (**C**H$_3$CO) ppm.

LRMS (ESI$^+$) m/z: 301.05 $[M+Na]^+$ Da.

HRMS (ESI$^+$) m/z: Calculated: 301.1410; Found: 301.1409 ($[M+Na]^+$) Da.

HPLC: Chiralpak® AD-H - (eluent: IPA/*n*-hexane 7.5:92.5) - 0.3 mL/min. Retention times: t_{maj} = 31.9 min & t_{min} = 35.1 min.

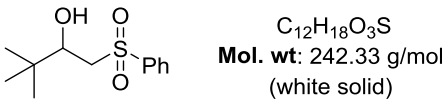
((2*R*,5*R*)-5-(2-Hydroxypropan-2-yl)-2-methyltetrahydrofuran-2-yl)methyl benzoate (2.122) and (+minor enantiomer (2*S*,5*S*)- 2.123 er. 4.2:1) (from (1*R*,2*S*)-TCC)



Following the procedure for the benzoylation of the (2*S*,5*S*)-diol (2*S*, 5*S*)- **2.121**, the mixture of enantiomeric diols **2.120/2.121**(5.00 mg, 0.03 mmol) was converted to the corresponding benzoates **2.122/2.123** (5.00 mg, 0.02 mmol, 62%). Physical and Spectroscopic data are consistent with that reported above. The sample was analysed by chiral HPLC, which showed an enantiomeric ratio of 80.9:19.1 (~4.2:1).

HPLC: Chiralpak® AD-H - (eluent: IPA/n-hexane 7.5:92.5) - 0.3 mL/min Retention times: t_{maj} =35.1 min & t_{min} = 31.9 min.

3,3-Dimethyl-1-(phenylsulfonyl)butan-2-ol (2.72)



To a solution of methyl phenyl sulfone (1.85 g, 11.6 mmol) in THF (60 mL) was added dropwise a solution of LDA (12.2 mL, 1.0M, 12.2 mmol) at –10 °C. The mixture was

stirred for 30 min, and allowed to warm to 0 °C. A solution of pivaldehyde (**2.71**, 1.00 g, 11.6 mmol) in THF (25 mL) was added dropwise to the anion of methyl phenyl sulfone solution at –78 °C. The mixture was stirred for 1 h at this temperature. H_2O (40 mL) was added, the aqueous layer was separated and re-extracted with CH_2Cl_2 (2 x 50 mL). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product as a yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/hexane (10 to 30 %) to give the title product as a racemic mixture **2.72** as a white solid (1.63 g, 6.73 mmol, 58%). 40% of the aldehyde was recovered.

mp: 53-54 °C.

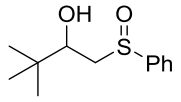
FT-IR ν_{max} (neat): 3528 (br), 2958 (m), 2897 (w), 2871 (w), 1290 (s), 1135 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 7.95 (2H, d, *J* = 8.3 Hz, 2 x C**H**, Ar), 7.69 (1H, m, C**H**, Ar), 7.60 (2H, t, *J* = 7.87 Hz, 2 x C**H**, Ar), 3.78 (1H, br dd, *J* = 9.9 and 1.2 Hz, C**H**OH), 3.29-3.09 (3H, m, O**H**, C$\mathbf{H}_2$), 0.87 (9H, s, 3 x C$\mathbf{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$): 139.2 (**C**, Ar), 133.9 (**C**H, Ar), 129.4 (2 x **C**H, Ar), 127.9 (2 x **C**H, Ar), 73.2 (**C**HOH), 58.8 (**C**H_2), 34.9 (**C**Me_3), 25.3 (2 x **C**H_3) ppm.
LRMS (ESI$^+$) m/z: 243 $[M+H]^+$ Da.

HRMS (ESI$^+$) m/z: Calculated: 265.0869; Found: 265.0869 ($[M+Na]^+$) Da.

3,3-dimethyl-1-(phenylsulfinyl)butan-2-ol (2.73)



$C_{12}H_{18}O_2S$
Mol. wt: 226.33 g/mol
(White solid)

To a solution of methyl phenyl sulfoxide (1.62 g, 11.6 mmol) in THF (60 mL) was added dropwise a solution of LDA (12.2 mL, 1.0M in THF/ Hexane, 12.2 mmol) at –10 °C. The mixture was stirred for 30 min, and allowed to warm to 0 °C. A solution of pivaldehyde (**2.71**, 1.00 g, 11.6 mmol) in THF (25 mL) was added dropwise to the anion of methyl phenyl sulfoxide solution at –78 °C. The mixture was stirred for 1 h at this temperature. H_2O (40 mL) was added, the aqueous layer was separated and re-extracted with Et_2O (4 x 100 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product as yellow oil. The crude

product was purified by column chromatography (SiO_2) eluting with EtOAc/hexane (5 to 30%) to give the title compound as inseparable diastereoisomers **2.73** as a white solid (2.15 g, 9.50 mmol, 82%, dr. 1.3:1 by ^{1}H NMR).

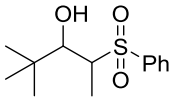
mp : 72-74 ◦C

FT-IR ν_{max} (neat): 3295 (br), 3036 (w), 2961 (m), 2868 (w), 1078 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73-7.46 (10H, m, 10 x C**H**, Ar), 3.90-3.81 (4H, m, 2 x C**H**OH, 2 x O**H**), 2.97 (1H, m, C**H**HSO), 2.88 (2H, d, *J* = 6.2 Hz, 2 x CH**H**SO), 2.74 (1H, d, *J* = 13.2 Hz, C**H**HSO), 0.92 and 0.96 (18H, m, 2 x **Me**$_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9 and 143.2 (**C**, Ar), 131.4 and 130.9 (**C**H, Ar), 129.5 and 129.3 (2 x **C**H, Ar), 124.0 (2 x **C**H, Ar), 76.3 and 73.4 (**C**HOH), 58.8 and 58.5 (**C**H_2), 35.3 and 34.9 (**C**Me_3), 25.4 (3 x **C**H_3) ppm.
LRMS (ES^+) m/z: 227 $[M+H]^+$ Da.

HRMS (ESI^+) m/z: Calculated: 249.0921; Found: 249.0921($[M+Na]^+$) Da.

2,2-Dimethyl-4-(phenylsulfonyl)pentan-3-ol (2.74)



$C_{13}H_{20}O_3S$
Mol.wt: 256.36 g/mol
(Yellow oil)

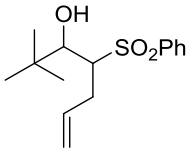
To a solution of *β*-hydroxyl sulfone **2.72** (100 mg, 0.43 mmol) in THF (4 mL) was added dropwise a solution of LDA (930 µL, 0.92M in THF/hexane, 0.43 mmol) at –78 °C. The mixture was stirred at 0 °C for 10 min, then re-cooled to –78 °C and was stirred for 20 min. Methyl iodide (26.7 µL, 0.429 mmol) to the dianion at –78 °C and the mixture was allowed to warm to rt and stirred for 4 h. The reaction was quenching with sat. NH_4Cl sol. (3 mL), the aqueous layer was separated and re-extracted with CH_2Cl_2 (3 x 4 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude as a yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/hexane (20 to 30%) to give the title product **2.74** as an inseparable mixture with the S.M as a yellow oil (85.7 mg, 0.33 mmol, 78%, ^{1}H NMR of the crude compound showed a ratio of the product to S.M~3:1).

