UNIVERSITY OF SOUTHAMPTON

Asymmetric Oxidative Cyclisation of Dienes

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ABSTRACT

FACULTY OF ENGINEERING, SCIENCE AND MATHEMATICS

CHEMISTRY

Doctor of Philosophy

PERMANGANATE OXIDATIVE CYCLISATION OF DIENES

by Alexander Richard Liam Cecil

The total synthesis of the *mono*-THF acetogenin *cis*-solamin has been accomplished *via* an asymmetric permanganate promoted oxidative cyclisation of a 1,5-diene. The asymmetric oxidative cyclisation formed the 2,5-disubstituted THF-diol core, creating the four new stereocentres with control of absolute stereochemistry, in excellent yield (75%). For the purpose of both unequivocally determining the absolute configuration of *cis*-solamin and obtaining biological data, three *cis*-solamin diastereoisomers were selectively synthesised *via* our concise oxidative cyclisation methodology.

The permanganate promoted chiral phase-transfer catalysed (CPTC) oxidative cyclisation of 1,5-dienes using a cinchonidine derived tertiary ammonium salt has been investigated, realising some excellent ee's (up to 94%). This excellent level of asymmetric induction was utilised in the formal synthesis of *cis*-solamin. The key steps were the CPTC oxidative cyclisation (52%, 93% ee) and the oxidative degradation of the naphthyl group to the carboxylic acid without epimerisation.

Aromatic ester and amides have shown themselves applicable to the CPTC oxidative cyclisation of 1,5-dienes, giving moderate to good asymmetric induction (up to 70% ee).

The racemic, asymmetric and CPTC permanganate promoted oxidative cyclisation of 1,6-dienes to furnish exclusively *cis*-THP-diols has been developed. Thus, the creation of up to four new stereocentres with complete control of relative and absolute stereochemistry has been accomplished.

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Acknowledgements

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Abbreviations

α	observed optical rotation
[α]	specific rotation [expressed without units
Å	angstrom(s)
Ac	acetyl
Acac	acetylacetonate
AIBN	2,2'-azoisobutyronitrile
aq	aqueous
Ar	aryl
Atm	atmosphere(s)
ATP	adenosine 5'-triphosphate
BINAP	2,2'-*bis*-(diphenylphosphino) -1,1'binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
br	broad (NMR and IR)
Bu	butyl
Bz	benzoyl
°C	degrees Celsius
calcd.	calculated
cat.	catalytic
CI	chemical ionisation
cm	centimetre(s)
cm^{-1}	wavemumber(s)
COD	1,5-cyclooctadiene
Cp	cyclopentadienyl
CPTC	chiral phase-transfer catalysed
CSA	camphor sulfonic acid
δ	chemical shift in parts per million downfield from tetramethylsilane
d	doublet (NMR)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DIBAL-H	diisobutylaluminium hydride
DIPEA	*N,N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	ethylene glycol dimethyl ether (1,2-dimethoxyethane)
DMF	dimethylforamide
DMOP	2,2-dimethoxypropane
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
d.r.	diastereomeric ratio
ee	enantiomeric excess
EI	electon impact
eq	equivalents
ES	electrospray
Et	ethyl
FT	Fourier transform
g	gram(s)
GC	gas chromatography
h	hour(s)
HMDS	hexamethyl disilazane
HMPA	hexamethylphosphoric triamide
HOBt	1-hydroxybenzotriazole
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectroscopy
Hz	hertz
IDCP	iodonium dicollidine perchlorate
IR	infrared

J	coupling constant (NMR)
L	ligand
LD_{50}	dose that is lethal in 50% of test subjects
LDA	lithium diisopropylamine
LHMDS	lithium hexamethyl disilazane
lit.	literature
μ	micro
m	multiplet (NMR) or medium (IR)
M	molar
M^+	parent molecular ion
MCPBA	3-chloroperbenzoic acid
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	mass spectrometry
MTT	3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide
MW	molecular weight
m/z	mass-to-charge ratio
NAD	nicotinamide adenine dinucleotide
NADH	reduced NAD
NBS	*N*-bromosuccinimide
NMO	*N*-morpholine oxide
NMR	nuclear magnetic resonance
Nu	nucleophile
obsc	obscured (spectoral)
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
ppm	part(s) per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
***i*-Pr**	isopropyl
Py	pyridine
q	quartet (NMR)
quin	quintet (NMR)
rt	room temperature
s	singlet (NMR) or strong (IR)
SM	starting material
sult	sultam protons (NMR)
t	triplet (NMR)
t	*tert*
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFPAA	trifluoroperacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethyl-1,2-ethylenediamine
TMS	trimethylsilyl
Ts	*para*-toluenesolfonyl (tosyl)
TS	transition state
vol	volume
v/v	volume-to-volume ratio
w	weak (IR)
w/v	weight-to-volume ratio
w/w	weight-to-weight ratio

Chapter 1

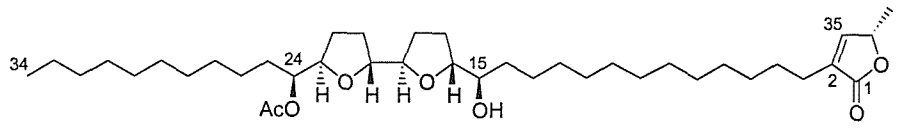
Annonaceous Acetogenins: Structure, Biological Activity and Synthesis

The chapter summarises the structural characteristics associated with *Annonaceous* acetogenins and their corresponding biological properties, and provides recent literature examples of their synthesis.

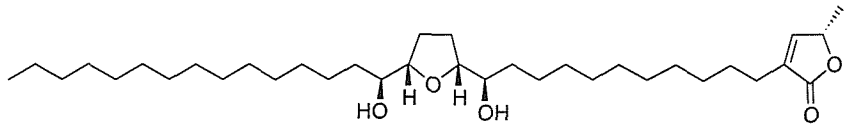
1.1 Introduction

The *Annonaceous* acetogenins are a class of natural products that are isolated from the plant family *Annonaceae.* This tropical plant family until recently was one of the least studied,[1] although containing 130 genera and over 2000 species. *Annonaceous* acetogenins have not been found in all the species examined, but there has been over 350 different *Annonaceous* acetogenins reported from at least 37 species.[2] In 1982 the first *Annonaceous* acetogenin was isolated from the roots of *Uvaria accuminata* and named uvaricin **1.1**. It was found to exhibit potent *in vivo* antitumour properties against P-388 lymphocytic leukaemia in mice.[3] This initial discovery has led to extensive research being undertaken into the *Annonaceous* acetogenins over the last 20 years. They have been shown to exhibit a remarkable range of biological activities, and now belong to one of the most rapidly growing classes of natural products.[2,4,5]

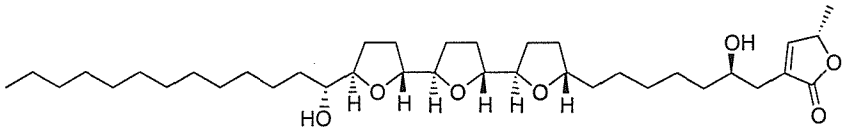
Structurally, the *Annonaceous* acetogenins are a series of C-35 / C-37 heterocyclic compounds that are derived from C-32 / C-34 fatty acids, combined with a propan-2-ol unit. They are generally characterised by a long aliphatic chain bearing a terminal unsaturated γ-lactone (butenolide). At the centre of the aliphatic chain are one, two or occasionally three tetrahydrofuran (THF) rings usually flanked by hydroxyl groups. The chain can also contain ketones, acetetates, hydroxyls, epoxides and unsaturation along its length (Figure 1.1).[2] Examples containing tetrahydropyran (THP) rings in conjunction with THF rings have also been isolated.[6]



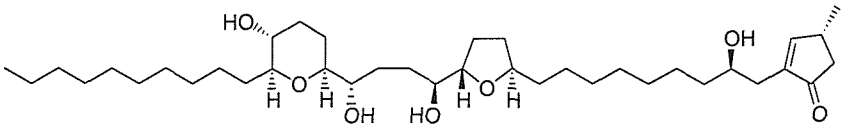
Uvaricin **1.1**



cis-Panatellin **1.2**



Goniocin **1.3**



Mucocin **1.4**

Figure 1.1 Examples of *Annonaceous* acetogenins

1.2 Structural Classification

The *Annonaceous* acetogenins can be classified in a number of ways, the most common and easiest to understand relates primarily to the number and position of the heterocyclic ring(s) at the centre, followed by sub-classification of the γ-lactone (Figure 2). Thus, the main classes are *mono*-THF **1.5**, *bis*-THF **1.6**, non-adjacent bis-THF **1.7**, *tris*-THF **1.8**, THP (non-classical) **1.9** and non-ring **1.10** based acetogenins. Within each of these major subclasses many diastereoisomers can exist. Each subclass can be further divided by the type of γ-lactone terminus present; hydroxylated **1.11**, ring hydroxylated **1.12** or *cis/trans* ketolactone **1.13**.

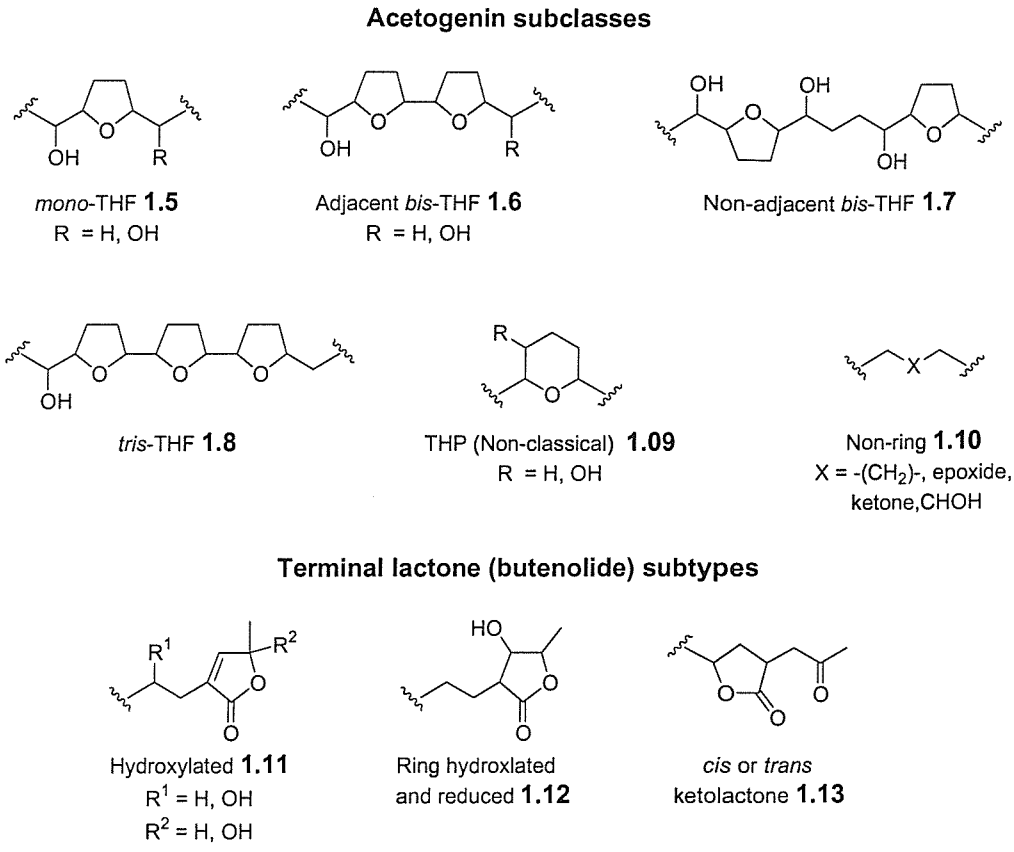


Figure 1.2 Acetogenin structural classification

1.3 Structural Activity Relationships

Studies into the cytotoxicity of *Annonaceous* acetogenins have given the following structural activity relationships (SAR's):[7-12]

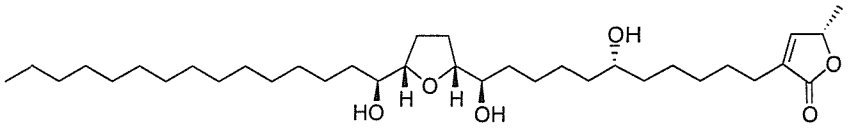
1. The order of potency is determined by the THF core, with adjacent *bis*-THF > non-adjacent *bis*-THF > *mono*-THF > non-ring THF.
2. The terminal butenolide and a central region of high polarity (THF) are crucial for activity. One without the other leads to inactivity.
3. The spacer between the THF ring and the butenolide is crucial for activity, 13 carbons being optimum.
4. The shorter C-35 acetogenins are more potent than the C-37 acetogenins if the structures are otherwise identical.
5. Three hydroxyl groups give optimum potency, two either side of the THF ring and one on the long hydrocarbon chain. More than four hydroxyls cause a dramatic decrease in potency.

1.4 Biological Activity and Mechanism of Action

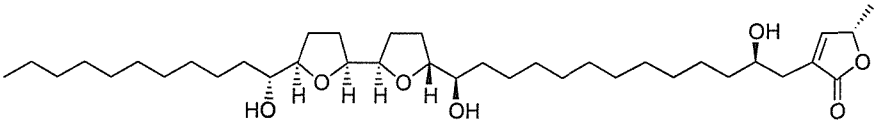
The *Annonaceous* acetogenins have been shown to exhibit a variety of biological activities including: insecticidal,[13,14] pesticidal,[9,15,16] antifeedant,[17] antiparasitic and antimicrobial.[18] Most importantly, many acetogenins exhibit highly selective cytotoxicity against tumour cell lines.[19-23] The SAR is demonstrated in the example of the *mono*-THF longicoricin **1.14**[24] versus the adjacent *bis*-THF trilobacin **1.15**.[15] The only structural differences between the two being the extra THF ring present in trilobacin **1.15** and the position of the third hydroxyl group on the alkyl spacer.

Compound	LD_{50} x 10^{-12} g/mL	Cell line
Longicoricin (**1.14**)	1250	Human pancreatic carcinoma
Trilobacin (**1.15**)	1	Human colon carcinoma
(+)-Parviflorin (**1.16**)	0.0013	Human lung carcinoma

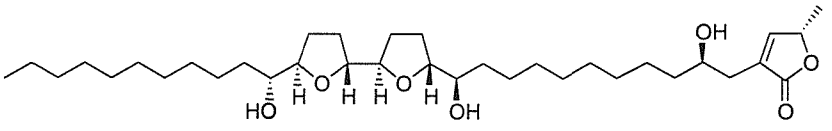
Table 1.1 LD_{50} values of three cytotoxic acetogenins



Longicoricin **1.14**



Trilobacin **1.15**



(+)-Parviflorin **1.16**

Figure 1.3 Structure of three cytotoxic acetogenins

(+)-Parviflorin **1.16** exhibits one of the most potent LD_{50}'s known for human lung carcinoma (Table 1.1 and Figure 1.3).[21,25] Recent research has shown that a number of *Annonaceous* acetogenins are cytotoxic toward multidrug resistant mammalian cancers.[26,27]

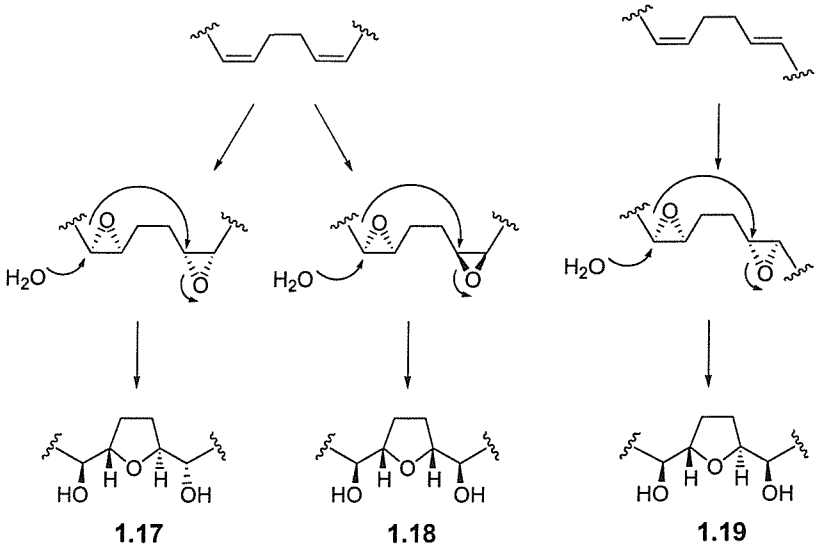
The *Annonaceous* acetogenins major site of action is inside the mitochondria of cells. The inhibitory effect is on the mitochondrial NADH:ubiquinone oxidoreductase or complex-I, a membrane bound enzyme.[28-33] This enzyme is involved in the transfer of electrons from NADH to O_2. Acetogenins prevent electron transfer between the Fe-S cluster 2 and the ubiquinone pool. The site of action is similar to ordinary inhibitors of complex-I such as piericidin-A and rotenone but there are few structural similarities with acetogenins.[10,34-38] The adjacent *bis*-THF acetogenins, bullatacin and rolliniastatin-I, are the most potent inhibitors of complex-I to date.[12,36,38] The effect of inhibiting complex-I is to stop the translocation of protons out of the mitochondria. Without the transmembranous electrochemical force the production of adenosine triphosphate (ATP) fails.[29] Depleted cellular ATP concentration leads to cell death (apoptosis). This mechanism of action is particularly effective against cancerous cells due to their higher demand for ATP.[39] The *Annonaceous* acetogenin family have been found to act on the ubiquinone-linked NADH oxidase found in the plasma membrane (lipid bilayer) of cancerous cells.[12,27,40] It has been proposed that the hydrophilic core of the acetogenins binds to the polar glycerol end groups of the phospholipid membrane, allowing the hydrophobic chains to penetrate the bilayer and interact with the ubiquinone-dependant site in the electron transport system *via* the terminal butenolide.[41] The cessation of ATP production in the cellular membrane inhibits the growth of cancer cells and leads to selective apoptosis.

The *Annonaceous* acetogenins have been found to have another mechanism of action for cell death, as a poison of DNA topoisomerase-I.[40] This enzyme is essential for DNA replication and transcription. It allows the formation of a transient protein-bridged break in a single strand, through which another strand may pass. This break in the DNA is accompanied by the formation of a covalent enzyme-DNA complex.[42] Topoisomerase-I poisons act by stabilising the cleavable complex, causing irreversible DNA strand breakage and cellular destruction.[43,44] An assay of *bis*- and *mono*-THF acetogenins gave IC_{50} values of 8.25 and 9.84 μM respectively compared to 6.1 μM for etoposide, the positive control.[40]

1.5 Biosynthesis

The *Annonaceous* acetogenins are long alkyl chain compounds with THF ring(s) at the centre and terminated by a butenolide. This suggests overwhelmingly that they are derived from a polyketide pathway. It is easy to visualise that they are built up by a method analogous to the well-known pathway for fatty acid biosynthesis, utilising acetyl-CoA, malonyl-CoA and propanyl-CoA as the two and three carbon building blocks. All the classes of THF rings can be synthesised by facially selective epoxidation of 1,5-dienes, 1,5,9-trienes and 1,5,9-triene ketones followed by cascade cyclisation initiated by nucleophilic attack from water or an intramolecular hydroxyl group. Thus, giving *mono*-THF, adjacent *bis*-THF, non-adjacent *bis*-THF and *tris*-THF acetogenins respectively. The geometry of the double bond is also key to the stereochemical outcome of the THF ring.[45]

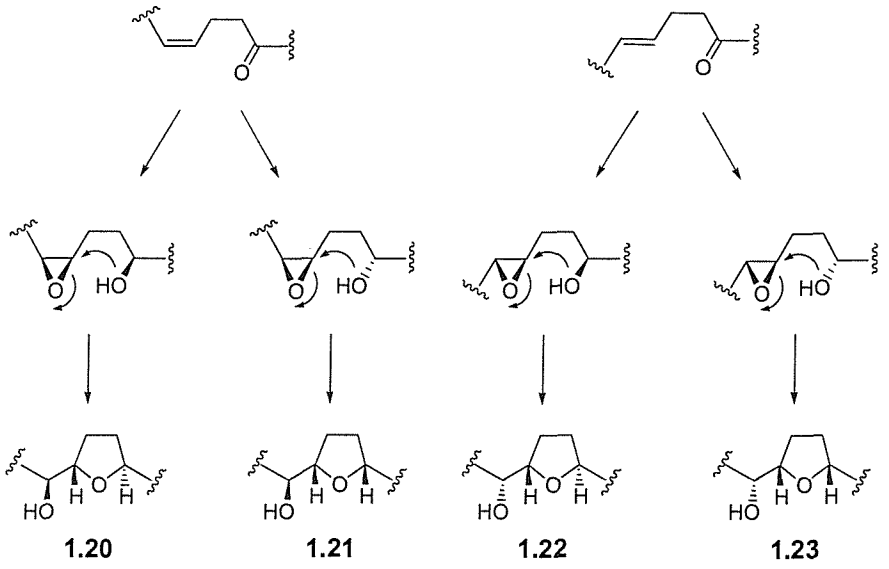
For a *mono*-THF with flanking hydroxyls (2,5-disubstituted), both *cis*- and *trans*-THF rings can be synthesised from a 1,5-diene, accounting for all the different stereochemical outcomes seen in Nature (Scheme 1.1). From a (*Z,Z*)-1,5-diene; with *bis*-epoxidation from the same face you get *threo-trans-threo* squamone type **1.17**, and with *bis*-epoxidation from opposite faces you get *threo-cis-threo cis*-panatelin type **1.18**. From a (*Z,E*)-1,5-diene with *bis*-epoxidation on the same face you get *threo-trans-erythro* annonacin-A type **1.19**.



Scheme 1.1 Proposed biosynthetic route to *mono*-THF-diols

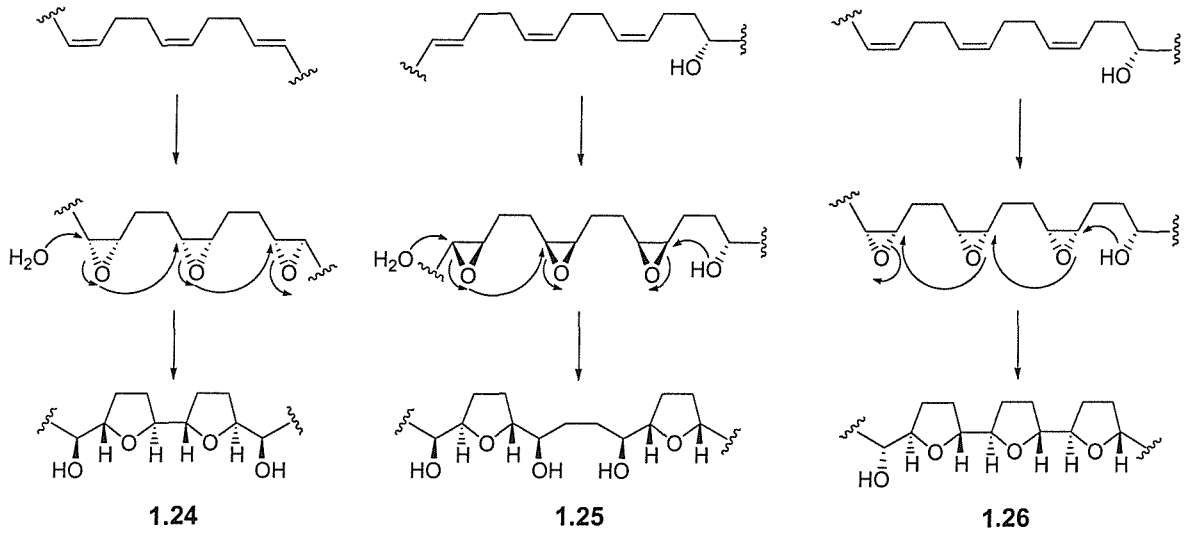
mono-THF acetogenins with only one flanking hydroxyl group are thought to be derived from either (*E*)- or (*Z*)-γ,δ-enones (Scheme 1.2). Epoxidation and ketone reduction allows

intramolecular cyclisation to occur, giving rise to *threo-trans* gigantetrocin-A type systems (**1.20**), *threo-cis* muricatetrocin-A type systems (**1.21**), *erythro-trans* muricatalin type systems (**1.22**), or structures of the *erythro-cis* type **1.23**.



Scheme 1.2 Proposed biosynthetic route to *mono*-THF's with one flanking hydroxyl group

Adjacent *bis*-THF acetogenins are thought to derive from epoxidation of 1,5,9-trienes, followed by cascade cyclisation initiated from one end by intermolecular nucleophilic attack from a water source (Scheme 1.3). It is proposed that non-adjacent *bis*-THF acetogenins are synthesised from keto-trienes. After epoxidation and keto-reduction, they undergo simultaneous attack at both ends from the intramolecular hydroxyl group and an intermolecular water source (Scheme 1.3). *tris*-THF acetogenins are believed to be formed from keto-trienes. After keto-reduction, an epoxidation cascade cyclisation occurs intramolecularly.



Scheme 1.3 Proposed biosynthetic route to adjacent and non-adjacent *bis* and *tris*-THF's

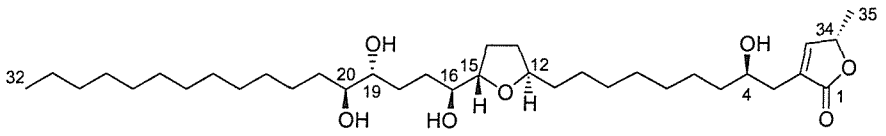
1.6 Synthesis of *mono*-THF *Annonaceous* Acetogenins

The following section summarises recent literature methodologies used in the synthesis of *mono*-THF acetogenins. There are a number of reviews already covering this area.[46-50] It does not include syntheses of acetogenins which fall outside this classification, even if they contain a *mono*-THF ring; such as the THP (non-classical) acetogenin mucocin (**1.4**), which was synthesised in a highly convergent manner by Evans *et al.*[51]

1.6.1 Steven V. Ley *et al.*

1.6.1.1 Synthesis of Muricatetrocin-C (1.27)[52,53]

Muricatetrocin-C (**1.27**) contains a *mono-trans*-THF flanked by only one hydroxyl group, a terminal butenolide (typical of most acetogenins) and 3 other hydroxyl groups along the carbon backbone (Figure 1.5). It was first isolated by McLaughlin *et al.* from the leaves of *Rollina mucosa*.[54]



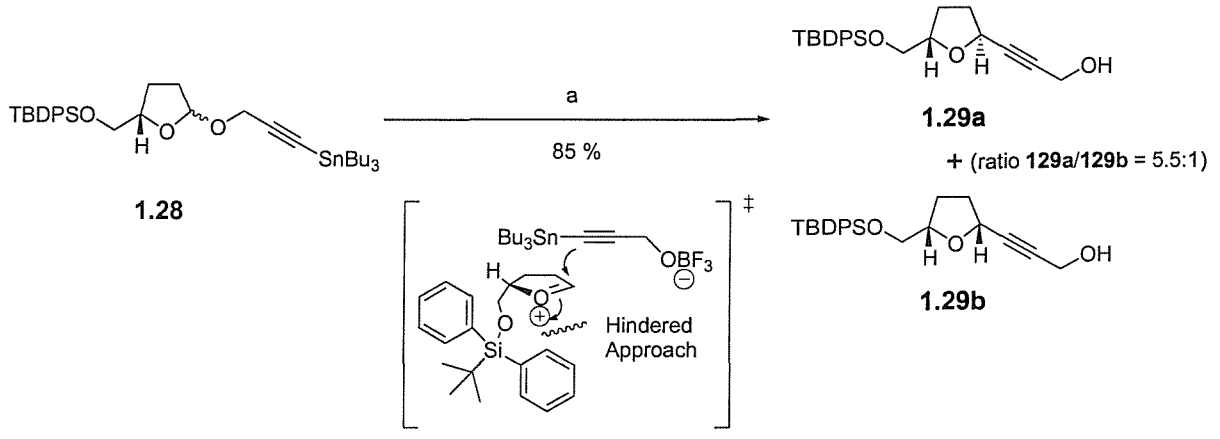
Muricatetrocin-C (**1.27**)

Figure 1.5 Structure of muricatetrocin-C (**1.27**)

The strategy of Ley and co-workers was to split the synthesis into three roughly equal parts; left (diol), centre (THF) and right (butenolide) sections, and thus complete a convergent synthesis. The diol fragment (C-17 to C-32) was derived from the desymmetrisation of a dimethyl tartrate derivative. The THF ring fragment (C-8 to C-16) was prepared by a Lewis acid mediated rearrangement of an alkynylstannane, and the chirality at C-4 in the butenolide fragment (C-1 to C-7 and C-33 to C-35) was introduced *via* a hetero Diels Alder reaction.

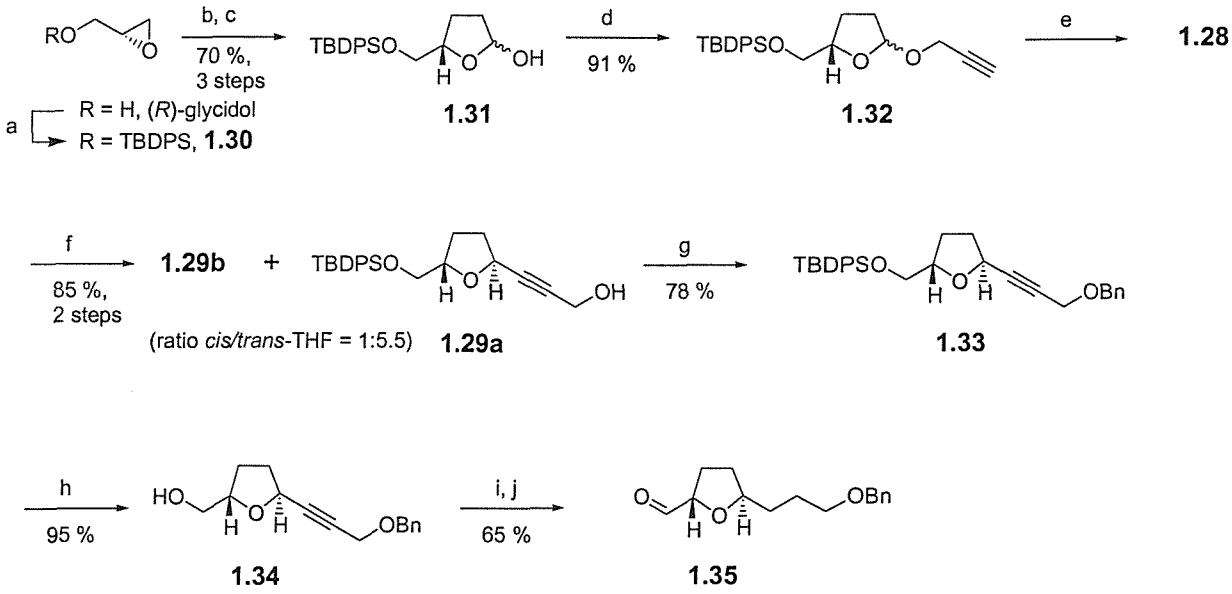
Synthesis of the THF Fragment

Ley and co-workers used an oxygen to carbon Lewis acid mediated rearrangement of an alkynylstannane **1.28** to set up the *trans*-THF stereochemistry found in muricatetrocin-C (**1.27**). The approach of the alkynylstannane was governed by the pendant bulky *tert*-butyldiphenylsilyloxymethyl group (Scheme 1.4). The ratio of the *trans*-THF product **1.29a** to the corresponding *cis*-THF product **1.29b** was 5.5:1 in favour of the desired *trans*-THF, which was separated by column chromatography after O-benzylation.



Scheme 1.4 Lewis acid mediated rearrangement to give *trans*-THF core. *Reagents and Conditions*: a) $BF_3 \cdot OEt_2$, CH_2Cl_2, –10 °C, 10 min.

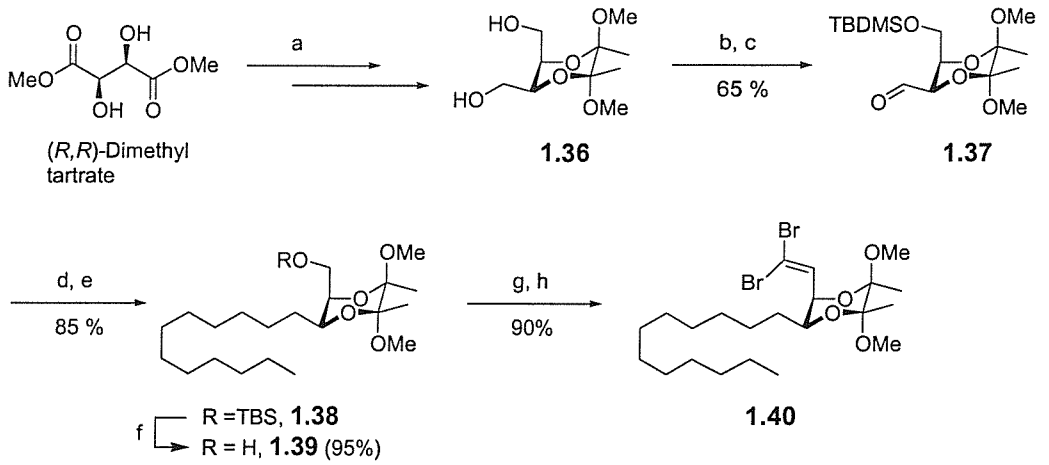
Compound **1.28** was prepared in five steps from (*R*)-glycidol as shown in scheme 1.5. After O-silylation, an allyl cuprate epoxide ring-opening and an ozonolysis furnished the known lactol **1.31** as a 3:2 mixture of epimers. Treatment of lactol **1.31** with excess propargylic alcohol gave propargylic ether **1.32** in excellent yield, again as a 3:2 mixture. Stannane **1.28** was prepared from propargylic ether **1.32** by deprotonation followed by addition of tributyltin chloride. The Lewis acid mediated rearrangement went in good yield from the crude mixture (Scheme 1.4). Subsequent benzylation of the 5.5:1 mixture of *trans/cis*-THF alcohols **1.29a/1.29b** allowed for separation of the diastereoisomers and gave *trans*-THF **1.32** in good yield. The TBDPS group was removed to give primary alcohol **1.34.** It was found necessary to firstly reduce out the triple bond before oxidising the primary alcohol up to the aldehyde. The reduction was carried out using Raney nickel and H_2. The oxidation was carried out under Swern conditions[55] and gave aldehyde **1.35**, ready for coupling to the left-hand-side (LHS) of the molecule.



Scheme 1.5 Synthesis of THF core fragment **1.35**. *Reagents and Conditions*: a) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, rt; b) allylMgBr, $CuLi_2Cl_4$, THF, –30 °C; c) O_3, CH_2Cl_2, –78 °C, then PPh_3; d) prop-2-yn-1-ol, Amberlyst A-15, benzene, reflux; e) *n*BuLi, THF, –78 °C, then Bu_3SnCl, –78 °C to rt; f) $BF_3{\bullet}OEt_2$, CH_2Cl_2, –10 °C; g) KHMDS, –78 °C, then BnBr, THF, –78 °C to rt; h) TBAF, THF, rt; i) Raney nickel, H_2, EtOH, rt; j) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C; then Et_3N.

Synthesis of the Left-Hand-Side Masked *anti*-Diol Fragment

The synthesis of the *anti*-diol was accomplished from the chemical desymmetrisation of a *meso*-dimethyl tartrate derivative. Thus, 2,3-butanediacetal protected (*R,R*)-dimethyl tartrate was converted to the corresponding (*R,S*)-diol **1.36** (Scheme 1.6).[56] Terminal differentiation of diol **1.36** was accomplished *via* deprotonation with NaH, then addition of TBSCl. This gave a 5:1 mixture of easily separable diastereoisomers. The equatorial alcohol was oxidised using Swern conditions.[55] Introduction of the alkyl chain was accomplished smoothly by Wittig reaction with the phosphorus ylid derived from 1-iodoundecane (*Z/E* 8:1). The olefin was then removed by reduction with Raney nickel/H_2 to give **1.38** in good yield. Deprotection, followed by oxidation furnished the axial aldehyde. The conversion to a suitable coupling partner required a one-carbon homologation reaction. Thus, the olefination was carried out using the Corey-Fuchs[57] procedure to give the *gem*-dibromo olefin **1.40**.



Scheme 1.6 Synthesis of masked *anti*-diol fragment **1.40**. *Reagents and Conditions*: a) reference[56] b) NaH, THF, pentane, 0 °C to rt, then TBSCl; c) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, then Et_3N; d) $CH_3(CH_2)_{10}PPh_3I$, *n*BuLi, THF, –78 °C; e) Raney nickel, H_2, EtOH; f) TBAF, THF; g) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, then Et_3N; h) PPh_3, CBr_4, CH_2Cl_2, 0 °C.

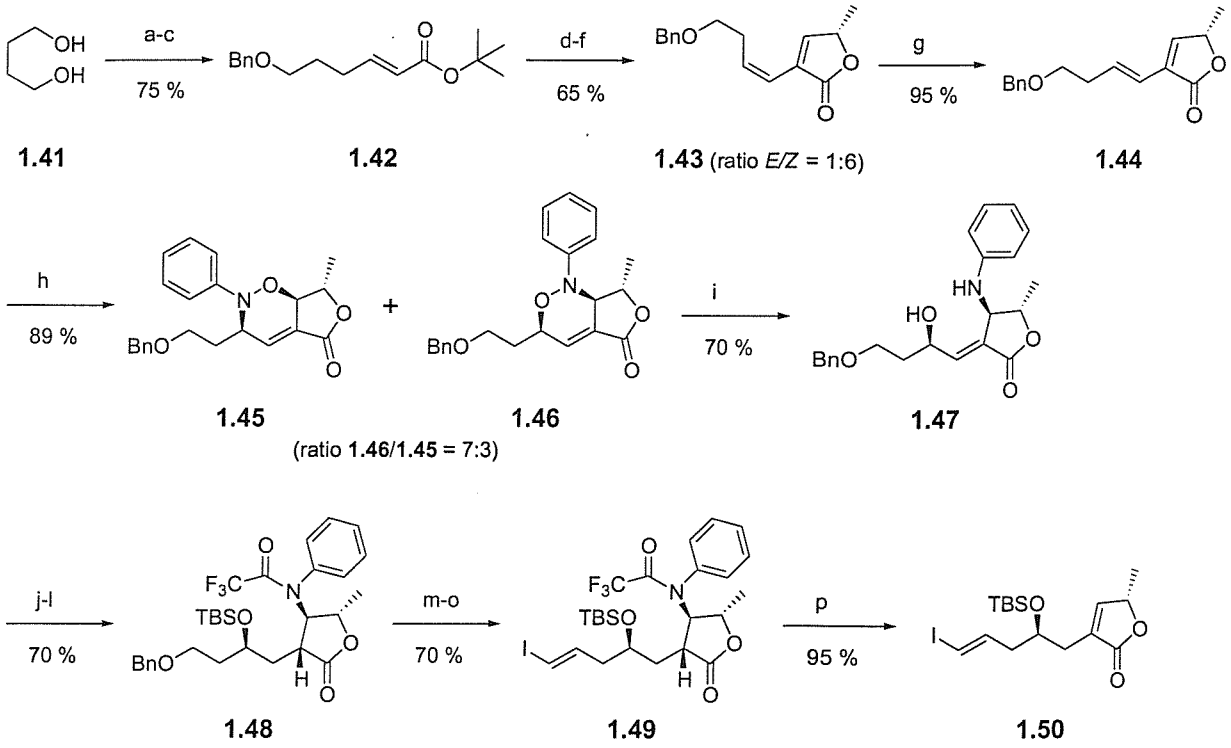
Synthesis of the Butenolide Fragment

Ley and co-workers prepared the butenolide fragment using novel methodology, installing the chirality at C-4 by a hetero Diels Alder (HDA) reaction. This required the dieneophile to deliver oxygen to C-4 and to accomplish this with complete facial selectivity. Therefore singlet oxygen was ruled out as it did not have the bulk required for steric control under the direction of methyl-35. They accomplished the stereoselective delivery of oxygen using

nitrosobenzene, which was also regioselective in the HDA reaction. Calculation of the frontier orbital coefficients demonstrated that delivery of oxygen to the C-4 position was favoured if the reaction proceeded with normal electron demand.

Starting with 1,4-butanediol **1.41**, *mono*-benzylation followed by tandem Swern-Wittig reaction afforded ester **1.42** (Scheme 1.7). The next three steps were carried out on the crude material. Aldol condensation between the enolate of **1.42** and (*S*)-2-(*tert*-butyldimethylsilyloxy)propanal,[58] then treatment with HCl/MeOH facilitated lactonisation and the formation of the β-hydroxy-γ-lactone. Elimination was accomplished by mesylation then base to give the α,β-unsaturated butenolide **1.43** in good yield, with a 1:6 (*E*/*Z*) ratio for the external double bond. Treatment with sunlamp irradiation with catalytic iodine gave the desired (*E*)-isomer **1.44** in greater than 20:1 ratio.[59] With diene **1.44** in hand, the key HDA reaction was investigated. It was found that nitrosobenzene stirred overnight in CH_2Cl_2/MeOH at 0 °C gave a mixture of regioisomers (7:3, **1.46:1.45**) favouring the desired product. Importantly, the correct regioisomer **1.46** was formed as one diastereoisomer (20:1). It appeared that the observed diastereoselectivity was limited only by the original geometry of the diene precursor. Cleavage of the N-O bond was achieved by $[Mo(CO)_3(CH_3CN)_3]$ in high yield giving amine **1.47**. Protection of the resulting alcohol, reduction of the double bond and protection of the amine as the trifluoroacetomide gave **1.48** as a single diastereoisomer in good yield. Next, the terminal benzyl group was converted to the vinyl iodine for palladium coupling. This was achieved by reductive removal of the benzyl group, oxidation of the resulting alcohol to the corresponding aldehyde followed by the Takai procedure[60] to give vinyl iodide **1.49** in high yield. Elimination of the trifluoroacetomide was accomplished in excellent yield by treatment with DBU giving the butenolide coupling fragment **1.50**.

This gave Ley and co-workers the three fragments of muricatetrocin-C (**1.27**); masked *anti*-diol **1.40**, THF **1.34** and butenolide **1.50**, which just required coupling and deprotection.

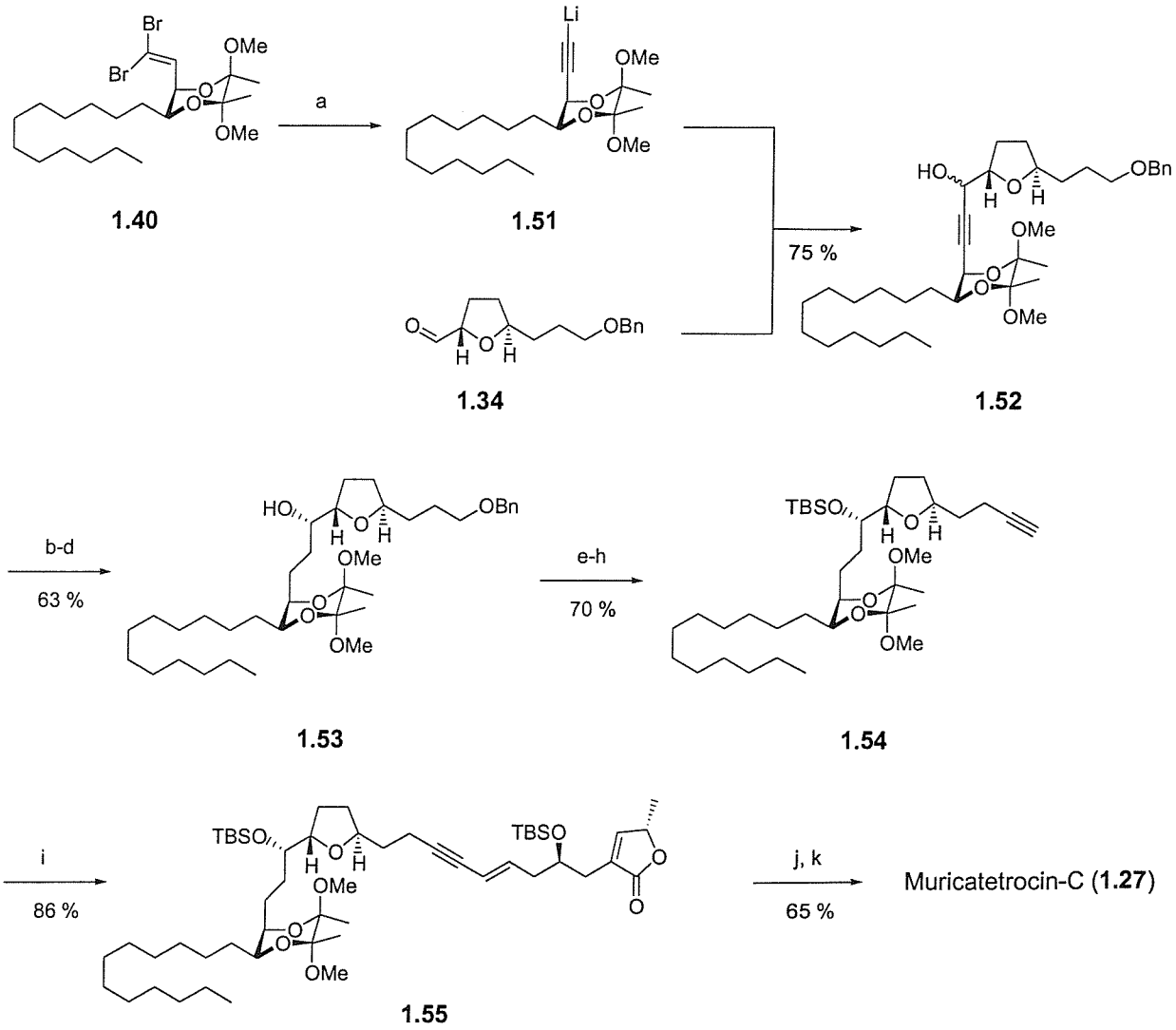


Scheme 1.7 Synthesis of butenolide fragment. *Reagents and Conditions*: a) NaH, BnBr, DMF, rt; b) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, then Et_3N; c) (*tert*-butoxycarbonylmethylene)- triphenylphosphorane, CH_2Cl_2, 0 °C to rt; d) LDA/HMPA/THF rt, then (*S*)-2-(*tert*-butyldimethylsilyloxy)propanal, –78 °C to rt; e) MeOH/HCl, (repeat), rt; f) MsCl, Et_3N, CH_2Cl_2, 0 °C; g) I_2, irradiation; h) PhNO, $MeOH/CH_2Cl_2$, 0 °C; i) $[Mo(CO)_6]$, MeCN, then **1.46**, H_2O, rt; j) TBSCl, imidazole, DMF, rt; k) PtO_2, H_2, EtOH, rt; l) TFAA, $(^iPr)_2NEt$, CH_2Cl_2, 0 °C; m) $Pd(OH)_2$, H_2, MeOH, rt; n) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, then Et_3N; o) $CrCl_2$, CHI_3, THF, 0 °C to rt; p) DBU, CH_2Cl_2, 0 °C.

Coupling the Fragments to Complete the Synthesis of Muricatetrocin-C (1.27)

The convergent assembly of muricatetrocin-C (**1.27**) from the three fragments was completed using the following chemistry. *gem*-Dibromoalkene **1.40** was treated with *n*-butyl lithium to give the acetylide **1.151** which was reacted with aldehyde **1.34**, giving the propargylic alcohol **1.52** in good yield but poor diastereoselectivity (1.8:1) (Scheme 1.8). Consequently, an oxidation-reduction sequence was carried out to set the desired stereochemistry a C-16. Reduction of the alkyne enabled separation of the two diastereoisomers. The (*R*)-epimer was oxidised to the ketone using Swern condition[55] and reduced to the desired (*S*)-alcohol **1.53** (4:1) using L-selectride. With the final stereogenic centre in place, **1.54** was prepared for coupling with **1.50**. Thus, silylation of the secondary

alcohol then hydrogenation, allowed Dess-Martin oxidation to the aldehyde.[61] One-carbon homologation using the Colvin-Gilbert-Seyferth reagent gave the terminal alkyne **1.54** in good yield. The final coupling was accomplished using the methods described by Hoye *et al.*[62] in a Sonogashira cross coupling reaction[63] with alkyne **1.54** and vinyl iodide **1.50**. Selective hydrogenation of enyne **1.55** with Wilkinson's catalyst followed by deprotection with aqueous trifluoroacetic acid afforded muricatetrocin-C (**1.27**).



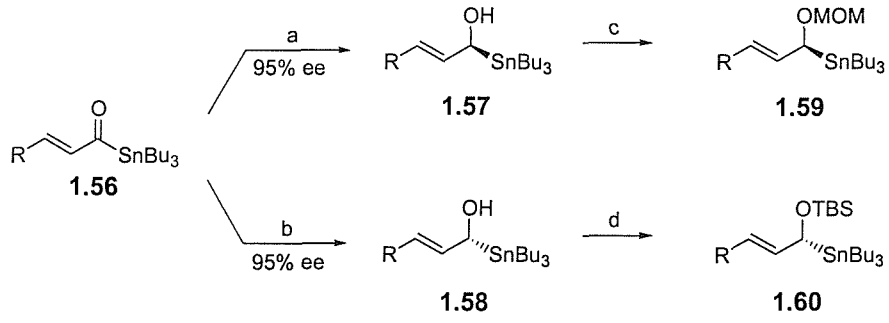
Scheme 1.8 Coupling of fragments to complete the synthesis of Muricatetrocin-C (**1.27**). *Reagents and Conditions:* a) *n*Buli, THF, –78 °C to rt; then **1.34**, –78 °C; b) Raney Nickel, H_2, EtOH, rt; c) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, then Et_3N; d) L-selectride, THF, –100 °C; e) TBSCl, imidazole, DMF, 45 °C; f) $Pd(OH)_2$, H_2, EtOH, rt; g) Dess-Martin periodinanne, CH_2Cl_2, 0 °C to rt; h) diethyl methyldiazophosphonate, *t*BuOK, THF, –78 °C to rt; i) **1.50**, $[Pd(PPh_3)_2Cl_2]$, CuI, Et_3N (0.32 mL, 2.2 mmol), rt; j) $[Rh(PPh_3)_3Cl]$, H_2, THF, rt; k) TFA/H_2O 9:1, 1 min, repeat.

1.6.2 James A. Marshall *et al.*

Marshall and co-workers have published extensively on the total synthesis of *Annonaceous* acetogenins, concentrating their efforts on *bis*-THF ring substrates.[64-71]

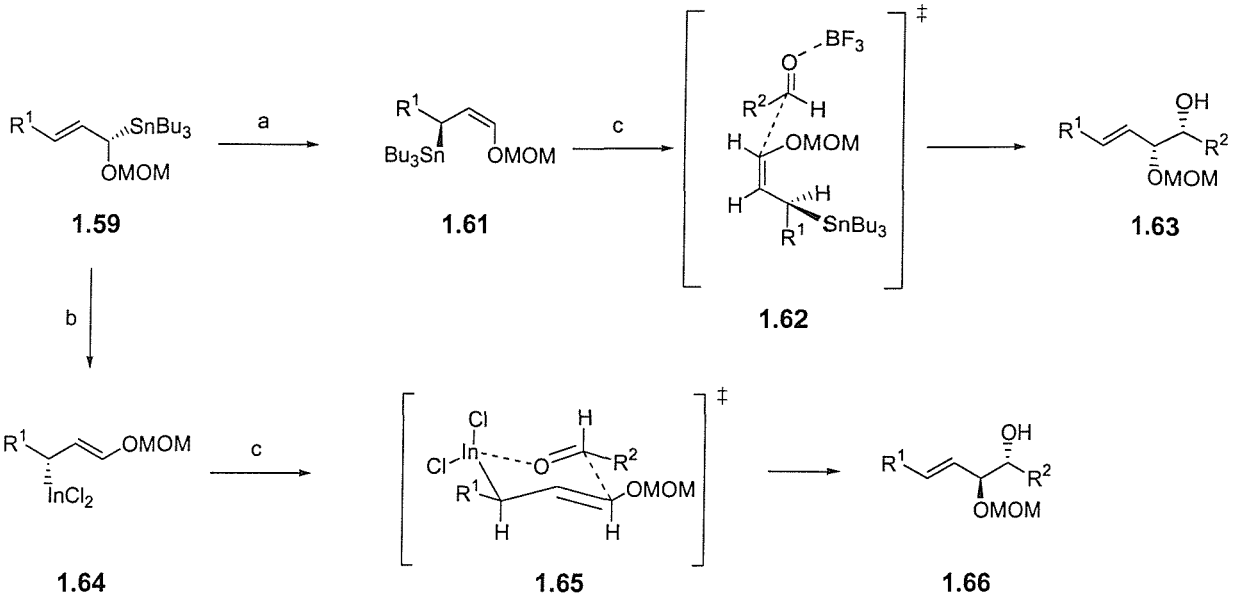
1.6.2.1 Introduction to Marshall's Stannane Chemistry

Marshall's interest in the synthesis of *Annonaceous* acetogenins began as a divergence from an existing project directed towards carbohydrate-based natural products. This project involved the development of a route to highly enantioenriched α- and γ-alkoxy allylic stannanes.[72] They were prepared by the reduction of an acylstannane **1.56** by a chiral hydride source, followed by the etherification of the resulting (*S*) or (*R*)-hydroxy stannane **1.57** or **1.58** with a reactive halide or triflate to form the corresponding protected stannane **1.59** or **1.60** (Scheme 1.9).



Scheme 1.9 Synthesis of α-alkoxy chiral stannanes. *Reagents and Conditions:* a) (*R*)-(+)-BINAL-H, THF, –78 °C; b) (*S*)-(-)-BINAL-H, THF, –78 °C; c) MOMCl, DIPEA, CH_2Cl_2, 0 °C; d) TMSOTf, *i*-Pr_2NEt, CH_2Cl_2, 0 °C.

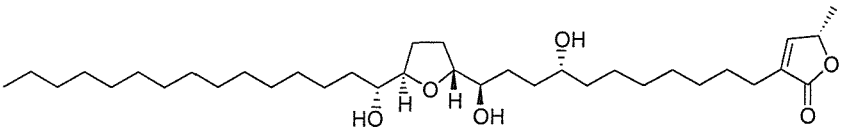
The α-alkoxy stannane **1.59** was found to undergo stereospecific isomerisation to the γ-isomer **1.61** with inversion (Scheme 1.10). Subsequent addition to aldehydes, in the presence of Lewis acid, furnished *mono*-protected *syn*-1,2-diols **1.63**, *via* an acylic transition state.[73] Pleasingly, pre-treatment of the α-alkoxy stannane **1.59** with indium trichloride followed by addition to aldehydes gave *mono*-protected *anti*-diols **1.66**, *via* a cyclic transition state.[74]



Scheme 1.10 Stereospecific isomerisation of α-alkoxy stannane and reaction with aldehydes. *Reagents and Conditions:* a) BF_3•OEt_2, –78 °C; b) $InCl_3$, –78 °C; c) R^2CHO.

1.6.2.2 Synthesis of Longifolicin (1.67)[75]

Marshall and co-workers used their α-and γ-OMOM allylic stannanes in the total synthesis of the *threo-trans-threo-mono*-THF acetogenin longifolicin (**1.67**) (Figure 1.6),[75] isolated from the roots of Asimina longifolia.[24]

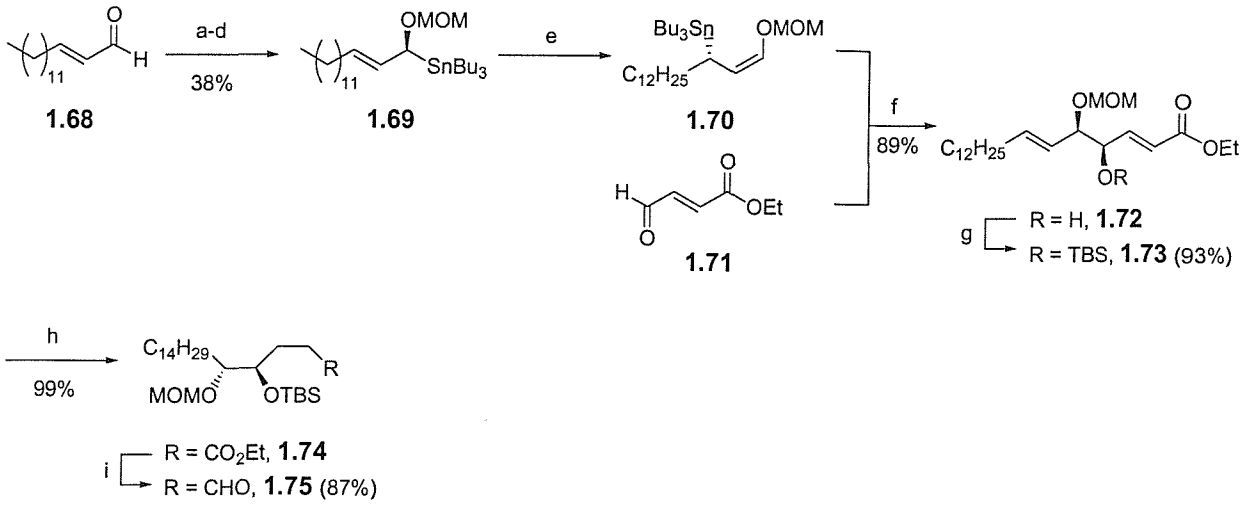


Longifolicin (**1.67**)

Figure 1.5 Structure of *threo- trans- threo-mono*-THF acetogenin longifolicin (**1.67**)

Preparation of the γ-OMOM Allyic Stannane and Subsequent *syn*-Diol

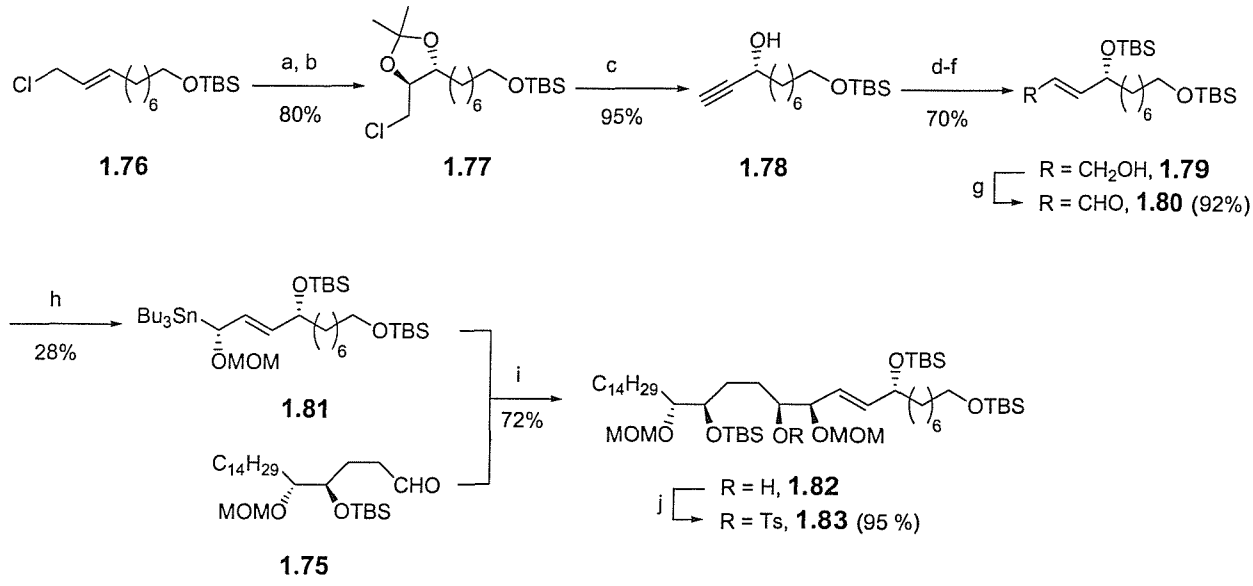
The α-MOM stannane **1.69** was prepared in four steps from enal **1.68** (Scheme 1.11).[73] Treatment of **1.69** with Lewis acid gave γ-MOM stannane **1.70**, which upon addition of aldehyde **1.71** gave *syn*-diol **1.72** in a 9:1 *syn:anti* ratio. Conversion to the TBS ether **1.73** and subsequent hydrogenation and reduction gave aldehyde **1.75** in good yield.



Scheme 1.11 Synthesis of the LHS *syn*-diol fragment. *Reagents and Conditions:* a) Bu_3SnLi; b) 1,1-(azodicarbonyl)dipiperidine; c) (*R*)-BINAL-H; d) MOMCl, (^{i}Pr)$_2$NEt; e) BF_3•OEt_2, CH_2Cl_2, –78 °C; f) BF_3•OEt_2, **1.71**, CH_2Cl_2, –78 °C; g) TBSCl, imidazole; h) H_2, Rh-Al_2O_3; i) DIBAL-H, hexane.

Preparation of the α-MOM Stannane and Subsequent *anti*-Diol

Preparation of stannane **1.81** commenced from the allylic chloride **1.76** (Scheme 1.12).[64] Asymmetric dihydroxylation[76] and protection of the resulting *syn*-diol gave acetonide **1.77**. This was converted to the alkynol **1.78** by treatment with *n*BuLi, before a series of transformations gave enal **1.80** in good yield. The final four steps (as for **1.69**) gave stannane **1.81**. The coupling to aldehyde **1.75** was accomplished by an *anti*-selective addition of an allylic indium derivative prepared *in situ* from (*R*)-α-OMOM stannane **1.81**, affording the adduct as a separable 9:1 mixture favouring the *anti* isomer **1.82**. Tosylation of the secondary alcohol gave **1.83** the precursor to Williamson cyclisation.

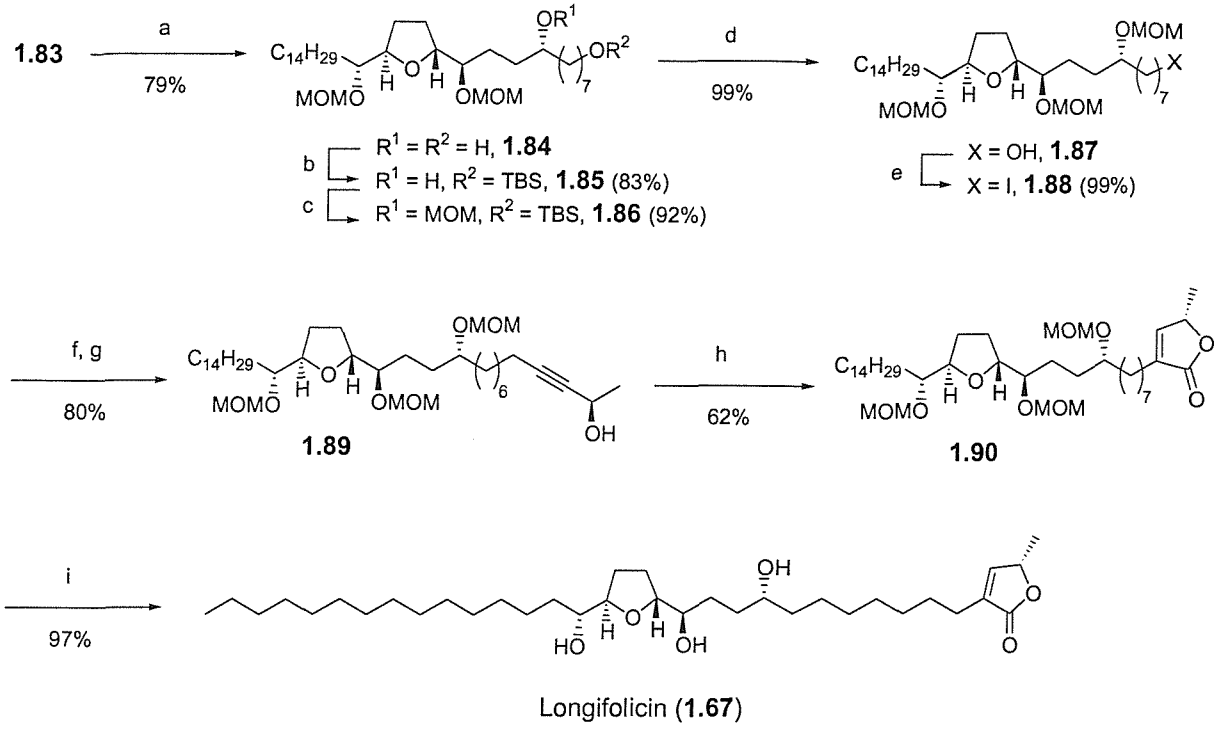


1.76 1.77 1.78 1.81 1.75

Scheme 1.12 Synthesis of *anti*-diol and pre-cursor for Williamson cyclisation. *Reagents and Conditions:* a) AD-mix β; b) $Me_2C(OMe)_2$, PPTS; c) BuLi, –35 °C; d) TBSCl, imidazole; e) CH_2O, *n*BuLi; f) Red-Al; g) MnO_2; h) Bu_3SnLi, THF; 1,1-(azodicarbonyl)dipiperidine; (*S*)-BINAL-H; MOMCl, (^{i}Pr)$_2$NEt, (four steps); i) $InBr_3$, Et_2O, –30 °C; j) *p*-TsCl, py.

THF Formation and Completion of Synthesis

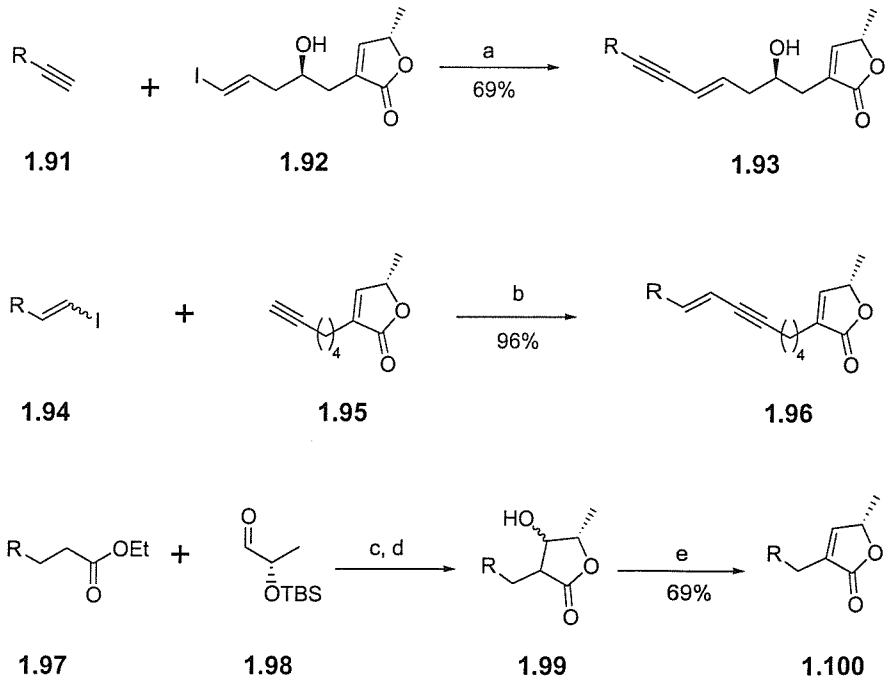
Desilylation of **1.83** commenced Williamson cyclisation affording *trans*-THF **1.84** in good yield (Scheme 1.13). The last stage of the synthesis entailed attachment of a butenolide moiety to the THF intermediate **1.84**. This was achieved through a chiral propargylic alcohol and application of their allenyl palladium hydrocarbonylation methodology.[47,64] Thus, iodide **1.88** was prepared and treated with the lithiated TBS ether derived from commercially available (*R*)-3-butyn-2-ol. After TBS cleavage, propargylic alcohol **1.89** was converted to the trifluoroacetate and subjected to their palladium hydrocarbonylation conditions affording butenolide **1.90**. The MOM protecting groups were cleaved giving longifolicin (**1.67**) in excellent yield.



Scheme 1.13 Completion of longifolicin (**1.67**) by Williamson cyclisation and allenyl Pd hydrocarbonylation. *Reagents and Conditions:* a) TBAF, THF, 45 °C; b) TBSCl, imidazole; c) MOMCl, (^{i}Pr)$_2$NEt; d) H_2, Rh-Al_2O_3; e) TBAF, THF; f) I_2, Ph_3P, imidazole; g) (*R*)-LiCCCH(OTBS)Me, HMPA; TBAF, THF (two steps); h) $(CF_3CO)_2O$, py; $Pd(PPh_3)_4$, CO, H_2O, THF; $AgNO_3$, Et_2O (three steps); i) HCl/THF/MeOH, 1:2:2.

1.6.2.3 Marshall's Alternative Approaches to the Installation of the Butenolide Fragment

Marshall's numerous acetogenin syntheses have some variation in the method of addition of the butenolide moiety (Scheme 1.14). This has entailed pre-formed butenolide fragments with a terminal vinyl iodide **1.92** ready for Sonogashira coupling[63] to a terminal alkyne **1.91**.[70] Or reversing this so that the butenolide contains the terminal alkyne **1.95**.[64,66] Both of these methods require selective hydrogenation to complete the synthesis. An alternative method was investigated, aldol condensation of an ethyl ester **1.97** with aldehyde **1.98** derived from (*S*)-lactic acid. Desilylation gave γ-lactone **1.99**, which on treatment with trifluoroacetic anhydride and base afforded the butenolide **1.100**.[68]



Scheme 1.14 Alternative approaches to the installation of the butenolide fragment. *Reagents and Conditions:* a) $Pd(Ph_3P)_2Cl_2$, Et_3N, CuI; b) $Pd(Ph_3P)_2Cl_2$, Et_3N, CuI; c) LDA; d) TBAF; e) $(CF_3CO)_2O$, Et_3N.

1.6.3 Yu-Lin Wu *et al.*

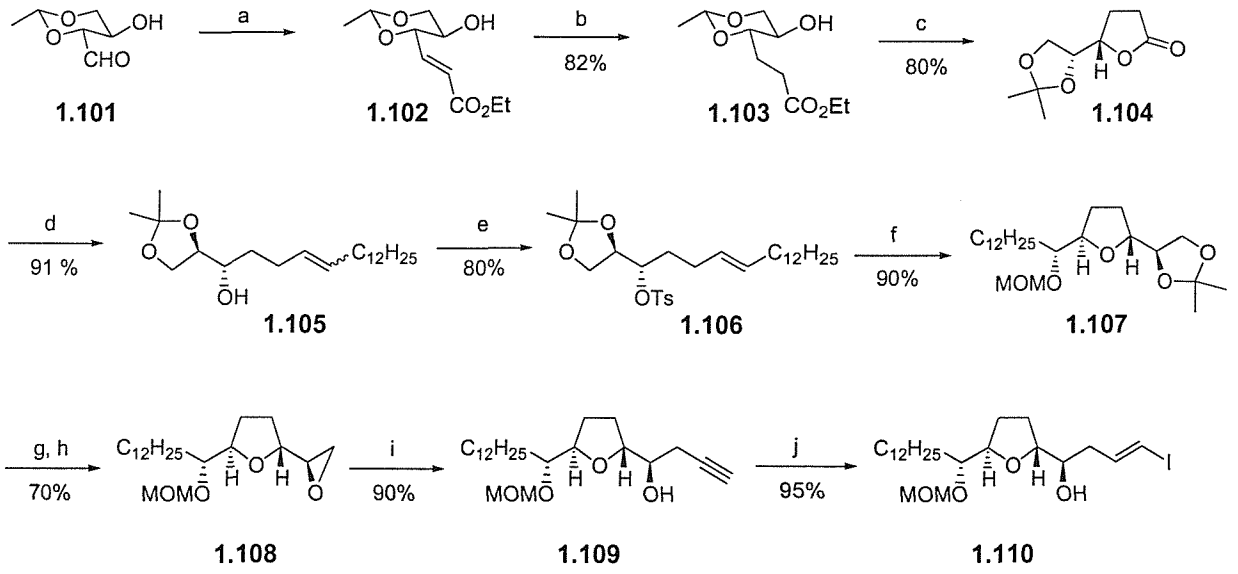
Wu and co-workers have published total syntheses of three *threo-trans-threo-mono*-THF *Annonaceous* acetogenins using carbohydrate derivatives as the source of the required chirality. Williamson cyclisations were employed to form the THF rings.[77-80]

1.6.3.1 Synthesis of 4-Deoxyannomontacin (1.119)[78]

Wu and co-workers strategy was similar to most groups; to couple the THF fragment to the pre-formed butenolide fragment *via* Hoye's Sonogashira coupling conditions.[62,63] They used chirality already in place from D-(+)-glucose combined with Sharpless asymmetric dihydroxylation[81] to bring about a Williamson cyclisation to form the *trans*-THF moiety.

Starting from known aldehyde **1.101**, which is easily obtainable from D-glucose,[82] a Wittig-Horner olefination gave ester **1.102** (Scheme 1.15). Hydrogenation followed by treatment with propane-1,3-dithiol in the presence of Lewis acid led to deprotection and lactonisation.

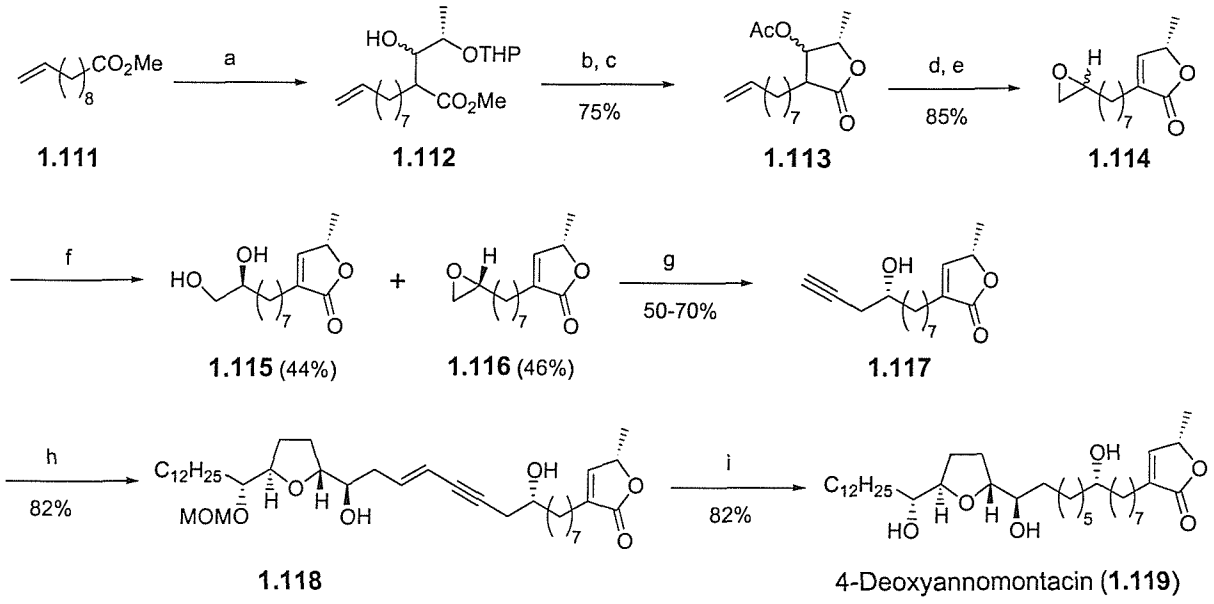
Subsequent protection of the diol gave acetonide **1.104** in good yield. Reduction of lactone **1.104** gave the corresponding lactol, which underwent Wittig olefination to give olefin **1.105** as a mixture of regioisomers. Photo-isomerisation[83] gave exclusively the (*E*)-isomer, which was followed by tosylation to obtain **1.106**. Asymmetric dihydroxylation[81] set up the desired stereochemistry at C-22 and a Williamson cyclisation furnished the desired THF **1.107**. Deprotection followed by epoxide formation gave **1.08**, which was converted to the propargylic alcohol **1.09** in excellent yield. Conversion of **1.09** to the vinyl iodide **1.110** went smoothly using tributyltin hydride and iodine-metal exchange.[84]



Scheme 1.15 Synthesis of THF coupling fragment from a carbohydrate derivative. *Reagents and Conditions:* a) Ph_3PCHCO_2Et, THF; b) Pd-C, H_2; c) propane-1,3-dithiol, $BF_3{\bullet}OEt_2$; then DMOP, CH_2Cl_2; d) DIBAL-H, CH_2Cl_2, –78 °C; $C_{13}H_{27}PPh_3Br$, *n*BuLi, –20 °C to rt; e) *hv*, PhSSPh, cyclohexane, 1,4-dioxane; then NaH, *N*-TsIm, THF; f) AD mix β, ^{t}BuOH/H_2O; then K_2CO_3, MeOH; then MOMCl, $(^i Pr)_2NEt$; g) AcOH, 60 °C; h) NaH, *N*-TsIm; i) TMS-acetylene, *n*BuLi, $BF_3{\bullet}OEt_2$, THF; then *n*-Bu_4NF, THF; j) Bu_3SnH, AIBN, 130 °C; then I_2, Et_2O.

The butenolide fragment was synthesised from ethyl (*S*)-lactate and used an enzyme resolution to control the stereochemistry at C-10. Thus, ester **1.111** was reacted in an aldol reaction with the aldehyde **1.123**, derived from ethyl (*S*)-lactate (Scheme 1.16). The alcohol was protected as the acetate before removal of the THP group caused lactonisation affording lactone **1.113**. Epoxidation of the olefin gave **1.114** as a mixture of isomers. Hydrolytic enzyme resolution gave the desired epoxide **1.116** and the unreacted diol **1.115**. Epoxide **1.116** was transformed into terminal alkyne **1.117** in excellent yield, which was coupled to

vinyl iodide **1.110** by Hoye's palladium conditions.[62,63] The selective reduction was carried out by diimide, generated *in situ*, as reported by Marshall *et al.*[65] The final deprotection was accomplished in good yield, completing the synthesis of 4-deoxyannomontacin (**1.119**).



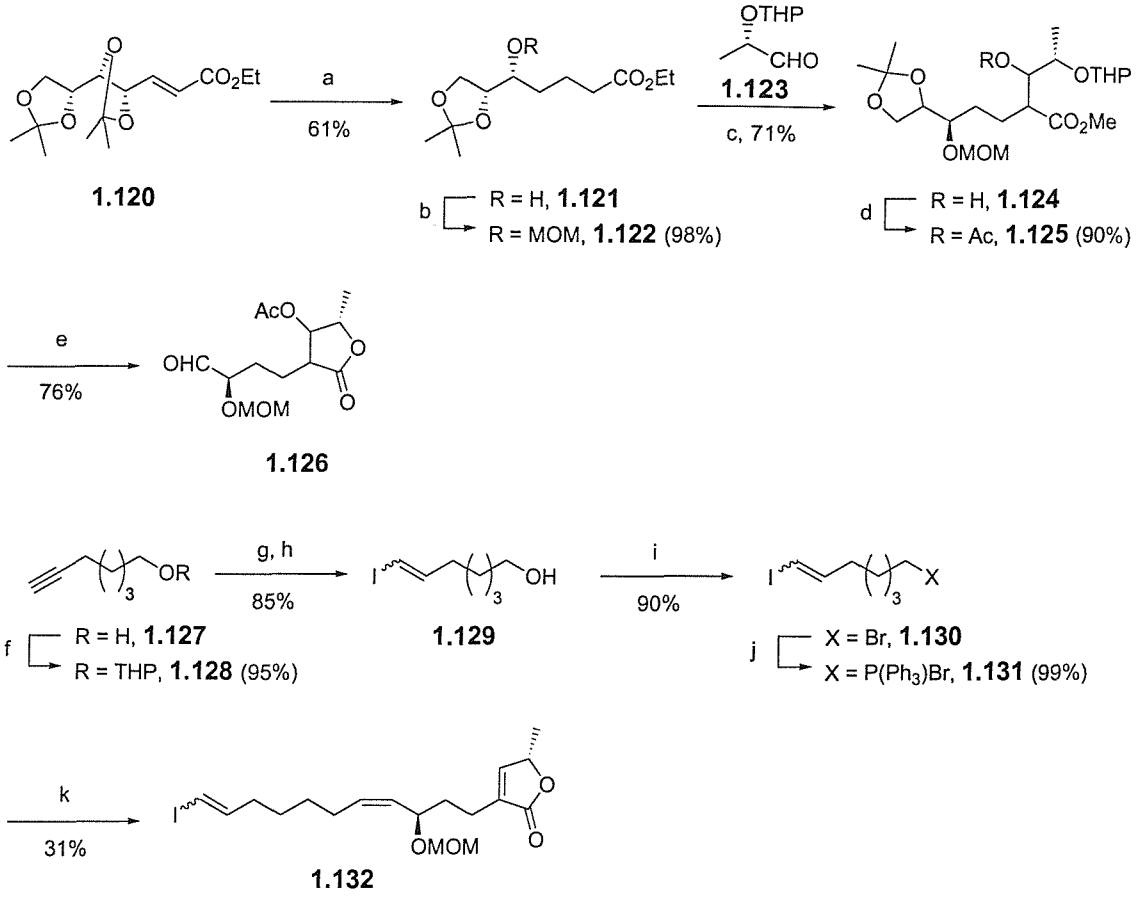
Scheme 1.16 Synthesis of butenolide fragment and completion of 4-deoxyannomontacin (**1.119**). *Reagents and Conditions:* a) reference[85]; b) Ac_2O, Py; c) H_2SO_4, THF; d) MCPBA, CH_2Cl_2; e) DBU, CH_2Cl_2; f) (*R,R*)-salenCo(OAc), H_2O, 40 °C; g) *n*BuLi, TMS-acetylene, BF_3•OEt_2, THF; then *n*-Bu_4NF, THF; h) **1.110**, $Pd(PPh_3)_2Cl_2$, Et_3N, CuI; i) $TsNHNH_2$, NaOAc, DME, H_2O, reflux; then BF_3•OEt_2, DMS.

1.6.3.2 Synthesis of Tonkinecin (1.134)[77,79]

Wu and co-workers published the synthesis of a related *mono-trans*-THF acetogenin using similar starting materials and chemistry. The synthesis of the butenolide fragment altered due to the position of the hydroxyl group shifting from C-10 to C-5. The THF fragment was constructed by the methods used for 4-deoxyannomontacin (**1.119**).

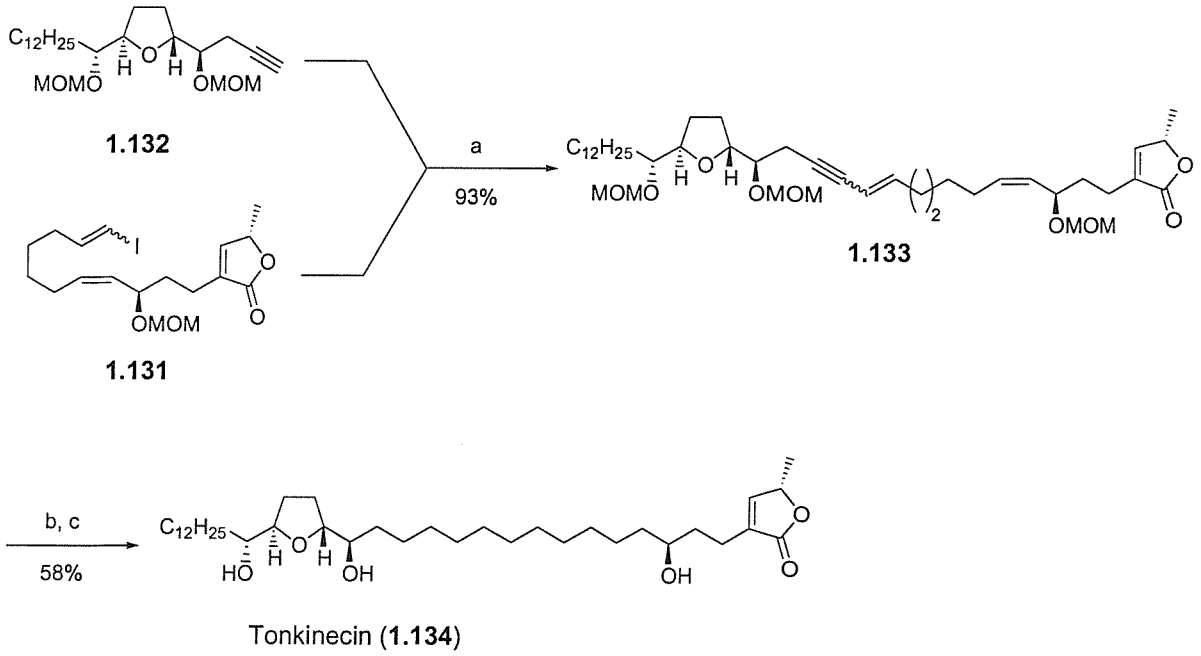
Starting from D-xylose, ester **1.120** was prepared in two steps by the known procedure.[86] Treatment with Mg in MeOH gave alcohol **1.121**, which was protected (Scheme 1.17). Ester **1.122** was reacted in an aldol reaction with aldehyde **1.123** giving alcohol **1.124**. Protection as the acetate was followed by treatment with periodic acid, which deprotected the OTHP group facilitating lactonisation and oxidatively cleaved the 1,2-diol, giving the γ-lactone

1.126. Hydroxy-alkyne **1.127** was protected and converted to the vinyl iodide before deprotection gave alcohol **1.129**. Formation of the bromide followed by reaction with triphenylphosphene gave the unstabilised phosphonium salt **1.131**. Olefination with aldehyde **1.126** gave butenolide **1.132** but in very low yield.



Scheme 1.17 Synthesis of butenolide fragment. *Reagents and Conditions:* a) Mg, MeOH, reflux; b) MOMCl, (^{i}Pr)$_2$NEt, CH_2Cl_2, 0 °C; c) LDA, HMPA, THF; then **1.123**; d) Ac_2O, Py; e) H_5IO_6, Et_2O; f) DHP, PPTS, CH_2Cl_2; g) Bu_3SnH, AIBN, 130 °C; then I_2; h) PTSA, MeOH; i) PPH_3, CBr_4, CH_2Cl_2, 0 °C; j) PPh_3, CH_3CN, reflux; k) LiHMDS, HMPA, THF; then **1.126**.

In this synthesis Wu and co-workers had swapped the coupling groups around for the palladium cross coupling, hence *bis*-MOM protected alkyne **1.132** was prepared by MOM protection of alkyne **1.109** (used in the synthesis of 4-deoxyannomontacin (**1.119**)). The coupling reaction was accomplished in excellent yield giving olefin **1.133** (Scheme 1.18). Hydrogenation by diimide then deprotection using the aforementioned conditions gave tonkinecin (**1.134**).



Tonkinecin (**1.134**)

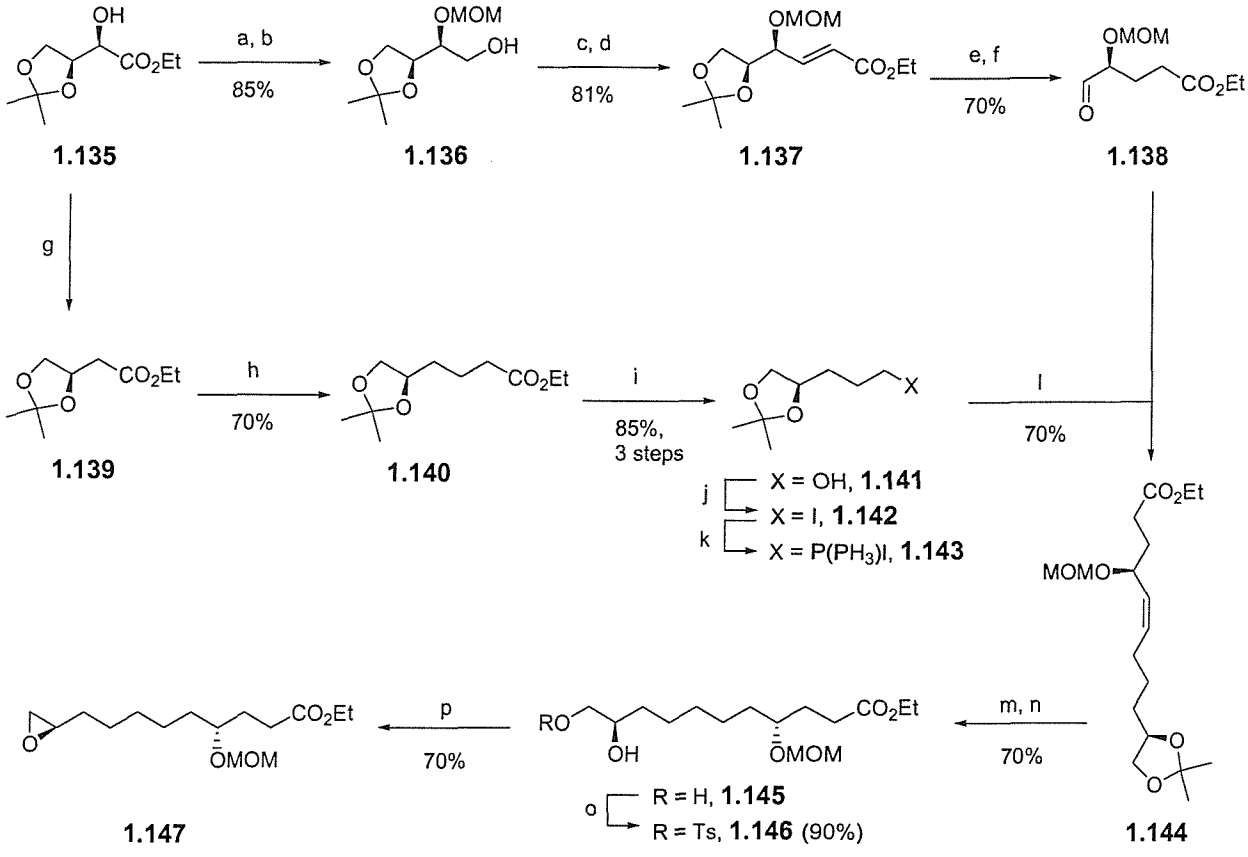
Scheme 1.18 Completion of tonkinecin (**1.134**). *Reagents and Conditions:* a) $[Pd(PPh_3)_2Cl_2]$, CuI, Et_3N; b) $TsNHNH_2$, NaOAc, DME, reflux; c) $BF_3 \cdot OEt_2$, DMS.

1.6.3.3 Synthesis of Annonacin (1.151)[77,80]

Wu and co-workers third synthesis of a *mono-trans*-THF acetogenin differed from the previous two by containing hydroxyl groups at positions C-4 and C-10. Their strategy remained unchanged for the THF fragment, continuing to use terminal alkyne **1.132** which was coupled *via* anion chemistry to the alkyl chain bearing the aforementioned hydroxyl groups. They then utilised their butenolide methodology to complete the synthesis of annonacin (**1.151**).

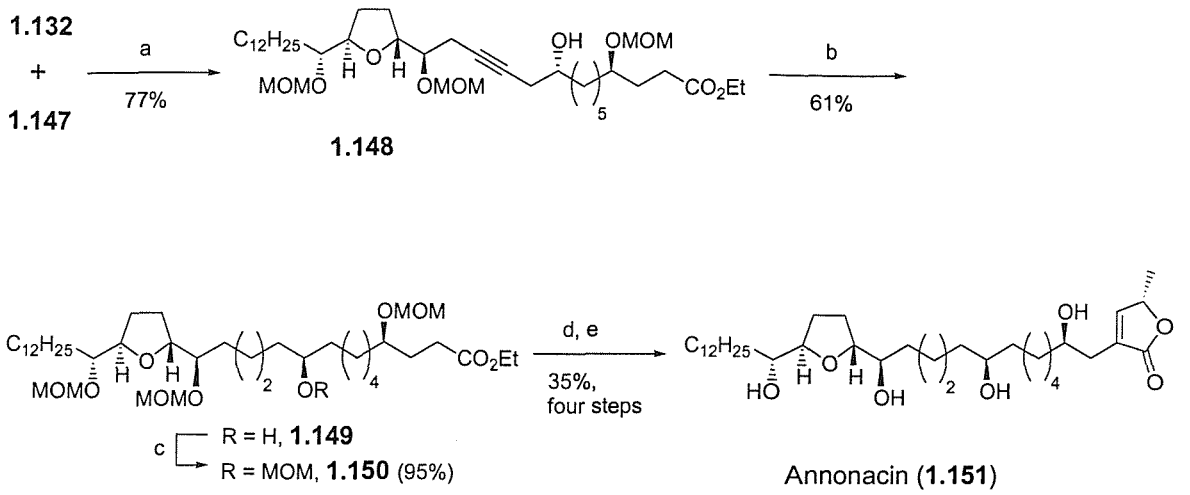
Wu and co-workers exploited the chirality in L-ascorbic acid to provide the chirality present at C-4 and C-10. Alcohol **1.135** was prepared by the known procedure from L-ascorbic acid.[87] At this point the synthesis split into two parts (Scheme 1.19). Protection followed by reduction gave primary alcohol **1.136**. Oxidation to the aldehyde followed by Wittig olefination gave the ester **1.137**. Hydrogenation then treatment with periodic acid gave aldehyde **1.138** ready for coupling. Meanwhile, treatment of alcohol **1.135** by the known procedure gave ester **1.139**.[88] Chain elongation was achieved by subsequent reduction, oxidation, Wittig olefination and hydrogenation giving ester **1.140**. Reduction to the alcohol followed by conversion to the iodide *via* the tosylate and then subjection to

triphenylphosphene gave the phosphonium salt **1.143** in good yield. Wittig olefination with aldehyde **1.138** gave *cis*-alkene **1.144**. Hydrogenation followed by deprotection of the 1,2-diol gave ester **1.145**. Tosylation of the primary alcohol then treatment with base gave epoxide **1.147**, which contained the hydroxyl stereocentres corresponding to C-4 and C-10 present in annonacin (**1.151**).



Scheme 1.19 Synthesis of alkyl chain containing stereocentres C-4 and C-10. *Reagents and Conditions:* a) MOMCl, (^{i}Pr)$_2$NEt; b) $LiAlH_4$, THF 0 °C; c) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, then ^{i}PrEt$_2$N; d) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, reflux; e) H_2/Pd-C, EtOH; f) (i) AcOH, H_2O, 45 °C; (ii) $NaIO_4$, CH_2Cl_2, H_2O; g) reference[87] h) (i) $LiAlH_4$, THF 0 °C; (ii) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, then Et_3N; (iii) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, reflux; (iv) H_2/Pd-C, EtOH; four steps i) $LiAlH_4$, THF 0 °C; j) (i) *p*-TsCl, Et_3N, CH_2Cl_2; (ii) NaI, acetone; k) PPh_3, Na_2CO_3, CH_3CN; l) NaHMDS, THF –78 °C; then **1.138**; m) H_2/Pd-C, $NaHCO_3$, EtOH; n) AcOH, H_2O; o) *p*-TsCl, Et_3N, Bu_2SnO, CH_2Cl_2; p) DBU, CH_2Cl_2.

Alkynol **1.148** was prepared by the coupling of epoxide **1.147** to the lithium acetylide of **1.132** (Scheme 1.20). Hydrogenation followed by MOM protection gave ester **1.150**, which was converted to the butenolide and then deprotected using the aforementioned conditions (Scheme 1.16), giving annonacin (**1.151**) in low yield.



Scheme 1.20 Synthesis of Annonacin **1.132**. *Reagents and Conditions:* a) **1.132**, *n*BuLi, THF, –78 °C; then BF_3•OEt_2, **1.147**; b) PtO_2, EtOH; c) MOMCl, (^{i}Pr)$_2$NEt; d) (i) LDA, THF, –78 °C; then **1.123**; (ii) AcOH, H_2O, THF; (iii) $(CF_3CO)_2O$, Et_3N; e) BF_3•OEt_2, DMS

Wu and co-workers have shown that their general convergent strategy is applicable to a number of *threo-trans-threo-mono*-THF acetogenins, utilising readily available carbohydrates and a hydroxyl acid as their chiral starting materials.

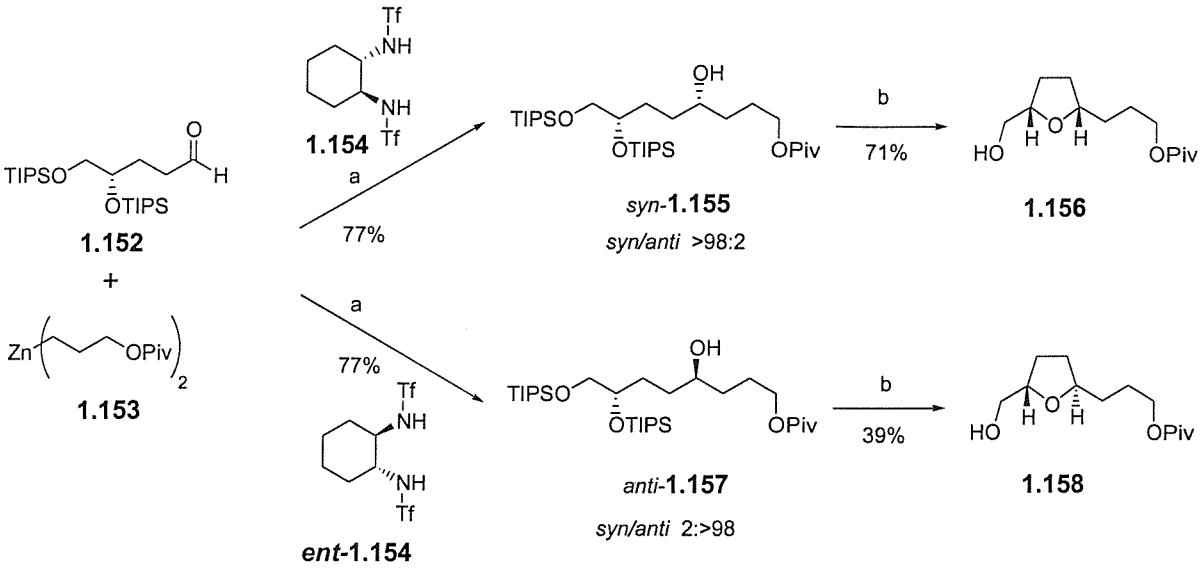
1.6.4 Ulrich Koert *et al.*

1.6.4.1 Introduction to Koert's Diorganozinc Chemistry

Koert was interested in developing a stereospecific method of synthesising both *cis*- and *trans*-2,5-disubstituted THF rings from a common intermediate. A Williamson cyclisation would be used to form the THF ring, hence a 1,4-diol, with complete control of stereochemistry (*syn* or *anti*), would be required.

Koert investigated the addition of functionalised diorganozinc reagents **1.153** to aldehydes (Scheme 1.21).[89] The control of the stereoselectivity was accomplished by a chiral catalyst **1.154** present in the reaction. They used enantiomerically pure aldehydes **1.152**, finding it necessary to block the inherent stereochemistry with a bulky TIPS protecting group to allow the chiral catalyst to have complete control. They were able to form either *syn*- or *anti*-diols

(**1.155** or **1.157**) with complete control in good yield. The THF ring was then formed by tosylation of the free alcohol followed by Williamson cyclisation.

