UNIVERSITY OF SOUTHAMPTON

FACULTY OF ENGINEERING, SCIENCE AND MATHEMATICS

SCHOOL OF CHEMISTRY

Stereoselective Oxidative Cyclisations of 1,5,9-Trienes; Synthetic Studies Towards Eurylene

Nadeem Sadiq Sheikh

A Thesis Submitted for the Degree of Doctor of Philosophy

April 2008

To my **Mother**
whose blessings lead me
and prayers shield me.

Declaration

The research described in this thesis was carried out by myself at the School of Chemistry, University of Southampton between October 2004 and September 2007, unless otherwise acknowledged. No part of this thesis has been submitted in any previous application for a higher degree.

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ABSTRACT

FACULTY OF ENGINEERING, SCIENCE AND MATHEMATICS
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STEREOSELECTIVE OXIDATIVE CYCLISATIONS OF 1,5,9-TRIENES; SYNTHETIC STUDIES TOWARDS EURYLENE

by

Nadeem Sadiq Sheikh

A novel synthetic route towards the stereoselective formation of *trans*-THF rings by permanganate promoted oxidative cyclisation of 1,5-diene precursors was developed. This methodology was applied to 1,5-dienoates and 1,5,9-trienoates to afford *trans*-THF regions of the natural products, (+)-linalool oxide and eurylene respectively. Synthesis of *trans*-THF aldehyde fragment **2.47** of eurylene was accomplished, using (+)-*trans*-cumylcyclohexanol as a chiral auxiliary to direct the stereoselective oxidative cyclisation of 1,5,9-triene **4.35** by permanganate.

An efficient synthesis of *cis*-THF triol fragment **2.38** of eurylene was also achieved by permanganate mediated oxidative cyclisation of 1,5,9-triene **3.9**, bearing (2*S*)-10,2-camphorsultam as a chiral auxiliary. *Trans*-THF aldehyde **2.47** and *cis*-THF triol **2.38** intersect with a reported synthesis of eurylene, hence achieving a formal synthesis of the natural product. Seven, out of eight, stereogenic centres present in eurylene were established by two permanganate induced stereoselective oxidative cyclisations.

Several coupling strategies were investigated to complete a total synthesis of eurylene. Successful formation of the complete carbon skeleton **6.56** was achieved, although it was not possible to attain selective reduction of the triple bond in **6.56**. The knowledge gained will be used to devise a revised end game, which will ultimately allow a total synthesis to be achieved.

CONTENTS

Acknowledgements

All praises be to the GREATEST CHEMIST of universe(s) and blessings upon the prophets of all ages, who were sent for the ultimate salvation of humanity.

A remarkably great episode of my life in Southampton is knocking at the doorway of a happy ending with indeed a heavy heart. Thanks to everyone who made this chapter memorable. My thoughts are wavering, however I give a try.

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Now moving to the leading players of this stage, who will keep hammering my nostalgia. I wonder is there any way to forget friendly and charismatic nature of Lynda, outstandingly comic presence of Stephen, hysterically unshaken attitude of Neville, sweet gestures of Claire, movies night-out with Sherif, travelling experiences with Iain, communicative fights with Ian, fun discussions with Ali, pleasant neighbourhood watch from Amy and supportive role of Mohammad. I am afraid, life is too short to think forgetting about you guys, I highly acknowledge your contribution in my life and say my sincere thanks for all you have offered.

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I am indebted to uncle Rustam (late) for his dedicated support, may his soul rest in peace. Thanks to aunt Kausar and uncle Irfan for their love and to my students for provoking me to meet my inside man and allowing him to express explicitly.

Abbreviations

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

HRMS	high resolution mass spectrometry
imid	imidazole
^{i}Pr	*iso*-propyl
IR	infrared
J	coupling constant (NMR)
LDA	lithium diisoprpylamide
LRMS	low resolution mass spectrometry
m	multiplet (NMR) or medium (IR)
m/z	mass to charge ratio
m-CPBA	3-chloroperoxybenzoic acid
MeCN	acetonitrile
MEM	methoxyethoxymethy
min	minute(s)
mmol	millimole(s)
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	mass spectrometry
NBSH	nitrobenzenesulfonylhydrazide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonnance
NOE	nuclear Overhauser effect
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PFP	pentaflourophenyl
Ph	phenyl
PMBM	*p*-methoxybenzylmethoxy
PMP	*p*-methoxyphenyl
ppm	parts per million
ppt.	precipitate(s)
psi	pound per square inch
PTC	phase-transfer catalyst
p-TSA	*p*-toluenesulfonic acid
py	pyridine
q	quartet (NMR)

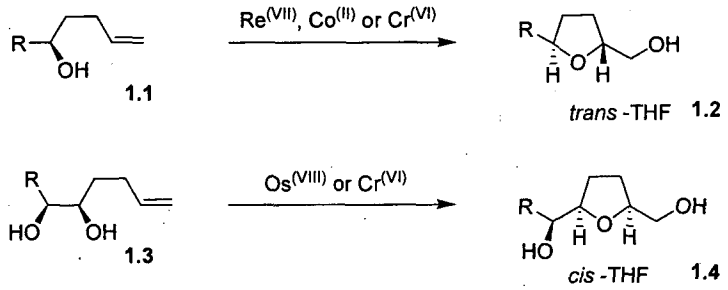
quin	quintet (NMR)
RCM	ring closing metathesis
RRCM	relay ring closing metathesis
rt	room temperature
s	singlet (NMR) or strong (IR)
sol.	solution
t	tertiary
t	triplet (NMR)
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBAPI	tetrabutylammunium periodate
TBDMS	*t*-butyldimethylsilyl
TBDPS	*t*-butyldiphenylsilyl
TEMPO	2,2,6,6-Tetramethylpiperidinyloxy
TFA	triflouroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammonium perruthenate
Ts	*p*-toluenesulfonyl (tosyl)
TTMSS	*tris*-trimethylsilylsilane
UV	ultraviolet
W	Watt
w	weak (IR)

Chapter 1 Routes to 2,5-Disubstituted Tetrahydrofurans

A large number of biologically active natural products contain 2,5-disubstituted tetrahydrofurans as a core structural unit.[1-5] Thus these heterocycles have attracted a lot of interest from a synthetic viewpoint. A range of metal oxidants have been explored and reported for the synthesis of 2,5-disubstituted tetrahydrofuran (THF) rings by metal mediated oxidative cyclisations of 5-hydroxyalkenes, 5,6-dihydroxyalkenes or 1,5-diene precursors.[6,7]

Oxidative cyclisation of 5-hydroxyalkenes has been carried out using $Re^{(VII)}$,$Co^{(II)}$ or $Cr^{(VI)}$ oxidants to afford *trans*-2,5-disubstituted THF rings, while oxidative cyclisation of 5,6-dihydroxyalkenes using $Os^{(VIII)}$ or $Cr^{(VI)}$ species have been reported to induce a *cis*-stereoselectivity in the incipient disubstituted THF ring (Scheme 1.1).[8-14]

Mechanistically, $Re^{(VII)}$ and $Os^{(VIII)}$ mediated oxidative cyclisations go through an intramolecular [3+2] cycloaddition after the hydroxyl alkene coordinates to the metal.[11,16] $Cr^{(VI)}$ promoted cyclisation is claimed to be based on either intramolecular [2+2] or [3+2] cycloaddition, while $Co^{(II)}$ catalysed oxidative cyclisation follows a radical pathway to afford the 2,5-disubstituted THF rings (Scheme 1.1).[10,13,14]



Scheme 1.1: Oxidative cyclisation of 5-hydroxyalkenes and 5,6-dihydroxyalkenes using different metal oxidants.

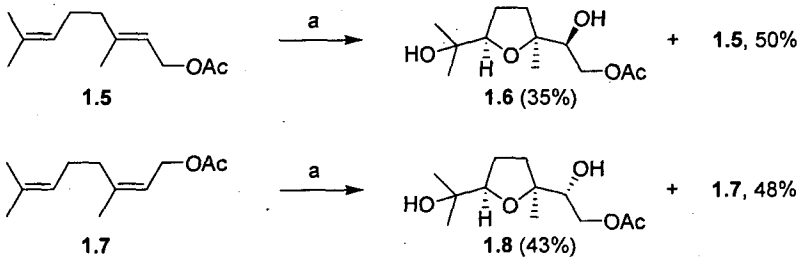
The oxidative cyclisation of 5-hydroxyalkenes and 5,6-dihydroxyalkenes have been reviewed in depth previously in our group.[17,18] Therefore in the following chapter, the main synthetic routes to 2,5-disubstituted tetrahydrofurans by metal-oxo reagents, directly from 1,5-diene precursors are summarised. Also oxidative cyclisations of 1,4-, 1,6-, and 1,7-diene precursors by metal oxidants are described.

1.1 Oxidative Cyclisation of Dienes

One powerful methodology to construct THF rings is an oxidative cyclisation protocol applied to 1,5-dienes. The metal-oxo agents which had been reported for this particular transformation are described in the sections below.

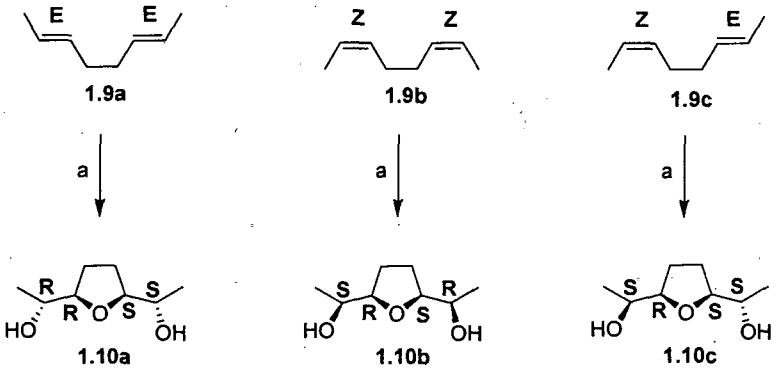
1.1.1 Permanganate Mediated Oxidative Cyclisation

Kötz *et al.* attempted to oxidise geranyl acetate (**1.5**) with potassium permanganate under slightly basic conditions in 1924.[19] Unfortunately the reaction product could not be identified and was described as "oxidodioxygeraniolmonoacetate". In 1965, Klein *et al.* investigated the same reaction and elucidated the product to be a *cis*-2,5-disubstituted THF diol **1.6** obtained in a moderate yield (Scheme 1.2).[20] Similarly neryl acetate (**1.7**) underwent cyclisation to afford the *cis*-THF diol **1.8**. The reaction proceeded in a stereospecific fashion and yielded only the *cis*-isomer. This stereoselectivity is of great importance as it offers potential for the stereocontrolled synthesis of THF containing natural products.



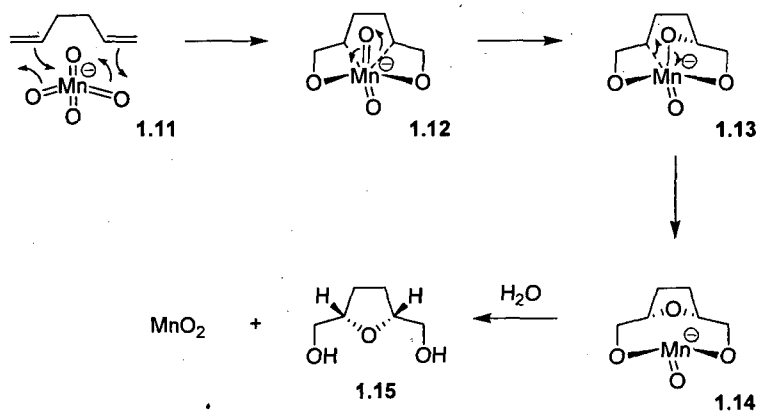
Scheme 1.2: First example of $KMnO_4$ mediated oxidative cyclisation. Reagents and conditions: (a) $KMnO_4$, acetone:H_2O (5:1), CO_2 bubbling, pH = 7.5, 0 °C, 30 min.

Walba *et al.* later investigated the stereoselectivity and the mechanism of potassium permanganate mediated cyclisations of 1,5-dienes.[21] The oxidative cyclisation of dienes **1.9a-c** led to the formation of corresponding diols **1.10a-c** in approximately 97% *cis*-stereoselectivity. The stereochemistry of the resultant THF depends on the geometry of the diene precursor (Scheme 1.3).



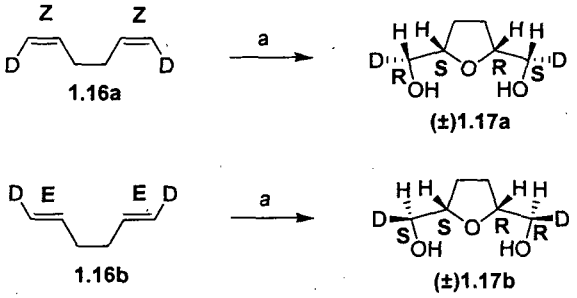
Scheme 1.3: The effect of alkene geometry on relative stereochemistry. Reagents and conditions: (a) $KMnO_4$, acetone:H_2O (5:1), CO_2 bubbling, pH = 7.5, –20 °C, 30 min.

The Sharpless mechanistic proposal for the oxidation of olefins by oxo-transition metal species was advanced by Walba *et al.* to permanganate mediated oxidative cyclisations (Scheme 1.4).[21,22] It was proposed that after the formation of *bis*-π-complex **1.11**, an octahedral $Mn^{(VII)}$ intermediate **1.12** is produced *via* two Sharpless-type [2+2] additions. Alkyl migration from $Mn^{(VII)}$ to one of the oxygen atoms with retention, yields $Mn^{(V)}$ intermediate **1.13**, which after a reductive elimination affords $Mn^{(III)}$ diester **1.14**. Oxidation of $Mn^{(III)}$ ester **1.14** followed by the hydrolysis affords MnO_2 and the desired *cis*-THF **1.15** with the observed relative stereochemistry.



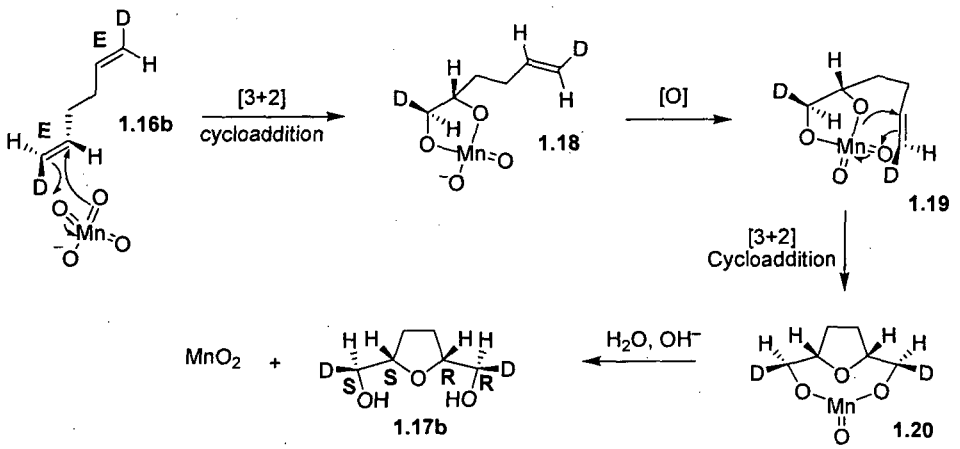
Scheme 1.4: Walba's proposed mechanism for permanganate mediated oxidative cyclisation.

Baldwin *et al.* also investigated the stereoselectivity of these reactions.[23] For this purpose, deuterated dienes **1.16a-b** were subjected to permanganate oxidative cyclisation and the *cis*-stereoselectivity of the resultant THF diols **1.17a-b** was confirmed by NMR analysis (Scheme 1.5).



Scheme 1.5: Baldwin's stereochemical investigation of the oxidative cyclisation. Reagents and conditions: (a) $KMnO_4$, acetone:H_2O (5:1), CO_2 bubbling, pH = 7.5, –20 °C, 30 min.

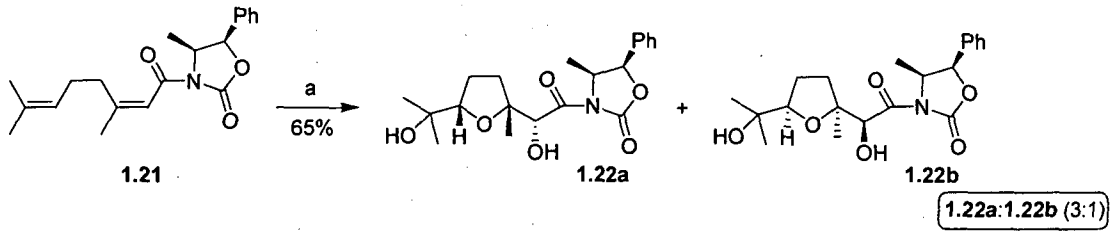
Baldwin *et al.* suggested a mechanism for the permanganate mediated oxidative cyclisation based on sequential [3+2] cycloadditions (Scheme 1.6).[23] It was proposed that after [3+2] cycloaddition to one double bond of diene **1.16b**, an intermediate $Mn^{(V)}$ ester **1.18** is formed. After rapid oxidation with permanganate, a second [3+2] intramolecular cycloaddition occurs on the remaining double bond and finally the basic hydrolysis of the diester **1.20** affords the *cis*-THF **1.17b**. This mechanism is also supported by evidence of the intermediacy of a cyclic $Mn^{(V)}$ ester in the reaction of alkenes with permanganate.[24]



Scheme 1.6: Baldwin's proposed mechanism for permanganate oxidative cyclisation.

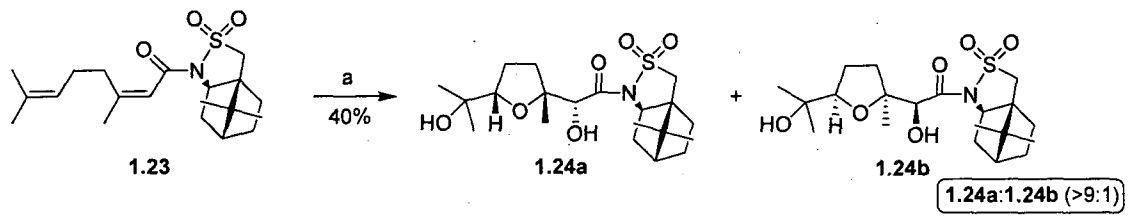
Clearly, by controlling the face and initial attack of the oxidant, the reaction could be performed asymmetrically. Walba *et al.* achieved this using 1,5-diene **1.21** bearing Evans' oxazolidinone as a chiral auxiliary (Scheme 1.7).[25,26] The oxidative cyclisation of dienoate **1.21** afforded *cis*-THF diols **1.22a,b** in a good yield and in a moderate

diastereoselectivity (d.r. 3:1), with the major diastereoisomer **1.22a** resulting from the *Re*-face attack on the conjugated double bond.



Scheme 1.7: Oxidative cyclisation of dienoate **1.21** bearing Evans' auxiliary. Reagents and conditions: (a) $KMnO_4$, acetone:H_2O (10:1), CO_2 bubbling, pH = 7.5, –30 °C, 30 min.

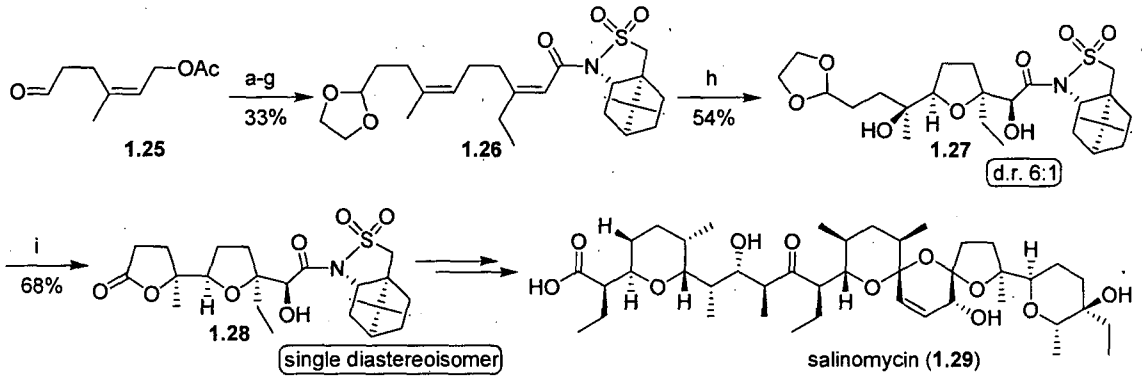
The stereoselectivity was enhanced by swapping Evans' auxiliary with Oppolzer's sultam.[27,28] The dienoate **1.23** was subjected to permanganate oxidation and the resultant *cis*-THF diols **1.24a,b** were obtained in a moderate yield with an improved diastereoselectivity (d.r. >9:1, Scheme 1.8). The major diastereoisomer **1.24a** was due to the attack from the *Re*-face of the enoyl olefin bond. The same facial preference was observed previously by Oppolzer *et al.* in dihydroxylation reactions.[27]



Scheme 1.8: Oxidative cyclisation of dienoate **1.23** 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.

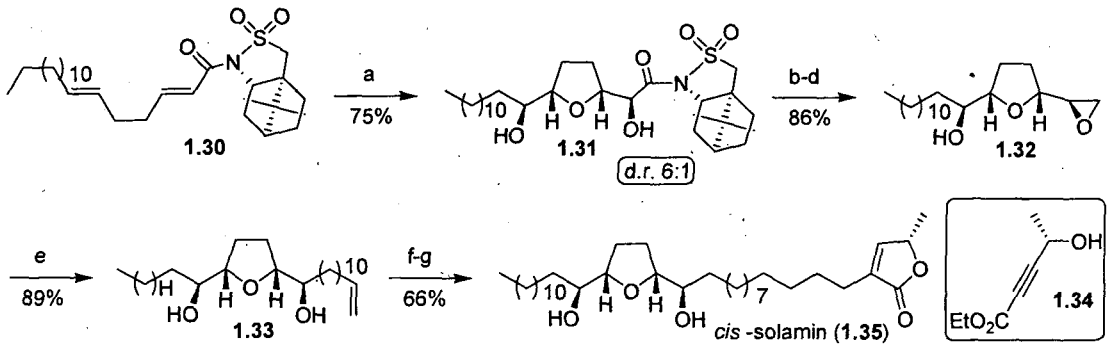
Permanganate based oxidative cyclisation has been employed in various natural product total syntheses to construct THF rings in racemic and enantioselective fashions.[29,30] The asymmetric variant of the oxidative cyclisation extended the utility of the reaction in total synthesis, and its first application was reported by Kocienski *et al.*[31] Dienoate **1.26** bearing (2*S*)-10,2-camphorsultam was synthesised using standard procedures in seven steps from a known aldehyde **1.25** (Scheme 1.9). The oxidative cyclisation of dienoate **1.26** using modified conditions yielded the THF adduct **1.27** in a good yield and diastereoselectivity (d.r. 6:1).[25] Treatment of THF diol **1.27** with an excess of ozone afforded a hydroxy ester which underwent cyclisation using PTSA to afford

corresponding lactone **1.28**. The minor diastereoisomer was separated at this stage and optically enriched lactone **1.28** was used in the subsequent steps to accomplish the total synthesis of salinomycin (**1.29**).



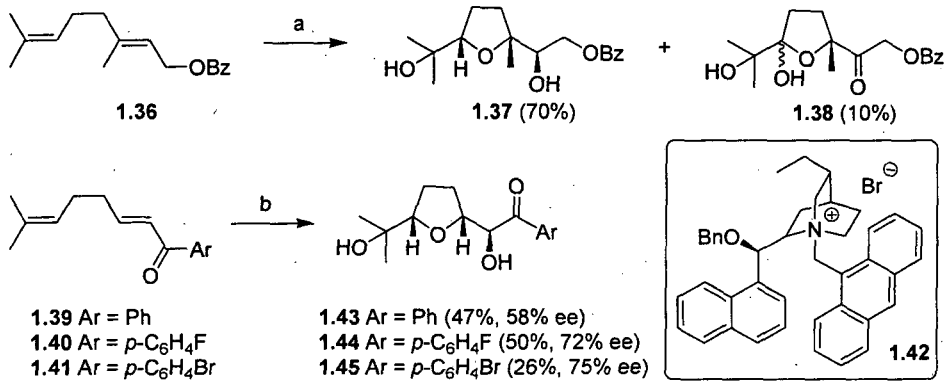
Scheme 1.9: Stereoselective synthesis of *cis*-THF diol **1.27**. Reagents and conditions: (a) $HOCH_2CH_2OH$, PTSA, PhH, reflux; (b) K_2CO_3, MeOH; (c) MsCl, LiCl, 2,6-lutidine, DMF, (d) $LiC{\equiv}CCH_2Li$, THF; (e) (I) *n*-BuLi, THF; (II) $ClCO_2Me$; (f) Et_2CuLi, THF; (g) (I) NaOH, MeOH; (II) $(COCl)_2$; (III) (2*S*)-bornane-10,2-camphorsultam, *n*-BuLi; (h) $KMnO_4$, pH = 6, acetate buffer, acetone-AcOH-H_2O; (i) (I) O_3, EtOAc; (II) PTSA, CH_2Cl_2.

The reaction has also been used extensively by Brown *et al.*[32,33] In the reported stereoselective synthesis of *cis*-solamin (**1.35**), dienoate **1.30** bearing (2*S*)-10,2-camphorsultam was subjected to permanganate mediated cyclisation to afford the THF diol **1.31** in a good yield and diastereoselectivity (d.r. 6:1, Scheme 1.10). Both diastereoisomers were separable at this stage. Reductive cleavage of the auxiliary from THF diol **1.31**, tosylation of primary alcohol and treatment with DBU afforded the epoxide **1.32**. Cupurate addition to epoxide **1.32** yielded the diol **1.33**, which was reacted with alkyne **1.34** to introduce the butenolide. Subsequent diimide reduction of the disubstituted alkene accomplished the synthesis of *cis*-solamin (**1.35**).



Scheme 1.10: Stereocontrolled synthesis of *cis*-solamin (**1.35**). Reagents and conditions: (a) $KMnO_4$, acetone:AcOH (3:2), (b) $NaBH_4$, THF, H_2O (c) Bu_2SnO, PhH, then TsCl, TBAB; (d) DBU, CH_2Cl_2; (e) $CH_2{=}CH(CH_2)_9MgBr$, CuI, THF; (f) Compound **1.34**, CpRu(cod)Cl, MeOH, reflux; (g) $TsNHNH_2$, NaOAc, THF/H_2O.

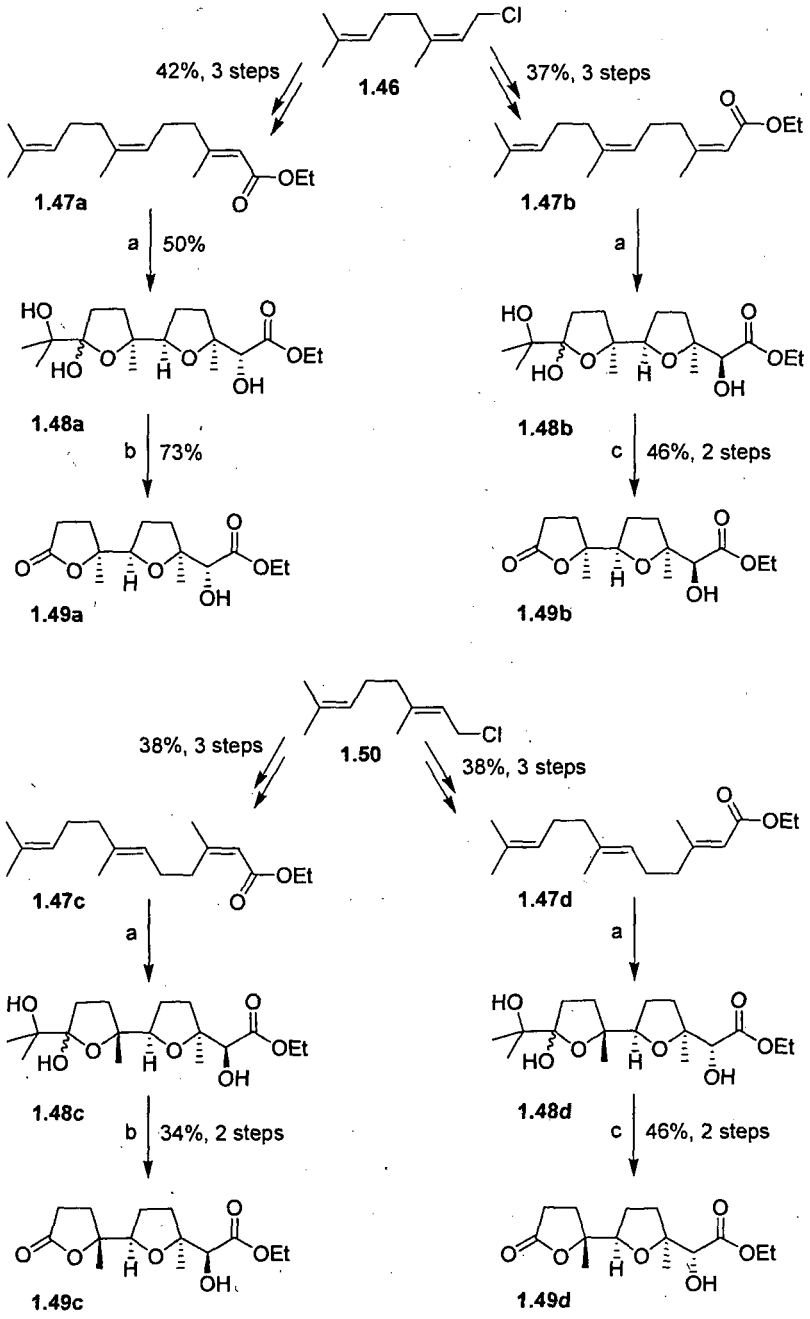
Brown *et al.* also reported the use of phase-transfer catalyst (PTC) for the permanganate induced oxidative cyclisation of 1,5 dienes.[34] Geranyl benzoate (**1.36**) was oxidised using potassium permanganate in the presence of adogen 464 (a phase-transfer catalyst) to afford the *cis*-THF **1.37** in a good yield along with ketol **1.38** as a major by-product (Scheme 1.11). The asymmetric oxidation of dienes **1.39-1.41** was also attempted using chiral phase-transfer catalyst **1.42** and corresponding *cis*-THF diols **1.43-1.45** were produced in moderate yields and promising enantiomeric excesses.



Scheme 1.11: Phase-transfer catalysts in $KMnO_4$ oxidative cyclisations. Reagents and conditions: (a) $KMnO_4$ (2.0 eq., 0.4 M aq.), AcOH (4.0 eq.), Adogen 464 (0.4 eq.)/Et_2O; (b) $KMnO_4$ (1.6 eq. powder), AcOH (6.5 eq.), chiral catalyst **1.42** (0.1 eq.)/CH_2Cl_2.

Brown *et al.* investigated the regioselective oxidative cyclisations of 1,5,9-trienes to explore a synthetic route for the preparation of useful *bis*-adjacent THF building blocks.[35,36] Farnesoate esters **1.47a-d** were synthesised using established methods and subjected to permanganate oxidative cyclisation to afford adjacent *bis*-THF lactols

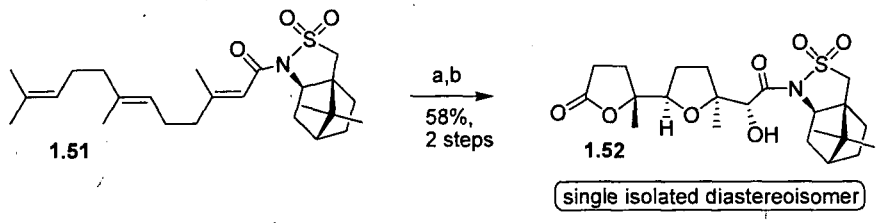
1.48a-d (Scheme 1.12).[37] Cleavage of vicinal diols **1.48a-d** yielded the desired lactones **1.49a-d** in good yields. The relative stereochemistry of lactones **1.49b** and **1.49c** also correlate with polyether antibiotics semduramycin and CP-54883 respectively.[38]



Scheme 1.12: Syntheses of adjacent *bis*-THF lactols **1.48a-d**. Reagents and conditions: (a) $KMnO_4$ (3.0 eq.), AcOH (4.0 eq.), pH = 6.2 buffer, acetone-H_2O; (b) $Pb(OAc)_4$, CH_2Cl_2, Na_2CO_3; (c) $NaIO_4$-SiO_2, CH_2Cl_2.

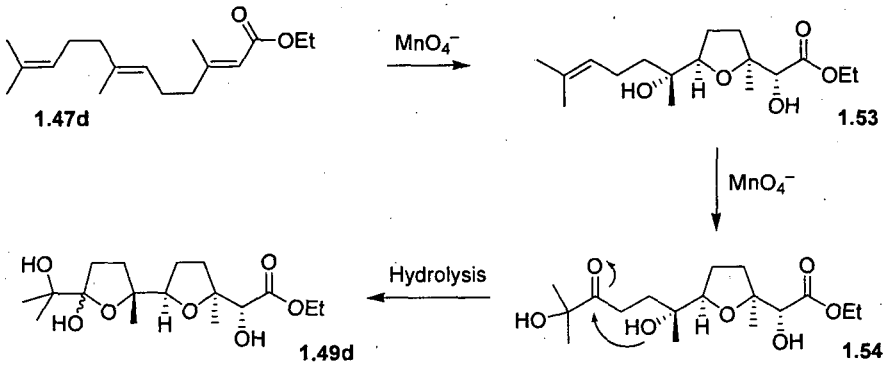
Later on, (2*R*)-10,2-camphorsultam was used to carry out the cyclisation in a stereoselective manner. The oxidation of triene **1.51** afforded the lactol which was

cleaved to lactone **1.52** in a good yield with an excellent level of diastereoselectivity (Scheme 1.13). The minor diastereoisomer was not detected in the ^{1}H NMR of the crude product of lactone **1.52**.



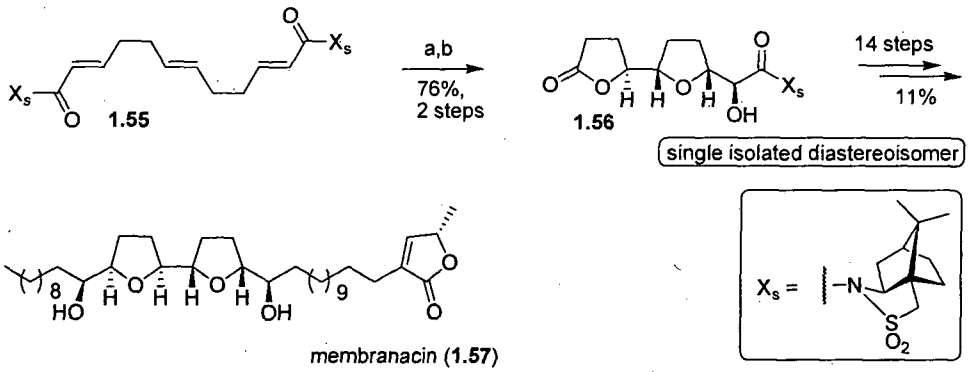
Scheme 1.13: Oxidative cyclisation of 1,5,9-triene **1.51**. Reagents and conditions: (a) $KMnO_4$ (3.0 eq.), AcOH (4.0 eq.), pH = 6.2 buffer, acetone-H_2O; (b) $NaIO_4$-SiO_2, CH_2Cl_2.

The mechanism of cyclisation of 1,5,9-triene **1.47d** is in accordance with the one proposed by Baldwin *et al.* for 1,5-diene system.[23] After the formation of *cis*-THF diol **1.53**, the oxidation of the remaining double bond affords the hydroxy ketone **1.54**, which subsequently undergoes an intramolecular cyclisation to furnish the lactol **1.49d** (Scheme 1.14).



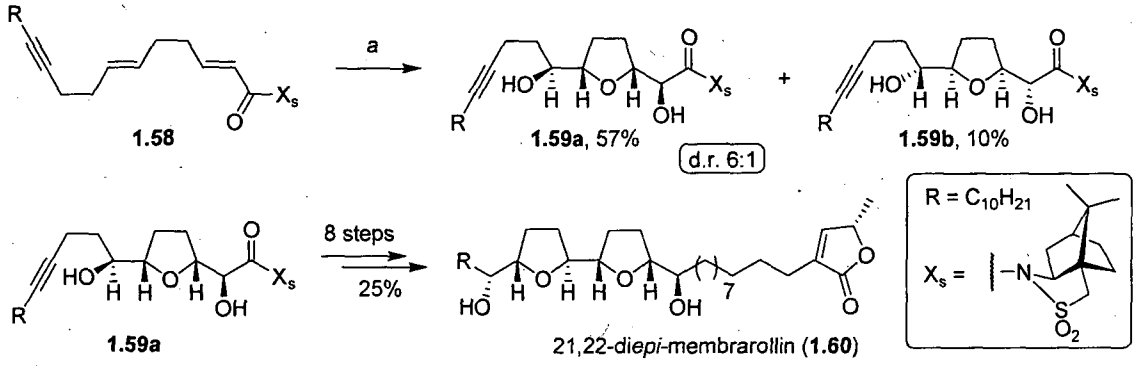
Scheme 1.14: Mechanism for the formation of *bis*-THF lactol **1.49d**.

Brown *et al.* also applied this bifuranyl synthesis approach to the synthesis of membranacin (**1.57**).[39] The requisite triene **1.55** bearing (2*S*)-10,2-camphorsultam was prepared using established methods.[40] Permanganate oxidation of the triene **1.55** followed by periodate cleavage afforded the lactone **1.56** as a single isolated diastereoisomer in a good yield (Scheme 1.15). The subsequent synthesis was accomplished in 14 steps to complete a stereoselective synthesis of membranacin (**1.57**).



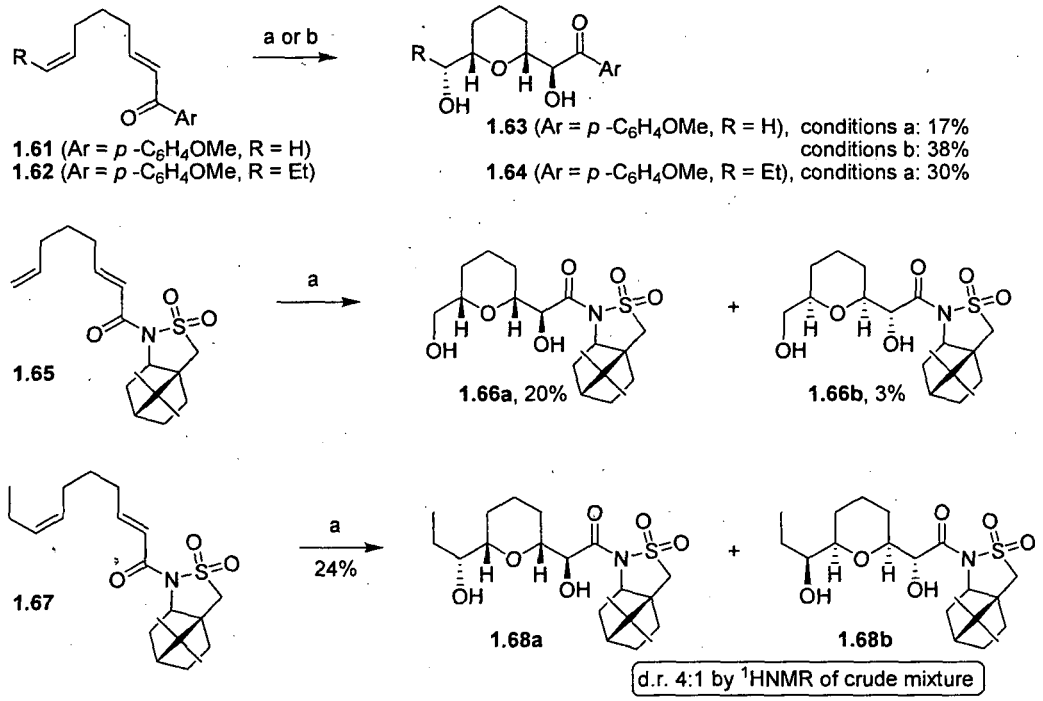
Scheme 1.15: Synthesis of membranacin (**1.57**). Reagents and conditions: (a) $KMnO_4$ (2.6 eq.), adogen 464 (5 mol%), acetone:AcOH (3:2); (b) $NaIO_4$-SiO_2, CH_2Cl_2.

Brown *et al.* also reported the synthesis of 21,22-di*epi*-membrarollin (**1.60**) by permanganate mediated oxidative cyclisation of dienyne **1.58** (Scheme 1.16).[41] The key oxidative cyclisation afforded the THF diols **1.59a,b** in a good yield and diastereoselectivity (d.r. 6:1 from ^1H NMR of the crude mixture). The diastereoisomers were separable and the synthesis was subsequently completed in 8 steps with diastereomerically pure *cis*-THF diol **1.59a**.



Scheme 1.16: Synthesis of 21,22-di*epi*-membrarollin (**1.60**). Reagents and conditions: (a) $KMnO_4$, acetone:AcOH (1:1).

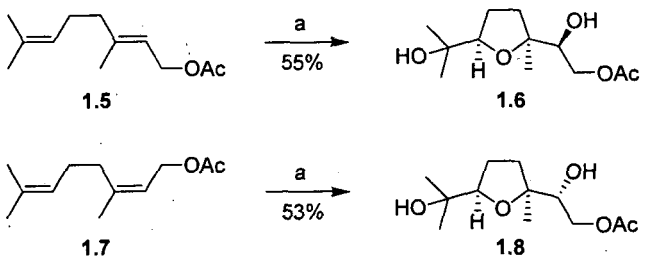
Brown *et al.* also reported the first examples of permanganate mediated oxidative cyclisations of 1,6-dienes to afford tetrahydropyrans with exclusive 2,6-*cis*-selectivity.[42] Aryl ketones **1.61** and **1.62** underwent permanganate oxidations to afford *cis*-tetrahydropyran (THP) diols **1.63** and **1.64** respectively in moderate yields (Scheme 1.17). Dienoyl sultams **1.65** and **1.67** were also oxidised stereoselectively to yield 2,6-disubstituted *cis*-THP diols **1.66a,b** and **1.68a,b** in moderate yields. Diastereoisomers **1.68a** and **1.68b** could not be separated by flash column chromatography.



Scheme 1.17: Synthesis of *cis*-2,6-disubstituted THP rings. Reagents and conditions: (a) $KMnO_4$ (1.4 eq.), acetone:AcOH (3:2); (b) $KMnO_4$ (1.4 eq.), adogen 464 (10 mol%), AcOH (16 eq.), CH_2Cl_2.

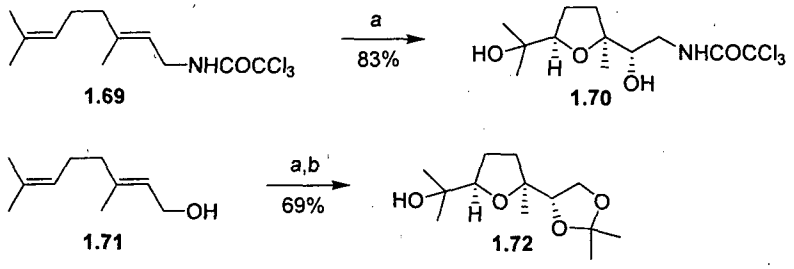
1.1.2 Osmium Tetroxide Catalysed Oxidation

Piccialli *et al.* were the first to report the catalytic osmium tetroxide mediated oxidative cyclisation using sodium periodate as a co-oxidant.[43] Gernayl acetate **(1.5)** and neryl acetate **(1.7)** were oxidised to the corresponding *cis*-THF diols **1.6** and **1.8** in moderate yields, 55% and 53% respectively (Scheme 1.18). Interestingly, changing the co-oxidant from sodium periodate to *N*-methylmorpholine-*N*-oxide (NMO) failed to yield the desired cyclised products even though NMO is a well known co-oxidant in the catalytic asymmetric dihydroxylation of olefins.[44]



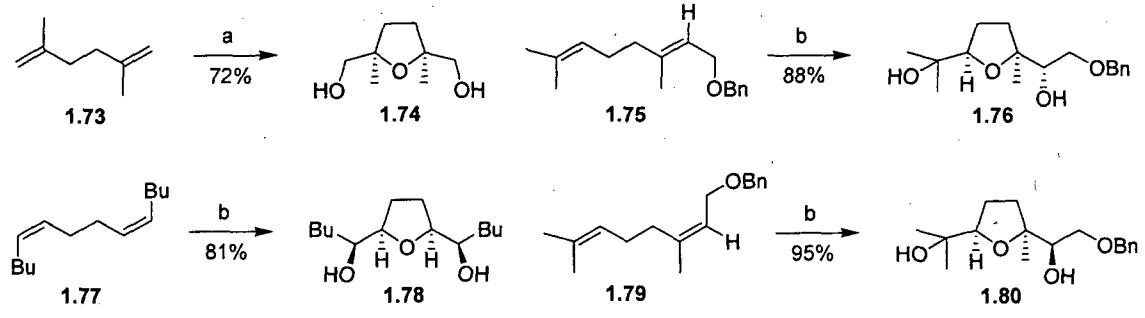
Scheme 1.18: First examples of OsO_4 mediated oxidative cyclisations. Reagents and conditions: (a) OsO_4 (5 mol%), $NaIO_4$ (4.0 eq.), DMF, 16 h.

Intensive work in the field of OsO_4 promoted oxidative cyclisation was carried out by Donohoe *et al.* and they explored the synthetic application of an OsO_4/TMEDA combination for the stereoselective oxidative cyclisation of 1,5-functionalised dienes in good yields.[45] Dienes **1.69** and **1.71** were oxidised in a regioslective fashion and it was expected to obtain the corresponding dihydroxylated products, however *cis*-THF diols **1.70** and **1.72** were obtained in good yields, during the attempted acidic decomplexation of the intermediate osmate esters (Scheme 1.19). It was thought that the OsO_4/TMEDA combination affords a hydrogen bond acceptor reagent which is an effective way to direct the regioselectivity during dihydroxylation of allylic alcohols such as **1.71**.[46]



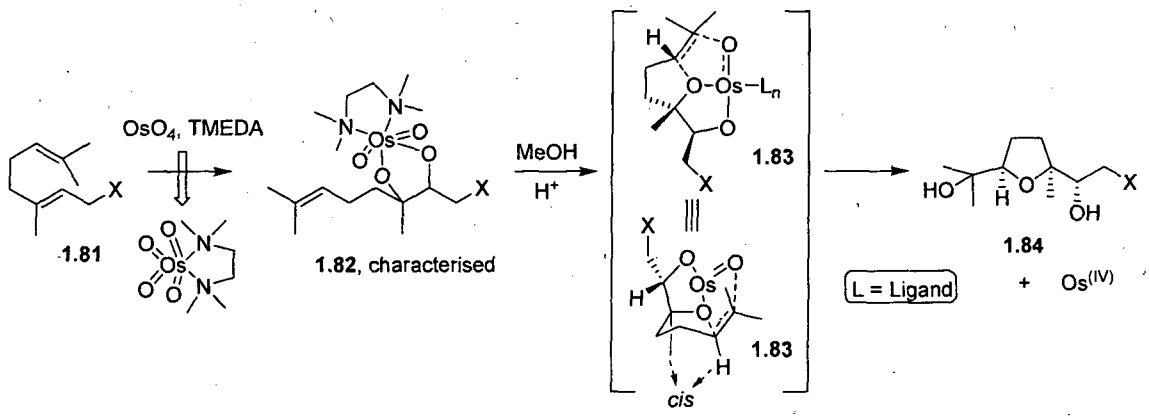
Scheme 1.19: Oxidation of dienes **1.69** and **1.71** using OsO_4/TMEDA complex. Reagents and conditions: (a) OsO_4 (1.0 eq), TMEDA (1.0 eq.), CH_2Cl_2, –78 °C then MeOH, HCl, rt; (b) $(MeO)_2CMe_2$, TFA.

To avoid the unattractive use of stoichiometric OsO_4, Donohoe *et al.* investigated the use of catalytic osmium along with Me_3NO as a co-oxidant under acidic conditions.[47] A wide range of dienes were subjected to catalytic OsO_4 promoted oxidative cyclisation to yield *cis*-THF diols, in good to excellent yields and as single diastereoisomers (Scheme 1.20).



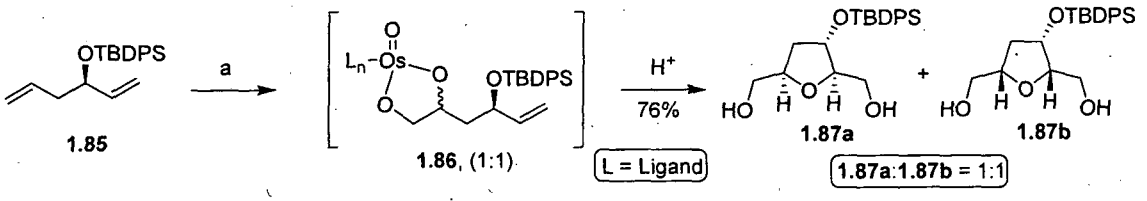
Scheme 1.20: Catalytic use of OsO_4 under acidic conditions. Reagents and conditions: (a) OsO_4 (5 mol%), Me_3NO (4.0 eq.), CSA (6.0 eq.), CH_2Cl_2; (b) OsO_4 (5 mol%), Me_3NO (4.0 eq.), TFA (excess), acetone:H_2O (9:1).

Donohoe *et al.* proposed the mechanism for OsO_4 cyclisation, which is believed to follow the same principle of cyclisation reported by Baldwin *et al.* for the permanganate mediated oxidative cyclisation of 1,5-dienes.[23] Initially one of the double bonds of diene **1.81** undergoes regioselective osmylation, controlled by hydrogen bonding to form osmate$^{(VI)}$ ester **1.82**, which has been characterised in some cases (Scheme 1.21). An intramolecular cyclisation takes place involving the reduction of active osmate$^{(VI)}$ to osmate$^{(IV)}$ to give osmate ester **1.83**. Subsequent hydrolysis of the ester **1.83** *in situ* affords the *cis*-THF adduct **1.84**. It is proposed that acid either serves to promote the rapid ligand exchange to permit the cyclisation or protonates the oxo-ligand species. In the later case, the metal would be more electron deficient hence more reactive in the cyclisation. The *cis*-selectivity of the five membered ring is believed to be due to the transition state **1.83**, in which the intact glycol osmium bonds impose the *cis*-stereochemistry across the incipient THF ring.[45]



Scheme 1.21: Proposed mechanism of OsO_4/TMEDA oxidation.

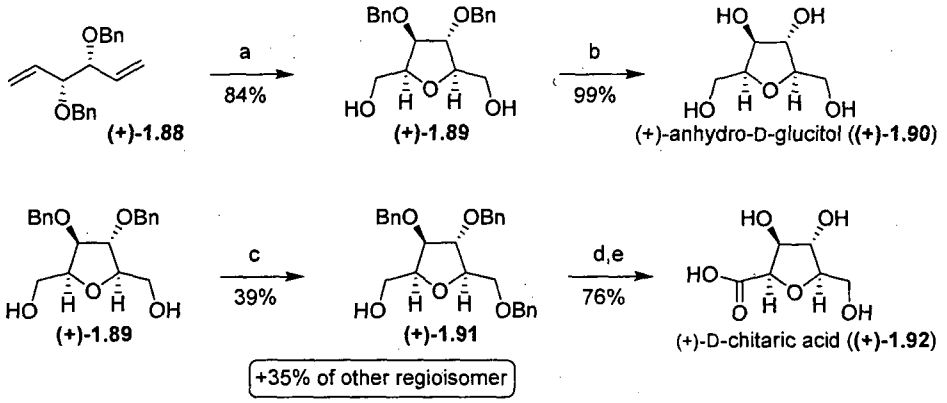
To investigate control of facial selectivity, Donohoe *et al.* introduced an internal stereodirecting substituent on the 1,5-diene precursor **1.85** and subjected it to OsO_4 catalysed oxidative cyclisation, affording exclusively *cis*-THF diols **1.87a,b** in a good yield (Scheme 1.22).[47] The reaction gave a 1:1 mixture of diastereoisomers.



Scheme 1.22: Oxidative cyclisation involving stereodirecting substituent. Reagents and conditions: (a) OsO_4 (5 mol%), Me_3NO (4.0 eq.), CSA (6.0 eq.), CH_2Cl_2.

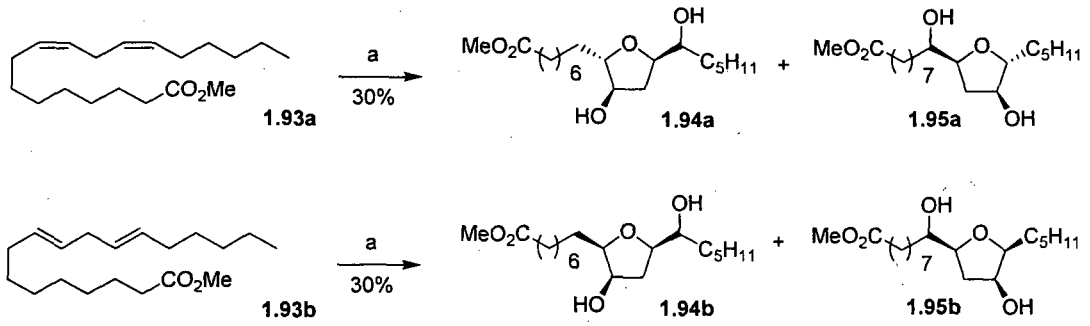
The synthetic applications of catalytic OsO_4 promoted oxidative cyclisation of 1,5-dienes was exploited by Donohoe *et al.* in a remarkably short and effective stereocontrolled synthesis of (+)-anhydro-D-glucitol (**1.90**) and (+)-D-chitaric acid (**1.92**, Scheme 1.23).[47] Enantiomerically enriched 1,5-diene **(+)-1.88**, bearing internally stereodirecting dibenzyl protected diols, was synthesised from D-mannitol in 4 steps, overall 51% yield.[48] Catalytic OsO_4 oxidative cyclisation of 1,5-diene **1.88** yielded a single stereoisomer of *cis*-THF diol **(+)-1.89** in an excellent yield. Deprotection completed a synthesis of (+)-anhydro-D-glucitol (**1.90**) in 6 steps, overall 42.5% yield.

Similarly enantiomerically enriched *cis*-THF diol **(+)-1.89** was selectively mono-protected, oxidised to the carboxylic acid and deprotected to complete the synthesis of (+)-D-chitaric acid (**1.92**) in total 8 steps, overall 12.7% yield.



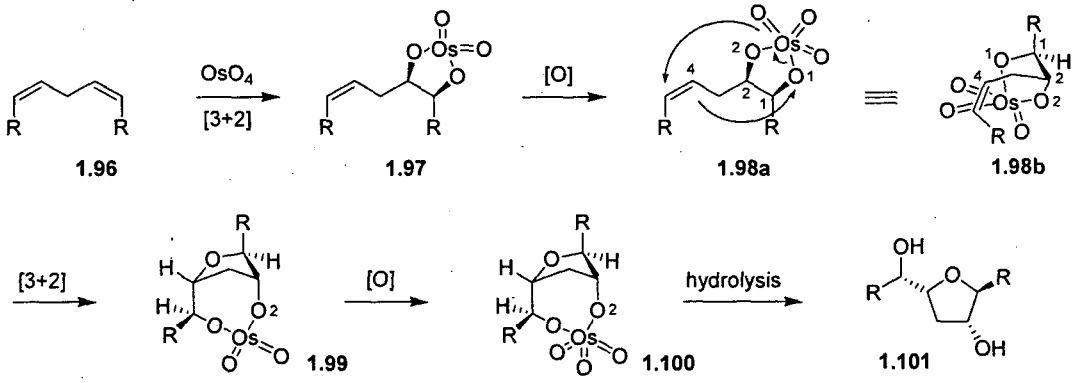
Scheme 1.23: Stereoselective synthesis of (+)-anhydro-D-glucitol (**1.90**) and (+)-D-chitaric acid (**1.92**). Reagents and conditions: (a) OsO_4 (5 mol%), Me_3NO (4.0 eq.), CSA (6.0 eq.), CH_2Cl_2; (b) H_2, Pd/C, EtOH; (c) BnBr, Ag_2O, toluene; (d) TEMPO (catalytic), $NaClO_2$, NaClO, MeCN; (e) H_2, Pd/C, MeOH.

Borhan *et al.* reported the oxidative cyclisation of 1,4-diene, *cis*-methyl linoleate (**1.93a**) using catalytic OsO_4 with Oxone® as co-oxidant in DMF to afford a 1:1 mixture of regioisomers **1.94a** and **1.95a** in a moderate yield (Scheme 1.24).[49] The same cyclisation using $KMnO_4$ and RuO_4 resulted in 20% and 12% yields respectively. Similarly oxidative cyclisation of *trans*-methyl linoleate (**1.93b**) using the same conditions yielded *cis*-2,3,5-trisubstituted THF diols **1.94b** and **1.95b** (d.r. 1:1).



Scheme 1.24: Oxidative cyclisation 1,4-dienes **1.93a,b**. Reagents and conditions: (a) OsO_4 (10 mol%), Oxone® (4.0 eq.), DMF.

The proposed mechanism for 1,4-diene oxidative cyclisation is analogous to the permanganate oxidation of 1,5-diene system.[23] Diene **1.96** undergoes [3+2] cycloaddition resulting in an osmate$^{(VI)}$ ester **1.97**, which is oxidised to Os$^{(VIII)}$ ester **1.98a**, (Scheme 1.25). THF ring formation takes place by the attack of C4 olefinic carbon on O1 as shown in Os$^{(VIII)}$ ester **1.98a**. To achieve this, the molecule must adopt conformation **1.98b**, which is very strained. This may be a reason for the modest yield. After this, the ester **1.98a** undergoes another intramolecular [3+2] cycloaddition on the internal olefin carbon of the remaining double bond to afford intermediate **1.99**, followed by the oxidation of Os$^{(VI)}$ to Os$^{(VIII)}$ to afford ester **1.100**. Finally hydrolysis yields the cyclised product **1.101**.

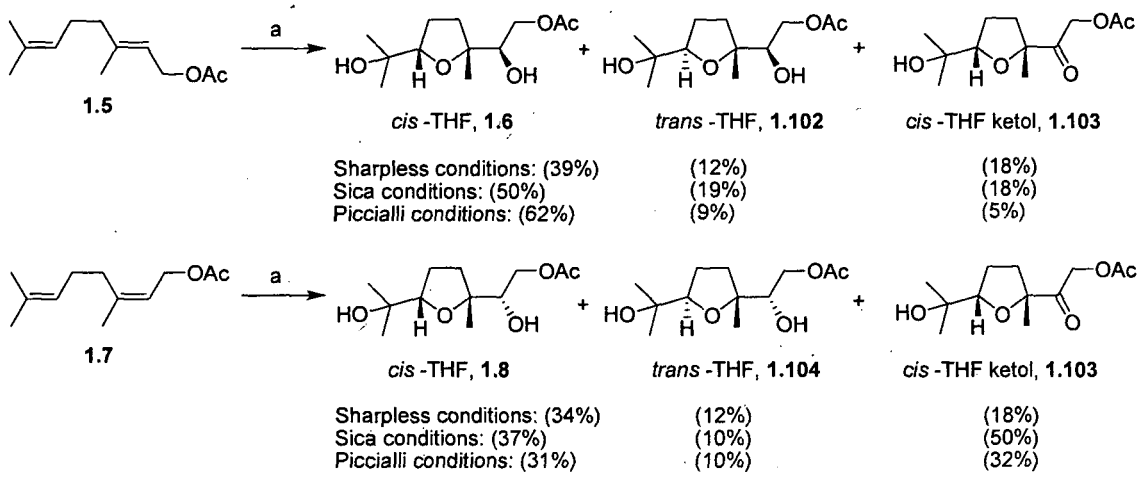


Scheme 1.25: Mechanistic proposal for the oxidation of 1,4-diene.

1.1.3 Ruthenium Tetroxide Promoted Cyclisation

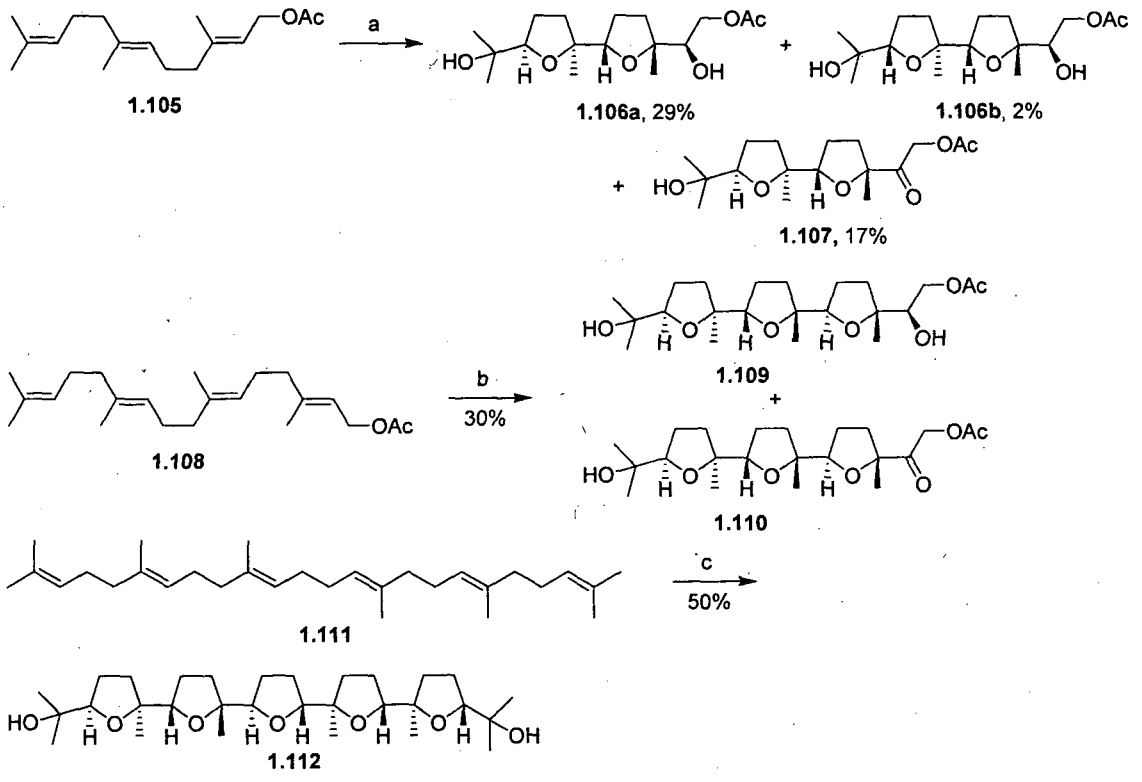
The use of ruthenium in the oxidative cyclisation of 1,5-dienes was first reported by Sharpless *et al.* (Scheme 1.26).[50] The focus of the study was to improve the catalytic conversion of primary alcohols to carboxylic acids using ruthenium and it was

discovered that the oxidation of geranyl acetate (**1.5**) and neryl acetate (**1.7**) led to the formation of *cis*-THF adducts **1.6** and **1.8** respectively as a mixture of *cis*- and *trans*-isomers (~3:1 ratio) while *cis*-THF ketol **1.103** was achieved as a major by-product. Sica *et al.* also investigated the same transformation and attempted to enhance the *cis*-selectivity of the reaction but could not achieve a significant improvement.[51] Piccialli *et al.* did have some success and the improved method also caused a decrease in the amount of over oxidation product **1.103**.[52]



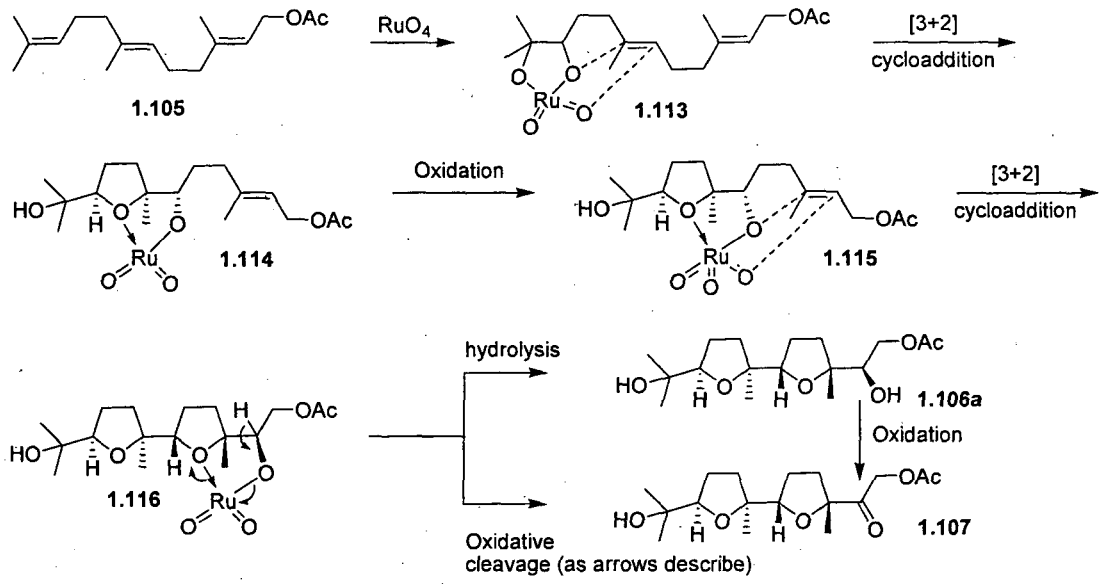
Scheme 1.26: Comparative studies of RuO_4 promoted oxidative cyclisation. Reagents and conditions: (a) *Sharpless conditions*: $RuCl_3.(H_2O)_n$, (2.2 mol%), $NaIO_4$ (3.1 eq.), CCl_4:CH_3CN:H_2O (2:2:3), 0 °C, 15 min; *Sica conditions*: $RuO_2.2H_2O$, (5.0 mol%), $NaIO_4$ (2.5 eq.), EtOAc:$(CH_3)_2CO$:H_2O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

Piccialli *et al.* have also investigated the RuO_4 catalysed polycyclisation of isoprenoid polyenes towards the syntheses of adjacently linked poly-THF rings.[53-56] Farnesyl acetate (**1.105**), geranylgeranylacetate (**1.108**) and squalene (**1.111**) underwent RuO_4 mediated oxidative polycyclisation to afford *bis*-, *tris*- and *penta*-THF diols **1.106a**, **1.109** and **1.112** respectively (Scheme 1.27). In the case of *tris*-THF product **1.109** and *penta*-THF product **1.112**, the relative configuration was determined by NMR studies and confirmed by synthesising the diols **1.109** and **1.112** *via* established methods.



Scheme 1.27: RuO_4 promoted polycyclisations of isoprenoid polyenes **1.105**, **1.108** and **1.111**. Reagents and conditions: (a) $RuO_2.2H_2O$ (20 mol%), $NaIO_4$ (4.0 eq.), EtOAc:CH_3CN:H_2O (3:3:1), 0 °C, 30 min; (b) $RuO_2.2H_2O$ (20 mol%), $NaIO_4$ (8.0 eq.), EtOAc:CH_3CN:H_2O (3:3:1), 0 °C, 30 min; (c) $RuO_2.2H_2O$ (20 mol%), $NaIO_4$ (8.0 eq.), EtOAc:CH_3CN:H_2O (3:3:1), 0 °C, 30 min.

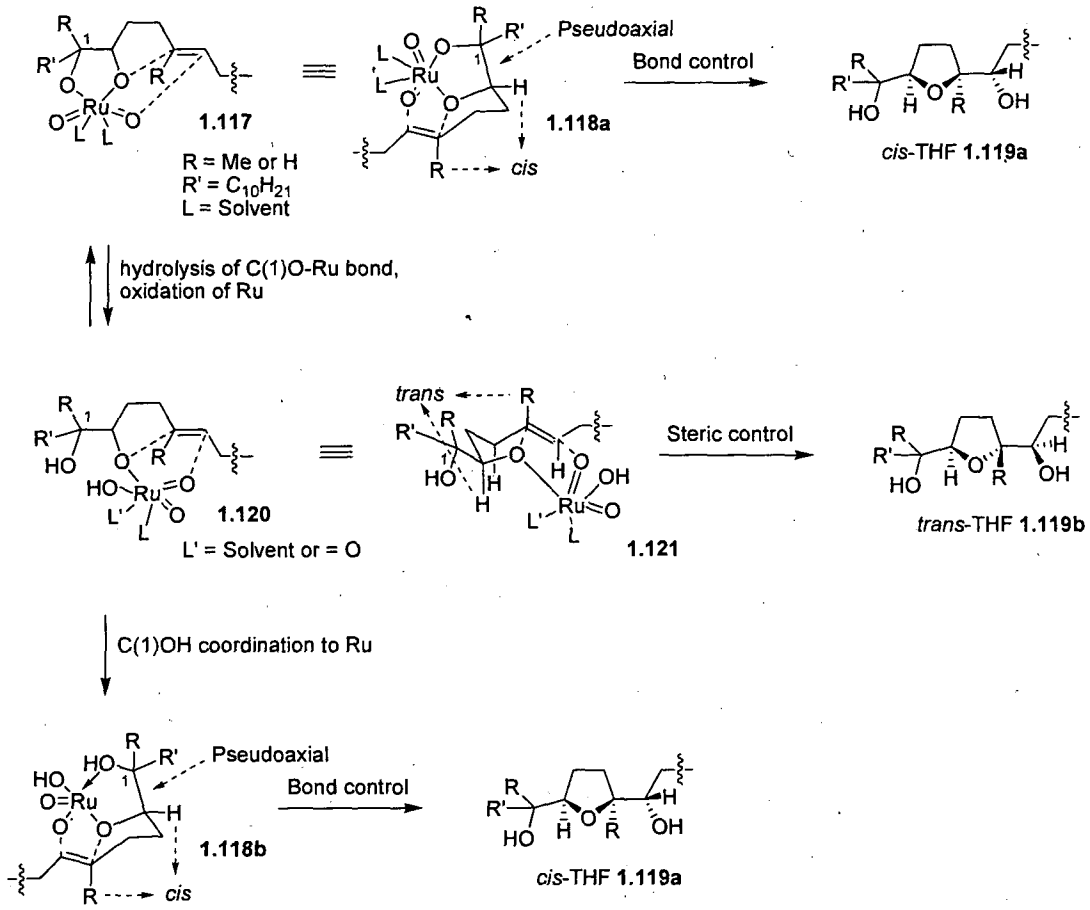
It is thought that the mechanism of this reaction is related to the proposals of Baldwin *et al.* for the permanganate oxidative cyclisation of 1,5-dienes.[23] Piccialli *et al.* also reported the mechanistic studies carried out for the formation of *bis*-THF adduct **1.105** (Scheme 1.28).[52] In the reported studies, it is believed that RuO_4 interacts with a double bond to form $Ru^{(VI)}$ diester **1.113**, followed by an intramolecular [3+2] cycloaddition and subsequent hydrolysis to initially yield THF product **1.114**. In order to achieve the active oxidation level of $Ru^{(VII)}$, $Ru^{(V)}$ is re-oxidised to form intermediate **1.115**, which undergoes another [3+2] oxidative cyclisation to form $Ru^{(V)}$ ester **1.116**. Hydrolysis of the ester **1.116** releases the *bis*-THF diol adduct **1.106a**, while oxidative cleavage leads to ketol **1.107**.



Scheme 1.28: Proposed mechanism for RuO_4 catalysed oxidative cyclisation of a 1,5,9-triene.

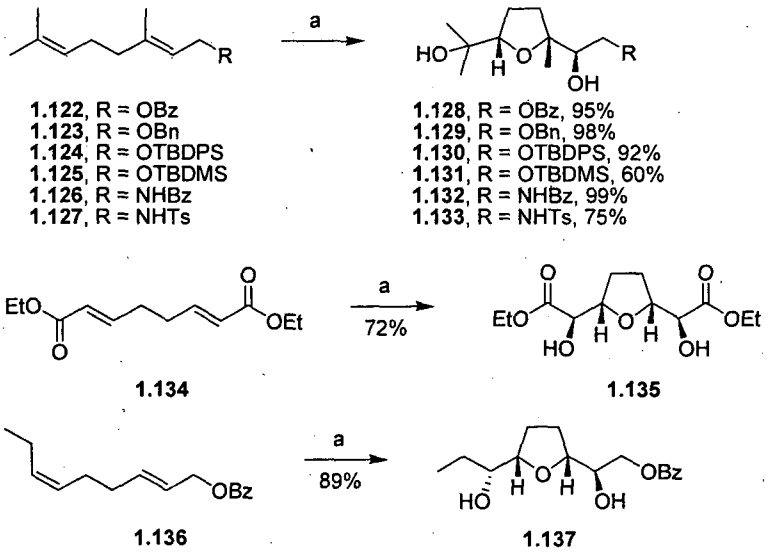
Piccialli *et al.* proposed models for the origin of *cis*- and *trans*-stereoselectivity of the THF rings resulting from RuO_4 oxidative cyclisations.[57] After the initial attack of the metal-oxo species, diester **1.117** is formed, which adopts a specific stereochemical arrangement **1.118a** to ensure the correct positioning of the remaining olefinic double bond involved in THF ring formation (Scheme 1.29). Such a chair-like conformation **1.118a**, on hydrolysis, results in *cis*-THF ring **1.119a**. It was also proposed that the hydrolysis of C(1)O-Ru bond would afford $Ru^{(VIII)}$ ester **1.120**. The coordination of C(1)OH with $Ru^{(VIII)}$ would lead to a chair like conformation **1.118b**, which is analogous to the reactive conformation **1.118a** and leads to *cis*-stereoselectivity of the incipient THF ring **1.119a** through the chelation control mechanism.

Alternatively, if no coordination of C(1)OH takes place with $Ru^{(VIII)}$, conformation **1.121** would result giving *trans*-THF **1.119b**, based on steric reasons. This open form of $Ru^{(VIII)}$ intermediate **1.121** is similar to the perrehenate ester involved in the *trans*-diastereoselective oxidative cyclisation of the bishomoallylic alcohols.[58,59]



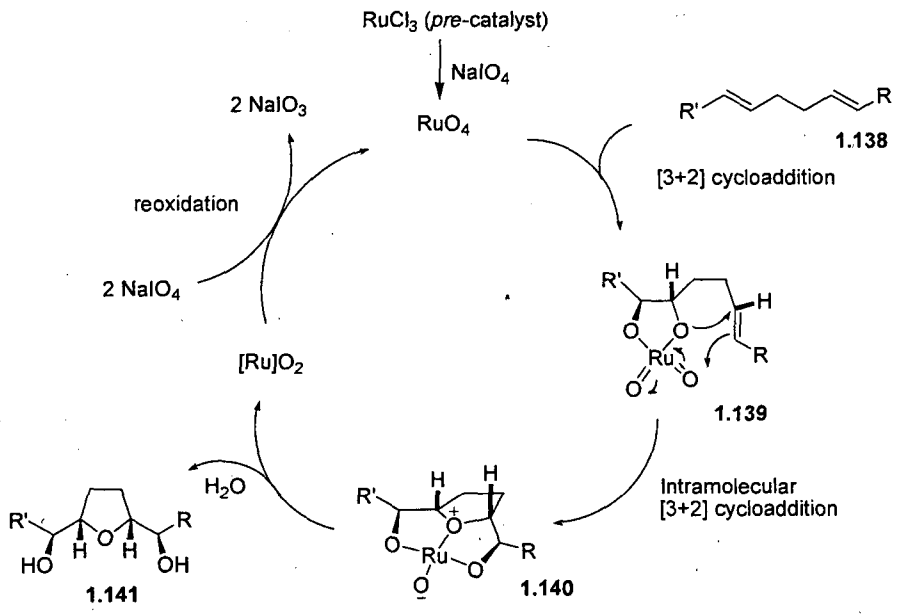
Scheme 1.29: Origin of *cis*- and *trans*-THFs resulting from RuO_4 catalysed oxidative cyclisation.

Stark *et al.* reported a catalytic RuO_4 mediated oxidative cyclisation of differently substituted 1,5-dienes to afford THF diols in a good to excellent yield and with high *cis*-stereoselectivity (d.r. >95:5, Scheme 1.30).[60,61] The corresponding *trans*-THF diols were not detected except in the case of diols **1.129** and **1.130**. $NaIO_4$ on wet silica was used as co-oxidant in a solvent mixture of THF and CH_2Cl_2 (9:1). A wide range of functional and protecting groups showed compatibility with the reaction conditions and irrespective of the double bond substitution pattern, the cyclisation proceeded in a good yield.



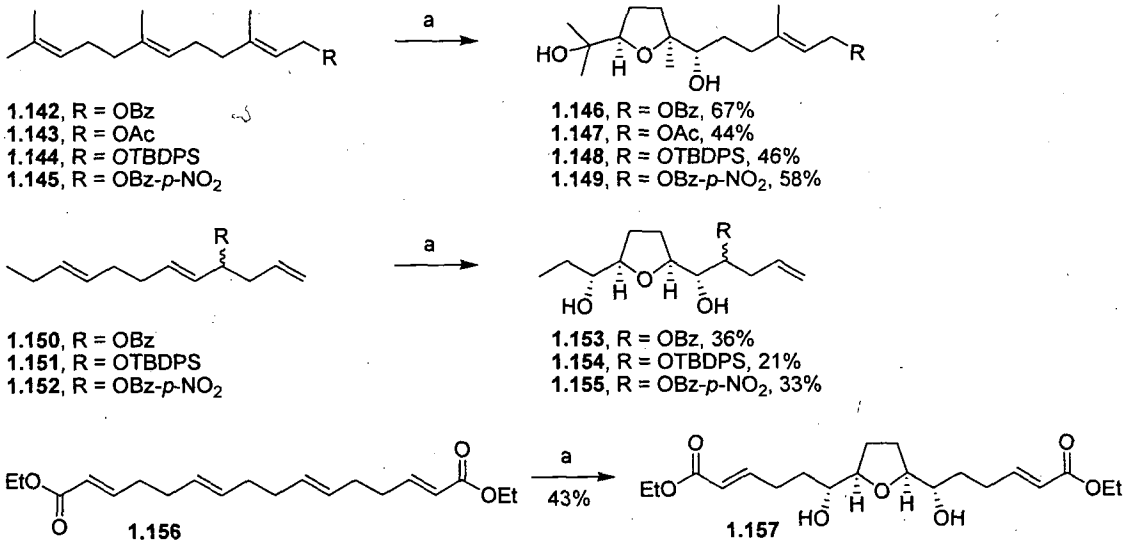
Scheme 1.30: Catalytic RuO_4 mediated cyclisation of 1,5-dienes. Reagents and conditions: (a) $RuCl_3$ (0.2 mol%), $NaIO_4$ on wet silica (3.0 eq.), THF:CH_2Cl_2 (9:1).

The mechanism proposed by Stark *et al.* for the RuO_4 cyclisation is analogous to the $KMnO_4$ and OsO_4 mediated oxidative cyclisations.[23,45] It is proposed that after the oxidation of pre-catalyst, an initial [3+2] cycloaddition takes place between RuO_4 and one of the double bond of diene **1.138** to afford $Ru^{(VI)}$ intermediate **1.139** (Scheme 1.31). The intermediate **1.139** undergoes another [3+2] intramolecular cyclisation to give $Ru^{(IV)}$ diester **1.140**, which on subsequent hydrolysis furnishes a *cis*-stereoselective THF diol **1.141** and RuO_2, which is oxidised back to RuO_4.



Scheme 1.31: Stark's proposed mechanism for catalytic RuO_4 promoted cyclisation.

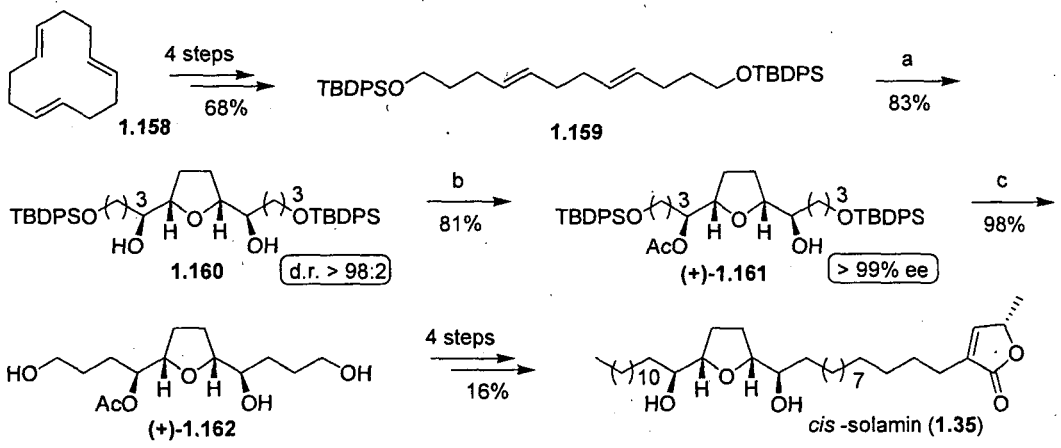
Stark *et al.* also reported the catalytic RuO_4 based mono-cyclisation of 1,5,9-trienes and polyenes, showing a good control of diastereoselectivity and regioselectivity.[62] Farnesol derivatives **1.142-1.145**, bearing a wide range of protecting groups, were oxidised to corresponding *cis*-THF diols **1.146-1.149** in good yields with high diastereoselectivity (d.r. >95:5, Scheme 1.32). Similarly non-terpenoid 1,5,9-trienes **1.150-1.152** were oxidised to *cis*-THF diols **1.153-1.155** in moderate yields and with the same level of diastereoselectivity. The methodology was extended to various polyenes including diester **1.156** and a good level of position selectivity and diastereoselectivity was observed along with moderate yields of the resultant *cis*-THF diol **1.157**. Interestingly, the cyclisations of polyenes did not go to complete conversion using previously reported optimised conditions for 1,5-diene substrates.[60] Changing the solvent from THF:CH_2Cl_2 (9:1) mixture to THF (100%) increased the reaction rates and yields. This may be due to faster hydrolysis in a polar solvent.



Scheme 1.32: Oxidative cyclisation of polyenes. Reagents and conditions: (a) $RuCl_3$ (1 mol%), $NaIO_4$ on wet silica (3.0 eq.), THF.

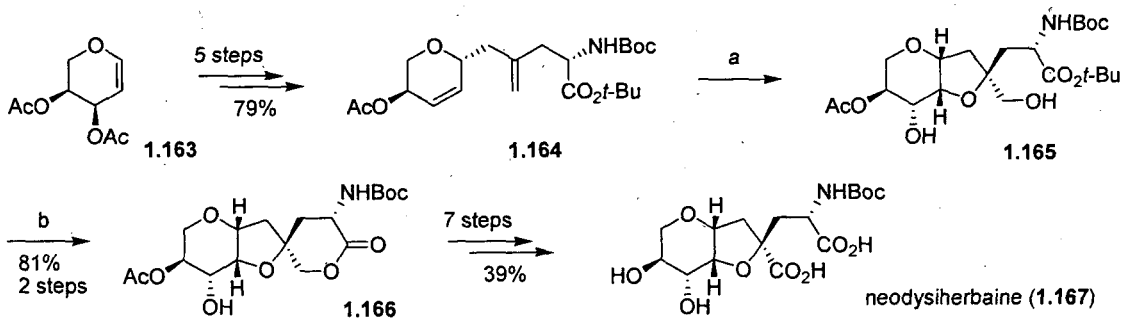
Stark *et al.* also has published a synthesis of *cis*-solamin (**1.35**) using catalytic RuO_4 mediated oxidative cyclisation in 11 steps with an overall yield of 7.5%.[63] Diene **1.159** was synthesised from commercially available (*E,E,E*)-1,5,9-cyclododecatriene (**1.158**) in 4 steps (Scheme 1.33). The oxidative cyclisation of diene **1.159** with $RuCl_3$ along with $NaIO_4$ on wet silica as co-oxidant afforded the *meso*-diol **1.160** in an excellent yield and as a single diastereoisomer. *Meso*-diol **1.160** was subjected to enzymatic esterification to afford enantiomerically pure acetate **(+)-1.161** (>99% *ee*) in a good

yield. The absolute configuration of acetate (+)-**1.161** was assigned by making Mosher esters method. Silyl deprotection of *cis*-THF afforded the triol **1.162**, which was subsequently converted to *cis*-solamin (**1.35**) in 4 steps using known method.[64]



Scheme 1.33: Stereoselective synthesis of *cis*-solamin (**1.35**). Reagents and conditions: (a) $RuCl_3$ (0.2 mol%), $NaIO_4$ on wet silica (3.0 eq.), THF, 0 °C, 6h; (b) lipase Amano AK, vinyl acetate, hexane, 60 °C, 5-7 days; (c) HF/py THF, py, rt, 24 h.

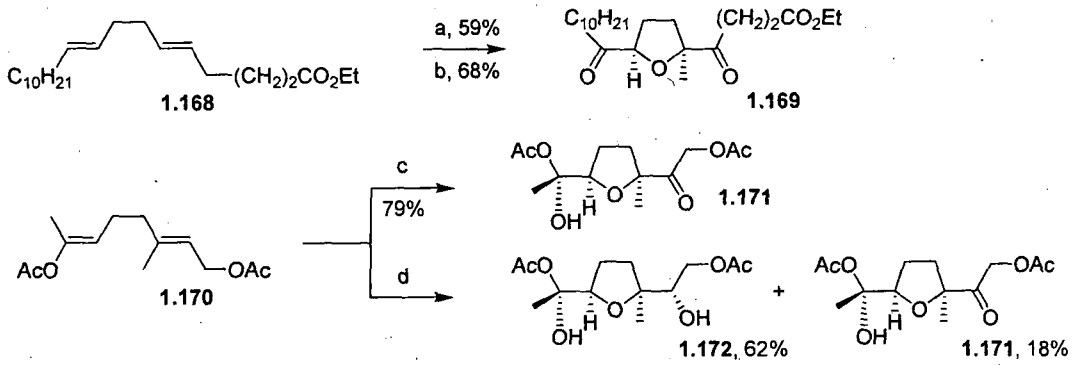
Lygo *et al.* have used the reaction in the synthesis of neodysiherbaine (**1.167**).[65] The requisite 1,5-diene **1.164** was synthesised from diacetate **1.163** in 5 steps and subjected to catalytic RuO_4 oxidative cyclisation to afford the desired THF diol **1.165** in 61% isolated yield (Scheme 1.34). However an unidentified contaminant meant that the diol **1.165** could not be purified. Alternatively, oxidative cyclisation of the diene **1.164** and treatment of the crude mixture with TsOH in $CHCl_3$ yielded the desired lactone **1.166** in an improved 81% yield over two steps, giving clean product. The rest of the synthesis was carried out with lactone **1.166** using established methods to complete the synthesis of neodysiherbaine (**1.167**).