FT-IR ν_{max} (neat): 3520 (m), 2952 (m), 22906 (w), 2872 (w), 1286 (s), 1137 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 7.93 (2H, m, 2 x C**H**, Ar), 7.69 (1H, m, C**H**, Ar), 7.59 (2H, m, 2 x C**H**, Ar), 4.00 (1H, d, *J* = 3.7 Hz, C**H**OH), 3.31 (1H, m, C**H**SO), 2.31 (1H, d, *J* = 3.7 Hz, O**H**), 1.37 (3H, d, *J* = 7.0 Hz, C$\mathbf{H}_3$), 0.88 (9H, s, 3 x C$\mathbf{H}_3$).
^{13}C NMR (100 MHz, $CDCl_3$): 137.2 (**C**, Ar), 133.8 (**C**H, Ar), 129.2 (2 x **C**H, Ar), 128.8 (2 x **C**H, Ar), 73.5 (CHOH), 60.6 (**C**HCH$_3$), 35.8 (**C**Me$_3$), 26.4 (2 x **C**H$_3$), 8.4 (**C**H$_3$) ppm.
LRMS (ESI$^+$) m/z: 279 $[M+Na]^+$ Da.

HRMS (ESI$^+$) m/z: Calculated: 279.1025; Found: 279.1026 ($[M+Na]^+$) Da.

2,2-Dimethyl-4-(phenylsulfonyl)hept-6-en-3-ol (2.76)



$C_{15}H_{22}O_3S$
Mol.wt: 282.40 g/mol
(Colourless oil)

To a solution of *β*-hydroxyl sulfone **2.72** (56.5 mg, 0.23 mmol) in THF (2.2 mL) was added LDA (240 µL, 2.0M in ethyl benzene, 0.48 mmol). The mixture was stirred at 0 °C for 10 min then at –78 °C for 20 min. Allyl bromide (25.0 mg, 0.21 mmol) was added at –78 °C then the mixture was stirred at rt for 6 h. Sat NH_4Cl sol. (1 mL) and H_2O (1 mL) were added, the aqueous layer was re-extracted with CH_2Cl_2 (3 x 4 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product as a yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/hexane (5 to 20%) to provide the title product **2.72** as a colourless oil (19.2 mg, 0.07 mmol, 29%). 42% of the *β*-hydroxyl sulfone was recovered.

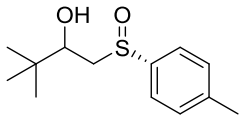
FT-IR ν_{max} (neat): 3525 (br), 2956 (m), 2916 (s), 2871 (s), 1302 (m), 1140 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ7.96-7.87 (2H, m, 2 x C**H**, Ar), 7.70-7.755 (1H, m, C**H**, Ar), 7.59 (2H, t, *J* = 7.8 Hz, 2 x C**H**, Ar), 5.65 (1H, dddd, *J* = 16.7, 10.4, 7.7 and 6.1 Hz, C**H**=C), 4.94-4.88 (2H, m, CH=C$\mathbf{H}_2$), 3.97 (1H, d, *J* = 3.6 Hz, C**H**OH), 3.23 (1H, dd, *J* = 8.0 and 2.0 Hz, C**H**SO), 2.79 (1H, m, C**H**HCH=C), 2.57 (1H, m, CH**H**CH=C), 2.45 (1H, d, *J* = 3.7 Hz, O**H**), 0.86 (9H, s, 3 x C$\mathbf{H}_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 137.5 (**C**, Ar), 135.6 (**C**H=C), 133.9 (**C**H, Ar), 129.3 (2 x **C**H, Ar), 129.0 (2 x **C**H, Ar), 116.6 (**C**H_2=CH), 74.4 (**C**HOH), 65.4 (**C**HSO), 35.8 (**C**$(CH_3)_3$), 27.3 (3 x CH_3) ppm.
LRMS (ES^+) m/z: 305 $[M+Na]^+$ Da.

HRMS (ESI^+) m/z: Calculated: 305.1182; Found: 305.1177 ($[M+Na]^+$) Da.

3,3-Dimethyl-1-((*S*)-p-tolylsulfinyl)butan-2-ol (2.105)



2.105

$C_{13}H_{20}O_2S$
Mol. wt: 240.36 g/mol
(White solid)

To a solution of (*S*)-(–)-methyl phenyl sulfoxide (500 mg, 3.24 mmol) in THF (16 mL) was added dropwise a solution of LDA (2.3 mL, 1.0M, 3.2 mmol) at –10 °C. The mixture was stirred for 45 min, and allowed to warm to 0 °C. A solution of pivalaldehyde (**2.71**, 279 mg, 3.24 mmol) in THF (6.9 mL) was then added at –78 °C. The mixture was stirred for 3 h at this temperature. H_2O (12 mL) was added, the aqueous layer was separated and re-extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude as a yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/hexane (10 to 80%) to give the title sulfoxide **2.105** as a white solid as inseparable diastereoisomers (425 mg, 1.77 mmol, 55%, dr . 1.2:1 by ^{1}H NMR, 28% of the aldehyde **2.71** was recovered, during the column chromatography some of the major isomer was collected as a single isomer).

mp: 93-95 °C.

FT-IR ν_{max} (neat): 3406, 3284 (br), 2965(w), 2947(m), 2932 (w), 2870 (m), 1257 (m), 1082 (s) cm^{-1}.

Data for the major isomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (2H, d, *J* = 8.0 Hz, 2 x C**H**, Ar), 7.36 (2H, d, *J* = 8.0 Hz, 2 x C**H**, Ar), 3.94 (1H, td, *J* = 6.0 and 2.0 Hz, C**H**OH), 3.83 (1H, d, *J* = 2.0 Hz, O**H**), 2.84 (2H, d, *J* = 6.0 Hz, C$\mathbf{H}_2$SO), 2.44 (3H, s, C$\mathbf{H}_3$), 0.92 (9H, s, 3 x C$\mathbf{H}_3$) ppm.

^{13}C NMR (100 MHz, CDCl3): δ 142.1 (**C**, Ar), 140.7 (**C**, Ar), 130.2 (2 x **C**H, Ar), 124.0 (2 x **C**H, Ar), 76.5 (**C**HOH), 58.6 (**C**H_2), 35.3 (**C**Me_3), 25.5 (3 x **C**H_3), 21.5 (**C**H_3Ph) ppm.

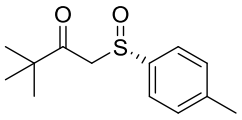
Data for the minor isomer:

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.53 (2H, d, *J* = 8.0 Hz, 2 x C**H**, Ar), 7.36 (2H, d, *J* = 8.0 Hz, 2 x C**H**, Ar), 3.79 (1H, m, C**H**OH), 3.37 (1H, m, O**H**), 3.0 (1H, m, C**H**HSO), 2.68 (1H, d, *J* = 11.6 Hz, CH**H**SO), 2.44 (3H, s, C**H**$_3$), 0.86 (9H, s, 3 x C**H$_3$**) ppm.
^{13}C NMR (100 MHz, CDCl$_3$): δ 141.4 (**C**, Ar),), 139.7 (**C**, Ar),), 130.0 (2 x **C**H, Ar), 124.0 (2 x **C**H, Ar), 73.8 (**C**HOH), 57.5 (**C**H_2), 34.9 (**C**Me_3), 25.4 (3 x **C**H_3), 21.4 (**C**H_3Ph) ppm.