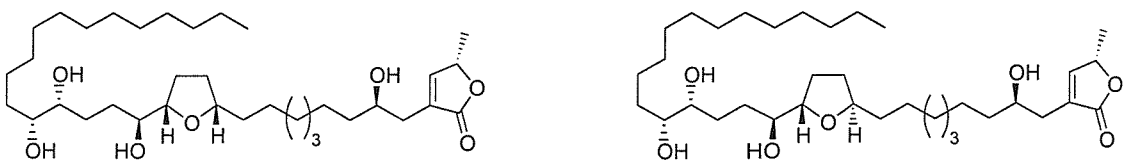


Scheme 1.21 Koert's stereoselective diorganozinc addition to aldehydes. *Reagents and Conditions:* a) $Ti(^{i}OPr)_4$, **1.154** 50 °C; then **1.153**, toluene; then **1.152**; b) (i) TsCl, Py; (ii) HF, H_2O, CH_3CN.

This gave Koert *et al.* a stereoselective method to prepare both *cis*- and *trans*-2,5-disubstituted THF rings from a common intermediate. They then used this methodology in the synthesis of *Annonaceous* acetogenins.

1.6.4.2 Synthesis of Muricatetrocin-A (1.159) and Muricatetrocin-B (1.160)[90]

Koert and co-workers used their diorganozinc chemistry to synthesise two acetogenins that differed only by their THF ring geometry; *threo-cis-mono*-THF muricatetrocin-A, (**1.159**) and *threo-trans-mono*-THF muricatetrocin-B (**1.160**) (Figure 1.6).



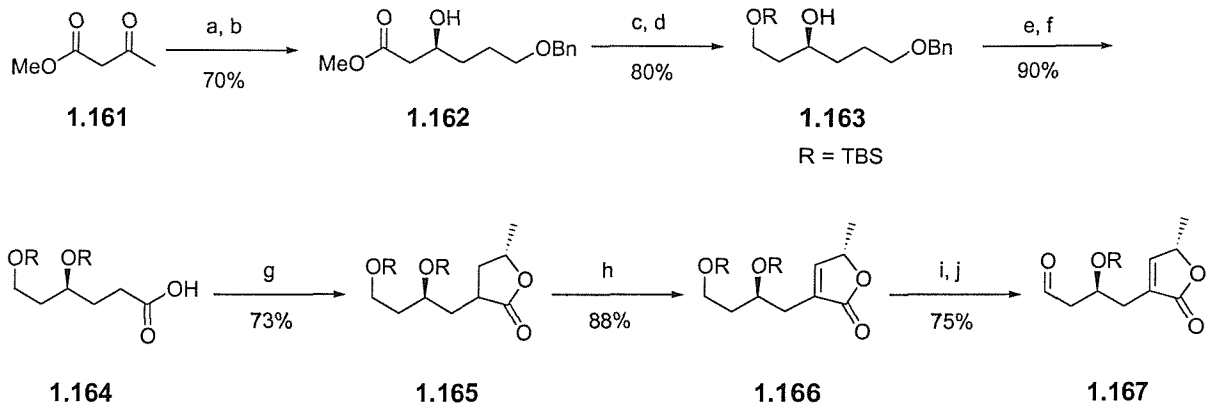
Muricatetrocin-A (**1.159**)

Muricatetrocin-B (**1.160**)

Figure 1.6 Structure of acetogenins muricatetrocin-A and muricatetrocin-B

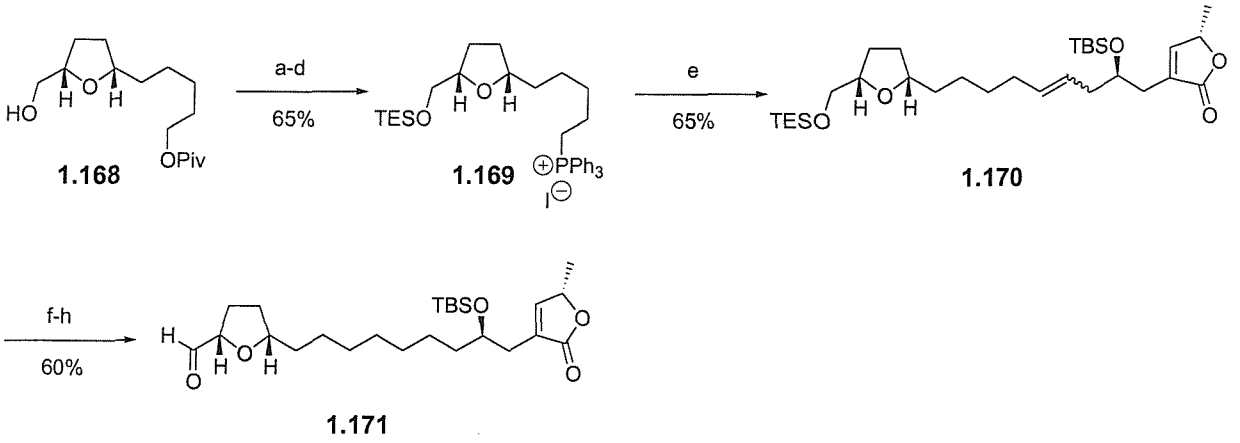
The *cis*- and *trans*-THF fragments were made in accordance with their published material (Scheme 1.21).[89] Herein, for the purpose of clarity only the synthesis of muricatetrocin-A (**1.159**) will be discussed, due to the almost identical approach and structure of muricatetrocin-B (**1.160**) (Figure 1.6).

The butenolide fragment was synthesised by their methodology.[91] Hence, the chirality at the C-4 position was put in place by a Noyori reduction with BINAP[92] giving alcohol **1.162** (Scheme 1.22). The γ-lactone **1.165** was formed by enolate addition to (*S*)-propene oxide, giving the C-34 stereocentre. After introduction of the double bond by selenium chemistry, aldehyde **1.167** was obtained by selective deprotection of the primary silyl ether followed by Dess-Martin oxidation.[61]



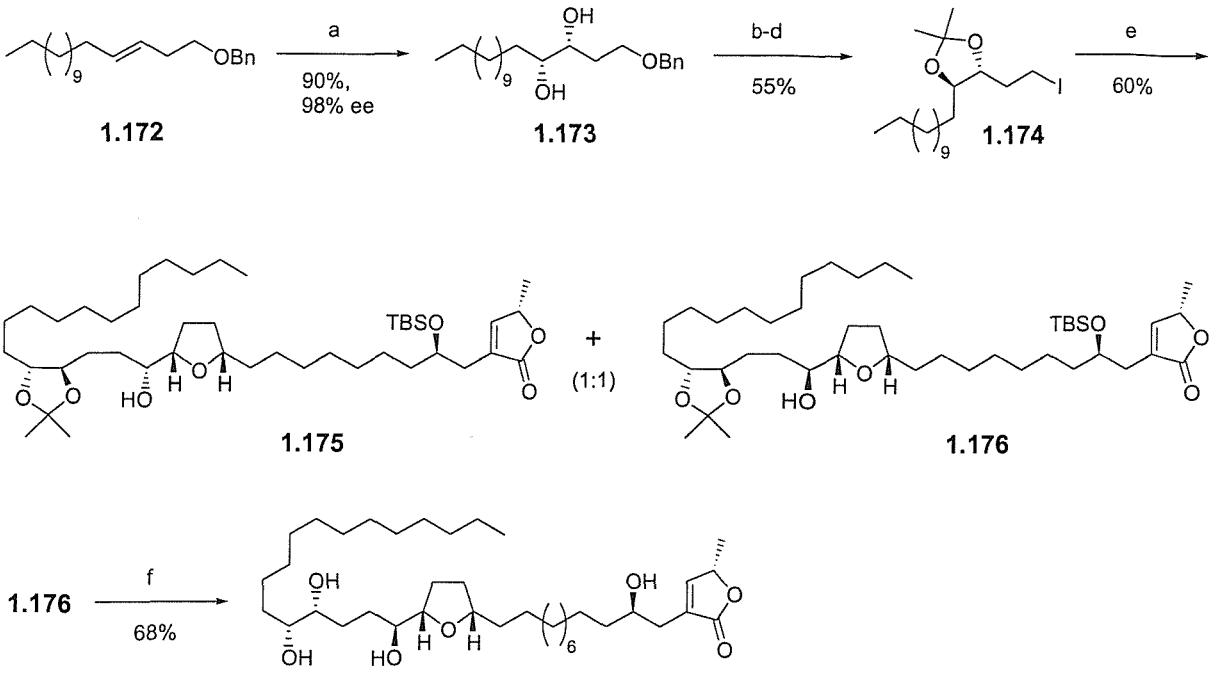
Scheme 1.22 Koert's butenolide fragment synthesis. *Reagents and Conditions:* a) NaH, *n*BuLi, –30 °C; then $Br(CH_2)_2OBn$, –10 °C; b) H_2 (5 bar), Ru^{II}(*S*)-BINAP, 95 °C; c) BH_3•DMS, THF, 60 °C; d) TBSCl, imidazole, DMAP, CH_2Cl_2; e) H_2, Pd-C, EtOAc; f) (i) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, then Et_3N; (ii) $NaClO_2$, NaH_2PO_4•$2H_2O$, methyl-2-butene, ^{t}BuOH, H_2O; g) (i) LDA, THF, 0 °C; then (*S*)-propene oxide; (ii) PivCl, Et_3N; h) (i) KHMDS, THF, 0 °C; then PhSeCl; (ii) magnesium monoperoxophthalate, THF, MeOH; i) CSA, CH_2Cl_2, MeOH; j) Dess-Martin periodinanne, Py, CH_2Cl_2.

The THF fragment **1.168** was converted to the phosphonium salt and coupled to aldehyde **1.167**. The LHS was then deprotected and oxidised to give aldehyde **1.171** (Scheme 1.23).



Scheme 1.23 Coupling of THF and butenolide fragments. *Reagents and conditions:* a) TESCl, imidazole, CH_2Cl_2; b) DIBAL-H, THF, –40 °C; c) I_2, PPh_3, imidazole, CH_2Cl_2; d) PPh_3, imidazole, CH_2Cl_2; e) NaHMDS, THF, 0 °C; then **1.167** –70 °C to 0 °C; f) $[Rh(PPh_3)_3Cl]$, H_2, benzene; g) CSA, CH_2Cl_2, MeOH; h) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, then Et_3N.

The *syn*-diol **1.173** was prepared by Sharpless dihydroxylation[81] (ee = 98%) (Scheme 1.24). Protection as the acetonide followed by conversion to the terminal iodide gave the LHS coupling fragment **1.174**. Addition of aldehyde **1.171** to the lithiated alkane **1.174** gave a 1:1 mixture of secondary alcohols **1.175** and **1.176**, which could be separated by chromatography. No stereocontrol could be obtained with addition to the *cis*-THF fragment. The synthesis was finished by deprotection of the silyl ethers giving muricatetrocin-A (**1.159**). Interestingly, when aldehyde **1.171** was added to the *trans*-THF fragment chelation controlled coupling was observed, giving only the desired diastereoisomer, although in only 34% yield. Deprotection of this gave muricatetrocin-B (**1.160**).



Scheme 1.24 Synthesis of muricatetrocin-A. *Reagents and Conditions:* a) AD-mix β, $MeSO_2NH_2$, H_2O, ^tBuOH, 0 °C; b) DMOP, CSA, CH_2Cl_2; H_2, Pd-C, EtOAc; I_2, PPh_3, imidazole, CH_2Cl_2, 0 °C, e) *t*BuLi, Et_2O, –105 °C; then $MgBr_2 \cdot Et_2O$, –105 °C to –25 °C; then **1.171** –5 °C; f) HF, CH_3CN, CH_2Cl_2; then CSA, MeOH.

To the best of our knowledge this is the first example of a *mono-cis*-THF acetogenin being selectively synthesised. Koert's diorganozinc chemistry is an effective way of selectively preparing either *cis*- or *trans*-2,5-disubstituted THF rings from a common aldehyde intermediate. The method is especially useful in the preparation of *cis*-THF rings that until recently have received little synthetic attention.

1.6.5 Tetsuaki Tanaka *et al.*

1.6.5.1 Synthesis of Mosin-B (1.201)[93]

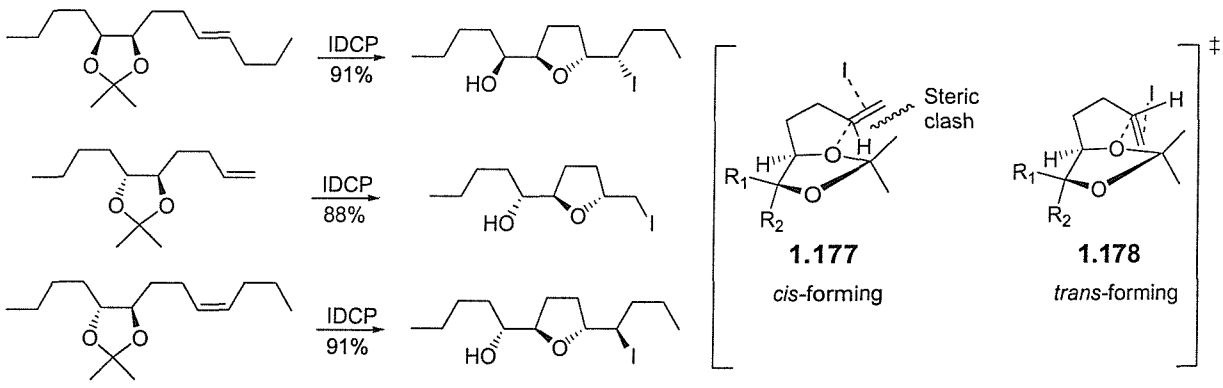
Tanaka and co-workers used an asymmetric desymmetrisation of a σ-symmetric diol to create the stereocentres required for forming the *erythro-trans-threo-mono*-THF ring. The THF formation was accomplished using an iodoetherification of a 5,6-O-isopropylidene alkene, chemistry developed by Mootoo *et al.*[94] It is worth noting that their assignment for

the absolute configuration of mosin-B (**1.201**) is based upon an optical rotation value that poorly matches the literature value.[19]

Mootoo's *trans*-2,5-Disubstituted THF's Formed By Iodoetherification[94,95]

The chemistry to form exclusively *trans*-THF's was developed to compliment their previous work into the formation of *cis*-2,5-disubstituted THF's.[96]

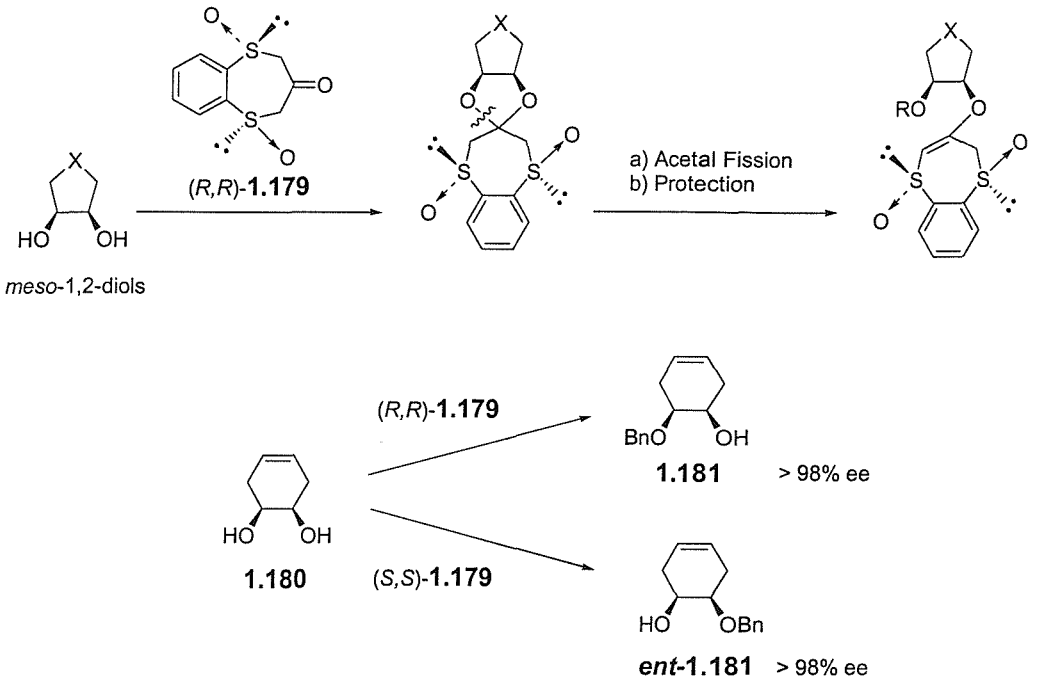
The iodoetherification proceeds with high selectivity towards the *trans*-THF due to steric constraints in the proposed transition states. Formation of a THF-oxonium ion can occur in two orientations (Scheme 1.25). To form the *cis*-THF the required transition state **1.177** would have high steric strain between the aliphatic chain and the acetonide methyl group. Whereas, transition state **1.178** leads to the *trans*-THF adduct, and is sterically much more favourable.[95] Mootoo's iodoetherifications generally take place in wet CH_2Cl_2 or CH_3CN with iodonium dicollidine perchlorate (IDCP) as the promoter.



Scheme 1.25 Iodoetherification of 5,6-O-isopropylidene alkenes.

Asymmetric Desymmetrisation of σ-Symmetric 1,2-Diols

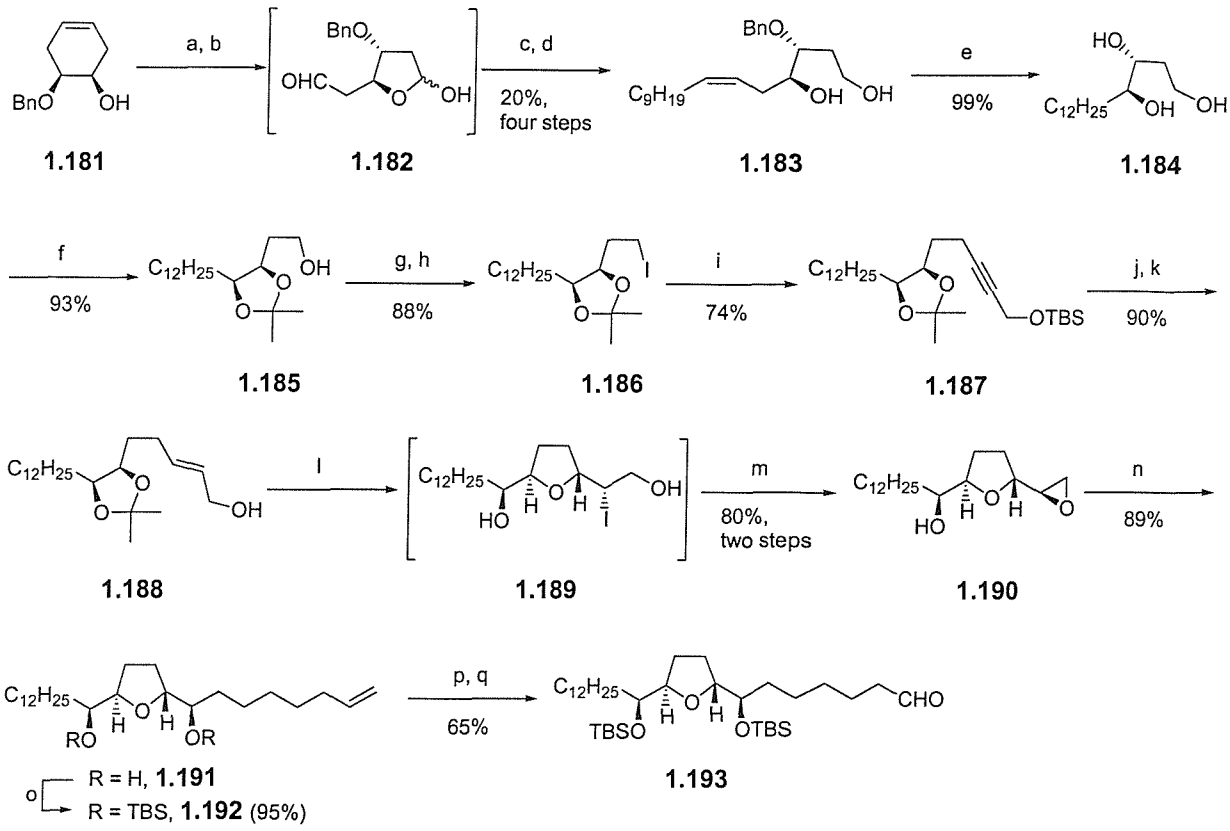
Tanaka and co-workers used asymmetric desymmetrisation methodology developed in their laboratory to produce alcohol **1.181** in high enantiomeric excess by means of a diastereoselective acetal fission using a C_2-symmetric *bis*-sulfoxide **1.179** (Scheme 1.26).[97]



Scheme 1.26 Asymmetric desymmetrisation of σ-symmetric 1,2-diols

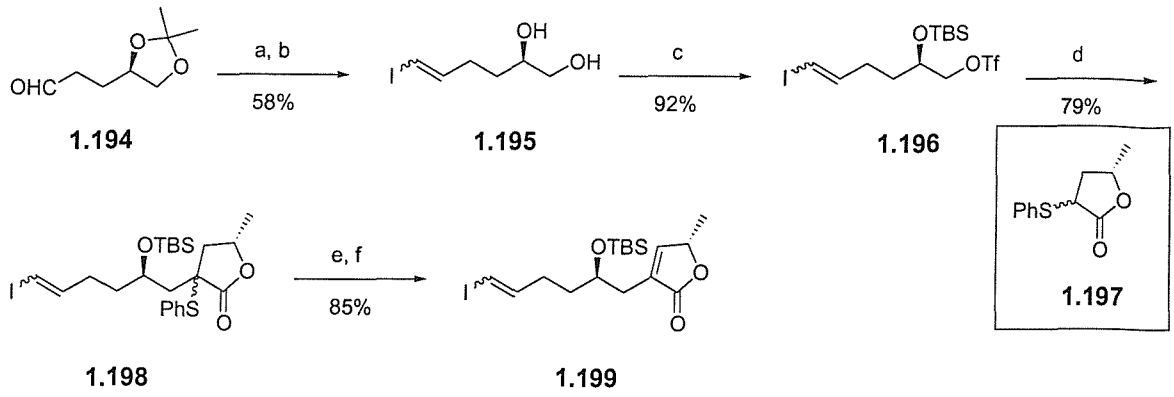
Synthesis of Mosin-B (1.201)

After the desymmetrisation of diol **1.180** had given enantiomerically pure alcohol **1.181**, Tanaka and co-workers began the synthesis of mosin-B's THF fragment (Scheme 1.27). Dihydroxylation followed by oxidative cleavage of the 1,2-diol gave lactol **1.182**. Wittig olefination introduced the left-hand side-chain then subsequent reduction and deprotection gave triol **1.184** in good yield. Protection of the 1,2-diol as the acetonide and conversion of the primary alcohol to the iodide gave **1.186**. Addition of the acetylide followed by TBS deprotection and hydrogenation gave the (*E*)-allyic alcohol **1.188**, which was the required substrate for Mootoo's iodoetherification reaction.[95] Treatment with IDCP gave exclusively *trans*-THF **1.189** in high yield. This potentially unstable intermediate was not isolated but subjected to base furnishing epoxide **1.190** with the desired *erythro-trans-threo*-THF geometry. Epoxide opening with an alkyl Grignard in the presence of copper bromide followed by TBS protection gave the terminal olefin **1.192**. Dihydroxylation followed by oxidative cleavage of the 1,2-diol gave aldehyde **1.193**, which was ready for coupling to the butenolide fragment **1.199**.



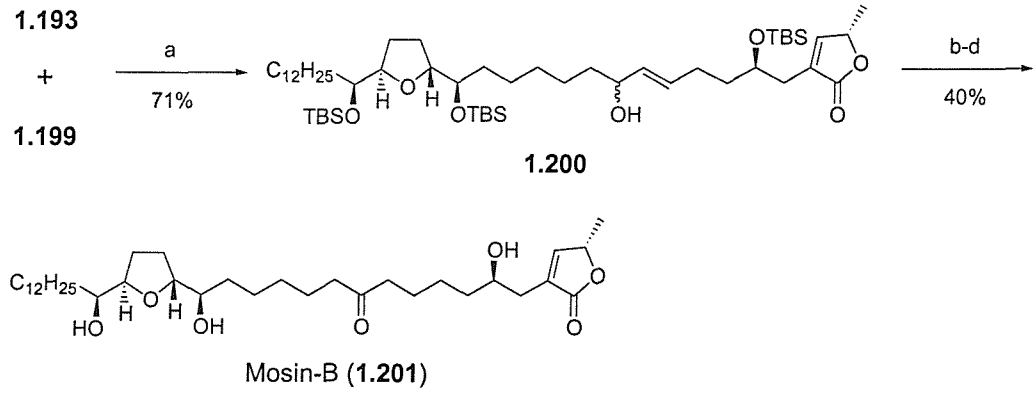
Scheme 1.27 Synthesis of mosin-B's THF fragment. *Reagents and Conditions:* a) OsO_4, NMO, acetone, H_2O; b) $NaIO_4$, acetone, H_2O; c) $Ph_3P(C_{10}H_{21})Br$, KHMDS, THF, –78 °C; d) $NaBH_4$, MeOH; e) H_2, Pd-C, MeOH, f) TsOH, acetone; g) MsCl, Et_3N, CH_2Cl_2; h) NaI, $NaHCO_3$, acetone, reflux; i) 1-*tert*-butyldimethylsilyloxy-2-propyne, *n*BuLi, THF, HMPA, 0 °C; j) TBAF, THF; k) $LiAlH_4$, THF, reflux; l) IDCP, CH_3CN, H_2O; m) K_2CO_3, MeOH; n) 6-bromo-1-hexene, Mg, CuBr, THF, 0 °C; o) TBSOTf, 2,6-lutidine, CH_2Cl_2; p) OsO_4, NMO, THF, acetone, H_2O; q) $NaIO_4$, CH_2Cl_2, acetone, H_2O.

Synthesis of the butenolide fragment **1.199** commenced by subjecting the known aldehyde **1.194** to Takai's olefination[60] followed by deprotection to give diol **1.195** (Scheme 1.28). In a one pot reaction,[98] primary triflation followed by secondary silylation gave vinyl iodide **1.196** in excellent yield. The coupling reaction of triflate **1.196** and γ-lactone **1.197** gave vinyl iodide **1.198** in good yield. Tanaka *et al.* did not specify how **1.197** was prepared; it is likely they used a method such as that of White *et al.*[99] Oxidation to the sulfoxide followed by thermal elimination gave the butenolide fragment **1.199** in good yield.



Scheme 1.28 Synthesis of Tanaka's butenolide fragment. *Reagents and Conditions:* a) $CrCl_2$, CHI_3, THF; b) Dowex 50W, MeOH; c) Tf_2O, 2,6-lutidine, CH_2Cl_2, –50 °C; then TBSOTf, 0 °C; d) **1.197**, KHMDS, THF, 0 °C; then **1.196**; e) MCPBA, CH_2Cl_2 0 °C; f) toluene, reflux.

The coupling of THF-aldehyde **1.193** and butenolide-vinyl iodide **1.199** was carried out using the Nozaki-Hiyama-Kishi reaction,[100] giving exclusively (*E*)-allylic alcohol **1.200** (Scheme 1.29). Oxidation, selective hydrogenation and deprotection completed the synthesis of mosin-B (**1.201**).



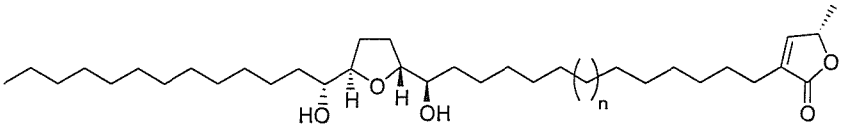
Scheme 1.29 Synthesis of mosin-B (**1.201**). *Reagents and Conditions:* a) $CrCl_2$, $NiCl_2$, DMF, DMS; b) SO_3•Py, DMSO, Et_3N, CH_2Cl_2; c) H_2, $[Rh(PPh_3)_3Cl]$, benzene; d) HF (aq), CH_3CN, THF.

1.6.6 Subhash C. Sinha and Ehud Keinan *et al.*

Sinha and Keinan have published numerous papers on the total synthesis of various *Annonaceous* acetogenins, although they have tended to specialise in *bis*-THF containing acetogenins in recent years.[101-105]

1.6.6.1 Synthesis of *trans*-Solamin (1.202) and Reticulatacin (1.203)[106]

Sinha and Keinan accomplished the stereoselective formation of all four asymmetric THF centres *via* Sharpless dihydroxylation[81] of a 1,5-diene. Subsequent double inversion at C-16 or C-18 meant all the centres (15*R*,16*R*,19*R*,20*R* for **1.202**) were put in place in their correct configuration by the asymmetric *bis*-dihydroxylation. Herein, for the purpose of clarity only the synthesis of *trans*-solamin (**1.202**) will be discussed, due to the almost identical approach and structure of reticulatacin (**1.203**) (Figure 1.7).



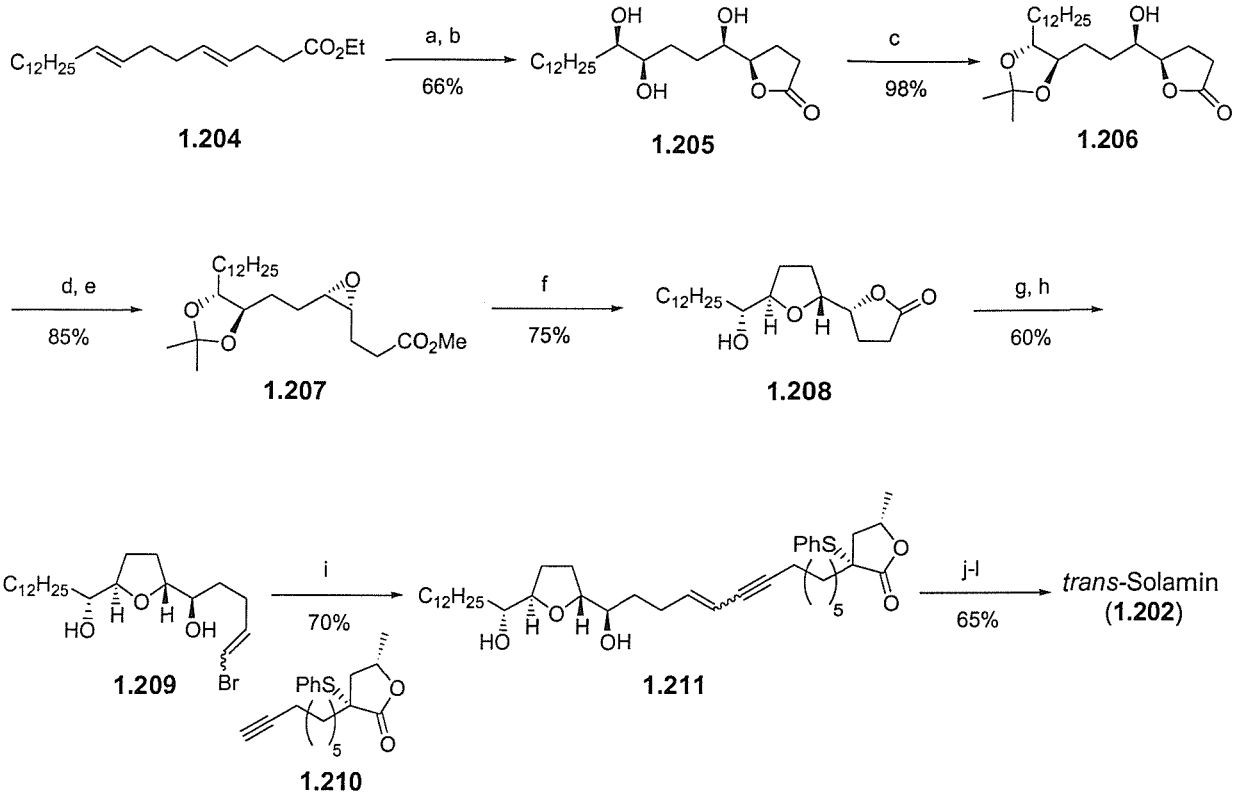
n = 1, *trans*-Solamin (**1.202**)

n = 3, Reticulatacin (**1.203**)

Figure 1.7 Structure and configuration of *trans*-solamin (**1.202**) and reticulatacin (**1.203**)

The synthesis began with the Sharpless *bis*-dihydroxylation[81] of 1,5-diene **1.204** (Scheme 1.30).[106] Subsequent ester hydrolysis then lactonisation gave **1.205** which was recrystallised to enantiomeric purity. The 1,2-diol was protected as the acetonide, then the remaining alcohol was tosylated and treated with base to provide epoxide **1.207** (Nb first inversion at C-16). Lewis acid removal of the acetonide promoted epoxide opening and lactonisation, forming THF **1.208** with the desired *threo-trans-threo* configuration (Nb second inversion at C-16). Reduction to the lactol then Wittig olefination gave vinyl bromide **1.209**, which was ready for palladium coupling. The butenolide fragment **1.210** was prepared following Hoye's procedure.[62] The vinyl bromide and terminal alkyne were joined in a Pd(0)-catalysed cross-coupling reaction, giving olefin **1.211**. Hydrogenation, oxidation of the sulfide to the sulfoxide and thermal elimination gave *trans*-solamin (**1.202**) in good yield.

Reticulatacin (**1.203**) was prepared in the same manner, except for a two carbon extension on the alkyl chain of the butenolide fragment.



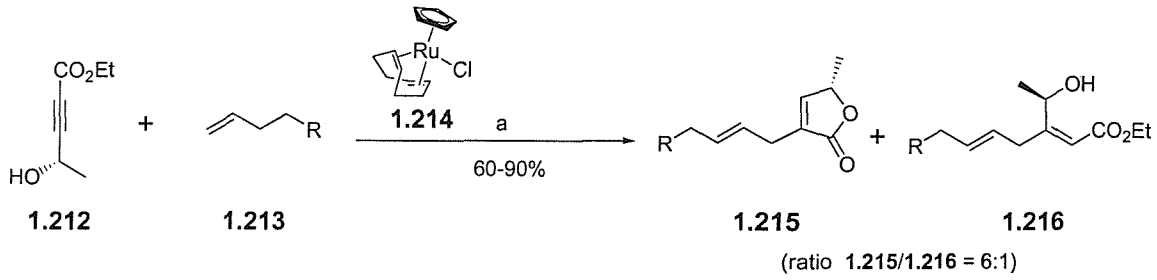
Scheme 1.30 Synthesis of *trans*-solamin (**1.202**) *via* Sharpless dihydroxylation. *Reagents and Conditions:* a) AD-mix β, ^{t}BuOH, H_2O, $CH_3SO_2NH_2$, 0 °C; b) NaOH, H_2O; then TsOH, CH_2Cl_2; c) DMOP, acetone, TsOH; d) TsCl, DMAP, Et_3N, CH_2Cl_2; e) K_2CO_3, MeOH; f) BF_3•Et_2O, CH_2Cl_2; g) DIBAL-H, THF, –50 °C; h) $BrCH_2PPh_3Br$, ^{t}BuOK, THF; i) **1.210**, $Pd(PPh_3)_4$, CuI, Et_3N; j) H_2, $[Rh(PPh_3)_3Cl]$, benzene; k) MCPBA, CH_2Cl_2; l) toluene, reflux.

1.6.7 Barry M. Trost *et al.*

Trost and co-workers have synthesised a number of acetogenins *via* novel methodology. They published elegant work on the synthesis of *bis*-THF acetogenins: (+)-parviflorin **1.16** and (+)-squamocin-K.[107] They also developed an extremely efficient and chemoselective method of preparing the butenolide moiety present in most acetogenins *via* a ruthenium-catalysed Alder-ene reaction.[108]

1.6.7.1 Trost's Butenolide Methodology

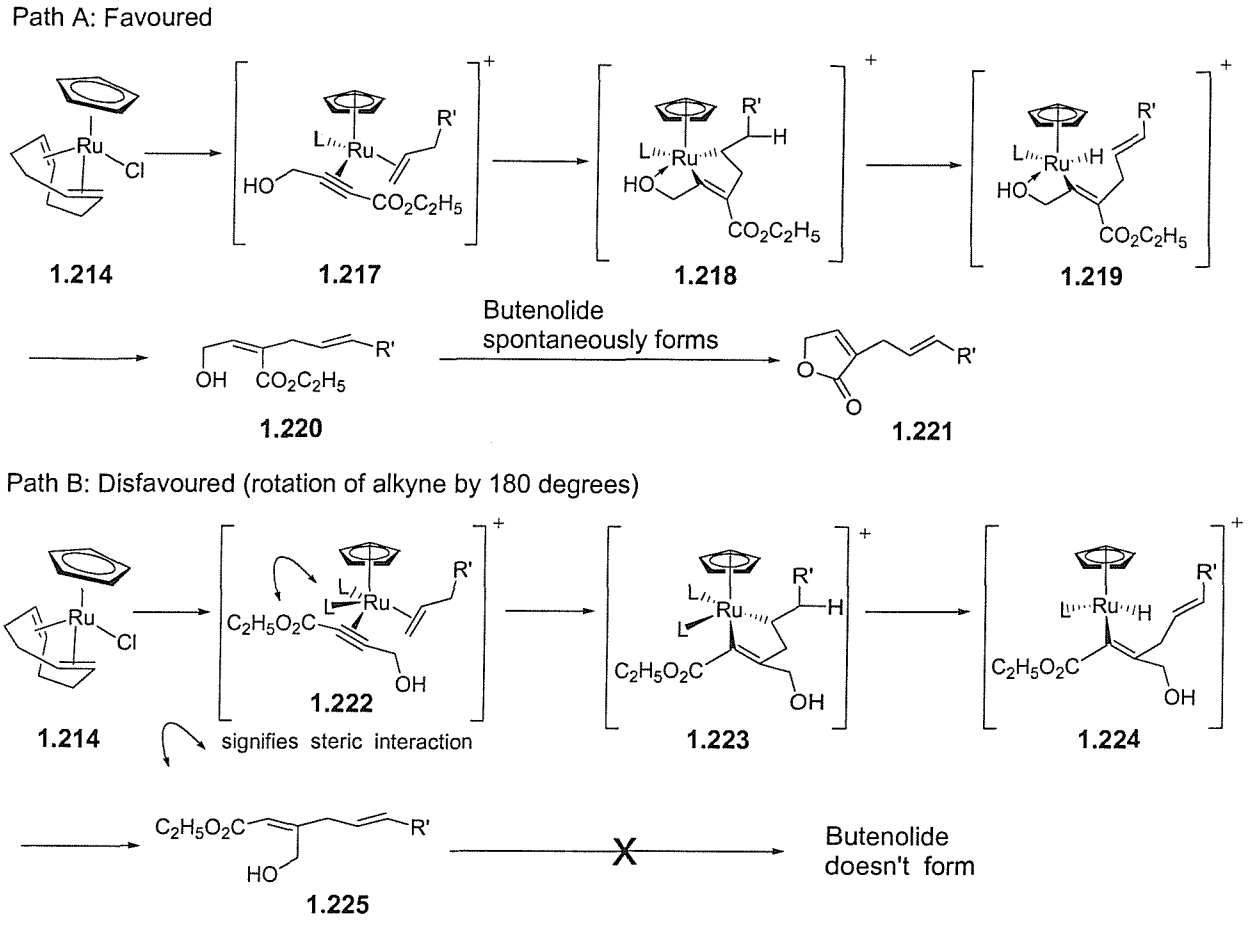
Trost wanted a method to prepare the butenolide moiety from an easily accessible functional group *via* a reaction that showed high chemoselectivity. Most groups synthesising acetogenins tended to pre-form the butenolide or γ-lactone fragment and then couple this to their central fragment. The ideal solution was to have a single reaction that formed the butenolide. Their solution was based on a ruthenium-catalysed Alder-ene reaction between a terminal olefin and a propargylic alcohol (Scheme 1.31).[108]



Scheme 1.31 Butenolide formation *via* Trost's ruthenium-catalysed Alder-ene reaction. *Reagents and Conditions:* a) [CpRu(COD)Cl] (**1.214**) 5 mol%, MeOH, reflux.

Trost *et al.* demonstrated that a variety of functional groups could be present in the terminal olefin substrate and did not affect the reaction. Importantly, alcohols which are present in nearly all acetogenins, had no effect on the reaction, even sulfide and sulfone groups can be present (though the rate of reaction does decrease). Hence, Trost had accomplished his goal; to develop a highly chemoselective butenolide forming reaction.

The mechanism proposed by Trost allows for the observed formation of cyclised and uncyclised products (Scheme 1.32). The two paths, A and B, are distinguished by the initial binding of the alkyne to the ruthenium complex **1.214**. As shown, the alkyne can bind in two geometries (**1.217** and **1.222**); path A is favoured and leads to butenolide formation, path B is disfavoured due to increased steric clash in the transition state and leads to uncyclised diene. Trost showed that the explanation for why one isomer cyclises and the other doesn't is due to an increase in energy required for geometry **1.225** to lactonise.[108]

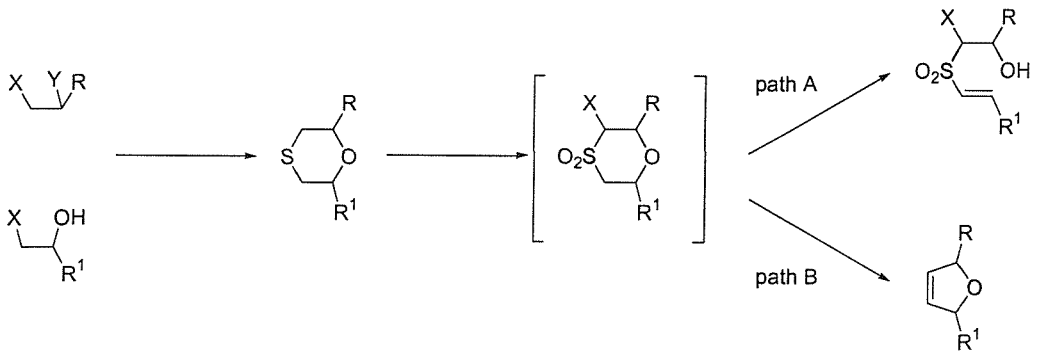


Scheme 1.32 Mechanism of Trost's ruthenium-catalysed Alder-ene reaction

1.6.7.2 Synthesis of *trans*-Solamin (1.202)[109]

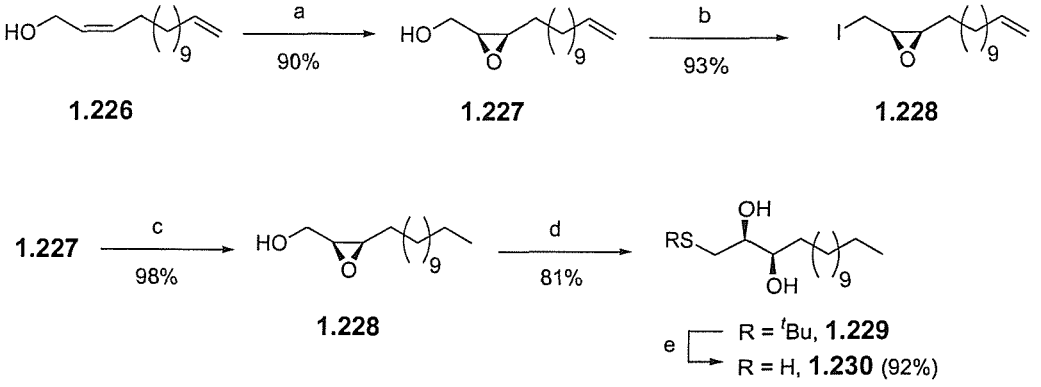
One year after Sinha and Keinan had published their route to *trans*-solamin (**1.202**) Trost and co-workers published their strategy based upon two novel approaches. Firstly, coupling of two nearly identical fragments *via* a Ramberg-Backlund olefination[110] to give a heterocycle and secondly, application of the ruthenium-catalysed Alder-ene reaction.[108]

For their synthesis to be successful Trost required γ-elimination (path B) to occur in preference over β-elimination (path A) after the fragments had been joined together (Scheme 1.33).



Scheme 1.33 Ramberg-Backlund olefination to give a heterocycle

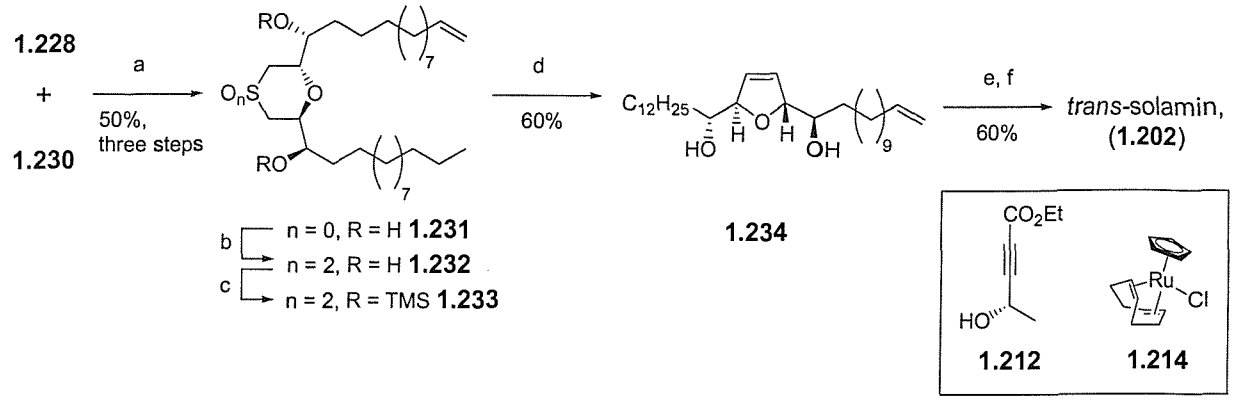
Allylic alcohol **1.226** was prepared according to the literature.[109,111] Sharpless asymmetric epoxidation[112] gave epoxide **1.227** in only 82% ee, however recrystallisation gave the epoxide > 99% ee (Scheme 1.34). At this intermediate (**1.227**) the synthesis split in two. Conversion of the primary alcohol to the iodide gave **1.228** and completed one half of the fragment. Hydrogenation followed by thiolate substitution[113] of the Payne rearranged[114] hydroxy epoxide gave diol **1.229**, which was converted to thiol **1.230** to complete the other half of the fragment.



Scheme 1.34 Synthesis of two similar fragments for Ramberg-Backlund olefination. *Reagents and Conditions:* a) L-(+)-DET, $Ti(O^iPr)_4$, ^{t}BuOH, 4-Å molecular sieves, CH_2Cl_2, –20 °C; b) I_2, PPh_3, imidazole, THF, 0 °C; c) H_2, Pd-C, hexane, EtOAc; d) ^{t}BuSH, NaOH, ^{t}BuOH, H_2O; e) $Hg(OAc)_2$, $PhOCH_3$, CF_3CO_2H, 0 °C.

Coupling of the two halves (**1.228** and **1.230**) to form oxathiane **1.231** was achieved under basic conditions (Scheme 1.35). Attempts to chlorinate were met with considerable difficulty, eventually an *in situ* chlorination-rearrangement on the *bis*-TMS protected sulfone **1.233** gave dihydrofuran **1.234** after deprotection. The ruthenium-catalysed Alder-

ene reaction with propargylic alcohol **1.212** was carried out in the presence of the disubstituted olefin, forming the butenolide in good yield. Selective hydrogenation of the aliphatic olefin and the furan olefin gave *trans*-solamin **1.202**.

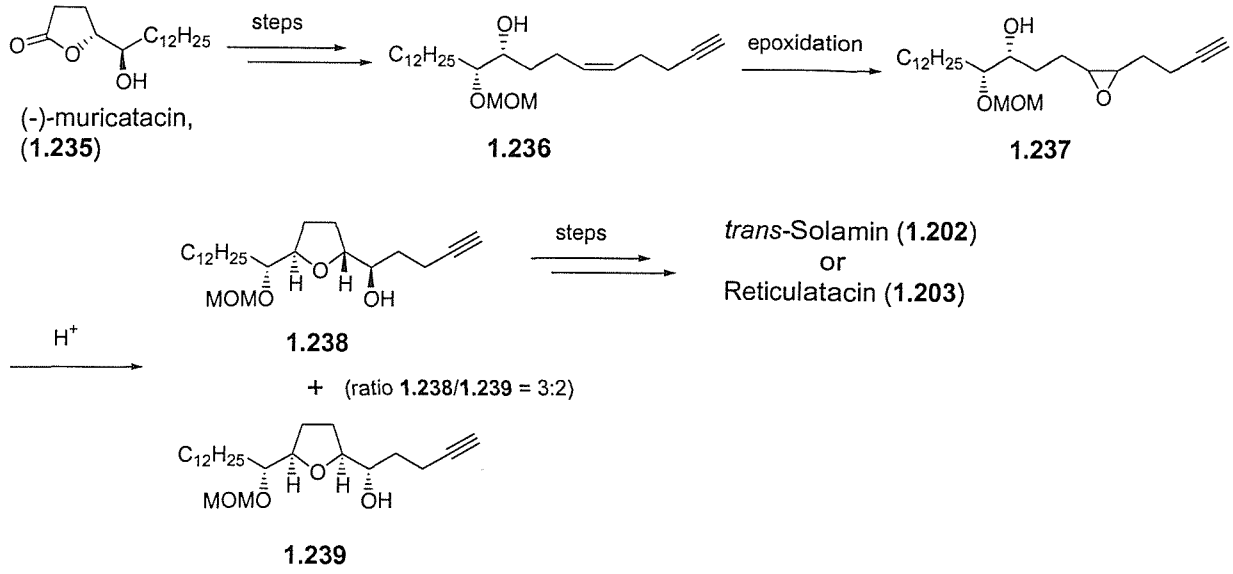


Scheme 1.35 Synthesis of *trans*-solamin **1.202**. *Reagents and Conditions:* a) (i) Cs_2CO_3, DMF; (ii) KOH, H_2O, ^{t}BuOH; b) MCPBA, benzene, hexane; c) TMSCl, Et_3N, CH_2Cl_2; d) (i) ^{t}BuOK, ^{t}BuOH, CCl_4; (ii) TsOH, H_2O, EtOH; e) [CpRu(COD)Cl] (**1.214**) 5 mol%, **1.212**, MeOH, reflux; f) H_2, [$Rh(PPh_3)_3Cl$], benzene, EtOH.

1.6.8 Hidefumi Makabe *et al.*

1.6.8.1 Synthesis of *trans*-Solamin (1.202) and Reticulatacin (1.203)[84]

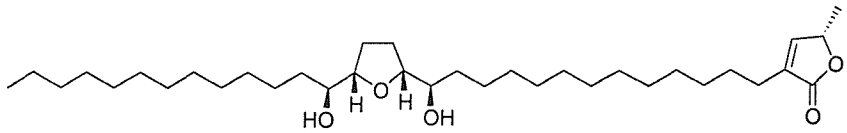
In the same year as Trost, Makabe and co-workers also synthesised *trans*-solamin (**1.202**) and reticulatacin (**1.203**). They utilised the fact that the left-hand stereocentres in the two acetogenins were present in (-)-muricatatacin **1.235**, an acetogenin derivative they had previously synthesised.[115] Conversion to the olefin **1.236** then epoxidation gave the racemic substrate **1.237** (Scheme 1.36). Their strategy was to then form the THF fragment by an acid-catalysed epoxide opening. This gave them a 3:2 mixture of *trans*- to *cis*-THF's (**1.238** and **1.239**) as they could not form the epoxide asymmetrically. The synthesis was completed by palladium cross-coupling with the pre-formed butenolide fragments, giving *trans*-solamin (**1.202**) and reticulatacin (**1.203**).



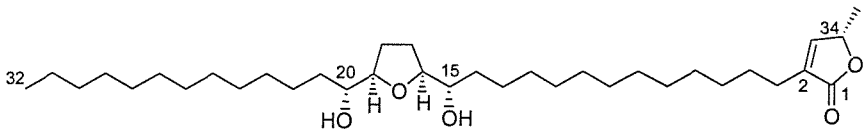
Scheme 1.36 Makabe's synthesis of *trans*-solamin (**1.202**) and reticulatacin (**1.203**)

1.6.8.2 Synthesis of *cis*-Solamin (1.240)[116]

The first total synthesis of *cis*-solamin (**1.240**) was published in 2002 by Makabe *et al.*[116] Previously, the absolute configuration of the THF-diol core had been unknown. Spectroscopic studies on the isolated natural product[117] could not distinguish between the possible relative configurations of the THF core, due to the length and flexibility of the alkyl chain linking the terminal butenolide. They could only conclude that the configuration of the THF region was *threo-cis-threo*. Therefore Makabe *et al.* decided to synthesise both diastereoisomers (**1.240** and **1.241**) and compare the spectroscopic data of the two with that of natural *cis*-solamin (Figure 1.8). Herein, for the purpose of clarity the structure of *cis*-solamin will be regarded as **1.240**, in accordance with the optical rotation findings of Makabe *et al.*[116]



cis-Solamin (**1.240**)

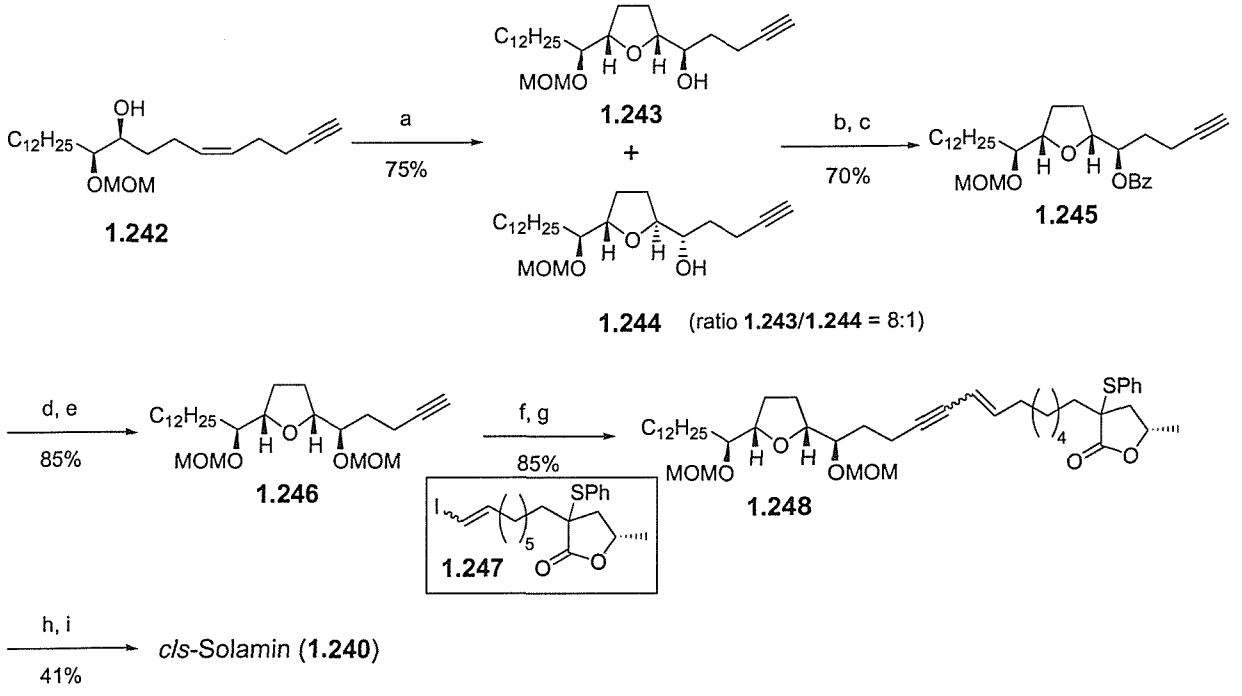


15,16,19,20-tetra *ent-cis*-Solamin (**1.241**)

Figure 1.8 The two possible structures of *cis*-solamin

Makabe and co-workers used exactly the same strategy as in their previous synthesis of *trans*-solamin (**1.202**), except that they employed a diastereoselective *t*-butyl hydroperoxide (TBHP)-$VO(acac)_2$ epoxidation.[118,119]

To synthesise both possible *cis*-solamin structures Makabe *et al.* synthesised homoallylic alcohol **1.242** and its enantiomer **1.236** (used previously in the synthesis of *trans*-solamin (**1.202**)) by their published methods.[115] Herein, for the purpose of clarity only the synthesis of *cis*-solamin **1.240** from homoallylic alcohol **1.242** will be discussed (Scheme 1.37). The diastereoselective TBHP-$VO(acac)_2$ epoxidation and subsequent THF formation was investigated. Conditions were achieved whereby the ratio of *cis*- to *trans*-THF (**1.243/1.244**) was 8:1 respectively. Separation of the diastereoisomers proved troublesome, requiring protection of the free alcohol as the benzoate ester. The diastereomers could then be separated by column chromatography. Hydrolysis of benzoate ester **1.245** and subsequent MOM protection gave optically pure alkyne **1.246**. Sonogashira cross coupling[62,63] to the pre-formed butenolide fragment **1.247**[84] gave olefin **1.248**. Hydrogenation followed by oxidation of the sulfide to the sulfoxide and thermal elimination gave *cis*-solamin (**1.240**) in good yield. 15,16,19,20-tetra *ent-cis*-solamin (**1.241**) was completed in exactly the same manner from homoallylic alcohol **1.236**.



Scheme 1.37 Makabe's synthesis of *cis*-solamin **1.240**. *Reagents and Conditions:* a) ^{t}BuOOH-$VO(acac)_2$, 4-Å molecular sieves, CH_2Cl_2; b) BzCl, Py; c) separation by

chromatography; d) NaOH, MeOH; e) MOMCl, (^{i}Pr)$_2$NEt; f) **1.247**, [Pd(PPh$_3$)$_2$Cl$_2$], CuI, Et$_3$N; g) H$_2$, [Rh(PPh$_3$)$_3$Cl]; h) MCPBA, toluene, reflux; i) BF$_3$•Et$_2$O, DMS.

Comparison of the spectroscopic data (IR, MS, ^{1}H NMR and ^{13}C NMR) for *cis*-solamin **1.240** and its diastereoisomer **1.241** showed that they were indistinguishable. However, Makabe reported that the optical rotations were substantially different: **1.240** ($[\alpha]^{21}_{D}$ = +26, MeOH, *c* 0.45) and **1.241** ($[\alpha]^{21}_{D}$ +42, MeOH, *c* 0.50). He therefore tentatively assigned structure **1.240** as corresponding to natural *cis*-solamin ($[\alpha]^{25}_{D}$ = +22, MeOH, *c* 0.55).[117]

1.7 Conclusions

The *Annonaceous* acetogenins show a remarkable range of biological activities, and belong to one of the most rapidly growing classes of natural products. Their biological activity has spurred a remarkable interest in their synthesis, especially towards the 2,5-disubstituted THF core.

These approaches have varied extensively and can use a combination of the chiral pool, asymmetric epoxidation, asymmetric dihydroxylation, Williamson cyclisation, iodoetherification and epoxide opening to form the THF ring.

However, none of the approaches have utilised a direct approach to the 2,5-disubstituted THF-diol core *via* oxidation of a 1,5-diene by a transition metal oxo species.

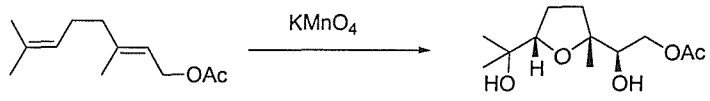
Chapter 2

Oxidative Cyclisation of 1,5-Dienes by Transition Metal Oxidants

The following chapter summarises the synthesis of 2,5-disubstitued tetrahydrofuran diols from 1,5-dienes by a variety of transition metal oxo species. The main focus of the chapter will be on permanganate promoted oxidative cyclisations.

2.1 Aqueous Permanganate Promoted Oxidative Cyclisation of 1,5-Dienes

The permanganate oxidation of 1,5-dienes under neutral conditions was reported by Kötz and Steche in 1924;[120] they reported a product which they could not identify. It was not until 1965 that Klein and Rojahn identified the product as a *cis*-2,5-disubstituted THF-diol.[121] They established the relative stereochemistry by solving the crystal structure of the product **2.2** obtained from the oxidation of geranyl acetate (**2.1**). They found that all three oxygens had been inserted from the same face, hence giving the *cis*-THF-diol **2.2** (Scheme 2.1).

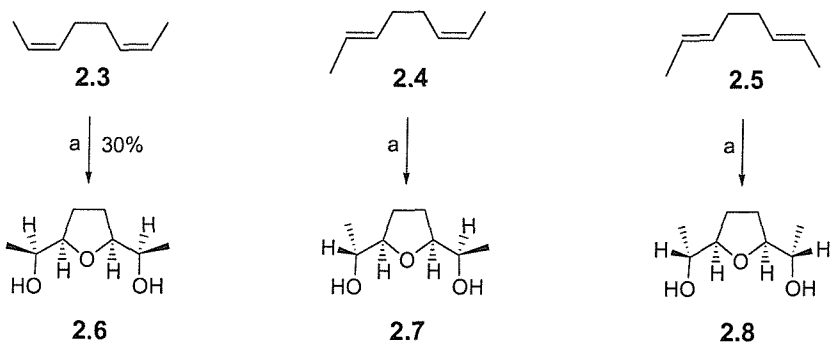


2.1 **2.2**

Scheme 2.1 Oxidative cyclisation of geranyl acetate by permanganate

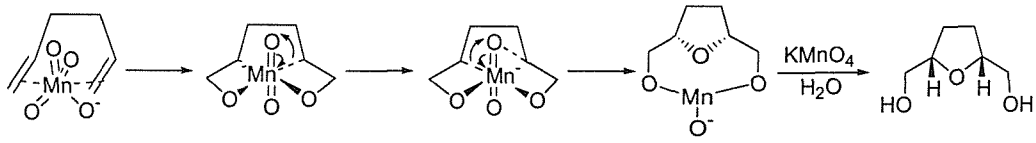
It was not until 1979 that further work on this reaction was carried out by the teams of Walba and Baldwin. They recognised the potential power of the reaction; inserting up to four new stereocentres with control of relative stereochemistry in a single step.

Walba carried out a series of oxidations on isomeric dienes **2.3-2.5**, concluding that the stereochemistry of the hydroxyl group was determined by the geometry of the alkene (Scheme 2.2).[122] They also found that the reaction favoured the *cis*-THF over the *trans*-THF by a ratio of 97:3 respectively.



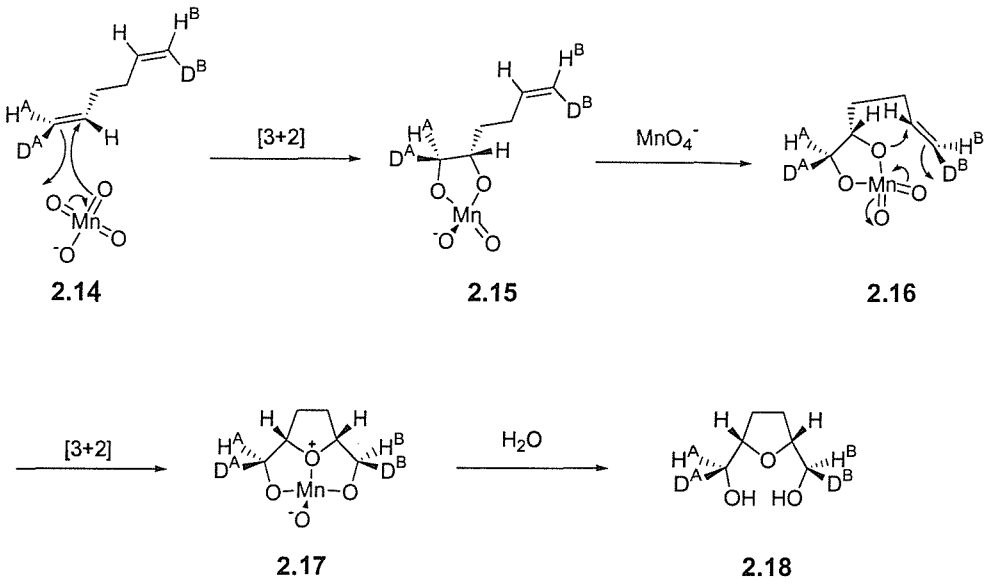
Scheme 2.2 Relative stereochemistry determined by alkene geometry. *Reagents and Conditions:* a) $KMnO_4$, H_2O, acetone, pH 7.5, CO_2 ebullition.

Walba went on to propose a possible mechanism,[122] bringing together ideas put forward by Sharpless for the oxidation of alkenes by transition metal oxo species.[123] The initial step involves the formation of a *bis*-π-complex **2.9** with the permanganate ion. Then two [2+2] cycloadditions between the metal-oxo and alkene affords octahedral manganese(VII) intermediate **2.10**. Double alkyl migration with retention onto oxygen with reductive elimination affords manganese(III) complex **2.12**. Subsequent oxidation and hydrolysis affords *cis*-THF-diol **2.13** and MnO_2.



Scheme 2.3 Mechanism proposed by Walba

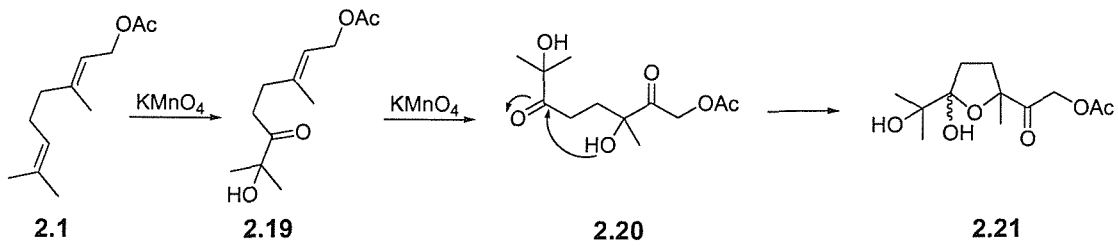
In the same year Baldwin published his findings on the oxidative cyclisation of deuterated dienes of known geometry.[124] He proposed that the first step was a [3+2] cycloaddition of permanganate to the double bond, forming cyclic manganese(V) ester **2.15** (Scheme 2.4). This unreactive species undergoes oxidation by permanganate to the reactive manganese(VI) species **2.16**. A further stereospecific [3+2] cycloaddition to the remaining double bond affords manganese(IV) species **2.17**. Hydrolysis gives the THF-diol **2.18** and MnO_2. This mechanism was supported to a degree by Wolfe and Ingold[125] and by Lee *et al.* as they showed evidence for the formation of manganese(V) esters in oxidations on isolated olefins.[126]



Scheme 2.4 Mechanism proposed by Baldwin

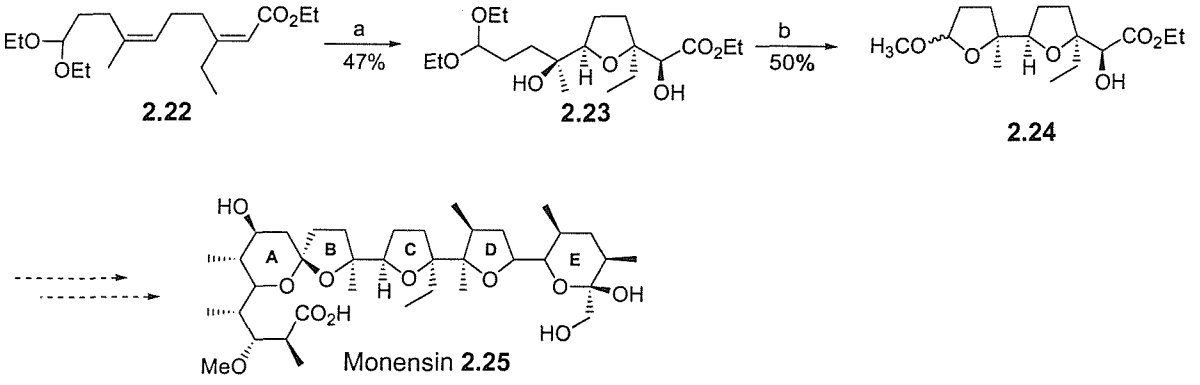
However, Wolfe and Ingold showed that when the oxidation was carried out in ^{18}O labelled water, there was incorporation of ^{18}O into the THF-diol.[125] They concluded that this indicated that a manganese species with a coordination number greater than four, incorporating water from the solvent, was involved in the mechanism. As neither mechanism could account for this, they decided to defer precise judgement on the nature of this intermediate and the exact mechanism remains unresolved.

The yield for the oxidative cyclisation, at this early stage, was often low. This was due to a number of side reactions that were occurring; the manganese(V) species **2.15** can undergo hydrolysis before the second cycloaddition. In the case of geranyl acetate (**2.1**) this results in the formation of α-hydroxy ketone **2.19**, which has been isolated. Further oxidation of the remaining double bond followed by hydrolysis leads to *bis*-α-hydroxy ketone **2.20**, which cyclises to give lactol **2.21** (Scheme 2.5).



Scheme 2.5 By-products of the oxidative cyclisation

Walba continued his work on the oxidative cyclisation, identifying some key intermediates in natural product synthesis.[127,128] He went on to synthesis the B / C ring fragment of monensin (**2.25**), putting the four stereocentres in place with correct relative stereochemistry in one step *via* the permanganate mediated oxidative cyclisation (Scheme 2.6). The oxidation of diene **2.22** was achieved in a yield of just 20%, however considering the complexity of incorporating four new stereocentres with control of relative stereochemistry it was considered a success. Treatment of **2.23** with trimethyl orthoformate and acid closed the B ring, giving **2.24** their fragment of monensin (**2.25**).

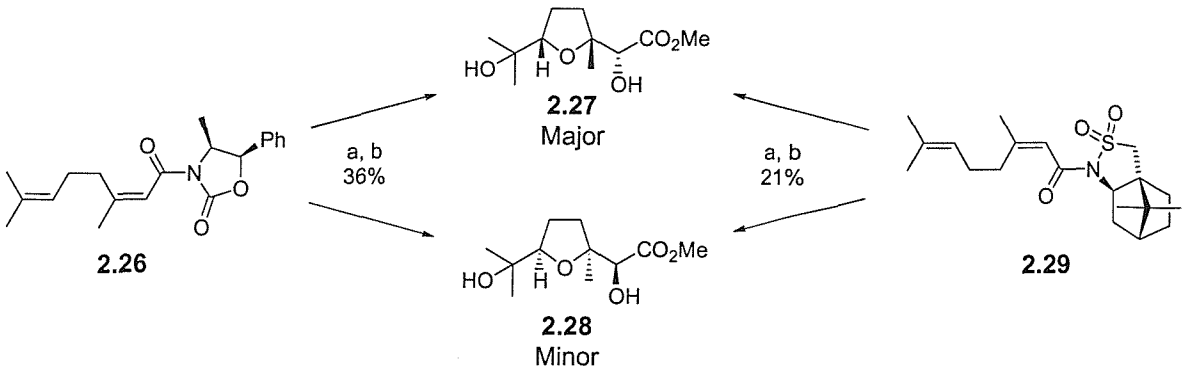


Scheme 2.6 Walba's Synthetic approach to monensin **2.25**. *Reagents and Conditions:* a) $KMnO_4$, H_2O, acetone, pH 7.5, CO_2 ebullition; b) $CH_3C(OMe)_3$, TsOH, benzene.

The oxidative cyclisation was already showing that it was capable of becoming an extremely powerful reaction, however the control of absolute stereochemistry would be a key requirement in achieving this.

Walba developed an asymmetric oxidative cyclisation,[129] by exploiting the fact that alkenes conjugated to a carbonyl group were known to be more reactive to permanganate oxidation than aliphatic substrates.[130] Hence, attachment of a chiral auxiliary through amide linkage was the perfect solution. Walba used Oppolzer's camphorsultam[131-136] and Evans oxazolinone[137-144] to induce asymmetry, both of which are well documented chiral auxiliaries. Use of the oxazolinone gave only 3:1 selectivity in the oxidative cyclisation of diene **2.26** (Scheme 2.7). This resulted from face selective addition of permanganate to the least hindered (*Re*) face of the conjugated double bond. The low selectively can be explained by the observation that Lewis acid chelation is required to give higher selectivity.[145] However, when the diene sultam **2.29** was cyclised a much higher degree of selectivity was achieved, in excess of 9:1 after transesterification (discussed Section 5.3).

This approach was also used by Kocienski and co-workers to provide the THF fragment in their elegant approach to the synthesis of salinomycin.[146]

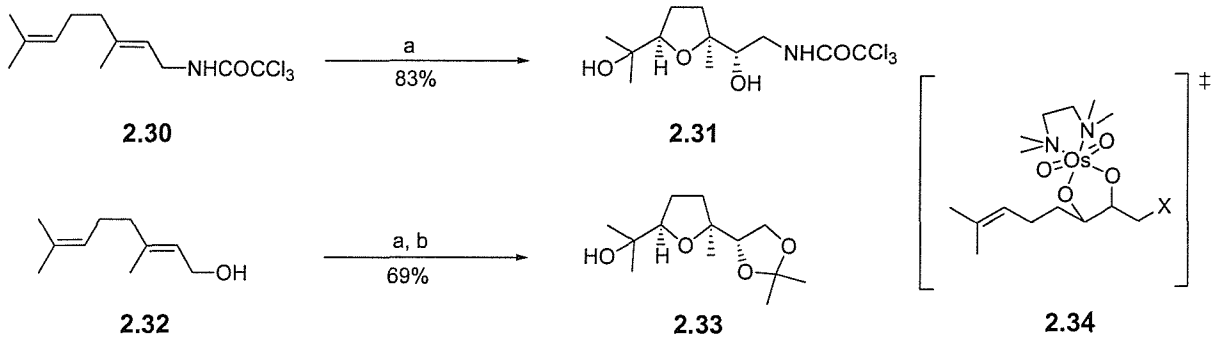


Scheme 2.7 Walba's permanganate promoted asymmetric oxidative cyclisation. *Reagents and Conditions:* a) $KMnO_4$, H_2O, acetone, pH 7.5, CO_2 ebullition, –30 °C; b) CH_3OMgBr.

2.2 Osmium Tetroxide Catalysed Oxidation of 1,5-Dienes

Piccialli and co-workers showed that treatment of geranyl acetate (**2.1**) with catalytic osmium tetroxide with sodium periodate as a co-oxidant gave exclusively *cis*-THF-diol **2.2** in a 55% yield (as for permanganate, Scheme 2.1).[147]

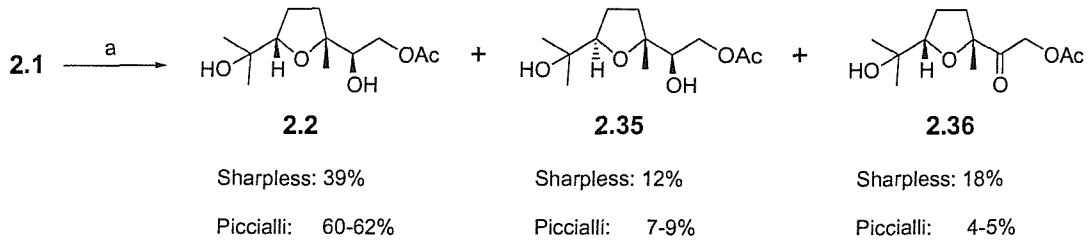
Donohoe and co-workers used a hydrogen bond acceptor complex of OsO_4 / TMEDA in the stereoselective formation of *cis*-THF-diols in high yield.[148] Thus, amido-diene **2.30** and hydroxy-diene **2.32** (both have a hydrogen bond donor adjacent to one alkene) were cyclised to the corresponding *cis*-THF-diols **2.31** and **2.32** respectively (Scheme 2.8). The initial step in the oxidative cyclisation was the formation of an osmate ester **2.34**, in accordance with the accepted mechanism for permanganate (Scheme 2.4).



Scheme 2.8 Osmium tetroxide / TMEDA oxidative cyclisation. *Reagents and Conditions:* a) OsO_4, TMEDA, CH_2Cl_2, –78 °C; then HCl, MeOH; b) $(MeO)_2CMe_2$, TFA.

2.3 Ruthenium Tetroxide Catalysed Oxidation of 1,5-Dienes

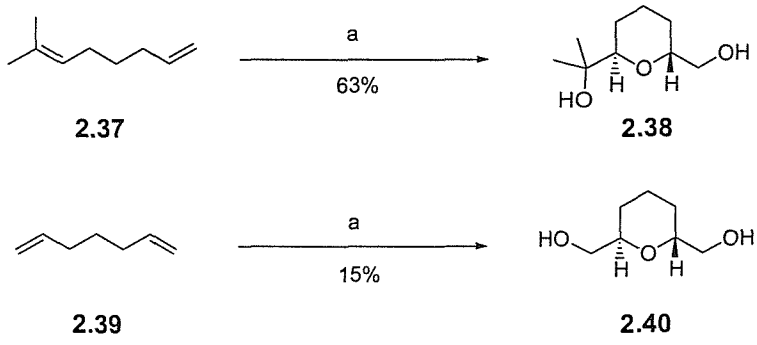
Whilst attempting to improve catalytic ruthenium tetroxide oxidations, Sharpless *et al.* found that their conditions cyclised geranyl acetate **2.1** to the corresponding THF-diol in 51% yield.[149] However, the control of the THF geometry was poor (3:1, *cis/trans*), and there was also a reasonable amount of *cis*-2-keto derivative **2.36** isolated. Later, Piccialli *et al.* greatly improved the stereoselectivity and yield using their modified conditions (Scheme 2.9).[150]



Scheme 2.9 Ruthenium tetroxide oxidative cyclisation. a) Sharpless: 2.2 mol% $RuCl_3{\bullet}(H_2O)_n$, 4.1 eq $NaIO_4$, CCl_4, CH_3CN, H_2O; Piccialli: 4% $RuO_2{\bullet}2H_2O$, 4 eq $NaIO_4$, EtOAc, CH_3CN, H_2O, 0 °C.

2.4 Ruthenium Tetroxide Catalysed Oxidation of 1,6-Dienes

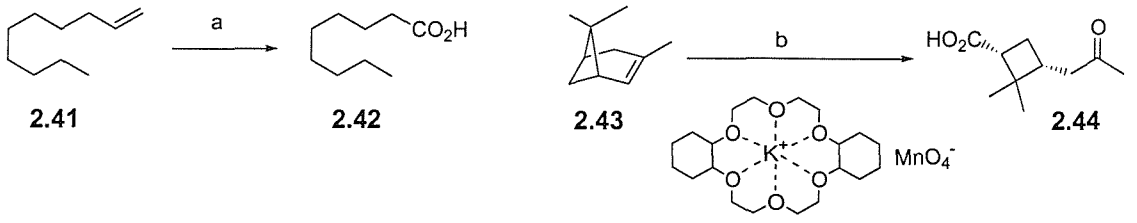
Piccialli used the Sharpless ruthenium oxidation conditions to stereoselectively cyclise two 1,6-dienes to their corresponding 2,6-disubstituted *trans*-THP-diols (Scheme 2.10).[151] To the best of our knowledge this is the only example of an oxidative cyclisation of a 1,6-diene by a transition metal oxo species. There are however examples of 6-hydroxy alkenes being oxidatively cyclised by acyl perrhenate to the corresponding *trans*-THP-diols.[152]



Scheme 2.10 Ruthenium tetroxide oxidative cyclisation of 1,6-dienes. *Reagents and Conditions:* a) 5 mol% $RuCl_3{\bullet}(H_2O)_n$, 4 eq $NaIO_4$, CCl_4, CH_3CN, H_2O, 0 °C.

2.5 Permanganate Phase-Transfer Oxidation of Olefins

Until 1971 all permanganate oxidations were carried out in water, with the addition of a miscible organic solvent to aid the solubility of the organic substrate. For non-polar substrates the oxidation often did not proceed well. In 1971, Starks used a biphasic mixture of water and benzene with tetrabutylammonium bromide as the phase-transfer catalyst to oxidatively cleave lipophilic substrate **2.41** to the carboxylic acid (Scheme 2.11).[153] The following year Sam and Simmons published the use of crown ethers as phase-transfer catalysts to affect the oxidative cleavage of alkenes.[154]



2.41 **2.42** **2.43** **2.44**

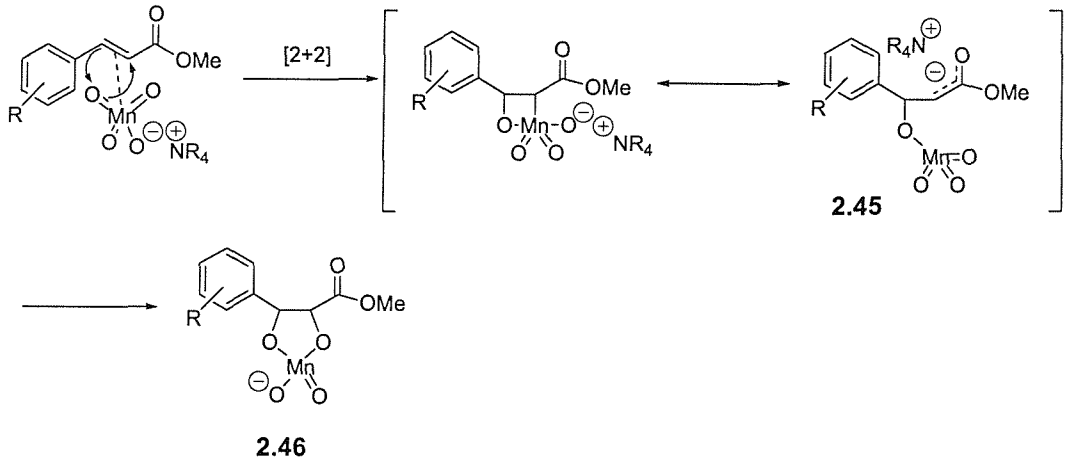
Scheme 2.11 Early phase-transfer catalysed permanganate oxidative cleavages. *Reagents and Conditions:* a) $KMnO_4$, $Bu_4N^+Br^-$, benzene, H_2O; b) $KMnO_4$, 18-crown ether, benzene, H_2O.

Phase-transfer oxidations with permanganate can be carried out in two ways: aqueous permanganate (liquid-liquid phase-transfer catalysis) or solid permanganate (solid-liquid phase-transfer catalysis). The factors effecting both of these methods are similar; the ability of the phase-transfer catalyst to carry the permanganate ion into the organic phase, and the extent to which they will exist as an ion pair once there.[155] The degree to which permanganate will be carried into the organic phase will depend on both the polarity of the solvent and phase-transfer catalyst, and the catalysts structure.

Lee *et al.* investigated the permanganate mediated phase-transfer oxidations of alkenes.[156-158] Using methyl cinamates as a model,[156] the rate of reaction was investigated by substituting the phenyl ring with either electron withdrawing or donating groups. They went on to study a range of alkyl ammonium phase-transfer catalysts, varying the chain lengths. They found that electron withdrawing groups on the aromatic ring increased the rate of reaction and concluded that the mechanism proceeded through an electron rich transition state (Scheme

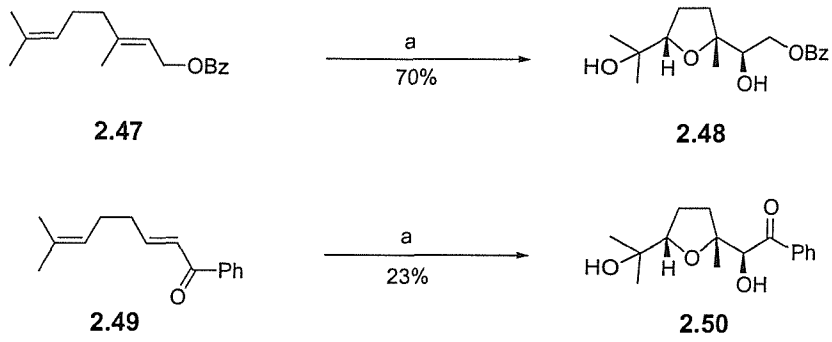
2.12). They also found that for the symmetrical tetraalkylammonium ions the longer the four alkyl chains became the slower the rate of reaction. However, the rate increased dramatically if one of the alkyl chains was replaced with a methyl group (similar to the structure of adogen 464). Lee and co-workers concluded that the presence of the smaller methyl group on the ammonium ion allowed the permanganate to get closer, thus forming a tighter ion pair, which resulted in an increased rate of reaction.

Lee proposed a mechanism which involves a [2+2] cycloaddition between the olefin and permanganate (Scheme 2.12). Subsequent rearrangement gave an enolate-like structure **2.45**, which is stabilised due to interaction with the ammonium ion. This electron rich intermediate is further stabilised by the presence of electron withdrawing groups on the phenyl ring. Further rearrangement gives the cyclic manganese(V) ester **2.46**.



Scheme 2.12 Lee's proposed mechanism for phase-transfer oxidations

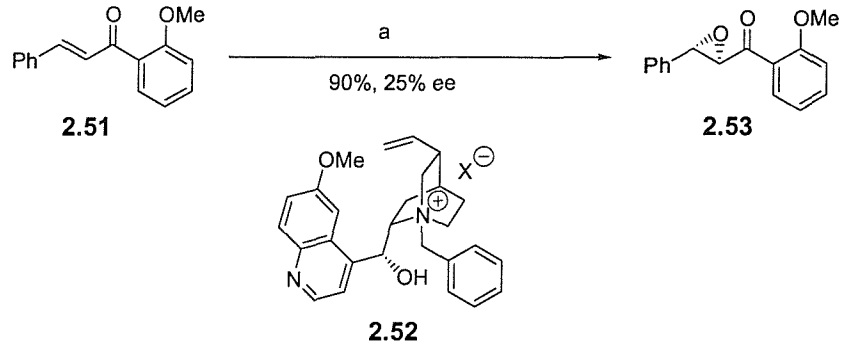
The first permanganate mediated phase-transfer catalysed oxidative cyclisations of 1,5-dienes were carried out in our group using a liquid-liquid system.[159,160] Dienes **2.47** and **2.49** were oxidatively cyclised to the corresponding THF's **2.48** and **2.50** respectively, with varying success (Scheme 2.13). Thus, the oxidative cyclisation of much more lipophilic substrates was allowed. It also enabled the development of an asymmetric oxidative cyclisation using a chiral ammonium salt.



Scheme 2.13 Permanganate mediated phase-transfer catalysed oxidative cyclisations. *Reagents and Conditions:* a) 0.4 M $KMnO_4$ (2 eq), AcOH (4 eq), adogen 464 (0.4 eq), Et_2O.

2.6 Chiral Phase-Transfer Oxidations

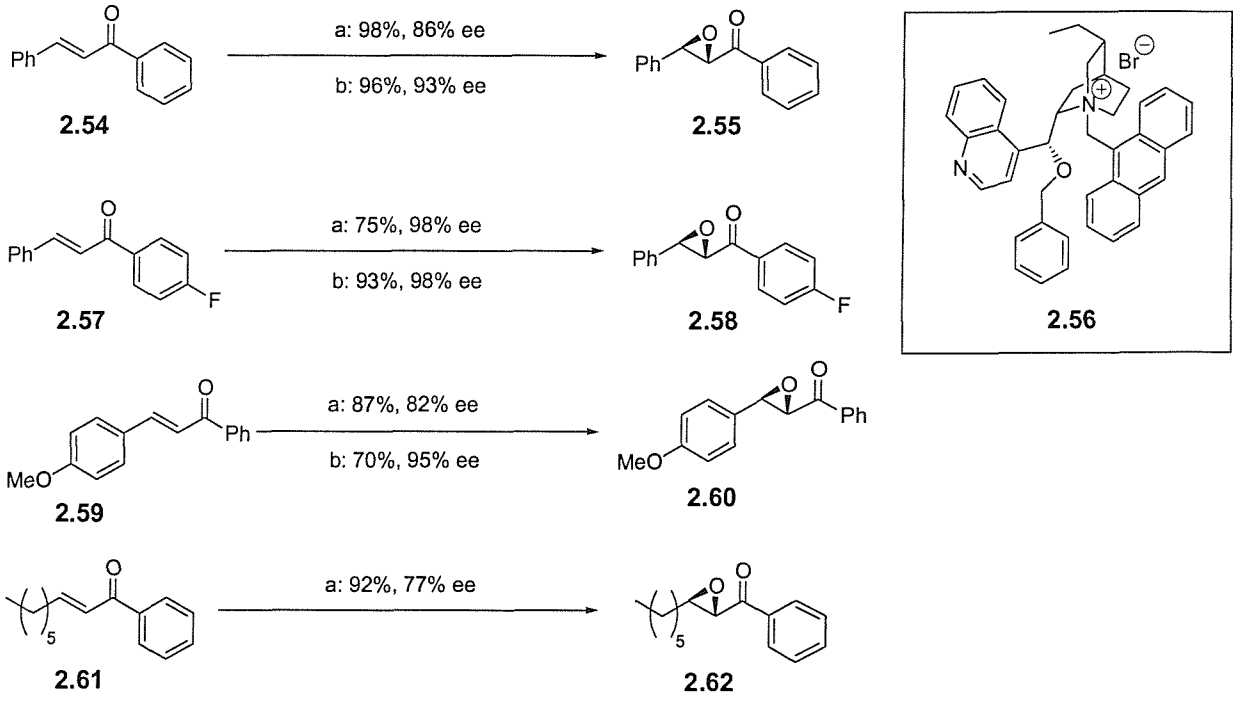
Chiral phase-transfer catalysts were introduced in the 1970's; inducing asymmetry into alkylations and Michael additions. Wynberg *et al.*, one of the pioneers of chiral phase-transfer catalysts, worked on the asymmetric epoxidation of chalcone derivatives (Scheme 2.14).[161] They used an alkaloid based ammonium salt, quinine **2.52**, as the chiral catalyst and found that it induced a reasonable enantiomeric excess of 25%. It was found that if the oxidant was changed to *t*-BuOOH or sodium hypochlorite,[162] the stereochemical outcome was reversed. Later it was suggested that this was due to hydrogen bonding between the hydrogen peroxide and the hydroxyl group.[163] Wynberg *et al.* published further work on asymmetric epoxidation using sodium hypochlorite and alkaloid ammonium salt quibec.[162]



Scheme 2.14 Early chiral phase-transfer catalysed oxidation of chalcone. *Reagents and Conditions:* a) H_2O_2 (aq), **2.52** (5 mol%), toluene.

A number of other groups have looked to improve the enantiomeric excess for the epoxidation of chalcones using a variety of catalysts, however without much success.[164-167]

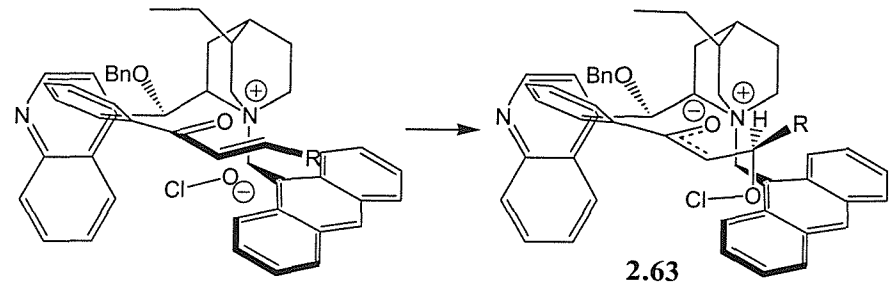
A breakthrough was made in the late 1990's by Lygo *et al.* who investigated the use of *Cinchona* alkaloids in the chiral phase-transfer catalysed epoxidation of α,β-unsaturated phenones.[163,168-171] They found that benzylation of the secondary alcohol in the catalyst led to a marked increase in enantiomeric excess, and that O-*benzyl*-*N*-anthracenylmethyl cinchodinium salts with sodium hypochlorite as the oxidant gave enantiomeric excesses between 70-98% (Scheme 2.15). They were able be prepare both enantiomers by starting with either cinchonidine or its enantiomer cinchonine, both showing equal inducement of chirality. Corey *et al.* also published very similar results for the asymmetric epoxidation of chalcones using the same cinchonidine derived catalyst.[172] Carrying out the reactions at –40 °C, Corey achieved high yields and enantiomeric excesses up to 98% (Scheme 2.15).



Scheme 2.15 Asymmetric epoxidation by cinchonidinium salt; Lygo and Corey's results. *Reagents and Conditions:* a) Lygo: **2.56** (1 mol%), 15% aq NaOCl (2 eq), toluene, 12-24 h, rt; b) Corey: **2.56** (10 mol%), KOCl aq, toluene, –40 °C, 12 h.

Lygo has proposed a transition state **2.63**, which is formed through a Michael-type addition, giving an enolate-like structure (Scheme 2.16). This intermediate is stabilised through

interaction with the proximate ammonium cation. Chirality is induced as the substrate is sterically restricted by the quinoline, benzyl and anthracene groups.



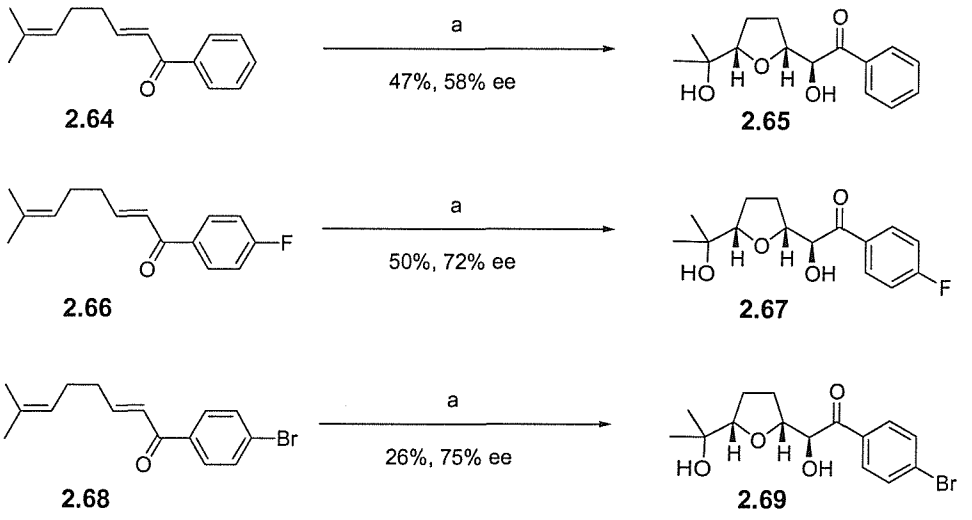
2.63

Scheme 2.16 Lygo's proposed intermediate in the phase-transfer catalysed nucleophilic epoxidation of olefins

The similarity between Lee's transition state **2.45** and the initial adduct **2.63** formed in the phase-transfer catalysed nucleophilic epoxidation of enones, led our group to suggest that chiral catalysts developed for the epoxidation reaction might also be applied to the phase-transfer oxidative cyclisation of dienes by permanganate.

2.7 Permanganate Promoted Chiral Phase-Transfer Catalysed Oxidative Cyclisations

The preliminary results carried out in our group for the chiral phase-transfer catalysed oxidative cyclisation of geranyl benzoate (**2.47**) were disappointing, resulting in an enantiomeric excess of < 3%. However, when the substrate was changed to α,β-unsaturated phenone **2.64** an enantiomeric excess of 39% was observed at 0 °C.[160] This was later improved to 58% ee by lowering the temperature to –30 °C and changing from an aqueous solution of permanganate and CH_2Cl_2 (liquid-liquid phase-transfer system) to solid permanganate in CH_2Cl_2 (solid-liquid phase-transfer system). Substitution on the phenyl ring (**2.66** and **2.68**) was briefly investigated and was discovered to increase the enantiomeric excess up to 75% for *p*-bromo derivative **2.69** (Scheme 2.17).[159]

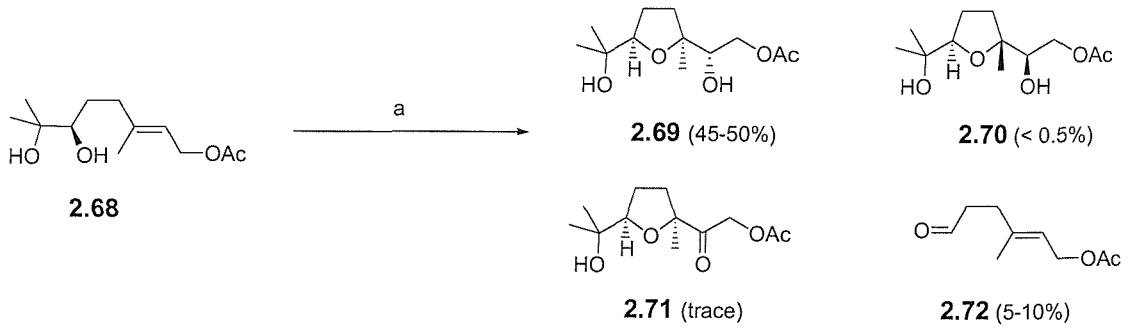


Scheme 2.17 Chiral phase-transfer catalysed oxidative cyclisation of 1,5-diene phenones. *Reagents and Conditions:* a) $KMnO_4$ (powder, 1.6 eq), **2.56** (10 mol%), AcOH (6.5 eq), CH_2Cl_2, –30 °C.

These preliminary results for the permanganate promoted chiral phase-transfer catalysed oxidative cyclisation were very encouraging and required further development.

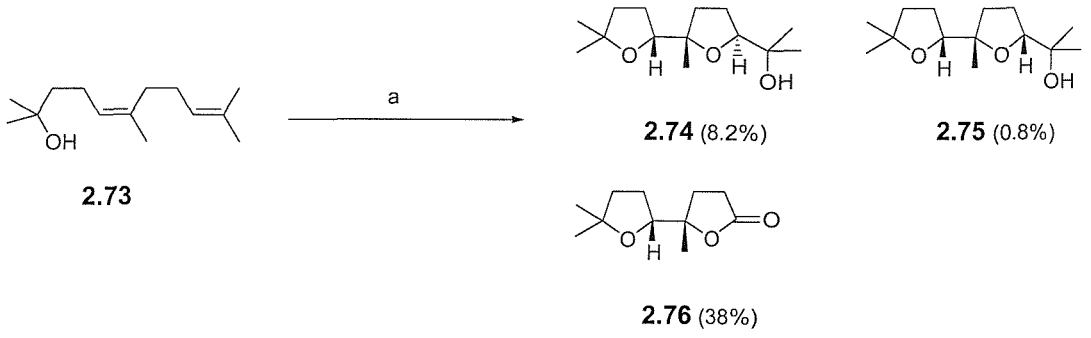
2.8 Chromium(VI) Mediated Oxidative Cyclisation of Hydroxyalkenes

The chromium(VI) mediated oxidative cyclisation of 5,6-dihydroxyalkenes to give *cis*-THF diols was developed by Walba *et al.* (Scheme 2.18).[173] Oxidation of alkene **2.68** by the chromium(VI) oxo species occurs with *syn*-selectivity (> 99:1) to give the *cis*-THF diol **2.69** in good yield. The over-oxidation of THF-diol **2.69** to ketone **2.71** was also observed, as well as aldehyde **2.72**, which resulted from oxidative cleavage of the 1,2-diol.