Scheme 1.34: Stereoselective synthesis of neodysiherbaine (**1.167**). Reagents and conditions: (a) RuO_2 (5 mol%), $NaIO_4$ (2.5 eq.), EtOAc:$(CH_3)_2CO$:H_2O (2:1:1), rt, 30 min; (b) TsOH (10 mol%), $CHCl_3$, rt, 48 h.

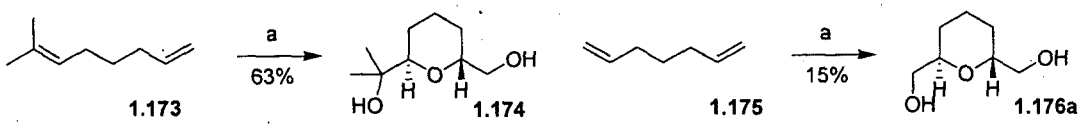
Piccialli *et al.* discovered that oxidative cyclisation could be achieved using ruthenate ion from TPAP.[66] In the presence of NMO as co-oxidant and excess of TPAP (2.0 eq.), 1,5-diene **1.168** was cyclised to *cis*-THF diketone **1.169** in a good yield (Scheme 1.35). When TPAP was used alone as oxidising agent in the absence of NMO, an incomplete conversion to THF diketone **1.169** was observed. The reaction became catalytic in TPAP, when the co-oxidant was changed from NMO to TBAPI and the yield increased from 59% to 68%.

Oxidative cyclisation of diacetate **1.170** using catalytic TPAP with TBAPI afforded the THF ketol **1.171** in a good yield. When the reaction was done in acidic conditions using NMO, a mixture of diol **1.172** and ketol **1.171** was obtained in 62% and 18% yields respectively. By changing the co-oxidant and reaction conditions, the major product of the oxidative cyclisation can be controlled which may be of synthetic importance.



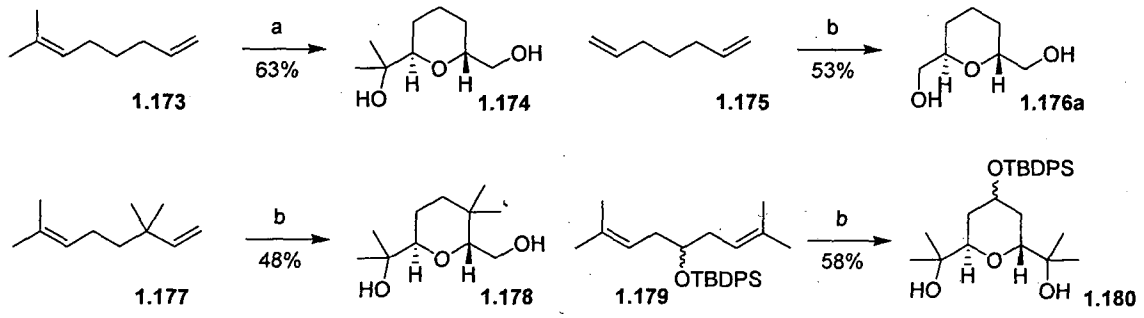
Scheme 1.35: Perruthenate promoted oxidative cyclisations of 1,5-dienes. Reagents and conditions: (a) TPAP (2.0 eq.), NMO (25 eq.), 4 Å MS, CH_2Cl_2; (b) TPAP (10 mol%), TBAPI (5.0 eq.), CH_2Cl_2; (c) TPAP (5 mol%), TBAPI (5.0 eq.), CH_2Cl_2; (d) TPAP (2.0 eq.), NMO (3.0 eq.), AcOH (500 eq.), 4 Å MS, CH_2Cl_2.

Piccialli also reported the synthesis of *trans*-2,6-THP diols by the RuO_4 mediated oxidative cyclisation of 1,6-dienes.[67] In the presence of $NaIO_4$ as co-oxidant, commercially available 1,6-dienes **1.173** and **1.175** were stereoselectively cyclised to the corresponding *trans*-THP diols **1.174** and **1.176a** respectively (Scheme 1.36).



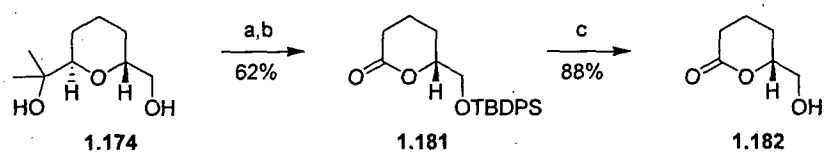
Scheme 1.36: Oxidative cyclisation of 1,6-dienes. Reagents and conditions: (a) $RuCl_3.2H_2O$ (5 mol%), $NaIO_4$ (4.0 eq.), EtOAc:CH_3CN:H_2O (3:3:1), 0 °C, 4 min.

Stark *et al.* also investigated the formation of *trans*-THP diols and reported this protocol for a wide range of 1,6-dienes, resulting in a good yield with high *trans*-diastereoselectivity (d.r. >95:5, Scheme 1.37).[68]



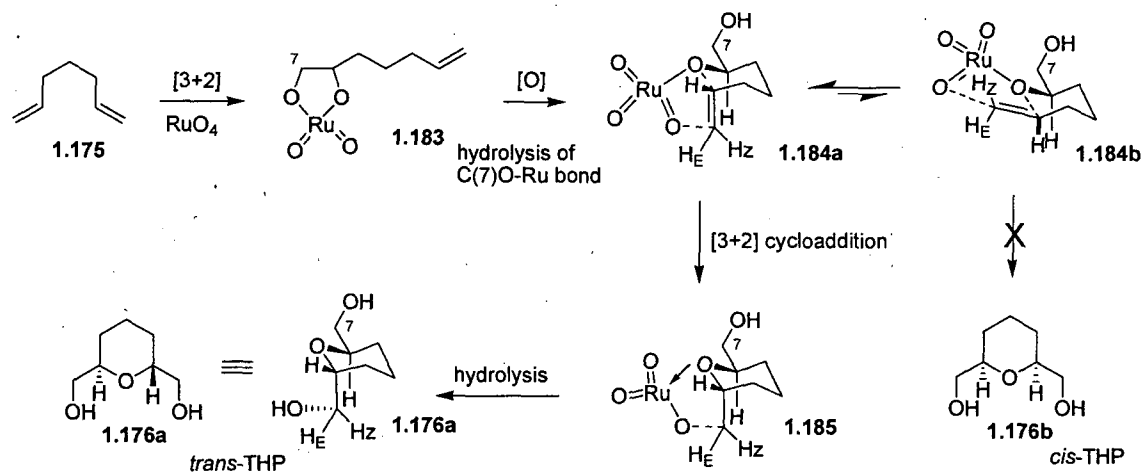
Scheme 1.37: Oxidative cyclisation of 1,6-dienes. Reagents and conditions: (a) $RuCl_3$ (1 mol%), $NaIO_4$ on wet silica (4.0 eq.), EtOAc:CH_3CN (1:1), 0 °C, 10 min; (b) $RuCl_3$ (5 mol%), $NaIO_4$ on wet silica (4.0 eq.), EtOAc:CH_3CN (1:1), 0 °C, 10 min.

Stark *et al.* also elaborated the applicability of this protocol by the synthesis of *δ*-lactone **1.182** (Scheme 1.38). The primary alcohol of *trans*-THP diol **1.174** was protected as a silyl ether, followed by the oxidative cleavage to *δ*-lactone **1.181**. Finally silyl deprotection yielded *δ*-lactone **1.182**, which has been reported as the key intermediate in the synthesis of leukotriene B_5, 5-hexadecanolide and 6-acetoxy 5-hexadecanolide.[69,70]



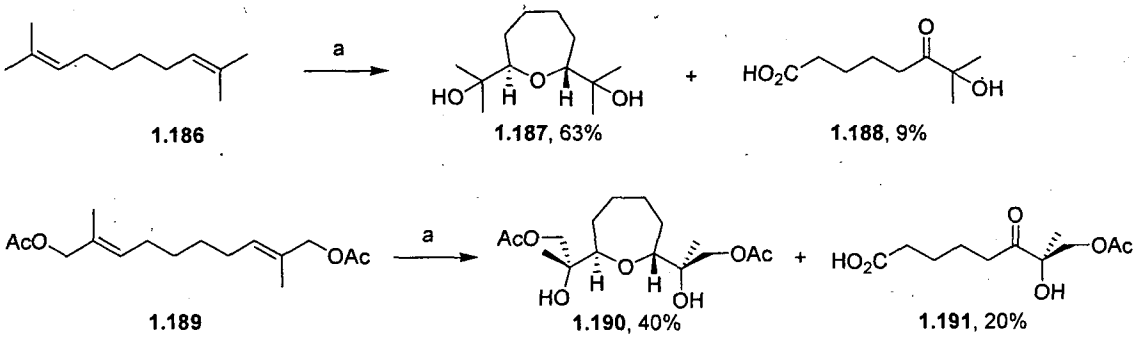
Scheme 1.38: Synthesis of *δ*-lactone **1.182**. Reagents and conditions: (a) TBDPSCl, Imid., CH_2Cl_2; (b) PCC, 4 Å MS, CH_2Cl_2; (c) TBAF, THF.

Piccialli proposed a mechanism for the oxidiative cyclisation of 1,6-dienes to afford *trans*-THP diols.[67] After initial [3+2] cycloaddition to $Ru^{(VI)}$ diester **1.183**, hydrolysis of the Ru-(C7)O bond and oxidation of $Ru^{(VI)}$ to $Ru^{(VIII)}$ affords intermediate **1.184a** (Scheme 1.39). There are two possible conformations for the second [3+2] cyclisation, **1.184a** and **1.184b**, leading to *trans*- and *cis*-THPs respectively. The open form chair like transition state **1.184a** also correlate with the models reported by McDonald *et al.* for the formation of THP alcohols from trishomoallylic alcohols.[71] The conformation **1.184b** leading to *cis*-THP formation is disfavoured due to more destabilising *gauche* interactions. Hydrolysis of intermediate **1.185** affords the *trans*-THP **1.176a**.



Scheme 1.39: Proposed mechanism for the formation of *trans*-THP diol **1.176a**.

Piccialli *et al.* also extended the RuO_4 based oxidations to the synthesis of 2,7-disubstituted *trans*-oxepane diols by cyclisation of 1,7-dienes.[72] Diene **1.186** was synthesised from cyclohexene and subjected to catalytic RuO_4 mediated oxidative cyclisation in the presence of $NaIO_4$ on wet silica as co-oxidant (Scheme 1.40). The cyclisation afforded *trans*-oxepane diols **1.187** in a good yield and high diastereoselectivity (d.r. >95:5) along with ketol **1.188**. Similarly diacetate **1.189** was oxidised to yield diol **1.190** in a moderate yield with a significant amount of the by-product, ketol **1.191**.



Scheme 1.40: Oxidative cyclisation of 1,7-dienes. Reagents and conditions: (a) $RuCl_3$ (5 mol%), $NaIO_4$ on wet silica (7.0 eq.), EtOAc:CH_3CN (1:1), 0 °C, 15 min.

1.2 Conclusions

A number of metal-oxo agents have been reported to bring about the oxidative cyclisation of 1,5-dienes to THF rings. Permanganate generally affects cyclisation in good yield, and it is environmental friendly compared to other metal-oxo reagents.

However, permanganate based oxidation requires a stoichiometric amount of the transition metal oxidant while osmium tetroxide and ruthenium tetroxide are catalytic, and require excesses of a co-oxidant such as TMEDA, Me_3NO, NMO, $NaIO_4$ and Oxone®. The advantage of using osmium tetroxide is that it gives high yields while ruthenium tetroxide affects polycyclisation.

Both osmium and ruthenium oxo-catalysts result in efficient oxidative cyclisation, but do not allow direct asymmetric oxidative cyclisation of 1,5-dienes, although indirect asymmetric oxidative cyclisations have been devised.[11,12,63] However, the use of internal stereodirecting groups for osmium tetroxide promoted asymmetric oxidative cyclisation has been investigated and reported.[47] One of the major advantages of permanganate oxidation is its effectiveness in direct asymmetric oxidative cyclisations. Permanganate has been used with chiral phase transfer catalysts and chiral auxiliaries to give effective control of absolute stereoselectivity.

Chapter 2 An Introduction to the Project

2.1 Previous Synthetic Pathways to Eurylene

Eurycoma longifolia is a tall slender shrub like tree which is native to Burma, Indochina, Thailand, and Southeast Asia. It belongs to the plant family Simaroubaceae and is commonly found as an under story in the lowland forests at up to 500 m above the sea level. The tree has many local 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. [73]

Eurylene (**2.1**) is one of the bioactive natural products isolated from Eurycoma longifolia by Itokawa *et al.*[74] The absolute stereostructure was elucidated by using X-ray crystallographic, stereoscopic and chemical methods.[74,75] In terms of total synthesis, the challenging features of this bicyclic squalenoid target include two THF rings bearing eight chiral centres. The left hand (C_1-C_{12}) segment contains a 2,5-*trans*-THF, and the right hand (C_{13}-C_{24}) fragment consists of a 2,5-*cis*-THF. The left hand and the right hand fragments of eurylene (**2.1**) are structurally and functionally similar, but there is a lack of C_2 axis of symmetry due to stereochemical differences between C_{10} and C_{15}, and C_{11} and C_{14} carbon pairs. In this section, the previous synthetic routes and our retrosynthetic approaches to eurylene (**2.1**) are summarised.

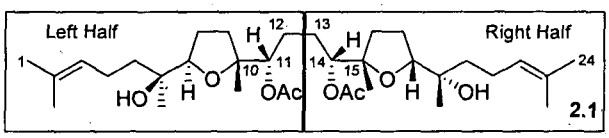


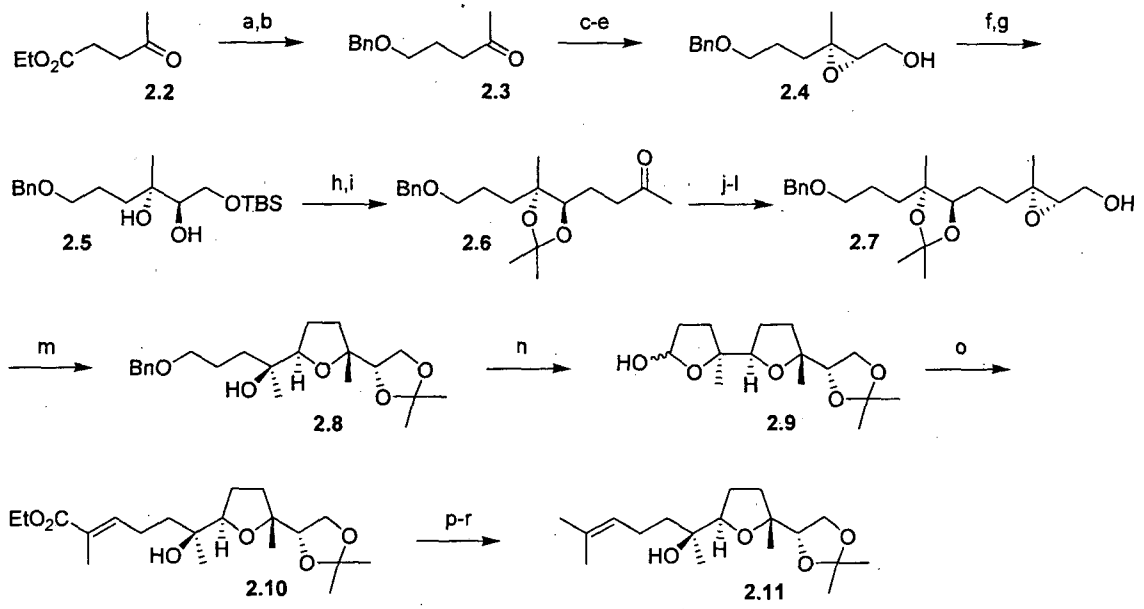
Figure 2.1: Eurylene (**2.1**).

2.1.1 Sharpless Asymmetric Epoxidation - Cyclisation

Gurjar *et al.* reported the first stereoselective synthesis of the *trans*-THF fragment **2.11** of eurylene (**2.1**), starting from a commercially available ester **2.2** (Scheme 2.1).[76] The ester **2.2** was reduced after protecting the ketone functionality. The resultant primary alcohol was protected and the ketone was deprotected to afford the benzyl ether **2.3**.

Horner-Wadsworth-Emmons olefination of the ketone **2.3** afforded the pure *E* isomer of the ester which was reduced to the corresponding allylic alcohol. Asymmetric epoxidation of the allylic alcohol afforded the epoxide **2.4** (>90% *ee*), which was subsequently converted to the triol (ratio 30:1) under basic conditions and chromatographically purified to afford the desired single isomer. Protection of the primary alcohol gave the diol **2.5**, which was protected as an acetonide. This was desilylated and oxidised to the aldehyde, which underwent Wittig olefination then catalytic hydrogenation to afford the ketone **2.6**.

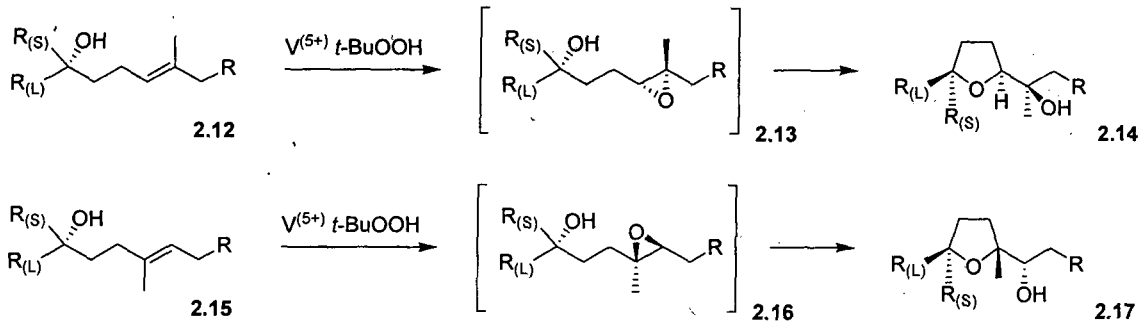
Horner-Wadsworth-Emmons olefination of ketone **2.6** afforded the methyl ester (*E*:*Z* ratio 13:1) which was reduced to the corresponding allylic alcohol. Asymmetric epoxidation of the allylic alcohol afforded the epoxide **2.7**. Acetonide deprotection of epoxide **2.7** under acidic conditions and subsequent ring closure afforded the *trans*-THF adduct which was isolated as acetonide derivative **2.8**. The structure of *trans*-THF **2.8** was assigned using ^{1}H NMR. Deprotection of benzyl ether, followed by Swern oxidation afforded the cyclic product **2.9**, which underwent olefination with stabilised ylide to afford *E* isomer of ester **2.10**, followed by DIBAL reduction to afford the allylic alcohol. The deoxygenation of allylic alcohol was carried out using Corey's protocol to finish the formal synthesis of acetonide protected *trans*-THF fragment **2.11** of eurylene (**2.1**) in 25 steps.[77]



Scheme 2.1: Synthesis of *trans*-THF fragment **2.11** of eurylene (**2.1**) by Gurjar *et al.* Reagents and conditions: (a) $HOCH_2CH_2OH$, PhH; (b) (I) $LiAlH_4$, THF; (II) NaH, BnBr, THF; (III) MeOH, PTSA; (c) $(EtO)_2P(O)CH_2COOEt$, NaH, PhH; (d) DIBAL-H, CH_2Cl_2; (e) (+)-DIPT, TBHP, $Ti(iOPr)_4$, CH_2Cl_2; (f) KOH, DMSO:H_2O (4:1); (g) TBSCl, imid., CH_2Cl_2; (h) (I) $Me_2C(OMe)_2$, PTSA, CH_2Cl_2; (II) Bu_4NF, THF; (i) (I) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (II) $CH_3COCH{=}PPh_3$, CH_2Cl_2; (III) Pd-C, H_2, $NaHCO_3$, MeOH; (j) $(EtO)_2P(O)CH_2COOEt$, NaH, PhH; (k) DIBAL-H, CH_2Cl_2; (l) (+)-DIPT, TBHP, $Ti(^iOPr)_4$, CH_2Cl_2; (m) (I) Amberlyst 15 Å, MeOH; (II) $Me_2C(OMe)_2$, PTSA, CH_2Cl_2; (n) (I) Pd-C, H_2, MeOH; (II) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (o) $Ph_3P{=}C(Me)COOEt$, CH_2Cl_2; (p) DIBAL-H, CH_2Cl_2; (q) Ac_2O, py, DMAP, CH_2Cl_2; (r) Py-SO_3 complex, THF then $LiAlH_4$.

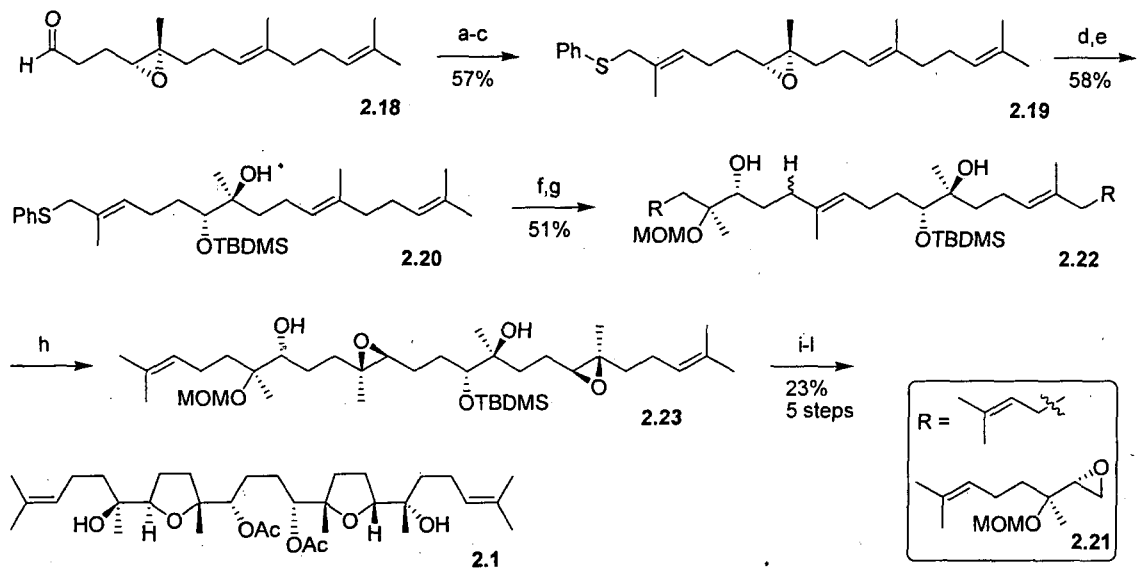
2.1.2 Vanadium Catalysed Oxidative Cyclisations

Ujihara *et al.* synthesised the *cis*-THF moiety **2.14** of eurylene (**2.1**) using vanadium$^{(V)}$ catalysed oxidative cyclisation of 5-substituted-4-alken-1-ol **2.12** via *syn*-epoxide **2.13**. The *trans*-THF adduct **2.17** was constructed by the same methodology applied to 4-substituted-4-alken-1-ol **2.15** via *anti*-epoxide **2.16** (Scheme 2.2).[78]



Scheme 2.2: Syntheses of *cis*-THF **2.14** and *trans*-THF **2.17** using vanadium catalysed oxidations.

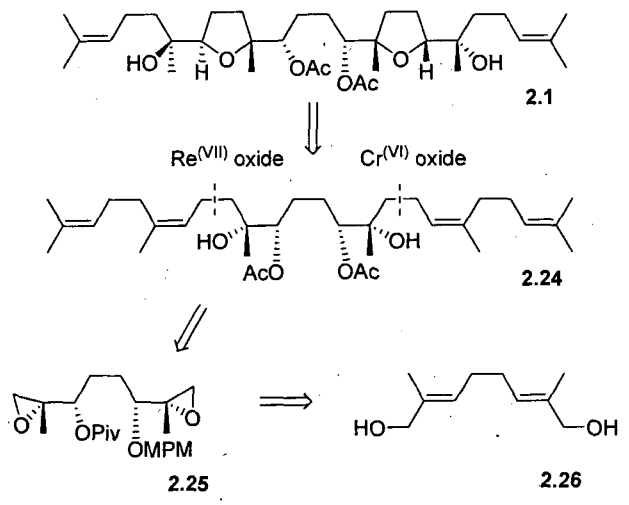
The synthesis commenced with the optically pure aldehyde **2.18**, previously reported by Kigoshi *et al.*[79] The aldehyde **2.18** underwent Horner-Wadsworth-Emmons olefination to afford the ethyl ester, which was subsequently reduced to alcohol and then converted to thioether **2.19** (Scheme 2.3). Hydrolysis of epoxide **2.19** and protection of the resultant secondary alcohol afforded silyl ether **2.20**. Coupling of silyl ether **2.20** with oxirane **2.21** yielded the *bis*-homoallylic alcohol that was desulfurised using Birch conditions to afford the diol **2.22**, which was subsequently converted to *bis*-epoxide **2.23**. Due to side reactions including deprotection and/or oxidation of terminal double bonds, the diastereomeric purity of *bis*-epoxide **2.23** could not be determined. Acid catalysed cyclisation of left hand epoxide and deprotection of the silyl group followed by the acid catalysed cyclisation of right hand epoxide with simultaneous cleavage of the methoxymethyl group afforded the *bis*-THF core structure. Finally acetylation of the secondary alcohols completed the first total synthesis of eurylene (**2.1**).



Scheme 2.3: First total synthesis of eurylene (**2.1**) by Ujihara *et al.* Reagents and conditions: (a) $(EtO)_2P(O)CH(CH_3)CO_2Et$, NaH, THF; (b) DIBAL-H, toluene; (c) PhSSPh, *n*-Bu_3P, CH_2Cl_2; (d) cat. $HClO_4$, THF:H_2O (6:1); (e) TBDMSOTf, 2,6-lutidine, CH_2Cl_2; (f) epoxide **2.21**, *n*-BuLi, TMEDA, HMPA, THF; (g) Li, NH_3:EtOH (1:1); (h) TBHP, cat. $VO(acac)_2$, MS 3Å, benzene then Me_2S; (i) cat. CSA; (j) TBAF, THF; (k) cat. HCl, THF:H_2O (10:1); (l) Ac_2O, py.

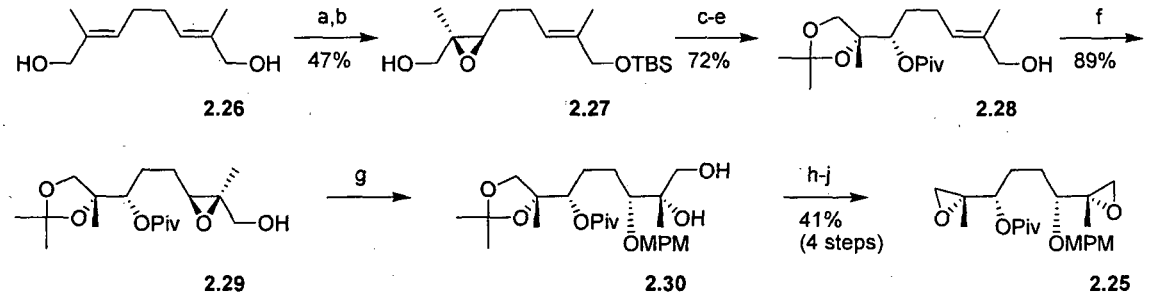
2.1.3 Rhenium and Chromium Oxidative Cyclisations

Morimoto *et al.* reported the synthesis of eurylene (**2.1**) by using rhenium$^{(VII)}$ oxidative cyclisation for the construction of the *trans*-THF ring while the *cis*-THF was synthesised by applying chromium$^{(VI)}$ oxide as an oxidant (Scheme 2.4).[80]



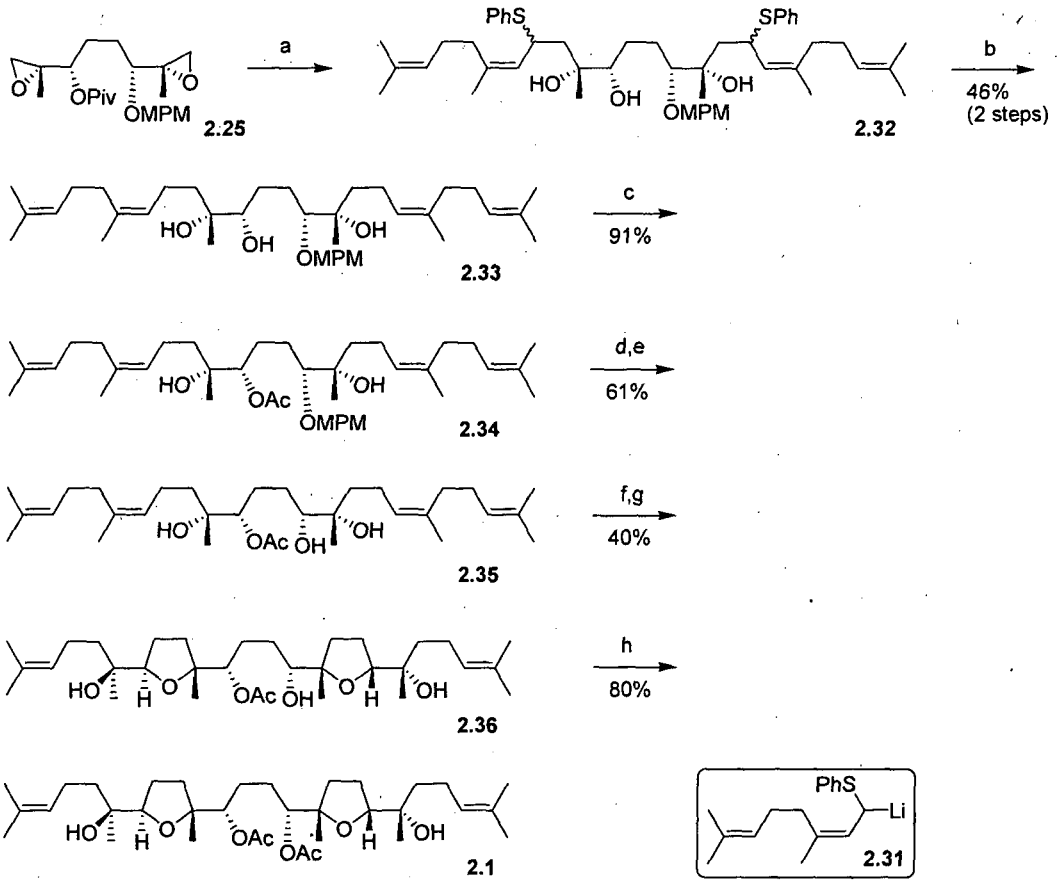
Scheme 2.4: Retrosynthetic analysis of eurylene (**2.1**) by Morimoto *et al.*

The synthesis started with the known diol **2.26**.[81] This was mono-protected then subjected to Sharpless asymmetric epoxidation to afford epoxy alcohol **2.27** in 98% *ee* (Scheme 2.5). The regioselective introduction of a pivalate group in to epoxide **2.27** yielded the diol as a single diastereoisomer which on subsequent acetonide protection and desilylation furnished allylic alcohol **2.28**. The asymmetric epoxidation of allylic alcohol **2.28** yielded epoxyalcohol **2.29**, which was subjected to epoxide opening reaction to afford the desired 1,2-diol **2.30** along with a by-product 1,3-diol in a ratio of 3:1. Cleavage of the acetonide **2.30**, mesylation of both primary hydroxy groups, and epoxide closure finally furnished the requisite *bis*-epoxide **2.25**.



Scheme 2.5: Stereoselective synthesis of diepoxide **2.25**. Reagents and conditions: (a) TBSCl, imid., CH_2Cl_2; (b) TBHP, $Ti(^iOPr)_4$, D-(–)-DET, MS 4Å (98% *ee*); (c) $Ti(iOPr)_4$, PivOH, PhH; (d) $Me_2C(OMe)_2$, CSA, CH_2Cl_2; (e) Bu_4NF, THF; (f) TBHP, $Ti(^iOPr)_4$, L-(+)-DET, MS 4Å, CH_2Cl_2; (g) $Ti(OMPM)_4$, MPMOH, PhH; (h) AcOH:H_2O, (4:1); (i) MsCl, py, CH_2Cl_2; (j) K_2CO_3, MeOH.

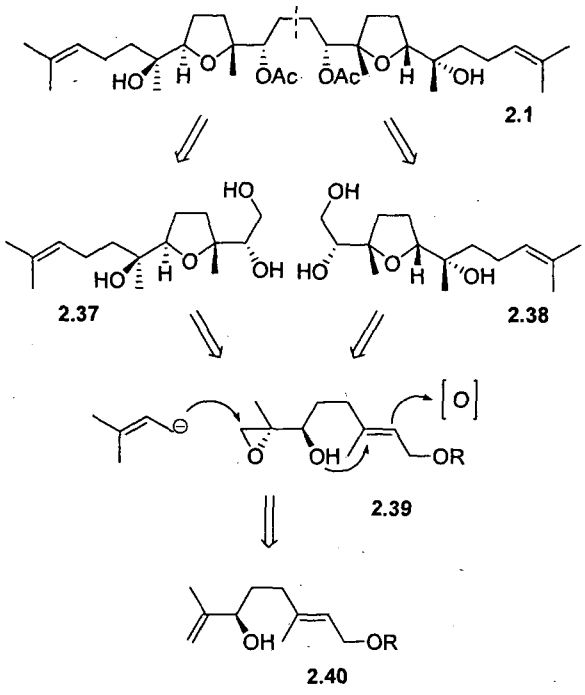
Alkylation of the lithio derivative of neryl phenyl sulfide **2.31** with *bis*-epoxide **2.25** achieved a bidirectional chain extension, yielding bisulfide **2.32** which was desulfurised under Bouvault-Blanc conditions to provide the triol **2.33** (Scheme 2.6).[82] Selective acetylation of the secondary alcohol afforded the mono-acetate **2.34**. MPM deprotection of acetate **2.34** with subsequent acidic hydrolysis furnished the triol **2.35**. Treatment of triol **2.35** with oxorhenium$^{(VII)}$ complex (8.0 eq.) and TFAA (10.0 eq.) afforded *trans*-mono-THF adduct which, on treatment with a stoichiometric amount of oxochromium$^{(VI)}$ complex afforded *cis*-THF **2.36**. Acetylation of **2.36** completed the total synthesis of eurylene (**2.1**).



Scheme 2.6: Total synthesis of eurylene (**2.1**) by Morimoto *et al.* Reagents and conditions: (a) sulfide **2.31**, TMEDA, THF; (b) Na, THF:^{i}PrOH, (2:1); (c) Ac_2O, py; (d) DDQ, MS 4Å, CH_2Cl_2; (e) AcOH:H_2O, (4:1); (f) [$(CF_3CO_2)ReO_3.2CH_3CN$], TFAA, CH_2Cl_2:CH_3CN (9:1); (g) PCC, CH_2Cl_2; (h) Ac_2O, py.

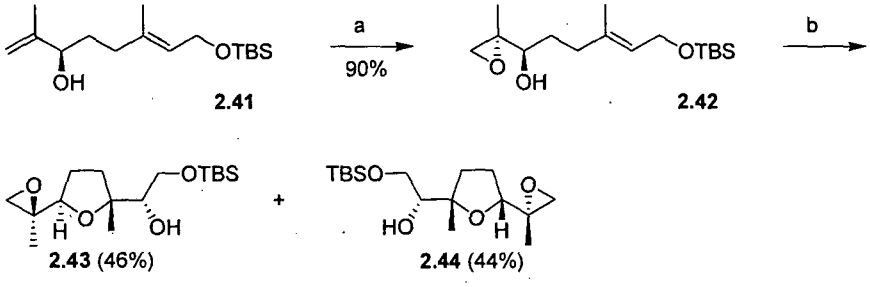
2.1.4 *m*-CPBA Epoxidation - Cyclisation

Kodama *et al.* achieved the synthesis of eurylene (**2.1**) by non-stereoselective THF ring formation (Scheme 2.7).[83] Their retrosynthetic approach disconnected eurylene (**2.1**) in to a left hand segment **2.37** and right hand fragment **2.38**, which come from a common diene precursor **2.40**.



Scheme 2.7: Retrosynthetic analysis of eurylene (**2.1**) by Kodama *et al.*

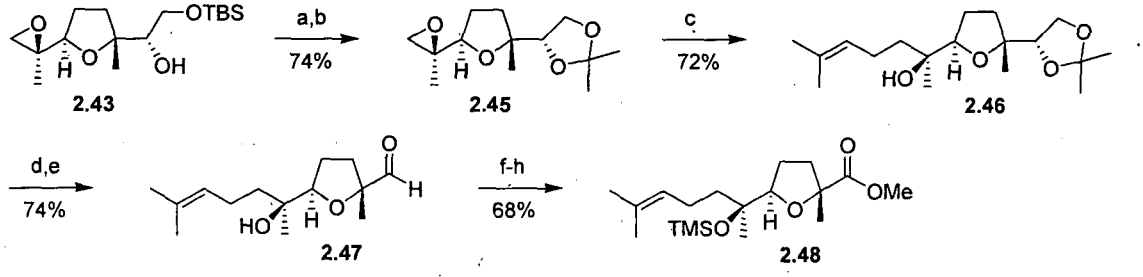
The (*R*)-allylic alcohol **2.41** was synthesised using baker's yeast reduction giving more than 99% *ee*.[84] The alcohol **2.41** was converted into epoxide **2.42** in 86% diastereomeric excess, which on treatment with *m*-CPBA afforded *trans*-THF **2.43** and *cis*-THF **2.44** unselectively and in almost equal amounts (Scheme 2.8). Due to the difference in polarity, the polar *trans*-THF moiety **2.43** was separated from the *cis*-THF adduct **2.44** and stereochemistry was determined by NOE experiments.



Scheme 2.8: THF ring formation in a non-stereoselective fashion.
Reagents and conditions: (a) $VO(acac)_2$, *t*-BuOOH, PhH; (b) *m*-CPBA, CH_2Cl_2.

To accomplish the synthesis of left hand fragment **2.48**, *trans*-THF product **2.43** was converted to acetonide **2.45** by sequential deprotection of silyl ether and protection of the resulting 1,2-diol (Scheme 2.9). Alkylation of epoxide **2.45** afforded the alcohol **2.46** in a good yield. The acetonide protecting group was hydrolyzed, the resulting 1,2-

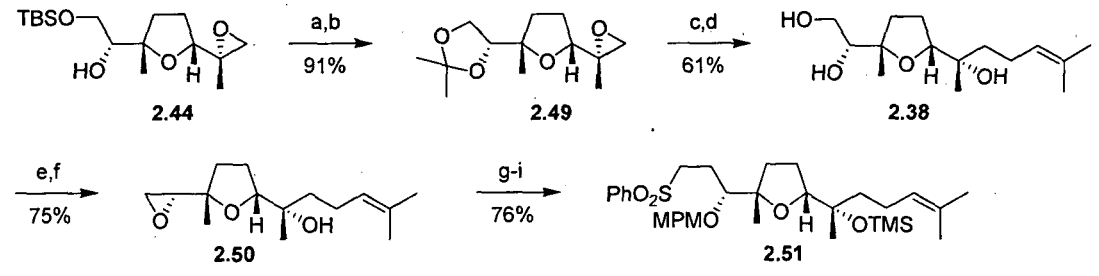
diol was oxidatively cleaved to give aldehyde **2.47**, which was further oxidized and esterified to afford the methyl ester **2.48**, the left hand fragment of eurylene (**2.1**).



2.43 **2.45** **2.46** **2.47** **2.48**

Scheme 2.9: Synthesis of left hand fragment **2.48** of eurylene (**2.1**). Reagents and conditions: (a) TBAF, THF; (b) $Me_2C(OMe)_2$, PTSA, CH_2Cl_2; (c) $Me_2C{=}CHCH_2MgCl$, CuI, THF; (d) PPTS, EtOH; (e) $NaIO_4$, aq. THF; (f) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, aq. *t*-BuOH; (g) MeI, K_2CO_3, DMF; (h) TMSCl, imid., DMF.

Similarly *cis*-THF **2.44** was transformed into acetonide **2.49**, which was subsequently alkylated, and the acetonide functionality was deprotected to afford 1,2-diol **2.38** (Scheme 2.10). The primary alcohol of 1,2-diol **2.38** was mesylated and treated under basic conditions to afford the epoxide **2.50**. Alkylation of epoxide **2.50** with the lithio-anion of methyl phenyl sulfone gave the diol, in which secondary and tertiary hydroxy groups were protected as MPM and TMS ethers respectively to afford the sulfone **2.51**, the right hand fragment of eurylene (**2.1**).

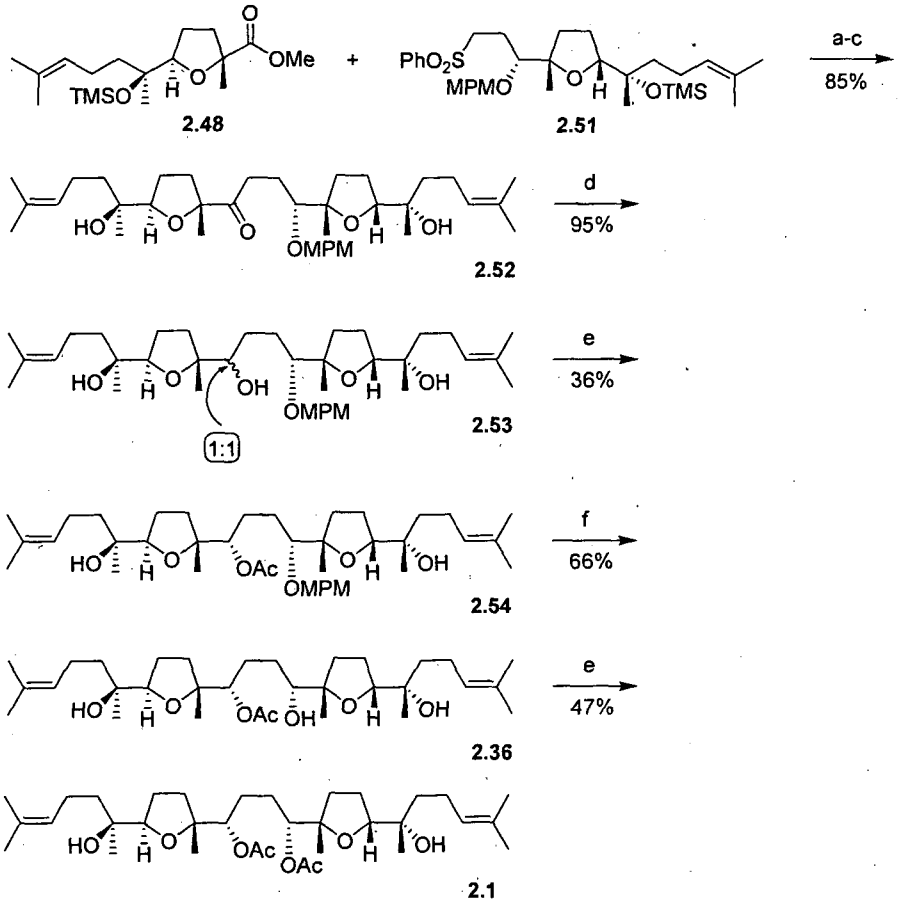


2.44 **2.49** **2.38** **2.50** **2.51**

Scheme 2.10: Synthesis of right hand fragment **2.51** of eurylene (**2.1**). Reagents and conditions: (a) TBAF, THF; (b) $Me_2C(OMe)_2$, PTSA, CH_2Cl_2; (c) $Me_2C{=}CHCH_2MgCl$, CuI, THF; (d) PPTS, EtOH; (e) MsCl, py; (f) K_2CO_3, MeOH; (g) $MeSO_2Ph$, *n*-BuLi, DMPU, THF; (h) MPMCl, NaH, DMF; (i) TMSCl, imid., DMF.

Lithio-anion of *cis*-THF **2.51** was coupled with the *trans*-THF ester **2.48** in a good yield (Scheme 2.11). Reductive desulfonylation, deprotection of the TMS group, and reduction of the resultant ketone **2.52** afforded a mixture of epimeric alcohols **2.53** (ca. 1:1). The epimers could not be separated and the mixture was acetylated and then

separated to give pure *bis*-THF adduct **2.54**. Deprotection of the MPM ether afforded 14-deacetyl eurylene (**2.36**). Acetylation of the secondary alcohol completed the synthesis of eurylene (**2.1**). The syntheses of epimeric eurylene, 14-deacetyl eurylene (**2.36**) and epimeric deacetyl eurylene were also reported.



Scheme 2.11: Total synthesis of eurylene (**2.1**) by Kodama *et al*. Reagents and conditions: (a) LiHMDS, DMPU, THF; (b) SmI_2, THF:MeOH (5:1); (c) 1 M HCl, MeOH; (d) $NaBH_4$, MeOH; (e) Ac_2O, py; (f) DDQ, CH_2Cl_2:$NaHCO_3$ (10:1).

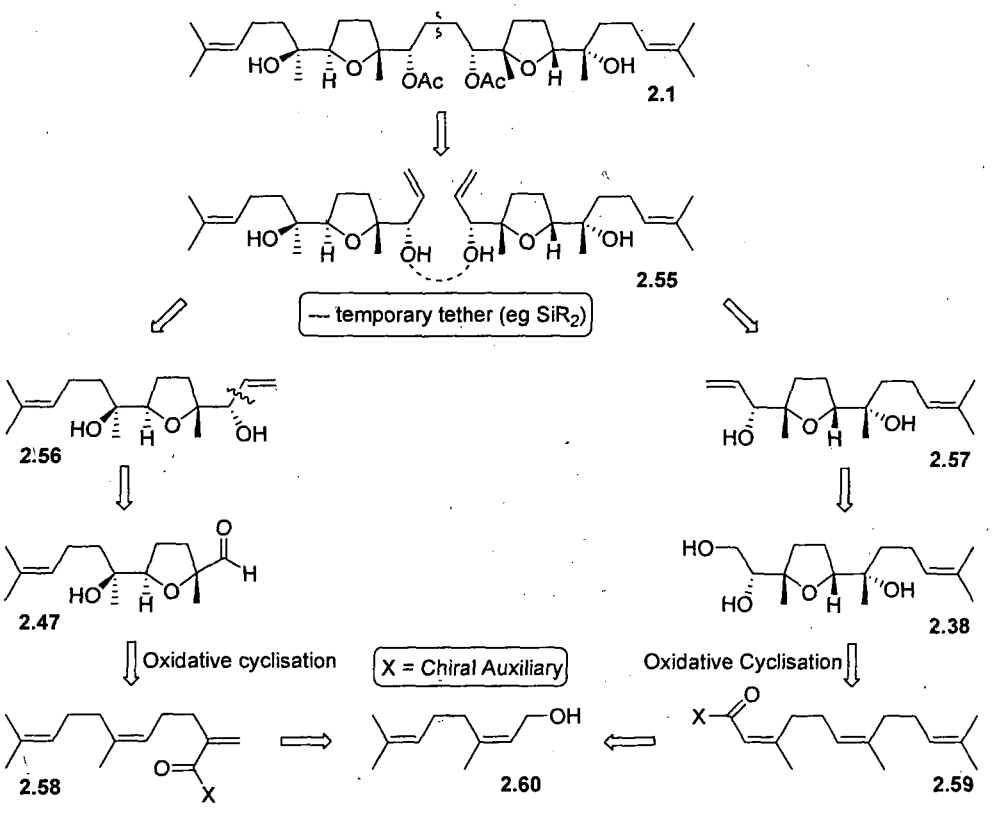
2.2 Our Proposed Approaches to Eurylene

Our approach towards the synthesis of eurylene (**2.1**) is based on permanganate mediated stereocontrolled oxidative cyclisations of 1,5,9-trienes **2.58** and **2.59**, bearing suitable chiral auxiliaries, to afford *trans*-THF **2.47** and *cis*-THF **2.38** fragments of eurylene (**2.1**) respectively (Scheme 2.12). The importance of this methodology is described by the fact that seven out of eight chiral centres can be fixed by these two key permanganate promoted oxidative cyclisations. Also herein, we report the illustration of a new approach towards the synthesis of *trans*-THF ring **2.47** by selective permanganate catalysed oxidative cyclisation of 1,5,9-triene **2.58**.

Trienes **2.58** and **2.59** can be synthesised from a cheap commercially available starting material nerol (**2.60**) employing number of established chemistries. Once the left hand *trans*-THF aldehyde **2.47** and the right hand *cis*-THF triol **2.38** of eurylene (**2.1**) are synthesised, the coupling of both fragments can be envisaged using various procedures. A brief description of the retrosynthetic analyses applying various coupling methodologies is summarised below.

2.2.1 Tethered Ring Closing Metathesis Protocol

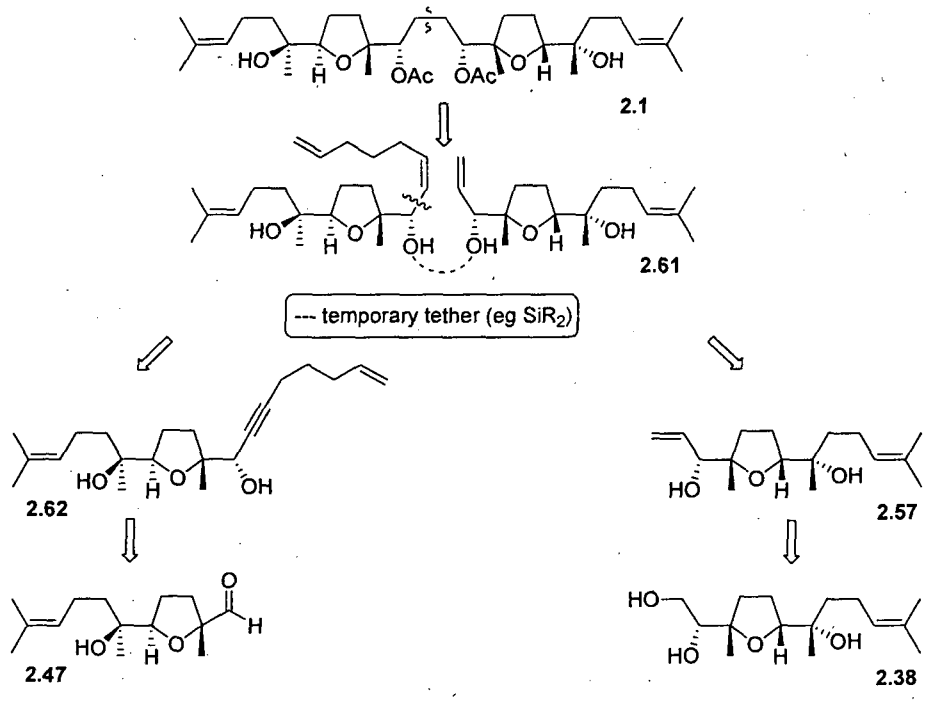
Asymmetric vinylation of *trans*-THF aldehyde **2.47** would fix the last stereocentre in the molecule and coupling of the resultant allylic alcohol **2.56** with the left hand allylic alcohol **2.57**, using a silicon tether would provide a suitable substrate for ring closing metathesis (Scheme 2.12).[85,86] The bridging of both allylic partners would be accomplished by RCM.[87] Selective reduction of the least substituted double bond, deprotection and acetylation of the secondary alcohols would accomplish a synthesis of eurylene (**2.1**).[88]



Scheme 2.12: Retrosynthesis of eurylene (**2.1**) using tethered RCM protocol.

2.2.2 Tethered Relay Ring Closing Metathesis Route

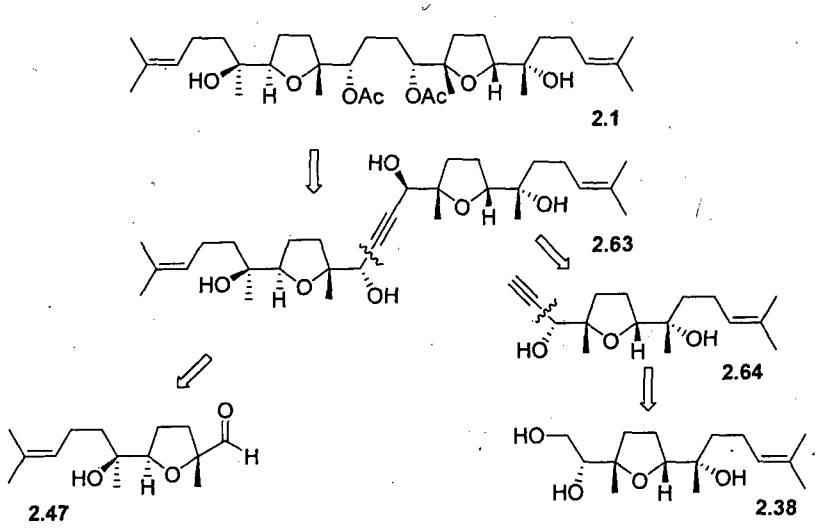
An alternative to simple ring closing metathesis is relay ring closing metathesis. Selective alkyne addition to the aldehyde fragment **2.47** would lead to a *trans*-THF adduct **2.62** (Scheme 2.13).[89] Reduction of the triple bond to a double bond and later coupling with allylic alcohol **2.57** using temporary silicon tether would provide a suitable substrate **2.61** for relay ring closing metathesis.[90] Selective reduction of the least hindered double bond, deprotection and acetylation of secondary alcohols would complete a synthesis of eurylene (**2.1**).[88]



Scheme 2.13: Retrosynthetic analysis of eurylene (**2.1**) by applying RRCM protocol.

2.2.3 Alkyne - Aldehyde Coupling Strategy

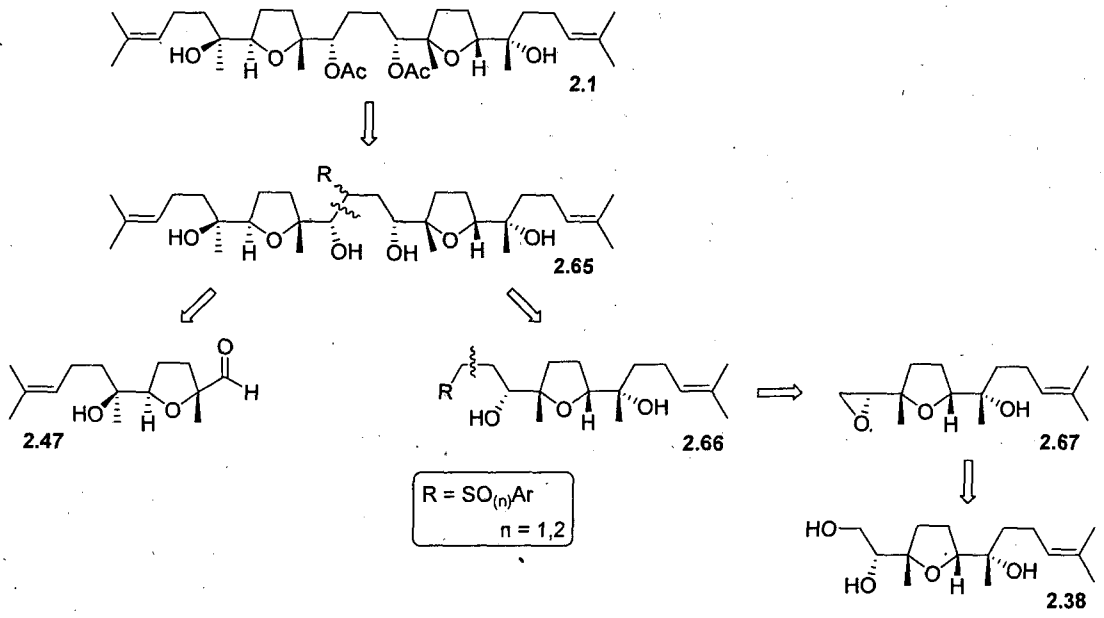
Alternatively, alkyne **2.64** can be selectively added to aldehyde fragment **2.47** to join both fragments of eurylene (**2.1**) and to fix the eighth stereocentre (Scheme 2.14).[89] Complete reduction of the triple bond of *bis*-THF adduct **2.63** using selective reducing agents and acetylation of both secondary alcohols would complete the synthesis of eurylene (**2.1**).[91]



Scheme 2.14: Retrosynthesis of eurylene (**2.1**) using enyne-aldehyde coupling strategy.

2.2.4 Carbanion Addition Approach

Finally ring opening of epoxide **2.67** with the anion of methyl aryl sulfone or sulfoxide would open another route towards the synthesis of eurylene (**2.1**, Scheme 2.15). The lithio-anion of *cis*-THF product **2.66** can then be added to aldehyde **2.47**, followed by the reductive cleavage of sulfur containing species **2.65** to afford deacetylated eurylene.[92] Acetylation of both secondary alcohols would complete the synthesis of eurylene (**2.1**).



Scheme 2.15: Retrosynthetic analysis of eurylene (**2.1**) applying carbanion addition approach.

2.3 Conclusions

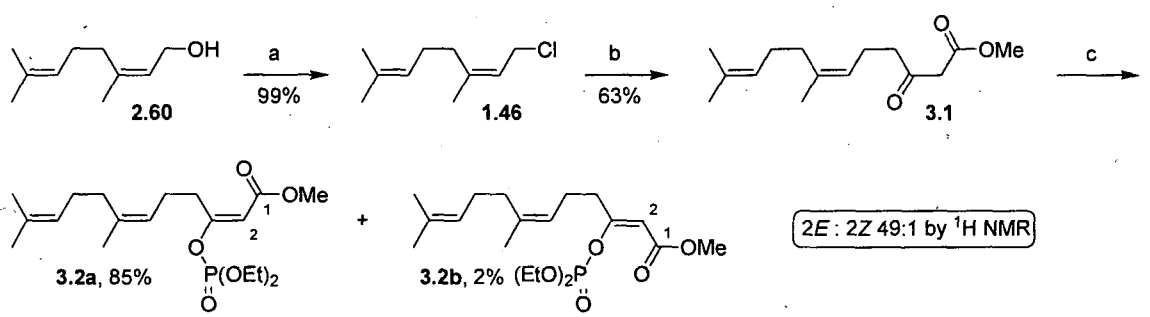
Previously reported syntheses of eurylene (**2.1**) have been described, along with our proposed retrosynthetic plans. Our synthetic strategy is based on stereoselective permanganate mediated oxidation of 1,5,9-trienes **2.58** and **2.59** bearing suitable chiral auxiliaries to establish seven out of eight stereocentres in just two key cyclisations (Scheme 2.12). Coupling of the key THF fragments, *trans*-THF aldehyde **2.47** and *cis*-THF triol **2.38** may be carried out using various pathways. Also, through the syntheses of aldehyde **2.47** and triol **2.38**, a formal synthesis of eurylene (**2.1**) would be accomplished as these key fragments intersect with Kodama's route to the natural product.[83]

Chapter 3 Synthesis of the Right Hand Fragment of Eurylene

The relative stereochemistry of the *cis*-THF fragment **3.12a** of eurylene (**2.1**) will be derived from that of the precursor 1,5,9-triene **3.9** (Scheme 3.7). The requisite triene was synthesised using a slight modification of the methodology developed by Weiler *et al.*[37,93] The *Z* configured central double bond originated from nerol (**2.60**), a cheap commercially available starting material. In this chapter, a stereoselective synthesis of the right hand fragment **2.38** of eurylene (**2.1**) by permanganate mediated oxidative cyclisation of 1,5,9-triene **3.9** will be discussed.

3.1 Synthesis of the 1,5,9-Triene 3.9

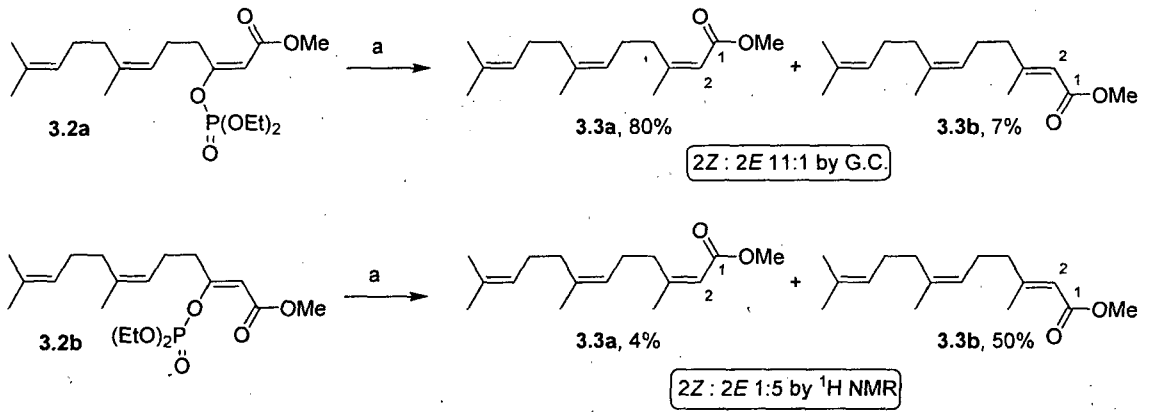
Chlorination of nerol (**2.60**) afforded neryl chloride (**1.46**) in a quantitative yield and the crude product was used in the next step without purification (Scheme 3.1).[94] The dianion of methyl acetoacetate was generated using NaH and *n*-BuLi and alkylated with neryl chloride (**1.46**) to yield the corresponding *β*-ketoester **3.1** in a moderate yield.[93,95] The *β*-ketoester **3.1** underwent stereoselective enol phosphate formation by treatment with $(EtO)_2POCl/Et_3N$ in DMPU and a catalytic DMAP to provide the 2*E* enol phosphate **3.2a** in a good yield and selectivity (isomer ratio 2*E*:2*Z* ~ 49:1 by ^1H NMR of crude product).[37] The enol phosphate isomers **3.2a,b** were readily separated by column chromatography, allowing full characterisation of both isomers **3.2a** and **3.2b**.



Scheme 3.1: Stereoselective synthesis of enol phosphates **3.2a,b**. Reagents and conditions: (a) MsCl (1.15 eq.), LiCl (1.1 eq.), 2,6-lutidine (1.2 eq.), DMF, 0 °C to rt, 4 h; (b) methyl acetoacetate (1.05 eq.), NaH (1.05 eq.), *n*-BuLi (1.05 eq.), THF, 0 °C to rt, 55 min; (c) $(EtO)_2POCl$ (1.12 eq.), DMAP (0.11 eq.), Et_3N (1.12 eq.), DMPU, –20 °C to rt, 17 h.

Stereoselective alkylation of 2*E* enol phosphate **3.2a** was carried out by treatment with $Me_2CuLiMgCl$, formed by the reaction of CuI with MeLi followed by MeMgCl, to

afford the desired 2*Z* triene methyl ester **3.3a** in a good yield and selectivity along with the 2*E* methyl ester **3.3b** (Scheme 3.2).[37,96] The best isomeric ratio, 2*Z*:2*E* 11:1 was estimated by G.C. analysis of the crude product (entry 3, Table 3.1). Fortunately the geometric isomers could be separated by flash column chromatography. Similarly 2*Z* enol phosphate **3.2b** was selectively alkylated using the same conditions to afford the triene methyl esters **3.3a,b** in a moderate yield, and with an isomeric ratio 2*Z*:2*E* 1:5 (by ^{1}H NMR of the crude product).



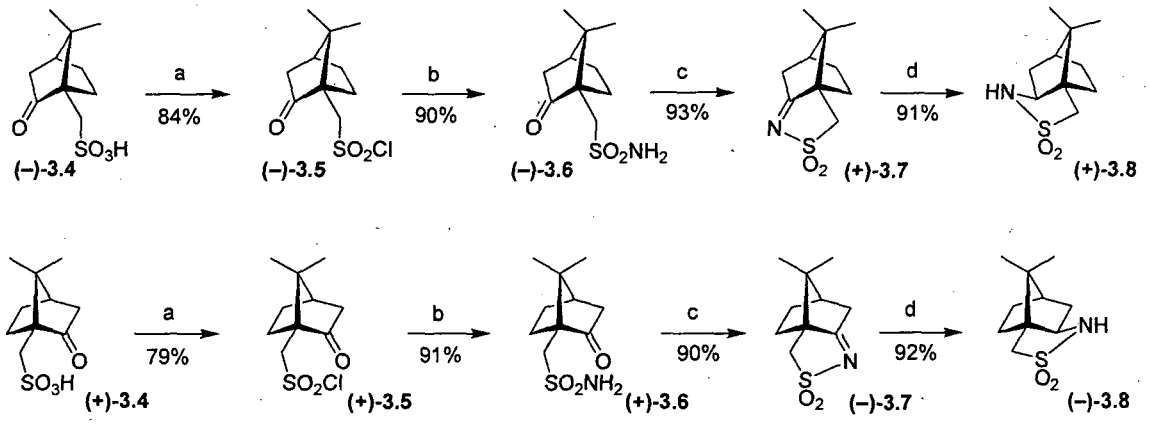
Scheme 3.2: Stereoselective alkylation of enol phosphates **3.2a,b**. Reagents and conditions: (a) CuI (3.0 eq.), MeLi (3.0 eq.), MeMgCl (5.0 eq.), THF, –35 to –5 °C, 2.25 h.

In order to investigate the selectivity of the cuprate reaction, alkylation of 2*E* enol phosphate **3.2a** was carried out using different solvents, varying reaction temperature and time (Table 3.1). Initially when THF was used as the solvent, the reaction did not go to complete conversion and a moderate selectivity was achieved (entries 1-2). However, when the reaction was repeated using purified CuI and freshly opened bottles of MeLi and MeMgCl, complete conversion was observed.[97] The desired 2*Z* triene **3.3a** was isolated in a good yield and with high selectivity (entry 3, Table 3.1). Both isomers were separated by flash chromatography and the rest of the synthesis was carried out with isomerically pure 2*Z* triene **3.3a**. In order to investigate effect of the solvent, the reaction was carried out in ether and CH_2Cl_2. Ether was found to lower the selectivity while with CH_2Cl_2 a poor conversion was observed with a moderate selectivity (entries 4-6, Table 3.1).

Entry	Solvent	Temp. (°C) [a]	Time (min) [a]	Yield of Triene **3.3a**, (%)[b]	2*Z* : 2*E* Ratio[c]	Yield of RSM **3.2a**, (%)
1.	THF	–60	90	20	4.2:1.0	65
2.	THF	–30	120	40	3.7:1.0	35
3.[d]	THF	–35	75	80	11.0:1.0	NI[e]
4.	Ether	–60	60	NI[e]	-	90
5.	Ether	–40	120	35	1.7:1.0	29
6.	CH_2Cl_2	–30	120	9	7.4:1.0	81

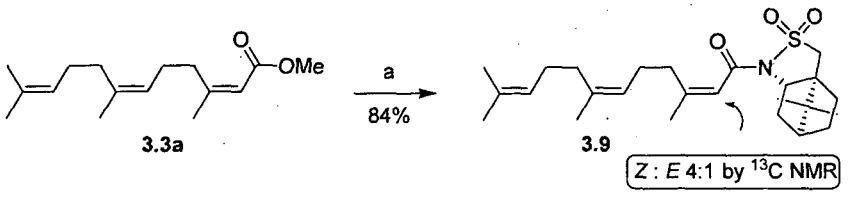
Table 3.1: Effect of the solvents, reaction temperature and time on the stereoselective alkylation of 2*E* enol phosphate **3.2a**. [a]Temperature and time describe the conditions after the addition of 2*E* enol phosphate **3.2a**; [b]Yield of pure 2*Z* ismomer; [c]Isomeric ratios were estimated by G.C. analysis of crude products; [d]Reaction carried out using purified CuI, fresh MeLi and MeMgCl; [e]NI: Not isolated.

For the substrate based stereocontrolled permanganate mediated oxidative cyclisation of the 1,5,9-triene system, a chiral auxiliary would be required to direct the attack of the metal-oxidant to one face of the enoyl alkene. From previous experience, it was clear that the use of (2*S*)-10,2-camphorsultam ((+)-**3.8**) would establish the required stereochemistry of the THF diol **3.12a**.[98] Therefore a large scale synthesis of the chiral auxiliary (+)-**3.8** was undertaken, starting with commercially available (1*R*)-camphorsulfonic acid ((–)-**3.4**). Chlorination of sulfonic acid (–)-**3.4** with PCl_5 afforded the sulfonyl chloride (–)-**3.5**, which was then treated with liquid NH_3 to yield the sulfonamide (–)-**3.6** (Scheme 3.3).[99] The amide derivative (–)-**3.6** was refluxed under acidic conditions to give the sulfonyl imine (+)-**3.7**, which on reduction with $NaBH_4$ afforded the required (2*S*)-10,2-camphorsultam ((+)-**3.8**).[100-102] Following the same synthetic pathway, the other enantiomer (2*R*)-10,2-camphorsultam ((–)-**3.8**) was synthesised starting with commercially available (1*S*)-camphorsulfonic acid ((+)-**3.4**).



Scheme 3.3: Synthesis of (2*S*)- and (2*R*)-10,2-camphorsultams ((+)- and (–)-**3.8**). Reagents and conditions: (a) PCl_5 (3.0 eq.), CH_2Cl_2, –10 °C to rt, 6 h; (b) liquid NH_3, CH_2Cl_2, 0 °C to rt, 4.5 h; (c) Amberlyst 15 Å, toluene, reflux, 3.5 h; (d) $NaBH_4$ (1.1 eq.), MeOH, –5 °C, 30 min.

In order to achieve the synthesis of trienoate **3.9**, (2*S*)-10,2-camphorsultam ((+)-**3.8**) was reacted with $(Me)_3Al$ and the resultant aluminium complex was treated with triene methyl ester **3.3a** in toluene under reflux to afford the triene **3.9** (Scheme 3.4).[103] The reaction proceeded smoothly but unfortunately isomerisation was observed at the enoyl olefin position, *Z*:*E* ~ 4:1 by ^{13}C NMR of the crude product. Both geometric isomers were partially enriched by flash chromatography.

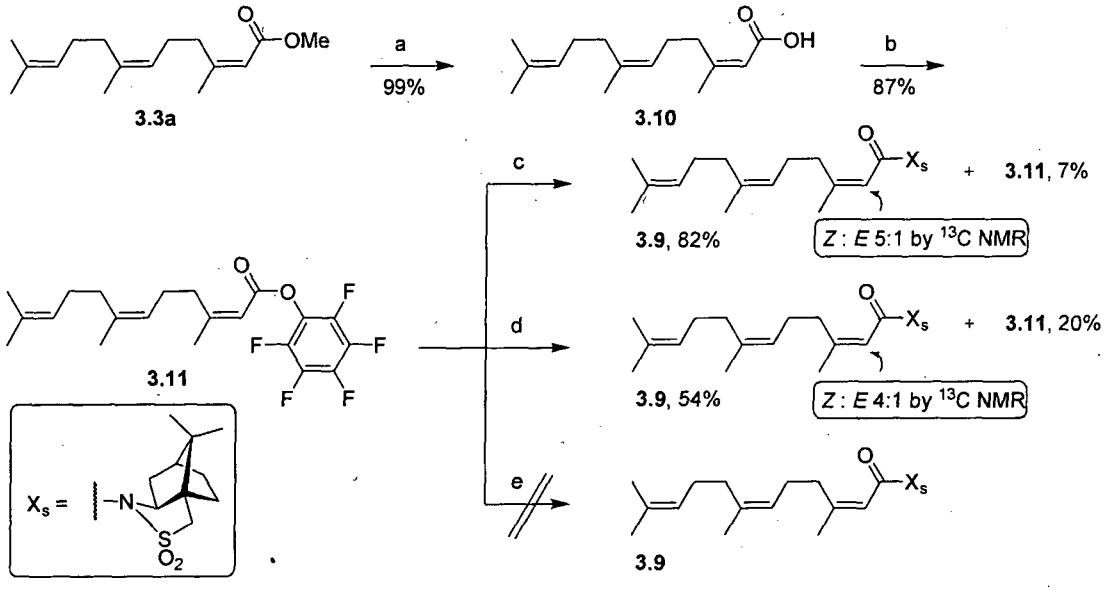


Scheme 3.4: Synthesis of trienoate **3.9**, bearing (2*S*)-10,2-camphorsultam ((+)-**3.8**). Reagents and conditions: (a) (2*S*)-10,2-camphorsultam ((+)-**3.8**, 1.25 eq.), Me_3Al (1.25 eq.), toluene, reflux, 22 h.

To avoid isomerisation of the enoyl olefin of triene **3.9**, an alternative strategy was designed. Unsaturated methyl ester **3.3a** was hydrolysed to the corresponding carboxylic acid **3.10** in an excellent yield (Scheme 3.5).[104] The crude material was used without purification and treated with pentaflourophenol in the presence of DCC to afford the activated pentaflourophenyl ester **3.11** in a good yield.

(2*S*)-10,2-camphorsultam ((+)-**3.8**) was deprotonated using NaHMDS as the base and the resultant pre-formed sodium salt of the auxiliary (+)-**3.8** was coupled with PFP ester **3.11** to afford the trienoate **3.9** in a good yield.[105] Unfortunately isomerisation at the enoyl alkene was observed, *Z*:*E* ~ 5:1 by ^{13}C NMR of crude product. Changing the solvent from THF to toluene did not improve the selectivity and resulted in only a 10% yield of the triene product **3.9** along with starting material **3.11** recovered in 75% yield.

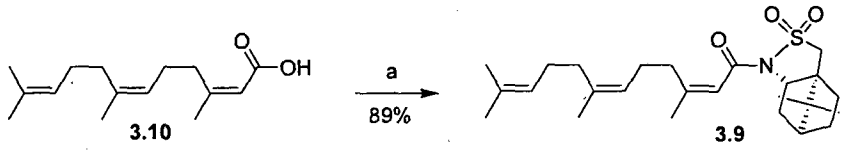
In an effort to avoid the isomerisation, *n*-BuLi was used as the base instead of NaHMDS, resulting in comparatively poor conversion and an isomeric ratio of *Z*:*E* ~ 4:1 (^{13}C NMR). The use of NaH as a base also proved unsuccessful, returning only the starting material.



Scheme 3.5: Synthesis of isomerically pure trienoate **3.9**, bearing (2*S*)-10,2-camphorsultam ((+)-**3.8**). Reagents and conditions: (a) NaOH (6.5 eq.), $NaHCO_3$ (0.53 eq.), MeOH:H_2O (1:1.7), reflux, 6 h; (b) C_6F_5OH (1.16 eq.), DCC (1.14 eq.), EtOAc, rt, 21 h; (c) NaHMDS (1.15 eq.), (2*S*)-10,2-camphorsultam ((+)-**3.8**, 1.05 eq.), THF, –20 °C to rt, 5.5 h; (d) *n*-BuLi (1.10 eq.), (2*S*)-10,2-camphorsultam ((+)-**3.8**, 1.05 eq.), THF, –78 °C to rt, 3 h; (e) NaH (1.2 eq.), (2*S*)-10,2-camphorsultam ((+)-**3.8**, 1.15 eq.), toluene, 0 °C to rt, 29 h.

Alternatively a different strategy reported by Liddle *et al.* was applied with a modified approach.[106] The carboxylic acid **3.10** was treated with a slight excess of $(COCl)_2$ and a catalytic DMF in *n*-hexane (Scheme 3.6).[107] The resultant acid chloride was immediately treated with the pre-formed sodium salt of (2*S*)-10,2-camphorsultam ((+)-**3.8**) in toluene to afford the trienoate **3.9** in a good yield. Gratifyingly, no isomerisation

at the enoyl olefin position was observed using this protocol and it was decided to adopt this route.

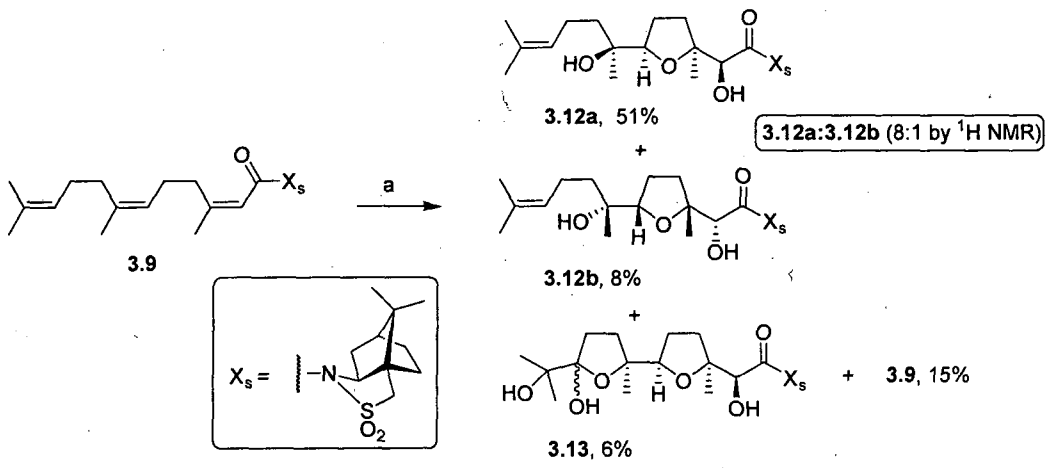


3.10 3.9

Scheme 3.6: Synthesis of trienoate **3.9**, bearing (2*S*)-10,2-camphorsultam (**(+)-3.8**). Reagents and conditions: (a) $(COCl)_2$ (5.0 eq.), DMF (1.0 eq.), *n*-hexane, rt 2 h then (2*S*)-10,2-camphorsultam (**(+)-3.8**, 1.1 eq.), NaH (1.15 eq.), toluene, 0 °C to rt, 9 h.

3.2 Oxidative Cyclisation of the 1,5,9-Triene 3.9

Trienoate **3.9** underwent sodium permanganate mediated oxidative cyclisation in a stereoselective fashion to afford the desired *cis*-THF diol **3.12a** in a good yield (51%) and diastereoselectivity (d.r. 8:1 by ^{1}H NMR of the crude product, Scheme 3.7).[35] An over-oxidised by-product, lactol **3.13** was also identified and characterised. Fortunately both diastereoisomers, **3.12a,b** and side product lactol **3.13** were separable by flash column chromatography and the subsequent synthesis was carried out using diastereomerically pure *cis*-THF diol **3.12a**. The isolated yields of *cis*-THF diols **3.12a,b** do not reflect the d.r. ratio observed by ^{1}H NMR of the crude product, which is probably because of the chromatographic purification step. On the basis of recovered starting material, the yield of major diastereoisomer **3.12a** was found to be 60%. During an investigative study of the oxidative cyclisation of triene **3.9**, it was found that the over oxidised product **3.13** was observed before the triene **3.9** had been completely converted to *cis*-THF diols **3.12a,b**. Shorter reaction times with use of an excess of oxidising agent did not appear to solve the problem, therefore it was decided to stop the cyclisation after the optimised reaction time and unreacted starting material was recovered and reused.



Scheme 3.7: Stereocontrolled oxidative cyclisation of the 1,5,9-triene **3.9**. Reagents and conditions: (a) $NaMnO_4$ (1.5 eq., 0.4 M aq.), AcOH (3.5 eq.), phosphate buffer (KH_2PO_4:NaH_2PO_4 8:2), acetone, –21 to –7 °C, 70 min.

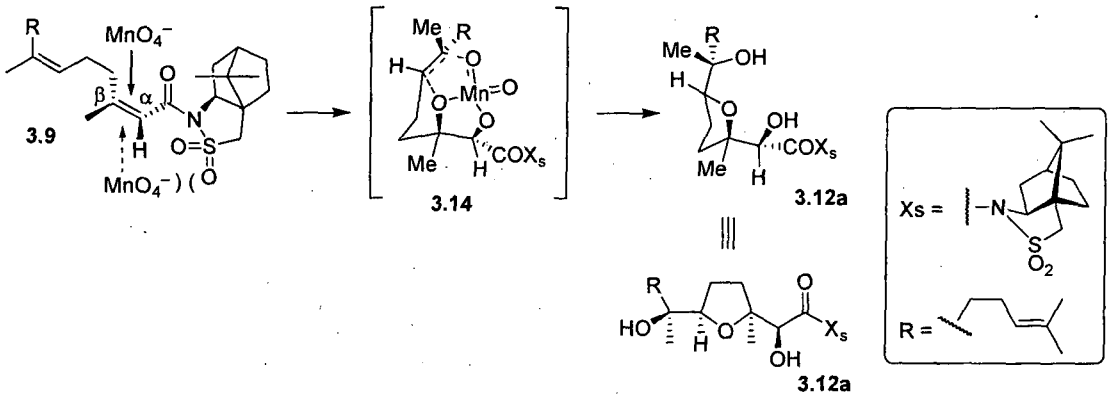
During the optimisation study of the stereoselective oxidation of the triene **3.9**, the effect of different equivalents of the oxidising agent, reaction temperature and time was investigated but unfortunately it could not produce a good combination of reaction conversion and product yield (Table 3.2). Excess of $KMnO_4$ and shorter reaction time resulted in the recovery of starting material in 80% yield (entry 1). Increasing the reaction temperature and time improved the conversion but promoted side reactions (entry 2). Decreasing the amount of $KMnO_4$ to 1.5 eq. improved the situation and a good combination of yield of the product **3.12a** and recovered starting material **3.9** was achieved (entries 3-6). A further decrease in the amount of $KMnO_4$ to 1.3 eq. reduced the reaction conversion (entries 7-9). The best result was obtained when 1.5 eq. of the oxidising agent was used and the reaction was conducted for an hour (entry 6).

Finally it was decided to use $NaMnO_4$ instead of $KMnO_4$. Changing oxidising agent and using the already optimised reaction conditions resulted in an improved yield of the product **3.12a** (entry 12). Gratifyingly, the diastereoisomers were readily separated by flash column chromatography.

Entry	Oxidant (eq.)	Temp. (°C)	Time (min)	Yield of **3.12a**, (%)[a]	Yield of RSM **3.9**, (%)
1.	$KMnO_4$ (1.7)	–40	10	2	80
2.	$KMnO_4$ (1.7)	–40 to –15	60	20	16
3.	$KMnO_4$ (1.5)	–40 to –12	90	19	13
4.	$KMnO_4$ (1.5)	–23 to –3	70	36	5
5.	$KMnO_4$ (1.5)	–20 to –2	70	33	7
6.	$KMnO_4$ (1.5)	–20 to –7	60	41	6
7.	$KMnO_4$ (1.3)	–40 to –20	120	12	31
8.	$KMnO_4$ (1.3)	–20 to –4	90	30	7
9.	$KMnO_4$ (1.3)	–30 to –10	60	36	11
10.	$NaMnO_4$ (1.5)	–45 to –10	90	25	4
11.	$NaMnO_4$ (1.5)	–35 to –10	45	32	20
12.	$NaMnO_4$ (1.5)	–21 to –7	70	51	15

Table 3.2: Effect of oxidising agent, reaction temperature and time on the oxidative cyclisation of triene **3.9** using aq. oxidant (0.4 M). [a]Yield refers to a single purified diastereoisomer; all reactions were carried out in acetone, AcOH (3.0-5.0 eq.) and in the presence of a buffer solution of 1/15 M aq. sol. of both KH_2PO_4 and NaH_2PO_4 in a volumetric ratio of 8:2 respectively. Change in the eq. of AcOH from 3.0 to 5.0 had no appreciable effect on the cyclisation.

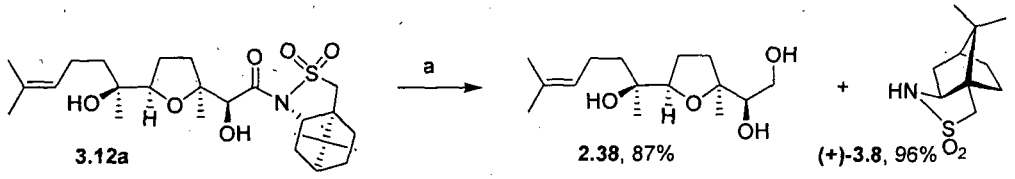
The origin of stereoselectivity for the oxidative cyclisation of trienoyl sultam **3.9** can be explained by the preferred orientation of enoyl olefin of triene **3.9** and relevant arrangement of C=O and NSO_2 moieties (Scheme 3.8). It is believed that based on steric and electronic reasons, the s-*cis* orientation of C=O/C(α)=C(β) and anti-position of C=O and NSO_2 groups are favoured.[108] These conditions lead to a conformer where approach of MnO_4^- from the C(β) *Si*-face would take place preferentially. Such an attack goes through the transition state **3.14** and on hydrolysis affords the required THF adduct **3.12a** as the major product.



Scheme 3.8: Origin of facial selectivity during the oxidative cyclisation of triene **3.9**.

3.3 Synthesis of the Right Hand Triol Fragment 2.38 of Eurylene (2.1), Intersection with Kodama's Intermediate

The reductive cleavage of the chiral auxiliary **(+)-3.8** from the optically pure *cis*-THF diol **3.12a** was carried out using $NaBH_4$ (4.0 eq.) in THF:H_2O (3:1) to afford the triol **2.38** in a disappointing 60% yield.[32] The reaction proceeded smoothly and TLC had indicated a complete, and one to one spot conversion. The low yield may be due to the coordination of excessive boron with the triol product **2.38**, and loss on the column during purification. The solvent system, THF:H_2O (3:1), could also influence the effective extraction of the polar triol product **2.38**, during the work-up. Therefore the same transformation was carried out using $NaBH_4$ (1.15 eq.) in THF:H_2O (25:1). The modified conditions dramatically affected the result and an improved 87% yield was achieved (Scheme 3.9). Triol **2.38** also corresponds to the right hand fragment of eurylene (**2.1**) reported by Kodama *et al.*, hence we successfully completed a formal synthesis of right hand fragment of eurylene (**2.1**). Spectroscopic and analytical data were in agreement with the literature.[83]



Scheme 3.9: Synthesis of right hand triol fragment **2.38** of eurylene (**2.1**). Reagents and conditions: (a) $NaBH_4$ (1.15 eq.), THF:H_2O (25:1), –5 °C, 4 h.