LRMS (ESI$^+$) m/z: 241 $[M+H]^+$ Da.

HRMS (ESI$^+$) m/z: Calculated: 263.1076; Found: 263.1079 ($[M+Na]^+$) Da.

(*S*)-3,3-Dimethyl-1-(*p*-tolylsulfinyl)butan-2-one (2.106)



$C_{13}H_{18}O_2S$
Mol.wt:238.35 g/mol
(White solid)

Following a procedure that reported by Sridhar *et al.*[104] to a solution of *β*-hydroxyl sulfoxide **2.105** (329 mg, 1.37 mmol) in CH_2Cl_2 (6.8 mL) was added Dess-Martin periodinane (755 mg, 1.78 mmol) at 0 °C. The mixture was stirred at this time for 2 h. The reaction mixture was diluted with CH_2Cl_2 (5.0 mL), the precipitate solid was filtrated, and the filtrate was washed with sat. $NaHCO_3$ sol. (25 mL), H_2O (25 mL), brine (25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product as a white solid. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/hexane (20 to 30 %) to give the title *β*-keto sulfoxide **2.106** as a white solid (298 mg, 1.25 mmol, 91%).

$[\alpha]^{24}_D$: –175 (*c* 0.718, $CHCl_3$); {lit. $[\alpha]^{25}_D$ = –180 (*c* 0.500, acetone)}.[113]

mp: 106-107 °C.

FT-IR ν_{max} (neat): 3957 (m), 2928 (m), 2929 (m), 2877 (m), 1697 (s), 1080 (s) cm^{-1}.

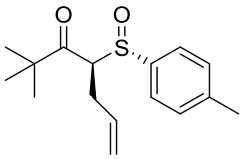
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (2H, d, *J* = 8 Hz, 2 x C**H**, Ar), 7.26-7.39 (2H, m, *J* = 8 Hz, 2 x C**H**, Ar), 4.17 (1H, d, *J* = 15.2 Hz, C**H**H), 3.82 (1H, d, *J* = 15.2 Hz, CH**H**), 2.42 (3H, s, C**H**$_3$Ph), 1.06 (9H, s, 3 x C**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 207.3 (C=O), 142.0 (**C**, Ar), 140.7 (**C**, Ar), 130.0 (2 x **C**H, Ar), 124.3 (2 x **C**H, Ar), 65.4 (**C**H_2), 44.6 (**C**Me_3), 25.5 (3 x **C**H_3), 21.4 (**C**H_3Ph) ppm.

LRMS (ESI$^+$) m/z: 239 $[M+H]^+$ Da.

HRMS (ESI$^+$) m/z: Calculated: 261.0920; Found: 261.0921($[M+Na]^+$) Da.

(*S*)-2,2-Dimethyl-4-((*S*)-p-tolylsulfinyl)hept-6-en-3-one (2.107)



$C_{16}H_{22}O_2S$
Mol. wt: 278.41 g/mol
(Yellow oil)

Following the procedure that reported by Maestro *et al.*,[109] to NaH (8.30 mg, 60% in mineral oil, 0.21 mmol) and TBAI (38.3 mg, 0.10 mmol) at rt was added a solution of *β*-keto sulfoixde **2.106** (50.0 mg, 0.21 mmol) in THF (1.2 mL). The mixture was stirred for 30 min. Allyl bromide (25.0 mg, 0.21 mmol) was added at rt and the mixture was stirred for 19 h. 5% HCl (400 µl) was added, the aqueous layer was re-extracted with CH_2Cl_2 (3 x 3 mL). The combined organic phases were washed with H_2O (5.0 mL) and brine (5.0 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product as a yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/hexane (0 to 25 %) to give the title product **2.107** as one isomer (6.00 mg, 0.02 mmol, 10%). The second distereoisomer was inseparable with the starting material. Elimination product was resulted as a main product (20.0 mg, 0.14 mmol, 70%).

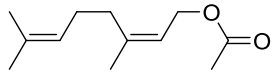
FT-IR ν_{max} (neat): 2986 (m), 2929 (w), 2870 (w), 2947(m), 1699 (s), 1049 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (2H, d, *J* = 8 Hz, 2 x C**H**, Ar), 7.34 (2H, d, *J* = 8 Hz, 2 x C**H**, Ar), 5.41-5.53 (1H, m, C**H**=CH_2), 4.97-5.01 (1H, m, C**H**H=C), 4.93-4.97 (1H, m, CH**H**=C), 4.36 (1H, dd, *J* = 10 and 4.0 Hz, C**H**CO), 2.44 (3H, m, C**H**$_3$Ph), 2.36 (1H, m, C**H**HCH=C), 2.21 (1H, m, CH**H**CH=C), 1.22 (9H, s, 3 x C**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 209.5 (C=O), 142.6 (**C**, Ar), 137.2 (**C**, Ar), 132.9 (**C**H=), 129.6 (2 x **C**H, Ar), 125.9 (2 x **C**H, Ar), 118.8 (**C**H_2=C), 69.5 (**C**HSO), 45.0 (**C**Me_3), 29.7 (**C**H_2CH=C), 26.0 (3 x **C**H_3), 21.5 (CH_3Ph) ppm.
LRMS (ESI$^+$) m/z: 279 $[M+H]^+$ Da.

HRMS (ESI$^+$) m/z: Calculated: 301.12.33; Found: 301.1228 ($[M+Na]^+$) Da.

(Z)-3,7-Dimethylocta-2,6-dien-1-yl acetate (1.69)



$C_{12}H_{20}O_2$
Mol. w: 196.29 g/mol
(Coulorless oil)

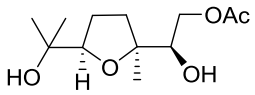
To a solution of Nerol (**1.58**, 6.0 g, 39 mmol) in pyridine (90 mL) was added Ac_2O (3.7 mL, 39 mmol). The mixture was stirred at 50 °C for 23 h. The reaction mixture concentrated *in vacuo* to afford the crude product as a brownish yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/hexane (5%) to give the title acetate **1.69** as a colorless oil (6.80 g, 34.6 mmol, 89%). Spectroscopic data are in agreement with the literature.[114]

FT-IR ν_{max}: 2968 (s), 2916 (s), 2833 (m), 1737 (s), 1445 (s), 1228 (s) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ 5.37 (1H, t, *J* = 7.3 Hz, C=C**H**CH_2O), 5.10 (1H, m, C=C**H**CH_2), 4.56 (2H, d, *J* = 7.3 Hz, C**H**$_2$Cl), 2.15-2.2.07 (4H, m, 2 x C**H**$_2$), 2.05 (3H, s, C**H**$_3$), 1.77 (3H, s, C**H**$_3$), 1.69 (3H, s, C**H**$_3$), 1.61 (3H, s, C**H**$_3$) ppm.

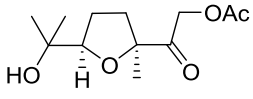
^{13}C NMR (75 MHz, $CDCl_3$): δ 171.07 (C=O), 142.64 (CH_3**C**=$CHCH_2O$), 132.16 (**C**=CH), 123.54 (C=**C**HCH_2O), 119.1 (C=**C**H), 61.09 (**C**H_2O), 32.14 (**C**H_2CCH_3), 26.62 (**C**H_2CH_2), 25.66 (**C**H_3), 23.45 (**C**H_3), 21.05 (**C**H_3), 17.63 (**C**H_3) ppm.