Scheme 2.18 Chromium(VI) mediated oxidative cyclisation of 5,6-dihydroxyalkenes. *Reagents and Conditions:* a) Collins reagent[174] or PCC.

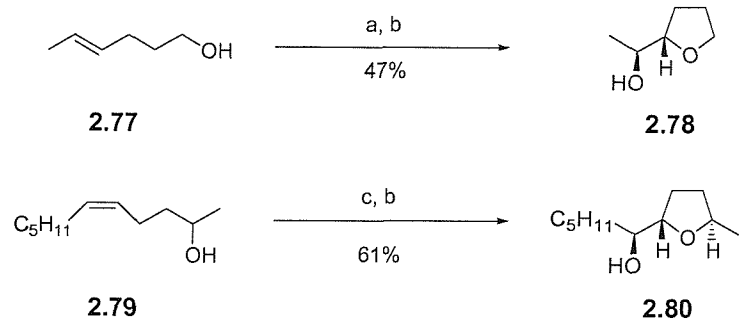
Later, McDonald and Towne demonstrated that tertiary 5-hydroxypolyenes underwent *syn*-oxidative cyclisation with PCC/AcOH to give predominantly *trans*-THF's and the corresponding over-oxidised lactones (Scheme 2.19).[175]



Scheme 2.19 Chromium(VI) mediated oxidative cyclisation of 5-hydroxypolyenes. *Reagents and Conditions:* a) PCC, AcOH, celite, CH_2Cl_2.

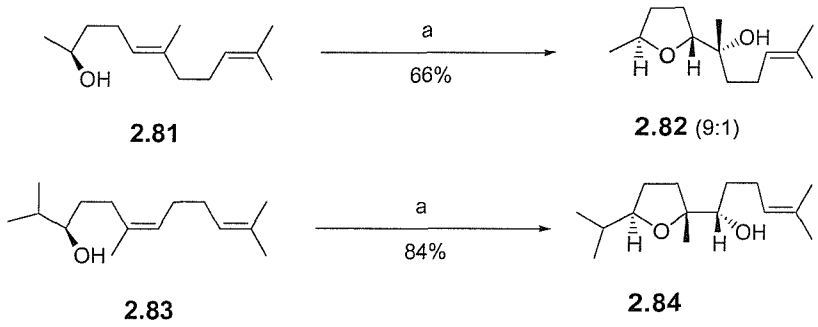
2.9 Rhenium(VII) Mediated Oxidative Cyclisation of 5-Hydroxyalkenes

Kennedy and Tang developed the rhenium(VII) oxo mediated *syn*-oxidative cyclisation of 5-hydroxyalkenes to give *trans*-2,5-disubstituted THF products (Kennedy cyclisation) (Scheme 2.20).[176-178] Whereas the chromium(VI) mediated cyclisation is limited to tertiary alcohol substrates,[175] Kennedy showed rhenium(VII) oxo species were compatible with both primary and secondary alcohols.



Scheme 2.20 Rhenium(VII) mediated oxidative cyclisation of 5-hydroxyalkenes. *Reagents and Conditions:* a) Re_2O_7, 2,6-lutidine, CH_2Cl_2; b) NaOOH, H_2O; c) ReO_3, H_5IO_6, CH_2Cl_2.

Improved yields were later realised by McDonald and Towne using acylperrhenate reagents for the oxidative cyclisation of 5-hydroxydienes (Scheme 2.21).[179,180] Again, the *trans*-2,5-disubstituted THF products, **2.82** and **2.84**, were obtained in both high selectivity and good yield.



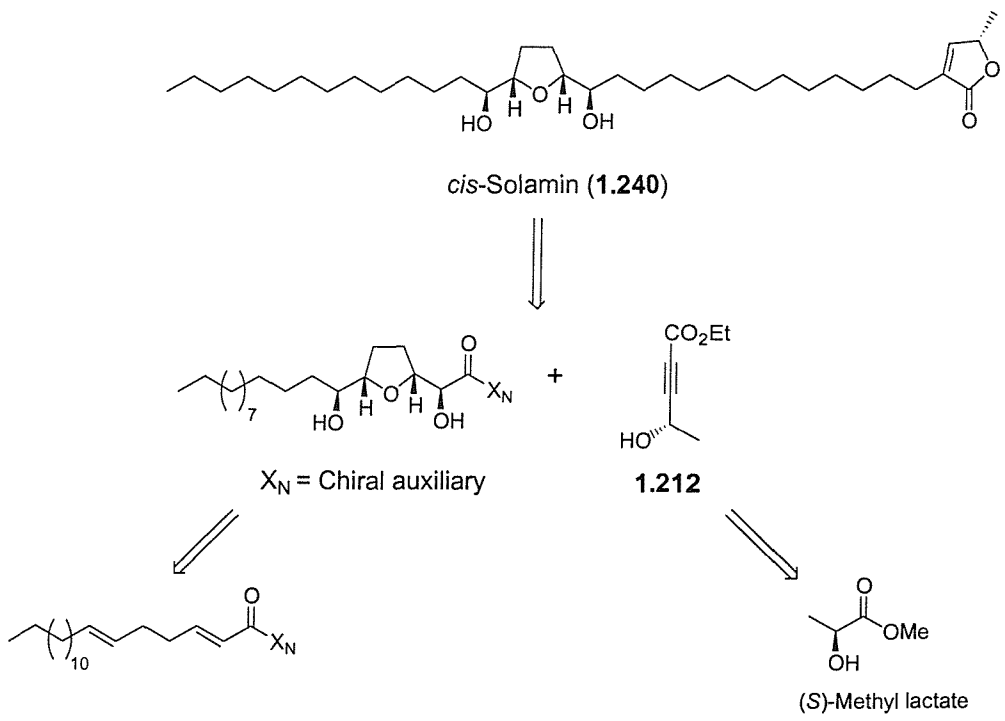
Scheme 2.21 Acylperrhenate mediated oxidative cyclisation of 5-hydroxydienes. *Reagents and Conditions:* a) $(CF_3CO_2)ReO_3$, 2,6-lutidine, CH_2Cl_2.

Chapter 3

An Introduction to the Proposed Work

3.1 Synthesis of *cis*-Solamin (1.240) *via* a Permanganate Promoted Oxidative Cyclisation

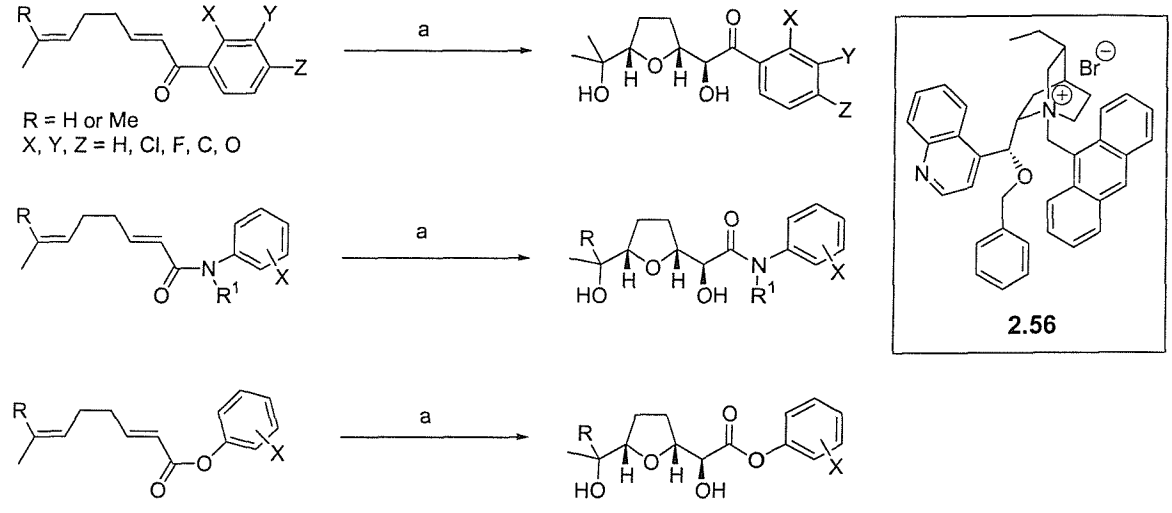
At the time of selecting *cis*-solamin (**1.240**) as a natural product target there had been no stereoselective total synthesis published. It contained the central 2,5-disubstituted *threo-cis-threo-mono*-THF-diol structure which could be synthesised in one step by the permanganate mediated oxidative cyclisation of a 1,5-diene. The absolute stereochemistry of the oxidative cyclisation would be controlled by a chiral auxiliary. We felt we could utilise some elegant chemistry reported by Trost *et al.* when forming the butenolide,[108] and complete one of the shortest and most efficient *mono*-THF acetogenin syntheses published (Scheme 3.1).



Scheme 3.1 Retrosynthesis of our route to *cis*-solamin (**1.240**)

3.2 Chiral Phase-Transfer Catalysed Oxidative Cyclisation and Formal Synthesis

With some good ee's already realised for the permanganate promoted chiral phase-transfer catalysed oxidative cyclisation,[159] the effect substrate structure has on the level of asymmetric induction would be investigated (Scheme 3.2). Halo-substitution at the 4-position of the phenyl ring had already shown a dramatic increase in enantiomeric excess. Therefore a range of substituted phenones would be investigated as well as investigating the scope of the reaction in terms of the functional groups which could be tolerated.

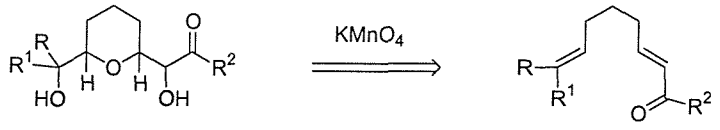


Scheme 3.2 Optimisation of the substrate structure for the optimal ee. *Reagents and Conditions:* a) $KMnO_4$ (powder, 1.6 eq), **2.56** (10 mol%), AcOH (6.5 eq), CH_2Cl_2.

Realisation of highly enantioselective phase-transfer catalysed oxidative cyclisation reactions would then allow us to investigate applications in total synthesis. *cis*-Solamin (**1.240**) would provide a suitable target (Scheme 3.1), although the methodology could be more generally applicable.

3.3 Permanganate Promoted Oxidative Cyclisation of 1,6-Dienes to Afford THP's

The permanganate mediated oxidative cyclisation of 1,6-dienes would also be investigated. To the best of our knowledge there are no literature examples of this reaction. If successful an application towards a natural product target would be attempted.



Scheme 3.3 Possible permanganate mediated oxidative cyclisation of a 1,6-diene

There are numerous examples of biologically active natural products containing a 2,6-disubstituted THP rings.[181,182] One such example is the *Annonaceous* acetogenin muconin (**3.1**), which was synthesised by Kitahara *et al.* (Figure 3.1).[183]

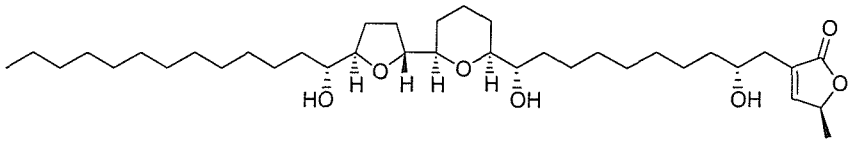


Figure 3.1 Structure of THP (non-classical) acetogenin muconin (**3.1**)

Results and Discussion

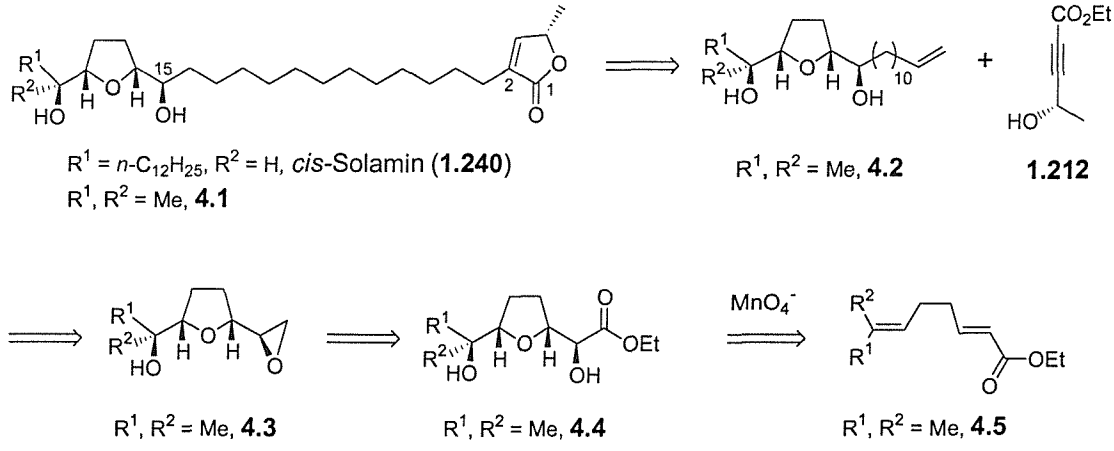
Chapter 4

Model Study Towards the Synthesis of *cis*-Solamin (1.240)

The following chapter summarises the results of our initial study into the feasibility of synthesising *mono*-THF acetogenins *via* a permanganate promoted oxidative cyclisation of a 1,5-diene.[184]

4.1 Synthesis and Oxidation of a Model 1,5-Diene

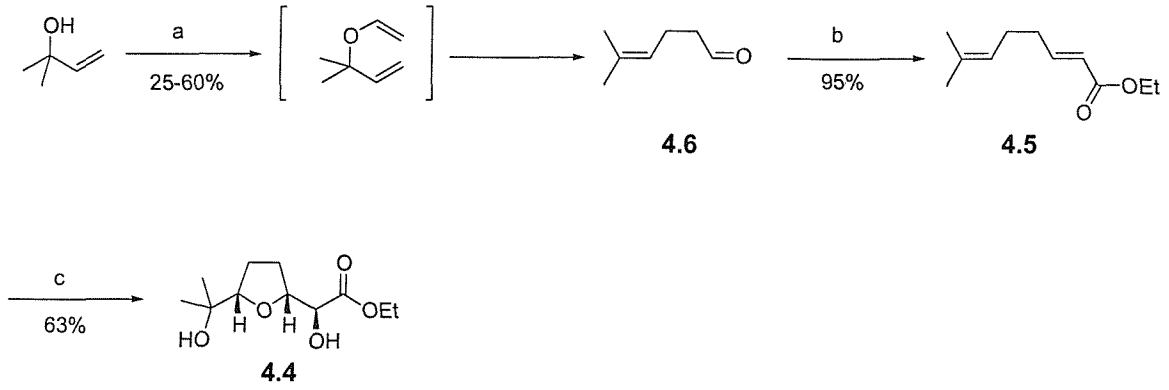
In order to assess our proposed route towards the synthesis of *mono*-THF acetogenins a model study was undertaken. The requirement of a simple 1,5-dienoate, which could be synthesised in large quantities in as few steps as possible was fundamental (Scheme 4.1). The 1,5-diene would be cyclised to provide the THF core of an acetogenin, the right-hand-side would then be extended and elaborated to give the terminal butenolide *via* Trost's methodology.[108]



Scheme 4.1 Approach to *mono-cis*-THF acetogenins employing a permanganate promoted oxidative cyclisation

The ester **4.5** was selected as our model 1,5-diene and was synthesised in two steps by well documented chemistry. Thus, 2-methyl-3-buten-2-ol was heated in a sealed tube with ethyl vinyl ether and a catalytic quantity of phosphoric acid,[185] affording aldehyde **4.6** in variable

yield *via* a Johnson-Claisen rearrangement (Scheme 4.2).[186] Wittig olefination with (carbethoxymethylene)-triphenylphosphorane provided exclusively (*E*)-1,5-dienoate **4.5** in excellent yield.[187] Oxidative cyclisation of dienoate **4.5** by potassium permanganate using previously optimised conditions,[188] afforded racemic *cis*-THF-diol **4.4** in good yield.



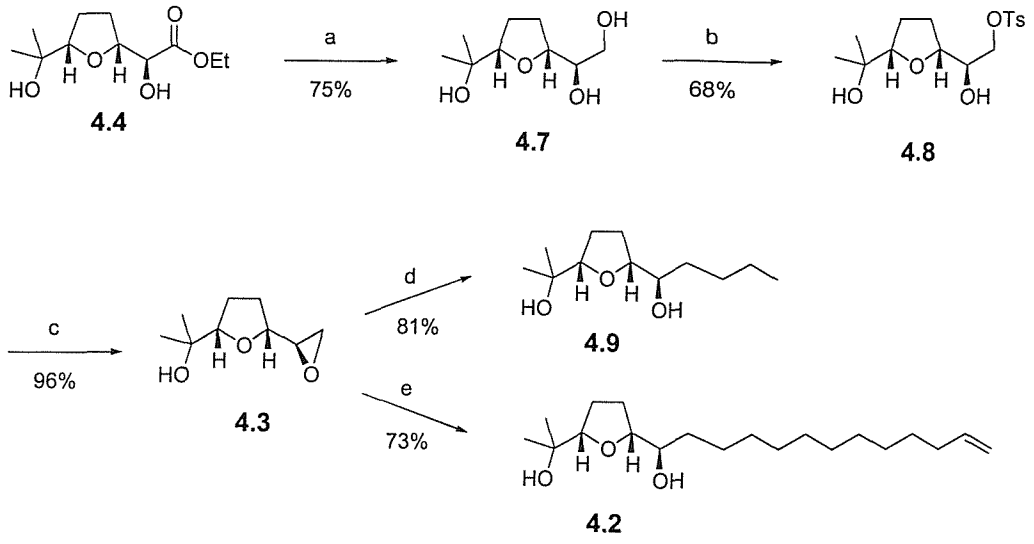
Scheme 4.2 Synthesis and oxidation of the model 1,5-diene. *Reagents and Conditions:* a) ethyl vinyl ether, H_3PO_4, 120 °C, 16 hr, then 2N HCl, acetone, rt, 1 hr; b) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 12 hr; c) $KMnO_4$ (0.4 M, 2 eq), AcOH (2.8 eq), pH 6.5, acetone, –25 °C.

The THF-diol **4.4** was synthesised as a single diastereoisomer from an achiral diene; for the total synthesis of *cis*-solamin (**1.240**) absolute stereochemistry would be controlled by replacing the ethyl ester group with a chiral auxiliary (Oppolzer's sultam). At this stage the primary interest was the optimisation of the chemistry required to construct the right-hand-side of the molecule.

4.2 Elaboration of the Right-Hand-Side

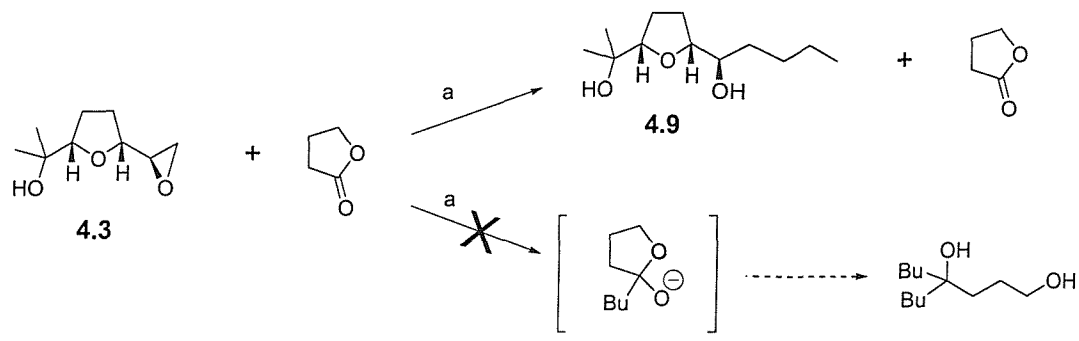
Reduction of α-hydroxy-ester **4.4** with $NaBH_4$ gave the polar triol **4.7** in good yield (Scheme 4.3). Apprehension about our ability to extract triol **4.7** into the organic phase was unwarranted. Triol **4.7** underwent selective tosylation of the primary alcohol, giving diol **4.8**. Formation of the key epoxide intermediate **4.3** occurred rapidly when a methylene chloride solution of **4.8** was treated with DBU. The selective epoxide opening was first investigated with commercially available butylmagnesium bromide and copper iodide, giving the desired diol **4.9** as the only isolated product. The C-3 to C-13 carbon atoms present in the target were then introduced using the aforementioned copper-catalysed

Grignard reaction to give **4.2**, which contained the terminal alkene allowing for the formation of the butenolide ring in the subsequent step.



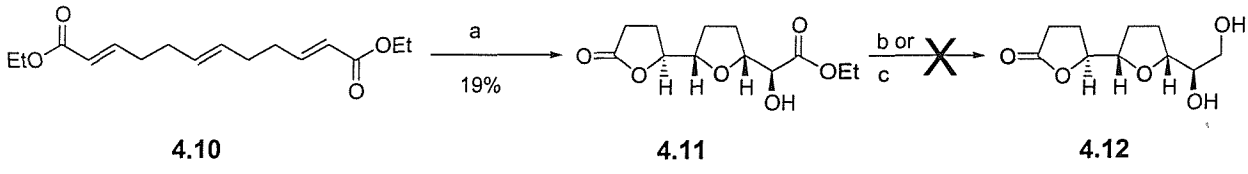
Scheme 4.3 Elaboration of the right-hand-side to the terminal olefin. *Reagents and Conditions:* a) $NaBH_4$, THF, H_2O; b) TsCl, DMAP, Et_3N, CH_2Cl_2; c) DBU, CH_2Cl_2; d) *n*BuMgCl, CuI, THF, 0 °C to –78 °C; then **4.3**; e) undec-10-enylmagnesium bromide, CuI, THF, 0 °C to –78 °C; then **4.3**.

Initially, the epoxide opening *via* a copper-catalysed Grignard reaction was selected as concurrent projects within our group required the selective epoxide opening in the presence of a lactone (the cyclisation of a 1,5,9-triene by permanganate gives a THF lactone, Scheme 4.5). The selective epoxide opening was investigated by a competition reaction. Thus, a 1:1 mixture of epoxide **4.3** and γ-butyrolactone were subjected to the copper-catalysed Grignard conditions for the formation of diol **4.9** (Scheme 4.4). Pleasingly, it was found that the epoxide reacted very rapidly at –78 °C to give the desired diol, whereas the lactone only started to react after the solution had been warmed to 0 °C (reaction monitored by GC at 10 °C intervals). Therefore it appeared that a selective epoxide opening would be possible in the presence of lactone functionality.



Scheme 4.4 Selective epoxide opening. *Reagents and Conditions:* a) *n*BuMgBr, CuI, THF, 0 °C to –78 °C; then **4.3**, γ–butyrolactone, –78 °C to –10 °C.

The synthesis of a THF-lactone was undertaken to confirm the preliminary results. The symmetrical triene **4.10** was prepared in three steps according to the known procedure.[189] Oxidative cyclisation by permanganate followed by subsequent treatment with $NaIO_4$ gave THF-lactone **4.11** as a crystalline solid (Scheme 4.5). X-ray crystallography clearly showed that all three oxygens had been inserted on the same face, as predicted by the accepted mechanisms (Figure 4.1). Attempts at the selective reduction of the α-hydroxy ester **4.11** to the diol **4.12** failed using either our previously successful conditions of $NaBH_4$, or the reported conditions of $NaBH_4$ with BH_3•DMS.[190] Ultimately, as the reduction would be carried out on a chiral auxiliary and not an ethyl ester this avenue was not pursued and the oxidation of 1,5,9-trienes and subsequent elaboration was handed over to a colleague.[191]



Scheme 4.5 Synthesis of THF-lactone and failed reduction. *Reagents and Conditions:* a) (i) $KMnO_4$, AcOH, phosphate buffer pH 6.5, acetone, –25 °C, 10 min; (ii) $NaIO_4$, acetone, H_2O; b) $NaBH_4$, BH_3•DMS, THF; c) $NaBH_4$, THF, H_2O.

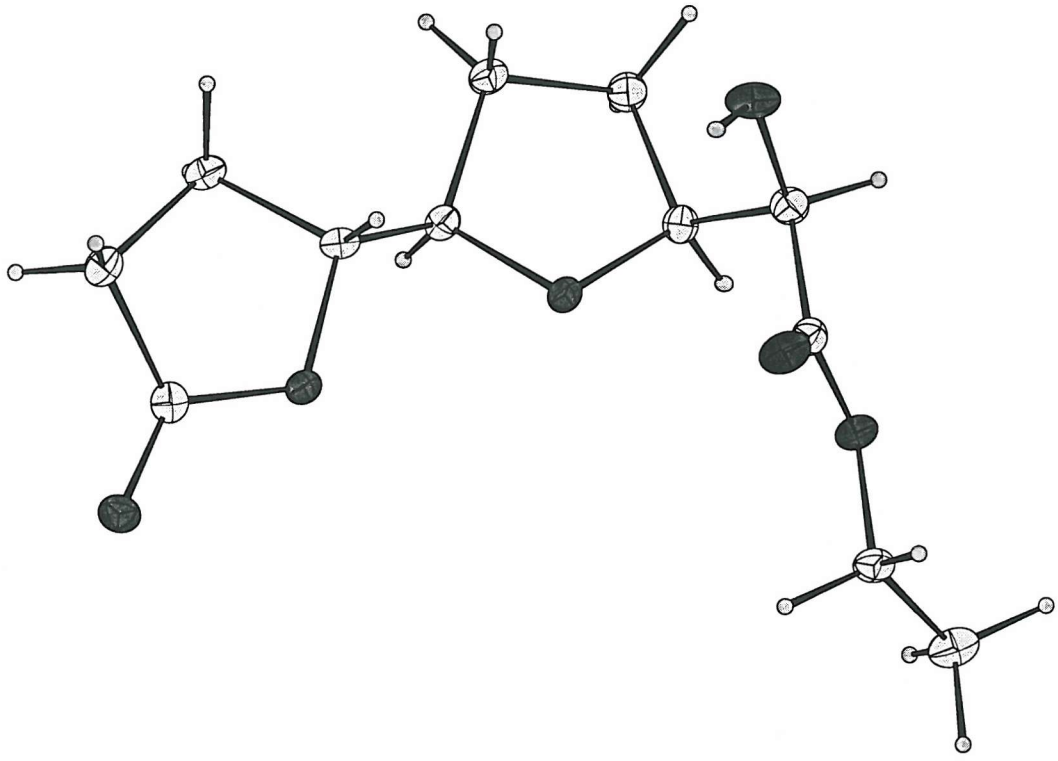
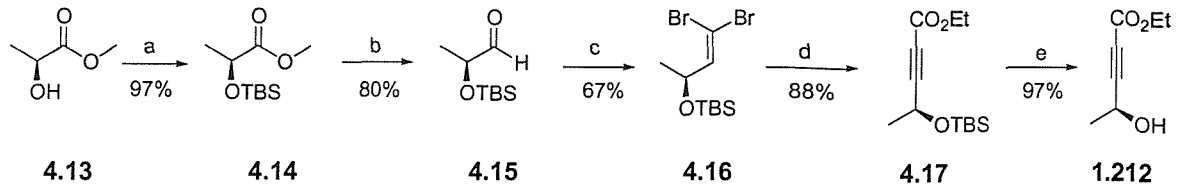


Figure 4.1 Crystal structure of THF-lactone **4.11**

4.3 Completion of the Model Study *via* Trost's Butenolide Methodology

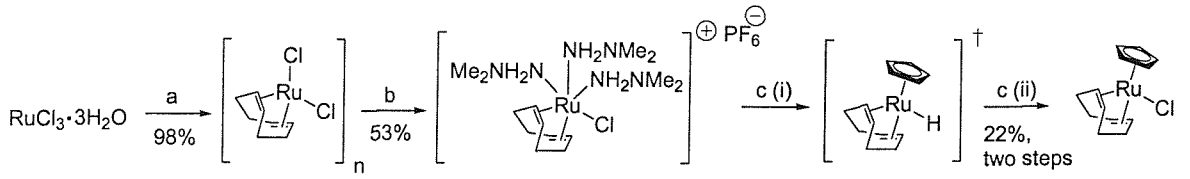
Trost's butenolide methodology[108] required the synthesis of a chiral propargylic alcohol and a ruthenium catalyst (Section 1.6.7.1). The propargylic alcohol was prepared in 5 steps from methyl-(*S*)-lactate **4.13** following the known procedure (Scheme 4.6).[108,192] Thus, formation of the silyl ether of **4.13** followed by DIBAL-H reduction gave aldehyde **4.15**. Olefination by the Corey-Fuchs[57] procedure gave the *gem*-dibromo alkene **4.16** in good yield. Treatment with *n*BuLi and subsequent trapping of the acetylide with ethyl chloroformate gave alkyne **4.17**, which was deprotected to give the desired propargylic alcohol **1.212**.



4.13 **4.14** **4.15** **4.16** **4.17** **1.212**

Scheme 4.6 Synthesis of propargylic alcohol. *Reagents and conditions:* a) TBSCl, Et_3N, DMAP, CH_2Cl_2; b) DIBAL-H, CH_2Cl_2, –78 °C; c) Ph_3P, CBr_4, –78 °C, CH_2Cl_2; d) *n*BuLi, THF, –78 °C; then ethyl chloroformate to rt; e) AcOH, THF, H_2O, 70 °C.

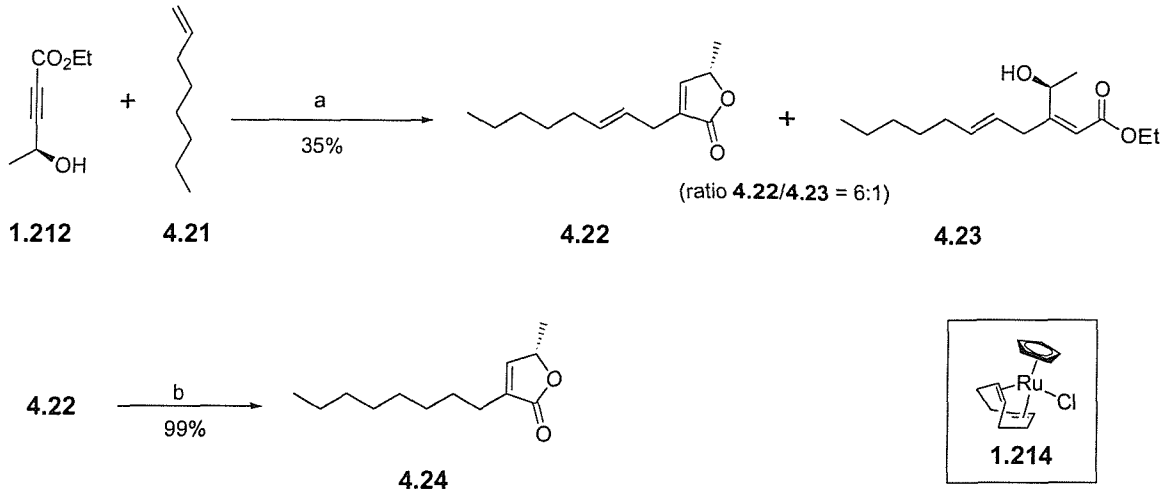
The ruthenium catalyst **1.214** was synthesised in three steps following the known procedure,[193-195] except for a modification whereby the ruthenium hydride complex **4.20** was not isolated as it was found to decompose almost instantaneously (Scheme 4.7). It is worth noting that the ruthenium catalyst **1.214** is a bright orange solid, which appears relatively stable; samples have been stored in our freezer for more than three years and do not appear to have decomposed.



4.18 **4.19** **4.20** **1.214**

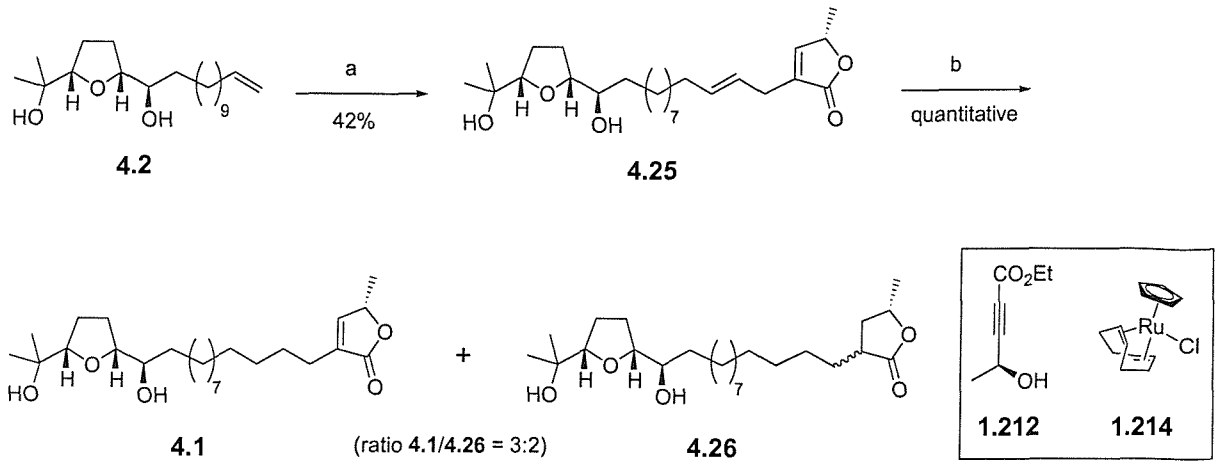
Scheme 4.7 Synthesis of ruthenium catalyst. *Reagents and conditions:* a) 1,5-cyclooctadiene, EtOH, reflux; b) (i) *N'N*-dimethylhydrazine, H_2O, MeOH, reflux; (ii) $[NH_4][PF_6]$ c) (i) ThCp, acetone, reflux; (ii) CCl_4, pentane.

We were now ready to attempt Trost's ruthenium-catalysed Alder-ene reaction,[108] selecting commercially available oct-1-ene as the first substrate. The desired butenolide **4.22** and its uncyclised regioisomer **4.23** (6:1 respectively) were isolated in disappointing yield (Scheme 4.8 and Scheme 1.32 for the mechanism). The reaction was not repeated to optimise the yield, but the substrate was carried forward to practice the selective reduction of the aliphatic double bond. Using conditions similar to those reported by Trost;[108] in a steel bomb **4.22** was treated with Wilkinson's catalyst under an atmosphere of H_2 (2-4 bar), giving the selectively reduced butenolide **4.24** in excellent yield.



Scheme 4.8 Ruthenium-catalysed Alder-ene reaction and selective reduction. *Reagents and Conditions:* a) 5 mol% CpRu(COD)Cl (**1.214**), MeOH, reflux b) $Rh(PPh_3)_3Cl$, H_2 (2-4 bar), benzene/EtOH.

Having successfully carried out the trial ruthenium-catalysed Alder–ene reaction we were now ready to attempt the reaction on our model alkene **4.2**. The aforementioned conditions gave the desired butenolide **4.25** in satisfactory yield in a 5:1 ratio with the uncyclised regioisomer (Scheme 4.9). The reaction of the racemic THF fragment **4.2** with the homochiral alkyne **1.212** gave a 1:1 mixture of diastereoisomers (not shown in Scheme 4.9) that were indistinguishable spectroscopically due to the length and flexibility of the aliphatic chain. With compound **4.25** in hand, it was possible to investigate the selective reduction of the disubstituted olefin. The reduction was carried out as before in a steel bomb at 2–4 atmospheres of H_2, giving a 3:2 mixture of the desired butenolide **4.1** and over reduced lactone **4.26** in quantitative yield. Although efforts to separate **4.1** and **4.26** were unsuccessful, we were confident that the over reduction observed here would be avoided when the synthesis of *cis*-solamin (**1.240**) was attempted through more careful control of H_2 pressure. Unfortunately, it was not possible to demonstrate this on the model substrate, as insufficient material was available to attempt the reaction a second time.



Scheme 4.9 Butenolide formation and subsequent reduction. *Reagents and Conditions:* a) 5 mol% CpRu(COD)Cl (**1.214**), **1.212**, MeOH, reflux b) $Rh(PPh_3)_3Cl$, H_2 (2-4 bar), benzene/EtOH.

It is noteworthy that the use of protecting groups was avoided during the assembly of the fragments, with both the copper-catalysed Grignard opening of epoxide **4.3** and the ruthenium-catalysed Alder-ene reaction proceeding in the presence of free hydroxyl groups.

Chapter 5

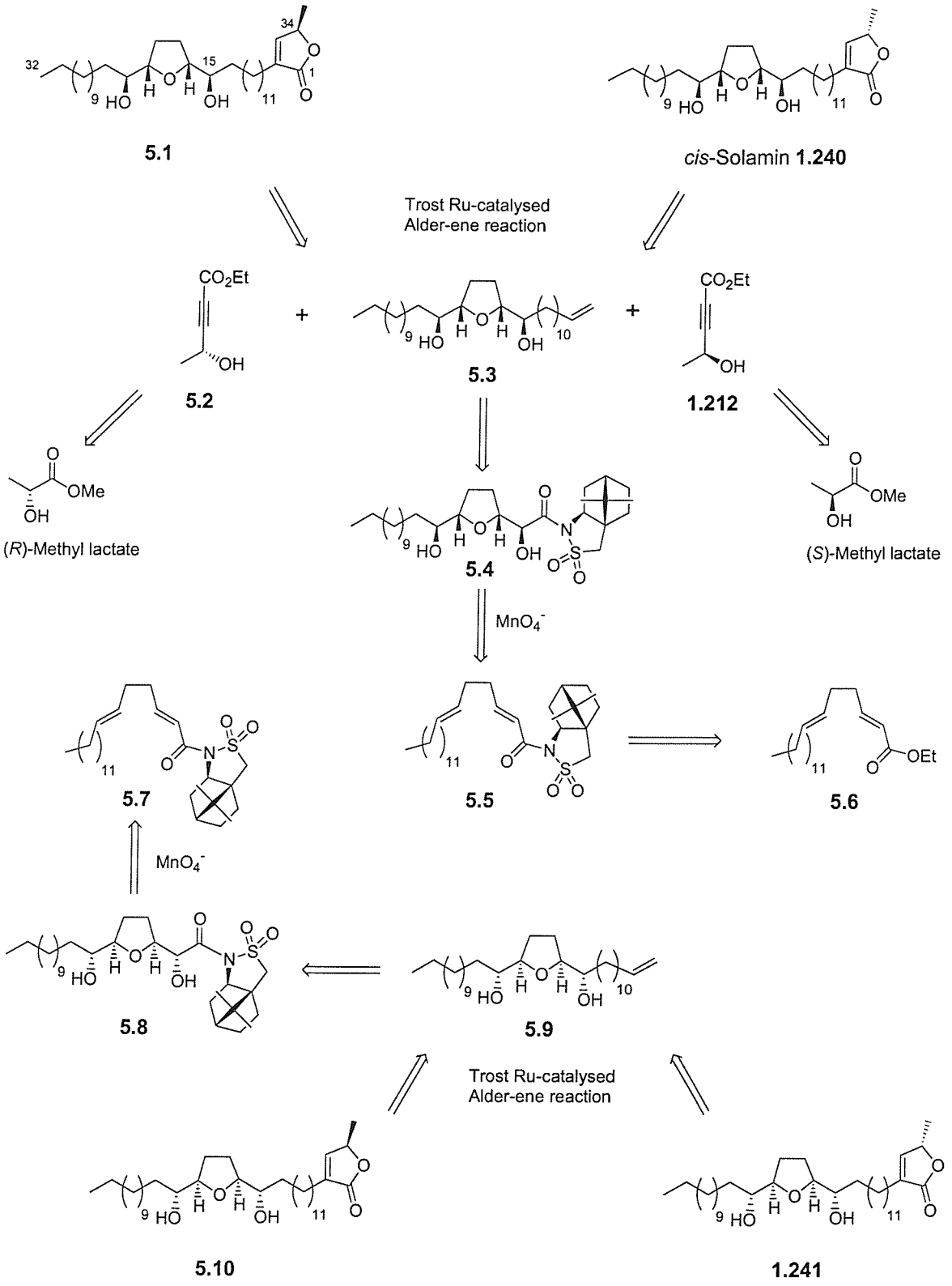
Total Synthesis of *cis*-Solamin (1.240)

The following chapter summarises our approach to the total synthesis of *cis*-solamin (**1.240**).[196,197] In an attempt to unambiguously assign the absolute stereochemistry of the *threo-cis-threo*-THF core,[117] all possible diastereoisomers of the natural product were synthesised.

5.1 Our Approach to *mono-cis*-THF Acetogenins

To control the absolute stereochemistry of the THF core the initial facial attack by permanganate on the α,β-unsaturated carbonyl has to be controlled, this can be accomplished using a chiral auxiliary. Work within our group,[191] and past publications had shown Oppolzer's camphor sultam to give good diastereoselectivity in the permanganate promoted oxidative cyclisation.[129,146] Both enantiomers of the sultam would be used to allow the synthesis of both *threo-cis-threo*-THF conformations (Scheme 5.1). The stereochemistry at C-34 would be introduced by the propargylic alcohol used in the ruthenium-catalysed Alder-ene reaction. Therefore, starting from either (*S*) or (*R*) methyl lactate would facilitate the required alkyne and enable the convergent synthesis of the *cis*-solamin diastereoisomers.

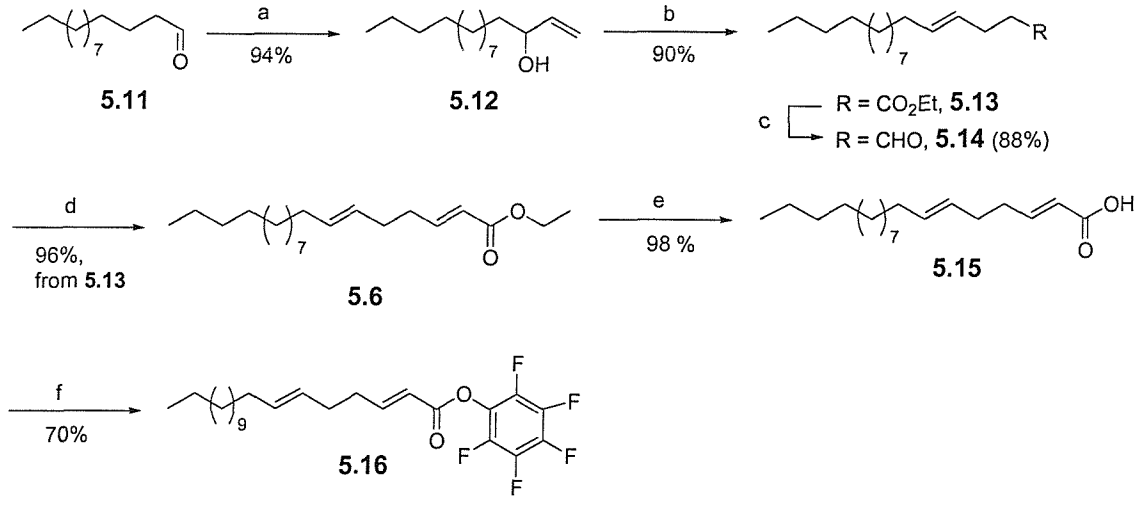
Our retrosynthetic analysis of *cis*-solamin (**1.240**) was designed to take advantage of the elegant ruthenium-catalysed methodology developed by Trost to introduce the butenolide portion of the molecule (Scheme 5.1). Strategically, the use of the highly chemoselective transition metal-catalysed Alder-ene reaction would minimise the requirement for protecting groups during the final stages of the synthesis. After disconnection of the butenolide, it becomes apparent that the C-3 to C-13 chain could be introduced by copper promoted opening of an epoxide derived from the product **5.4** of the permanganate mediated oxidative cyclisation of diene **5.5**. Asymmetric induction would be provided by a chiral auxiliary present in the 1,5-dienoate **5.5**.



Scheme 5.1 Approach to the *mono*-THF acetogenin *cis*-solamin and its diastereoisomers

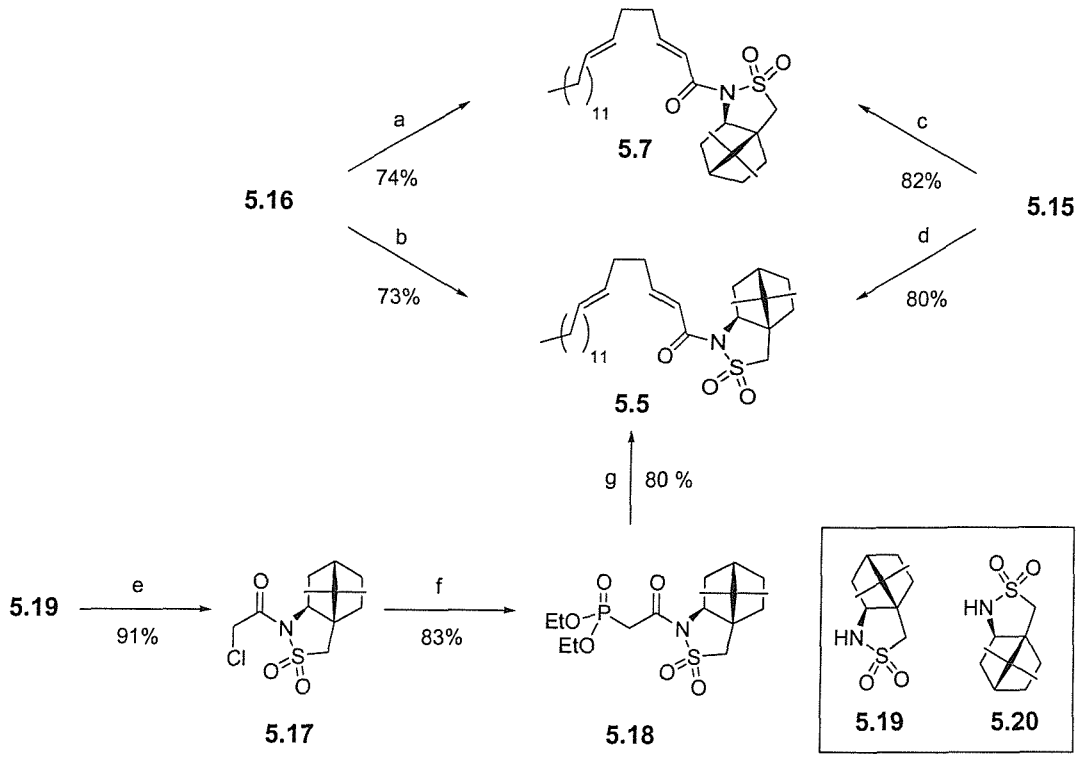
5.2 Preparation of the 1,5-Dienoates for the Asymmetric Oxidative Cyclisation

Starting from the aldehyde **5.11**, addition of vinyl Grignard afforded allylic alcohol **5.12**, which underwent a Johnson-Claisen rearrangement to give enoate **5.13** in excellent overall yield (Scheme 5.2).[198] Elaboration of **5.13** to dienoate **5.6** was best achieved without isolation of the intermediate aldehyde **5.14**, in a one-pot reduction-olefination reaction,[199] although care was required during the reduction step as any remaining ester **5.13** co-eluted with the desired dienoate **5.6**. The synthesis of the oxidative cyclisation precursor was originally completed by hydrolysis of **5.6** and activation of the resulting unsaturated acid **5.15** as its pentafluorophenol ester **5.16**, prior to substitution with the anion of the appropriate sultam.



Scheme 5.2 Synthesis towards 1,5-dienoate. *Reagents and conditions*: a) CH_2=CHMgBr, THF, –20 °C; b) triethyl orthoacetate, propionic acid, xylene, reflux; c) DIBAL-H, toluene, –60 °C; d) i) DIBAL-H, toluene, –60 °C; ii) triethyl phosphonoacetate, NaH –40 °C to rt; e) NaOH, $NaHCO_3$, MeOH, H_2O, reflux; f) pentafluorophenol, DCC, EtOAc.

On a larger scale the by-product from acylation, pentafluorophenol, proved inconvenient to separate from **5.5** leading to the use of the acid chloride derived from **5.15** as the acylating agent (Scheme 5.3). The sequence used to introduce the auxiliary proceeded in a satisfactory yield of 75%, but at the expense of three extra synthetic steps in the overall linear sequence. Therefore a more convergent route from aldehyde **5.14** to 1,5-diene **5.5** was subsequently developed by making use of phosphonate **5.18** already carrying the sultam auxiliary.[200] Both enantiomers of Oppolzer's sultam (**5.19** and **5.20**) were synthesised in four steps from the corresponding camphorsulfonic acid by the methods of Bartlett and Towson.[201-203]

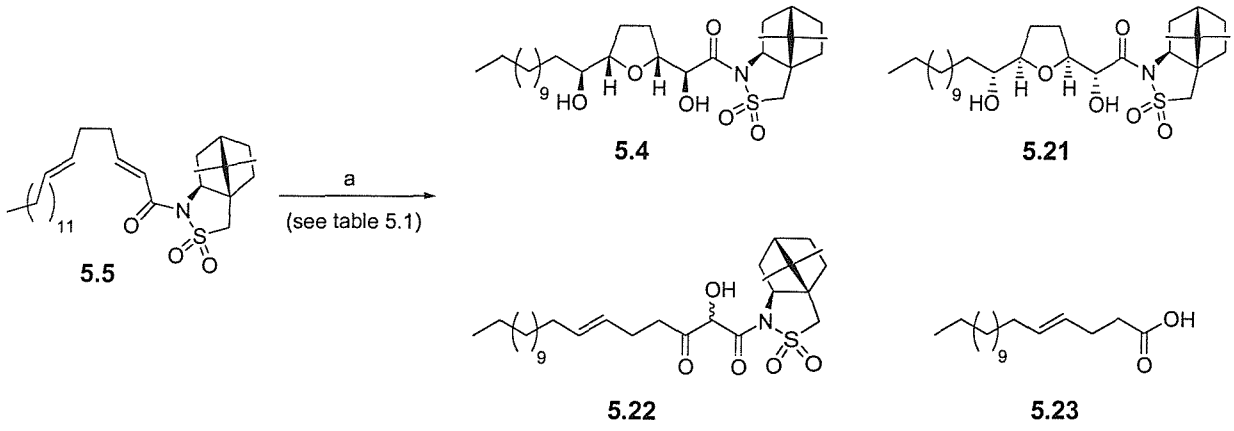


Scheme 5.3 Methods employed for the coupling of the chiral auxiliary. *Reagents and Conditions:* a) **5.20**, *n*BuLi, THF, –60 °C to –10 °C; b) **5.19**, *n*BuLi, THF, –60 °C to –10 °C; c) (i) DMF, $(COCl)_2$, CH_2Cl_2, 0 °C; (ii) **5.20**, NaH, CH_2Cl_2, 0 °C; d) i) DMF, $(COCl)_2$, CH_2Cl_2, 0 °C; (ii) **5.19**, NaH, CH_2Cl_2, 0 °C; e) NaH, CH_2Cl_2; then chloroacetyl chloride, –60 °C to 0 °C; f) triethyl phosphite, xylene, 145 °C; g) NaH, CH_2Cl_2; then **5.14**, 0 °C.

5.3 Permanganate Promoted Asymmetric Oxidative Cyclisation of Dienoyl Sultam

Prior to this work the asymmetric oxidative cyclisation of dienoates had been shown to provide an effective tool for the synthesis of polyether antibiotic fragments, where the starting olefins were tri-substituted.[129,204,205] However, other reports on the permanganate promoted oxidative cyclisation of dienes containing mono- and di-substituted olefins were far less encouraging in terms of isolated yields (5–33%).[206,207] In fact our first attempts at the oxidative cyclisation of **5.5** under our previously optimised aqueous conditions,[188] gave similarly disappointing results (Scheme 5.4). Isolating the desired product **5.4** (stereochemical outcome discussed later) in only 18% yield along with a major component **5.22** (40%) that arose from mono-oxidation of the enoate olefin (Table 5.1, entry 1). Other minor products included the diastereoisomeric THF-diol **5.21**, and acid **5.23** that probably

resulted from oxidative cleavage of the enol tautomer of **5.22**. The previously successful oxidative cyclisation of model dienoate **4.5** (Scheme 4.2) led us to speculate that the reluctance of **5.5** to undergo the cyclisation reaction was related to poor solvation of the hydrophobic C-21 to C-32 alkyl chain in acetone/water, causing aggregation in an aqueous environment.



Scheme 5.4 Permanganate promoted asymmetric oxidative cyclisation. *Reagents and Conditions:* a) $KMnO_4$, AcOH, solvent, additive (see table 5.1).

Entry	Solvent	AcOH	**5.4/5.21**[a] (d.r.)[b]
1	Acetone/H_2O/ pH 6.5 buffer	3 eq	21%, (7:1)
2[c]	CH_2Cl_2	8 eq	31%, (6.5:1)
3[c]	Toluene	8 eq	50%, (obsc)
4[c]	EtOAc	8 eq	55%, (6:1)
5[c]	Acetone	16 eq	62%, (6.5:1)
6[c]	Acetone	co-solvent[d]	75%, (6.5:1)[e]

Table 5.1 Results from the oxidative cyclisation of dienoate **5.5** (see Scheme 5.4). [a] Combined isolated yield of THF-diols **5.4** and **5.21**; [b] Ratio of **5.4**:**5.21** estimated from ^1H NMR; [c] Reaction carried out with the addition of 10 mol% adogen 464; [d] AcOH/acetone (2:3); [e] Reaction carried out without adogen 464 gave identical results.

In order to improve the solubility of the diene **5.5**, the oxidative cyclisation reaction was investigated under phase-transfer (solid-liquid) conditions in a variety of solvents (Table 5.1, entries 2–5).[159] Improved yields of the desired THF product **5.4** were realised, with the best results occurring in acetone or EtOAc using adogen 464 as phase-transfer catalysts (Table 5.1, entries 4–5). However, ultimately it was found that addition of powdered $KMnO_4$ (1.3 eq) to the substrate **5.5** dissolved in a mixed solvent system of AcOH/acetone (2:3) provided the conditions of choice for the oxidative cyclisation of dienoate systems of this type. Furthermore, both the substrate and the oxidant were soluble in AcOH/acetone (2:3) avoiding the need for any phase-transfer reagent.

Little change in diastereoselectivity was observed under the various conditions investigated, with a d.r. estimated as 6.5:1 in favour of **5.4**. The diastereoselectivity was estimated by integration of the H15 and H16 signals from the major and minor diastereoisomers in the ^1H NMR spectrum of the crude reaction mixture. Determination of an accurate d.r. was complicated due to the incomplete resolution of the $H16_{minor}$ signal from the $H15/H16_{major}$ signals. The d.r. value of 6.5:1 was also confirmed from the isolated yields of **5.4** and **5.21**. Considering the consistent d.r. values obtained from reactions run in solvents of very different polarity, it seems unlikely that chelation control is involved in determining the facial selectivity of the initial attack upon the enoate olefin.[129]

Oppolzer's Sultam: Control of Facial-Selectivity

The stereochemistry of the major product was predicted on the basis of previous use of this auxiliary in the permanganate mediated oxidative cyclisation of dienes.[129,146] The selectivity can be explained if the following conditions for the face-selective reaction with the enoate double bond are adhered to:[131]

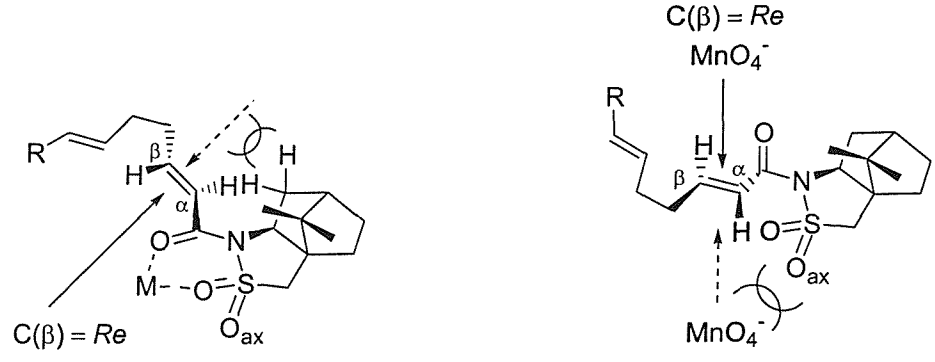
1. The reactive conformation of the CO-CC bond must be unambiguous. Of the two possible conformations which allow conjugation of the π-system, the *s-cis*-orientation is favoured both for steric reasons ($O < NR_2$), and due to the fact that (*Z*)-enolates of amides are more stable than (*E*)-enolates.
2. The orientation of the carbonyl group must be unambiguous. It must lie parallel or antiparallel to the N-S bond. Other orientations are energetically less favourable due to the lack of mesomeric stabilisation with the amide nitrogen atom.

3. In the most favoured conformation, one face of the double bond must be effectively blocked by the chiral auxiliary, thus allowing selective attack of the other face by the reagent.

In the case of the sultam the orientation of the carbonyl group may be influenced by the reaction conditions. Addition of a Lewis acid with two available coordination sites results in a *syn*-relationship between C=O and SO_2, due to the formation of chelate **5.24** (Figure 5.1). The upper face of the alkene is blocked by the camphor framework, and the reagent must attack from the lower C(β) *Re*-face.

In the absence of a chelating Lewis acid (our system) there is an *anti*-relationship between C=O and SO_2, transition state **5.25** (Figure 5.1). This is due both to steric and, in particular, stereoelectronic considerations, as this conformation minimises the dipole moment. Here the camphor framework is too distant to shield the alkene, however the *pseudo*-axial oxygen atom of the SO_2 group effectively blocks the lower face, and reagent attack occurs from the upper C(β) *Re*-face. The sultam therefore induces identical stereoselectivity whether or not Lewis acid chelation is available.

In the permanganate mediated oxidative cyclisation of 1,5-diene **5.5**, THF-diol **5.4** was the predicted product according to this model. Dipolar organisation of the carbonyl and SO_2 groups and an s-*cis*-arrangement of the C=O and C(α)–C(β) bonds would give a conformer where approach of MnO_4^- from the C(β) *Re*-face would be favoured **5.25** (Figure 5.1). This conformation was observed in the crystal structure obtained for diene **5.7** (Figure 5.2).



5.24 **5.25**

Figure 5.1 Diastereoselective oxidation of dienoyl sultam by MnO_4^-

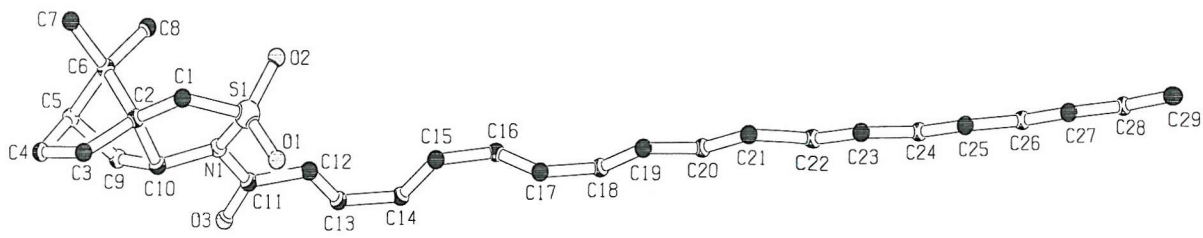
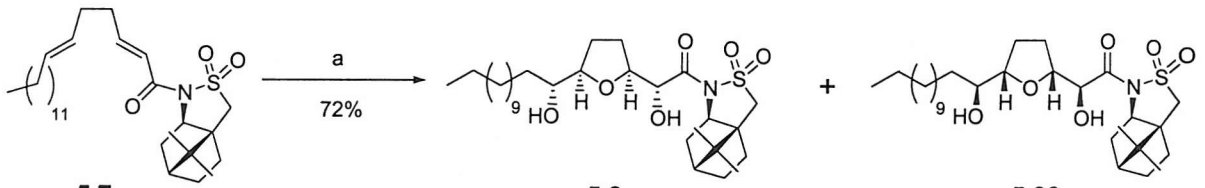


Figure 5.2 Crystal structure of dienoyl sultam **5.7** showing adoption of the predicted conformation

The oxidative cyclisation of dienoyl sultam **5.7** (the enantiomer of dienoyl sultam **5.5**) gave the corresponding THF diastereoisomers **5.8** and **5.26** in similarly good yield (Scheme 5.5).



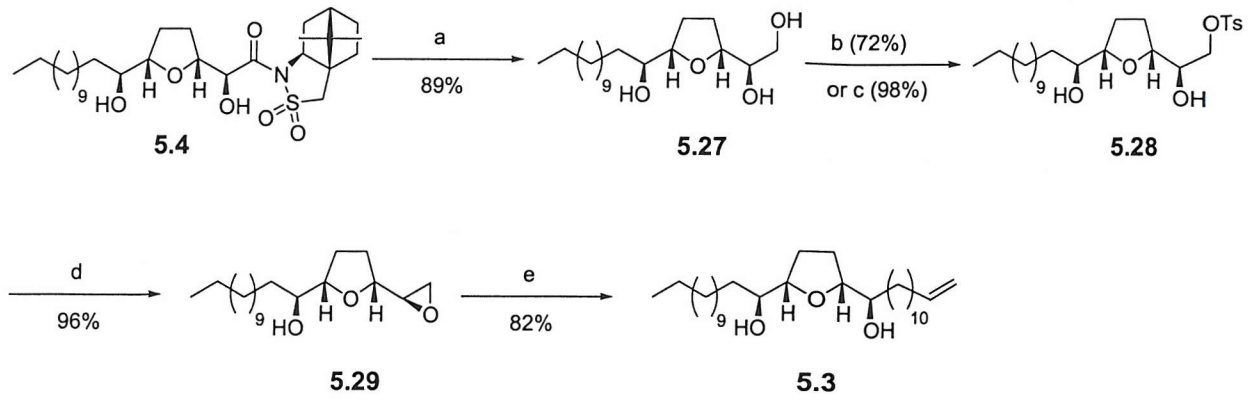
Scheme 5.5 Oxidative cyclisation of dienoyl sultam. *Reagents and Conditions:* a) $KMnO_4$ (1.3 eq), AcOH/acetone (2:3).

5.4 Introduction of the C-3 to C-15 Fragment

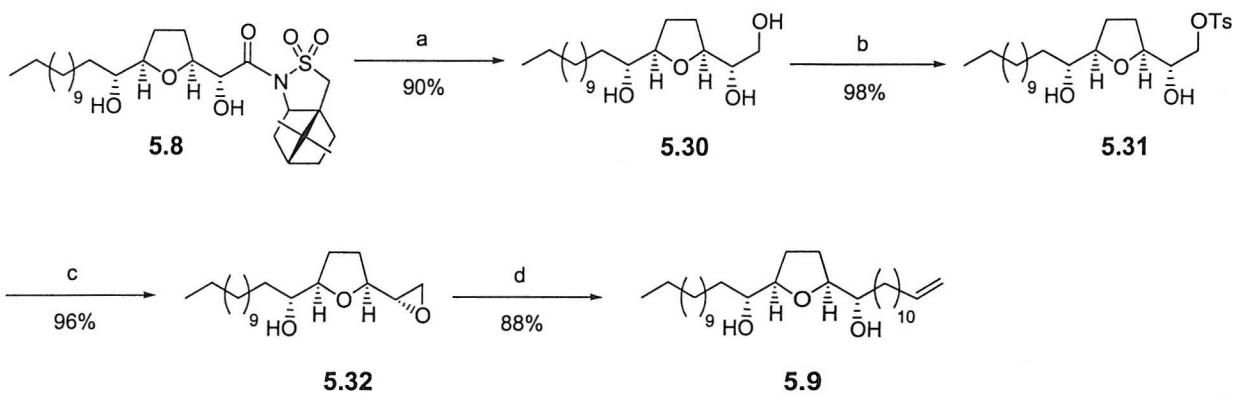
The following sequence was carried out on both *threo-cis-threo*-THF conformations *via* identical chemistry (Scheme 5.6 & 5.7). Herein, for the purpose of clarity only the synthesis of terminal olefin **5.3** containing the stereochemistry present in *cis*-solamin (**1.240**) will be discussed (Scheme 5.6). The yields were generally improved when the route was repeated with the THF configuration not corresponding to *cis*-solamin (**1.240**) (Scheme 5.7).

Following separation of the diastereoisomeric THF-diols **5.4** and **5.21** by column chromatography, the sultam was cleaved by reduction of **5.4** using $NaBH_4$ to afford triol **5.27** and the recovered auxiliary in excellent yield (Scheme 5.6). Closure of the epoxide **5.29** was carried out by DBU treatment of tosylate **5.28**, obtained by direct mono-tosylation of **5.27** or more efficiently *via* a stannylene derivative of the 1,2-diol. As anticipated, copper-

promoted addition to epoxide **5.29** proceeded without the need for protection of the C-20 hydroxyl group, affording the C-3 to C-32 fragment **5.3** of *cis*-solamin (**1.240**) in 82% yield.



Scheme 5.6 Introduction of the C-15 to C-3 fragment of *cis*-solamin. *Reagents and Conditions:* a) $NaBH_4$, THF/H_2O (3:1) –10 °C to 0 °C; b) TsCl, Et_3N, DMAP, CH_2Cl_2; c) Bu_2SnO, benzene, reflux; then TsCl, TBAB; d) DBU, CH_2Cl_2, 0 °C to rt; e) $CH_2{=}CH(CH_2)_9MgBr$, CuI, THF, –60 °C to –20 °C.

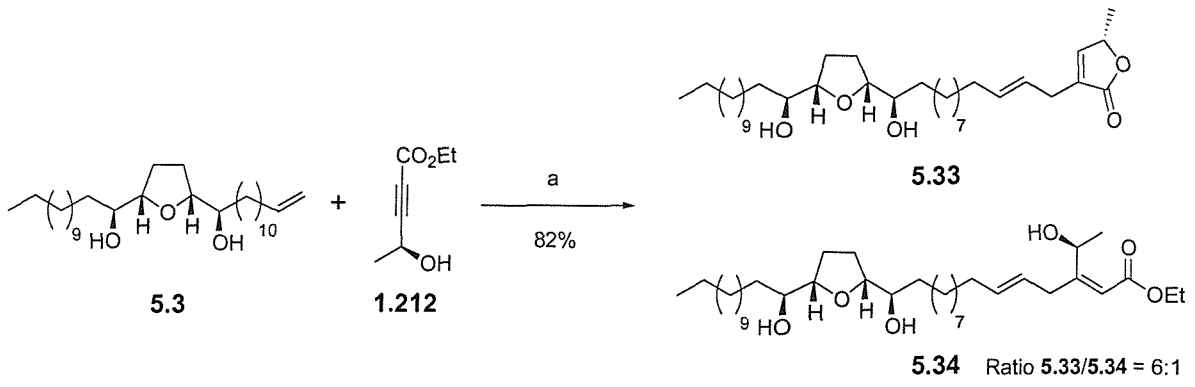


Scheme 5.7 Introduction of the C-15 to C-3 fragment. *Reagents and Conditions:* a) $NaBH_4$, THF/H_2O (3:1) –10 °C to 0 °C; b) Bu_2SnO, benzene, reflux; then TsCl, TBAB; c) DBU, CH_2Cl_2, 0 °C to rt; d) $CH_2{=}CH(CH_2)_9MgBr$, CuI, THF, –60 °C to –20 °C.

5.5 Completion of *cis*-Solamin (1.240) and its Diastereoisomers

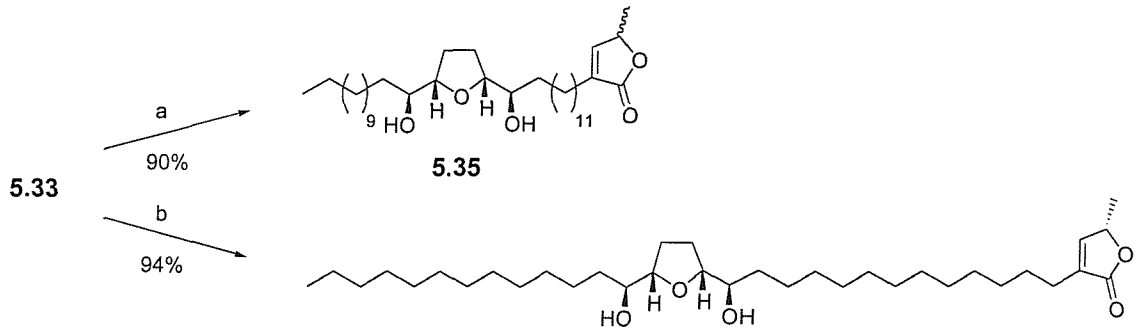
Formal Alder-ene reaction of the terminal olefin **5.3** with alkyne **1.212** was carried out by refluxing the reactants and a catalytic amount of the Ru(II) complex **1.214** in MeOH for 3 h,[107,108] delivering a 6:1 (NMR) mixture of products derived from addition to either end of the alkyne (Scheme 5.8). As noted previously by Trost, the undesired minor regioisomeric

adduct **5.34** is reluctant to cyclise to the corresponding butenolide due to developing $A_{1,2}$ strain, facilitating chromatographic separation of the two products.



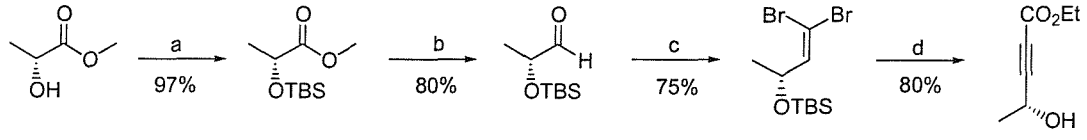
Scheme 5.8 Ruthenium-catalysed butenolide formation. *Reagents and Conditions:* a) CpRu(COD)Cl (**1.214**), MeOH, reflux.

The final step in the synthesis required selective reduction of the C-4/C-5 double bond, a transformation that was well precedented in the literature using careful catalytic hydrogenation in the presence of Wilkinson's catalyst.[46] Initial attempts conducted on a small-scale led to some over reduction of the butenolide ring, and although it was possible to achieve separation of *cis*-solamin (**1.240**) from the mixture by preparative HPLC, complete epimerisation of the C-34 stereocentre in one of our synthetic samples **5.35** was observed (Scheme 5.9). Evidence for epimerisation of the C-34 stereocentre was provided by chiral HPLC using a Chiralcel OD-H HPLC column, eluting with *i*-PrOH/hexane (5:95), which gave two peaks with a ratio of 1:1. The same sample only showed one set of signals in its ^{1}H and ^{13}C NMR spectra. It was subsequently found that diimide reduction provided a convenient and reliable means of reducing **5.33** to *cis*-solamin (**1.240**), without any detectable epimerisation at C-34.[64]

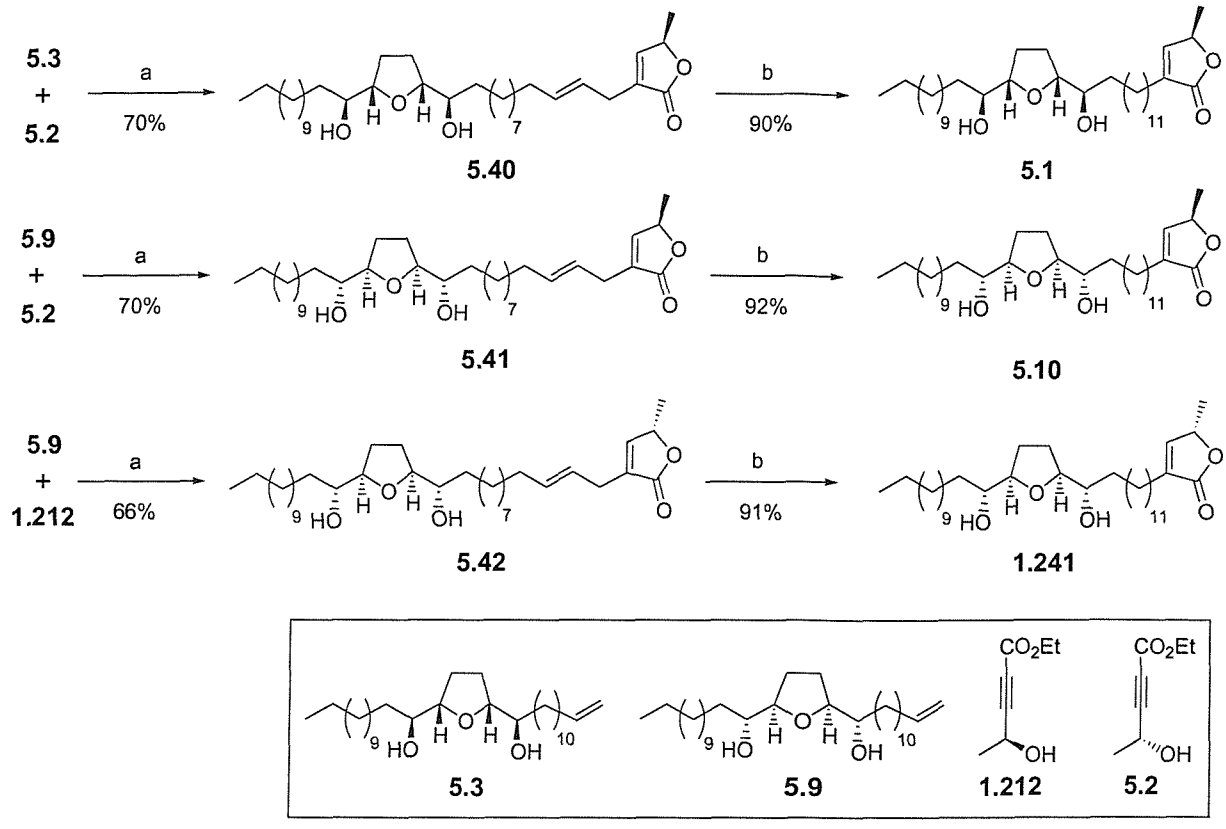


Scheme 5.9 Selective reduction to give *cis*-solamin. *Reagents and Conditions:* a) H_2 (1-2 bar), $Rh(PPh_3)_3Cl$, benzene, EtOH; b) $TsNHNH_2$, NaOAc, THF/H_2O, reflux.

Due to our interest in the relative cytotoxicity of *cis*-solamin analogues and the uncertainty regarding the absolute stereochemistry of the *threo-cis-threo*-THF-diol unit present in the natural product, the three possible diastereoisomers were prepared. In order to create the opposite stereochemistry at C-34, propargylic alcohol **5.2** was synthesised from methyl-(*R*)-lactate **5.36** using the known procedure (Scheme 5.10).[108,192] Thus, terminal olefin **5.3** was coupled to alkyne **5.2** and terminal olefin **5.9** was coupled to both alkyne **5.2** and **1.212** to give butenolides **5.40**, **5.41** and **5.42** respectively in good yield (Scheme 5.11).[108] Subsequent selective reduction gave *cis*-solamin diastereoisomers **5.1**, **5.10** and **1.241** respectively.



Scheme 5.10 Synthesis of the enantiomeric propargylic alcohol. *Reagents and Conditions:* a) TBSCl, Et_3N, DMAP, CH_2Cl_2; b) DIBAL-H, CH_2Cl_2, –78 °C; c) Ph_3P, CBr_4, –78 °C, CH_2Cl_2; d) (i) nBuLi, THF, –78 °C; then ethyl chloroformate to rt; (ii) AcOH, THF, H_2O, 70 °C.



Scheme 5.10 Synthesis of *cis*-solamin diastereoisomers. *Reagents and Conditions:* a) CpRu(COD)Cl (**1.214**), MeOH, reflux; b) $TsNHNH_2$, NaOAc, THF/H_2O, reflux.

The four synthetic *cis*-solamin isomers were indistinguishable from each other and natural *cis*-solamin on the basis of their IR, MS, ^1H NMR and ^{13}C NMR spectra, due to the length and flexibility of the chain connecting the THF-diol and butenolide regions. Optical rotation values obtained for each of the pairs of diastereoisomers (**1.240** & **1.241**, **5.1** & **5.10**) were also very similar and consistent with previous observations that the contribution from the butenolide ring dominates that from a *pseudo*-symmetrical THF region in acetogenins (Table 5.2).[208] Although, all four isomers could be separated by chiral HPLC and were shown to be isomerically pure, it was not possible to determine whether *cis*-solamin had the structure **1.240** or **1.241** due to the lack of an authentic sample of the natural product. When samples **1.240** and **1.241** were combined our HPLC method showed two distinct peaks (Figure 5.3). Therefore if an authentic sample of natural *cis*-solamin could be acquired it would be possible to unequivocally assign its structure.

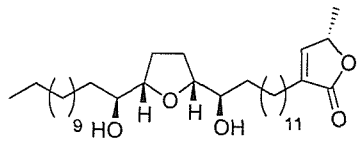
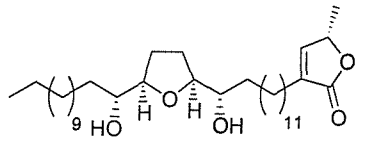
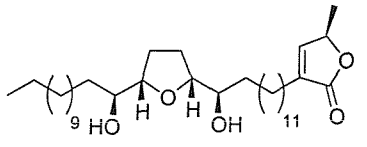
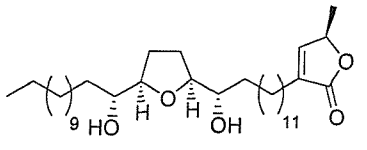
Structure	Optical rotation[a] $[\alpha]^{24}_D$	HPLC retention time[b]
 **1.240**	+11.3	14.5 min
 **1.241**	+11.8	17.3 min
 **5.1**	-11.3	15.7 min
 **5.10**	-11.7	18.7 min
Natural *cis*-solamin	+22[c]	Unknown

Table 5.2 Optical rotation and HPLC data for *cis*-solamin and its isomers. [a] All optical rotation experiments for the synthetic samples were carried out in MeOH. [b] Each of the four isomers (**1.240**, **5.11**, **5.1** and **5.10**) gave a separate and single peak on a Chiral CD-Ph HPLC column, 230 nm, eluting with *i*-PrOH/hexane (15:85). [c] Lit $[\alpha]^{25}_D$ +22 (MeOH, *c* 0.55).[117]

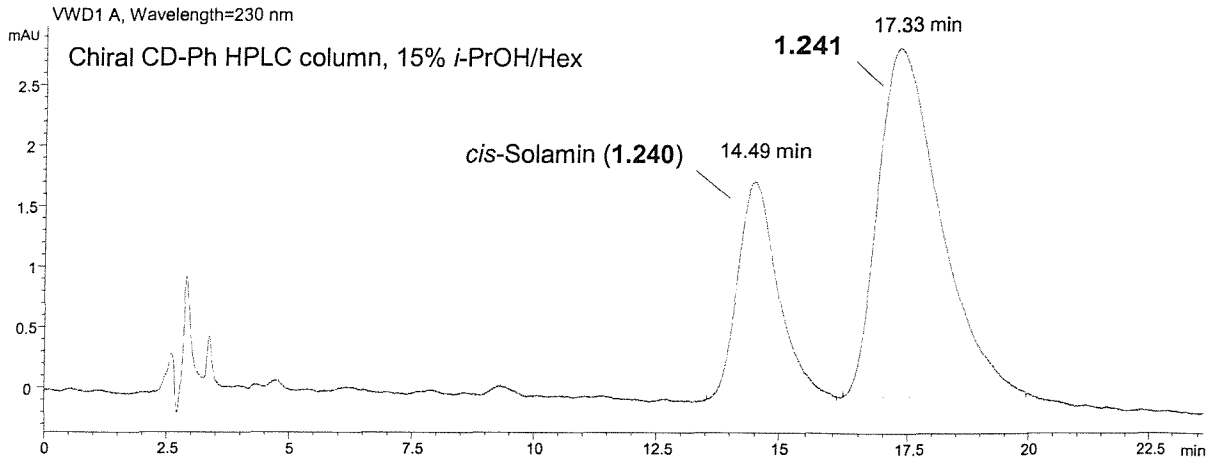


Figure 5.3 Chiral HPLC trace showing separation of compounds **1.240** and **1.241**. *Conditions:* Chiral CD-Ph HPLC column, 230 nm, eluting with *i*-PrOH/hexane (15:85).

Makabe *et al.* published optical rotation values for **1.240** ($[\alpha]^{21}_{D}$ = +26, MeOH, *c* 0.45) and its isomer **1.241** ($[\alpha]^{21}_{D}$ +42, MeOH, *c* 0.50).[116] Both of these values are significantly different from our observed values. It is worth noting that the optical rotation of the 4,5-di-dehydro precursors (**5.33**, **5.40**, **5.41** and **5.42**) closely matched their corresponding *cis*-solamin isomer and it therefore appears likely that our values for the optical rotation are correct. Until a sample of natural *cis*-solamin can be obtained the absolute configuration of the *threo-cis-threo*-THF core remains unresolved as either **1.240** or **1.241**. Therefore until otherwise refuted, structure **1.240** will be regarded as corresponding to natural *cis*-solamin, in agreement with the findings of Makabe and co-workers.

5.6 Conclusion

A concise, efficient and high yielding synthesis of *cis*-solamin (**1.240**) (11 steps, 20% overall yield) and its diastereoisomers using an asymmetric oxidative cyclisation of a 1,5-diene as the key step has been completed. It has been shown for the first time that permanganate promoted oxidations of substrates containing disubstituted olefins can be achieved in high yield (75%). No protecting groups were required throughout the linear synthesis and no step delivered a yield less than 70%.

Our research has shown that the permanganate promoted asymmetric oxidative cyclisation of disubstituted 1,5-dienes is an extremely efficient route to *mono*-THF acetogenins. This methodology could be used to synthesise a variety of *mono*-THF acetogenins and analogues, enabling biological testing to provide valuable insight into the structural activity relationship governing acetogenins.

Chapter 6

Biological Activity of *cis*-Solamin Analogues

The following chapter summarises the biological data that has been obtained courtesy of Dr Maria Vicent (Welsh School of Pharmacy, Cardiff University), who carried out the biological testing of the synthetic samples.

6.1 Biological Activity

The availability of samples of the natural product, its stereoisomers and synthetic intermediates presented an opportunity to examine their biological activity (Figure 6.1).[197] To study the relative influence of the structural and stereochemical features on biological activity, the cytotoxicity and haemolytic activity were evaluated. Understanding the structure activity relationship of these properties is important in relation to the selection of potential candidates for further development as anticancer agents. Cytotoxicity gives an indication of the antitumour activity and the haemolysis model relates to the mechanism of action and also the potential for later intravenous administration.

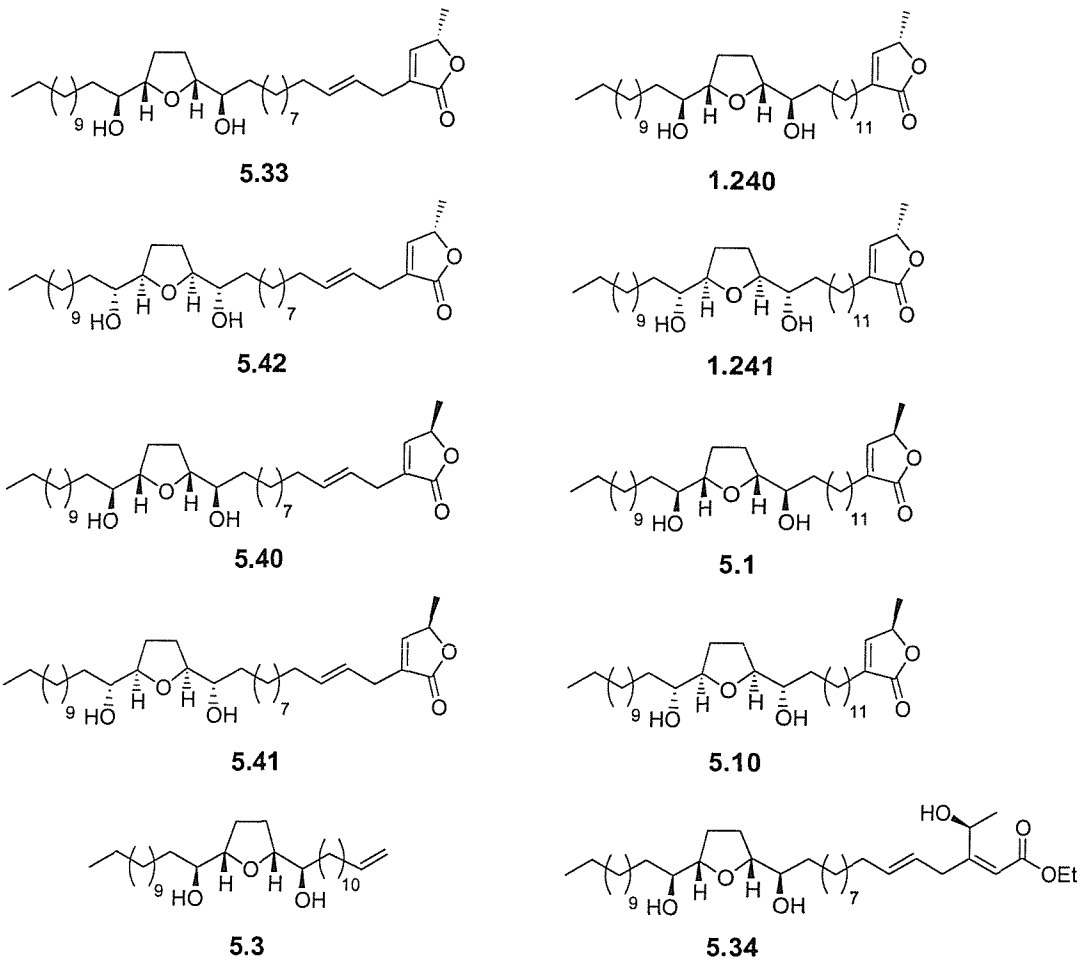


Figure 6.1 Compounds evaluated for their cytotoxic and haemolytic activity

The *in vitro* cytotoxicity of acetogenin derivatives were evaluated using an MTT cell viability assay (72 h incubation) against a B16F10 murine melanoma cell line.[209] Results are expressed as a percentage of viability of cells grown in the absence of drug, but also with 3 % DMSO medium (Table 6.1, Figure 6.2).

Entry	Compound	IC_{50}[a] (μM)	Hb[b] (% control)
1	**5.33**	0.27 ± 0.01	84.0 ± 1.2
2	**5.42**	3.0 ± 0.8	20.4 ± 5.0
3	**5.40**	2.2 ± 0.4	24.7 ± 4.8
4	**5.41**	5.5 ± 0.8	92.1 ± 1.7
5	**1.240**	2.8 ± 0.2	7.0 ± 0.8
6	**1.241**	7.0 ± 1.6	3.6 ± 0.7
7	**5.10**	23.2 ± 0.1	2.9 ± 0.8
8	**5.1**	6.4 ± 0.8	5.6 ± 0.5
9	**5.3**	> 447	1.5 ± 0.4
10	**5.34**	> 336	1.0 ± 0.6

Table 6.1 *In vitro* cytotoxicity and haemolytic properties of acetogenin derivatives. [a] IC_{50} values against B16F10 murine melanoma cell line (seeding density 5x 10^4 cells/mL, 3% DMSO in medium). (n=3, mean ± SD); [b] Haemolysis (% control 1% Triton X-100) at concentration of 0.3 mg/mL, 3 % DMSO in PBS, (n=3, mean ± SD).

All the acetogenin derivatives were active at μM concentrations except for **5.3** and **5.35** (IC_{50} > 447 and 336 μM, respectively). These results are consistent with the previous observation that the terminal lactone ring is a fundamental requirement for antitumoural activity in acetogenins.[2,5,45,48,210] The unsaturated precursor **5.33** to *cis*-solamin (**1.240**) was most potent (IC_{50} = 0.27 ± 0.01 μM) (Figure 6.2). In fact **5.33** was at least 10 times more active than the rest of the acetogenin analogues described and even 100 times more active than **5.10** (IC_{50} = 23.2 ± 0.1 μM). The results are also consistent with previous findings that the absolute stereochemistry of the γ-lactone ring and THF core are not crucial to activity.[211,212] *cis*-Solamin (**1.240**) and its diastereoisomer **5.1** (stereochemistry reversed at C-34) show roughly equal activity (IC_{50} = 2.8 ± 0.2 and 6.4 ± 0.8 μM, respectively), as do compounds **5.40** and **5.41** (IC_{50} = 2.2 ± 0.4 and 5.5 ± 0.8 μM, respectively) where the THF configuration is reversed. Keinan and Sinha found that *trans*-solamin (**1.202**) also displayed similar activity (IC_{50} = 5.1 μM against SK-Mel-28, melanoma).[106] Thus, it appears the

the γ-lactone and the THF core are not a crucial structural feature in determining the cytotoxicity of acetogenins.

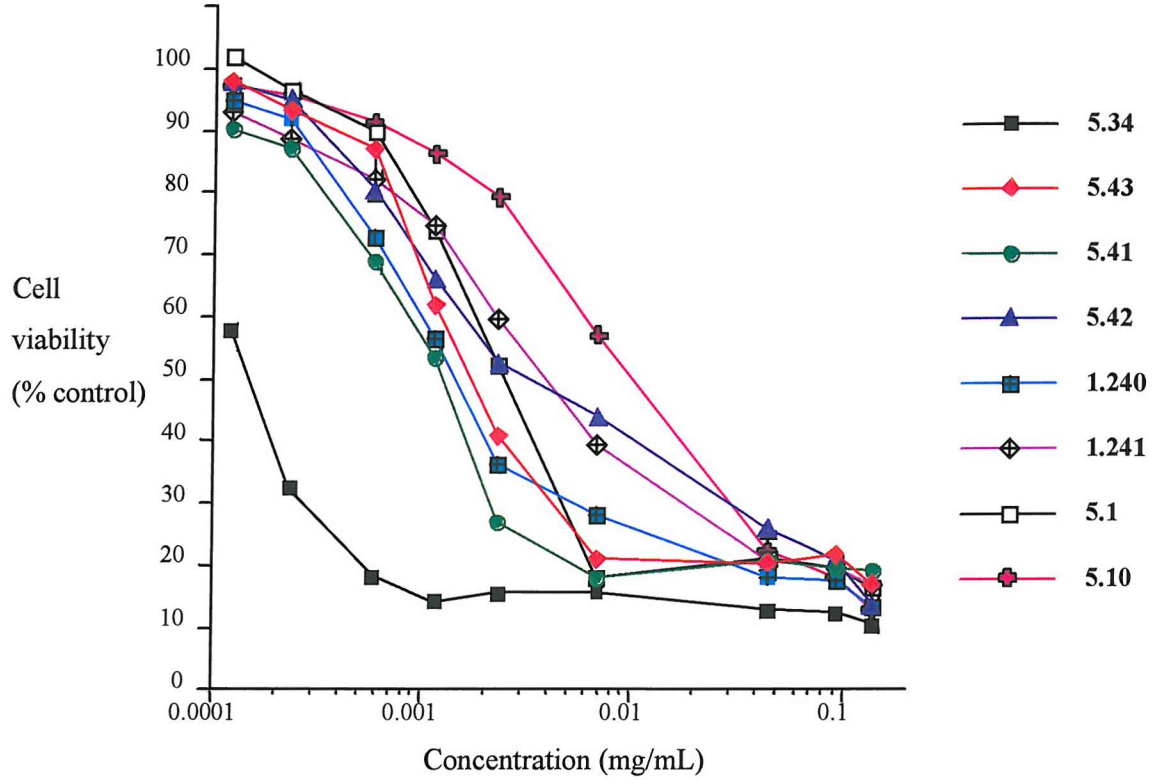


Figure 6.2 IC_{50} values against B16F10 cell line for acetogenin derivatives

However, the haemolytic properties of the acetogenin derivatives studied were clearly related to their structures (Table 6.1 and Figure 6.3). For instance, comparison of the compounds containing the C-4/C-5 unsaturation (Table 6.1, entries 1-4) with the corresponding saturated spacer compounds (Table 6.1, entries 4-8), shows that the presence of the double bond (reduced flexibility) leads to a marked increase in haemolysis. In addition, comparison of the two sets of enantiomers **5.33/5.41** and **5.40/5.42**, which display differences in the relative chirality between the central THF-diol and the butenolide units, showed a distinct decrease in haemolysis (going from 84-92% to approximately 20%).

Further studies using other models are required to better understand structural activity relationships of membrane interactions, but these are the first to investigate such membrane properties.

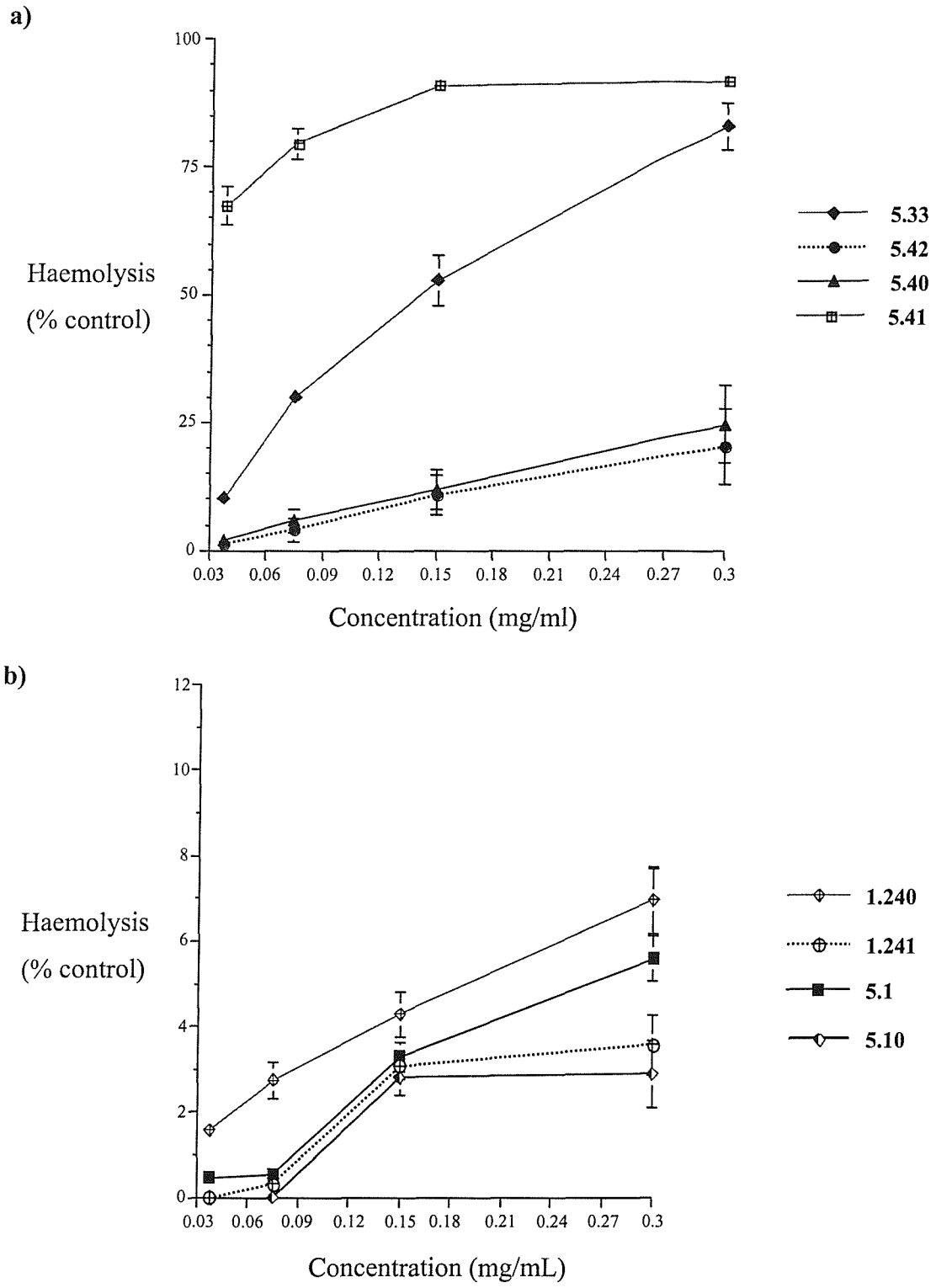


Figure 6.3 1 h Red blood cell lysis assays for acetogenin derivatives. a) *cis*-Solamin unsaturated derivatives; b) *cis*-solamin saturated derivatives. Haemolysis (% control, 1% Triton X-100), 3% DMSO in PBS (n=3, mean ± SD).

Chapter 7

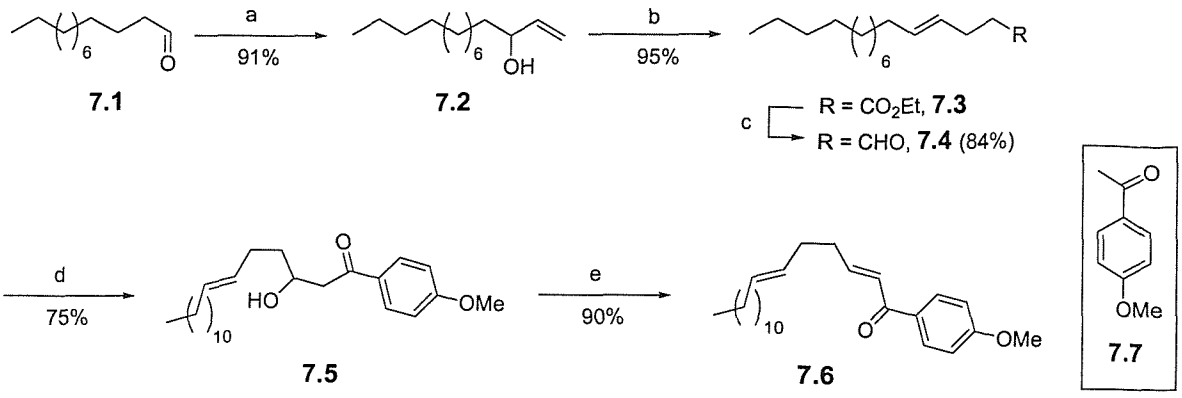
Chiral Phase-Transfer Catalysed Oxidative Cyclisation

The following chapter summarises the results obtained for the chiral phase-transfer catalysed (CPTC) oxidative cyclisation of various 1,5-dienes. Earlier the mechanism for the phase-transfer permanganate oxidation of α,β-unsaturated carbonyls (Section 2.5) and the chiral phase-transfer catalysed nucleophilic epoxidation of α,β-unsaturated phenones (Section 2.6) were discussed. The similarity in the proposed transition states led to the first asymmetric permanganate promoted oxidative cyclisation of 1,5-dienes using a chiral phase-transfer catalyst to be carried out (Section 2.7).[159]

7.1 Preparation of Disubstituted 1,5-Diene Phenones

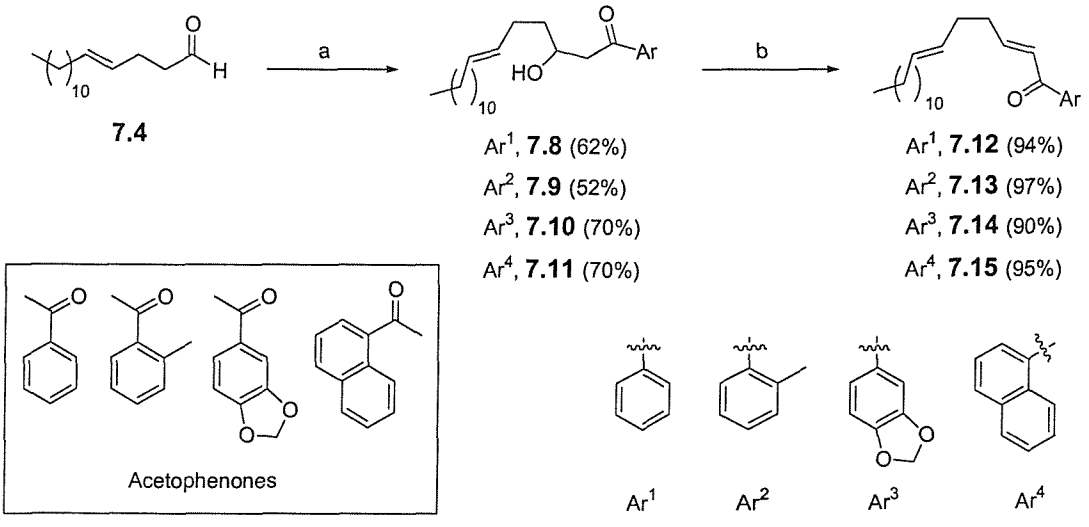
Using the methodology previously applied in the synthesis of *cis*-solamin (**1.240**), aldehyde **7.4** was prepared in two steps from dodecanal (**7.1**) (Scheme 7.1). Thus, addition of vinyl Grignard afforded allylic alcohol **7.2**, which underwent a Johnson-Claisen rearrangement to give enoate **7.3** in excellent overall yield.[213,214] Treatment of enoate **7.3** with DIBAL-H gave aldehyde **7.4**, a useful precursor in the synthesis of 1,5-dienes. Previously, all dienes had been synthesised *via* a Wittig or Horner-Emmons olefination. However, attempts to perform these olefinations with electron rich aromatic Wittig reagents, such as *p*-methoxy, typically gave poor yields (< 20%). Our desire to synthesise electron rich aromatic dienes came from our belief that increasing the electron richness of the aromatic region may lead to improved ee's with the catalyst **2.56**.