3.4 Conclusions

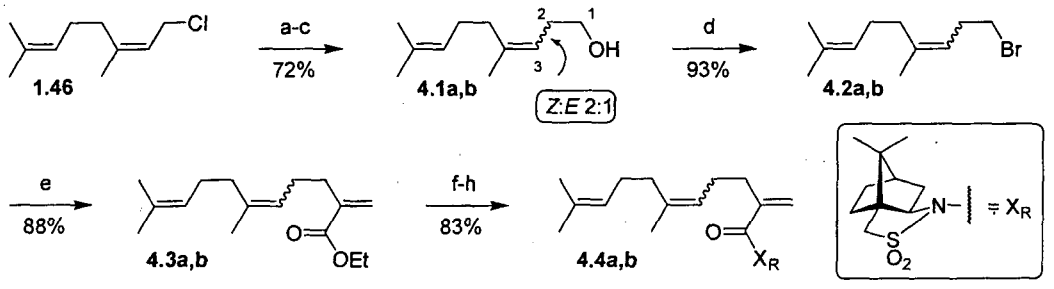
A short and efficient stereocontrolled formal synthesis of right hand triol fragment **2.38** of eurylene (**2.1**) was achieved in 8 steps (19.5% overall yield) using permanganate mediated oxidative cyclisation of the readily accessible triene **3.9**. The use of (2*S*)-10,2-camphorsultam ((+)-**3.8**) to influence the asymmetric induction proved to be very successful and an excellent level of stereoselectivity was obtained (see Scheme 3.7). Fortunately both diastereoisomers **3.12a,b** could be separated by flash column chromatography and subsequent steps were carried out with optically enriched *cis*-THF diol **3.12a**.

Chapter 4 Synthesis of the Left Hand Fragment of Eurylene

In this chapter, a stereocontrolled synthesis of the left hand aldehyde fragment **2.47** of eurylene (**2.1**) will be described. The stereoselective synthesis of the *trans*-THF ring of eurylene proceeded via selective oxidative cyclisation of a 1,5,9-triene and subsequent radical deoxygenation of the hydroxymethyl group.

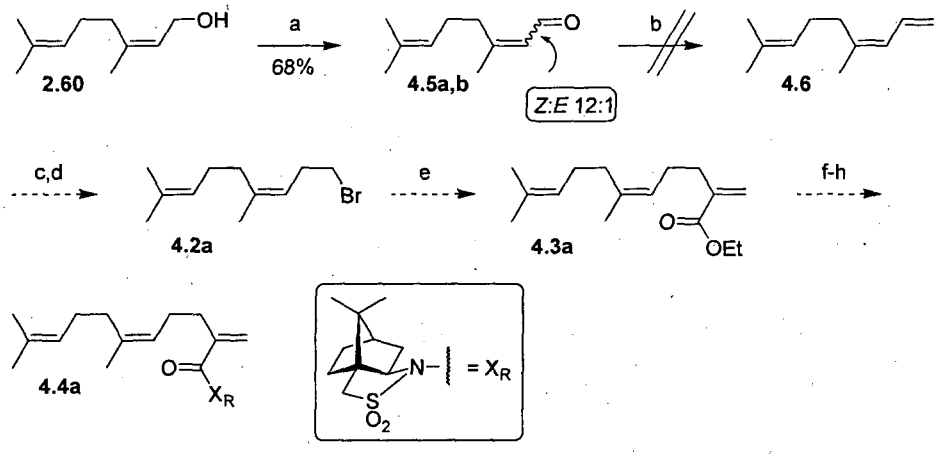
4.1 Synthesis of the 1,5,9-Triene 4.4a

Previously in our group, attempts to synthesise isomerically pure *Z* triene **4.4a** proved unsuccessful.[98] The attempted route included treatment of neryl chloride (**1.46**) with NaCN in DMF to afford the corresponding cyanide, which was hydrolysed to the carboxylic acid under basic conditions (Scheme 4.1). Unfortunately ^{13}C NMR of the crude carboxylic acid revealed isomerisation at the C-3 position giving a *cis*:*trans* ratio of 2:1. Geometric isomers could not be separated and the subsequent synthesis was carried out with a mixture of olefin isomers. $LiAlH_4$ reduction of the resultant carboxylic acid afforded a mixture of homonerol (**4.1a**) and homogeraniol (**4.1b**), which underwent transformation to their corresponding bromides **4.2a,b** in good yields. Treatment of bromides **4.2a,b** with triethyl phosphonoacetate gave the phosphonates which were subjected to a Horner-Wadsworth-Emmons reaction with formaldehyde to produce the triene ethyl esters **4.3a,b**. Trienes **4.3a,b** were hydrolysed, activated as PFP esters and coupled with (2*R*)-10,2-camphorsultam ((–)-**3.8**) to furnish the trienes **4.4a,b**, still as an inseparable mixture of *cis*- and *trans*- isomers (*Z*:*E* 2:1).



Scheme 4.1: Synthesis of trienoate **4.4a,b**. Reagents and conditions: (a) NaCN, DMF, 0 °C to rt, 20 h; (b) KOH (aq.), MeOH, reflux, 20 h; (c) $LiAlH_4$, Et_2O, 0 °C to rt, 3 h; (d) PPh_3, CBr_4, CH_2Cl_2, rt, 2 h; (e) NaH, DMSO, triethyl phosphonoacetate, 50 °C, 5 h then K_2CO_3, CH_2O, rt, 12 h then 60 °C, 3.5 h; (f) NaOH, $NaHCO_3$, MeOH, H_2O, reflux; (g) C_6F_5OH, DCC, EtOAc, rt; (h) *n*-BuLi, (2*R*)-10,2-camphorsultam ((–)-**3.8**), THF, –78 °C to rt.

Due to difficulties in preparing isomerically pure homoneryl bromide (**4.2a**) in the past, other synthetic routes were investigated to synthesise the required *cis*-bromide. The first methodology attempted was a strategy described by Leopold *et al.* with some modifications.[109] Nerol (**2.60**) was subjected to Swern oxidation to give aldehydes **4.5a,b** in a moderate yield and in a *cis:trans* ratio of 12:1 (by ^{1}H NMR of the crude product, Scheme 4.2).[110] At this stage, the isomers could not be separated by standard flash column chromatography. Attempted Wittig methylenation of isomeric aldehydes **4.5a,b** to furnish triene **4.6** proved unsuccessful and starting aldehydes **4.5a,b** were recovered in 60% yield. Due to isomerisation in the oxidation step, our failure to separate both isomers **4.5a,b** and difficulties associated with Wittig olefination, this approach was abandoned.

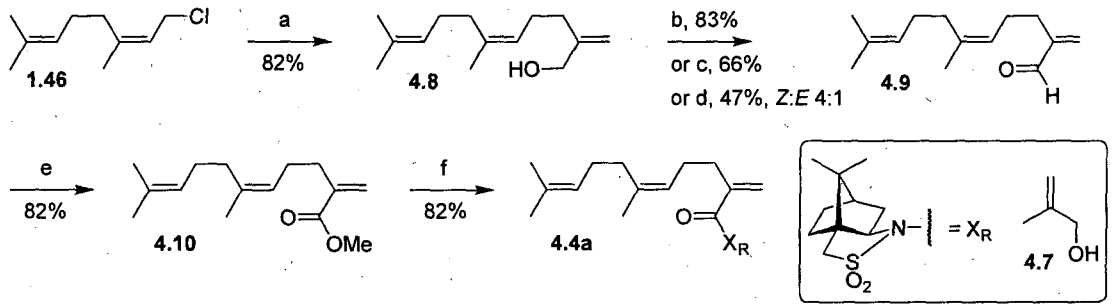


Scheme 4.2: Towards the synthesis of trienoate **4.4a**. Reagents and conditions: (a) $(COCl)_2$ (1.15 eq.), Et_3N (5 eq.), DMSO (2.4 eq.), CH_2Cl_2, –60 °C to rt, 2 h; (b) PhLi (5.7 eq.), $MePh_3P^+I^-$ (1.36 eq.), PhLi (5.7 eq.), THF, rt, 4 h; (c) (I) $(Me_2CHC(Me)H)_2BH$; (II) H_2O_2, NaOH; (d) PPh_3, CBr_4, CH_2Cl_2; (e) NaH, DMSO, triethyl phosphonoacetate, then K_2CO_3, CH_2O; (f) NaOH, $NaHCO_3$, MeOH, H_2O; (g) C_6F_5OH, DCC, EtOAc; (h) *n*-BuLi, (2*R*)-10,2-camphorsultam (**(–)-3.8**), THF.

Due to difficulties in synthesising isomerically pure homoneryl bromide (**4.2a**), an alternate route was explored. Neryl chloride (**1.46**) was alkylated with the dianion generated from methallyl alcohol (**4.7**) to yield allylic alcohol **4.8** in a good yield (Scheme 4.3).[111-113] Gratifyingly no isomerisation of the central *Z* double bond was observed. Allylic alcohol **4.8** was oxidised to aldehyde **4.9** using modified Swern conditions, which resulted in isomerisation of the *Z* double bond to give a *cis:trans* ratio of 4:1 (by ^{1}H NMR of the crude product).[114] The reactivity of other oxidising agents

were investigated and finally $BaMnO_4$ and MnO_2 were found to be mild oxidising agents, affording isomerically pure aldehyde **4.9**.[115,116] However after optimisation of experimental procedures, MnO_2 was found to be superior to $BaMnO_4$ in terms of yields and reaction times.

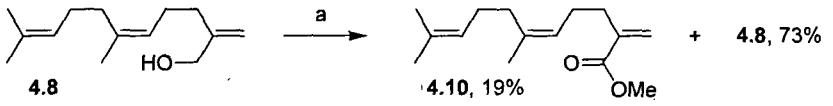
Aldehyde **4.9** was treated with NaCN/AcOH to generate the cyanohydrin *in situ* which was oxidised to the acyl cyanide and subsequent nucleophilic attack of MeOH afforded the triene methyl ester **4.10**, without isomerisation of the *Z* double bond.[116,117] For a stereoselective oxidative cyclisation, a chiral auxiliary would be required to direct the metal oxidant to one face of the enoyl alkene. From previous studies of chiral auxiliaries, it was clear that the use of (2*R*)-10,2-camphorsultam (**(–)-3.8**) would provide the required relative stereochemistry of resultant *trans*-THF **4.13**.[98] Coupling of triene ester **4.10** with a pre-formed aluminium complex of (2*R*)-10,2-camphorsultam (**(–)-3.8**) furnished the desired isomerically pure trienoate **4.4a** in a good yield, ready for the key permanganate promoted oxidative cyclisation (Scheme 4.3).[103]



Scheme 4.3: Synthesis of isomerically pure trienoate **4.4a**. Reagents and conditions: (a) alcohol **4.7** (2.3 eq.), *n*-BuLi (4.0 eq., 2.3 M in hexanes), TMEDA (4.0 eq.), Et_2O , –78 °C to rt, 24 h; (b) MnO_2 (17 eq.), *n*-hexane, 0 °C to rt, 1.5 h; (c) $BaMnO_4$ (5.2 eq.), CH_2Cl_2, rt, 43 h; (d) SO_3-Py complex (6 eq.), Et_3N (6.6 eq.), DMSO, rt, 2 h; (e) NaCN (3.5 eq.), AcOH (2.5 eq.), MnO_2 (10 eq.), MeOH, rt, 18 h; (f) (2*R*)-10,2-camphorsultam (**(–)-3.8**, 1.25 eq.), Me_3Al (1.25 eq.), toluene, reflux, 41 h.

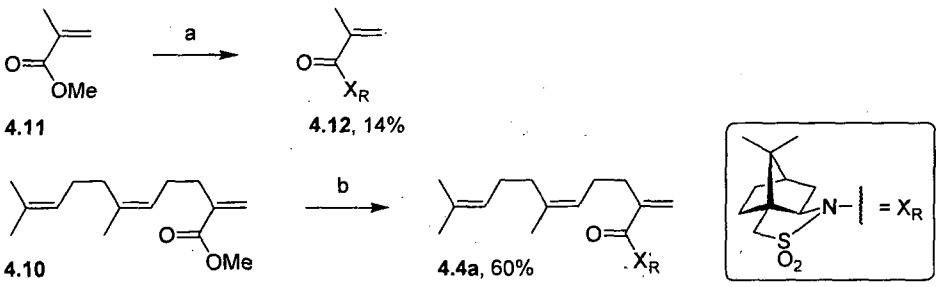
Before oxidative cyclisation of triene **4.4a** was carried out, an attempt was made to shorten the synthesis of the triene ester **4.10**. The transformation from allylic alcohol **4.8** to methyl ester **4.10** proceeded via aldehyde **4.9**, this aldehyde **4.9** was used without purification. A one-pot synthesis of the trienoate **4.10** was attempted from the allylic alcohol **4.8**.[118] Unfortunately the reaction conversion was relatively poor and the

maximum isolated yield of ester **4.10** was 19% (Scheme 4.4). The starting allylic alcohol **4.8** was recovered in 73% yield after purification.



Scheme 4.4: One pot oxidation of allylic alcohol **4.10**. Reagents and conditions: (a) MnO_2 (25 eq.), NaCN (3.4 eq.), AcOH (2.3 eq.), MeOH, rt, 18 h;

As the coupling reaction of triene ester **4.10** with (2*R*)-10,2-camphorsultam (**(–)-3.8**) required long reaction times, *i.e.* 41 hours, the use of microwave irradiation was studied. Initially methyl ester **4.11** was added to a pre-formed aluminium complex of (2*R*)-10,2-camphorsultam (**(–)-3.8**) in a microwave tube and the reaction mixture was irridiated (Scheme 4.5). A poor yield of the product **4.12** was isolated along with 58% recovery of the starting chiral auxiliary **(–)-3.8**. The starting ester **4.11** could not be recovered, probably because of its high volatility. The same reaction was attempted with the triene ester **4.10** resulting 60% yield of the trienoate **4.4a** and 23% yield of the starting auxiliary **(–)-3.8**. The starting ester **4.10** was also recovered in 12% yield. Instead of optimising the reaction conditions to drive the reaction to the completion, permanganate oxidative cyclisation of triene **4.4a** was investigated.

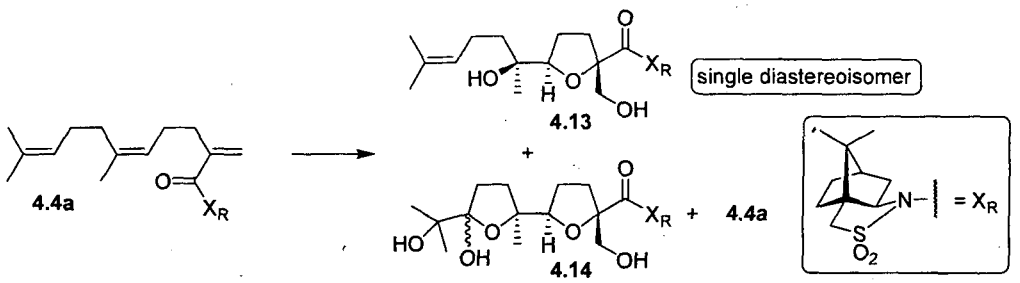


Scheme 4.5: Microwave study for the coupling of (2*R*)-10,2-camphorsultam (**(–)-3.8**) to enoates. Reagents and conditions: (a) (2*R*)-10,2-camphorsultam (**(–)-3.8**, 1.25 eq.), $(Me)_3Al$ (1.25 eq.), toluene, 130 °C, 250 psi, 250 W, 30 min; (b) (2*R*)-10,2-camphorsultam (**(–)-3.8**, 1.05 eq.), Me_3Al (1.05 eq.), toluene, 130 °C, 250 psi, 250 W, 1 h.

4.2 Oxidative Cyclisation of the 1,5,9-Triene 4.4a

Permanganate oxidation of the triene **4.4a** afforded the *trans*-THF **4.13** as a single diastereoisomer along with a major by-product, *bis*-THF triol **4.14**, as a result of over

oxidation (Scheme 4.6).[35] The starting triene **4.4a** was also recovered cleanly. The yields of both products **4.13** and **4.14** and recovered starting material **4.4a** varied depending upon the reaction conditions, which have been tabulated (Tables 4.1-4.4). The relative stereochemistry of the THF diol **4.13** was assigned based on earlier results from our laboratory.[98]



Scheme 4.6: Permanganate mediated oxidative cyclisation of trienoate **4.4a**.

Initially oxidative cyclisation of triene **4.4a** was carried out using $KMnO_4$ as metal oxidant (Table 4.1). Changing the amount of oxidant, AcOH, and reaction time did not significantly improve the yield of the required THF diol **4.13**. It is clear from the investigation that excess oxidising agent and longer reaction times, not surprisingly, increased the yield of over oxidised product **4.14** (entries 1-3), while shorter reaction times and less oxidant afforded comparatively superior results (entry 4). Subsequently $KMnO_4$ was replaced with the oxidant $NaMnO_4$ (0.4 M aq.) as this has the advantage of greater aqueous solubility in comparison to $KMnO_4$.

Entry	$KMnO_4$ (eq.)[a]	AcOH (eq.)	Temp. (°C)	Time (min)	Yield of THF 4.13, (%)[b]	Yield of triol 4.14, (%)	Yield of RSM 4.4a, (%)
1.	1.7	2.8	−35 to −5	120	15	30	18
2.	1.7	2.8	−35 to −20	90	6	24	22
3.	1.7	6.0	−35 to 0	60	18	19	16
4.	1.4	6.0	−20 to 3	60	19	12	24

Table 4.1: Attempted optimisation of the oxidative cyclisation of trienoate **4.4a** using aq. $KMnO_4$. [a]0.4 M; [b]yield refers to a single purified diastereoisomer; all reactions were conducted in acetone and in the presence of a buffer solution of 1/15 M aqueous solutions of KH_2PO_4 and NaH_2PO_4 in a volumetric ratio of 8:2 respectively.

When $NaMnO_4$ was used as oxidant, much cleaner reactions were observed based on crude ^{1}H NMR spectra and improved mass recoveries were achieved compared to $KMnO_4$ oxidative cyclisations (Table 4.2). However the yield of THF diol **4.13** did not increase and the best isolated yield was 16% (entry 4).

Entry	$NaMnO_4$ (eq.)[a]	AcOH (eq.)	Temp. (°C)	Time (min)	Yield of THF 4.13, (%)[b]	Yield of triol 4.14, (%)	Yield of RSM 4.4a, (%)
1.	1.7	3.0	−35 to −10	60	15	13	42
2.	1.5	3.5	−20 to −2	75	12	20	44
3.	1.5	3.5	−35 to −2	40	10	11	41
4.	1.4	3.0	−35 to −5	75	16	2	42

Table 4.2: Optimisation studies for the oxidative cyclisation of trienoate **4.4a** using aq. $NaMnO_4$. [a]0.4 M; [b]yield refers to a single purified diastereoisomer; all reactions were conducted in acetone in the presence of a buffer solution of 1/15 M aqueous solution of KH_2PO_4 and NaH_2PO_4 in a volumetric ratio of 8:2 respectively.

The use of phase-transfer catalyst (PTC) had been reported to affect the reactivity and the yield of oxidative cyclisation.[34] Adogen 464 was used as PTC along with the metal oxidant (Table 4.3). Under these conditions, $KMnO_4$ was found to be comparatively better than $NaMnO_4$ and afforded the best yield for oxidative cyclisation (entry 2). Changing the solvent from ether to CH_2Cl_2 gave no isolated product, returning clean starting triene **4.4a** after purification. Further optimisation studies to improve the yield of the THF diol **4.13** failed, resulting in degradation of the starting triene **4.4a**.

Entry	Oxidant (eq.)[a]	Adogen 464 (eq.)	Solvent	Yield of THF 4.13, (%)[b]	Yield of triol 4.14, (%)	Yield of RSM 4.4a, (%)
1.	$KMnO_4$ (1.7)	0.4	Ether	22	-[c]	33
2.	$KMnO_4$ (1.5)	0.5	Ether	25	-[c]	40
3.	$KMnO_4$ (2.0)	0.5	CH_2Cl_2	-[c]	-[c]	57
4.	$NaMnO_4$ (1.5)	0.4	Ether	13	-[c]	43

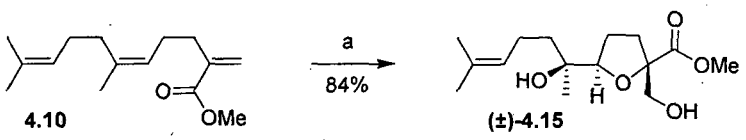
Table 4.3: Use of phase-transfer catalyst for the oxidative cyclisation of trienoate **4.4a**. [a]0.4 M aq.; [b]yield refers to a single purified diastereoisomer; [c]No product observed; all reactions were carried out in the presence of 4.0 eq. of AcOH at rt for 30 minutes except entry 4, which was carried out at –35 to 0 °C for 1 hour.

Taking some encouragement from phase-transfer experiments (entry 2, Table 4.3), solid $KMnO_4$ was used as the metal oxidant instead of aq. $KMnO_4$ (Table 4.4). Different solvents were used to investigate the effect on the reaction yield. Unfortunately in most of the cases, no product was observed from inspection of the ^1H NMR of the crude reaction mixture and starting material **4.4a** was recovered (entries 1-5). When the oxidation was carried out in acetone, an 18% yield of the desired THF diol **4.13** was obtained (entry 6).

Entry	$KMnO_4$ (eq.)[a]	AcOH (eq.)	Solvent	Time (min)	Yield of THF 4.13, (%)[b]	Yield of triol 4.14, (%)	Yield of RSM 4.4a, (%)
1.	2.0	10.0	Ether	30	-[c]	-[c]	81
2.	2.0	4.0	Ether	30	-[c]	-[c]	89
3.	1.7	3.0	Ether	30	-[c]	-[c]	85
4.	1.5	4.0	*t*-BuOH	120	-[c]	-[c]	88
5.	1.5	4.0	EtOAc	120	-[c]	-[c]	85
6.	1.5	4.0	Acetone	60	18	-[c]	45

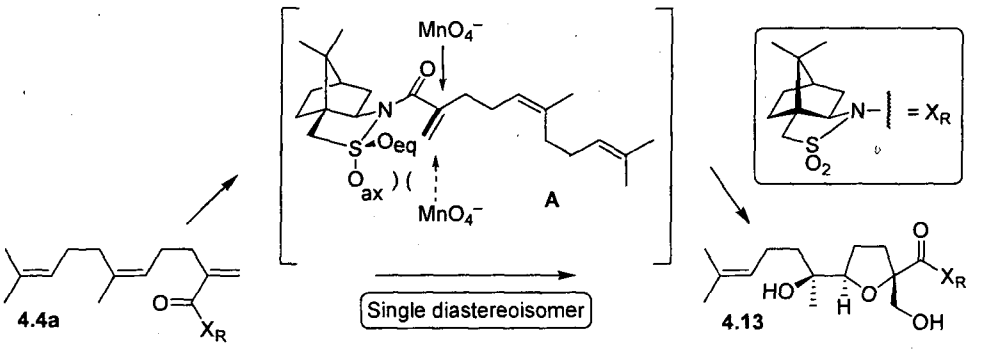
Table 4.4: Use of phase-transfer catalyst for the oxidative cyclisation of trienoate **4.4a**. [a]Solid; [b]yield refers to a single purified diastereoisomer; [c]No product observed; all reactions were carried out at rt using 0.5 eq. of phase-transfer catalyst-Adogen 464.

Although (2*R*)-10,2-camphorsultam ((–)-**3.8**) provided a single diastereoisomer as a result of permanganate oxidative cyclisation of 1,5,9-triene **4.4a**, the yield of the THF diol **4.13** was far from satisfactory. It was presumed that the low yield for the oxidation of trienoate **4.4a** was due to the presence of the bulky chiral auxiliary (–)-**3.8**, which shields the enoyl olefin from the initial reaction with permanganate, hence reducing the reactivity of the enoyl olefin. In order to establish whether an efficient selective oxidation of such a 1,5,9-triene system was viable, the permanganate oxidation of methyl ester **4.10** was performed, affording the racemic THF diols (±)-**4.15** in an excellent yield (Scheme 4.7).[35] The selective oxidation of methyl ester **4.10** indicated that such 1,5,9-triene systems could undergo oxidative cyclisations in a selective fashion and the low yields of cyclisations using **4.4a** was most probably due to the effect of the chiral auxiliary, (2*R*)-10,2-camphorsultam ((–)-**3.8**).



Scheme 4.7: Permanganate oxidative cyclisation of triene ester **4.10**. Reagents and conditions: (a) $NaMnO_4$ (1.4 eq., 0.4 M aq.), AcOH (3.5 eq.), phosphate buffer (KH_2PO_4:NaH_2PO_4 8:2), acetone, –20 to –10 °C, 30 min.

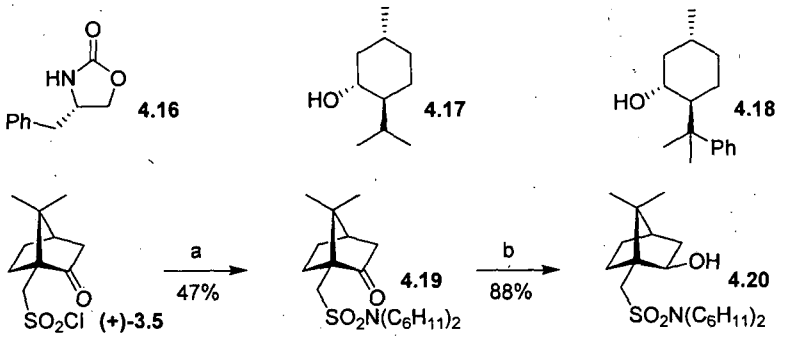
The selectivity obtained using (2*R*)-10,2-camphorsultam ((–)-**3.8**) can be explained by a reactive conformation **A**, in which the anti-position of the C=O and the NSO_2 moieties is favoured for steric and stereoelectronic reasons (Scheme 4.8).[108] In the reactive conformation **A**, the axial oxygen atom blocks the *Si*-face and the attack takes place preferentially from the *Re*-face. Such a *Re*-face attack rationalises the high diastereoselectivity obtained during the oxidative cyclisation of trienoyl sultam **4.4a**. However, in this system it is believed that approach from the *Re*-face may also be impeded to some extent, leading to competitive oxidation at other sites.



Scheme 4.8: Rationalisation of the diastereoselectivity obtained using (2*R*)-10,2-camphorsultam (**(–)-3.8**).

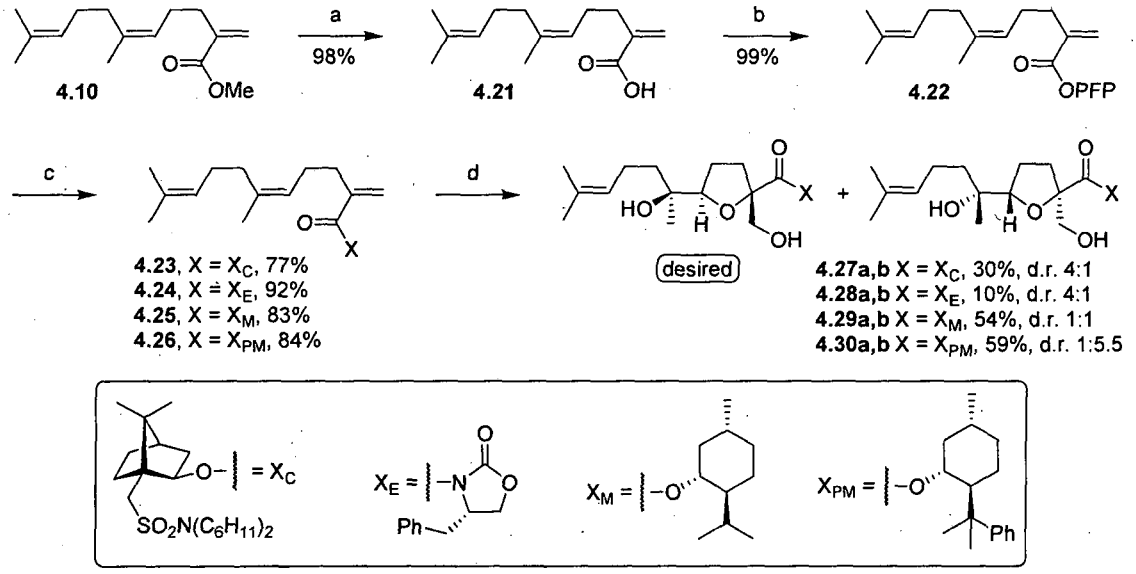
4.3 Towards the Synthesis of *trans*-THFs 4.36a,b

A successful oxidation of methyl ester **4.10** to afford racemic THF diols **(±)-4.15** and low yielding oxidative cyclisation of trienoate **4.4a** prompted investigation of the effect of alternative chiral auxiliaries on the permanganate oxidative cyclisation of the 1,5,9-triene system. To determine the optimum conditions for maximum yield and diastereoselectivity, camphor, oxazolidine and cyclohexyl based auxiliaries were investigated. Evans' auxiliary **4.16** was already available in our laboratory, while (2*S*)-menthol (**4.17**) and (–)-8-phenylmenthol (**4.18**) were commercially available. The camphor based auxiliary **4.20** was synthesised using the methodology reported by Oppolzer *et al.*[119] Amidation of previously synthesised (1*S*)-camphorsulfonyl chloride (**(+)-3.5**) with diisopropyl amine afforded the sulfonamide **4.19** in a moderate yield (Scheme 4.9). Selective reduction of **4.19** using L-selectride gave the required chiral auxiliary **4.20** in a good yield.



Scheme 4.9: Chiral auxiliaries **4.16-4.19** and synthesis of camphor based chiral auxiliary **4.20**. Reagents and conditions: (a) Dicyclohexylamine (2.0 eq.), isoquinoline (2.0 eq.), DMAP (0.2 eq.), DMF, 0 °C, 1 h; (b) L-Selectride (1.1 eq.), THF, –78 to 20 °C, 1.25 h.

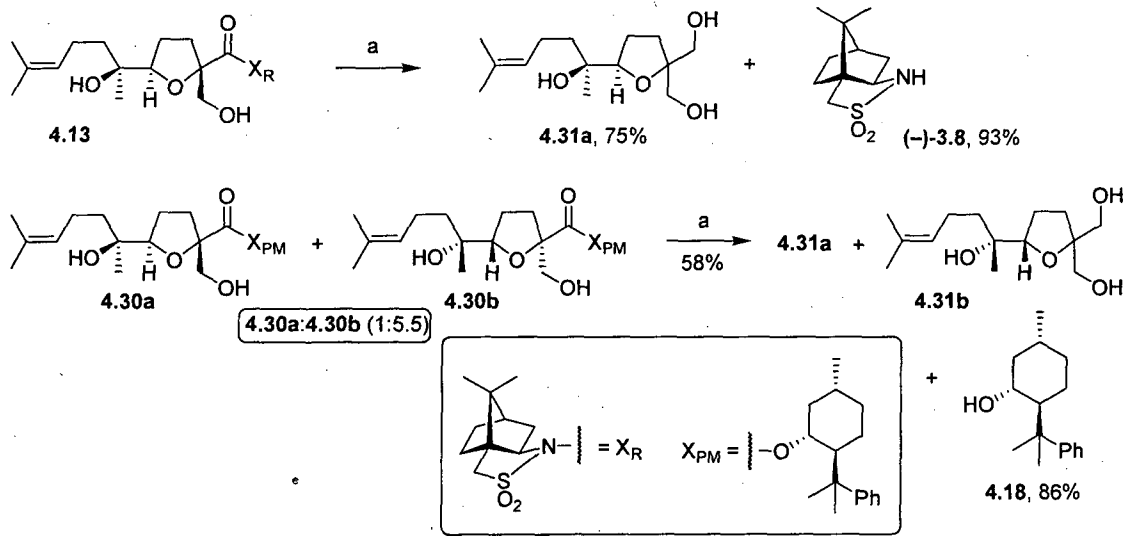
In order to couple the chiral auxiliaries **4.16-4.18** and **4.20** with triene methyl ester **4.10**, the ester **4.10** was hydrolysed to the carboxylic acid **4.21** (Scheme 4.10).[104] The crude acid was treated with pentafluorophenol and DCC to afford the activated PFP ester **4.22**, which on reaction with pre-formed sodium salts of auxiliaries **4.16-4.18** and **4.20** afforded the trienoates **4.23-4.26** in good yields.[105] Selective permanganate oxidative cyclisations of the trienoates **4.23-4.26** gave THF diols **4.27-4.30(a,b)**. In case of the oxidative cyclisation of triene **4.24**, the yield (10%) of oxidised product represents a single major diastereoisomer **4.28a**. The minor diastereoisomer **4.28b** could not be isolated. The poor crude mass recovery and the loss of product during purification are the reasons for such a result. Unfortunately the diastereoisomers **4.27a,b** and **4.29-4.30 (a,b)** could not be separated by flash column chromatography.



Scheme 4.10: Permanganate oxidative cyclisations of trienoates **4.23-4.26**. Reagents and conditions: (a) NaOH (6.5 eq.), $NaHCO_3$ (0.5 eq.), MeOH:H_2O (5:4), reflux, 9 h; (b) C_6F_5OH (1.15 eq.), DCC (1.14 eq.), EtOAc, rt, 21 h; (c) chiral auxiliary (**4.16-4.18** and **4.20**, 1.1 eq.), NaHMDS (1.15 eq.), THF, –20 °C to rt, 2 h; (d) $NaMnO_4$ (1.5 eq., 0.4 M aq.), AcOH (3.0 eq.), phosphate buffer (KH_2PO_4:NaH_2PO_4 8:2), acetone, –35 to –15 °C, 30 min.

Using the commercially available chiral auxiliary, (–)-8-phenylmenthol (**4.18**) for the oxidative cyclisation of triene **4.26** provided a good combination of yield and diastereoselectivity (Scheme 4.10). In this case, the (–)-enantiomer of 8-phenylmenthol (**4.18**) afforded the desired diastereoisomer **4.30a** as the minor product. The relative stereochemistry of THF diol **4.30a** was determined by converting it to a known compound **4.31a**, prepared previously by the reduction of the THF diol **4.13** (Scheme

4.11). The diol **4.13** was synthesised as a single diastereoisomer and its relative stereochemistry had been determined, based on the earlier results from our laboratory.[98] By comparing the signs of optical rotations of enantiomerically pure triol **4.31a** and diastereomeric mixture of triol **4.31a,b** (d.r. 1:5.5), it was known that (+)-enantiomer of 8-phenylmenthol was needed to afford the desired diastereoselective outcome of the permanganate oxidative cyclisation.

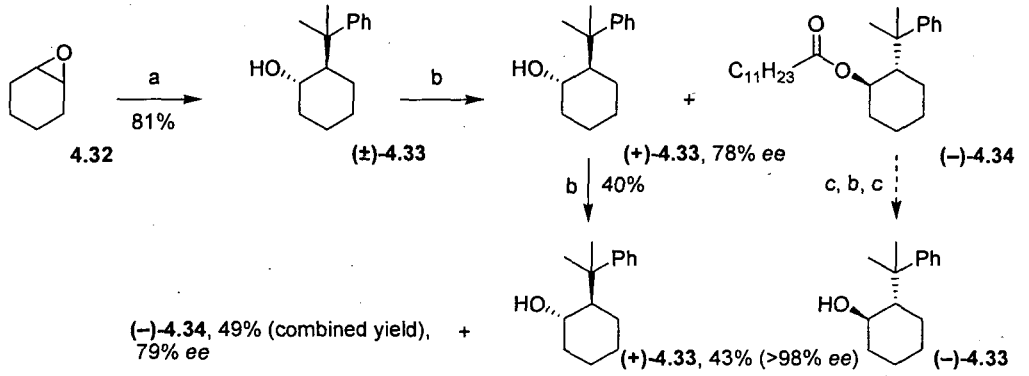


Scheme 4.11: Determination of relative stereochemistry of THF diols **4.30a,b**. Reagents and conditions: (a) $NaBH_4$ (4.0 eq.), THF:H_2O (3:1), –10 to 0 °C, 2 h.

Unfortunately, the (+)-enantiomer of 8-phenylmenthol was not commercially available and it required seven steps to prepare using a known method.[120] Whitesell *et al.* reported that (+)-*trans*-cumylcyclohexanol (TCC) **(+)-4.33** had been used as an alternate to (+)-8-phenylmenthol, therefore the synthesis of this cyclohexyl based auxiliary was undertaken.[121-123]

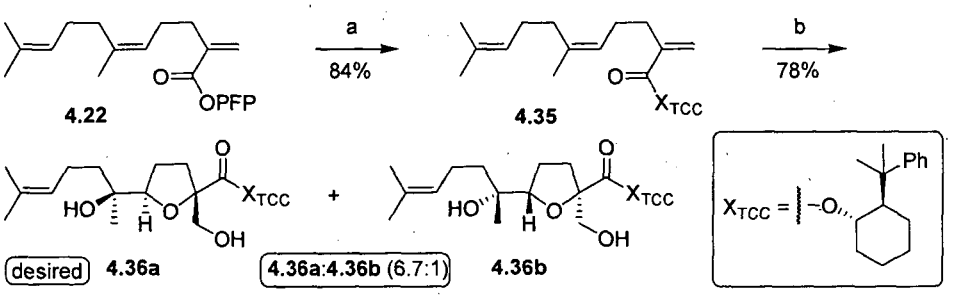
The synthesis of racemic TCC **(±)-4.33** was achieved in one step using a modified approach, reported by Comins *et al.*[124,125] Ring opening of cyclohexene epoxide (**4.32**) by α-cumyl anion afforded the racemic alcohol **(±)-4.33** in a good yield (Scheme 4.12). Enzymatic resolution of the racemic alcohol **(±)-4.33** was carried out using Candida rugosa (Amano AY30) and the resultant enantiomerically enriched TCC **(+)-4.33** (78% *ee*) was separated from the enriched laurate ester **(–)-4.34**. The enantiomerically enriched alcohol **(+)-4.33** was re-subjected to the same enzymatic resolution and TCC **(+)-4.33** was achieved in 43% overall yield (>98% *ee*) along with the enriched ester **(–)-4.34** in 49% combined yield (79% *ee*). The synthesis of (–)-TCC **(–)-4.33** was not

undertaken, as this enantiomer **(–)-4.33** was not needed urgently however sponification of laurate ester **(–)-4.34**, subsequent enzymatic resolution and finally hydrolysis would result in enantiomerically enriched alcohol **(–)-4.33**.[125]



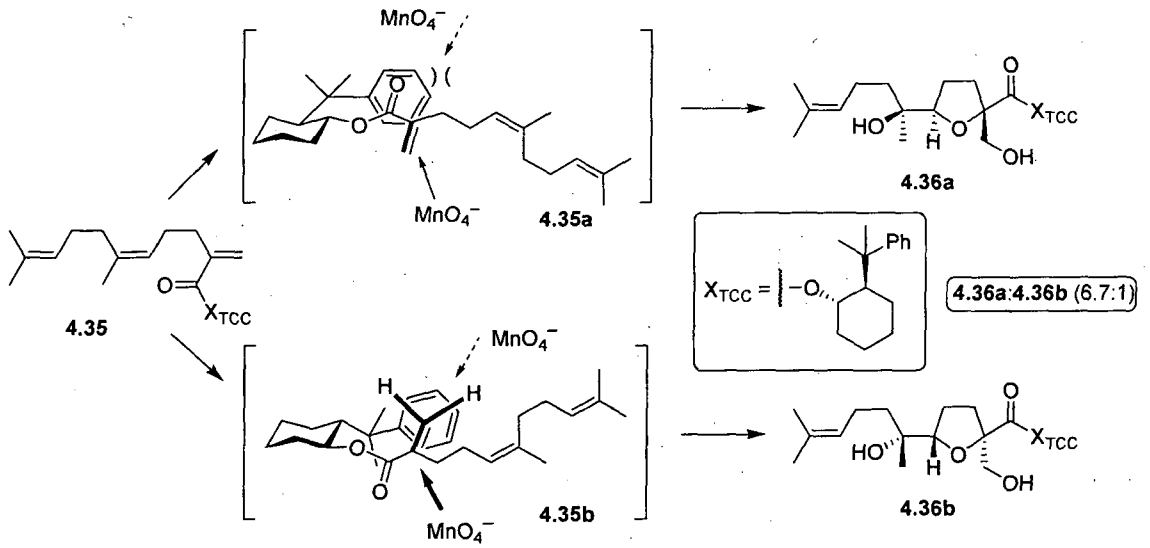
Scheme 4.12: Synthesis of (+)-TCC **(+)-4.33**. Reagents and conditions: (a) Cumene (4.0 eq.), *n*-BuLi (1.10 eq.), *t*-BuOK (1.15 eq.), 0 °C to rt, 2 days; (b) lauric acid (1.0 eq.), Amano AY30 (3.0 g for 1.0 g of racemic alcohol **(±)-4.33**), cyclohexane, 40 °C, 2-3 days; (c) KOH, EtOH, reflux.

After successful preparation of TCC **(+)-4.33**, triene PFP ester **4.22** was treated with a pre-formed sodium salt of TCC **(+)-4.33** to afford the triene **4.35** in a good yield (Scheme 4.13). The key step of permanganate oxidative cyclisation with triene **4.35** proceeded very smoothly providing the THF diols **4.36a,b** in an excellent yield with good diastereoselectivity (d.r. 6.7:1). However, diastereoisomers appeared as a single spot on TLC analysis using various eluent systems and could not be separated by flash column chromatography. In order to investigate the subsequent steps to the target aldehyde fragment **2.47**, the synthesis was continued using the diastereomeric mixture of THF diols **4.36a,b**.



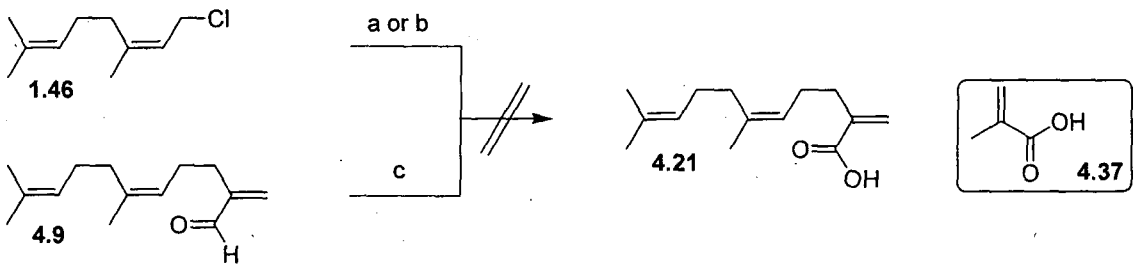
Scheme 4.13: Permanganate oxidative cyclisation of triene **4.35** bearing TCC **(+)-4.33**. Reagents and conditions: (a) chiral auxiliary **(+)-4.33** (1.05 eq.), NaHMDS (1.10 eq.), THF, –20 to 5 °C, 1.5 h; (b) $NaMnO_4$ (1.5 eq., 0.4 M aq.), AcOH (3.5 eq.), phosphate buffer (KH_2PO_4:NaH_2PO_4 8:2), acetone, –20 to –8 °C, 40 min.

It is proposed that the stereoselectivity observed is due to blockage of the *Si*-face by the tertiary centre bearing the phenyl ring, as indicated in the conformation **4.35a** (Scheme 4.14). Due to shielding of *Si*-face, attack of the oxidant would take place preferentially from the *Re*-face, affording the desired THF diol diastereoisomer **4.36a** as the major product. Such a *Re*-face attack also corresponds with attack of the oxidant on the enoyl olefin when triene bearing (2*R*)-10,2-camphorsultam ((–)-**3.8**) was subjected to oxidative cyclisation (See Scheme 4.7). As a result of *Si*-face attack, as shown in conformation **4.35b**, the minor diastereoisomer **4.36b** was obtained.



Scheme 4.14: Rationalisation of the diastereoselectivity obtained using (+)-TCC (+)-**4.33**.

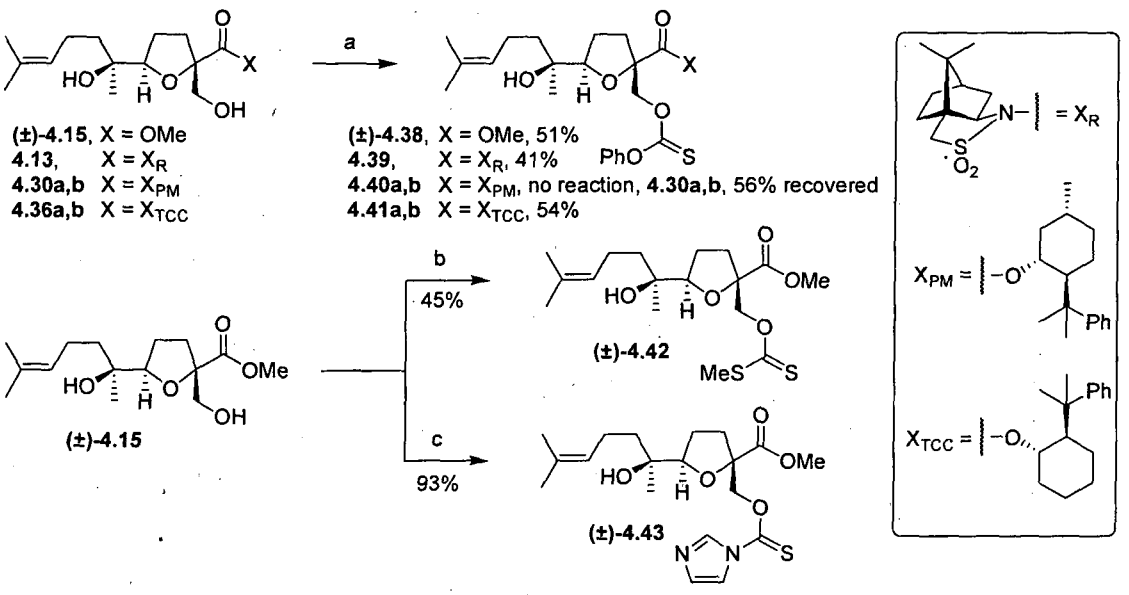
After achieving a good combination of yield and diastereoselectivity for the oxidative cyclisation of triene **4.35**, investigations to shorten the synthesis of triene **4.35** were carried out. In order to shorten the synthetic route to carboxylic acid **4.21**, various methodologies were tried to reduce the number of steps. Alkylation of neryl chloride (**1.46**) with methacrylic acid (**4.37**) failed to afford the desired carboxylic acid **4.21** under various conditions (Scheme 4.15). This may be due to the poor solubility of methacrylic acid (**4.37**) which affected formation of the dianion. Similarly in our hands, oxidation of aldehyde **4.9** to yield carboxylic acid **4.21** was not possible.[126]



Scheme 4.15: Strategies to shorten the synthetic route to acid **4.21**. Reagents and conditions: (a) acid **4.37** (2.2 eq.), *n*-BuLi (4.0 eq.), TMEDA (4.0 eq.), Et_2O, –78 °C to rt, 24 h; (b) acid **4.37** (2.2 eq.), NaH (2.2 eq.), *n*-BuLi (2.0 eq.), TMEDA (2.0 eq.), Et_2O, –78 °C to rt, 18 h; (c) $NaClO_2$ (3 eq.), 1-methyl-1-cyclohexene (4.9 eq.), sulfamic acid (1.0 eq.), CH_2Cl_2, 0 °C to rt, 3 h.

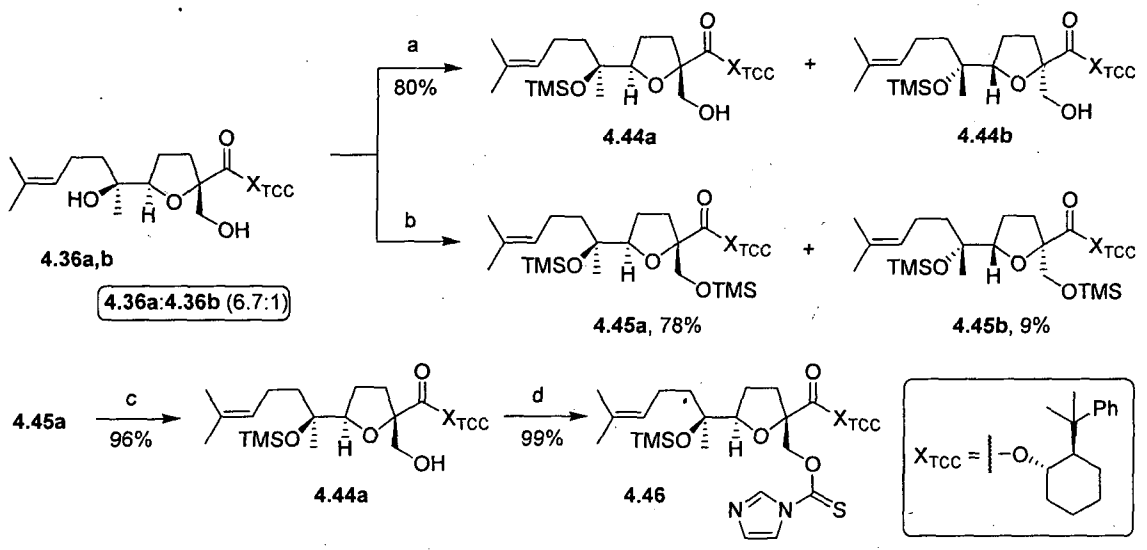
4.4 Synthesis of *trans*-THF 4.50 by Radical Deoxygenation

To accomplish radical deoxygenation of the primary alcohol of THF diols, racemic THF **(±)-4.15**, isomerically pure THF diol **4.13**, and diastereomeric mixture **4.36a,b** were transformed to their corresponding thionoformates using chlorothionoformate, pyridine and catalytic DMAP in 51%, 40% and 54% yields respectively (Scheme 4.16).[127,128] THF diols **4.30a,b** did not undergo thionoformate formation using prescribed reaction conditions, and the starting diols were recovered in 56% yield. Thionoformate formation gave moder ate yields, which may be due to interference by the tertiary hydroxyl group. Alternatively racemic THF **(±)-4.15** was treated with CS_2 and MeI to afford the racemic xanthate **(±)-4.42** in a moderate yield.[129] Attempts to improve the yield failed. Finally an imidazolide strategy was investigated. Gratifyingly the conversion of racemic THF **(±)-4.15** into the corresponding racemic THF thiocarbonyl imidazolide **(±)-4.43** proceeded in an excellent yield.[130]



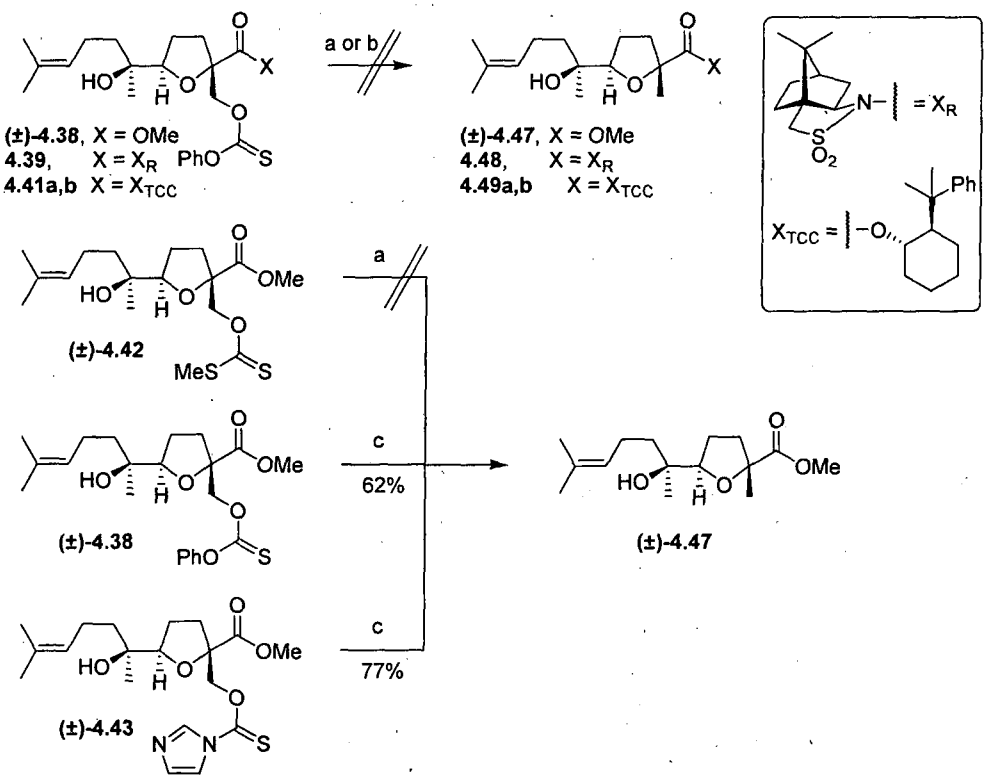
Scheme 4.16: Preparation of desired substrates for radical cleavage of the primary alcohols. Reagents and conditions: (a) PhOC(=S)Cl (5.0 to 10.0 eq.), DMAP (0.05 eq.), pyridine (5.0 to 10.0 eq.), CH_2Cl_2, –10 °C, 6 h; (b) CS_2 (2.5 eq.), imid. (0.05 eq.), NaH (2.5 eq.), MeI (2.5 eq.), THF, –5 °C to rt, 1 h; (c) $imid_2(C=S)$ (3.0 eq.), DMAP (0.3 eq.), CH_2Cl_2, rt, 4 h.

The diastereomeric mixture of THF diols **4.36a,b** were converted to its thiocarbonyl imidazolide **4.46** using the same conditions. To prevent interference of the free tertiary hydroxyl group, it was protected as a TMS ether. However, as primary hydroxyls are more reactive towards TMS ether formation, both hydroxyl groups were initially protected and then the primary hydroxyl was deprotected selectively under basic conditions in a one pot process to afford a diastereomeric mixture of mono-protected THFs **4.44a,b** in 80% yield (Scheme 4.17). The diastereoisomers **4.44a,b** could not be separated by flash column chromatography. Alternatively, *bis*-protected THF adducts **4.5a,b** were isolated and gratifyingly these were separated by column chromatography at this stage. The rest of the synthesis was carried out with diastereomerically pure *bis*-protected THF **4.45a**. Deprotection of the primary hydroxyl group afforded the mono-protected THF **4.44a** which was subsequently treated with thiocarbonyldimidazole to afford the imidazolide **4.46** in an excellent yield.[130]



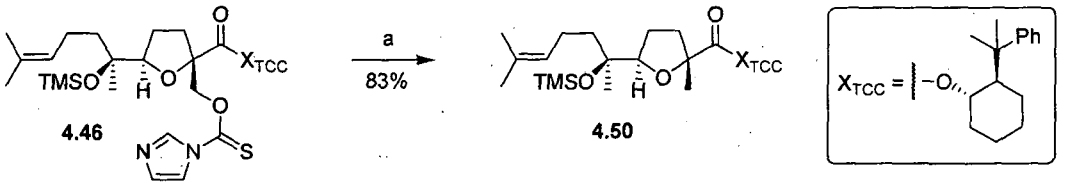
Scheme 4.17: Separation of diastereoisomers **4.36a,b** and synthesis of imidazolide **4.46**. Reagents and conditions: (a) TMSCl (10.0 eq.), imid. (12.0 eq.), DMF, –5 to 0 °C, 30 min; then K_2CO_3 (0.2 eq.), MeOH, –10 to 10 °C, 2.5 h; (b) TMSCl (10.0 eq.), imid. (12.0 eq.), DMF, –5 to 0 °C, 30 min; (c) K_2CO_3 (0.4 eq.), MeOH, –10 to 10 °C, 2.5 h; (d) $imid_2(C=S)$ (3.0 eq.), DMAP (0.3 eq.), CH_2Cl_2, rt, 8 h.

Radical cleavage of racemic thionoformates **(±)-4.38**, isomerically enriched thionoformate **4.39**, the diastereomeric mixture of thionoformates **4.41a,b** and racemic xanthate **(±)-4.42**, using Barton-McCombie deoxygenation protocol proved unsuccessful (Scheme 4.18).[127,131] As an alternative to Bu_3SnH, $(Bu_4N)_2S_2O_8$ has also been reported as a radical source to bring about the same transformation.[132] $(Bu_4N)_2S_2O_8$ was prepared using the literature procedure.[133] Unfortunately it also failed to afford the deoxygenated product for thionoformates **(±)-4.38**, **4.39** and **4.41a,b**. Ultimately racemic thionoformates **(±)-4.38** and racemic imidazolide **(±)-4.43** were deoxygenated using *tris*-trimethylsilyl silane (TTMSS) as a radical source in good yields.[134]



Scheme 4.18: Radical cleavage of thionoformates, disulfide and xanthate. Reagents and conditions: (a) Bu_3SnH (1.5 eq.), AIBN (0.5 eq.), toluene, reflux, 5 h; (b) $(Bu_4N)_2S_2O_8$ (3.0 eq.), HCO_2Na (6.0 eq.), Na_2CO_3 (8.0 eq.), DMF, 75 °C, 45 min; (c) TTMSS (4.0 eq.), AIBN (0.3 eq.), toluene, 85 °C, 2 h.

After optimisation of the radical cleavage reaction using TTMSS, optically enriched imidazolide **4.46** was treated with TTMSS to afford the desired mono-protected THF **4.50** in a good yield (Scheme 4.19).



Scheme 4.19: Radical cleavage of optically enriched thiocarbonyl imidazolide **4.46**. Reagents and conditions: (a) TTMSS (6.5 eq.), AIBN (0.5 eq.), toluene, 85 °C, 1.25 h.

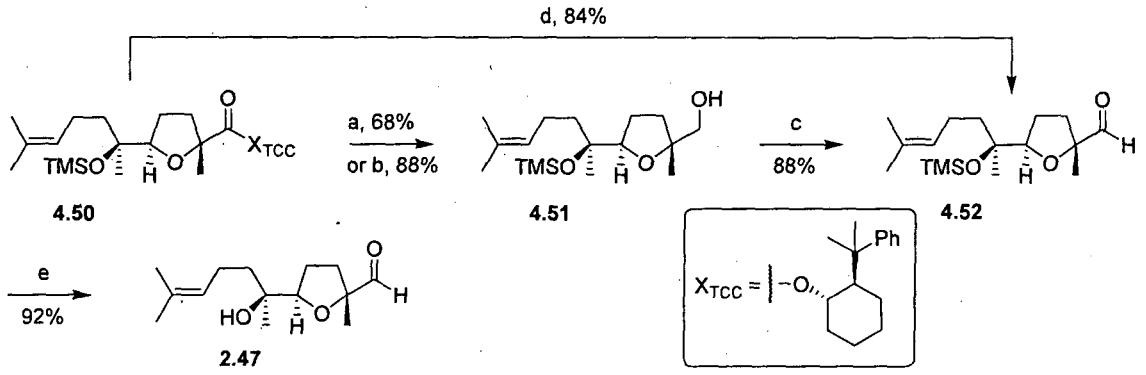
As the radical intermediates had the potential to undergo side reactions, deoxygenation was carried out in the presence of differing amounts of TTMSS (Table 4.5). It was found that excess of TTMSS directly affected the reaction rate and forced the reaction to completion in a shorter time, and improved the isolated yield of the product **4.50**.

Entry*	TTMSS (eq.)	AIBN (eq.)	Time (h)	Yield (%)
1.	2.0	0.3	4	60
2.	4.0	0.5	1.5	79
3.	6.5	0.5	1.25	83

Table 4.5: Optimisation studies towards the radical cleavage of imidazolide **4.46**. *All reactions were carried out in toluene at 85 °C.

4.5 Synthesis of the Left Hand Aldehyde Fragment 2.47 of Eurylene (2.1), Intersection with Kodama's Intermediate

Reductive cleavage of the chiral auxiliary from the *trans*-THF fragment **4.50** using $NaBH_4$ afforded the alcohol **4.51** and the chiral auxiliary **(+)-4.33** in 68% and 88% yields respectively. Due to the low yield of the desired product, the chiral auxiliary **(+)-4.33** from THF fragment **4.50** was reductively cleaved using DIBAL-H and an improved yield (88%) of the alcohol **4.51** was achieved along with 91% yield of the auxiliary **(+)-4.33** (Scheme 4.20).[135] Alcohol **4.51** was oxidised to aldehyde fragment **4.52** in a good yield using Dess-Martin periodinane.[136] Alternatively, treatment of mono-protected THF **4.50** bearing the auxiliary **(+)-4.33** with DIBAL-H at –78 °C with carefully quenching of the reaction at the same temperature afforded the aldehyde fragment **4.52** directly in a good yield. Silyl deprotection of the tertiary hydroxyl group under acidic conditions furnished the desired *trans*-THF aldehyde fragment **2.47**, which corresponds to the left hand fragment of eurylene (**2.1**) reported by Kodama *et al.*[83] *Trans*-THF aldehyde fragment **2.47** displayed analytical and spectroscopic data that were consistent with those reported.[83]



Scheme 4.20: Synthesis of *trans*-THF fragment **2.47** of eurylene (**2.1**). Reagents and conditions: (a) $NaBH_4$ (1.2 eq.), THF:H_2O (25:1), –5 °C to rt 4 h; (b) DIBAL-H (3.0 eq.), CH_2Cl_2, –78 °C to rt, 4 h; (c) DMP (1.5 eq.), CH_2Cl_2, rt, 4.5 h; (d) DIBAL-H (4.0 eq.), CH_2Cl_2, –78 °C, 2 h; (e) HCl (1 N aq.), THF, rt, 30 min.

4.6 Conclusions

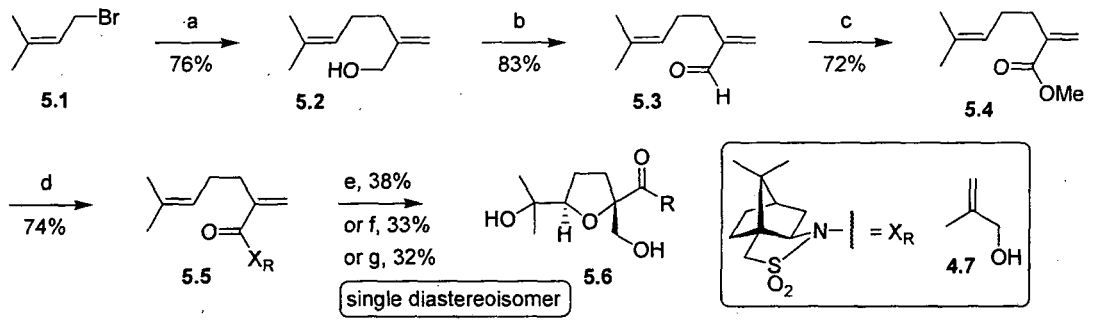
An efficient stereocontrolled synthesis of left hand aldehyde fragment **2.47** of eurylene (**2.1**) was achieved in 13 linear steps (16.2% overall yield) using permanganate promoted oxidative cyclisation of readily accessible 1,5,9-triene **4.35**. The use of (2*R*)-10,2-camphorsultam ((–)-**3.8**) afforded the required THF diol **4.13** as a single diastereoisomer but in a disappointing low yield. The effect of different chiral auxiliaries on stereoselective oxidative cyclisation of the 1,5,9-triene precursor was investigated and (+)-TCC (+)-**4.33** was found to afford the best combination of yield and diastereoselectivity (see Scheme 4.13). The diastereoisomers **4.45a,b** were separated by column chromatography and the synthesis of the left hand fragment **2.47** of eurylene was accomplished using diastereomerically and enantiomerically pure *bis*-protected THF adduct **4.45a**.

Chapter 5 Synthesis of *trans*-THFs; Towards the Synthesis of (+)-Linalool Oxide

In this chapter, progress towards stereocontrolled synthesis of (+)-linalool oxide (**5.27**) will be described.

5.1 Synthesis and Oxidative Cyclisations of 1,5-Dienes 5.5 and 5.10

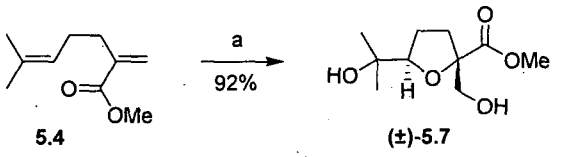
Following the methodology applied to the synthesis of trienoate **4.4a**, dienoate **5.5** was prepared in 4 steps (34% overall yield, Scheme 5.1).[111-113,116-117,103] Oxidative cyclisation of 1,5-diene **5.5** was carried out using the optimised conditions developed previously to afford the *trans*-THF **5.6** as a single diastereoisomer in a moderate yield along with the recovery of starting dienoate **5.5** (30-45% yield).[35] The highest yield of the *trans*-THF **5.6** was achieved when oxidative cyclisation was carried out using a phase-transfer catalyst, Adogen 464 (condition e, Scheme 5.1). The relative stereochemistry of the resultant diol **5.6** was assigned based on earlier results from our laboratory.[98]



Scheme 5.1: Oxidative cyclisation of 1,5-diene **5.5**, bearing (2*R*)-10,2-camphorsultam (**(–)-3.8**). Reagents and conditions: (a) alcohol **4.7** (2.3 eq.), *n*-BuLi (4.0 eq.), TMEDA (4.0 eq.), Et_2O, –78 °C to rt, 24 h; (b) MnO_2 (17 eq.), *n*-hexane, 0 °C to rt, 1 h; (c) NaCN (3.5 eq.), AcOH (2.5 eq.), MnO_2 (10.0 eq.), MeOH, rt, 18 h; (d) (2*R*)-10,2-camphorsultam (**(–)-3.8**, 1.25 eq.), Me_3Al (1.25 eq.), toluene, reflux, 40 h; (e) $KMnO_4$ (2.0 eq., 0.4 M aq.), AcOH (4.0 eq.), Adogen 464 (0.5 eq.), ether, rt, 30 min; (f) $NaMnO_4$ (1.5 eq., 0.4 M aq.), AcOH (3.0 eq.), phosphate buffer (KH_2PO_4:NaH_2PO_4 8:2), acetone, –35 to –10 °C, 1 h; (g) $NaMnO_4$ (1.7 eq., 0.4 M aq.), AcOH (3.0 eq.), phosphate buffer (KH_2PO_4:NaH_2PO_4 8:2), acetone, –40 to 0 °C, 1 h.

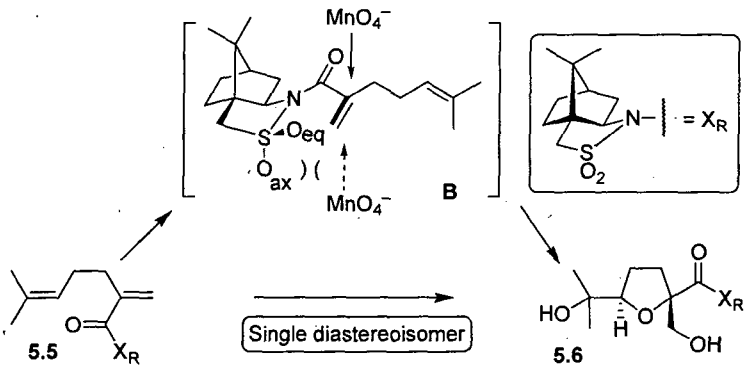
The low yield of the oxidative cyclisation of diene **5.5** can be attributed due to the bulky chiral auxiliary **(–)-3.8** as observed for the oxidative cyclisation of related trienoyl

sultam **4.4a** (see Scheme 4.6). Therefore diene ester **5.4** was subjected to permanganate oxidation, resulting in an excellent yield of racemic THF **(±)-5.7** (Scheme 5.2). The successful oxidative cyclisation of methyl ester **5.4** confirmed that the steric bulk of (2*R*)-10,2-camphorsultam **((–)-3.8)** was one of the major reasons for the low yield of oxidative cyclisation of diene **5.5**.



Scheme 5.2: Oxidative cyclisation of diene ester **5.4**. Reagents and conditions: (a) $NaMnO_4$ (1.5 eq., 0.4 M aq.), AcOH (3.0 eq.), phosphate buffer (KH_2PO_4:NaH_2PO_4 8:2), acetone, –35 to –10 °C, 40 min.

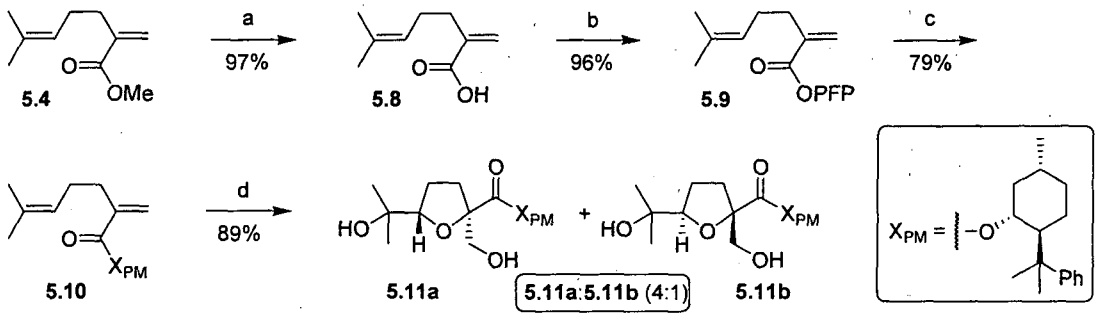
The steric hindrance caused by chiral auxiliary **(–)-3.8** can be explained by the reactive conformation **B**, in which the anti-position of the C=O and the NSO_2 moieties is favoured (Scheme 5.3).[108] The axial oxygen atom blocks the *Si*-face and the attack takes place preferentially from the *Re*-face, resulting in *trans*-THF **5.6** as a single diastereoisomer.



Scheme 5.3: Rationalisation of the diastereoselectivity obtained using (2*R*)-10,2-camphorsultam **((–)-3.8)**.

Due to the low yield of oxidative cyclisation for diene **5.5**, the commercially available chiral auxiliary, (–)-8-phenylmenthol (**4.18**) was used. Firstly, the diene ester **5.4** was hydrolysed under basic conditions and the resultant carboxylic acid **5.8** was converted to its PFP ester **5.9** by treating with pentaflourophenol and DCC (Scheme 5.4).[104] Treatment of the diene ester **5.9** with the sodium salt of the auxiliary **4.18** furnished diene **5.10**, subsequent permanganate mediated oxidative cyclisation afforded THF diols

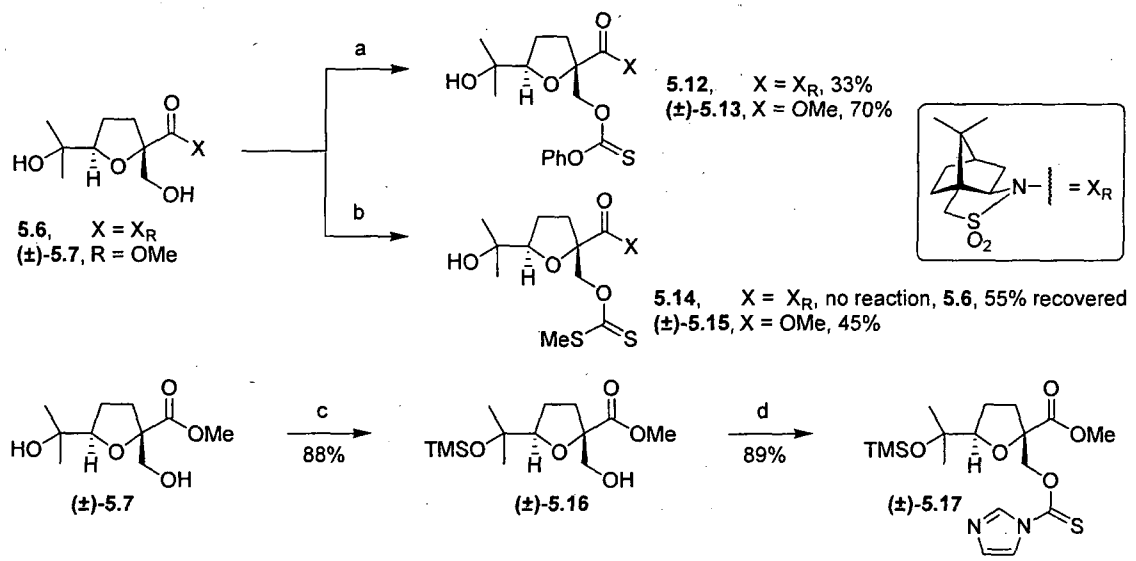
5.11a,b in an excellent yield and reasonably good diastereoselectivity (d.r. 4:1). Unfortunately the diastereoisomers **5.11a,b** could not be separated by flash column chromatography.



Scheme 5.4: Oxidative cyclisation of diene **5.10** bearing (–)-8-phenylmenthol (**4.18**). Reagents and conditions: (a) NaOH (6.5 eq.), $NaHCO_3$ (0.5 eq.), MeOH:H_2O (5:4), reflux, 7 h; (b) C_6F_5OH (1.15 eq.), DCC (1.14 eq.), EtOAc, rt, 23 h; (c) chiral auxiliary **4.18** (1.05 eq.), NaHMDS (1.10 eq.), THF, –20 °C to rt, 1.5 h; (d) $NaMnO_4$ (1.5 eq., 0.4 M aq.), AcOH (3.5 eq.), phosphate buffer (KH_2PO_4:NaH_2PO_4 8:2), acetone, –22 to –8 °C, 40 min.

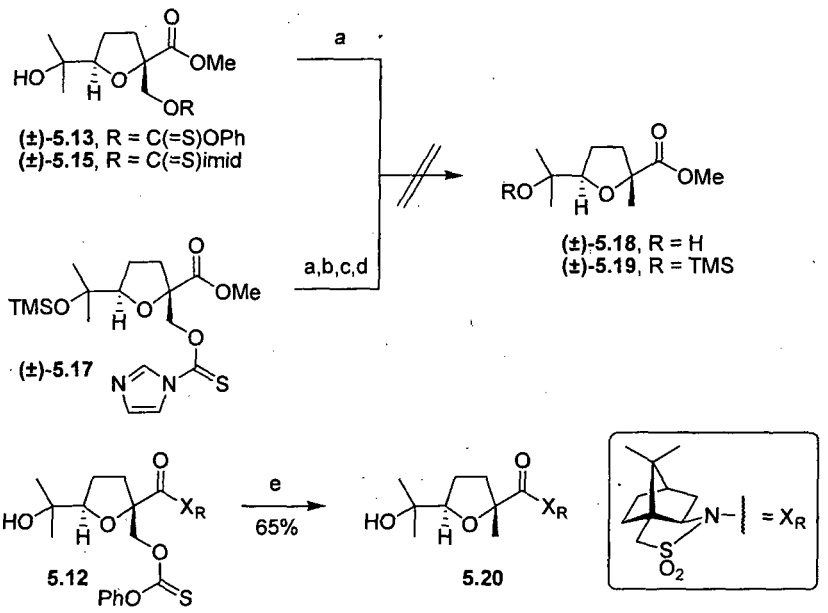
5.2 Synthesis of *trans*-THF 5.24 by Radical Deoxygenation

To provide substrates for the reductive deoxygenation of the primary alcohol, THF diol **5.6** and racemic THF (±)-**5.7** were converted to their corresponding thionoformates and xanthates. Treatment of *trans*-THF **5.6** bearing (2*R*)-10,2-camphorsultam ((–)-**3.8**) and racemic THF diol (±)-**5.7** with chlorothionoformate, pyridine and catalytic DMAP afforded the desired thionoformates **5.12** and (±)-**5.13** in 33% and 70% yields respectively (Scheme 5.5).[127,128] Alternatively treatment of the racemic diol (±)-**5.7** with CS_2 and MeI in the presence of NaH and imidazole afforded the racemic xanthate (±)-**5.15** in a moderate yield, whilst the xanthate formation for the diol **5.6** proved unsuccessful and starting material was recovered in 55% yield after purification.[129] Moving to another approach for radical deoxygenation, the tertiary hydroxyl group of racemic THF (±)-**5.7** was protected as trimethylsilyl (TMS) ether (±)-**5.16** and this was treated with thiocarbonyldiimidazole in the presence of imidazole to afford the racemic thiocarbonyl imidazolide (±)-**5.17** in an excellent yield.[130]



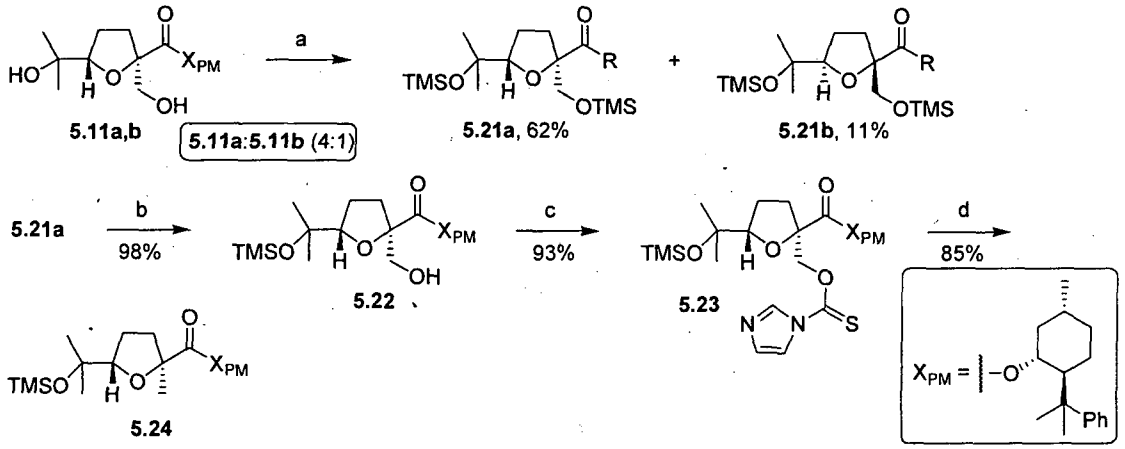
Scheme 5.5: Preparation of desired substrates for radical cleavage of the primary alcohol. Reagents and conditions: (a) PhOC(=S)Cl (5.0 to 10.0 eq.), DMAP (0.05 eq.), pyridine (5.0 to 10.0 eq.), CH_2Cl_2, –10 °C, 4 to 8 h; (b) CS_2 (2.5 eq.), imid. (0.05 eq.), NaH (2.5 eq.), MeI (2.5 eq.), THF, –5 °C to rt, 2 h; (c) TMSCl (10.0 eq.), imid. (12.0 eq.), DMF, –5 to 0 °C, 30 min; then K_2CO_3 (0.2 eq.), MeOH, –10 to 10 °C, 2.5 h (d) $imid_2(C{=}S)$ (3.0 eq.), DMAP (0.3 eq.), CH_2Cl_2, rt, 6 h.

Radical cleavage of racemic substrates **(±)-5.13**, **(±)-5.15** failed to afford the desired racemic THF **(±)-5.18** on treatment with $(Bu_4N)_2S_2O_8$ (Scheme 5.6).[132] The same result was observed with racemic imidazolide **(±)-5.17**. The use of excess Na_2CO_3 and Et_3N had been reported to accelerate the reaction; therefore racemic imidazolide **(±)-5.17** was subjected to these modified conditions but no product was observed.[132] Treatment of racemic imidazolide **(±)-5.17** with Bu_3SnH and 20 mol% AIBN also failed to effect the radical deoxygenation.[127,131] During all these radical reactions, the starting materials were degraded. Gratifyingly, treatment of the thionoformate **5.12** with Bu_3SnH afforded the required *trans*-THF product **5.20** in a good yield.[131]



Scheme 5.6: Radical deoxygenation to synthesise racemic *trans*-THF **(±)-5.18** and diastereomerically pure *trans*-THF **5.20**. Reagents and conditions: (a) $(Bu_4N)_2S_2O_8$ (3.0 eq.), HCO_2Na (6.0 eq.), DMF, 70 °C, 30 min; (b) $(Bu_4N)_2S_2O_8$ (3.0 eq.), HCO_2Na (6.0 eq.), Na_2CO_3 (8.0 eq.), DMF, 70 °C, 30 min; (c) $(Bu_4N)_2S_2O_8$ (3.0 eq.), HCO_2Na (6.0 eq.), Et_3N (8.0 eq.), DMF, 70 °C, 30 min; (d) Bu_3SnH (1.2 eq.), AIBN (0.2 eq.), toluene, reflux, 5 h; (e) Bu_3SnH (3.0 eq.), AIBN (0.5 eq.), toluene, reflux, 4 h.

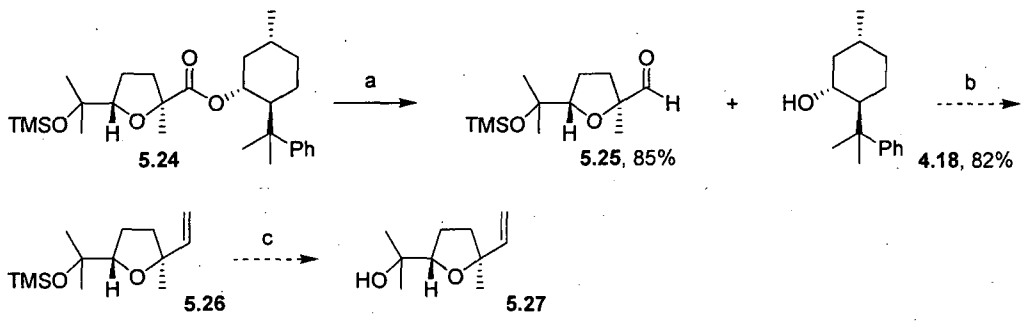
After establishing a procedure for successful thiocarbonyl imidazolide formation and efficient radical deoxygenation, the diastereomeric mixture of diols **5.11a,b** were subjected to the same conditions. Protection of both hydroxyl groups of diol **5.11a,b** enabled separation of the diastereoisomers and the rest of the synthesis was continued with optically enriched *bis*-protected diastereoisomer **5.21a** (Scheme 5.7). Selective deprotection of the primary alcohol and subsequent treatment of mono-protected THF **5.22** with thiocarbonyldiimidazole afforded the imidazolide **5.23** in an excellent yield.[130] Treatment of **5.23** with TTMSS and AIBN afforded the THF fragment **5.24** in a good yield.[134]



Scheme 5.7: Separation of diastereoisomers **5.11a,b** and synthesis of *trans*-THF **5.24**. Reagents and conditions: (a) TMSCl (10.0 eq.), imid. (12.0 eq.), DMF, –10 to 0 °C, 30 min; (b) K_2CO_3 (0.1 eq.), MeOH, –10 to 10 °C, 4 h; (c) $imid_2(C{=}S)$ (3.0 eq.), DMAP (0.3 eq.), CH_2Cl_2, rt, 14 h; (d) TTMSS (4.0 eq.), AIBN (0.25 eq.), toluene, 85 °C, 2.25 h.

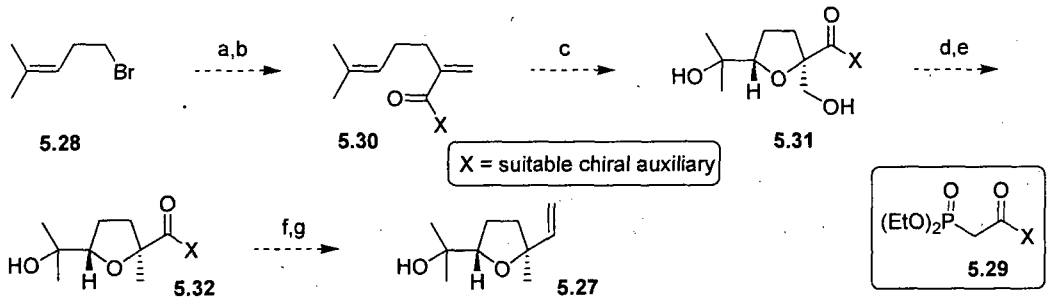
5.3 Towards the Synthesis of (+)-Linalool Oxide

Reductive cleavage of the (–)-8-phenylmenthol (**4.18**) from the *trans*-THF fragment **5.24** afforded the aldehyde fragment **5.25** and the auxiliary **4.18** in 85% and 82% yields respectively (Scheme 5.8). The planned strategy was to effect homologation of aldehyde **5.25** by one carbon to the *trans*-THF **5.26**, followed by deprotection of the tertiary TMS ether to complete the total synthesis of (+)-linalool oxide (**5.27**).[137,138] When Wittig methylenation of the aldehyde fragment **5.25** was attempted, complete consumption of aldehyde **5.25** by TLC was observed, however, olefination product **5.26** could not be isolated. Due to time constraints, this particular transformation was not repeated.



Scheme 5.8: Towards the synthesis of (+)-linalool oxide (**5.27**). Reagents and conditions: (a) DIBAL-H (4.0 eq.), CH_2Cl_2, –78 °C, 3 h; (b) $MePh_3P^+I^-$ (5.0 eq.), *t*-BuO^-K^+ (5.0 eq.), THF, rt to reflux, 10 h; (c) 1 N HCl (aq.), THF, rt.

The present route requires 7 steps for the synthesis of dienoate **5.10** and an additional protection-deprotection sequence, in order to separate diastereoisomers **5.21a,b**. To overcome these limitations a short, stereoselective route to (+)-linalool oxide (**5.27**) is proposed (Scheme 5.9). Treatment of commercially available prenyl bromide (**5.28**) with phosphonate **5.29** bearing a suitable chiral auxiliary would afford the requisite diene **5.30**, ready for oxidative cyclisation. Radical deoxygenation of the primary alcohol of THF diol **5.31**, reductive cleavage of the auxiliary and finally Wittig methylenation would accomplish a short synthesis of (+)-linalool oxide (**5.27**).



Scheme 5.9: Proposed short route for the synthesis of (+)-linalool oxide (**5.27**). Reagents and conditions: (a) phosphonate **5.29**, NaH, DMSO; (b) CH_2O, K_2CO_3; (c) $NaMnO_4$, AcOH, acetone; (d) $imid_2(C{=}S)$, imid., CH_2Cl_2; (e) TMTSS, toluene; (f) DIBAL-H, CH_2Cl_2; (g) $MePh_3P^+I^-$, *t*-BuO^-K^+, THF.