LRMS (ESI$^+$) m/z: 235 $[M+K]^+$ Da.

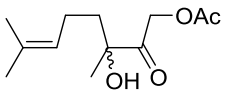
***Rac*-2-Hydroxy-2-(5-(2-hydroxypropan-2-yl)-2-methyltetrahydrofuran-2-yl)ethyl acetate (1.70)**



1.70 (28%)



1.125 (24%)



2.79 (18%)

$C_{12}H_{22}O_5$
Mol. w.: 246.30 g/mol
(white solid)

To a vigorously stirred mixture of methyl neryoate (**1.69**, 4.00 g, 20.4 mmol) and phosphate buffer (KH_2PO_4/Na_2HPO_4, pH 7, 40.8 mL) in acetone (250 mL) at –35 °C was added a solution of $NaMnO_4$ (76.4 mL, 0.4M aq., 30.6 mmol) containing AcOH (3.50 mL, 61.1 mmol). The purple mixture was stirred rapidly for 1 h. The reaction was quenched with sat. aq. $Na_2S_2O_5$ (250 mL) and the mixture was stirred at rt to dissolve all of the precipitated manganese. Acetone was removed *in vacuo,* and the solution was extracted with CH_2Cl_2 (2 x 250 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude as a yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with MeOH/EtOAc/DCM (0.5:20:79.5 then 0.5:30:69.5) to provide the title compound **1.70** (1.40 g, 5.68 mmol, 28%) along with lactol **1.125** (1.20 g, 4.91, 24%) and lactol **2.79** (825 mg, 3.61 mmol, 18%). Spectroscopic data are in agreement with the literature.[115]

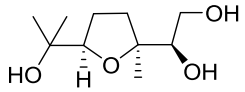
FT-IR ν_{max} (neat): 3403 (br), 2973 (m), 2935 (w), 2876 (w), 1724 (s), 1452 (m), 1372 (m), 1237 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.39 (1H, dd, *J* = 11.6, 2.4 Hz, CH**H**OAC), 3.96 (1H, dd, *J* = 11.6, 8.1 Hz, C**H**HOAC), 3.85-3.81 (2H, m, CH (THF ring), C**H**OH), 3.27 (1H, br s, OH) 2.55 (1H, br s, OH), 2.20 (1H, m, THF ring), 2.10 (3H, s, C**H**$_3$CO$_2$), 2.051.87 (2H, m, THF ring), 1.58 (1H, dt, *J* = 12.4, 8.2 Hz, THF ring), 1.29 (3H, s, C**H**$_3$), 1.22 (3H, s, C**H**$_3$), 1.12 (3H, s, C**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5 (C=O), 85.0 (**C**CH$_3$, THF ring), 84.3 (**C**OH), 75.1 (**C**(CH$_3$)$_2$OH), 71.6 (CHOH), 66.2 (**C**H$_2$OAc), 33.0 (**C**H$_2$, THF ring), 27.7 (**C**H$_2$, THF ring), 26.5 (**C**H$_2$, THF ring), 25.3 (**C**H$_3$COH), 23.1 (**C**H$_3$COO), 20.9 (**C**H$_3$CO) ppm.

LRMS (ESI$^+$) m/z: 247 $[M+H]^+$ Da.

***Rac*-1-(5-(2-hydroxypropan-2-yl)-2-methyltetrahydrofuran-2-yl)ethane-1,2-diol (2.80)**



$C_{10}H_{20}O_4$
Mol. w.: 204.27 g/mol
(Yellow oil)

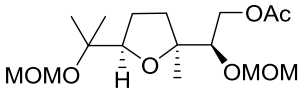
To a solution of the acetate **1.70** (306 mg, 1.24 mmol) in MeOH (9.0 mL) was added K_2CO_3 (687 mg, 4.96 mmol). The mixture was stirred at rt for 1 h, H_2O was added and

MeOH was removed *in vacuo*. The solution was re-extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title triol **2.80** as a yellow oil (152 mg, 0.74 mmol, 60%).

FT-IR ν_{max} (neat): 3461 (br), 2972 (m), 2931 (w), 2876 (w), 1377 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.95 (1H, br, O**H**), 3.81 (1H, t, *J* = 7.2 Hz, C**H**O, THF), 3.70 (2H, m, C**H**$_2$OH), 3.54 (1H, m, C**H**OH), 3.09 (2H, br. 2 x O**H**), 2.14 (1H, ddd, *J* = 12.2, 8.7 and 6.0 Hz, C**H**, THF ring), 2.02-1.88 (2H, m, C**H**$_2$, THF ring), 1.55 (1H, m, C**H**, THF), 1.29 (3H, s, C**H**$_3$), 1.19 (3H, s, C**H**$_3$), 1.14 (3H, s, C**H**$_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): 84.8 (**C**O, THF ring), 84.5 (**C**HO, THF ring), 76.7 (**C**Me$_2$OH), 72.0 (**C**HOH), 63.4 (**C**H$_2$OH), 32.0 (**C**H$_2$, THF ring), 27.7 (**C**H$_2$, THF ring), 26.6 (**C**H$_2$, THF ring), 25.5 (**C**H$_3$COH), 23.6 (**C**H$_3$CO) ppm.
LRMS (ESI$^+$) m/z: 227 ([M+H]$^+$) Da.

***Rac*.- 2-(methoxymethoxy)-2-(5-(2-(methoxymethoxy)propan-2-yl)-2-methyltetrahydrofuran-2-yl)ethyl acetate (2.89)**



$C_{16}H_{30}O_7$
Mol. wt.: 334.41 g/mol
(Yellow oil)

To a solution of the acetate **1.70** (900 mg, 3.65 mmol) in CH_2Cl_2 (34 mL) was added dropwise DIPEA (3.18 mmol) and MOM-Cl (833 µL, 10.3 mmol) at 0 °C. The mixture was stirred at rt for 24 h. Et_2O (35 mL), the solution was re-washed with HCl (10% aq., 3 x 35 mL), brine (34 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product as a yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with EtOAc/hexane (10%) to give the title di-protected acetate **2.89** as a yellow oil (387 g, 1.16 mmol, 32%) along with partial deprotection acetate as a yellow oil (405 mg, 1.49 mmol, 41%). Following the same procedure above, the mono protected alcohol was converted to the title diprotected acetate **2.89** (252 mg, 0.75 mmol, 50%). The mono-protected acetate was recovered (104 mg, 0.358 mmol, 24%).

FT-IR ν_{max} (neat): 2975 (w), 2937 (w), 2889 (w), 2845 (w), 2822 (w), 1740 (s), 1463 cm^{-1}.