Due to the vast array of commercially available aceto-aromatics an aldol/dehydration strategy was seen as an excellent method of creating 1,5-dienes with the required (*E*)-geometry from unsaturated aldehyde **7.4** (Scheme 7.1). Thus, aldol reaction of 4-methoxy acetophenone (**7.7**) with aldehyde **7.4** gave β-hydroxy phenone **7.5** in good yield. Dehydration was accomplished by mesylation then treatment with DBU giving 1,5-diene **7.6** in excellent yield.



Scheme 7.1 Synthesis of disubstituted 1,5-dienes *via* an aldol/dehydration strategy. *Reagents and Conditions:* a) CH_2=CHMgBr, THF, –20 °C; b) triethyl orthoacetate, propionic acid, xylene, reflux; c) DIBAL-H, CH_2Cl_2, –60 °C; d) 4-methoxy acetophenone (**7.7**), LDA, THF, –60 °C; then **7.4**; e) (i) MsCl, Et_3N, CH_2Cl_2; (ii) DBU, CH_2Cl_2.

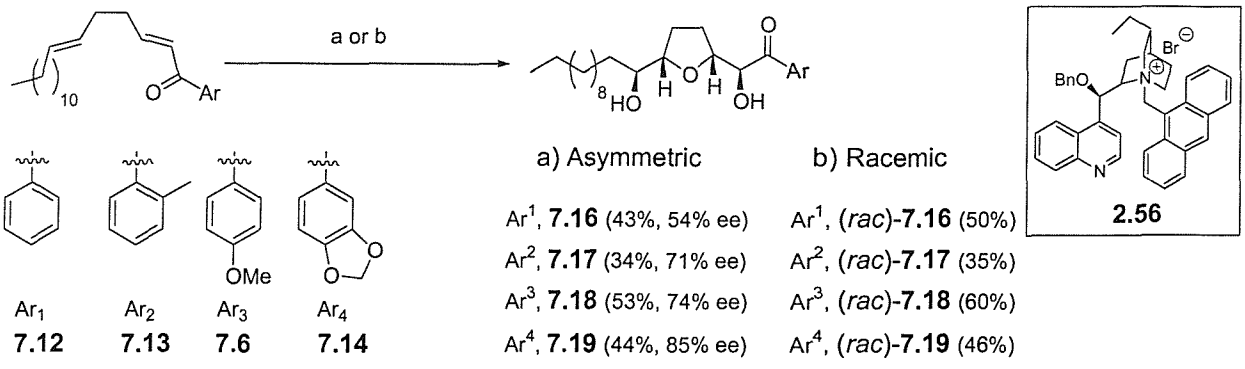
Using this methodology a number of different diene-phenones were synthesised (Scheme 7.2). Care has to be taken during the aldol reaction as the aliphatic aldehyde **7.4** is only sparingly soluble in a wide range of appropriate solvents at temperatures < –60 °C (THF, Et_2O, CH_2Cl_2, $CHCl_3$ and toluene) and will precipitate out causing a marked reduction in yield. The dehydrations all proceeded in good yield to furnish exclusively the desired (*E*)-1,5-dienes.



Scheme 7.2 Synthesis of disubstituted 1,5-dienes. *Reagents and Conditions:* a) acetophenone analogue, LDA, THF, –60 °C; then **7.4**; b) (i) MsCl, Et_3N, CH_2Cl_2; (ii) DBU, CH_2Cl_2.

7.2 Chiral Phase-Transfer Catalysed Oxidative Cyclisation of Disubstituted 1,5-Diene Phenones

Following on from the initial work on the chiral phase-transfer catalysed oxidative cyclisation of 1,5-dienes,[159] the tertiary ammonium salt **2.56** was synthesised in three steps from cinchonidine according to the known procedure.[160] The chiral phase-transfer catalysed oxidative cyclisations were carried out on the prepared 1,5-dienes using previously optimised conditions (Scheme 7.3).[160] The dienes were also cyclised under racemic conditions in order to obtain both enantiomers for chiral HPLC. Pleasingly, improved ee's were obtained for the substrates with aromatic substitution. The highest ee (85%) was observed for the electron rich 3,4-methylenedioxy-derivative **7.19**, with both *p*-methoxy-derivative **7.18** and *o*-methyl-derivative **7.17** giving much improved ee's (74% and 71%, respectively) over the unsubstituted phenone **7.16** (54% ee).



Scheme 7.3 Chiral phase-transfer catalysed oxidative cyclisations. *Reagents and Conditions:* asymmetric a) $KMnO_4$ (1.6 eq), AcOH (8 eq), 10 mol% cinchonidine derivative **2.56**, CH_2Cl_2, –60 °C, 3 h; racemic b) $KMnO_4$ (1.3 eq), AcOH (16 eq), adogen 464 (10 mol%), CH_2Cl_2, –30 °C to –10 °C.

The effect of the solvent on the yield and ee were then briefly investigated for the oxidative cyclisation of dienes **7.6** and **7.14** (Figure 7.1). Previous results had shown that an increase in solvent polarity gave a marked decrease in ee.[160] Therefore, an investigation was undertaken to discover whether a decrease in the solvent system polarity gave rise to an increase in ee. A less polar solvent system should allow for a tighter ion pair to form in the transition state and hence increase the ee. The results showed that increasing the proportion of toluene had little effect on the ee, but decreased the yield substantially. The dual solvent system (1:1 CH_2Cl_2/toluene) gave good results for the oxidation of diene **7.6**; however the

yield dropped remarkably for diene **7.14**. A further decrease in yield was observed when toluene was the sole solvent. This can be explained as tertiary ammonium salt **2.56** is only partially soluble in toluene at –60 °C. As the results showed that a reduction in solvent polarity had a negative effect on the reaction outcome, the investigation into the optimum solvent system was halted and CH_2Cl_2 was judged to be the solvent of choice for the CPTC oxidative cyclisation of dienes of this type.

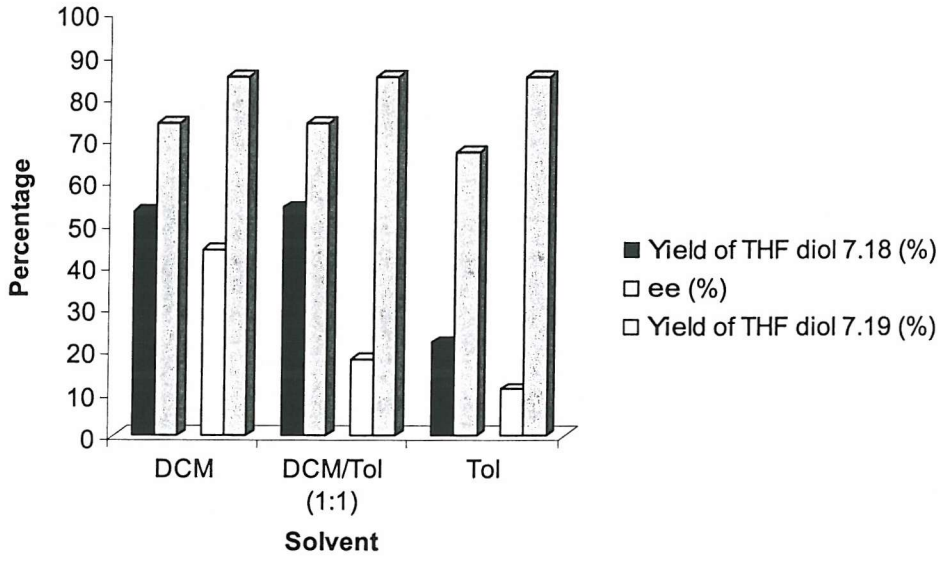
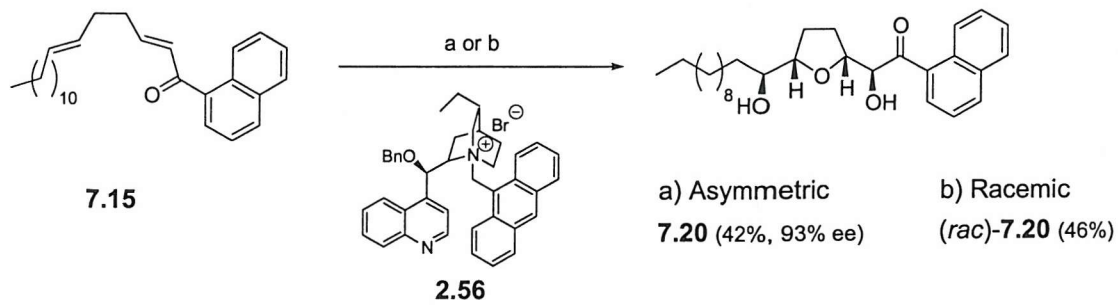


Figure 7.1 Effect of Solvent on the chiral phase-transfer catalysed oxidative cyclisation. *Reagents and Conditions:* $KMnO_4$ (1.6 eq), 10 mol% cinchonidine derivative **2.56**, AcOH (8 eq), solvent, –60 °C, 3 h.

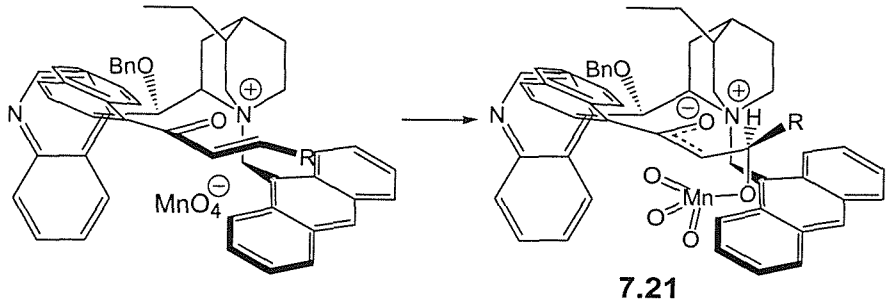
With these promising ee's in hand the next substrate that was cyclised was 1-napthphone **7.15** (Scheme 7.4). The yield obtained, after the standard 3 h reaction time at –60 °C, was moderate (42%, SM remained). However, the asymmetric induction was excellent (93% ee).



Scheme 7.4 Asymmetric induction achieved by 1-naphthone group. *Reagents and Conditions:* a) $KMnO_4$ (1.6 eq), AcOH (8 eq), 10 mol% cinchonidine derivative **2.56**,

CH_2Cl_2, –60 °C, 3 h; racemic b) $KMnO_4$ (1.3 eq), AcOH (16 eq), adogen 464 (10 mol%), CH_2Cl_2, –30 °C to –10 °C.

To get this level of asymmetric induction the following geometry in the transition state is required (Scheme 7.5): the α,β-enone in the complex is situated so that the naphthyl group is wedged between the ethyl and quinoline substituents and simultaneously the carbonyl oxygen is placed as close to N^+ as permitted by Van der Waals forces. Upon attack by permanganate the negative charge which is developed (Section 2.5, Scheme 2.12) at the carbonyl oxygen in transition state **7.21** is electrostatically stabilised by the proximate N^+ of tertiary ammonium salt **2.56**. This leads to the major product having the stereochemistry depicted (Scheme 7.4), which was unambiguously proven by crystal structure (Figure 7.3) and formal synthesis (Section 7.4), and was in agreement with the predicted facial attack in the asymmetric nucleophilic epoxidation of α,β-unsaturated phenones using **2.56**.[168,172]



7.21

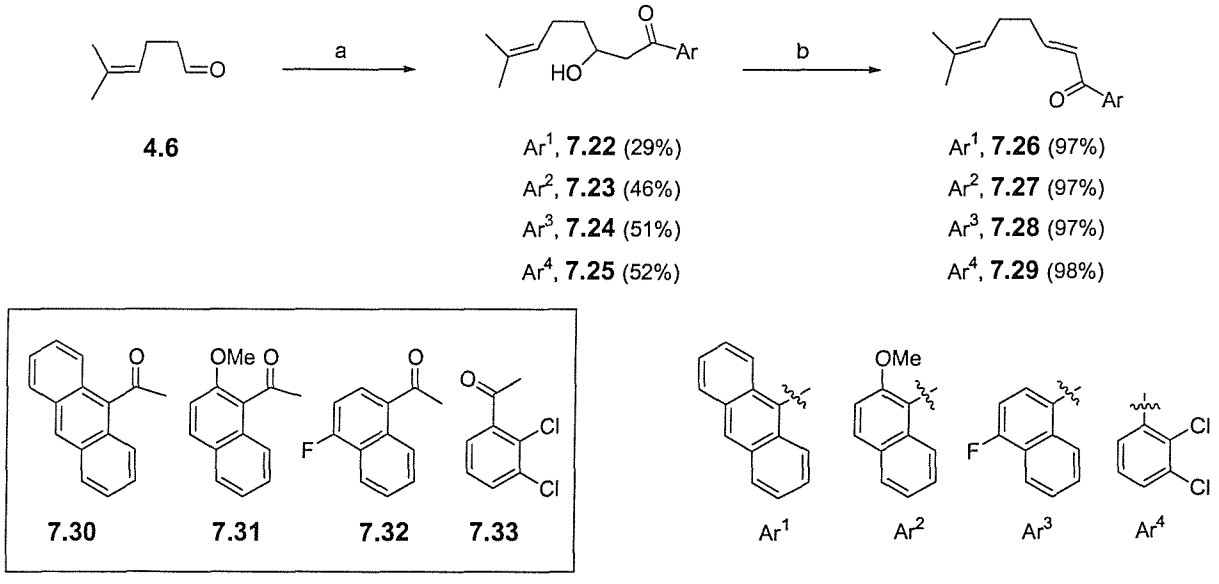
Scheme 7.5 Predicted transition state for the permanganate promoted oxidative cyclisation by tertiary ammonium salt **2.56**

The level of asymmetric induction shown for the 1-napthphone group was sufficiently high (93% ee = d.r. 27:1) to consider the first formal synthesis of an acetogenin *via* a transition metal-oxo species promoted chiral phase-transfer catalysed oxidative cyclisation (Section 7.4).

The yields obtained for the chiral phase-transfer catalysed oxidative cyclisation of disubstituted dienes to give 2,5-disubstituted THF-diols containing four new chiral centres (54-93% ee) were moderate to good (34-53%). Especially when considering that until our publication of the synthesis of *cis*-solamin (**1.240**),[196] the general perception was that the permanganate promoted oxidative cyclisation of disubstituted olefins was low yielding.[206,207]

7.3 Preparation and Oxidation of 1-Naphthone Analogues

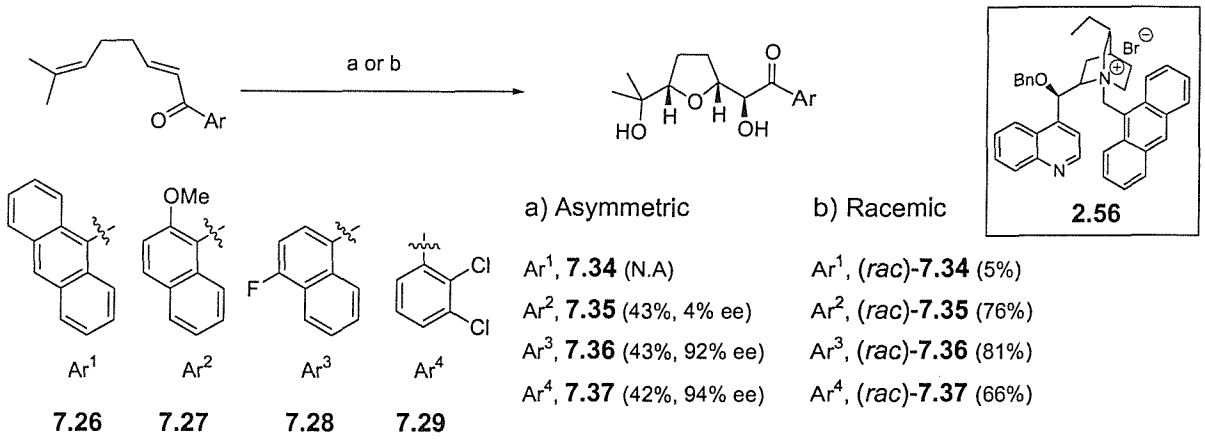
Having achieved an excellent level of asymmetric induction with the 1-naphthone group, a series of analogues were synthesised (Scheme 7.6). To categorically prove the absolute stereochemistry a crystalline derivative of the cyclised product was required, from which the crystal structure could be solved. The long aliphatic chain was extremely detrimental to obtaining a crystal structure so aldehyde **4.6**, used in our initial model study, was seen as the solution. The analogues selected were structurally similar to 1-naphthone, either containing substitution on the ring or, in the case of 2,3-dichloroacetophenone (**7.33**), *ortho*, *meta* substitution equivalent to the second ring of the 1-naphthyl group. Commercially available 2-hydroxy-1-acetonaphthone was methylated in quantitative yield to give methoxy naphthone **7.31** according to the known procedure.[215] The aldol reactions all proceeded in moderate yield to give the corresponding β-hydroxy naphthones, except for the 9-anthryl derivative **7.22**. Dehydration by mesylation then treatment with DBU furnished the 1,5-dienes in near quantitative yield.



Scheme 7.6 Synthesis of 1,5-diene naphthone analogues. *Reagents and Conditions:* a) acetophenone analogue, LDA, THF, –60 °C; then **4.6**; b) (i) MsCl, Et_3N, CH_2Cl_2; (ii) DBU, CH_2Cl_2.

The four naphthone analogues (**7.26**, **7.27**, **7.28** and **7.29**) were then racemically cyclised using the optimised AcOH/acetone (2:3) system to give the corresponding racemic THF-diols (Scheme 7.7). Diene **7.26**, containing the 9-anthryl group, practically refused to

undergo the oxidative cyclisation (5%), giving a complex mixture of products. However, the two naphthyl dienes **7.27** and **7.28** underwent oxidative cyclisation in the best yields achieved to date (76% and 81%, respectively). The asymmetric oxidative cyclisations were equally pleasing, with both 4-fluoro-naphthone **7.28** and 2,3-dichlorophenone **7.29** undergoing an equal level of asymmetric induction (92% and 94% ee, respectively) as naphthone **7.15** (93% ee). The similarity in shape between phenone **7.29** and naphthone **7.15** is apparent; both rings substituted in the 2- and 3-positions. This structural similarity gives an almost identical level of asymmetric induction. It appears that additional substitution in the 4-position of the 1-naphthone group **7.28** has neither a beneficial or detrimental effect. Interestingly, when the 2-position of the naphthone group was substituted, **7.27**, asymmetric induction was completely removed (93 to 4% ee). This can be accounted for by steric hindrance, the substituted naphthyl group is too large to be wedged between the ethyl and quinoline substituents on the tertiary ammonium salt **2.56**.



Scheme 7.7 Asymmetric oxidation of naphthone analogues. a) $KMnO_4$ (1.6 eq), AcOH (8 eq), 10 mol% cinchonidine derivative **2.56**, CH_2Cl_2, –60 °C, 3 h; racemic b) $KMnO_4$ (1.3 eq), adogen 464 (10 mol%), AcOH/acetone (2:3), –30 °C to 0 °C.

Pleasingly, the THF-diols **7.35**, **7.36** and **7.37** were crystalline solids, with the crystal of 4-fluoro-naphthone **7.36** obtained as a single enantiomer after recrystallisation (EtOAc/hexane) (Figure 7.2). However, to establish the absolute stereochemistry a heavy atom (usually Br in organic compounds) was required in the structure.

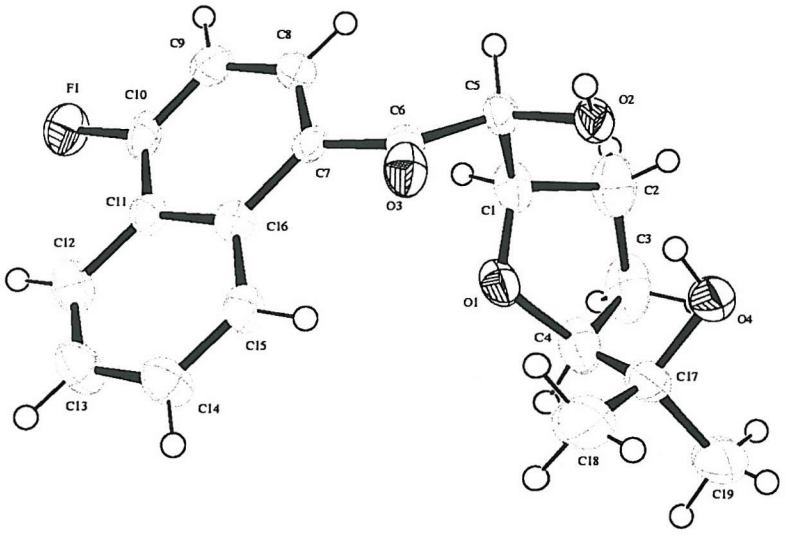
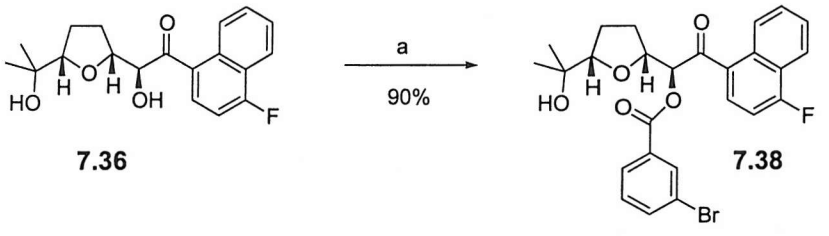


Figure 7.2 Crystal structure of THF-diol **7.36** as a single enantiomer

Using conditions optimised for acylation of THF-diols (Section 7.4, Scheme 7.11), **7.36** was selectively benzoylated at the secondary alcohol with 3-bromobenzoyl chloride without any detectable epimerisation (Scheme 7.8). After recrystallisation (EtOAc/hexane) crystals were obtained of a single enantiomer corresponding to the predicted stereochemistry (Figure 7.3, Scheme 7.5), though the bromobenzoate group was found to be in two orientations due to rotation and its unsymmetrical structure. The absolute stereochemistry of **7.38** was consistent with the observed facial attack in the asymmetric nucleophilic epoxidation of phenones using tertiary ammonium salt **2.56**.[168,172]



7.36 **7.38**

Scheme 7.8 Introduction of a heavy atom by formation of a benzoate derivative of **7.36**. *Reagents and Conditions:* a) bromobenzoyl chloride, Py, DMAP, CH_2Cl_2, 0 °C.

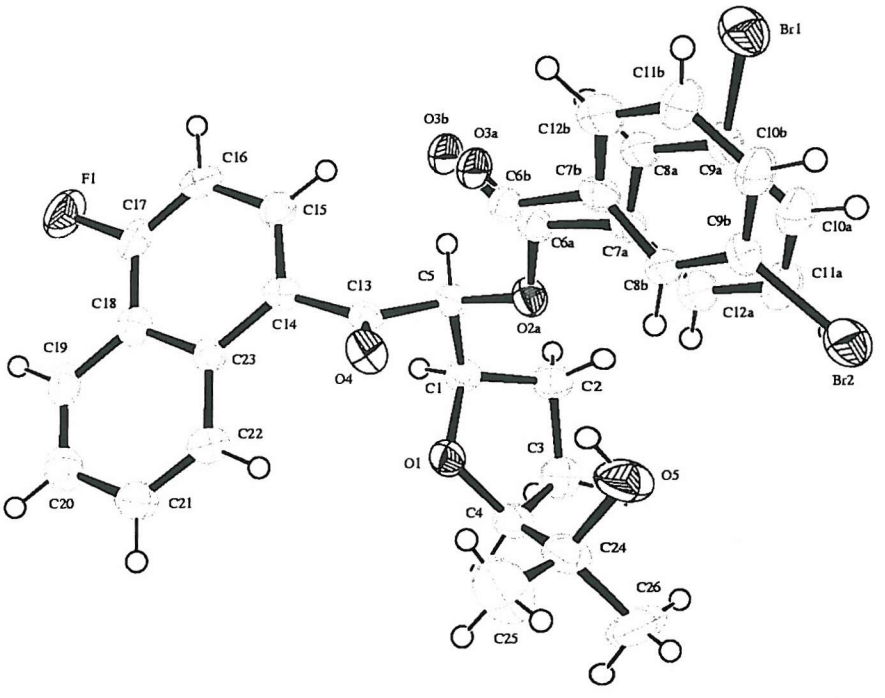


Figure 7.3 Crystal structure of bromobenzoyl derivative **7.38**, which unequivocally proved absolute stereochemistry for the oxidative cyclisation using tertiary ammonium salt **2.56**

Having accomplished an excellent level of asymmetric induction using 1,5-diene phenones (Figure 7.4) and ascertaining the absolute stereochemistry, the formal synthesis of *cis*-solamin (**1.240**) was instigated.

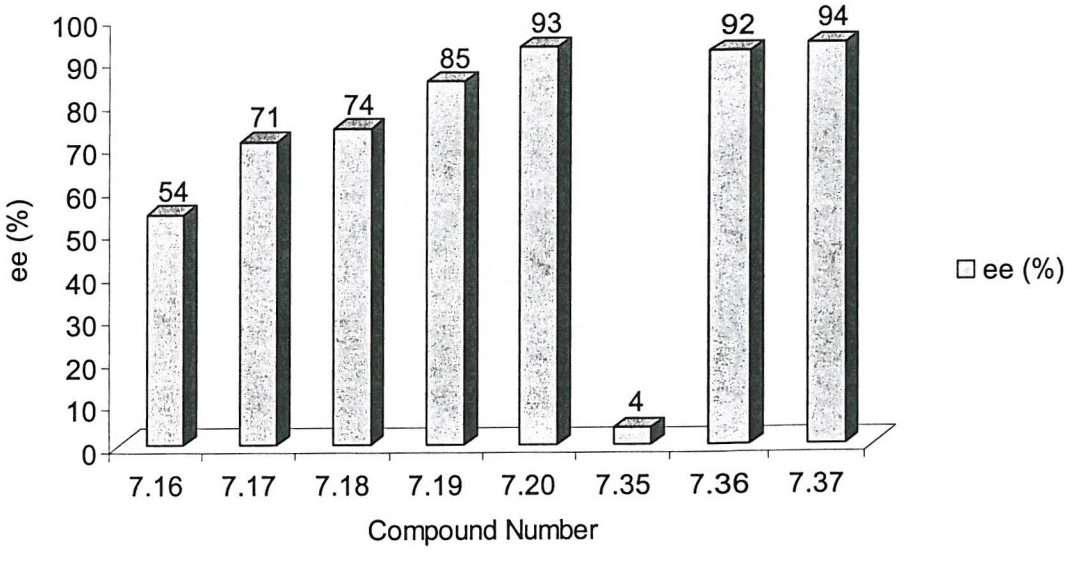
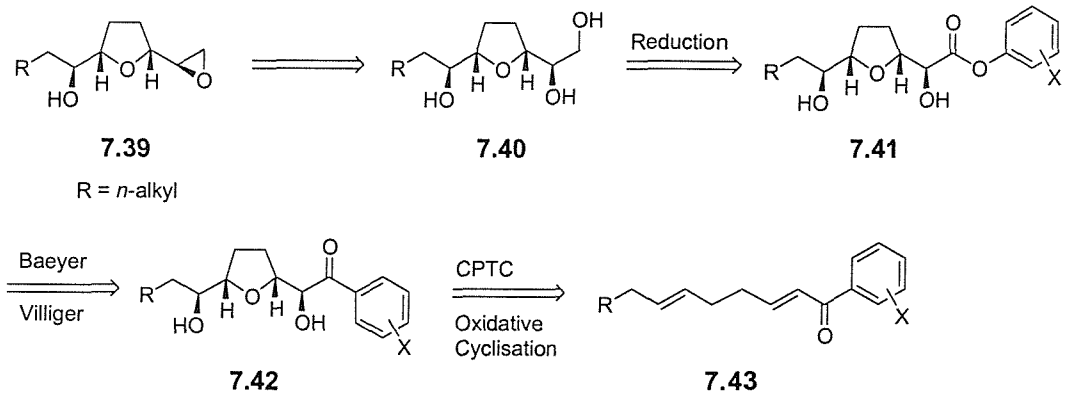


Figure 7.4 Effect of the phenone structure on the ee for the asymmetric oxidative cyclisation

7.4 Formal Synthesis of *cis*-Solamin (1.240) *via* CPTC Oxidative Cyclisation

With excellent ee's obtained for the asymmetric oxidative cyclisation of phenones (up to 94%), it was necessary to demonstrate that the phenone functional group could be transformed into a useful functional group, such as an epoxide, and complete a formal synthesis of a natural product (Scheme 7.9). It was proposed this could be achieved by performing a Baeyer-Villiger reaction[216,217] on the phenone **7.42**, giving the aromatic ester **7.41** which could then be reduced to form the 1,2-diol **7.40**. Conversion to the epoxide **7.39** could be accomplished by the methods employed in our synthesis of *cis*-solamin (**1.240**) (Section 5.4).



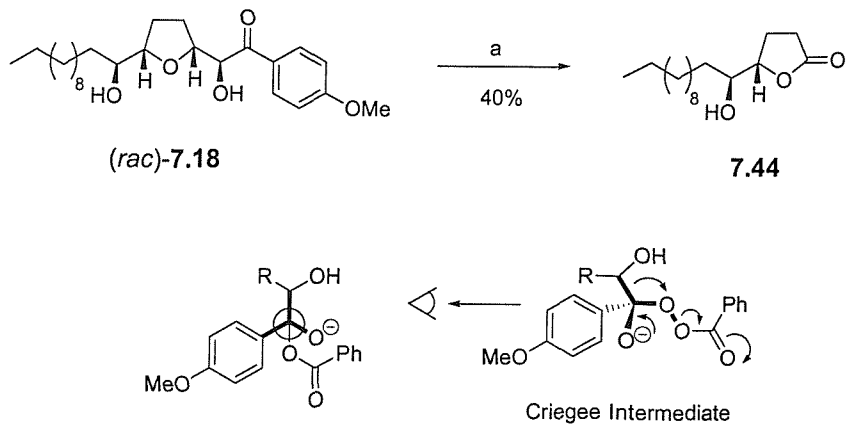
7.39 R = *n*-alkyl **7.40** **7.41** **7.42** **7.43**

Scheme 7.9 Baeyer-Villiger approach to the CPTC formal synthesis of acetogenins

In the Baeyer-Villiger reaction the migrating group (decomposition of the Criegee intermediate) is determined by two prevalent factors:

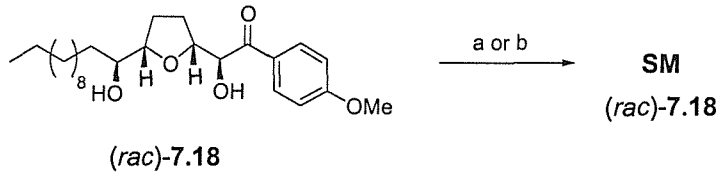
1. Groups which can best support a positive charge are more likely to migrate.
2. Migration occurs from the favoured rotomer of the Criegee intermediate, which has the bulkier group antiperiplanar to the leaving group (Scheme 7.10).

Hence electron donating groups on the phenyl ring should aid its migration. Unfortunately when the Baeyer-Villiger reaction was carried out on phenone (*rac*)-**7.18**, the alkyl group migrated causing the oxygen insertion to be on the left-hand-side of the carbonyl and after a series of transformations culminating in an oxidation gave lactone **7.44** as the only identifiable product (Scheme 7.10).



Scheme 7.10 Attempted Baeyer-Villiger reaction. *Reagents and Conditions:* a) MCPBA, CH_2Cl_2.

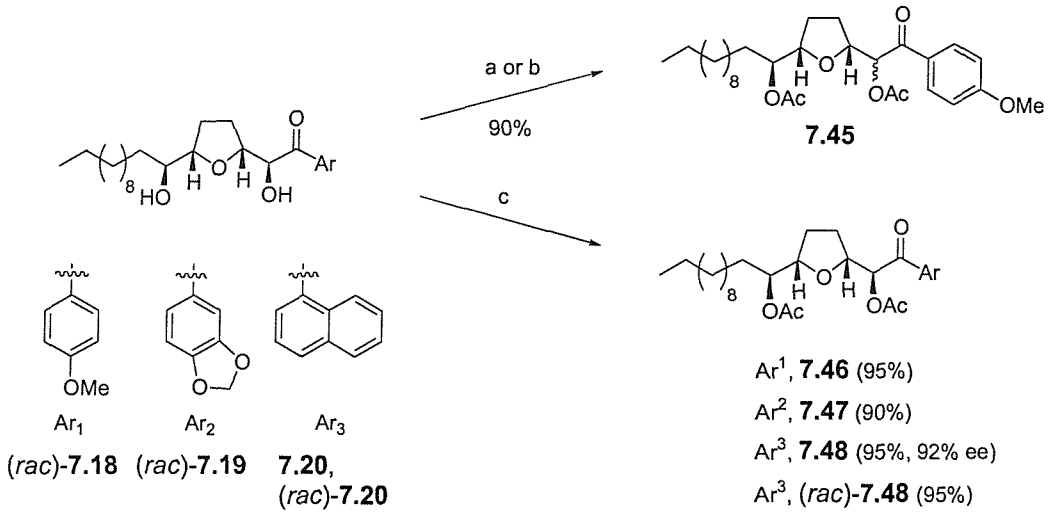
Protection of the hydroxyl groups was then investigated, with the intention of performing the Baeyer-Villiger reaction on the *bis*-protected phenone. The initial attempt involved the formation of silyl-ethers, however this proved futile due to steric hindrance. As expected TBSCl and TIPSCl were too bulky to react and due to the presence of the carbonyl the more reactive triflates were not used. At this point it was decided to move away from silyl protecting groups and try to form the *bis*-acetate. This was first attempted under mild enzymatic conditions using isoprenylacetate as the donor (Scheme 7.11). Neither enzyme acylated either of the hydroxyl groups present in phenone (*rac*)-**7.18**.



Scheme 7.11 Failed enzyme acylation. *Reagents and conditions:* a) NOVOZYM435, isoprenylacetate, 40 °C, 3 days; b) Lipase Ps 'Amano', isoprenylacetate, 40 °C, 3 days.

The chemical acylation using acetyl chloride and base was then investigated on a range of the prepared THF-diol phenones. At first Et_3N was used as the base, the alcohols were acylated but the stereocentre α to the carbonyl was completely epimerised, giving **7.45** in good yield (Scheme 7.11). Switching to Hünnig's base resulted in the same epimerisation. Pyridine was tried but the reaction would not go to completion, with a mixture of *bis*- and *mono*-acetates isolated. However, there appeared to be no epimerisation (^{1}H NMR). The

addition of catalytic DMAP with pyridine improved the rate of reaction but it still refused to go to completion, pleasingly there was still no epimerisation. The reaction was finally got to go to completion by using stoichiometric amounts of DMAP with excess pyridine, giving the *bis*-acetate in near quantitative yield with no detectable epimerisation. A sample of **7.48** was analysed by chiral HPLC resulting in a 92% ee, before acylation **7.20** showed a 93% ee. The racemic *bis*-acetate (*rac*)-**7.20** was isolated as colourless plates, which allowed the crystal structure to be solved and confirmed the relative stereochemistry (Figure 7.5).



Scheme 7.11 Acylation of THF phenones. *Reagents and Conditions:* a) AcCl, Et_3N, CH_2Cl_2, 0 °C; b) AcCl, $(^iPr)_2NEt$, CH_2Cl_2, 0 °C; c) AcCl, Py (10 eq), DMAP (2 eq), CH_2Cl_2, 0 °C, 2 h.

The Baeyer-Villiger reaction was then attempted but to no avail (Scheme 7.12). MCPBA gave no reaction under any of the conditions tried: CH_2Cl_2 at rt, CH_2Cl_2 at reflux or $CHCl_3$ at reflux for 3 days. The stronger peracid, trifluoroperacetic anhydride (TFPAA), was then used. The rate determining step of the Baeyer-Villiger reaction is the migration, therefore using the peracid with the best leaving group should enhance the rate. However, no reaction was observed with TFPAA, with quantitative recovery of starting material after 3 days. The *bis*-acetyl protection had the desired effect of stopping the alkyl migration, however this did not make the aromatic migration prevalent, instead no migration was observed.

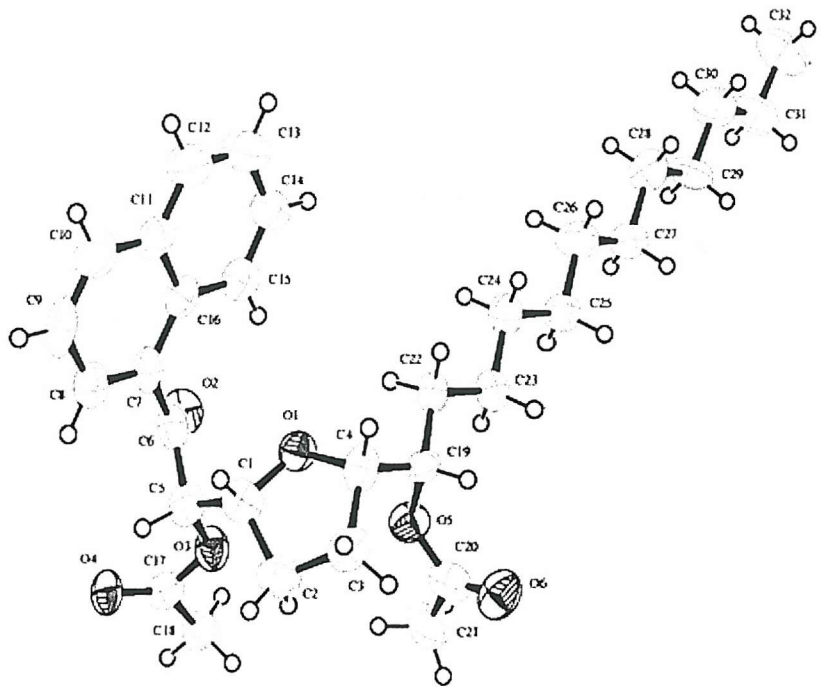
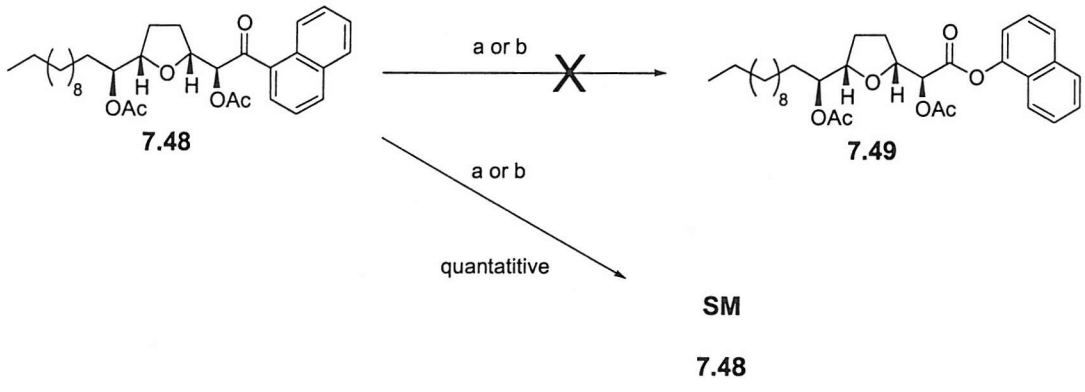


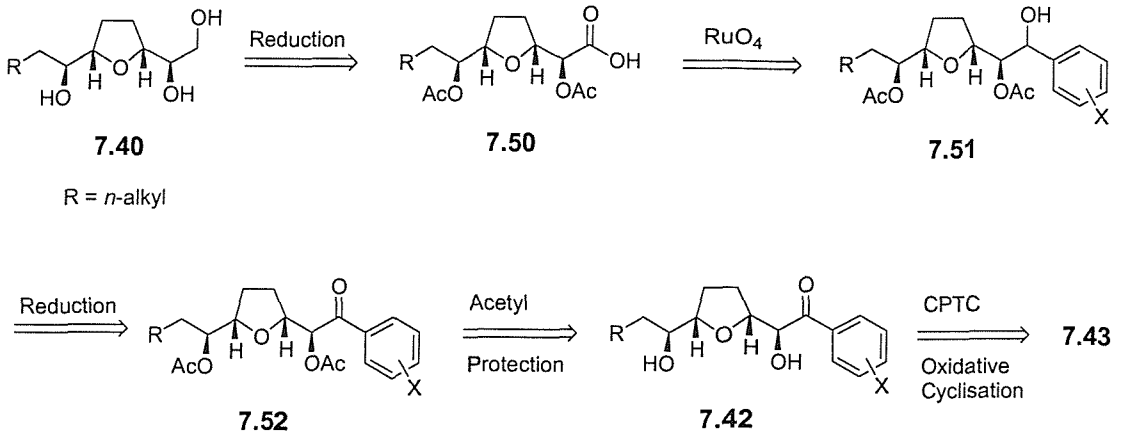
Figure 7.5 Crystal structure of *bis*-acetate (*rac*)-**7.48**



Scheme 7.12 Failed Baeyer-Villiger Reaction on the protected phenone. *Reagents and Conditions:* a) MCPBA, $CHCl_3$, reflux; b) TFAA, H_2O_2 (30% w/v), CH_2Cl_2.

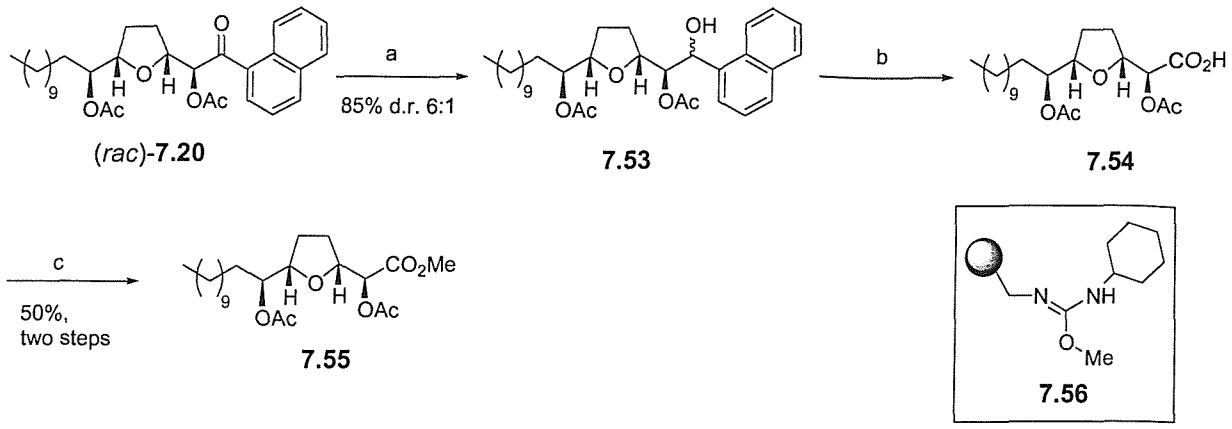
At this stage, other possible functional group transformations applicable to our system were examined. The use of ruthenium tetroxide in the oxidative degradation of electron rich aromatics to give carboxylic acids was seen as a plausible solution.[218-220] There were examples in the literature where α–stereocentres were not epimerised[221] and other examples where an α,β-diol was cleaved and oxidised to the corresponding acid.[222] The idea was to

combine both of these reported observations; oxidatively degrading back to the α-hydroxyl group (present in **7.51**), which would be oxidised to the acid, without epimerising any of the stereocentres (Scheme 7.13). Reduction of the acid **7.50** would lead to the 1,2-diol **7.40**, which with the correct alkyl chain length would be an intermediate from the synthesis of *cis*-solamin (**1.240**), thus completing the formal synthesis.



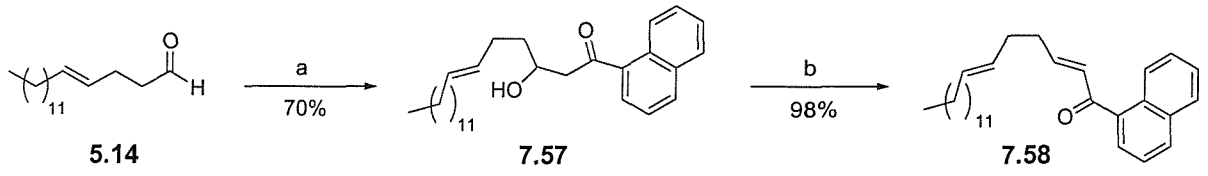
Scheme 7.13 Ruthenium tetroxide approach to the CPTC formal synthesis of acetogenins

The predicted route was optimised with the material already available, thus THF naphthone **7.20** and (*rac*)-**7.20** (both one-carbon short of the alkyl chain length corresponding to that of *cis*-solamin (**1.240**)) were used. Sodium borohydride reduction of the ketone (*rac*)-**7.20** gave secondary alcohol **7.53** (d.r. 6:1) in good yield (Scheme 7.14). Gratifyingly, this allowed ruthenium tetroxide, generated *in situ*,[222,223] to oxidatively degrade the naphthone group to acid **7.54**. This was a pleasing result as there was a lot of potential for side-reactions to occur, not to mention possible epimerisation under the extremely harsh oxidising conditions. The acid **7.54** was not purified but converted to its methyl ester to enable column chromatography and full characterisation. This was accomplished using resin bound reagent **7.56**,[224] a source of Me^+ after protonation on nitrogen, as there is a strong driving force for the formation of urea. Direct reduction of the crude acid **7.54** was attempted on a small scale with BH_3•DMS, however no alcohol was isolated. Therefore methylation of the crude acid **7.54** was deemed the priority to prove its formation and allow purification and full characterisation as the methyl ester **7.55**.



Scheme 7.14 Optimisation of the formal synthesis route. *Reagents and Conditions:* a) $NaBH_4$, MeOH, -15 °C; b) 20 mol % $RuCl_3 \cdot H_2O$, H_5IO_6, CH_3CN, CCl_4, H_2O; c) **7.56**, THF, reflux.

With the required functional group transformations almost completed the formal synthesis of *cis*-solamin (**1.240**) *via* a permanganate promoted chiral phase-transfer catalysed oxidative cyclisation commenced. Thus, aldehyde **5.14** was reacted in an aldol reaction with 1-acetonaphthone (**7.19**) to give β–hydroxy ketone **7.57** in good yield (Scheme 7.15). Dehydration by mesylation then treatment with DBU gave 1,5-diene **7.58** in near quantitative yield.



Scheme 7.15 Formal synthesis: synthesis of the 1,5-diene naphthone. *Reagents and Conditions:* a) 1-acetonaphthone (**7.19**), LDA, THF, –60 °C; then **5.14**; b) (i) MsCl, Et_3N, CH_2Cl_2; (ii) DBU, CH_2Cl_2.

With a plentiful amount of 1,5-diene **7.58** a study into the effect of temperature on the ee of the oxidative cyclisation was undertaken (Figure 7.6). To ensure good asymmetric induction ion pair formation between permanganate and the catalyst **2.56**, and binding of the substrate diene to the catalyst **2.56** are crucial. As these are entropically disfavoured processes, a reduction in the reaction temperature should facilitate tighter binding of permanganate and

the diene with the catalyst **2.56** and give enhanced asymmetric induction. With this in mind, the temperature of the reaction was to be raised to more convenient temperatures and the reduction in ee was to be measured. It was hoped that a rise in temperature would support only a slight loss of ee but allow an increase in reaction rate and hence an increased yield.

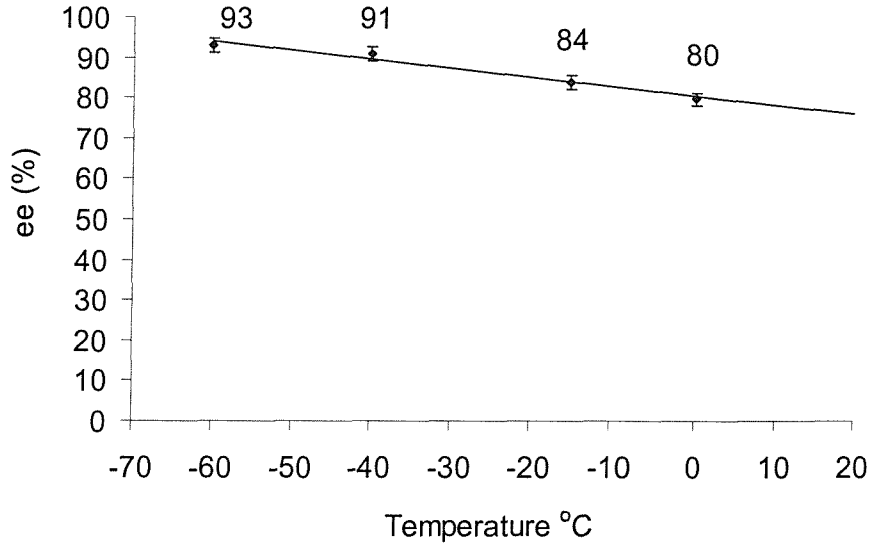
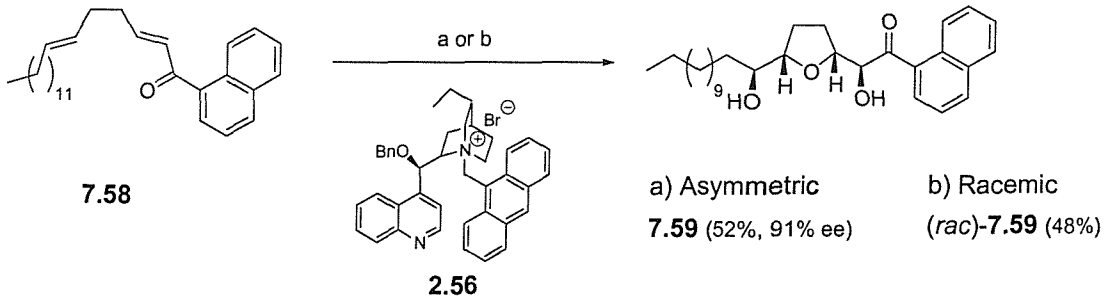


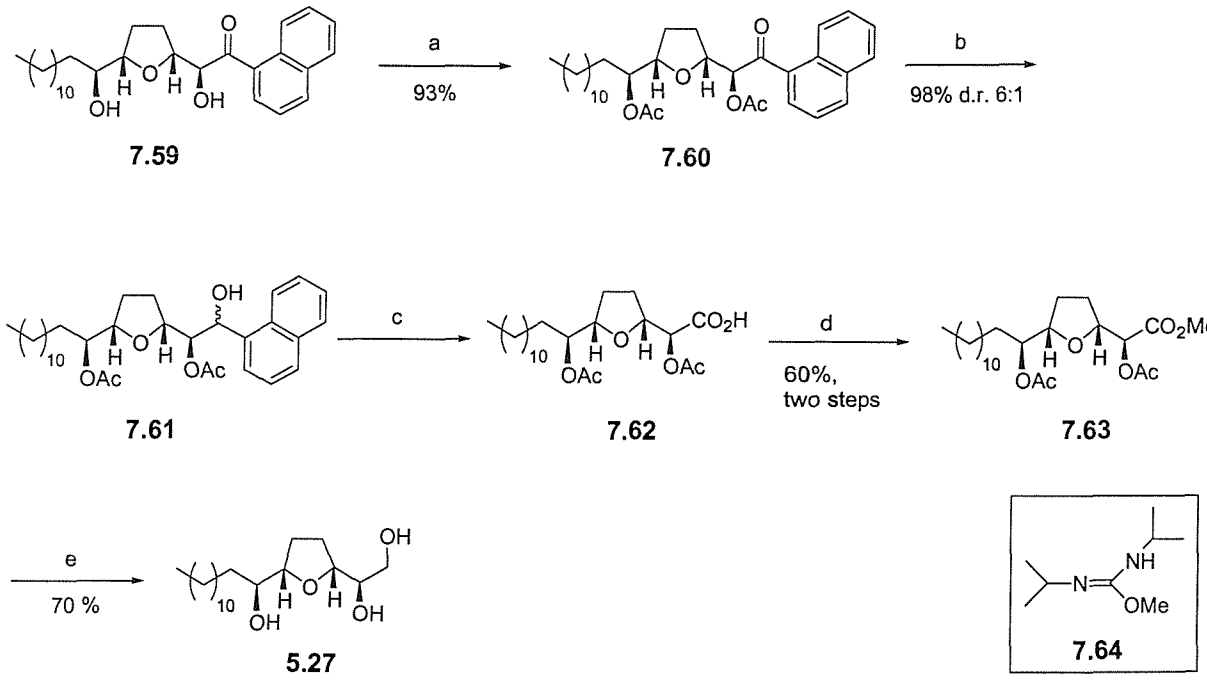
Figure 7.6 Effect of temperature on the asymmetric induction for diene **7.58**

At –40 °C an excellent 91% ee was obtained (only a 2% reduction for a decrease of 20 °C), and when repeated on a larger scale (0.5 g) a good yield (52%) was achieved for the permanganate promoted CPTC oxidative cyclisation, which was superior to the yield (48%) obtained under the racemic conditions (Scheme 7.16).



Scheme 7.16 Asymmetric induction achieved by 1-naphthone group at –40 °C. *Reagents and Conditions:* asymmetric a) $KMnO_4$ (1.6 eq), AcOH (8 eq), 10 mol% cinchonidine derivative **2.56**, CH_2Cl_2, –40 °C, 3 h; racemic b) $KMnO_4$ (1.3 eq), adogen 464 (10 mol%), AcOH/acetone (2:3), –30 °C to –10 °C.

Protection of the hydroxyl groups as the corresponding acetates was achieved using the aforementioned conditions in excellent yield to give ketone **7.60**, which was reduced with sodium borohydride to the secondary alcohol **7.61** (d.r. 6:1) (Scheme 7.17). The oxidative degradation of the α-hydroxy naphthyl group to the carboxylic acid was realised using ruthenium tetroxide, which was generated *in situ*.[222,223] Methylation of the crude acid **7.62** with isourea **7.64** gave the methyl ester **7.63** in good yield with no detectible epimerisation (^{1}H NMR). Reduction of the methyl ester and acetates was accomplished in one-step using lithium aluminium hydride giving triol **5.27** in good yield and completing the formal synthesis of *cis*-solamin (**1.240**).

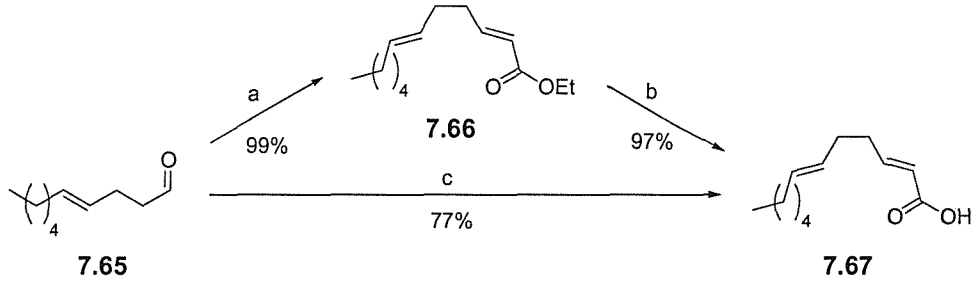


Scheme 7.17 Completion of the formal synthesis of *cis*-solamin (**1.240**). *Reagents and Conditions:* a) AcCl, Py (10 eq), DMAP (2 eq), CH_2Cl_2, 0 °C, 2 h; b) $NaBH_4$, MeOH, -15 °C; c) 20 mol % $RuCl_3 \cdot H_2O$, H_5IO_6, CH_3CN, CCl_4, H_2O; d) *O*-methyl-*N*-*N'*diisopropylisourea (**7.64**), THF, reflux; e) $LiAlH_4$, Et_2O, 0 °C.

The optical rotation value obtained for triol **5.27** prepared *via* CPTC oxidative cyclisation ($[\alpha]^{24}_D = -10.3$ (MeOH, *c* 0.17), > 90% ee) closely matched the homochiral **5.27** prepared *via* dienoyl sultam oxidation ($[\alpha]^{25}_D$ −10.5 (MeOH, *c* 0.40). This also proved the absolute stereochemistry of the THF-diol produced in the CPTC oxidative cyclisation using cinchonidine derived salt **2.56** (discussed in Section 7.2).

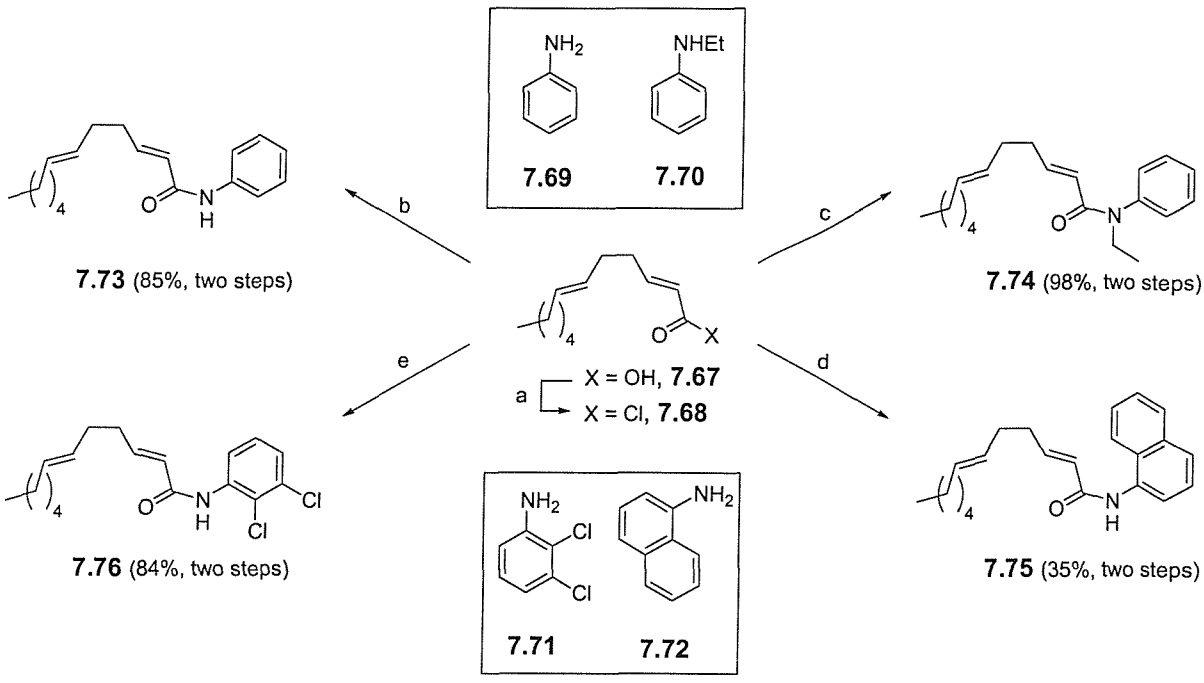
7.5 Chiral Phase-Transfer Catalysed Oxidative Cyclisation of Amides and Esters

Having completed a comprehensive investigation into the effect of the phenone structure in the CPTC oxidative cyclisation our attention turned towards amide and ester functional groups. Previously, the attempted oxidative cyclisation of a phenyl ester had failed to yield any THF product,[160] however no amides had been investigated. It was felt that the asymmetric oxidative cyclisation of these functional groups would be an important addition to the scope of the reaction. Due to the unpredictability and risk (explosion) involved in the formation of aldehyde **4.6**, and not to mention its particularly pungent odour, a new route to a 1,5-diene was undertaken (Scheme 7.18). Starting from the commercially available aldehyde **7.65** (also quite malodorous) Horner-Emmons olefination with triethyl phosphonoacetate gave 1,5-dienoate **7.66** in near quantitative yield. Subsequent hydrolysis gave the dienoic acid **7.67** in excellent yield. A one-step method from commercially available aldehyde **7.65** was also utilised; a Knoevenagel condensation with malonic acid in pyridine gave the 1,5-dienoic acid **7.67** in good yield. Both of these methods were an efficient way of preparing large quantities of dienoic acid **7.67**, from which a selection of amides and esters were synthesised.



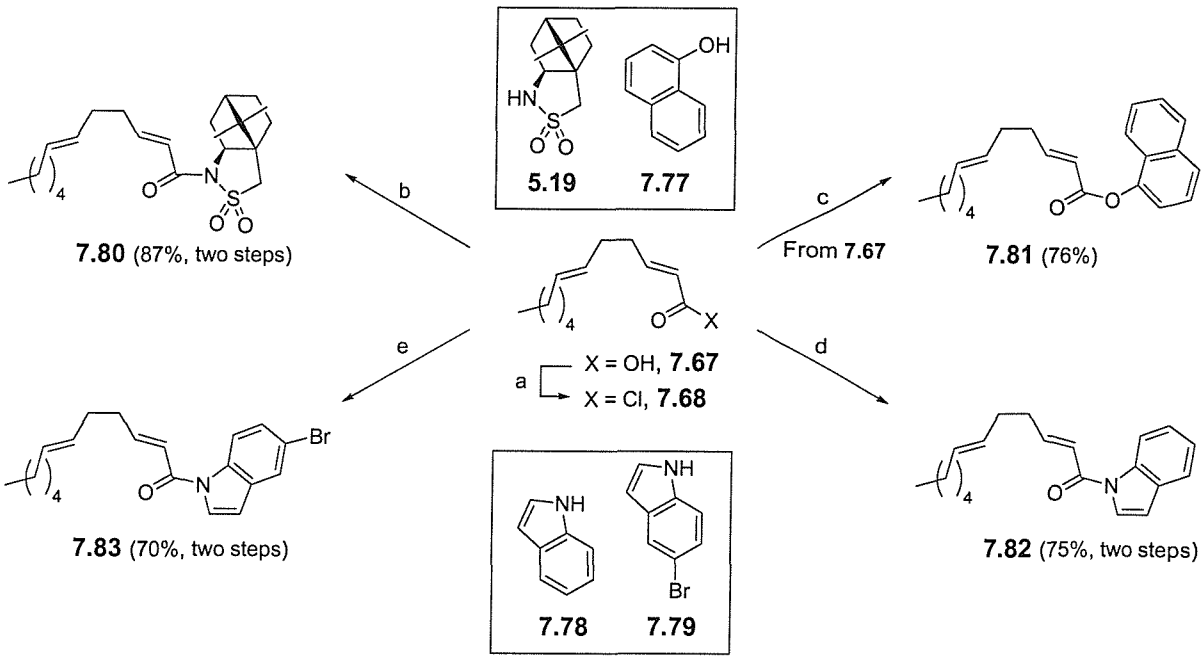
Scheme 7.18 Synthesis of 1,5-dienoic acid. *Reagents and Conditions:* a) triethyl phosphonoacetate, NaH, CH_2Cl_2; then **7.65**; b) MeOH, NaOH, $NaHCO_3$, H_2O, reflux; c) malonic acid, Py, rt; then reflux.

As there were no examples of CPTC oxidative cyclisations of amides, and due to the failed oxidative cyclisation of a phenyl ester,[160] the former was chosen as the main functional group to investigate. The substrates which gave the best ee's in the phenone series were the 1-naphthyl and 2,3-dichlorophenyl groups, therefore it seemed logical to mimic these structures with the corresponding amide and ester substrates. Hence amines **7.69**, **7.70**, **7.71** and **7.72** were acetylated using the acid chloride **7.68** derived from dienoic acid **7.67**, giving the corresponding secondary and tertiary amides **7.73**, **7.74**, **7.75** and **7.76** (Scheme 7.19).



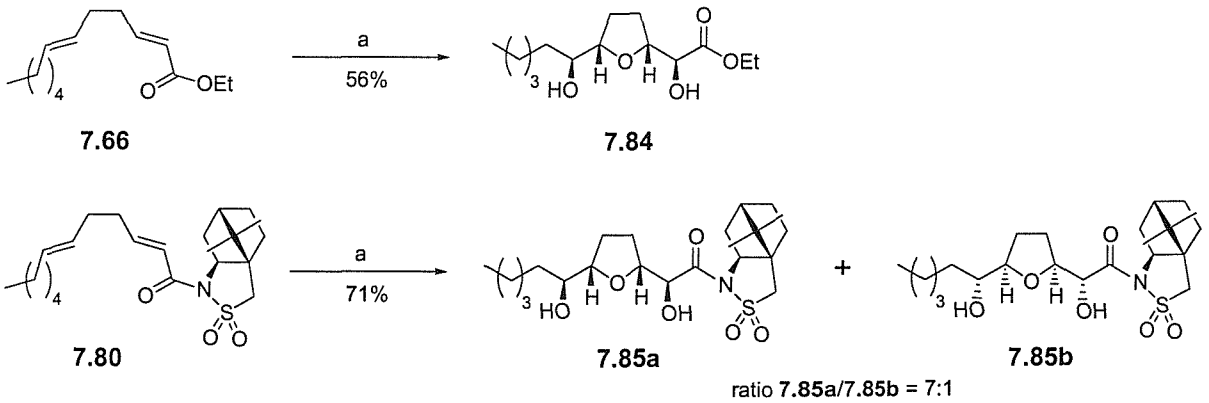
Scheme 7.19 Amine acylation with a diene acid chloride. *Reagents and Conditions:* a) DMF, $(COCl)_2$, CH_2Cl_2, 0 °C; b) aniline (**7.69**), **7.68**, NaOH, CH_2Cl_2; c) **7.70**, **7.68**, NaOH, CH_2Cl_2; d) 1-naphthylamine (**7.72**), **7.68**, NaOH, CH_2Cl_2; e) **7.71**, **7.68**, NaOH, CH_2Cl_2;

The 1-naphthyl ester **7.81** was prepared from acid **7.67** by esterification with 1-naphthol (**7.77**) using DCC as the coupling reagent (Scheme 7.20). This allowed direct comparison between the three functional groups (phenone, amide and ester), which all contained the 1-naphthyl structure (**7.58**, **7.76** and **7.81**, respectively). Indoles were also seen as being potentially useful substrates, mimicking the 1-naphthone structure but containing the more versatile amide bond. As the amide bond would be attached to the nitrogen atom contained in the five-membered ring, the one-atom extension between the carbonyl and the aromatic group, present in the other amides, is removed. The phenyl ring in the indole structure is joined at the 2- and 3-positions, similar to the substitution in the phenone substrates which gave the highest ee's. Therefore it was hoped that equivalent ee's to the phenone series would be observed with indoles. Thus, amides **7.82** and **7.83** were prepared from indole (**7.78**) and 5-bromoindole (**7.79**), acylating with acid chloride **7.68** in good yield. Dienoyl sultam **7.80** was also prepared using the aforementioned conditions.



Scheme 7.20 Formation of amide and ester dienes. *Reagents and Conditions:* a) DMF, $(COCl)_2$, CH_2Cl_2, 0 °C; b) **5.19**, NaH, CH_2Cl_2, 0 °C; then **7.68**; c) 1-naphthol (**7.77**), **7.67**, DCC, CH_2Cl_2 d) indole (**7.78**), **7.68**, NaOH, CH_2Cl_2; e) indole **7.79**, **7.68**, NaOH, CH_2Cl_2.

The racemic oxidative cyclisation was first carried out on the prepared 1,5-diene ester **7.66** and sultam **7.80** to give the corresponding THF-diols in good yield (Scheme 7.21). The 7:1 ratio of THF-diol **7.85a/7.85b** was based on isolated yield.



Scheme 7.21 Racemic oxidative cyclisation of dienes. *Reagents and Conditions:* a) $KMnO_4$ (1.3 eq), adogen 464 (10 mol%), AcOH/acetone (2:3), –30 °C to 0 °C.

The oxidative cyclisations were then carried out on the prepared 1,5-diene ester and amides (from Scheme 7.19 and Scheme 7.20) using the racemic AcOH/acetone 2:3 method to give

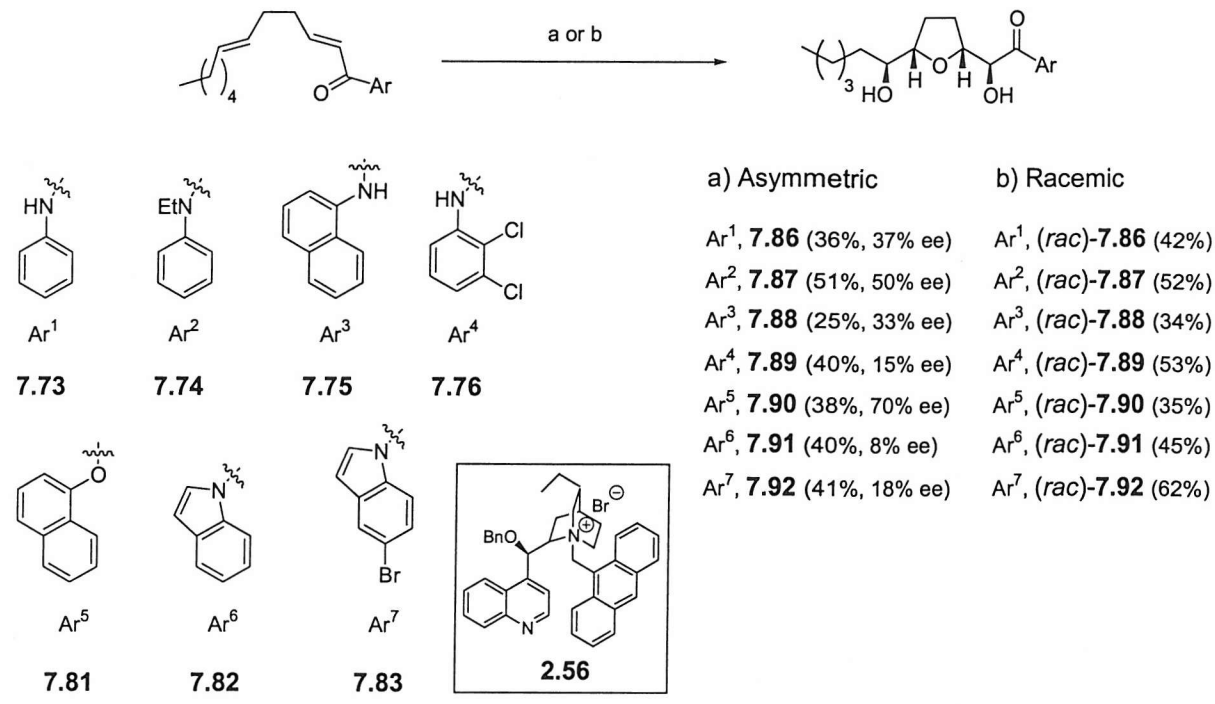
both enantiomers of the corresponding THF-diols (Scheme 7.22). The yields varied from good to poor (62-34%), with the bromoindole THF (*rac*)-**7.92** isolated in the highest yield (62%) as a crystalline solid (EtOAc/hexane). It was pleasing to ascertain that indoles and both secondary and tertiary amides were cyclised under the seemingly harsh oxidising conditions in good yield. The presence of the free N-H in the cyclisation did not prevent the oxidative cyclisation, although it did appear to lower the yield. Comparing otherwise identical secondary and tertiary amides **7.86** and **7.87** shows a decrease in yield from 52% to 42%, respectively. Interestingly, the naphthyl ester was oxidatively cyclised to give THF-diol (*rac*)-**7.90** (35%). Although isolated in low yield, this contradicted the previous finding that phenyl esters were unsuitable substrates for the permanganate promoted phase-transfer oxidative cyclisation.[160]

Next, the CPTC oxidative cyclisations were carried out on the aforementioned dienes to give the corresponding enantiomerically enriched THF-diols (Scheme 7.22, Figure 7.7). Generally the ee's obtained were very disappointing (8-70%), with the naphthyl ester **7.90** possessing the highest level of asymmetric induction (70% ee). The addition of the oxygen-atom spacer appeared to have decreased the asymmetric induction substantially (93% to 70% ee for **7.58**/**7.90**). This marked decrease in ee was even more significant in the amide series; with naphthyl-amide **7.88** (33% ee) and 2,3-dichlorophenyl-amide **7.89** (15% ee) losing nearly all the asymmetric induction which was present in the corresponding phenones (93% ee and 94% ee for **7.58** and **7.37**, respectively). Surprisingly, the secondary and tertiary phenyl amides (**7.86** and **7.87**) contained a slightly higher level of asymmetric induction (37% and 50%, respectively). However, this was still well below the levels observed for the phenone series.

The THF indole **7.91** showed practically no asymmetric induction (8% ee) with only a slight increase observed for the bromo derivative **7.92** (18% ee), which was isolated as a crystalline solid (EtOAc/hexane) and its crystal structure solved. The crystals were a 1:1 mixture of enantiomers, preventing the absolute stereochemistry from being confirmed.

The functional group compatibility of the permanganate promoted CPTC oxidative cyclisation was pleasing; secondary, tertiary and indole amides were all cyclised in good yield with some promising ee's (8-70% ee, Figure 7.7). As of yet, no amide or ester substrate has been identified which can rival the phenone series for asymmetric induction.

However, both the permanganate promoted CPTC oxidative cyclisation and the racemic method have proved themselves applicable to the cyclisation of aromatic amides and esters.



Scheme 7.22 Asymmetric induction achieved by diene ester and amides. *Reagents and Conditions:* a) $KMnO_4$ (1.6 eq), AcOH (8 eq), 10 mol% cinchonidine derivative **2.56**, CH_2Cl_2, –60 °C, 3 h; racemic b) $KMnO_4$ (1.3 eq), adogen 464 (10 mol%), AcOH/acetone (2:3), –30 °C to –10 °C.

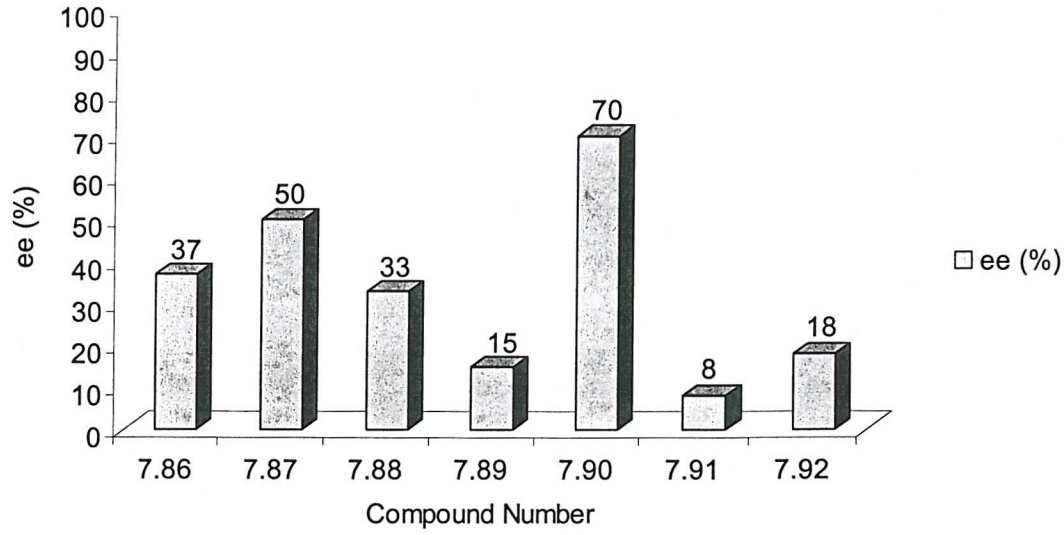


Figure 7.7 Effect of the amide and ester group on the ee for the asymmetric oxidative cyclisation

7.6 Conclusion

The permanganate promoted CPTC oxidative cyclisation of 1,5-dienes has been investigated, realising excellent ee's for the phenone series (Figure 7.8). Two functional groups, 1-naphthyl and 2,3-dichlorophenyl, display ee's in excess of 90%.

This excellent level of asymmetric induction was utilised *via* the formal synthesis of *cis*-solamin (**1.240**). The key steps were the permanganate promoted CPTC oxidative cyclisation (52%, 93% ee) and the oxidative degradation of the naphthyl group to the carboxylic acid without epimerisation.

The permanganate promoted CPTC oxidative cyclisation was demonstrated to induce moderate levels of asymmetry in a selection of aromatic amides (Figure 7.8). This was the first example of the CPTC oxidative cyclisation of substrates of this type. The reaction allowed both secondary and tertiary amides, as well as indole amides to be cyclised to the corresponding THF-diols in reasonable yield.

The permanganate promoted CPTC oxidative cyclisation was demonstrated to induce good levels of asymmetry for a naphthyl ester (Figure 7.8). This was also the first example of the CPTC oxidative cyclisation of an aromatic ester.

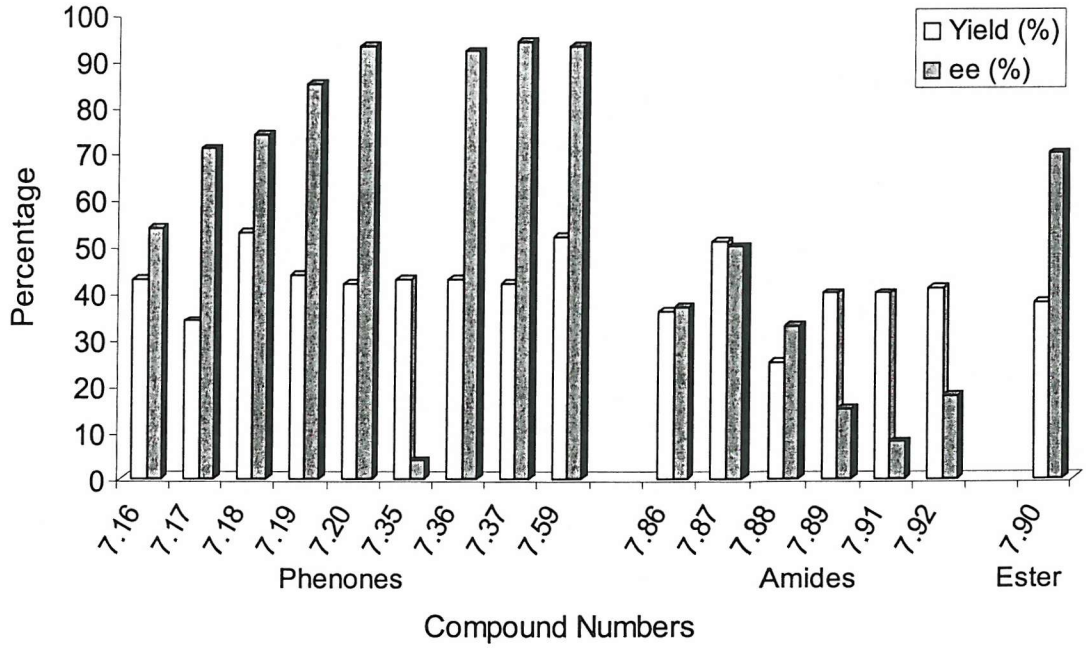


Figure 7.8 Summary of the permanganate promoted CPTC oxidative cyclisation results

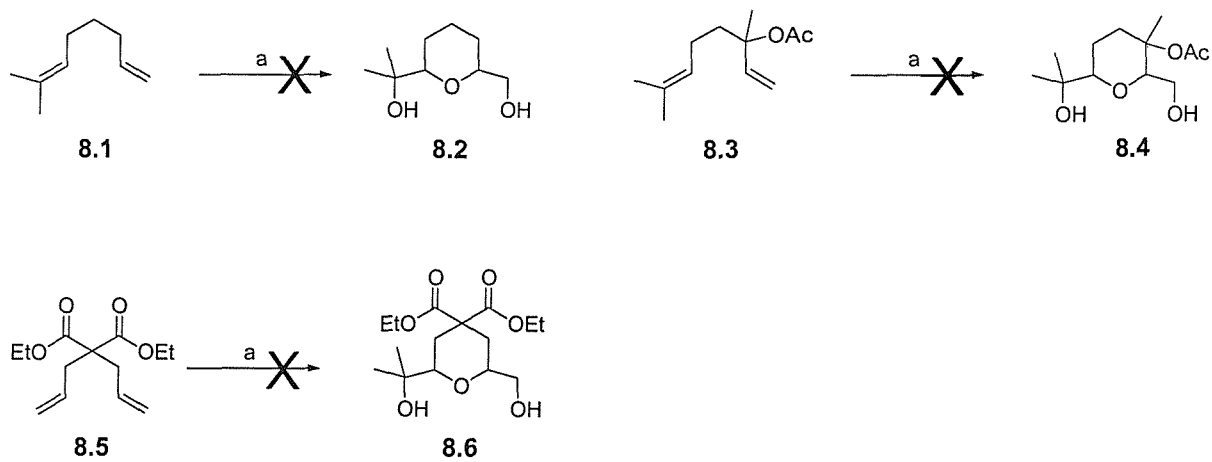
Chapter 8

Permanganate Promoted Oxidative Cyclisation of 1,6-Dienes

The chapter summarises the results obtained for the oxidative cyclisation of *mono-* and di-substituted 1,6-dienes. The focus of the research was to demonstrate the potential of the reaction and to prove the relative stereochemistry of the THP product. The only literature example of 1,6-diene oxidative cyclisation by a transition metal oxo species is the use of ruthenium tetroxide, which gives exclusively *trans*-THP-diols (Section 2.4).[151]

8.1 Attempted Oxidative Cyclisation of Commercially Available 1,6-Dienes

Although it was suspected that permanganate would not oxidatively cyclise solely aliphatic (inactivated) double bonds, a number of substrates containing the desired 1,6-diene were commercially available. Thus, 1,6-dienes **8.1**, **8.3**, **8.5** were purchased and using the AcOH/acetone (2:3) method the oxidative cyclisation was attempted (Scheme 8.1). However, mainly starting material was recovered and the crude ^{1}H NMR's showed no signals corresponding to the THF region.



8.1 **8.2** **8.3** **8.4**

8.5 **8.6**

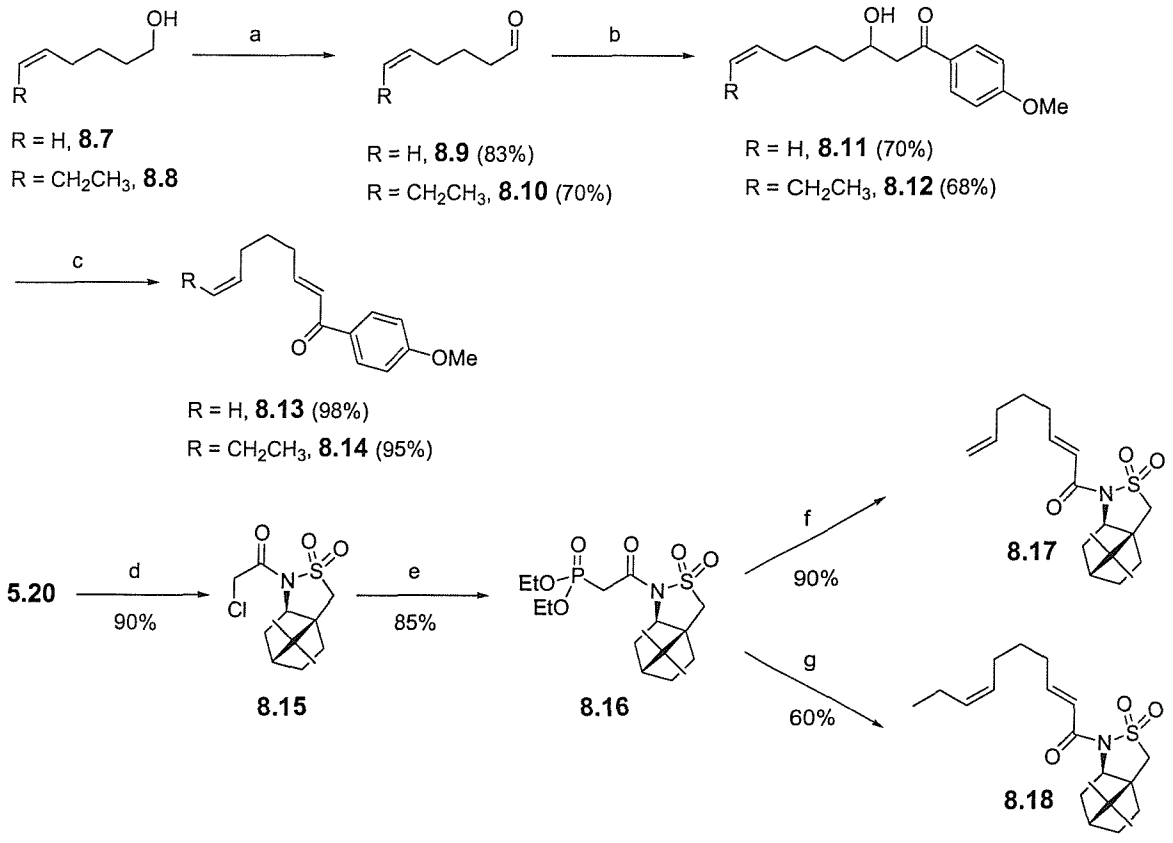
Scheme 8.1 Attempted oxidative cyclisation with commercially available 1,6-dienes. *Reagents and Conditions:* a) $KMnO_4$ (1.3 eq), adogen 464 (10 mol%), AcOH/acetone (2:3), –30 °C to –10 °C.

This was not an unexpected result as 1,5-diene substrates of this type give poor yields in the permanganate promoted oxidative cyclisation. Therefore, in order to test the plausibility of

1,6-diene oxidative cyclisation diene phenone and dienoyl sultam substrates, which give excellent yields (up to 81% and 75%, respectively) in the 1,5-diene series, were synthesised.

8.2 Preparation of 1,6-Diene Substrates

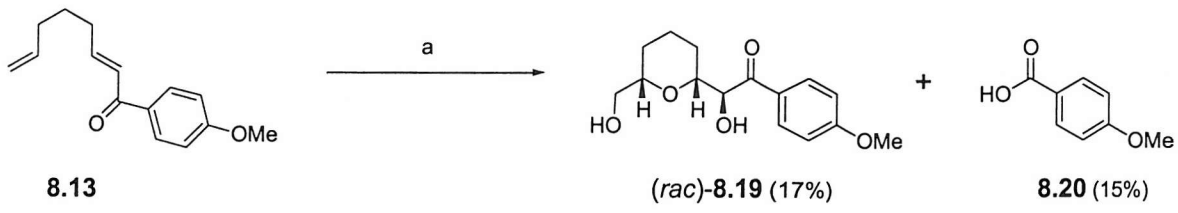
There were no appropriate starting materials containing disubstituted (*E*)-olefin with oxygen functionality present in the correct position. However, alcohols **8.7** and **8.8** containing a *mono*-olefin and a di-substituted (*Z*)-olefin were available. Thus, Swern oxidation[55] gave the corresponding aldehydes in good yield (Scheme 8.2). The corresponding 1,6-diene *p*-methoxy phenones (**8.13** and **8.14**) were synthesised by aldol reaction then dehydration using the aforementioned conditions. The sultam was introduced using phosphonate **8.16**, already containing the auxiliary (the enantiomer of phosphonate **5.18** used in the Section 5.2), in good yield.



Scheme 8.2 Synthesis of 1,6-dienes. *Reagents and Conditions:* a) DMSO, $(COCl)_2$, CH_2Cl_2, -60 °C, then Et_3N; b) **7.7**, LDA, THF, –60 °C; then aldehyde; c) (i) MsCl, Et_3N, CH_2Cl_2; (ii) DBU, CH_2Cl_2; d) NaH, CH_2Cl_2; then chloroacetyl chloride, –60 °C to 0 °C; e) triethyl phosphite, xylene, 145 °C; f) NaH, CH_2Cl_2; then **8.9**, 0 °C; g) NaH, CH_2Cl_2; then **8.10**, 0 °C.

8.3 Permanganate Promoted Oxidative Cyclisation of 1,6-Dienes

With the four 1,6-dienes in hand, the oxidative cyclisation was attempted on the simplest diene **8.13** using the AcOH/acetone (2:3) method (Scheme 8.3). Pleasingly, THP-diol (*rac*)-**8.19** (17%) was isolated as one of two main products, the other being benzoic acid **8.20** (15%). The crude ^{1}H NMR showed that the permanganate promoted oxidative cyclisation had furnished only one diastereoisomer of the THP ring. Detailed 2-D NMR experiments showed that the reaction led to exclusive formation of the *cis*-THP ring, and this was later confirmed by X-ray crystallography (Figure 8.1). Recrystallisation (EtOAc/hex or Et_2O/hex) gave racemic colourless blocks from which the crystal structure showed that all oxygens had been inserted from the same face to give *cis*-THP-diol (*rac*)-**8.19** (in accord with the oxidative cyclisation of 1,5-dienes).



8.13 (*rac*)-**8.19** (17%) **8.20** (15%)

Scheme 8.3 Permanganate promoted oxidative cyclisation of a 1,6-diene. *Reagents and Conditions:* a) $KMnO_4$ (1.3 eq), adogen 464 (10 mol%), AcOH/acetone (2:3), –30 °C to –10 °C.

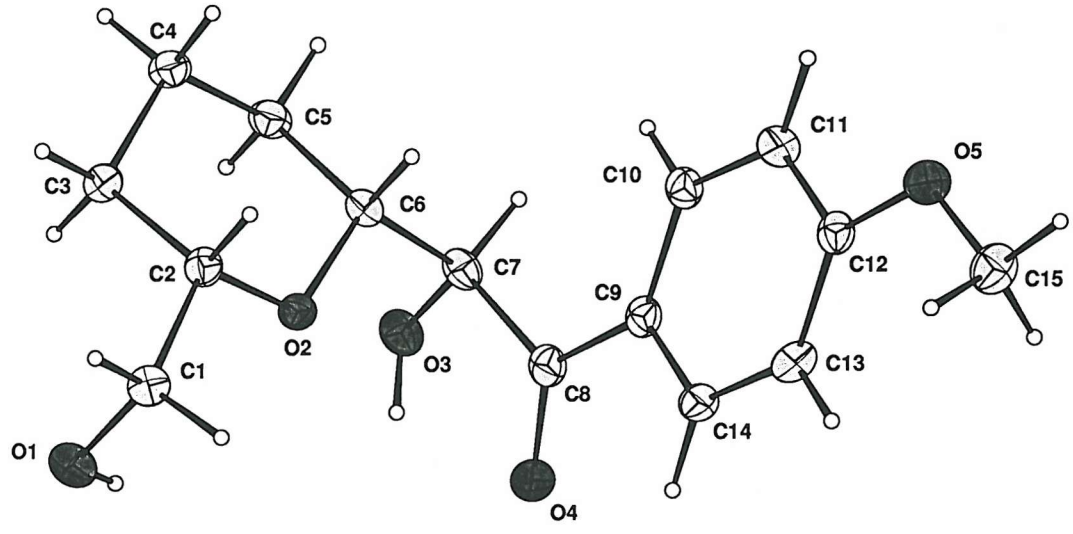
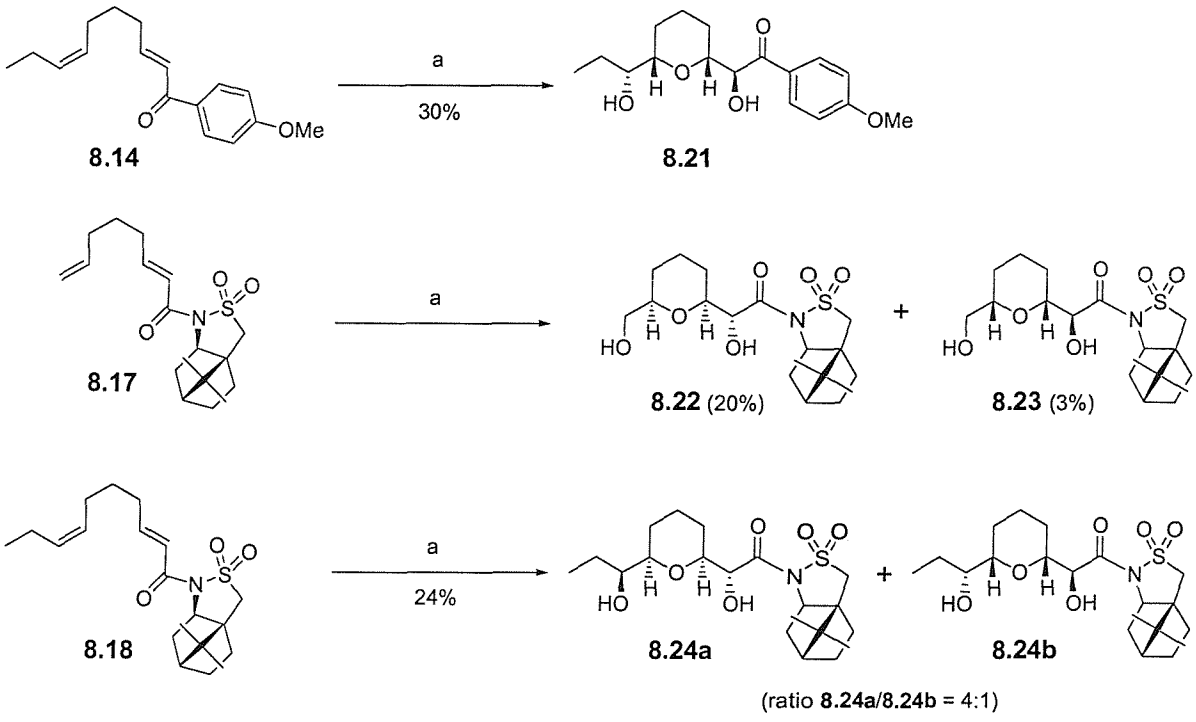


Figure 8.1 Crystal structure of *cis*-THP-diol (*rac*)-**8.19**

The oxidative cyclisation of the remaining three 1,6-dienes were carried out, with improved yields obtained for the disubstituted olefins (30% and 24% for **8.21** and **8.24**, respectively) (Scheme 8.4). Unfortunately, THP diastereoisomers **8.24a/8.24b** could not be separated and were isolated as a 4:1 mixture after column chromatography. However, the diastereoisomeric oxidative cyclisation products **8.22** and **8.23** were separated by column chromatography.



Scheme 8.4 Permanganate promoted oxidative cyclisation of a 1,6-dienes. *Reagents and Conditions:* a) $KMnO_4$ (1.3 eq), adogen 464 (10 mol%), AcOH/acetone (2:3), –15 °C.

The rate of reaction was noted to be extremely fast, with all the starting material used up after only minutes of adding permanganate. With this in mind, it was proposed that a decrease in temperature would not inhibit the reaction, whereas it might lead to improved yields. The AcOH/acetone (2:3) method was not applicable at temperatures below –30 °C as the solution freezes. Therefore conditions similar to the asymmetric CPTC oxidative cyclisation were investigated for the racemic cyclisation of 1,6-diene **8.13** (Table 8.1, entry 3). The yield more than doubled, increasing from 17% to 38% (Table 8.1, entries 1 and 3). The aqueous permanganate conditions were also applied; giving the THP (*rac*)-**8.19** in low yield (5%).

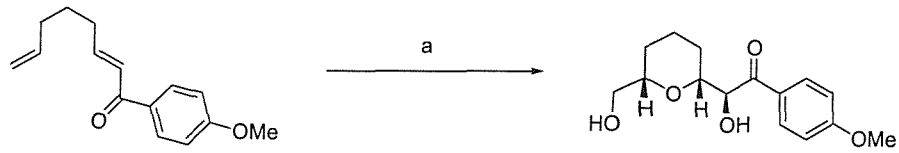
Entry	CPTC Oxidative Cyclisation Conditions	**8.19**[a]
1	AcOH/acetone (2:3), –30 °C[b]	17%
2	Aqueous –25 °C[c]	5%
3	CH_2Cl_2, –60 °C[d]	38%

Table 8.1 Effect of the oxidative cyclisation conditions on the yield of THP (*rac*)-**8.19**. [a] Yield of THP (*rac*)-**8.19** from diene **8.13**. *Reagents and Conditions:* [b] $KMnO_4$ (1.3 eq), adogen 464 (10 mol%), AcOH/acetone (2:3), –15 °C; [c] $KMnO_4$ (0.4 M, 2 eq,), AcOH (3 eq), phosphate buffer pH 6.5, acetone, –25 °C; [d] $KMnO_4$ (1.4 eq), adogen 464 (10 mol%), AcOH (16 eq), CH_2Cl_2, –60 °C.

If the observed increase in yield (17% to 38% for **8.13**) was witnessed in the oxidative cyclisation of disubstituted dienes **8.14** and **8.18** the respective yields would be in the region of 50-65%.