The permanganate oxidative cyclisation methodology and subsequent steps for the synthesis of (+)-linalool oxide (**5.27**) has been investigated and optimised. Therefore by using the (+)-enantiomer of 8-phenylmenthol or its analogue (+)-TCC **(+)-4.33**, a synthesis of the other enantiomer, (–)-linalool oxide could be achieved.

5.4 Conclusions

Permanganate promoted oxidative cyclisation of 1,5-diene **5.5**, bearing (2*R*)-10,2-camphorsultam (**(–)-3.8**), afforded *trans*-THF **5.6** as a single diastereoisomer in a moderate yield. The use of commercially available chiral auxiliary (–)-8-phenylmenthol (**4.18**) gave a good combination of yield and diastereoselectivity of THF diols **5.11a,b** (see Scheme 5.4). Gratifyingly, the diastereoisomers **5.21a,b** were separated by column chromatography and a key aldehyde fragment **5.25** of (+)-linalool oxide was stereoselectively synthesised in 13 steps, overall yield 8.8%. Due to time constraints, the

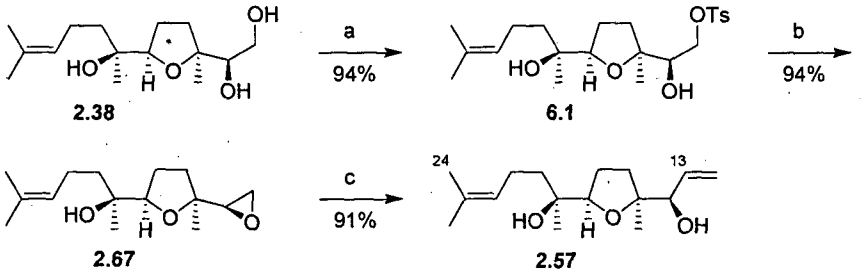
total synthesis of (+)-linalool oxide (**5.27**) was not accomplished and an alternative approach is proposed to minimise the number of reaction steps (see Scheme 5.9).

Chapter 6 Towards the Total Synthesis of Eurylene

Following successful stereoselective syntheses of the two fragments of eurylene using a permanganate mediated oxidative cyclisation, various coupling strategies were investigated to accomplish a total synthesis. In this chapter, approaches towards a total synthesis of eurylene (**2.1**) will be described.

6.1 Tethered Ring Closing Metathesis Protocol

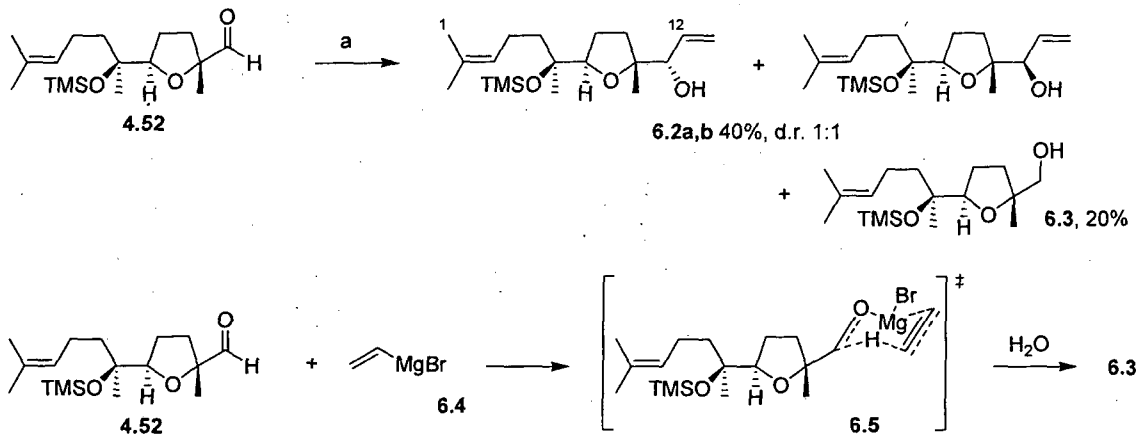
Retrosynthetic analysis for this route has been described in Chapter two (see Scheme 2.12). To carry out the silicon tethering chemistry, allylic alcohols **2.57** and **6.2a** were required. The allylic alcohol **2.57** encompassing the right hand fragment was synthesised by selective tosylation of triol **2.38** to afford tosylate **6.1**, followed by ring closure under basic conditions to furnish epoxide **2.67** in an excellent yield (Scheme 6.1).[139] The sulfur ylide was formed by treating $Me_3S^+I^-$ with *n*-BuLi and this was subsequently treated with the epoxide **2.67** to afford the desired allylic alcohol **2.57** in a good yield.[140] In this way, the synthesis of a C13-C24 fragment of eurylene (**2.1**) was accomplished.



Scheme 6.1: Synthesis of allylic alcohol **2.57**. Reagents and conditions: (a) Bu_2SnO (1.2 eq.), TsCl (1.3 eq.), TBAB (0.5 eq.), PhH, 95 °C to rt, 23 h; (b) K_2CO_3 (1.2 eq.), MeOH, rt, 40 min; (c) $Me_3S^+I^-$ (10.0 eq.), *n*-BuLi (10.0 eq., 2.3 M in hexanes), THF, –10 °C to rt, 5 h.

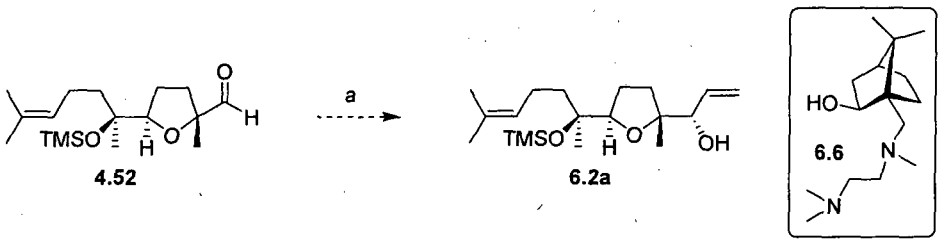
To complete the synthesis of the left hand C1-C12 allylic alcohol **6.2a**, *trans*-THF aldehyde fragment **4.52** was treated with commercially available vinyl magnesium bromide (**6.4**, Scheme 6.2).[141,142] No substrate based stereocontrol was observed and epimers **6.2a,b** were isolated as a 1:1 mixture. Partial separation was possible by flash column chromatography. Surprisingly, alcohol **6.3** was identified as a major side

product which is thought to be due to the migration of the hydrogen atom from the terminal carbon of vinyl group, through a 6-membered transition state **6.5**.



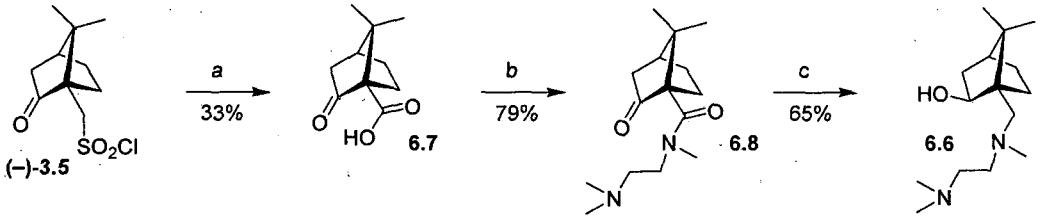
Scheme 6.2: Vinylation of aldehyde fragment **4.52**. Reagents and conditions: (a) CH_2=CHMgBr (**6.4**, 2.0 eq.), THF, –78 to –35 °C, 1 h.

Due to the configuration of *trans*-THF aldehyde **4.52**, no substrate controlled stereoselectivity was observed therefore it was decided to investigate the chiral reagent controlled vinylation. Oppolzer *et al.* had reported the stereoselective alkyl addition to aldehydes using various chiral reagents.[143] The same methodology with slight modification was selected to bring about this particular transformation (Scheme 6.3).



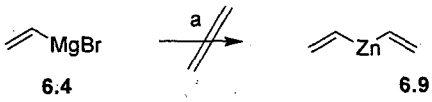
Scheme 6.3: Proposed synthesis of allylic alcohol **6.2a**. Reagents and conditions: (a) chiral auxiliary **6.6**, $(CH_2$=$CH)_2Zn$ (**6.9**), THF.

As the chirophore **6.6** and divinylzinc (**6.9**) were not commercially available, preparation of these reagents was necessary. Tridentate ligand **6.6** was prepared by using the methodology reported by Oppolzer *et al.*[144] (1*R*)-Camphorsulfonyl chloride ((–)-**3.5**) was oxidised to ketopinic acid **6.7**, and subsequently treated with *N,N,N'*-trimethylethylenediamine to afford the ketoamide **6.8** (Scheme 6.4).[145] Reduction of amide **6.8** gave the required tridentate ligand **6.6**.[144]



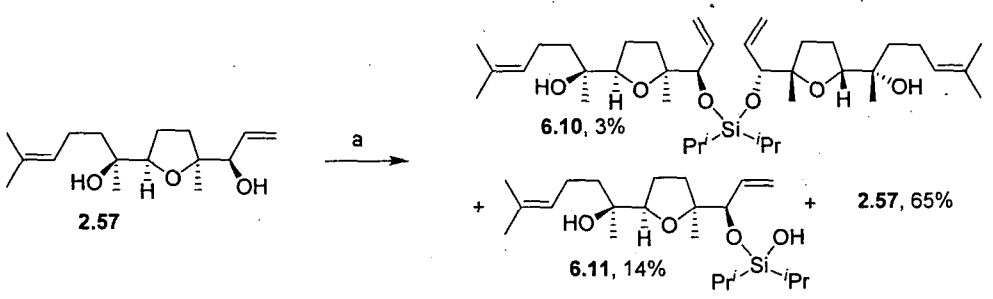
Scheme 6.4: Synthesis of tridentate ligand **6.7**. Reagents and conditions: (a) $KMnO_4$ (1.6 eq.), Na_2CO_3 (2.4 eq.), H_2O, 95 °C, 1 h; (b) *N,N,N'*-trimethylethylenediamine (2.2 eq.), $SOCl_2$ (7.0 eq.), pyridine (0.1 eq.), PhH, 0 °C to rt, 2.25 h; (c) $LiAlH_4$ (5.0 eq.), THF, –40 to 0 °C, 4.5 h.

Similarly for the synthesis of divinylzinc (**6.9**), a method reported by Bartocha *et al.* was investigated, but unfortunately our efforts to synthesise divinylzinc (**6.9**) failed (Scheme 6.5).[146]



Scheme 6.5: Attempted synthesis of divinylzinc **6.9**. Reagents and conditions: (a) CH_2=CHMgBr (**6.5**, 1.0 eq.), $ZnCl_2$ (0.425 eq.), THF, 0 to 55 °C, 12 h.

In order to establish the viability of tethered RCM route, self tethering of right hand allylic alcohol **2.57** was tried, giving the desired *bis*-THF diol **6.10** in a disappointing 3% yield (Scheme 6.6).[86] Diol **6.10** was not cleanly isolated and found to be contaminated with an unidentified product. A hydrolysed product **6.11** and the starting material **2.57** were isolated in 14% and 65% yields respectively. Due to time constraints, the tethering chemistry was not further investigated.

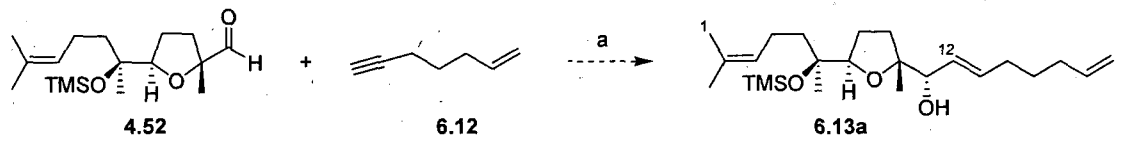


Scheme 6.6: Synthesis of silicon tethered diol **6.10**. Reagents and conditions: (a) $^iPr_2SiCl_2$ (0.5 eq.), imid. (5.0 eq.), CH_2Cl_2, rt, 15 h.

Due to failure in the synthesis of the C1-C12 allylic alcohol partner **6.2a**, an investigation for this approach was abandoned.

6.2 Tethered Relay Ring Closing Metathesis Route

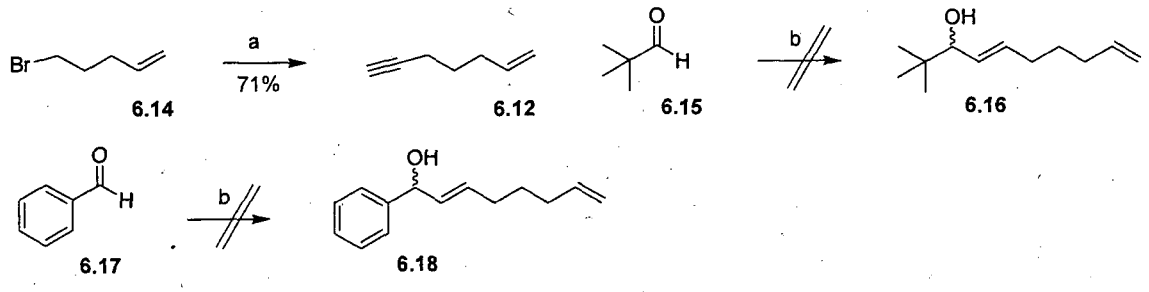
A synthetic plan for the coupling of key fragments of eurylene (**2.1**) using relay ring closing metathesis (RRCM) has been described in Chapter two (see Scheme 2.13). It was believed that the relatively slow rates of RCM for silicon tethered allylic alcohols might be overcome by using the RRCM strategy.[90] The right hand allylic alcohol **2.57** was readily synthesised from triol **2.38** (Scheme 6.1). Initial focus was to apply the hydroboration methodology to furnish the requisite vinyl zinc reagent and couple it with the left hand aldehyde **4.52** to afford allylic alcohol **6.13a** (Scheme 6.7).[147-149]



4.52 6.12 6.13a

Scheme 6.7: Proposed synthesis of allylic alcohol **6.13a**. Reagents and conditions: (a) cyclohexene, $BH_3.SMe_2$, Et_2Zn, chiral auxiliary **6.6**, hexane.

Enyne **6.12** was prepared in a moderate yield by treating bromopentene **6.14** with lithiumacetylene ethylenediamine complex in DMSO (Scheme 6.8).[150] Before the enyne **6.12** was added to aldehyde **4.52**, a model study was conducted. Treatment of trimethylacetaldehyde (**6.15**) and benzaldehyde (**6.17**) with alkyenyl zinc reagent prepared from enyne **6.12** did not afford the desired allylic alcohols **6.16** and **6.18** respectively.[148-149] As the addition of alkenyl zinc reagent to the model substrates **6.15** and **6.17** failed therefore this approach was not extended to the real substrate **4.52**.



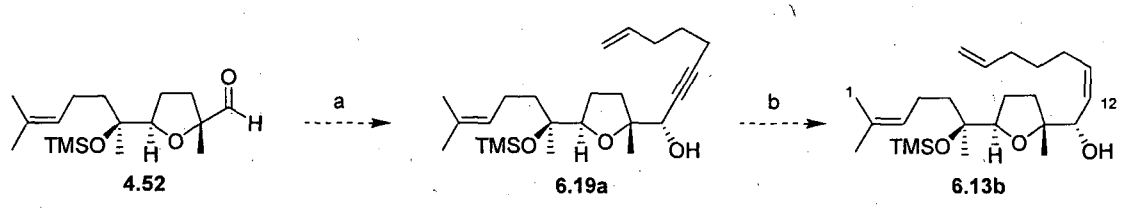
6.14 6.12 6.15 6.16

6.17 6.18

Scheme 6.8: Synthesis of enyne **6.12** and model study to investigate the hydroboration methodology. Reagents and conditions: (a) Lithiumacetylene ethylenediamine complex (1.5

eq.), DMSO, 0 °C to rt, 2 h; (b) cyclohexene (2.0 eq.), $BH_3.SMe_2$ (1.0 eq.), Et_2Zn (1.05 eq.), enyne **6.12** (1.0 eq.), chiral auxiliary **6.6** (0.1 eq.), hexane, 0 °C to rt, 4 h.

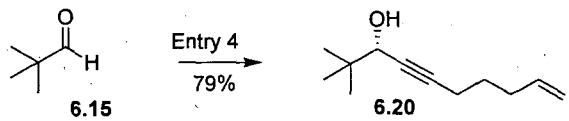
An alternative approach involved a stereoselective enyne addition of **6.12** to aldehyde **4.52**, followed by Lindlar reduction of the triple bond to afford the C1-C12 allylic alcohol **6.13b** (Scheme 6.9).[151,88]



4.52 6.19a 6.13b

Scheme 6.9: Proposed synthesis of allylic alcohol **6.13b**. Reagents and conditions: (a) $Zn(OTf)_2$, Et_3N, (+)-*N*-methylephedrine, enyne **6.12**, toluene; (b) Lindlar catalyst, quinoline, hexane, $H_{2(g)}$.

In a model study, treatment of trimethylacetaldehyde (**6.15**) with enyne **6.12** using Carreira's protocol furnished the propargylic alcohol **6.20** in a good yield.[151,152] An optimisation was carried out with different reaction conditions and the results are summarised (Table 6.1).

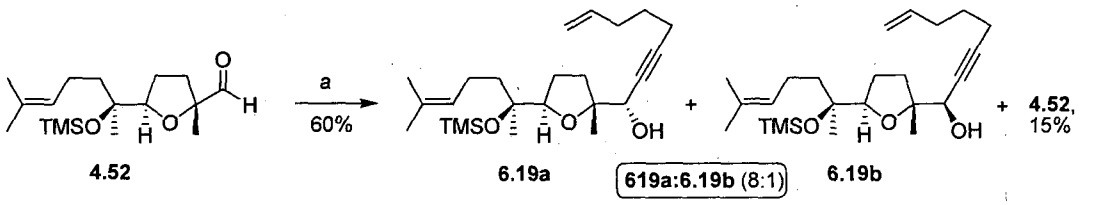


6.15 6.20

Entry*	**$Zn(OTf)_2$** (eq.)	**Et_3N** (eq.)	**(–)-*N*-methylephedrine** (eq.)	**Reaction*** (M conc.)	**Observation**
1.	0.2	0.5	0.2	0.97	Poor conversion by TLC, 5% product yield.
2.	0.2	0.5	0.2	No Solvent	No reaction by TLC.
3.	1.2	1.2	1.2	1.0	57% product yield.
4.	1.5	1.5	1.5	0.36	79% product yield.

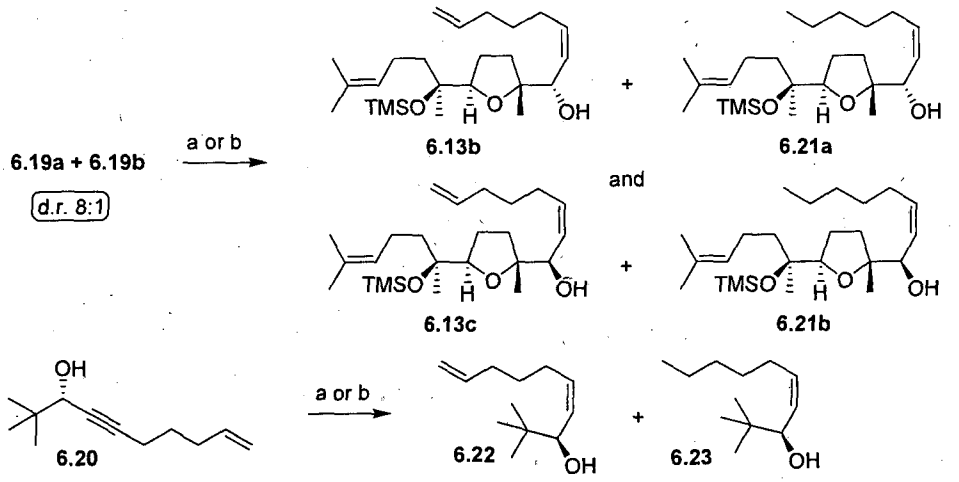
Table 6.1: Optimisation studies for the enyne **6.12** addition to aldehyde **6.15** using Carreira's protocol. *All reactions were conducted at 60 °C for 20 h using 1.2 eq. of enyne **6.12**.

After optimisation, aldehyde fragment **4.52** was treated with enyne **6.12** to afford the epimeric propargylic alcohols **6.19a,b** (d.r. 8:1) in 60% yield (Scheme 6.10). The reaction did not proceed to completion and starting aldehyde **4.52** was also recovered in 15% yield. The relative stereochemistry of the resultant propargylic alcohols **6.19a,b** was tentatively assigned based on literature data.[151,152] Unfortunately the epimeric precursors **6.19a,b** could not be separated by flash column chromatography.



Scheme 6.10: Synthesis of propargylic alcohols **6.19a,b**. Reagents and conditions: (a) $Zn(OTf)_2$ (1.2 eq.), Et_3N (1.2 eq.), (+)-*N*-methylephedrine (1.2 eq.), enyne **6. 12** (1.2 eq.), toluene, 60 °C, 20 h.

Lindlar reduction of propargylic alcohols **6.19a,b** proved to be unselective, resulting in partial reduction of the terminal double bond (Scheme 6.11).[88] The desired allylic alcohols **6.13b,c** could not be separated from the over reduced products **6.21a,b** by flash chromatography. Similar results were obtained using a model enyne **6.20**, with significant over reduction to give a mixture of **6.22** and **6.23**. Alternatively Lindlar catalyst was poisoned with $MnCl_2$ and used to induce the selective reduction.[153] Unfortunately it did not improve the reaction, and again over reduction was observed.

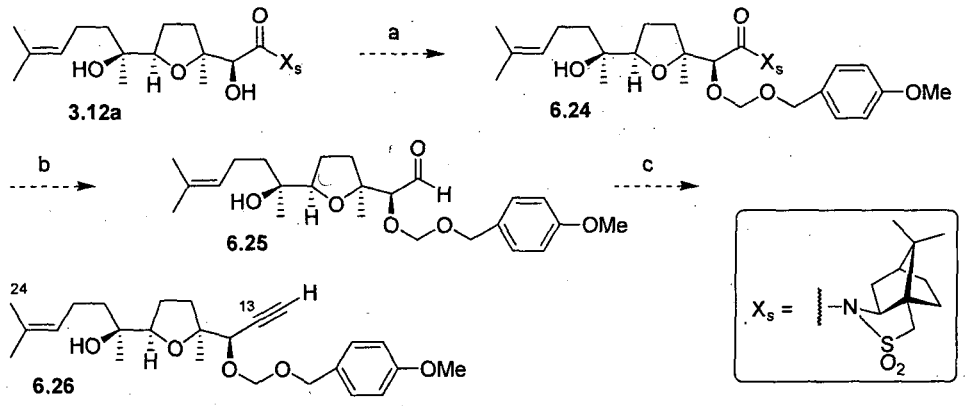


Scheme 6.11: Reductions of propargylic alcohols **6.19a,b** and **6.20**. Reagents and conditions: (a) Lindlar catalyst (0.05 eq.), quinoline (0.155 eq.), hexane, $H_{2(g)}$, rt, 30 min; (b) $MnCl_2$-Pd-$CaCO_3$ (0.05 eq.), quinoline (0.155 eq.), hexane, $H_{2(g)}$, rt, 15 min.

Unfortunately selective reduction of the triple bond to an alkene proved unsuccessful and due to time limitations, the tethered relay ring closing metathesis approach was abandoned.

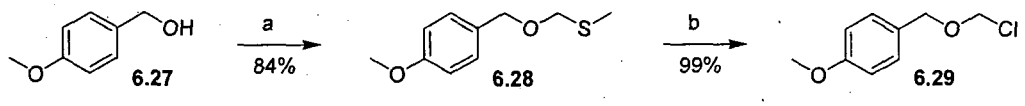
6.3 Alkyne - Aldehyde Coupling Strategy

During the course of the investigation into the relay ring closing metathesis strategy, it was found that enyne **6.12** could be added to the left hand *trans*-THF fragment **4.52** in a good yield and diastereoselectivity (see Scheme 6.10). Therefore it was decided to transform the *cis*-THF diol **3.12a** into the C13-C24 protected propargylic alcohol **6.26** and subsequently added to the C1-C12 aldehyde fragment **4.52** (Scheme 6.12).



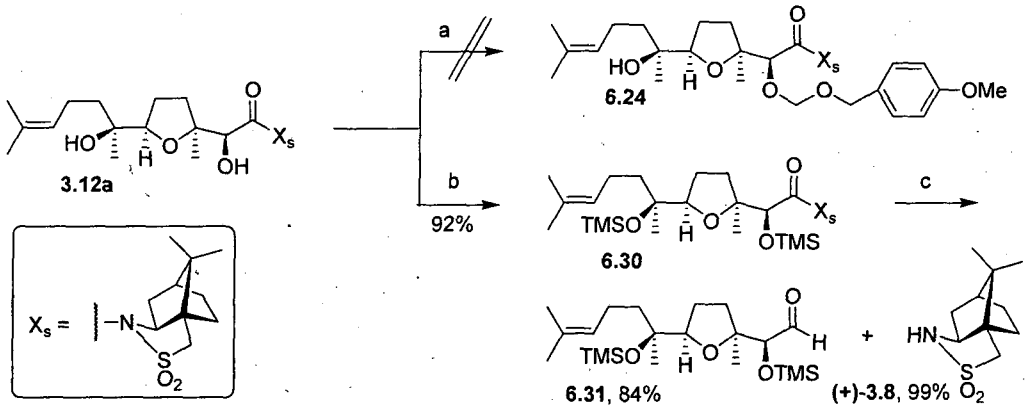
Scheme 6.12: Synthetic plan for C13-C24 right hand propargylic alcohol **6.26**. Reagents and conditions: (a) PMBMCl **6.29**, (^{i}Pr)$_2$EtN, CH_2Cl_2; (b) DIBAL-H, CH_2Cl_2, –78 °C; (c) phosphonate **6.33**, K_2CO_3, MeOH.

Initially we set out to protect the secondary alcohol of *cis*-THF diol **3.12a** as its *p*-methoxybenzyloxymethyl ether. PMBMCl **6.29** was synthesised by treating chloromethyl methyl sulfide with *p*-methoxybenzyl alcohol (**6.27**) to afford thioether **6.28** (Scheme 6.13).[154] Thioether **6.28** was treated with sulfuryl chloride to afford the required PMBMCl **6.29** in an excellent yield.[155]



Scheme 6.13: Preparation of *p*-methoxybenzylmethyl chloride (**6.29**). Reagents and conditions: (a) CH_3SCH_2Cl (1.0 eq.), NaH (2.0 eq.), NaI (1.0 eq.), DME, 0 °C to rt, 4.5 h; (b) SO_2Cl_2 (1.05 eq.), CH_2Cl_2, –78 °C, 30 min.

After preparation of the chloride **6.29**, selective protection of the secondary alcohol of diol **3.12a** was attempted without success (Scheme 6.14). Therefore both hydroxyl groups of *cis*-THF diol **3.12a** were protected as TMS ethers to afford THF product **6.30**. Subsequent reductive cleavage of the chiral auxiliary **(+)-3.8** afforded the aldehyde fragment **6.31** in good yield.

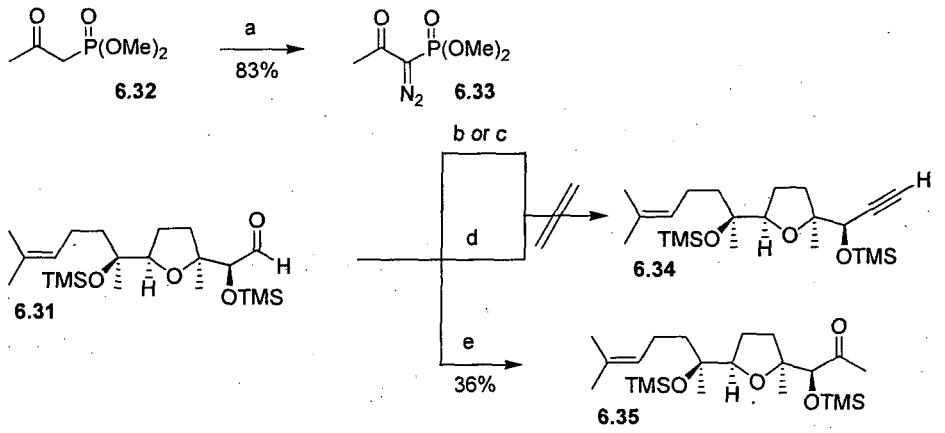


Scheme 6.14: Synthesis of *bis*-protected aldehyde **6.31**. Reagents and conditions: (a) PMBMCl **6.29** (1.2 eq.), $^{i}Pr_2EtN$ (2.2 eq.), CH_2Cl_2, rt, 8 h; (b) TMSCl (12.0 eq.), imid. (15.0 eq.), DMF, –5 °C, 45 min; (c) DIBAL-H (4.0 eq.), CH_2Cl_2, –78 °C, 2 h.

With aldehyde **6.31** in hand, a modified Bestmann-Ohira reagent **6.33** was employed to transform the aldehyde to alkyne **6.34**.[156,157] The reagent **6.33** was prepared in good yield by treating commercially available phosphonate **6.32** with tosyl azide (Scheme 6.15).[158]

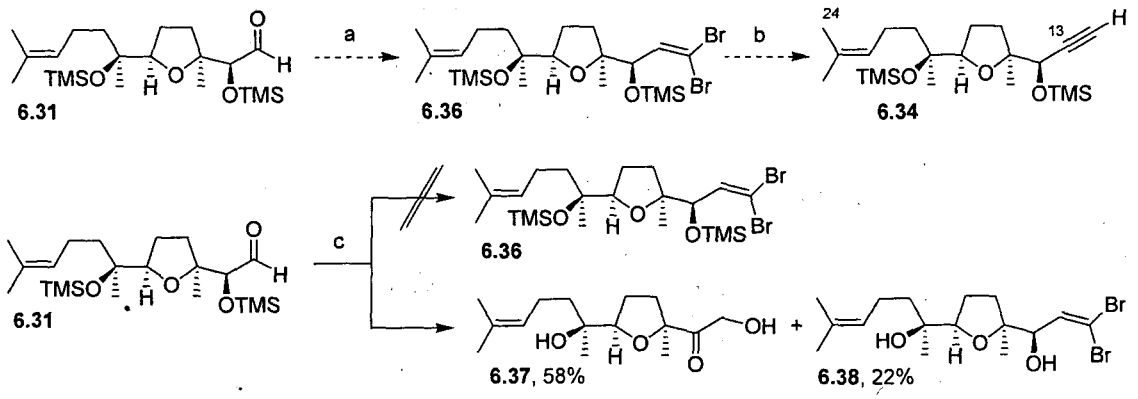
Initially when the modified Bestmann-Ohira reagent **6.33** was treated with aldehyde **6.31**, using the K_2CO_3/MeOH system, none of the desired alkyne product **6.34** was observed by crude ^{1}H NMR.[159] An unidentified crude mixture was obtained, showing deprotection of both hydroxyl groups. Changing the base to Cs_2CO_3/^{i}PrOH did not lead to any improvement.[158]

The phosphonate **6.33** was deacetylated using NaOMe and then treated with *bis*-protected aldehyde **6.31**. Unfortunately no conversion to the desired product was observed and the starting material was recovered. Finally, treatment of aldehyde **6.31** with $TMSCHN_2$ using LDA as a base afforded the rearranged ketone **6.35** (Scheme 6.15).[160]



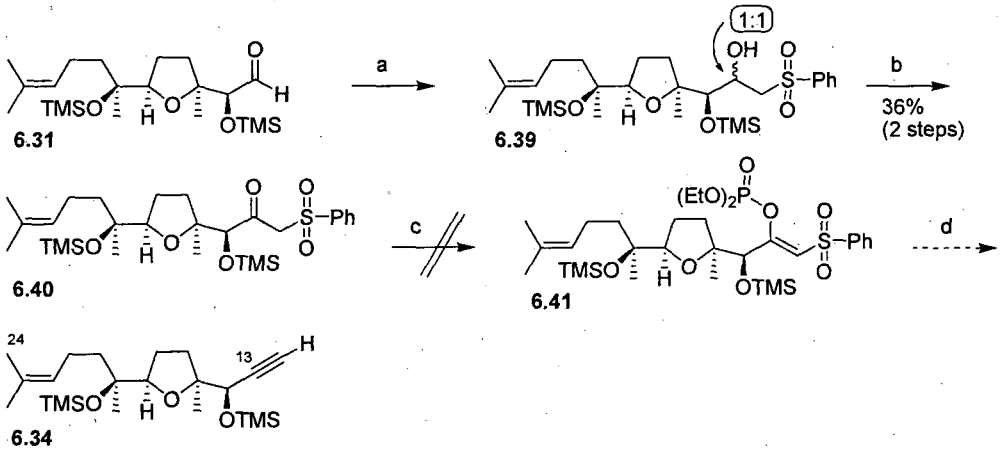
Scheme 6.15: Towards the synthesis of alkyne **6.34**. Reagents and conditions: (a) TsN_3 (1.10 eq.), NaH (1.10 eq.), THF, 0 °C, 1.15 h; (b) phosphonate **6.33** (2.0 eq.), K_2CO_3 (2.0 eq.), MeOH, 0 °C to rt, 5 h; (c) phosphonate **6.33** (2.0 eq.), Cs_2CO_3 (3.0 eq.), ^iPrOH, –40 to 0 °C, 12 h; (d) phosphonate **6.33** (4.0 eq.), NaOMe (3.5 eq.), THF, –78 °C to rt, 6 h; (e) TMSCHN (1.2 eq., 2.0 M in Et_2O), LDA (1.2 eq., 1.8 M in Et_2O), THF, –78 to –10 °C, 6 h.

As Bestmann-Ohira conditions and the $TMSCHN_2$ reagent failed to transform aldehyde **6.31** to alkyne **6.34**, a different approach was considered. The Corey-Fuchs reaction is a two step protocol to carry out the same transformation.[161-162] In this pathway, treatment of an aldehyde with CBr_4/PPh_3 affords a dibromoolefin, which subsequently releases an alkyne on treatment with *n*-BuLi (Scheme 6.16). Treatment of aldehyde **6.31** with CBr_4/PPh_3, afforded an unexpected rearranged ketone **6.37** (58%) and deprotected dibromoolefin **6.38** (22%), instead of the desired *bis*-protected dibromoolefin **6.36**. Due to the difficulties associated with the formation of required dibromoolefin **6.36**, this route was abandoned.



Scheme 6.16: Attempted Corey-Fuchs protocol for the synthesis of alkyne **6.34**. Reagents and conditions: (a) Zn dust, CBr_4, PPh_3, CH_2Cl_2; (b) *n*-BuLi, THF, aq. work-up; (c) Zn dust (6 eq.), CBr_4 (6 eq.), PPh_3 (6 eq.), CH_2Cl_2, –78 °C to rt, 2 h.

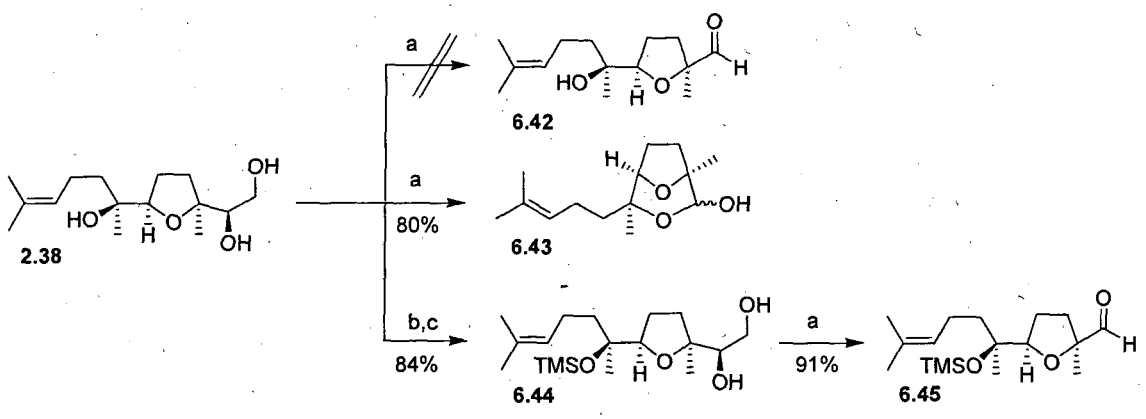
The synthesis of alkyne **6.34**, using conventional methods had not been successful, therefore a different strategy was explored to prepare the right hand C13-C24 alkyne fragment. Treatment of *bis*-protected aldehyde **6.31** with lithiated methyl phenyl sulfone afforded the sulfone **6.39**, which was subsequently oxidised to ketosulfone **6.40** in a moderate yield (Scheme 6.17).[163,136] Phosphonation of the ketosulfone **6.40** failed to afford the desired phosphonate **6.41**[164] and due to time constraints, this route was not further investigated.



Scheme 6.17: Synthesis of alkyne **6.34**. Reagents and conditions: (a) CH_3SO_2Ph (1.10 eq.), n-BuLi (1.10 eq., 2.4 M in hexanes), THF, –78 to –10 °C, 1.5 h; (b) DMP (1.2 eq.), $NaHCO_3$ (0.2 eq.), CH_2Cl_2, rt, 4 h; (c) $(EtO)_2POCl$ (1.15 eq.), NaH (1.20 eq.), THF, rt, 4 h; (d) SmI_2, THF.

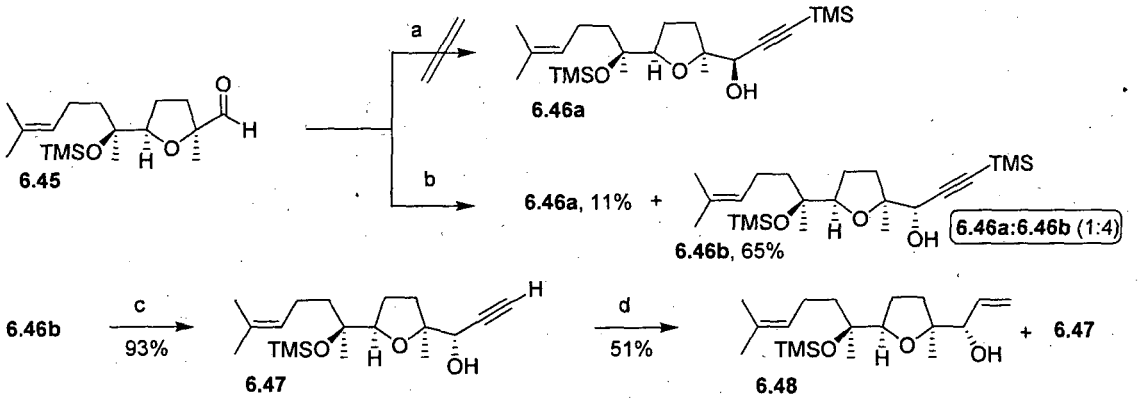
A number of reported routes were tried, however the transformation of aldehyde **6.31** to alkyne **6.34** proved unsuccessful. Finally an oxidative cleavage of the triol **2.38** to aldehyde **6.45** was performed, followed by TMS acetylene addition to afford the propargylic alcohol **6.46a,b** (Schemes 6.18 and 6.19). This approach was unattractive as it involved destroying a chiral centre of the triol **2.38**, which required re-establishment. However, the objective of this route was to investigate the coupling of both fragments of eurylene (**2.1**) and explore the subsequent steps to the natural product.

Oxidative cleavage of triol **2.38**, on treatment with $NaIO_4$ resulted in bicyclic adduct **6.43**, instead of the desired aldehyde **6.42** (Scheme 6.18).[165] To avoid formation of this bicyclic substrate **6.43**, the tertiary hydroxyl of triol **2.38** was protected selectively as its TMS ether and the resultant diol **6.44** was oxidatively cleaved to afford the desired aldehyde **6.45** in good yield.



Scheme 6.18: Synthesis of aldehyde **6.45**. Reagents and conditions: (a) $NaIO_4$ (1.25 eq.), acetone:H_2O (2:1), rt, 4 h; (b) TMSCl (10.0 eq.), imid. (12.0 eq.), DMF, –10 to 15 °C, 2 h; (c) K_2CO_3 (0.25 eq.), MeOH, –10 °C to rt, 10 h.

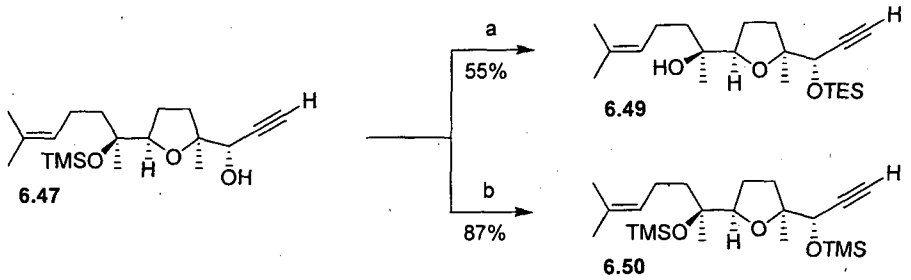
Selective addition of TMS acetylene to aldehyde **6.45** using Carriera's conditions failed to afford the desired enyne **6.46a** (Scheme 6.19).[151,152] Alternatively lithiated TMS acetylene was added to the aldehyde **6.45** to yield the enyne **6.46a,b** (d.r. 1:4 by ^1H NMR of the crude product). Major epimer **6.46a** was separated from the epimeric mixture with **6.46b**, resulting in a 65% yield of the pure epimer **6.46b** and 11% isolated yield of the minor epimer **6.46a**. The minor isomer **6.46a** was contaminated with an unidentified product. The rest of the synthesis was carried out with optically pure enyne **6.46b**. To establish relative stereochemistry of epimers **6.46a,b**, deprotection of the TMS alkyne of epimeric alcohol **6.46b**, followed by Lindlar reduction afforded an inseparable mixture of allylic alcohol **6.48** and starting alkyne **6.47**.[88] The relative stereochemistry of the allylic alcohol **6.48** was tentatively assigned by comparing with the previously prepared optically enriched allylic alcohol **2.57** (see Scheme 6.1).



Scheme 6.19: Synthesis of alkyne **6.47**. Reagents and conditions: (a) $Zn(OTf)_2$ (1.2 eq.), Et_3N (1.2 eq.), (–)-*N*-methylephedrine (1.2 eq.), TMSC≡CH (1.2 eq.), toluene, 60 °C, 20 h; (b)

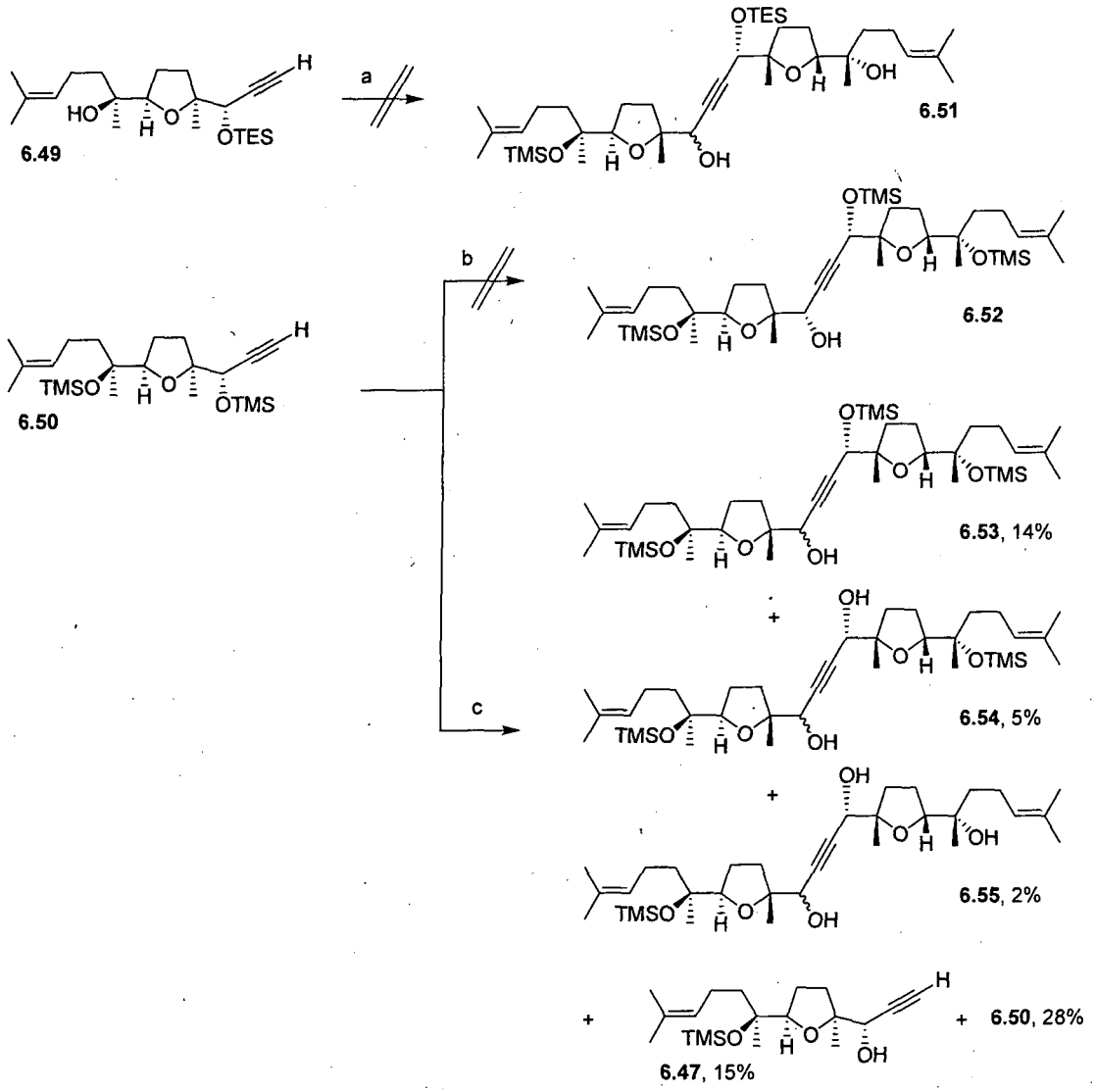
TMSC≡CH (1.5 eq.), n-BuLi (1.5 eq., 2.3 M in hexanes), –78 to 0 °C, 7.5 h; (c) K_2CO_3 (0.50 eq.), MeOH, rt, 10 h; (d) Lindlar catalyst (0.03 eq.), quinoline (0.02 eq.), hexane, $H_{2(g)}$, rt, 25 min.

Before coupling the right hand alkyne fragment **6.47** with left hand aldehyde fragment **4.52**, the secondary hydroxyl group was protected as TES ether **6.49** but this resulted in the deprotection of the tertiary hydroxyl group (Scheme 6.20). Alternatively the secondary hydroxyl was protected as a TMS ether to afford the alkyne **6.50** in good yield.



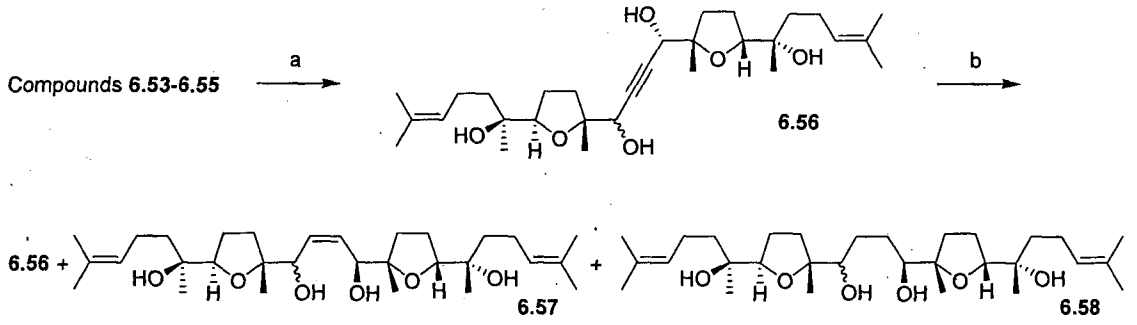
Scheme 6.20: Synthesis of alkynes **6.49** and **6.50**. Reagents and conditions: (a) TESCl (5.0 eq.), imid. (5.0 eq.), CH_2Cl_2, –10 to 15 °C, 2 h; (b) TMSCl (4.0 eq.), imid. (4.0 eq.), DMF, –5 to 12 °C, 1.5 h.

Coupling of alkyne **6.49** with aldehyde **4.52** failed to afford the required *bis*-THF adduct **6.51** and starting materials were recovered (Scheme 6.21). Alkyne **6.50** also failed to couple with aldehyde **4.52**, using Carriera's procedure to afford the desired *bis*-THF product **6.52**.[151-152] Treatment of lithiated alkyne **6.50** with aldehyde **4.52** afforded *bis*-THF products **6.53-6.55**, along with the deprotected propargylic alcohol **6.47** and starting alkyne **6.50**. As small quantities of compounds **6.53-6.55** were obtained, the characterisation was carried out only by ^{1}H NMR and mass spectroscopic analysis.



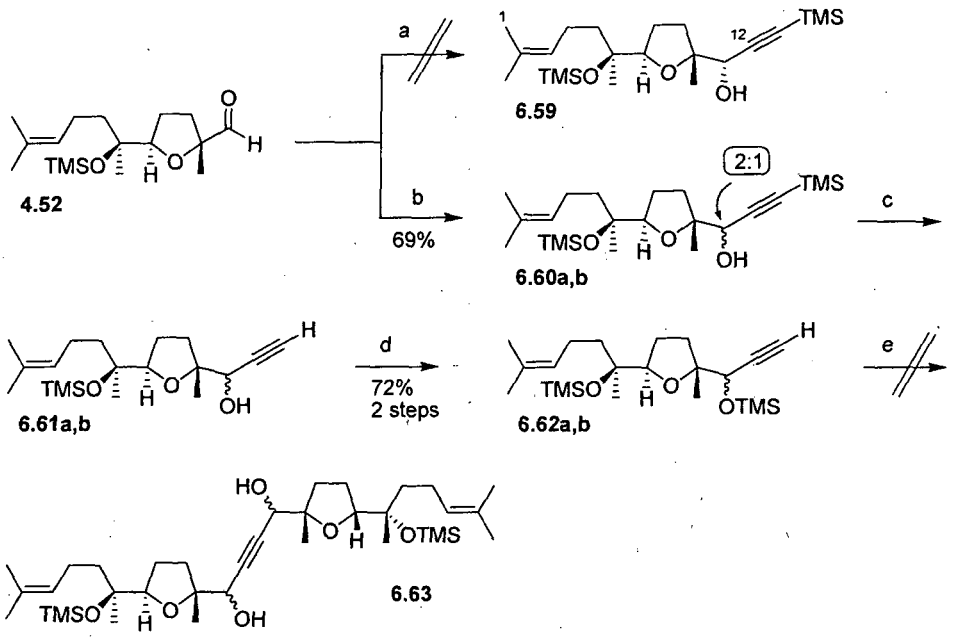
Scheme 6.21: Investigation of enyne-aldehyde fragments coupling. Reagents and conditions: (a) aldehyde **4.52** (1.0 eq.), *n*-BuLi (1.5 eq., 2.3 M in hexanes), THF, –78 °C to rt, 5 h; (b) $Zn(OTf)_2$ (1.2 eq.), Et_3N (1.2 eq.), (+)-*N*-methylephedrine (1.2 eq.), aldehyde **4.52** (1.2 eq.), toluene, 60 °C, 20 h; (c) aldehyde **4.52** (1.02 eq.), *n*-BuLi (2.0 eq., 2.3 M in hexanes), THF, –78 °C to rt, 4.5 h.

To allow investigation of the selective reduction of the triple bond to olefin, *bis*-THF products **6.53-6.55** were combined and subjected to mildly acidic conditions to afford tetrol **6.56** (Scheme 6.22). Tetraol **6.56** was treated with nitrobenzenesulfonyl hydrazide (NBSH) and Et_3N in a NMR tube, using CD_2Cl_2 as the solvent to investigate the reduction.[91,166] The ^1H NMR was taken at different time intervals and the reaction followed. Unfortunately a mixture of products **6.56-6.58** was obtained. Due to time constraints, the alkyne-aldehyde fragments coupling and selective reduction of the triple bond could not be investigated further.



Scheme 6.22: Investigation for the selective reduction of the triple bond. Reagents and conditions: (a) 1N HCl, THF, rt, 30 min; (b) NBSH (3.0 eq.), Et_3N (3.0 eq.), CD_2Cl_2, rt to 30 °C, 20 h.

As the right hand alkyne fragment failed to couple with the left hand aldehyde fragment, the chemistry was reversed to add the left hand alkyne to the right hand aldehyde fragment. Treatment of TMS acetylene with *trans*-THF aldehyde fragment **4.52** using Carriera's protocol failed to afford the desired TMS protected C1-C12 enyne **6.59** (Scheme 6.23).[151,152] However, treatment of lithiated TMS acetylene with the aldehyde **4.52** yielded the enynes **6.60a,b** as an epimeric mixture (d.r. 2:1). Due to time limitations, the relative stereochemistry of the resultant epimeric alcohols **6.60a,b** was not determined and investigation of coupling with the right hand aldehyde fragment **6.45** was continued. Also characterisation for the compounds in this scheme was carried out by ^1H NMR and mass analysis only. Deprotection of the TMS group from the alkyne of the epimers **6.60a,b** afforded the epimeric mixture **6.61a,b**, this was protected at its secondary alcohol to afford the C1-C12 alkyne fragment **6.62a,b**. Treatment of alkynes **6.62a,b** with the right hand aldehyde **6.45** failed to afford the *bis*-THF diols **6.63** and starting materials were recovered. Due to time constraints, the alkyne-aldehyde fragments coupling could not be investigated further.



Scheme 6.23: Investigation of enyne-aldehyde fragments coupling. Reagents and conditions: (a) $Zn(OTf)_2$ (1.5 eq.), Et_3N (1.5 eq.), (+)-*N*-methylephedrine (1.5 eq.), TMSC≡CH (1.2 eq.), toluene, 60 °C, 15 h; (b) TMSC≡CH (5.0 eq.), *n*-BuLi (5.0 eq., 2.3 M in hexanes), –78 °C to rt, 5 h; (c) K_2CO_3 (1.0 eq.), MeOH, rt, 7 h; (d) TMSCl (4.0 eq.), imid. (4.0 eq.), DMF, –5 to 10 °C, 3 h; (e) aldehyde **6.45** (1.05 eq.), *n*-BuLi (1.10 eq., 2.4 M in hexanes), THF, –60 °C to rt, 5 h.

6.4 Conclusions

A number of synthetic methodologies were investigated to couple the right hand *cis*-THF and the left hand *trans*-THF fragments of eurylene (**2.1**) in order to accomplish a total synthesis. Significant issues included the conversion of aldehyde **6.31** to a suitable alkyne fragment, and achieving selective alkynyl additions to either left or right hand fragments. Simple alkynyl anions were coupled effectively to both fragments, but without selectivity, although this did allow the carbon skeleton of eurylene (**2.1**) to be assembled. Future efforts will focus on the asymmetric addition of carbanions to the left hand aldehyde fragment **4.52**.

Chapter 7 Concluding Remarks and Future Work

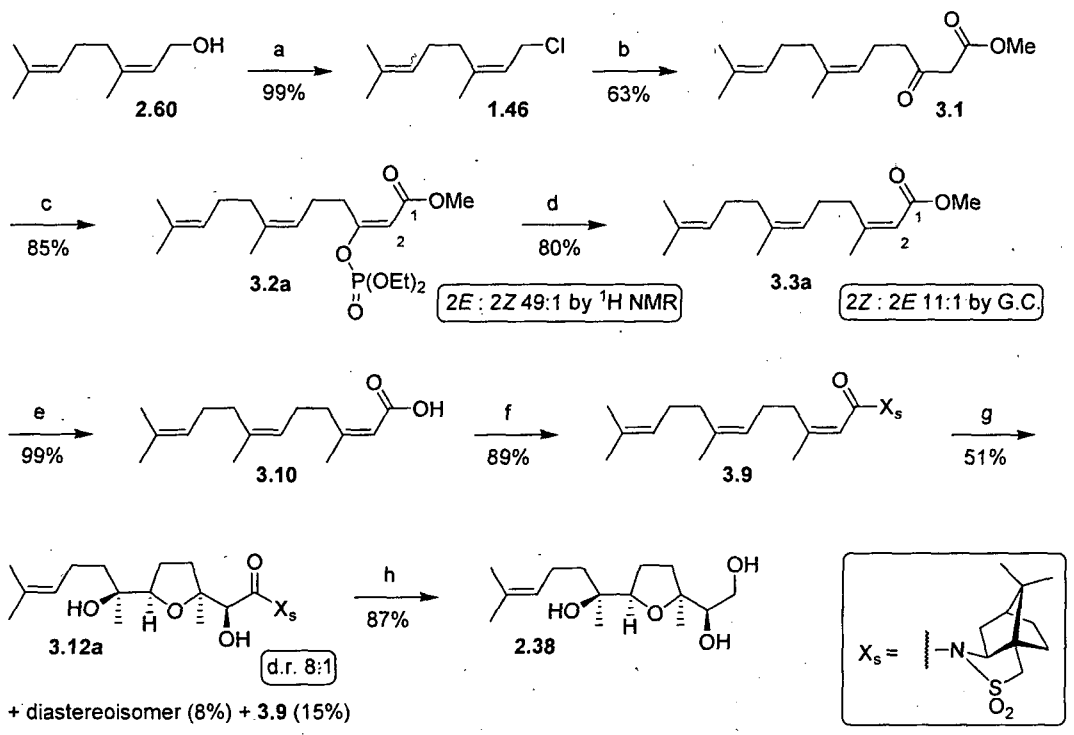
A brief review of synthetic routes of 2,5-disubstituted THF rings by metal promoted oxidative cyclisations of 1,5-dienes has been given. Previous syntheses of the target molecule, eurylene (**2.1**) have also been summarised.

A short and efficient stereocontrolled formal synthesis of right hand triol fragment **2.38** of eurylene (**2.1**) was achieved in 8 steps (19.5% overall yield, Scheme 7.1) using permanganate promoted oxidative cyclisation of the readily accessible triene **3.9**. A chiral auxiliary, (2*S*)-10,2-camphorsultam (**(+)-3.8**) was successfully applied to influence the asymmetric induction and an excellent level of stereoselectivity was obtained (see Scheme 3.7).

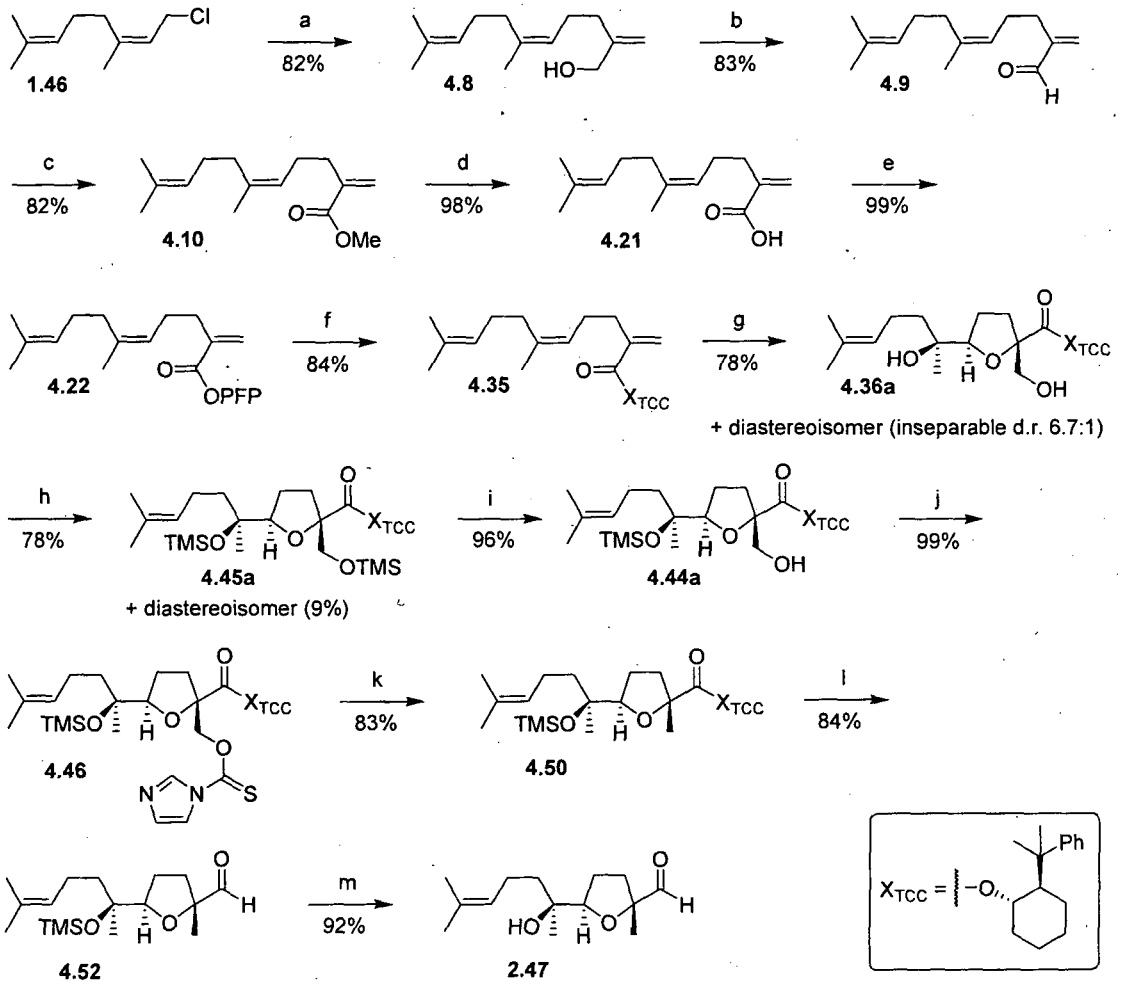
An efficient stereocontrolled synthesis of left hand aldehyde fragment **2.47** of eurylene (**2.1**) was achieved in 13 linear steps (16.9% overall yield, Scheme 7.2) using permanganate mediated oxidative cyclisation of readily accessible 1,5,9-triene **4.35**. The use of (2*R*)-10,2-camphorsultam (**(–)-3.8**) afforded the required THF diol **4.13** as a single diastereoisomer but in a disappointing low yield. The effect of different chiral auxiliaries on the stereoselective oxidative cyclisation of 1,5,9-triene was investigated and TCC **(+)-4.33** was found to afford the best combination of yield and diastereoselectivity (see Scheme 4.13).

A key aldehyde fragment **5.25** of (+)-linalool oxide (**5.27**) was stereoselectively synthesised by permanganate mediated oxidative cyclisation of 1,5-diene **5.10** in 13 steps, overall yield 8.8%. Due to time constraints, the total synthesis of (+)-linalool oxide (**5.27**) was not accomplished and an alternative approach is proposed to reduce the number of reaction steps (see Scheme 5.9).

A number of synthetic methodologies were tried to investigate the coupling of the right hand *cis*-THF and left hand *trans*-THF fragments of eurylene (**2.1**) to accomplish a total synthesis. Unfortunately attempted procedures failed to complete a total synthesis, however investigations have led to a better understanding of the issues that need to be overcome to couple the two fragments.

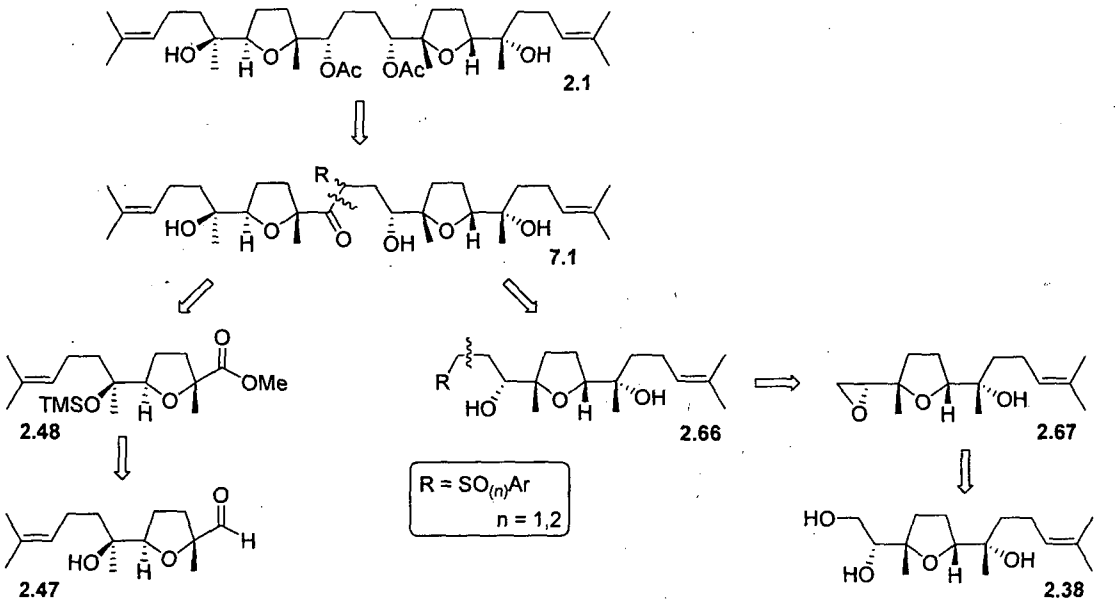


Scheme 7.1: Formal synthesis of right hand triol fragment **2.38** of eurylene. Reagents and conditions: (a) MsCl (1.15 eq.), LiCl (1.1 eq.), 2,6-lutidine (1.2 eq.), DMF, 0 °C to rt, 4 h; (b) methyl acetoacetate (1.05 eq.), NaH (1.05 eq.), *n*-BuLi (1.05 eq.), THF, 0 °C to rt, 55 min; (c) $(EtO)_2POCl$ (1.12 eq.), DMAP (0.11 eq.), Et_3N (1.12 eq.), DMPU, –20 °C to rt, 17 h; (d) CuI (3.0 eq.), MeLi (3.0 eq.), MeMgCl (5.0 eq.), THF, –35 to –5 °C, 2.25 h; (e) NaOH (6.5 eq.), $NaHCO_3$ (0.5 eq.), MeOH:H_2O (1:1.7), reflux, 6 h; (f) $(COCl)_2$ (5.0 eq.), DMF (1.0 eq.), *n*-hexane, rt 2 h then (2*S*)-10,2-camphorsultam (**(+)-3.8**, 1.1 eq.), NaH (1.15 eq.), toluene, 0 °C to rt, 9 h; (g) $NaMnO_4$ (1.5 eq., 0.4 M aq.), AcOH (3.5 eq.), phosphate buffer (KH_2PO_4:NaH_2PO_4 8:2), acetone, –21 to –7 °C, 70 min; (h) $NaBH_4$ (1.15 eq.), THF:H_2O (25:1), –5 °C, 4 h.



Scheme 7.2: Formal synthesis of left hand aldehyde fragment **2.47** of eurylene. Reagents and conditions: (a) $CH_3C(=CH_2)CH_2OH$ (2.3 eq.), *n*-BuLi (4.0 eq., 2.3 M in hexanes), TMEDA (4.0 eq.), Et_2O, –78 °C to rt, 24 h; (b) MnO_2 (17 eq.), *n*-hexane, 0 °C to rt, 1.5 h; (c) NaCN (3.5 eq.), AcOH (2.5 eq.), MnO_2 (10 eq.), MeOH, rt, 18 h; (d) NaOH (6.5 eq.), $NaHCO_3$ (0.5 eq.), MeOH:H_2O (5:4), reflux, 9 h; (e) C_6F_5OH (1.15 eq.), DCC (1.14 eq.), EtOAc, rt, 21 h; (f) chiral auxiliary **(+)-4.33** (1.05 eq.), NaHMDS (1.10 eq.), THF, –20 to 5 °C, 1.5 h; (g) $NaMnO_4$ (1.5 eq., 0.4 M aq.), AcOH (3.5 eq.), phosphate buffer (KH_2PO_4:NaH_2PO_4 8:2), acetone, –20 to –8 °C, 40 min; (h) TMSCl (10.0 eq.), imid. (12.0 eq.), DMF, –5 to 0 °C, 30 min; (i) K_2CO_3 (0.4 eq.), MeOH, –10 to 10 °C, 2.5 h; (j) $imid_2(C=S)$ (3.0 eq.), DMAP (0.3 eq.), CH_2Cl_2, rt, 8 h; (k) TTMSS (6.5 eq.), AIBN (0.5 eq.), toluene, 85 °C, 1.25 h; (l) DIBAL-H (4.0 eq.), CH_2Cl_2, –78 °C, 2 h; (m) HCl (1 N aq.), THF, rt, 30 min.

The future work includes the coupling of right hand *cis*-THF fragment with the left hand *trans*-THF fragment of eurylene (**2.1**), using a carbanion addition approach followed by the reductive cleavage of sulfur containing species (See scheme 2.15).[92] Alternatively addition of the lithio-anion of *cis*-THF product **2.66** to the *trans*-THF ester **2.48** would afford the *bis*-THF ketone **7.1** (Scheme 7.3). Reductive cleavage of sulfur species, followed by selective reduction of the ketone **7.1** and acetylation of secondary alcohols would accomplish a stereoselective synthesis of eurylene (**2.1**).[163,167,168]



Scheme 7.3: Future work towards a synthesis of eurylene (**2.1**).

Chapter 8 Experimental

8.1 General Procedures

All air/ moisture sensitive reactions were carried out under an inert atmosphere, in oven dried glassware. The solvents THF and Et_2O (from Na/benzophenone) and CH_2Cl_2 (from CaH_2) were distilled before use, and where appropriate, other reagents and solvents were purified by standard techniques.[97] TLC was performed on aluminium-precoated plates coated with silica gel 60 with an F_{254} indicator; visualised under UV light (254 nm) and/or by staining with $KMnO_4$ (10% aq.). Flash column chromatography was performed with Merck Kieselgel 60 silica gel.

Fourier-transform infrared (FT-IR) spectra are reported in wavenumbers (cm^{-1}) and were collected on a Nicolet 380 fitted with a Diamond platform, as solids or neat liquids. The abbreviations s (strong), m (medium), w (weak) and br (broad) are used when reporting the spectra.

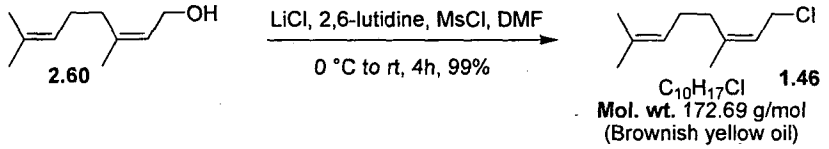
^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solution using a Bruker AC300 or and AV300 (300 and 75 MHz respectively) or on a Bruker DPX400 (400 and 100 MHz respectively). ^{19}F and ^{31}P NMR spectra were recorded in $CDCl_3$ solution on a Bruker AV300 (282 and 121 MHz respectively). Chemical shifts are reported in δ units using $CHCl_3$ as an internal standard (δ 7.27 ppm ^1H and δ 77.00 ppm ^{13}C). Coupling 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), sxt (sextet), br (broad), and m (multiplet).

Melting points were obtained using a Gallenkamp Electrothermal apparatus and are uncorrected. Optical rotations were measured using PolAAr 2001 polarimeter with 589 nm light source. Low-resolution mass spectra were obtained on a Fisons VG platform single quadrapole mass spectrometer in either chemical ionisation or electron impact ionisation mode or a Micromass platform mass analyser with an electrospray ion source. Enantiomeric excesses were determined by chiral HPLC analysis, performed on a Hewlett-Packard 1090 series II HPLC using a Chiralcel-OJ column (Daicell Chemical Industries, Ltd.), eluting with IPA/hexane. The phosphate buffer solution used in the

aqueous permanganate promoted oxidative cyclisations was an aqueous 8:2 mixture of 1/15 M KH_2PO_4 and 1/15 M NaH_2PO_4 at pH 6.5. For the ease of retrieval of information, the experimental details are arranged as the synthesis of *cis*-THF triol **2.38**, then *trans*-THF aldehyde **2.47**, followed by the experimental details of other reactions.

8.2 Experimental Details

(2*Z*)-1-Chloro-3,7-dimethylocta-2,6-diene (1.46)



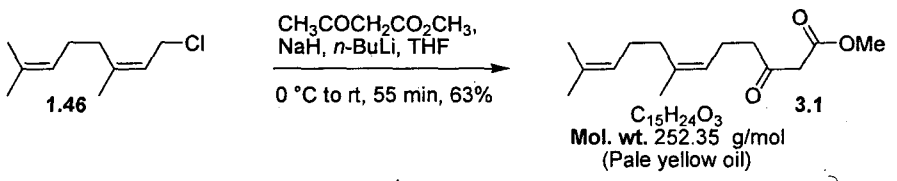
2.60

$C_{10}H_{17}Cl$ **1.46**
Mol. wt. 172.69 g/mol
(Brownish yellow oil)

To a solution of nerol (**2.60**, 25.0 g, 157 mmol) in 2,6-lutidine (22.0 mL, 188 mmol) was added a solution of LiCl (7.33 g, 173 mmol) dissolved in dry DMF (130 mL). The mixture was cooled to 0 °C and MsCl (14.0 mL, 179 mmol) was added dropwise to the reaction mixture. The reaction was allowed to warm to room temperature and the resultant yellow coloured mixture was stirred for 4 hours, at which the reaction mixture was quenched by dissolving in Et_2O (150 mL) and washing with water (3 x 250 mL), HCl (2 N, 2 x 50 mL), brine (50 mL) and sat. aq. $NaHCO_3$ (40 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude product **1.46** as a brownish yellow oil (26.9 g, 156 mmol, 99%). The spectroscopic data was in agreement with the literature.[94] The crude material was used in the next step without purification.

FT-IR ν_{max} (neat)	2968 (m), 2930 (m), 2859 (w), 1661(w), 1447 (s), 734 (s) cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	δ 5.46 (1H, t, J = 8.1 Hz, =C**H**CH_2Cl), 5.12 (1H, m, =C**H**CH_2), 4.09 (2H, d, J = 8.1 Hz, C**H**$_2$Cl), 2.13 (4H, br, 2 x C**H**$_2$), 1.78 (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 142.68 (CH_3**C**), 132.36 ((CH_3)$_2$**C**), 123.49 (=**C**HCH_2Cl), 121.17 (=**C**HCH_2), 40.94 (**C**H$_2$Cl), 31.90 (**C**H$_2$CCH_3), 26.49 (**C**H$_2$CH_2), 25.65 (CH_3), 23.45 (**C**H$_3$), 17.65 (**C**H$_3$) ppm.
LRMS (EI) m/z	172 (M^+, 1.2%), 136 (43%), 121 (34%), 93 (78%), 69 (100%).

Methyl (6*Z*)-7,11-dimethyl-3-oxo-6,10-dodecadienoate (3.1)

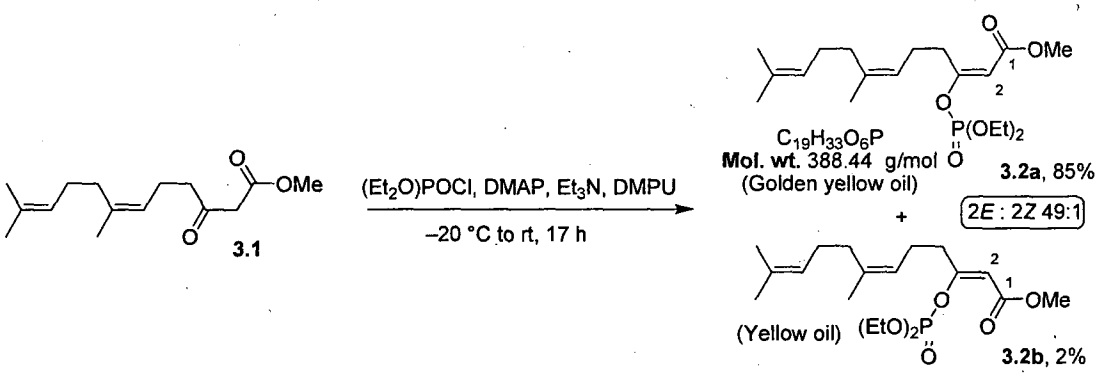


Following the procedure reported by Weiler *et al.*,[37] to an ice-cooled suspension of NaH (1.22 g, 30.4 mmol) in dry THF (30 mL) was added dropwise methyl acetoacetate (3.28 mL, 30.4 mmol). After 10 minutes, *n*-BuLi (16.0 mL, 1.9 M in hexanes, 30.4 mmol) was added and the mixture was stirred for a further 15 min. A solution of neryl chloride (**1.46**, 5.0 g, 29.0 mmol) in dry THF (5 mL) was added to the reaction and the orange mixture was allowed to warm to room temperature. After 30 min a solution of HCl (2N, 40 mL) and Et_2O (50 mL) was added. The aqueous phase was extracted with Et_2O (3 x 50 mL). The organic phases were combined, washed with water until neutral, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude as a golden yellow oil (6.34 g). Purification by column chromatography (SiO_2 eluting with Et_2O/hexane (5 to 15%)) gave the title *β*-ketoester **3.1** as a pale yellow oil (4.57 g, 18.1 mmol, 63%).

FT-IR ν_{max} (neat)	2962 (m), 2915 (m), 2856 (w), 1747 (s), 1717 (s), 1436 (m), 1237 (m) cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	δ 5.10-4.99 (2H, m, 2 x =C**H**CH_2), 3.74 (3H, s, O**CH$_3$**), 3.44 (2H, s, **CH$_2$**$COOCH_3$), 2.56 (2H, t, *J* = 7.4 Hz, **CH$_2$**CO), 2.29 (2H, q, *J* = 7.4 Hz, **CH$_2$**CH_2CO), 2.05-2.04 (4H, m, 2 x **CH$_2$**), 1.69 (6H, s, 2 x **CH$_3$**), 1.61 (3H, s, **CH$_3$**) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 202.31 (**C**OCH_2), 167.58 (**C**$OOCH_3$), 136.89 (CH_3**C**), 131.71 ($(CH_3)_2$**C**), 124.09 ($(CH_3)_2C$=**C**H), 122.84 (CH_3C=**C**H), 52.28 ($COOCH_3$), 49.08 (**C**H_2COOCH_3), 43.29 (**C**H_2COCH_2), 31.86 (**C**H_2CCH_3), 26.46 (**C**H_2CH_2CO), 25.68 (**C**H_2CH_2), 23.32 (**C**H_3), 21.97 (**C**H_3), 17.62 (**C**H_3) ppm.
LRMS (ES^+) m/z	275 (100%, $[M+Na]^+$), 527 (40%, $[2M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 275.1617; Found: 275.1617 ($[M+Na]^+$).

Methyl (2*E*, 6*Z*)-3-[(diethoxyphosphoryl)oxy]-7,11-dimethyl-2,6,10-dodecatrienoate (3.2a);

Methyl (2*Z*, 6*Z*)-3-[(diethoxyphosphoryl)oxy]-7,11-dimethyl-2,6,10-dodecatrienoate (3.2b)



To an ice-cooled solution of DMAP (240 mg, 1.96 mmol) and Et_3N (2.78 mL, 19.9 mmol) in DMPU (35 mL) was added a solution of β-keto ester **3.1** (4.5 g, 17.8 mmol) in DMPU (5 mL). After 1 hour, the mixture was cooled to –20 °C and $(EtO)_2POCl$ (2.98 mL, 19.9 mmol) was added dropwise (**Note**: A strong magnetic stirrer was required as the reaction mixture became viscous after the addition of $(EtO)_2POCl$). The reaction mixture was allowed to warm to room temperature and stirred for 16 hours. The mixture was diluted with Et_2O (100 mL) and acidified with HCl (2 N, 40 mL). The aqueous phase was extracted with Et_2O (2 x 100 mL) and the combined organic phases were washed with sat. aq. $CuSO_4$ solution (2 x 25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an orange oil as crude product (6.87 g, isomeric ratio 2*E*:2*Z* ~49:1 by crude ^{1}H NMR). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (10 to 30%)) afforded the title 2*E* isomer **3.2a** as a bright yellow oil (5.92 g, 15.22 mmol, 85%) followed by 2*Z*-isomer **3.2b** as a yellow oil (134 mg, 0.35 mmol, 2%). Spectroscopic data was in agreement with the literature.[37]

Spectroscopic data for **3.2a**:

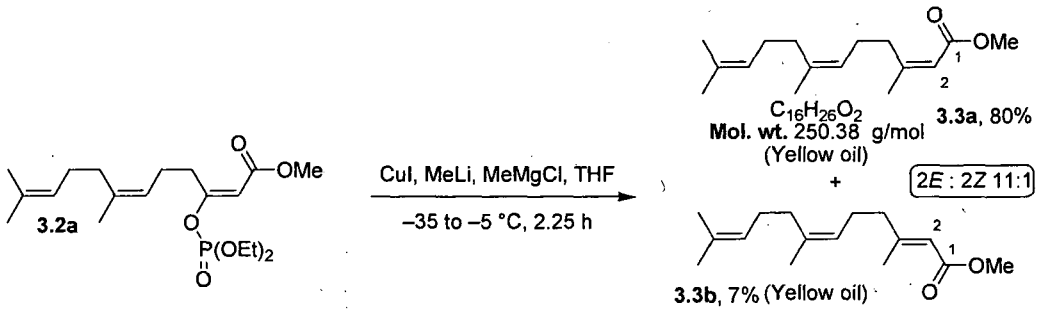
FT-IR ν_{max} (neat)	2965 (m), 2913 (m), 2857 (w), 1721 (s), 1643 (s), 1437 (w), 1030 (s) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$)	δ 5.86 (1H, s, =C**H**COO), 5.17-5.12 (2H, m, 2 x =C**H**CH_2), 4.18 (4H, quin, *J* = 7.4 Hz, POC**H**$_2$), 3.69 (3H, s, OC**H**$_3$), 2.82 (2H, t, *J* = 7.4 Hz, C**H**$_2$), 2.28 (2H, q, *J* = 7.4 Hz, C**H**$_2$), 2.04 (4H, 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, $POCH_2C\mathbf{H_3}$) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 166.56 ($\mathbf{C}OOCH_3$), 166.48 ($\mathbf{C}OP$), 136.63 ($CH_3\mathbf{C}$), 131.55 ($(CH_3)_2\mathbf{C}$), 124.22 ($(CH_3)_2C{=}\mathbf{C}H$), 123.20 ($CH_3C{=}\mathbf{C}H$), 105.01 ($\mathbf{C}HCOO$), 64.79 (d, J = 6.0 Hz, $PO\mathbf{C}H_2$), 64.71 ($PO\mathbf{C}H_2$), 51.22 ($O\mathbf{C}H_3$), 32.10 ($\mathbf{C}H_2CCH_3$), 32.02 ($\mathbf{C}H_2COP$), 26.57 ($\mathbf{C}H_2CH_2$), 25.65 ($\mathbf{C}H_3$), 25.21 ($\mathbf{C}H_3$), 23.34 ($\mathbf{C}H_2CH_2COP$), 17.59 ($\mathbf{C}H_3$), 16.08 (d, J = 6.6 Hz, $POCH_2\mathbf{C}H_3$), 15.99 ($OCH_2\mathbf{C}H_3$) ppm.
^{31}P NMR (121 MHz, $CDCl_3$)	δ –7.47 (s) ppm.
LRMS (ES^+) m/z	411 (100%, $[M+Na]^+$), 799 (30%, $[2M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 411.1907; Found: 411.1911 ($[M+Na]^+$).

Spectroscopic data for **3.2b**:

^{1}H NMR (400 MHz, $CDCl_3$)	δ 5.36 (1H, s, $=C\mathbf{H}COO$), 5.10 (2H, t, J = 6.2 Hz, 2 x $=C\mathbf{H}CH_2$), 4.26 (4H, quin, J = 7.4 Hz, $PO\mathbf{C}H_2$), 3.70 (3H, s, $O\mathbf{C}H_3$), 2.45 (2H, t, J = 7.3 Hz, $C\mathbf{H}_2$), 2.27 (2H, q, J = 7.3 Hz, $C\mathbf{H}_2$), 2.04 (4H, s, 2 x $C\mathbf{H}_2$), 1.69 (6H, s, 2 x $C\mathbf{H}_3$), 1.61 (3H, s, $C\mathbf{H}_3$), 1.37 (6H, t, J = 7.3, $POCH_2C\mathbf{H}_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 164.21 ($\mathbf{C}OOCH_3$), 161.62 ($\mathbf{C}OP$), 137.09 ($CH_3\mathbf{C}$), 131.73 ($(CH_3)_2\mathbf{C}$), 124.06 ($(CH_3)_2C{=}\mathbf{C}H$), 122.58 ($CH_3C{=}\mathbf{C}H$), 104.94 ($\mathbf{C}HCOO$), 64.76 (d, J = 5.1 Hz, $PO\mathbf{C}H_2$), 64.69 ($PO\mathbf{C}H_2$), 51.06 ($O\mathbf{C}H_3$), 35.43 ($\mathbf{C}H_2CCH_3$), 31.95 ($\mathbf{C}H_2COP$), 26.45 ($\mathbf{C}H_2CH_2$), 25.67 ($\mathbf{C}H_3$), 24.73 ($\mathbf{C}H_3$), 23.30 ($\mathbf{C}H_2CH_2COP$), 17.62 ($\mathbf{C}H_3$), 16.08 (d, J = 5.1 Hz, $POCH_2\mathbf{C}H_3$), 16.02 ($POCH_2\mathbf{C}H_3$) ppm.