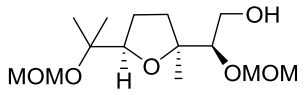
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.75 (1H, d, *J* = 2.0 Hz, OC**H**HO), 4.73 (1H, d, *J* = 1.6 Hz, OCH**H**O), 4.69 (1H, d, *J* = 2.2 Hz, OC**H**HO), 4.67 (1H, d, *J* =1.8 Hz, OCH**H**O), 4.41 (1H, dd, *J* = 11.9 and 2.3 Hz, C**H**HOAc), 4.11 (1H, dd, *J* = 11.7 and 7.6 Hz, CH**H**OAc), 3.85 (1H, t, *J* = 7.6 Hz, C**H**O, THF ring), 3.67 (1H, dd, *J* = 7.5 and 2.3 Hz, C**H**OMOM), 3.36 (3H, s, CH_3O), 3.32 (3H, s, CH_3), 2.07-2.0 (4H, m, CH (THF ring) and CH_3), 1.78-1.94 (2H, m, CH_2, THF ring), 1.59 (1H, m, CH_2, THF ring), 1.18 (3H, s, C**H**$_3$), 1.17 (3H, s, C**H**$_3$), 1.16 (3H, s, C**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ170.8 (**C**=O), 97.4 (O**C**H_2O), 91.2 (O**C**H_2O), 84.8 (**C**O, THF), 83.7 (**C**HOMOM), 80.3 (**C**HO, THF ring), 77.3 (**C**Me_2), 65.5 (**C**H_2OAc), 55.7 (**C**H_3O), 55.0 (**C**H_3O), 35.0 (**C**H_2, THF ring), 26.1 (**C**H_2, THF ring), 22.9 (**C**H_3), 22.3 (**C**H_3), 21.6 (**C**H_3), 20.9 (**C**H_3) ppm.

LRMS (ESI$^+$) m/z: 357 $[M+Na]^+$ Da.

HRMS (ESI$^+$) m/z: Calculated: 357.1884; Found: 351.1889 ($[M+Na]^+$) Da.

2-(Methoxymethoxy)-2-(5-(2-(methoxymethoxy)propan-2-yl)-2-methyltetrahydrofuran-2-yl)ethan-1-ol (2.90)



$C_{14}H_{28}O_6$
Mol. wt.: 292.37 g/ mol
(Yellow oil)

Following the procedure for hydrolysis of acetate **2.80**, the di-protected acetate **2.89** (387 mg, 1.157 mmol) was hydrolysed to alcohol **2.90** as a yellow oil (311 mg, 1.06 mmol, 92%).

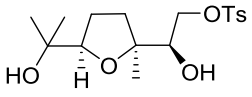
FT-IR ν_{max} (neat): 3473 (br m), 2974 (w), 2937 (w), 2887 (w), 2847 (w), 2823 (w), 1465 (m), 1092 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.59-4.52 (3H, m, 3 x OC**H**HO), 4.47 (1H, d, *J* = 6.6 and 2.3 Hz, OCH**H**O), 3.70-3.64 (2H, m, C**H**O (THF ring), C**H**HOH), 3.40 (1H, ddd, *J* = 11.5, 6.2 and 5.0 Hz, CH**H**O), 3.31-3.28 (2H, m, C**H**HO and OH), 3.22 (3H, s, CH_3), 3.17 (3H, s, CH_3O), 1.80 (1H, m, C**H**H, THF ring), 1.72-1.65 (2H, m, C**H**$_2$, THF ring), 1.46 (H, m, CH**H**, THF ring), 1.03 (3H, s, C**H**$_3$), 1.00 (3H, s, C**H**$_3$), 0.99 (3H, s, C**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 97.4 (O**C**H_2O), 91.3 (O**C**H_2O), 85.6 (**C**O, THF ring), 85.3 (**C**HOMOM), 84.5 (**C**HO, THF ring), 76.7 (**C**Me_2), 62.4 (**C**H_2OH), 55.8 (**C**H_3O), 55.2 (**C**H_3O), 35.8 (**C**H_2, THF), 26.1 (**C**H_2, THF), 22.9 (**C**H_3), 22.88 (**C**H_3), 21.5 (**C**H_3) ppm.

LRMS (ESI$^+$) m/z: 315 (30%, $[M+Na]^+$) Da.

2-Hydroxy-2-(5-(2-hydroxypropan-2-yl)-2-methyltetrahydrofuran-2-yl)ethyl4-methylbenzenesulfonate (2.81)



$C_{17}H_{26}O_6S$
Mol. wt.: 358.45 g/mmol
(White oil)

Following the procedure for selective tosylation of RHF triol **1.42**, the triol **2.80** (152 mg, 0.74 mmol) was tosylated to the title tosylate **2.81** as a white oil (293 mg, 0.67 mmol, 90%).

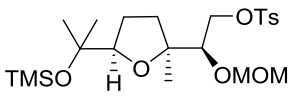
FT-IR ν_{max} (neat): 3528 (br. w), 3384 (br. w), 2973 (w), 2930 (w), 2875 (w), 1452 (m), 1357 (m), 1173 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (2H, d, *J* = 7.8 Hz, 2 x SCC**H**, Ar), 7.35 (2H, d, *J* = 7.8 Hz, 2 x SCCHC**H,** Ar), 4.25 (1H, dd, *J* = 10.4 and 2.5 Hz, C**H**OH), 3.97 (1H, dd, *J* = 10.4 and 7.6 Hz, C**H**O, THF ring), 3.82-3.77 (2H, m, C**H$_2$**OS), 3.50 (1H, s, O**H**), 2.45 (3H, s, C**H$_3$**, Ar), 2.38 (1H, br., O**H**), 2.14 (1H, ddd, *J* = 12.6, 8.3 and 6.0 Hz, C**H**H, THF ring), 1.95-1.83 (2H, m, C**H**$_2$, THF), 1.56 (H, dt, *J* = 12.6 and 8.2 Hz, CH**H**, THF ring), 1.22 (3H, s, C**H**$_3$), 1.13 (3H, s, C**H**$_3$), 1.09 (3H, s, C**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.9 (**C**CH_3, Ar), 132.7 (**C**S, Ar), 129.9 (2 x **C**HCS, Ar), 127.9 (2 x **C**HCHCS, Ar), 85.1 (**C**HO, THF ring), 84.0 (**C**O, THF ring), 74.8 (**C**HOH), 71.7 (**C**Me_2OH), 71.6 (**C**H_2OS), 33.5 (**C**H_2, THF ring), 27.7 (**C**H_3), 26.4 (**C**H_2, THF ring), 25.2 (**C**H_3), 22.8 (**C**H_3), 21.6 (**C**H_3) ppm.

LRMS (ESI$^+$) m/z: 381 ($[M+Na]^+$) Da.

2-(Methoxymethoxy)-2-(2-methyl-5-(2-((trimethylsilyl)oxy)propan-2-yl)tetrahydrofuran-2-yl)ethyl 4-methylbenzenesulfonate (2.82)



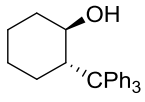
$C_{22}H_{38}O_7SSi$
Mol. wt.: 474.68 g/mol
(Yello oil)

Following the procedure for protection of acetate **2.89** with MOM-Cl, The tosylate **2.81** (242 mg, 0.67 mmol) was reacted with MOMCl (56.0 µL, 0.74 mmol) to give a mono-protected tosylat as a yellow oil (90.0 mg, 0.22 mmol, 33%). (58.7 mg, 0.164 mmol, 24%) was recovered of starting material tosylate **2.81**. To a solution of the resulted protected tosylat (90 mg, 0.223 mmol) in CH_2Cl_2 (3 mL) was added imidazole (91.0 mg, 1.34 mmol) and TMSCl (141 µL, 1.12 mmol) at –5 °C. The mixture was stirred for 1 h. Sat. aq. NH_4Cl (1.5 mL) and H_2O (2.0 mL) were added. The organic phase was separated and the aqueous phase was re-extracted with Et_2O (3 x 5 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title protected tosylate **2.82** as a yellow oil (95 mg, 0.2 mmol, 89%).