8.4 Permanganate Promoted CPTC Oxidative Cyclisation of a 1,6-Diene Phenone

The CPTC methodology developed for the oxidative cyclisation of 1,5-dienes was directly applied to 1,6-diene **8.13** (Scheme 8.5). The asymmetric induction observed in THP **8.19** (73% ee) was equivalent to the corresponding THF **7.18** (74% ee). However, the yield was disappointing (4%), with recovered starting material (> 80%) making up the majority of the material after the standard 3 h reaction time. Due to time constraints the CPTC oxidative cyclisation was not further investigated. The reaction has shown its potential; selectively forming *cis*-THP-diols containing up to four new stereocentres with complete control of relative and absolute stereochemistry from an achiral 1,6-diene. However, it requires optimisation to improve the yields to the levels enjoyed by the comparable 1,5-diene CPTC oxidative cyclisation.

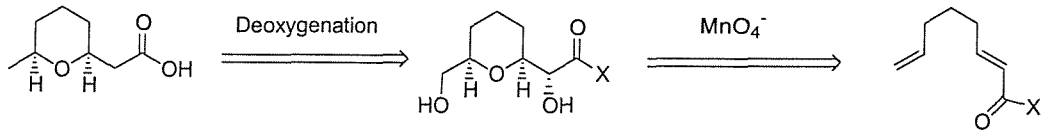


8.13 **8.19** (4%, 73% ee)

Scheme 8.5 Permanganate promoted CPTC oxidative cyclisation of a 1,6-diene. *Reagents and Conditions:* a) a) $KMnO_4$ (1.6 eq), AcOH (8 eq), 10 mol% cinchonidine derivative **2.56**, CH_2Cl_2, –60 °C.

8.5 Synthesis Towards a Civet Constituent *via* an Oxidative Cyclisation of a 1,6-Diene

A search of the literature identified (+)-(*S*,*S*)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid (**8.25**),[225] a glandular component of the civet cat (*Viverra civette*), as containing the desired *cis*-THP ring which we could synthesise *via* an oxidative cyclisation of a 1,6-diene (Scheme 8.6).



8.25 **8.26** **8.27**

X = sultam, asymmetric oxidative cyclisation

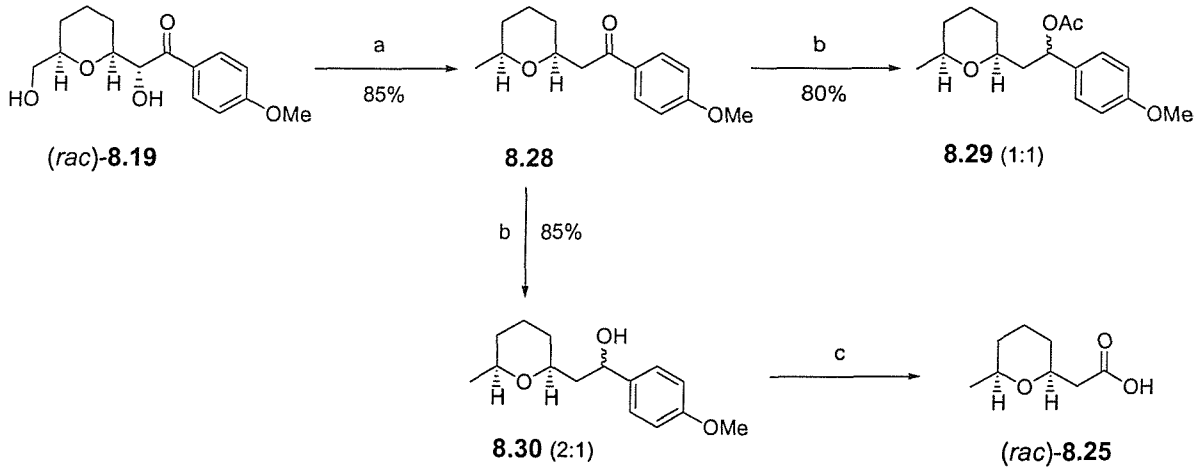
X = Ar, CPTC oxidative cyclisation

Scheme 8.6 Retrosynthesis of (+)-(*S*,*S*)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid (**8.25**)

There are several total syntheses of the civet constituent **8.25** in the literature.[226-229] Our approach using the oxidative cyclisation of 1,6-diene **8.27** to give THP **8.26** as the key step and subsequent deoxygenation made the proposed synthesis of **8.25** exceptionally concise. The control of absolute stereochemistry in the oxidative cyclisation could be accomplished using either the sultam or chiral phase-transfer catalyst ***ent*-2.56**, derived from cinchonine.

First the racemic synthesis of **8.25** was investigated, starting from advanced THP intermediate (*rac*)-**8.19**. The *bis*-deoxygenation was accomplished in excellent yield (85%) to give THP **8.28** (Scheme 8.6). Thus, diol (*rac*)-**8.19** was *bis*-mesylated and then, in a one

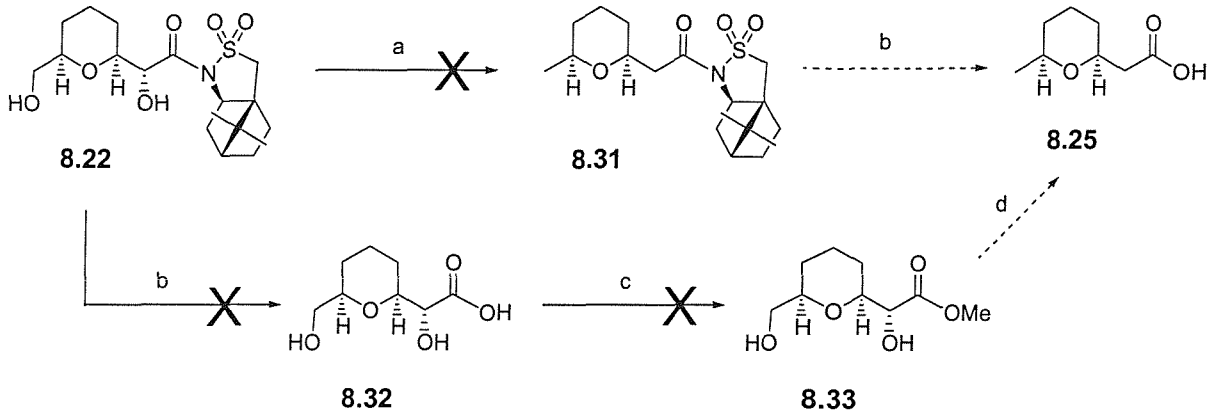
pot procedure, halogenated and reduced using sodium iodide and tributyltin hydride respectively. The initial attempt at the reduction of the ketone proceeded in good yield to give the corresponding alcohol, however this was accidentally transesterified in the acidic work up conditions to give acetate **8.29**. When the reaction was repeated the desired secondary alcohol **8.30** was obtained as a 2:1 inseparable mixture of diastereoisomers. The final step in the synthesis was the oxidative degradation of the electron rich aromatic group using ruthenium tetroxide to give (*rac*)-(*S,S*)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid (**8.25**). The reaction was monitored by MS (ES-), watching for the appearance of a peak at 189 Da (corresponding to $[M-H]^-$). After 3 h the peak appeared strong, however after 4 h the reaction was worked up and no material identifiable as (*rac*)-**8.25** could be isolated. The reaction could not be repeated due to lack of material and time, therefore it is inconclusive whether this route would be applicable for the synthesis of (+)-(*S,S*)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid (**8.25**) *via* the permanganate promoted CPTC oxidative cyclisation of 1,6-diene phenones.



Scheme 8.6 Synthesis Towards (*rac*)-(*S,S*)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid (**8.25**). *Reagents and Conditions:* a) (i) MsCl, Py, CH_2Cl_2; (ii) NaI, Bu_3SnH, AIBN, DME, 80 °C; b) $NaBH_4$, MeOH, 0 °C; c) 20 mol % $RuCl_3 \cdot H_2O$, H_5IO_6, CH_3CN, CCl_4, H_2O.

The asymmetric synthesis of (+)-(*S,S*)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid (**8.25**) commenced from advanced intermediate THP **8.22**. Attempts to deoxygenate **8.22**, using the radical conditions applied to diol phenone (*rac*)-**8.19**, failed to give any of the reduced product **8.31** (Scheme 8.7). The starting material was consumed and no identifiable products were isolated. The radical conditions employed have been shown to be stable for α-iodo-*N*-acylsultam substrates.[182,230] However, the reaction failed again when it was repeated even though the *bis*-mesylate, which was definitely formed, was columned to remove any salts

before being subjected to the radical conditions. The alternative was to first remove the sultam by hydrolysis and then carry out the deoxygenation. This also proved futile as the extremely polar acid **8.32** could not be isolated as either the free acid or its methyl ester **8.33**. This may have been due to our inability to extract acid **8.32** into the organic phase. Unfortunately, owing to time constraints these two remaining steps which would complete the synthesis of (+)-(*S*,*S*)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid (**8.25**) were not further investigated.



Scheme 8.7 Asymmetric synthesis of (+)-(*S*,*S*)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid (**8.25**). *Reagents and Conditions:* a) (i) MsCl, Py, CH_2Cl_2; (ii) NaI, Bu_3SnH, AIBN, DME, 80 °C; b) $LiOH{\bullet}H_2O$, THF, H_2O, 0 °C; c) *O*-methyl-*N*-*N*'diisopropylisourea (**7.64**), THF, reflux; d) (i) MsCl, Py, CH_2Cl_2; (ii) NaI, Bu_3SnH, AIBN, DME, 80 °C; (iii) NaOH, MeOH, H_2O, reflux.

8.6 Conclusion

The first permanganate promoted oxidative cyclisation of 1,6-dienes has been accomplished in moderate yields (23-38%). The THP-diol products have been shown to be formed with an exclusive *cis*-geometry, with all oxygens inserted from the same face (in accord with the oxidative cyclisation of 1,5-dienes). The reaction has shown its potential, and yields in excess of 50% should be realised with a little optimisation.

The permanganate promoted CPTC oxidative cyclisation of 1,6-dienes has been accomplished, with levels of asymmetric induction equal to the 1,5-diene series obtained. However, the reaction requires optimisation to improve the yield to levels witnessed in the 1,5-diene series.

The synthesis of civet constituent **8.25** was attempted to demonstrate an application for the permanganate promoted oxidative cyclisation of 1,6-dienes. However, due to time constraints the deoxygenation of the asymmetric THP-diol was not achieved, leaving the synthesis a couple of steps short of being completed.

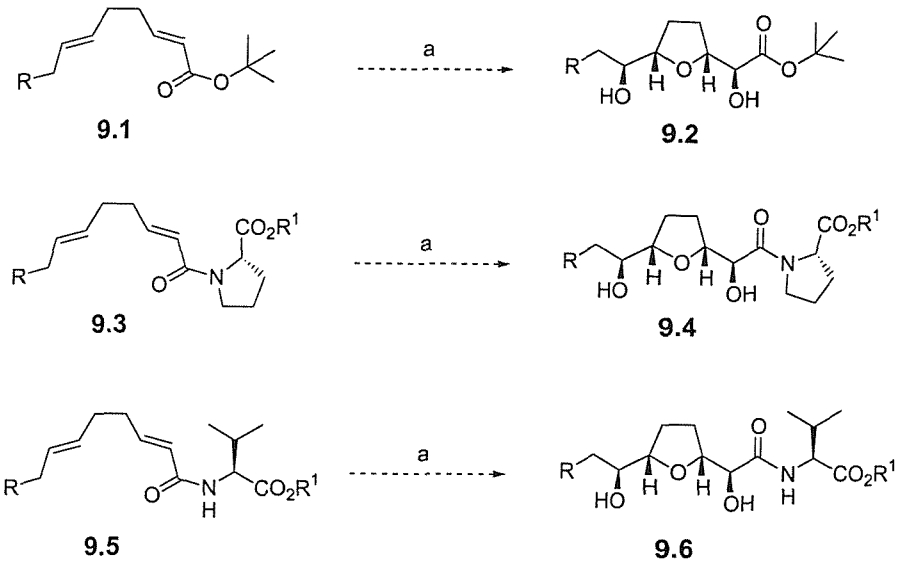
Chapter 9

Concluding Remarks and Future Work

An elegant approach to the synthesis of *mono*-THF acetogenins has been demonstrated utilising an asymmetric permanganate promoted oxidative cyclisation of dienoyl sultam. Subsequent elaboration gave *cis*-solamin (**1.240**) and analogues, which enabled their cytotoxicity and haemolytic properties to be evaluated. The biological data proved to be of some interest giving an insight into the structural activity relationships (SAR's) of acetogenins. However, further biological studies are required to fully understand these relationships. The developed methodology would allow the concise synthesis of acetogenin analogues, creating a library of compounds from which biological evaluation could provide an in depth study into the SAR's governing acetogenins.

The permanganate promoted CPTC oxidative cyclisation of 1,5-dienes has been investigated, realising excellent ee's (up to 94% ee). This excellent level of asymmetric induction was utilised *via* the formal synthesis of *cis*-solamin (**1.240**). The key steps were the permanganate promoted CPTC oxidative cyclisation (52%, 93% ee) and the oxidative degradation of the naphthyl group to the carboxylic acid without epimerisation.

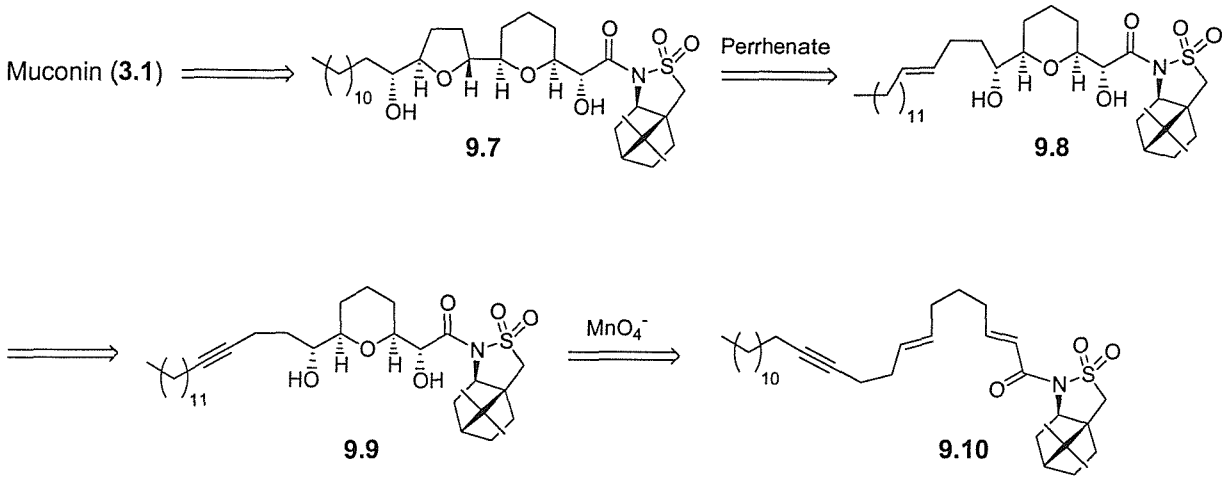
Aromatic ester and amides have shown themselves applicable to the CPTC oxidative cyclisation of 1,5-dienes, giving moderate to good asymmetric induction (up to 70% ee). Further development of the permanganate promoted CPTC oxidative cyclisation could be accomplished by examining the level of asymmetric induction induced in non-aromatic dienes (Scheme 9.1). This could be realised using the optimised method for the formation of benzoates from THF-diols, thus allowing chiral HPLC analysis. Bulky esters such as *t*-Bu may give excellent ee's. Amino acid analogues (such as **9.3** and **9.5**) could also be examined in the CPTC oxidative cyclisation. It would be interesting to see whether the stereochemistry present in amino acids, such as proline or valine, increase the level of asymmetric induction observed using either tertiary ammonium salt **2.56** or ***ent*-2.56**. The free carboxylic acid would probably require esterification to enable easier purification.



9.1 **9.2** **9.3** **9.4** **9.5** **9.6**

Scheme 9.1 Interesting substrates for the CPTC oxidative cyclisation. *Reagents and Conditions:* a) $KMnO_4$ (1.6 eq), AcOH (8 eq), 10 mol% cinchonidine derivative **2.56**, CH_2Cl_2.

The racemic, asymmetric and CPTC permanganate promoted oxidative cyclisation of 1,6-dienes to furnish exclusively *cis*-THP-diols has been developed. Moderate yields (up to 38%) have been accomplished with minimal optimisation. This methodology could be utilised in the total or formal synthesis of many natural products containing 2,6-disubstituted THP rings,[181,231] such as the acetogenin muconin (**3.1**) (Scheme 9.2). 1,6-Diene **9.10** could be oxidatively cyclised to give THP-diol **9.9**. Reduction to the (*E*)-alkene **9.8** and Kennedy cyclisation[176-178,232] using perrhenate would install the central THF-THP core present in muconin (**3.1**).



9.7 **9.8** **9.9** **9.10**

Scheme 9.2 Approach to muconin (**3.1**) *via* oxidative cyclisation of a 1,6-diene.

Chapter 10

Experimental

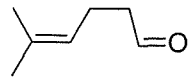
10.1 General Methods

All air and/or moisture sensitive reactions were carried out under an inert atmosphere, in oven-dried glassware. "Brine" refers to a saturated aqueous solution of sodium chloride. Dichloromethane and dichloroethane were dried by distillation from CaH_2 and THF was distilled from Na/benzophenone prior to use. Where appropriate, all other solvents and reagents were purified according to standard methods.[233] Reactions were monitored by TLC using aluminium-backed plates coated with silica gel 60 containing a fluorescence indicator active at 254 nm; the chromatograms were visualised under UV light (254 nm) and by staining with, most commonly, 20 % phosphomolybdic acid in EtOH, cerium sulphate/ammonium molybdate in 2M H_2SO_4 (aq) or 10% aqueous $KMnO_4$. Flash column chromatography was performed with 40-63 μm silica gel (Merck). ^{1}H-NMR and ^{13}C-NMR were recorded on Bruker AC300, Bruker AM300 or Bruker DPX400 spectrometers in deuterated chloroform ($CDCl_3$) with chloroform (δ 7.27 ppm ^{1}H, δ 77.15 ppm ^{13}C) as the internal standard. Fourier transform infrared (FTIR) spectra were recorded on a Perkin-Elmer 1600 FT-IR instrument, a Bio-Rad FTS 135 instrument using a Golden Gate adaptor or a Nicolet Impact 400 instrument using a Thunderdome adaptor. Absorptions were recorded in wave numbers (cm^{-1}) and are described as strong (s), medium (m), weak (w) or broad (br). Melting points were obtained in open capillary tubes and are uncorrected. Low-resolution mass spectra were obtained on a Fisons VG platform single quadropole mass spectrometer in either chemical ionisation or electron impact ionisation mode or a Micromass platform mass analyser with an electrospray ion source. Chiral analytical HPLC was performed on either a HP1050 or a HP1090 Series II LC system using a normal phase Chiralcel OD-H, Chiralcel OB-H, Chiralpak AD-H or Chiral CD-Ph column with 230 nm or 254 nm detection, eluting with *i*-PrOH/hexane mixtures. Preparative normal phase HPLC was performed on a Perkin-Elmer Series 3B LC system using a normal phase Phenomenex Luna silica column (21.2 x 250 mm, 10 μm), eluting with either EtOAc/hexane or *i*-PrOH/hexane mixtures. GC analysis was carried out using a Varian 3800 fitted with an autosampler connected to a Hewlett Packard 3396 Series II integrator. Where the experimental procedure is reported as using the method of an analogous procedure, the quantities of all reagents required scaling according to the molar amount used. The buffer

solution used in the aqueous permanganate promoted oxidative cyclisation is an aqueous 4:1 mixture of 1/16 M KH_2PO_4 & 1/16 M Na_2HPO_4 at pH 6.5.

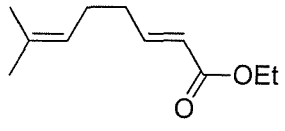
10.2 Experimental Details

5-Methyl-hex-4-enal (**4.6**)



The procedure was carried out as described by Marbet *et al.*[185] In a thick walled sealed glass tube, ethyl vinyl ether (40 mL, 418 mmol), 2-methyl-3-buten-2-ol (20 mL, 191 mmol) and H_3PO_4 (0.2 mL) were heated to 110 °C for 16 h. The light yellow solution was then cooled to rt, whereupon acetone (50 mL) and 2M HCl (50 mL) were added. After 2 h Et_2O (100 mL) was added and the organic phase separated. The aqueous phase was extracted with Et_2O (2 x 100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (20 g). Purification by vacuum distillation (30 mbar, 50 °C) gave aldehyde **4.6** (11.35 g, 101 mmol, 53%) as a colourless oil: spectroscopic data was in agreement with the literature;[160] IR ν_{max} (neat) 1725 (s), 1640 (m), 1446 (s), 1377 (s), 1102 (s), 1059 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.76 (1H, t, J = 1.5 Hz, **CH**O), 5.13-5.05 (1H, m, **CH**=C(CH_3)$_2$), 2.46 (2H, dt, J = 1.5, 6.6 Hz, **CH$_2$**CHO), 2.31 (2H, q, J = 6.6 Hz, **CH$_2$**CH=C(CH_3)$_2$), 1.69 (3H, s, (**CH$_3$**)$_2$CCH), 1.63 (3H, s, (**CH$_3$**)$_2$CCH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.9 (CH), 133.4 (C), 122.3 (CH), 44.1 (CH_2), 25.8 (CH_3), 21.0 (CH_2), 17.8 (CH_3); LRMS (GCCI) 2.29 min, *m/z* 130 (30%, $[M+NH_4]^+$), 113 (30%, $[M+H]^+$), 94 (100%).

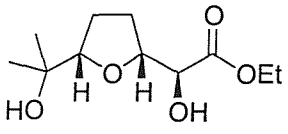
Ethyl (2*E*)-7-methylocta-2,6-dienoate (**4.5**)



To a solution of the aldehyde **4.6** (9.90 g, 88 mmol) in CH_2Cl_2 (160 mL) at rt was added (carbethoxymethylene)-triphenylphosphorane (36.8 g, 106 mmol) as a single batch. After 12 h the solution was concentrated *in vacuo*. The resulting organic residue was extracted with

hexane (5 x 75 mL, crushing the solid $Ph_3P{=}O$ with a pestle & mortar) to give a yellow solution, which was concentrated *in vacuo* to give a yellow oil (16 g). Purification by vacuum distillation (10 mbar, 110 °C) gave diene **4.5** (13.66 g, 75 mmol, 85%) as a colourless oil: spectroscopic data was in agreement with the literature;[160] IR ν_{max} (neat) 1722 (s), 1655 (m), 1446 (m), 1368 (m), 1265 (m), 1185 (s), 1043 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.97 (1H, dt, J = 15.5, 6.6 Hz, C**H**=CHCO$_2$), 5.82 (1H, d, J = 15.5 Hz, C**H**CO$_2$), 5.10 (1H, t, J = 6.6 Hz, C**H**=C(CH$_3$)$_2$), 4.19 (2H, q, J = 7.3 Hz, OC**H**$_2$CH$_3$), 2.21 (2H, dt, J = 2.0, 6.6, Hz, C**H**$_2$CH=CHCO$_2$), 2.15 (2H, dt, J = 2.0, 6.6 Hz, C**H**$_2$CH=C(CH$_3$)$_2$), 1.69 (3H, s, C**H**$_3$C), 1.63 (3H, s, C**H**$_3$C), 1.3 (3H, t, J = 7.3 Hz, C**H**$_3$CH$_2$O); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9 (C), 149.1 (CH), 132.9 (C), 123.0 (CH), 121.5 (CH) 60.3 (CH_2), 32.6 (CH_2), 26.7 (CH_2), 25.8 (CH_3), 17.9 (CH_3), 14.2 (CH_3); LRMS (GCCI) 4.27 min, *m/z* 200 (50%, $[M+NH_4]^+$), 183 (100%, $[M+H]^+$).

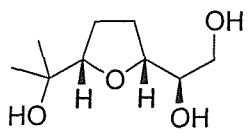
(*rac*)-Ethyl (2*S*)-2-hydroxy-2-[(2*R*,5*S*)-5-(1-hydroxy-1-methylethyl)tetrahydro-2-furanyl]-ethanoate (**4.4**).



At –25 °C a solution of 0.4 M $KMnO_4$ (aq, 6.60 mL, 2.6 mmol) and acetic acid (265 μL, 4.6 mmol) was added dropwise over 10 min to a solution of the diene **4.5** (300 mg, 1.7 mmol), buffer (1.16 mL) and acetone (20 mL). The reaction was quenched after a further 2 min by addition of ice cold $Na_2S_2O_5$ (sat. aq, 40 mL) and ice (20 g). Et_2O (50 mL) and NaCl (10 g) were added and the organic phase was separated. The aqueous phase was extracted with Et_2O (2 x 50 mL). The combined organic phases were then washed with $NaHCO_3$ (20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow oil (350 mg). Purification by column chromatography on silica gel (30% EtOAc/hexane → 60%) gave THF **4.4** (241 mg, 1.0 mmol, 63%) as a white solid: mp 44-45 °C; IR ν_{max} (neat) 3350 (br), 1737 (s), 1465 (m), 1364 (s), 1264 (s), 1199 (s), 1158 (s), 1121 (s), 1078 (s), 1026 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.43 (1H, ddd, J = 2.0, 4.4, 6.6 Hz, OC**H**CHOH), 4.34-4.21 (2H, m, OC**H**$_2$CH$_3$), 4.14 (1H, d, J = 2.0 Hz, C**H**OHC=O), 3.78 (1H, t, J = 7.0 Hz, OC**H**COH(CH$_3$)$_2$), 3.22 (2H, br, OH), 2.20-1.83 (4H, m, OCHC**H**$_2$C**H**$_2$), 1.34 (3H, t, J = 7.2 Hz, C**H**$_3$CH$_2$O) 1.29 (3H, s, C**H**$_3$C), 1.15 (3H, s, C**H**$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.6 (C), 86.7 (CH), 80.0 (CH), 74.0 (CH), 72.1 (C), 61.9 (CH_2), 28.2 (CH_2), 28.1 (CH_3), 26.3 (CH_2), 25.2 (CH_3), 14.3

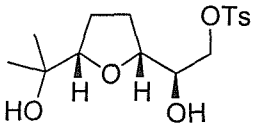
(CH_3); LRMS (GCCI) 4.72 min, *m/z* 233 (10%, $[M+H]^+$), 250 (20%, $[M+NH_4]^+$), 215 (100%, $[(M+H)-H_2O]^+$); HRMS (EI) $C_{11}H_{21}O_5^{+\cdot}$ Calcd. 233.1389 found 233.1391.

(*rac*)-(1*R*)-1-[(2*R*,5*S*)-5-(1-Hydroxy-1-methyl-ethyl)-tetrahydro-furan-2-yl]-ethane-1,2-diol (**4.7**).



At rt to a solution of THF **4.4** (200 mg, 0.86 mmol) in THF (25 mL) and H_2O (0.5 mL) was added $NaBH_4$ (66 mg, 1.7 mmol). After 16 h HCl (2M, 2 mL), brine (10 mL) and Et_2O (30 mL) were added. The organic phase was separated and the aqueous phase extracted with Et_2O (2 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a colourless oil. Purification by column chromatography on silica gel (5% MeOH/CH_2Cl_2 →10%) gave THF-triol **4.7** (123 mg, 0.65 mmol, 75%) as a white solid: mp 49-51 °C; IR ν_{max} (neat) 3442 (s), 3309 (s), 3139 (s), 1464 (m), 1444 (m), 1373 (s), 1297 (m), 1232 (m), 1163 (s), 1152 (s), 1129 (s), 1080 (s), 1066 (s), 1050 (s) cm^{-1}; ^1H NMR (300 MHz) δ 4.11-4.05 (1H, m, OC**H**CHOH), 3.80 (1H, t, *J* = 7.0 Hz, OC**H**C$(CH_3)_2$OH), 3.75-3.42 (3H, m, C**H**$_2$OH, C**H**OHCH_2OH), 1.83-2.10 (4H, m, OCHC**H**$_2$C**H**$_2$), 1.20 (3H, s, C**H**$_3$C), 1.05 (3H, s, C**H**$_3$C); ^{13}C NMR (75 MHz, $CDCl_3$); 86.7 (CH), 80.2 (CH), 74.2 (CH), 72.0 (C), 65.3 (CH_2), 28.5 (CH_2), 27.9 (CH_3), 26.0 (CH_2), 25.4 (CH_3); LRMS (GCCI) 4.49 min, *m/z* 191 (10%, $[M+H]^+$), 208 (20%, $[M+NH_4]^+$), 173 (100%, $[(M+H)-H_2O]^+$); HRMS (CI) $C_9H_{19}O_4^+$ Calcd. 191.1283 found 191.1280.

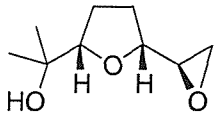
(*rac*)-Toluene-4-sulfonic acid (2*R*)-2-hydroxy-2-[(2*R*,5*S*)-5-(1-hydroxy-1-methyl-ethyl)-tetrahydro-furan-2-yl]-ethyl ester (**4.8**)



To a solution of the THF triol **4.7** (55 mg, 0.29 mmol), tosyl chloride (55 mg, 0.29 mmol) and DMAP (4 mg, 0.03, 10 mol%) in CH_2Cl_2 (10 mL) was added Et_3N (0.30 mL, 0.29 mmol). After 16 h 2M HCl (2 mL), CH_2Cl_2 (20 mL) and brine (20 mL) were added and the

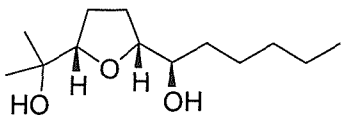
organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to give a colourless oil (160 mg). Purification by column chromatography using silica gel (30% EtOAc/CH_2Cl_2) gave tosylate **4.8** (69 mg, 0.20 mmol, 68%) as a colourless oil; IR ν_{max} (neat) 3360 (br), 1596 (m), 1456 (m), 1358 (s), 1190 (s), 1175 (s), 1096 (s), 1076 (s) cm^{-1}; ^1H NMR (300 MHz) δ 7.73 (2H, d, J = 8.0 Hz, C**H**), 7.27 (2H, d, J = 8.0 Hz, C**H**), 4.02 (2H, dd, J = 1.8, 4.5 Hz, C**H**$_2$OTs), 3.99-3.94 (1H, m, OC**H**CHOH), 3.70-3.58 (2H, m, OC**H**C(CH$_3$)$_2$OH, C**H**OHCH$_2$OTs), 3.26 (2H, br, O**H**), 2.35 (3H, s, C**H**$_3$Ar), 1.72-1.98 (4H, m, C**H**$_2$C**H**$_2$CHCHOH), 1.15 (3H, s, (C**H**$_3$)$_2$COH) 1.04 (3H, s, (C**H**$_3$)$_2$COH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 145.1 (C), 133.0 (C), 130.1 (CH), 128.2 (CH), 86.6 (CH), 78.4 (CH), 72.3 (C), 71.9 (CH), 71.8 (CH), 28.4 (CH_2), 27.9 (CH_3), 26.1 (CH_2), 25.9 (CH_3), 21.8 (CH_3); LRMS (ES^+) *m/z* 711 (50%, $[2M+Na]^+$), 367 (100%, $[M+Na]^+$), 345 (25%, $[M+H]^+$); HRMS (CI) $C_{16}H_{25}O_6S^+$ Calcd. 345.1372 found 345.1360.

(*rac*)-2-[(2*S*,5*R*)-5-[(2*R*)-Oxiranyl]-tetrahydro-furan-2-yl]-propan-2-ol (**4.3**).



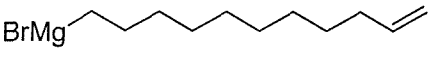
To a solution of tosylate **4.8** (186 mg, 0.54 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added DBU (170 mg, 1.08 mmol) dropwise. The solution was brought to rt and stirred for 12 h before being concentrated *in vacuo* to give a yellow oil. Purification by column chromatography on silica gel (2.5% MeOH/CH_2Cl_2) gave epoxide **4.3** (89 mg, 0.52 mmol, 96%) as a colourless oil; IR ν_{max} (neat) 3455 (br), 1470 (m), 1381 (m), 1361 (m), 1258 (m), 1177 (m), 1156 (s), 1109 (s), 1071 (s), 1032 (s) cm^{-1}; ^1H NMR (300 MHz) δ 4.11 (1H, ddd, J = 3.0, 5.5, 7.5 Hz, OC**H**CHOCH$_2$), 3.78 (1H, t, J = 7.0 Hz, C**H**C(CH$_3$)$_2$OH), 3.09-3.02 (2H, m, C**H**OCH$_2$, O**H**), 2.85 (1H, dd, J = 3.0, 5.0 Hz, C**H**HO), 2.79 (1H, dd, J = 4.0, 5.0 Hz, C**H**HO), 1.81-2.18 (4H, m, C**H**$_2$C**H**$_2$), 1.20 (3H, s, C**H**$_3$C), 1.05 (3H, s, C**H**$_3$C); ^{13}C NMR (75 MHz, $CDCl_3$) 87.1 (CH), 76.7 (CH), 71.4 (C), 54.7 (CH), 44.3 (CH_2), 29.6 (CH_2), 28.0 (CH_3), 25.8 (CH_2), 25.2 (CH_3); LRMS (GCCI) 5.74 min, *m/z* 190 (25%, $[M+NH_4]^+$), 173 (20%, $[M+H]^+$), 155 (100%, $[(M+H)-H_2O]^+$); HRMS (CI) $C_9H_{17}O_3S^+$ Calcd. 173.1178 found 173.1181.

(*rac*)-(1*R*)-1-[(2*R*,5*S*)-5-(1-Hydroxy-1-methylethyl)tetrahydro-2-furanyl]hexan-1-ol (**4.9**).



At 0 °C 2.0 M butylmagnesium chloride in THF (240 μL, 0.48 mmol) was added dropwise to a suspension of CuI (25 mg, 0.13 mmol) in THF (8 mL). The solution was then cooled to –78 °C whereupon it went grey. The THF epoxide **4.3** (20 mg, 0.12 mmol) in THF (2 mL) was then added dropwise. The reaction was quenched after 2 h with a saturated aqueous solution of NH_4Cl / NH_3 (9:1, 20 mL). Et_2O (30 mL) and brine (20 mL) were added and the organic phase was separated, dried (Na_2SO_4) and concentrated *in vacuo* to give an oil (24 mg). Purification by column chromatography on silica gel (35% EtOAc/hexane) gave the THF-diol **4.9** (22 mg, 0.10 mmol, 81%) as a colourless oil: IR ν_{max} (neat) 3371 (br), 1463 (s), 1376 (s), 1360 (m), 1159 (s), 1084 (s), 953 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.84 (1H, q, J = 6.5 Hz, OC**H**CHOH), 3.76 (1H, t, J = 7.0 Hz, C**H**C(CH_3)$_2$OH), 3.46-3.42 (1H, m, C**H**OHCH_2), 2.29 (2H, br, OH), 1.94-1.62 (4H, m, CH_2CH_2CHOCHOH), 1.49-1.35 (2H, m, CH_2CHOH), 1.35-1.19 (6H, m, (CH_2)$_3$CH_3), 1.26 (3H, s, CH_3C), 1.07 (3H, s, CH_3C), 0.87 (3H, t, J = 6.5 Hz, CH_3CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 86.5 (CH), 82.9 (CH), 74.8 (CH), 72.0 (C), 34.5 (CH_2), 32.3 (CH_2), 28.8 (CH_2), 27.8 (CH_3), 26.4 (CH_2), 25.8 (CH_2), 25.4 (CH_3), 22.3 (CH_2), 14.3 (CH_3); LRMS (GCCI) 11.96 min, *m/z* 213 (100%, [(M+H)-H_2O]$^+$), 248 (5%, [M+NH_4]$^+$); HRMS (CI) Calcd. for $C_{13}H_{27}O_3^+$ *m/z* 231.1960, found 231.1956.

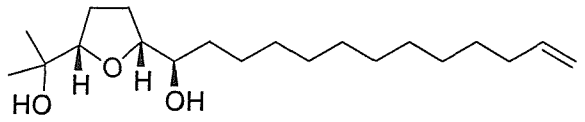
Undec-10-enylmagnesium bromide



Mg turnings (118 mg, 4.8 mmol) were heated under nitrogen to 300 °C. After cooling to rt, THF (8 mL) and one iodine crystal (< 1 mg) were added turning the solution light yellow. 11-bromoundec-1-ene (0.1 mL, 0.4 mmol) was added dropwise and the solution heated at reflux for 5 minutes until the solution had become colourless. At this point the remaining 11-bromoundec-1-ene (0.9 mL, 3.6 mmol) was added and the solution stirred for 30 min giving

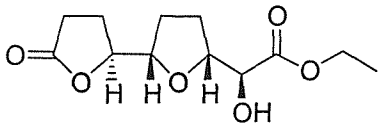
undec-10-enylmagnesium bromide. This was then transferred to a Schlenk tube and stored under nitrogen. Before use its concentration was determined by titration.

(*rac*)-(1*R*)-1-[(2*R*,5*S*)-5-(1-Hydroxy-1-methylethyl)tetrahydro-2-furanyl]-12-tridecen-1-ol (**4.2**).



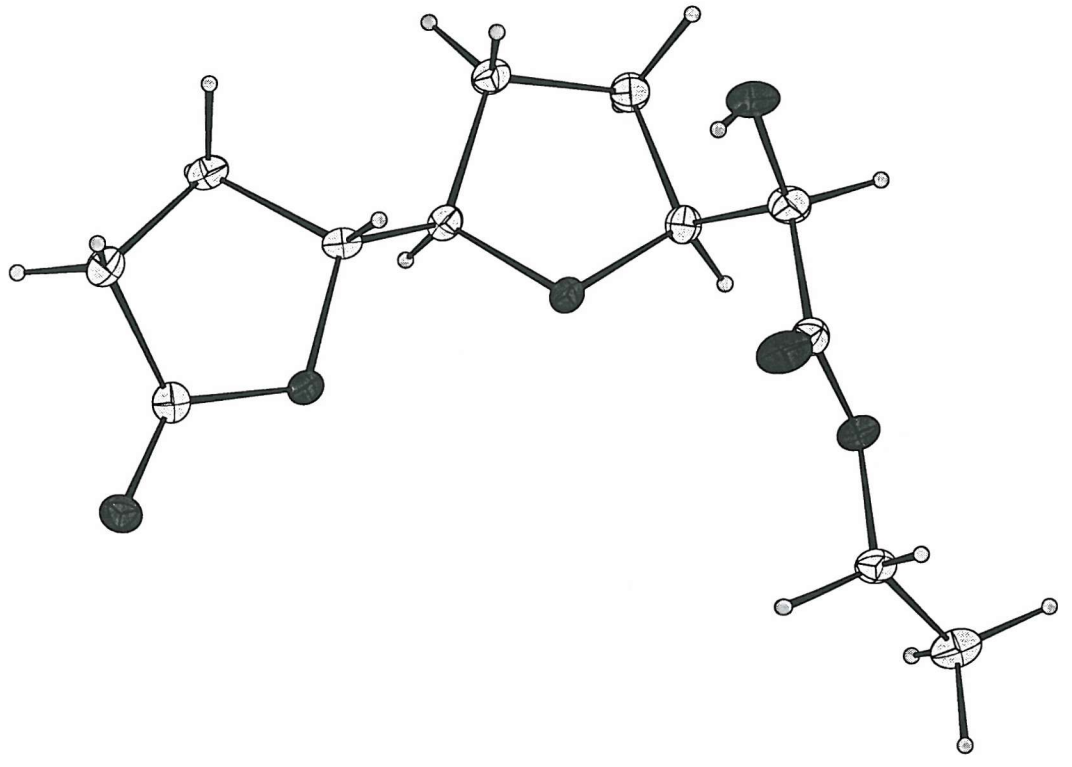
A solution of undec-10-enylmagnesium bromide in THF (3.5 mL, 0.7 mmol) was added to a suspension of CuI (28 mg, 0.15 mmol) in THF (10 mL) at 0 °C. After 10 min stirring, the solution was cooled to –78 °C whereupon it went grey. A solution of epoxide **4.3** (25 mg, 0.14 mmol) in THF (2 mL) was added dropwise. After 45 min the reaction mixture was quenched by the addition of an aqueous solution of saturated NH_4Cl / NH_4OH (9:1, 30 mL). Et_2O (60 mL) was added and the organic phase separated. The organic phase was then washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow oil (250 mg). Purification by column chromatography on silica gel (30% EtOAc/hexane) gave the title THF-diol **4.2** (32 mg, 0.10 mmol, 73%) as a white solid: mp 30-33 °C; IR ν_{max} (neat) 3376 (br), 1640 (m), 1463 (s), 1377 (m), 1362 (m), 1162 (s), 1081 (s), 995 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.74 (1H, tdd, J = 6.5, 10.0, 17.0 Hz, C**H**=CH_2), 4.92 (1H, dd, J = 2.0, 17.0 Hz, C**H**H=CH), 4.85 (1H, dd, J = 2.0, 10.0 Hz, C**H**H=CH), 3.76 (1H, q, J = 6.5 Hz, OC**H**CHOH), 3.71 (1H, t, J = 7.0 Hz, OC**H**C$(CH_3)_2$OH), 3.40-3.34 (1H, m, C**H**OHCH_2), 2.49 (2H, br, OH), 1.98 (2H, q, J = 6.5 Hz, C$\mathbf{H_2}$CH=CH_2), 1.90-1.61 (4H, m, C$\mathbf{H_2}$C$\mathbf{H_2}$ (THF)), 1.48-1.18 (18H, m, (C$\mathbf{H_2}$)$_9$CH_2CH=CH_2), 1.20 (3H, s, C$\mathbf{H_3}$C), 1.06 (3H, s, C$\mathbf{H_3}$C); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 139.6 (CH), 114.5 (CH_2), 86.5 (CH), 82.9 (CH), 74.8 (CH), 72.0 (C), 34.6 (CH_2), 34.2 (CH_2), 30.1 (CH_2), 30.0 (CH_2), 30.0 (CH_2), 30.0 (CH_2), 29.9 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.8 (CH_2), 27.9 (CH_3), 26.5 (CH_2), 26.1 (CH_2), 25.5 (CH_3); LRMS (ES^+) *m/z* 675 (50%, $[2M+Na]^+$), 653 (5%, $[2M+H]^+$), 349 (100, $[M+Na]^+$); HRMS (EI) calcd. for $C_{20}H_{39}O_3^{+\cdot}$ *m/z* 327.2899, found 327.2901.

(*rac*)-(2*S*)-2-Hydroxy-((2*R*,5*S*,5'*S*)-5'-oxooctahydo-[2,2']bifuranyl-5-yl)-acetic acid ethyl ester (**4.11**)

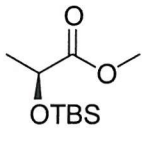


At –25 °C to a solution of triene **4.10** (3.8 g, 13.6 mmol) and buffer (17 mL) in acetone (250 mL) was added dropwise a solution of $KMnO_4$ (0.4 M, 94.9 mL, 38 mmol) and acetic acid (3.26 mL). After 20 min an ice-cold solution of $Na_2S_2O_5$ (aq, 1000 mL) was added to quench the reaction, followed by citric acid (10% w/v aq, 200 mL). After a further 10 min Et_2O (400 mL) was added and the organic separated. The aqueous was saturated with NaCl (50 g) and extracted with CH_2Cl_2 (3 x 300 mL). The combined organic phases were washed with $NaHCO_3$ (75 mL) before being dried ($MgSO_4$) and concentrated *in vacuo* to give a colourless oil (2.6 g). Purification by column chromatography through a plug of silica gel (30% EtOAc/CH_2Cl_2) gave a mixture of predominantly lactol and the title lactone **4.11** (1.6 g).

At 0 °C to the solution of lactol and lactone **4.11** (1.6 g, 4.8 mmol) in acetone (100 mL) was added a solution of $NaIO_4$ (2.0 g, 9.6 mmol) in H_2O (100 mL). The mixture was allowed to warm to rt and after 3 h Et_2O (250 mL) and brine (50 mL) were added. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 60 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give an oil (1.2 g). Purification by column chromatography on silica gel (25% EtOAc/CH_2Cl_2) gave the title lactone **4.11** (681 mg, 26 mmol, 19%, 2 steps) as colourless oil that crystallised on standing to thin colourless blocks: IR ν_{max} (neat) 3415 (br), 1771 (s), 1742 (s), 1172 (m), 1128 (s) 1082 (m) cm^{-1}; ^1H NMR (400 MHz) δ 4.53 (1H, ddd, J = 3.0, 5.0, 7.0 Hz, OC**H**), 4.34-4.21 (3H, m, OC**H**, O**CH**$_2$CH$_3$), 4.05 (1H, d, J = 2.5 Hz, C**H**OH), 3.99 (1H, dt, J = 3.0, 7.0 Hz, OC**H**), 2.64 (1H, ddd, J = 7.3, 10.0, 17.3 Hz, C**H**HCO$_2$), 2.44 (1H, ddd, J = 6.0, 10.0, 16.0 Hz, C**H**HCO$_2$) 2.32-2.20 (2H, m, C**H**$_2$CH$_2$CO$_2$), 2.19-1.89 (4H, m, C**H**$_2$C**H**$_2$CHCHOH), 1.31 (3H, t, J = 7.0 Hz, C**H**$_3$CH$_2$O); ^{13}C NMR (100 MHz) δ 177.7 **C**, 172.6 **C**, 81.8 **C**H, 80.6 **C**H, 80.3 **C**H, 72.8 **C**H, 61.8 **C**H$_2$, 28.1 **C**H$_2$, 27.6 **C**H$_2$, 27.5 **C**H$_2$, 24.7 **C**H$_2$, 14.3 **C**H$_3$; LRMS (GCCI) 8.96 min, *m/z* 276 (100%, $[M+NH_4]^+$), 259 (40%, $[M+H]^+$); Elemental calcd. for $C_{12}H_{18}O_6$: C, 55.81; H, 7.02. Found: C, 55.51; H, 7.22; X-Ray (racemic mixture).



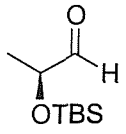
Ethyl (2*S*)-2-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxypropanoate (**4.14**)



The procedure was carried out as described by Massad *et al.*[192] Under an atmosphere of N_2, at 0 °C to a solution of methyl-(*S*)-lactate (**4.13**) (6.9 mL, 72 mmol) in THF (75 mL) was added Et_3N (26.1 mL, 188 mmol), DMAP (0.88 g, 7 mmol) and TBSCl (14.1 g, 94 mmol). The cloudy white solution was allowed to warm to rt and stir for 18 h. The reaction mixture was diluted with Et_2O (50 mL) then washed sequentially with citric acid (10% w/v aq, 50 mL), H_2O (50 mL), saturated aqueous sodium bicarbonate (50 mL) and H_2O (50 mL) before drying ($MgSO_4$). Evaporation of the solvents gave the crude product as an oil (18.2 g). Purification by vacuum distillation (bp 95 °C, 30 mbar) gave the title silyl-ether **4.14** (15.2 g, 70 mmol, 97%) as a colourless oil: spectroscopic data was in agreement with the literature;[192] IR ν_{max} (neat) 2870 (m), 1759 (m), 1738 (m) 1145 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.33 (1H, q, J = 6.9 Hz, C**H**O(TBDMS)CH_3), 3.72 (3H, s, C**H**$_3$O), 1.40 (3H, d, J

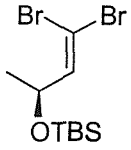
= 6.9 Hz, $CH_3CHO(TBDMS)$), 0.90 (9H, s, $(CH_3)_3C$), 0.09 (3H, s, CH_3Si), 0.07 (3H, s, CH_3Si); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7 (C), 68.5 (CH), 52.0 (CH_3), 25.9 (CH_3), 21.5 (CH_3), 18.5 (C), –4.6 (CH_3), –4.7 (CH_3); LRMS (GCCI) 3.57 min, 219 (100%, $[M+H]^+$).

(2*S*)-2-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxypropanal (**4.15**)



The procedure was carried out as described by Massad *et al.*[192] Under an atmosphere of N_2, at –78 °C to a solution of ester **4.14** (2.00 g, 9.2 mmol) in CH_2Cl_2 (25 mL) was added DIBAL-H in hexanes (11 mL, 11 mmol) dropwise over 10 min. After 5 h the reaction was quenched by addition of NH_4Cl (sat aq, 20 mL) and H_2O (10 mL) and warmed to rt. The organic phase was separated and the aqueous phase extracted with Et_2O (3 x 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a colourless oil (1.5 g). Purification by column chromatography on silica gel (40% CH_2Cl_2/hexane) gave aldehyde **4.15** (1.365 g, 80%) as a colourless oil: spectroscopic data was in agreement with the literature;[192] IR ν_{max} (neat) 1740 (m), 1450 (m) 1360 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.62 (1H, d, *J* = 1.5 Hz, **CHO**), 4.10 (1H, dq, *J* = 6.9, 1.5 Hz, **CHO**(TBDMS)CH_3), 1.28 (3H, d, *J* = 6.9 Hz, $CH_3CHO(TBDMS)$), 0.91 (9H, s, $(CH_3)_3C$), 0.11 (3H, s, CH_3Si), 0.09 (3H, s, CH_3Si); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7 (CH), 74.0 (CH), 25.9 (CH_3), 18.7 (CH_3), 18.3 (C), –4.6 (CH_3), –4.7 (CH_3); LRMS (GCCI) 5.54 min, 189 (20%, $[M+H]^+$) 131 (100%).

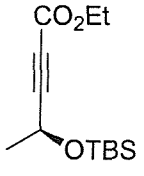
(3*S*)-1,1-Dibromo-3-[(*tert*-butyldimethylsilyl)oxy]-1-butene (**4.16**)



The procedure was carried out as described by Trost *et al.*[108] Under an atmosphere of N_2, at 0 °C to a solution of carbon tetrabromide (4.2 g, 12.7 mmol) in CH_2Cl_2 (6 mL) was added a solution of triphenylphosphine (6.7 g, 25.5 mmol) in CH_2Cl_2 (20 mL) dropwise. After 15 min the yellow solution was cooled to –78 °C whereupon a solution of aldehyde **4.15** (1.20

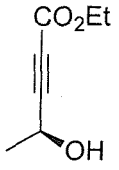
g, 6.4 mmol) in CH_2Cl_2 (7 mL) was added dropwise. After 1 h the reaction mixture was brought to rt and pentane (80 mL) was added. After 30 min the precipitate was removed by filtration, the organic filtrate was concentrated *in vacuo*, before being solvated in CH_2Cl_2 (5 mL). Pentane (20 mL) was added and the precipitate was removed by filtration. Evaporation of solvents gave an oil that was purified by column chromatography on silica gel (hexane) to give *gem*-dibromoalkene **4.16** (1.471 g, 67%) as a colourless oil: spectroscopic data was in agreement with the literature;[108] IR ν_{max} (neat) 1619 (m), 1471 (m) 1462 (m), 1369 (m), 1361 (m), 1253 (s), 1134 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.43 (1H, d, J = 8.0 Hz, C**H**=CBr_2), 4.45 (1H, dq, J = 8.0, 5.9 Hz, C**H**O(TBDMS)CH_3), 1.23 (3H, d, J = 5.9 Hz, CH_3CHO(TBDMS)), 0.89 (9H, s, (C**H**$_3$)$_3$C), 0.09 (3H, s, C**H**$_3$Si), 0.08 (3H, s, C**H**$_3$Si); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2 (CH), 87.7 (C), 70.0 (CH), 25.9 (CH_3), 22.9 (CH_3), 18.3 (C), –4.5 (CH_3), –4.7 (CH_3); LRMS (GCCI) 8.44 min, 344 (4%, $[M+H]^+$), 304 (40%, $[M+NH_4\text{-}^tBu]^+$), 154 (100%).

Ethyl (4*S*)-4-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy-2-pentynoate (**4.17**)



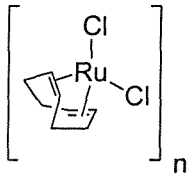
The procedure was carried out as described by Trost *et al.*[108] Under an atmosphere of N_2, at –78 °C to a solution of *gem*-dibromoalkene **4.16** (3.00 g, 8.7 mmol) in THF (25 mL) was added *n*BuLi in hexanes (13.1 mL, 1.6 M, 20.9 mmol) dropwise over 20 min. After 1 h of stirring at –78 °C, ethyl chloroformate (2.37 g, 21.8 mmol) was added dropwise. After 10 min the reaction mixture was warmed to rt and poured into NH_4Cl (sat aq, 20 mL). The organic phase was separated and the aqueous phase extracted with Et_2O (2 x 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a orange/yellow oil (2.51 g). Purification by column chromatography on silica gel (10% CH_2Cl_2/hexane) gave the alkyne **4.17** (1.963 g, 7.7 mmol, 88%) as a yellow oil: spectroscopic data was in agreement with the literature;[108] IR ν_{max} (neat) 2239 (m), 1716 (s), 1449 (m), 1368 (m), 1244 (s), 1102 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.61 (1H, d, J = 6.9 Hz, C**H**OHCH_3), 4.22 (2H, q, J = 7.1 Hz, CH_3C**H**$_2$O), 1.45 (3H, d, J = 6.9 Hz,C**H**$_3$CHOH), 1.30 (3H, t, J = 7.1 Hz, C**H**$_3$CH$_2$O), 0.92 (9H, s, (C**H**$_3$)$_3$C), 0.11 (3H, s, C**H**$_3$Si), 0.09 (3H, s, C**H**$_3$Si); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7 (C), 88.2 (C), 75.4 (C), 62.1 (CH_2), 58.8 (CH), 25.8 (CH_3) 24.6 (CH_3), 18.3 (C), 14.1 (CH_3), –4.6 (CH_3), –4.9 (CH_3).

Ethyl (4*S*)-4-hydroxy-2-pentynoate (**1.212**)



The procedure was carried out as described by Trost *et al.*[108] To a solution of silyl-ether **4.17** (1.963 g, 7.7 mmol) in THF was added H_2O (5 mL) and acetic acid (14 mL). The mixture was heated at 70 °C for 12 h. The reaction mixture was cooled to rt and quenched with $NaHCO_3$ (aq, 80 mL and solid 2 g). Et_2O (100 mL) was added and the organic phase separated, the aqueous phase was extracted with Et_2O (2 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a pale yellow oil (1.15 g). Purification by column chromatography on silica gel (25% EtOAc/hexane) gave propargylic alcohol **1.212** (1.062g, 7.5 mmol, 97%) as a colourless oil: spectroscopic data was in agreement with the literature;[108] $[\alpha]^{20}_D$ –26.7 ($CHCl_3$, *c* 0.23), Lit. $[\alpha]^{25}_D$ –28.4 ($CHCl_3$, *c* 0.21); IR ν_{max} (neat) 3410 (m) 2244 (m), 1710 (s), 1445 (m), 1368 (m), 1244 (s), 1122 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.65 (1H, d, *J* = 6.9 Hz, C**H**OHCH$_3$), 4.24 (2H, q, *J* = 7.0 Hz, CH$_3$C**H**$_2$O), 2.29 (1H, br, O**H**), 1.52 (3H, d, *J* = 6.9 Hz,C**H**$_3$CHOH), 1.32 (3H, t, *J* = 7.0 Hz, C**H**$_3$CH$_2$O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4 (C), 88.3 (C), 75.9 (C), 62.2 (CH_2), 58.0 (CH), 23.3 (CH_3), 14.0 (CH_3); LRMS (GCCI) 3.61 min, 142 (100%, $[M+NH_4]^+$).

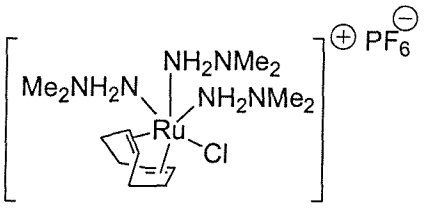
Di-μ-chloro(η^4-1,5-cyclooctadiene)ruthenium(II) (**4.18**)



The procedure was carried out as described by Albers *et al.*[193] Under an atmosphere of N_2, into a Schlenk flask (100 mL) was added $RuCl_3 \cdot H_2O$ (4.96 g, 19 mmol), 1,5-cyclooctadiene (5.76 g, 53 mmol) and EtOH (50 mL). The mixture was heated at reflux for 50 hr. The mixture was allowed to cool to rt before the resulting brown solid was collected by filtration and washed with EtOH (200 mL). Drying under vacuum gave the ruthenium complex **4.18** (5.232 g, 18.7 mmol, 98%) as a brown solid: spectroscopic data was in agreement with the

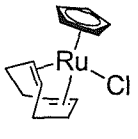
literature;[193] IR ν_{max} (neat) 2945 (m), 1475 (m) 1431 (m), 1337 (m), 1091 (s), 999 (s), 837 (s) cm^{-1}.

(η^4-1,5-Cyclooctadiene)*tris*(*N'N'*-dimethylhydrazine)(hydrido)ruthenium(II) hexafluorophosphate (**4.19**)



The procedure was carried out as described by Ashworth *et al.*[195] except for an additional H_2O wash to purify the title compound **4.19**. Under an atmosphere of nitrogen, *N,N*-dimethylhydrazine (20 mL, 260 mmol) and H_2O (5 mL) were added to a suspension of **4.18** (2.17 g, 7.8 mmol) in MeOH (25 mL). The suspension was refluxed for 20 min producing a dark brown solution, which was allowed to cool to rt. An aqueous solution (20 mL) of $[NH_4]^+[PF_6]^-$ (2.0 g, 12 mmol) was added. The resulting solid was filtered, washing with the filtrate followed by degassed H_2O (60 mL), to give a cream solid. On drying under vacuum the ruthenium complex **4.19** (2.212 g, 4.1 mmol, 53%) was obtained as a cream solid: spectroscopic data was in agreement with the literature;[195] mp 115-117 °C Lit. 114-116 °C; IR ν_{max} (neat) 3245 (s), 3059 (s) 2041 (m, RuH), 1604 (s), 1160 (m), 1151 (s), 918 (s), 842 (s, PF).

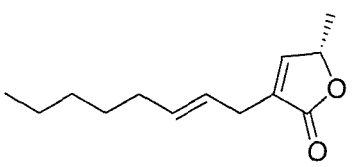
Chloro(η^4-1,5-cyclooctadiene)(η^5-cyclopentadienyl)ruthenium(II) (**1.214**).



The procedure was carried out by an adaptation of the method described by Albers *et al.*,[194] whereby the hydride complex was not isolated. Under an atmosphere of argon a suspension of ruthenium complex **4.19** (0.98 g, 1.8 mmol) and thallium cyclopentadiene (0.543 g, 2.0 mmol) in degassed acetone (40 mL) was refluxed for 35 min. After cooling to rt, the air and light sensitive solution was filtered and the filtrate concentrated *in vacuo* to give a sticky brown residue. Repeated extractions with degassed pentane (3 x 15 mL) gave a yellow

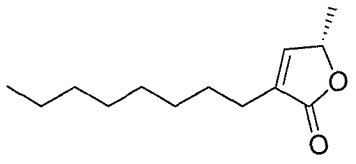
solution, which was filtered (care- very air and light sensitive compound) into a solution of degassed pentane (5 mL) and CCl_4 (1 mL). On addition an orange suspension formed, this was stirred for 5 min before being filtered. Orange crystals of the title ruthenium complex **1.214** (0.120 g, 0.4 mmol, 22%) were obtained after drying under vacuum, which required no further purification: spectroscopic data was in agreement with the literature;[194] mp 227-232 °C, Lit 228-232 °C; IR ν_{max} (neat) 2949 (m) 1471 (m), 1429 (m), 1340 (m), 1302 (m), 1166 (m), 1101 (s), 1012 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.36-5.28 (2H, m, C**H**), 4.97 (5H, s, $C_5\mathbf{H}_5$), 4.45-4.36 (2H, m, C**H**), 2.64-2.58 (2H, m, $C\mathbf{H}_2$), 2.10-1.99 (6H, m, $C\mathbf{H}_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 87.4 (CH), 86.2 (CH), 78.9 (CH), 32.9 (CH_2), 28.4 (CH_2).

(2*E*)-(5*S*)-5-Methyl-3-oct-2-enyl-5*H*-furan-2-one (**4.22**)



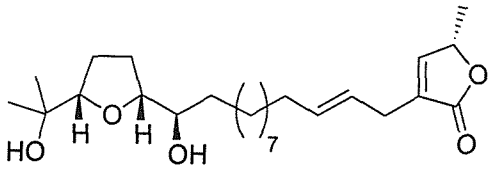
The procedure was carried out as described by Trost *et al.*[108] Under an atmosphere of argon, a solution of alkyne **1.212** (100 mg, 0.7 mmol) and oct-1-ene (**4.21**) (79 mg, 0.7 mmol) in MeOH (2 mL) was added to a bright orange solution of ruthenium complex **1.214** (9.3 mg, 0.03 mmol) in MeOH (0.5 mL). The solution was heated at reflux for 2.5 h. On cooling to rt the solution was diluted with Et_2O (20 mL), filtered and concentrated *in vacuo* to give a dark orange oil (130 mg). Purification by column chromatography on silica gel (10% EtOAc/hexane) gave butenolide **4.22** (41 mg, 0.2 mmol, 28%) as a yellow oil; spectroscopic data was in agreement with the literature;[108] IR ν_{max} (neat) 1756 (s), 1655 (w), 1457 (m), 1375 (m), 1320 (s), 1197 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.00 (1H, d, J = 1.5 Hz, =C**H**CHCH$_3$), 5.57 (1H, dt, J = 15.4, 6.6 Hz, C**H**CH$_2$CCO$_2$), 5.48 (1H, dt, J = 15.4, 6.6 Hz, C**H**=CHCH$_2$CCO$_2$), 5.01 (1H, dq, J = 6.8, 1.5 Hz, C**H**CH$_3$), 2.96 (2H, d, J = 6.6 Hz, C**H**$_2$CCO$_2$), 2.04 (2H, dt, J = 6.6, 7.0 Hz, C**H**$_2$(CH$_2$)$_3$CH$_3$), 1.42 (3H, d, J = 6.8 Hz, C**H**$_3$CH), 1.35-1.22 (6H, m, (**CH**$_2$)$_3$CH$_3$), 0.90 (3H, t, J = 6.7 Hz, C**H**$_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5 (C), 149.4 (CH), 134.2 (CH), 133.5 (C), 124.2 (CH), 77.6 (CH), 32.4 (CH_2), 31.4 (CH_2), 29.0 (CH_2), 28.4 (CH_2), 22.5 (CH_2), 19.2 (CH_3), 14.1 (CH_3).

(5*S*)-5-Methyl-3-octyl-5*H*-furan-2-one (**4.24**)



In a sealed steel bomb was placed butenolide **4.22** (35 mg, 0.17 mmol) and Wilkinson's catalyst (15 mg, 0.016 mmol) in a solution of 1:1 benzene/EtOH (3 mL). After 3 cycles of nitrogen/evacuation, H_2 (~3 bar) was introduced. The mixture was stirred at rt for 18 h. After releasing the pressure, chloroform (20 mL) was added and the mixture filtered, resulting in a brown liquor that was concentrated *in vacuo* . Purification by column chromatography on silica gel (10% EtOAc/hexane) gave butenolide **4.24** (35 mg, 0.17 mmol, 99%) as a yellow oil: IR ν_{max} (neat) 1753 (s), 1465 (m), 1375 (m), 1318 (s), 1197 (m), 1177 (m), 1116 (m), 1077 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.92 (1H, d, J = 1.0 Hz, C**H**CHCH$_3$), 4.92 (1H, dq, J = 1.5, 6.5 Hz, C**H**CH$_3$), 2.19 (2H, t, J = 7.5 Hz, C**H$_2$**(CH$_2$)$_6$CH$_3$), 1.51-1.43 (2H, m, C**H$_2$**(CH$_2$)$_5$CH$_3$), 1.33 (3H, d, J = 7.0 Hz, C**H$_3$**CH), 1.30-1.15 (10H, m, (**CH$_2$**)$_5$CH$_3$), 0.81 (3H, t, J = 6.7 Hz, C**H$_3$**CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4 (C), 149.3 (CH), 134.7 (C), 77.8 (CH), 32.2 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 27.8 (CH_2), 25.6 (CH_2), 23.1 (CH_2), 19.6 (CH_3), 14.5 (CH_3); LRMS (GCCI) 8.13 min, 228 (100%, $[M+NH_4]^+$), 211 (40%, $[M+H]^+$); HRMS (EI) Calcd. for $C_{13}H_{22}O_2^{+\cdot}$ *m/z* 210.1620, found 210.1614.

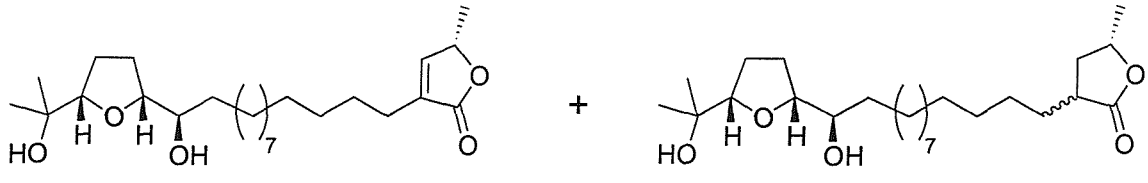
(5*S*)-3-(*E*,13*R**)-13-Hydroxy-13-[(2*R**,5*S**)-5-(1-hydroxy-1-methylethyl)tetrahydro-2-furanyl]-2-tridecenyl-5-methyl-2,5-dihydro-2-furanone (**4.25**)



Using the ruthenium Alder-ene conditions reported by Trost *et al.*[108] Under an atmosphere of argon, a bright orange solution of ruthenium complex **1.214** (3 mg, 0.02 mmol, 5 mol%) in degassed CH_3OH (1 mL) was added to a solution of alkene **4.2** (56 mg, 0.17 mmol) and alkyne **1.212** (24.5 mg, 0.17 mmol) in degassed CH_3OH (4 mL). The solution was heated at reflux for 2.5 h. After cooling to rt the mixture was diluted with Et_2O (30 mL), filtered and concentrated *in vacuo* to give an orange oil (75 mg). Purification by column chromatography

on silica gel (2.5% CH_3OH/CH_2Cl_2) gave butenolide **4.25** (30 mg, 0.07 mmol, 42%) as a yellowish oil: IR ν_{max} (neat) 3420 (br), 2849 (s), 1739 (s), 1462 (s), 1376 (m), 1240 (s), 1084 (m) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.99 (1H, d, J = 1.5 Hz, C**H**=CCO_2), 5.56 (1H, dt, J = 15.1, 6.5 Hz, C**H**=$CHCH_2CCO_2$), 5.46 (1H, dt, J = 15.1, 6.5 Hz, $CHCH_2CCO_2$), 5.01 (1H, dq, J = 1.5, 6.5 Hz, $CHCH_3$), 3.83 (1H, q, J = 6.2 Hz, OC**H**CHOH), 3.76 (1H, t, J = 7.0 Hz, $OCHC(CH_3)_2OH$), 3.44 (1H, q, J = 5.5 Hz, C**H**OH), 2.94 (2H, d, J = 6.5 Hz, CH_2CCO_2), 2.50 (2H, br, O**H**), 2.04 (2H, q, J = 6.6 Hz, CH_2CH_2CH=CH), 1.96-1.69 (4H, m, CH_2CH_2 (THF)), 1.51-1.25 (16H, m, $(CH_2)_8CHOH$), 1.40 (3H, d, J = 6.5 Hz, CH_3CH), 1.27 (3H, s, CH_3C), 1.13 (3H, s, CH_3C); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.6 (C), 149.5 (CH), 134.3 (CH), 133.7 (C), 124.4 (CH), 86.3 (CH), 82.6 (CH), 77.7 (CH), 74.6 (CH), 71.7 (C), 34.3 (CH_2), 32.6 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.5 (CH_2), 28.5 (CH_2), 27.6 (CH_3), 26.2 (CH_2), 25.9 (CH_2), 25.2 (CH_3), 19.3 (CH_3); LRMS (ES^+) *m/z* 868 (30%, $[2M+Na]^+$), 445 (100%, $[M+Na]^+$), 423 (25%, $[M+H]^+$); HRMS (ES^+) calcd. for $C_{25}H_{42}O_5Na^+$ *m/z* 445.2924, found 445.2923.

Inseparable mixture of:
3-(13*R**)-13-Hydroxy-13-[(2*R**,5*S**)-5-(1-hydroxy-1-methylethyl)tetrahydro-2-furanyl]tridecyl-(5*S*)-5-methyl-2,5-dihydro-2-furanone (**4.1**) &
3-(13*R**)-13-hydroxy-13-[(2*R**,5*S**)-5-(1-hydroxy-1-methylethyl)tetrahydro-2-furanyl]tridecyl-(5*S*)-5-methyltetrahydro-2-furanone (**4.26**)



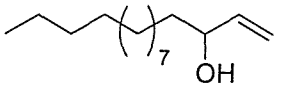
4.1 (ratio **4.1**/**4.26** = 3:2) **4.26**

In a steel bomb were placed butenolide **4.25** (30 mg, 0.07 mmol) and Wilkinson's catalyst (7 mg, 0.007 mmol) in a 1:1 solution of benzene/EtOH (3 mL). After 3 cycles of nitrogen/evacuation, H_2 (2-4 bar) was introduced. The mixture was stirred at rt for 18 h. After releasing the pressure, $CHCl_3$ (10 mL) was added and the mixture filtered, resulting in a brown liquor that was concentrated *in vacuo* and then purified by column chromatography on silica gel (50% EtOAc/hexane). This gave a yellow oil that contained butenolide **4.1** and the over reduced lactone **4.26** as a 3:2 inseparable mixture (28 mg, 95%).

Compound **4.1** (selected data): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.99 (1H, d, J = 1.5 Hz, C**H**=CCO_2), 4.99 (1H, dq, J = 1.5, 6.5 Hz, C**H**CH_3), 3.84 (1H, q, J = 6.2 Hz, OC**H**CHOH), 3.76 (1H, t, J = 7.0 Hz, OC**H**$C(CH_3)_2OH$), 3.44 (1H, q, J= 5.5 Hz, C**H**OH), 2.24 (2H, t, J = 7.4 Hz, CH_2CCO_2); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.9 (C), 148.9 (CH), 134.3 (CH), 86.2 (CH), 82.6 (CH), 75.1 (CH), 74.4 (CH); LRMS (ES^+) of mixture *m/z* 447 (100%, $[M+Na]^+$), 425 (65%, $[M+H]^+$).

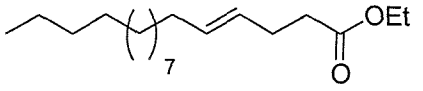
Compound **4.26** (selected data): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.51-4.41 (1H, m, C**H**CH_3), 3.84 (1H, q, J = 6.2 Hz, OC**H**CHOH), 3.76 (1H, t, J = 7.0 Hz, OC**H**$C(CH_3)_2OH$), 3.44 (1H, q, J= 5.5 Hz, C**H**OH) (THF protons coincidental for both compounds); LRMS (ES^+) of mixture *m/z* 449 (70%, $[M+Na]^+$), 427 (40%, $[M+H]^+$).

Pentadec-1-en-3-ol (**5.12**)



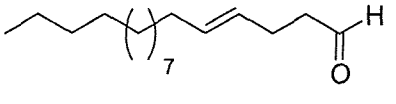
Under an atmosphere of N_2 at –20 °C to a solution of vinyl magnesium bromide (1.0 M, 91 mL, 91 mmol) in THF (150 mL) was added a solution of tridecanal (**5.11**) (18.0 g, 91 mmol) in THF (20 mL) dropwise. After 2 h a saturated solution of NH_4Cl (100 mL) and H_2O (50 mL) were added and the mixture acidified with 1 M HCl (50 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (26 g). Purification by column chromatography on silica gel (3% EtOAc/hexane → 8%) gave the allylic alcohol **5.12** (19.31 g, 86 mmol, 94%) as a colourless oil that solidified on standing to a white solid: spectroscopic data agreed with the literature;[198] mp 26-9 °C; IR ν_{max} (neat) 3312 (br), 2980 (m), 2915 (s), 1470 (m), 923 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (1H, ddd J = 6.3, 10.3, 16.8 Hz, C**H**=CH_2, 5.22 (1H, dt, J = 17.3, 1.3 Hz, C**H**H=CH), 5.10 (1H, dt, J = 10.5, 1.3 Hz, C**H**H=CH), 4.09 (1H, q, J = 6.3 Hz, C**H**OH), 1.58-1.47 (3H, m, CH_2CHOH, O**H**), 1.42-1.20 (20H, m, CH_2), 0.89 (3H, t, J = 6.5 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5 (CH), 114.6 (CH_2), 73.4 (CH), 37.2 (CH_2), 32.0 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 25.5 (CH_2), 22.8 (CH_2), 14.2 (CH_3).

(4*E*)-Heptadec-4-enoic acid ethyl ester (**5.13**)



The procedure was carried out using the method described by Keinan *et al.*[198] Under an atmosphere of N_2 to a solution of allylic alcohol **5.12** (6.30 g, 28 mmol) and triethyl orthoacetate (10.45 mL, 56 mmol) in xylene (300 mL) was added propionic acid (0.22 mL, 3 mmol). The reaction was heated at reflux for 3 h, after cooling to rt the solution was concentrated *in vacuo* to 20 mL whereupon Et_2O (100 mL) and $NaHCO_3$ (sat. aq, 50 mL) were added. The organic phase was separated, the aqueous phase extracted with Et_2O (2 x 50 mL). The combined organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification by vacuum distillation (0.5 mbar, 156 °C) gave ester **5.13** (7.82 g, 26 mmol, 95%) as a colourless oil: spectroscopic data agreed with the literature;[198] IR ν_{max} (neat) 2928 (s), 1740 (s), 1459 (m), 1169 (m), 968 (m); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.46 (1H, td J = 6.1, 15.3 Hz, C**H**=CH, 5.39 (1H, td, J = 5.5, 15.8 Hz, C**H**=CH), 4.12 (2H, q, J = 7.1 Hz, C**H$_2$**O), 2.41-2.25 (4H, m, C**H$_2$**), 1.96 (2H, q, J = 6.2 Hz, C**H$_2$**CH=CH), 1.37-1.19 (23H, m), 0.88 (3H, t, J = 6.4 Hz, C**H$_3$**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4 (C), 132.0 (CH), 128.0 (CH), 60.4 (CH_2), 34.6 (CH_2), 32.7 (CH_2), 32.1 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.1 (CH_2), 22.8 (CH_2), 14.4 (CH_3), 14.3 (CH_3).

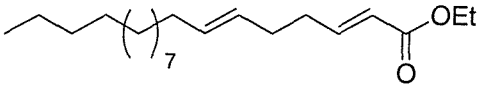
(4*E*)-Heptadec-4-enal (**5.14**)



At –78 °C to a solution of ester **5.13** (2.00 g, 7.1 mmol) in CH_2Cl_2 (160 mL) was added dropwise DIBAL-H in hexane (1M, 9.2 mL, 9.2 mmol) *via* syringe pump over 20 min. After 3 h the reaction was quenched by the addition of MeOH (40 mL), after 10 min H_2O (40 mL) was added and finally 2 M HCl (20 mL) after a further 5 min. The Organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 50 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated *in vacuo* to give a colourless oil (1.72 g). Purification by column chromatography on silica gel (2.5% EtOAc/hexane → 3%) gave aldehyde **5.14** (1.57 g, 6.2 mmol, 88%) as a white solid: mp 34-36 °C; IR ν_{max} (neat) 2924 (s), 2853 (s), 1735 (s), 1365 (s), 1217 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.77 (1H, t, J

= 1.7 Hz, CHO), 5.47 (1H, td, J = 6.8, 15.3 Hz, CH=CH), 5.40 (1H, td, J = 6.8, 15.3 Hz, CH=CH), 2.52-2.47 (2H, m, CH_2CHO), 2.34 (2H, br q, J = 6.8 Hz, CH_2), 1.96 (2H, br q, J = 6.8 Hz, CH_2), 1.37-1.22 (20H, m, CH_2), 0.89 (3H, t, J = 7.0 Hz, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 202.5 (C), 132.3 (CH), 127.7 (CH), 43.7 (CH_2), 32.6 (CH_2), 32.1 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 25.3 (CH_2), 22.8 (CH_2), 14.2 (CH_3); LRMS (GCEI) 8.23 min, *m/z* 252 (5%, $M^{+\cdot}$), 84 (100%); Elemental calcd. for $C_{16}H_{30}O$: C, 80.88; H, 12.78. Found, C, 80.85; H, 12.73.

(2*E*,6*E*)-Nonadeca-2,6-dienoic acid ethyl ester (**5.6**)

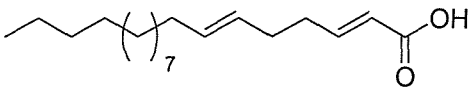


Under an atmosphere of N_2 at –60 °C a solution of ester **5.13** (2.00 g, 6.8 mmol) in CH_2Cl_2 (80 mL) had added dropwise DIBAL-H in hexane (1.0 M, 8.4 mL, 8.4 mmol) via syringe pump over 20 min. The reaction mixture was stirred for a further 2 h.

Meanwhile, under an atmosphere of N_2 at rt a solution of triethyl phosphonoacetate (2.0 mL, 10.0 mmol) in THF (50 mL) had added in several batches NaH (0.40 g, 10 mmol, 60% in mineral oil). After 10 min stirring the solution was cooled to –40 °C.

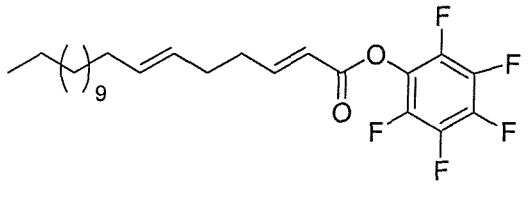
The organo-aluminium solution (aldehyde, rf: 0.37, 5% EtOAc/hexane) was allowed to warm to –40 °C whereupon it was transferred *via* cannula into the –40 °C Horner-Emmons anion solution. After 30 min the solution was allowed to warm to rt over an hour, whereupon H_2O (100 mL), 1 M HCl (20 mL) and Et_2O (250 mL) were added. The organic phase was separated and the aqueous phase extracted with Et_2O (3 x 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (2.5 g). Purification by column chromatography on silica gel (EtOAc/hexane 1:65) gave the title diene ester **5.6** (2.10 g, 6.5 mmol, 96%) as a colourless oil: IR ν_{max} (neat) 2921 (s), 1724 (s), 1654 (m), 1266 (m), 1173 (m), 1047 (m); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (1H, td, J = 6.8, 15.6 Hz, CH=$CHCO_2Et$), 5.82 (1H, td, J = 1.5, 15.6 Hz, $CHCO_2Et$), 5.45 (1H, td J = 6.2, 15.3 Hz, CH=CH, 5.37 (1H, td, J = 6.2, 15.3 Hz, CH=CH), 4.18 (2H, q, J = 7.2 Hz, CH_2O), 2.31-2.21 (2H, m, CH_2CH=CH), 2.20-2.10 (2H, m, CH_2CH=CH), 1.96 (2H, q, J = 6.2 Hz, CH_2CH=CH), 1.40-1.16 (23H, m), 0.88 (3H, t, J = 6.4 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9 (C), 148.9 (CH), 132.0 (CH), 128.5 (CH), 121.6 (CH), 60.3 (CH_2), 32.7 (CH_2), 32.4 (CH_2), 32.1 (CH_2), 31.2 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 22.9 (CH_2), 14.4 (CH_3), 14.3 (CH_3).

(2*E*,6*E*)-Nonadeca-2,6-dienoic acid (**5.15**)



To a solution of diene ester **5.6** (1.77 g, 5.5 mmol) in MeOH (9 mL) was added a solution of NaOH (1.18 g, 30 mmol) and $NaHCO_3$ (0.23 g, 3.0 mmol) in H_2O (30 mL). The solution was refluxed for 5 h, after cooling to 0 °C the reaction was quenched with citric acid (10% w/v aq, 100 mL). Et_2O (200 mL) was added and the organic phase separated, the aqueous phase was extracted with Et_2O (2 x 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give diene acid **5.15** (1.60 g, 5.4 mmol, 98%) as a white solid that required no further purification: mp 63-65 °C; IR ν_{max} (neat) 2580(br), 1694(s), 1660(s), 1469(m), 1373(m), 1289(m), 1250(m), 1214(m); ^{1}H NMR (300 MHz, DMSO) δ 12.36 (1H, br, COO**H**), 6.78 (1H, td, J = 6.7, 15.6 Hz, C**H**=CHCO$_2$H), 5.75 (1H, d, J = 15.6 Hz, C**H**CO$_2$H), 5.42 (1H, td J = 6.6, 15.3 Hz, C**H**=CH, 5.35 (1H, td, J = 6.6, 15.3 Hz, C**H**=CH), 2.28-2.16 (2H, m, C**H**$_2$CH=CH), 2.15-2.05 (2H, m, C**H**$_2$CH=CH), 2.00-1.88 (2H, m, C**H**$_2$CH=CH), 1.40-1.15 (20H, m), 0.85 (3H, t, J = 6.5 Hz, C**H**$_3$); ^{13}C NMR (75 MHz, DMSO) δ 167.1 (C), 148.2 (CH), 130.9 (CH), 128.7 (CH), 122.1 (CH), 31.9 (CH_2), 31.3 (CH_2), 30.4 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 28.7 (CH_2), 28.4 (CH_2), 22.1 (CH_2), 13.9 (CH_3); LRMS (ES$^-$) *m/z* 293 (100%, [M-H]$^-$); Elemental calcd. for $C_{19}H_{34}O_2$: C, 77.50; H, 11.64. Found: C, 77.38; H, 11.53.

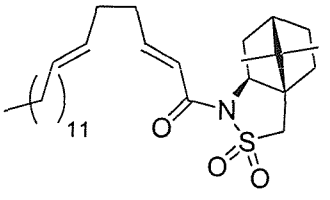
(2*E*,6*E*)-Nonadeca-2,6-dienoic acid pentafluorophenyl ester (**5.16**)



Under an atmosphere of N_2 at rt to a solution of diene acid **5.15** (180 mg, 0.6 mmol) and DCC (130 mg, 0.6 mmol) in EtOAc (50 mL) was added a solution of pentafluorophenol (110 mg, 0.6 mmol) in EtOAc (10 mL). After 48 h the mixture was filtered. The filtrate was concentrated *in vacuo* to give a yellow oil that was purified by column chromatography on silica gel (CH_2Cl_2/hexane 1:9) to give title PFP ester **5.16** (200 mg, 0.4 mmol, 70%) as a yellow oil: IR ν_{max} (neat) 1753 (s), 1649 (m), 1173 (m), 1125 (s) 1085 (m); ^{1}H NMR (300

MHz, $CDCl_3$) δ 7.29 (1H, td, J = 6.8, 15.6 Hz, C**H**=CHCOPFP), 6.07 (1H, td, J = 1.5, 15.6 Hz, C**H**COPFP), 5.50 (1H, td J = 6.2, 15.1 Hz, C**H**=CH), 5.40 (1H, td, J = 6.2, 15.1 Hz, C**H**=CH), 2.45-2.34 (2H, m, C**H**$_2$CH=CH), 2.29-2.18 (2H, m, C**H**$_2$CH=CH), 2.00 (2H, q, J = 6.8 Hz, C**H**$_2$CH=CH), 1.40-1.16 (20H, m), 0.89 (3H, t, J = 6.5 Hz, C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4 (C), 154.8 (CH), 132.6 (CH), 127.9 (CH), 118.3 (CH), 32.9 (CH_2), 32.7 (CH_2), 32.1 (CH_2), 30.8 (CH_2), 29.9 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 22.8 (CH_2), 14.2 (CH_3), Nb quaternary Ar C's not observed due to ^{19}F splitting; LRMS (GCCI) 16.10 min, *m/z* 461 (1%, $[M+H]^+$), 277 (100%, $[M-PFP]^+$) 184 (10%, $[PFP]^+$); HRMS (EI) Calcd. for $C_{25}H_{33}O_2F_5^{+\cdot}$ *m/z* 460.2401. Found 460.2403.

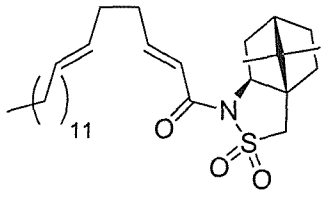
Method 1: (2*S*)-*N*-((2*E*,6*E*)-2,6-Nonadecadienoyl)-camphor-10,2-sultam (**5.5**)



At –60 °C under nitrogen, *n*BuLi in hexanes (0.17 mL, 0.31 mmol) was added dropwise to a solution of the (2*S*)-sultam **5.19** (68 mg, 0.31 mmol) in THF (7.5 mL). The solution was allowed to warm to –20 °C over 30 min whereupon a solution of PFP-ester **5.16** (138 mg, 0.3 mmol) in THF (4 mL) was added dropwise. After 20 min, allowing the reaction mixture to warm to –10 °C, NH_4Cl (sat aq, 5 mL) and Et_2O (20 mL) were added. The organic phase was separated and the aqueous phase was extracted with Et_2O (2 x 10 mL). The combined organic phases were washed with $NaHCO_3$ (sat aq, 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (250 mg). Purification was achieved by removal of PFP under vacuum (0.5 mbar, 100 °C) followed by column chromatography on silica gel (10% Et_2O/hexane → 20%) gave dienoyl sultam **5.5** (108 mg, 0.22 mmol, 73%) as a white solid: mp 42-44 °C; $[\alpha]^{24}_D$ +62.0 ($CHCl_3$, *c* 0.77); IR ν_{max} (neat) 1671 (s), 1630 (s), 1334 (s), 1294 (s), 1215 (s), 1133 (s); 1H-NMR (400 MHz, $CDCl_3$) δ 7.09 (1H, dt, J = 15.1, 7.0 Hz, C**H**=CHCON), 6.56 (1H, dt, J = 15.1, 1.5 Hz, =C**H**CON), 5.46 (1H, dt, J = 15.3, 6.3 Hz, CH_2C**H**=C**H**CH_2), 5.38 (1H, dt, J = 15.3, 6.3 Hz, CH_2C**H**=C**H**CH_2), 3.93 (1H, dd, J = 5.0, 7.5 Hz, CHN), 3.51 (1H, d, J = 13.6 Hz, C**H**HSO_2), 3.44 (1H, d, J = 13.6 Hz, C**H**HSO_2), 2.31 (2H, q, J = 7.0 Hz, C**H**$_2$CH=CHCON), 2.20-2.05 (4H, m), 2.00-1.84 (5H, m), 1.46-1.26 (22H, m), 1.18 (3H, s, C**H**$_3$C), 0.98 (3H, s, C**H**$_3$C), 0.89 (3H, t, J = 6.8 Hz, C**H**$_3$$CH_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.2 (C), 150.5 (CH), 132.0 (CH), 128.3 (CH), 121.1 (CH), 65.3 (CH), 53.3 (CH_2), 48.5 (C), 47.9 (C), 44.8 (CH), 38.6 (CH_2), 33.0 (CH_2), 32.7 (CH_2),

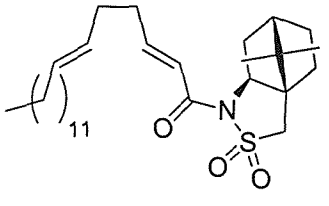
32.6 (CH_2), 32.0 (CH_2), 31.1 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 26.6 (CH_2), 22.8 (CH_2), 21.0 (CH_3), 20.0 (CH_3), 14.3 (CH_3); LRMS (ES^+) *m/z* 515 (100%, $[M + Na]^+$); Elemental calcd. for $C_{29}H_{49}NO_3S$: C, 70.83; H, 10.01; N, 2.85. Found: C, 70.71; H, 9.96; N, 2.79.

Method 2: (2*S*)-*N*-((2*E*,6*E*)-2,6-Nonadecadienoyl)-camphor-10,2-sultam (**5.5**)



At 0 °C under nitrogen, two drops of DMF were added to a stirred solution of diene acid **5.15** (2.23 g, 7.7 mmol) and oxalyl chloride (0.81 mL, 9.2 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred for 2 h before being concentrated *in vacuo* and then solvated in CH_2Cl_2 (2 mL). Meanwhile, at rt under nitrogen NaH (60% in mineral oil, 0.339 g, 8.5 mmol) was added to a solution of (2*S*)-sultam **5.19** (1.82 g, 8.5 mmol) in CH_2Cl_2 (20 mL). After 10 min the anion solution was cooled to 0 °C and the acid chloride solution (prepared above) was added dropwise. After 1 h the reaction was quenched by addition of H_2O (5 mL), brine (5 mL) and CH_2Cl_2 (20 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel (10% Et_2O/hexane → 20%) gave dienoyl sultam **5.5** (3.03 g, 6.2 mmol, 80%) as a white solid.

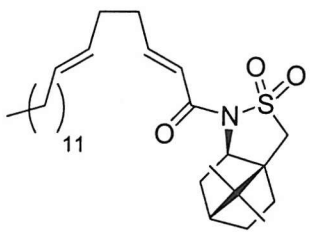
Method 3: (2*S*)-*N*-((2*E*,6*E*)-2,6-Nonadecadienoyl)-camphor-10,2-sultam (**5.5**)



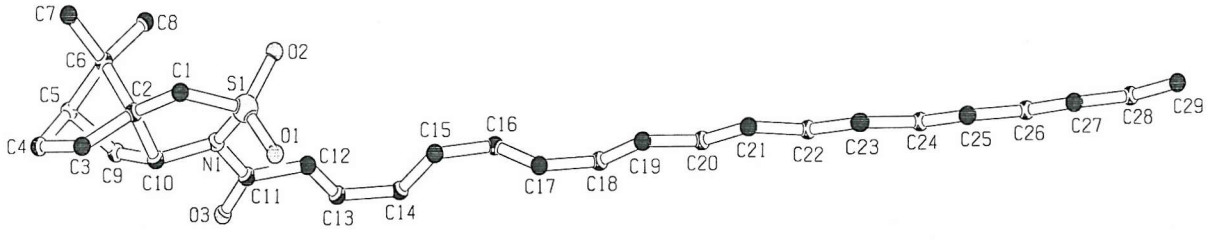
Under N_2 at 0 °C, to a solution of sultam phosphonate **5.18** (409 mg 1.04 mmol) in CH_2Cl_2 (25 mL) was added in one batch NaH (42 mg, 1.04 mmol, 60% in mineral oil). The reaction was allowed to warm to rt and was stirred for 20 min before being cooled to 0 °C. A solution of aldehyde **5.14** (250 mg, 0.99 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The reaction mixture was stirred for 16 h before addition of a saturated aqueous solution of NH_4Cl (10 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 10

mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification by column chromatography on silica gel (10% Et_2O/hexane → 20%) gave dienoyl sultam **5.5** (389 mg, 0.79 mmol, 80%) as a white solid.

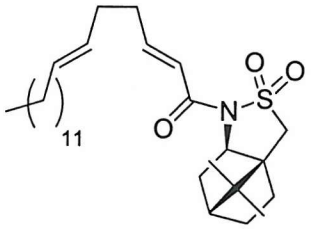
Method 1: (2*R*)-*N*-((2*E*,6*E*)-2,6-Nonadecadienoyl)-camphor-10,2-sultam (**5.7**)



The title compound was prepared according to the method outlined for **5.5**, except using: acid **5.15** (2.00 g, 6.89 mmol), oxalyl chloride (0.72 mL, 8.27 mmol), DMF (2 drops), (2*R*)-sultam **5.20** (1.63 g, 7.60 mmol) and NaH (0.30 g, 7.60 mmol). Gave the title dienoyl sultam **5.7** (2.78 g, 5.65 mmol, 82%) as a white solid (recrystallised EtOAc/hexane to give colourless plates): mp 41-43 °C; $[\alpha]^{24}_D$ –61.1 ($CHCl_3$, *c* 0.40); spectroscopic data identical to compound **5.5**; Elemental calcd. for $C_{29}H_{49}NO_3S$: C, 70.83; H, 10.01; N, 2.85. Found: C, 70.69; H, 9.95; N, 2.83; X-ray (single enantiomer).

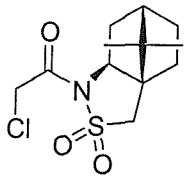


Method 2: (2*R*)-*N*-((2*E*,6*E*)-2,6-Nonadecadienoyl)-camphor-10,2-sultam (**5.7**)



At 0 °C under nitrogen, two drops of DMF were added to a stirred solution of diene acid **5.15** (2.20 g, 7.5 mmol) and oxalyl chloride (0.80 mL, 9.1 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred for 2 h before being concentrated *in vacuo* and then solvated in CH_2Cl_2 (2 mL). Meanwhile, at rt under nitrogen NaH (60% in mineral oil, 0.324 g, 8.1 mmol) was added to a solution of (2*R*)-sultam **5.20** (1.74 g, 8.1 mmol) in CH_2Cl_2 (20 mL). After 10 min the anion solution was cooled to 0 °C and the acid chloride solution (prepared above) was added dropwise. After 1 h the reaction was quenched by addition of H_2O (5 mL), brine (5 mL) and CH_2Cl_2 (20 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel (10% Et_2O/hexane → 20%) gave dienoyl sultam **5.7** (3.03 g, 6.2 mmol, 82%) as a white solid.

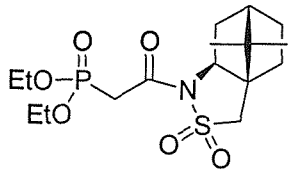
(2*S*)-*N*-(2-Chloroethanoyl)-camphor-10,2-sultam (**5.17**)



The procedure was carried out using the method described by Oppolzer *et al.*[200] Under an atmosphere of N_2, to a solution of (2*S*)-sultam **5.19** (7.00 g, 32.5 mmol) in CH_2Cl_2 (300 mL) was added in several batches NaH (60% mineral-oil, 1.30g, 32.5 mmol). After 30 min the reaction was cooled to –60 °C whereupon chloroacetyl chloride (3.11 mL, 39 mmol) was added dropwise. The reaction was allowed to warm to rt over 2 h, whereupon NH_4Cl (sat aq, 50 mL) and H_2O (100 mL) were added. The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 75 mL). The combined organic fractions were washed with $NaHCO_3$ (sat aq, 40 mL) before being dried ($MgSO_4$) and concentrated *in vacuo* to give a white solid (9 g). Purification by column chromatography on silica gel (12% EtOAc/hexane → 15%) gave the title chloride **5.17** (8.53 g, 29.3 mmol, 91%) as a white crystalline solid: mp 120-122 °C; IR ν_{max} (neat) 2953 (s), 1699 (s), 1323 (s), 1267 (s), 1235 (s), 1213 (s), 1132 (s), 1065 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.51 (2H, s, CH_2Cl), 3.92 (1H, dd, J = 5.1, 7.5 Hz, CHN), 3.54 (1H, d, J = 13.8 Hz, $CHHSO_2$), 3.47 (1H, d, J = 13.8 Hz, $CHHSO_2$), 2.24-2.04 (2H, m, CH_2CHN), 2.01-1.82 (3H, m, sult), 1.49-1.31 (2H, m, sult), 1.15 (3H, s, CH_3C), 0.98 (3H, s, CH_3C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8 (C), 65.6 (CH), 52.8 (CH_2), 49.3 (C), 48.0 (C), 44.6 (CH), 42.5 (CH_2), 38.1 (CH_2), 32.9 (CH_2), 26.5 (CH_2), 20.9 (CH_3),

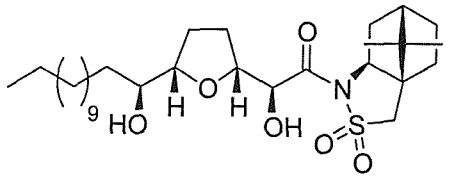
20.0 (CH_3); LRMS (ES^+) *m/z* 314 (100%, $[M + Na]^+$), 292 (90%, $[M + H]^+$); Elemental calcd. for $C_{12}H_{18}O_3NSCl$: C, 49.40; H, 6.22; N, 4.80. Found: C, 49.22; H, 5.99; N, 4.66.

Diethyl-2-oxo-2-*N*-((2*S*)-camphor-10-2-sultam)-ethylphosphonate (**5.18**)



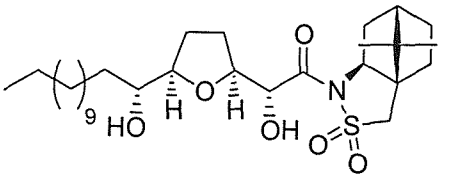
The procedure was carried out using the method described by Oppolzer *et al.*[200] Under an atmosphere of N_2 a solution of chloride **5.17** (7.30 g, 26.3 mmol) and triethyl phosphite (6.85 mL, 39.9 mmol) in xylene (100 mL) was heated at reflux for 48 h. The solution was concentrated *in vacuo* to give a yellow oil. Excess triethyl phosphite was removed under vacuum (0.5 mbar, 150 °C). Purification by column chromatography on silica gel (25% EtOAc/hexane → 80%) gave phosphonate **5.18** (8.58 g, 21.8 mmol, 83%) as a colourless oil: $[\alpha]^{25}_D$ +58.9 ($CHCl_3$, *c* 1.0); IR ν_{max} (neat) 2962 (s), 1692 (s), 1329 (s), 1257 (s), 1169 (m), 1134 (m), 1054 (s), 1024 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.24-4.11 (4H, m, OCH_2CH_3 x 2), 3.88 (1H, dd, *J* = 5.0, 7.8 Hz, CHN), 3.56 (1H, dd, *J* = 15.6, 22.6 Hz, PCHH), 3.50 (1H, d, *J* = 13.8 Hz, $CHHSO_2$), 3.43 (1H, d, *J* = 13.8 Hz, $CHHSO_2$), 3.19 (1H, dd, *J* = 15.6, 22.6 Hz, PCHH), 2.20-2.03 (2H, m, CH_2CHN), 1.97-1.77 (3H, m, sult), 1.45-1.22 (2H, m, sult), 1.33 (6H, dt, *J* = 2.8, 7.3 Hz, CH_3CH_2), 1.17 (3H, s, CH_3C), 0.96 ((3H, s, CH_3C); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.7 (d, J_{c-p} = 6.8 Hz, C), 65.4 (CH), 62.9 (d, J_{c-p} = 6.8 Hz, $POCH_2$), 62.6 (d, J_{c-p} = 5.8 Hz, $POCH_2$), 53.0 (CH_2), 48.4 (C), 47.9 (C), 44.7 (CH), 38.3 (CH_2), 35.1 (d, J_{c-p} = 136.3 Hz, PCH_2), 32.9 (CH_2), 26.6 (CH_2), 20.8 (CH_3), 20.0 (CH_3), 16.5 (d, J_{c-p} = 4.8 Hz, CH_3CH_2OP), 16.4 (d, J_{c-p} = 4.8 Hz, CH_3CH_2OP); LRMS (ES^+) *m/z* 416 (100%, $[M + Na]^+$); Elemental calcd. for $C_{16}H_{28}O_6NSP$: C, 48.85; H, 7.17; N, 3.56. Found: C, 48.66; H, 7.05; N, 3.37.