Methyl (2*Z*, 6*Z*)-3,7,11-trimethyl-2,6,10-dodecatrienoate (3.3a);
Methyl (2*E*, 6*Z*)-3,7,11-trimethyl-2,6,10-dodecatrienoate (3.3b)



To a suspension of CuI (7.20 g, 37.9 mmol) in THF (70 mL) at 0 °C was added dropwise MeLi (23.7 mL, 1.6 M in Et_2O, 37.9 mmol). The resultant orange mixture was stirred at 0 °C for 15 min, before cooling to –35 °C. MeMgCl (21.0 mL, 3.0 M in THF, 63.1 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 **3.2a** (4.90 g, 12.6 mmol) in THF (10 mL), and the mixture was stirred at –35 °C for 1.5 hours, then quenched by pouring quickly onto ice-cold sat. aq. NH_4Cl (60 mL). The mixture was diluted with Et_2O (500 mL) and organic phase was separated, washed with sat. aq. NH_4Cl (30 mL), brine (2 x 30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give light brownish muddy colour oil (3.19 g, isomeric ratio 2*Z*:2*E* 11:1 by G.C. analysis). Purification by column chromatography (SiO_2 eluting with 100% hexane and then 3% EtOAc/hexane) afforded the 2*Z* isomer **3.3a** as a yellow oil (2.53 g, 10.1 mmol, 80%) and 2*E* isomer **3.3b** as a yellow oil (218 mg, 0.87 mmol, 7%). Spectroscopic data was in agreement with that reported in the literature.[37]

Spectroscopic data for **3.3a**:

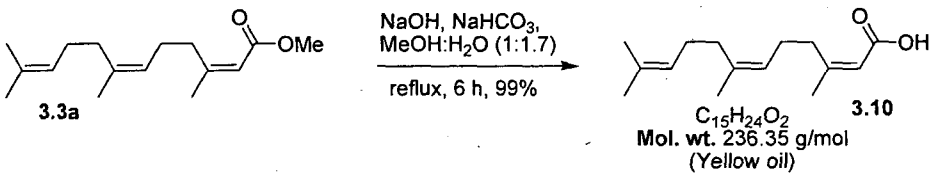
FT-IR ν_{max} (neat)	2965 (m), 2915 (m), 2856 (w), 1720 (s), 1647 (m), 1435 (m), 1162 (s), 1148 (s) cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	δ 5.66 (1H, s, =C**H**COO), 5.19-5.13 (2H, m, 2 x =C**H**CH_2), 3.68 (3H, s, OCH_3), 2.65 (2H, t, *J* = 7.7 Hz, CH_2), 2.17 (2H, q, *J* = 7.7 Hz, CH_2), 2.14-2.05 (4H, m, 2 x CH_2), 1.89 (3H, s, CH_3C=CHCOO), 1.69 (6H, s, 2 x CH_3), 1.62 (3H, s, CH_3) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 166.67 (**C**$OOCH_3$), 160.40 (**C**=CHCOO), 135.83 (CH_3**C**), 131.49 ((CH_3)$_2$**C**), 124.40 ((CH_3)$_2$C=**C**H), 124.35

	(CH_3C=**C**H), 115.80 (**C**HCOO), 50.71 (O**C**H_3), 33.68 (**C**H_2CCH_3), 31.90 (**C**H_2CCH_3), 26.63 (**C**H_2CH_2), 26.58 (**C**H_2CH_2), 25.68 (**C**H_3), 25.35 (**C**H_3), 23.32 (**C**H_3), 17.60 (**C**H_3) ppm.
LRMS (ES^+) m/z	273 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 251.2007; Found: 251.2007 ($[M+H]^+$).

Spectroscopic data for **3.3b**:

^{1}H NMR (300 MHz, $CDCl_3$)	δ 5.68 (1H, s, =C**H**COO), 5.12-5.09 (2H, m, 2 x =C**H**CH_2), 3.70 (3H, s, OC**H**$_3$), 2.17-2.16 (6H, m, 3 x C**H**$_2$), 2.04 (2H, br, C**H**$_2$), 2.04 (3H, s, C**H**$_3$C=CHCOO), 1.69 (6H, s, 2 x C**H**$_3$), 1.62 (3H, s, C**H**$_3$) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 167.25 (**C**$OOCH_3$), 160.07 (**C**=CHCOO), 136.27 (CH_3**C**), 131.69 ((CH_3)$_2$**C**), 124.16 ((CH_3)$_2$C=**C**H), 123.64 (CH_3C=**C**H), 115.19 (**C**HCOO), 50.75 (O**C**H_3), 41.20 (**C**H_2CCH_3), 31.96 (**C**H_2CCH_3), 26.51 (**C**H_2CH_2), 25.84 (**C**H_2CH_2), 25.70 (**C**H_3), 23.32 (**C**H_3), 18.82 (**C**H_3), 17.62 (**C**H_3) ppm.

(2*Z*, 6*Z*)-3,7,11-Trimethyl-2,6,10-dodecatrienoic acid (3.10)



3.3a

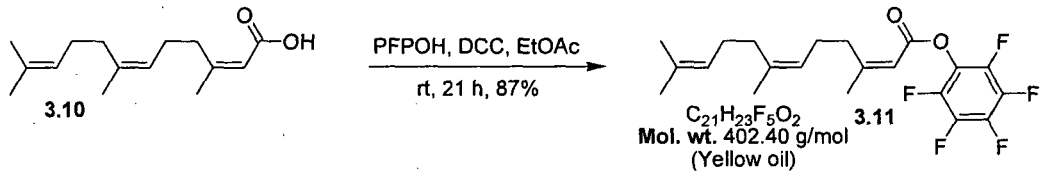
$C_{15}H_{24}O_2$ **3.10**
Mol. wt. 236.35 g/mol
(Yellow oil)

According to the method of Kulkarni *et al.*,[104] at room temperature, to a solution of NaOH (3.87 g, 96.9 mmol) and $NaHCO_3$ (663 mg, 4.50 mmol) in water (87 mL) was added to a solution of trienoate **3.3a** (3.73 g, 14.9 mmol) in MeOH (60 mL). The resulting solution was heated to reflux and stirred for 6 hours. The reaction was cooled, washed with hexane (25 mL) and acidified with HCl (10% aq., 25 mL) while keeping the temperature at 0 °C. The methanol was evaporated and the resultant residue was dissolved in ether (100 mL) and water (50 mL). The organic phase was separated, the aqueous phase was re-extracted with ether (3 × 50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford the crude acid **3.10** as a yellow oil (3.48 g, 14.7 mmol,

99%) which was used in the next step without purification. Spectroscopic data was in agreement with that reported in the literature.[35]

FT-IR ν_{max} (neat)	2964 (m), 2913 (m), 2857 (m), 1690 (s), 1638 (m), 1442 (w), 1258 (m) cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	δ 5.69 (1H, s, =C**H**COO), 5.18-5.14 (2H, m 2 x =C**H**CH_2), 5.13 (1H, br, O**H**), 2.66 (2H, t, J = 7.8 Hz, C$\mathbf{H_2}$), 2.22-2.14 (2H, m, C$\mathbf{H_2}$), 2.05 (4H, br, 2 x C$\mathbf{H_2}$), 1.93 (3H, s, C$\mathbf{H_3}$C=CHCOO), 1.70 (6H, s, 2 x C$\mathbf{H_3}$), 1.62 (3H, s, C$\mathbf{H_3}$) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 171.27 (**C**OOH), 163.44 (**C**=CHCOO), 136.06 (CH_3**C**), 131.52 ((CH_3)$_2$**C**), 124.30 ((CH_3)$_2$C=**C**H), 124.23 (CH_3C=**C**H), 115.61 (**C**HCOO), 33.87 (**C**$H_2$$CH_3$), 31.85 (**C**$H_2$$CH_3$), 26.61 (**C**$H_2$$CH_2$), 26.57 (**C**$H_2$$CH_2$), 25.69 (**C**$H_3$), 23.33 (**C**$H_3$), 19.56 (**C**$H_3$), 17.60 (**C**$H_3$) ppm.
LRMS (ES^-) m/z	235 (100%, $[M-H]^-$).
HRMS (ES^-) m/z	Calculated: 235.1703; Found: 235.1699 ($[M-H]^-$).

Pentafluorophenyl (2*Z*,6*Z*)-3,7,11-trimethyl-2,6,10-dodecatrienoate (3.11)

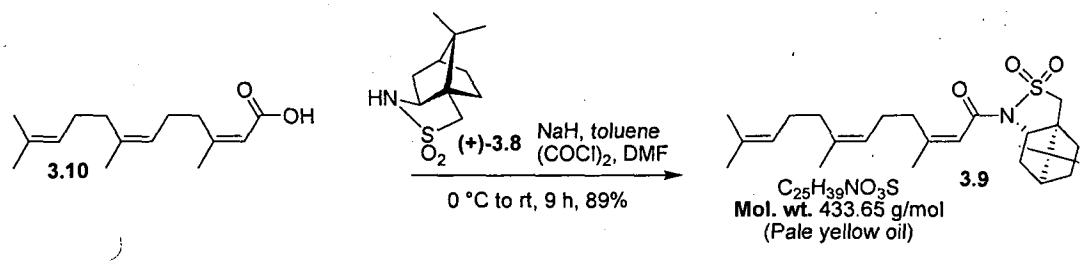


To a solution of acid **3.10** (1.02 g, 4.32 mmol) and pentafluorophenol (922 mg, 5.02 mmol) in EtOAc (10 mL) was added dropwise a solution of DCC (1.02 mg, 4.92 mmol) in EtOAc (20 mL) and the resultant mixture was stirred for 21 hours (**Note**: EtOAc was dried over 4Å MS overnight). The mixture was diluted with hexane (50 mL) and the white solid residue was removed by filtration. The organic phase was washed with sat. aq. $NaHCO_3$ (2 × 40 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield a yellow oil as crude product **3.11** (1.79 g). Purification by column chromatography (SiO_2 eluting with 100% hexane and then 0.5% Et_2O/hexane) afforded the title PFP ester **3.11** as a yellow oil (1.51 g, 3.75 mmol, 87%). Spectroscopic data was in agreement with the literature.[35]

FT-IR ν_{max} (neat)	2965 (w), 2916 (w), 2857 (w), 1761 (m), 1637 (m), 1515 (s),

	1442 (m), 1002 (s), 997 (s) cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	δ 5.96 (1H, s, =C**H**COO), 5.15 (2H, t, *J* = 7.4 Hz, 2 x =C**H**CH_2), 2.70 (2H, t, *J* = 7.8 Hz, CH_2), 2.21 (2H, q, *J* = 7.4 Hz, CH_2), 2.04 (4H, br s, 2 x CH_2), 2.04 (3H, s, CH_3C=CHCOO), 1.69 (6H, s, 2 x CH_3), 1.60 (3H, s, CH_3) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 168.08 (**C**OO), 161.21 (**C**=CHCOO), 136.53 (CH_3**C**), 131.58 ((CH_3)$_2$**C**), 124.20 ((CH_3)$_2$C=**C**H), 123.65 (CH_3C=**C**H), 112.68 (**C**HCOO), 34.35 (**C**$H_2$$CH_3$), 31.88 (**C**$H_2$$CH_3$), 26.61 (**C**$H_2$$CH_2$), 26.44 (**C**$H_2$$CH_2$), 25.96 (**C**$H_3$), 25.63 (**C**$H_3$), 23.29 (**C**$H_3$), 17.54 (**C**$H_3$) ppm. (Aromatic carbons were not observed).
LRMS (ES^+) m/z	425 (30%, $[M+Na]^+$).

***N*-((*2Z,6Z*)-3,7,11-Trimethyl- 2,6,10- dodecatrienoyl)-(2*S*)-camphor-10,2-sultam (3.9)**



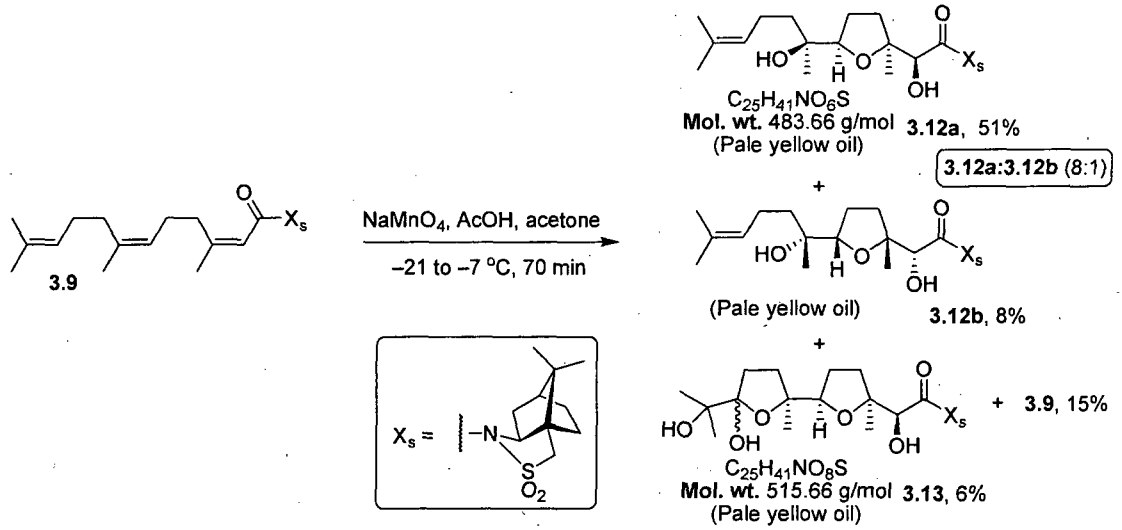
According to the method of Liddle *et al.*,[106] to a dispersion of NaH (678 mg, 16.9 mmol), in dry toluene (40 mL) at 0 °C, a solution of (2*S*)-10,2-camphorsultam (**(+)-3.8**, 3.50 g, 16.2 mmol) in dry toluene (40 mL) was added dropwise and the resulting mixture was stirred at room temperature for 1 hour.

To a solution of acid **3.10** (3.48 g, 14.73 mmol) in *n*-hexane (23 mL) was added DMF (1.14 mL, 14.7 mmol), followed by the dropwise addition of $(COCl)_2$ (6.50 mL, 73.7 mmol). Evolution of gas was observed. The reaction was stirred for 2 hours at room temperature, evaporated to dryness and the resulting residue was dissolved in dry toluene (10 mL). This solution was added dropwise to the pre-formed sodium salt of (2*S*)-10,2-camphorsultam (**(+)-3.8**) in toluene, which was pre-cooled to 0 °C. The resulting mixture was allowed to warm to room temperature and was stirred for 6 hours. The reaction was quenched with sat. aq. NH_4Cl (40 mL) and diluted with EtOAc (40

mL). The organic phase was separated and the aqueous phase was re-extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine (2 × 30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product **3.9** as a yellow oil (6.23 g). Purification by column chromatography (SiO_2 eluting with 5% EtOAc/ hexane) afforded the title trienoate **3.9** as a pale yellow oil (5.68 g, 13.1 mmol, 89%). Spectroscopic data was in agreement with the literature.[35]

$[\alpha]^{28.5}_D$	+47.50 (*c* 1.026, $CHCl_3$).
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}.
^1H NMR (300 MHz, $CDCl_3$)	δ 6.32 (1H, s, =C**H**CON), 5.19-5.14 (2H, m, 2 x =C**H**), 3.92 (1H, t, *J* = 6.2 Hz, C**H**N), 3.50 (1H, d, *J* = 13.9 Hz, C**H**HSO$_2$), 3.42 (1H, d, *J* = 13.9 Hz, CH**H**SO$_2$), 2.68-2.51 (2H, m, C**H$_2$**), 2.19-2.05 (8H, m, 4 x C**H$_2$**), 1.96 (3H, s, C**H$_3$**C=CHCON), 1.95-1.88 (3H, m, C**H** and C**H$_2$**), 1.69 (6H, s, 2 × C**H$_3$**), 1.62 (3H, s, C**H$_3$**), 1.46-1.33 (2H, m, C**H$_2$**CH$_2$S), 1.19 (3H, s, C**H$_3$**), 0.98 (3H, s, C**H$_3$**) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 163.93 (**C**ON), 162.73 (**C**=CHCON), 135.83 (CH_3**C**), 131.42 ((CH_3)$_2$**C**), 124.42 ((CH_3)$_2$C=**C**), 124.40 (CH_3C=**C**), 116.13 (**C**HCON), 65.12 (**C**HN), 53.22 (**C**CH$_2$SO$_2$), 48.15 (**C**H$_2$SO$_2$), 47.74 (**C**(CH$_3$)$_2$), 44.75 (**C**HC(CH$_3$)$_2$), 38.72 (**C**H$_2$CHN), 34.80 (**C**H$_2$CH$_2$CCH$_2$S), 32.88 (**C**H$_2$CCH$_2$S), 31.93 (**C**H$_2$CCH$_3$), 26.63 (**C**H$_2$CCH$_3$), 26.58 (**C**H$_2$CH$_2$), 26.52 (**C**H$_2$CH$_2$), 25.84 (**C**H$_3$), 25.70 (**C**H$_3$), 23.32 (**C**H$_3$), 20.86 (**C**H$_3$), 19.90 (**C**H$_3$), 17.63 (**C**H$_3$) ppm.
LRMS (ES^+) m/z	889 (100%, $[2M+Na]^+$), 456 (90%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 434.2724; Found: 434.2731 ($[M+H]^+$).

N-[(S)-2-((2S,5R)-Tetrahydro-5-((S)-2-hydroxy-6-methylhept-5en-2-yl)-2-methylfuran-2-yl)]-2-hydroxy-(2S)-10,2-camphorsultam (3.12a);
N-[(R)-2-((2R,5S)-Tetrahydro-5-((R)-2-hydroxy-6-methylhept-5en-2-yl)-2-methylfuran-2-yl)]-2-hydroxy-(2S)-10,2-camphorsultam (3.12b);
N-[(2S)-2-Hydroxy-2-((2S,2'S,5R)-5'-hydroxy-5'-(1-hydroxy-1-methyl-ethyl)-5,2'-dimethyl-octahydro-[2,2']bifuranyl-5-yl)ethanoyl]-(2S)-10,2-camphorsultam (3.13)



According to Brown *et al.*,[35] to a vigorously stirred mixture of triene **3.9** (1.45 g, 3.34 mmol) and phosphate buffer (14.6 mL) in acetone (106 mL) at –21 °C was added a solution of $NaMnO_4$ (12.6 mL, 0.4 M aq., 5.02 mmol) containing AcOH (670 μL, 11.7 mmol). The purple mixture was stirred rapidly for 70 min during which time the temperature of the acetone bath was raised to –7 °C and the reaction mixture had turned to dark brown. The reaction was quenched with sat. aq. $Na_2S_2O_5$ (aq. 100 mL) to dissolve all of the precipitated manganese salt. The mixture was diluted with brine (20 mL) and EtOAc (50 mL) and the organic phase was separated. The aqueous phase was repeatedly re-extracted using EtOAc (4 x 60 mL). The organic extracts were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as a yellow oil (1.42 g). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (5 to 20%)) afforded the major diastereoisomer, THF diol **3.12a** as a pale yellow oil (819 mg, 1.70 mmol, 51%) followed by the minor diastereoisomer, THF diol **3.12b** as a pale yellow oil (128 mg, 0.26 mmol, 8%). Finally lactol **3.13** was isolated as a pale yellow oil (109 mg, 0.21 mmol, 6%), which was found contaminated with minor diastereoisomer **3.12b**. The starting material **3.9** was also isolated as a pale yellow oil (217 mg, 0.50 mmol, 15%).

Spectroscopic data for **3.12a**:

$[\alpha]^{24}_D$	+57.08 (*c* 0.48, $CHCl_3$).
FT-IR ν_{max} (neat)	3495 (br), 2963 (m), 2936 (m), 2880 (w), 1698 (m), 1453 (w), 1327 (s), 1133 (s), 731 (s) cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	δ 5.11 (1H, t, *J* = 7.0 Hz, =C**H**CH_2), 4.63 (1H, s, C**H**OH), 3.92 (1H, dd, *J* = 7.3 and 5.1 Hz, C**H**N), 3.87 (1H, t, *J* = 7.1 Hz, C**H**, THF), 3.74 (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), 3.11 (1H, br, O**H**), 2.31-2.01 (6H, m, 3 x C**H**$_2$), 1.99-1.74 (5H, m, C**H** and C**H**$_2$), 1.67 (3H, s, C**H**$_3$), 1.62 (3H, s, C**H**$_3$), 1.52-1.21 (4H, m, 2 x C**H**$_2$), 1.30 (6H, s, 2 x C**H**$_3$), 1.27 (3H, s, C**H**$_3$), 0.98 (3H, s, C**H**$_3$) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 170.13 (**C**ON), 131.60 ((CH_3)$_2$**C**), 124.55 ((CH_3)$_2$C=**C**), 83.91 (**C**H, THF), 83.86 (**C**OH), 75.58 (**C**HOH), 73.38 (**C**CH_3, THF), 65.26 (**C**HN), 53.06 (**C**H_2SO_2), 48.75 (**C**CH_2SO_2), 47.82 (**C**HC(CH_3)$_2$), 44.56 (**C**(CH_3)$_2$), 38.35 (CH_2**C**HN), 38.10 (CH_2CH_2**C**CH_2S), 33.27 (**C**H_2, THF), 32.83 (CH_2**C**CH_2S), 26.40 (**C**H_2CH_2), 26.00 (**C**H_2, THF), 25.66 (**C**H_2), 25.84 (**C**H_3), 25.70 (**C**H_3), 23.32 (**C**H_3), 20.86 (**C**H_3), 19.90 (**C**H_3), 17.63 (**C**H_3) ppm.
LRMS (ES^+) m/z	989 (100%, $[2M+Na]^+$), 506 (40%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 506.2547; Found: 506.2552 ($[M+Na]^+$).

Spectroscopic data for **3.12b**:

$[\alpha]^{29}_D$	+28.23 (*c* 0.82, $CHCl_3$).
^1H NMR (400 MHz, $CDCl_3$)	δ 5.12-5.08 (1H, m, (CH_3)$_2$C=C**H**), 4.66 (1H, s, C**H**OH), 3.97 (1H, dd, *J* = 7.8 and 4.8 Hz, C**H**N), 3.81 (1H, dd, *J* = 8.2, 6.7 Hz, C**H**, THF), 3.53 (1H, d, *J* = 13.7 Hz, C**H**HSO_2), 3.48 (1H, d, *J* = 13.7 Hz, CH**H**SO_2), 3.46 (1H, br, O**H**), 3.22 (1H, br, O**H**), 2.30-1.89 (11H, m, C**H** and 5 x C**H**$_2$), 1.74 (3H, s, C**H**$_3$), 1.68 (3H, s, C**H**$_3$), 1.61-1.17 (4H, m, 2 x C**H**$_2$), 1.25 (3H, s, C**H**$_3$), 1.23 (3H, s, C**H**$_3$), 1.21 (3H, s, C**H**$_3$), 0.98 (3H, s, C**H**$_3$)

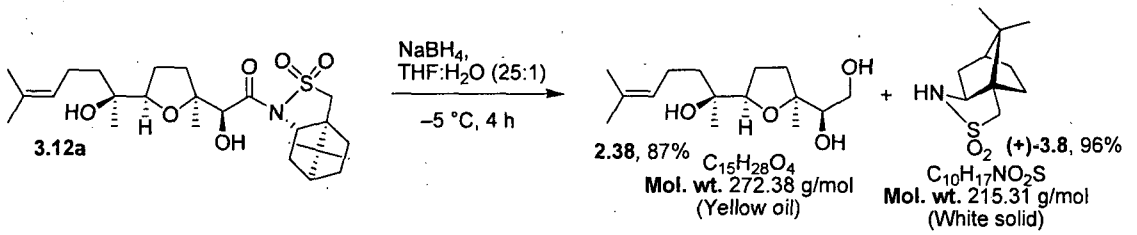
	ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 172.97 (**C**ON), 131.55 ($(CH_3)_2$**C**), 124.55 =**C**HCH_2), 84.74 (**C**H, THF), 84.45 (**C**OH), 75.81 (CCH_3, THF), 72.45 (**C**HOH), 65.50 (**C**HN), 53.20 (CH_2SO_2), 48.29 (CCH_2SO_2), 47.79 ($CHC(CH_3)_2$, 44.71 ($C(CH_3)_2$), 38.41 (CH_2CHN), 38.33 ($CH_2CH_2CCH_2S$), 34.56 (CH_2, THF), 32.99 (CH_2CCH_2S), 26.46 (CH_2, THF), 25.67 (CH_2), 25.38 (CH_2), 24.47 (CH_3), 22.97 (CH_3), 22.22 (CH_3), 21.06 (CH_3), 19.85 (CH_3), 17.64 (CH_3) ppm.

Selected spectroscopic data for **3.13**:

$[\alpha]^{29}_D$	+37.55 (*c* 1.39, $CHCl_3$).
FT-IR ν_{max} (neat)	3406 (br), 2967 (m), 2936 (m), 2877 (w), 1698 (m), 1445 (w), 1329 (m), 908 (s), 727 (s) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$)	δ 4.55 (1H, s, C**H**OH), 4.26 (1H, br, O**H**), 4.01 (1H, t, *J* = 7.3 Hz, C**H**N), 3.91 (1H, td, *J* = 7.5, 6.0 Hz, C**H**, THF), 3.54-3.44 (2H, m, 2 x O**H**), 3.53 (1H, d, *J* = 13.7 Hz, C**H**HSO$_2$), 3.45 (1H, d, *J* = 13.7 Hz, CH**H**SO$_2$), 2.41-2.02 (8H, m, C**H$_2$**), 1.86-1.25 (4H, m, 2 x C**H$_2$**), 1.31 (3H, s, C**H$_3$**), 1.26 (3H, s, C**H$_3$**), 1.26-1.16 (3H, m, C**H** and C**H$_2$**), 1.25 (3H, s, C**H$_3$**), 1.19 (3H, s, C**H$_3$**), 1.18 (3H, s, C**H$_3$**), 0.96 (3H, s, C**H$_3$**) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 169.54 (**C**ON), 109.24 (**C**OH, THF), 86.69 (**C**OH, THF), 84.77 (**C**H, THF), 82.95 (**C**HOH), 75.26 (CCH_3, THF), 73.52 (CCH_3, THF), 65.27 (**C**HN), 53.11 (CH_2SO_2), 48.65 (CCH_2SO_2), 47.74 ($CHC(CH_3)_2$), 44.55 ($C(CH_3)_2$), 38.10 (CH_2CHN), 32.73 ($CH_2CH_2CCH_2S$), 29.91 (CH_2), 27.76 (CH_2CCH_2S), 26.36 (CH_2), 24.72 (CH_2), 24.57 (CH_2), 24.10 (CH_3), 23.99 (CH_3), 20.80 (CH_3), 19.81 (CH_3), 15.20 (CH_3), 14.13 (CH_3) ppm.
LRMS (ES^+) m/z	538 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 538.2445; Found: 538.2443 ($[M+Na]^+$).

(*R*)-1-((2*S*,5*R*)-Tetrahydro-5-((*S*)-2-hydroxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-yl)ethane-1,2-diol (2.38);

(2*S*)-10,2-Camphorsultam ((+)-3.8)

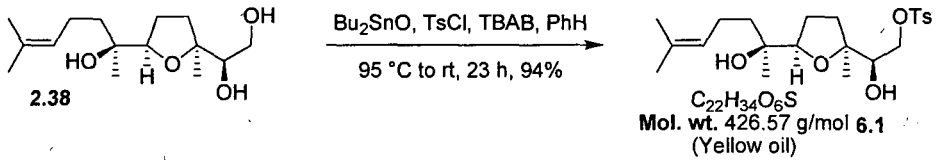


To a stirrerd solution of *cis*-THF diol **3.12a** (624 mg, 1.29 mmol) in THF:H_2O (25:1, 5mL) was added $NaBH_4$ (56 mg, 1.48 mmol) at –10 °C and the mixture was allowed to warm to rt and was stirred for 3 hours whereupon the reaction mixture was quenched by adding HCl (2 N, 2 mL) and diluted with EtOAc (20 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (2 x 25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as a pale yellow oil (615 mg). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (30 to 80%)) afforded the title THF triol **2.38** as a yellow oil (305 mg, 1.12 mmol, 87%) and (2*S*)-10,2-camphorsultam (**(+)-3.8**) as a white solid (267 mg, 1.24 mmol, 96%). Spectroscopic and analytic data were in agreement with the literature.[83]

$[\alpha]^{26}_D$	+6.38 (*c* 1.20, $CHCl_3$), {lit. $[\alpha]^{25.4}_D$ = +6.34 (*c* 1.33, $CHCl_3$)}.[83]
FT-IR ν_{max} (neat)	3392 (br), 2967 (m), 2929 (m), 2875 (w), 1453 (m), 1374 (m), 1084 (m) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$)	δ 5.12 (1H, t, *J* = 7.0 Hz, =C**H**CH_2), 3.84 (1H, t, *J* = 7.3 Hz, C**H**, THF), 3.73-3.69 (2H, m, C**H**$_2$OH), 3.56 (1H, dd, *J* = 11.7, 8.0 Hz, C**H**OH), 2.53 (2H, br, 2 x O**H**), 2.19-1.85 (5H, m, O**H** and 2 x C**H**$_2$), 1.69 (3H, s, C**H**$_3$), 1.63 (3H, s, C**H**$_3$), 1.59-1.33 (4H, m, 2 x C**H**$_2$), 1.28 (3H, s, C**H**$_3$), 1.20 (3H, s, C**H**$_3$) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 132.12 ($(CH_3)_2$**C**), 124.19 ($(CH_3)_2$C=**C**H), 84.66 (**C**OH), 83.81 (**C**HOH), 77.42 (**C**H, THF), 73.99 (**C**CH_3, THF), 63.35 (**C**H_2OH), 38.50 (**C**H_2COH), 32.61 (**C**H_2, THF), 26.40 (**C**H_2, THF), 25.68 (**C**H_3), 24.20 (**C**H_3), 23.76 (**C**H_3), 22.27 (**C**H_2CH_2), 17.66 (**C**H_3) ppm.
LRMS (ES^+) m/z	295 (100%, $[M+Na]^+$).

HRMS (ES^+) m/z Calculated: 295.1880; Found: 295.1878 ($[M+Na]^+$).

(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 (6.1)

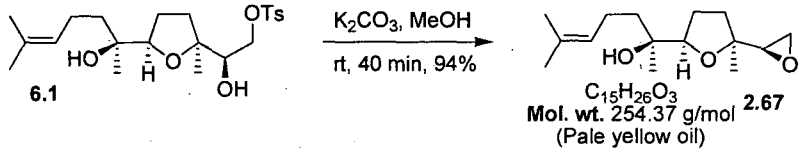


Following the method reported by Kong *et al.*,[139] to the solution of THF triol **2.38** (425 mg, 1.56 mmol) in anhydrous benzene (35 mL) was added Bu_2SnO (475 mg, 1.87 mmol) and the mixture was heated to reflux (oil bath temperature 95 °C) for 3 hours. The reaction was cooled to room temperature using a water bath, then TsCl (385 mg, 2.02 mmol) and TBAB (255 mg, 0.78 mmol) were added and the reaction was stirred for 22 hours. The reaction mixture was concentrated *in vacuo* to yield the crude product **6.1** as yellow oil (714 mg). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (20 to 50%)) afforded the title tosylate **6.1** as a yellow oil (625 mg, 1.47 mmol, 94%).

$[\alpha]^{25}_D$	+25.6 (*c* 0.71, $CHCl_3$).
FT-IR ν_{max} (neat)	3418 (br, w), 2968 (m), 2925 (m), 2877 (w), 1450 (w), 1175 (s) cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	δ 7.81 (2H, d, *J* = 8.4 Hz, 2 x SCC**H**), 7.36 (2H, d, *J* = 8.0 Hz, 2 x SCCHC**H**), 5.10 (1H, t, *J* = 7.0 Hz, =C**H**CH_2), 3.52 (1H, dd, *J* = 10.6, 2.6 Hz, C**H**OH), 3.99 (1H, t, *J* = 7.3 Hz, C**H**, THF), 3.84-3.79 (2H, m, C$\mathbf{H_2}$OTs), 3.25 (1H, br, O**H**), 2.46 (3H, s, C$\mathbf{H_3}$, Ar), 2.18-1.81 (6H, m, C$\mathbf{H_2}$ and 2 x C$\mathbf{H_2}$, THF), 1.69 (3H, s, C$\mathbf{H_3}$), 1.62 (3H, s, C$\mathbf{H_3}$), 1.59-1.27 (2H, m, C$\mathbf{H_2}$), 1.22 (3H, s, C$\mathbf{H_3}$), 1.15 (3H, s, C$\mathbf{H_3}$) ppm. (One O**H** was not observed).
^{13}C NMR (75 MHz, $CDCl_3$)	δ 144.95 (**C**CH_3, Ar), 132.87 ($(CH_3)_2$**C**), 131.99 (**C**S, Ar), 129.90 (2 x **C**HCS, Ar), 127.96 (2 x **C**HCHCS, Ar), 124.24 ($(CH_3)_2$C=**C**), 84.44 (**C**HOH), 83.82 (**C**OH), 75.03 (**C**H, THF), 73.62 (**C**CH_3, THF), 71.59 (**C**H_2OTs), 38.23 (**C**H_2COH), 33.45 (**C**H_2, THF), 26.09 (**C**H_2, THF), 25.66

	(CH_3), 24.02 (CH_3), 22.93 (CH_3), 22.20 (CH_2CH_2), 21.63 (CH_3), 17.64 (CH_3) ppm.
LRMS (ES^+) m/z	449 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 427.2149; Found: 427.2135 ($[M+H]^+$).

(*S*)-2-((2*R*,5*S*)-Tetrahydro-5-methyl-5-((*R*)-oxiran-2-yl)-furan-2-yl)-6-methylhept-5-en-2-ol (2.67)

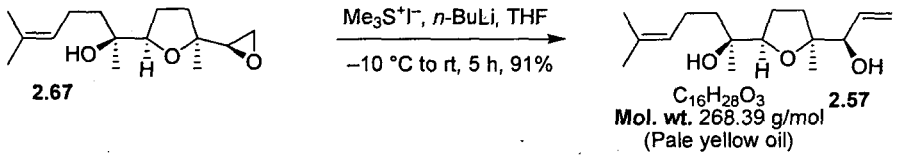


At room temperature, a solution of tosylate **6.1** (625 mg, 1.47 mmol) in dry MeOH (15 mL) was stirred with anhydrous K_2CO_3 (245 mg, 1.20 eq.) and stirred for 40 min, during which time, the reaction mixture turned milky in appearance. The methanol was removed *in vacuo* and the resultant residue was dissolved in water (4 mL) and EtOAc (15 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product **2.67** as a yellow oil (435 mg). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (20 to 40%)) afforded the title epoxide **2.67** as a pale yellow oil (348 mg, 1.37 mmol, 94%). Spectroscopic data was in agreement with the literature.[83]

$[\alpha]^{25}_D$	+8.4 (*c* 0.61, $CHCl_3$), {lit. $[\alpha]^{19.8}_D$ = +9.98 (*c* 1.15, $CHCl_3$)}.[83]
FT-IR ν_{max} (neat)	3477 (br, w), 2962 (m), 2925 (m), 2868 (w), 1446 (w), 1368 (m), 1066 (s) cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	δ 5.12 (1H, t, *J* = 7.0 Hz, =C**H**CH_2), 3.86 (1H, t, *J* = 7.3 Hz, C**H**, THF), 3.07 (1H, dd, *J* = 4.6, 2.7 Hz, C**H**HO), 2.77 (1H, t, *J* = 4.6 Hz, C**H**CH_2), 2.61 (1H, dd, *J* = 4.6 and 2.7 Hz, CH**H**O), 2.13-1.72 (5H, m, O**H** and 2 x C**H**$_2$, THF), 1.69 (3H, s, C**H**$_3$), 1.62 (3H, s, C**H**$_3$), 1.58-1.31 (4H, m, 2 x C**H**$_2$), 1.23 (3H, s, C**H**$_3$), 1.22 (3H, s, C**H**$_3$) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 131.54 ((CH_3)$_2$**C**), 124.61 ((CH_3)$_2$C=**C**), 84.95 (**C**H, THF), 81.89 (**C**OH), 73.15 (**C**CH_3, THF), 56.39 (**C**HCH_2), 44.62 (**C**H_2O), 37.54 (**C**H_2CO), 32.62 (**C**H_2, THF), 26.03 (**C**H_2,

	THF), 25.66 ($\mathbf{C}H_3$), 23.91 ($\mathbf{C}H_3$), 23.40 ($\mathbf{C}H_3$), 22.14 ($\mathbf{C}H_2CH_2$), 17.62 ($\mathbf{C}H_3$) ppm.
LRMS (ES^+) m/z	277 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 277.1774; Found: 277.1765 ($[M+Na]^+$).

(*S*)-1-((2*R*,5*S*)-Tetrahydro-5-((*R*)-1-hydroxyallyl)-5-methylfuran-2-yl)-6-methylhept-5-en-2-ol (2.57)

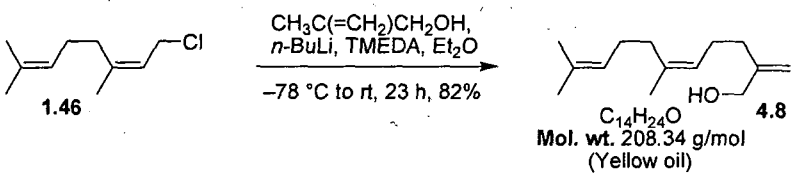


To $Me_3S^+I^-$ (2.77 g, 13.6 mmol) in dry THF (15 mL) at –10 °C was added *n*-BuLi (5.9 mL, 2.3 M in hexanes, 13.6 mmol) and the mixture was stirred for 30 min, during which time the reaction mixture turned milky in appearance. The epoxide **2.67** (345 mg, 1.36 mmol) was dissolved in dry THF (3 mL) and added to the reaction mixture. The reaction was stirred at –10 °C for 30 min, allowed to warm to room temperature and stirred for a further 4 hours. The reaction mixture was then diluted with H_2O (10 mL) and brine (10 mL), the aqueous phase was extracted with EtOAc (3 x 25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product **2.57** as a yellow oil (350 mg). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (20 to 30%)) afforded the allylic alcohol **2.57** as a pale yellow oil (332 mg, 1.24 mmol, 91%).

$[\alpha]^{25}_D$	+4.0 (*c* 1.0, $CHCl_3$).
FT-IR ν_{max} (neat)	3358 (br), 2969 (m), 2929 (m), 2871 (w), 1450 (w), 1373 (m), 1099 (s) cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	δ 5.84 (1H, ddd, *J* = 16.9, 10.4 and 6.2 Hz, C**H**=CH_2), 5.38 (1H, d, *J* = 16.9 Hz, CH=C**H**H), 5.21 (1H, d, *J* = 10.4 Hz, CH=CH**H**), 5.11 (1H, t, *J* = 7.0 Hz, =C**H**CH_2), 4.11 (1H, d, *J* = 6.2 Hz, C**H**OH), 3.89 (1H, t, *J* = 7.4 Hz, C**H**, THF), 3.30 (1H, br, O**H**), 2.43 (1H, br, O**H**), 2.22-1.82 (4H, m, 2 x $\mathbf{C}H_2$, THF), 1.69 (3H, s, $\mathbf{C}H_3$), 1.62 (3H, s, $\mathbf{C}H_3$), 1.54-1.33 (4H, m, 2 x $\mathbf{C}H_2$), 1.28 (3H, s, $\mathbf{C}H_3$), 1.18 (3H, s, $\mathbf{C}H_3$) ppm.
^{13}C NMR	δ 136.87 (**C**HCH_2), 131.94 ((CH_3)$_2$**C**), 124.30 ((CH_3)$_2$C=**C**),

(75 MHz, $CDCl_3$)	117.14 (**C**H_2), 85.37 (**C**OH), 84.33 (**C**H, THF), 78.66 (**C**HOH), 73.92 (**C**CH_3, THF), 38.46 (**C**H_2CO), 31.48 (**C**H_2, THF), 26.57 (**C**H_2, THF), 25.65 (**C**H_3), 24.51 (**C**H_3), 24.20 (**C**H_3), 22.23 (CH_2**C**H_2), 17.63 (**C**H_3) ppm.
LRMS (ES^+) m/z	291 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 291.1931; Found: 291.1923 ($[M+Na]^+$).

(5*Z*)-6,10-Dimethyl-2-methyleneundeca-5,9-dien-1-ol (4.8)

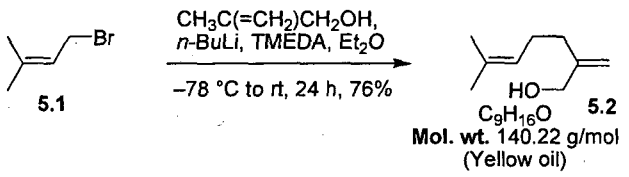


Following a method reported by Taber *et al.*,[113] TMEDA (17.8 mL, 118 mmol) was added dropwise to *n*-BuLi (51 mL, 2.3 M in hexane, 118 mmol) at –78 °C resulting in a white precipitation. After stirring for 10 min, methallyl alcohol (5.5 mL, 70 mmol) was added dropwise (75 mL distilled Et_2O was added after addition of methallyl alcohol). The cooling bath was removed and stirring was continued for 22 hours at rt, during which time a dark orange mass was observed in the reaction mixture. Subsequently, the reaction mixture was chilled to –78 °C and neryl chloride (**1.46**, 5.1 g, 29.5 mmol) in distilled Et_2O (10 mL) was added. The cooling bath was removed and the resultant yellow mixture was allowed to warm to rt and stirred for 1 hour. The reaction was chilled to 0 °C and quenched with HCl (10% aq. 250 mL). The organic phase was extracted with Et_2O (5 x 100 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude **4.8** as a dark yellow oil (6.85 g). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (5% to 20%)) afforded the title triene alcohol **4.8** as a yellow oil (5.02 g, 24.1 mmol, 82%).

FT-IR ν_{max} (neat)	3344 (br), 2963 (s), 2914 (s), 2855 (m), 1652 (w), 1447 (s), 1376 (m), 1022 (m) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$)	δ 5.14 (2H, t, *J* = 6.7 Hz, 2 x =C**H**CH_2), 5.04 (1H, s, =C**H**H), 4.89 (1H, s, =CH**H**), 4.08 (2H, d, *J* = 4.0 Hz, C**H**$_2$OH), 2.18 (2H, q, *J* = 7.5 Hz, C**H**$_2$), 2.10 (2H, d, *J* = 7.5 Hz, C**H**$_2$), 2.05 (4H, br, 2 x C**H**$_2$), 1.69 (6H, s, 2 x C**H**$_3$), 1.62 (3H, s, C**H**$_3$), 1.44 (1H, t, *J* = 4.0 Hz, CH_2O**H**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$)	δ 148.86 (**C**=CH_2), 135.72 (CH_3**C**), 131.60 ((CH_3)$_2$**C**), 124.50 (C=**C**HCH_2), 124.24 (C=**C**HCH_2), 109.28 (=**C**H_2), 65.97 (**C**H_2OH), 33.27 (**C**H_2C=CH_2), 31.99 (**C**H_2C=CH), 26.55 (**C**$H_2$$CH_2$), 26.19 ($CH_2$**C**$H_2$), 25.70 (**C**$H_3$), 23.35 (**C**$H_3$), 17.62 (**C**$H_3$) ppm.
LRMS (EI) m/z	208 ($M^{+\cdot}$, 3%), 165 (18%), 109 (22%), 93 (42%), 81 (63%), 69 (100%), 41 (93%).
HRMS (EI) m/z	Calculated: 208.18272; Found: 208.18286 ($M^{+\cdot}$).

6-Methyl-2-methylenehept-5-en-1-ol (5.2)



Following the procedure for the preparation of alcohol **4.8**, the bromide **5.1** (10.5 g, 71.0 mmol) afforded a brownish orange oil as the crude **5.2** (9.58 g). Purification by column chromatography (SiO_2 eluting with 5% Et_2O/pentane) afforded the title alcohol **5.2** as a yellow oil (7.59 g, 54.0 mmol, 76%).

FT-IR ν_{max} (neat)	3340 (br), 2965 (m), 2914 (s), 2856 (m), 1447 (s), 1021 (s), 895 (s) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$)	δ 5.12 (1H, tsept, J = 6.7, 1.5 Hz, =C**H**CH_2), 5.03 (1H, d, J = 1.4 Hz, =C**H**H), 4.89 (1H, d, J = 1.4 Hz, =CH**H**), 4.10 (2H, d, J = 6.0 Hz, C**H**$_2$OH), 2.17-2.08 (4H, m, 2 x C**H**$_2$), 1.70 (3H, s, C**H**$_3$), 1.62 (3H, s, C**H**$_3$), 1.48 (1H, t, J = 6.0 Hz, O**H**) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 148.95 (**C**=CH_2), 131.94 ((CH_3)$_2$**C**), 123.86 (C=**C**HCH_2), 109.37 (=**C**H_2), 66.03 (**C**H_2OH), 33.06 (**C**H_2C=CH_2), 26.46 (**C**$H_2$$CH_2$), 25.64 (**C**$H_3$), 17.69 (**C**$H_3$) ppm.
LRMS (EI) m/z	140 ($M^{+\cdot}$, 0.5%), 107 (10%), 79 (13%), 69 (74%).

(5*Z*)-6,10-Dimethyl-2-methyleneundeca-5,9-dienal (4.9)

Procedure 1

Following the method of Corey *et al.*,[116] a mixture of alcohol **4.8** (4.50 g, 21.6 mmol) and active MnO_2 (38.0 g, 367 mmol) in hexane (215 mL) at 0 °C, was stirred for 1 hour. After that the ice bath was removed and stirring was continued for a further 30 min at room temperature. Filtration through celite and concentration *in vacuo* afforded the title aldehyde **4.9** as a colourless oil (3.70 g, 17.97 mmol, 83%). The crude material was used in the next step without further purification.

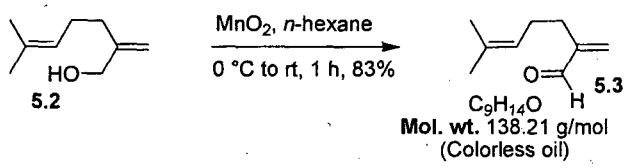
Procedure 2

Following the method of Hauser *et al.*,[115] $BaMnO_4$ (14.6 g, 51.2 mmol) was added portion-wise to the alcohol **4.8** (2.05 g, 9.85 mmol) in dry CH_2Cl_2 (400 mL). The suspension was stirred at room temperature for 43 hours. Filtration through celite and concentration *in vacuo* afforded crude **4.9** as a pale yellow oil (1.51 g). Purification by column chromatography (SiO_2 eluting with 10% EtOAc/hexane) gave the title aldehyde **4.9** as a colourless oil (1.34 g, 6.50 mmol, 66%).

FT-IR ν_{max} (neat)	2963 (m), 2917 (m), 2854 (w), 1691 (s), 1444 (m), 939 (m) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 9.54 (1H, s, C**H**O), 6.25 (1H, d, *J* = 0.8 Hz, =C**H**H), 5.99 (1H, d, *J* = 0.8 Hz, =CH**H**), 5.13-5.08 (2H, m, 2 x =C**H**CH_2), 2.28 (2H, t, *J* = 7.6 Hz, C$\mathbf{H_2}$), 2.20-2.11 (2H, m, C$\mathbf{H_2}$), 2.09-1.99 (4H, m, 2 x C$\mathbf{H_2}$), 1.70 (6H, s, 2 x C$\mathbf{H_3}$), 1.61 (3H, s, C$\mathbf{H_3}$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 194.58 (**C**HO), 149.92 (**C**=CH_2), 136.24 (CH_3**C**), 133.99 (=**C**H_2), 131.61 ((CH_3)$_2$,**C**), 124.22 (C=**C**HCH_2), 123.94 (C=**C**HCH_2), 31.96 (**C**H_2C=CH_2), 28.19 (**C**H_2=CH), 26.55 (**C**H_2CH_2), 25.96 (CH_2**C**H_2), 25.68 (**C**H_3), 23.32 (CH_3), 17.60 (**C**H_3) ppm.
LRMS (EI) m/z	206 (M^+, 18%), 163 (52%), 135 (38%), 109 (44%), 81 (64%), 69 (100%), 55 (48).

HRMS (EI) m/z Calculated: 206.1671; Found: 206.1679 ($M^{+\cdot}$).

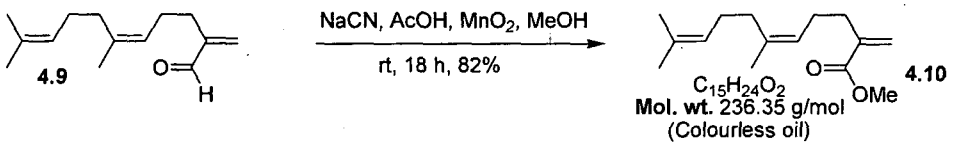
6-Methyl-2-methylenehept-5-enal (5.3)



Following the procedure 1 for the preparation of aldehyde **4.9**, alcohol **5.2** (6.0 g, 42.8 mmol) afforded aldehyde **5.3** as a colourless oil (4.90 g, 35.4 mmol, 83%). The crude material was used in the next step without purification.

FT-IR ν_{max} (neat)	2967 (w), 2917 (m), 2856 (w), 1692 (s), 1440 (w), 942 (m) cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	δ 9.54 (1H, s, **CHO**), 6.25 (1H, s, =C**H**H), 5.99 (1H, s, =CH**H**), 5.01 (1H, t, J = 7.1 Hz, =C**H**CH_2), 2.28 (2H, q, J = 7.1 Hz, C**H**$_2$), 2.15 (2H, q, J = 7.1 Hz, C**H**$_2$), 1.69 (3H, s, C**H**$_3$), 1.60 (3H, s, C**H**$_3$) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 194.65 (**C**HO), 149.90 (**C**=CH_2), 134.07 (=**C**H_2), 132.49 ($(CH_3)_2$**C**), 123.22 (C=**C**HCH_2), 27.95 (**C**H_2C=CH_2), 26.17 (**C**H_2CH_2), 25.61 (**C**H_3), 17.69 (**C**H_3) ppm.
LRMS (EI) m/z	138 ($M^{+\cdot}$, 17%), 109 (16%), 95 (48%), 69 (100%), 53 (31%).
HRMS (EI) m/z	Calculated: 138.1045; Found: 138.1042 ([$M^{+\cdot}$]).

(5*Z*)-Methyl 6,10-dimethyl-2-methyleneundeca-5,9-dienoate (4.10)

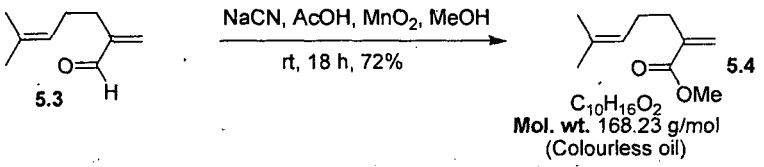


Following the procedure reported by Corey *et al.*,[116] the mixture of aldehyde **4.9** (2.72 g, 13.2 mmol) in dry MeOH (150 mL) and active MnO_2 (13.5 g, 132 mmol) and NaCN (2.26 g, 46.2 mmol) in the presence of glacial acetic acid (1.75 mL, 30.6 mmol) was stirred at room temperature for 18 hours. The evolved $HCN_{(g)}$ was scrubbed in sodium hypochlorite (25%). After filtering through celite, the filtrate was concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2 (200 mL), washed with water (3 x 50 mL) and brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford the crude **4.10** as an

orange yellow oil (2.92 g). Purification by column chromatography (SiO_2 eluting with 5% Et_2O/hexane) gave the title ester **4.10** as a colourless oil (2.55 g, 10.8 mmol, 82%).

FT-IR ν_{max} (neat)	2963 (m), 2922 (m), 2855 (w), 1721 (s), 1438 (m), 1194 (m), 942 (m) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 6.15 (1H, s, C=C**H**H), 5.53 (1H, s, C=CH**H**), 5.15-5.11 (2H, m, 2 x C=C**H**), 3.76 (3H, s, O**CH$_3$**), 2.33 (2H, t, *J* = 7.1 Hz, **CH$_2$**), 2.17 (2H, q, *J* = 7.1 Hz, **CH$_2$**), 2.04 (4H, br s, 2 x **CH$_2$**), 1.69 (6H, s, 2 x **CH$_3$**), 1.62 (3H, s, **CH$_3$**) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 167.72 (**C**OOCH$_3$), 140.36 (**C**=CH$_2$), 136.05 (CH$_3$**C**), 131.55 ((CH$_3$)$_2$**C**), 124.76 (C=**C**H$_2$), 124.28 (C=**C**HCH$_2$), 124.05 (C=**C**HCH$_2$), 51.69 (O**C**H$_3$), 32.28 (**C**H$_2$C=CH$_2$), 31.96 (**C**H$_2$C=CH), 26.72 (**C**H$_2$CH$_2$), 26.58 (**C**H$_2$CH$_2$), 26.67 (**C**H$_3$), 23.33 (**C**H$_3$), 17.60 (**C**H$_3$) ppm.
LRMS (EI) m/z	236 ($M^{+\cdot}$, 26%), 193 (74%), 137 (46%), 107 (78%), 91 (66%), 81 (69%), 69 (100%).
HRMS (EI) m/z	Calculated: 236.1777; Found: 236.1779 ($M^{+\cdot}$).

Methyl 6-methyl-2-methylenehept-5-enoate (5.4)

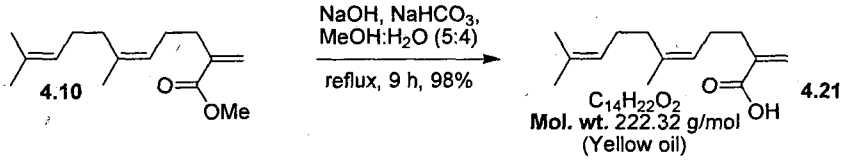


Following the procedure for the preparation of ester **4.10**, the aldehyde **5.3** (4.90 g, 35.5 mmol) afforded an orange oil as the crude **5.4** (4.96 g). Purification by column chromatography (SiO_2 eluting with 5 % Et_2O/pentane) afforded the title ester **5.4** as a colourless oil (4.28 g, 25.43 mmol, 72%).

FT-IR ν_{max} (neat)	2950 (w), 2923 (m), 2858 (w), 1721 (s), 1438 (m), 1170 (m), 940 (m) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 6.14 (1H, s, C=C**H**H), 5.53 (1H, s, C=CH**H**), 5.12 (1H, t, *J* = 7.0 Hz, C=C**H**), 3.76 (3H, s, O**CH$_3$**), 2.33 (2H, t, *J* = 7.0 Hz, **CH$_2$**), 2.16 (2H, q, *J* = 7.0 Hz, **CH$_2$**), 1.69 (3H, s, **CH$_3$**), 1.60 (3H, s, **CH$_3$**) ppm.
^{13}C NMR	δ 167.76 (**C**OOCH$_3$), 140.34 (**C**=CH$_2$), 132.32 ((CH$_3$)$_2$**C**),

(100 MHz, $CDCl_3$)	124.78 (C=**C**H_2), 123.33 (C=**C**HCH$_2$), 51.70 (O**C**H$_3$), 32.06 (**C**H$_2$C=CH$_2$), 26.92 (**C**H$_2$CH$_2$), 25.62 (**C**H$_3$), 17.65 (**C**H$_3$) ppm.
LRMS (EI) m/z	168 ($M^{+\cdot}$, 12%), 126 (9%), 93 (13%), 69 (100%), 53 (28%).
HRMS (EI) m/z	Calculated: 168.1150; Found: 168.1147 ([$M^{+\cdot}$]).

(5*Z*)-6,10-Dimethyl-2-methyleneundeca-5,9-dienoic acid (4.21)

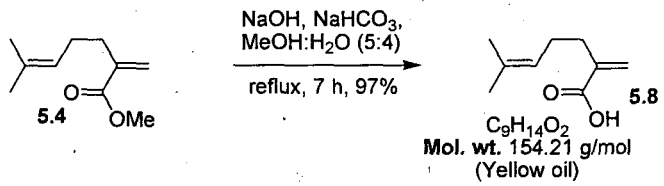


According to the method of Kulkarni *et al.*,[104] at room temperature, a solution of NaOH (4.80 mg, 120 mmol) and $NaHCO_3$ (819 mg, 9.75 mmol) in water (33 mL) was added to a solution of methyl ester **4.10** (4.43 g, 18.74 mmol) in MeOH (40 mL). The resulting solution was heated to reflux and stirred for 9 hours. The reaction was cooled to 0 °C, washed with hexane (30 mL) and carefully acidified with HCl (2 M, 30 mL), while maintaining the temperature at 0 °C. The organic phase was separated and the aqueous phase was extracted with ether (4 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude **4.21** as a yellow oil (4.07 g, 18.31 mmol, 98%) which was used in the next step without purification.

FT-IR ν_{max} (neat)	2962 (m), 2909 (m), 2856 (w), 1691 (s), 1440 (m), 1218 (w), 947 (m) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$)	δ 6.26 (1H, s, C=C**H**H), 5.61 (1H, s, C=CH**H**), 5.13-5.11 (2H, m, 2 x C=C**H**CH$_2$), 2.36-2.31 (2H, m, C**H$_2$**), 2.19-2.17 (2H, m, C**H$_2$**), 2.04 (4H, br s, 2 x C**H$_2$**), 1.69 (6H, s, 2 x C**H$_3$**), 1.61 (3H, s, C**H$_3$**) ppm. (OH signal was not observed).
^{13}C NMR (75 MHz, $CDCl_3$)	δ 172.38 (**C**OOH), 139.75 (**C**=CH$_2$), 136.20 (CH$_3$**C**), 131.60 ((CH$_3$)$_2$**C**), 127.11 (C=**C**H$_2$), 124.92 (C=**C**HCH$_2$), 123.92 (C=**C**HCH$_2$), 31.96 (**C**H$_2$C=CH$_2$), 31.89 (**C**H$_2$C=CH), 26.70 (**C**H$_2$CH$_2$), 26.57 (**C**H$_2$CH$_2$), 25.66 (**C**H$_3$), 23.32 (**C**H$_3$), 17.58 (**C**H$_3$) ppm.
LRMS (ES^-) m/z	221 (100%, [M–H]$^-$).

HRMS (ES$^-$) m/z Calculated: 221.15470; Found: 221.15414 ([M–H]$^-$).

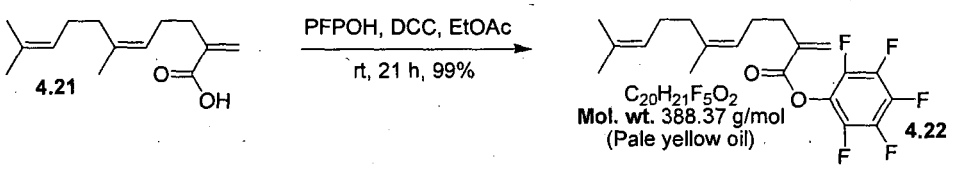
6-Methyl-2-methylenehept-5-enoic acid (5.8)



Following the procedure for the preparation of acid **4.21**, the basic hydrolysis of ester **5.4** (2.34 g, 13.7 mmol) afforded the crude **5.8** as a yellow oil (2.04 g, 13.2 mmol, 97%). The crude material was used in the next step without purification.

FT-IR ν_{max} (neat)	2966 (m), 2915 (m), 2857 (w), 1691 (s), 1439 (m), 1302 (m), 1221 (m), 946 (m) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$)	δ 6.30 (1H, s, C=C**H**H), 5.65 (1H, s, C=CH**H**), 5.12 (1H, t, *J* = 7.0 Hz, C=C**H**), 2.36-2.31 (2H, m, C**H$_2$**), 2.22-2.18 (2H, m, C**H$_2$**), 1.70 (3H, s, C**H$_3$**), 1.61 (3H, s, C**H$_3$**) ppm. (OH signal was not observed).
^{13}C NMR (75 MHz, $CDCl_3$)	δ 172.63 (**C**OOCH$_3$), 139.77 (**C**=CH$_2$), 132.47 ((CH$_3$)$_2$**C**), 127.13 (C=**C**H$_2$), 123.20 (C=**C**HCH$_2$), 31.64 (**C**H$_2$C=CH$_2$), 26.88 (**C**H$_2$CH$_2$), 25.60 (**C**H$_3$), 17.67 (**C**H$_3$) ppm.
LRMS (ES$^-$) m/z	153 (100%, [M–H]$^-$).
HRMS (ES$^-$) m/z	Calculated: 153.0921; Found: 153.0918 ([M–H]$^-$).

(5*Z*)-Perflourophenyl 6,10-dimethyl-2-methyleneundeca-5,9-dienoate (4.22)

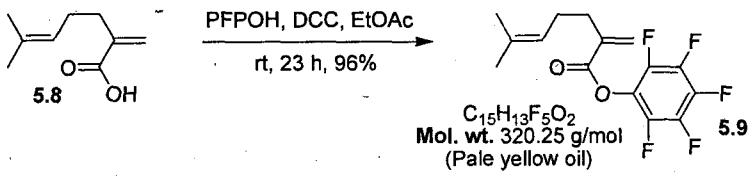


To a solution of acid **4.21** (4.07 g, 18.3 mmol) and pentafluorophenol (3.92 g, 21.3 mmol) in EtOAc (25 mL) at room temperature, was dropwise added a solution of DCC (4.40 g, 21.1 mmol) in EtOAc (50 mL). After stirring for 21 hours, the mixture was diluted in hexane (50 mL) and white solids were removed by filtration. The organic layer was washed with sat. aq. $NaHCO_3$ (3 × 50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow oil (7.44 g). Purification by column

chromatography (SiO_2 eluting with 10 % Et_2O/hexane) afforded the title triene ester **4.22** as a pale yellow oil (7.01 g, 18.1 mmol, 99%).

FT-IR ν_{max} (neat)	2967 (w), 2928 (m), 2857 (w), 1758 (s), 1516 (s), 1072 (s), 994 (s) cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	δ 6.49 (1H, s, C=C**H**H), 5.87 (1H, s, C=CH**H**), 5.15 (2H, t, J = 7.3 Hz, 2 x C=C**H**), 2.46 (2H, t, J = 7.3 Hz, C**H₂**), 2.26 (2H, q, J = 7.3 Hz, C**H₂**), 2.05 (4H, br s, 2 x C**H₂**), 1.69 (6H, s, 2 x C**H₃**), 1.61 (3H, s, C**H₃**) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 162.95 (**C**OO), 137.83 (**C**=CH_2), 136.77 (CH_3**C**), 131.67 ((CH_3)$_2$**C**), 129.33 (C=**C**H_2), 124.14 (C=**C**HCH_2), 123.33 (C=**C**HCH_2), 34.94 (**C**H_2C=CH_2), 32.26 (**C**H_2C=CH), 26.60 (**C**H_2CH_2), 25.65 (**C**H_2CH_2), 24.70 (**C**H_3), 23.33 (**C**H_3), 17.57 (**C**H_3) ppm (Aromatic carbons were not observed)
^{19}F NMR (282 MHz, $CDCl_3$)	δ –152.94 (2F, d, J = 20.3 Hz, F $_{(ortho)}$), –158.54 (1F, t, J = 21.4 Hz, F $_{(para)}$), –162.80 (2F, dd, J = 21.4 and 20.3Hz, F $_{(meta)}$) ppm.
LRMS (EI) m/z	388 ($M^{+\cdot}$, 2%), 345 (16%), 205 (24%), 137 (44%), 109 (64%), 69 (100%).
HRMS (EI) m/z	Calculated: 388.14617; Found: 388.14692 ([$M^{+\cdot}$]).

Perflourophenyl 6-methyl-2-methylenehept-5-enoate (5.9)

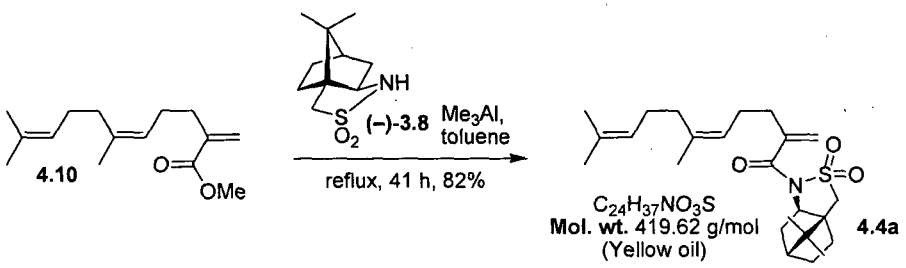


Following the procedure for the preparation of triene ester **4.22**, the acid **5.8** (2.0 g, 12.6 mmol) afforded the crude **5.9** as a pale yellow oil (4.19 g). Purification by column chromatography (SiO_2 eluting with 100% hexane) afforded the title triene ester **5.9** as a pale yellow oil (3.84 g, 12.0 mmol, 96%).

FT-IR ν_{max} (neat)	2967 (w), 2928 (m), 2857 (w), 1758 (s), 1516 (s), 1072 (s), 994 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$)	δ 6.48 (1H, s, C=C**H**H), 5.87 (1H, s, C=CH**H**), 5.13 (1H, t, *J* = 7.1 Hz, C=C**H**), 2.46 (2H, t, *J* = 7.1 Hz, C**H**$_2$), 2.26 (2H, q, *J* = 7.1 Hz, C**H**$_2$), 1.71 (3H, s, C**H**$_3$), 1.62 (3H, s, C**H**$_3$) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 162.96 (**C**OO), 137.78 (**C**=CH$_2$), 133.08 ((CH$_3$)$_2$**C**), 129.40 (C=**C**H$_2$), 122.62 (C=**C**HCH$_2$), 32.09 (**C**H$_2$C=CH$_2$), 26.79 (**C**H$_2$CH$_2$), 25.62 (**C**H$_3$), 17.65 (**C**H$_3$) ppm. (Aromatic carbons were not observed).
^{19}F NMR (282 MHz, $CDCl_3$)	δ –152.94 (2F, d, *J* = 20.3 Hz, F$_{(ortho)}$), –158.55 (1F, t, *J* = 21.4 Hz, F$_{(para)}$), –162.80 (2F, dd, *J* = 21.4 and 20.3 Hz, F$_{(meta)}$) ppm.
LRMS (EI) m/z	320 ($M^{+\cdot}$, 5%), 184 (40%), 137 (100%), 109 (68%), 69 (92%), 53 (56%).
HRMS (EI) m/z	Calculated: 320.0836; Found: 320.0839 ([$M^{+\cdot}$]).

***N*-((*Z*)-Methyl 6,10-dimethyl-2-methyleneundeca-5,9-dienoyl)-(2*R*)-camphor-10,2-sultam (4.4a)**

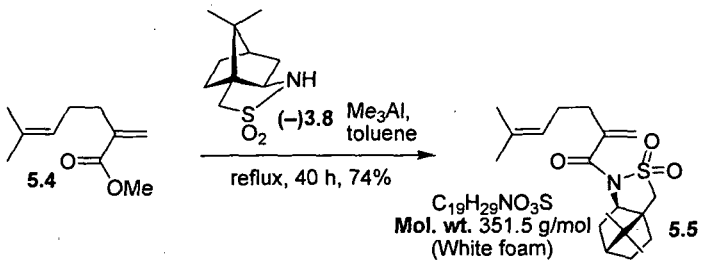


According to the method of Oppolzer *et al.*,[103] to the solution of (2*R*)-10,2-camphorsultam (**(–)-3.8**, 2.4 g, 11.1 mmol) in distilled toluene (54 mL) was added dropwise Me_3Al (5.6 mL, 2.0 M in hexane, 11.1 mmol) at room temperature. After stirring for 15 min, a solution of ester **4.10** (2.1 g, 8.88 mmol) in distilled toluene (2 mL) was added and the resulting mixture was refluxed for 41 hours, at which CH_2Cl_2 (50 mL), water (30 mL) and Rochelle salt (30 mL) were added and stirred for 1 hour. The organic phase was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford a yellow oil as the crude product **4.4a** (4.05 g). Purification by column chromatography (SiO_2 eluting with 20% EtOAc/hexane) afforded the title trieneoate **4.4a** as a yellow oil (3.04 g, 7.24 mmol, 82%).

$[\alpha]^{25}_D$	–41.8 (*c* 0.33, $CHCl_3$).
FT-IR ν_{max} (neat)	2960 (m), 2914 (m), 1680 (s), 1336 (s), 1196 (m), 1132 (m),

	1063 (m), 976 (w) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 5.76 (1H, s, =C**H**H), 5.63 (1H, s, =CH**H**), 5.15 (2H, t, *J* = 7.0 Hz, 2 x C=C**H**CH_2), 4.05 (1H, dd, *J* = 7.3, 4.8 Hz, C**H**N), 3.51 (1H, d, *J* = 13.6 Hz, C**H**HSO_2), 3.40 (1H, d, *J* = 13.6 Hz, CH**H**SO_2), 2.39-2.19 (4H, m, 2 x C**H**$_2$), 2.06 (4H, s, 2 x C**H**$_2$), 2.05-1.90 (5H, m, C**H** and 2 x C**H**$_2$), 1.69 (6H, s, 2 x C**H**$_3$), 1.61 (3H, s, C**H**$_3$), 1.44-1.38 (2H, m, C**H**$_2$), 1.24 (3H, s, C**H**$_3$), 1.00 (3H, s, C**H**$_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 171.10 (**C**ON), 143.15 (**C**=CH_2), 135.94 (CH_3**C**), 131.50 ((CH_3)$_2$**C**), 124.34 (C=**C**H$_2$), 124.12 (C=**C**HCH$_2$), 123.49 (C=**C**HCH$_2$), 65.53 (**C**HN), 53.60 (**C**CH$_2$), 47.92 (**C**H$_2$SO$_2$), 47.70 (**C**(CH$_3$)$_2$), 45.20 (**C**HC(CH$_3$)$_2$), 38.38 (**C**H$_2$CHN), 33.21 (**C**H$_2$C), 32.76 (**C**H$_2$C=CH$_2$), 31.94 (**C**H$_2$C=CH), 26.55 (**C**H$_2$CH$_2$C), 26.48 (**C**H$_2$CH$_2$), 26.04 (**C**H$_2$CH$_2$), 25.69 (**C**H$_3$), 23.33 (**C**H$_3$), 21.25 (**C**H$_3$), 19.87 (**C**H$_3$), 17.63 (**C**H$_3$) ppm.
LRMS (ES^+) m/z	442 (100%, $[M+Na]^+$), 420 (20%, $[M+H]^+$).
HRMS (ES^+) m/z	Calculated: 442.2386; Found: 442.2380 ($[M+Na]^+$).
Elemental Analysis	Calculated for $C_{24}H_{37}NO_3S$: C, 68.70; H, 8.89; N, 3.34. Found: C, 68.70; H, 8.95; N, 3.24.

_N_-(6-Methyl-2-methylene-hept-5-enoyl)-(2_R_)-camphor-10,2-sultam (5.5)

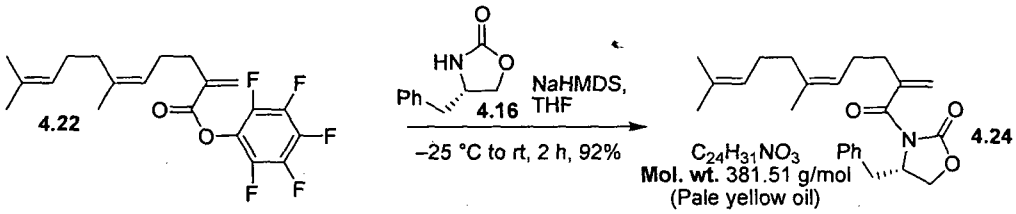


Following the procedure for the preparation of trienoate **4.4a**, the ester **5.5** (500 mg, 2.97 mmol) afforded the crude **5.5** as a yellow oil (835 mg). Purification by column chromatography (SiO_2 eluting with 10% EtOAc/hexane) afforded the title dienoate **5.5** as a white foam (774 mg, 2.20 mmol, 74%).

$[\alpha]^{23}_D$	–39.2 (*c* 0.22, $CHCl_3$).
FT-IR ν_{max} (neat)	2961 (m), 2919 (m), 2882 (m), 1679 (s), 1334 (s), 1194 (m), 1132 (m), 1063 (m), 976 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$)	δ 5.75 (1H, s, C=C**H**H), 5.64 (1H, s, C=CH**H**), 5.14 (1H, t, *J* = 6.8 Hz, C=C**H**CH_2), 4.05 (1H, dd, *J* = 7.5, 5.0 Hz, C**H**N), 3.51 (1H, d, *J* = 13.6 Hz, C**H**HSO_2), 3.40 (1H, d, *J* = 13.6 Hz, CH**H**SO_2), 2.38-2.31 (2H, m, C**H**$_2$), 2.20 (2H, q, *J* = 7.0 Hz, C**H**$_2$), 2.06-1.90 (5H, m, C**H** and 2 x C**H**$_2$,), 1.68 (3H, s, C**H**$_3$), 1.62 (3H, s, C**H**$_3$), 1.47-1.33 (2H, m, C**H**$_2$), 1.23 (3H, s, C**H**$_3$), 1.00 (3H, s, C**H**$_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 171.11 (**C**ON), 143.16 (**C**=CH_2), 132.21 ($(CH_3)_2$**C**), 123.55 (C=**C**H_2), 123.41 (C=**C**HCH_2), 65.54 (**C**HN), 53.60 (**C**H_2SO_2), 47.92 (**C**CH_2), 47.70 (**C**$(CH_3)_2$), 45.20 (**C**$HC(CH_3)_2$), 38.38 (CH_2**C**=CH_2), 33.20 (**C**H_2CHN), 32.57 (**C**H_2CH), 26.47 (**C**H_2CH_2), 26.32 (**C**H_2C), 25.61 (**C**H_3), 21.25 (**C**H_3), 19.87 (**C**H_3), 17.63 (**C**H_3) ppm.
LRMS (ES^+) m/z	374 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 352.1941; Found: 352.1937 ($[M+H]^+$).

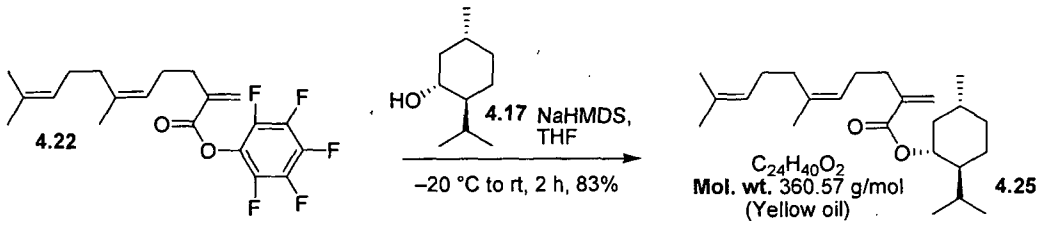
(*S*)-3-((*Z*)-6,10-Dimethyl-2-methyleneundeca-5,9-dienoyl)-4-benzyloxazolidin-2-one (4.24)



To a solution of (*S*)-benzyloxazolidinone (**4.16**, 16 mg, 0.09 mmol) in dry THF (5 mL) at –78 °C, was added NaHMDS (0.09 mL, 1.0 M in THF, 0.09 mmol) at –25 °C. The solution was allowed to warm to –25 °C over 1.5 hours whereupon a solution of the triene **4.22** (35 mg, 0.09 mmol) in dry THF (2 mL) was added dropwise. The solution was then allowed to warm to room temperature. After stirring at room temperature for 30 min, the reaction was diluted in Et_2O (25 mL) and quenched with sat. aq. NH_4Cl (15 mL). The organic phase was separated, washed with sat. aq. $NaHCO_3$ (2 x 20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow oil as the crude **4.24** (79 mg). Purification by column chromatography (SiO_2 eluting with 25% EtOAc/hexane) afforded the title triene **4.24** as a pale yellow oil (30 mg, 0.08 mmol, 92%).

$[\alpha]^{25.5}_D$	+22.60 (*c* 0.365, $CHCl_3$).
FT-IR ν_{max} (neat)	2966 (w), 2913 (w), 2856 (w), 1781 (s), 1515 (s), 1350 (s), 1210 (s), 977 (s), 701 (m) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 7.36-7.19 (5H, m, Ar), 5.45 (1H, s, =C**H**H), 5.44 (1H, s, =CH**H**), 5.16-5.11 (2H, m, 2 x C=C**H**CH_2), 4.72 (1H, dddd, *J* = 9.4, 8.0, 4.4, 3.5 Hz, C**H**N), 4.28-4.22 (2H, m, CH_2OCO), 3.39 (1H, dd, *J* = 13.5, 3.5 Hz, C**H**HPh), 2.82 (1H, dd, *J* = 13.5, 9.4 Hz, CH**H**Ph), 2.44-2.39 (2H, m, CH_2), 2.22-2.19 (2H, m, CH_2), 2.05 (4H, br s, 2 x CH_2), 1.70 (3H, s, CH_3), 1.68 (3H, s, CH_3), 1.61 (3H, s, CH_3) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 171.02 (**C**ON), 152.86 (**C**OO), 143.9 (**C**=CH_2), 136.35 (**C**CH, Ar), 135.03 (CH_3**C**), 131.61 ((CH_3)$_2$**C**), 129.38 (2 x **C**H, $Ar_{(meta)}$), 128.96 (2 x **C**H, $Ar_{(ortho)}$), 127.37 (**C**H, $Ar_{(para)}$), 124.20 (=**C**CH_2), 123.71 (=**C**CH_2), 119.43 (=**C**H_2), 66.46 (**C**H_2Ph), 55.30 (N**C**HCH_2), 37.70 (**C**H_2O), 33.28 (**C**H_2C=CH_2), 31.97 (**C**H_2C=CH), 26.52 (**C**H_2CH_2), 26.27 (**C**H_2CH_2), 25.66 (**C**H_3), 23.35 (**C**H_3), 17.72 (**C**H_3) ppm.
LRMS (ES^+) m/z	404 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 404.2196; Found: 404.2193 ($[M+Na]^+$).

(*Z*)-(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 6,10-dimethyl-2-methyleneundeca-5,9-dienoate (4.25)

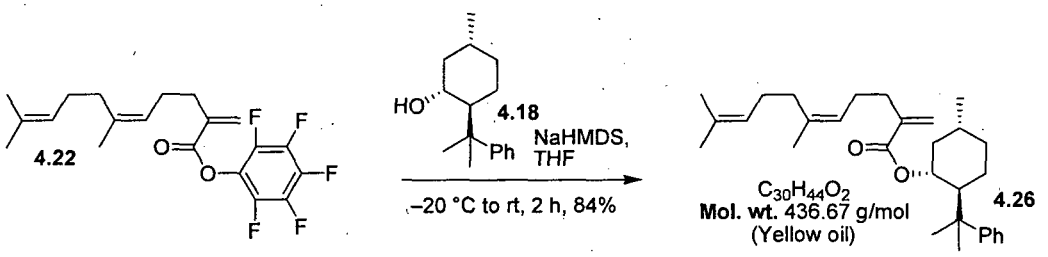


Following the procedure for the preparation of triene **4.24**, the ester **4.22** (200 mg, 0.52 mmol) afforded the crude **4.25** as a yellow oil (192 mg). Purification by column chromatography (SiO_2 eluting with 5% EtOAc/hexane) afforded the title triene **4.25**, bearing (2*S*)-menthol (**4.17**), as a yellow oil (156 mg, 0.42 mmol, 83%).

$[\alpha]^{26}_D$	–40.38 (*c* 0.52, $CHCl_3$).
FT-IR ν_{max} (neat)	2955 (m), 2922 (m), 2866 (w), 1712 (s), 1453 (m), 1300 (m),

	1177 (m), 984 (w) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 6.12 (1H, s, C=C**H**H), 5.49 (1H, s, C=CH**H**), 5.16-5.11 (2H, m, 2 x =C**H**CH_2), 4.76 (1H, td, *J* = 10.8, 4.3 Hz, OC**H**), 2.32 (2H, t, *J* = 7.0 Hz, C**H**$_2$), 2.16 (2H, q, *J* = 7.0 Hz, C**H**$_2$), 2.10-1.99 (5H, m, C**H** and 2 x C**H**$_2$), 1.77 (1H, m, C**H**), 1.68 (6H, s, 2 x C**H**$_3$), 1.61 (3H, s, C**H**$_3$), 1.53-1.41 (3H, m, C**H** and C**H**$_2$), 1.13-0.92 (4H, m, 2 x C**H**$_2$), 0.92 (3H, d, *J* = 6.0 Hz, C**H**$_3$CH), 0.89 (3H, d, *J* = 6.0 Hz, C**H**$_3$CH), 0.77 (3H, d, *J* = 7.0 Hz, C**H**$_3$CH) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 166. 82 (**C**OO), 141.02 (**C**=CH_2), 135.95 (CH_3**C**), 131.51 ((CH_3)$_2$**C**), 124.30 (=**C**H$_2$), 124.22 (C=**C**HCH$_2$), 124.16 (C=**C**HCH$_2$), 74.35 (O**C**H), 47.16 (**C**HCH(CH_3)$_2$), 40.88 (**C**H$_2$CH(CH_3)), 34.30 (**C**H$_2$C=CH$_2$), 32.29 (**C**H$_2$C=CH), 31.93 (**C**HCH$_3$), 31.39 (**C**H$_2$CH$_2$CH), 26.87 (**C**H$_2$CH$_2$), 26.58 (**C**H$_2$CH$_2$), 26.40 (**C**H$_3$), 25.68 (**C**H(CH_3)$_2$), 23.51 (**C**H$_2$CH), 23.36 (**C**H$_3$), 22.02 (**C**H$_3$), 20.76 (**C**H$_3$), 17.63 (**C**H$_3$), 16.37 (**C**H$_3$) ppm.
LRMS (ES^+) m/z	383 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 383.2920; Found: 383.2924 ($[M+Na]^+$).

(*Z*)-(1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl 6,10-dimethyl-2-methyleneundeca-5,9-dienoate (4.26)

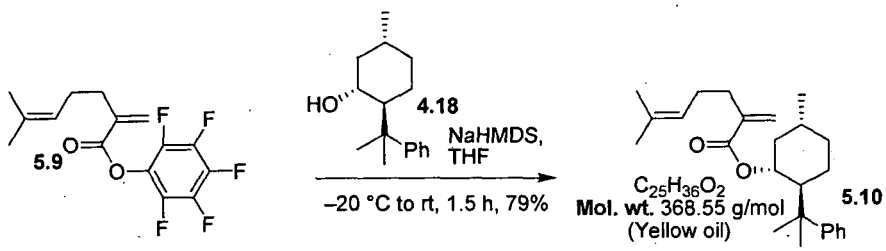


Following the procedure for the preparation of triene **4.24**, the ester **4.22** (150 mg, 0.39 mmol) afforded the crude **4.26** as a yellow oil (175 mg). Purification by column chromatography (SiO_2 eluting with 5% EtOAc/hexane) afforded the title triene **4.26**, bearing (–)-8-phenylmenthol (**4.18**), as a yellow oil (143 mg, 0.33 mmol, 84%).

$[\alpha]^{24}_D$	–26.38 (*c* 1.75, $CHCl_3$)
FT-IR ν_{max} (neat)	2955 (m), 2916 (m), 2852 (m), 1706 (s), 1442 (m), 1176 (s),

	1150 (m), 1125 (m), 761 (m), 698 (s) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$)	δ 7.30-7.11 (5H, m, Ar), 5.72 (1H, s, C=C**H**H), 5.32 (1H, s, C=CH**H**), 5.16-5.11 (2H, m, 2 x =C**H**CH_2), 4.95 (1H, td, J = 10.8, 4.3 Hz, OC**H**), 2.20-1.92 (10H, m, 5 x$C\mathbf{H_2}$), 1.72 (6H, s, 2 x $C\mathbf{H_3}$), 1.72-1.46 (2H, m, $C\mathbf{H_2}$), 1.65 (3H, s, $C\mathbf{H_3}$), 1.35 (3H, s, $C\mathbf{H_3}$), 1.26 (3H, s, $C\mathbf{H_3}$), 1.17-0.91 (4H, m, 2 x $C\mathbf{H_2}$), 0.90 (3H, d, J = 6.5 Hz, $C\mathbf{H_3}$CH) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 166.26 (**C**OO), 151.44 (**C**CH, Ar), 140.60 (**C**=CH_2), 135.71 ($CH_3\mathbf{C}$), 131.51 ($(CH_3)_2\mathbf{C}$), 127.98 (2 x **C**H, $Ar_{(meta)}$), 125.43 (2 x **C**H, $Ar_{(ortho)}$), 125.03 (**C**H, $Ar_{(para)}$), 124.36 (=$\mathbf{C}H_2$), 124.33 (C=**C**HCH_2), 124.30 (C=**C**HCH_2), 74.60 (O**C**H), 50.54 (**C**HCPh), 41.78 (**C**Ph), 39.83 ($\mathbf{C}H_2CH(CH_3)$), 34.61 ($\mathbf{C}H_2C=CH_2$), 31.99 ($\mathbf{C}H_2C=CH$), 31.84 ($\mathbf{C}HCH_3$), 31.32 ($\mathbf{C}H_2CH_2CH$), 26.86 ($\mathbf{C}H_2CH_2$), 26.84 ($\mathbf{C}H_2CH_2$), 26.71 ($\mathbf{C}H_3$), 26.60 ($\mathbf{C}H(CH_3)_2$), 26.42 ($\mathbf{C}H_3$), 25.70 ($\mathbf{C}H_3$), 23.37 ($\mathbf{C}H_3$), 21.76 ($\mathbf{C}H_3$), 17.64 ($\mathbf{C}H_3$) ppm.
LRMS (ES$^+$) m/z	459 (100%, $[M+Na]^+$).
HRMS (ES$^+$) m/z	Calculated: 459.3234; Found: 459.3234 ($[M+Na]^+$).

(1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl 6-methyl-2-methylenehept-5-enoate (5.10)

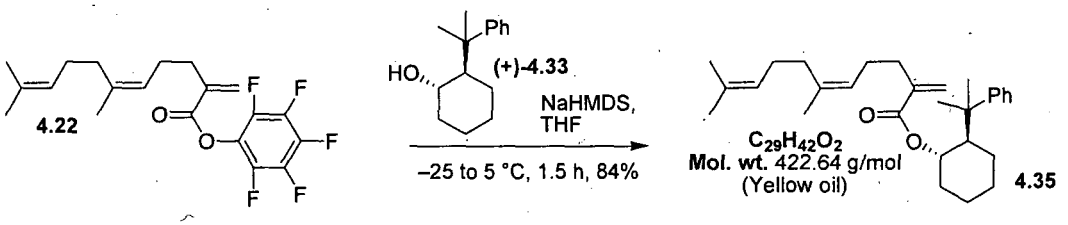


Following the procedure for the preparation of triene **4.24**, diene ester **5.9** (418 mg, 1.30 mmol) afforded the crude **5.10** as a yellow oil (425 mg). Purification by column chromatography (SiO_2 eluting with 5 % EtOAc/hexane) afforded the title diene **5.10**, bearing chiral auxiliary (–)-8-phenylmenthol (**4.18**), as a yellow oil (380 mg, 1.03 mmol, 79%).