FT-IR ν_{max} (neat): 2954 (w), 2935 (w), 2920 (s), 2850 (m), 1462 (m), 1260 (m), 1119 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (2H, d, *J* = 8.3 Hz, 2 x SCC**H**, Ar), 7.35 (2H, d, *J* = 8.3 Hz, 2 x SCCHC**H,** Ar), 4.71 (1H, d, *J* = 7.3 Hz, OC**H**HO), 4.62 (1H, d, *J* = 7.3 Hz, OCH**H**O), 4.30 (1H, dd, *J* = 9.5 and 1.6 Hz, CH**H**OS), 3.90 (1H, t, *J* = 10.4, C**H**O, THF), 3.75 (1H, dd, *J* = 9.5 and 1.6 Hz, C**H**HOS), 3.34 (3H, s, C**H$_3$**O), 2.45 (3H, s, C**H$_3$**, Ar**)**, 2.96-1.80 (1H, m, 3 x C**H**H, THF ring), 1.95-1.83 (2H, m, C**H$_2$**, THF), 1.56 (1H, dt, *J* = 12.6 and 8.2 Hz, CH**H**, THF ring), 1.59 (1H, dd, 12.1 and 7.7 Hz, C**H**H, THF), 1.10 (6H, s, 2 x C**H$_3$**), 1.07 (3H, s, C**H$_3$**), 0.13 (9H, s, 3 x C**H$_3$**) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ 144.6 (**C**CH_3, Ar), 132.0 (**C**S, Ar), 129.8 (2 x **C**HCS, Ar), 128.0 (2 x **C**HCHCS, Ar), 91.3 (O**C**H_2O), 86.1 (**C**HO, THF ring), 84.1 (**C**O, THF ring), 76.9 (**C**HOH), 75.4 (**C**Me_2O), 72.9 (**C**H_2OS), 55.1 (**C**H_3O), 36.3 (**C**H_2, THF ring), 25.7 (**C**H_2, THF ring), 22.9 (**C**H_3), 22.5 (**C**H_3), 21.6 (**C**H_3), 20.6 (**C**H_3), 0.5 (3 x **C**H_3) ppm.
LRMS (ESI$^+$) m/z: 497 ($[M+Na]^+$) Da.

(±)- *trans*-2-Trityl cyclohexanol (TTC)



$C_{25}H_{26}O$
Mol. wt. 342.47 g/mol
(White solid)

To a solution of triphenylmethane (45.20 g, 183.1 mmol) in THF (200 mL) under Ar was added dropwise ^{n}BuLi (83.30 mL, 457.7 mmol) at –78 ^{o}C over 27 min producing

an orange solution. The mixture was stirred at 0 ^{o}C for 40 min then the resulting red solution of the trityl anion was re-cooled to –78 ^{o}C. Cyclohexene oxide (47.30 mL, 457.7 mmol) was added and the reaction mixture was stirred for 15 min. The cooling bath was removed, and the reaction mixture was stirred at rt for 14 h. The mixture was quenched with water (100 mL) and the phases separated. The aqueous layer was re-extracted with EtOAc (3 x 80 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a yellow oil. Hexane (150 mL) was added to the oil and was removed *in vacuo* to give a white solid that was washed with hexane to afford a crude product as a white powder. The crude product was recrystallized over EtOH to give the title product as a white powder (35.0 g, 102.2 mmol, 55%). Spectroscopic data are in agreement with the literature.[39] The sample was analysed by chiral HPLC, which showed an enantiomeric ratio of 50:50.

FT-IR ν_{max} (neat): 3582 (m), 3400 (br), 3086 (w), 3055 (w), 3000 (w), 2933 (m), 2854 (m), 1594 (w), 1491 (m), 1446 (m) cm^{-1}.

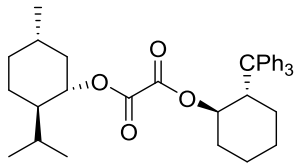
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48-7.15 (15H, m, C**H**, Ar), 3.27 (1H, t, *J* = 10.2 Hz, C**H**OH), 3.15-3.07 (1H, m, C**H**CPh_3), 2.06 (1H, d, *J* = 14.3, CH_2), 1.96-1,91 (1H, m,C**H**H), 1.48 (1H, d, *J* = 4.5 Hz, O**H**) 1.76-1.34 (4H, m, C$\mathbf{H}_2$), 1.17-1.03 (1H, m, C$\mathbf{H}_2$), 0.57-0.43 (1H, m, C$\mathbf{H}_2$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 129.5 (br, 6 x **C**H, Ar), 127.7 (6 x **C**H, Ar), 125.8 (3 x **C**H, Ar), 73.6 (**C**HOH), 60.7 (**C**Ph_3), 48.8 (**C**HCPh_3), 37.1 (**C**H_2), 28.9 (**C**H_2), 26.2 (**C**H_2), 25.2 (**C**H_2) ppm. (Quaternary aromatic carbons signals were not observed).

LRMS (ESI^{+}) m/z: 365 ($[M+Na]^{+}$) Da.

HPLC: Chiralcel® OD-H-(eluent: IPA/n-hexane 5:95) - 0.5 mL/min Retention times: $t_{(+)}$ = 13.8 min & $t_{(-)}$ = 17.2 min.

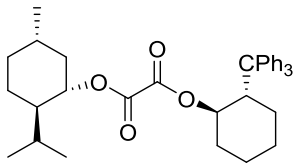
(*1R,2S,5R*)-2-Isopropyl-5-methylcyclohexyl ((*1R,2S*)-*2*-tritylcyclohexyl) oxalate (2.18) and (*1R,2S,5R*)-2-Isopropyl-5-methylcyclohexyl ((*1S,2R*)-*2*-tritylcyclohexyl) oxalate (2.19).



$C_{37}H_{44}O_4$
Mol.wt.: 552.74 g/mol
(Whitefoamy solid)

Using a procedure described by the Brown group,[39] to a solution of oxalyl chloride (41.60 mL, 491.8 mmol) in CH_2Cl_2 (297 mL) was added a solution of (+)-menthol (30.70 g, 196.7 mmol) in CH_2Cl_2 (297 mL) via a pressure equalizing dropping funnel at 0 ^oC over 50 min. The reaction mixture was stirred for 30 min at 0 ^oC, warmed to rt and the reaction monitored by TLC. When complete consumption of (+)-menthol was shown by TLC, the solvent and excess oxalyl chloride were removed *in vacuo* giving (+)-menthol-chloro-oxoacetate as a colourless liquid. (±)-TTC (64.0 g, 186.9 mmol) was dissolved in CH_2Cl_2 (137.5 mL) and pyridine (39.60 mL, 491.8 mmol), the mixture was added dropwise via a pressure equalizing dropping funnel to a solution of (+)-menthol-chloro-oxoacetate in CH_2Cl_2 (297 mL) at 0 ^oC under Ar. The reaction was monitored by TLC and upon complete consumption of (±)-TTC the reaction mixture was quenched with sat. NH_4Cl sol. (250 mL), the phases separated and the organic layer washed with HCl (2.0N, 3 x 130 mL), sat. aq. $NaHCO_3$ (200 mL) and brine (130 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title compounds **2.18/2.19** as a white foamy solid (90.7 gm, 164 mmol, 88%). The compound was used in the next reaction with a further purification.