(2*S*)-*N*-[(2*S*)-2-Hydroxy-2-(2*R*,5*S*)-5-((1*S*)-1-hydroxytridecyl)tetrahydro-2-furanylethanoyl)]-camphor-10,2-sultam (**5.4**)



AcOH/Acetone 2:3 method: At –30 °C under N_2, powdered $KMnO_4$ (221 mg, 1.4 mmol) was added in one batch to a rapidly stirred solution of diene **5.5** (500 mg, 1.0 mmol) and adogen 464 (10 mol%, 40 mg, 0.01 mmol) in AcOH/acetone (25 mL 2:3). The reaction mixture was allowed to warm to –10 °C over 1 h whereupon quenching occurred by addition of ice cold $Na_2S_2O_5$ (sat aq, 20 mL). EtOAc (40 mL) was added and the organic phase separated. The aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (600 mg). Purification by column chromatography on silica gel (30% Et_2O/hexane → 60%) gave the major THF diastereoisomer **5.4** (358 mg, 0.63 mmol, 65%) as a gummy oil and the minor THF diastereoisomer **5.21** (56 mg, 0.10 mmol, 10%) as a white solid. Two by-products were also isolated: hydroxy ketone **5.22** (42 mg, 0.08 mmol, 8%) as a yellow solid and acid **5.23** (8 mg, 0.03 mmol 3%) as a white solid. Data for **5.4**: $[\alpha]^{20}_D$ +40.0 ($CHCl_3$, *c* 0.44); IR ν_{max} (neat) 3524 (m), 1699 (s), 1467 (s), 1304 (s), 1295 (s), 1214 (s), 1131 (s), 1106 (s); 1H-NMR (400 MHz, $CDCl_3$) δ 4.60-4.55 (2H, m, CHOHCON, CHO), 3.96 (1H, dd, J = 5.0, 7.5 Hz, CHN), 3.87 (1H, dt, J = 4.5, 7.3 Hz, CHO), 3.52 (1H, d, J = 13.8 Hz, $CHHSO_2$), 3.48-3.43 (1H, m, CHOH), 3.45 (1H, d, J = 13.8 Hz, $CHHSO_2$), 2.29-2.21 (3H, m, CH_2 THF, CHHCHN), 2.13-2.03 (6H, m, CH_2 THF, 4H sultam), 1.55-1.20 (24H, m), 1.16 (3H, s, CH_3C), 0.98 (3H, s, CH_3C), 0.89 (3H, t, J = 6.8 Hz, CH_3CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.8 (C), 83.3 (CH), 78.7 (CH), 74.1 (CH), 73.7 (CH), 65.9 (CH), 53.2 (CH_2), 49.1 (C), 48.0 (C), 44.7 (CH), 38.4 (CH_2), 34.7 (CH_2), 33.0 (CH_2), 32.0 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 28.5 (CH_2), 28.3 (CH_2), 26.5 (CH_2), 25.9 (CH_2) 22.8 (CH_2), 21.0 (CH_3), 20.0 (CH_3), 14.2 (CH_3); LRMS (ES^+) *m/z* 1106 (5%, $[2M + Na]^+$), 564 (100%, $[M + Na]^+$), 542 (5%, $[M + H]^+$); HRMS (ES^+) Calcd. for $C_{29}H_{51}NO_6SNa^+$ *m/z* 564.3329. Found 564.3326; Elemental calcd. for $C_{29}H_{51}NO_6S$: C, 64.29; H, 9.49; N, 2.58. Found: C, 64.24; H, 9.55; N, 2.56.

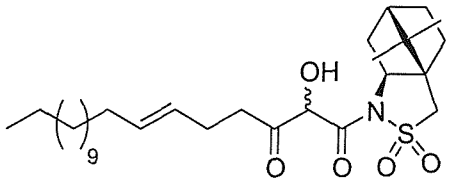
(*2S*)-*N*-[(*2R*)-2-Hydroxy-2-(*2S*,*5R*)-5-((*1R*)-1-hydroxytridecyl)tetrahydro-2-furanylethanoyl)]-camphor-10,2-sultam (**5.21**)



Data for minor THF diastereoisomer **5.21**: mp 95-97 °C; $[\alpha]^{24}_D$ +102.8 (MeOH, *c* 0.38); IR ν_{max} (neat) 3498 (m), 1698 (s), 1465 (s), 1304 (s), 1296 (s), 1216 (s), 1132 (s), 1105 (s); 1H-

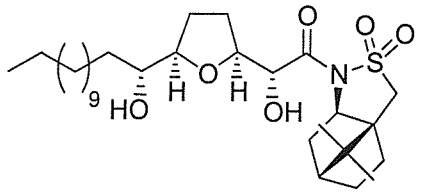
NMR (400 MHz, $CDCl_3$) δ 4.67 (1H, br s, CHOHCON), 4.51 (1H, ddd, J = 2.3, 5.0, 7.5 Hz, CHO), 3.96 (1H, t, J = 6.5 Hz, CHN), 3.77 (1H, dt, J = 4.5, 7.3 Hz, CHO LHS), 3.65 (1H, br, OH), 3.50 (1H, d, J = 13.7 Hz, $CHHSO_2$), 3.49-3.39 (1H, m, CHOH), 3.45 (1H, d, J = 13.7 Hz, $CHHSO_2$), 2.25-2.14 (1H, m, CHHCHN), 2.10-1.83 (8H, m), 1.60 (1H, br, OH), 1.51-1.20 (24H, m), 1.16 (3H, s, CH_3C), 0.98 (3H, s, CH_3C), 0.89 (3H, t, J = 6.8 Hz, CH_3CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.3 (C), 83.1 (CH), 80.3 (CH), 74.3 (CH), 73.8 (CH), 65.0 (CH), 53.1 (CH_2), 49.1 (C), 48.1 (C), 44.6 (CH), 37.8 (CH_2), 34.7 (CH_2), 32.7 (CH_2), 32.1 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 28.3 (CH_2), 27.9 (CH_2), 26.7 (CH_2), 25.8 (CH_2) 22.8 (CH_2), 20.5 (CH_3), 20.0 (CH_3), 14.2 (CH_3); LRMS (ES^+) *m/z* 1105 (20%, $[2M + Na]^+$), 564 (100%, $[M + Na]^+$), 542 (5%, $[M + H]^+$), HRMS (ES^+) Calcd. for $C_{29}H_{51}NO_6SNa^+$ *m/z* 564.3329. Found 564.3328; Elemental calcd. for $C_{29}H_{51}NO_6S$: C, 64.29; H, 9.49; N, 2.58. Found: C, 64.20; H, 9.61; N, 2.57.

(2*S*)-1-*N*-((6*E*)-2-Hydroxy-6-nonadecene-1,3-dioxo)-camphor-10,2-sultam (**5.22**)



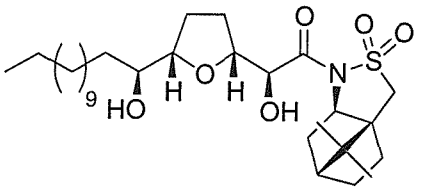
Data for hydroxy ketone **5.22**: (obtained as a 5:1 inseparable mixture of diastereoisomers, spectroscopic data for major isomer only): mp 66-69 °C; IR ν_{max} (neat) 3524 (m), 1699 (s), 1467 (s), 1304 (s), 1295 (s), 1214 (s), 1131 (s), 1106 (s); 1H-NMR (400 MHz, $CDCl_3$) δ 5.44 (1H, td, J = 6.5, 15.0 Hz, CH=CH), 5.35 (1H, td, 6.3, 15.3 Hz, CH=CH), 5.35 (1H, d, 7.5 Hz, CHOH), 3.95 (1H, dd, J = 5.0, 7.5 Hz, CHN), 3.92 (1H, d, J = 7.5 Hz, OH), 3.52 (1H, d, J = 13.6 Hz, $CHHSO_2$), 3.45 (1H, d, J = 13.6 Hz, $CHHSO_2$), 2.80 (1H, td, J = 7.3, 17.5 Hz, CHHCO), 2.64 (1H, td, J = 7.2, 17.5 Hz, CHHCO), 2.29 (2H, q, J = 6.8 Hz, CH_2CH=CH), 2.21-2.01 (2H, m, CH_2CHN), 1.94-1.86 (5H, m), 1.49-1.20 (22H, m), 1.16 (3H, s, CH_3C), 0.98 (3H, s, CH_3C), 0.89 (3H, t, J = 6.8 Hz, CH_3CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 203.3 (C), 168.3 (C), 132.1 (CH), 127.6 (CH), 76.6 (CH), 65.2 (CH), 53.0 (CH_2), 49.2 (C), 48.0 (C), 44.7 (CH), 39.4 (CH_2), 37.9 (CH_2), 32.9 (CH_2), 32.6 (CH_2), 32.0 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 26.6 (CH_2), 26.2 (CH_2), 22.8 (CH_2), 20.6 (CH_3), 20.1 (CH_3), 14.2 (CH_3); LRMS (ES^+) *m/z* 1069 (100%, $[2M + Na]^+$), 546 (50%, $[M + Na]^+$); Elemental calcd. for $C_{29}H_{49}NO_5S$: C, 66.50; H, 9.43; N, 2.67. Found: C, 66.23; H, 9.27; N, 2.55.

(*2R*)-*N*-[(2*R*)-2-Hydroxy-2-(2*S*,5*R*)-5-((1*R*)-1-hydroxytridecyl)tetrahydro-2-furanylethanoyl)]-camphor-10,2-sultam (**5.8**)



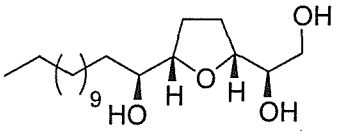
AcOH/Acetone 2:3 method: At –30 °C under N_2, powdered $KMnO_4$ (221 mg, 1.4 mmol) was added in one batch to a rapidly stirred solution of diene **5.7** (500 mg, 1.0 mmol) and adogen 464 (10 mol%, 40 mg, 0.01 mmol) in AcOH/acetone (25 mL 2:3). The reaction mixture was allowed to warm to –10 °C over 1 h whereupon quenching occurred by addition of ice cold $Na_2S_2O_5$ (sat aq, 20 mL). EtOAc (40 mL) was added and the organic phase separated. The aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (600 mg). Purification by column chromatography on silica gel (30% Et_2O/hexane → 60%) gave the major THF diastereoisomer **5.8** (335 mg, 0.62 mmol, 62%) as a gummy oil and the minor THF diastereoisomer **5.26** (51 mg, 0.10 mmol, 10%) as a gummy oil. Data for **5.8**: $[\alpha]^{20}_D$ – 39.1 ($CHCl_3$, *c* 0.40); IR ν_{max} (neat) 3524 (m), 1699 (s), 1467 (s), 1304 (s), 1295 (s), 1214 (s), 1131 (s), 1106 (s); 1H-NMR (400 MHz, $CDCl_3$) δ 4.60-4.55 (2H, m, C**H**OHCON, C**H**O), 3.96 (1H, dd, *J* = 5.0, 7.5 Hz, C**H**N), 3.87 (1H, dt, *J* = 4.5, 7.3 Hz, C**H**O), 3.52 (1H, d, *J* = 13.8 Hz, C**H**HSO$_2$), 3.48-3.42 (1H, m, C**H**OH), 3.45 (1H, d, *J* = 13.8 Hz, C**H**HSO$_2$), 2.29-2.21 (3H, m, C**H$_2$** THF, C**H**HCHN), 2.14-2.03 (6H, m, C**H$_2$** THF, 4H sultam), 1.57-1.18 (24H, m), 1.16 (3H, s, C**H$_3$**C), 0.98 (3H, s, C**H$_3$**C), 0.89 (3H, t, *J* = 6.8 Hz, C**H$_3$**CH$_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.8 (C), 83.3 (CH), 78.7 (CH), 74.1 (CH), 73.7 (CH), 65.9 (CH), 53.2 (CH_2), 49.1 (C), 48.0 (C), 44.7 (CH), 38.4 (CH_2), 34.7 (CH_2), 33.0 (CH_2), 32.0 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 28.5 (CH_2), 28.3 (CH_2), 26.5 (CH_2), 25.9 (CH_2) 22.8 (CH_2), 21.0 (CH_3), 20.0 (CH_3), 14.2 (CH_3); LRMS (ES^+) *m/z* 564 (100%, $[M + Na]^+$), 542 (10%, $[M + H]^+$); Elemental calcd. for $C_{29}H_{51}NO_6S$: C, 64.29; H, 9.49; N, 2.58. Found: C, 64.19; H, 9.52; N, 2.54.

(*2R*)-*N*-[(2*S*)-2-Hydroxy-2-(2*R*,5*S*)-5-((1*S*)-1-hydroxytridecyl)tetrahydro-2-furanylethanoyl)]-camphor-10,2-sultam (**5.26**)



Data for minor THF diastereoisomer **5.26**: $[\alpha]^{24}_{D}$ –94.6 (MeOH, *c* 0.40); IR ν_{max} (neat) 3498 (m), 1698 (s), 1465 (s), 1304 (s), 1296 (s), 1216 (s), 1132 (s), 1105 (s); 1H-NMR (400 MHz, $CDCl_3$) δ 4.67 (1H, br s, CHOHCON), 4.51 (1H, ddd, *J* = 2.3, 5.0, 7.5 Hz, CHO), 3.96 (1H, t, *J* = 6.5 Hz, CHN), 3.77 (1H, dt, *J* = 4.5, 7.3 Hz, CHO LHS), 3.65 (1H, br, OH), 3.50 (1H, d, *J* = 13.7 Hz, $CHHSO_2$), 3.49-3.39 (1H, m, CHOH), 3.45 (1H, d, *J* = 13.7 Hz, $CHHSO_2$), 2.25-2.14 (1H, m, CHHCHN), 2.10-1.83 (8H, m), 1.63 (1H, br, OH), 1.56-1.21 (24H, m), 1.16 (3H, s, CH_3C), 0.98 (3H, s, CH_3C), 0.89 (3H, t, *J* = 6.8 Hz, CH_3CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.3 (C), 83.1 (CH), 80.3 (CH), 74.3 (CH), 73.8 (CH), 65.0 (CH), 53.1 (CH_2), 49.1 (C), 48.1 (C), 44.6 (CH), 37.8 (CH_2), 34.7 (CH_2), 32.7 (CH_2), 32.1 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 28.3 (CH_2), 27.9 (CH_2), 26.7 (CH_2), 25.8 (CH_2) 22.8 (CH_2), 20.5 (CH_3), 20.0 (CH_3), 14.2 (CH_3); LRMS (ES^+) *m/z* 1105 (20%, $[2M + Na]^+$), 564 (100%, $[M + Na]^+$), 542 (5%, $[M + H]^+$), Found 564.3328; Elemental calcd. for $C_{29}H_{51}NO_6S$: C, 64.29; H, 9.49; N, 2.58. Found: C, 64.30; H, 9.57; N, 2.57.

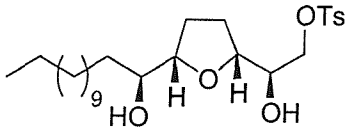
(1*R*)-1-(2*R*,5*S*)-5-[(1*S*)-1-hydroxytridecyl]tetrahydro-2-furanylethane-1,2-diol (**5.27**)



To a solution of the THF-sultam **5.4** (215 mg, 0.40 mmol) in a 3:1 mixture of THF/H_2O (12 mL) at –10 °C was added $NaBH_4$ (30 mg, 0.80 mmol) in one batch. The mixture was allowed to warm to 0 °C over 2 h whereupon HCl (2M, 5 mL) and EtOAc (10 mL) were added. The organic phase was separated and the aqueous phase extracted with EtOAc (2 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a colourless oil. Purification by column chromatography on silica gel (3% MeOH/CH_2Cl_2 → 5%) gave triol **5.27** (118 mg, 0.36 mmol, 89%) as a white solid: mp 47-48 °C; $[\alpha]^{25}_{D}$ –10.5 (MeOH, *c* 0.40); IR ν_{max} (neat) 3238 (br), 1460 (s), 1415 (m), 1327 (m), 1118 (s), 1078 (s),

1056 (s); 1H-NMR (400 MHz, CD_3OD) δ 4.02 (1H, dt, *J* = 3.7, 6.7 Hz, CHO), 3.84 (1H, br q, *J* = 6.0 Hz, CHO), 3.66 (1H, dd, *J* = 5.3, 11.0 Hz, CHHOH), 3.62 (1H, dd, *J* = 6.3, 11.0 Hz, CHHOH), 3.54 (1H, br q, *J* = 5.5 Hz, CHOH), 3.45 (1H, br q, J = 5.3 Hz, CHOH), 2.04-1.77 (4H, m, CH_2 x 2 THF), 1.58-1.47 (2H, m, CH_2CHOH), 1.45-1.26 (20H, m), 0.94 (3H, t, *J* = 7.0 Hz, CH_3CH_2); ^{13}C-NMR (100 MHz, CD_3OD) δ 83.8 (CH), 80.9 (CH), 75.3 (CH), 74.9 (CH), 65.2 (CH_2), 35.2 (CH_2), 33.1 (CH_2), 30.8 x 6 (CH_2), 30.5 (CH_2), 28.9 (CH_2), 28.6 (CH_2), 27.0 (CH_2), 23.8 (CH_2), 14.7 (CH_3); LRMS (ES^+) *m/z* 684 (40%, $[2M + Na]^+$), 353 (100%, $[M + Na]^+$); HRMS (ES^+) Calcd. for $C_{26}H_{44}O_4Na^+$ *m/z* 330.2770. Found 330.2768; Elemental calcd. for $C_{19}H_{38}O_4$: C, 69.05; H, 11.59. Found: C, 68.82; H, 11.41.

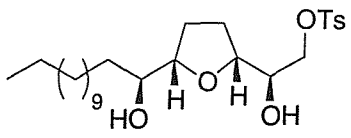
Method 1: (2*R*)-2-hydroxy-2-(2*R*,5*S*)-5-[(1*S*)-1-hydroxytridecyl]tetrahydro-2-furanylethyl-4-methyl-1-benzenesulfonate (**5.28**)



To a solution of the THF triol **5.27** (100 mg, 0.30 mmol), tosyl chloride (50 mg, 0.31 mmol) and DMAP (4 mg, 0.03 mmol) in CH_2Cl_2 (6 mL) was added Et_3N (46 μL). After 4 h HCl (2M, 2 mL), brine (5 mL) and CH_2Cl_2 (10 mL) were added. The organic phase was separated and the aqueous was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a colourless oil. Purification by column chromatography using silica gel (20% EtOAc/hexane → 40%) gave the tosylate **5.28** (105 mg, 0.22 mmol, 72%) as a white solid: mp 70-72 °C; $[\alpha]^{25}_D$ −10.4 ($CHCl_3$, *c* 0.40); IR ν_{max} (neat) 3425 (s), 3309 (br), 1596 (m), 1469 (s), 1365 (s), 1171 (s), 1114 (s); 1H-NMR (400 MHz, $CDCl_3$) δ 7.80 (2H, d, *J* = 8.3 Hz, CH), 7.34 (2H, d, *J* = 8.3 Hz, CH), 4.09 (2H, d, *J* = 6.0 Hz, CH_2OTs), 4.00 (1H, dt, *J* = 2.8, 6.8 Hz, $OCHCHOHCH_2OTs$), 3.84 (1H, dt, *J* = 4.0, 7.0 Hz, $OCHCHOHCH_2CH_2$), 3.74 (1H, dt, *J* = 2.8, 6.0 Hz, $CHOHCH_2OTs$ RHS), 3.44-3.40 (1H, m, $CHOHCH_2CH_2$), 2.78 (2H, br, OH), 2.45 (3H, s, CH_3Ar), 2.02-1.81 (4H, m, CH_2 x 2 THF), 1.47-1.40 (2H, m, CH_2CHOH), 1.34-1.20 (20H, m), 0.88 (3H, t, *J* = 7.0 Hz, CH_3CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 145.0 (C), 132.9 (C), 130.0 (CH), 128.1 (CH), 82.7 (CH), 78.6 (CH), 74.2 (CH), 71.8 (CH), 71.6 (CH_2), 34.6 (CH_2), 32.0 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 28.2 (CH_2), 27.9 (CH_2), 25.9 (CH_2), 22.8 (CH_2), 21.8 (CH_3), 14.2 (CH_3); LRMS (ES^+) *m/z* 991 (60%, $[2M + Na]^+$), 969 (10%, $[2M + H]^+$), 507 (100%, $[M + Na]^+$),

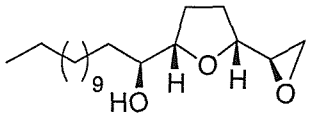
485 (30%, $[M + H]^+$); Elemental calcd. for $C_{26}H_{44}O_6S$: C, 64.43; H, 9.15. Found: C, 64.39; H, 9.08.

Method 2: (2*R*)-2-hydroxy-2-(2*R*,5*S*)-5-[(1*S*)-1-hydroxytridecyl]tetrahydro-2-furanylethyl-4-methyl-1-benzenesulfonate (**5.28**)



To a solution of the THF triol **5.27** (256 mg, 0.78 mmol) in benzene (10 mL) was added Bu_2SnO (232 mg, 0.94 mmol). The reaction mixture was heated at reflux for 3 h where upon it was cooled to rt. TsCl (164 mg, 0.86 mmol) was added followed 10 min later by TBAB (256 mg, 0.78 mmol). After a further 30 min the reaction mixture was concentrated *in vacuo*. Purification by column chromatography using silica gel (20% EtOAc/hexane → 40%) gave the tosylate **5.28** (370 mg, 0.77 mmol, 98%) as a white solid: characterisation as above.

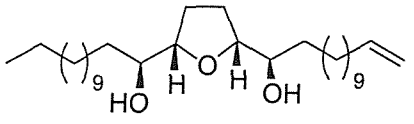
(1*S*)-1-[(2*S*,5*R*)-5-[(2*R*)-oxiran-2-yl]tetrahydro-2-furanyl]-tridecan-1-ol (**5.29**)



To a solution of tosylate **5.28** (95 mg, 0.20 mmol) in CH_2Cl_2 (6 mL) at 0 °C was added DBU (64 μL, 0.4 mmol) dropwise by syringe. The solution was allowed to warm to rt, after 2 h the solution was concentrated *in vacuo* to give a yellow oil that was purified through a plug of silica (40% EtOAc/hexane) to give epoxide **5.29** (59 mg, 0.19 mmol, 96%) as a white solid: mp 36-40 °C; $[\alpha]^{24}_D$ −10.1 ($CHCl_3$, *c* 0.40); IR ν_{max} (neat) 3320 (br), 1465 (s), 1418 (m), 1321 (m), 1122 (s); 1H-NMR (300 MHz, d4-MeOH) δ 4.06 (1H, dt, *J* = 3.1, 6.6 Hz, **CH**O RHS), 3.88 (1H, dt, *J* = 4.2, 7.2 Hz, **CH**O LHS), 3.45-3.29 (1H, m, **CH**OH), 3.03 (1H, td, *J* = 3.1, 4.0 Hz, **CH**-O-CH_2), 2.82 (1H, dd, *J* = 2.9, 5.1 Hz, **CH**HO), 2.80 (1H, br, OH), 2.78 (1H, dd, *J* = 4.0, 5.1 Hz, **CH**HO), 2.20-1.80 (4H, m, **CH_2** x 2 THF), 1.57-1.12 (22H, m), 0.88 (3H, t, *J* = 7.0 Hz, **CH_3**CH_2); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 83.1 (CH), 77.2 (CH), 74.3 (CH), 54.7 (CH), 44.5 (CH_2), 34.8 (CH_2), 32.1 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 28.2 (CH_2), 26.0 (CH_2), 22.8 (CH_2), 14.3 (CH_3); LRMS (ES^+) *m/z* 647 (100%, $[2M + Na]^+$),

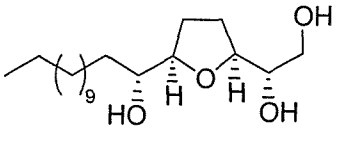
335 (10%, $[M + Na]^+$); Elemental calcd. for $C_{19}H_{36}O_3$: C, 73.03; H, 11.61. Found: C, 72.95; H, 11.55.

(1*R*)-1-(2*R*,5*S*)-5-[(1*S*)-1-hydroxytridecyl]tetrahydro-2-furanyl-12-tridecen-1-ol (**5.3**)



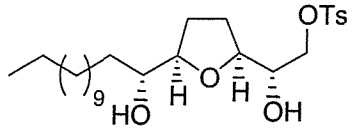
At –60 °C, Undec-10-enylmagnesium bromide in THF (0.4 M, 2.4 mL, 0.95 mmol) was added dropwise to a suspension of CuI (91 mg, 0.48 mmol) in THF (7 mL). The mixture was warmed to –30 °C (solution grey colour) and after 20 min cooled back down to –60 °C whereupon a solution of epoxide **5.29** (60 mg, 0.19 mmol) in THF (5 mL) was added dropwise. The mixture was allowed to warm to –20 °C over 1 h whereupon it was quenched by addition of an aqueous solution of NH_4Cl /NH_3 (9:1, 15 mL). EtOAc (20 mL) was added and the organic phase separated, the aqueous was extracted with EtOAc (2 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a colourless oil. Purification by column chromatography on silica gel (10% EtOAc/hexane → 15%) gave the title olefin **5.3** (73 mg, 0.16 mmol, 82%) as a white solid: mp 55-57 °C; $[\alpha]^{25}_D$ –0.9 ($CHCl_3$, *c* 1.1); IR ν_{max} (neat) 3380 (br), 1462 (s), 1367 (s), 1169 (s), 1117 (s); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.81 (1H, tdd, *J* = 6.8,10.1, 17.0 Hz, C**H**=CH_2), 4.99 (1H, dd, *J* = 1.4, 17.0 Hz, C**H**H=CH), 4.93 (1H, dd, *J* = 1.4, 10.1 Hz, C**H**H=CH), 3.84-3.80 (2H, m, C**H**O x 2), 3.42 (2H, br q, *J* = 5.5 Hz, C**H**OH x 2), 2.58 (2H, br s, **OH**), 2.04 (2H, q, *J* = 7.2 Hz, CH_2CH=CH_2), 1.99-1.86 (2H, m, C**H**$_2$ THF), 1.81-1.69 (2H, m, C**H**$_2$ THF) 1.56-1.18 (40H, m), 0.88 (3H, t, *J* = 7.0 Hz, CH_3CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 139.3 (CH), 114.2 (CH_2), 82.9 (CH), 74.5 (CH), 34.2 (CH_2), 33.9 (CH_2), 32.0 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.2 (CH_2), 25.8 (CH_2), 22.8 (CH_2), 14.2 (CH_3); LRMS (ES^+) *m/z* 955 (90%, $[2M + Na]^+$), 489 (100%, $[M + Na]^+$); Elemental calcd. for $C_{30}H_{58}O_3$: C, 77.19; H, 12.52. Found: C, 77.15; H, 12.37.

(1*S*)-1-(2*S*,5*R*)-5-[(1*R*)-1-hydroxytridecyl]tetrahydro-2-furanylethane-1,2-diol (**5.30**)



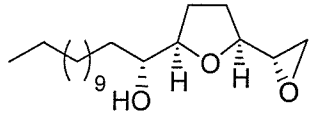
The title compound was prepared according to the method outlined for **5.27**, except using: THF-sultam **5.8** (250 mg, 0.46 mmol). Gave the title triol **5.30** (137 mg, 0.41 mmol, 90%) as a white solid (^{1}H, ^{13}C, IR, LRMS spectroscopic data identical to **5.27**): mp 46-47 °C; $[\alpha]^{25}_D$ +10.5 (MeOH, *c* 0.40); Elemental calcd. for $C_{19}H_{38}O_4$: C, 69.05; H, 11.59. Found: C, 68.93; H, 11.42.

(2*S*)-2-hydroxy-2-(2*S*,5*R*)-5-[(1*R*)-1-hydroxytridecyl]tetrahydro-2-furanylethyl 4-methyl-1-benzenesulfonate (**5.31**)



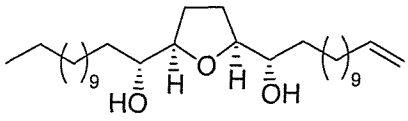
The title compound was prepared according to the method outlined for **5.28**, except using: THF triol **5.30** (128 mg, 0.39 mmol). Gave the title tosylate **5.31** (185 mg, 0.38 mmol, 98%) as a white solid (^{1}H, ^{13}C, IR, LRMS spectroscopic data identical to **5.28**): mp 70-72 °C; $[\alpha]^{25}_D$ +10.6 ($CHCl_3$, *c* 0.36); Elemental calcd. for $C_{26}H_{44}O_6S$: C, 64.43; H, 9.15. Found: C, 64.34; H, 9.05.

(1*R*)-1-(2*R*,5*S*)-5-[(2*S*)oxiran-2-yl]tetrahydro-2-furanyltridecan-1-ol (**5.32**)



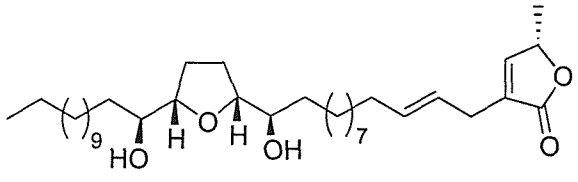
The title compound was prepared according to the method outlined for **5.29**, except using: tosylate **5.31** (180 mg, 0.37 mmol). Gave the title epoxide **5.32** (111 mg, 0.36 mmol, 96%) as a white solid (^{1}H, ^{13}C, IR, LRMS spectroscopic data identical to **5.29**): mp 37-40 °C; $[\alpha]^{20}_D$ +10.3 ($CHCl_3$, *c* 0.62); Elemental calcd. for $C_{19}H_{36}O_3$: C, 73.03; H, 11.61. Found: C, 73.01; H, 11.57.

(1*S*)-1-(2*S*,5*R*)-5-[(1*R*)-1-hydroxytridecyl]tetrahydro-2-furanyl-12-tridecen-1-ol (**5.9**)



The title compound was prepared according to the method outlined for **5.3**, except using: epoxide **5.32** (96 mg, 0.31 mmol). Gave the title olefin **5.9** (127 mg, 0.27 mmol, 88%) as a white solid (^{1}H, ^{13}C, IR, LRMS spectroscopic data identical to **5.3**): mp 55-57 °C; $[\alpha]^{25}_D$ – 0.3 ($CHCl_3$, *c* 1.0); Elemental calcd. for $C_{30}H_{58}O_3$: C, 77.19; H, 12.52. Found: C, 77.24; H, 12.31.

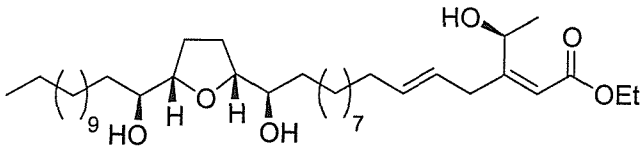
(5*S*)-3-((2*E*,13*R*)-13-hydroxy-13-(2*R*,5*S*)-5-[(1*S*)-1-hydroxytridecyl]tetrahydro-2-furanyl-2-tridecenyl)-5-methyl-2,5-dihydro-2-furanone (**5.33**)



Under an atmosphere of argon, a bright orange solution of CpRu(COD)Cl (**1.214**) (1 mg, 0.006 mmol) in degassed CH_3OH (0.5 mL) was added to a solution of the olefin **5.3** (26 mg, 0.06 mmol) and alkyne **1.212** (10 mg, 0.07 mmol) in degassed CH_3OH (1.5 mL). The solution was heated at reflux for 3 h, before cooling to rt and dilution with Et_2O (10 mL). The solution was then concentrated *in vacuo* to give an orange gum which was passed through a plug of silica (40% acetone/hexane). Purification by column chromatography on silica gel (1% MeOH/CH_2Cl_2 → 2%) gave a 6:1 ratio of the title butenolide **5.33** (22 mg, 0.039 mmol, 70%) as a white solid and the uncyclised enoate **5.34** (4 mg, 0.006 mmol, 12%) as a white solid. Data for **5.33**: mp 60-62 °C; $[\alpha]^{20}_D$ +10.6 (MeOH, *c* 0.39); IR ν_{max} (neat) 3350 (br), 1758 (s), 1462 (s), 1365 (s), 1171 (s), 1115 (s), 1078 (s); 1H-NMR (400 MHz, $CDCl_3$) δ 6.99 (1H, d, *J* = 1.8 Hz, C**H**=C), 5.57 (1H, dt, *J* = 15.3, 6.5 Hz, C**H**=CHCH$_2$C), 5.47 (1H, dt, *J* = 15.3, 6.5 Hz, =C**H**CH$_2$C), 5.03 (1H, qq, *J* = 1.8, 6.8 Hz, C**H**CH$_3$), 3.87-3.83 (2H, m, C**H**O x 2), 3.47-3.39 (2H, m, C**H**OH x 2), 2.96 (2H, d, *J* = 6.5, CH$_2$C), 2.50 (2H, br s, O**H** x 2), 2.03 (2H, q, *J* = 7.1 Hz, CH$_2$C**H**$_2$CH=CH), 1.98-1.89 (2H, m, C**H**$_2$ THF), 1.81-1.71 (2H, m, C**H**$_2$ THF), 1.54-1.22 (38H, m), 1.42 (3H, d, *J* = 6.8 Hz, C**H**$_3$CH), 0.89 (3H, t, *J* = 7.0 Hz, C**H**$_3$CH$_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.6 (C), 149.5

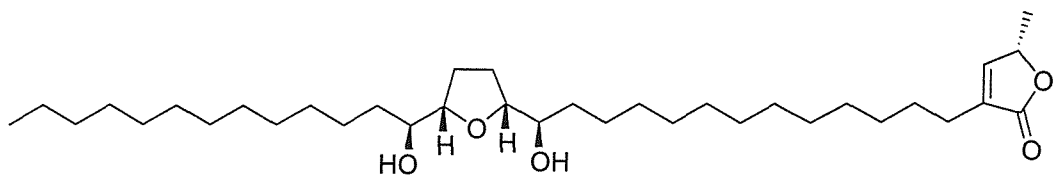
(CH), 134.3 (CH), 133.7 (C), 124.4 (CH), 82.8 (CH), 77.7 (CH), 74.5 (CH) 34.3 (CH_2), 32.6 (CH_2), 32.1 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 25.9 (CH_2), 22.8 (CH_2), 19.3 (CH_3), 14.2 (CH_3); LRMS (ES^+) *m/z* 1148 (20%, $[2M + Na]^+$), 1126 (10%, $[2M + H]^+$), 586 (100%, $[M + Na]^+$), 564 (100%, $[M + H]^+$); HRMS (ES^+) $C_{35}H_{63}O_5^+$ Calcd. 563.4670 found 563.4662; Elemental calcd. for $C_{35}H_{62}O_5$: C, 74.68; H, 11.10. Found: C, 74.65; H, 11.09.

16-Hydroxy-3-(1-hydroxy-ethyl)-16-[5-(1-hydroxy-tridecyl)-tetrahydro-furan-2-yl]-hexadeca-2,5-dienoic acid ethyl ester (**5.34**)



Data for **5.34**: mp 32-34 °C; IR ν_{max} (neat) 3333 (br), 1730 (s), 1462 (s), 1365 (s), 1171 (s), 1115 (s), 1076 (s); 1H-NMR (400 MHz, $CDCl_3$) δ 6.01 (1H, d, *J* = 1.1 Hz, C**H**=C), 5.51 (1H, dt, *J* = 15.3, 6.5 Hz, C**H**=CHCH$_2$C), 5.43 (1H, dt, *J* = 15.3, 6.5 Hz, =C**H**CH$_2$C), 4.34 (1H, dq, *J* = 1.1, 6.5 Hz, C**H**OHCH$_3$), 4.18 (2H, q, *J* = 7.0 Hz, OCH$_2$CH$_3$), 3.86-3.78 (2H, m, C**H**O x 2), 3.56 (1H, dd, *J* = 6.0, 13.8 Hz, =CHC**H**HC=), 3.47-3.38 (2H, m, C**H**OH x 2), 3.07 (1H, dd, *J* = 6.7, 13.8 Hz, =CHC**H**HC=), 2.39 (1H, br s, O**H**), 2.02-1.89 (4H, m, C**H**$_2$), 1.82-1.70 (2H, m, C**H**$_2$), 1.53-1.19 (44H, m, C**H**$_2$, C**H**$_3$CHOH, C**H**$_3$CH$_2$O), 0.89 (3H, t, *J* = 7.0 Hz, C**H**$_3$CH$_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.7 (C), 163.4 (C), 133.1 (CH), 126.7 (CH), 114.2 (CH), 82.8 (CH), 74.5 (CH), 70.8 (CH), 60.0 (CH_2), 34.3 (CH_2), 32.9 (CH_2), 32.6 (CH_2), 32.1 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 25.8 (CH_2), 22.8 (CH_2), 22.4 (CH_3), 14.4 (CH_3), 14.2 (CH_3); LRMS (ES^+) *m/z* 631 (100%, $[M + Na]^+$), 609 (100%, $[M + H]^+$); HRMS (ES^+) $C_{37}H_{69}O_6^+$ Calcd. 609.5089 found 609.5085.

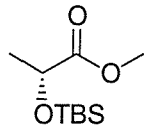
cis-Solamin (**1.240**)



To a solution of 4,5-di-dehydro-*cis*-solamin **5.33** (20 mg, 0.036 mmol) and $TsNHNH_2$ (40 mg, 0.22 mmol) in THF (1 mL) was added a solution of NaOAc (18 mg, 0.22 mmol) in H_2O

(1 mL). The mixture was heated at 80 °C for 18 h. After cooling to rt, K_2CO_3 (sat aq, 2 mL) was added and the mixture stirred for 1 h. CH_2Cl_2 (5 mL) was added and the organic phase separated, the aqueous was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a white solid. Purification by column chromatography (40% EtOAc/Hex) gave *cis*-solamin (**1.240**) (19 mg, 0.034, 94%) as a white solid: mp 67-69 °C; $[\alpha]^{24}_D$ +11.3 (MeOH, *c* 0.87), Lit $[\alpha]^{25}_D$ +22 (MeOH, *c* 0.55);[117] IR ν_{max} (neat) 3390 (br), 1760 (s), 1464 (s), 1367 (s), 1169 (s), 1118 (s), 1080 (s); 1H-NMR (400 MHz, $CDCl_3$) δ 6.99 (1H, d, J = 1.8 Hz, C**H**=C), 5.00 (1H, dq, J = 1.8, 6.8 Hz, C**H**CH_3), 3.87-3.83 (2H, m, C**H**O x 2), 3.47-3.39 (2H, m, C**H**OH x 2), 2.26 (2H, t, J = 7.1, C**H**$_2$C), 2.00-1.88 (2H, m, C**H**$_2$ THF), 1.81-1.71 (2H, m, C**H**$_2$ THF), 1.62-1.10 (44H, m), 1.42 (3H, d, J = 6.8 Hz, C**H**$_3$CH), 0.89 (3H, t, J = 7.0 Hz, C**H**$_3$CH$_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 174.0 (C), 148.9 (CH), 134.5 (C), 82.8 (CH), 77.6 (CH), 74.5 (CH) 34.2 (CH_2), 32.1 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 28.3 (CH_2), 25.9 (CH_2), 25.2 (CH_2), 22.8 (CH_2), 19.3 (CH_3), 14.2 (CH_3); LRMS (ES^+) *m/z* 1152 (20%, $[2M + Na]^+$), 1130 (10%, $[2M + H]^+$), 587 (80%, $[M + Na]^+$), 565 (100%, $[M + H]^+$); HRMS (ES^+) $C_{35}H_{65}O_5^+$ Calcd. 565.4827 found 565.4821; Elemental calcd. for $C_{34}H_{64}O_5$: C, 73.86; H, 11.67. Found: C, 73.72; H, 11.53; Chiral CD-Ph, 15% *i*-PrOH/Hex, 14.5 min.

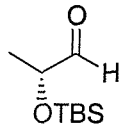
Ethyl (2*R*)-2-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxypropanoate (**5.37**)



Under an atmosphere of N_2, at 0 °C to a solution of methyl-(*R*)-lactate (**5.36**) (5.04 mL, 48 mmol) in THF (75 mL) was added Et_3N (14.9 mL, 106 mmol), DMAP (0.61 g, 5 mmol) and TBSCl (8.03 g, 53 mmol). The cloudy white solution was allowed to warm to rt and stir for 18 h. The reaction mixture was diluted with Et_2O (100 mL) then washed sequentially with citric acid (10% w/v aq, 75 mL), H_2O (50 mL) and saturated aqueous sodium bicarbonate (50 mL) before drying ($MgSO_4$). Evaporation of the solvents gave the crude product as an oil (12 g). Purification by vacuum distillation (bp 95 °C, 30 mbar) gave the title silyl-ether **5.37** (10.15 g, 46.6 mmol, 97%) as a colourless oil (spectroscopic data was identical to **4.14**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.33 (1H, q, J = 6.9 Hz, C**H**O(TBDMS)CH_3), 3.72 (3H, s, C**H**$_3$O), 1.40 (3H, d, J = 6.9 Hz, C**H**$_3$CHO(TBDMS)), 0.90 (9H, s, (C**H**$_3$)$_3$C), 0.09 (3H, s,

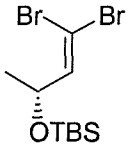
CH_3Si), 0.07 (3H, s, CH_3Si); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7 (C), 68.5 (CH), 52.0 (CH_3), 25.9 (CH_3), 21.5 (CH_3), 18.5 (C), –4.6 (CH_3), –4.7 (CH_3).

(2*R*)-2-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxypropanal (**5.38**)



Under an atmosphere of N_2, at –78 °C to a solution of ester **5.37** (9.29 g, 42.6 mmol) in CH_2Cl_2 (600 mL) was added DIBAL-H in hexanes (47 mL, 47 mmol) dropwise over 25 min. After 3 h the reaction was quenched by addition of NH_4Cl (sat aq, 200 mL) and H_2O (100 mL) and warmed to rt. The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 200 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a colourless oil (8 g). Purification by column chromatography on silica gel (40% CH_2Cl_2/hexane → 60%) gave aldehyde **5.38** (6.50 g, 81%) as a colourless oil (spectroscopic data was identical to **4.15**): ^1H NMR (300 MHz, $CDCl_3$) δ 9.62 (1H, d, J = 1.5 Hz, C**H**O), 4.10 (1H, dq, J = 6.9, 1.5 Hz, C**H**O(TBDMS)CH_3), 1.28 (3H, d, J = 6.9 Hz, CH_3CHO(TBDMS)), 0.91 (9H, s, (CH_3)$_3$C), 0.11 (3H, s, CH_3Si), 0.09 (3H, s, CH_3Si); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7 (CH), 74.0 (CH), 25.9 (CH_3), 18.7 (CH_3), 18.3 (C), –4.6 (CH_3), –4.7 (CH_3).

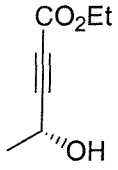
(3*R*)-1,1-Dibromo-3-[(*tert*-butyldimethylsilyl)oxy]-1-butene (**5.39**)



Under an atmosphere of N_2, at 0 °C to a solution of carbon tetrabromide (10.35 g, 31.2 mmol) in CH_2Cl_2 (70 mL) was added a solution of triphenylphosphine (16.37 g, 62.4 mmol) in CH_2Cl_2 (20 mL). After 15 min the yellow solution was cooled to –78 °C and a solution of **5.38** (2.93 g, 15.6 mmol) in CH_2Cl_2 (5 mL) was added dropwise. After 1 h the reaction mixture was brought to rt and pentane (200 mL) was added. After 30 min the precipitate was removed by filtration, the organic filtrate was concentrated *in vacuo*, before being solvated in CH_2Cl_2 (5 mL). Pentane (20 mL) was added and the precipitate was removed by filtration.

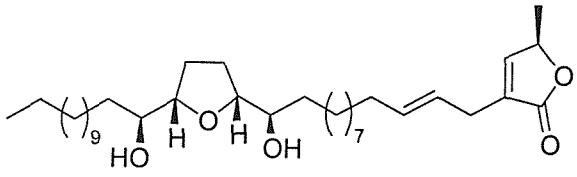
Evaporation of solvents gave an oil that was purified by column chromatography on silica gel (hexane) to give dibromide **5.39** (4.65 g, 13.6 mmol, 87%) as a colourless oil (spectroscopic data was identical to **4.16**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.43 (1H, d, J = 8.0 Hz, C**H**=CBr_2), 4.45 (1H, dq, J = 8.0, 5.9 Hz, C**H**O(TBDMS)CH_3), 1.23 (3H, d, J = 5.9 Hz, CH_3CHO(TBDMS)), 0.89 (9H, s, (CH_3)$_3$C), 0.09 (3H, s, CH_3Si), 0.08 (3H, s, CH_3Si); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2 (CH), 87.7 (C), 70.0 (CH), 25.9 (CH_3), 22.9 (CH_3), 18.3 (C), –4.5 (CH_3), –4.7 (CH_3).

Ethyl (4*R*)-4-hydroxy-2-pentynoate (**5.2**)



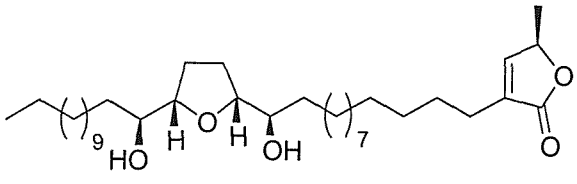
Under an atmosphere of N_2, at –78 °C to a solution of vinyl bromide **5.39** (4.63 g, 13.5 mmol) in THF (60 mL) was added *n*BuLi in hexanes (14.2 mL, 32.45 mmol) dropwise over 20 min. After 1 h ethyl chloroformate (3.23 mL, 33.75 mmol) was added dropwise. After 10 min the reaction mixture was warmed to rt and poured into NH_4Cl (sat aq, 40 mL). The organic phase was separated and the aqueous phase extracted with Et_2O (2 x 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. To this oil in THF (7 mL) was added H_2O (7 mL) and acetic acid (21 mL). The mixture was heated at 70 °C for 12 h. The reaction mixture was cooled to rt and quenched with $NaHCO_3$ (aq, 100 mL and solid 3 g). Et_2O (100 mL) was added and the organic phase separated, the aqueous phase was extracted with Et_2O (2 x 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a pale yellow oil. Purification by column chromatography on silica gel (15% EtOAc/hexane → 25%) gave propargylic alcohol **5.2** (1.51 g, 10.6 mmol, 80%) as a colourless oil; $[\alpha]^{20}_D$ +27.2 ($CHCl_3$, *c* 0.85); IR ν_{max} (neat) 3410 (m) 2244 (m), 1710 (s), 1445 (m), 1368 (m), 1244 (s), 1122 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.65 (1H, d, J = 6.9 Hz, C**H**OHCH$_3$), 4.24 (2H, q, J = 7.0 Hz, CH_3C**H**$_2$O), 2.29 (1H, br, O**H**), 1.52 (3H, d, J = 6.9 Hz,C**H**$_3$CHOH), 1.32 (3H, t, J = 7.0 Hz, C**H**$_3$CH$_2$O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4 (C), 88.3 (C), 75.9 (C), 62.2 (CH_2), 58.0 (CH), 23.3 (CH_3), 14.0 (CH_3); LRMS (GCCI) 3.61 min, 142 (100%, $[M+NH_4]^+$); HRMS (EI) Calcd. for $C_7H_{10}O_3^{+\cdot}$ *m/z* 142.0630, found 142.0627.

(5*R*)-3-((2*E*,13*R*)-13-hydroxy-13-(2*R*,5*S*)-5-[(1*S*)-1-hydroxytridecyl]tetrahydro-2-furanyl-2-tridecenyl)-5-methyl-2,5-dihydro-2-furanone (**5.40**)



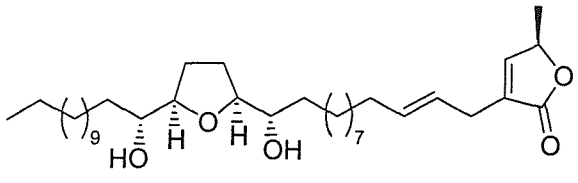
The title compound was prepared according to the method outlined for **5.33**, except using: olefin **5.3** (40 mg, 0.09 mmol), alkyne **5.2** (16 mg, 0.11 mmol) and CpRu(COD)Cl (**1.214**) (3 mg, 0.01 mmol). Gave the title butenolide **5.40** (34 mg, 0.06 mmol, 70%) as a white solid (^{1}H, ^{13}C, IR, LRMS spectroscopic data identical to **5.33**): mp 63-65 °C; $[\alpha]^{24}_D$ –8.3 (MeOH, *c* 0.54); Elemental calcd. for $C_{35}H_{62}O_5$: C, 74.68; H, 11.10. Found: C, 74.64; H, 11.07.

(5*R*)-3-((13*R*)-13-hydroxy-13-(2*R*,5*S*)-5-[(1*S*)-1-hydroxytridecyl]tetrahydro-2-furanyltridecyl)-5-methyl-2,5-dihydro-2-furanone (**5.1**)



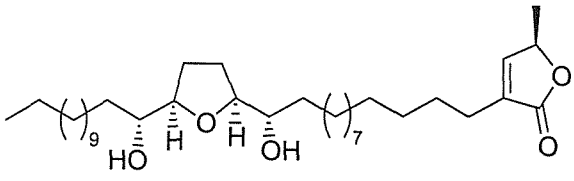
The title compound was prepared according to the method outlined for **1.240**, except using: butenolide **5.40** (24 mg, 0.04 mmol), $TsNHNH_2$ (48 mg, 0.26 mmol) and NaOAc (21 mg, 0.26 mmol). Gave the title compound **5.1** (23 mg, 0.04, 90%) as a white solid (^{1}H, ^{13}C, IR, LRMS spectroscopic data identical to **1.240**): mp 68-70 °C; $[\alpha]^{24}_D$ –11.3 (MeOH, *c* 0.68); Elemental calcd. for $C_{34}H_{64}O_5$: C, 73.86; H, 11.67. Found: C, 73.78; H, 11.61; Chiral CD-Ph, 15% *i*-PrOH/Hex, 15.7 min.

(5*R*)-3-((2*E*,13*S*)-13-hydroxy-13-(2*S*,5*R*)-5-[(1*R*)-1-hydroxytridecyl]tetrahydro-2-furanyl-2-tridecenyl)-5-methyl-2,5-dihydro-2-furanone (**5.41**)



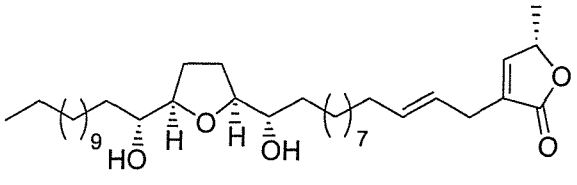
The title compound was prepared according to the method outlined for **5.33**, except using: olefin **5.9** (45 mg, 0.10 mmol), alkyne **5.2** (19 mg, 0.14 mmol) and CpRu(COD)Cl (**1.214**) (3 mg, 0.01 mmol). Gave the title butenolide **5.41** (39 mg, 0.06 mmol, 70%) as a white solid (^{1}H, ^{13}C, IR, LRMS spectroscopic data identical to **5.33**): mp 63-65 °C; $[\alpha]^{24}_D$ –8.9 (MeOH, *c* 0.42); Elemental calcd. for $C_{35}H_{62}O_5$: C, 74.68; H, 11.10. Found: C, 74.59; H, 11.02.

(5*R*)-3-((13*S*)-13-hydroxy-13-(2*S*,5*R*)-5-[(1*R*)-1-hydroxytridecyl]tetrahydro-2-furanyltridecyl)-5-methyl-2,5-dihydro-2-furanone (**5.10**)



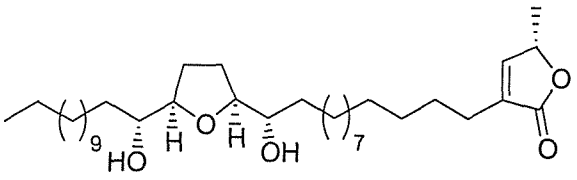
The title compound was prepared according to the method outlined for **1.240**, except using: butenolide **5.41** (24 mg, 0.04 mmol), $TsNHNH_2$ (48 mg, 0.26 mmol) and NaOAc (21 mg, 0.26 mmol). Gave the title compound **5.10** (23 mg, 0.04, 92%) as a white solid (^{1}H, ^{13}C, IR, LRMS spectroscopic data identical to **1.240**): mp 71-72 °C; $[\alpha]^{24}_D$ –11.7 (MeOH, *c* 1.02); Elemental calcd. for $C_{34}H_{64}O_5$: C, 73.86; H, 11.67. Found: C, 73.68; H, 11.47; Chiral CD-Ph, 15% *i*-PrOH/Hex, 18.7 min.

(5*S*)-3-((2*E*,13*S*)-13-hydroxy-13-(2*S*,5*R*)-5-[(1*R*)-1-hydroxytridecyl]tetrahydro-2-furanyl-2-tridecenyl)-5-methyl-2,5-dihydro-2-furanone (**5.42**)



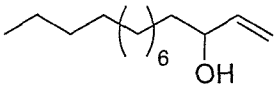
The title compound was prepared according to the method outlined for **5.33**, except using: olefin **5.9** (45 mg, 0.10 mmol), alkyne **1.212** (19 mg, 0.14 mmol) and CpRu(COD)Cl (**1.214**) (3 mg, 0.01 mmol). Gave the title butenolide **5.42** (36 mg, 0.06 mmol, 66%) as a white solid (^{1}H, ^{13}C, IR, LRMS spectroscopic data identical to **5.33**): mp 64-67 °C; $[\alpha]^{24}_D$ +9.3 (MeOH, *c* 0.48); Elemental calcd. for $C_{35}H_{62}O_5$: C, 74.68; H, 11.10. Found: C, 74.61; H, 11.08.

(5*S*)-3-((13*S*)-13-hydroxy-13-(2*S*,5*R*)-5-[(1*R*)-1-hydroxytridecyl]tetrahydro-2-furanyltridecyl)-5-methyl-2,5-dihydro-2-furanone (**1.241**)



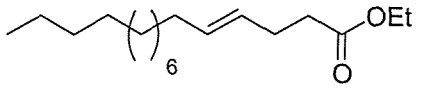
The title compound was prepared according to the method outlined for **1.240**, except using: butenolide **5.42** (24 mg, 0.04 mmol), $TsNHNH_2$ (48 mg, 0.26 mmol) and NaOAc (21 mg, 0.26 mmol). Gave the title compound **1.241** (23 mg, 0.04, 91%) as a white solid (^1H, ^{13}C, IR, LRMS spectroscopic data identical to **1.240**): mp 69-70 °C; $[\alpha]^{24}_D$ +11.8 (MeOH, *c* 0.85); Elemental calcd. for $C_{34}H_{64}O_5$: C, 73.86; H, 11.67. Found: C, 73.80; H, 11.63; Chiral CD-Ph, 15% *i*-PrOH/Hex, 17.3 min.

Tetradec-1-en-3-ol (**7.2**)



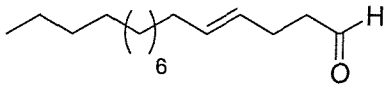
Under an atmosphere of N_2, at –20 °C to a solution of vinyl magnesium bromide (1.0 M, 87 mL, 87 mmol) in THF (150 mL) was added a solution of tridecanal (**7.1**) (16.0 g, 87 mmol) in THF (15 mL) dropwise. After 2 h a saturated solution of NH_4Cl (100 mL) and H_2O (50 mL) were added and the mixture acidified with 1 M HCl (50 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (25 g). Purification by column chromatography on silica gel (3% EtOAc/hexane → 9%) gave the allylic alcohol **7.2** (16.78 g, 79 mmol, 91%) as a colourless oil: IR ν_{max} (neat) 3385 (br), 2980 (m), 1469 (m), 989 (s), 919 (s); ^1H NMR (300 MHz) δ 5.86 (1H, ddd *J* = 6.3, 10.3, 16.9 Hz, C**H**=CH_2, 5.20 (1H, dt, *J* = 17.1, 1.3 Hz, C**H**H=CH), 5.08 (1H, dt, *J* = 10.3, 1.3 Hz, CH**H**=CH), 4.08 (1H, q, *J* = 6.3 Hz, C**H**OH), 1.80 (1H, br, O**H**), 1.57-1.47 (2H, m, CH_2CHOH), 1.37-1.19 (18H, m, CH_2), 0.88 (3H, t, *J* = 6.5 Hz, CH_3); ^{13}C NMR (75 MHz) δ 141.5 (CH), 114.6 (CH), 37.2 (CH_2), 32.1 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 25.4 (CH_2), 22.8 (CH_2), 14.3 (CH_3).

(4*E*)-Hexadec-4-enoic acid ethyl ester (**7.3**)



Under an atmosphere of N_2 to a solution of allylic alcohol **7.2** (5.94 g, 28 mmol) and triethyl orthoacetate (10.45 mL, 56 mmol) in xylene (300 mL) was added propionic acid (0.22 mL, 3 mmol). The reaction was heated at reflux for 3 h, after cooling to rt the solution was concentrated *in vacuo* to 20 mL whereupon Et_2O (100 mL) and $NaHCO_3$ (sat. aq, 50 mL) were added. The organic phase was separated, the aqueous phase extracted with Et_2O (2 x 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification by vacuum distillation (Bp 151 °C, 0.5 mbar) gave ester **7.3** (7.33 g, 26 mmol, 95%) as a colourless oil: IR ν_{max} (neat) 2928 (s), 1740 (s), 1459 (m), 1169 (m), 968 (m); ^{1}H NMR (300 MHz) δ 5.45 (1H, td *J* = 6.3, 15.5 Hz, C**H**=CH, 5.38 (1H, td, *J* = 5.9, 15.5 Hz, C**H**=CH), 4.13 (2H, q, *J* = 7.2 Hz, C**H**$_2$O), 2.41-2.25 (4H, m, C**H**$_2$), 1.96 (2H, q, *J* = 6.3 Hz, C**H**$_2$CH=CH), 1.40-1.16 (21H, m), 0.88 (3H, t, *J* = 6.4 Hz, C**H**$_3$); ^{13}C NMR (75 MHz) δ 173.4 (C), 132.0 (CH), 128.0 (CH, 60.4 (CH_2), 34.6 (CH_2), 32.7 (CH_2), 32.1 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.1 (CH_2), 22.8 (CH_2), 14.4 (CH_3), 14.3 (CH_3).

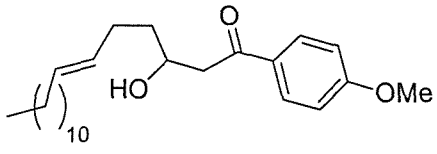
(4*E*)-Hexadec-4-enal (**7.4**)



At –78 °C to a solution of ester **7.3** (2.00 g, 7.1 mmol) in CH_2Cl_2 (160 mL) was added dropwise DIBAL-H in hexane (1M, 9.2 mL, 9.2 mmol) *via* syringe pump over 20 min. After 3 h the reaction was quenched by the addition of MeOH (40 mL), after 10 min H_2O (40 mL) was added and finally 2 M HCl (20 mL) after a further 5 min. The Organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 50 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated *in vacuo* to give a colourless oil (1.72 g). Purification by column chromatography on silica gel (2.5% EtOAc/hexane→ 3%) gave aldehyde **7.4** (1.41 g, 5.9 mmol, 84%) as a white solid: mp 35-37 °C; No spectroscopic data reported in the literature; IR ν_{max} (neat) 2915 (s), 2848 (s), 1732 (s), 1361 (s), 1219(s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.77 (1H, t, *J* = 1.6 Hz, C**H**O), 5.48 (1H, td, *J* = 6.1, 15.3 Hz,

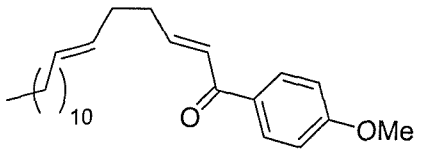
CH=CH), 5.39 (1H, td, J = 6.2, 15.4 Hz, CH=CH), 2.50 (2H, dt, J = 1.6, 7.0 Hz, CH_2CHO), 2.34 (2H, br q, J = 7.0 Hz, CH_2), 1.97 (2H, br q, J = 6.8 Hz, CH_2), 1.40-1.17 (18H, m, CH_2), 0.89 (3H, t, J = 7.0 Hz, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 202.6 (C), 132.3 (CH), 127.7 (CH), 43.7 (CH_2), 32.6 (CH_2), 32.1 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 25.3 (CH_2), 22.8 (CH_2), 14.3 (CH_3); LRMS (GCEI) 7.99 min, *m/z* 238 (1%, $M^{+\cdot}$), 84 (100%); HRMS (EI) $C_{16}H_{30}O^{+\cdot}$ Calcd. 238.2297 found 238.2298; Elemental calcd. for $C_{16}H_{30}O$: C, 80.61; H, 12.68. Found, C, 80.23; H, 12.29.

(6*E*)-3-Hydroxy-1-(4-methoxyphenyl)octadec-6-en-1-one (**7.5**)



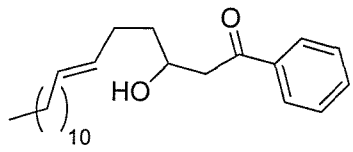
At –60 °C to a freshly prepared solution of LDA (2.0 mmol) in THF (20 mL) was added dropwise a solution of *p*-methoxyacetophenone (**7.7**) (302 mg, 2.0 mmol) in THF (2 mL). After 30 min a solution of aldehyde **7.4** (479 mg, 2.0 mmol) in THF (5 mL) was added dropwise over 20 min. After a further 30 min the reaction was quenched by addition of NH_4Cl (sat aq, 20 mL), brine (10 mL), H_2O (10 mL) and CH_2Cl_2 (30 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 20 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated *in vacuo* to give a colourless oil. Purification by column chromatography on silica gel (6% EtOAc/hexane → 15%) gave alcohol **7.5** (576 mg, 1.5 mmol, 75%) as a white solid: mp 64-66 °C; IR ν_{max} (neat) 3384 (br), 2916 (s), 2848 (s), 1674 (s), 1605 (s), 1579 (m), 1509 (m), 1256 (s), 1177 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.94 (2H, d, J = 8.8 Hz, CH), 6.94 (2H, d, J = 9.0 Hz, CH), 5.48 (1H, td, J = 6.0, 15.3 Hz, CH=CH), 5.42 (1H, td, J = 5.8, 15.3 Hz, CH=CH), 4.22 (1H, ddt, J = 2.8, 4.5, 8.3, Hz, CHOH), 3.88 (3H, s, OCH_3), 3.47 (1H, br, OH), 3.13 (1H, dd, J = 2.8, 17.3 Hz, CHHC=O), 2.99 (1H, dd, J = 9.0, 17.3 Hz, CHHC=O), 2.27-2.07 (2H, m, CH_2), 1.98 (2H, br q, J = 5.8 Hz, CH_2), 1.75 (1H, dtd, J = 6.0, 8.5, 13.8 Hz, CHHCHOH), 1.62 (1H, dddd, J = 4.5, 6.8, 8.7, 15.6 Hz, CHHCHOH), 1.39-1.17 (18H, m, CH_2), 0.89 (3H, t, J = 7.0 Hz, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 199.6 (C), 164.0 (C), 131.4 (CH), 130.5 (CH), 130.1 (C), 129.5 (CH), 114.0 (CH), 67.6 (CH), 55.6 (CH_3), 44.6 (CH_2), 36.5 (CH_2), 32.7 (CH_2), 32.1 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.8 (CH_2), 22.8 (CH_2), 14.2 (CH_3); LRMS (EI) *m/z* 388 ($M^{+\cdot}$, 5%), 370 ($[M-H_2O]^{+\cdot}$, 10%) 135 (100%); HRMS (EI) $C_{25}H_{40}O_3^{+\cdot}$ Calcd. 388.2978 found 388.2981.

(2*E*,6*E*)-1-(4-Methoxyphenyl)octadeca-2,6-dien-1-one (**7.6**)



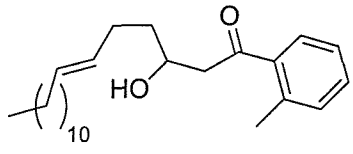
At 0 °C to a solution of β-hydroxy ketone **7.5** (576 mg, 1.5 mmol) in CH_2Cl_2 (25 mL) was added dropwise methane sulfonyl chloride (0.18 mL, 2.2 mmol) and Et_3N (0.32 mL, 2.2 mmol). The reaction mixture was allowed to warm to rt and stir for 2 h before addition of brine (10 mL) and H_2O (10 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 10 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated *in vacuo* before being solvated in CH_2Cl_2 (20 mL). The reaction mixture was cooled to 0 °C whereupon DBU (0.45 mL, 3 mmol) was added dropwise. The reaction was allowed to warm to rt over 30 min whereupon H_2O (10 mL), 2 M HCl (5 mL) and brine (10 mL) were added. The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 20 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated *in vacuo* to give a colourless oil. Purification by column chromatography on silica gel (6% EtOAc/hexane → 10%) gave diene **7.6** (498 mg, 1.4 mmol, 90%) as a white solid: mp 46-48 °C; IR ν_{max} (neat) 2916 (s), 2848 (s), 1668 (s), 1617 (s), 1604 (s), 1578 (m), 1510 (m), 1468 (s), 1252 (s), 1178 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.94 (2H, d, J = 8.9 Hz, C**H**), 7.04 (1H, td, J = 6.6, 15.3 Hz, C**H**=CH), 6.94 (2H, d, J = 9.0 Hz, C**H**), 6.89 (1H, td, J = 1.5, 15.3 Hz, C**H**=CH), 5.49 (1H, td, J = 6.3, 15.2 Hz, C**H**=CH), 5.42 (1H, td, J = 6.1, 15.2 Hz, C**H**=CH), 3.88 (3H, s, OC**H**$_3$), 2.39 (2H, br q, J = 7.3 Hz, C**H**$_2$CH=CHC=O), 2.22 (2H, br q, J = 7.0 Hz, C**H**$_2$CH$_2$CH=CHC=O), 1.99 (2H, br q, J = 6.3 Hz, C**H**$_2$), 1.39-1.17 (18H, m, C**H**$_2$), 0.89 (3H, t, J = 7.0 Hz, C**H**$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 189.3 (C), 163.4 (C), 148.3 (CH), 132.0 (CH), 130.0 (C), 129.9 (CH), 128.6 (CH), 125.9 (CH), 113.9 (CH), 55.6 (CH_3), 42.4 (CH_2), 33.0 (CH_2), 32.7 (CH_2), 32.1 (CH_2), 31.4 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 22.8 (CH_2), 14.2 (CH_3); LRMS (EI) *m/z* 370 (5%, $M^{+\cdot}$), 176 (100%); HRMS (EI) $C_{25}H_{38}O_2^{+\cdot}$ Calcd. 370.2872 found 370.2869; Elemental calcd. for $C_{25}H_{38}O_2$: C, 81.03; H, 10.34. Found: C, 80.79; H, 10.47.

(6*E*)-3-Hydroxy-1-phenyloctadec-6-en-1-one (**7.8**)



The title compound was prepared according to the method outlined for **7.5**, except using: acetophenone (300 mg, 1.3 mmol). Purification by column chromatography on silica gel (10% EtOAc/hexane → 15%) gave alcohol **7.8** (280 mg, 0.8 mmol, 62%) as a white solid: mp 50-52 °C; IR ν_{max} (neat) 3355 (br), 2920 (s), 2848 (s), 1680 (s), 1597 (w), 1447 (s), 1380 (s), 1295 (s), 1241 (s), 1192 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.96 (2H, dd, J = 1.5, 8.5 Hz, C**H**), 7.59 (1H, dt, J = 1.4, 7.5 Hz, C**H**), 7.46 (2H, t, J = 7.3 Hz, C**H**), 5.49 (1H, td, J = 6.0, 15.3 Hz, C**H**=CH), 5.44 (1H, td, J = 5.8, 15.3 Hz, C**H**=CH), 4.24 (1H, ddt, J = 2.8, 4.8, 8.7, Hz, C**H**OH), 3.18 (1H, dd, J = 3.0, 17.6 Hz, C**H**HC=O), 3.06 (1H, dd, J = 8.8, 17.6 Hz, C**H**HC=O), 2.27-2.10 (2H, m, C**H**$_2$), 1.98 (2H, br q, J = 7.2 Hz, C**H**$_2$), 1.75 (1H, dtd, J = 6.0, 8.5, 13.8 Hz, C**H**HCHOH), 1.62 (1H, dddd, J = 4.5, 6.8, 8.8, 15.6 Hz, C**H**HCHOH), 1.39-1.21 (18H, m, C**H**$_2$), 0.89 (3H, t, J = 7.0 Hz, C**H**$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 201.0 (C), 137.0 (C), 133.6 (CH), 131.5 (CH), 129.6 (CH), 128.8 (CH), 128.2 (CH), 67.5 (CH), 45.1 (CH_2), 36.5 (CH_2), 32.7 (CH_2), 32.1 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.8 (CH_2), 22.8 (CH_2), 14.2 (CH_3); LRMS (EI) *m/z* 358 (3%, $M^{+\cdot}$), 340 (10%, $[M\text{-}H_2O]^{+\cdot}$) 105 (100%); Elemental calcd. for $C_{24}H_{38}O_2$: C, 80.39; H, 10.68. Found, C, 80.23; H, 10.85.

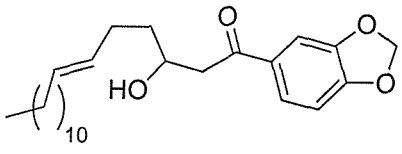
(6*E*)-3-Hydroxy-1-(2-methylphenyl)octadec-6-en-1-one (**7.9**)



The title compound was prepared according to the method outlined for **7.5**, except using: 1-methylactophenone (500 mg, 2.1 mmol). Purification by column chromatography on silica gel (10% EtOAc/hexane → 15%) gave alcohol **7.9** (420 mg, 1.1 mmol, 52%) as a colourless oil: IR ν_{max} (neat) 3446 (br), 2918 (s), 2852 (s), 1678 (s), 1601 (w), 1571 (w), 1456 (s), 1286 (s), 1208 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.69 (1H, d, J = 8.1 Hz, C**H**), 7.44 (1H, dt, J = 1.3, 7.8 Hz, C**H**), 7.34-7.29 (2H, m, C**H**), 5.50 (1H, td, J = 5.8, 15.3 Hz, C**H**=CH), 5.44

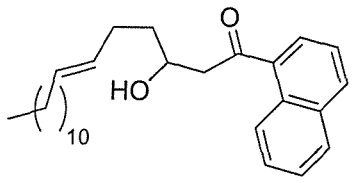
(1H, td, J = 5.8, 15.3 Hz, C**H**=CH), 4.25 (1H, ddt, J = 2.8, 4.8, 8.7, Hz, C**H**OH), 3.21 (1H, br, O**H**), 3.15 (1H, dd, J = 3.0, 17.6 Hz, C**H**HC=O), 3.01 (1H, dd, J = 9.0, 17.6 Hz, C**H**HC=O), 2.55 (3H, s, CH_3), 2.27-2.09 (2H, m, CH_2), 2.00 (2H, br q, J = 5.8 Hz, CH_2), 1.72 (1H, dtd, J = 6.0, 8.4, 13.8 Hz, CHHCHOH), 1.62 (1H, dddd, J = 4.8, 6.8, 8.8, 15.6 Hz, CHHCHOH), 1.40-1.22 (18H, m, CH_2), 0.90 (3H, t, J = 7.0 Hz, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 204.9 (C), 138.5 (C), 137.7 (C), 132.2 (CH), 131.8 (CH), 131.6 (CH), 129.4 (CH), 128.8 (CH), 125.9 (CH), 67.7 (CH), 47.9 (CH_2), 36.5 (CH_2), 32.7 (CH_2), 32.1 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.8 (CH_2), 22.8 (CH_2), 21.5 (CH_3), 14.2 (CH_3); LRMS (EI) *m/z* 372 (3%, $M^{+\cdot}$), 354 (15%, $[M\text{-}H_2O]^{+\cdot}$) 119 (100%); HRMS (EI) $C_{25}H_{40}O_2^{+\cdot}$ Calcd. 372.3028 found 372.3029.

(6*E*)-1-(1,3-Benzodioxol-5-yl)-3-hydroxyoctadec-6-en-1-one (**7.10**)



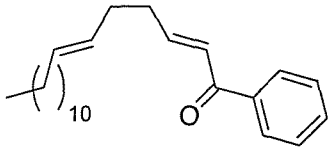
The title compound was prepared according to the method outlined for **7.5**, except using: 3,4-(methylenedioxy)acetophenone (643 mg, 2.7 mmol). Purification by column chromatography on silica gel (10% EtOAc/hexane → 20%) gave alcohol **7.10** (760 mg, 1.9 mmol, 70%) as a white solid: mp 56-58 °C; IR ν_{max} (neat) 3385 (br), 2915 (s), 2848 (s), 1671 (s), 1605 (m), 1498 (s), 1445 (s), 1254 (s), 1110 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.54 (1H, dd, J = 1.8, 8.3 Hz, C**H**), 7.45 (1H, d, J = 1.7 Hz, C**H**), 6.85 (1H, d, J = 8.0 Hz, C**H**), 6.04 (2H, s, OCH_2O), 5.47 (1H, td, J = 6.0, 15.3 Hz, C**H**=CH), 5.41 (1H, td, J = 5.8, 15.3 Hz, C**H**=CH), 4.21 (1H, ddt, J = 2.8, 4.5, 8.4, Hz, C**H**OH), 3.28 (1H, br, OH), 3.14 (1H, dd, J = 2.8, 17.3 Hz, C**H**HC=O), 2.98 (1H, dd, J = 9.0, 17.3 Hz, C**H**HC=O), 2.30-2.06 (2H, m, CH_2), 1.98 (2H, br q, J = 5.9 Hz, CH_2), 1.70 (1H, dtd, J = 6.0, 8.5, 13.8 Hz, C**H**HCHOH), 1.60 (1H, dddd, J = 4.5, 6.8, 8.8, 15.6 Hz, C**H**HCHOH), 1.39-1.17 (18H, m, CH_2), 0.89 (3H, t, J = 7.0 Hz, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 199.0 (C), 152.3 (C), 148.4 (C), 131.9 (C), 131.4 (C), 129.5 (CH), 124.7 (CH), 108.1 (CH), 107.9 (CH), 102.1 (CH_2), 67.6 (CH), 44.8 (CH_2), 36.5 (CH_2), 32.7 (CH_2), 32.1 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.8 (CH_2), 22.8 (CH_2), 14.3 (CH_3); LRMS (EI) *m/z* 402 (5%, $M^{+\cdot}$), 384 (8%, $[M\text{-}H_2O]^{+\cdot}$) 149 (100%); HRMS (EI) $C_{25}H_{38}O_4^{+\cdot}$ Calcd. 402.2770 found 402.2771.

(6*E*)-3-Hydroxy-1-(1-naphthyl)octadec-6-en-1-one (**7.11**)



The title compound was prepared according to the method outlined for **7.5**, except using: 1-acetonaphthone (494 mg, 2.1 mmol). Purification by column chromatography on silica gel (10% EtOAc/hexane → 20%) gave alcohol **7.11** (588 mg, 1.5 mmol, 70%) as a colourless oil: IR ν_{max} (neat) 3385 (br), 3054 (s), 2983 (s), 2848 (s), 1673 (s), 1605 (m), 1498 (s), 1422 (s), 1261 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.65 (1H, d, J = 8.5 Hz, C**H**), 8.01 (1H, d, J = 8.3 Hz, C**H**), 7.94-7.86 (2H, m, C**H**), 7.66-7.46 (3H, m, C**H**), 5.54-5.39 (2H, m, C**H**=CH), 4.32 (1H, ddt, J = 3.0, 4.5, 8.1, Hz, C**H**OH), 3.25 (1H, dd, J = 2.8, 17.2 Hz, C**H**HC=O), 3.17 (1H, dd, J = 9.0, 17.3 Hz, C**H**HC=O), 2.28-2.11 (2H, m, C**H**$_2$), 1.98 (2H, br q, J = 6.5 Hz, C**H**$_2$), 1.72 (1H, dtd, J = 6.0, 8.3, 13.8 Hz, C**H**HCHOH), 1.60 (1H, dddd, J = 4.8, 6.8, 8.8, 15.5 Hz, C**H**HCHOH), 1.39-1.21 (18H, m, C**H**$_2$), 0.89 (3H, t, J = 7.0 Hz, C**H**$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 205.1 (C), 135.7 (C), 134.1 (C), 133.3 (CH), 131.5 (CH), 130.2 (C), 129.4 (CH), 128.6 (CH), 128.3 (CH), 128.2 (CH), 126.7 (CH), 125.9 (CH), 124.5 (CH), 68.0 (CH), 48.5 (CH_2), 36.6 (CH_2), 32.7 (CH_2), 32.1 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.8 (CH_2), 22.8 (CH_2), 14.2 (CH_3); LRMS (EI) *m/z* 408 (1%, $M^{+\cdot}$), 390 (5%, $[M\text{-}H_2O]^{+\cdot}$) 155 (100%); HRMS (EI) $C_{28}H_{40}O_2^{+\cdot}$ Calcd. 408.3034 found 408.3034.

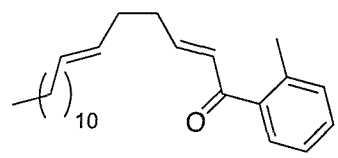
(2*E*,6*E*)-1-Phenyloctadeca-2,6-dien-1-one (**7.12**)



The title compound was prepared according to the method outlined for **7.6**, except using: β-hydroxy ketone **7.8** (179 mg, 0.5 mmol). Purification by column chromatography on silica gel (3% EtOAc/hexane → 5%) gave diene **7.12** (160 mg, 0.5 mmol, 94%) as a white solid: mp 33-34 °C: IR ν_{max} (neat) 2922 (s), 2852 (s), 1674 (s), 1656 (s), 1621 (s), 1456 (s), 1296 (s), 1272 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.96 (2H, dd, J = 1.5, 8.5 Hz, C**H**), 7.59 (1H, dt, J = 1.4, 7.5 Hz, C**H**), 7.50 (2H, t, J = 7.3 Hz, C**H**), 7.01 (1H, td, J = 6.8, 15.8 Hz, C**H**=CH), 6.81 (1H, td, J = 1.3, 15.8 Hz, CH=CH), 5.42 (1H, td, J = 6.5, 15.3 Hz, C**H**=CH),

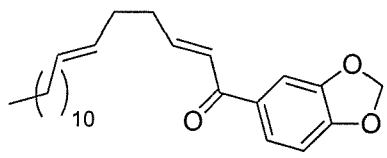
5.36 (1H, td, J = 6.3, 15.3 Hz, C**H**=CH), 2.34 (2H, br q, J = 8.0 Hz, C**H**$_2$CH=CHC=O), 2.18 (2H, br q, J = 7.0 Hz, C**H**$_2$CH$_2$CH=CHC=O), 1.96 (2H, br q, J = 6.5 Hz, C**H**$_2$), 1.37-1.21 (18H, m, C**H**$_2$), 0.89 (3H, t, J = 7.0 Hz, C**H**$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 191.1 (C), 149.5 (CH), 138.2 (C), 132.7 (CH), 132.1 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 126.4 (CH), 33.0 (CH_2), 32.7 (CH_2), 32.1 (CH_2), 31.3 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 22.8 (CH_2), 14.3 (CH_3); LRMS (EI) *m/z* 340 (5%, $M^{+\cdot}$), 146 (100%); Elemental calcd. for $C_{24}H_{36}O$: C, 84.65; H, 10.65. Found, C, 84.82; H, 10.70.

(2*E*,6*E*)-1-(2-Methylphenyl)octadeca-2,6-dien-1-one (**7.13**)



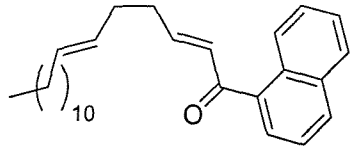
The title compound was prepared according to the method outlined for **7.6**, except using: β-hydroxy ketone **7.9** (264 mg, 0.71 mmol). Purification by column chromatography on silica gel (3% EtOAc/hexane → 5%) gave diene **7.13** (243 mg, 0.71 mmol, 97%) as a colourless oil: IR ν_{max} (neat) 2922 (s), 2852 (s), 1674 (s), 1656 (s), 1621 (s), 1456 (s), 1296 (s), 1272 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.39-7.32 (2H, m, C**H**), 7.26-7.20 (2H, m, C**H**), 6.70 (1H, td, J = 6.8, 15.8 Hz, C**H**=CH), 6.47 (1H, td, J = 1.3, 15.8 Hz, C**H**=CH), 5.46 (1H, td, J = 6.5, 15.3 Hz, C**H**=CH), 5.38 (1H, td, J = 6.3, 15.3 Hz, C**H**=CH), 2.39 (3H, s, C**H**$_3$), 2.34 (2H, br q, J = 8.0 Hz, C**H**$_2$CH=CHC=O), 2.18 (2H, br q, J = 7.0 Hz, C**H**$_2$CH$_2$CH=CHC=O), 1.98 (2H, br q, J = 6.5 Hz, C**H**$_2$), 1.37-1.21 (18H, m, C**H**$_2$), 0.89 (3H, t, J = 7.0 Hz, C**H**$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 197.2 (C), 151.1 (CH), 139.2 (C), 136.8 (C), 132.2 (CH), 131.3 (CH), 131.1 (CH), 130.3 (CH), 128.3 (CH), 128.1 (CH), 125.4 (CH), 32.8 (CH_2), 32.7 (CH_2), 32.1 (CH_2), 31.2 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 22.8 (CH_2), 20.2 (CH_3), 14.2 (CH_3); LRMS (EI) *m/z* 354 (5%, $M^{+\cdot}$), 119 (100%); HRMS (EI) $C_{25}H_{38}O^{+\cdot}$ Calcd. 354.2923 found 354.2932.

(2*E*,6*E*)-1-(1,3-Benzodioxol-5-yl)octadeca-2,6-dien-1-one (**7.14**)



The title compound was prepared according to the method outlined for **7.6**, except using: β-hydroxy ketone **7.10** (690 mg, 1.7 mmol). Purification by column chromatography on silica gel (8% EtOAc/hexane → 10%) gave diene **7.14** (590 mg, 1.4 mmol, 90%) as a white solid: mp 36-38 °C; IR ν_{max} (neat) 2914 (s), 2848 (s), 1665 (s), 1620 (s), 1605 (s), 1498 (s), 1470 (s), 1446 (s), 1335 (m), 1295 (s), 1252 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.54 (1H, dd, J = 1.8, 8.3 Hz, C**H**), 7.45 (1H, d, J = 1.7 Hz, C**H**), 7.02 (1H, td, J = 6.7, 15.3 Hz, C**H**=CH), 6.85 (1H, d, J = 8.0 Hz, C**H**), 6.83 (1H, td, J = 1.5, 15.3 Hz, C**H**=CH), 6.05 (2H, s, O**CH$_2$**O), 5.48 (1H, td, J = 6.3, 15.3 Hz, C**H**=CH), 5.41 (1H, td, J = 6.3, 15.3 Hz, C**H**=CH), 2.37 (2H, br q, J = 7.5 Hz, C**H$_2$**CH=CHC=O), 2.22 (2H, br q, J = 6.8 Hz, C**H$_2$**CH$_2$CH=CHC=O), 1.97 (2H, br q, J = 6.5 Hz, C**H$_2$**), 1.39-1.18 (18H, m, C**H$_2$**), 0.89 (3H, t, J = 7.0 Hz, C**H$_3$**); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 188.8 (C), 151.6 (C), 148.6 (CH), 148.3 (C), 132.9 (C), 132.0 (CH), 128.5 (CH), 125.8 (CH), 124.8 (CH), 108.6 (CH), 107.9 (CH), 101.9 (CH), 55.6 (CH_3), 42.4 (CH_2), 33.0 (CH_2), 32.7 (CH_2), 32.1 (CH_2), 31.4 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 22.8 (CH_2), 14.2 (CH_3); LRMS (EI) *m/z* 384 (10%, $M^{+\cdot}$), 190 (100%); Elemental calcd. for $C_{25}H_{36}O_3$: C, 78.08; H, 9.44. Found: C, 77.81; H, 9.53.

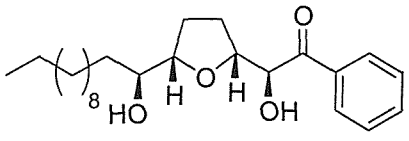
(2*E*,6*E*)-1-(1-Naphthyl)octadeca-2,6-dien-1-one (**7.15**)



The title compound was prepared according to the method outlined for **7.6**, except using: β-hydroxy ketone **7.11** (420 mg, 1.0 mmol). Purification by column chromatography on silica gel (3% EtOAc/hexane → 5%) gave diene **7.15** (371 mg, 1.0 mmol, 95%) as a yellowish oil: IR ν_{max} (neat) 2922 (s), 2846 (s), 1665 (m), 1646 (s), 1620 (s), 1612 (s), 1464 (s), 1446 (s), 1375 (s), 1289 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.25 (1H, dd, J = 2.0, 7.3 Hz, C**H**), 7.97 (1H, d, J = 8.3 Hz, C**H**), 7.89 (1H, dd, J = 2.5, 6.0 Hz, C**H**), 7.65 (1H, dd, J = 1.2, 7.0 Hz, C**H**), 7.58-7.46 (3H, m, C**H**), 6.84 (1H, td, J = 6.8, 15.8 Hz, C**H**=CH), 6.66 (1H, td, J = 1.5, 15.8 Hz, C**H**=CH), 5.46 (1H, td, J = 6.3, 15.3 Hz, C**H**=CH), 5.38 (1H, td, J = 6.3, 15.3 Hz, C**H**=CH), 2.36 (2H, br q, J = 7.3 Hz, C**H$_2$**CH=CHC=O), 2.19 (2H, br q, J = 6.8 Hz, C**H$_2$**CH$_2$CH=CHC=O), 1.97 (2H, br q, J = 6.8 Hz, C**H$_2$**), 1.37-1.21 (18H, m, C**H$_2$**), 0.89 (3H, t, J = 7.0 Hz, C**H$_3$**); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 196.3 (C), 151.3 (CH), 137.1 (C), 133.9 (C), 132.2 (CH), 131.5 (CH), 131.4 (CH), 130.6 (C), 128.5 (CH), 128.3 (CH), 127.3 (CH), 127.1 (CH), 126.5 (CH), 125.8 (CH), 124.5 (CH), 32.9 (CH_2), 32.7 (CH_2), 32.0 (CH_2),

31.3 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 22.8 (CH_2), 14.3 (CH_3); LRMS (EI) *m/z* 390 (10%, $M^{+\cdot}$), 196 (100%); HRMS (EI) $C_{28}H_{38}O^{+\cdot}$ Calcd. 390.2923 found 390.2914.

(2*S*)-2-Hydroxy-2-[(2*R*,5*S*)-5-[(1*S*)-1-hydroxydodecyl]tetrahydrofuran-2-yl]-1-phenylethanone (**7.16**)

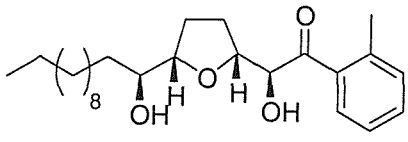


At –60 °C to a solution of diene **7.12** (138 mg, 0.41 mmol), chiral catalyst **2.56** (28 mg, 0.04 mmol), AcOH (160 μL, 2.7 mmol) in CH_2Cl_2 (6 mL) was added in one batch powdered $KMnO_4$ (104 mg, 0.66 mmol). After 3 h vigorous stirring the reaction was quenched with $Na_2S_2O_5$ (sat aq, 8 mL), H_2O (2 mL) and CH_2Cl_2 (5 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow oil. Purification by column chromatography on silica gel (15% EtOAc/hexane → 30%) gave THF-diol **7.16** (69 mg, 0.18 mmol, 43%, 54% ee) as a colourless oil: IR ν_{max} (neat) 3462 (br), 2922 (s), 2853 (s), 1684 (s), 1598 (w), 1580 (w), 1449 (s), 1264 (s), 1127 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.92 (2H, dd, *J* = 1.2, 8.4 Hz, C**H**), 7.62 (1H, dt, *J* = 1.3, 7.5 Hz, C**H**), 7.50 (2H, t, *J* = 7.8 Hz, C**H**), 5.09 (1H, d, *J* = 1.8 Hz, C**H**OHC=O), 4.40 (1H, ddd, *J* = 2.0, 6.3, 8.3 Hz, C**H**CHOHC=O), 3.72 (1H, dt, *J* = 5.3, 6.8 Hz, C**H**CHOH), 3.32 (1H, dt, *J* = 5.0, 7.3 Hz, C**H**OH), 2.25 (1H, dq, *J* = 12.3, 7.6 Hz, C**H**H THF), 2.06 (1H, dq, *J* = 12.6, 7.5 Hz, C**H**H THF), 1.87 (2H, q, *J* = 7.5 Hz, C**H**$_2$ THF), 1.50-1.19 (20H, m, C**H**$_2$), 0.89 (3H, t, *J* = 7.0 Hz, C**H**$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 199.9 (C), 134.4 (C), 134.0 (CH), 129.0 (CH), 128.7 (CH), 83.4 (CH), 80.2 (CH), 75.4 (CH), 74.2 (CH), 34.3 (CH_2), 32.0 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 28.3 (CH_2), 28.1 (CH_2), 25.8 (CH_2), 22.8 (CH_2), 14.2 (CH_3); LRMS (ES^+) *m/z* 803 (80%, $[2M+Na]^+$), 413 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{24}H_{38}O_4Na^+$ Calcd. 413.2662 found 413.2666; 54% ee (Chiralcel OD-H, 10% *i*-PrOH/Hex, 6.4, 7.5 min).

(*rac*)-(2*S*)-2-Hydroxy-2-[(2*R*,5*S*)-5-[(1*S*)-1-hydroxydodecyl]tetrahydrofuran-2-yl]-1-phenylethanone ((*rac*)-**7.16**)

At –30 °C to a solution of diene **7.12** (50 mg, 0.15 mmol), adogen 464 (14 μL, 0.01 mmol), AcOH (0.14 mL, 2.3 mmol) in acetone (2 mL) was added in one batch powdered $KMnO_4$ (23 mg, 0.14 mmol). The reaction mixture was allowed to warm to –10 °C over 1.5 h whereupon it was quenched with $Na_2S_2O_5$ (sat aq, 3 mL), H_2O (2 mL) and CH_2Cl_2 (3 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic fractions were then dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow oil. Purification by column chromatography on silica gel (15% EtOAc/hexane → 30%) gave THF-diol (*rac*)-**7.16** (29 mg, 0.08 mmol, 50%) as a colourless oil: characterisation data as above.

(2*S*)-2-Hydroxy-2-[(2*R*,5*S*)-5-[(1*S*)-1-hydroxydodecyl]tetrahydrofuran-2-yl]-1-(2-methylphenyl)ethanone (**7.17**)



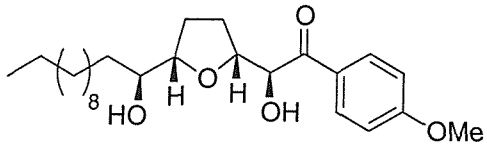
The title compound was prepared according to the method outlined for **7.16**, except using: diene **7.13** (150 mg, 0.42 mmol). Purification by column chromatography on silica gel (15% EtOAc/hexane → 25%) gave THF-diol **7.17** (58 mg, 0.14 mmol, 34%, 71% ee) as a colourless oil: IR ν_{max} (neat) 3380 (br), 2922 (s), 2852 (s), 1675 (s), 1602 (s), 1573 (m), 1463 (m), 1257 (s), 1171 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.47 (1H, dd, J = 1.3, 7.8 Hz, C**H**), 7.42 (1H, dt, J = 1.3, 7.5 Hz, C**H**), 7.31 (1H, d, J = 7.6 Hz, C**H**), 7.27 (1H, t, J = 7.5 Hz, C**H**), 4.92 (1H, d, J = 1.7 Hz, C**H**OHC=O), 4.18 (1H, dt, J = 2.0, 6.7 Hz, C**H**CHOHC=O), 3.72 (1H, dt, J = 4.8, 6.3 Hz, C**H**CHOH), 3.37 (1H, dt, J = 4.5, 7.8 Hz, C**H**OH), 2.48 (3H, s, C**H**$_3$), 2.30-2.17 (1H, m, C**H**$_2$ THF), 2.00-1.78 (3H, m, C**H**$_2$ THF), 1.51-1.18 (20H, m, C**H**$_2$), 0.89 (3H, t, J = 7.0 Hz, C**H**$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 203.6 (C), 138.9 (C), 135.3 (C), 132.3 (CH), 131.9 (CH), 127.8 (CH), 125.7 (CH), 83.1 (CH), 79.8 (CH), 76.9 (CH), 74.1 (CH), 34.4 (CH_2), 32.0 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 28.5 (CH_2), 28.3 (CH_2), 28.0 (CH_2), 25.8 (CH_2), 22.8 (CH_2), 20.5 (CH_3), 14.2 (CH_3); LRMS (ES$^+$) *m/z* 832 (100%, [2M+Na]$^+$), 427 (40%, [M+Na]$^+$); HRMS (ES$^+$)

$C_{25}H_{40}O_4Na^+$ Calcd. 427.2819 found 427.2818; 71% ee (Chiralcel OB-H, 1% *i*-PrOH/Hex, 11.5, 13.0 min).

(*rac*)-(2*S*)-2-Hydroxy-2-[(2*R*,5*S*)-5-[(1*S*)-1-hydroxydodecyl]tetrahydrofuran-2-yl]-1-(2-methylphenyl)ethanone ((*rac*)-**7.17**)

The title compound was prepared according to the method outlined for (*rac*)-**7.16**, except using: diene **7.13** (50 mg, 0.14 mmol). Purification by column chromatography on silica gel (15% EtOAc/hexane → 25%) gave THF-diol (*rac*)-**7.17** (20 mg, 0.05 mmol, 35%) as a colourless oil: characterisation data as above.

(2*S*)-2-Hydroxy-2-[(2*R*,5*S*)-5-[(1*S*)-1-hydroxydodecyl]tetrahydrofuran-2-yl]-1-(4-methoxyphenyl)ethanone (**7.18**)

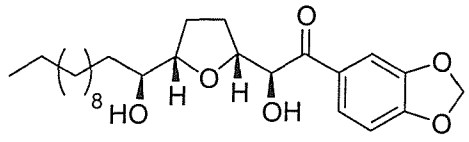


The title compound was prepared according to the method outlined for **7.16**, except using: diene **7.6** (50 mg, 0.13 mmol). Purification by column chromatography on silica gel (15% EtOAc/hexane → 25%) gave THF-diol **7.18** (29 mg, 0.07 mmol, 53%, 74% ee) as a colourless oil: IR ν_{max} (neat) 3450 (br), 2922 (s), 2852 (s), 1673 (s), 1600 (s), 1573 (m), 1512 (m), 1463 (m), 1257 (s), 1171 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.92 (2H, d, J = 9.0 Hz, C**H**), 6.97 (2H, d, J = 9.0 Hz, C**H**), 5.04 (1H, d, J = 1.8 Hz, C**H**OHC=O), 4.38 (1H, ddd, J = 1.8, 6.3, 7.5 Hz, C**H**OCHOHC=O), 3.88 (3H, s, OC**H$_3$**), 3.71 (1H, br q, J = 6.5 Hz, C**H**OCHOH), 3.32 (1H, td, J = 5.0, 7.3 Hz, C**H**OHCH$_2$), 2.28-2.17 (1H, m, C**H**H THF), 2.03 (1H, dq, J = 12.3, 7.5 Hz, C**H**H THF), 1.86 (2H, br q, J = 6.8 Hz, C**H$_2$** THF), 1.49-1.18 (20H, m, C**H$_2$**), 0.89 (3H, t, J = 7.0 Hz, C**H$_3$**); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 198.0 (C), 164.3 (C), 131.0 (CH), 127.0 (C), 114.2 (CH), 83.4 (CH), 80.5 (CH), 74.8 (CH), 74.2 (CH), 55.7 (CH_3), 34.5 (CH_2), 32.0 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 28.3 (CH_2), 28.1 (CH_2), 25.8 (CH_2), 22.8 (CH_2), 14.3 (CH_3); LRMS (ES$^+$) *m/z* 863 (50%, $[2M+Na]^+$), 443 (100%, $[M+Na]^+$), 421 (60%, $[M+H]^+$); HRMS (ES$^+$) $C_{25}H_{40}O_5Na^+$ Calcd. 443.2768 found 443.2772; 74% ee (Chiralcel OB-H, 2.5% *i*-PrOH/Hex, 25.0, 29.1 min).

(*rac*)-(2*S*)-2-Hydroxy-2-[(2*R*,5*S*)-5-[(1*S*)-1-hydroxydodecyl]tetrahydrofuran-2-yl]-1-(4-methoxyphenyl)ethanone ((*rac*)-**7.18**)

The title compound was prepared according to the method outlined for (*rac*)-**7.16**, except using: diene **7.6** (50 mg, 0.13 mmol). Purification by column chromatography on silica gel (15% EtOAc/hexane → 25%) gave THF-diol (*rac*)-**7.18** (27 mg, 0.07 mmol, 60%) as a colourless oil: characterisation data as above.

(2*S*)-1-(1,3-Benzodioxol-5-yl)-2-hydroxy-2-[(2*R*,5*S*)-5-[(1*S*)-1-hydroxydodecyl]tetrahydrofuran-2-yl]ethanone (**7.19**)

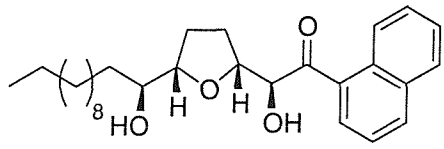


The title compound was prepared according to the method outlined for **7.16**, except using: diene **7.14** (50 mg, 0.13 mmol). Purification by column chromatography on silica gel (20% EtOAc/hexane → 35%) gave THF-diol **7.19** (25 mg, 0.07 mmol, 44%, 85% ee) as a colourless oil: IR ν_{max} (neat) 3476 (br), 2922 (s), 2852 (s), 1667 (s), 1602 (m), 1502 (m), 1445 (s), 1425 (m), 1258 (s), 1096 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.50 (1H, dd, J = 1.5, 8.3 Hz, C**H**), 7.41 (1H, d, J = 1.5 Hz, C**H**), 6.87 (1H, d, J = 8.3 Hz, C**H**), 6.05 (2H, s, O**CH$_2$**O), 4.98 (1H, d, J = 1.5 Hz, C**H**OHC=O), 4.38 (1H, ddd, J = 2.0, 6.3, 7.5 Hz, C**H**CHOHC=O), 4.00 (1H, br, O**H**), 3.71 (1H, td, J = 5.0, 6.8 Hz, C**H**CHOH), 3.33 (1H, td, J = 4.8, 7.0 Hz, C**H**OH), 2.50 (1H, br, O**H**), 2.28-2.16 (1H, m, C**H**H THF), 2.03 (1H, dq, J = 12.3, 7.5 Hz, C**H**H THF), 1.86 (2H, br q, J = 6.8 Hz, **CH$_2$** THF), 1.49-1.18 (20H, m, **CH$_2$**), 0.88 (3H, t, J = 7.0 Hz, **CH$_3$**); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 197.6 (C), 152.7 (C), 148.6 (C), 128.8 (C), 125.1 (CH), 108.5 (CH), 108.3 (CH), 102.2 (CH_2), 83.6 (CH), 80.5 (CH), 75.0 (CH), 74.1 (CH), 34.3 (CH_2), 32.0 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 28.3 (CH_2), 28.1 (CH_2), 26.0 (CH_2), 25.8 (CH_2), 22.8 (CH_2), 14.2 (CH_3); LRMS (ES^+) *m/z* 891 (50%, $[2M+Na]^+$), 457 (100%, $[M+Na]^+$), 435 (40%, $[M+H]^+$); HRMS (ES^+) $C_{25}H_{38}O_6Na^+$ Calcd. 457.2561 found 457.2567; 85% ee (ChiralPak AD-H, 10% *i*-PrOH/Hex, 13.5, 22.4 min).