$[\alpha]^{30}_D$	–31.1 (*c* 1.13, $CHCl_3$)
FT-IR ν_{max} (neat)	2954 (m), 2920 (m), 2862 (w), 1706 (s), 1176 (s), 1129 (m),

	763 (m), 699 (s) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 7.28-7.10 (5H, m, Ar), 5.69 (1H, d, J = 1.5 Hz, C=C**H**H), 5.30 (1H, d, J = 1.5 Hz, C=CH**H**), 5.11-5.06 (1H, m, =**CH**CH_2), 4.92 (1H, td, J = 10.8, 4.3 Hz, O**CH**), 2.11-2.05 (6H, m, 3 x CH_2), 1.70 (3H, s, CH_3), 1.70-1.32 (2H, m, CH_2), 1.62 (3H, s, CH_3), 1.33 (3H, s, CH_3), 1.27 (3H, s, CH_3), 1.17-0.91 (4H, m, 2 x CH_2), 0.90 (3H, d, J = 6.5 Hz, CH_3CH) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 166.26 (**C**OO), 151.43 (**C**CH, Ar), 140.57 (**C**=CH_2), 131.95 ($(CH_3)_2$**C**), 127.97 (2 x **C**H, $Ar_{(meta)}$), 125.43 (2 x **C**H, $Ar_{(ortho)}$), 125.03 (**C**H, $Ar_{(para)}$), 124.38 (=CH_2), 123.60 (C=**C**HCH_2), 74.61 (O**C**H), 50.55 (**C**HCPh), 41.78 (**C**Ph), 39.83 (CH_2**C**H(CH_3)), 34.62 (CH_2**C**=CH_2), 31.65 (**C**HCH_3), 31.33 (CH_2**C**H_2CH), 26.93 (CH_2**C**H_2), 26.85 (2 x **C**H_3), 26.44 (CH_2**C**H), 25.65 (**C**H_3), 21.78 (**C**H_3), 17.71 (**C**H_3) ppm.
LRMS (ES^+) m/z	391 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 391.2608; Found: 391.2605 ($[M+Na]^+$).

(*Z*)-(1*R*,2*R*)-2-(2-Phenylpropan-2-yl)cyclohexyl 6,10-dimethyl-2-methyleneundeca-5,9-dienoate (4.35)

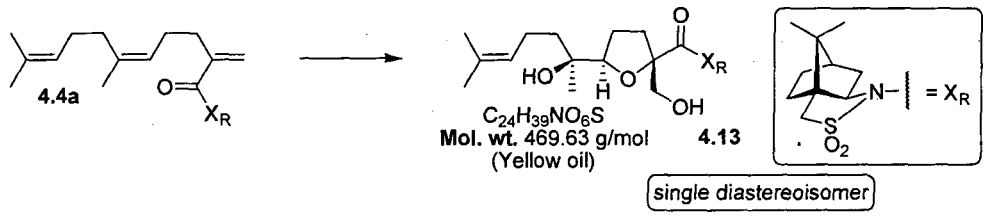


Following the procedure for the preparation of triene **4.24**, triene ester **4.22** (1.5 g, 3.86 mmol) afforded the crude **4.35** as a yellow oil (1.55 g). Purification by column chromatography (SiO_2 eluting with 100% hexane and then 20% CH_2Cl_2/hexane) afforded the title triene **4.35**, bearing the chiral auxiliary **(+)-4.33**, as a yellow oil (1.37 g, 3.24 mmol, 84%).

$[\alpha]^{25}_D$	+15.4 (*c* 1.25, $CHCl_3$)
FT-IR ν_{max} (neat)	2962 (m), 2921 (m), 2856 (w), 1708 (s), 1442 (m), 1180 (m), 1148 (m), 1119 (w), 1021 (m), 698 (m) cm^{-1}.
^1H NMR	δ 7.30-7.11 (5H, m, Ar), 5.72 (1H, s, C=C**H**H), 5.32 (1H, s,

(400 MHz, $CDCl_3$)	C=CH**H**), 5.16-5.11 (2H, m, 2 x =C**H**CH_2), 4.92 (1H, td, *J* = 10.8, 4.3 Hz, OC**H**), 2.15-1.96 (10H, m, 5 x CH_2), 1.72 (6H, s, 2 x CH_3), 1.72-1.35 (5H, m, C**H** and 2 x CH_2), 1.32 (6H, s, 2 x CH_3), 1.26 (3H, s, CH_3), 1.19-1.02 (2H, m, CH_2) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 166.24 (**C**OO), 151.42 (**C**CH, Ar), 140.60 (**C**=CH_2), 135.72 (CH_3**C**), 131.56 ((CH_3)$_2$**C**), 127.98 (2 x **C**H, $Ar_{(meta)}$), 125.44 (**C**H, $Ar_{(para)}$), 125.04 (2 x **C**H, $Ar_{(ortho)}$), 124.33 (C=**C**H_2), 124.29 (2 x C=**C**H), 74.99 (O**C**H), 50.99 (**C**HCPh), 40.01 (**C**Ph), 33.36 (CH_2**C**HCH), 31.99 (CH_2**C**=CH_2), 31.96 (CH_2CH_2), 27.28 (CH_2CH_2**C**H_2CH), 26.83 (CH_2CH_2), 26.67 (CH_2CH_2), 26.60 (CH_3), 26.44 (CH_3), 25.98 (CH_3), 25.70 (CH_2CH_2), 24.73 (CH_3), 23.36 (CH_2), 17.62 (CH_3) ppm.
LRMS (ES^+) m/z	445 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 445.3077; Found: 445.3068 ($[M+Na]^+$).

***N*-[(*S*)-2-((2*S*,5*R*)-Tetrahydro-5-((*S*)-2-hydroxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-oyl)]-2-hydroxy-(2*R*)-camphor-10,2-sultam (4.13)**



Procedure 1

Following the method of Brown *et al.*,[35] to a vigorously stirred mixture of trieneoate **4.4a** (103 mg, 0.25 mmol) and phosphate buffer (0.5 mL) in acetone (5.4 mL) at –35 °C was added a solution of $NaMnO_4$ (0.86 mL, 0.4 M aq., 0.34 mmol) containing AcOH (0.04 mL, 0.74 mmol). The purple mixture was stirred rapidly for 75 min, during which time the temperature of the acetone cooling bath had raised to 5 °C and the reaction mixture had turned dark brown. At this stage, the reaction was quenched with sat. aq. $Na_2S_2O_5$ (8 mL) to dissolve all of the precipitated manganese salt and then repeatedly extracted using CH_2Cl_2 (4 x 40mL). The organic extracts were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the yellow oil. ^1H NMR of the crude product showed that diol **4.13** was present as a single diastereoisomer. Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (10 to 60%))

afforded the title THF diol **4.13** as a yellow oil (19 mg, 0.04 mmol, 16%). The less polar starting triene **4.4a** was also recovered as a yellow oil (43mg, 0.11, 42%).

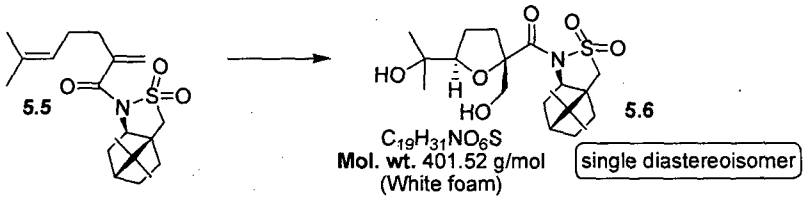
Procedure 2

To a vigorously stirred mixture of trieneoate **4.4a** (105 mg, 0.25 mmol) with adogen 464 (46.4 mg, 0.1 mmol) in ether (10 mL) at room temperature, was added a solution of $KMnO_4$ (1.06 mL, 0.4 M aq., 0.43 mmol) containing AcOH (0.05 mL, 0.75 mmol). The purple mixture was stirred rapidly for 30 min during which time the reaction mixture had turned dark brown. At this stage, the reaction was quenched with sat. aq. $Na_2S_2O_5$ (10 mL) to dissolve all of the precipitated manganese salt and then repeatedly extracted using CH_2Cl_2 (4 x 30mL). The organic extracts were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the yellow oily crude. ^1H NMR of the crude product showed that diol **4.13** was present as a single diastereoisomer. Purification by column chromatography (SiO_2 eluting with EtOAc/CH_2Cl_2 (10%) and then EtOAc/hexane (10 to 60%)) afforded the title THF **4.13** as a yellow oil (29 mg, 0.06 mmol, 25%). The less polar starting triene **4.4a** was also recovered as a yellow oil (42mg, 0.10 mmol, 40%).

$[\alpha]^{20}_D$	-21.9 (*c* 1.55, $CHCl_3$).
FT-IR ν_{max} (neat)	3450 (br), 2960 (m), 2935 (m), 2882 (w), 1675 (m), 1339 (s), 1140 (s), 1061 (s) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 5.11 (1H, t, J = 7.0 Hz, =C**H**CH_2), 4.19 (1H, dd, J = 8.6, 6.8 Hz, C**H**N), 4.09 (1H, dd, J = 7.7, 4.2 Hz, C**H**, THF), 3.99 (1H, d, J = 11.0, Hz, C**H**HOH), 3.68 (1H, d, J = 11.0, Hz, CH**H**OH), 3.54 (1H, d, J = 13.4 Hz, C**H**HSO_2), 3.44 (1H, d, J = 13.4 Hz, CH**H**SO_2), 2.52 (2H, br, 2 x O**H**), 2.33-1.86 (11H, m, C**H**H, 4 x C**H**$_2$ and 2 x C**H**$_2$, THF), 1.68 (3H, s, C**H**$_3$), 1.62 (3H, s, C**H**$_3$), 1.56-1.24 (4H, m, 2 x C**H**$_2$), 1.34 (3H, s, C**H**$_3$), 1.21 (3H, s, C**H**$_3$), 1.00 (3H, s, C**H**$_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 176.77 (**C**ON), 131.75 ($(CH_3)_2$**C**), 124.48 ((=**C**HCH_2), 88.98 (CCH_2OH, THF), 88.21 (**C**H, THF), 73.42 (**C**OH), 67.76 (**C**HN), 67.10 (**C**H_2OH), 54.84 (**C**H_2S), 47.72 (**C**CH_2S), 47.50 (**C**$(CH_3)_2$), 45.48 (**C**$HC(CH_3)_2$), 39.38 (**C**H_2CHN), 37.33 (**C**H_2COH), 35.06 (**C**H_2C), 33.70 (**C**H_2, THF), 26.13 (**C**H_2, THF), 25.67 (**C**H_2CH_2C), 25.53 (**C**H_3), 24.25 (**C**H_3), 22.12

	($\mathbf{C}H_2CH_2$), 21.83 ($\mathbf{C}H_3$), 19.90 ($\mathbf{C}H_3$), 17.64 ($\mathbf{C}H_3$) ppm.
LRMS (ES^+) m/z	492 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 470.25708; Found: 470.25791 ($[M+H]^+$).

_N_-[(2_S_,5_R_)-Tetrahydro-2-(hydroxymethyl)-5-(2-hydroxypropan-2-yl)furanoyl]-2-(2_R_)-camphor-10,2-sultam (5.6)



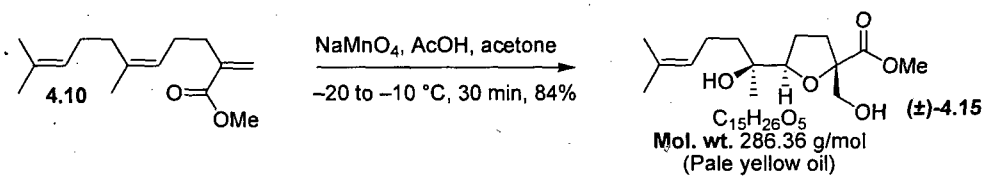
Following Procedure 1 for the preparation of THF diol **4.13**, the permanganate oxidation of dienoate **5.5** (100 mg, 0.28 mmol) afforded a yellow oily crude. ^{1}H NMR of the crude product showed that diol **5.6** was present as a single diastereoisomer. Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (20 to 40%)) afforded the title THF diol **5.6** as a white foam (37 mg, 0.09 mmol, 33%).

Following Procedure 2 for the preparation of THF diol **4.13**, the permanganate oxidative cyclisation of dienoate **5.5** (250 mg, 0.71 mmol) afforded the yellow oily crude. ^{1}H NMR of the crude product showed that diol **5.6** was present as a single diastereoisomer. Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (20 to 40%) afforded the title THF diol **5.6** as a white foam (108 mg, 0.27 mmol, 38%).

$[\alpha]^{23}_D$	-35.7 (c 1.05, $CHCl_3$).
FT-IR ν_{max} (neat)	3440 (br), 2962 (m), 2930 (m), 2882 (w), 1672 (s), 1335 (s), 1138 (s), 909 (s), 727 (s) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$)	δ 4.15 (1H, dd, J = 8.8, 6.5 Hz, C**H**N), 4.08 (1H, dd, J = 7.5, 4.5 Hz, C**H**, THF), 3.99 (1H, d, J = 11.0 Hz, C**H**HOH), 3.66 (1H, d, J = 11.0 Hz, CH**H**OH), 3.54 (1H, d, J = 13.4 Hz, C**H**HSO_2), 3.43 (1H, d, J = 13.4 Hz, CH**H**SO_2), 2.83 (2H, br, 2 x O**H**), 2.33-2.03 (3H, m, C**H** and $\mathbf{CH_2}$, THF), 1.93-1.83 (6H, m, 2 x C**H**H, $\mathbf{CH_2}$, THF), 1.43-1.25 (2H, m, $\mathbf{CH_2}$), 1.28 (3H, s, $\mathbf{CH_3}$), 1.21 (3H, s, $\mathbf{CH_3}$), 1.15 (3H, s, $\mathbf{CH_3}$), 0.99 (3H, s, $\mathbf{CH_3}$) ppm.
^{13}C NMR	δ 176.78 (**C**ON), 89.18 ($\mathbf{C}CH_2$, THF), 88.44 (**C**H, THF), 71.48

(100 MHz, $CDCl_3$)	(($CH_3)_2$**C**), 67.77 (**C**HN), 66.96 (**C**H_2OH), 54.80 (**C**H_2S), 47.71 (**C**CH_2S), 47.49 (**C**$(CH_3)_2$), 45.49 (**C**HC$(CH_3)_2$), 39.38 (**C**H_2CHN), 34.96 (**C**H_2C), 33.68 (**C**H_2, THF), 27.47 (**C**H_2, THF), 26.10 (**C**H_2CH_2C), 25.99 (**C**H_3), 24.48 (**C**H_3), 21.82 (**C**H_3), 19.88 (**C**H_3) ppm.
LRMS (ES^+) m/z	424 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 424.1764; Found: 424.1764 ($[M+Na]^+$).

***Rac.*(2*S*,5*R*)-Methyl tetrahydro-5-((*S*)-2-hydroxy-6-methylhept-5-en-2-yl)-2-(hydroxymethyl)furan-2-carboxylate ((±)-4.15)**

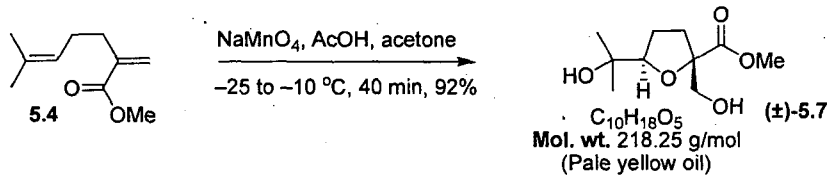


Following Procedure 1 for the preparation of THF diol **4.13**, permanganate mediated oxidative cyclisation of triene ester **4.10** (725 mg, 3.07 mmol) afforded the crude **(±)-4.15** as a yellow oil (915 mg). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (10 to 50%)) afforded the title racemic THF diol **(±)-4.15** as a pale yellow oil (739 mg, 2.58 mmol, 84%).

FT-IR ν_{max} (neat)	3410 (br), 2966 (m), 2924 (m), 2879 (w), 1732 (s), 1436 (m), 1273 (m), 1105 (s), 1056 (s) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$)	δ 5.11 (1H, t, *J* = 7.0 Hz, =C**H**CH_2), 4.09 (1H, t, *J* = 7.3 Hz, C**H**, THF), 3.86 (1H, d, *J* = 11.5 Hz, C**H**HOH), 3.83 (1H, d, *J* = 11.5 Hz, CH**H**OH), 3.76 (3H, s, OC**H**$_3$), 3.73 (1H, br, O**H**), 2.19-1.91 (6H, m, C**H**$_2$ and 2 x C**H**$_2$, THF), 1.70 (3H, s, C**H**$_3$), 1.63 (3H, s, C**H**$_3$), 1.49-1.36 (3H, m, O**H** and C**H**$_2$), 1.30 (3H, s, C**H**$_3$) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 174.46 (**C**OO), 132.02 (($CH_3)_2$**C**), 124.19 (=**C**HCH_2), 87.07 (**C**H, THF), 86.44 (**C**CH_2OH, THF), 73.48 (**C**OH), 66.27 (**C**H_2OH), 52.29 (O**C**H_3), 38.14 (**C**H_2COH), 32.16 (**C**H_2, THF), 25.66 (**C**H_3), 25.62 (**C**H_2, THF), 24.04 (**C**H_3), 22.15 (**C**H_2CH_2), 17.64 (**C**H_3) ppm.
LRMS (ES^+) m/z	309 (100%, $[M+Na]^+$).

HRMS (ES^+) m/z Calculated: 309.1672; Found: 309.1673 ($[M+Na]^+$).

***Rac.*(2*S*,5*R*)-Methyl tetrahydro-2-(hydroxymethyl)-5-(2-hydroxypropan-2-yl)furan-2-carboxylate ((±)-5.7)**

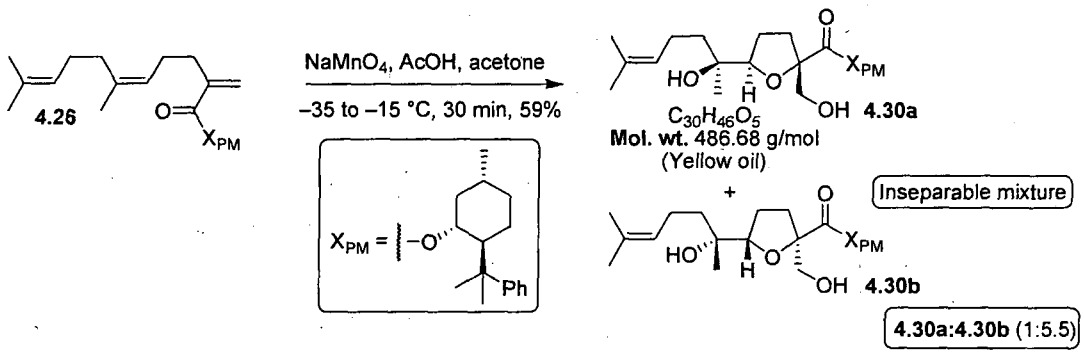


Following Procedure 1 for the preparation of THF diol **4.13**, oxidative cyclisation of diene ester **5.4** (1.20 mg, 7.13 mmol) afforded the crude **(±)-5.7** as a yellow oil (1.55 g). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (20 to 60%)) afforded the title racemic THF diol **(±)-5.7** as a pale yellow oil (1.43 g, 6.56 mmol, 92%).

FT-IR ν_{max} (neat)	3383 (br), 2971 (m), 2877 (m),1728 (s), 1452 (m), 1103 (s), 1051 (s) cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	δ 4.05 (1H, t, *J* = 7.3 Hz, C**H**, THF), 3.87 (1H, d, *J* = 11.3 Hz, C**H**HOH), 3.77 (1H, d, *J* = 11.3 Hz, CH**H**OH), 3.75 (3H, s, OC**H$_3$**), 2.97 (2H, br, 2 x O**H**), 2.21-2.0 (2H, m, C**H$_2$**, THF), 1.92 (2H, q, *J* = 7.3 Hz, C**H$_2$**CH$_2$, THF), 1.30 (3H, s, C**H$_3$**), 1.14 (3H, s, C**H$_3$**) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 174.52 (**C**OO), 87.60 (**C**H, THF), 86.78 (**C**CH$_2$OH, THF), 71.49 ((CH$_3$)$_2$**C**), 66.09 (**C**H$_2$OH), 52.30 (O**C**H$_3$), 32.00 (**C**H$_2$, THF), 27.43 (**C**H$_2$, THF), 26.02 (**C**H$_3$), 24.98 (**C**H$_3$) ppm.
LRMS (ES^+) m/z	241 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 241.1046; Found: 241.1041 ($[M+Na]^+$).

(2*S*,5*R*)-((1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl) tetrahydro-5-((*S*)-2-hydroxy-6-methylhept-5-en-2-yl)-2-(hydroxymethyl)furan-2-carboxylate (4.30a);

(2*R*,5*S*)-((1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl) tetrahydro-5-((*R*)-2-hydroxy-6-methylhept-5-en-2-yl)-2-(hydroxymethyl)furan-2-carboxylate (4.30b)



Following Procedure 1 for the preparation of THF diol **4.13**, permanganate promoted oxidative cyclisation of triene ester **4.26** (245 mg, 0.56 mmol) afforded the crude as a yellow oil in a diastereomeric ratio (220 mg, **4.30a**:**4.30b** = 1:5.5). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (10 to 25%)) afforded an inseparable diasteromeric mixture of THF diols **4.30a,b** as a yellow oil (160 mg, 0.33 mmol, 59%).

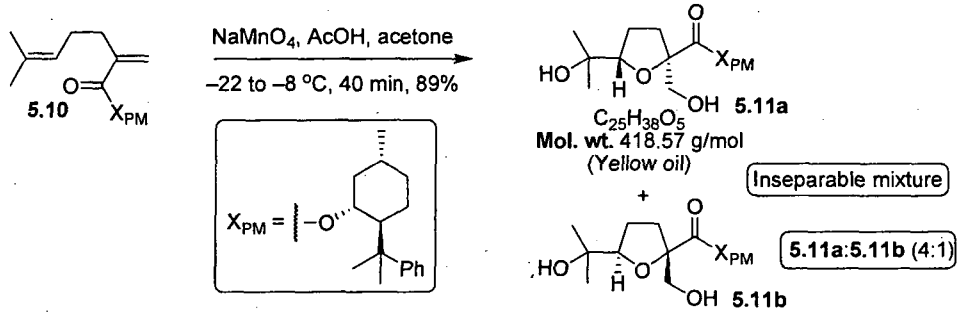
$[\alpha]^{25}_D$	–12.22 (*c* 1.35, $CHCl_3$).
FT-IR ν_{max} (neat)	3428 (br), 2951 (m), 2921 (m), 2868 (m), 1720 (s), 1453 (m), 1089 (s), 1051 (s), 731 (s), 699 (s) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$)	δ 7.30-7.16 (5H, m, 5 x C**H**, Ar), 5.12 (1H, tt, *J* = 7.0, 1.3 Hz, =C**H**CH_2), 4.91_{min} and 4.82_{maj} (1H, td, *J* = 10.5, 4.2 Hz, OC**H**), 4.08_{maj} and 3.93_{min} (1H, t, *J* = 7.0 Hz, C**H**, THF), 3.69_{maj} and 3.60_{min} (1H, d, *J* = 11.3 Hz, C**H**HOH), 3.56_{maj} and 3.45_{min} (1H, d, *J* = 11.3 Hz, CH**H**OH), 2.15-1.86 (9H, m, C**H**, 2 x CH_2 and 2 x CH_2, THF), 1.70 (3H, s, CH_3), 1.64 (3H, s, CH_3), 1.59-1.20 (8H, m, 2 x O**H**, 3 x CH_2), 1.37 (3H, s, CH_3), 1.28 (3H, s, CH_3), 1.04-0.79 (4H, m, 2 x CH_2), 0.86 (3H, d, *J* = 6.5 Hz, CH_3CH) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 173.58 (**C**OO), 150.51 (**C**CH, Ar), 131.98 ($(CH_3)_2$**C**), 128.07_{maj} and 128.04_{min} (2 x **C**H, $Ar_{(meta)}$), 125.67_{maj} and

125.60$_{min}$ (2 x **C**H, Ar$_{(ortho)}$), 125.35 (**C**H, Ar$_{(para)}$), 124.26 (C=**C**HCH$_2$), 87.15$_{maj}$ and 86.81$_{min}$ (**C**H, THF), 86.21$_{min}$ and 85.83$_{maj}$ (**C**CH$_2$OH, THF), 76.16 (O**C**H), 73.41$_{min}$ and 73.31$_{maj}$ (**C**OH), 66.06$_{maj}$ and 65.73$_{min}$ (**C**H$_2$OH), 50.36$_{maj}$ and 50.19$_{min}$ (**C**HCPh), 41.61$_{min}$ and 41.45$_{maj}$ (**C**Ph), 40.15 (**C**H$_2$COH), 38.19 (**C**H$_2$CH(CH$_3$), 34.52 (**C**H$_2$CH$_2$CH), 32.20$_{min}$ and 31.31$_{maj}$ (**C**H$_2$, THF), 28.81 (**C**HCH$_3$), 28.36 (**C**H$_3$), 27.19 (**C**H$_3$), 25.69 (**C**H$_2$C), 25.43 (**C**H$_2$, THF), 24.10$_{min}$ and 24.06$_{maj}$ (**C**H$_2$CH$_2$), 22.17 (**C**H$_3$), 21.72 (**C**H$_3$), 17.68 (**C**H$_3$), 15.26 (**C**H$_3$) ppm.

LRMS (ES$^+$) m/z 509 (100%, [M+Na]$^+$).

HRMS (ES$^+$) m/z Calculated: 509.3237; Found: 509.3237 ([M+Na]$^+$).

(2*R*,5*S*)-((1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl) tetrahydro-2-(hydroxymethyl)-5-(2-hydroxypropan-2-yl)furan-2-carboxylate (5.11a); (2*S*,5*R*)-((1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl) tetrahydro-2-(hydroxymethyl)-5-(2-hydroxypropan-2-yl)furan-2-carboxylate (5.11b)



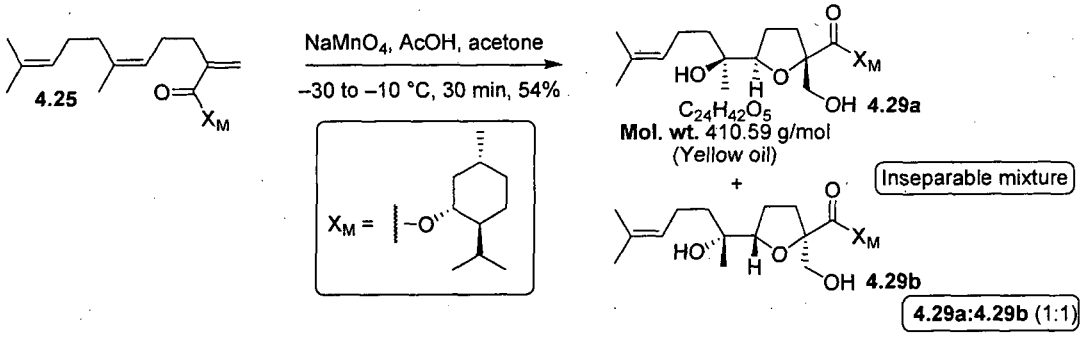
Following the Procedure 1 for the preparation of THF diol **4.13**, permanganate promoted oxidative cyclisation of diene ester **5.10** (375 mg, 1.02 mmol) afforded the crude as a yellow oil in a diastereomeric ratio (411 mg, **5.11a**:**5.11b** = 4:1). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (5 to 40%)) afforded an inseparable diasteromeric mixture of THF diols **5.11a,b** as a yellow oil (378 mg, 0.90 mmol, 89%).

$[\alpha]^{28}_D$ –15.4 (*c* 0.915, $CHCl_3$).

FT-IR ν_{max} (neat) 3390 (br), 2957 (m), 2923 (m), 2871 (m), 1721 (s), 1457 (m), 1089 (s), 1051 (s), 765 (m), 732 (s), 701 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$)	δ 7.31-7.16 (5H, m, Ar), 4.92_{min} and 4.80_{maj} (1H, td, J = 10.7, 4.4 Hz, OC**H**), 4.05_{maj} and 3.93_{min} (1H, t, J = 7.1 Hz, C**H**, THF), 3.74-3.47 (2H, m, C**H$_2$**OH), 2.73 (1H, br, O**H**), 2.34 (1H, br, O**H**), 2.05-1.88 (5H, m, C**H** and 2 x C**H$_2$**, THF), 1.49-1.26 (5H, m, C**H** and 2 x C**H$_2$**), 1.37 (3H, s, C**H$_3$**), 1.29 (3H, s, C**H$_3$**), 1.27 (3H, s, C**H$_3$**), 1.25 (3H, s, C**H$_3$**), 1.15-0.75 (2H, m, C**H$_2$**), 0.86 (3H, d, J = 6.5 Hz, C**H$_3$**CH) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 173.59_{maj} and 173.09_{min} (**C**OO), 150.76_{maj} and 150.51_{min} (**C**CH, Ar), 128.03 (2 x **C**H, $Ar_{(meta)}$), 125.66_{maj} and 125.58_{min} (2 x **C**H, $Ar_{(ortho)}$), 125.34 (**C**H, $Ar_{(para)}$), 87.67_{maj} and 87.35_{min} (**C**H, THF), 86.46_{maj} and 85.06_{min} (**C**CH$_2$OH, THF), 76.18_{maj} and minor (O**C**H), 71.41_{maj} and 71.30_{min} (**C**OH), 65.96_{maj} and 65.59_{min} (**C**H$_2$OH), 50.33_{maj} and 49.96_{min} (**C**HCPh), 41.59_{maj} and 41.42_{min} (**C**Ph), 40.12_{maj} and 38.17_{min} (**C**H$_2$CH(CH$_3$)), 34.50_{maj} and 34.43_{min} (**C**H$_2$CH$_2$CH), 32.11_{maj} and 31.30_{min} (**C**H$_2$, THF), 28.75 (**C**HCH$_3$), 27.54_{maj} and 27.42_{min} (**C**H$_2$, THF), 27.50 (**C**H$_3$), 27.16 (**C**H$_3$), 26.09 (**C**H$_2$C), 25.66_{maj} and 25.47_{min} (**C**H$_3$), $25.17_{maj\ and\ min}$ (**C**H$_3$), 21.72_{maj} and 14.19_{min} (**C**H$_3$) ppm.
LRMS (ES$^+$) m/z	441 (40%, [M+Na]$^+$), 859 (100%, [2M+Na]$^+$).
HRMS (ES$^+$) m/z	Calculated: 441.2611; Found: 441.2607 ([M+Na]$^+$).

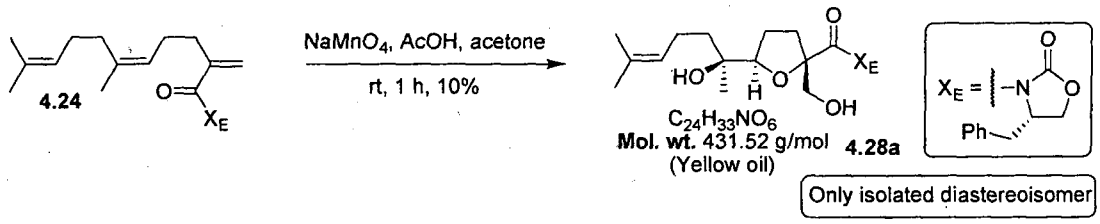
(2*S*,5*R*)-((1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl) tetrahydro-5-((*S*)-2-hydroxy-6-methylhept-5-en-2-yl)-2-(hydroxymethyl)furan-2-carboxylate (4.29a); (2*R*,5*S*)-((1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl) tetrahydro-5-((*R*)-2-hydroxy-6-methylhept-5-en-2-yl)-2-(hydroxymethyl)furan-2-carboxylate (4.29b)



Following Procedure 1 for the preparation of THF diol **4.13**, permanganate promoted oxidative cyclisation of triene ester **4.25** (51 mg, 0.14 mmol) afforded the crude as a yellow oil in a diastereomeric ratio (45 mg, **4.29a**:**4.29b** = 1:1). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (5 to 40%) afforded an inseparable 1:1 diasteromeric mixture of THF diols **4.29a,b** as a yellow oil (31 mg, 0.08 mmol, 54%).

$[\alpha]^{26.5}_D$	–41.0 (*c* 0.90, $CHCl_3$).
FT-IR ν_{max} (neat)	3423 (br), 2955 (m), 2923 (m), 2869 (w), 1721 (s), 905 (s), 729 (s) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 5.12 (1H, tt, *J* = 7.0, 1.3 Hz, =C**H**CH_2), 4.72 (1H, ddddd, *J* = 13.8, 10.9, 7.3, 4.4, 3.1 Hz, OC**H**), 4.06 (1H, td, *J* = 7.1, 3.7 Hz, C**H**, THF), 3.86 and 3.83 (1H, d, *J* = 11.3 Hz, C**H**HOH), 3.76 and 3.74 (1H, d, *J* = 11.3 Hz, CH**H**OH), 2.28-1.67 (11H, m, C**H**, 3 x C**H₂** and 2 x C**H₂**, THF), 1.68 (3H, s, C**H₃**), 1.67 (3H, s, C**H₃**), 11.43-0.92 (11H, m, C**H** and 5 x C**H₂**), 0.92 (3H, d, *J* = 4.6 Hz, C**H₃**CH), 0.90 (3H, d, *J* = 4.6 Hz, C**H₃**CH), 0.77 and 0.75 (3H, d, *J* = 7.3 Hz, C**H₃**CH) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 173.38 (**C**OO), 131.94 ((CH₃)₂**C**), 124.24 (=**C**HCH₂), 86.92 and 86.82 (**C**H, THF), 86.52 and 86.17 (**C**CH₂OH, THF), 75.19 (O**C**H), 73.45 and 73.33 (**C**OH), 66.21 and 66.18 (**C**H₂OH), 47.11 and 46.98 (**C**HCH(CH₃)₂), 40.66 (**C**H₂CH(CH₃)), 38.22 (**C**H₂CH₂CH), 34.20 (**C**H₂COH), 32.17 (**C**H₂, THF), 31.97 and 31.37 (**C**HCH₃), 26.43 (**C**H₂CH₂), 26.18 (**C**H₃), 25.67 (**C**H(CH₃)₂), 25.61 (**C**H₂, THF), 23.98 (**C**H₂CH), 23.54 and 23.20 (**C**H₃), 22.15 and 21.19 (**C**H₃), 20.80 and 20.67 (**C**H₃), 17.64 (**C**H₃), 16.36 and 16.01 (**C**H₃) ppm.
LRMS (ES^+) m/z	433 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 411.3105; Found: 411.3110 ($[M+H]^+$).

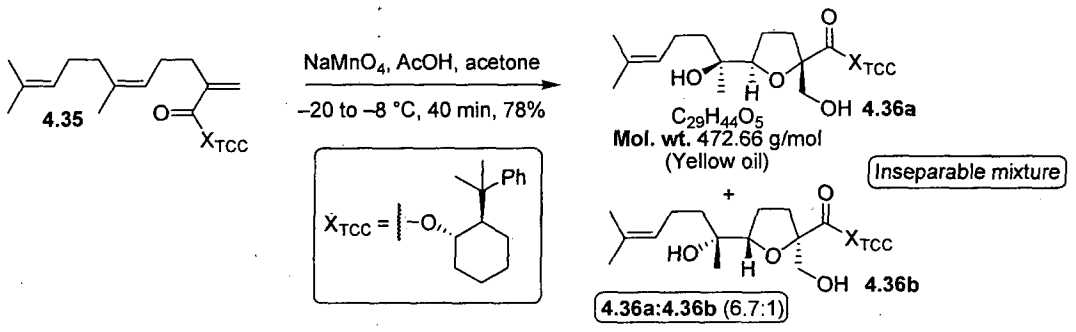
N-[2-((2S,5R)-Tetrahydro-5-((S)-2-hydroxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-oyl)]-2-hydroxy-(S)-4-benzyloxazolidin-2-one (4.28a)



Following Procedure 1 for the preparation of THF diol **4.13**, permanganate promoted oxidative cyclisation of triene ester **4.24** (28 mg, 0.07 mmol) afforded the crude as a yellow oil in a diastereomeric ratio (12 mg, **4.28a**:**4.28b** = 4:1). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (20 to 60%)) afforded only isolated diasteromer **4.28a** as a yellow oil (4 mg, 0.01 mmol, 10%).

FT-IR ν_{max} (neat)	3451 (br), 2968 (m), 2926 (m), 2875 (w), 1782 (s), 1696 (m), 1350 (m), 1212 (m), 1117 (m), 1053 (m), 702 (w) cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	δ 7.32-7.18 (5H, m, Ar), 5.07 (1H, tt, *J* = 7.0, 1.3 Hz, =C**H**CH_2), 4.72 (1H, dddd, *J* = 9.4, 8.0, 4.4, 3.5 Hz, C**H**N), 4.24 (1H, d, *J* = 11.7 Hz, C**H**HOH), 4.19-4.12 (2H, m, CH_2OCO), 4.01 (1H, dd, *J* = 8.8, 6.6 Hz, C**H**, THF), 3.83 (1H, d, *J* = 11.7 Hz, CH**H**OH), 3.26 (1H, dd, *J* = 13.5, 3.5 Hz, C**H**HPh), 2.76 (1H, dd, *J* = 13.5, 9.4 Hz, CH**H**Ph), 2.34-2.25 (3H, m, O**H** and CH_2, THF), 2.13-1.85 (5H, m, O**H**, CH_2 and CH_2, THF), 1.65 (3H, s, CH_3), 1.58 (3H, s, CH_3), 1.47-1.19 (2H, m, CH_2), 1.29 (3H, s, CH_3) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 173.37 (**C**ON), 152.27 (**C**OO), 135.13 (**C**CH, Ar), 132.01 ($(CH_3)_2$**C**), 129.44 (2 x **C**H, $Ar_{(meta)}$), 128.94 (2 x **C**H, $Ar_{(ortho)}$), 127.35 (**C**H, $Ar_{(para)}$), 124.21 (=**C**HCH_2), 89.58 (**C**OH), 86.74 (**C**H, THF), 73.11 (**C**CH_2OH, THF), 66.63 (**C**H_2OH), 66.55 (**C**H_2Ph), 56.73 (N**C**HCH_2), 37.97 (**C**H_2O), 31.64 (**C**H_2, THF), 30.88 (**C**H_2C), 25.90 (**C**H_2, THF), 25.67 (**C**H_3), 24.16 (**C**H_3), 22.14 (**C**H_2CH_2), 17.64 (**C**H_3) ppm.
LRMS (ES^+) m/z	454 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 454.2200; Found: 454.2204 ($[M+Na]^+$).

(2*S*,5*R*)-((1*S*,2*R*)-2-(2-Phenylpropan-2-yl)cyclohexyl) tetrahydro-5-((*S*)-2-hydroxy-6-methylhept-5-en-2-yl)-2-(hydroxymethyl)furan-2-carboxylate (4.36a); (2*R*,5*S*)-((1*S*,2*R*)-2-(2-Phenylpropan-2-yl)cyclohexyl) tetrahydro-5-((*R*)-2-hydroxy-6-methylhept-5-en-2-yl)-2-(hydroxymethyl)furan-2-carboxylate (4.36b)



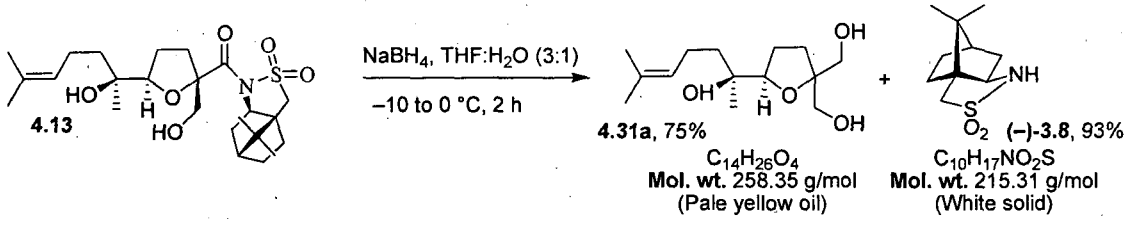
Following Procedure 1 for the preparation of THF diol **4.13**, permanganate promoted oxidative cyclisation of triene ester **4.35** (1.07 g, 2.53 mmol) afforded the crude **4.36a,b** as a yellow oil in a diastereomeric ratio (1.05 g, **4.36a**:**4.36b** = 6.7:1). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (10 to 20%)) afforded an inseparable diasteromeric mixture of THF diols **4.36a,b** as a yellow oil (931 mg, 1.97 mmol, 78%).

$[\alpha]^{26}_D$	+2.25 (*c* 0.6, $CHCl_3$).
FT-IR ν_{max} (neat)	3412 (br), 2966 (m), 2929 (m), 2856 (w), 1716 (s), 1279 (w), 1091 (s), 1050 (s), 756 (w), 731 (m), 698 (s) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$)	δ 7.28-7.14 (5H, m, 5 x C**H**, Ar), 5.10 (1H, t, *J* = 7.0 Hz, =C**H**CH_2), 4.87_{min} and 4.76_{maj} (1H, td, *J* = 10.0, 4.3 Hz, OC**H**), 4.05_{min} and 3.95_{maj} (1H, t, *J* = 7.0 Hz, C**H**, THF), 3.68_{maj} and 3.59_{min} (1H, d, *J* = 11.3 Hz, C**H**HOH), 3.53_{maj} and 3.49_{min} (1H, d, *J* = 11.3 Hz, CH**H**OH), 2.73 (1H, br, O**H**), 2.19-1.80 (12H, m, O**H**, C**H**, 3 x C**H**$_2$, 2 x C**H**$_2$, THF), 1.68 (3H, s, C**H**$_3$), 1.62 (3H, s, C**H**$_3$), 1.68-1.39 (4H, m, 2 x C**H**$_2$), 1.38 (3H, s, C**H**$_3$), 1.37-0.85 (2H, m, C**H**$_2$) 1.24 (6H, s, 2 x C**H**$_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 173.52_{maj} and 173.08_{min} (**C**OO), 150.67_{maj} and 150.45_{min} (**C**CH, Ar), 131.93 ((CH$_3$)$_2$**C**), 128.07_{maj} and 128.03_{min} (2 x **C**H, $Ar_{(meta)}$), 125.69_{maj} and 125.63_{min} (2 x **C**H, $Ar_{(ortho)}$), 125.37_{maj} and 125.35_{min} (**C**H, $Ar_{(para)}$), 124.26_{maj} and 124.24_{min} (C=**C**HCH$_2$), 87.10_{maj} and 86.80_{min} (**C**H, THF), 86.23_{maj} and

	85.88$_{min}$ (**C**CH$_2$OH, THF), 77.31$_{maj}$ and 77.20$_{min}$ (**O**CH), 76.50$_{maj}$ and 76.42$_{min}$ (**C**OH), 66.07$_{maj}$ and 65.69$_{min}$ (**C**H$_2$OH), 50.78$_{maj}$ and 50.43$_{min}$ (**C**HCPh), 40.33 (**C**Ph), 38.21$_{maj}$ and 38.17$_{min}$ (**C**H$_2$COH), 33.12$_{maj}$ and 33.02$_{min}$ (**C**H$_2$CHCH), 31.56$_{maj}$ and 31.41$_{min}$ (**C**H$_2$, THF), 28.79$_{maj}$ and 28.35$_{min}$, (**C**H$_2$CH$_2$CH$_2$CH), 27.54$_{maj}$ and 27.42$_{min}$ (**C**H$_2$), 25.81 (**C**H$_2$CH$_2$), 25.70$_{maj}$ and 25.67$_{min}$ (**C**H$_3$), 25.55$_{maj}$ and 25.39$_{min}$ (**C**H$_3$), 24.54$_{maj}$ and 24.49$_{min}$ (**C**H$_2$, THF), 24.08$_{maj}$ and 24.04$_{min}$ (**C**H$_3$), 22.65$_{maj}$ and 22.16$_{min}$ (**C**H$_2$CH$_2$), 17.66$_{maj}$ and 17.64$_{min}$ (**C**H$_3$), 14.17$_{maj}$ and 14.08$_{min}$ (**C**H$_3$) ppm.
LRMS (ES$^+$) m/z	495.5 (95%, [M+Na]$^+$), 968 (100%, [2M+Na]$^+$).
HRMS (ES$^+$) m/z	Calculated: 495.3081; Found: 495.3088 ([M+Na]$^+$).

(5*R*)-Tetrahydro-5-((*S*)-2-hydroxy-6-methylhept-5-en-2-yl)-2-hydroxymethylfuran-2-ol (4.31a);

(2*R*)-10,2-Camphorsultam ((–)-3.8)



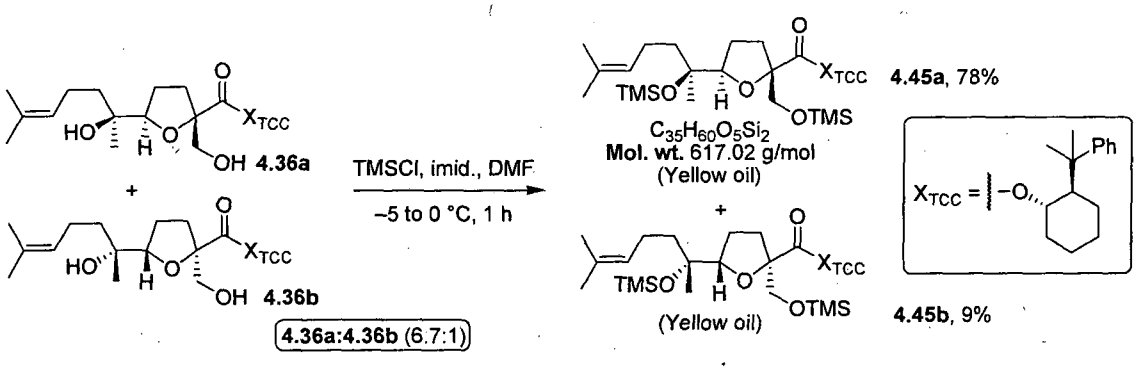
To a solution of THF diol **4.13**, (75 mg, 0.16 mmol) in THF:H$_2$O (3:1, 4 mL) at –10 °C was added NaBH$_4$ (25 mg, 0.64 mmol) in two batches. The mixture was stirred and allowed to warm to 0 °C over a period of 2 hours, whereupon HCl (2 N, 4 mL) and EtOAc (10 mL) were added. The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were dried (Na$_2$SO$_4$), filtered and concentrated *in vacuo* to give the crude as a pale yellow oil (70 mg). Purification by column chromatography (SiO$_2$ eluting with 60% EtOAc/hexane and 100% EtOAc) afforded the title triol **4.31a** as a pale yellow oil (31 mg, 0.12 mmol, 75%) and less polar (2*R*)-10,2-camphorsultam (**(–)-3.8**) as a white solid (32 mg, 0.15 mmol, 93%).

$[\alpha]^{24}_D$	–2.06 (*c* 1.53, CHCl$_3$).
FT-IR ν_{max} (neat)	3475 (br), 2960 (m), 2962 (m), 2917 (m), 2868 (w), 1417 (s),

	1368 (s), 1046 (s) cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	δ 5.11 (1H, tt, J = 7.0, 1.4 Hz, =C**H**CH_2), 4.00-3.80 (7H, m, 2 x CH_2, 2 x O**H**, and C**H**, THF), 2.17-1.72 (6H, m, CH_2 and 2 x CH_2, THF), 1.68 (3H, s, CH_3), 1.62 (3H, s, CH_3), 1.66-1.17 (3H, m, O**H** and CH_2), 1.24 (3H, s, CH_3) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 131.70 ($(CH_3)_2C$), 124.33 (=**C**HCH_2), 85.57 (**C**H, THF), 78.04 (**C**CH_2OH, THF), 72.32 (**C**OH), 69.65 (**C**H_2OH), 69.19 (**C**H_2OH), 37.44 (CH_2**C**OH), 30.82 (**C**H_2, THF), 25.64 (CH_3), 25.08 (**C**H_2, THF), 24.09 (CH_3), 22.08 (CH_2**C**H_2), 17.11 (CH_3) ppm.
LRMS (ES^+) m/z	281 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 281.1723; Found: 281.1719 ($[M+Na]^+$).

(2*S*,5*R*)-((1*S*,2*R*)-2-(2-Phenylpropan-2-yl)cyclohexyl) tetrahydro-5-((*S*)-2-trimethylsiloxy-6-methylhept-5-en-2-yl)-2-(methoxytrimethylsilyl)furan-2-carboxylate (4.45a);

(2*R*,5*S*)-((1*S*,2*R*)-2-(2-Phenylpropan-2-yl)cyclohexyl) tetrahydro-5-((*R*)-2-trimethylsiloxy-6-methylhept-5-en-2-yl)-2-(trimethylsilyl)furan-2-carboxylate (4.45b)



To a solution of THF diols **4.36a,b** (1.03 g, 2.17 mmol) in DMF (20 mL) was added imidazole (1.80 g, 26.5 mmol), followed by the addition of TMSCl (2.80 mL, 21.9 mmol) at –5 °C. The reaction mixture was stirred for 1 hour, during which the temperature raised to 0 °C. The reaction was quenched with sat. aq. NH_4Cl (5 mL) and H_2O (10 mL). The aqueous phase was extracted with Et_2O (2 x 60 mL) and combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude **4.45a,b** as a yellow oil (1.25 g). Purification by column chromatography (SiO_2 eluting with CH_2Cl_2/hexane (10 to 50%)) afforded the title THF **4.45a** (single

diastereoisomer by ^{1}H NMR) as a yellow oil (1.04 g, 1.69 mmol, 78%). The more polar minor diastereoisomer **4.45b** was also isolated as a yellow oil (123 mg, 0.2 mmol, 9%). Note: Some of the mixed fractions of **4.45a,b** were separated by chiral HPLC, eluting with 30% CH_2Cl_2/hexane.

Spectroscopic data for major diastereoisomer **4.45a**:

$[\alpha]^{26}_D$	+7.36 (c 1.04, $CHCl_3$).
FT-IR ν_{max} (neat)	2957 (m), 2918 (m), 2860 (w), 1725 (s), 1249 (s), 1097 (br), 872 (m), 836 (br), 751 (s), 699 (s) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$)	δ 7.27-7.11 (5H, m, 5 x C**H**, Ar), 5.10 (1H, t, *J* = 7.0 Hz, =C**H**CH_2), 4.81 (1H, td, *J* = 10.0, 4.3 Hz, OC**H**), 4.04 (1H, t, *J* = 7.0 Hz, C**H**, THF), 3.80 (1H, d, *J* = 10.1 Hz, C**H**HOSi$(CH_3)_3$), 3.56 (1H, d, *J* = 10.1 Hz, CH**H**OSi$(CH_3)_3$), 2.08-1.38 (7H, m, C**H**, C**H$_2$**, and 2 x C**H$_2$**, THF), 1.85-1.38 (8H, m, 4 x C**H$_2$**), 1.68 (3H, s, C**H$_3$**), 1.62 (3H, s, C**H$_3$**), 1.32 (3H, s, C**H$_3$**), 1.31-0.81 (2H, m, C**H$_2$**), 1.26 (3H, s, C**H$_3$**), 1.20 (3H, s, C**H$_3$**), 0.11 (9H, s, COSi(C**H$_3$**)$_3$), 0.07 (9H, s, CH_2OSi(C**H$_3$**)$_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 173.58 (**C**OO), 150.77 (**C**CH, Ar), 131.03 ((CH$_3$)$_2$**C**), 127.97 (2 x **C**H, Ar$_{(meta)}$), 125.82 (2 x **C**H, Ar$_{(ortho)}$), 125.25 (**C**H, Ar$_{(para)}$), 124.92 (C=**C**HCH$_2$), 87.59 (**C**H, THF), 85.19 (**C**CH$_2$OH, THF), 76.58 (**C**OSi$(CH_3)_3$), 76.12 (O**C**H), 66.51 (**C**H$_2$OSi$(CH_3)_3$), 50.91 (**C**HCPh), 40.72 (**C**Ph), 40.59 (**C**H$_2$COSi$(CH_3)_3$), 33.15 (**C**H$_2$CHCH), 31.65 (**C**H$_2$, THF), 30.04 (**C**H$_2$), 27.70 (**C**H$_2$CH$_2$CH$_2$CH), 25.85 (**C**H$_3$), 25.69 (**C**H$_2$), 25.46 (**C**H$_2$), 24.59 (**C**H$_2$, THF), 23.94 (**C**H$_3$), 22.64 (**C**H$_3$), 22.35 (**C**H$_2$CH$_2$), 17.72 (**C**H$_3$), 2.67 (3C, COSi(**C**H$_3$)$_3$), –0.49 (3C, CH_2OSi(**C**H$_3$)$_3$) ppm.
LRMS (ES$^+$) m/z	639 (100%, $[M+Na]^+$).
HRMS (ES$^+$) m/z	Calculated: 639.3871; Found: 639.3888 ($[M+Na]^+$).

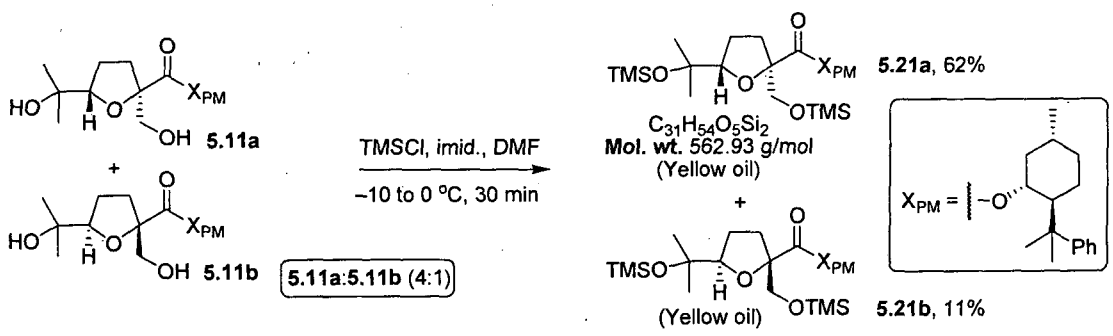
Spectroscopic data for minor diastereoisomer **4.45b**:

$[\alpha]^{27}_D$	+4.74 (c 1.475, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$)	δ 7.31-7.14 (5H, m, 5 x C**H**, Ar), 5.09 (1H, tt, *J* = 7.0, 1.4 Hz, =C**H**CH_2), 4.84 (1H, td, *J* = 10.0, 4.3 Hz, OC**H**), 3.97 (1H, t, *J* = 7.0 Hz, C**H**, THF), 3.62 (1H, d, *J* = 10.6 Hz, C**H**HOSi$(CH_3)_3$), 3.58 (1H, d, *J* = 10.6 Hz, CH**H**OSi$(CH_3)_3$), 2.13-1.68 (7H, m, C**H**, $C\mathbf{H}_2$, and 2 x $C\mathbf{H}_2$, THF), 1.85-1.28 (8H, m, 4 x $C\mathbf{H}_2$), 1.68 (3H, s, $C\mathbf{H}_3$), 1.62 (3H, s, $C\mathbf{H}_3$), 1.43 (3H, s, $C\mathbf{H}_3$), 1.31 (3H, s, $C\mathbf{H}_3$), 1.31-0.86 (2H, m, $C\mathbf{H}_2$), 1.26 (3H, s, $C\mathbf{H}_3$), 0.13 (9H, s, COSi$(C\mathbf{H}_3)_3$), 0.10 (9H, s, CH_2OSi$(C\mathbf{H}_3)_3$) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 172.62 (**C**OO), 150.43 (**C**CH, Ar), 131.08 ($(CH_3)_2\mathbf{C}$), 127.95 (2 x **C**H, $Ar_{(meta)}$), 125.92 (2 x **C**H, $Ar_{(ortho)}$), 125.29 (**C**H, $Ar_{(para)}$), 124.78 (C=**C**HCH_2), 87.33 (**C**H, THF), 85.39 (**C**CH_2OH, THF), 76.57 (**C**OSi$(CH_3)_3$), 76.26 (O**C**H), 66.10 ($\mathbf{C}H_2$OSi$(CH_3)_3$), 51.02 (**C**HCPh), 40.68 (**C**Ph), 40.59 ($\mathbf{C}H_2$COSi$(CH_3)_3$), 33.14 ($\mathbf{C}H_2$CHCH), 31.01 ($\mathbf{C}H_2$, THF), 30.41 ($\mathbf{C}H_2$), 27.77 ($\mathbf{C}H_2CH_2CH_2$CH), 25.82 ($\mathbf{C}H_3$), 25.66 ($\mathbf{C}H_2$), 25.51 ($\mathbf{C}H_2$), 24.59 ($\mathbf{C}H_2$, THF), 23.63 ($\mathbf{C}H_3$), 22.82 ($\mathbf{C}H_3$), 22.46 ($\mathbf{C}H_2CH_2$), 17.66 ($\mathbf{C}H_3$), 2.67 (3C, COSi$(\mathbf{C}H_3)_3$), –0.53 (3C, CH_2OSi$(\mathbf{C}H_3)_3$) ppm.

(2*R*,5*S*)-((1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl) tetrahydro-2-(methoxytrimethylsilyl)-5-(2-trimethylsiloxy-propan-2-yl)furan-2-carboxylate (5.21a);

(2*S*,5*R*)-((1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl) tetrahydro-2-(methoxytrimethylsilyl)-5-(2-trimethylsiloxy-propan-2-yl)furan-2-carboxylate (5.21b)



Following the method for the preparation of *bis*-protected *trans*-THF **4.45a,b**, THF diols **5.11a,b** (378 mg, 0.90 mmol) afforded the crude as a yellow oil (412 mg). Purification by column chromatography (SiO_2 eluting with CH_2Cl_2/hexane (10 to 30%)) afforded the title THF **5.21a** (single major diastereoisomer by ^1H NMR) as a yellow oil (315 mg, 0.56 mmol, 62%). The more polar minor diastereoisomer **5.21b** was also isolated as a yellow oil (54 mg, 0.10 mmol, 11%).

Spectroscopic data for major diastereoisomer **5.21a**:

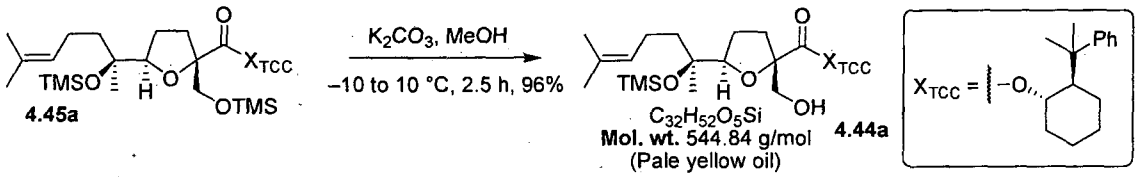
$[\alpha]^{30}_D$	–16.1 (*c* 1.01, $CHCl_3$).
FT-IR ν_{max} (neat)	2954 (m), 2915 (m), 2865 (w), 1726(s), 1249 (s), 1094 (s), 1039 (m), 872 (m), 836 (s), 751 (m), 700 (m) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 7.32-7.16 (5H, m, 5 x C**H**, Ar), 4.85 (1H, td, *J* = 10.6, 4.3 Hz, OC**H**), 4.00 (1H, m, C**H**, THF), 3.83 (1H, d, *J* = 10.1 Hz, C**H**HOSi$(CH_3)_3$), 3.57 (1H, d, *J* = 10.1 Hz, CH**H**OSi$(CH_3)_3$), 2.05-1.79 (5H, m, C**H** and 2 x C$\mathbf{H_2}$, THF), 1.70-1.24 (5H, m, C**H** and 2 x C$\mathbf{H_2}$), 1.41 (3H, s, C$\mathbf{H_3}$), 1.28 (3H, s, C$\mathbf{H_3}$), 1.23 (6H, s, 2 x C$\mathbf{H_3}$), 1.15-0.79 (2H, m, C$\mathbf{H_2}$), 0.85 (3H, s, d, *J* = 6.5 Hz, C$\mathbf{H_3}$CH), 2.59 (9H, s, COSi(C$\mathbf{H_3}$)$_3$), –0.48 (9H, s, CH_2OSi(C$\mathbf{H_3}$)$_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 173.50 (**C**OO), 150.85 (**C**CH, Ar), 127.96 (2 x **C**H, $Ar_{(meta)}$), 125.73 (2 x **C**H, $Ar_{(ortho)}$), 125.22 (**C**H, $Ar_{(para)}$), 87.80 (**C**CH_2O, THF), 87.58 (**C**H, THF), 75.87 (O**C**H), 75.00 (**C**OSi$(CH_3)_3$), 66.73 (**C**H_2OSi$(CH_3)_3$), 50.41 (**C**HCPh), 41.61 (**C**Ph), 40.31 (**C**H_2CH(CH_3)), 34.59 (**C**H_2CH_2CH), 31.50 (**C**H_2, THF), 31.29 (**C**HCH_3), 29.77 (**C**H_3), 27.94 (**C**H_3), 27.34 (**C**H_2, THF), 25.52 (**C**H_2C), 25.14 (**C**H_3), 24.27 (**C**H_3), 21.77 (**C**H_3), 2.59 (3C, COSi(**C**H_3)$_3$), –0.48 (3C, CH_2OSi(**C**H_3)$_3$) ppm.
LRMS (ES^+) m/z	585 (65%, $[M+Na]^+$), 1148 (100%, $[2M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 585.3407; Found: 585.3405 ($[M+Na]^+$).

Spectroscopic data for minor diastereoisomer **5.21b**:

$[\alpha]^{27}_D$	–15.5 (*c* 1.405, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$)	δ 7.32-7.16 (5H, m, 5 x **CH**, Ar), 4.86 (1H, td, *J* = 10.6, 4.3 Hz, O**CH**), 3.89 (1H, m, **CH**, THF), 3.75 (1H, d, *J* = 10.1 Hz, **CH**HOSi$(CH_3)_3$), 3.69 (1H, d, *J* = 10.1 Hz, CH**H**OSi$(CH_3)_3$), 2.17-1.79 (5H, m, **CH** and 2 x **CH$_2$**, THF), 1.52-1.1.21 (3H, m, **CH** and **CH$_2$**), 1.44 (3H, s, **CH$_3$**), 1.31 (3H, s, **CH$_3$**), 1.23 (3H, s, **CH$_3$**), 1.21 (3H, s, **CH$_3$**), 1.03-0.79 (4H, m, **CH$_2$**), 0.84 (3H, s, d, *J* = 6.3 Hz, **CH$_3$**CH), 0.12 (9H, s, COSi$(CH_3)_3$), 0.10 (9H, s, $CH_2OSi(CH_3)_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 172.80 (**C**OO), 150.41 (**C**CH, Ar), 127.94 (2 x **C**H, $Ar_{(meta)}$), 125.92 (2 x **C**H, $Ar_{(ortho)}$), 125.29 (**C**H, $Ar_{(para)}$), 87.74 (**C**CH_2O, THF), 87.54 (**C**H, THF), 75.97 (O**C**H), 74.92 (**C**OSi$(CH_3)_3$), 66.38 ($CH_2OSi(CH_3)_3$), 50.60 (**C**HCPh), 41.63 (**C**Ph), 40.51 ($CH_2CH(CH_3)$), 34.55 (CH_2CH_2CH), 31.34 ($CHCH_3$), 31.29 (CH_2, THF), 30.73 ((CH_3), 27.82 (CH_3), 27.49 (CH_3), 25.59 (CH_2, THF), 25.42 (CH_2C), 23.34 (CH_3), 21.75 (CH_3), 2.57 (3C, COSi$(CH_3)_3$), –0.54 (3C, $CH_2OSi(CH_3)_3$) ppm.

(2*S*,5*R*)-((1*S*,2*R*)-2-(2-Phenylpropan-2-yl)cyclohexyl) tetrahydro-5-((*S*)-2-trimethylsiloxy-6-methylhept-5-en-2-yl)-2-(hydroxymethyl)furan-2-carboxylate (4.44a)

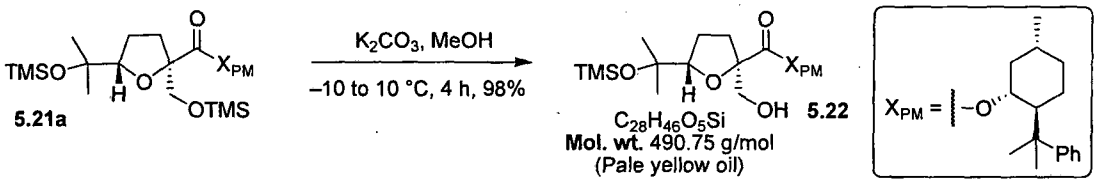


To a solution of THF **4.45a** (650 mg, 1.05 mmol) in MeOH (20 mL) was added dried powdered K_2CO_3 (64 mg) at –10 °C. The resultant milky mixture was stirred for 2.5 hours, while maintaining the temperature. The reaction was quenched by adding H_2O (2 mL) and MeOH was evaporated. The resultant residue was partitioned between Et_2O (30 mL) and H_2O (15 mL), and the organic phase was separated. The aqueous phase was re-extracted with Et_2O (2 x 30 mL), and the combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product **4.44a** as a yellow oil (585 mg). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane

(10 to 20%)) afforded the title THF **4.44a** as a pale yellow oil (552 mg, 1.01 mmol, 96%).

$[\alpha]^{25}_D$	+2.85 (*c* 1.035, $CHCl_3$).
FT-IR ν_{max} (neat)	3483 (br), 2962 (m), 2933 (m), 2860 (w), 1725 (s), 1447 (m), 1250 (s), 1084 (m), 1047 (m), 1020 (m), 839 (s), 700 (s) cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	δ 7.28-7.12 (5H, m, 5 x C**H**, Ar), 5.06 (1H, t, *J* = 7.0 Hz, =C**H**CH_2), 4.78-4.72 (1H, td, *J* = 10.0, 4.3 Hz, OC**H**), 4.08 (1H, t, *J* = 7.0 Hz, C**H**, THF), 3.68 (1H, dd, *J* = 8.2, 4.9 Hz, C**H**HOH), 3.52 (1H, dd, *J* = 8.2, 4.9 Hz, CH**H**OH), 2.62 (1H, dd, *J* = 8.2, 4.9 Hz, CH_2**OH**), 2.06-1.87 (7H, m, C**H**, $C\mathbf{H_2}$, and 2 x $C\mathbf{H_2}$, THF), 1.86-1.41 (8H, m, 4 x $C\mathbf{H_2}$), 1.68 (3H, s, $C\mathbf{H_3}$), 1.61 (3H, s, $C\mathbf{H_3}$), 1.41 (3H, s, $C\mathbf{H_3}$), 1.35-0.87 (2H, m, $C\mathbf{H_2}$), 1.32 (3H, s, $C\mathbf{H_3}$), 1.27 (3H, s, $C\mathbf{H_3}$), 0.11 (9H, s, $COSi(C\mathbf{H_3})_3$) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 173.62 (**C**OO), 150.40 (**C**CH, Ar), 131.63 ($(CH_3)_2\mathbf{C}$), 128.03 (2 x **C**H, $Ar_{(meta)}$), 125.72 (2 x **C**H, $Ar_{(ortho)}$), 125.36 (**C**H, $Ar_{(para)}$), 124.21 (C=**C**HCH_2), 86.32 (**C**H, THF), 85.89 (**C**CH_2, THF), 76.57 ($COSi(CH_3)_3$), 76.33 (OCH), 66.19 (CH_2OH), 50.83 (**C**HCPh), 41.21 (**C**Ph), 40.40 ($CH_2COSi(CH_3)_3$), 33.07 (CH_2CHCH), 32.40 (CH_2, THF), 29.19 (CH_3), 27.61 ($CH_2CH_2CH_2CH$), 25.99 (CH_2), 25.82 (CH_2), 25.65 (CH_3), 25.00 (CH_3), 24.56 (CH_2, THF), 24.15 (CH_3), 23.13 (CH_2CH_2), 17.68 (CH_3), 2.57 (3C, $COSi(CH_3)_3$) ppm.
LRMS (ES^+) m/z	567 (100%, $[M+Na]^+$), 1112 (60%, $[2M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 567.3476; Found: 567.3461 ($[M+Na]^+$).

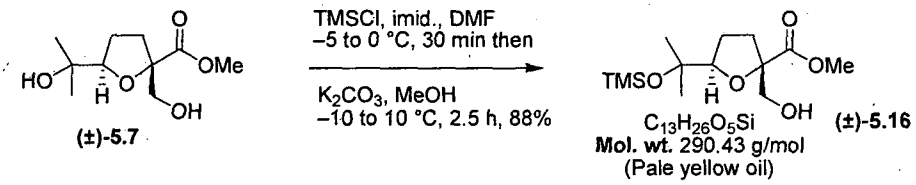
(2*R*,5*S*)-((1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl) tetrahydro-2-(hydroxymethyl)-5-(2-trimethylsiloxy-propan-2-yl)furan-2-carboxylate (5.22)



Following the procedure for the preparation of *trans*-THF **4.44a**, THF **5.21a** (307 mg, 0.55 mmol) afforded the crude **5.22** as a yellow oil (270 mg). Purification by column chromatography (SiO_2 eluting with CH_2Cl_2/hexane (60 to 100%)) afforded the title THF **5.22** as a pale yellow oil (262 mg, 0.53 mmol, 98%).

$[\alpha]^{26}_D$	–7.34 (*c* 1.07, $CHCl_3$).
FT-IR ν_{max} (neat)	3478 (br), 2955 (m), 2922 (m), 2871 (m), 1725 (s), 1251 (m), 1172 (m), 1050 (m), 841 (s), 761 (m), 701 (m) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$)	δ 7.28-7.13 (5H, m, 5 x C**H**, Ar), 4.75 (1H, td, *J* = 10.6, 4.3 Hz, OC**H**), 3.94 (1H, m, C**H**, THF), 3.68 (1H, dd, *J* = 11.3, 3.7 Hz, C**H**HOH), 3.53 (1H, dd, *J* = 11.3, 9.4 Hz, CH**H**OH), 2.89 (1H, dd, *J* = 9.4, 3.7 Hz, O**H**), 2.15-1.84 (5H, m, C**H** and 2 x C**H**$_2$, THF), 1.56-1.20 (5H, m, C**H** and 2 x C**H**$_2$), 1.36 (3H, s, C**H**$_3$), 1.33 (3H, s, C**H**$_3$), 1.27 (3H, s, C**H**$_3$), 1.17 (3H, s, C**H**$_3$), 1.00-0.74 (2H, m, C**H**$_2$), 0.84 (3H, s, d, *J* = 6.4 Hz, C**H**$_3$CH), 0.14 (9H, s, COSi(C**H**$_3$)$_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 173.49 (**C**OO), 150.39 (**C**CH, Ar), 128.01 (2 x **C**H, Ar$_{(meta)}$), 125.68 (2 x **C**H, Ar$_{(ortho)}$), 125.37 (**C**H, Ar$_{(para)}$), 88.59 (**C**CH$_2$OH, THF), 86.13 (**C**H, THF), 75.91 (O**C**H), 75.02 (**C**OSi(CH$_3$)$_3$), 65.92 (**C**H$_2$OH), 50.42 (**C**HCPh), 41.41 (**C**Ph), 40.19 (**C**H$_2$CH(CH$_3$)), 34.53 (**C**H$_2$CH$_2$CH), 32.55 (**C**H$_2$, THF), 31.28 (**C**HCH$_3$), 29.32 (**C**H$_3$), 27.37 (**C**H$_3$), 27.23 (**C**H$_2$, THF), 27.07 (**C**H$_2$C), 26.45 (**C**H$_3$), 24.93 (**C**H$_3$), 21.73 (**C**H$_3$), 2.35 (3C, COSi(**C**H$_3$)$_3$) ppm.
LRMS (ES$^+$) m/z	513 (100%, $[M+Na]^+$).
HRMS (ES$^+$) m/z	Calculated: 513.3007; Found: 513.3020 ($[M+Na]^+$).

Rac.(2_S_,5_R_)-Methyl tetrahydro-2-(hydroxymethyl)-5-(2-trimethylsiloxy-2-yl)furan-2-carboxylate ((±)-5.16)

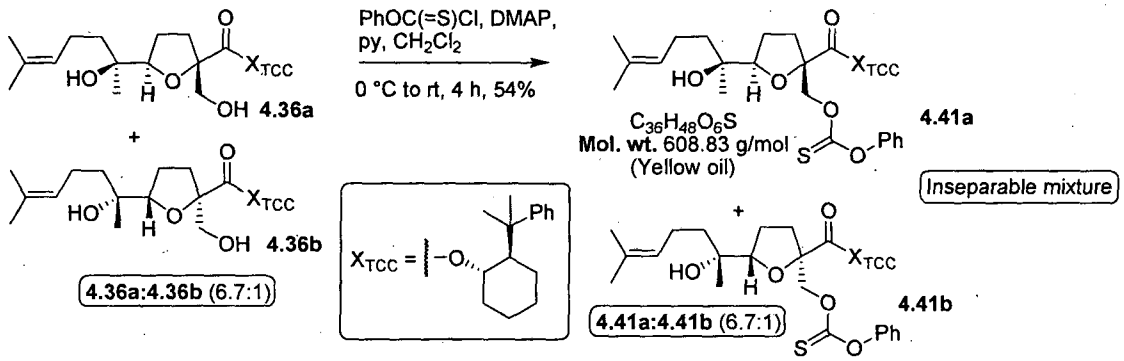


To a stirred solution of racemic THF **(±)-5.7** (397 mg, 1.68 mmol) and imidazole (1.14 g, 16.8 mmol) in DMF (3 mL) was added TMSCl (0.65 mL, 5.04 mmol) at 0 °C. The mixture was stirred at this temperature for 15 min. After this stage, anhydrous MeOH (2 mL) was added in the reaction mixture followed by the addition of K_2CO_3 (2 mg in 1 mL anhydrous MeOH). The reaction mixture was stirred at 0 °C for 1.5 hours, whereupon it was quenched by acetic acid (5% aq., 5 mL). The organic phase was separated and the aqueous phase was re-extracted with Et_2O (2 x 20 mL). The combined organic phases were dried (Na_2SO_4), concentrated *in vacuo* to afford the crude **(±)-5.16** as a pale yellow oil (443 mg). Purification by column chromatography (SiO_2 eluting with with EtOAc/hexane (10 to 20%)) afforded the title racemic alcohol **(±)-5.16** as a pale yellow oil (428 mg, 1.47 mmol, 88%).

FT-IR ν_{max} (neat)	3465 (br), 2950 (m), 2890 (w), 2868 (w), 1732 (s), 1242 (m), 1169 (m), 1037 (s), 837 (s) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 3.96 (1H, t, J = 7.3 Hz, C**H**, THF), 3.84 (1H, dd, J = 11.3, 4.0 Hz, C**H**HOH), 3.74 (3H, s, OC**H**$_3$), 3.71 (1H, dd, J = 11.3, 9.0 Hz, CH**H**OH), 2.91 (1H, dd, J = 9.0, 4.0 Hz, O**H**), 2.27-1.86 (4H, m, 2 x C**H**$_2$), 1.37 (3H, s, C**H**$_3$), 1.18 (3H, s, C**H**$_3$), 0.15 (9H, s, Si,(C**H**$_3$)$_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 174.48 (**C**OO), 88.56 (**C**CH$_2$OH, THF), 86.81 (**C**H, THF), 75.18 ((CH$_3$)$_2$**C**), 66.14 (**C**H$_2$OH), 52.16 (O**C**H$_3$), 32.41 (**C**H$_2$, THF), 27.37 (**C**H$_2$, THF), 26.97 (**C**H$_3$), 26.30 (**C**H$_3$), 2.33 (3C, Si(**C**H$_3$)$_3$) ppm.
LRMS (ES^+) m/z	313 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 313.1442; Found: 313.1442 ($[M+Na]^+$).

***O*-((2*S*,5*R*)-2-(((1*S*,2*R*)-2-(2-Phenylpropan-2-yl)cyclohexyloxy)carbonyl) tetrahydro-5-((*S*)-2-hydroxy-6-methylhept-5-en-2-yl)furan-2-yl)methyl-*O*-phenyl carbonothioate (4.41a);**

***O*-((2*R*,5*S*)-2-(((1*S*,2*R*)-2-(2-Phenylpropan-2-yl)cyclohexyloxy)carbonyl) tetrahydro-5-((*R*)-2-hydroxy-6-methylhept-5-en-2-yl)furan-2-yl)methyl-*O*-phenyl carbonothioate (4.41b)**

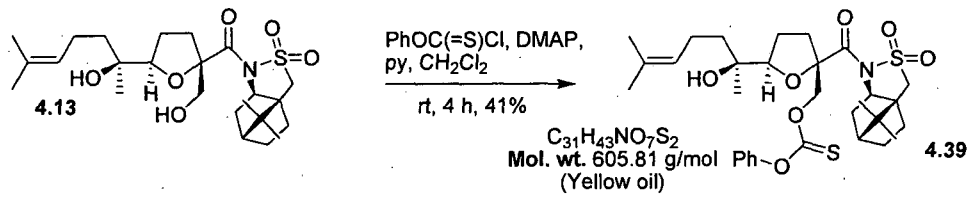


According to the method of Ireland *et al.*,[128] to a solution of THF diols **4.36a,b** (20 mg, 0.04 mmol, d.r. 6.7:1), pyridine (34 μL, 0.42 mmol) and catalytic DMAP (20 mol%) in CH_2Cl_2 (2 mL) was added phenyl chlorothionoformate (59 μL, 0.42 mmol) at 0 °C. The bright yellow mixture was stirred for 4 hour at room temperature, diluted with CH_2Cl_2 (10 mL) and washed with HCl (2 N, 10 mL) and water (2 x 10 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude product **4.41a,b** as a bright yellow oil in a diastereomeric ratio (35 mg, **4.41a**:**4.41b** = 6.7:1). Purification by column chromatography (SiO_2 eluting with CH_2Cl_2/hexane (50 to 100%)) afforded an inseparable mixture of title thionoformates **4.41a,b** as a yellow oil (14 mg, 0.02 mmol, 54%).

$[\alpha]^{25}_D$	+ 1.03 (*c* 0.35, $CHCl_3$).
FT-IR ν_{max} (neat)	3550 (br), 2966 (m), 2925 (m), 2860 (w), 1720 (s), 1487 (m), 1295 (s), 1197 (s), 1107 (m), 760 (w), 731 (m), 694 (m) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$)	δ 7.40 (2H, td, *J* = 7.5, 1.8 Hz, 2 x C**H**, Ar), 7.35-7.25 (6H, m, 6 x C**H**, Ar), 7.21-7.08 (2H, m, 2 x C**H**, Ar), 5.10 (1H, tt, *J* = 7.1 and 1.3 Hz, =C**H**CH_2), 4.93_{min} and 4.83_{maj} (1H, td, *J* = 10.0, 4.2 Hz, OC**H**), 4.69 (1H, d, *J* = 11.3 Hz, C**H**HOCS), 4.53 (1H, d, *J* = 11.3 Hz, CH**H**OCS), 4.14_{maj} and 4.02_{min} (1H, t, *J* = 7.0 Hz, C**H**, THF), 2.22-1.81 (12H, m, O**H**, C**H**, 3 x $C\mathbf{H}_2$, 2 x $C\mathbf{H}_2$, THF), 1.70 (3H, s, $C\mathbf{H}_3$), 1.64 (3H, s, $C\mathbf{H}_3$), 1.59-1.34

	(4H, m, 2 x CH_2), 1.38 (3H, s, CH_3), 1.33-0.98 (2H, m, CH_2) 1.28 (6H, s, 2 x CH_3) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 195.22 (C=S), 171.90 (COO), 153.42 (CCH, Ar), 150.62 (CCH, Ar), 131.69 ($(CH_3)_2C$), 129.50 (2 x CH, $Ar_{(meta)}$), 128.14 (2 x CH, $Ar_{(meta)}$), 126.55 (CH, $Ar_{(para)}$), 125.63 (2 x CH, $Ar_{(ortho)}$), 125.37 (CH, $Ar_{(para)}$), 124.44 ($C=CHCH_2$), 121.84 (2 x CH, $Ar_{(ortho)}$), 87.80 (CH, THF), 84.22 (CCH_2OCS, THF), 75.57 (OCH), 72.71 (COH), 50.67 (CHCPh), 40.27 (CPh), 37.81 (CH_2COH), 32.81 (CH_2CHCH), 31.99 (CH_2, THF), 28.14 ($CH_2CH_2CH_2CH$), 27.45 (CH_2), 25.93 (CH_2CH_2), 25.81 (CH_3), 25.67 (CH_3), 25.26 (CH_3), 24.57 (CH_2, THF), 24.10 (CH_3), 22.14 (CH_2CH_2), 17.66 (CH_3) ppm.
LRMS (ES^+) m/z	626 (50%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 626.3510; Found: 626.3521 ($[M+Na]^+$).

_N_-[_O_-((2_S_,5_R_)-2-Methyl-_O_-phenylcarbonothioatyl) tetrahydro-5-((_S_)-2-hydroxy-6-methylhept-5-en-2-yl)furan-2-yl)]-2-(2_R_)-camphor-10,2-sultam (4.39)

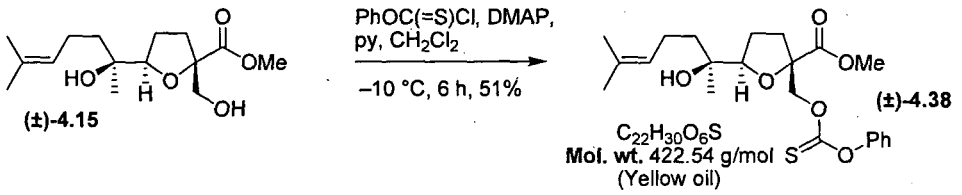


Following the procedure for the preparation of thionoformates **4.41a,b**, enantiomerically pure THF diol **4.13** (140 mg, 0.30 mmol) afforded the crude **4.39** as a golden yellow oil (130 mg). Purification by column chromatography (SiO_2 eluting with 20% EtOAc/hexane) afforded the title thionoformate **4.39** as a yellow oil (72 mg, 0.12 mmol, 41%).

$[\alpha]^{26}_D$	–25.93 (_c_ 0.835, $CHCl_3$).
FT-IR ν_{max} (neat)	3509 (br), 2961 (m), 2935 (m), 2832 (w), 1751 (w), 1676 (m), 1196 (s), 907 (s), 729 (s) cm^{-1}.
^1H NMR (100 MHz, $CDCl_3$)	δ 7.47-7.37 (2H, m, 2 x CH, $Ar_{(meta)}$), 7.34-7.09 (3H, m, 3 x CH, Ar), 5.10 (1H, tt, J = 7.0, 1.4 Hz, $=CHCH_2$), 4.98 (1H, d,

	J = 11.0, Hz, C**H**HOCS), 4.87 (1H, d, J = 11.0 Hz, CH**H**OCS), 4.20 (1H, dd, J = 8.6, 6.8 Hz, C**H**N), 4.09 (1H, dd, J = 7.9, 4.8 Hz, C**H**, THF), 33.54 (1H, d, J = 13.5 Hz, C**H**HSO$_2$), 3.44 (1H, d, J = 13.5 Hz, CH**H**SO$_2$), 2.51-1.74 (12H, m, O**H**, C**H**H, 3 x C**H$_2$** and 2 x C**H$_2$**, THF), 1.68 (3H, s, C**H$_3$**), 1.62 (3H, s, C**H$_3$**), 1.56-1.24 (4H, m, 2 x C**H$_2$**), 1.31 (3H, s, C**H$_3$**), 1.23 (3H, s, C**H$_3$**), 1.02 (3H, s, C**H$_3$**) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 195.10 (**C**=S), 175.18 (**C**ON), 153.50 (**C**CH, Ar), 131.38 ((CH$_3$)$_2$**C**), 129.45 (2 x **C**H, Ar$_{(meta)}$), 126.51 (**C**H, Ar$_{(para)}$), 124.75 (=**C**HCH$_2$), 121.26 (2 x **C**H, Ar$_{(ortho)}$), 88.71 (**C**H, THF), 87.32 (**C**CH$_2$O, THF), 75.45 (**C**H$_2$OCS), 72.99 (**C**OH), 67.60 (**C**HN), 54.58 (**C**H$_2$S), 47.93 (**C**CH$_2$S), 47.58 (**C**(CH$_3$)$_2$), 45.44 (**C**HC(CH$_3$)$_2$), 39.23 (**C**H$_2$CHN), 36.87 (**C**H$_2$COH), 35.20 (**C**H$_2$C), 33.67 (**C**H$_2$, THF), 26.17 (**C**H$_2$, THF), 25.67 (**C**H$_3$), 24.41 (**C**H$_3$), 24.11 (**C**H$_2$CH$_2$C), 22.11 (**C**H$_2$CH$_2$), 21.73 (**C**H$_3$), 19.92 (**C**H$_3$), 17.65 (**C**H$_3$) ppm.
LRMS (ES$^+$) m/z	628 (100%, [M+Na]$^+$).
HRMS (ES$^+$) m/z	Calculated: 606.2554; Found: 606.2568 ([M+H]$^+$).

***Rac.* *O*-((2*S*,5*R*)-2-(Methoxycarbonyl) tetrahydro-5-((*S*)-2-hydroxy-6-methylhept-5-en-2-yl)furan-2-yl)methyl *O*-phenyl carbonothioate ((±)-4.38)**

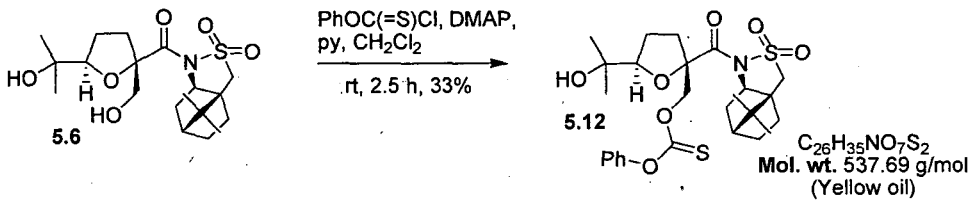


Following the procedure for the preparation of thionoformates **4.41a,b**, racemic THF **(±)-4.15** (81 mg, 0.28 mmol) afforded the crude **(±)-4.38** as a yellow oil (98 mg). Purification by column chromatography (SiO_2 eluting with CH_2Cl_2/hexane (60 to 90%)) afforded the title thionoformate **(±)-4.38** as a yellow oil (60 mg, 0.14 mmol, 51%).