(–)-(*1R,2S,5R*)-2-Isopropyl-5-methylcyclohexyl (*1R,2S*)-2-tritylcyclohexyl oxalate (2.18)



$C_{37}H_{44}O_4$
Mol. wt.: 552.74 g/mol
(White solid)

The mixture of **2.18/2.19** (90.7 g, 164 mmol) was suspended in MeOH (250 mL) and heated under reflux for 30 min. The suspension was filtrated through a hot sintered funnel and the solid washed with hot MeOH (2 x 100 mL). Ths whole process was repeated nine times. The solid was then analysed by TLC (eluent: CH_2Cl_2- hexane 1:1-1.0 mg in 1.0 mL sample concentration (CH_2Cl_2)) showing a single diastereomer. The solid was collected and concentrated *in vacuo* and gave the title compound **2.18** as a white solid (20.30 g, 36.73 mmol, 22% yield, 100% *de*). Diastereomeric purity was confirmed by analytical HPLC-ODH column, eluent system 1% IPA in hexane-0.5 mL/min flow rate, 20 min, 254 nm. Spectroscopic data are in agreement with the literature.[39] The sample was analysed by chiral HPLC, which showed a diastereomeric ratio of 100:0.

$[\alpha]^{26}_{D}$: –8.2 (*c* 1.01, $CHCl_3$).

FT-IR ν_{max} (neat): 3079 (w), 3029 (w), 3056 (w), 2929 (m), 2864 (m), 1758 (s), 1731 (s), 1493 (m), 1447 (m) cm^{-1}.

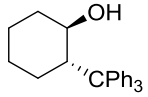
^{1}H NMR (300MHz, $CDCl_3$): δ 7.97-7.12 (15H, m, C**H,** Ar), 4.65 (1H, td, *J* = 4.8 and 4.4 Hz, C**H**OR), 4.15 (1H, td, *J* = 10.2 and 4.0 Hz, C**H**OR\), 3.64-3.56 (1H, m, C**H**CPh_3), 2.13 (1H, d, *J* = 13.6 Hz, CH_2), 2.03-1.98 (1H, m, C**H**$_2$), 1.86-1.61 (8H, m), 1.52-1.15 (5H, m), 1.1- 0.85 (8H, m), 0.76 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 157.9 and 157.7 (**C**=O), 129.8 (6 x **C**H, Ar), 127.4 (6 x **C**H, Ar), 125.6 (3 x **C**H, Ar $_r$), 78.5 (**C**HOR), 77.5 (**C**HOR), 60.8 (**C**Ph_3), 46.3 (**C**HCPh_3), 36.3 (**C**H$CH(CH_3)_2$), 40.1 (**C**H_2), 34.0 (**C**H_2), 32.7(**C**H_2), 31.4 (**C**HCH_3), 28.9 (**C**H_2), 26.0(**C**H_3), 26.0 (**C**H_2), 24.7 (**C**H_2), 23.3 (**C**H_2), 22.0 (**C**H$(CH_3)_2$), 20.7 (**C**H_3), 16.2 (**C**H_3) ppm. (Quaternary aromatic carbons signal were not observed).

LRMS (ESI$^+$) m/z: 275 ($[M+Na]^+$) Da.

HPLC: Chiralcel® OD-H-(eluent: IPA/n-hexane 1:99) - 1 mL/min Retention times: $t_{(–)}$ = 11.2 min.

(+)-(1*R*,2*S*)-2-Tritylcyclohexanol (1.186)



$C_{25}H_{26}O$
Mol. wt.: 342.47 g/mol
(White solid)

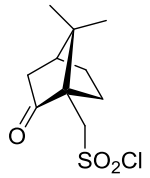
(–)-**2.18** (20.3 g, 36.7 mmol) was suspended in MeOH (276 mL) and H_2O (55 mL), KOH (5.20 g, 91.8 mmol) was added and the reaction was heated under reflux for 26 h. The flask was cooled to rt and concentrated in *vacuo* to afford a white solid. The residue was treated with H_2O (100 mL) and EtOAc (500 mL) was added. The organic phase was separated and the aqueous layer was re-extracted with EtOAc (3 x 100 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* gave a white solid compound. The solid was treated with hexane and the insoluble precipitate collected by filtration giving the title (+)-TTC **1.186** as a white solid (10.9 g, 31.8 mmol, 87%, 99.6 *ee*). Enantiopurity was confirmed by analytical HPLC-ODH column, eluent system 5% IPA in hexane-0.5 mL/min flow rate, 30 min, 254 nm. The sample was analysed by chiral HPLC, which showed an enantiomeric ratio of 99.8:0.2. Spectroscopic date were consistent with that reported for *racemic* TTC.

$[\alpha]^{23.5}_{D}$: +25.3 (*c* 1.01, $CHCl_3$).

HPLC: Chiralcel® OD-H-(eluent: IPA/n-hexane 1:99) - 0.5 mL/min Retention times: t_{maj} = 13.9 min & t_{min} = 17.5min.

Analytical data consistent with (±)-TTC.

(–)-Camphorsulfonyl chloride (2.49)



$C_{10}H_{15}ClO_3S$
Mol. wt. 250.74 g/mol
(Brownish yellow oil)

PCl_5 (98.0 g, 448 mmol) was added in one batch to (–)-(1*R*)-camphorsulfonic acid (**2.48**, 34.7 g, 149 mmol) at –10 °C. Both solids were stirred using an overhead stirrer. The evolved $HCl_{(g)}$ was scrubbed in NaOH (aq. sol. 1.0M). After 10 min, when gas evolution ceased, the reaction was warmed to rt and stirring was continued for 6 h. At this stage, CH_2Cl_2 (100 mL) was added to the reaction mixture at rt and it was cooled to –10 °C before it was quenched by the careful, dropwise addition of cold water (100 mL) (**Note**: Extreme care should be taken while addition of cold water as the reaction is highly exothermic and $HCl_{(g)}$ is given off). The organic phase was separated and the aqueous phase was re-extracted with CH_2Cl_2 (2 x 175 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title sulfonyl chloride **2.49** as a brownish yellow solution (50.00 g, 199.4 mmol, >99%). The crude product was used in next step without any purification. Spectroscopic data are in agreement with the literature.[12,95]

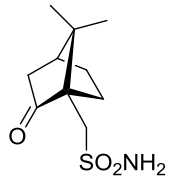
FT-IR ν_{max} (neat): 2960(m), 2926 (w), 2862(w), 1741 (s), 1365 (s), 1167 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.33 (1H, d, *J* = 14.7 Hz, C**H**HSO_2), 3.73 (1H, d, *J* = 14.5 Hz, CH**H**SO_2), 2.48-2.42 (2H, m, C**H_2**), 2.18-2.06 (2H, m, C**H_2**), 2.03 (1H, d, *J* = 18.6 Hz, C**H**H), 1.78(1H, ddd, *J* = 14.0, 9.4, 4.8 Hz, C**H**H), 1.5 (1H, ddd, *J* = 12.8, 9.1, 3.9 Hz ,C**H**H), 1.15 (3H, s, C**H_3**), 0.94 (3H, s, C**H_3**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 212.7 (**C**O), 64.3 (**C**H_2SO_2), 59.7 (**C**Me_2), 48.2 (**C**H_2CO), 42.8 (**C**CH_2SO_2), 42.3 (**C**$HCMe_2$), 26.9 (**C**H_2C), 25.3 (**C**H_2CH_2C), 19.8 (**C**H_3), 19.7 (**C**H_3) ppm.