(*rac*)-(2*S*)-1-(1,3-Benzodioxol-5-yl)-2-hydroxy-2-[(2*R*,5*S*)-5-[(1*S*)-1-hydroxydodecyl]tetrahydrofuran-2-yl]ethanone ((*rac*)-**7.19**)

The title compound was prepared according to the method outlined for (*rac*)-**7.16**, except using: diene **7.14** (200 mg, 0.52 mmol). Purification by column chromatography on silica gel (20% EtOAc/hexane → 35%) gave THF-diol (*rac*)-**7.19** (105 mg, 2.4 mmol, 46%) as a colourless oil: characterisation data as above.

(2*S*)-2-Hydroxy-2-[(2*R*,5*S*)-5-[(1*S*)-1-hydroxydodecyl]tetrahydrofuran-2-yl]-1-(1-naphthyl)ethanone (**7.20**)

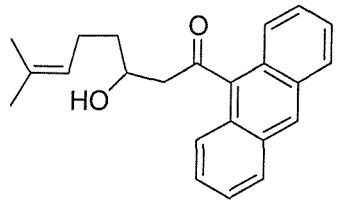


The title compound was prepared according to the method outlined for **7.16**, except using: diene **7.15** (50 mg, 0.13 mmol). Purification by column chromatography on silica gel (20% EtOAc/hexane → 30%) gave THF-diol **7.20** (26 mg, 0.06 mmol, 42%, 93% ee) as a colourless oil: IR ν_{max} (neat) 3470 (br), 3058 (s), 2926 (s), 2850 (s), 1682 (s), 1460 (s), 1422 (s), 1266 (s), 1091 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.38 (1H, d, J = 8.5 Hz, C**H**), 8.04 (1H, d, J = 8.3 Hz, C**H**), 7.90 (1H, d, J = 8.5 Hz, C**H**), 7.73 (1H, d, J = 7.3 Hz, C**H**), 7.64-7.48 (3H, m, C**H**), 5.10 (1H, d, J = 1.8 Hz, C**H**OHC=O), 4.23 (1H, ddd, J = 2.0, 6.3, 8.0 Hz, C**H**CHOHC=O), 3.65 (1H, dt, J = 5.0, 6.8 Hz, C**H**CHOH), 3.38 (1H, dt, J = 4.5, 7.8 Hz, C**H**OH), 2.32-2.20 (1H, m, C**H**$_2$ THF), 2.02-1.75 (3H, m, C**H**$_2$ THF), 1.52-1.18 (20H, m, C**H**$_2$), 0.90 (3H, t, J = 7.0 Hz, C**H**$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 203.5 (C), 134.2 (C), 133.5 (C), 133.2 (CH), 130.4 (C), 128.5 (CH), 128.2 (CH), 127.0 (CH), 126.9 (CH), 125.6 (CH), 124.2 (CH), 83.2 (CH), 80.0 (CH), 77.5 (CH), 74.1 (CH), 34.4 (CH_2), 32.0 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 28.2 (CH_2), 28.0 (CH_2), 25.8 (CH_2), 22.8 (CH_2), 14.3 (CH_3); LRMS (ES^+) *m/z* 903 (20%, $[2M+Na]^+$), 463 (100%, $[M+Na]^+$), 441 (10%, $[M+H]^+$); HRMS (ES^+) $C_{28}H_{40}O_4Na^+$ Calcd. 463.2819 found 463.2810; 93% ee (Chiralcel OB-H, 2.5% *i*-PrOH/Hex, 13.8, 15.6 min).

(*rac*)-(2*S*)-2-Hydroxy-2-[(2*R*,5*S*)-5-[(1*S*)-1-hydroxydodecyl]tetrahydrofuran-2-yl]-1-(1-naphthyl)ethanone ((*rac*)-**7.20**)

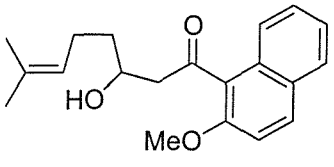
The title compound was prepared according to the method outlined for (*rac*)-**7.16**, except using: diene **7.15** (200 mg, 0.51 mmol). Purification by column chromatography on silica gel (20% EtOAc/hexane → 35%) gave THF-diol (*rac*)-**7.20** (104 mg, 2.4 mmol, 46%) as a colourless oil: characterisation data as above.

1-Anthracen-9-yl-3-hydroxy-7-methyl-oct-6-en-1-one (**7.22**)



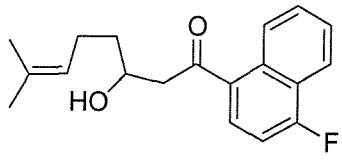
The title compound was prepared according to the method outlined for **7.5**, except using: 9-acetoanthracene (**7.30**) (295 mg, 1.34 mmol) and aldehyde **4.6** (150 mg, 1.34 mmol) instead. Purification by column chromatography on silica gel (8% EtOAc/hexane → 12%) gave β-hydroxy ketone **7.22** (130 mg, 0.39 mmol, 29%) as a yellow oil: IR ν_{max} (neat) 3453 (br), 2922 (s), 1692 (s), 1446 (s), 1376 (s), 1161 (s), 1107 (s), 1064 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.51 (1H, s, C**H**), 8.06-8.03 (2H, m, C**H**), 7.86 (2H, d, J = 8.5 Hz, C**H** x 2), 7.56-7.47 (4H, m, C**H**), 5.19-5.11 (1H, m, =C**H**), 4.54-4.47 (1H, m, C**H**OH), 3.27-3.18 (2H, m, CH_2C=O), 2.18 (2H, q, J = 7.0 Hz, CH_2CH=), 1.71 (3H, s, CH_3C), 1.67-1.48 (2H, m, CH_2CHOH), 1.64 (3H, s, CH_3C); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 211.5 (C), 135.9 (C), 132.5 (C), 131.2 (C), 129.0 (CH), 128.6 (CH), 127.1 (CH), 127.0 (C), 125.7 (CH), 124.3 (CH), 123.8 (CH), 67.4 (CH), 53.1 (CH_2), 36.5 (CH_2), 25.9 (CH_3), 24.2 (CH_2), 17.8 (CH_3); LRMS (EI) *m/z* 332 (5%, $M^{+\cdot}$), 217 (100%); HRMS (EI) $C_{23}H_{24}O_2^{+\cdot}$ Calcd. 332.1776 found 332.1773.

3-Hydroxy-1-(2-methoxy-naphthalen-1-yl)-7-methyl-oct-6-en-1-one (**7.23**)



The title compound was prepared according to the method outlined for **7.5**, except using: 2-methoxy-1-acetonaphthone (**7.31**) (268 mg, 1.34 mmol) and aldehyde **4.6** (150 mg, 1.34 mmol) instead. Purification by column chromatography on silica gel (10% EtOAc/hexane → 18%) gave alcohol **7.23** (193 mg, 0.62 mmol, 46%) as a yellow oil: IR ν_{max} (neat) 3473 (br), 2921 (s), 1688 (s), 1593 (s), 1510 (s), 1432 (s), 1273 (s), 1250 (s), 1180 (s), 1067 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.90 (1H, d, J = 9.0 Hz, C**H**), 7.80 (1H, d, J = 8.3 Hz, C**H**), 7.72 (1H, d, J = 8.3 Hz, C**H**), 7.48 (1H, ddd, J = 1.2, 6.8, 8.3 Hz, C**H**), 7.38 (1H, ddd, J = 1.2, 6.8, 8.3 Hz, C**H**), 7.28 (1H, d, J = 9.0 Hz, C**H**), 5.18-5.11 (1H, m, =C**H**), 4.34-4.27 (1H, m, C**H**OH), 3.97 (3H, s, OC**H**$_3$), 3.21 (1H, br, O**H**), 3.17 (1H, dd, J = 2.8, 17.6 Hz, C**H**HC=O), 3.02 (1H, dd, J = 9.0, 17.6 Hz, CHHC=O), 2.23-2.07 (2H, m, C**H**$_2$CH=), 1.70 (3H, s, C**H**$_3$C), 1.68-1.46 (2H, m, C**H**$_2$CHOH), 1.63 (3H, s, C**H**$_3$C); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 208.6 (C), 135.9 (C), 132.2 (C), 131.8 (CH), 130.5 (C), 129.0 (C), 128.3 (CH), 128.0 (CH), 124.7 (C), 124.4 (CH), 124.0 (CH), 123.6 (CH), 112.8 (CH), 67.9 (CH), 56.6 (CH_3), 51.9 (CH_2), 36.8 (CH_2), 25.8 (CH_3), 24.2 (CH_2), 17.8 (CH_3); LRMS (EI) *m/z* 312 (3%, $M^{+\cdot}$), 185 (100%); HRMS (EI) $C_{20}H_{24}O_3^{+\cdot}$ Calcd. 312.1725 found 312.1726.

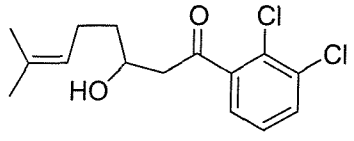
1-(4-Fluoro-naphthalen-1-yl)-3-hydroxy-7-methyl-oct-6-en-1-one (**7.24**)



The title compound was prepared according to the method outlined for **7.5**, except using: 4-fluoro-1-acetonaphthone (**7.32**) (252 mg, 1.34 mmol) and aldehyde **4.6** (150 mg, 1.34 mmol) instead. Purification by column chromatography on silica gel (8% EtOAc/hexane → 12%) gave alcohol **7.24** (205 mg, 0.68 mmol, 51%) as a colourless oil: IR ν_{max} (neat) 3440 (br), 2923 (s), 1671 (s), 1600 (s), 1574 (s), 1510 (s), 1424 (s), 1220 (s), 1145 (s), 1051 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.80 (1H, d, J = 8.8 Hz, C**H**), 8.18 (1H, d, J = 8.3 Hz, C**H**), 7.94 (1H, dd, J = 5.5, 8.3 Hz, C**H**), 7.71-7.59 (2H, m, C**H** x 2), 7.17 (1H, dd, J = 8.3, 9.8 Hz, C**H**), 5.19-5.13 (1H, m, =C**H**), 4.34-4.26 (1H, m, C**H**OH), 3.22 (1H, dd, J = 3.8, 17.1 Hz, C**H**HC=O), 3.16 (1H, dd, J = 8.0, 17.1 Hz, CHHC=O), 2.26-2.11 (2H, m, C**H**$_2$CH=), 1.71 (3H, s, C**H**$_3$C), 1.70-1.48 (2H, m, C**H**$_2$CHOH), 1.65 (3H, s, C**H**$_3$C); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 203.5 (C), 161.5 (d, $J_{C\text{-}F}$ = 258.9 Hz, C), 132.5 (C), 132.4 (d, $J_{C\text{-}F}$ = 5.8 Hz, C), 131.7 (d, $J_{C\text{-}F}$ = 4.8 Hz, C), 129.6 (d, $J_{C\text{-}F}$ = 9.7 Hz, CH), 129.4 (CH), 127.1 (d, $J_{C\text{-}F}$ = 1.9 Hz, CH), 126.1 (CH), 124.3 (d, $J_{C\text{-}F}$ = 15.5 Hz, C), 123.9 (CH), 121.0 (d, $J_{C\text{-}F}$ = 6.8

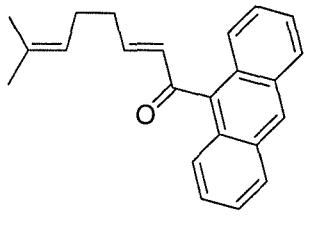
Hz, CH), 108.3 (d, $J_{C\text{-}F}$ = 20.3 Hz, CH), 68.1 (CH), 48.2 (CH_2), 36.8 (CH_2), 25.9 (CH_3), 24.3 (CH_2), 17.9 (CH_3); ^{19}F-NMR (282 MHz, $CDCl_3$) δ 48.3 (1F, s, CF); LRMS (EI) *m/z* 300 (3%, $M^{+\cdot}$), 173 (100%); HRMS (EI) $C_{19}H_{21}O_2F^{+\cdot}$ Calcd. 300.1526 found 300.1530.

1-(2,3-Dichloro-phenyl)-3-hydroxy-7-methyl-oct-6-en-1-one (**7.25**)



The title compound was prepared according to the method outlined for **7.5** except using: 2,3-dichloro-1-acetophenone (**7.33**) (252 mg, 1.34 mmol) and aldehyde **4.6** (150 mg, 1.34 mmol) instead. Purification by column chromatography on silica gel (12% EtOAc/hexane → 15%) gave alcohol **7.25** (207 mg, 0.69 mmol, 52%) as a colourless oil: IR ν_{max} (neat) 3417 (br), 2921 (s), 1703 (s), 1448 (s), 1410 (s), 1374 (s), 1229 (s), 1183 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.59 (1H, dd, *J* = 1.8, 7.8 Hz, C**H**), 7.36 (1H, dd, *J* = 1.8, 7.8 Hz, C**H**), 7.30 (1H, t, *J* = 7.8 Hz, C**H**), 5.16-5.09 (1H, m, =C**H**), 4.31-4.22 (1H, m, C**H**OH), 3.16 (1H, dd, *J* = 2.8, 17.5 Hz, C**H**HC=O), 3.03 (1H, dd, *J* = 9.0, 17.5 Hz, C**H**HC=O), 2.71 (1H, br, O**H**), 2.29-2.06 (2H, m, C**H**$_2$CH=), 1.71 (3H, s, C**H**$_3$C), 1.68-1.46 (2H, m, C**H**$_2$CHOH), 1.63 (3H, s, C**H**$_3$C); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 203.5 (C), 141.7 (C), 134.3 (C), 132.6 (C), 132.5 (CH), 129.0 (C), 127.9 (CH), 126.6 (CH), 123.7 (CH), 67.8 (CH), 50.0 (CH_2), 36.7 (CH_2), 25.8 (CH_3), 24.2 (CH_2), 17.8 (CH_3); LRMS (EI) *m/z* 302 (1%, $M^{+\cdot}$, $^{35}Cl^{37}Cl$), 300 (3%, $M^{+\cdot}$, $^{35}Cl_2$), 173 (100%); HRMS (EI) $C_{15}H_{18}O_2Cl_2^{+\cdot}$ Calcd. 300.0684 found 312.0683.

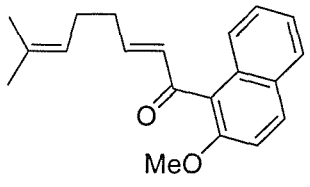
(6*E*)-1-Anthracen-9-yl-7-methyl-octa-2,6-dien-1-one (**7.26**)



The title compound was prepared according to the method outlined for **7.6**, except using: β-hydroxy ketone **7.22** (110 mg, 0.33 mmol). Purification by column chromatography on silica gel (3% EtOAc/hexane → 5%) gave diene **7.26** (100 mg, 0.32 mmol, 97%) as a yellowish oil: IR ν_{max} (neat) 2922 (m), 1650 (s), 1445 (m), 1354 (w), 1287 (w), 1216 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.51 (1H, s, C**H**), 8.05-8.02 (2H, m, C**H**), 7.87-7.81 (2H, m, C**H**), 7.51-

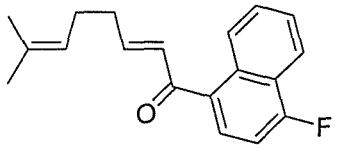
7.44 (4H, m, C**H**), 6.67 (1H, dt, *J* = 15.8, 1.5 Hz, =C**H**C=O), 6.45 (1H, dt, 15.8, 6.8 Hz, C**H**=CHC=O), 5.01-4.94 (1H, m, $(CH_3)_2C$=C**H**), 2.24 (2H, q, *J* = 6.8 Hz, CH_2CH=), 2.05 (2H, q, *J* = 6.8 Hz, CH_2CH=), 1.61 (3H, s, CH_3C), 1.41 (3H, s, CH_3C); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 200.8 (C), 154.4 (CH), 134.8 (C), 133.7 (CH), 133.0 (C), 131.2 (C), 128.7 (CH), 128.4 (C), 128.2 (CH), 126.5 (CH), 125.5 (CH), 125.4 (CH), 122.6 (CH), 33.0 (CH_2), 26.4 (CH_2), 25.7 (CH_3), 17.7 (CH_3); LRMS (GCEI) 10.81 min, *m/z* 314 (90%, $M^{+\cdot}$), 69 (100%); HRMS (EI) $C_{23}H_{22}O^{+\cdot}$ Calcd. 314.1671 found 314.1675.

(6*E*)-1-(2-Methoxy-naphthalen-1-yl)-7-methyl-octa-2,6-dien-1-one (**7.27**)



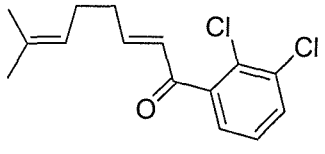
The title compound was prepared according to the method outlined for **7.6**, except using: β-hydroxy ketone **7.23** (170 mg, 0.54 mmol). Purification by column chromatography on silica gel (5% EtOAc/hexane → 10%) gave diene **7.27** (154 mg, 0.52 mmol, 97%) as a yellowish oil: IR ν_{max} (neat) 2929 (m), 1651 (s), 1620 (s), 1593 (s), 1509 (s), 1432 (s), 1339 (s), 1282 (s), 1251 (s), 1236 (s), 1070 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.90 (1H, d, *J* = 9.0 Hz, C**H**), 7.81 (1H, d, *J* = 8.3 Hz, C**H**), 7.61 (1H, d, *J* = 8.3 Hz, C**H**), 7.44 (1H, ddd, *J* = 1.3, 6.8, 8.3 Hz, C**H**), 7.36 (1H, ddd, *J* = 1.3, 6.8, 8.3 Hz, C**H**), 7.30 (1H, d, *J* = 9.0 Hz, C**H**), 6.58 (1H, dt, *J* = 15.8, 6.8 Hz, C**H**=CHC=O), 6.49 (1H, dt, 15.8, 1.3 Hz, =C**H**C=O), 5.08-5.01 (1H, m, $(CH_3)_2C$=C**H**), 2.26 (2H, q, *J* = 6.8 Hz, CH_2CH=), 2.11 (2H, q, *J* = 6.8 Hz, CH_2CH=), 1.65 (3H, s, CH_3C), 1.51 (3H, s, CH_3C); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 198.0 (C), 153.9 (C), 151.8 (CH), 133.0 (CH), 132.8 (C), 131.7 (C), 131.0 (CH), 128.9 (C), 128.1 (CH), 127.4 (CH), 124.3 (CH), 124.1 (CH), 123.8 (C), 122.9 (CH), 113.3 (CH), 56.8 (CH_3), 32.9 (CH_2), 26.6 (CH_2), 25.8 (CH_3), 17.8 (CH_3); LRMS (GCEI) 9.85 min, *m/z* 294 (15%, $M^{+\cdot}$), 185 (100%); HRMS (EI) $C_{20}H_{22}O_2^{+\cdot}$ Calcd. 294.1620 found 294.1622.

(6*E*)-1-(4-Fluoro-naphthalen-1-yl)-7-methyl-octa-2,6-dien-1-one (**7.28**)



The title compound was prepared according to the method outlined for **7.6**, except using: β-hydroxy ketone **7.24** (110 mg, 0.33 mmol). Purification by column chromatography on silica gel (3% EtOAc/hexane → 5%) gave diene **7.28** (100 mg, 0.32 mmol, 97%) as a yellowish oil: IR ν_{max} (neat) 2913 (m), 1669 (s), 1649 (s), 1615 (s), 1600 (s), 1576 (s), 1509 (s), 1425 (s), 1289 (s), 1225 (s), 1144 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.40-8.34 (1H, m, C**H**), 8.18-8.14 (1H, m, C**H**), 7.67 (1H, dd, J = 5.5, 7.8 Hz, C**H**), 7.65-7.57 (2H, m, C**H** x 2), 7.16 (1H, dd, J = 8.0, 9.8 Hz, C**H**), 6.86 (1H, dt, J = 15.6, 6.8 Hz, C**H**=CHC=O), 6.67 (1H, dt, 15.6, 1.3 Hz, =C**H**C=O), 5.17-5.09 (1H, m, $(CH_3)_2$C=C**H**), 2.34 (2H, q, J = 6.8 Hz, CH_2CH=), 2.19 (2H, q, J = 6.8 Hz, CH_2CH=), 1.71 (3H, s, CH_3C), 1.60 (3H, s, CH_3C); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 194.9 (C), 160.6 (d, J_{C-F} = 256.0 Hz, C), 151.3 (CH), 133.1 (d, J_{C-F} = 4.8 Hz, C), 133.0 (C), 132.6 (d, J_{C-F} = 4.8 Hz, C), 131.0 (CH), 128.5 (CH), 128.2 (d, J_{C-F} = 9.7 Hz, CH), 126.8 (d, J_{C-F} = 1.9 Hz, CH), 126.0 (d, J_{C-F} = 2.9 Hz, CH), 124.2 (d, J_{C-F} = 15.5 Hz, C), 122.9 (CH), 120.9 (d, J_{C-F} = 6.8 Hz, CH), 108.3 (d, J_{C-F} = 21.3 Hz, CH), 33.1 (CH_2), 26.7 (CH_2), 25.8 (CH_3), 17.9 (CH_3); ^{19}F-NMR (282 MHz, $CDCl_3$) δ 45.0 (1F, s, CF); LRMS (GCEI) 9.44 min, *m/z* 282 (10%, $M^{+\cdot}$), 69 (100%); HRMS (EI) $C_{19}H_{19}OF^{+\cdot}$ Calcd. 282.1420 found 282.1423.

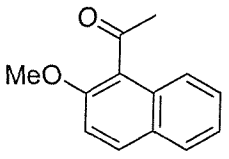
(6*E*)-1-(2,3-Dichloro-phenyl)-7-methyl-octa-2,6-dien-1-one (**7.29**)



The title compound was prepared according to the method outlined for **7.6**, except using: β-hydroxy ketone **7.25** (150 mg, 0.53 mmol). Purification by column chromatography on silica gel (5% EtOAc/hexane) gave diene **7.29** (138 mg, 0.51 mmol, 98%) as a yellowish oil: IR ν_{max} (neat) 2919 (m), 1661 (s), 1619 (s), 1448 (m), 1409 (s), 1288 (s), 1195 (m), 1134 (m) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.54 (1H, dd, J = 1.8, 8.0 Hz, C**H**), 7.27 (1H, t, J = 8.0 Hz, C**H**), 7.21 (1H, dd, J = 1.8, 8.0 Hz, C**H**), 6.66 (1H, dt, J = 15.6, 6.8 Hz, C**H**=CHC=O), 6.42 (1H, dt, 15.6, 1.3 Hz, =C**H**C=O), 5.13-5.05 (1H, m, $(CH_3)_2$C=C**H**), 2.32 (2H, q, J = 6.8 Hz, CH_2CH=), 2.17 (2H, q, J = 6.8 Hz, CH_2CH=), 1.69 (3H, s, CH_3C), 1.59 (3H, s, CH_3C); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 193.8 (C), 153.3 (CH), 141.4 (C), 134.0 (C), 133.2 (C), 131.7 (CH), 130.5 (CH), 129.5 (C), 127.5 (CH), 126.9 (CH), 122.7 (CH), 33.1 (CH_2), 26.6

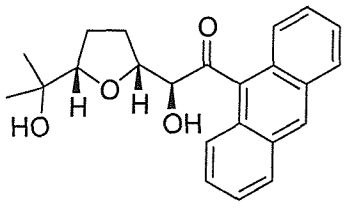
(CH_2), 25.8 (CH_3), 17.9 (CH_3); LRMS (GCEI) 8.91 min, *m/z* 284 (10%, $M^{+\cdot}$, $^{35}Cl^{37}Cl$), 282 (30%, $M^{+\cdot}$, $^{35}Cl_2$), 69 (100%); HRMS (EI) $C_{15}H_{16}OCl_2^{+\cdot}$ Calcd. 282.0578 found 282.0583.

1-(2-Methoxy-naphthalen-1-yl)-ethanone (**7.31**)



The procedure was carried out according to Catalan *et al.*[215] To a solution of 2-hydroxy-1-acetonaphthone (1.00 g, 5.4 mmol) and MeI (2.0 mL, 32 mmol) in acetone (30 mL) was added K_2CO_3 (4.5 g, 33 mmol). The reaction mixture was heated at reflux for 12 h. After cooling to rt the mixture was filtered (EtOAc). To the filtrate was added EtOAc (30 mL), H_2O (20 mL) and brine (20 mL). The organic phase was separated and the aqueous phase extracted with EtOAc (2 x 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a white solid. Purification by column chromatography on silica gel (8% EtOAc/Hex → 12%) gave methoxy-naphthone **7.31** (1.08 g, 5.4 mmol, 99%) as a white solid: spectroscopic data agreed with the literature;[215] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.89 (1H, d, *J* = 9.0 Hz, C**H**), 7.81-7.76 (2H, m, C**H** x 2), 7.49 (1H, ddd, *J* = 1.2, 6.8, 8.3 Hz, C**H**), 7.38 (1H, ddd, *J* = 1.2, 6.8, 8.3 Hz, C**H**), 7.29 (1H, d, *J* = 9.0 Hz, C**H**), 3.98 (3H, s, O**CH**$_3$), 2.66 (3H, s, **CH**$_3$C=O); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 205.2 (C), 154.1 (C), 131.6 (CH), 130.4 (C), 129.0 (C), 128.3 (CH), 127.8 (CH), 125.3 (C), 124.2 (CH), 123.8 (CH), 112.9 (CH), 56.5 (CH_3), 32.8 (CH_3).

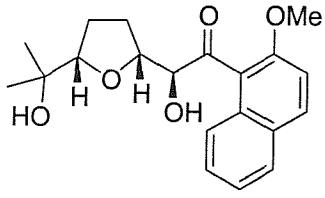
(*rac*)-1-Anthracen-9-yl-(2*S*)-2-hydroxy-2-[(2*R*,5*S*)-5-(1-hydroxy-1-methyl-ethyl)-tetrahydro-furan-2-yl]-ethanone ((*rac*)-**7.34**)



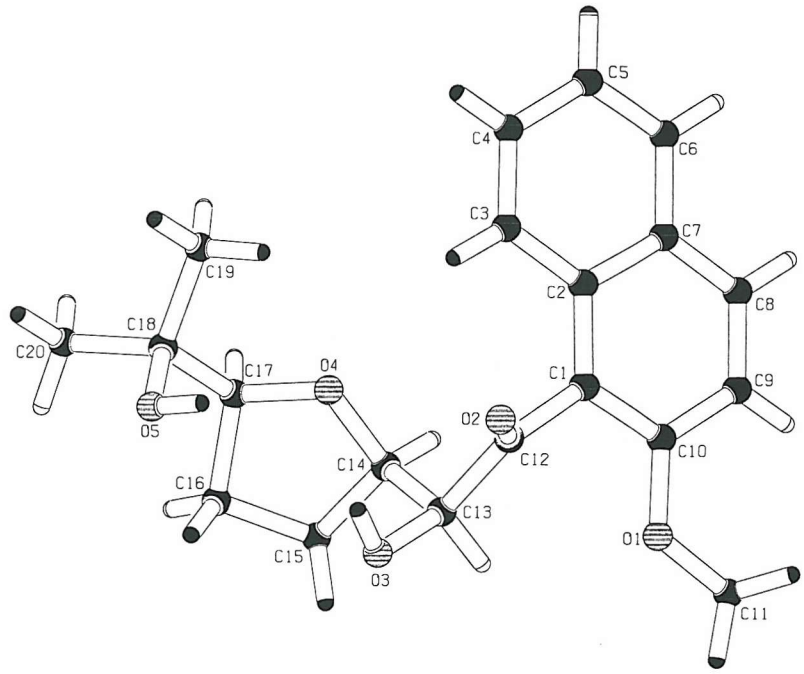
The title compound was prepared according to the method outlined for (*rac*)-**7.16**, except using: diene **7.26** (50 mg, 0.16 mmol). Purification by column chromatography on silica gel (25% EtOAc/hexane → 30%) gave THF-diol (*rac*)-**7.34** (3 mg, 0.008 mmol, 5%) as a yellow

oil: IR ν_{max} (neat) 3388 (br), 2926 (s), 1676 (s), 1591 (s), 1284 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.56 (1H, s, C**H**), 8.09-7.93 (4H, m, C**H**), 7.55-7.48 (4H, m, C**H**), 4.99 (1H, d, J = 1.5 Hz, C**H**OHC=O), 4.01 (1H, ddd, J = 1.5, 5.5, 7.0 Hz, OC**H**CHOH), 3.68 (1H, t, J = 7.0 Hz, OC**H**COH$(CH_3)_2$), 2.18-1.96 (2H, m, CH_2), 1.92-1.45 (4H, m, CH_2, O**H** x 2), 1.42 (3H, s, CH_3C), 1.19 (3H, s, CH_3C); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 209.5 (C), 131.1 (C), 129.8 (CH), 128.9 (CH), 128.4 (CH), 127.1 (CH), 125.8 (CH), 125.3 (C), 125.0 (C), 86.3 (CH), 81.7 (CH), 78.1 (CH), 72.0 (C), 28.8 (CH_2), 28.2 (CH_3), 26.0 (CH_2), 25.2 (CH_3); LRMS (ES^+) *m/z* 387 (100%, $[M+Na]^+$), 382 (70%, $[M+NH_4]^+$); HRMS (EI) $C_{23}H_{24}O_4Na^+$ Calcd. 387.1567 found 387.1564.

(2*S*)-2-Hydroxy-2-[(2*R*,5*S*)-5-(1-hydroxy-1-methyl-ethyl)-tetrahydro-furan-2-yl]-1-(2-methoxy-naphthalen-1-yl)-ethanone (**7.35**)



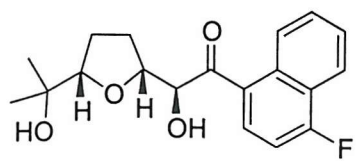
The title compound was prepared according to the method outlined for **7.16**, except using: diene **7.27** (50 mg, 0.17 mmol). Purification by column chromatography on silica gel (35% EtOAc/hexane → 45%) gave THF-diol **7.35** (25 mg, 0.07 mmol, 43%, 4% ee) as a white solid which was recrystallised ($CHCl_3$) to give colourless plates: mp 103-105 °C; IR ν_{max} (neat) 3518 (s), 2941 (m), 1676 (s), 1593 (s), 1512 (s), 1461 (s), 1342 (s), 1276 (s), 1256 (s), 1145 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.96-7.91 (2H, m, C**H**), 7.79 (1H, m, C**H**), 7.46 (1H, ddd, J = 1.3, 6.8, 8.3 Hz, C**H**), 7.36 (1H, ddd, J = 1.3, 6.8, 8.3 Hz, C**H**), 7.28 (1H, d, J = 9.0 Hz, C**H**), 5.08 (1H, d, J = 1.8 Hz, C**H**C=O), 4.20 (1H, ddd, J = 1.8, 6.0, 7.8 Hz, OC**H**CHOH), 3.95 (3H, s, OCH_3), 3.57 (1H, t, J = 7.0 Hz, OC**H**COH$(CH_3)_2$), 2.20 (1H, ddt, J = 8.8, 11.5, 6.0 Hz, C**H**H), 2.02 (1H, ddt, J = 8.8, 11.8, 7.0 Hz, C**H**H), 1.92 (1H, ddt, J = 7.0, 11.5, 8.3 Hz, C**H**H), 1.71 (1H, dddd, J = 6.0, 7,0, 7.8, 15.1 Hz, C**H**H), 1.27 (3H, s, CH_3C), 1.12 (3H, s, CH_3C); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 206.1 (C), 155.0 (C), 133.1 (CH), 131.6 (C), 129.2 (C), 128.0 (CH), 127 .8 (CH), 125.0 (CH), 124.6 (CH), 120.8 (C), 112.5 (CH), 86.8 (CH), 80.1 (CH), 79.1 (CH), 71.8 (C), 56.6 (CH_3), 28.5 (CH_2), 27.9 (CH_3), 26.1 (CH_2), 25.1 (CH_3); LRMS (ES^+) *m/z* 711 (100%, $[2M+Na]^+$), 706 (50%, $[2M+NH_4]^+$), 367 (40%, $[M+Na]^+$), 345 (30%, $[M+H]^+$); Elemental calcd. for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.54; H, 7.00; 4% ee (Chiralcel OD-H, 10% *i*-PrOH/Hex, 13.5, 16.7 min); X-ray (racemic mixture).



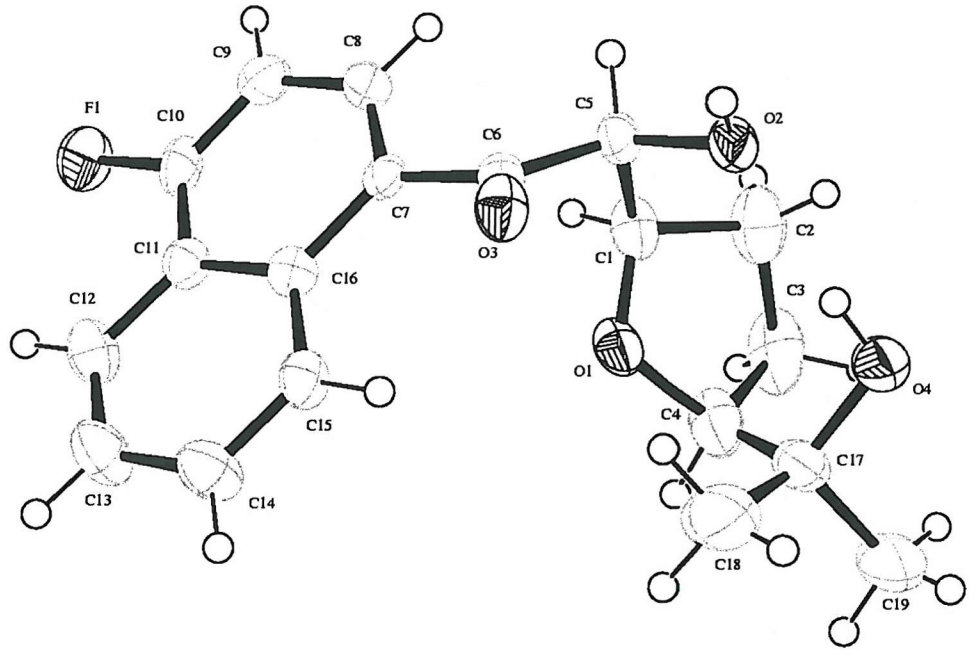
(*rac*)-(2*S*)-2-Hydroxy-2-[(2*R*,5*S*)-5-(1-hydroxy-1-methyl-ethyl)-tetrahydro-furan-2-yl]-1-(2-methoxy-naphthalen-1-yl)-ethanone ((*rac*)-**7.35**)

AcOH/Acetone 2:3 method: At –30 °C under N_2, powdered $KMnO_4$ (39 mg, 0.25 mmol) was added in one batch to a rapidly stirred solution of diene **7.27** (55 mg, 0.19 mmol) and adogen 464 (10 mol%, 8 mg, 0.02 mmol) in AcOH/acetone (2 mL 2:3). The reaction mixture was allowed to warm to –10 °C over 1 h whereupon quenching occurred by addition of ice cold $Na_2S_2O_5$ (sat aq, 3 mL) and H_2O (2 mL). EtOAc (5 mL) was added and the organic phase separated. The aqueous phase was extracted with EtOAc (2 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (70 mg). Purification by column chromatography on silica gel (30% EtOAc/hexane → 40%) gave THF-diol (*rac*)-**7.35** (50 mg, 0.15 mmol, 76%) as a white solid: mp 103-105 °C; characterisation data as above.

1-(4-Fluoro-naphthalen-1-yl)-(2*S*)-2-hydroxy-2-[(2*R*,5*S*)-5-(1-hydroxy-1-methyl-ethyl)-tetrahydro-furan-2-yl]-ethanone (**7.36**)

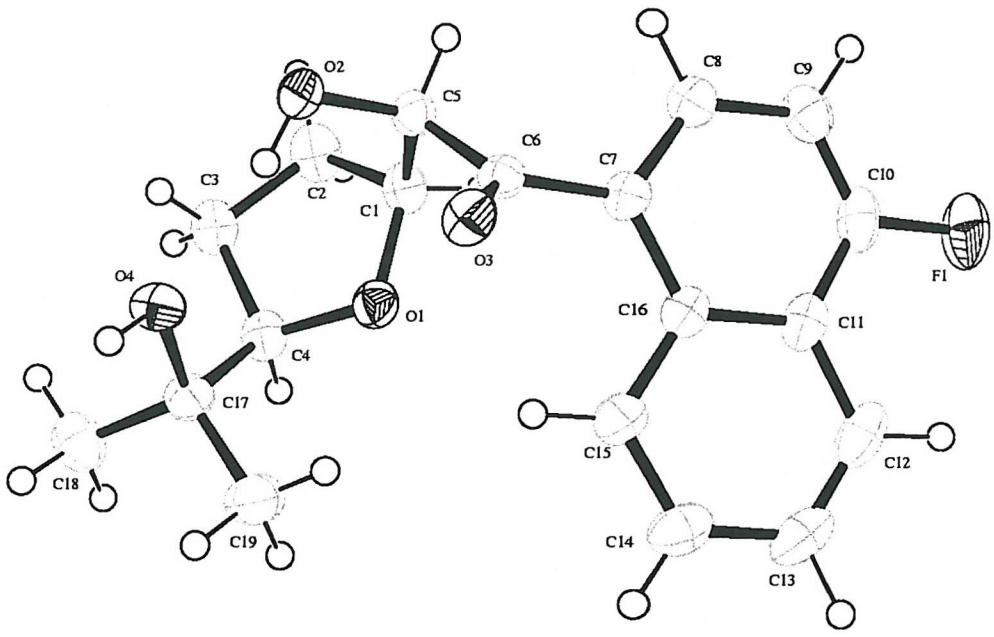


The title compound was prepared according to the method outlined for **7.16**, except using: diene **7.28** (40 mg, 0.14 mmol). Purification by column chromatography on silica gel (30% EtOAc/hexane → 40%) gave THF-diol **7.36** (20 mg, 0.06 mmol, 43%, 92% ee) as colourless crystals (EtOAc/Hex): mp 103-105 °C; $[\alpha]^{25}_{D}$ –72.6 (MeOH, *c* 0.12); IR ν_{max} (neat) 3394 (br), 2980 (s), 1692 (s), 1511 (s), 1275 (s), 1122 (s), 1073 (s), 1047 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.50 (1H, d, *J* = 8.3 Hz, C**H**), 8.18 (1H, dd, *J* = 1.8, 8.0 Hz, C**H**), 7.75 (1H, dd, *J* = 5.3, 8.0 Hz, C**H**), 7.70-7.60 (2H, m, C**H**), 7.18 (1H, dd, *J* = 8.0, 9.8 Hz, C**H**), 5.09 (1H, d, *J* = 1.8 Hz, C**H**OHC=O), 4.21 (1H, ddd, *J* = 2.0, 5.5, 7.8 Hz, C**H**OCHOHC=O), 4.12 (1H, br s, O**H**), 3.56 (1H, dd, *J* = 6.5, 7.6 Hz, C**H**OC(CH_3)$_2$OH), 2.53 (1H, br s, O**H**), 2.23-2.13 (1H, m, C**H**$_2$), 2.02-1.83 (2H, m, C**H**$_2$), 1.72-1.60 (1H, m, C**H**$_2$), 1.22 (3H, s, C**H**$_3$C), 1.11 (3H, s, C**H**$_3$C); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 202.4 (C), 161.6 (d, J_{C-F} = 258.9 Hz, C), 132.6 (d, J_{C-F} = 5.6 Hz, C), 129.7 (d, J_{C-F} = 2.9 Hz, C), 129.2 (CH), 128.0 (d, J_{C-F} = 9.7 Hz, CH), 127.4 (CH), 125.9 (d, J_{C-F} = 1.9 Hz, CH), 124.5 (d, J_{C-F} = 15.5 Hz, C), 121.0 (d, J_{C-F} = 5.8 Hz, CH), 108.2 (d, J_{C-F} = 20.3 Hz, CH), 86.9 (CH), 80.0 (CH), 77.7 (CH), 71.8 (C), 28.4 (CH_2), 27.9 (CH_3), 26.2 (CH_2), 25.0 (CH_3); ^{19}F-NMR (282 MHz, $CDCl_3$) δ 48.0 (1F, s, CF); LRMS (ES^+) *m/z* 687 (50%, $[2M+Na]^+$), 355 (100%, $[M+Na]^+$); Elemental calcd. for $C_{19}H_{21}O_4F$: C, 68.66; H, 6.37. Found: C, 68.44; H, 6.33; 93% ee (Chiralcel OD-H, 10% *i*-PrOH/Hex, 9.8, 18.8 min); X-ray (single enantiomer).

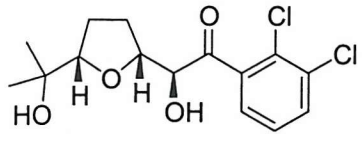


(*rac*)-1-(4-Fluoro-naphthalen-1-yl)-(2*S*)-2-hydroxy-2-[(5*S*,2*R*)-5-(1-hydroxy-1-methyl-ethyl)-tetrahydro-furan-2-yl]-ethanone ((*rac*)-**7.36**)

The title compound was prepared according to the method outlined for (*rac*)-**7.35**, except using: diene **7.28** (53 mg, 0.19 mmol). Purification by column chromatography on silica gel (30% EtOAc/hexane → 40%) gave THF-diol (*rac*)-**7.36** (51 mg, 0.15 mmol, 81%) as colourless crystals (EtOAc/Hex): characterisation data as above; X-ray (racemic mixture).



1-(2,3-Dichloro-phenyl)-(2*S*)-2-hydroxy-2-[(2*R*,5*S*)-5-(1-hydroxy-1-methyl-ethyl)-tetrahydro-furan-2-yl]-ethanone (**7.37**)

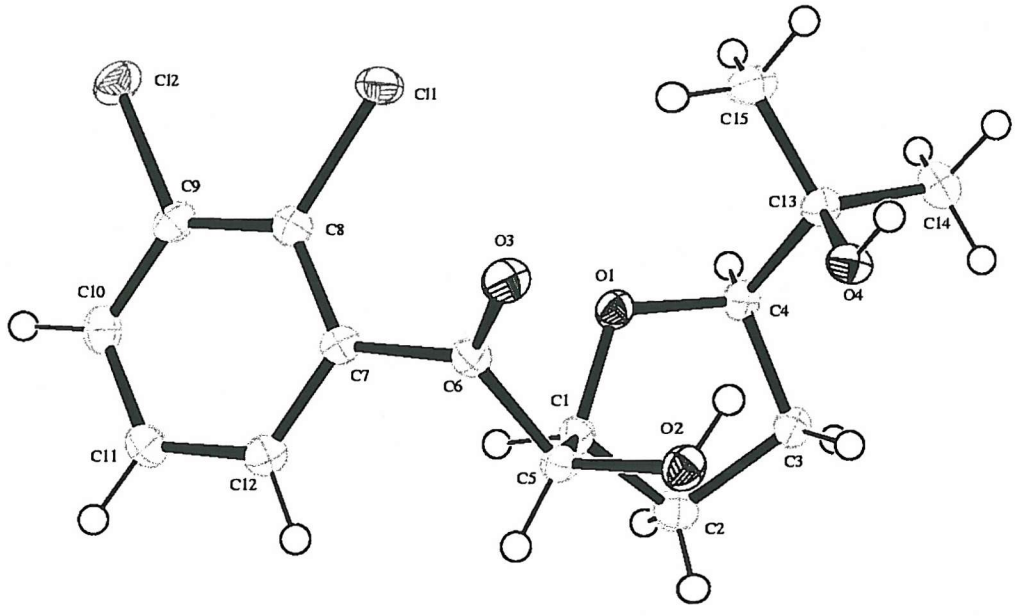


The title compound was prepared according to the method outlined for **7.16**, except using: diene **7.29** (48 mg, 0.18 mmol). Purification by column chromatography on silica gel (30% EtOAc/hexane → 35%) gave THF-diol **7.37** (25 mg, 0.08 mmol, 42%, 94% ee) as white solid: mp 89-91 °C; IR ν_{max} (neat) 3404 (s), 3269 (s), 2975 (m), 1707 (s), 1408 (s), 1275 (s), 1193 (s), 1159 (s), 1108 (s), 1080 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.65 (1H, dd, *J* =

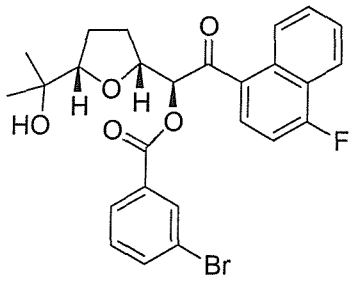
1.8, 7.8 Hz, CH), 7.43 (1H, dd, J = 1.8, 7.8 Hz, CH), 7.37 (1H, t, J = 7.8 Hz, CH), 4.98 (1H, d, J = 2.0 Hz, CHOHC=O), 4.33 (1H, ddd, J = 2.0, 5.0, 7.0 Hz, OCHCHOH), 3.75 (1H, dd, J = 6.8, 7.5 Hz, OCHCOH(CH_3)$_2$), 2.26-2.17 (1H, m, CHH), 2.12-1.94 (2H, m, CHH x 2), 1.84-1.75 (1H, m, CHH), 1.30 (3H, s, CH_3C), 1.18 (3H, s, CH_3C); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 202.9 (C), 139.2 (C), 134.3 (C), 132.7 (CH), 129.4 (C), 127.9 (CH), 127.3 (CH), 86.9 (CH), 79.3 (CH), 78.7 (CH), 72.0 (C), 28.3 (CH_2), 27.9 (CH_3), 26.3 (CH_2), 25.2 (CH_3); LRMS (ES^+) *m/z* 357 (60%, $[M+Na]^+$ ^{37}Cl), 355 (100%, $[M+Na]^+$ ^{35}Cl), 352 (20%, $[M+NH_4]^+$ ^{37}Cl), 350 (50%, $[M+NH_4]^+$ ^{35}Cl); Elemental calcd. for $C_{15}H_{18}O_4Cl_2$: C, 54.07; H, 5.44. Found: C, 53.92; H, 5.46; 94% ee (Chiralcel OD-H, 5% *i*-PrOH/Hex, 12.9, 13.5 min).

(*rac*)-1-(2,3-Dichloro-phenyl)-(2*S*)-2-hydroxy-2-[(2*R*,5*S*)-5-(1-hydroxy-1-methyl-ethyl)-tetrahydro-furan-2-yl]-ethanone ((*rac*)-**7.37**)

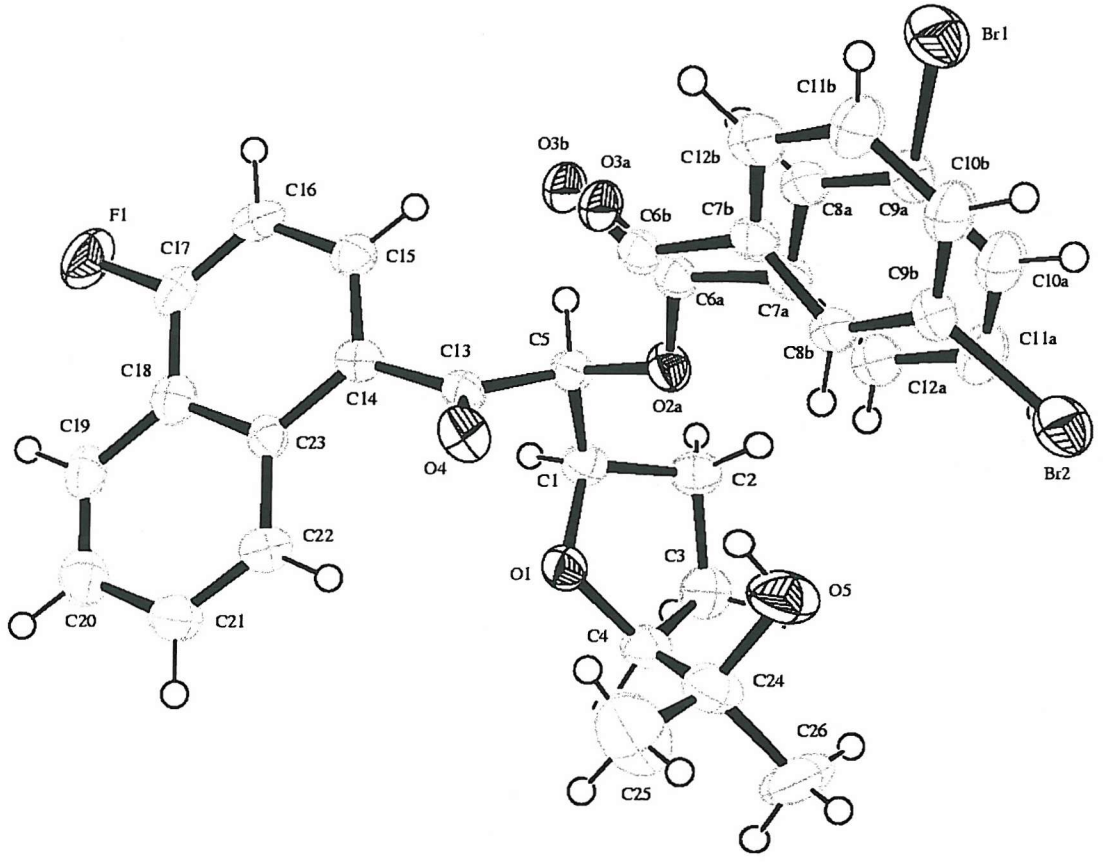
The title compound was prepared according to the method outlined for (*rac*)-**7.35**, except using: diene **7.29** (40 mg, 0.15 mmol). Purification by column chromatography on silica gel (30% EtOAc/hexane → 35%) gave THF-diol (*rac*)-**7.37** (33 mg, 0.10 mmol, 66%) as colourless crystals (EtOAc/Hex): mp 89-91 °C; characterisation data as above; X-ray (racemic mixture).



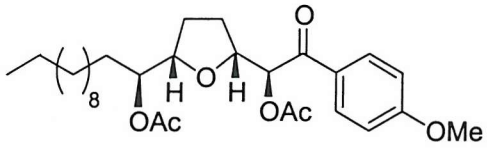
3-Bromo-benzoic acid 2-(4-fluoro-naphthalen-1-yl)-(1*S*)-1-[(2*R*,5*S*)-5-(1-hydroxy-1-methyl-ethyl)-tetrahydro-furan-2-yl]-2-oxo-ethyl ester (**7.38**)



Under N_2 at 0 °C to a solution of THF-diol **7.36** (20 mg, 0.06 mmol) in CH_2Cl_2 (0.5 mL) was added pyridine (50 μL, 0.6 mmol), bromobenzoyl chloride (66 mg, 0.3 mmol) and DMAP (18 mg, 0.15 mmol). After 30 min the reaction was quenched by addition of NH_4Cl (sat aq, 1 mL), citric acid (10% w/v aq, 0.5 mL), H_2O (0.5 mL) and CH_2Cl_2 (1 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 1 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow oil. Purification by column chromatography on silica gel (10% EtOAc/Hex→ 20%) gave the bromobenzoate **7.38** (27 mg, 0.05 mmol, 90%) as colourless needles (EtOAc/Hex): mp100-103 °C; $[\alpha]^{25}_D$ –6.5 ($CHCl_3$, *c* 0.77); IR ν_{max} (neat) 3548 (br), 2976 (s), 1723 (s), 1706 (s), 1573 (s), 1426 (s), 1288 (s), 1262 (s), 1230 (s), 1123 (s), 1069 (s), 1045 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.55 (1H, d, *J* = 8.3 Hz, C**H**), 8.40 (1H, t, *J* = 1.7 Hz, C**H**), 8.20-8.13 (2H, m, C**H**), 8.03 (1H, dd, *J* = 5.3, 8.0 Hz, C**H**), 7.73 (1H, ddd, *J* = 1.0, 2.0, 8.0 Hz, C**H**), 7.70-7.60 (2H, m, C**H**), 7.38 (1H, t, *J* = 8.0 Hz, C**H**), 7.22 (1H, dd, *J* = 8.0, 9.8 Hz, C**H**), 6.20 (1H, d, *J* = 3.5 Hz, C**H**OC=O), 4.56 (1H, dt, *J* = 7.8, 3.5 Hz, C**H**OCHOC=O), 3.74 (1H, dd, *J* = 6.2, 8.0 Hz, C**H**OC(CH$_3$)$_2$OH), 2.24-1.97 (3H, m, C**H$_2$**), 1.90-1.79 (1H, m, C**H**H), 1.31 (3H, s, C**H$_3$**C), 1.20 (3H, s, C**H$_3$**C); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 196.6 (C), 165.5 (C), 161.5 (d, $J_{C\text{-}F}$ = 257.9 Hz, C), 136.6 (CH), 133.3 (CH), 132.6 (d, $J_{C\text{-}F}$ = 5.8 Hz, C), 131.3 (CH), 130.5 (d, $J_{C\text{-}F}$ = 3.9 Hz, C), 130.3 (CH), 129.2 (CH), 128.7 (CH), 128.4 (d, $J_{C\text{-}F}$ = 10.6 Hz, CH), 127.3 (CH), 125.8 (CH), 124.4 (d, $J_{C\text{-}F}$ = 16.4 Hz, C), 122.8 (C), 121.0 (d, $J_{C\text{-}F}$ = 5.8 Hz, CH), 108.4 (d, $J_{C\text{-}F}$ = 20.3 Hz, CH), 87.6 (CH), 80.6 (CH), 77.2 (CH), 70.9 (C), 28.7 (CH_2), 28.3 (CH_3), 26.0 (CH_2), 24.9 (CH_3); ^{19}F-NMR (282 MHz, $CDCl_3$) δ 48.1 (1F, s, CF); LRMS (ES^+) *m/z* 1053 (100%, $[2M+Na]^+$, 1 x ^{79}Br, 1 x ^{81}Br), 539 (50%, $[M+Na]^+$, ^{81}Br), 537 (45%, $[M+Na]^+$, ^{79}Br); Elemental calcd. for $C_{26}H_{24}O_5FBr$: C, 60.59; H, 4.69. Found: C, 60.55; H, 4.67; X-ray (single enantiomer).



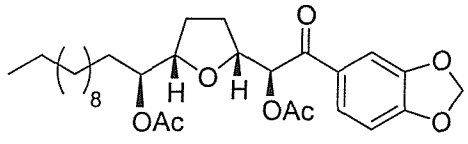
(1*S*)-1-[(2*R*,5*S*)-5-[(1*S*)-1-(Acetyloxy)dodecyl]tetrahydrofuran-2-yl]-2-(4-methoxyphenyl)-2-oxoethyl acetate (**7.46**)



At 0 °C to a solution of THF-diol (*rac*)-**7.18** (100 mg, 0.24 mmol) in CH_2Cl_2 (10 mL) was added dropwise pyridine (0.19 mL, 2.4 mmol), acetyl chloride (86 μL, 1.2 mmol) and DMAP (73 mg, 0.6 mmol). After 1.5 h the reaction was quenched by addition of NH_4Cl (sat aq, 10 mL) and H_2O (5 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated *in vacuo* to give a colourless oil. Purification by column chromatography on silica gel (15% EtOAc/hexane → 20%) gave THF-acetate **7.46** (114 mg, 0.23 mmol, 95%) as a colourless oil: IR ν_{max} (neat) 2926 (s), 2850 (s), 1734 (s), 1677 (m), 1597 (s), 1460 (s), 1370 (s), 1237 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.02 (2H, d, J = 9.0 Hz, C**H**),

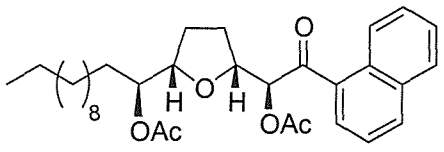
6.94 (2H, d, J = 9.0 Hz, C**H**), 5.80 (1H, d, J = 5.8 Hz, C**H**OAcC=O), 4.82 (1H, td, J = 7.3, 5.3 Hz, C**H**OAc), 4.36 (1H, br q, J = 6.3 Hz, C**H**CHOAcC=O), 3.99 (1H, br q, J = 6.0 Hz, C**H**CHOAc), 3.88 (3H, s, OC**H**$_3$), 2.13 (3H, s, C**H**$_3$C=O), 2.05 (3H, s, C**H**$_3$C=O), 1.98-1.55 (4H, m, C**H**$_2$ THF), 1.50-1.38 (2H, m, C**H**$_2$CHOAc), 1.36-1.10 (18H, m, C**H**$_2$), 0.89 (3H, t, J = 7.0 Hz, C**H**$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 194.5 (C), 170.9 (C), 170.5 (C), 164.1 (C), 131.6 (CH), 129.1 (C), 114.0 (CH), 80.5 (CH), 78.7 (CH), 77.2 (CH), 75.4 (CH), 55.7 (CH_3), 32.1 (CH_2), 31.1 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 27.8 (CH_2), 27.7 (CH_2), 25.5 (CH_2), 22.9 (CH_2), 21.3 (CH_3), 20.8 (CH_3), 14.3 (CH_3); LRMS (ES$^+$) *m/z* 1031 (50%, $[2M+Na]^+$), 527 (100%, $[M+Na]^+$), 505 (20%, $[M+H]^+$); HRMS (ES$^+$) $C_{29}H_{44}O_7Na^+$ Calcd. 527.2971 found 527.2972.

(1*S*)-1-[(2S,5*R*)-5-((1*S*)-1-(Acetyloxy)-2-(1,3-benzodioxol-5-yl)-2-oxoethyl)tetrahydrofuran-2-yl]dodecyl acetate (**7.47**)



The title compound was prepared according to the method outlined for THF-diol **7.46**, except using: methylenedioxy-THF-diol (*rac*)-**7.19** (104 mg, 0.24 mmol). Purification by column chromatography on silica gel (20% EtOAc/hexane → 25%) gave THF-acetate **7.47** (112 mg, 0.22 mmol, 90%) as a slightly yellow oil: IR ν_{max} (neat) 2926 (s), 2852 (s), 1734 (s), 1666 (s), 1602 (m), 1502 (m), 1445 (s), 1425 (m), 1258 (s), 1096 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.68 (1H, dd, J = 1.8, 8.3 Hz, C**H**), 7.48 (1H, d, J = 1.7 Hz, C**H**), 6.86 (1H, d, J = 8.0 Hz, C**H**), 6.04 (2H, s, OC**H**$_2$O), 5.75 (1H, d, J = 5.8 Hz, C**H**OAcC=O), 4.79 (1H, td, J = 7.6, 5.3 Hz, C**H**OAc), 4.35 (1H, br q, J = 6.3 Hz, C**H**CHOAcC=O), 3.98 (1H, br q, J = 6.8 Hz, C**H**CHOAc), 2.13 (3H, s, C**H**$_3$C=O), 2.05 (3H, s, C**H**$_3$C=O), 1.97-1.57 (4H, m, C**H**$_2$ THF), 1.50-1.41 (2H, m, C**H**$_2$CHOAc), 1.34-1.18 (18H, m, C**H**$_2$), 0.88 (3H, t, J = 7.0 Hz, C**H**$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 194.1 (C), 170.9 (C), 170.5 (C), 152.3 (C), 148.2 (C), 130.8 (C), 126.7 (CH), 108.9 (CH), 108.1 (CH), 102.0 (CH_2), 80.4 (CH), 78.6 (CH), 76.9 (CH), 75.3 (CH), 32.0 (CH_2), 31.1 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 27.8 (CH_2), 27.6 (CH_2), 25.4 (CH_2), 22.8 (CH_2), 21.2 (CH_3), 20.8 (CH_3), 14.2 (CH_3); LRMS (ES$^+$) *m/z* 1058 (30%, $[2M+Na]^+$), 541 (100%, $[M+Na]^+$), 519 (10%, $[M+H]^+$); HRMS (ES$^+$) $C_{29}H_{42}O_8Na^+$ Calcd. 541.2772 found 541.773.

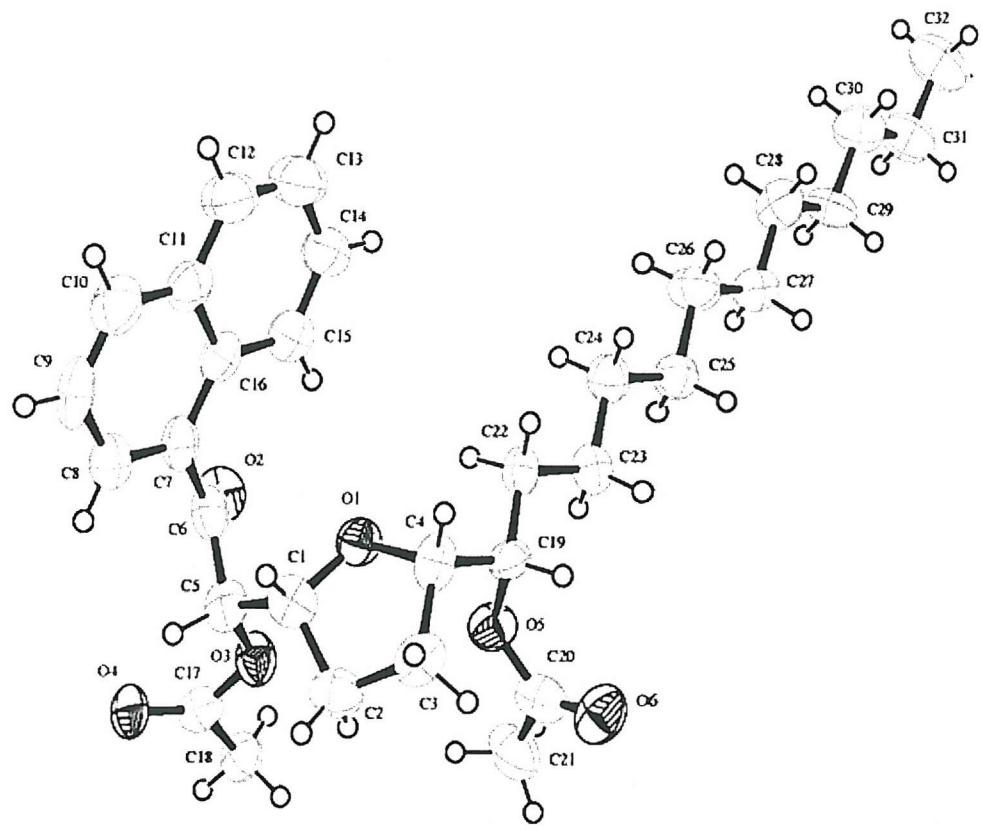
(1*S*)-1-[(2*R*,5*S*)-5-[(1*S*)-1-Acetyloxy-dodecyl]tetrahydrofuran-2-yl]-2-(1-naphthyl)-2-oxoethyl acetate (**7.48**)



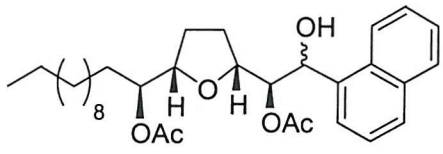
The title compound was prepared according to the method outlined for **7.46**, except using: naphthyl-THF-diol **7.20** (44 mg, 0.01 mmol). Purification by column chromatography on silica gel (15% EtOAc/hexane → 20%) gave THF-acetate **7.48** (52 mg, 0.01 mmol, 95%, 92% ee) as a colourless gummy oil: IR ν_{max} (neat) 2920 (s), 2852 (s), 1744 (s), 1723 (s), 1465 (m), 1372 (s), 1233 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.38 (1H, dd, *J* = 1.0, 8.3 Hz, C**H**), 8.06 (1H, dd, *J* = 1.2, 7.3 Hz, C**H**), 7.99 (1H, d, *J* = 8.3 Hz, C**H**), 7.86 (1H, dd, *J* = 1.5, 8.0 Hz, C**H**), 7.60-7.50 (3H, m, C**H**), 5.80 (1H, d, *J* = 4.5 Hz, C**H**OAcC=O), 4.89 (1H, dt, *J* = 5.3, 7.8 Hz, C**H**OAc), 4.41 (1H, dt, *J* = 4.6, 7.3 Hz, C**H**CHOAcC=O), 3.94 (1H, dt, *J* = 5.3, 7.0 Hz, C**H**CHOAc), 2.14 (3H, s, C**H**$_3$C=O), 2.04 (3H, s, C**H**$_3$C=O), 1.94-1.50 (6H, m, 2 x C**H**$_2$ THF, C**H**$_2$), 1.34-1.21 (18H, m, C**H**$_2$), 0.90 (3H, t, *J* = 7.0 Hz, C**H**$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 199.7 (C), 170.8 (2 x C), 134.4 (C), 134.0(C), 132.7 (CH), 130.4 (C), 128.4 (CH), 127.9 (2 x CH), 126.6 (CH), 125.6 (CH), 124.3 (CH), 80.4 (CH), 79.9 (CH), 78.0 (CH), 75.2 (CH), 32.0 (CH_2), 31.1 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 28.4 (CH_2), 27.8 (CH_2), 27.7 (CH_2), 25.4 (CH_2), 22.8 (CH_2), 21.2 (CH_3), 20.8 (CH_3), 14.2 (CH_3); LRMS (ES^+) *m/z* 1071 (50%, $[2M+Na]^+$), 547 (100%, $[M+Na]^+$), 525 (10%, $[M+H]^+$); HRMS (ES^+) $C_{32}H_{44}O_6Na^+$ Calcd. 547.3030 found 547.3031; 91% ee (Chiralcel OD-H, 10% *i*-PrOH/Hex, 6.6, 8.6 min).

(*rac*)-(1*S*)-1-[(2*R*,5*S*)-5-[(1*S*)-1-Acetyloxy-dodecyl]tetrahydrofuran-2-yl]-2-(1-naphthyl)-2-oxoethyl acetate ((*rac*)-**7.48**)

The title compound was prepared according to the method outlined for **7.46**, except using: naphthyl-THF-diol (*rac*)-**7.20** (50 mg, 0.01 mmol). Purification by column chromatography on silica gel (15% EtOAc/hexane → 20%) gave THF-acetate (*rac*)-**7.48** (56 mg, 0.01 mmol, 95%) a colourless oil which crystallised on standing to give colourless platelets: mp 48-50 °C; characterisation data as above; X-ray (racemic mixture).



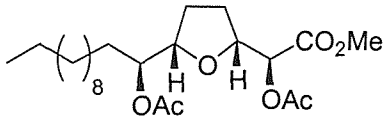
(1*S*)-1-[(2*S*,5*R*)-5-[(1*S*)-1,2-Dihydroxy-2-(1-naphthyl)ethyl]tetrahydrofuran-2-yl]dodecyl acetate (**7.53**)



At –10 °C to a solution of ketone (*rac*)-**7.20** (25 mg, 0.05 mmol) in MeOH (1 mL) was added $NaBH_4$ (2 mg, 0.05 mmol) in one batch. After 1.5 h the reaction was quenched by addition of 2 M HCl (1 mL), brine (2 mL) and CH_2Cl_2 (5 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 3 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated *in vacuo* to give a colourless oil. Purification by column chromatography on silica gel (30% EtOAc/hexane) gave an inseparable mixture of diastereoisomers (6:1) of secondary alcohol **7.53** (21 mg, 0.04 mmol, 85%) as an oil (characterisation of major isomer only): IR ν_{max} (neat) 3483 (br), 2924 (s), 2854 (s), 1737 (s), 1464 (m), 1370 (s), 1233 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.38 (1H, d, J = 8.5 Hz, C**H**), 7.88-7.71 (3H, m, C**H**), 7.62-7.44 (3H, m, C**H**), 5.88 (1H, d, J = 1.8 Hz, C**H**OH), 5.21

(1H, dd, J = 2.0, 4.3 Hz, CHOAcCHOH), 5.08-5.01 (1H, m, CHOCHOAc), 4.55 (1H, br s, OH), 4.09 (1H, ddd, J = 2.0, 5.5, 7.8 Hz, CHOCHOAcCHOH), 4.02-3.94 (1H, m, $CHOAcCH_2$), 2.18 (3H, s, CH_3C=O), 2.12 (3H, s, CH_3C=O), 1.96-1.56 (6H, m, 2 x CH_2 THF, CH_2), 1.42-1.21 (18H, m, CH_2), 0.90 (3H, t, J = 7.0 Hz, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.0 (C), 170.9 (C), 136.8 (C), 133.6 (C), 130.5 (C), 128.8 (CH), 128.2 (CH), 126.5 (CH), 125.7 (CH), 125.6 (CH), 124.1 (CH), 123.0 (CH), 81.3 (CH), 77.6 (CH), 75.4 (CH), 75.0 (CH), 71.7 (CH), 32.0 (CH_2), 31.3 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 28.2 (CH_2), 28.0 (CH_2), 27.7 (CH_2), 25.4 (CH_2), 22.8 (CH_2), 21.2 (CH_3), 21.1 (CH_3), 14.2 (CH_3); LRMS (ES^+) *m/z* 1075 (80%, $[2M+Na]^+$), 549 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{32}H_{46}O_6Na^+$ Calcd. 549.3187 found 549.3185.

Methyl (2*S*)-(acetyloxy)[(2*R*,5*S*)-5-[(1*S*)-1-(acetyloxy)dodecyl]tetrahydrofuran-2-yl]acetate (**7.55**)

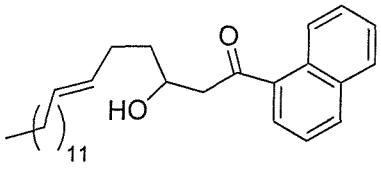


At rt to a vigorously stirred biphasic solution of secondary alcohol **7.53** (20 mg, 0.04 mmol), H_5IO_6 (130 mg, 0.57 mmol) in $CCl_4/CH_3CN/H_2O$ (2:2:3, 1.4 mL) was added in one portion $RuCl_3 \cdot H_2O$ (1.6 mg, 0.008 mmol) (After 20 min stirring organic phase was bright orange). After 3 h Et_2O (5 mL) and brine (2 mL) were added and the solution stirred for a further 5 min whereupon the organic phase was separated and the aqueous phase extracted with Et_2O (2 x 5 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated *in vacuo* to give a crude material which was passed through a plug of silica (10% $MeOH/CH_2Cl_2$) yielding a colourless oil (12 mg) that was shown to contain acid **7.54** by MS (ES^-).

To a solution of the oil (12 mg) in THF (0.5 mL) was added resin bound reagent **7.56** (30 mg, 0.05 mmol). The reaction mixture was heated at reflux for 6 h. The reaction was filtered, the resin was taken up in CH_2Cl_2 (2 x 5 mL) and filtered again. The filtrate was concentrated *in vacuo* to give a yellowish oil, purification by column chromatography on silica gel (20% EtOAc/hexane) gave THF-methyl ester **7.55** (8 mg, 0.02 mmol, 50%) as a colourless oil: IR ν_{max} (neat) 2924 (s), 2854 (s), 1740 (s), 1459 (s), 1436 (s), 1232 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.01 (1H, d, J = 5.5 Hz, $CHOAcCO_2Me$), 4.90 (1H, dt, J = 4.8, 8.4 Hz, CHCHOAc), 4.38-4.30 (1H, m, $CHCHOAcCO_2Me$), 4.08-3.97 (1H, m, CHOAc), 2.18 (3H, s, CH_3C=O), 2.09 (3H, s, CH_3C=O), 2.02-1.83 (2H, m, CH_2 THF), 1.80-1.49 (4H, m, CH_2

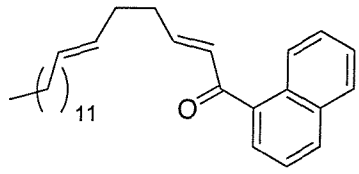
THF, CH_2), 1.35-1.18 (18H, m, CH_2), 0.89 (3H, t, J = 7.0 Hz, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.8 (C), 170.7 (C), 168.7 (C), 80.5 (CH), 77.9 (CH), 75.3 (CH), 74.5 (CH), 52.5 (CH_3), 32.0 (CH_2), 30.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 27.7 (CH_2), 27.6 (CH_2), 25.5 (CH_2), 22.8 (CH_2), 21.2 (CH_3), 20.7 (CH_3), 14.2 (CH_3); LRMS (ES^+) *m/z* 879 (50%, $[2M+Na]^+$), 451 (100%, $[M+Na]^+$), 429 (10%, $[M+H]^+$); HRMS (ES^+) $C_{23}H_{40}O_7Na^+$ Calcd. 451.2666 found 451.2665.

(6*E*)-3-Hydroxy-1-(1-naphthyl)nonadec-6-en-1-one (**7.57**)



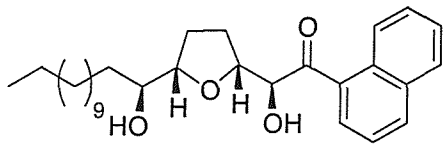
The title compound was prepared according to the method outlined for **7.5**, except using: 1-acetonaphthone (3.70 g, 14.7 mmol) and aldehyde **5.14** (3.70 g, 14.7 mmol) instead. Purification by column chromatography on silica gel (10% EtOAc/hexane → 15%) gave β-hydroxy ketone **7.57** (4.34g, 10.0 mmol, 70%) as a white solid: mp 31-32 °C; IR ν_{max} (neat) 3462 (br), 2922 (s), 2852 (s), 1674 (s), 1508 (m), 1463 (s), 1354 (m), 1287 (s), 1230 (s), 1100 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.65 (1H, d, J = 8.5 Hz, C**H**), 8.01 (1H, d, J = 8.3 Hz, C**H**), 7.92-7.87 (2H, m, C**H**), 7.65-7.48 (3H, m, C**H**), 5.49 (1H, td, J = 5.8, 15.2 Hz, C**H**=CH), 5.42 (1H, td, J = 6.0, 15.3 Hz, C**H**=CH), 4.32 (1H, ddt, J = 3.3, 4.5, 8.1, Hz, C**H**OH), 3.25 (1H, dd, J = 3.3, 17.2 Hz, C**H**HC=O), 3.18 (1H, dd, J = 8.5, 17.3 Hz, C**H**HC=O), 2.29-2.10 (2H, m, CH_2), 1.97 (2H, br q, J = 7.2 Hz, CH_2), 1.72 (1H, dtd, J = 6.0, 8.3, 13.8 Hz, C**H**HCHOH), 1.60 (1H, dddd, J = 4.8, 6.7, 8.8, 15.6 Hz, C**H**HCHOH), 1.41-1.19 (20H, m, CH_2), 0.89 (3H, t, J = 7.0 Hz, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 205.1 (C), 135.7 (C), 134.1 (C), 133.3 (CH), 131.5 (CH), 130.2 (C), 129.4 (CH), 128.6 (CH), 128.3 (CH), 128.2 (CH), 126.7 (CH), 125.8 (CH), 124.5 (CH), 68.0 (CH), 48.5 (CH_2), 36.6 (CH_2), 32.7 (CH_2), 32.1 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.8 (CH_2), 22.8 (CH_2), 14.2 (CH_3); LRMS (EI) *m/z* 422 (3%, $M^{+\cdot}$), 404 (8%, $[M-H_2O]^{+\cdot}$), 155 (100%); HRMS (ES^+) $2[C_{29}H_{42}O_2]Na^+$ Calcd. 867.6262 found 867.6285; Elemental calcd. for $C_{29}H_{42}O_2$: C, 82.41; H, 10.02. Found: C, 82.08; H, 9.95.

(2*E*,6*E*)-1-(1-Naphthyl)nonadeca-2,6-dien-1-one (**7.58**)



The title compound was prepared according to the method outlined for **7.6**, except using: β-hydroxy ketone **7.57** (4.34 g, 10.3 mmol). Purification by column chromatography on silica gel (3% EtOAc/hexane → 5%) gave diene **7.58** (4.10 mg, 10.1 mmol, 98%) as a yellowish oil: IR ν_{max} (neat) 2922 (s), 2852 (s), 1670 (m), 1650 (s), 1617 (s), 1508 (m), 1462 (s), 1287 (s), 1251 (s), 1231 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.25 (1H, dd, J = 2.0, 7.3 Hz, C**H**), 7.96 (1H, d, J = 8.3 Hz, C**H**), 7.91-7.87 (1H, m, Hz, C**H**), 7.66 (1H, dd, J = 1.2, 7.0 Hz, C**H**), 7.58-7.46 (3H, m, C**H**), 6.84 (1H, td, J = 6.7, 15.7 Hz, C**H**=CH), 6.66 (1H, td, J = 1.3, 15.8 Hz, C**H**=CH), 5.46 (1H, td, J = 6.3, 15.3 Hz, C**H**=CH), 5.38 (1H, td, J = 6.3, 15.1 Hz, C**H**=CH), 2.37 (2H, q, J = 7.0 Hz, C**H**$_2$CH=CHC=O), 2.20 (2H, q, J = 6.8 Hz, C**H**$_2$CH$_2$CH=CHC=O), 1.98 (2H, q, J = 6.8 Hz, C**H**$_2$), 1.37-1.22 (20H, m, C**H**$_2$), 0.90 (3H, t, J = 6.9 Hz, C**H**$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 196.4 (C), 151.3 (CH), 137.1 (C), 133.9 (C), 132.2 (CH), 131.5 (CH), 131.4 (CH), 130.7 (C), 128.5 (CH), 128.3 (CH), 127.4 (CH), 127.1 (CH), 126.5 (CH), 125.8 (CH), 124.5 (CH), 32.9 (CH_2), 32.7 (CH_2), 32.1 (CH_2), 31.2 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 22.8 (CH_2), 14.2 (CH_3); LRMS (EI) *m/z* 404 (10%, $M^{+\cdot}$), 196 (100%); HRMS (EI) $C_{29}H_{40}O^{+\cdot}$ Calcd. 404.3081 found 404.3079.

(2*S*)-2-Hydroxy-2-[(2*R*,5*S*)-5-[(1*S*)-1-hydroxytridecyl]tetrahydrofuran-2-yl]-1-(1-naphthyl)ethanone (**7.59**)



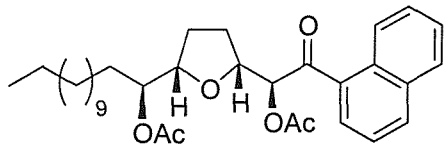
The title compound was prepared according to the method outlined for **7.16** except at –40 °C and using: diene **7.58** (500 mg, 1.24 mmol). Purification by column chromatography on silica gel (20% EtOAc/hexane → 40%) gave THF-diol **7.59** (293 mg, 0.64 mmol, 52%, 91% ee) as a waxy white solid: mp 45-47 °C; $[\alpha]^{25}{}_D$ –92.6 ($CHCl_3$, c 0.85); IR ν_{max} (neat) 3384 (br), 2922 (s), 1695 (s), 1465 (s), 1275 (s), 1245 (s), 1090 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.39 (1H, dd, J = 1.5, 8.5 Hz, C**H**), 8.04 (1H, d, J = 8.3 Hz, C**H**), 7.90 (1H, dd, J =

1.8, 7.8 Hz, CH), 7.73 (1H, dd, J = 1.0, 7.1 Hz, CH), 7.63-7.49 (3H, m, CH), 5.10 (1H, d, J = 1.8 Hz, CHOHC=O), 4.23 (1H, ddd, J = 2.0, 6.3, 8.0 Hz, CHCHOHC=O), 3.65 (1H, dt, J = 5.0, 6.8 Hz, CHCHOH), 3.38 (1H, dt, J = 7.7, 5.0 Hz, CHOH), 2.32-2.20 (1H, m, CHH), 2.02-1.76 (3H, m, CH_2), 1.51-1.09 (22H, m, CH_2), 0.90 (3H, t, J = 7.0 Hz, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 203.5 (C), 134.2 (C), 133.5 (C), 133.2 (CH), 130.4 (C), 128.5 (CH), 128.2 (CH), 127.0 (CH), 126.9 (CH), 125.7 (CH), 124.3 (CH), 83.2 (CH), 80.0 (CH), 77.4 (CH), 74.2 (CH), 34.4 (CH_2), 32.1 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 28.2 (CH_2), 28.0 (CH_2), 25.8 (CH_2), 22.8 (CH_2), 14.2 (CH_3); LRMS (ES^+) *m/z* 931 (50%, $[2M+Na]^+$), 477 (100%, $[M+Na]^+$); Elemental calcd. for $C_{29}H_{42}O_4$: C, 76.61; H, 9.31. Found: C, 76.73; H, 9.38; 91% ee (Chiralcel OB-H, 2.5% *i*-PrOH/Hex, 17.0, 22.5 min).

(*rac*)-(2*S*)-2-Hydroxy-2-[(2*R*,5*S*)-5-[(1*S*)-1-hydroxytridecyl]tetrahydrofuran-2-yl]-1-(1-naphthyl)ethanone ((*rac*)-**7.59**)

The title compound was prepared according to the method outlined for (*rac*)-**7.35**, except using: diene **7.58** (50 mg, 0.12 mmol). Purification by column chromatography on silica gel (20% EtOAc/hexane → 40%) gave THF-diol (*rac*)-**7.59** (27 mg, 0.06 mmol, 48%) as a white solid: mp 45-47 °C; characterisation data as above.

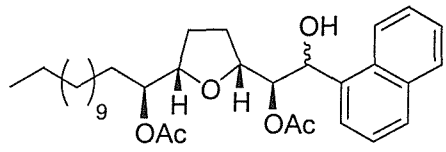
(1*S*)-1-[(2*R*,5*S*)-5-[(1*S*)-1-Acetyloxy-tridecyl]tetrahydrofuran-2-yl]-2-(1-naphthyl)-2-oxoethyl acetate (**7.60**)



The title compound was prepared according to the method outlined for **7.46**, except using: naphthyl-THF-diol **7.59** (240 mg, 0.53 mmol). Purification by column chromatography on silica gel (15% EtOAc/hexane → 20%) gave THF-acetate **7.60** (264 mg, 0.01 mmol, 93%) as a colourless oil: $[\alpha]^{24}{}_D$ –20.2 ($CHCl_3$, *c* 1.39)IR ν_{max} (neat) 2923 (s), 2853 (s), 1738 (s), 1722 (s), 1464 (m), 1371 (s), 1235 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.37 (1H, dd, J = 1.0, 8.3 Hz, CH), 8.06 (1H, dd, J = 1.2, 7.3 Hz, CH), 7.99 (1H, d, J = 8.3 Hz, CH), 7.86 (1H, dd, J = 1.5, 8.0 Hz, CH), 7.60-7.48 (3H, m, CH), 5.80 (1H, d, J = 4.5 Hz, CHOAcC=O), 4.89 (1H, dt, J = 5.3, 7.8 Hz, CHOAc), 4.41 (1H, dt, J = 4.6, 7.3 Hz, CHCHOAcC=O), 3.94 (1H, dt, J = 5.3, 7.0 Hz, CHCHOAc), 2.14 (3H, s, CH_3C=O), 2.04 (3H, s, CH_3C=O), 1.94-

1.50 (6H, m, 2 x CH_2 THF, CH_2), 1.34-1.21 (20H, m, CH_2), 0.89 (3H, t, J = 7.0 Hz, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 198.7 (C), 170.8 (2 x C), 134.5 (C), 134.0(C), 132.7 (CH), 130.5 (C), 128.4 (CH), 128.0 (2 x CH), 126.6 (CH), 125.6 (CH), 124.3 (CH), 80.4 (CH), 79.9 (CH), 78.0 (CH), 75.2 (CH), 32.0 (CH_2), 31.1 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 27.8 (CH_2), 27.7 (CH_2), 25.5 (CH_2), 22.8 (CH_2), 21.2 (CH_3), 20.8 (CH_3), 14.2 (CH_3); LRMS (ES^+) *m/z* 1099 (100%, $[2M+Na]^+$), 561 (50%, $[M+Na]^+$), 556 (70%, $[M+NH_4]^+$); Elemental calcd. for $C_{33}H_{46}O_6$: C, 73.57; H, 8.61. Found: C, 73.42; H, 8.81.

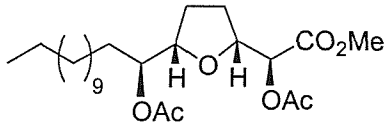
(1*S*)-1-[(2*S*,5*R*)-5-[(1*S*)-1,2-Dihydroxy-2-(1-naphthyl)ethyl]tetrahydrofuran-2-yl]tridecyl acetate (**7.61**)



At –10 °C to a solution of ketone **7.59** (50 mg, 0.09 mmol) in MeOH (1.5 mL) was added $NaBH_4$ (4 mg, 0.11 mmol) in one batch. After 25 min the reaction was quenched by addition of 2 M HCl (1 mL), H_2O (5 mL) and CH_2Cl_2 (5 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 3 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated *in vacuo* to give a colourless oil. Purification by column chromatography on silica gel (20% EtOAc/hexane → 30%) gave an inseparable mixture of diastereoisomers (6:1) of secondary alcohol **7.60** (49 mg, 0.09 mmol, 98%) as an oil: IR ν_{max} (neat) 3465 (br), 2924 (s), 2854 (s), 1738 (s), 1370 (s), 1231 (s), 1025 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.38 (1H, d, J = 8.5 Hz, C**H**, major), 8.12 (1H, d, J = 8.5 Hz, C**H** minor), 7.88-7.75 (5H, m, 3 x C**H** major, 2 x C**H** minor), 7.72 (1H, d, J = 7.0 Hz, C**H** minor), 7.62-7.46 (6H, m, 3 x C**H** major, 3 x C**H** minor), 5.90-5.84 (1H, br s , C**H**OH major), 5.83 (1H, d, J = 4.3 Hz, C**H**OH minor), 5.34 (1H, dd, J = 2.8, 4.3 Hz, C**H**OAcCHOH minor), 5.20 (1H, dd, J = 2.0, 4.3 Hz, C**H**OAcCHOH major), 5.08-5.01 (2H, m, C**H**OCHOAcCH_2 major/minor), 4.55 (1H, d, J = 7.0 Hz, O**H** major), 4.21 (1H, ddd, J = 2.8, 5.8, 7.8 Hz, C**H**OCHOAcCHOH minor), 4.09 (1H, ddd, J = 2.0, 5.5, 7.8 Hz, C**H**OCHOAcCHOH major), 4.03-3.93 (2H, m, C**H**OAcCH_2 major/minor), 3.65 (1H, br, O**H** minor), 2.19 (3H, s, CH_3C=O minor), 2.18 (3H, s, CH_3C=O major), 2.13 (3H, s, CH_3C=O minor), 2.18 (3H, s, CH_3C=O major), 1.96-1.57 (12H, m, 2 x CH_2 THF major/minor, CH_2CHOAc major/minor), 1.42-1.21 (40H, m, 10 x CH_2 major/minor), 0.90 (3H x 2, t, J = 7.0 Hz, CH_3CH_2 major/minor); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.0 (C major), 170.9 (C

major), 170.8 (C minor), 170.7 (C minor), 136.8 (C major), 136.2 (C minor), 133.9 (C minor), 133.6 (C major), 130.6 (C minor), 130.5 (C major), 129.1 (CH, minor), 128.8 (CH major), 128.6 (CH, minor), 128.2 (CH major), 126.5 (CH major), 126.2 (CH, minor), 125.7 (CH major), 125.6 (CH major), 125.6 (CH, minor), 125.3 (CH, minor), 124.9 (CH, minor), 124.1 (CH major), 123.3 (CH major), 123.0 (CH, minor), 81.3 (CH major), 80.8 (CH, minor), 79.6 (CH, minor), 77.6 (CH major), 75.9 (CH, minor), 75.4 (CH major), 75.2 (CH, minor), 75.0 (CH major), 71.6 (CH major), 71.3 (CH, minor), 32.0 (CH_2), 31.3 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 28.2 (CH_2, minor), 28.0 (CH_2 major), 27.8 (CH_2, minor), 27.7 (CH_2 major), 25.4 (CH_2), 22.8 (CH_2), 21.3 (CH_3, minor), 21.2 (CH_3 major), 21.1 (CH_3 major), 20.9 (CH_3, minor), 14.2 (CH_3); LRMS (ES^+) *m/z* 1103 (100%, $[2M+Na]^+$), 563 (90%, $[M+Na]^+$), 558 (95%, $[M+NH_4]^+$); Elemental calcd. for $C_{33}H_{48}O_6$: C, 73.30; H, 8.95. Found: C, 73.26; H, 9.10.

Methyl (2*S*)-(acetyloxy)[(2*R*,5*S*)-5-[(1*S*)-1-(acetyloxy)tridecyl]tetrahydrofuran-2-yl]acetate (**7.63**)

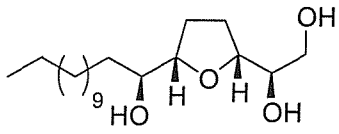


At rt to a vigorously stirred biphasic solution of secondary alcohol **7.61** (45 mg, 0.08 mmol), H_5IO_6 (285 mg, 1.25 mmol) in $CCl_4/CH_3CN/H_2O$ (2:2:3, 2.5 mL) was added in one portion $RuCl_3 \cdot H_2O$ (3.4 mg, 0.017 mmol) (After 20 min stirring organic phase was bright orange). After 3 h Et_2O (5 mL) and brine (2 mL) were added and the solution stirred for a further 5 min whereupon the organic phase was separated and the aqueous phase extracted with Et_2O (2 x 5 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated *in vacuo* to give a crude material which was passed through a plug of silica (10% $MeOH/CH_2Cl_2$) yielding a colourless oil (36 mg) that was shown to contain acid **7.62** by MS (ES^-).

To a solution of the crude oil (36 mg) in THF (4 mL) was added *O*-Methyl-*N*-*N'*diisopropylisourea (22 mg, 0.13 mmol). The reaction mixture was heated at reflux for 4 h. The reaction was concentrated *in vacuo* to give a yellowish oil. Purification by column chromatography on silica gel (10% EtOAc/hexane → 15%) gave THF-methyl ester **7.63** (22 mg, 0.05 mmol, 60%, 2 steps) as a colourless oil: $[\alpha]^{24}_D$ –17.6 ($CHCl_3$, *c* 0.77); IR ν_{max} (neat) 2924 (s), 2854 (s), 1741 (s), 1462 (m), 1438 (m), 1232 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.00 (1H, d, *J* = 5.5 Hz, CHOAcCO_2Me), 4.89 (1H, dt, *J* = 8.0, 5.3 Hz, CHOCHOAcCH_2),

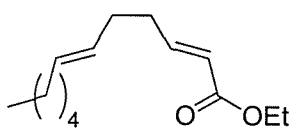
4.35 (1H, dt, J = 5.5, 6.8 Hz, CHCHOAcCO$_2$Me), 4.03 (1H, dt, J = 5.3, 6.5 Hz, CHOAcCH$_2$), 2.18 (3H, s, CH$_3$C=O), 2.08 (3H, s, CH$_3$C=O), 2.02-1.83 (3H, m, CH$_2$ THF), 1.81-1.69 (1H, m, CHH THF), 1.47-1.37 (2H, m, CH$_2$CHOAc), 1.37-1.17 (20H, m, CH$_2$), 0.89 (3H, t, J = 7.2 Hz, CH$_3$); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 170.8 (C), 170.6 (C), 168.7 (C), 80.5 (CH), 77.9 (CH), 75.3 (CH), 74.6 (CH), 52.4 (CH$_3$), 32.0 (CH$_2$), 30.9 (CH$_2$), 29.8 (CH$_2$), 29.7 (CH$_2$), 29.6 (CH$_2$), 29.5 (CH$_2$), 27.7 (CH$_2$), 27.6 (CH$_2$), 25.5 (CH$_2$), 22.8 (CH$_2$), 21.2 (CH$_3$), 20.7 (CH$_3$), 14.2 (CH$_3$); LRMS (ES$^+$) *m/z* 907 (95%, [2M+Na]$^+$), 465 (100%, [M+Na]$^+$); HRMS (ES$^+$) $C_{24}H_{42}O_7Na^+$ Calcd. 465.2823 found 465.2828.

(1*R*)-1-(2*R*,5*S*)-5-[(1*S*)-1-Hydroxytridecyl]tetrahydro-2-furanylethane-1,2-diol (**5.27**)



Under an atmosphere of N_2, at 0 °C to a solution of THF-methyl ester **7.63** (10 mg, 0.02 mmol) in Et_2O (2 mL) was added $LiALH_4$ (4 mg, 0.1 mmol) in one batch. After 30 min the reaction was quenched by addition of EtOAc (5 mL) followed by NH_4Cl (sat aq, 5 mL). The organic phase was separated and the aqueous phase extracted with EtOAc (2 x 5 mL). The combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo* to give a colourless oil. Purification by column chromatography on silica gel (3% MeOH/CH_2Cl_2→ 5%) gave triol **5.27** (4.6 mg, 0.014 mmol, 70%) as a white solid (^{1}H, ^{13}C, IR, LRMS spectroscopic data identical to homochiral **5.27** prepared from **5.4**): mp 47-48 °C; $[\alpha]^{24}_D$ –10.3 (MeOH, *c* 0.17); Elemental calcd. for $C_{19}H_{38}O_4$: C, 69.05; H, 11.59. Found: C, 68.84; H, 11.46; > 90% ee.

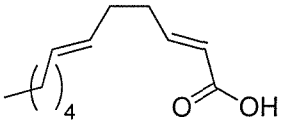
(2*E*,6*E*)-Dodeca-2,6-dienoic acid ethyl ester (**7.66**)



Under an atmosphere of N_2, at 0 °C a solution of triethyl phosphonoacetate (7.0 mL, 35.0 mmol) in THF (80 mL) had added in several batches NaH (1.40 g, 35.0 mmol, 60% in mineral oil). The mixture was allowed to warm to rt and stir for 10 min before being cooled

back down to –10 °C. 4-decanal (**7.65**) (5.00 g, 32.4 mmol) was added dropwise over 5 min causing a gelatinous solid to form. The reaction mixture was warmed to rt and CH_2Cl_2 (100 mL) was added. After 1 h the solution was quenched by addition of NH_4Cl (sat aq, 50 mL) and H_2O (20 mL). the organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification by vacuum distillation (106 °C, 0.5 mbar) gave the title diene ester **7.66** (7.16 g, 32.0 mmol, 99%) as a colourless oil: IR ν_{max} (neat) 2926 (s), 1721 (s), 1655 (m), 1265 (s), 1180 (s), 1158 (s), 1042 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (1H, td, *J* = 6.8, 15.6 Hz, C**H**=CHCO$_2$Et), 5.82 (1H, td, *J* = 1.5, 15.6 Hz, C**H**CO$_2$Et), 5.45 (1H, td *J* = 6.8, 15.3 Hz, C**H**=CH, 5.37 (1H, td, *J* = 6.8, 15.8 Hz, C**H**=CH), 4.18 (2H, q, *J* = 7.0 Hz, C**H**$_2$O), 2.26 (2H, q, *J* = 6.8 Hz, C**H**$_2$CH=CH), 2.15 (2H, q, *J* = 6.8 Hz, C**H**$_2$CH=CH), 1.96 (2H, q, *J* = 6.8 Hz, C**H**$_2$CH=CH), 1.39-1.20 (6H, m), 0.89 (3H, t, *J* = 7.3 Hz, C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8 (C), 148.8 (CH), 132.0 (CH), 128.5 (CH), 121.6 (CH), 60.2 (CH_2), 32.6 (CH_2), 32.4 (CH_2), 31.5 (CH_2), 31.1 (CH_2), 29.3 (CH_2), 22.6 (CH_2), 14.4 (CH_3), 14.2 (CH_3); LRMS (GCEI) 7.43 min, *m/z* 224 (60%, $M^{+\cdot}$), 114 (100%); HRMS (EI) $C_{14}H_{24}O_2^{+\cdot}$ Calcd. 224.1776 found 224.1778.

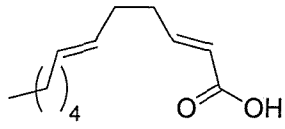
Method 1: (2*E*,6*E*)-Dodeca-2,6-dienoic acid (**7.67**)



To a solution of diene ester **7.66** (3.04 g, 13.6 mmol) in MeOH (16 mL) was added a solution of NaOH (2.94 g, 73.4 mmol) and $NaHCO_3$ (0.50 g, 6 mmol) in H_2O (56 mL). The solution was refluxed for 4 h, after cooling to 0 °C the reaction was quenched with 2M HCl (aq, 50 mL). CH_2Cl_2 (100 mL) was added and the organic phase separated, the aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a slightly yellow oil. Purification by vacuum distillation (160 °C, 0.5 mbar) gave diene acid **7.67** (2.37 g, 13.2 mmol, 97%) as a colourless sticky gum: IR ν_{max} (neat) 3100 (br), 2924 (s), 1693 (s), 1650 (s), 1420 (s), 1286 (s) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 11.25 (1H, br, COO**H**), 7.10 (1H, dt, *J* = 15.6, 6.8 Hz, C**H**=CHC=O), 5.83 (1H, dt, *J* = 15.6, 1.3 Hz, C**H**C=O), 5.47 (1H, dt, *J* = 15.5, 6.1 Hz, CH_2C**H**=C**H**CH_2), 5.37 (1H, dt, *J* = 15.5, 6.1 Hz, CH_2C**H**=C**H**CH_2), 2.30 (2H, q, *J* = 6.8 Hz, C**H**$_2$CH=), 2.17 (2H, q, *J* = 6.8 Hz, C**H**$_2$CH=), 1.98 (2H, q, *J* = 6.8 Hz, C**H**$_2$CH=), 1.44-1.19

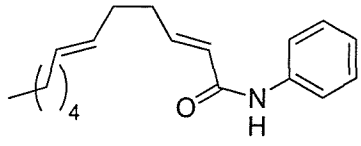
(6H, m, CH_2), 0.89 (3H, t, J = 7.0 Hz, CH_3CH_2); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.3 (C), 151.9 (CH), 132.2 (CH), 128.2 (CH), 121.0 (CH), 32.6 (CH_2), 32.5 (CH_2), 31.5 (CH_2), 31.0 (CH_2), 29.3 (CH_2), 22.7 (CH_2), 14.2 (CH_3); LRMS (ES^-) *m/z* 195 (100%, $[M-H]^-$); Elemental calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.35; H, 10.33.