FT-IR ν_{max} (neat)	3513 (br), 2967 (m), 2917 (m), 2865 (m), 1737 (s), 1293 (m), 1199 (s), 1115 (m), 771 (w) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$)	δ 7.47-7.35 (2H, m, 2 x **C**H, Ar$_{(meta)}$), 7.28 (1H, m, **C**H, Ar$_{(para)}$), 7.15-7.06 (2H, m, 2 x **C**H, Ar$_{(ortho)}$), 5.10 (1H, tt, J =

	7.0, 1.4 Hz, =C**H**CH_2), 4.84-4.79 (2H, m, C$\mathbf{H_2}$O), 4.13 (1H, t, *J* = 7.3 Hz, C**H**, THF), 3.78 (3H, s, OC$\mathbf{H_3}$), 2.30-1.77 (6H, m, C$\mathbf{H_2}$, and 2 x C$\mathbf{H_2}$, THF), 1.84 (1H, br, O**H**), 1.67 (3H, s, C$\mathbf{H_3}$), 1.61 (3H, s, C$\mathbf{H_3}$), 1.58-1.29 (2H, m, C$\mathbf{H_2}$), 1.28 (3H, s, C$\mathbf{H_3}$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 195.07 (**C**=S), 172.85 (**C**OO), 153.38 (**C**CH, Ar), 131.76 ($(CH_3)_2$**C**), 129.49 (2 x **C**H, $Ar_{(meta)}$), 126.59 (**C**H, $Ar_{(para)}$), 124.34 (=**C**HCH_2), 121.83 (2 x **C**H, $Ar_{(ortho)}$), 87.77 (**C**H, THF), 84.35 (**C**CH_2O, THF), 75.38 (**C**H_2O), 72.87 (**C**OH), 52.60 (O**C**H_3), 37.79 (**C**H_2COH), 32.91 (**C**H_2, THF), 25.65 (**C**H_3), 25.21 (**C**H_2, THF), 24.01 (CH_2**C**H_2), 22.12 (**C**H_3), 17.64 (**C**H_3) ppm.
LRMS (ES^+) m/z	445 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 445.1655; Found: 445.1651 ($[M+Na]^+$).

***N*-[*O*-((2*S*,5*R*)-2-Methyl *O*-phenylcarbonothioatyl) tetrahydro-5-(2-hydroxypropan-2-yl)furan-2-yl]-2-(2*R*)-camphor-10,2-sultam (5.12)**

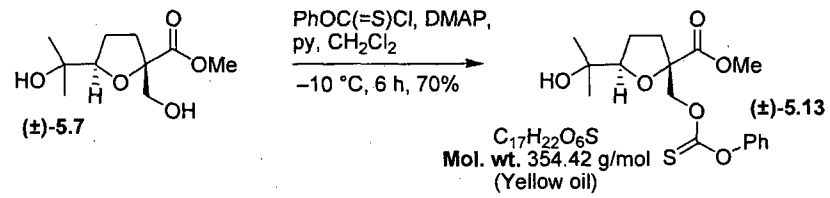


Following the method for the preparation of thionoformates **4.41a,b**, enantiomerically pure THF diol **5.6** (235 mg, 0.59 mmol) afforded the crude **5.12** as a yellow oil (220 mg). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (10 to 25%)) afforded the title thionoformate **5.12** as a yellow oil (104 mg, 0.19 mmol, 33%).

$[\alpha]^{24}_D$	–37.0 (*c* 0.7, $CHCl_3$).
FT-IR ν_{max} (neat)	3535 (br), 2967 (m), 2950 (m), 2870 (w), 1677 (m), 1340 (m), 1287 (m), 1200 (s), 1051 (w) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$)	δ 7.41 (2H, t, *J* = 8.0 Hz, 2 x **C**H, $Ar_{(meta)}$), 7.29 (1H, m, **C**H, $Ar_{(para)}$), 7.11 (2H, t, *J* = 8.0 Hz, 2 x **C**H, $Ar_{(orth)}$), 4.98 (1H, d, *J* = 11.0 Hz, C**H**HO), 4.85 (1H, d, *J* = 11.0 Hz, CH**H**O), 4.16 (1H, t, *J* = 7.0 Hz, C**H**N), 4.10 (1H, dd, *J* = 7.5, 4.5 Hz, C**H**,

	THF), 3.55 (1H, d, J = 13.4 Hz, C**H**HSO$_2$), 3.46 (1H, d, J = 13.4 Hz, CH**H**SO$_2$), 2.84 (1H, br, O**H**), 2.50-1.87 (8H, m, 2 x C**H$_2$** and 2 x C**H$_2$**, THF), 1.45-1.28 (3H, m, C**H** and C**H$_2$**), 1.28 (3H, s, C**H$_3$**), 1.23 (3H, s, C**H$_3$**), 1.18 (3H, s, C**H$_3$**), 1.01 (3H, s, C**H$_3$**) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 195.08 (**C**=S), 175.27 (**C**ON), 153.49 (**C**CH, Ar), 129.47 (2 x **C**H, Ar$_{(meta)}$), 126.53 (**C**H, Ar$_{(para)}$), 121.93 (2 x **C**H, Ar$_{(ortho)}$), 88.89 (**C**CH$_2$, THF), 87.46 (**C**H, THF), 75.42 (**C**H$_2$O), 71.29 ((CH$_3$)$_2$**C**), 67.62 (**C**HN), 54.59 (**C**H$_2$S), 47.92 (**C**CH$_2$S), 47.57 (**C**(CH$_3$)$_2$), 45.48 (**C**HC(CH$_3$)$_2$), 39.24 (**C**H$_2$CHN), 35.30 (**C**H$_2$C), 33.69 (**C**H$_2$, THF), 27.31 (**C**H$_2$CH$_2$C), 26.16 (**C**H$_2$, THF), 25.98 (**C**H$_3$), 23.98 (**C**H$_3$), 21.77 (**C**H$_3$), 19.91 (**C**H$_3$) ppm.
LRMS (ES$^+$) m/z	560 (100%, [M+Na]$^+$).
HRMS (ES$^+$) m/z	Calculated: 560.1747; Found: 560.1749 ([M+Na]$^+$).

***Rac. O*-((2*S*,5*R*)-2-(Methoxycarbonyl) tetrahydro-5-(2-hydroxypropan-2-yl)furan-2-yl)methyl *O*-phenyl carbonothioate ((±)-5.13)**

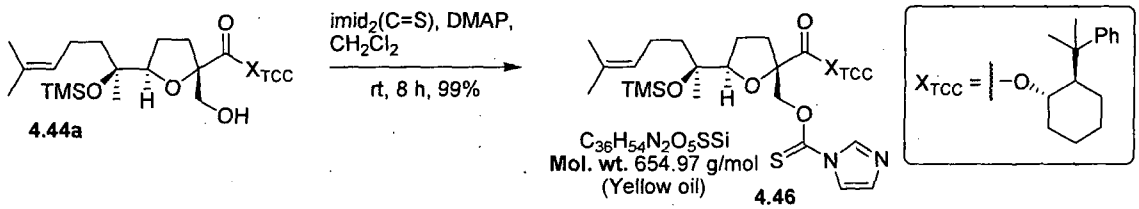


Following the procedure for the preparation of thionoformates **4.41a,b**, racemic THF **(±)-5.7** (145 mg, 0.66 mmol) afforded the crude **(±)-5.13** as a yellow oil (215 mg). Purification by column chromatography (SiO_2 eluting with CH_2Cl_2/hexane (40 to 90%)) afforded the title thionoformate **(±)-5.13** as a yellow oil (164 mg, 0.46 mmol, 70%).

FT-IR ν_{max} (neat)	3383 (br), 2971 (m), 2877 (w),1728 (s), 1295 (m), 1201 (s), 1042 (m), 772 (w), 690 (m) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$)	δ 7.45-7.35 (2H, m, 2 x **C**H, Ar$_{(meta)}$), 7.27 (1H, m, **C**H, Ar$_{(para)}$), 7.10-7.06 (2H, m, 2 x **C**H, Ar$_{(ortho)}$), 4.84 (1H, d, J = 11.3 Hz, C**H**HO), 4.79 (1H, d, J = 11.3 Hz, CH**H**O), 4.12 (1H, t, J = 7.3 Hz, C**H**, THF), 3.78 (3H, s, OC**H$_3$**), 2.29-2.12 (3H,

	m, OH and CH_2, THF), 2.07-1.89 (2H, m, CH_2, THF), 1.29 (3H, s, CH_3), 1.15 (3H, s, CH_3) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 194.98 (C=S), 172.73 (COO), 153.31 (CCH, Ar), 129.45 (2 x CH, $Ar_{(meta)}$), 126.55 (CH, $Ar_{(para)}$), 121.75 (2 x CH, $Ar_{(ortho)}$), 88.23 (CH, THF), 84.53 (CCH_2O, THF), 75.29 (CH_2O), 71.04 ($(CH_3)_2C$), 52.57 (OCH_3), 32.84 (CH_2, THF), 27.31 (CH_2, THF), 25.61 (CH_3), 24.66 (CH_3) ppm.
LRMS (ES^+) m/z	377 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 377.1029; Found: 377.1026 ($[M+Na]^+$).

(2*S*,5*R*)-((1*S*,2*R*)-2-(2-Phenylpropan-2-yl)cyclohexyl) tetrahydro-5-((*S*)-2-trimethylsiloxy-6-methylhept-5-en-2-yl)-2-(*O*-methoxy-1*H*-imidazol-1-carbothioyl)furan-2-carboxylate (4.46)

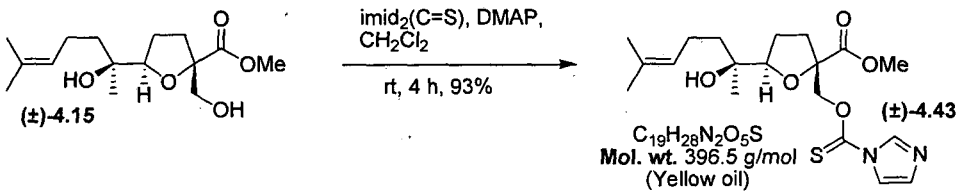


To a solution of enantiomerically pure THF **4.44a** (551 mg, 1.01 mmol) in CH_2Cl_2 (20 mL) was added DMAP (38mg, 0.30 mmol) and thiocarbonyl diimidazole (570 mg, 3.0 mmol). The resultant bright yellow solution was stirred at room temperature for 8 hours. The reaction was concentrated *in vacuo* to give crude **4.46** as a golden yellow oil (671 mg). Purification by column chromatography (SiO_2 eluting with 10% EtOAc/hexane) afforded the title thiocarbonyl imidazolide **4.46** as a yellow oil (654 mg, 1.0 mmol, 99%).

$[\alpha]^{25}_D$	–8.86 (*c* 1.14, $CHCl_3$).
FT-IR ν_{max} (neat)	2957 (m), 2933 (m), 2859 (w), 1728 (s), 1463 (m), 1391 (s), 1332 (s), 1287 (s), 1248 (s), 1197 (s), 1107 (m), 760 (w), 731 (m), 694 (m) cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	δ 8.28 (1H, t, *J* = 1.2 Hz, NCHN), 7.58 (1H, dd, *J* = 1.7, 1.2 Hz, CHN), 7.26-7.11 (5H, m, Ar), 6.98 (1H, dd, *J* = 1.7, 0.8 Hz, NCHCH), 5.05 (1H, t, *J* = 7.0 Hz, $=CHCH_2$), 4.82 (1H, td, *J* = 10.0, 4.3 Hz, OCH), 4.68 (1H, d, *J* = 10.8 Hz, CHHO),

	4.35 (1H, d, J = 10.8 Hz, CH**H**O), 4.16 (1H, t, J = 6.4 Hz, C**H**, THF), 2.08-1.76 (7H, m, C**H**, C**H**$_2$, and 2 x C**H**$_2$, THF), 1.66 (3H, s, C**H**$_3$), 1.60-1.28 (8H, m, 4 x C**H**$_2$), 1.59 (3H, s, C**H**$_3$), 1.41 (3H, s, C**H**$_3$), 1.20-0.87 (2H, m, C**H**$_2$), 1.20 (6H, s, 2 x C**H**$_3$), 0.06 (9H, s, COSi(C**H**$_3$)$_3$) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 183.76 (**C**=S), 171.87 (**C**OO), 150.80 (**C**CH, Ar), 136.95 (N**C**HN), 131.47 ((CH$_3$)$_2$**C**), 130.79 (N**C**HCH), 128.18 (2 x **C**H, Ar$_{(meta)}$), 125.51 (2 x **C**H, Ar$_{(ortho)}$), 125.36 (**C**H, Ar$_{(para)}$), 124.38 (C=**C**H), 117.80 (**C**HN), 87.02 (**C**H, THF), 84.06 (**C**CH$_2$O, THF), 77.42 (**C**OSi(CH$_3$)$_3$), 76.43 (O**C**H), 75.67 (**C**H$_2$OC=S), 50.35 (**C**HCPh), 40.74 (**C**Ph), 40.22 (**C**H$_2$COSi(CH$_3$)$_3$), 32.97 (**C**H$_2$CHCH), 32.81 (**C**H$_2$, THF), 28.00 (**C**H$_3$), 27.39 (**C**H$_2$CH$_2$CH$_2$CH), 25.82 (2 x **C**H$_3$), 25.65 (**C**H$_2$), 25.46 (**C**H$_2$), 24.49 (**C**H$_2$, THF), 23.16 (**C**H$_3$), 22.57 (**C**H$_2$CH$_2$), 17.64 (**C**H$_3$), 2.58 (3C, COSi(**C**H$_3$)$_3$) ppm.
LRMS (ES$^+$) m/z	677 (100%, [M+Na]$^+$).
HRMS (ES$^+$) m/z	Calculated: 655.3595; Found: 655.3585 ([M+H]$^+$).

***Rac.*(2*S*,5*R*)-Methyl tetrahydro-5-((*S*)-2-hydroxy-6-methylhept-5-en-2-yl)-2-(*O*-methoxy-1*H*-imidazol-1-carbothioyl) furan-2-carboxylate ((±)-4.43)**

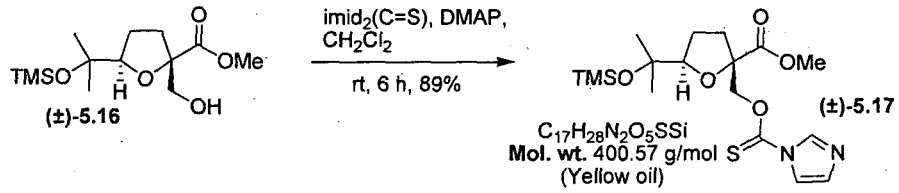


Following the method for the preparation of thiocarbonyl imidazolide **4.46**, racemic THF **(±)-4.15** (29 mg, 0.10 mmol) afforded the crude **(±)-4.43** as a yellow oil (48 mg). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (10 to 30%)) afforded the title racemic thiocarbonyl imidazolide **(±)-4.43** as a yellow oil (37 mg, 0.09 mmol, 93%).

FT-IR ν_{max} (neat)	3360 (br), 2967 (m), 2917 (m), 2868 (w), 1736 (s), 1389 (s), 1332 (s), 1286 (s), 1231 (m), 1106 (m), 997 (s) cm^{-1}.
^{1}H NMR	δ 8.34 (1H, s, NC**H**N), 7.62 (1H, t, J = 1.4 Hz, C**H**N), 7.03

(300 MHz, $CDCl_3$)	(1H, dd, J = 1.4, 0.8 Hz, NC**H**CH), 5.10 (1H, tt, J = 7.0, 1.4 Hz, =C**H**CH_2), 4.89 (2H, s, C**H**$_2$O), 4.09 (1H, dd, J = 7.9, 6.9 Hz, C**H**, THF), 3.80 (3H, s, OC**H**$_3$), 2.37-1.89 (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**$_3$), 1.57-1.31 (3H, m, O**H** and C**H**$_2$), 1.26 (3H, s, C**H**$_3$) ppm.
^{13}C NMR	δ 183.92 (**C**=S), 172.70 (**C**OO), 137.03 (N**C**HN), 131.97
(75 MHz, $CDCl_3$)	((C**H**$_3$)$_2$**C**), 131.03 (N**C**HCH), 124.13 (=**C**HCH$_2$), 117.88 (**C**HN), 87.70 (**C**H, THF), 84.20 (**C**CH$_2$O, THF), 73.48 (**C**H$_2$O), 66.27 (**C**OH), 52.74 (O**C**H$_3$), 37.94 (**C**H$_2$COH), 33.00 (**C**H$_2$, THF), 25.65 (**C**H$_3$), 25.15 (**C**H$_2$, THF), 23.95 (**C**H$_3$), 22.07 (**C**H$_2$CH$_2$), 17.63 (**C**H$_3$) ppm.
LRMS (ES$^+$) m/z	419 (100%, [M+Na]$^+$).
HRMS (ES$^+$) m/z	Calculated: 397.1792 ; Found: 397.1787 ([M+H]$^+$).

Rac.(2_S_,5_R_)-Methyl tetrahydro-2-(_O_-methoxy-1_H_-imidazol-1-carbothioyl)-5-(2-trimethylsiloxy-2-yl) furan-2-carboxylate ((±)-5.17)

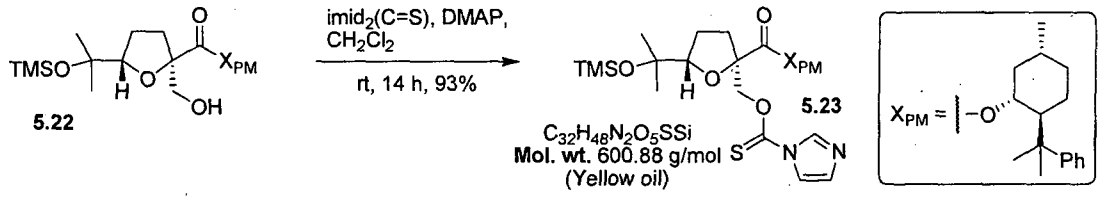


Following the method for the preparation of thiocarbonyl imidazolide **4.46**, racemic mono-protected THF **(±)-5.16** (320 mg, 1.10 mmol) afforded crude **(±)-5.17** as a yellow oil (445 mg). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (10 to 20%)) afforded the title racemic thiocarbonyl imidazolide **(±)-5.17** as a yellow oil (409 mg, 1.02 mmol, 89%).

FT-IR ν_{max} (neat)	2965 (m), 2953 (m), 2840 (w), 1737 (s), 1390 (s), 1330 (s), 1286 (s), 1246 (s), 1173 (w), 1037 (m), 955 (m), 839 (s) cm^{-1}.
^{1}H NMR	δ 8.30 (1H, s, NC**H**N), 7.60 (1H, t, J = 1.4 Hz, C**H**N), 7.03
(400 MHz, $CDCl_3$)	(1H, dd, J = 1.4, 0.8 Hz, NC**H**CH), 4.91 (1H, d, J = 10.8 Hz, C**H**HO), 4.73 (1H, d, J = 10.8 Hz, CH**H**O), 4.04 (1H, m, C**H**, THF), 3.79 (3H, s, OC**H**$_3$), 2.28-1.93 (4H, m, 2 x C**H**$_2$, THF), 1.27 (3H, s, C**H**$_3$), 1.19 (3H, s, C**H**$_3$), 0.12 (9H, s, Si,(C**H**$_3$)$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$)	δ 183.69 (**C**=S), 173.01 (**C**OO), 136.87 (N**C**HN), 130.86 (N**C**HCH), 117.88 (**C**HN), 89.14 (**C**H, THF), 84.76 (**C**CH_2O, THF), 75.84 (CH_2OCS), 74.80 (($CH_3)_2$**C**), 52.68 (OCH_3), 33.12 (CH_2, THF), 27.26 (CH_2, THF), 26.18 (CH_3), 25.47 (CH_3), 2.48 (3C, Si($CH_3)_3$) ppm.
LRMS (ES^+) m/z	423 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 423.1386; Found: 423.1392 ($[M+Na]^+$).

(2*R*,5*S*)-((1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl) tetrahydro-2-(*O*-methoxy-1*H*-imidazol-1-carbothioyl)-5-(2-trimethylsiloxypropan-2-yl)furan-2-carboxylate (5.23)

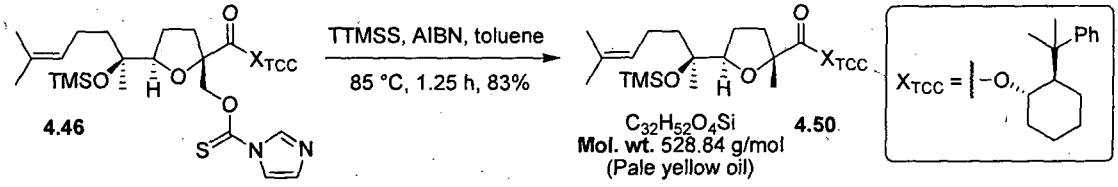


Following the procedure for the preparation of thiocarbonyl imidazolide **4.46**, enantiomerically pure mono-protected THF **5.22** (260 mg, 0.53 mmol) afforded crude **5.23** as a yellow oil (310 mg). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (5 to 25%)) afforded the title thiocarbonyl imidazolide **5.23** as a yellow oil (297 mg, 0.49 mmol, 93%).

$[\alpha]^{27}_D$	+7.85 (*c* 1.21, $CHCl_3$).
FT-IR ν_{max} (neat)	2955 (m), 2915 (m), 2865 (w), 1730 (m), 1463 (m), 1391 (s), 1332 (s), 1287 (s), 1248 (s), 1176 (m), 1037 (m), 955 (m), 840 (s), 764 (m), 701 (m) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$)	δ 8.31 (1H, t, *J* = 1.0 Hz, NC**H**N), 7.60 (1H, t, *J* = 1.0 Hz, C**H**N), 7.30-7.12 (5H, m, Ar), 6.98 (1H, dd, *J* = 1.6, 1.0 Hz, NC**H**CH), 4.82 (1H, td, *J* = 10.6, 4.3 Hz, OC**H**), 4.71 (1H, d, *J* = 10.8 Hz, C**H**HO), 4.39 (1H, d, *J* = 10.8 Hz, CH**H**O), 4.04 (1H, t, *J* = 6.5 Hz, C**H**, THF), 2.04-1.73 (5H, m, C**H** and 2 x CH_2, THF), 1.55-1.36 (5H, m, C**H** and 2 x CH_2), 1.34 (3H, s, CH_3), 1.21 (3H, s, CH_3), 1.20 (3H, s, CH_3), 1.19 (3H, s, CH_3), 1.03-0.69 (2H, m, CH_2), 0.73 (3H, d, *J* = 6.4 Hz, CH_3CH), 0.07 (9H, s, COSi($CH_3)_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$)	δ 183.78 (**C**=S), 171.89 (**C**OO), 150.84 (**C**CH, Ar), 137.01 (NCHN), 130.72 (N**C**HCH), 128.14 (2 x **C**H, $Ar_{(meta)}$), 125.45 (2 x **C**H, $Ar_{(ortho)}$), 125.32 (**C**H, $Ar_{(para)}$), 117.88 (**C**HN), 89.17 (**C**H, THF), 84.45 (**C**CH_2OH, THF), 76.61 (O**C**H), 75.87 (**C**H_2OCS), 74.64 (**C**O$Si(CH_3)_3$), 49.88 (**C**HCPh), 41.40 (**C**Ph), 39.99 (**C**H_2CH(CH_3)), 34.33 (**C**H_2CH_2CH), 32.77 (**C**H_2, THF), 31.17 (**C**HCH_3), 27.92 (**C**H_3), 27.40 (**C**H_3), 26.99 (**C**H_2, THF), 25.98 (**C**H_3), 25.92 (**C**H_2C), 25.59 (**C**H_3), 21.53 (**C**H_3), 2.46 (3C, CO$Si(CH_3)_3$) ppm.
LRMS (ES^+) m/z	623 (80%, $[M+Na]^+$), 601 (550%, $[M+H]^+$).
HRMS (ES^+) m/z	Calculated: 601.3126; Found: 601.3111 ($[M+H]^+$).

(2*S*,5*R*)-((1*S*,2*R*)-2-(2-Phenylpropan-2-yl)cyclohexyl) tetrahydro-5-((*S*)-2-trimethylsiloxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-carboxylate (4.50)

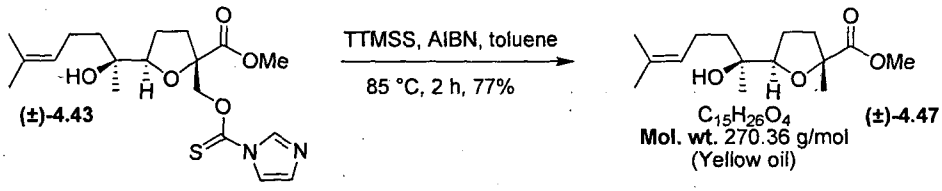


To a solution of thiocarbonyl imidazolide **4.46** (538 mg, 0.82 mmol) in toluene (35 mL) was added AIBN (69 mg, 0.41 mmol), followed by dropwise addition of TTMSS (1.70 mL, 5.33 mmol). The resultant solution was stirred at 85 °C for 75 min, then concentrated *in vacuo* to afford crude **4.50** as a pale yellow oil (410 mg). Purification by column chromatography (SiO_2 eluting with CH_2Cl_2/hexane (10 to 45%)) afforded the title THF **4.50** as a pale yellow oil (359 mg, 0.68 mmol, 83%).

$[\alpha]^{25.5}_D$	+5.27 (*c* 1.10, $CHCl_3$).
FT-IR ν_{max} (neat)	2958 (s), 2934 (s), 2859 (m), 1724 (s), 1447 (m), 1372 (m), 1249 (m), 1122 (m), 1062 (m), 838 (s), 762 (m), 700 (m) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$)	δ 7.28-7.12 (5H, m, Ar), 5.09 (1H, t, *J* = 7.0 Hz, =C**H**CH_2), 4.77 (1H, td, *J* = 10.0, 4.3 Hz, OC**H**), 3.98 (1H, t, *J* = 7.0 Hz, C**H**, THF), 2.06-1.71 (7H, m, C**H**, C**H**$_2$, and 2 x C**H**$_2$, THF), 1.67 (3H, s, C**H**$_3$), 1.67-1.37 (6H, m, 3 x C**H**$_2$), 1.61 (3H, s, C**H**$_3$), 1.35 (3H, s, C**H**$_3$), 1.35-0.87 (4H, m, 2 x C**H**$_2$), 1.34 (3H, s, C**H**$_3$), 1.26 (3H, s, C**H**$_3$), 1.20 (3H, s, C**H**$_3$), 0.06 (9H,

	s, $COSi(CH_3)_3$) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 170.08 (**C**OO), 150.56 (**C**CH, Ar), 131.11 ($(CH_3)_2$**C**), 128.00 (2 x **C**H, $Ar_{(meta)}$), 125.76 (2 x **C**H, $Ar_{(ortho)}$), 125.32 (**C**H, $Ar_{(para)}$), 124.84 (C=**C**HCH_2), 85.31 (**C**H, THF), 83.76 (**C**CH_3, THF), 76.68 ($COSi(CH_3)_3$), 75.89 (O**C**H), 50.85 (**C**HCPh), 40.67 (**C**Ph), 40.50 ($CH_2COSi(CH_3)_3$), 36.53 (CH_2**C**HCH), 33.12 (CH_2, THF), 29.69 (CH_3), 27.64 ($CH_2CH_2CH_2$**C**H), 25.83 (CH_3), 25.69 (CH_2), 24.57 (CH_2), 24.44 (2 x CH_3), 24.02 (CH_2, THF), 22.73 (CH_3), 22.40 (CH_2CH_2), 17.70 (CH_3), 2.70 (3C, $COSi(CH_3)_3$) ppm.
LRMS (ES^+) m/z	551 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 551.3527; Found: 551.3529 ($[M+Na]^+$).

***Rac.*(2*R*,5*R*)-Methyl tetrahydro-5-((*S*)-2-hydroxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-carboxylate ((±)-4.47)**

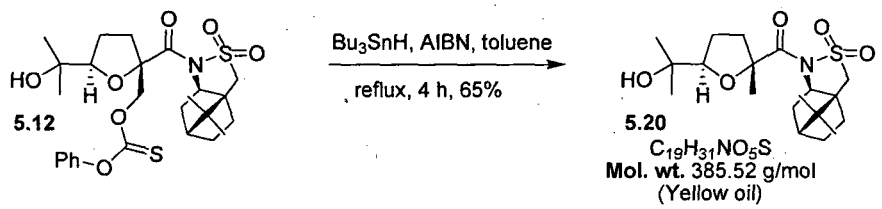


Following the method for the radical deoxygenation of thiocarbonyl imidazolide **4.50**, racemic THF imidazolide **(±)-4.43** (36 mg, 0.09 mmol) afforded crude **(±)-4.47** as a yellow oil (29 mg). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (5 to 20%)) afforded the title racemic THF **(±)-4.47** as a yellow oil (19 mg, 0.07 mmol, 77%).

FT-IR ν_{max} (neat)	3508 (br), 2972 (m), 2937 (m), 2915 (w), 1736 (s), 1455 (m), 1375 (m), 1272 (m), 1120 (s), 839 (w) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 5.13 (1H, tt, J = 7.1, 1.3 Hz, =C**H**CH_2), 4.00 (1H, t, J = 7.2 Hz, C**H**, THF), 3.74 (3H, s, O**C**H_3), 2.29 (1H, m, C**H**H, THF), 2.17-1.94 (2H, m, CH_2, THF), 1.92-1.79 (3H, m, C**H**H, THF and CH_2), 1.69 (3H, s, CH_3), 1.63 (3H, s, CH_3), 1.53 (1H, m, C**H**H), 1.39 (1H, ddd, J = 13.6, 11.4, 5.7 Hz, C**H**H), 1.49 (3H, s, CH_3), 1.25 (3H, s, CH_3) ppm.
	OH signal was not observed.

^{13}C NMR (100 MHz, $CDCl_3$)	δ 175.68 (**C**OO), 131.74 ((CH$_3$)$_2$**C**), 124.45 (=**C**HCH$_2$), 86.56 (**C**H, THF), 83.52 (**C**CH$_3$, THF), 72.74 (**C**OH), 52.19 (O**C**H$_3$), 37.52 (**C**H$_2$COH), 36.77 (**C**H$_2$, THF), 25.68 (**C**H$_3$), 25.37 (**C**H$_2$, THF), 24.89 (**C**H$_3$), 23.87 (**C**H$_3$), 22.12 (**C**H$_2$CH$_2$), 17.64 (**C**H$_3$) ppm.
LRMS (ES$^+$) m/z	293 (100%, [M+Na]$^+$).
HRMS (ES$^+$) m/z	Calculated: 293.1723; Found: 293.1720 ([M+Na]$^+$).

***N*-[(2*S*,5*R*)-Tetrahydro-5-(2-hydroxypropan-2-yl)-2-methylfuranoyl]-2-(2*R*)-camphor-10,2-sultam (5.20)**

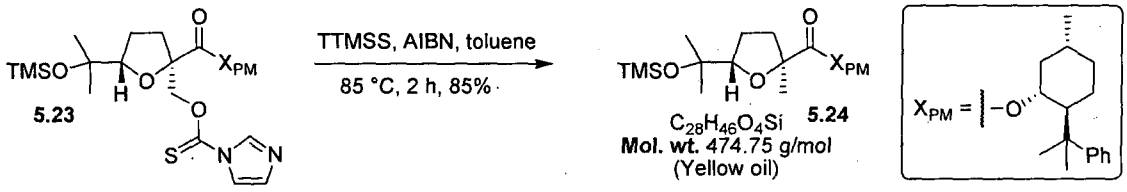


To a solution of thionoformate **5.12** (45 mg, 0.08 mmol) in toluene (2.0 mL) was added AIBN (7 mg, 0.04 mmol), followed by dropwise addition of Bu_3SnH (67 μL, 0.24 mmol). The resultant solution was heated to reflux for 4 hours. The reaction was concentrated in *vacuo* to afford crude **5.20** as a yellow oil (25 mg). Purification by column chromatography (SiO_2 eluting with CH_2Cl_2/hexane (10 to 30%)) afforded the title THF **5.20** as a yellow oil (19 mg, 0.05 mmol, 65%).

$[\alpha]^{26}_D$	–32.97 (*c* 0.37, $CHCl_3$).
FT-IR ν_{max} (neat)	3516 (br), 2962 (m), 2960 (m), 2879 (w), 1677 (m), 1456 (m), 1335 (s), 1163 (s), 1134 (s), 1062 (m), 912 (m), 728 (s) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$)	δ 4.08 (1H, m, C**H**N), 4.00 (1H, t, *J* = 7.0 Hz, C**H**, THF), 3.51 (1H, d, *J* = 13.4 Hz, C**H**HSO$_2$), 3.40 (1H, d, *J* = 13.4 Hz, CH**H**SO$_2$), 2.75 (1H, br, O**H**), 2.32 (1H, dd, *J* = 12.6, 8.0 Hz, C**H**H, THF), 2.10-1.69 (7H, m, 2 x C**H**$_2$, C**H**H and C**H**$_2$, THF), 1.53 (3H, s, C**H**$_3$), 1.42-1.25 (3H, m, C**H**H and C**H**$_2$), 1.19 (3H, s, C**H**$_3$), 1.21 (3H, s, C**H**$_3$), 1.13 (3H, s, C**H**$_3$), 0.99 (3H, s, C**H**$_3$) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 178.45 (**C**ON), 87.77 (**C**H, THF), 87.46 (**C**CH$_3$, THF), 71.29 ((CH$_3$)$_2$**C**), 67.68 (N**C**H), 54.59 (**C**H$_2$S), 47.80 (**C**(CH$_3$)$_2$),

	47.48 ($\mathbf{C}CH_2S$), 45.58 ($\mathbf{C}HC(CH_3)_2$), 39.47 ($\mathbf{C}H_2CHN$), 39.34 ($\mathbf{C}H_2C$), 33.82 ($\mathbf{C}H_2$, THF), 26.80 ($\mathbf{C}H_3$), 26.13 ($\mathbf{C}H_2$, THF), 25.86 ($\mathbf{C}H_2CH_2C$), 24.46 ($\mathbf{C}H_3$), 23.51 ($\mathbf{C}H_3$), 21.88 ($\mathbf{C}H_3$), 19.90 ($\mathbf{C}H_3$) ppm.
LRMS (ES^+) m/z	408 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 408.1815; Found: 408.1808 ($[M+Na]^+$).

(2*R*,5*S*)-((1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl) tetrahydro-2-methyl-5-(2-trimethylsiloxypropan-2-yl)furan-2-carboxylate (5.24)



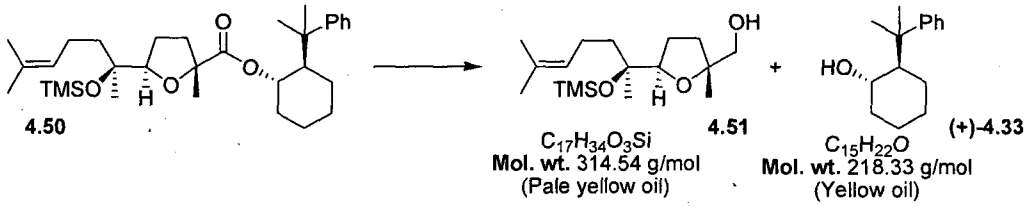
Following the radical deoxygenation procedure for the preparation of THF **4.50**, enantiomerically pure THF thiocarbonyl imidazolide **5.23** (292 mg, 0.49 mmol) afforded crude **5.24** as a yellow oil (235 mg). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (5 to 15%)) afforded the title THF **5.24** as a yellow oil (196 mg, 0.42 mmol, 85%).

$[\alpha]^{28}_D$	–18.03 (*c* 1.37, $CHCl_3$).
FT-IR ν_{max} (neat)	2954 (m), 2918 (m), 2865 (m), 1725 (s), 1456 (m), 1371 (m), 1248 (s), 1169 (s), 1092 (m), 1041 (s), 837 (s), 762 (m), 700 (s) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 7.28-7.14 (5H, m, Ar), 4.76 (1H, td, *J* = 10.7, 4.3 Hz, OC**H**), 3.90 (1H, dd, *J* = 7.5, 6.0 Hz, C**H**, THF), 1.99-1.79 (5H, m, C**H** and 2 x $\mathbf{C}H_2$, THF), 1.69-1.36 (5H, m, C**H** and 2 x $\mathbf{C}H_2$), 1.35 (3H, s, $\mathbf{C}H_3$), 1.33 (3H, s, $\mathbf{C}H_3$), 1.26 (3H, s, $\mathbf{C}H_3$), 1.20 (3H, s, $\mathbf{C}H_3$), 1.18 (3H, s, $\mathbf{C}H_3$),1.00-0.70 (2H, m, $\mathbf{C}H_2$), 0.83 (3H, d, *J* = 6.4 Hz, $\mathbf{C}H_3CH$), 0.10 (9H, s, $COSi(\mathbf{C}H_3)_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 175.10 (**C**OO), 150.59 (**C**CH, Ar), 127.98 (2 x **C**H, $Ar_{(meta)}$), 125.71 (2 x **C**H, $Ar_{(ortho)}$), 125.29 (**C**H, $Ar_{(para)}$), 87.45 (**C**H, THF), 83.96 ($\mathbf{C}CH_3$ THF), 75.63 (O**C**H), 74.77 ($\mathbf{C}OSi(CH_3)_3$), 50.41 (**C**HCPh), 41.52 (**C**Ph), 40.27 ($\mathbf{C}H_2CH(CH_3)$), 36.56 ($\mathbf{C}H_2CH_2CH$), 34.56 ($\mathbf{C}H_2$, THF), 31.29 ($\mathbf{C}HCH_3$), 29.65

	(CH_3), 27.86 (CH_3), 27.31 (CH_2, THF), 26.11 (CH_2C), 25.28 (CH_3), 24.53 (CH_3), 23.96 (CH_3), 21.76 (CH_3), 2.57 (3C, $COSi(CH_3)_3$) ppm.
LRMS (ES^+) m/z	497 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 497.3058; Found: 497.3058 ($[M+Na]^+$).

(2*R*,5*R*)-Tetrahydro-5-((*S*)-2-trimethylsilyloxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-methanol (4.51);

(1*S*,2*R*)-2-(2-Phenylpropan-2-yl)cyclohexanol ((+)-4.33)



Procedure 1

To a stirred solution of THF **4.50** (100 mg, 0.19 mmol) in THF:H_2O (25:1, 4 mL) was added $NaBH_4$ (8.60 mg, 0.23 mmol) at –5 °C. The reaction mixture was allowed to warm to rt over 4 hours whereupon it was quenched by adding HCl (2 N, 2 mL) and diluted with EtOAc (10 mL). The organic phase was separated and the aqueous phase was re-extracted with EtOAc (2 x 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude as a pale yellow oil (89 mg). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (10 to 20%)) afforded the title THF alcohol **4.51** as a yellow oil (41 mg, 0.13 mmol, 68%) and the less polar chiral auxiliary **(+)-4.33** as a pale yellow oil (37 mg, 0.17 mmol, 88%).

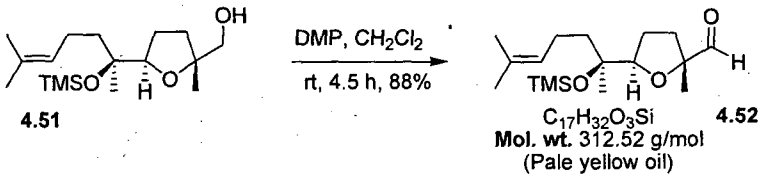
Procedure 2

To a solution of THF **4.50** (46 mg, 0.09 mmol) in CH_2Cl_2 (3 mL) was added DIBAL-H (260 μL, 0.26 mmol) at –78 °C. The reaction mixture was stirred and allowed to warm to room temperature over 4 hours. At this stage, the reaction was quenched by adding sat. aq. NH_4Cl (1 mL) and Rochelle's salt (1 mL) and the solution was stirred for 30 min at room temperature. The solution was diluted with CH_2Cl_2 (5 mL) and the organic phase was separated. The aqueous phase was re-extracted with CH_2Cl_2 (10 mL) and the combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude as a pale yellow oil (49 mg). Purification by column chromatography (SiO_2 eluting with CH_2Cl_2 (100%) and then EtOAc/hexane (10

to 20%)) afforded the title alcohol **4.51** as a pale yellow oil (24 mg, 0.08 mmol, 88%) and the less polar chiral auxiliary **(+)-4.33** as a yellow oil (17 mg, 0.08 mmol, 91%).

$[\alpha]^{24.5}_D$	–2.98 (*c* 1.19, $CHCl_3$).
FT-IR ν_{max} (neat)	3444 (br), 2965 (m), 2929 (m), 2864 (w), 1453 (w), 1249 (s), 1045 (s), 838 (s), 753 (m) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 5.10 (1H, tt, *J* = 7.0, 1.0 Hz, =C**H**CH_2), 3.80 (1H, m, C**H**, THF), 3.49-3.39 (2H, m, C$\mathbf{H_2}$OH), 2.01-1.85 (5H, m, O**H**, and 2 x C$\mathbf{H_2}$, THF), 1.69 (3H, s, C$\mathbf{H_3}$), 1.69-1.40 (4H, m, 2 x C$\mathbf{H_2}$), 1.61 (3H, s, C$\mathbf{H_3}$), 1.22 (3H, s, C$\mathbf{H_3}$), 1.19 (3H, s, C$\mathbf{H_3}$), 0.13 (9H, s, COSi(C$\mathbf{H_3}$)$_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 131.17 ((CH_3)$_2$**C**), 124.78 (C=**C**HCH_2), 85.42 (**C**H, THF), 83.19 (**C**CH_3, THF), 76.55 (**C**OSi(CH_3)$_3$), 68.45 (**C**H_2OH), 40.30 (**C**H_2COSi(CH_3)$_3$), 33.56 (**C**H_2, THF), 26.47 (**C**H_2, THF), 25.67 (**C**H_3), 23.92 (**C**H_3), 22.94 (**C**H_3), 22.47 (**C**H_2CH_2), 17.62 (**C**H_3), 2.67 (3C, COSi(**C**H_3)$_3$) ppm.
LRMS (ES^+) m/z	337 (60%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 337.2169; Found: 337.2168 ($[M+Na]^+$).

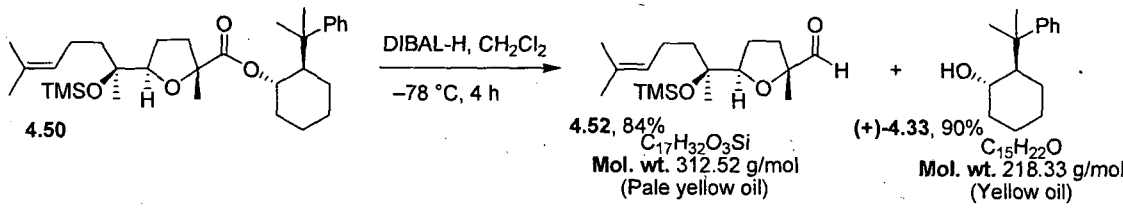
(2*R*,5*R*)-Tetrahydro-5-((*S*)-2-trimethylsiloxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-carbaldehyde (4.52)



To a solution of THF **4.51** (22 mg, 0.07 mmol) in CH_2Cl_2 was added DMP (45 mg, 0.11 mmol) at room temperature and the reaction mixture was stirred for 4.5 hours. At this stage, the reaction mixture was filtered through a short silica pad and concentrated *in vacuo* to afford the crude aldehyde **4.52** as a pale yellow oil (19 mg, 0.06 mmol, 88%). The crude material was used in next step without purification. The spectroscopic data is mentioned underneath.

(2*R*,5*R*)-Tetrahydro-5-((*S*)-2-trimethylsiloxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-carbaldehyde (4.52);

(1*S*,2*R*)-2-(2-Phenylpropan-2-yl)cyclohexanol ((+)-4.33)



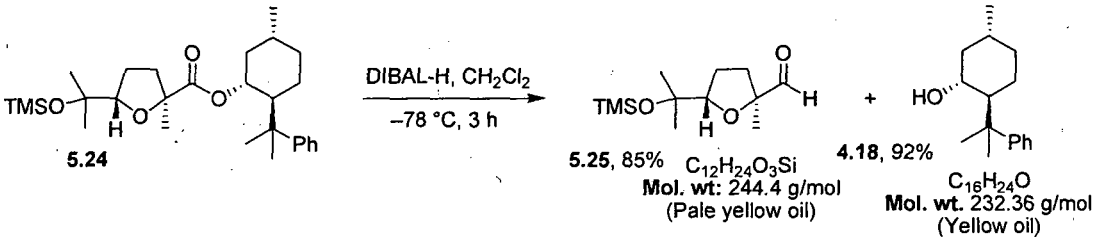
To a solution of THF **4.50** (420 mg, 0.79 mmol) in CH_2Cl_2 (12 mL) was added DIBAL-H (2.4 mL, 2.37 mmol) at –78 °C and the resultant solution was stirred for 4 hours, while keeping the temperature at –78 °C. The reaction was quenched by adding sat. aq. NH_4Cl (5 mL) and the temperature was allowed to rise to room temperature. Rochelle's salt (5 mL, aq. sat.) was added and the solution was stirred for 30 min at room temperature. The solution was diluted with CH_2Cl_2 (10 mL) and the organic phase was separated. The aqueous phase was re-extracted with CH_2Cl_2 (2 x 20 mL), and the combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude as a pale yellow oil (385 mg). Purification by column chromatography (SiO_2 eluting with CH_2Cl_2 (100%) and then EtOAc/hexane (10 to 20%)) afforded the title aldehyde **4.52** as a pale yellow oil (208 mg, 0.67 mmol, 84%) followed by the chiral auxiliary **(+)-4.33** as a yellow oil (155 mg, 0.71 mmol, 90%).

$[\alpha]^{26}_D$	+6.84 (*c* 0.585, $CHCl_3$).
FT-IR ν_{max} (neat)	2966 (m), 2925 (m), 2852 (w), 2790 (w), 1736 (s), 1453 (m), 1374 (m), 1249 (s), 1116 (w), 1046 (m), 837 (s), 753 (m) cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	δ 9.58 (1H, s, **CHO**), 5.11 (1H, tt, J = 7.1, 1.4 Hz, =**CH**CH_2), 3.87 (1H, t, J = 7.3 Hz, **CH**, THF), 2.16-1.76 (4H, m, 2 x **CH**$_2$, THF), 1.69 (3H, s, **CH**$_3$), 1.67-1.36 (4H, m, 2 x **CH**$_2$), 1.62 (3H, s, **CH**$_3$), 1.29 (3H, s, **CH**$_3$), 1.27 (3H, s, **CH**$_3$), 0.13 (9H, s, COSi(**CH**$_3$)$_3$) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 203.56 (**C**HO), 131.30 ((**C**H$_3$)$_2$**C**), 124.61 (C=**C**HCH$_2$), 86.62 (**C**H, THF), 86.13 (**C**CH$_3$, THF), 76.49 (**C**OSi(CH$_3$)$_3$), 40.56 (**C**H$_2$COSi(CH$_3$)$_3$), 32.59 (**C**H$_2$, THF), 25.88 (**C**H$_2$, THF), 25.64 (**C**H$_3$), 22.98 (**C**H$_3$), 22.47 (**C**H$_2$CH$_2$), 20.96 (**C**H$_3$), 17.60 (**C**H$_3$), 2.66 (3C, COSi(**C**H$_3$)$_3$) ppm.

LRMS (ES^+) m/z	335 (65%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 335.2013 ; Found: 335.2010 ($[M+Na]^+$).

(2*S*,5*S*)-Tetrahydro-2-methyl-5-(2-trimethylsilyl-oxy-propan-2-yl)furan-2-carbaldehyde (5.25);

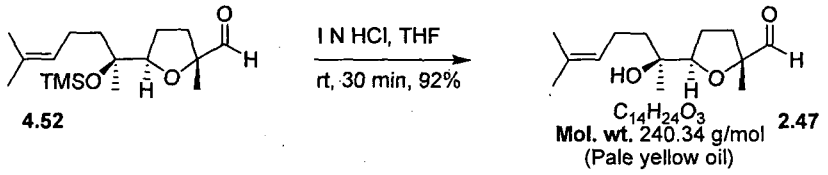
(1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexanol (4.18)



Following the DIBAL-H reduction procedure for the preparation of aldehyde **4.52**, enantiomerically pure THF **5.24** (189 mg, 0.40 mmol) afforded the crude as a yellow oil (175 mg). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (5 to 15%)) afforded the title aldehyde **5.25** as a pale yellow oil (83 mg, 0.34 mmol, 85%) followed by the chiral auxiliary **4.18** as a yellow oil (86 mg, 0.37 mmol, 92%).

$[\alpha]^{29}_D$	–1.46 (*c* 1.265, $CHCl_3$).
FT-IR ν_{max} (neat)	2975 (m), 2888 (w), 2786 (w), 1736 (s), 1249 (s), 1174 (m), 1061 (m), 1041 (s), 839 (s), 753 (m) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 9.58 (1H, s, **CHO**), 3.81 (1H, t, *J* = 7.0 Hz, **CH**, THF), 2.09 (1H, ddd, *J* = 12.0, 8.0, 6.8 Hz **CH**, THF), 1.96 (1H, ddt, *J* = 12.0, 8.0, 6.8 Hz **CH**, THF), 1.83 (1H, m, **CH**, THF), 1.68 (1H, ddd, *J* = 12.0, 8.0, 6.8 Hz **CH**, THF), 1.30 (3H, s, $\mathbf{CH_3}$), 1.26 (3H, s, $\mathbf{CH_3}$), 1.20 (3H, s, $\mathbf{CH_3}$), 0.12 (9H, s, $COSi(\mathbf{CH_3})_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 204.07 (**C**HO), 88.58 (**C**H, THF), 84.96 (**C**CH_3, THF), 74.77 ($\mathbf{C}OSi(CH_3)_3$), 33.25 ($\mathbf{C}H_2$, THF), 27.90 ($\mathbf{C}H_3$), 26.55 ($\mathbf{C}H_2$, THF), 26.15 ($\mathbf{C}H_3$), 21.30 ($\mathbf{C}H_3$), 2.93 (3C, $COSi(\mathbf{C}H_3)_3$) ppm.
LRMS (ES^+) m/z	267 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 267.1387; Found: 267.1385 ($[M+Na]^+$).

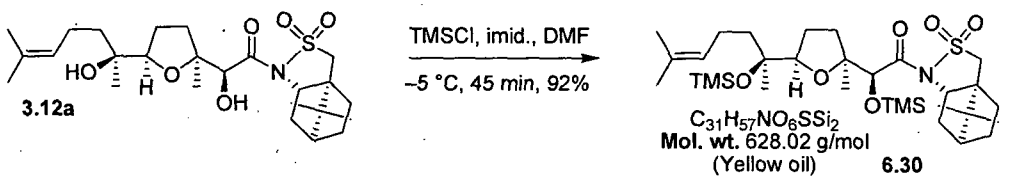
(2*R*,5*R*)-Tetrahydro-5-((*S*)-2-hydroxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-carbaldehyde (2.47)



To a solution of aldehyde **4.52** (12 mg, 0.038 mmol) in THF (2.5 mL) at room temperature, was added HCl (I N aq., 150 μL) and stirred for 15 min. The mixture was diluted with sat. aq. $NaHCO_3$ (2 mL) and extracted with Et_2O (10 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude product **2.47** as a pale yellow oil (11 mg). Purification by column chromatography (SiO_2 eluting with 25% EtOAc/hexane) afforded the title aldehyde **2.47** as a pale yellow oil (8.5 mg, 0.035 mmol, 92%). Spectroscopic data was in agreement with the literature.[83]

$[\alpha]^{27}_D$	+2.09 (*c* 0.335, $CHCl_3$), {lit. $[\alpha]^{14.9}_D$ +1.73 (*c* 1.101, $CHCl_3$)}.[83]
FT-IR ν_{max} (neat)	3446 (br), 2971 (m), 2928 (m), 2870 (w), 2795 (w), 1735 (s), 1455 (m), 1375 (m), 1116 (m), 1033 (m) cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	δ 9.58 (1H, s, C**H**O), 5.10 (1H, tt, *J* = 7.0, 1.2 Hz, =C**H**CH_2), 3.87 (1H, dd, *J* = 8.8, 6.3 Hz, C**H**, THF), 2.19-1.71 (5H, m, O**H** and 2 x C**H**$_2$, THF), 1.70 (3H, s, C**H**$_3$), 1.63 (3H, s, C**H**$_3$), 1.50-1.38 (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 (75 MHz, $CDCl_3$)	δ 202.76 (**C**HO), 131.85 ($(CH_3)_2$**C**), 124.31 (C=**C**HCH_2), 87.08 (**C**H, THF), 86.28 (**C**CH_3, THF), 72.52 (**C**OH), 37.51 (**C**H_2COH), 32.70 (**C**H_2, THF), 25.66 (**C**H_2, THF), 25.41 (**C**H_3), 24.03 (**C**H_3), 22.10 (CH_2**C**H_2), 21.07 (**C**H_3), 17.64 (**C**H_3) ppm.
LRMS (ES^+) m/z	263 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 263.1618; Found: 263.1617 ($[M+Na]^+$).

N-[(S)-2-((2S,5R)-Tetrahydro-5-((S)-2-trimethylsilyloxy-6-methylhept-5en-2-yl)-2-methylfuran-2-yl)]-2-trimethylsilyloxy-(2S)-10,2-camphorsultam (6.30)



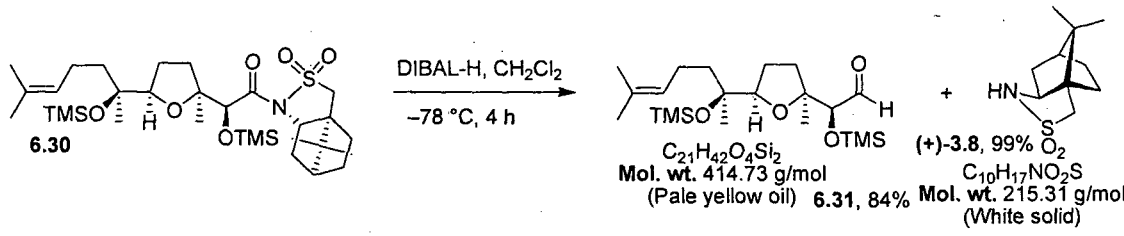
$C_{31}H_{57}NO_6SSi_2$
Mol. wt. 628.02 g/mol
(Yellow oil) **6.30**

To a solution of THF diol **3.12a** (210 mg, 0.43 mmol) in dry DMF (6 mL) was added imidazole (443 mg, 6.51 mmol) at –5 °C, followed by TMSCl (497 μL, 5.38 mmol). The reaction mixture was stirred for 45 min at the same etemperature. The reaction was quenched with H_2O (5 mL). The aqueous phase was extracted with Et_2O (2 x 20 mL), and the combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product **6.30** as a yellow oil (265 mg). Purification by column chromatography (SiO_2 eluting with CH_2Cl_2/hexane (5 to 7.5%)) afforded the title THF **6.30** as a yellow oil (251 mg, 0.40 mmol, 92%).

$[\alpha]^{24.5}_D$	+40 (*c* 0.325, $CHCl_3$).
FT-IR ν_{max} (neat)	2961 (m), 2911 (m), 2880 (w), 1707 (s), 1457 (m), 1338 (s), 1249 (s), 1108 (m), 841 (s), 757 (m) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 5.14 (1H, tt, *J* = 7.1, 1.3 Hz, =C**H**CH_2), 4.81 (1H, s, C**H**OSi), 3.88 (1H, dd, *J* = 7.5 and 5.3 Hz, C**H**N), 3.78 (1H, t, *J* = 7.4 Hz, C**H**, THF), 3.53 (1H, d, *J* = 13.8 Hz, C**H**HSO_2), 3.45 (1H, d, *J* = 13.8 Hz, CH**H**SO_2), 2.35 (1H, ddd, *J* = 12.0, 10.0, 6.0 Hz, C**H**, THF), 2.25 (1H, m, C**H**, THF), 1.99-2.16 (4H, m, CH_2 and CH_2, THF), 1.97-1.79 (5H, m, C**H** and 2 x CH_2), 1.77-1.24 (4H, m, CH_2), 1.69 (3H, s, CH_3), 1.68 (3H, s, CH_3), 1.62 (3H, s, CH_3), 1.17 (6H, s, 2 x CH_3), 0.97 (3H, s, CH_3), 0.15 (9H, s, COSi(CH_3)$_3$), 0.10 (9H, s, CHOSi(CH_3)$_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 170.92 (**C**ON), 130.82 ((CH_3)$_2$**C**), 125.16 ((CH_3)$_2$C=**C**), 84.91 (**C**CH_3, THF), 80.93 (**C**H, THF), 76.68 (**C**OSi(CH_3)$_3$), 75.16 (**C**HOSi(CH_3)$_3$), 65.93 (**C**HN), 53.27 (**C**H_2SO_2), 48.19 (**C**CH_2SO_2), 47.69 (**C**(CH_3)$_2$), 44.51 (**C**HC(CH_3)$_2$), 40.22 (CH_2**C**HN), 38.68 (CH_2**C**O), 33.19 (CH_2CH_2**C**CH_2S), 31.76 (CH_2, THF), 26.59 (CH_2**C**CH_2S), 26.00 (CH_2, THF), 25.69 (CH_3), 22.52 (CH_2**C**H_2), 22.00 (CH_3), 21.59 (CH_3), 21.15

	(CH_3), 19.89 (CH_3), 17.59 (CH_3), 2.63 (3C, $COSi(CH_3)_3$), 0.42 (3C, $CHOSi(CH_3)_3$) ppm..
LRMS (ES^+) m/z	650 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 650.3337; Found: 650.3340 ($[M+Na]^+$).

(*S*)-2-((2*S*,5*R*)-Tetrahydro-5-((*S*)-2-trimethylsilyloxy-6-methylhept-5en-2-yl)-2-methylfuran-2-yl)-2-trimethylsilyloxyacetaldehyde (6.31);
(2*S*)-10,2-Camphorsultam ((+)-3.8)

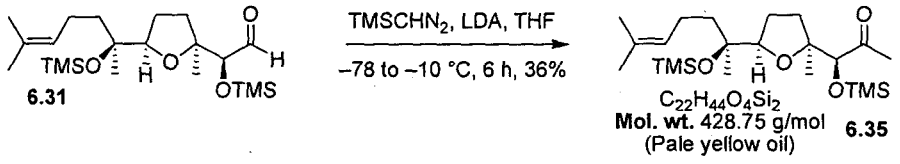


Following the DIBAL-H reduction procedure for the preparation of aldehyde **4.52**, *bis*-protected THF **6.30** (97 mg, 0.15 mmol) afforded the crude as a yellow oil (101 mg). Purification by column chromatography (SiO_2 eluting with CH_2Cl_2/hexane (30 to 90%)) afforded the title aldehyde **6.31** as a pale yellow oil (54 mg, 0.13 mmol, 84%) and chiral auxiliary **(+)-3.8** as a yellow oil (33 mg, 0.16 mmol, 99%).

$[\alpha]^{24.5}_D$	+99.8 (*c* 0.49, $CHCl_3$).
FT-IR ν_{max} (neat)	2966 (m), 2936 (m), 2869 (w), 1735 (s), 1374 (m), 1250 (s), 1099 (m), 912 (m), 839 (s), 753 (m) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 9.87 (1H, s, C**H**O), 5.08 (1H, m, =C**H**CH_2), 4.03 (1H, s, C**H**OSi), 3.97 (1H, dd, *J* = 8.5, 6.5 Hz, C**H**, THF), 2.10-1.82 (4H, m, 2 x C**H**$_2$, THF), 1.77-1.43 (4H, m, 2 x C**H**$_2$), 1.69 (3H, s, C**H**$_3$), 1.62 (3H, s, C**H**$_3$), 1.27 (3H, s, C**H**$_3$), 1.17 (3H, s, C**H**$_3$), 0.14 (9H, s, $COSi(CH_3)_3$), 0.13 (9H, s, $CHOSi(CH_3)_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 203.88 (**C**HO), 131.43 ($(CH_3)_2$**C**), 124.46 ($(CH_3)_2$C=**C**), 84.98 (**C**H, THF), 84.67 (**C**CH_3, THF), 81.39 (**C**H$OSi(CH_3)_3$), 76.68 (**C**$OSi(CH_3)_3$), 40.81 (**C**H_2CO), 36.04 (**C**H_2, THF), 25.66 (**C**H_2, THF), 25.24 (**C**H_3), 23.92 (**C**H_3), 22.95 (CH_2**C**H_2), 20.07 (**C**H_3), 17.62 (**C**H_3), 2.73 (3C, $COSi(CH_3)_3$), 0.09 (3C, $CHOSi(CH_3)_3$) ppm.

LRMS (ES^+) m/z	437 (75%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 437.2514; Found: 437.2510 ($[M+Na]^+$).

(*S*)-1-((2*S*,5*R*)-Tetrahydro-5-((*S*)-2-trimethylsilyloxy-6-methylhept-5en-2-yl)-2-methylfuran-2-yl)-1-trimethylsiloxypropane-2-one (6.35)



To a solution of LDA (39 μL, 1.8 M in THF/heptane/ethylbenzene, 0.069 mmol) in THF (0.5 mL) at –78 °C was added $TMSCHN_2$ (35 μL, 2.0 M in ether, 0.069 mmol) and the resultant mixture was stirred at the same temperature for 1 hour. At this stage, the solution of aldehyde **6.31** (24 mg, 0.058 mmol) in THF (0.1 mL) was added and the reaction mixture was stirred for additional 5 hours during which the temperature raised to –10 °C. The reaction was quenched by adding H_2O (2 mL), the aqueous phase was extracted with ether (3 x 15 mL), and the combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product **6.35** as a yellow oil (25 mg). Purification by column chromatography (SiO_2 eluting with CH_2Cl_2/hexane (5 to 50%)) afforded the title ketone **6.35** as pale yellow oil (10 mg, 0.021 mmol, 36%). The purification did not proceed very using the above mentioned eluent system and the ^{13}C NMR of the product showed minor peaks of starting material, aldehyde **6.31**.

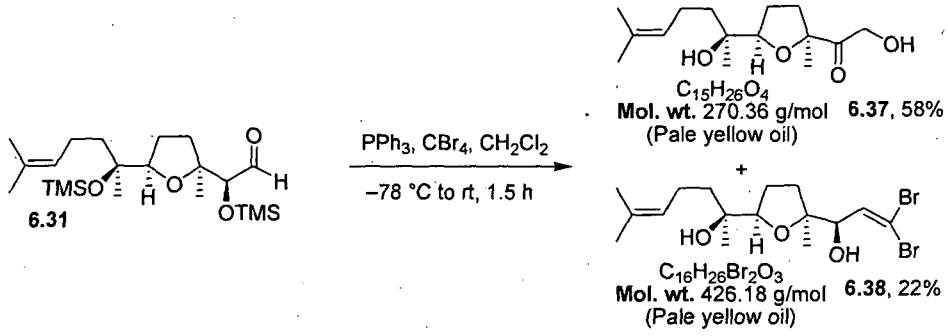
$[\alpha]^{26}_D$	+82.83 (*c* 0.23, $CHCl_3$).
FT-IR ν_{max} (neat)	2960 (m), 2930 (m), 2865 (w), 1722(m), 1452 (w), 1374 (w), 1251(s), 1093 (m), 840 (s), 753 (m) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 5.12-5.07 (1H, tt, *J* = 7.0, 1.0 Hz, =C**H**CH_2), 4.02 (1H, s, C**H**OSi), 3.92 (1H, t, *J* = 7.3 Hz, C**H**, THF), 2.24 (3H, s, C(O)C**H**$_3$), 2.04-1.82 (4H, m, 2 x C**H**$_2$, THF), 1.70 (3H, s, C**H**$_3$), 1.64 (3H, s, C**H**$_3$), 1.63-1.26 (4H, m, 2 x C**H**$_2$), 1.21 (3H, s, C**H**$_3$), 1.09 (3H, s, C**H**$_3$), 0.13 (9H, s, COSi(C**H**$_3$)$_3$), 0.11 (9H, s, CHOSi(C**H**$_3$)$_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) (selected data)	δ 209.82 (**C**(O)CH_3), 131.28 ($(CH_3)_2$**C**), 124.65 ($(CH_3)_2$C=**C**), 84.42 (**C**H, THF), 83.62 (**C**CH_3, THF), 82.91 (**C**OSi$(CH_3)_3$), 81.94 (**C**HOSi$(CH_3)_3$), 40.89 (**C**H_2CO), 35.52 (**C**H_2, THF),

28.39 (CH_3), 25.66 (CH_3), 25.28 (CH_2, THF), 23.06 (CH_3), 22.58 (CH_2CH_2), 21.02 (CH_3), 17.58 (CH_3), 2.69 (3C, $COSi(CH_3)_3$), 0.09 (3C, $CHOSi(CH_3)_3$) ppm.

LRMS (ES^+) m/z 451 (100%, $[M+Na]^+$).

1-((2*S*,5*R*)-Tetrahydro-5-((*S*)-2-hydroxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-yl)-2-hydroxyethanone (6.37);

(*S*)-2-((2*R*,5*S*)-5-((*R*)-3,3-Dibromo-1-hydroxyallyl)-tetrahydro-6-methylhept-5-en-2-yl)-2-methylfuran-2-yl)-2-ol (6.38)



To a solution of CBr_4 (66 mg, 0.20 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C was added a solution of Ph_3P (104 mg, 0.40 mmol) in CH_2Cl_2 (0.5 mL) dropwise. After 15 min, the reaction mixture was cooled to –78 °C and a solution of aldehyde **6.31** (40 mg, 0.096 mmol) in dichloromethane (0.5 mL) was added dropwise. The mixture was stirred at this temperature for 1 hour and then allowed to warm to room temperature. Pentane (5 mL) was added and stirred for 30 minutes. The precipitate was separated by filtering through a short plug of silica and washed with pentane (10 mL). The filtrate was concentrated in *vacuo* and re-dissolved in dichloromethane (10 mL). Pentane (5 mL) was added and stirred for 30 minutes. Filteration and concentration *in vacuo* afforded a yellow oil as the crude (40 mg). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (2 to 10%)) afforded the title ketone **6.37** as a pale yellow oil (15 mg, 0.056 mmol, 58%) and dibromoolefin **6.38** as a pale yellow oil (9 mg, 0.021 mmol, 22%). The ketone **6.37** was found contaminated with an unidentified product *i.e.* ca 10%.

Selected spectroscopic data for **6.37**:

$[\alpha]^{26.5}_D$ +20.38 (*c* 0.395, $CHCl_3$).

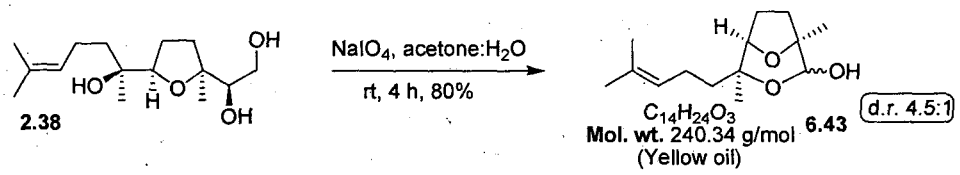
FT-IR ν_{max} (neat) 3441 (br), 2972 (m), 2930 (m), 2890 (w), 1720 (s), 1449 (m),

	1375 (m), 1110 (m), 1005 (m) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 5.12 (1H, t, J = 7.1 Hz, =C**H**CH_2), 4.58 (1H, d, J = 18.2 Hz, C**H**HOH), 4.50 (1H, d, J = 18.2 Hz, CH**H**OH), 3.94 (1H, t, J = 7.3 Hz, C**H**, THF), 3.02 (1H, br, O**H**), 2.26-1.87 (5H, m, O**H** and 2 x C$\mathbf{H_2}$, THF) 1.70 (3H, s, C$\mathbf{H_3}$), 1.63 (3H, s, C$\mathbf{H_3}$), 1.61-1.24 (4H, m, 2 x C$\mathbf{H_2}$), 1.41 (3H, s, C$\mathbf{H_3}$), 1.28 (3H, s, C$\mathbf{H_3}$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 213.44 (**C**O), 132.03 (($CH_3)_2$**C**), 124.19 (($CH_3)_2$C=**C**), 87.15 (**C**CH_3, THF), 86.03 (**C**H, THF), 72.92 (**C**OH), 65.07 (**C**H_2OH), 38.22 (**C**H_2CO), 32.57 (**C**H_2, THF), 25.67 (**C**H_2, THF), 25.48 (**C**H_3), 23.97 (**C**H_3), 22.63 (**C**H_2CH_2), 17.64 (**C**H_3), 14.09 (**C**H_3) ppm. Additional signals: δ 60.40, 36.58, 30.32, 25.47, 23.90, 22.12, 21.01, 14.18 ppm.
LRMS (ES^+) m/z	293 (100%, $[M+Na]^+$).

Spectroscopic data for **6.38**:

$[\alpha]^{26}_D$	–4.22 (*c* 0.545, $CHCl_3$).
FT-IR ν_{max} (neat)	3282 (br), 2970 (m), 2926 (m), 2895 (w), 1455 (m), 1372 (m), 1083 (s), 1061 (m), 802 (m), 750 (w) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 6.41 (1H, d, J = 9.1 Hz, C**H**=CBr_2), 5.12 (1H, t, J = 7.1 Hz, =C**H**CH_2), 4.36 (1H, d, J = 9.1 Hz, C**H**CH=CBr_2), 3.87 (1H, t, J = 7.5 Hz, C**H**, THF), 3.56 (1H, br, O**H**), 2.28-1.88 (5H, m, O**H** and 2 x C$\mathbf{H_2}$, THF), 1.70 (3H, s, C$\mathbf{H_3}$), 1.63 (3H, s, C$\mathbf{H_3}$), 1.60-1.20 (4H, m, 2 x C$\mathbf{H_2}$), 1.30 (3H, s, C$\mathbf{H_3}$), 1.22 (3H, s, C$\mathbf{H_3}$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 137.49 (**C**H=CBr_2), 132.19 (($CH_3)_2$**C**), 124.13 (($CH_3)_2$C=**C**), 93.34 (**C**Br_2), 85.38 (**C**CH_3, THF), 84.30 (**C**H, THF), 77.91 (**C**HOH), 74.17 (**C**OH), 38.48 (**C**H_2CO), 32.22 (**C**H_2, THF), 26.56 (**C**H_3), 25.68 (**C**H_2, THF), 24.19 (**C**H_3), 22.63 (**C**H_2CH_2), 17.67 (**C**H_3), 15.25 (**C**H_3) ppm.
LRMS (ES^+) m/z	449 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 447.0141; Found: 449.0149 ($[M+Na]^+$).

(1*S*,4*S*,5*R*)-1,4-Dimethyl-4-(4-methylpent-3-enyl)-3,8-dioxa-bicyclo[3.2.1]octan-2-ol (6.43)

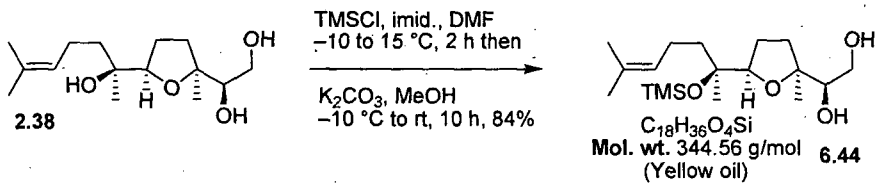


To a stirred solution of triol **2.38** (39 mg, 0.14 mmol) in acetone:H_2O (2:1, 1.2 mL) was added $NaIO_4$ (39 mg, 0.18 mmol) and the reaction mixture was stirred for 4 hours at room temperature. The reaction was quenched by adding H_2O (2 mL). The aqueous phase was extracted with Et_2O (2 x 10 mL), and the combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product **6.43** as a yellow oil (31 mg). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (20 to 30%) afforded the title THF **6.43** (d.r. 4.5:1) as a yellow oil (27 mg, 0.11 mmol, 80%).

$[\alpha]^{27}_D$	+51.80 (*c* 1.25, $CHCl_3$).
FT-IR ν_{max} (neat)	3392 (br), 2968 (m), 2922 (m), 2865 (w), 1448 (w), 1375 (w), 1102 (s), 1051 (s), 874 (w) 839 (w) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 5.06 (1H, tt, *J* = 7.0, 1.4 Hz, =C**H**CH_2), 4.81_{maj} (1H, d, *J* = 6.0 Hz, C**H**OH), 4.54_{min} (1H, d, *J* = 7.5 Hz, C**H**OH), 3.95_{min} (1H, d, *J* = 7.0 Hz, C**H**, THF), 3.81_{maj} (1H, d, *J* = 7.2 Hz, C**H**, THF), 2.79_{min} (1H, d, *J* = 7.5 Hz, CHO**H**), 2.59_{maj} (1H, d, *J* = 6.0 Hz, CHO**H**), 2.18-1.80 (4H, m, 2 x C**H**$_2$, THF), 1.68_{maj} (3H, s, C**H**$_3$), 1.62-1.33 (4H, m, 2 x C**H**$_2$), 1.56_{maj} (3H, s, C**H**$_3$), 1.57_{min} (3H, s, C**H**$_3$), 1.52_{min} (3H, s, C**H**$_3$), 1.41_{maj} (3H, s, C**H**$_3$), 1.38_{maj} (3H, s, C**H**$_3$), 1.35_{min} (3H, s, C**H**$_3$), 1.30_{min} (3H, s, C**H**$_3$) ppm. Aldehyde peak at 9.5 ppm was also observed *i.e.* ca 5 %.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 132.12 ((C**H**$_3$)$_2$**C**), 124.19_{min} and 123.99_{maj} ((C**H**$_3$)$_2$C=**C**), 96.05_{min} and 94.30_{maj} (**C**HOH), 82.14_{min} and 81.82_{maj} (**C**CH$_3$, THF), 80.10_{maj} and 79.36_{min} (**C**H, THF), 77.32 (**C**CH$_3$), 39.38_{min} and 38.74_{maj} (**C**H$_2$, THF), 27.60 (**C**H$_2$, THF), 25.63_{maj} and 24.43_{min} (**C**H$_3$), 25.23_{maj} and 24.02_{min} (**C**H$_2$CCH$_3$), 21.82_{maj} and 21.18_{min} (**C**H$_2$CH$_2$), 20.36 (**C**H$_3$), 19.82 (**C**H$_3$),

	17.64 (CH_3) ppm.
LRMS (ES^+) m/z	263 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 263.1618; Found: 263.1612 ($[M+Na]^+$).

(*R*)-1-((2*S*,5*R*)-Tetrahydro-5-((*S*)-2-trimethylsiloxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-yl)ethane-1,2-diol (6.44)

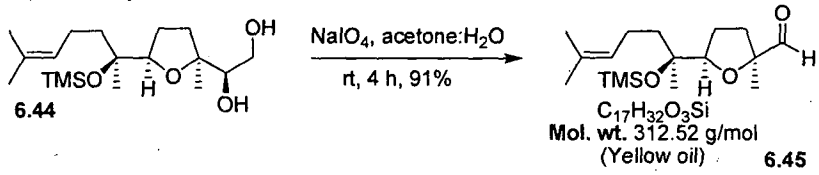


To a stirring solution of triol **2.38** (260 mg, 0.96 mmol) and imidazole (523 mg, 7.68 mmol) in DMF (3 mL) was added TMSCl (1.23 mL, 9.6 mmol) at –10 °C. The mixture was stirred for 2 hours, during which the temperature was raised to 15 °C. Then the mixture was cooled to –10 °C and anhydrous K_2CO_3 (4.4 mg, 2 mL of dry MeOH) was added followed by stirring at room temperature for 10 hours and MeOH was removed *in vacuo*. To the resultant residue, Et_2O (10 mL) and H_2O (10 mL) was added. The organic phase was separated and the aqueous phase was re-extracted with Et_2O (2 x 15 mL), dried (Na_2SO_4), concentrated *in vacuo* afforded the crude **6.44** as a yellow oil (345 mg). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (10 to 25%)) afforded the diol **6.44** as a yellow oil (278 mg, 0.81 mmol, 84%).

$[\alpha]^{24}_D$	+6.96 (*c* 0.395, $CHCl_3$).
FT-IR ν_{max} (neat)	3385 (br), 2967 (m), 2927 (m), 2873 (w), 1452 (w), 1374 (w), 1250 (s), 1084 (s), 837 (s), 753 (m) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 5.12 (1H, tt, *J* = 7.0, 1.4 Hz, =C**H**CH_2), 3.86 (1H, t, *J* = 7.4 Hz, C**H**, THF), 3.63-3.73 (2H, m, C**H**$_2$OH), 3.56 (1H, m, C**H**OH), 2.33 (1H, dd, *J* = 7.8, 4.0 Hz, CH_2O**H**), 2.11 (1H, ddd, *J* = 12.3, 9.6, 5.3 Hz, C**H**H, THF), 2.03-1.82 (8H, m, O**H**, 3 x C**H**$_2$ and CH**H**, THF), 1.69 (3H, s, C**H**$_3$), 1.61 (3H, s, C**H**$_3$), 1.33 (3H, s, C**H**$_3$), 1.17 (3H, s, C**H**$_3$), 0.16 (9H, s, COSi(C**H**$_3$)$_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 131.72 ((CH_3)$_2$**C**), 124.08 ((CH_3)$_2$C=**C**), 84.72 (**C**CH_3, THF), 82.73 (**C**H, THF), 77.58 (**C**OSi(CH_3)$_3$), 77.32 (**C**HOH),

	63.29 ($\mathbf{C}H_2OH$), 41.09 ($\mathbf{C}H_2CO$), 32.18 ($\mathbf{C}H_2$, THF), 26.72 ($\mathbf{C}H_2$, THF), 25.64 ($\mathbf{C}H_3$), 24.67 ($\mathbf{C}H_3$), 23.67 ($\mathbf{C}H_3$), 23.39 ($\mathbf{C}H_2CH_2$), 17.66 ($\mathbf{C}H_3$), 2.60 (3C, $COSi(\mathbf{C}H_3)_3$) ppm.
LRMS (ES^+) m/z	367 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 367.2275; Found: 367.2270 ($[M+Na]^+$).

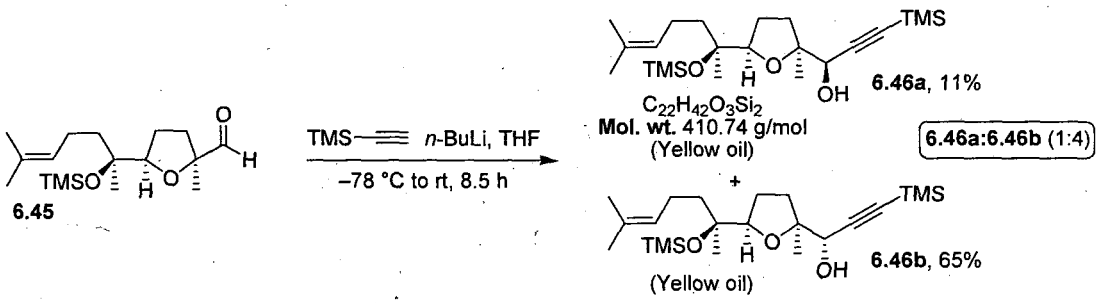
(2*S*,5*R*)-Tetrahydro-5-((*S*)-2-trimethylsiloxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-carbaldehyde (6.45)



Following the procedure for the preparation of THF **6.43**, THF diol **6.44** (272 mg, 0.79 mmol) afforded the crude **6.45** as a yellow oil (240 mg). Purification by column chromatography (SiO_2 eluting with CH_2Cl_2/hexane (10 to 40%)) afforded the title THF aldehyde **6.45** as a yellow oil (225 mg, 0.72 mmol, 91%).

$[\alpha]^{26}_D$	–3.83 (*c* 1.03, $CHCl_3$).
FT-IR ν_{max} (neat)	2967 (m), 2930 (w), 2862 (w), 1737 (s), 1445 (w), 1374 (w), 1250 (s), 1092 (m), 1044 (m), 837 (s), 753 (m) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 9.61 (1H, s, **C**HO), 5.08 (1H, t, J = 7.0 Hz, =**C**HCH$_2$), 4.02 (1H, t, J = 7.4 Hz, C**H**, THF), 2.11 (1H, dt, J = 12.1, 6.1 Hz, C**H**H, THF), 2.06-1.83 (4H, m, C**H**H, C**H**$_2$ and CH**H**, THF), 1.71-1.39 (3H, m, CH**H** and C**H**$_2$), 1.69 (3H, s, C**H**$_3$), 1.61 (3H, s, C**H**$_3$), 1.31 (3H, s, C**H**$_3$), 1.26 (3H, s, C**H**$_3$), 0.12 (9H, s, $COSi(\mathbf{C}H_3)_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 203.92 (**C**HO), 131.48 ($(CH_3)_2\mathbf{C}$), 124.38 ($(CH_3)_2C=\mathbf{C}$), 86.78 ($\mathbf{C}CH_3$, THF), 85.65 (**C**H, THF), 76.69 ($\mathbf{C}OSi(CH_3)_3$), 40.64 ($\mathbf{C}H_2CO$), 34.13 ($\mathbf{C}H_2$, THF), 26.39 ($\mathbf{C}H_2$, THF), 25.67 ($\mathbf{C}H_3$), 23.75 ($\mathbf{C}H_3$), 22.85 ($\mathbf{C}H_2CH_2$), 21.13 ($\mathbf{C}H_3$), 17.62 ($\mathbf{C}H_3$), 2.64 (3C, $COSi(\mathbf{C}H_3)_3$) ppm.
LRMS (ES^+) m/z	335 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 335.2013; Found: 335.2012 ($[M+Na]^+$).

(*R*)-2-((2*S*,5*R*)-Tetrahydro-5-((*S*)-2-trimethylsiloxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-yl)-3-(trimethylsilyl)prop-2-ynyl)-1-ol (6.46a);
(*S*)-2-((2*S*,5*R*)-Tetrahydro-5-((*S*)-2-trimethylsiloxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-yl)-3-(trimethylsilyl)prop-2-ynyl)-1-ol (6.46b)



To a solution of TMS acetylene (91 μL, 0.54 mmol) in THF (1.5 mL) at –78 °C was added *n*-BuLi (235 μL, 2.3 M in hexanes, 0.54 mmol) and the mixture was stirred for 1 hour, during which the temeprature of the acetone-bath raised to –60 °C. The acetone-bath was replaced with an ice-bath and aldehyde **6.45** (85 mg, 0.27 mmol) in THF (0.5 mL) was added. The resultant mixture was stirred and allowed to warm to room temperature over 7.5 hours. At this stage, the reaction was quenched with H_2O (2 mL) and diluted with Et_2O (5 mL). The organic phase was separated and the aqueous phase was re-extracted with Et_2O (2 x 10 mL). The organic phases were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product **6.46ab** as a yellow oil (99 mg, **6.46a**:**6.46b** (1:4)). Purification by column chromatography (SiO_2 eluting with CH_2Cl_2/hexane (10 to 40%)) afforded the title THF **6.46b** as a yellow oil (72 mg, 0.18 mmol, 65%). The minor diastereoisomer **6.46a** was isolated as a yellow oil (12 mg, 0.029 mmol, 11%) and was found contaminated with unidentified product *i.e.* 20%.

Spectroscopic data for **6.46b**:

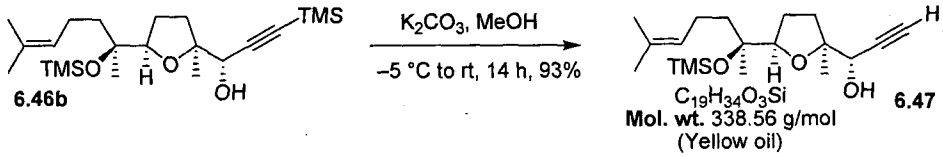
$[\alpha]^{26}_D$	+23.96 (*c* 0.53, $CHCl_3$).
FT-IR ν_{max} (neat)	3421 (br), 2964 (m), 2926 (w), 2865 (w), 1448 (w), 1374 (w), 1250 (s), 1073 (m), 841 (s), 759 (m) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 5.06 (1H, t, *J* = 7.0 Hz, =C**H**CH_2), 4.13 (1H, d, *J* = 7.0 Hz, C**H**OH), 3.93 (1H, dd, *J* = 9.3, 6.3 Hz, C**H**, THF), 3.35 (1H, d, *J* = 7.0 Hz, CHO**H**), 2.14-1.72 (6H, m, C**H**$_2$ and 2 x C**H**$_2$, THF), 1.69 (3H, s, C**H**$_3$), 1.62-1.39 (2H, m, C**H**$_2$), 1.62 (3H, s,

	CH_3), 1.35 (6H, s, 2 x CH_3), 0.17 (18H, s, 2 x $Si(CH_3)_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 131.61 ($(CH_3)_2C$), 124.22 ($(CH_3)_2C=C$), 104.98 ($C\equiv C$), 89.37 ($\equiv CSi(CH_3)_3$), 85.02 (CH, THF), 84.92 (CCH_3, THF), 77.32 ($COSi(CH_3)_3$), 69.52 (CHOH), 40.72 (CH_2CO), 35.61 (CH_2, THF), 26.58 (CH_2, THF), 25.64 (CH_3), 24.71 (CH_3), 23.22 (CH_2CH_2), 22.84 (CH_3), 17.62 (CH_3), 2.63 (3C, $COSi(CH_3)_3$), –0.13 (3C, $\equiv CSi(CH_3)_3$) ppm.
LRMS (ES^+) m/z	433 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 433.2565; Found: 433.2565 ($[M+Na]^+$).