LRMS (ESI$^+$) m/z: 273 ([M+Na]$^+$) Da.

(–)-(+)-(1*R*)-Camphorsulfonamide (2.50)



$C_{10}H_{17}NO_3S$
Mol. wt. 231.31 g/mol
(White solid)

To the rapidly stirred solution of (–)-sulfonyl chloride **2.49** (37.40 g, 149.0 mmol) in CH_2Cl_2 (170 mL) at 0 °C, was added a solution of NH_4OH (140 mL) using a dropping funnel. A white ppt. was formed and the reaction mixture was stirred for 5 h. At this stage, H_2O (100 mL) was added and the organic phase was separated from the aqueous phase. The aqueous phase was re-extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title (–)-sulfonamide **2.50** as a white solid (29.0 g, 125 mmol, 84%). The crude product was used in next step without purification. Spectroscopic data are in agreement with the literature.[12,95]

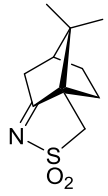
FT-IR ν_{max} (neat): 3298 (m), 3223 (w), 3124 (w), 2964 (m), 1731 (s), 1333 (s), 1152 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.43 (2H, br, N**H$_2$**), 3.50 (1H, d, *J* = 15.0 Hz, C**H**HSO$_2$), 3.13 (1H, d, *J* = 15.2 Hz, CH**H**SO$_2$), 2.46-2.40 (2H, m, C**H$_2$**), 2.27-1.99 (5H, m, C**H**H and 2 x C**H$_2$**), 1.98 (1H, m, C**H**H), 1.48 (1H, m, C**H**H), 1.01 (3H, s, C**H$_3$**), 0.93 (3H, s, C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 217.6 (**C**O), 59.3 (**C**Me$_2$), 53.9 (**C**H$_2$SO$_2$), 49.1 (**C**CH$_2$SO$_2$), 43.0 (**C**H$_2$CO), 42.8 (**C**HCMe$_2$), 27.0 (**C**H$_2$C), 26.7 (**C**H$_2$CH$_2$C), 19.9 (**C**H$_3$), 19.4 (**C**H$_3$) ppm.

LRMS (ESI$^+$) m/z: 254 ([M+Na]$^+$) Da.

(+)-(1*R*)-Camphorsulfonylimine (2.51)



$C_{10}H_{15}NO_2S$
Mol. wt. 213.3 g/mol
(White crystal)

To the suspension of (–)-sulfonamide **2.50** (28.80 g, 124.5 mmol) in toluene (185 mL) was added amberlyst 15 (4.0 g) and the resultant mixture was heated to reflux using Dean-Stark apparatus for 4 h. At this stage, the reaction was cooled to rt and CH_2Cl_2 (250 mL) was added to dissolve the white ppt. The solution was filtered and concentrated *in vacuo* to afford the crude product as a white solid. The crude product was recrystallized from absolute ethanol gave the title **(+)**-sulfonylimmine **2.51** as white crystals (17.8 g, 83.5 mmol, 67%). Spectroscopic data are in agreement with the literature.[12,95]

mp : 223-228 ^{o}C, (Lit. 223-229 ^{o}C).[12]

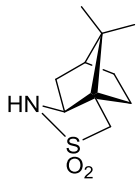
FT-IR ν_{max} (neat): 3004 (w), 2968 (m), 2893 (w), 1644 (m), 1316 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.18 (1H, d, *J* = 13.2 Hz, C**H**HSO_2), 2.98 (1H, d, *J* = 13.2 Hz, C**H**HSO_2), 2.78 (1H, C**H**$C(CH_3)_2$), 2.39 (H, d, *J* = 19.3 Hz, C**H**H), 2.26 (1H, m, CH**H**) 2.09-2.04 (2H, m, C**H$_2$**), 1.79 (1H, t, *J* = 9.5 Hz, C**H**$HCCH_2S$), 1.47 (1H, t, *J* = 9.5 Hz, C**H**$HCCH_2S$), 1.09 (3H, s, C**H$_3$**), 0.88 (3H, s, C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.3 (**C**N), 64.5 (**C**CH_2S), 49.4 (**C**H_2SO_2), 47.4 (**C**Me_2), 44.6 (**C**$HCMe_2$), 35.9 (**C**H_2C=N), 28.4 (**C**H_2CH_2C), 26.6 (**C**H_2C), 19.4 (**C**H_3), 19.0 (**C**H_3) ppm.

LRMS (ESI^{+}) m/z: 214 ($[M+H]^{+}$) Da.

(+)-(*2S*)-10,2-Camphorsultam (2.52)



$C_{10}H_{17}NO_2S$
Mol. wt. 215.31 g/mol
(White crystal)

To the stirring solution of sulfonylimine **2.51** (12.6 g, 59.1 mmol) in CH_3OH (88 mL) at –5 °C, was added $NaBH_4$ (the addition should be in a portionwise (3.60 g, 95.1 mol). After 1 h, the reaction was quenched dropwise with citric acid (10% aq., 17 mL) and diluted with CH_2Cl_2 (50 mL). The resultant suspension was concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2 (100 mL) and H_2O (50 mL). The organic phase was separated and the aqueous phase was re-extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to

afford the crude product as a white solid. The crude product was recrystallized with absolute ethanol which gave the title (+)-(*2S*)-10, 2-camphorsultam (**2.52**) as a white crystal (11.1 g, 51.5 mmol, 88%). Spectroscopic data are in agreement with the literature.[12,95]

$[\alpha]^{19}_{D}$: +32.9 (*c* 1.58, $CHCl_3$), {lit. $[\alpha]^{22}_{D}$ = +32.9 (*c* 0.1, $CHCl_3$)}.[12]

mp : 180-181, (Lit. 181-183 ^{o}C).[12]

FT-IR ν_{max} (neat): 3288 (s), 3000 (m), 2959 (s), 2875(w), 1329 (s), 1133 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.22 (1H, d, *J* = 5.9 Hz, N**H**), 3.42 (1H, td, *J* = 7.8, 4.9 Hz, C**H**N), 3.11 (2H, dd, *J* = 17.6, 13.7 Hz, C**H_2**SO2), 2.0-1.83 (5H, m, C**H** and 2 x C**H_2**), 1.45 (1H, m, C**H**H), 1.31 (1H, m, C**H**H), 1.13 (3H, s, C**H_3**), 0.93 (3H, s, C**H_3**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 62.8 (**C**HN), 55.0 (**C**H_2SO_2), 50.3 (**C**CH_2SO_2), 47.2 (**C**Me_2), 44.7 (**C**$HCMe_2$), 36.0 (**C**H_2CHN), 31.8 (**C**H_2CH_2C), 26.8 (**C**H_2C), 20.5 (**C**H_3), 20.4 (**C**H_3) ppm.

LRMS (ESI^+) m/z: 215 ($[M+H]^+$) Da.

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