Spectroscopic data for **6.46a**:

^1H NMR (400 MHz, $CDCl_3$)	δ 5.06 (1H, tt, J = 7.0, 1.0 Hz, $=CHCH_2$), 4.30 (1H, s, CHOH), 3.90 (1H, dd, J = 9.3, 6.3 Hz, CH, THF), 3.35 (1H, s, CHOH), 2.15-1.75 (6H, m, CH_2 and 2 x CH_2, THF), 1.69 (3H, s, CH_3), 1.67-1.25 (2H, m, CH_2), 1.61 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.31 (3H, s, CH_3), 0.17 (9H, s, $Si(CH_3)_3$), 0.16 (9H, s, $Si(CH_3)_3$) ppm. Additional peaks δ 2.50-1.93 (m), 1.56 (s)
^{13}C NMR (100 MHz, $CDCl_3$)	δ 131.76 ($(CH_3)_2C$), 124.05 ($(CH_3)_2C=C$), 104.48 ($C\equiv C$), 89.75 ($\equiv CSi(CH_3)_3$), 85.81 (CH, THF), 84.72 (CCH_3, THF), 77.43 ($COSi(CH_3)_3$), 70.43 (CHOH), 41.08 (CH_2CO), 33.02 (CH_2, THF), 27.11 (CH_2, THF), 25.64 (CH_3), 24.98 (CH_3), 24.88 (CH_2CH_2), 23.44 (CH_3), 17.64 (CH_3), 2.60 (3C, $COSi(CH_3)_3$), –0.16 (3C, $\equiv CSi(CH_3)_3$) ppm. Additional peaks δ 65.85 and 15.27 ppm.

(*S*)-2-((2*S*,5*R*)-Tetrahydro-5-((*S*)-2-trimethylsiloxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-yl)-1-hydroxypropyne (6.47)

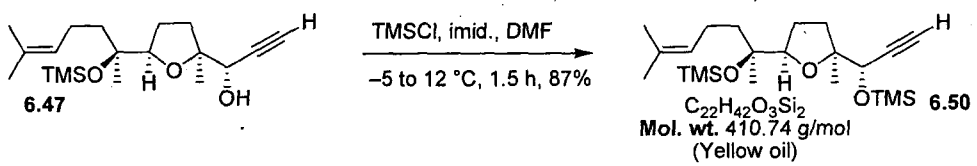


Following the procedure for the selective deprotection of TMS group to prepare THF **4.44a**, selective deprotection of THF **6.46b** (71 mg, 0.17 mmol) afforded the crude

product **6.47** as a yellow oil (61 mg). Purification by column chromatography (SiO_2 eluting with CH_2Cl_2/hexane (10 to 40%)) afforded the title propargylic alcohol **6.47** as a yellow oil (54 mg, 0.16 mmol, 93%)

$[\alpha]^{22}_D$	+28.6 (*c* 0.79, $CHCl_3$).
FT-IR ν_{max} (neat)	3421 (br), 2966 (m), 2926 (w), 2873 (w), 1455 (w), 1373 (w), 1251 (s), 1070 (m), 839 (s), 755 (m) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 5.06 (1H, t, *J* = 7.0 Hz, =C**H**CH_2), 4.13 (1H, dd, *J* = 7.5, 2.0 Hz, C**H**OH), 3.95 (1H, dd, *J* = 9.3, 6.3 Hz, C**H**, THF), 3.53 (1H, d, *J* = 7.5 Hz, CHO**H**), 2.39 (1H, d, *J* = 2.0 Hz, ≡C**H**), 2.17-1.71 (6H, m, C**H**$_2$ and 2 x C**H**$_2$, THF), 1.69 (3H, s, C**H**$_3$), 1.59-1.44 (2H, m, C**H**$_2$), 1.60 (3H, s, C**H**$_3$), 1.37 (6H, s, 2 x C**H**$_3$), 0.18 (9H, s, Si(C**H**$_3$)$_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 131.70 ((CH$_3$)$_2$**C**), 124.11 ((CH$_3$)$_2$C=**C**), 84.99 (**C**H, THF), 84.79 (**C**CH$_3$, THF), 83.12 (**C**≡CH), 77.37 (**C**OSi(CH$_3$)$_3$), 72.84 (C≡**C**H), 68.93 (**C**HOH), 40.88 (**C**H$_2$CO), 35.52 (**C**H$_2$, THF), 26.52 (**C**H$_2$, THF), 25.64 (**C**H$_3$), 24.86 (**C**H$_3$), 23.35 (**C**H$_2$CH$_2$), 23.01 (**C**H$_3$), 17.62 (**C**H$_3$), 2.59 (3C, COSi(**C**H$_3$)$_3$) ppm.
LRMS (ES^+) m/z	361 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 361.2169; Found: 361.2169 ($[M+Na]^+$).

(*S*)-2-((2*S*,5*R*)-Tetrahydro-5-((*S*)-2-trimethylsiloxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-yl)-1-trimethylsiloxypropyne (6.50)

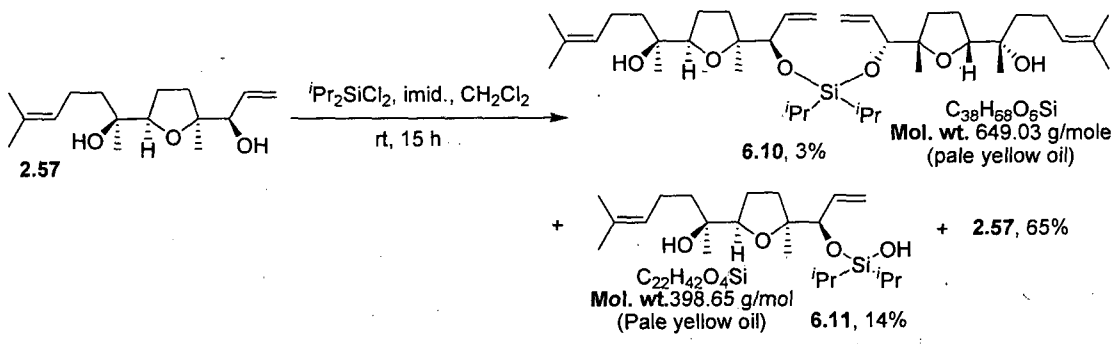


Following the procedure for the preparation of THF **4.45a,b**, protection of the secondary propargylic alcohol **6.47** (24 mg, 0.07 mmol) afforded the crude product **6.50** as a yellow oil (29 mg). Purification by column chromatography (SiO_2 eluting with CH_2Cl_2/hexane (10 to 40%)) afforded the enyne **6.50** as a yellow oil (26 mg, 0.06 mmol, 87%)

$[\alpha]^{25}_D$	+13.78 (*c* 1.27, $CHCl_3$).

FT-IR ν_{max} (neat)	2964 (m), 2926 (w), 2865 (w), 1448 (w), 1373 (w), 1250 (s), 1090 (s), 840 (s), 753 (m) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 5.11 (1H, t, J = 7.0 Hz, =C**H**CH_2), 4.22 (1H, d, J = 2.0 Hz, C**H**OSi$(CH_3)_3$), 3.89 (1H, t, J = 7.2 Hz, C**H**, THF), 2.31 (1H, d, J = 2.0 Hz, ≡C**H**), 2.09-1.84 (6H, m, C**H**$_2$ and 2 x C**H**$_2$, THF), 1.68 (3H, s, C**H**$_3$), 1.6361.44 (2H, m, C**H**$_2$), 1.61 (3H, s, C**H**$_3$), 1.26 (3H, s, C**H**$_3$), 1.18 (3H, s, C**H**$_3$), 0.18 (9H, s, Si(C**H**$_3)_3$), 0.12 (9H, s, COSi(C**H**$_3)_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 130.90 ($(CH_3)_2$**C**), 124.97 ($(CH_3)_2$C=**C**), 85.29 (**C**H, THF), 84.19 (**C**CH_3, THF), 83.63 (**C**≡CH), 76.68 (**C**OSi$(CH_3)_3$), 72.52 (C≡**C**H), 69.47 (**C**HOSi$(CH_3)_3$), 40.07 (**C**H_2CO), 34.18 (**C**H_2, THF), 26.56 (CH_2**C**H_2), 25.69 (**C**H_3), 27.78 (**C**H_3), 22.28 (**C**H_2, THF), 21.39 (**C**H_3), 17.62 (**C**H_3), 2.66 (3C, COSi(**C**$H_3)_3$), 0.14 (3C, CHOSi(**C**$H_3)_3$) ppm.
LRMS (ES^+) m/z	433 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 433.2565; Found: 433.2565 ($[M+Na]^+$).

(*S*,*S*)-1,1'-((2*R*,2'*R*,5S,5'*S*)-Tetrahydro-5,5'-((*R*,*R*)-1-diisopropylsiloxyallyl)-5,5'-methylfuran -2,2'-yl)-6,6'-methylhept-5,5'-en-2,2'-ol (6.10);
(*S*)-1-((2*R*,5*S*)-Tetrahydro-5-((*R*)-1-diisopropylhydroxysiloxyallyl)-5-methylfuran-2-yl)-6-methylhept-5-en-2-ol (6.11);
(*S*)-1-((2*R*,5*S*)-Tetrahydro-5-((*R*)-1-hydroxyallyl)-5-methylfuran-2-yl)-6-methylhept-5-en-2-ol (2.57)



At room temperature, to a solution of allylic alcohol **2.57** (50 mg, 0.19 mmol) in CH_2Cl_2 (1 mL) was added imidazole (64 mg, 0.93 mmol) and $^iPr_2SiCl_2$ (18 μL, 0.093 mmol) and the resultant mixture was stirred for 15 hours. The reaction was quenched by adding H_2O (1 mL) and diluted with CH_2Cl_2 (5 mL). The organic phase was separated, dried

(Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as a yellow oil (52 mg). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (2 to 15%) afforded the title THF **6.11** as a pale yellow oil (10 mg, 0.025 mmol, 14%) along with the less polar *bis*-THF product **6.10** as a pale yellow oil (4 mg, 0.006 mmol, 3%). The THF product **6.10** was contaminated with unidentified product. The unreacted starting allylic alcohol **2.57** was also recovered as a yellow oil (33 mg, 0.12 mmol, 66%).

Spectroscopic data for **6.11**:

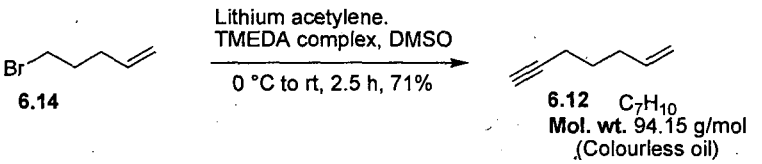
$[\alpha]^{28.5}_D$	+16.89 (*c* 0.45, $CHCl_3$).
FT-IR ν_{max} (neat)	3325 (br), 2966 (m), 2943 (m), 2867 (w), 1450 (w), 1373 (m), 1102 (m), 886 (m), 866 (m0, 834 (m), 692 (m) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$)	δ 5.89 (1H, ddd, *J* = 17.1, 10.5 and 6.5 Hz, C**H**=CH_2), 5.30 (1H, dt, *J* = 17.1, 1.5 Hz, CH=C**H**H), 5.18 (1H, d, *J* = 10.5 Hz, CH=C**H**H), 5.11 (1H, tt, *J* = 7.0, 1.2 Hz, =C**H**CH_2), 4.30 (1H, d, *J* = 6.5 Hz, C**H**OSi), 3.76 (1H, dd, *J* = 8.8, 6.5 Hz, C**H**, THF), 2.19 (1H, ddd, *J* = 12.3, 9.8, 4.5 Hz, C**H**H, THF), 2.13-1.79 (4H, m, O**H**, C**H**H and C**H**$_2$, THF), 1.69 (3H, s, C**H**$_3$), 1.62 (3H, s, C**H**$_3$), 1.53-0.88 (7H, m, C**H**H, and 3 x C**H**$_2$), 1.45 (3H, s, C**H**$_3$), 1.14 (3H, s, C**H**$_3$), 1.06 (6H, s, 2 x C**H**$_3$), 1.05 (6H, s, 2 x C**H**$_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 138.21 (**C**HCH_2), 131.80 ($(CH_3)_2$**C**), 124.38 ($(CH_3)_2$C=**C**), 116.54 (**C**H$_2$), 84.87 (**C**OH), 83.79 (**C**H, THF), 78.11 (**C**HOSi), 72.94 (**C**CH_3, THF), 38.66 (**C**H_2CO), 31.60 (**C**H_2, THF), 25.71 (**C**H_3), 25.67 (CH_2**C**H_2), 25.44 (**C**H_3), 23.54 (**C**H_3), 22.29 (**C**H_2, THF), 17.66 (**C**H_3), 17.73 (2 x **C**H_3), 17.25 (2 x **C**H_3), 12.87 (**C**H$(CH_3)_2$), 12.62 (**C**H$(CH_3)_2$) ppm.
LRMS (ES^+) m/z	421 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 421.2745; Found: 421.2744 ($[M+Na]^+$).

Selective spectroscopic data for **6.10**:

FT-IR ν_{max} (neat)	3421 (br), 2966 (m), 2944 (m), 2867 (w), 1464 (w), 1374 (m), 1096 (s), 1053 (s), 886 (m), 690 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$)	δ 5.59 (2H, ddd, *J* = 17.1, 10.5 and 6.5 Hz, 2 x C**H**=CH_2), 5.44-5.32 (4H, m, 2 x CH=C**H**$_2$), 5.18 (2H, tt, *J* = 7.0, 1.2 Hz, 2 x =C**H**CH_2), 4.95 (1H, br, O**H**), 4.45 (2H, d, *J* = 8.4 Hz, 2 x C**H**OSi), 3.89-3.33 (2H, m, 2 x C**H**, THF), 3.45 (1H, br, O**H**), 2.25-1.72 (8H, m, 4 x C**H**$_2$, THF), 1.69 (6H, s, 2 x C**H**$_3$), 1.61 (6H, s, 2 x C**H**$_3$), 1.65-0.89 (10H, m, 2 x C**H**, and 4 x C**H**$_2$), 1.53 (6H, s, 2 x C**H**$_3$), 1.13 (6H, s, 2 x C**H**$_3$), 1.06 (6H, s, 2 x C**H**$_3$), 1.05 (6H, s, 2 x C**H**$_3$) ppm.
LRMS (ES^+) m/z	672 (45%, $[M+Na]^+$).

Hept-1-en-6-yne (6.12)

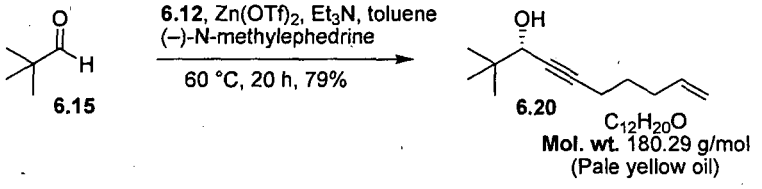


To a solution of lithiumacetylene.trimethylethylenediamine complex (5.14g, 50.3 mmol) in DMSO (45 mL) at 0 °C, was added bromopentene (**6.14**, 5.0 g, 33.5 mmol) in DMSO (5 mL). The resultant mixture was stirred at room temperature for 2.5 hours. At this stage, H_2O (15 mL) was added slowly while keeping the temperature below 35 °C. The title enyne **6.12** was distilled along with H_2O at 140 °C (760 mm Hg), extracted with Et_2O (30 mL), dried (Na_2SO_4) and ether was distilled at 50 °C (760 mm Hg) to isolate the title alkenyne **6.12** as a colourless oil (2.24 g, 23.8 mmol, 71%). Spectroscopic data were in agreement with the literature.[150]

FT-IR ν_{max} (neat)	3077 (w), 2976 (w), 2932 (m), 2859 (w), 2835 (w), 1641 (m), 1436 (m), 991 (m), 911 (s) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$)	δ 5.80 (1H, dddd, *J* = 17.0, 10.2, 6.8, 6.7 Hz, C**H**=CH_2), 5.03 (1H, dq, *J* = 17.0, 1.6 Hz, CH=C**H**H), 4.98 (1H, m, CH=CH**H**), 2.24-2.13 (4H, m, 2 x C**H**$_2$), 1.96 (1H, t, *J* = 2.7 Hz, C≡C**H**), 1.64 (2H, qd, *J* = 7.3, 7.1 Hz, C**H**$_2$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 137.68 (**C**H=CH_2), 115.24 (CH=**C**H_2), 84.28 (**C**≡CH), 68.36 (C≡**C**H), 32.62 (**C**H_2CH), 27.64 (**C**H_2CH_2CH), 17.76 (**C**$H_2CH_2CH_2CH$) ppm.
LRMS (EI) m/z	94 (M^+, 11%), 91 (90%), 79 (100%), 67 (50%), 53 (40%),

41 (70%).

(*S*)-2,2-Dimethyldec-9-en-4-yn-3-ol (6.20)



Procedure

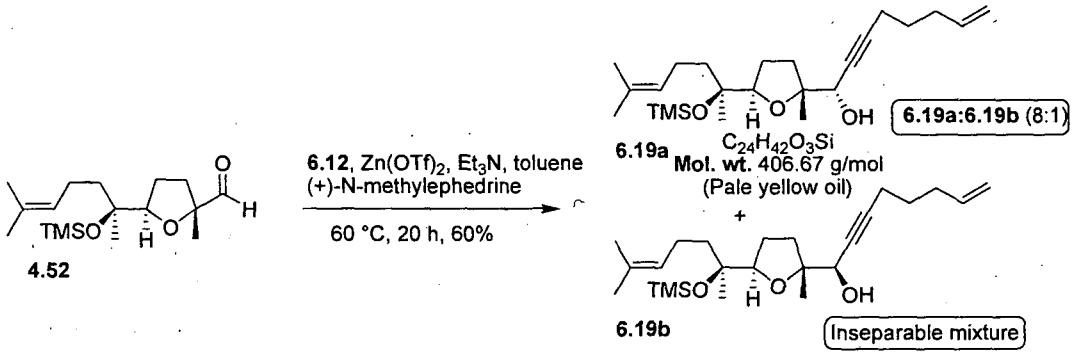
Following the procedure reported by Carreira *et al.*,[151] $Zn(OTf)_2$ (1.6 g, 4.35 mmol) was added in a 5 mL schlenck flask. Vacuum (0.2 mbar) was applied and the flask was heated at 125 °C for 10 hours. At this, the flask was cooled to room temperature, the vacuum was released and (–)-*N*-methylephedrine (788 mg, 4.35 mmol) was added. Vacuum (0.2 mbar) was applied for 30 min and released. The flask was charged with nitrogen, toluene (8 mL) and Et_3N (606 μL, 4.35 mmol) were added and the reaction mixture was stirred for 2 hours at room temperature. At this stage, enyne **6.12** (506 μL, 4.35 mmol) was added and stirred for 30 min. After this the aldehyde **6.15** (250 mg, 2.9 mmol) in toluene (0.5 mL) was added and the resultant mixture was heated at 60 °C and stirred for 20 hours. The reaction was quenched by adding sat. aq. NH_4Cl (4 mL) and diluted with Et_2O (10 mL). The organic phase was separated and the aqueous phase was re-extracted with Et_2O (2 x 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give crude product **6.20** as a yellow oil (460 mg). Purification by column chromatography (SiO_2 eluting with 5% EtOAc/hexane) afforded the title enyne **6.20** as a pale yellow oil (411 mg, 2.28 mmol, 79%).

FT-IR ν_{max} (neat)	3398 (br), 3077 (w), 2954 (m), 2921 (w), 2867 (w), 1641 (m), 1363 (m), 1001 (s), 912 (s) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 5.80 (1H, dddd, J = 17.0, 13.3, 10.0, 6.5 Hz, C**H**=CH_2), 5.04 (1H, dq, J = 17.0, 1.6 Hz, CH=C**H**H), 4.99 (1H, m, CH=CH**H**), 4.00 (1H, dt, J = 6.0, 2.0 Hz, C**H**OH), 2.24 (2H, td, J = 7.0, 2.0 Hz, C**H**$_2$), 2.21-2.12 (2H, m, C**H**$_2$), 1.68 (1H, d, J = 6.0 Hz, CHO**H**), 1.62 (2H, qd, J = 7.3, 7.0 Hz, C**H**$_2$), 0.99 (9H, s, 3 x C**H**$_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 137.8 (**C**H=CH_2), 115.17 (CH=**C**H$_2$), 85.82 (**C**≡C), 80.12 (C≡**C**), 71.61 (**C**HOH), 35.38 (**C**$(CH_3)_2$), 32.78 (**C**H$_2$CH),

	27.92 (CH_2CH_2CH), 125.27 (3C, 3 x CH_3), 18.05 ($CH_2CH_2CH_2CH$) ppm.
LRMS (EI) m/z	180 (M^+, 20%), 163 (30%), 122 (50%), 107 (60%), 95 (80%), 57 (100%).

(*S*)-1-((2*R*,5*R*)-Tetrahydro-5-((*S*)-2-trimethylsiloxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-yl)oct-7-en-2-yn-1-ol (6.19a)

(*R*)-1-((2*R*,5*R*)-Tetrahydro-5-((*S*)-2-trimethylsiloxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-yl)oct-7-en-2-yn-1-ol (6.19b)

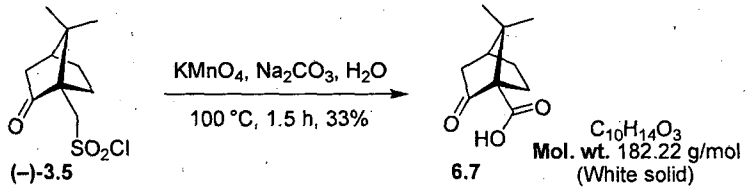


Following the procedure for the preparation of enyne **6.20**, the aldehyde **4.52** (27 mg, 0.112 mmol) afforded crude product **6.19a,b** as a yellow oil (38 mg). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (2 to 7.5%)) afforded the title enynes **6.19a,b** as a pale yellow oil (27 mg, 0.07 mmol, 60%, d.r. 8:1). The less polar starting aldehyde **4.52** was also recovered after purification as a pale yellow oil (6 mg, 0.02 mmol, 17%).

$[\alpha]^{28}_D$	–13.9 (*c* 1.09, $CHCl_3$).
FT-IR ν_{max} (neat)	3451 (br), 3075 (w), 2968 (m), 2922 (m), 2858 (w), 1249 (s), 1064 (m), 1045 (m), 838 (s), 753 (m) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 5.80 (1H, dddd, *J* = 17.0, 13.3, 10.0, 6.5 Hz, C**H**=CH_2), 5.10 (1H, td, *J* = 7.0, 1.2 Hz, =C**H**CH_2), 5.03 (1H, dq, *J* = 17.0, 1.6 Hz, CH=C**H**H), 4.97 (1H, m, CH=CH**H**), 4.21 (1H, br, C**H**OH), 3.90_{min} and 3.79_{maj} (1H, dd, *J* = 8.0, 6.3 Hz, C**H**, THF), 2.38 (1H, d, *J* = 3.2 Hz, CHO**H**), 2.23 (2H, td, *J* = 7.0, 2.0 Hz, C$\mathbf{H_2}$), 2.15 (2H, q, *J* = 7.0 Hz, C$\mathbf{H_2}$), 2.05-1.71 (6H, m, C$\mathbf{H_2}$ and 2 x C$\mathbf{H_2}$, THF), 1.69 (3H, s, C$\mathbf{H_3}$), 1.65-1.26 (4H, m, 2 x C$\mathbf{H_2}$), 1.60 (3H, s, C$\mathbf{H_3}$), 1.31 (3H, s, C$\mathbf{H_3}$), 1.22 (3H, s,

	CH_3), 0.12 (9H, s, $COSi(CH_3)_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 137.8 ($CH=CH_2$), 131.22 ($(CH_3)_2C$), 124.74 ($C=CHCH_2$), 115.15 ($CH=CH_2$), 85.79 (CH, THF), 85.69 (CCH_3, THF), 85.00 (C≡C), 78.55 (C≡C), 76.49 ($COSi(CH_3)_3$), 68.22 (CHOH), 40.28 ($CH_2COSi(CH_3)_3$), 34.32 (CH_2CH), 32.77 (CH_2, THF), 27.78 (CH_2CH_2CH), 26.40 (CH_2, THF), 25.68 (CH_3), 22.85 (CH_3), 21.29 (CH_2CH_2), 21.19 (CH_3), 18.05 ($CH_2CH_2CH_2CH$) 17.62 (CH_3), 2.67 (3C, $COSi(CH_3)_3$) ppm.
LRMS (ES^+) m/z	429 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 429.2755; Found: 429.2788 ($[M+Na]^+$).

7,7-Dimethyl-2-oxobicyclo[2.2'.1]heptane-1-carboxylic acid (6.7)

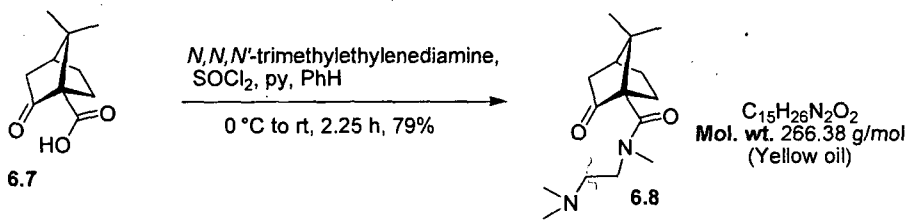


Following the procedure reported by Bartlett *et al.*,[145] a solution of Na_2CO_3 (6.0 g, 53.0 mmol) in H_2O (55 mL) was added in a beaker and placed on a steambath. The solution was stirred vigorously. When the steambath water started boiling one-third of a solution of $KMnO_4$ (6.0 g, 39.5 mmol) in H_2O (35 mL) was added to the hot solution of Na_2CO_3, followed by the addition of (1*R*)-camphorsulfonyl chloride ((–)-**3.5**, 6.0 g, 24.0 mmol). After stirring for 10 min, half of the remaining portion of $KMnO_4$ was added and stirred for a further 10 min. At this stage, the remaining solution of $KMnO_4$ was added and reaction mixture was stirred for 1 hour. The reaction was quenched by adding sat. aq. Na_2SO_3 (5 mL), cooled and acidified with H_2SO_4 (20% aq., 25 mL). The mixture was heated and precipitated MnO_2 was dissolved by adding powdered Na_2SO_3. The resulting solution was cooled to room temperature and organics were extracted with Et_2O (40 mL). The aqueous phase was re-extracted with Et_2O (2 x 25 mL), and combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the acid product **6.7** as a white solid (1.45 g, 7.96 mmol, 33%).

$[\alpha]^{25.5}_D$	+84.46 (*c* 1.02, $CHCl_3$).
mp	232-234 °C, (Lit. 233-234 °C).[145]
FT-IR ν_{max} (neat)	2962 (m), 2920 (m), 2876 (w), 1747 (s), 1689 (s), 1317 (m),

	908 (s), 730 (s) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$)	δ 2.61 (1H, dt, *J* = 18.8, 3.9 Hz, C**H**H), 2.47-2.40 (1H, m, C**H**H), 2.21-2.09 (2H, m, C**H$_2$**), 2.04 (1H, d, *J* = 18.8 Hz, C**H**H), 1.81 (1H, ddd, *J* = 13.9, 9.3, 4.4 Hz, C**H**H), 1.45 (1H, m, C**H**H), 1.23 (3H, s, C**H$_3$**), 1.12 (3H, s, C**H$_3$**) ppm. (OH signal was not observed).
^{13}C NMR (100 MHz, $CDCl_3$)	δ 215.12 (**C**O), 172.75 (**C**OOH), 66.11 (**C**COOH) 49.98 (**C**(CH$_3$)$_2$), 43.82 (**C**HC(CH$_3$)$_2$), 43.44 (**C**H$_2$CO), 27.74 (**C**H$_2$C), 27.06 (**C**H$_2$CH$_2$C), 20.62 (**C**H$_3$), 20.04 (**C**H$_3$) ppm.
LRMS (ES^-) m/z	181 (100%, $[M-H]^-$).
HRMS (ES^+) m/z	Calculated: 205.0835; Found: 205.0835 ($[M+Na]^+$).

_N_-(2-(Methylamino-4-dimethylamino)ethyl)-_N_-7,7-dimethyl-2-oxobicyclo[2.2'.1] heptane-1-carboxamide (6.8)

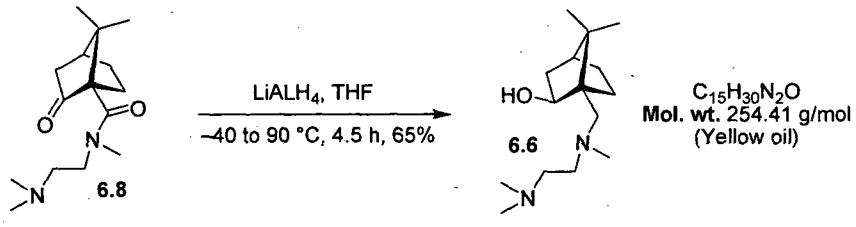


According to the method reported by Oppolzer *et al.*,[144] to the solution of acid **6.7** (1.45 g, 7.96 mmol) in $SOCl_2$ (6.6 mL, 55.47 mmol) was added pyridine (55 μL, 79.0 mmol) and stirred at room temperature for 2 hours. At this stage, the solvent was co-evaporated with benzene (10 mL). The residue was dissolved in benzene (10 mL) and cooled to 0 °C. To this *N,N,N'*-trimethylethylenediamine (2.07 mL, 102.2 mmol) was added and stirred for 10 min. The reaction was allowed to warm to room temperature and quenched with H_2O (5 mL). The organic phase was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford crude product **6.8** as a yellow oil (1.85 g). Purification by column chromatography (SiO_2 eluting with 95% EtOAc/Et_3N) afforded the title amide **6.8** as a yellow oil (1.68 g, 6.29 mmol, 79%).

FT-IR ν_{max} (neat)	2945 (m), 2820 (w), 2796 (m), 1739 (s), 1628 (s), 1397 (m), 1016 (m) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$)	δ 3.48 (2H, br, NC**H$_2$**), 2.99 (2H, br, 2.52 NCH$_2$C**H$_2$**), 2.52 (1H, dd, *J* = 4.6, 2.3 Hz, C**H**H), 2.44 (1H, m, C**H**H), 2.26 (9H,

	s, NCH_3 and $N(CH_3)_2$), 2.13-2.02 (2H, m, CH_2), 1.97 (1H, t, J = 4.6 Hz, CHH), 1.91 (1H, d, J = 18.6 Hz, CHH), 1.45 (1H, dt, J = 12.8, 5.5 Hz, CHH), 1.22 (3H, s, CH_3), 1.19 (3H, s, CH_3) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 212.31 (CO), 168.94 (CON), 67.64 (CCON) 56.23 (NCH_2CH_2), 50.62 ($C(CH_3)_2$), 47.55 (NCH_2), 45.76 (2C, $N(CH_3)_2$), 44.29 (CH_2CO), 43.81 (NCH_3), 43.32 ($CHC(CH_3)_2$), 27.34 (CH_2C), 27.02 (CH_2CH_2C), 21.52 (CH_3), 20.82 (CH_3) ppm.
LRMS (ES^+) m/z	267 (100%, $[M+H]^+$).

_N_-((2_S_)-1-(((2-(Methylamino)methyl)-4-dimethylamino)ethyl)-_N_-7,7-dimethylbicyclo[2.2'.1] heptan-2-ol (6.6)

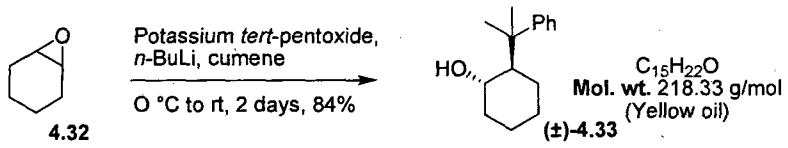


Following the reported method of Oppolzer *et al.*,[144] To a solution of $LiAlH_4$ (1.03 g, 27.1 mmol) in THF (5 mL) at –40 °C was added a solution of amide **6.8** (1.44 g, 5.41 mmol) in THF (8 mL) and the resultant mixture was stirred for 1.5 hours, while maintaining the temperature at –40 °C. The reaction was then stirred at –20 °C for 1 hour, then at 0 °C for 1 hour, and finally the mixture was heated to reflux for 1 hour. At this stage, the reaction was cooled to 0 °C and quenched with NaOH (20% aq., 10 mL) and diluted with Et_2O (50 mL). The organic phase was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give crude product **6.6** as a yellow oil (1.10 g). Bulb-to-bulb kugelrohr distillation (200 °C, 0.2 mbar) afforded the title tridentate ligand **6.6** as a yellow oil (895 mg, 3.52 mmol, 65%).

$[\alpha]^{28}_D$	–50.0 (*c* 1.375, $CHCl_3$).
FT-IR ν_{max} (neat)	3177 (br), 2948 (m), 2876 (w), 2788 (m), 1455 (s), 1076 (s), 1033 (s) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 3.90 (1H, dd, J = 8.0, 3.8 Hz, CHOH), 2.92 (1H, d, J = 12.8 Hz, CHHN), 2.70-2.53 (2H, m, CH_2), 2.31 (3H, s, NCH_3),

	2.30-2.10 (3H, m, C**H**H and C**H$_2$**), 2.21 (6H, s, N(C**H$_3$**)$_2$), 1.93 (1H, d, J = 12.8 Hz, CH**H**N), 1.79-0.98 (7H, m, O**H** and 3 x C**H$_2$**), 1.13 (3H, s, C**H$_3$**), 0.80 (3H, s, C**H$_3$**) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 77.32 (**C**HOH), 76.68 (**C**CH$_2$N), 57.06 (NCH$_2$**C**H$_2$), 56.70 (**C**CH$_2$N), 54.95 (N**C**H$_2$), 51.85 (**C**(CH$_3$)$_2$), 47.55 (**C**HC(CH$_3$)$_2$), 45.79 (N**C**H$_3$), 45.00 (N**C**H$_3$), 44.85 (N**C**H$_3$), 39.40 (**C**H$_2$CHOH), 33.29 (**C**H$_2$C), 27.87 (**C**H$_2$CH$_2$C), 20.85 (**C**H$_3$), 20.35 (**C**H$_3$) ppm.
LRMS (ES$^+$) m/z	255 (100%, [M+H]$^+$).
HRMS (ES$^+$) m/z	Calculated: 255.2431; Found: 255.2427 ([M+H]$^+$).

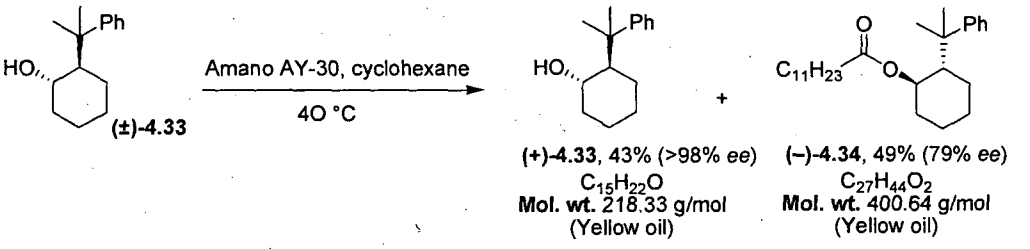
***Rac.* (1*S*,2*R*)-2-(2-Phenylpropan-2-yl)cyclohexanol ((±)-4.33)**



4.32 (±)-4.33

Following the method reported by Comins *et al.*,[125] with slight modifications, a three necked nitrogen filled flask was charged with potassium *tert*-pentaoxide (39.3 mL, 1.7 M in toluene, 66.8 mmol) and the toluene was removed under vacuum (**Note**: Extreme care should be taken as the base is highly flammable). The flask was charged with nitrogen, followed by the addition of neat cumene (28.5 mL, 232 mmol) at room temperature. To this, *n*-BuLi (27.8 mL, 2.3 M in hexanes, 63.9 mmol) was added and the resultant mixture was stirred at room temperature for 2 days (**Note**: a strong magnetic stirrer was required). At this stage, the dark purple gummy suspension was treated with dropwise addition of neat cyclohexene oxide **4.32** (6.0 mL, 58.1 mmol) over 10 min, while keeping the temperature below 30 °C. The reaction mixture was stirred for 3 hours and then cooled to 0 °C. The reaction was quenched by dropwise addition of sat. aq. NH_4Cl (50 mL) and diluted with Et_2O (200 mL). The organic phase was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford crude product as a yellow oil. Bulb-to-bulb kugelrohr distillation (100 °C, 0.5 mbar) afforded the racemic alcohol **(±)-4.33** as a yellow oil (10.7 g, 49.0 mmol, 84%). **Note**: Spectroscopic data of racemic alcohol **(±)-4.33** is identical to the enantiomerically pure alcohol **(+)-4.33**, which is described underneath.

(1*S*,2*R*)-2-(2-Phenylpropan-2-yl)cyclohexanol ((+)-4.33);
(1*R*,2*S*)-2-(2-Phenylpropan-2-yl)cyclohexyl dodecanoate ((–)-4.34)



Following the procedure reported by Comins *et al.*,[125] to a solution of racemic alcohol **(±)-4.33** (10.7 g, 49.0 mmol) in cyclohexane (115 mL) at 40 °C was added lauric acid (9.8 g, 49.0 mmol) and Candida rugosa (Amano AY30, 28.6 g). The progress of laurate ester **(–)-4.34** formation and enantiomeric excess of unreacted alcohol was monitored by chiral HPLC (Chiralcel-OJ column, Daicell Chemical Industries, Ltd., 10% IPA/hexane, 0.4 mL/min). After 45% conversion to ester **(–)-4.34** (48 hours), the enzyme was filtered and air dried (4 days, 28.5 g). The filterate was concentrated *in vacuo* to afford the yellow oil (20.3 g). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (3 to 10%)) afforded a mixture of lauric acid and (+)-TCC **(+)-4.33** as a yellow oil (10.9 g, 79% *ee*) and less polar laurate ester **(–)-4.34** as a yellow oil (8.9 g).

The mixture of lauric acid and (+)-TCC **(+)-4.33** was dissolved in cyclohexane (100 mL) and subjected to enzymatic resolution by adding air-dried Candida rugosa (Amano AY30, 28.5 g) at 40 °C. The reaction was monitored by chiral HPLC and stirred for 2 days. Filtration of enzyme and concentration of the filtrate *in vacuo* afforded the crude as a yellow oil (10.6 g). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (3 to 10%) afforded a mixture of lauric acid and (+)-TCC **(+)-4.33** as a yellow oil (9.65 g, >98% *ee*) and laurate ester **(–)-4.34** as a yellow oil (0.75 g).

The mixture of lauric acid and (+)-TCC **(+)-4.33** was dissolved in hexane (25 mL) and to this was added K_2CO_3 (5.0 g). The mixture was stirred for 1 hour at room temperature to precipitate the potassium laurate. Filtration of precipitates and concentration of the filtrate *in vacuo* afforded (+)-TCC **(+)-4.33** as a yellow oil (4.60 g, 21.07 mmol, 43%, 98% ee, eluation times $t_{(+)\text{-TCC }(+)\text{-4.33}}$ 17.2 min, $t_{(-)\text{-TCC}}$ 14.5 min, $t_{(-)\text{-ester }(-)\text{-4.34}}$ 8.2 min). The analytical data was in agreement with the literature.[125]

Spectroscopic data for **(+) 4.33**

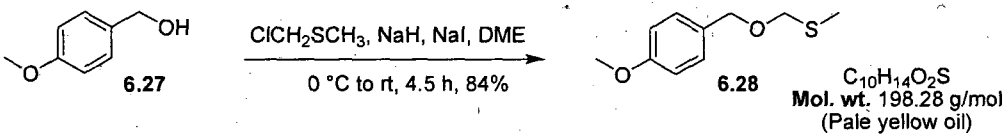
$[\alpha]^{27}_D$	+28.4 (*c* 1.72, $CHCl_3$), {lit. $[\alpha]^{22}_D$ +29.6 (*c* 1.7, $CHCl_3$)}.[125]
FT-IR ν_{max} (neat)	3399 (m), 2925 (m), 2856 (w), 1442 (m), 1042 (s), 760 (s), 694 (s) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 7.43-7.40 (2H, m, 2 x C**H**, $Ar_{(ortho)}$), 7.36-7.31 (2H, m, 2 x C**H**, $Ar_{(meta)}$), 7.20 (1H, tt, *J* = 7.3, 1.3 Hz, C**H**, $Ar_{(para)}$), 3.51 (1H, td, *J* = 10.0, 4.3 Hz, C**H**OH), 1.88-1.68 (6H, m, O**H**, C**H** and 2 x C**H_2**), 1.45 (3H, s, C**H_3**), 1.31 (3H, s, C**H_3**), 1.22-0.96 (4H, m, 2 x C**H_2**) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 151.32 (**C**CH, Ar), 128.42 (2 x **C**H, $Ar_{(meta)}$), 125.83 (2 x **C**H, $Ar_{(ortho)}$), 125.76 (**C**H, $Ar_{(para)}$), 73.43 (**C**OH), 54.67 (**C**HCPh), 39.95 (**C**Ph), 36.78 (**C**H_2COH), 28.65 (**C**H_3), 26.91 (**C**$H_2CH_2CH_2$COH), 26.29 (CH_2**C**H_2COH), 25.05 (**C**H_2CH), 24.29 (**C**H_3) ppm.
LRMS (EI) m/z	218 (M^+, 6%), 200 (28%), 131 (18%), 118 (100%), 105 (52%), 91 (58%), 79 (36%).
HRMS (EI) m/z	Calculated: 218.1671; Found: 218.1667 (M^+).

Spectroscopic data for **(–) 4.34**

FT-IR ν_{max} (neat)	2953 (m), 2917 (s), 2849 (w), 1729 (m), 1701 (s), 1465 (w), 1303 (w), 1192 (w), 938 (m), 699 (m), cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 7.32-7.24 (4H, m, 4 x C**H**, $Ar_{(ortho) \text{ and } (meta)}$), 7.13 (1H, m, C**H**, $Ar_{(para)}$), 4.79 (1H, td, *J* = 10.0, 4.3 Hz, C**H**OH), 2.36 (2H, t, *J* = 7.5 Hz, C**H_2**COO), 2.06 (1H, td, *J* = 11.2, 3.4 Hz, C**H**H), 1.91-1.61 (6H, m, 3 x C**H_2**), 1.45-1.04 (20H, m, 10 x C**H_2**), 1.33 (3H, s, C**H_3**), 1.22 (3H, s, C**H_3**), 0.90 (3H, t, *J* = 7.0 Hz, CH_2C**H_3**) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 173.12 (**C**OO), 151.66 (**C**CH, Ar), 127.85 (2 x **C**H, $Ar_{(meta)}$), 125.36 (2 x **C**H, $Ar_{(ortho)}$), 124.96 (**C**H, $Ar_{(para)}$), 74.26 (**C**OH), 50.83 (**C**HCPh), 39.85 (**C**Ph), 34.34 (**C**H_2COO), 34.05 (**C**H_2COH), 33.39 (**C**H_2), 31.89 (**C**H_2), 29.58 (**C**H_2), 29.44 (**C**H_2), 29.42 (**C**H_2), 29.31 (**C**H_2), 29.23 (**C**H_2), 29.05 (**C**H_2), 27.86 (**C**H_3), 27.04 (**C**H_2), 25.98 (**C**H_2), 24.96 (**C**H_3), 24.63

	($\mathbf{C}H_2$), 22.67 ($\mathbf{C}H_2$), 14.08 ($\mathbf{C}H_3$) ppm.
LRMS (ES^+) m/z	823 (100%, $[2M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 423.3234; Found: 423.3233 ($[M+Na]^+$).

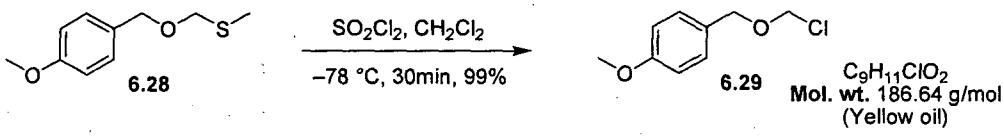
((4-Methoxybenzyloxy)methyl)(methyl)sulfane (6.28)



Following the method reported by Cory *et al.*,[154] to a stirred suspension of NaH (579 mg, 14.47 mmol) in dry DME (8 mL) was added 4-methoxybenzylalcohol (**6.27**, 1.0 g, 7.24 mmol) at 0 °C. To this reaction mixture was added NaI (1.10 g, 7.24 mmol) and then chloromethyl methyl sulfide (0.63 mL, 7.24 mmol). After stirring at 0 °C for 1 hour, the reaction mixture was warmed to room temperature and then further stirred for 3.5 hours, poured into H_2O (20 mL) and extracted with ether (2 x 30 mL). The combined organic phases were washed with brine (15 mL), dried (K_2CO_3), filtered and concentrated *in vacuo* to afford crude **6.28** as a yellow oil (1.45 g). Purification by column chromatography (SiO_2 eluting with Et_2O/hexane (5 to 20%) afforded the title thioether **6.28** as a pale yellow oil (1.21 g, 6.10 mmol, 84%). The spectroscopic data are in agreement with the literature.[154]

FT-IR ν_{max} (neat)	2954 (m), 2919 (m), 2834 (m), 1612 (s), 1511 (s), 1244 (s), 1054 (s), 1032 (s), 816 (s), 679 (s) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 7.29 (2H, d, J = 8.5 Hz, 2 x $OCCH_2C\mathbf{H}$, Ar), 6.90 (2H, d, J = 8.5 Hz, 2 x $OCC\mathbf{H}$, Ar), 4.67 (2H, s, $C\mathbf{H_2}O$), 4.56 (2H, s, $C\mathbf{H_2}S$), 3.82 (3H, s, $OC\mathbf{H_3}$), 2.19 (3H, s, $S,C\mathbf{H_3}$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 159.35 ($O\mathbf{C}CH$, Ar), 129.77 (2 x $OCCH_2\mathbf{C}H$, Ar), 129.76 ($\mathbf{C}CH_2$, Ar), 113.88 (2 x $OC\mathbf{C}H$, Ar), 74.05 ($\mathbf{C}H_2S$), 69.05 ($\mathbf{C}H_2O$), 55.27 ($O\mathbf{C}H_3$), 13.86 ($S\mathbf{C}H_3$) ppm.
LRMS (EI) m/z	198 (M^+, 3%), 168 (8%), 150 (15%), 121 (100%).
HRMS (EI) m/z	Calculated: 198.0714; Found: 198.0708 (M^+).

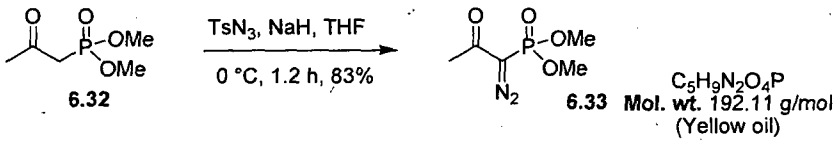
1-((Chloromethoxy)methyl)-4-methoxybenzene (6.29)



To a solution of thioether **6.28** (100 mg, 0.50 mmol) in dry CH_2Cl_2 (1.5 mL) at –78 °C, was added a solution of sulfuryl chloride (44 μL, 0.53 mmol) in CH_2Cl_2 (1 mL) and the resultant solution was stirred for 30 min. The solution was concentrated *in vacuo* to afford crude product **6.29** as a yellow oil (93 mg, 0.50 mmol, 99%). The spectroscopic data were in agreement with the literature.[155]

FT-IR ν_{max} (neat)	2954 (m), 2919 (m), 2831 (w), 1613 (s), 1513 (s), 1303 (m), 1248 (s), 1109 (s), 1033 (s), 819 (s), 640 (s) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 7.31 (2H, d, J = 8.5 Hz, 2 x $OCCH_2\mathbf{CH}$, Ar), 6.91 (2H, d, J = 8.5 Hz, 2 x $OC\mathbf{CH}$, Ar), 5.51 (2H, s, $\mathbf{CH_2}Cl$), 4.70 (2H, s, $\mathbf{CH_2}O$), 3.83 (3H, s, OCH_3) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 159.81 (**O**CCH, Ar), 130.22 (2 x $OCH_2\mathbf{C}H$, Ar), 127.53 (**C**CH_2, Ar), 114.02 (2 x O**C**CH, Ar), 81.43 (**C**H_2Cl), 70.69 (**C**H_2O), 55.29 (OCH_3) ppm.
LRMS (EI) m/z	186 (M^+, 0.4%), 83 (10%), 113 (15%), 57 (40%), 149 (100%).

Dimethyl (1-diazo-2-oxopropyl) phosphonate (6.33)

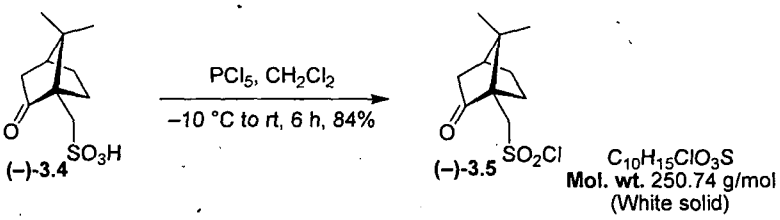


To a suspension of NaH (53 mg, 1.32 mmol) in THF (3.2 mL) at 0 °C, was added a solution of phosphonate **6.32** (200 mg, 1.20 mmol) in THF (3.2mL) and the reaction mixture was stirred for 1 hour. To this was added tosyl azide (260 mg, 1.32 mmol) and after 10 min, the reaction mixture was filtered through celite, concentrated *in vacuo* and purified by column chromatography (SiO_2 eluting with EtOAc/hexane (50 to 80%)) to afford the title phosphonate **6.33** as a yellow oil (191 mg, 0.99 mmol, 83%). The spectroscopic data were in agreement with literature.[157]

FT-IR ν_{max} (neat)	3519 (br), 3005 (w), 2956 (w), 2850 (w), 2120 (s), 1656 (s) 1266 (s), 1019 (s), 836 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$)	δ 3.85 (6H, d, J = 11.9 Hz, P(OC**H**$_3$)$_2$), 2.28 (3H, s, C(O)C**H**$_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 189.74 (**C**=O, d, J = 13.6 Hz), 53.53 (2C, P(O**C**H$_3$)$_2$, d, J = 5.5 Hz), 27.49 (C(O)**C**H$_3$) ppm. (**C**=N$_2$ was not observed)
^{31}P NMR (121 MHz, $CDCl_3$)	δ 14.92 (s) ppm.
LRMS (ES$^+$) m/z	215 (100%, [M+Na]$^+$), 407 (25%, [2M+Na]$^+$).
HRMS (ES$^+$) m/z	Calculated: 215.0192; Found: 215.0194 ([M+Na]$^+$).

(1*R*)-10-Camphorsulfonyl chloride ((–)-3.5)

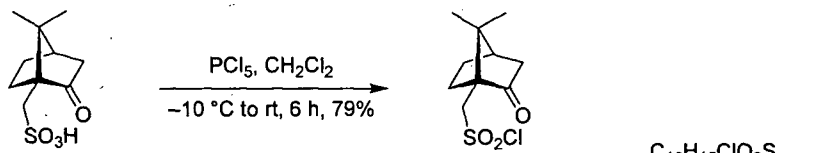


Following the method reported by Bartlett *et al.*,[99] PCl_5 (98 g, 448 mmol) was added in one batch to (1*R*)-camphorsulfonic acid (**(–)-3.4**, 34.7 g, 149 mmol) at –10 °C. Both solids were stirred using an overhead stirrer. The evolved $HCl_{(g)}$ was scrubbed in NaOH (1 M, aq.). After 10 min when gas evolution was ceased, the reaction was warmed to room temperature and stirring was continued for 6 hours. At this stage, CH_2Cl_2 (100 mL) was added to the reaction mixture 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 adding cold water as the reaction is highly exothermic and $HCl_{(g)}$ is given off). The aqueous phase was extracted with CH_2Cl_2 (250 mL), and the organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to afford sulfonyl chloride **(–)-3.5** as a white solid (31.2 g, 124 mmol, 84%). The crude material was used in the next step without any purification. The analytical data was in agreement with the literature.[99]

$[\alpha]^{25}_D$	–30.0 (*c* 0.48, $CHCl_3$).
mp	64-66 °C, (Lit. 66-68 °C).[99]
FT-IR ν_{max} (neat)	2962 (m), 2920 (m), 2830 (w), 1741 (s), 1377 (s), 1280 (w), 1160 (s), 1045 (s) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$)	δ 4.31 (1H, d, J = 14.6 Hz, C**H**HSO$_2$), 3.73 (1H, d, J = 14.6 Hz, CH**H**SO$_2$), 2.62-2.41 (2H, m, C**H**$_2$), 2.17-2.07 (2H, m,

	CH_2), 1.99 (1H, d, J = 18.6 Hz, CHH), 1.78 (1H, ddt, J = 13.8, 9.3, 4.5 Hz, CHH), 1.49 (1H, m, CHH), 1.14 (3H, s, CH_3), 0.93 (3H, s, CH_3) ppm
^{13}C NMR (100 MHz, $CDCl_3$)	δ 212.67 (CO), 64.27 (CH_2SO_2), 59.70 ($C(CH_3)_2$), 48.15 (CH_2CO), 42.81 (CCH_2SO_2), 42.30 ($CHC(CH_3)_2$), 26.86 (CH_2C), 25.28 (CH_2CH_2C), 19.74 (CH_3), 19.63 (CH_3) ppm.
LRMS (ES^+) m/z	273 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 273.0323; Found: 273.0327 ($[M+Na]^+$).

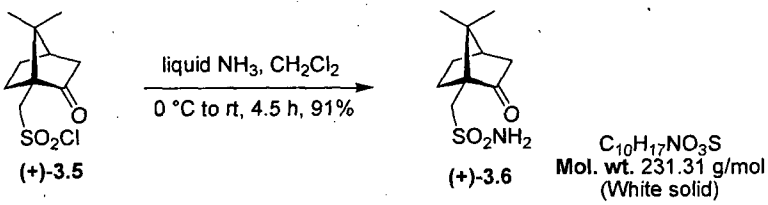
(1*S*)-10-Camphorsulfonyl chloride ((+)-3.5)



Following the procedure for the preparation of (1*R*)-sulfonyl chloride **(–)-3.5**, (1*S*)-camphorsulfonic acid (**(+)-3.4**, 65.0 g, 279 mmol) afforded the sulfonyl chloride **(+)-3.5** as a white solid (55.4 g, 221 mmol, 79%). The crude material was used in the next step without any purification. Spectroscopic data were in agreement with the literature.[99]

$[\alpha]^{26}_D$	+31.5 (*c* 1.0, $CHCl_3$).
mp	64-65 °C, (Lit. 66-68 °C).[99]

(1*S*)-10-Camphorsulfonamide ((+)-3.6)

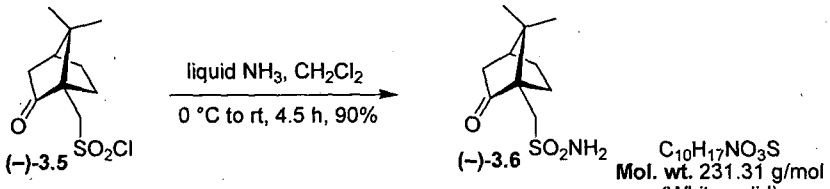


To the rapidly stirred solution of (1*S*)-sulfonyl chloride **(+)-3.5** (55.43 g, 221 mmol) in CH_2Cl_2 (250 mL) at 0 °C, was added liquid NH_3 (210 mL) using dropping funnel. A white ppt. was formed and the reaction mixture was stirred for 4.5 hours. At this stage, H_2O (100 mL) was added and the organic phase was separated from the aqueous phase. The aqueous phase was re-extracted with CH_2Cl_2 (2 x 100 mL). The combined organic phases were dried (Na_2SO_4), concentrated *in vacuo* to give sulfonamide **(+)-3.6** as a

white solid (46.5 g, 201 mmol, 91%). The crude material was used in the next step without purification. Spectroscopic data were in agreement with the literature.[100]

$[\alpha]^{26}_D$	+23.19 (*c*1.34, $CHCl_3$).
mp	122-125 °C, (Lit. 125-128 °C).[100]
FT-IR ν_{max} (neat)	2960 (m), 2935 (m), 2832 (w), 1731 (s), 1336 (s), 1152 (s) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 5.39 (2H, br, NH_2), 3.49 (1H, d, *J* = 15.1 Hz, $CHHSO_2$), 3.73 (1H, d, *J* = 15.1 Hz, $CHHSO_2$), 2.62-2.41 (2H, m, CH_2), 2.48-1.98 (3H, m, CH and CH_2), 1.99 (1H, d, *J* = 18.6 Hz, CHH), 1.50 (1H, m, CHH), 1.15 (3H, s, CH_3), 0.93 (3H, s, CH_3) ppm
^{13}C NMR (100 MHz, $CDCl_3$)	δ 217.54 (CO), 59.34 ($C(CH_3)_2$), 53.97 (CH_2SO_2), 49.06 (CCH_2SO_2), 43.06 (CH_2CO), 42.30 ($CHC(CH_3)_2$), 27.04 (CH_2C), 26.77 (CH_2CH_2C), 19.94 (CH_3), 19.37 (CH_3) ppm.
LRMS (ES^+) m/z	253 (100%, $[M+Na]^+$).

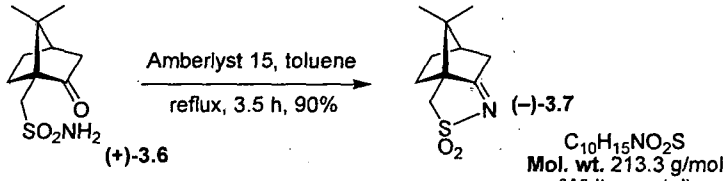
(1*R*)-10-Camphorsulfonamide ((–)-3.6)



Following the procedure for the preparation of (1*S*)-sulfonamide **(+)-3.6**, (1*R*)-sulfonyl chloride **(–)-3.5** (18.6 g, 74.2 mmol) afforded the sulfonamide **(–)-3.6** as a white solid (15.5 g, 67.0 mmol, 90%). The crude material was used in the next step without purification. Spectroscopic data were in agreement with the literature.[100]

$[\alpha]^{26}_D$	–22.40 (*c*1.0, $CHCl_3$).
mp	123-126 °C, (Lit. 125-128 °C).[100]

(1*S*)-10-Camphorsulfonylimine ((–)-3.7)

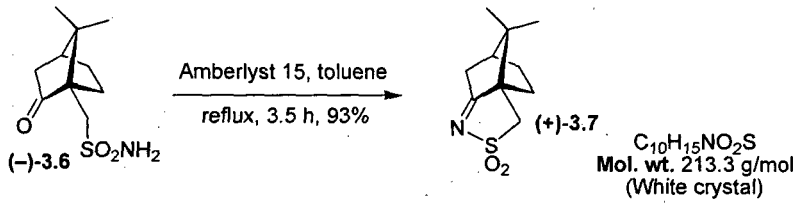


$C_{10}H_{15}NO_2S$
Mol. wt. 213.3 g/mol
(White crystal)

To the suspension of (1*S*)-sulfonamide **(+)-3.6** (46.5 g, 201 mmol) in toluene (300 mL) was added amberlyst 15 Å (5.5 g) and the resultant mixture was heated to reflux using Dean-Stark apparatus for 3.5 hours. At this stage, the reaction was cooled to room temperature and CH_2Cl_2 (250 mL) was added to dissolve the white ppt. The solution was filtered and concentrated *in vacuo* to give a brownish sludge as crude product (39.5 g). The crude product was recrystallization from absolute ethanol (625 mL) to afford the white crystals of sulfonylimmine **(–)-3.7** (38.6 g, 181 mmol, 90%). Spectroscopic data were in agreement with the literature.[100]

$[\alpha]^{25}_D$	–31.8 (*c* 1.91, $CHCl_3$), {lit. $[\alpha]_D$ = –32.3 (*c* 1.9, $CHCl_3$)}.[100]
mp	223-227 °C, (Lit. 222-224 °C).[102]
FT-IR ν_{max} (neat)	2960 (m), 2935 (m), 2832 (w), 1639 (s), 1311 (s), 1168 (m), 1132 (m), 807 (m) cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	δ 3.18 (1H, d, *J* = 13.3 Hz, C**H**HSO$_2$), 2.98 (1H, d, *J* = 13.3 Hz, C**H**HSO$_2$), 2.77 (1H, ddd, *J* = 19.4, 4.6, 2.6 Hz, C**H**C(CH$_3$)$_2$), 2.45-2.22 (2H, m, C**H$_2$**), 2.08-2.16 (2H, m, C**H$_2$**), 1.78 (1H, t, *J* = 9.5 Hz, C**H**HCCH$_2$S), 1.48 (1H, t, *J* = 9.5 Hz, C**H**HCCH$_2$S), 1.09 (3H, s, C**H$_3$**), 0.88 (3H, s, C**H$_3$**) ppm
^{13}C NMR (75 MHz, $CDCl_3$)	δ 195.35 (**C**N), 64.44 (**C**CH$_2$S), 49.37 (**C**H$_2$SO$_2$), 47.92 (**C**(CH$_3$)$_2$, 44.58 (**C**HC(CH$_3$)$_2$), 35.86 (**C**H$_2$C=N), 28.36 (**C**H$_2$CH$_2$C), 26.57 (**C**H$_2$C), 19.40 (**C**H$_3$), 18.93 (**C**H$_3$) ppm.
LRMS (ES^+) m/z	235 (100%, $[M+Na]^+$).

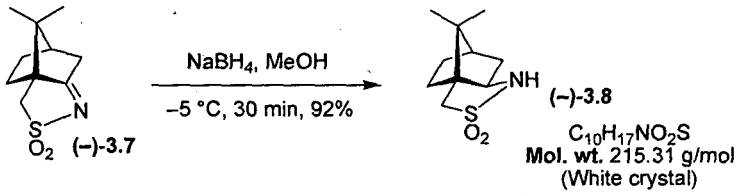
(1*R*)-10-Camphorsulfonylimine ((+)-3.7)



Following the procedure for the preparation of (1*S*)-sulfonylimmine **(–)-3.7**, sulfonamide **(–)-3.6** (15.5 g, 67.0 mmol) afforded the crude product as a brownish sludge (15.0 g). The crude product was recrystallization from absolute ethanol (125 mL) to afford the white crystals of (1*R*)-sulfonylimmine **(+)-3.7** (13.2 g, 62.0 mmol, 93%). Spectroscopic data were in agreement with the literature.[100]

$[\alpha]^{26}_D$	+32.0 (*c* 1.9, $CHCl_3$).
mp	222-226 °C, (Lit. 222-224 °C).[102]

(2*R*)-10,2-Camphorsultam ((–)-3.8)

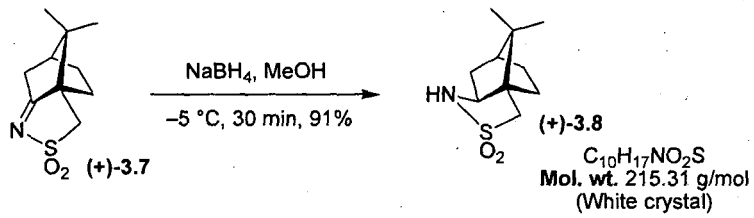


To the stirring solution of (1*S*)-sulfonyl imine **(–)-3.7** (38.6 g, 180 mmol) in CH_3OH (250 mL) at –5 °C, was added $NaBH_4$ (7.53 g, 199 mol). After 30 min, the reaction was quenched with citric acid (10% aq., 50 mL) and diluted with CH_2Cl_2 (100 mL). The resultant suspension was concentrated *in 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 extracted with CH_2Cl_2 (3 x 200 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to give a white solid (36.4 g), which was recrystallized with absolute ethanol (60 mL) to afford the (2*R*)-10,2-camphorsultam ((–)-**3.8**) as a white crystal (35.9 g, 167 mmol, 92%). Spectroscopic data were in agreement with the literature.[101-102]

$[\alpha]^{24}_D$	–31.7 (*c* 1.0, $CHCl_3$), {lit. $[\alpha]_D$ = –31.26 (*c* 1.0, $CHCl_3$)}.[102]
mp	181-183 °C, (Lit. 182-184 °C).[102]
FT-IR ν_{max} (neat)	3290 (s), 2996 (m), 2922 (m), 2891 (m), 1330 (s), 1295 (m),

	1135 (s), 1066 (m), 763 (m), 653 (m) cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	δ 4.11 (1H, br, N**H**), 3.43 (1H, td, J = 7.8, 4.9 Hz, C**H**N), 3.13 (1H, d, J = 13.8 Hz, C**H**HSO$_2$), 3.09 (1H, d, J = 13.8 Hz, CH**H**SO$_2$), 2.07-1.80 (5H, m, C**H** and 2 x C**H**$_2$), 1.46 (1H, t, J = 9.0 Hz, CH**H**), 1.39 (1H, m, CH**H**), 1.13 (3H, s, C**H**$_3$), 0.94 (3H, s, C**H**$_3$) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 62.85 (**C**HN), 55.06 (**C**H$_2$SO$_2$), 50.34 (**C**CH$_2$SO$_2$), 47.46 (**C**(CH$_3$)$_2$, 44.71 (**C**HC(CH$_3$)$_2$), 36.06 (**C**H$_2$CHN), 31.86 (**C**H$_2$CH$_2$C), 26.78 (**C**H$_2$C), 20.49 (**C**H$_3$), 20.42 (**C**H$_3$) ppm.
LRMS (ES^+) m/z	215 (100%, $[M+Na]^+$).

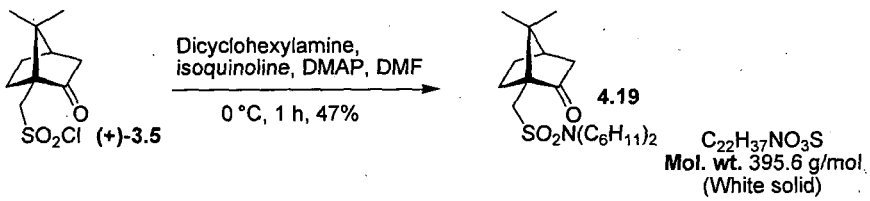
(2*S*)-10,2-Camphorsultam ((+)-3.8)



Following the procedure for the preparation of (2*R*)-10,2-camphorsultam (**(–)-3.8**), sulfonyl immine **(+)-3.7** (13.2 g, 61.3 mol) afforded the crude product **(+)-3.8** as a white solid (12.9 g). The crude product was recrystallization from absolute ethanol (50 mL) to afford (2*S*)-10,2-camphorsultam (**(+)-3.8**) as a white crystal (12.0 g, 55.8 mmol, 91%). Spectroscopic data were in agreement with the literature.[101-102]

$[\alpha]^{22}_D$	+32.9 (*c* 1.0, $CHCl_3$).
mp	182-184 °C, (Lit. 182-184 °C).[102]

(1*S*)-10-Camphordicyclohexylsulfonamide ((+)-4.19)

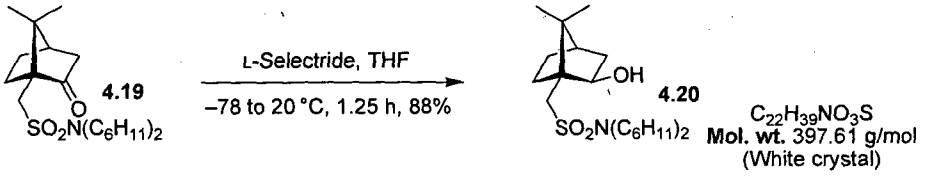


To a stirred mixture of DMAP (429 mg, 3.5 mmol), isoquinoline (4.3 mL, 35.1 mmol) and dicyclohexylamine (7.0 mL, 35.1 mmol) in DMF (15 mL) at 0 °C, was added a solution of (1*S*)-sulfonyl chloride **(+)-3.5** (4.4 g, 17.6 mmol) in DMF (15 mL). The

reaction mixture was stirred at 0 °C for 1 hour. At this stage, the reaction was diluted with CH_2Cl_2 (25 mL) and quenched with citric acid (10% aq., 30 mL). The organic phase was separated, dried (Na_2SO_4) and concentrated *in vacuo* to give crude as a white solid (3.81 g). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (5 to 50%)) afforded the title sulfonyl amine **4.19** as a white solid (3.26 g, 8.24 mmol, 47%). Analytical data was in agreement with the literature.[119]

$[\alpha]^{28}_D$	–25.6 (*c* 0.665, $CHCl_3$)
mp	132-135 °C, (Lit. 134-135 °C).[119]
FT-IR ν_{max} (neat)	2929 (s), 2853 (m), 1744 (s), 1452 (w), 1325 (s), 1143 (s), 1046 (s), 981 (m) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 3.32 (1H, d, *J* = 14.3 Hz, C**H**HSO$_2$), 2.79 (1H, d, *J* = 14.3 Hz, C**H**HSO$_2$), 2.63 (1H, m, C**H**H), 2.38 (1H, *J* = dd, 18.3, 3.3 Hz, C**H**H), 2.17-1.55 (21H, m, C**H**H and 9 x C**H**$_2$), 1.44-1.03 (6H, m, 3 x C**H**$_2$), 1.19 (3H, s, C**H**$_3$), 0.90 (3H, s, C**H**$_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 215.67 (**C**O), 59.03 (**C**(CH$_3$)$_2$), 57.67 (**C**CH$_2$SO$_2$), 52.23 (**C**H$_2$SO$_2$), 43.00 (**C**H$_2$CO), 42.59 (3 x **C**HC), 32.95 (2 x **C**H$_2$), 32.57 (2 x **C**H$_2$), 26.86 (**C**H$_2$), 26.46 (4 x **C**H$_2$), 25.33 (2 x **C**H$_2$), 25.21 (**C**H$_2$), 20.32 (**C**H$_3$), 19.87 (**C**H$_3$) ppm.
LRMS (ES^+) m/z	418 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 396.2567; Found: 396.2566 ($[M+H]^+$).

(2*R*)-10-Camphordicyclohexylsulfonyl-2-ol ((+)-4.20)

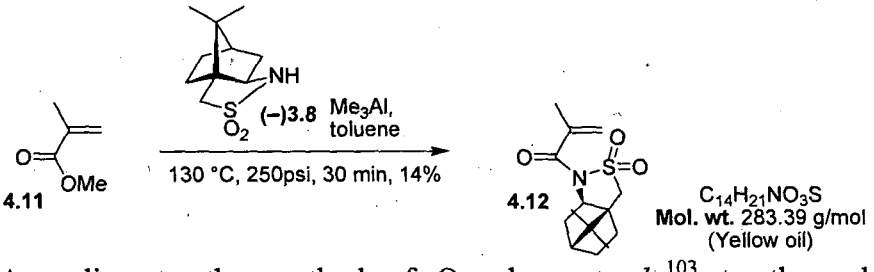


To a solution of sulfonyl amine **4.19** (3.11 g, 7.86 mmol) in THF (15 mL) at –78 °C, was dropwise added L-selectride (8.65 mL, 1 N in THF, 8.65 mmol) and the resultant mixture was stirred for 30 min. The reaction was stirred and allowed to warm to 20 °C over 45 minutes. The reaction was cooled to 0 °C and quenched by dropwise addition of H_2O (3 mL), EtOH (10 mL), NaOH (3 N aq., 15 mL), H_2O_2 (30% aq.) and K_2CO_3 (10% aq., 10 mL). The organic material was extracted with Et_2O:THF (1:1, 50 mL) to afford crude product **4.20**, which was recrystallised from hexane (20 mL) to give the auxiliary

4.20 as a white crystal (2.76 g, 6.94 mmol, 88%). Analytical data was in agreement with the literature.[119]

$[\alpha]^{28}_D$	+32.4 (*c* 0.37, $CHCl_3$)
mp	162-164 °C, (Lit. 163-164 °C).[119]
FT-IR ν_{max} (neat)	3511 (br), 2930 (s), 2854 (m), 1452 (m), 1319 (s), 1136 (s), 1048 (m), 981 (m) cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 4.10 (1H, dd, *J* = 7.5, 3.5 Hz, C**H**OH), 3.50 (1H, d, *J* = 3.5 Hz, CHO**H**), 3.25 (1H, d, *J* = 13.3 Hz, C**H**HSO$_2$), 2.64 (1H, d, *J* = 13.3 Hz, CH**H**SO$_2$), 1.82-1.53 (23H, m, C**H**H and 11 x C**H$_2$**), 1.40-1.03 (6H, m, 3 x C**H$_2$**), 1.07 (3H, s, C**H$_3$**), 0.81 (3H, s, C**H$_3$**) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ 76.55 (**C**HOH), 57.81 (2 x **C**HC), 55.28 (**C**H$_2$SO$_2$), 50.89 (**C**(CH$_3$)$_2$), 48.44 (**C**CH$_2$SO$_2$), 44.51 (**C**HC), 38.28 (**C**H$_2$COH), 32.92 (2 x **C**H$_2$), 32.72 (2 x **C**H$_2$), 30.99 (**C**H$_2$), 27.34 (**C**H$_2$), 26.44 (**C**H$_2$), 26.42 (3 x **C**H$_2$), 25.15 (2 x **C**H$_2$), 20.60 (**C**H$_3$), 19.95 (**C**H$_3$) ppm.
LRMS (ES^+) m/z	420 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 398.2724; Found: 398.2732 ($[M+H]^+$).

_N_-(3-Methyl-2-methylene-propylate)-(2_R_)-camphor-10,2-sultam (4.12)

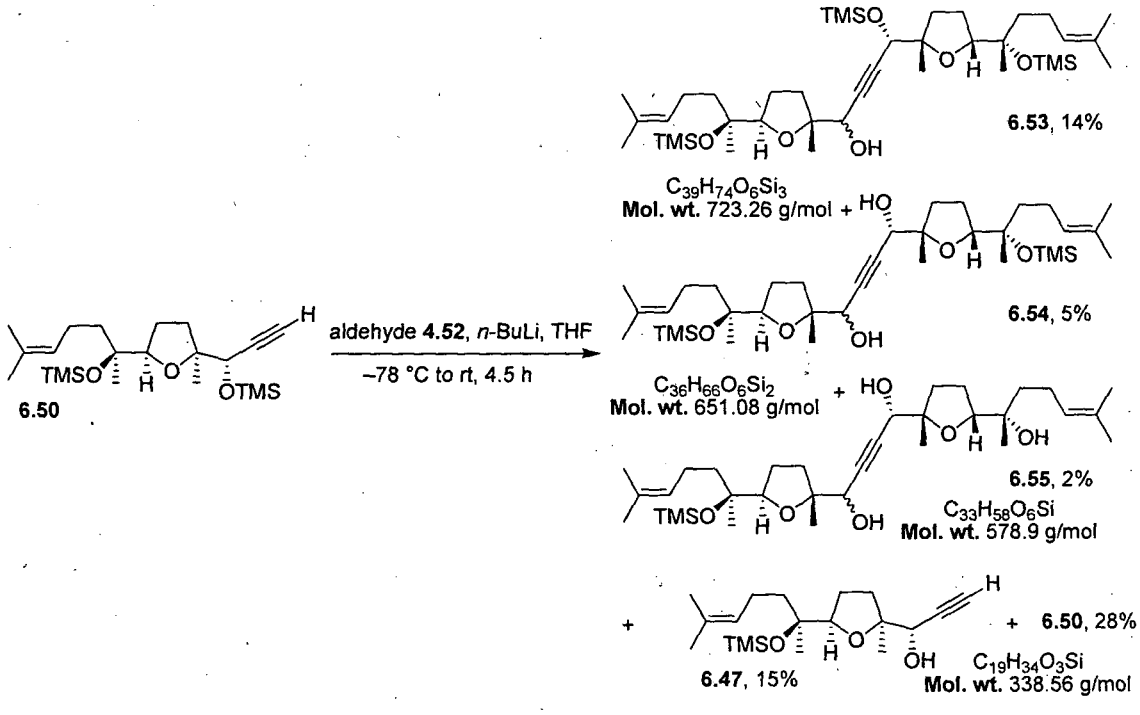


According to the method of Oppolzer *et al.*,[103] to the solution of (2*R*)-10,2-camphorsultam (**(–)-3.8**, 270 mg, 1.25 mmol) in distilled toluene (4 mL) was added dropwise Me_3Al (0.63 mL, 2.0 M hexane, 1.25 mmol) at room temperature. After stirring for 15 min, a solution of ester **4.11** (100 mg, 1.0 mmol) in distilled toluene (0.5 mL) was added and the resulting mixture was placed in microwave at 130 °C, 250 psi and 250 W for 30 min. The mixture was taken out from microwave and diluted with CH_2Cl_2 (5 mL), water (2 mL) and Rochelle salt (2 mL, sat. aq.) and stirred for 1 hour. The organic phase was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the white solid as a crude product. Purification by column chromatography (SiO_2

eluting with 20% EtOAc/hexane) afforded the title product **4.12** as a yellow oil (45 mg, 0.16 mmol, 14%). The chiral auxiliary **(–)-3.8** was also recovered as a white solid (190 mg, 0.88 mmol, 58%).

$[\alpha]^{26}_D$	–37.0 (*c* 0.45, $CHCl_3$).
FT-IR ν_{max} (neat)	2961 (m), 2919 (m), 2882 (m), 1679 (s), 1334 (s), 1194 (m), 1132 (m), 1063 (m), 976 (w) cm^{-1}.
FT-IR ν_{max} (neat)	2961 (m), 2919 (m), 2882 (m), 1679 (s), 1334 (s) cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	δ 5.70 (1H, br, C=C**H**H), 5.66 (1H, d, *J* = 1.5 Hz, C=CH**H**), 4.05 (1H, dd, *J* = 7.5, 5.0 Hz, C**H**N), 3.52 (1H, d, *J* = 13.8 Hz, C**H**HSO$_2$), 3.40 (1H, d, *J* = 13.5 Hz, CH**H**SO$_2$), 2.06-1.90 (5H, m, C**H**H and 2 x C**H$_2$**,), 2.01 (3H, s, C**H$_3$**), 1.44-1.38 (2H, m, C**H$_2$**), 1.24 (3H, s, C**H$_3$**), 1.01 (3H, s, C**H$_3$**) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 171.25 (**C**ON), 138.98 (**C**=CH$_2$), 124.31 (C=**C**H$_2$), 65.44 (**C**HN), 53.56 (**C**H$_2$SO$_2$), 48.02 (**C**CH$_2$), 47.71 (**C**(CH$_3$)$_2$), 45.26 (**C**HC(CH$_3$)$_2$), 38.35 (**C**H$_2$CHN), 33.28 (**C**H$_2$CH), 26.47 (**C**H$_2$C), 21.32 (**C**H$_3$), 19.89 (**C**H$_3$), 18.71 (**C**H$_3$) ppm.
LRMS (ES^+) m/z	306 (100%, $[M+Na]^+$).
HRMS (ES^+) m/z	Calculated: 306.1134; Found: 306.1132 ($[M+H]^+$).

(*S*)-1-((2*R*,5*R*)-Tetrahydro-5-((*S*)-2-trimethylsiloxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-yl)-4-((2*S*,5*R*)-tetrahydro-5-((*S*)-2-trimethylsiloxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-yl)but-2-yne-4-trimethylsiloxy-1ol (6.53);
(*S*)-1-((2*R*,5*R*)-Tetrahydro-5-((*S*)-2-trimethylsiloxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-yl)-4-((2*S*,5*R*)-tetrahydro-5-((*S*)-2-trimethylsiloxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-yl)but-2-yne-1,4-diol (6.54);
(*S*)-1-((2*R*,5*R*)-Tetrahydro-5-((*S*)-2-trimethylsiloxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-yl)-4-((2*S*,5*R*)-tetrahydro-5-((*S*)-2-hydroxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-yl)but-2-yne-1,4-diol (6.55);
(*S*)-2-((2*S*,5*R*)-Tetrahydro-5-((*S*)-2-trimethylsiloxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-yl)-1-hydroxypropyne (6.47)



Following the procedure for the preparation of enynes **6.46a,b**, alkyne **6.50** (25 mg, 0.06 mmol) was coupled with aldehyde **4.52** (19.5 mg, 0.06 mmol) to afford the crude product as a yellow oil (33 mg). Purification by column chromatography (SiO_2 eluting with CH_2Cl_2/hexane (10 to 90%) and then EtOAc/hexane (10 to 40%)) afforded the *bis*-THF **6.53** as a yellow oil (12 mg, 0.02 mmol, 14%) contaminated with unidentified product, along with **6.54** (5 mg, 0.006 mmol, 5%), **6.55** (1mg, 0.001 mmol, 2%), **6.47** (2 mg, 0.006 mmol, 10%). The starting enyne **6.50** (7 mg, 0.02 mmol, 28%) and starting aldehyde **4.52** (1mg, 0.004 mmol, 5%) were also recovered. Due to time constraints, the characterisation was done by ^1H NMR and mass spectrometric analysis.

Selective spectroscopic data for **6.53**:

^{1}H NMR (400 MHz, $CDCl_3$)	δ 5.12-5.09 (2H, m, 2 x =C**H**CH_2), 4.23 (1H, m, C**H**), 3.89 (1H, t, *J* = 7.0 Hz, C**H**, THF), 3.80 (1H, m, C**H**, THF), 3.42 (1H, t, *J* = 5.5 Hz, C**H**), 2.38-1.73 (9H, m, O**H** and 4 x CH_2, THF), 1.55-1.22 (8H, m, 4 x CH_2), 1.69 (6H, s, 2 x CH_3), 1.61 (6H, s, 2 x CH_3), 1.23 (3H, s, CH_3), 1.20 (3H, s, CH_3), 1.19 (3H, s, CH_3), 1.17 (3H, s, CH_3), 0.13 (9H, s, Si(CH_3)$_3$), 0.12 (18H, s, Si(CH_3)$_3$) ppm.
LRMS (ES^+) m/z	746 (100%, $[M+Na]^+$).

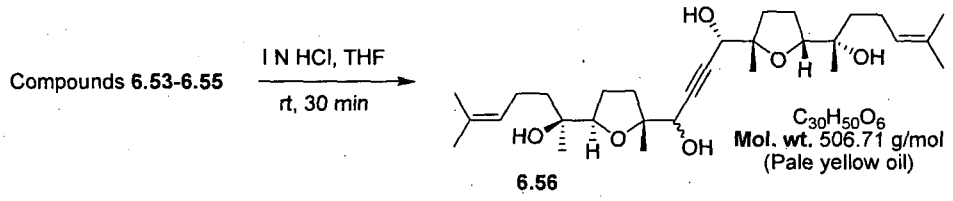
Selective Spectroscopic data for **6.54**:

^{1}H NMR (300 MHz, $CDCl_3$)	δ 5.12-5.03 (2H, m, 2 x =C**H**CH_2), 4.30-4.16 (2H, m, 2 x C**H**OH), 3.96-3.78 (2H, m, 2 x C**H**, THF), 3.34 (1H, dd, *J* = 7.0, 2.3 Hz, CHO**H**), 3.34 (1H, dd, *J* = 7.7, 4.0 Hz, CHO**H**), 2.05-1.89 (8H, m, 4 x CH_2, THF), 1.57-1.27 (8H, m, 4 x CH_2), 1.69 (3H, s, CH_3), 1.61 (3H, s, CH_3), 1.60 (3H, s, CH_3), 1.57 (3H, s, CH_3), 1.34 (3H, s, CH_3), 1.32 (3H, s, CH_3), 1.23 (3H, s, CH_3), 1.22 (3H, s, CH_3), 0.16 (9H, s, Si(CH_3)$_3$), 0.12 (9H, s, Si(CH_3)$_3$) ppm.
LRMS (ES^+) m/z	674 (100%, $[M+Na]^+$).

Selective Spectroscopic data for **6.55**:

^{1}H NMR (400 MHz, $CDCl_3$)	δ 5.12-5.01 (2H, m, 2 x =C**H**CH_2), 4.27-4.25 (2H, m, 2 x C**H**OH), 3.89 (1H, m, C**H**, THF), 3.82 (1H, dd, *J* = 8.0, 6.5 Hz, C**H**, THF), 2.96 (1H, br, O**H**), 2.75 (1H, d, *J* = 4.8 Hz, O**H**), 2.62 (1H, d, *J* = 3.3 Hz, O**H**), 2.28-1.69 (8H, m, 4 x CH_2, THF), 1.53-0.88 (8H, m, 4 x CH_2), 1.69 (3H, s, CH_3), 1.63 (3H, s, CH_3), 1.62 (3H, s, CH_3), 1.56 (3H, s, CH_3), 1.34 (3H, s, CH_3), 1.28 (3H, s, CH_3), 1.27 (3H, s, CH_3), 1.22 (3H, s, CH_3), 0.12 (9H, s, Si(CH_3)$_3$) ppm.
LRMS (ES^+) m/z	602 (100%, $[M+Na]^+$).

(*S*)-1-((2*R*,5*R*)-Tetrahydro-5-((*S*)-2-hydroxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-yl)-4-((2*S*,5*R*)-tetrahydro-5-((*S*)-2-hydroxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-yl)but-2-yne-1,4-diol (6.56)



Following the procedure for the preparation of aldehyde **2.47**, compounds **6.53-6.55** (16 mg) were desilylated to afford a crude product **6.56** as a yellow oil (9 mg). Purification by column chromatography (SiO_2 eluting with EtOAc/hexane (30 to 60%)) afforded the *bis*-THF **6.56** as a yellow oil (8 mg). Characterisation was carried out by IR, ^{1}H NMR and mass spectrometric analysis.

FT-IR ν_{max} (neat)	3377 (br), 2970 (s), 2829 (m), 2872 (w), 1450 (w), 1375 (m), 1058 (s) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$)	δ 5.15-5.05 (2H, m, 2 x =C**H**CH_2), 4.32-4.20 (2H, m, 2 x C**H**OH), 3.94-3.82 (2H, m, 2 x C**H**, THF), 3.11 (2H, br, O**H**), 2.93 (1H, d, J = 5.3 Hz, O**H**), 2.70 (1H, d, J = 4.8 Hz, O**H**), 2.35-1.80 (8H, m, 4 x C**H$_2$**, THF), 1.79-1.19 (8H, m, 4 x C**H$_2$**), 1.69 (6H, s, 2 x C**H$_3$**), 1.62 (6H, s, 2 x C**H$_3$**), 1.34 (3H, s, C**H$_3$**), 1.29 (3H, s, C**H$_3$**), 1.28 (3H, s, C**H$_3$**), 1.21 (3H, s, C**H$_3$**) ppm.
LRMS (ES$^+$) m/z	529 (100%, $[M+Na]^+$).

Chapter 9 References

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