Method 2: (2*E*,6*E*)-Dodeca-2,6-dienoic acid (**7.67**)



To a neat solution 4-decenal (**7.65**) (5.00 g, 32.4 mmol) and malonic acid (4.04 g, 38.9 mmol) was added pyridine (2.2 mL, 26.9 mmol). After 12 h at rt the solution was heated to 100 °C for 6 h, whereupon 2M HCl (15 mL) was added. The organic phase was separated and the aqueous phase extracted with EtOAc (3 x 25 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give an orange oil. Purification by column chromatography on silica gel (1:9:0.2 EtOAc/hexane/AcOH → 3:17:0.2) followed by vacuum distillation (0.5 mbar, 160 °C) gave the title acid **7.67** (4.90 g, 25 mmol, 77%) as a colourless sticky gum.

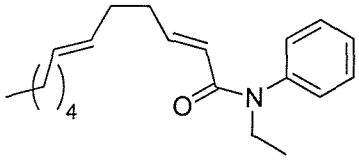
(2*E*,6*E*)-Dodeca-2,6-dienoic acid phenylamide (**7.73**)



At 0 °C under nitrogen, two drops of DMF were added to a stirred solution of diene acid **7.67** (300 mg, 1.4 mmol) and oxalyl chloride (0.15 mL, 1.7 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 2 h before being concentrated *in vacuo* and then solvated in CH_2Cl_2 (4 mL). To this solution was added aniline (**7.69**) (0.14 mL, 1.5 mmol) followed by NaOH (62 mg, 0.15 mmol). After 1.5 h H_2O (5 mL) was added and the organic phase separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification by column chromatography on silica gel (8% EtOAc/hexane → 12%) gave the title amide **7.73** (340 mg, 1.3 mmol, 85%) as a white solid: mp 63-65 °C; IR ν_{max} (neat) 3286 (s), 2926 (s), 1666 (s),

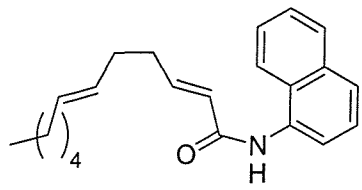
1632 (s), 1599 (s), 1529 (s), 1442 (s), 1337 (s), 1251 (s) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.66-7.50 (3H, m, C**H** x 2, N**H**), 7.32 (2H, t, *J* = 7.5 Hz, C**H**), 7.10 (1H, t, *J* = 7.5 Hz, C**H**), 6.98 (1H, dt, *J* = 15.6, 6.8 Hz, C**H**=CHC=O), 5.96 (1H, d, *J* = 15.6 Hz, C**H**C=O), 5.46 (1H, dt, *J* = 15.3, 6.2 Hz, CH_2C**H**=C**H**CH_2), 5.38 (1H, dt, *J* = 15.3, 6.2 Hz, CH_2C**H**=C**H**CH_2), 2.33-2.10 (4H, m, C**H**$_2$CH=), 1.97 (2H, q, *J* = 7.0 Hz, C**H**$_2$CH=), 1.41-1.20 (6H, m, C**H**$_2$), 0.89 (3H, t, *J* = 7.0 Hz, C**H**$_3$$CH_2$); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 164.3 (C), 146.0 (CH), 138.2 (C), 131.9 (CH), 129.1 (CH), 129.0 (CH), 128.5 (CH), 124.3 (CH), 120.0 (CH), 32.6 (CH_2), 32.4 (CH_2), 31.5 (CH_2), 31.3 (CH_2), 29.3 (CH_2), 22.6 (CH_2), 14.2 (CH_3); LRMS (ES^+) *m/z* 565 (20%, $[M+Na]^+$), 543 (100%, $[M+H]^+$), 272 (10%, $[M+H]^+$); Elemental calcd. for $C_{18}H_{25}ON$: C, 79.66; H, 9.28; N, 5.16. Found: C, 79.56; H, 9.38; N, 5.18.

(2*E*,6*E*)-Dodeca-2,6-dienoic acid ethyl-phenyl-amide (**7.74**)



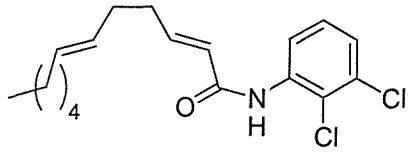
The title compound was prepared according to the method outlined for **7.73**, except using: amine **7.70** (0.19 mL, 1.5 mmol). Purification by column chromatography on silica gel (4% EtOAc/hexane → 12%) gave the title amide **7.74** (409 mg, 1.3 mmol, 98%) as a colourless oil: IR ν_{max} (neat) 2926 (s), 1662 (s), 1593 (s), 1498 (s), 1391 (s), 1255 (s), 1130 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.41 (2H, tt, *J* = 1.3, 7.5 Hz, C**H**), 7.34 (1H, tt, *J* = 1.3, 7.5 Hz, C**H**), 7.15 (2H, dd, *J* = 1.3, 7.5 Hz, C**H**), 6.90 (1H, dt, *J* = 15.1, 6.8 Hz, C**H**=CHC=O), 5.65 (1H, d, *J* = 15.1 Hz, C**H**C=O), 5.36 (1H, dt, *J* = 15.3, 6.3 Hz, CH_2C**H**=C**H**CH_2), 5.29 (1H, dt, *J* = 15.3, 6.3 Hz, CH_2C**H**=C**H**CH_2), 3.82 (2H, q, NC**H**$_2$) 2.14-2.06 (2H, m, C**H**$_2$CH=), 2.01 (2H, q, *J* = 6.3 Hz, C**H**$_2$CH=), 1.93 (2H, q, *J* = 6.3 Hz, C**H**$_2$CH=), 1.37-1.18 (6H, m, C**H**$_2$), 1.14 (3H, t, *J* = 7.0 Hz, C**H**$_3$$CH_2$N), 0.88 (3H, t, *J* = 6.8 Hz, C**H**$_3$$CH_2$ CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.7 (C), 145.9 (CH), 142.3 (C), 131.5 (CH), 129.5 (CH), 128.8 (CH), 128.6 (CH), 127.7 (CH), 122.1 (CH), 32.6 (CH_2), 32.5 (CH_2), 31.5 (CH_2), 31.3 (CH_2), 29.3 (CH_2), 22.6 (CH_2), 14.2 (CH_3), 13.2 (CH_3); LRMS (GCEI) 9.11 min, *m/z* 299 (40%, $M^{+\cdot}$), 121 (100%); Elemental calcd. for $C_{20}H_{29}ON$: C, 80.22; H, 9.76; N, 4.68. Found: C, 79.98; H, 10.08; N, 4.64.

(2*E*,6*E*)-Dodeca-2,6-dienoic acid naphthalen-1-ylamide (**7.75**)



The title compound was prepared according to the method outlined for **7.73**, except using: 1-naphthylamine (**7.72**) (215 mg, 1.5 mmol). Purification by column chromatography on silica gel (4% EtOAc/hexane → 12%) gave the title amide **7.75** (150 mg, 0.47 mmol, 35%) as a white solid: mp 120-122 °C; IR ν_{max} (neat) 3253 (s), 2924 (s), 1665 (s), 1630 (s), 1537 (s), 1503 (s), 1356 (s), 1269 (s), 1164 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2CO$) δ 9.18 (1H, br s, N**H**), 8.17-8.13 (1H, m, C**H**), 8.10-8.02 (1H, m, C**H**), 7.93 (1H, dd, *J* = 3.0, 6.5 Hz, C**H**), 7.74 (1H, d, *J* = 8.3 Hz, C**H**), 7.56-7.46 (3H, m, C**H**), 6.99 (1H, dt, *J* = 15.3, 6.8 Hz, C**H**=CHC=O), 6.44 (1H, d, *J* = 15.3 Hz, C**H**C=O), 5.57-5.44 (2H, m, CH_2**CH**=**CH**CH_2), 2.34 (2H, q, *J* = 6.8 Hz, **CH$_2$**CH=), 2.22 (2H, q *J* = 6.3 Hz, **CH$_2$**CH=), 2.02 (2H, q, *J* = 6.8 Hz, **CH$_2$**CH=), 1.44-1.24 (6H, m, **CH$_2$**), 0.89 (3H, t, *J* = 7.0 Hz, **CH$_3$**CH_2); ^{13}C-NMR (100 MHz, $(CD_3)_2CO$) δ 165.0 (C), 145.3 (CH), 135.1 (CH), 134.7 (C), 132.2 (CH), 131.6 (C), 129.8 (CH), 129.2 (CH), 126.7 (CH), 126.6 (CH), 126.4 (CH), 125.8 (CH), 125.6 (C), 122.8 (CH), 121.4 (br, (CH), 33.2 (CH_2), 32.8 (CH_2), 32.1 (CH_2), 30.2 (CH_2), 29.3 (CH_2), 23.2 (CH_2), 14.3 (CH_3); LRMS (ES^+) *m/z* 681 (100%, $[2M+K]^+$), 360 (95%, $[M+K]^+$), 322 (30%, $[M+H]^+$); Elemental calcd. for $C_{22}H_{27}ON$: C, 82.20; H, 8.47; N, 4.36. Found: C, 82.13; H, 8.59; N, 4.46.

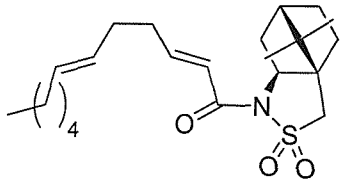
(2*E*,6*E*)-Dodeca-2,6-dienoic acid (2,3-dichloro-phenyl)-amide (**7.76**)



The title compound was prepared according to the method outlined for **7.73**, except using: 2,3-dichloro aniline (**7.71**) (243 mg, 1.5 mmol). Purification by column chromatography on silica gel (4% EtOAc/hexane → 5%) gave the title amide **7.76** (400 mg, 1.2 mmol, 84%) as a white solid: mp 77-79 °C; IR ν_{max} (neat) 3271 (s), 2925 (s), 1668 (s), 1638 (s), 1580 (s), 1524 (s), 1424 (s), 1408 (s), 1346 (s), 1278 (s), 1184 (s), 1159 (s), 1052 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.43 (1H, dd, *J* = 2.5, 6.8 Hz, C**H**), 7.72 (1H, br s, N**H**), 7.26-7.20 (2H, m,

CH), 7.03 (1H, dt, J = 15.1, 6.8 Hz, CH=CHC=O), 5.99 (1H, d, J = 15.1 Hz, CHC=O), 5.47 (1H, dt, J = 15.4, 6.3 Hz, CH_2CH=$CHCH_2$), 5.42 (1H, dt, J = 15.4, 6.3 Hz, CH_2CH=$CHCH_2$), 2.34 (2H, q, J = 6.8 Hz, CH_2CH=), 2.20 (2H, q, J = 6.3 Hz, CH_2CH=), 2.00 (2H, q, J = 6.3 Hz, CH_2CH=), 1.41-1.21 (6H, m, CH_2), 0.89 (3H, t, J = 6.8 Hz, CH_3CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.0 (C), 147.3 (CH), 136.6 (C), 132.8 (CH), 132.2 (CH), 128.3 (CH), 128.0 (CH), 125.2 (CH), 124.0 (CH), 121.3 (C), 119.6 (C), 32.6 (CH_2), 32.4 (CH_2), 31.5 (CH_2), 31.3 (CH_2), 29.3 (CH_2), 22.6 (CH_2), 14.2 (CH_3); LRMS (GCEI) 10.16 min, *m/z* 341 (2%, $M^{+\cdot}$, ^{37}Cl), 339 (5%, $M^{+\cdot}$, ^{35}Cl), 69 (100%) Elemental calcd. for $C_{18}H_{23}ONCl_2$: C, 63.53; H, 6.81; N, 4.11. Found: C, 63.69; H, 7.01; N, 4.16.

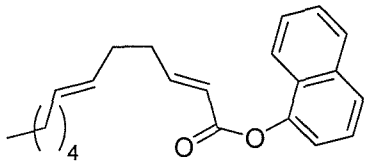
(2*S*)-*N*-((2*E*,6*E*)-2,6-Dodecadienoyl)-camphor-10,2-sultam (**7.80**)



At 0 °C under nitrogen, two drops of DMF were added to a stirred solution of diene acid **7.67** (1.135 g, 5.8 mmol) and oxalyl chloride (0.61 mL, 6.9 mmol) in CH_2Cl_2 (15 mL). The mixture was stirred for 3 h before being concentrated *in vacuo* and solvated in CH_2Cl_2 (2 mL). Meanwhile, at rt under nitrogen NaH (60% in mineral oil, 0.232 g, 5.8 mmol) was added in several batches to a solution of (2*S*)-sultam **5.19** (1.248 g, 5.8 mmol) in CH_2Cl_2 (20 mL). After 10 min the anion solution was cooled to 0 °C and had the acid chloride solution (prepared above) added dropwise. After 1 h the reaction was quenched by addition of NH4Cl (sat aq, 20 mL), H_2O (5 mL) and CH_2Cl_2 (20 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification by column chromatography on silica gel (10% Et_2O/hexane → 15%) gave dienoyl sultam **7.80** (1.99 g, 5.1 mmol, 87%) as a colourless oil: $[\alpha]^{24}_D$ +60.1 ($CHCl_3$, *c* 0.80); IR ν_{max} (neat) 2925 (s), 1681 (s), 1639 (s), 1331 (s), 1266 (s), 1217 (s), 1134 (s); 1H-NMR (400 MHz, $CDCl_3$) δ 7.09 (1H, dt, J = 15.3, 6.8 Hz, CH=CHC=O), 6.56 (1H, dt, J = 15.3, 1.5 Hz, =CHCON), 5.46 (1H, dt, J = 15.3, 6.3 Hz, CH_2CH=$CHCH_2$), 5.38 (1H, dt, J = 15.3, 6.3 Hz, CH_2CH=$CHCH_2$), 3.93 (1H, dd, J = 5.0, 7.5 Hz, CHN), 3.51 (1H, d, J = 13.8 Hz, $CHHSO_2$), 3.44 (1H, d, J = 13.8 Hz, $CHHSO_2$), 2.31 (2H, q, J = 6.8 Hz, CH_2CH=CHCON), 2.21-2.05 (4H, m), 2.02-1.84 (5H, m), 1.47-1.22 (8H, m), 1.18 (3H, s, CH_3C), 0.98 (3H, s, CH_3C), 0.89 (3H, t, J = 6.8 Hz, CH_3CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.3 (C), 150.4 (CH),

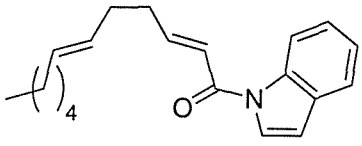
132.0 (CH), 128.3 (CH), 121.2 (CH), 65.3 (CH), 53.3 (CH_2), 48.6 (C), 47.9 (C), 44.9 (CH), 38.7 (CH_2), 33.0 (CH_2), 32.7 (CH_2), 32.6 (CH_2), 31.5 (CH_2), 31.1 (CH_2), 29.3 (CH_2), 26.6 (CH_2), 22.6 (CH_2), 21.0 (CH_3), 20.0 (CH_3), 14.2 (CH_3); LRMS (GCEI) 11.50 min, *m/z* 393 (40%, $M^{+\cdot}$), 283 (100%); HRMS (EI) $C_{22}H_{35}O_3NS^{+\cdot}$ Calcd. 393.2338, found 393.2348.

(2*E*,6*E*)-Dodeca-2,6-dienoic acid naphthalen-1-yl ester (**7.81**)



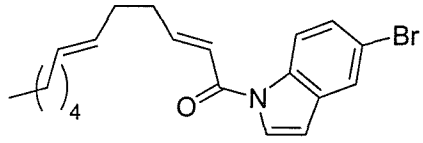
Under an atmosphere of N_2, to a solution of acid **7.67** (102 mg, 0.52 mmol) in CH_2Cl_2 (2 mL) was added 1-naphthol (**7.77**) (81 mg, 0.56 mmol) and DCC (117 mg, 0.56 mmol). After 16 h the reaction mixture was filtered and the filtrate concentrated *in vacuo* to give a brown oil. Purification by column chromatography on silica gel (3% EtOAc/hexane/AcOH → 5%) gave naphthyl-ester **7.81** (126 mg, 0.39 mmol, 76%) as a colourless oil: IR ν_{max} (neat) 2924 (s), 1742 (s), 1650 (s), 1390 (s), 1221 (s), 1138 (s), 1079 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.89-7.85 (2H, m, C**H**), 7.74 (1H, d, *J* = 8.3 Hz, C**H**), 7.53-7.43 (3H, m, C**H**), 7.34-7.22 (2H, m, C**H**, C**H**=CHC=O), 6.19 (1H, dt, *J* = 15.8, 1.5 Hz, C**H**C=O), 5.52 (1H, dt, *J* = 15.3, 6.6 Hz, CH_2C**H**=CHCH_2), 5.45 (1H, dt, *J* = 15.3, 6.6 Hz, CH_2C**H**=CHCH_2), 2.41 (2H, q, *J* = 6.8 Hz, C$\mathbf{H_2}$CH=), 2.26 (2H, q, *J* = 6.6 Hz, C$\mathbf{H_2}$CH=), 2.02 (2H, q, *J* = 6.6 Hz, C$\mathbf{H_2}$CH=), 1.43-1.22 (6H, m, C$\mathbf{H_2}$), 0.89 (3H, t, *J* = 7.0 Hz, C$\mathbf{H_3}$$CH_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.1 (C), 151.8 (CH), 146.8 (C), 134.8 (C), 132.3 (CH), 128.3 (CH), 128.1 (CH), 127.1 (C), 126.5 (CH), 126.4 (CH), 126.0 (CH), 125.5 (CH), 121.5 (CH), 120.7 (CH), 118.2 (CH), 32.7 (CH_2), 32.6 (CH_2), 31.5 (CH_2), 31.1 (CH_2), 29.3 (CH_2), 22.7 (CH_2), 14.2 (CH_3); LRMS (GCEI) 10.20 min, *m/z* 322 (30%, $M^{+\cdot}$), 144 (100%); HRMS (EI) $C_{22}H_{26}O_2^{+\cdot}$ Calcd. 322.1933 found 322.1938.

(2*E*,6*E*)-1-Indol-1-yl-dodeca-2,6-dien-1-one (**7.82**)



At 0 °C under nitrogen, two drops of DMF were added to a stirred solution of diene acid **7.67** (0.568 g, 2.9 mmol) and oxalyl chloride (0.31 mL, 3.4 mmol) in CH_2Cl_2 (8 mL). The mixture was stirred for 3 h before being concentrated *in vacuo* and solvated in CH_2Cl_2 (5 mL). To this solution of acid chloride was added indole (0.37 g, 3.2 mmol) followed by NaOH (0.13 g, 3.2 mmol). After 1.5 h H_2O (5 mL) was added and the organic phase separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow mixture. Purification by column chromatography on silica gel (3% EtOAc/hexane → 4%) gave amide **7.82** (641mg, 2.2 mmol, 75%) as a colourless oil: IR ν_{max} (neat) 2924 (s), 1691 (s), 1642 (s), 1454 (s), 1349 (s), 1205 (s), 1062 (s) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.50 (1H, d, J = 8.3 Hz, C**H**), 7.59 (1H, d, J = 7.4 Hz, C**H**), 7.54 (1H, d, J = 3.9 Hz, C**H**), 7.40-7.20 (2H, m, C**H**), 7.13 (1H, dt, J = 15.6, 6.8 Hz, C**H**=CHC=O), 6.69 (1H, d, J = 3.9 Hz, C**H**), 5.89 (1H, dt, J = 15.6, 1.5 Hz, C**H**C=O), 5.47 (1H, dt, J = 15.3, 6.3 Hz, CH_2C**H**=CHCH_2), 5.37 (1H, dt, J = 15.3, 6.3 Hz, CH_2C**H**=CHCH_2), 2.33 (2H, q, J = 6.8 Hz, **CH_2**CH=), 2.18 (2H, q, J = 6.3 Hz, **CH_2**CH=), 2.12-1.93 (2H, m, **CH_2**CH=), 1.41-1.20 (6H, m, **CH_2**), 0.89 (3H, t, J = 7.0 Hz, **CH_3**CH_2); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 164.1 (C), 151.1 (CH), 135.9 (C), 132.3 (CH), 130.4 (C), 128.3 (CH), 125.0 (CH), 124.8 (CH), 123.8 (CH), 121.2 (CH), 120.9 (CH), 116.9 (CH), 109.0 (CH), 32.7 (CH_2), 32.6 (CH_2), 31.5 (CH_2), 30.8 (CH_2), 29.3 (CH_2), 22.6 (CH_2), 14.2 (CH_3); LRMS (GCEI) 9.94 min, *m/z* 295 (50%, $M^{+\cdot}$), 117 (100%); HRMS (EI) $C_{20}H_{25}ON^{+\cdot}$ Calcd. 295.1936 found 295.1935.

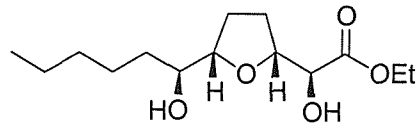
(2*E*,6*E*)-1-(5-Bromo-indol-1-yl)-dodeca-2,6-dien-1-one (**7.83**)



At 0 °C under nitrogen, two drops of DMF were added to a stirred solution of diene acid **7.67** (300 mg, 1.4 mmol) and oxalyl chloride (0.15 mL, 1.7 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 2 h before being concentrated *in vacuo* and then solvated in CH_2Cl_2 (4 mL). To this solution was added 5-bromo-indole (**7.79**) (302 mg, 1.5 mmol) followed by NaOH (62 mg, 0.15 mmol). After 1.5 h H_2O (5 mL) was added and the organic phase separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification by column chromatography on silica gel (3% EtOAc/hexane → 4%) gave the title amide **7.83**

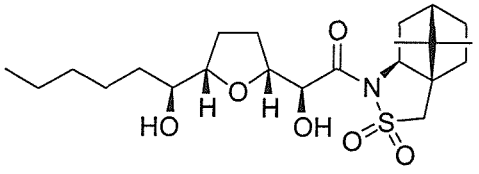
(393 mg, 1.1 mmol, 70%) as a colourless oil: IR ν_{max} (neat) 2924 (s), 1693 (s), 1639 (s), 1446 (s), 1375 (s), 1301 (s), 1197 (s), 1057 (s) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.38 (1H, d, *J* = 8.8 Hz, C**H**), 7.71 (1H, d, *J* = 2.0 Hz, C**H**), 7.53 (1H, d, *J* = 3.9 Hz, C**H**), 7.45 (1H, dd, *J* = 2.0, 8.8 Hz, C**H**), 7.13 (1H, dt, *J* = 15.6, 6.8 Hz, C**H**=CHC=O), 6.59 (1H, d, *J* = 3.9 Hz, C**H**), 5.88 (1H, dt, *J* = 15.6, 1.5 Hz, C**H**C=O), 5.52-5.33 (2H, m,CH_2C**H**=C**H**CH_2), 2.32 (2H, q, *J* = 6.8 Hz, C**H**$_2$CH=), 2.18 (2H, q, *J* = 7.0 Hz, C**H**$_2$CH=), 2.10-1.93 (2H, m, C**H**$_2$CH=), 1.45-1.19 (6H, m, C**H**$_2$), 0.89 (3H, t, *J* = 7.0 Hz, C**H**$_3$$CH_2$); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 164.2 (C), 151.8 (CH), 134.7 (C), 132.4 (CH), 132.4 (C), 128.2 (CH), 127.9 (CH), 125.9 (CH), 123.6 (CH), 120.7 (CH), 118.3 (CH), 117.1 (C), 108.1 (CH), 32.7 (CH_2), 32.6 (CH_2), 31.5 (CH_2), 30.8 (CH_2), 29.3 (CH_2), 22.6 (CH_2), 14.2 (CH_3); LRMS (GCEI) 11.05 min, *m/z* 375 (10%, $M^{+\cdot}$, ^{81}Br), 373 (10%, $M^{+\cdot}$, ^{79}Br), 117 (100%); HRMS (EI) $C_{20}H_{25}ON^{79}Br^{+\cdot}$ Calcd. 373.1041 found 373.1046.

Ethyl (2*S*)-2-hydroxy-[(2*R*,5*S*)-5-((1*S*)-1-hydroxy-hexyl)-tetrahydro-furan-2-yl]-ethanoate (**7.84**)



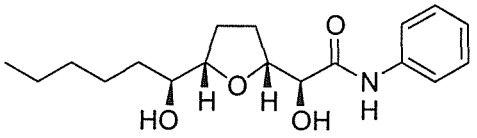
The title compound was prepared according to the method outlined for (*rac*)-**7.35**, except using: diene **7.66** (1.00 g, 4.5 mmol). Purification by column chromatography on silica gel (20% EtOAc/hexane → 30%) gave THF-diol **7.84** (0.68 g, 2.5 mmol, 56%) as colourless oil; IR ν_{max} (neat) 3447 (br), 2931 (s), 1737 (s), 1446 (s), 1369 (s), 1201 (s), 1131 (s), 1078 (s), 1025 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.37 (1H, ddd, *J* = 2.0, 5.8, 7.5 Hz, OC**H**CHOHC=O), 4.33-4.22 (2H, m, OC**H**$_2$$CH_3$), 4.10 (1H, d, *J* = 2.0, Hz, C**H**OHC=O), 3.84 (1H, dt, *J* = 4.5, 6.8 Hz, OC**H**CHOHCH_2), 3.56 (1H, br, O**H**), 3.43 (1H, dt, *J* = 4.5, 7.5 Hz, C**H**OHCH_2), 2.66 (1H, br, O**H**), 2.20-2.09 (1H, m, C**H**H), 2.07-1.88 (3H, m, C**H**H x 3), 1.53-1.22 (8H, m, C**H**$_2$ x 4), 1.31 (3H, t, *J* = 7.0 Hz, C**H**$_3$$CH_2$O), 0.89 (3H, t, *J* = 6.8 Hz, C**H**$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.4 (C), 83.1 (CH), 80.0 (CH), 74.1 (CH), 73.2 (CH), 34.5 (CH_2), 32.0 (CH_2), 28.4 (CH_2), 27.8 (CH_2), 25.4 (CH_2), 22.7 (CH_2), 14.3 (CH_3), 14.1 (CH_3); LRMS (ES^+) *m/z* 571 (60%, $[2M+Na]^+$), 293 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{14}H_{26}O_5Na^+$ Calcd. 297.1672 found 297.1669.

(2*S*)-*N*-[(2*S*)-2-Hydroxy-2-((2*R*,5*S*)-5-((1*S*)-1-hydroxyhexyl)tetrahydro-2-furanylethanoyl)]-camphor-10,2-sultam (**7.85a**)



The title compound was prepared according to the method outlined for (*rac*)-**7.35**, except using: diene **7.80** (540 mg, 1.37 mmol). Purification by column chromatography on silica gel (20% EtOAc/hexane → 45%) gave a 7:1 ratio of diastereoisomeric THF-diols: **7.85a** (369 mg, 0.82 mmol, 61%) as colourless oil and **7.85b** (52 mg, 0.12 mmol, 9%) as a colourless oil. Data for **7.85a**; $[\alpha]^{25}_{D}$ +41.5 (MeOH, *c* 1.00); IR ν_{max} (neat) 3437 (br), 2934 (s), 1690 (s), 1329 (s), 1275 (s), 1218 (s), 1134 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.61-4.54 (2H, m, C**H**OHC=O, OC**H**CHOHC=O), 3.97 (1H, dd, *J* = 5.0, 8.0 Hz, NC**H**), 3.87 (1H, dt, *J* = 4.5, 7.3 Hz, OC**H**CHOHCH$_2$), 3.52 (1H, d, *J* = 13.6 Hz, C**H**HSO$_2$), 3.49-3.43 (1H, m, C**H**OHCH$_2$), 3.45 (1H, d, *J* = 13.6 Hz, C**H**HSO$_2$), 2.28-2.21 (1H, m, C**H**HCHN), 2.15-2.02 (3H, m, C**H$_2$** THF, C**H**HCHN), 1.99-1.83 (4H, m, C**H$_2$** THF, 2H sult), 1.57-1.24 (10H, m, C**H$_2$** x 4, 2H sult), 1.16 (3H, s, C**H$_3$**C), 0.98 (3H, s, C**H$_3$**C), 0.89 (3H, t, *J* = 6.5 Hz, C**H$_3$**); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.8 (C), 83.2 (CH), 78.7 (CH), 74.1 (CH), 73.7 (CH), 65.9 (CH), 53.2 (CH_2), 49.2 (C), 48.0 (C), 44.6 (CH), 38.4 (CH_2), 34.7 (CH_2), 33.0 (CH_2), 32.0 (CH_2), 28.5 (CH_2), 28.3 (CH_2), 26.5 (CH_2), 25.6 (CH_2) 22.8 (CH_2), 21.0 (CH_3), 20.0 (CH_3), 14.2 (CH_3); LRMS (ES^+) *m/z* 904 (70%, $[2M+NH_4]^+$), 466 (50%, $[M+Na]^+$), 444 (100%, $[M+H]^+$); HRMS (ES^+) $C_{22}H_{37}O_6NSNa^+$ Calcd. 466.2234 found 466.2235.

(2*S*)-2-Hydroxy-2-[(2*R*,5*S*)-5-((1*S*)-1-hydroxy-hexyl)-tetrahydro-furan-2-yl]-*N*-phenyl-acetamide (**7.86**)



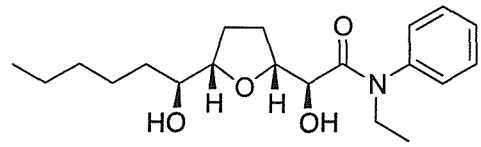
The title compound was prepared according to the method outlined for **7.16**, except using: diene **7.73** (50 mg, 0.18 mmol). Purification by column chromatography on silica gel (20% EtOAc/hexane → 50%) gave THF-diol **7.86** (21 mg, 0.06 mmol, 36%, 37% ee) as a white solid: mp 90-93 °C; $[\alpha]^{25}_{D}$ +26.3 ($CHCl_3$, *c* 0.77); IR ν_{max} (neat) 3299 (br), 2930 (s), 1677

(s), 1599 (s), 1531 (s), 1442 (s), 1275 (s), 1260 (s), 1062 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.73 (1H, s, NH), 7.57 (2H, d, *J* = 7.6 Hz, CH), 7.31 (2H, t, *J* = 7.6 Hz, CH), 7.11 (1H, t, *J* = 7.6 Hz, CH), 4.96 (1H, br, OH), 4.51 (1H, dt, *J* = 2.8, 7.0 Hz, CHOCHOHC=O), 4.11 (1H, d, *J* = 2.8 Hz, CHOHC=O), 3.92 (1H, dt, *J* = 3.5, 6.8 Hz, CHOCHOHCH$_2$), 3.51 (1H, dt, *J* = 8.0, 3.5 Hz, CHOHCH$_2$), 3.01 (1H, br, OH), 2.17-1.81 (4H, m, CH$_2$), 1.59-1.16 (8H, m, CH$_2$), 0.87 (3H, t, *J* = 6.8 Hz, CH$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.0 (C), 137.4 (C), 129.1 (CH), 124.6 (CH), 120.0 (CH), 82.3 (CH), 79.9 (CH), 74.6 (CH), 74.4 (CH), 34.6 (CH_2), 31.9 (CH_2), 28.6 (CH_2), 27.9 (CH_2), 25.5 (CH_2), 22.7 (CH_2), 14.1 (CH_3); LRMS (ES^+) *m/z* 660 (100%, $[2M+NH_4]^+$), 643 (80%, $[2M+H]^+$); Elemental calcd. for $C_{18}H_{27}O_4N$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.17; H, 8.55; N, 4.24; 37% ee (Chiralcel OD-H, 10% *i*-PrOH/Hex, 10.1, 15.5 min).

(*rac*)-(2*S*)-2-Hydroxy-2-[(2*R*,5*S*)-5-((1*S*)-1-hydroxy-hexyl)-tetrahydro-furan-2-yl]-*N*-phenyl-acetamide ((*rac*)-**7.86**)

The title compound was prepared according to the method outlined for (*rac*)-**7.35**, except using: diene **7.73** (100 mg, 0.37 mmol). Purification by column chromatography on silica gel (20% EtOAc/hexane → 50%) gave THF-diol (*rac*)-**7.86** (50 mg, 0.16 mmol, 42%) as a white solid: mp 90-93 °C; characterisation data as above.

N-Ethyl-(2*S*)-2-hydroxy-2-[(2*R*,5*S*)-5-((1*S*)-1-hydroxy-hexyl)-tetrahydro-furan-2-yl]-*N*-phenyl-acetamide (**7.87**)



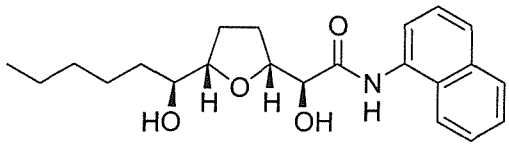
The title compound was prepared according to the method outlined for **7.16**, except using: diene **7.74** (50 mg, 0.17 mmol). Purification by column chromatography on silica gel (20% EtOAc/hexane → 35%) gave THF-diol **7.87** (30 mg, 0.09 mmol, 51%, 50% ee) as a white solid: mp 90-93 °C; $[\alpha]^{27}_D$ –8.5 (MeOH, *c* 1.89); IR ν_{max} (neat) 3429 (br), 2931 (s), 1644 (s), 1594 (s), 1498 (s), 1143 (s), 1380 (s), 1297 (s), 1123 (s), 1072 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.47-7.34 (3H, m, CH), 7.23 (2H, d, *J* = 7.3 Hz, CH), 4.06 (1H, br s, CHOHC=O), 3.99 (1H, dq, *J* = 14.2, 7.3 Hz, NCHHCH$_3$), 3.84-3.70 (2H, m, CHO x 2), 3.59 (1H, dq, *J* = 14.2, 7.3 Hz, NCHHCH$_3$), 3.37 (1H, dt, *J* = 8.3, 4.3 Hz, CHOH), 1.95-1.72 (3H, m, CH$_2$),

1.69-1.58 (1H, m, CHH), 1.56-1.20 (8H, m, CH_2), 1.15 (3H, t, J = 7.3 Hz, CH_3CH_2N), 0.88 (3H, t, J = 6.8 Hz, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.0 (C), 140.6 (C), 130.0 (CH), 128.7 (CH), 128.6 (CH), 83.3 (CH), 78.6 (CH), 73.7 (CH), 71.3 (CH), 34.7 (CH_2), 32.0 (CH_2), 28.3 (CH_2), 28.0 (CH_2), 25.6 (CH_2), 22.7 (CH_2), 14.1 (CH_3), 12.8 (CH_3); LRMS (ES^+) *m/z* 721 (80%, $[2M+Na]^+$), 372 (100%, $[2M+Na]^+$); Elemental calcd. for $C_{20}H_{31}O_4N$: C, 68.74; H, 8.94; N, 4.01. Found: C, 68.59; H, 9.02; N, 3.81; 50% ee (Chiralcel OB-H, 1.5% *i*-PrOH/Hex, 25.5, 28.6 min).

(*rac*)-*N*-Ethyl-(2*S*)-2-hydroxy-2-[(2*R*,5*S*)-5-((1*S*)-1-hydroxy-hexyl)-tetrahydro-furan-2-yl]-*N*-phenyl-acetamide ((*rac*)-**7.87**)

The title compound was prepared according to the method outlined for (*rac*)-**7.35**, except using: diene **7.74** (100 mg, 0.33 mmol). Purification by column chromatography on silica gel (20% EtOAc/hexane → 35%) gave THF-diol (*rac*)-**7.87** (59 mg, 0.17 mmol, 52%) as a colourless oil: characterisation data as above.

(2*S*)-2-Hydroxy-2-[(2*R*,5*S*)-5-((1*S*)-1-hydroxy-hexyl)-tetrahydro-furan-2-yl]-*N*-naphthalen-1-yl-acetamide (**7.88**)



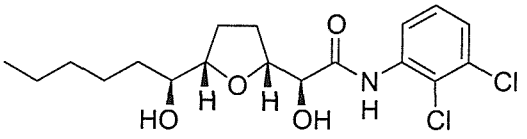
The title compound was prepared according to the method outlined for **7.16**, except using: diene **7.75** (35 mg, 0.11 mmol). Purification by column chromatography on silica gel (30% EtOAc/hexane → 60%) gave THF-diol **7.88** (10 mg, 0.03 mmol, 25%, 33% ee) as a colourless oil: IR ν_{max} (neat) 3361 (br), 2927 (s), 1663 (s), 1530 (s), 1465 (s), 1401 (s), 1346 (s), 1131 (s), 1076 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.17 (1H, br s, NH), 8.00 (1H, d, J = 7.3 Hz, CH), 7.96-7.89 (1H, m, CH), 7.88-7.82 (1H, m, CH), 7.69 (1H, d, J = 8.3 Hz, CH), 7.52-7.43 (3H, m, CH), 5.12 (1H, br, OH), 4.62 (1H, dt, J = 2.3, 7.0 Hz, CHOCHOHC=O), 4.23 (1H, d, J = 2.3 Hz, CHOHC=O), 3.99 (1H, ddd, J = 2.8, 5.8, 7.3 Hz, $CHOCHOHCH_2$), 3.54 (1H, ddd, J = 2.8, 5.0, 8.0 Hz, $CHOHCH_2$), 2.78 (2H, br, OH), 2.24-1.91 (4H, m, CH_2), 1.65-1.48 (2H, m, CH_2CHOH), 1.47-1.14 (6H, m CH_2), 0.84 (3H, t, J = 6.8 Hz, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.6 (C), 134.2 (C), 132.1 (C), 128.8 (CH), 127.2 (C), 126.4 (CH), 126.1 (CH), 125.9 (CH), 125.8 (CH), 121.0 (CH), 120.4 (CH), 82.1

(CH), 80.1 (CH), 75.1 (CH), 74.8 (CH), 34.8 (CH_2), 31.9 (CH_2), 28.7 (CH_2), 28.1 (CH_2), 25.6 (CH_2), 22.7 (CH_2), 14.1 (CH_3); LRMS (ES^+) *m/z* 394 (100%, $[M+Na]^+$); Elemental calcd. for $C_{22}H_{29}O_4N$: C, 71.13; H, 7.87; N, 3.77. Found: C, 70.98; H, 7.92; N, 3.61; 33% ee (ChiralPak AD-H, 5% *i*-PrOH/Hex, 31.6, 47.6 min).

(*rac*)-(2*S*)-2-Hydroxy-2-[(2*R*,5*S*)-5-((1*S*)-1-hydroxy-hexyl)-tetrahydro-furan-2-yl]-*N*-naphthalen-1-yl-acetamide ((*rac*)-**7.88**)

The title compound was prepared according to the method outlined for (*rac*)-**7.35**, except using: diene **7.75** (50 mg, 0.16 mmol). Purification by column chromatography on silica gel (30% EtOAc/hexane → 60%) gave THF-diol (*rac*)-**7.88** (20 mg, 0.06 mmol, 34%) as a colourless oil: characterisation data as above.

N-(2,3-Dichloro-phenyl)-(2*S*)-2-hydroxy-2-[(2*R*,5*S*)-5-((1*S*)-1-hydroxy-hexyl)-tetrahydro-furan-2-yl]-acetamide (**7.89**)

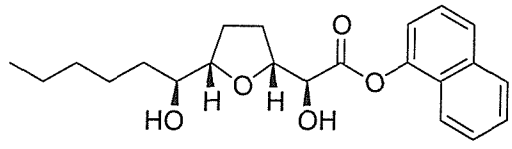


The title compound was prepared according to the method outlined for **7.16**, except using: diene **7.76** (50 mg, 0.15 mmol). Purification by column chromatography on silica gel (15% EtOAc/hexane → 30%) gave THF-diol **7.89** (24 mg, 0.06 mmol, 40%, 15% ee) as a white solid: mp 99-101 °C; $[\alpha]^{27}_D$ –3.9 (MeOH, *c* 0.31); IR ν_{max} (neat) 3349 (br), 2928 (s), 1679 (s), 1583 (s), 1518 (s), 1455 (s), 1406 (s), 1189 (s), 1049 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.40 (1H, s, N**H**), 8.43 (1H, t, *J* = 5.0 Hz, C**H**), 7.21 (2H, d, *J* = 5.0 Hz, C**H**), 4.60 (1H, dt *J* = 2.1, 6.8 Hz, C**H**OCHOHC=O), 4.16 (1H, d, *J* = 2.1 Hz, C**H**OHC=O), 3.99 (1H, ddd, *J* = 2.5, 5.8, 7.3 Hz, C**H**OCHOHCH$_2$), 3.57 (1H, dd, *J* = 2.5, 4.8, 7.3 Hz, C**H**OHCH$_2$), 1.93-1.64 (4H, m, C**H**$_2$), 1.63-1.20 (8H, m, C**H**$_2$), 0.86 (3H, t, *J* = 6.8 Hz, C**H**$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.5 (C), 136.1 (C), 132.9 (C), 127.9 (CH), 125.4 (CH), 121.8 (C), 119.2 (C), 82.0 (CH), 80.0 (CH), 75.2 (CH), 75.1 (CH), 34.7 (CH_2), 31.8 (CH_2), 28.9 (CH_2), 28.1 (CH_2), 25.5 (CH_2), 22.7 (CH_2), 14.1 (CH_3); LRMS (ES^+) *m/z* 801 (100%, $[2M+Na]^+$, ^{35}Cl x 2), 412 (50%, $[M+Na]^+$, ^{35}Cl); Elemental calcd. for $C_{18}H_{25}O_4NCl_2$: C, 55.39; H, 6.46; N, 3.59. Found: C, 55.20; H, 6.50; N, 3.46; 15% ee (Chiralcel OD-H, 10% *i*-PrOH/Hex, 6.7, 7.9 min).

(*rac*)-*N*-(2,3-Dichloro-phenyl)-(2*S*)-2-hydroxy-2-[(2*R*,5*S*)-5-((1*S*)-1-hydroxy-hexyl)-tetrahydro-furan-2-yl]-acetamide ((*rac*)-**7.89**)

The title compound was prepared according to the method outlined for (*rac*)-**7.35**, except using: diene **7.76** (100 mg, 0.29 mmol). Purification by column chromatography on silica gel (20% EtOAc/hexane → 30%) gave THF-diol (*rac*)-**7.89** (60 mg, 0.15 mmol, 53%) as a white solid: mp 99-101 °C; characterisation data as above.

(2*S*)-2-Hydroxy-[(2*R*,5*S*)-5-((1*S*)-1-hydroxy-hexyl)-tetrahydro-furan-2-yl]-acetic acid naphthalen-1-yl ester (**7.90**)

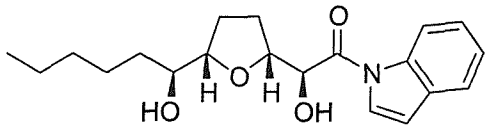


The title compound was prepared according to the method outlined for **7.16**, except using: diene **7.81** (50 mg, 0.16 mmol). Purification by column chromatography on silica gel (30% EtOAc/hexane) gave THF-diol **7.90** (22 mg, 0.06 mmol, 38%, 70% ee) as a colourless oil: $[\alpha]^{25}_{D}$ +37.5 ($CHCl_3$, *c* 0.16); IR ν_{max} (neat) 3376 (br), 2928 (s), 1762 (s), 1462 (m), 1391 (m), 1260 (s), 1223 (s), 1123 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.08-8.01 (1H, m, C**H**), 7.91-7.85 (1H, m, C**H**), 7.75 (1H, d, *J* = 8.3 Hz, C**H**), 7.54-7.44 (3H, m, C**H**), 7.26 (1H, dd, *J* = 1.0, 7.5 Hz, C**H**), 4.81 (1H, ddd, *J* = 2.0, 5.5, 7.8 Hz, OC**H**CHOHC=O), 4.56 (1H, d, *J* = 2.0 Hz, C**H**OHC=O), 4.04 (1H, dt, *J* = 3.7, 7.0 Hz, OC**H**CHOHCH$_2$), 3.55 (1H, ddd, *J* = 3.7, 4.0, 8.3 Hz, C**H**OHCH$_2$), 2.33 (1H, ddt, *J* = 7.8, 11.8, 4.8 Hz, C**H**H), 2.23-1.98 (3H, m, C**H**H x 3), 1.62-1.21 (8H, m, C**H$_2$**), 0.89 (3H, t, *J* = 7.0 Hz, C**H$_3$**); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.3 (C), 146.7 (C), 134.8 (C), 128.1 (CH), 126.9 (C), 126.8 (CH), 126.7 (CH), 126. 6 (CH), 125.5 (CH), 121.6 (CH), 118.0 (CH), 83.1 (CH), 80.3 (CH), 74.1 (CH), 74.0 (CH), 34.8 (CH_2), 32.0 (CH_2), 28.5 (CH_2), 28.0 (CH_2), 25.6 (CH_2), 22.7 (CH_2), 14.1 (CH_3); LRMS (ES^+) *m/z* 762 (10%, $[2M+Na]^+$), 762 (100%, $[M+NH_4]^+$), 395 (10%, $[M+Na]^+$), 390 (70%, $[M+NH_4]^+$), 373 (10%, $[M+H]^+$); HRMS (ES^+) $C_{22}H_{28}O_5Na^+$ Calcd. 395.1829 found 395.1824; 70% ee (Chiralcel OD-H, 10% *i*-PrOH/Hex, 12.2, 17.2 min).

(*rac*)-(2*S*)-2-Hydroxy-[(2*R*,5*S*)-5-((1*S*)-1-hydroxy-hexyl)-tetrahydro-furan-2-yl]-acetic acid naphthalen-1-yl ester ((*rac*)-**7.90**)

The title compound was prepared according to the method outlined for (*rac*)-**7.35**, except using: diene **7.81** (55 mg, 0.17 mmol). Purification by column chromatography on silica gel (30% EtOAc/hexane) gave THF-diol (*rac*)-**7.90** (22 mg, 0.06 mmol, 35%) as a colourless oil: characterisation data as above.

(2*S*)-2-Hydroxy-2-[(2*R*,5*S*)-5-((1*S*)-1-hydroxy-hexyl)-tetrahydro-furan-2-yl]-1-indol-1-yl-ethanone (**7.91**)

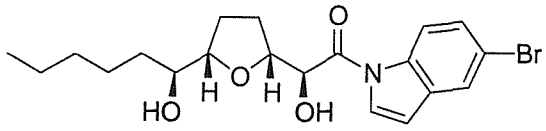


The title compound was prepared according to the method outlined for **7.16**, except using: diene **7.82** (50 mg, 0.17 mmol). Purification by column chromatography on silica gel (15% EtOAc/hexane → 30%) gave THF-diol **7.91** (24 mg, 0.07 mmol, 40%, 8% ee) as a colourless oil: IR ν_{max} (neat) 3415 (br), 2928 (s), 1702 (s), 1453 (s), 1337 (s), 1206 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.48 (1H, d, *J* = 8.3 Hz, C**H**), 7.58 (1H, d, *J* = 7.5 Hz, C**H**), 7.48 (1H, d, *J* = 3.8 Hz, C**H**), 7.39 (1H, t, *J* = 7.5 Hz, C**H**), 7.31 (1H, t, *J* = 7.5 Hz, C**H**), 6.70 (1H, d, *J* = 3.8 Hz, C**H**), 4.90 (1H, d, *J* = 2.5 Hz, C**H**OHC=O), 4.48 (1H, ddd, *J* = 2.5, 5.5, 7.8 Hz, C**H**CHOHC=O), 3.80 (1H, dt, *J* = 4.8, 7.0 Hz, C**H**OCHOHCH$_2$), 3.35 (1H, dt, *J* = 8.0, 4.8 Hz, C**H**OHCH$_2$), 3.13 (2H, br, O**H**), 2.34-1.80 (4H, m, C**H**$_2$), 1.55-1.16 (8H, m, C**H**$_2$), 0.88 (3H, t, *J* = 7.0 Hz, C**H**$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.4 (C), 136.0 (C), 130.4 (C), 125.7 (CH), 124.5 (CH), 124.1 (CH), 121.1 (CH), 116.9 (CH), 110.4 (CH), 83.6 (CH), 80.0 (CH), 74.0 (CH), 73.0 (CH), 34.3 (CH_2), 31.9 (CH_2), 28.2 (CH_2), 25.4 (CH_2), 22.7 (CH_2), 14.2 (CH_3); LRMS (ES^+) *m/z* 713 (90%, $[2M+Na]^+$), 368 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{20}H_{27}O_4Na^+$ Calcd. 368.1832 found 368.1835; 8% ee (Chiralcel OD-H, 10% *i*-PrOH/Hex, 11.6, 12.9 min).

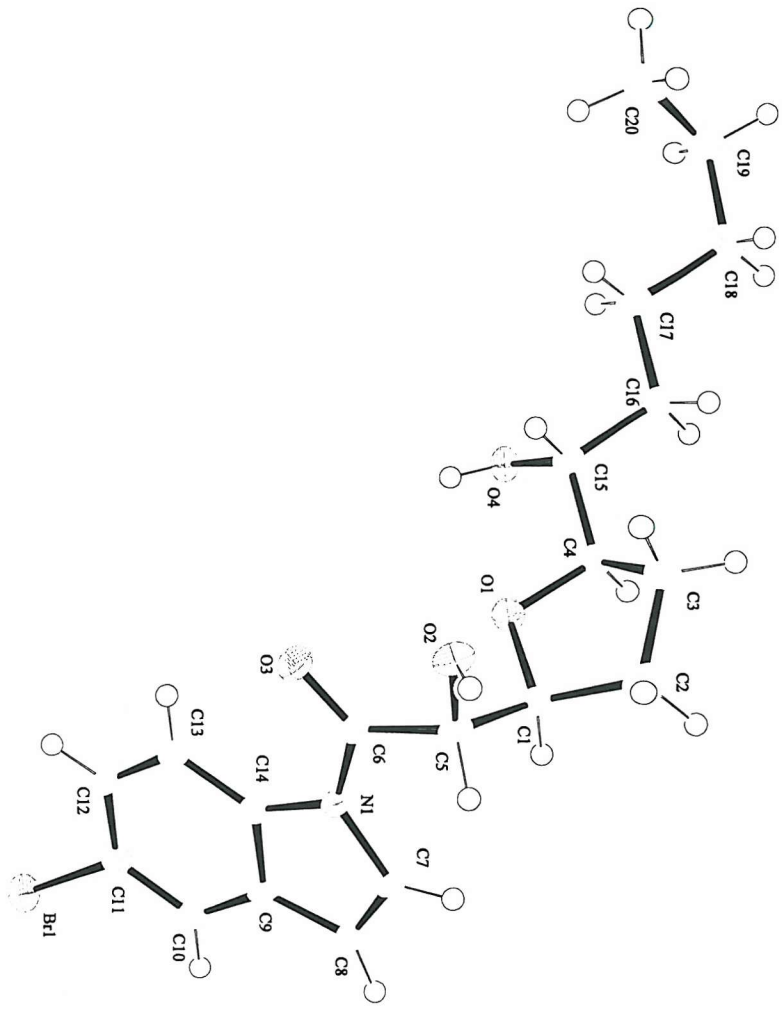
(*rac*)-(2*S*)-2-Hydroxy-2-[(2*R*,5*S*)-5-((1*S*)-1-hydroxy-hexyl)-tetrahydro-furan-2-yl]-1-indol-1-yl-ethanone ((*rac*)-**7.91**)

The title compound was prepared according to the method outlined for (*rac*)-**7.35**, except using: diene **7.82** (100 mg, 0.34 mmol). Purification by column chromatography on silica gel (15% EtOAc/hexane → 30%) gave THF-diol (*rac*)-**7.91** (52 mg, 0.15 mmol, 45%) as a colourless oil: characterisation data as above.

1-(5-Bromo-indol-1-yl)-(2*S*)-2-hydroxy-2-[(2*R*,5*S*)-5-((1*S*)-1-hydroxy-hexyl)-tetrahydro-furan-2-yl]-ethanone (**7.92**)



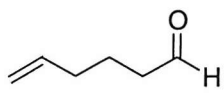
The title compound was prepared according to the method outlined for **7.16**, except using: diene **7.83** (50 mg, 0.13 mmol). Purification by column chromatography on silica gel (15% EtOAc/hexane → 30%) gave THF-diol **7.92** (23 mg, 0.05 mmol, 41%, 18% ee) as a white solid (recyrstallised EtOAc/hexane to give colourless platelets): mp 119-121 °C; $[\alpha]^{25}_{D}$ –3.6 (MeOH, *c* 0.68); IR ν_{max} (neat) 3399 (br), 2934 (s), 1712 (s), 1449 (s), 1316 (s), 1144 (s), 1087 (s), 1061 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.35 (1H, d, *J* = 8.8 Hz, C**H**), 7.70 (1H, d, *J* = 1.8 Hz, C**H**), 7.51 (1H, d, *J* = 3.8 Hz, C**H**), 7.47 (1H, dd, *J* = 1.8, 8.8 Hz, C**H**), 6.63 (1H, d, *J* = 3.8 Hz, C**H**), 4.86 (1H, d, *J* = 3.8 Hz, C**H**OHC=O), 4.46 (1H, ddd, *J* = 2.8, 5.5, 8.0 Hz, C**H**CHOHC=O), 3.81 (1H, dt, *J* = 4.8, 7.3 Hz, C**H**OCHOHCH$_2$), 3.37 (1H, dt, *J* = 7.8, 4.8 Hz, C**H**OHCH$_2$), 2.26-2.03 (2H, m, C**H**$_2$), 2.01-1.81 (2H, m, C**H**$_2$), 1.50-1.17 (8H, m, C**H**$_2$), 0.88 (3H, t, *J* = 7.0 Hz, C**H**$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.3 (C), 134.7 (C), 132.0 (C), 128.5 (CH), 125.4 (CH), 123.8 (CH), 118.3 (CH), 117.8 (C), 109.4 (CH), 83.6 (CH), 79.9 (CH), 74.0 (CH), 73.2 (CH), 34.4 (CH_2), 31.9 (CH_2), 28.2 (CH_2), 25.4 (CH_2), 22.7 (CH_2), 14.1 (CH_3); LRMS (ES^+) *m/z* 871 (100%, $[2M+Na]^+$, $^{79}Br^{81}Br$), 448 (60%, $[M+Na]^+$, ^{81}Br), 446 (50%, $[M+Na]^+$, ^{79}Br); Elemental calcd. for $C_{20}H_{26}O_4NBr$: C, 56.61; H, 6.18; N, 3.30. Found: C, 56.47; H, 6.24; N, 3.20; 18% ee (Chiralcel OD-H, 10% *i*-PrOH/Hex, 9.5, 12.0 min); X-ray (racemic mixture).



(*rac*)-1-(5-Bromo-indol-1-yl)-(2*S*)-2-hydroxy-2-[(2*R*,5*S*)-5-((1*S*)-1-hydroxy-hexyl)-tetrahydro-furan-2-yl]-ethanone ((*rac*)-**7.92**)

The title compound was prepared according to the method outlined for (*rac*)-**7.35**, except using: diene **7.83** (100 mg, 0.27 mmol). Purification by column chromatography on silica gel (15% EtOAc/hexane → 30%) gave THF-diol (*rac*)-**7.92** (71 mg, 0.17 mmol, 62%) as a white solid: mp 119-121 °C; characterisation data as above.

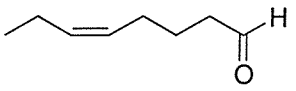
Hex-5-enal (**8.9**)



At –60 °C to a solution of oxalyl chloride (8.62 mL, 98.8 mmol) in CH_2Cl_2 (150 mL) was added DMSO (10.9 mL, 153 mmol) dropwise (care). After 5 min a solution of alcohol **8.7** (9.00 g, 89.9 mmol) in CH_2Cl_2 (10 mL) was added dropwise. After a further 30 min Et_3N

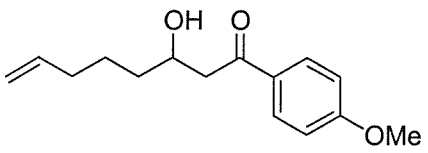
(62.7 mL, 445 mmol) was added dropwise. The reaction was allowed to warm to rt over 40 min, whereupon H_2O (150 mL) was added. The organic phase was separated and washed sequentially with citric acid (10% w/v aq, 2 x 200 mL) and H_2O (2 x 50 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification by vacuum distillation (15 mbar, 80 °C) gave aldehyde **8.9** (7.31 g, 74.6 mmol, 83%) as a colourless oil: IR ν_{max} (neat) 2939 (w), 1723 (s), 1641 (w), 1260 (w) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.77 (1H, t, J = 1.7 Hz, **CH**O), 5.76 (1H, ddt, J = 9.8, 16.7, 6.9 Hz, **CH**=CH_2), 5.07-4.97 (2H, m, **CH$_2$**=CH), 2.45 (2H, dt, J = 2.0, 6.9 Hz, **CH$_2$**CHO), 2.09 (2H, q, J = 6.9 Hz, **CH$_2$**CH=), 1.73 (2H, quin, J = 6.9 Hz, CH_2**CH$_2$**CH_2).

(5Z)-Oct-5-enal (**8.10**)



The title compound was prepared according to the method outlined for **8.9**, except using: alcohol **8.8** (5.00 g, 39.0 mmol) instead. Purification by vacuum distillation (15 mbar, 110 °C) gave aldehyde **8.10** (3.41 g, 27.3 mmol, 70%) as a colourless oil: IR ν_{max} (neat) 2964 (s), 1725 (s), 1454 (w), 1068 (w) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.78 (1H, t, J = 1.7 Hz, **CH**O), 5.42 (1H, dtt, J = 10.8,1.5, 7.2 Hz, **CH**=CH), 5.29 (1H, dtt, J = 10.8, 1.5, 7.2 Hz, **CH**=CH), 2.44 (2H, dt, J = 1.7, 7.2 Hz, **CH$_2$**CHO), 2.09 (2H, q, J = 7.2 Hz, **CH$_2$**CH=), 2.01 (2H, d, quin, J = 1.5, 7.2 Hz, **CH$_2$**CH_3), 1.70 (2H, quin, J = 7.2 Hz, CH_2**CH$_2$**CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 202.8 (CH), 133.1 (CH), 127.8 (CH), 43.4 (CH_2), 26.5 (CH_2), 22.2 (CH_2), 20.7 (CH_2), 14.3 (CH_2).

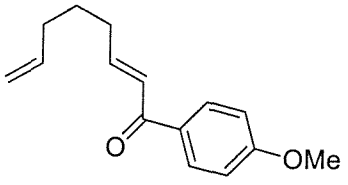
3-Hydroxy-1-(4-methoxy-phenyl)-oct-7-en-1-one (**8.11**)



The title compound was prepared according to the method outlined for **7.5**, except using: 4-methoxy-1-acetophenone (**7.7**) (5.36 g, 35.7 mmol) and aldehyde **8.9** (3.50 g, 35.7 mmol) instead. Purification by column chromatography on silica gel (15% EtOAc/hexane → 20%) gave β-hydroxy ketone **8.11** (6.20 g, 25.0 mmol, 70%) as a white solid: mp 54-55 °C; IR ν_{max}

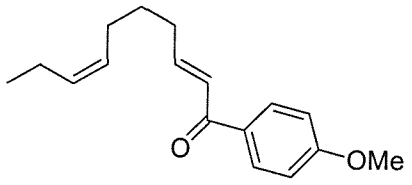
(neat) 3482 (br), 2932 (s), 1665 (s), 1598 (s), 1259 (s), 1219 (m), 1170 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.94 (2H, d, *J* = 9.0 Hz, C**H**), 6.94 (2H, d, *J* = 9.0 Hz, C**H**), 5.83 (1H, ddt, *J* = 10.3, 17.1, 6.8 Hz, C**H**=CH_2), 5.07 (1H, dq, *J* = 17.1, 2.0 Hz, C**H**H=CH), 5.01 (1H, ddt, *J* = 2.0, 10.2, 1.3 Hz, CH**H**=CH), 4.28-4.21 (1H, m, C**H**OH), 3.88 (3H, s, CH_3O), 3.40 (1H, br, O**H**), 3.13 (1H, dd, *J* = 2.5, 17.3 Hz, C**H**HC=O), 2.96 (1H, dd, *J* = 9.0, 17.3 Hz, CH**H**C=O), 2.19-2.11 (2H, m, CH_2), 1.69-1.43 (4H, m, CH_2), ^{13}C-NMR (100 MHz, $CDCl_3$) δ 199.6 (C), 164.0 (C), 138.8 (CH), 130.5 (CH), 130.0 (C), 114.8 (CH_2), 114.0 (C), 67.9 (CH), 55.6 (CH_3), 44.7 (CH_2), 36.1 (CH_2), 33.8 (CH_2), 25.0 (CH_2); LRMS (ES^+) *m/z* 249 (100%, $[M+H]^+$); Elemental calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.71; H, 8.34.

(2*E*)-1-(4-Methoxy-phenyl)-octa-2,7-dien-1-one (**8.13**)



The title compound was prepared according to the method outlined for **7.6**, except using: β-hydroxy ketone **8.11** (2.80 g, 11.3 mmol). Purification by column chromatography on silica gel (5% EtOAc/hexane → 7%) gave diene **8.13** (2.54 g, 11.0 mmol, 98%) as a yellow oil: IR ν_{max} (neat) 2931 (s), 1666 (s), 1618 (s), 1599 (s), 11259 (s), 1172 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.95 (2H, d, *J* = 9.0 Hz, C**H**), 7.05 (1H, dt, *J* = 15.3, 6.8 Hz, C**H**=CHCO), 6.95 (2H, d, *J* = 9.0 Hz, C**H**), 6.90 (1H, dt, *J* = 15.3, 1.2 Hz, =C**H**CO), 5.82 (1H, ddt, *J* = 10.0, 16.8, 6.8 Hz, C**H**=CH_2), 5.04 (1H, dq, *J* = 16.8, 1.8 Hz, C**H**H=CH), 5.00 (1H, ddt, *J* = 1.8, 10.0, 1.2 Hz, CH**H**=CH), 3.88 (3H, s, OCH_3), 2.34 (2H, dq, *J* = 1.2, 6.8 Hz, CH_2CH=), 2.13 (2H, dq, *J* = 1.2, 6.8 Hz, CH_2CH=), 1.64 (2H, quin, *J* = 6.8 Hz, $CH_2CH_2CH_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 189.2 (C), 163.4 (C), 148.5 (CH), 138.2 (CH), 131.0 (CH), 130.9 (C), 125.9 (CH), 115.2 (CH_2), 113.9 (CH), 55.8 (CH_3), 33.3 (CH_2), 32.2 (CH_2), 27.5 (CH_2); LRMS (GCEI) 8.52 min, *m/z* 230 (60%, $M^{+\cdot}$), 135 (100%); Elemental calcd. for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.37; H, 8.00.

(2E,7Z)-1-(4-Methoxy-phenyl)-deca-2,7-dien-1-one (**8.14**)

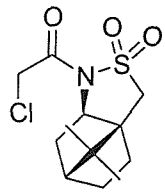


At –60 °C to a freshly prepared solution of LDA (1.2 mmol) in THF (10 mL) was added a solution of 4-methoxyacetophenone (**7.7**) (180 mg, 1.2 mmol) in THF (2 mL) dropwise. After 30 min a solution of aldehyde **8.10** (150 mg, 1.2 mmol) in THF (2 mL) was added dropwise. After 30 min the reaction was quenched by addition of NH_4Cl (sat aq, 10 mL), brine (5 mL), H_2O (10 mL) and CH_2Cl_2 (30 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 20 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated *in vacuo* to give a colourless oil. Purification by column chromatography on silica gel (10% EtOAc/hexane → 20%) gave alcohol **8.12** (226 mg, 0.82 mmol, 68%) as a colourless oil.

At 0 °C to a solution of alcohol **8.12** (226 mg, 0.82 mmol) in CH_2Cl_2 (10 mL) was added dropwise methane sulfonyl chloride (126 μL, 1.64 mmol) and Et_3N (228 μL, 1.64 mmol). The reaction mixture was allowed to warm to rt, after 2 h brine (10 mL) and H_2O (10 mL) were added. The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* before being solvated in CH_2Cl_2 (10 mL). The reaction mixture was cooled to 0 °C whereupon DBU (245 μL, 1.64 mmol) was added dropwise and the reaction mixture was allowed to warm to rt. After 30 min H_2O (5 mL), 2 M HCl (3 mL) and brine (5 mL) were added. The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 10 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated *in vacuo* to give a colourless oil. Purification by column chromatography on silica gel (4% EtOAc/hexane → 5%) gave diene **8.14** (201 mg, 0.78 mmol, 65%, 2 steps) as a yellow oil: IR ν_{max} (neat) 2931 (s), 1666 (s), 1618 (s), 1598 (s), 1574 (m), 1257 (s), 1231 (s), 1170 (s), 1027 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (2H, d, J = 8.8 Hz, C**H**), 7.06 (1H, dt, J = 15.5, 7.0 Hz, C**H**=CHCO$_2$Et), 6.95 (2H, d, J = 8.8 Hz, C**H**), 6.90 (1H, dt, J = 15.5, 1.5 Hz, C**H**CO$_2$Et), 5.48-5.27 (2H, m, CH$_2$C**H**=C**H**CH$_2$), 3.88 (3H, s, OC**H**$_3$), 2.32 (2H, dq, J = 1.5, 7.0 Hz, C**H**$_2$CH=), 2.15-1.99 (4H, m, C**H**$_2$CH=CH x 2), 1.59 (2H, quin, J = 7.0 Hz, CH$_2$C**H**$_2$CH$_2$), 0.97 (3H, t, J = 7.5 Hz, C**H**$_3$CH$_2$CH=); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.2 (C), 163.4 (C), 148.8 (CH), 132.6 (CH), 130.9 (CH), 128.3 (CH), 125.7 (CH), 113.8 (CH), 55.6 (CH_3), 32.4 (CH_2), 28.4 (CH_2), 26.7 (CH_2), 20.7 (CH_2), 20.7 (CH_2), 14.5 (CH_3); LRMS

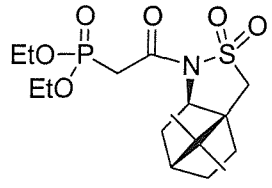
(GCCI) 9.13 min, *m/z* 259 (40%, $[M+H]^+$), 135 (100%); HRMS (EI) $C_{17}H_{22}O_2^{+\cdot}$ Calcd. 258.1620, found 258.1617.

(2*R*)-*N*-(2-Chloroethanoyl)-camphor-10,2-sultam (**8.15**)



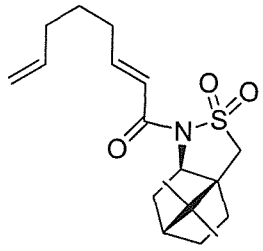
The title compound was prepared according to the method outlined for **5.17**, except using: (2*R*)-sultam (7.00 g, 32.5 mmol) instead. Gave chloride **8.15** (8.50 g, 29.2 mmol, 90%) as a white crystalline solid (spectroscopic data identical to **5.17**): mp 120-122 °C; Elemental calcd. for $C_{12}H_{18}O_3NSCl$: C, 49.40; H, 6.22; N, 4.80. Found: C, 49.28; H, 6.04; N, 4.69.

Diethyl-2-oxo-2-*N*-((2*R*)-camphor-10-2-sultam)-ethylphosphonate (**8.16**)



The title compound was prepared according to the method outlined for **5.18**, except using: chloride **8.15** (7.30 g, 26.3 mmol) instead. Gave phosphonate **8.16** (8.79 g, 22.4 mmol, 85%) as a colourless oil (spectroscopic data identical to **5.18**): $[\alpha]^{25}_D$ –58.7 ($CHCl_3$, *c* 0.80); Elemental calcd. for $C_{16}H_{28}O_6NSP$: C, 48.85; H, 7.17; N, 3.56. Found: C, 48.73; H, 7.08; N, 3.36.

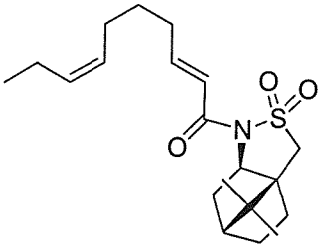
(2*R*)-*N*-((2*E*)-2,6-Octadienoyl)-camphor-10,2-sultam (**8.17**)



At 0 °C to a solution of sultam phosphonate **8.16** (3.00 g 7.63 mmol) in CH_2Cl_2 (60 mL) was added in several batches NaH (305 mg, 7.63 mmol, 60% in mineral oil). The reaction was

allowed to warm to rt and was stirred for 20 min before being cooled to 0 °C. A solution of aldehyde **8.9** (0.83 mg, 8.4 mmol) in CH_2Cl_2 (2 mL) was added dropwise. After 2 h the reaction was quenched by addition of NH_4Cl (sat aq, 30 mL) and H_2O (15 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification by column chromatography on silica gel (5% EtOAc/hexane → 15%) gave dienoyl sultam **8.17** (2.66 g, 6.87 mmol, 90%) as a white solid: mp 67-68 °C; $[\alpha]^{25}_D$ –78.9 ($CHCl_3$, *c* 0.62); IR ν_{max} (neat) 2957 (s), 1682 (s), 1639 (s), 1331 (s), 1276 (s), 1237 (s), 1218 (s), 1134 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.09 (1H, dt, *J* = 15.1, 7.0 Hz, C**H**=CHCO$_2$Et), 6.56 (1H, dt, *J* = 15.1, 1.5 Hz, C**H**CO$_2$Et), 5.78 (1H, ddt, *J* = 10.3, 17.1, 7.0 Hz, C**H**=CH$_2$), 5.03 (1H, dq, *J* = 17.1, 1.5 Hz, C**H**H=CH), 4.98 (1H, ddt, *J* = 2.0, 10.3, 1.5 Hz, C**H**H=CH), 3.93 (1H, dd, *J* = 5.0, 7.5 Hz, C**H**N), 3.51 (1H, d, *J* = 13.8 Hz, C**H**HSO$_2$), 3.44 (1H, d, *J* = 13.8 Hz, C**H**HSO$_2$), 2.27 (2H, dq, *J* = 1.5, 7.0 Hz, C**H**$_2$CH=CHCO), 2.20-2.06 (4H, m, C**H**$_2$CHN, C**H**$_2$CH=), 1.98-1.84 (3H, m, sult), 1.59 (2H, quin, *J* = 7.0, CH$_2$C**H**$_2$CH$_2$), 1.48-1.32 (2H, m, sult), 1.19 (3H, s, C**H**$_3$C), 0.98 (3H, s, C**H**$_3$C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3 (C), 150.6 (CH), 138.1 (CH), 121.3 (CH), 115.3 (CH_2), 65.3 (CH), 53.3 (CH_2), 48.6 (C), 47.9 (C), 44.9 (CH), 38.7 (CH_2), 33.3 (CH_2), 33.0 (CH_2), 32.0 (CH_2), 27.3 (CH_2), 26.6 (CH_2), 21.0 (CH_3), 20.1 (CH_3); LRMS (ES^+) *m/z* 360 (100%, $[M+Na]^+$), 338 (20%, $[M+H]^+$); Elemental calcd. for $C_{18}H_{27}O_3NS$: C, 64.06; H, 8.06; N, 4.15. Found: C, 64.07; H, 8.13; N, 4.08.

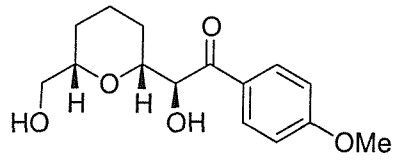
(2*R*)-*N*-((2*E*,7*Z*)-2,6-Decadienoyl)-camphor-10,2-sultam (**8.18**)



At 0 °C to a solution of sultam phosphonate **8.16** (623 mg 1.60 mmol) in CH_2Cl_2 (10 mL) was added in one batch NaH (64 mg, 1.60 mmol, 60% in mineral oil). The reaction was allowed to warm to rt and was stirred for 20 min before being cooled to 0 °C. A solution of aldehyde **8.10** (200 mg, 1.60 mmol) in CH_2Cl_2 (2 mL) was added dropwise. After 16 h the reaction was quenched by addition of NH_4Cl (sat aq, 10 mL) and H_2O (5 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow

oil. Purification by column chromatography on silica gel (5% EtOAc/hexane → 10%) gave dienoyl sultam **8.18** (365 mg, 1.00 mmol, 60%) as a colourless oil: $[\alpha]^{25}_{D}$ –85.6 ($CHCl_3$, *c* 1.00); IR ν_{max} (neat) 2960 (s), 1682 (s), 1639 (s), 1330 (s), 1281 (s), 1236 (s), 1218 (s), 1134 (s), 1116 (s), 1063 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.10 (1H, dt, *J* = 15.1, 7.0 Hz, C**H**=CHCO$_2$Et), 6.56 (1H, dt, *J* = 15.1, 1.5 Hz, C**H**CO$_2$Et), 5.40 (1H, dtt, *J* = 10.8, 1.5, 7.0 Hz, C**H**=CH), 5.29 (1H, dtt, *J* = 10.8, 1.5, 7.0 Hz, C**H**=CH), 3.93 (1H, dd, *J* = 5.0, 7.5 Hz, C**H**N), 3.51 (1H, d, *J* = 13.8 Hz, C**H**HSO$_2$), 3.44 (1H, d, *J* = 13.8 Hz, C**H**HSO$_2$), 2.26 (2H, dq, *J* = 1.5, 7.0 Hz, C**H**$_2$CH=CHCO), 2.20-1.98 (6H, m, C**H**$_2$CHN, C**H**$_2$CH= x 2), 1.97-1.83 (3H, m, sult), 1.54 (2H, quin, *J* = 7.0, CH$_2$C**H**$_2$CH$_2$), 1.47-1.31 (2H, m, sult), 1.18 (3H, s, C**H**$_3$C), 0.98 (3H, s, C**H**$_3$C), 0.96 (3H, t, *J* = 7.2 Hz, C**H**$_3$CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3 (C), 150.8 (CH), 132.6 (CH), 128.2 (CH), 121.1 (CH), 65.3 (CH), 53.3 (CH_2), 48.6 (C), 47.9 (C), 44.9 (CH), 38.7 (CH_2), 33.0 (CH_2), 32.2 (CH_2), 28.1 (CH_2), 26.7 (CH_2), 26.6 (CH_2), 21.0 (CH_3), 20.7 (CH_2), 20.0 (CH_3), 14.4 (CH_3); LRMS (ES^+) *m/z* 753 (100%, $[2M+Na]^+$), 388 (70%, $[M+Na]^+$), 366 (50%, $[M+H]^+$); HRMS (ES^+) $(C_{12}H_{20}O_2)_2Na^+$ Calcd. 753.3942, found 753.3944.

(2*S*)-2-Hydroxy-2-((2*R*,6*S*)-6-hydroxymethyl-tetrahydro-pyran-2-yl)-1-(4-methoxy-phenyl)-ethanone (**8.19**)

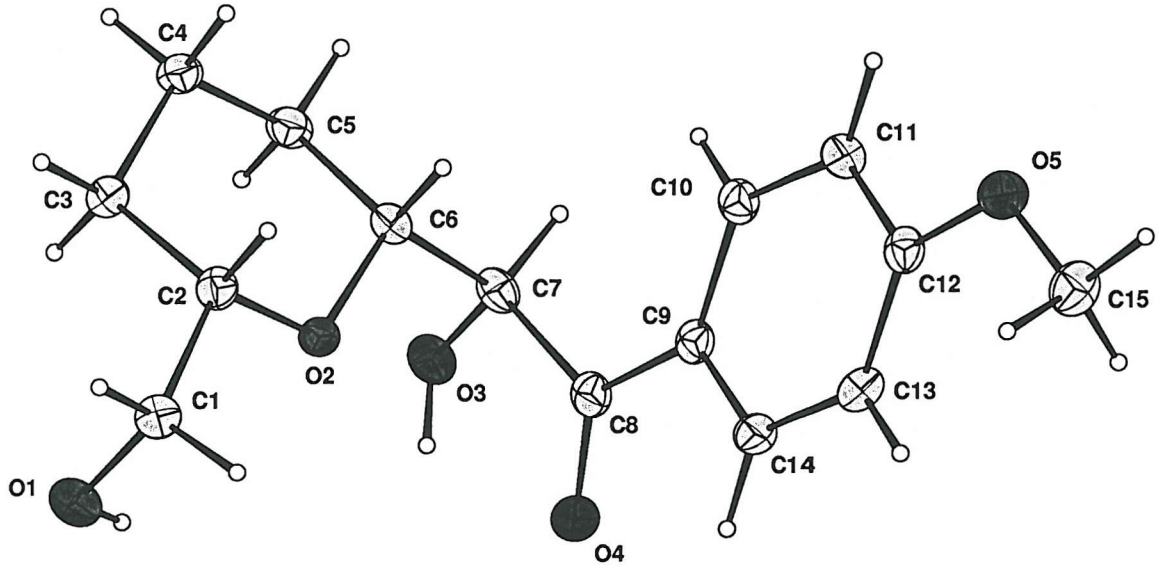


At –60 °C to a solution of diene **8.13** (100 mg, 0.43 mmol), chiral catalyst **2.56** (26 mg, 0.04 mmol), AcOH (0.2 mL, 3.4 mmol) in CH_2Cl_2 (4 mL) was added in one batch powdered $KMnO_4$ (110 mg, 0.70 mmol). After 3 h vigorous stirring the reaction was quenched with $Na_2S_2O_5$ (sat aq, 5 mL), H_2O (2 mL) and CH_2Cl_2 (5 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic fractions were then dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow oil. Purification by column chromatography on silica gel (50% EtOAc/hexane → 90%) gave THP-diol **8.19** (5 mg, 0.02 mmol, 4%, 73% ee) a white solid: mp 105-106 °C; $[\alpha]^{25}_{D}$ –12.2 (MeOH, *c* 0.19); IR ν_{max} (neat) 3420 (br), 2937 (m), 1672 (s), 1598 (s), 1573 (s), 1310 (s), 1256 (s), 1173 (s), 1085 (s), 1041 (s) cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 7.91 (2H, d, *J* = 9.0 Hz, C**H**), 6.96 (2H, d, *J* = 9.0 Hz, C**H**), 4.96 (1H, d, *J* = 2.8 Hz, C**H**OHC=O), 3.97 (1H, br, O**H**), 3.87 (3H, s, OC**H**$_3$), 3.75 (1H, ddd, *J* = 2.8, 5.3, 8.0 Hz, OC**H**CHOHC=O), 3.44

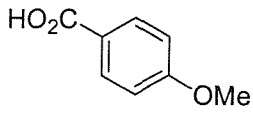
(1H, dd, J = 3.5, 11.5 Hz, CHHOH), 3.38 (1H, dd, J = 6.7, 11.5 Hz, CHHOH), 3.26 (1H, dddd, J = 2.3, 3.5, 5.8, 11.4 Hz, OCHCH$_2$OH), 2.23 (1H, br, OH), 1.90 (1H, ddt, 9.8, 12.8, 3.5 Hz, CHHCHO), 1.68-1.60 (2H, m, CH$_2$), 1.56-1.44 (1H, m, CHH), 1.39 (1H, ddt, J = 3.5, 13.0, 2.8 Hz, CHHCHO), 1.28-1.12 (1H, m, CHH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 198.4 (C), 164.2 (C), 130.9 (CH), 127.5 (C), 114.1 (CH), 78.9 (CH), 78.6 (CH), 75.4 (CH), 66.0 (CH_2), 55.6 (CH_3), 26.8 (CH_2), 26.6 (CH_2), 22.8 (CH_2); LRMS (ES$^+$) *m/z* 583 (100%, [2M+Na]$^+$), 303 (90%, [M+Na]$^+$); Elemental calcd. for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.26; H, 7.18; 73% ee (Chiralcel OB-H, 5% *i*-PrOH/Hex, 41.6, 50.1 min).

(*rac*)-(2*S*)-2-Hydroxy-2-((2*R*,6*S*)-6-hydroxymethyl-tetrahydro-pyran-2-yl)-1-(4-methoxy-phenyl)-ethanone ((*rac*)-**8.19**)

At –60 °C to a solution of diene **8.13** (80 mg, 0.35 mmol), adogen 464 (18 mg, 0.04 mmol), AcOH (0.3 mL, 5.6 mmol) in CH_2Cl_2 (2 mL) was added in one batch powdered $KMnO_4$ (77 mg, 0.49 mmol). After 1.5 h the reaction was quenched with $Na_2S_2O_5$ (sat aq, 3 mL), H_2O (2 mL) and CH_2Cl_2 (3 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic fractions were then dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow oil. Purification by column chromatography on silica gel (50% EtOAc/hexane → 80% then 2% MeOH) gave THP-diol (*rac*)-**8.19** (33 mg, 0.12 mmol, 35%) as a white solid (recrystallisation EtOAc/hexane or Et_2O/hexane gave colourless blocks) and benzoic acid **8.20** (20 mg, 0.13 mmol, 38%) as a white solid. Data for THP-diol (*rac*)-**8.19**: mp 105-107 °C; characterisation data as above; X-ray (racemic mixture).

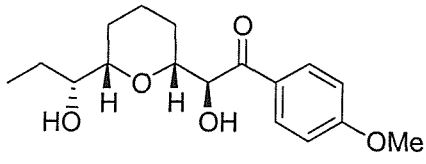


4-Methoxy-benzoic acid (**8.20**)



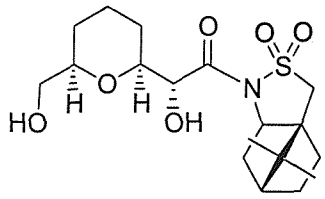
Data for **8.20**: ^{1}H-NMR (400 MHz, $(CD_3)_2SO$) δ 12.17 (1H, br, COO**H**), 7.49 (2H, d, J = 8.8 Hz, C**H**), 6.61 (2H, d, J = 8.8 Hz, C**H**), 3.42 (3H, s, OC**H**$_3$); ^{13}C-NMR (100 MHz, $(CD_3)_2SO$) δ 167.1 (C), 163.0 (C), 131.5 (CH), 123.1 (C), 114.0 (CH), 55.6 (CH_3).

(*rac*)-(2*S*)-2-Hydroxy-2-[(2*R*,6*S*)-6-((1*R*)-1-hydroxy-propyl)-tetrahydro-pyran-2-yl]-1-(4-methoxy-phenyl)-ethanone (**8.21**)



At –15 °C under N_2, powdered $KMnO_4$ (51.4 mg, 0.33 mmol) was added in one batch to a rapidly stirred solution of diene **8.14** (60 mg, 0.23 mmol) in AcOH/acetone (2 mL 2:3). After 35 min the reaction was quenched by addition of $Na_2S_2O_5$ (sat aq, 5 mL) and H_2O (3 mL). EtOAc (10 mL) was added and the organic phase separated. The aqueous was extracted with EtOAc (2 x 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (600 mg). Purification by column chromatography on silica gel (40% EtOAc/hexane → 50%) gave THP-diol **8.21** (21 mg, 0.10 mmol, 30%) as colourless oil: IR ν_{max} (neat) 3465 (br), 2937 (s), 1675 (s), 1600 (s), 1574 (m), 1512 (m), 1310 (m), 1258 (s), 1173 (s), 1112 (s), 1087 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.92 (2H, d, J = 8.8 Hz, C**H**), 6.97 (2H, d, J = 8.8 Hz, C**H**), 4.99 (1H, d, J = 2.8 Hz, C**H**OHC=O), 3.89 (3H, s, OC**H**$_3$), 3.77 (1H, dt, J = 11.1, 2.8 Hz, OC**H**CHOHC=O), 3.40 (1H, dt, J = 8.3, 4.3 Hz, C**H**OHCH$_2$), 3.11 (1H, ddd, J = 2.3, 4.3, 11.2 Hz, OC**H**CHOHCH$_2$), 1.97-1.17 (8H, m, C**H**$_2$ THP x 3, C**H**$_2$CH$_3$), 0.87 (3H, t, J = 7.3 Hz, C**H**$_3$CH$_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 198.4 (C), 164.2 (C), 131.1 (CH), 127.7 (C), 114.0 (CH), 80.5 (CH), 79.4 (CH), 75.2 (CH), 74.9 (CH), 55.7 (CH_3), 26.6 (CH_2), 24.8 (CH_2), 24.5 (CH_2), 22.8 (CH_2), 10.2 (CH_3); LRMS (ES$^+$) *m/z* 639 (100%, [2M+Na]$^+$), 331 (80%, [M+Na]$^+$); Elemental calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.33; H, 7.71.

(*2R*)-*N*-[(2*R*)-2-Hydroxy-2-((2*S*,5*R*)-6-(hydroxymethyl)tetrahydro-2-pyranyl)ethanoyl]-camphor-10,2-sultam (**8.22**)

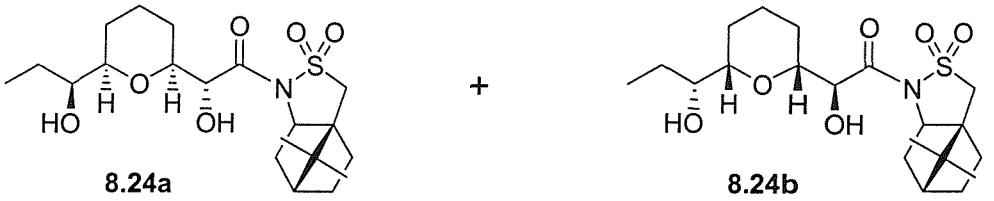


At –60 °C to a solution of diene **8.17** (200 mg, 0.59 mmol), adogen 464 (28 mg, 0.06 mmol), AcOH (2.8 mL, 47 mmol) in CH_2Cl_2 (10 mL) was added in one batch powdered $KMnO_4$ (131 mg, 0.83 mmol). After 2.5 h the reaction was quenched by addition of $Na_2S_2O_5$ (sat aq, 5 mL) and H_2O (5 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow oil. Purification by column chromatography on silica gel (40% EtOAc/hexane → 80% then 2% MeOH) gave diastereoisomeric THF-diol **8.22** (46 mg, 0.12 mmol, 20%) as a colourless oil and THF-diol **8.23** (7 mg, 0.02 mmol 3%) as a colourless oil. Data for **8.22**: $[\alpha]^{25}_D$ –52.9 ($CHCl_3$, *c* 1.69); IR ν_{max} (neat) 3422 (br), 2947 (m), 1691 (s), 1332 (s), 1215 (s), 1136 (s), 1046 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.55 (1H, d, *J* = 3.3 Hz, C**H**OHC=O), 3.97-3.92 (2H, m, C**H**N, OC**H**CHOHCO), 3.58-3.42 (3H, m, C**H**$_2$OH, OC**H**C**H**$_2$OH), 3.51 (1H, d *J* = 13.8 Hz, C**H**HSO$_2$), 3.44 (1H, d *J* = 13.8 Hz, C**H**HSO$_2$), 2.88 (2H, br, O**H** x 2), 2.31-2.19 (1H, m, C**H**HCHN), 2.12-2.03 (1H, m, CHHCHN), 2.10-1.79 (4H, m, 3H sult, C**H**HCHO), 1.67-1.51 (2H, m, C**H**$_2$), 1.51-1.19 (5H, m, 2H sult, 3H C**H**$_2$), 1.15 (3H, s, C**H**$_3$C), 0.97 (3H, s, C**H**$_3$C); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.1 (C), 78.5 (CH), 76.4 (CH), 73.4 (CH), 66.1 (CH_2), 65.8 (CH), 53.1 (CH_2), 49.1 (C), 48.0 (C), 44.7 (CH), 38.3 (CH_2), 33.0 (CH_2), 26.9 (CH_2), 26.8 (CH_2), 26.5 (CH_2), 22.6 (CH_2), 20.9 (CH_3), 20.0 (CH_3); LRMS (ES^+) *m/z* 797 (50%, $[2M+Na]^+$), 410 (100%, $[M+Na]^+$); Elemental calcd. for $C_{18}H_{29}O_6NS$: C, 55.79; H, 7.54; N, 3.61. Found: C, 55.76; H, 7.34; N, 3.53.

Inseparable mixture of:

(*2R*)-*N*-[(2*R*)-2-Hydroxy-2-((2*S*,5*R*)-6-((1*S*)-1-hydroxypropyl)tetrahydro-2-pyranyl)ethanoyl)]-camphor-10,2-sultam (**8.24a**) &

(*2R*)-*N*-[(2*S*)-2-Hydroxy-2-((2*R*,5*S*)-6-((1*R*)-1-hydroxypropyl)tetrahydro-2-pyranyl)ethanoyl)]-camphor-10,2-sultam (**8.24b**)



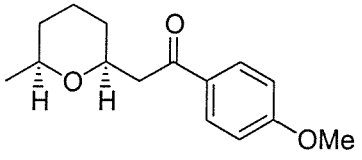
8.24a + **8.24b**

(ratio **8.24a**/**8.24b** = 4:1 after chromatography)

At –15 °C under N_2, powdered $KMnO_4$ (64 mg, 0.40 mmol) was added in one batch to a rapidly stirred solution of diene **8.18** (105 mg, 0.29 mmol) in AcOH/acetone (4 mL 2:3). After 30 min the reaction was quenched by addition of $Na_2S_2O_5$ (sat aq, 3 mL) and H_2O (2 mL). EtOAc (10 mL) was added and the organic phase separated. The aqueous was extracted with EtOAc (2 x 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification by column chromatography on silica gel (25% EtOAc/hexane → 45%) gave a 4:1 mixture of THF diastereoisomers **8.24a/8.24b** (29 mg, 0.07 mmol, 24%) as colourless oil: $[\alpha]^{25}_D$ –50.0 ($CHCl_3$, *c* 0.77); IR ν_{max} (neat) 3445 (s), 2958 (s), 1694 (s), 1457 (m), 1332 (s), 1290 (s), 1218 (s), 1136 (s), 1087 (s), 1058 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.59 (1H, d, *J* = 1.7 Hz, **CH**OHC=O minor), 4.51 (1H, d, *J* = 3.3 Hz, **CH**OHC=O major), 3.99-3.90 (4H, m, OC**H**CHOHC=O, C**H**N major/minor), 3.57-3.40 (2H, m, C**H**OHCH$_2$ major/minor), 3.51 (2H, d, *J* = 13.8 Hz, C**H**HSO$_2$ major/minor), 3.44 (2H, d, *J* = 13.8 Hz, C**H**HSO$_2$ major/minor), 3.38 (1H, ddd, *J* = 2.0, 3.5, 11.3 Hz, OC**H**CHOHCH$_2$ major), 3.21 (1H, ddd, *J* = 2.0, 3.7, 11.3 Hz, OC**H**CHOHCH$_2$ minor), 2.23-2.18 (2H, m, C**H**HCHN major/minor), 2.15-1.19 (26H, m, 10H sult, C**H$_2$** x 8 major/minor), 1.16 (3H, s, C**H$_3$**C major), 1.13 (3H, s, C**H$_3$**C minor), 0.98 (3H, s, C**H$_3$**C major), 0.96 (3H, t, *J* = 7.5 Hz, C**H$_3$**CH$_2$ major), 0.95 (3H, s, C**H$_3$**C minor), 0.94 (3H, t, *J* = 7.5 Hz, C**H$_3$**CH$_2$ minor); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1 (C, major), 170.9 (C, minor), 80.5 (CH, major), 80.4 (CH, minor), 78.9 (CH, minor), 77.0 (CH, major), 75.2 (CH, minor), 75.0 (CH, major), 74.3 (CH, minor), 73.7 (CH, major), 65.9 (CH, major), 65.0 (CH, minor), 53.2 (CH_2, major), 53.0 (CH_2, minor), 49.1 (C), 48.0(C), 44.7 (CH), 38.3 (CH_2, major), 37.9 (CH_2, minor), 33.0 (CH_2, major), 32.7 (CH_2, minor), 27.1 (CH_2, major), 26.8 (CH_2, minor), 26.5 (CH_2, major), 26.5 (CH_2, minor), 25.0 (CH_2, major), 24.9 (CH_2, minor), 24.5 (CH_2,

major), 24.3 (CH_2, minor), 22.8 (CH_2), 20.9 (CH_3, major), 20.5 (CH_3, minor), 20.0 (CH_3, major), 20.0 (CH_3, minor), 10.4 (CH_3); LRMS (ES^+) *m/z* 853 (40%, $[2M+Na]^+$), 438 (100%, $[M+Na]^+$); Elemental calcd. for $C_{20}H_{33}O_6NS$: C, 57.81; H, 8.00; N, 3.37. Found: C, 57.59; H, 7.96; N, 3.31.

(*rac*)-1-(4-Methoxy-phenyl)-2-((2*S*,6*R*)-6-methyl-tetrahydro-pyran-2-yl)-ethanone (**8.28**)

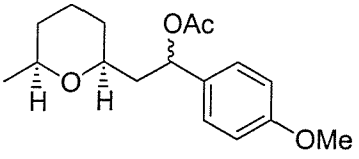


Under an atmosphere of N_2, to a solution of THP-diol (*rac*)-**8.19** (28 mg, 0.10 mmol) in CH_2Cl_2 (2 mL) was added dry pyridine (32 μL, 0.40 mmol) and methane sulfonyl chloride (31 μL, 0.40 mmol). After 4 h H_2O (2 mL) was added and the organic phase separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 3 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification through a quick plug of silica (30% EtOAc/CH_2Cl_2) gave the *bis*-mesylate (44 mg, 0.10 mmol) as a white foam.

Under an atmosphere of N_2, to a solution of the *bis*-mesylate (44 mg, 0.10 mmol) in DME (3 mL) was added NaI (90 mg, 0.60 mmol), Bu_3SnH (67 μL, 0.25 mmol) and AIBN (3 mg, 0.02 mmol). The reaction mixture was heated at 80 °C for 4 h then cooled to rt whereupon NaI (90 mg, 0.60 mmol) and AIBN (2 mg, 0.01 mmol) were added. The reaction mixture was heated at 80 °C for a further 2 h before quenching by addition of MeOH (2 mL). The solution was concentrated *in vacuo* and then taken up in EtOAc (10 mL). H_2O (10 mL) was added and the organic phase separated and washed with KF (10% w/v, aq) before being dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification by column chromatography on silica gel (15% EtOAc/hexane) gave THP **8.28** (21 mg, 0.09 mmol, 85%) as a colourless oil: IR ν_{max} (neat) 2931 (m), 1675 (s), 1600 (s), 1510 (m), 1260 (s), 1214 (s), 1172 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.95 (2H, d, *J* = 8.8 Hz, C**H**), 6.93 (2H, d, *J* = 8.8 Hz, C**H**), 3.96 (1H, dddd, *J* = 2.0, 6.0, 6.8, 13.1 Hz, OC**H**CH_2C=O), 3.87 (3H, s, OC**H**$_3$), 3.50 (1H, ddq, *J* = 2.0, 11.0, 6.0 Hz, OC**H**CH_3), 3.26 (1H, dd, *J* = 6.0, 15.8 Hz, C**H**HC=O), 2.93 (1H, dd, *J* = 6.8, 15.8 Hz, CHHC=O), 1.86-1.68 (2H, m, C**H**$_2$), 1.65-1.50 (2H, m, C**H**$_2$), 1.39-1.12 (2H, m, C**H**$_2$), 1.14 (3H, d, *J* = 6.0 Hz, C**H**$_3$CHO); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 197.1 (C), 163.6 (C), 130.7 (CH), 130.6 (C), 113.8 (CH), 74.5 (CH), 74.2 (CH), 55.6 (CH_3), 45.4 (CH_2), 33.3 (CH_2), 31.6 (CH_2), 23.7 (CH_2), 22.3 (CH_3); LRMS

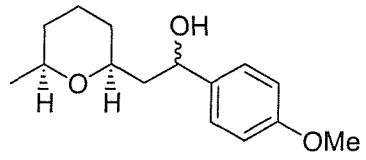
(GCCI) 8.58 min, *m/z* 249 (50%, $[M+H]^+$), 135 (100%); HRMS (EI) $C_{15}H_{20}O_3^{+\cdot}$ Calcd. 248.1412, found 248.1412.

(*rac*)-Acetic acid 1-(4-methoxy-phenyl)-2-((2*S*,6*S*)-6-methyl-tetrahydro-pyran-2-yl)-ethyl ester (**8.29**)



At 0 °C to a solution of ketone **8.28** (12 mg, 0.05 mmol) in MeOH (1 mL) was added $NaBH_4$ (4 mg, 0.1 mmol). After 20 min the reaction was quenched by careful addition of 2M HCl (1 mL), H_2O (5 mL) and EtOAc (10 mL). The organic phase was separated and the aqueous phase extracted with EtOAc (2 x 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a colourless oil. Purification by column chromatography on silica gel (15% EtOAc/hexane → 30%) gave a 1:1 inseparable mixture of diastereoisomers (A/B) of THP-acetate **8.29** (11 mg, 0.04 mmol, 80%) as a colourless oil: IR ν_{max} (neat) 2931 (m), 2930 (s), 1737 (s), 1514 (s), 1370 (m), 1236 (s), 1081 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.29 (4H, d, *J* = 8.8 Hz, C**H** x 2 A/B), 6.87 (2H, d, *J* = 8.8 Hz, C**H** x 2), 6.85 (2H, d, *J* = 8.8 Hz, C**H** x 2), 5.98-5.90 (2H, m, C**H**OAc A/B), 3.81 (3H, s, OC**H**$_3$), 3.80 (3H, s, OC**H**$_3$), 3.42-3.18 (3H, m, OC**H**CH$_3$ A/B, OC**H**CH$_2$CHOAc), 3.09 (1H, dddd, *J* = 2.0, 4.3, 8.8, 13.0 Hz, OC**H**CH$_2$CHOAc), 2.17 (1H, ddd, *J* = 6.8, 8.8, 13.8 Hz, C**H**HCHOAc), 2.04 (3H, s, C**H**$_3$C=O), 2.03 (3H, s, C**H**$_3$C=O), 2.01-1.70 (7H, m, C**H**H x 2 A/B, C**H**HCHOAc A/B, C**H**HCHOAc), 1.62-1.33 (6H, m, C**H**H x 3 A/B), 1.28-1.07 (2H, m, C**H**H A/B), 1.18 (3H, d, *J* = 6.0 Hz, C**H**$_3$CHO), 1.16 (3H, d, *J* = 6.0 Hz, C**H**$_3$CHO); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.4 (C), 170.3 (C), 159.3 (C), 159.3 (C), 133.5 (C), 133.0 (C), 128.2 (CH), 128.0 (CH), 113.9 (CH), 74.7 (CH), 74.2 (CH), 74.1 (CH), 73.9 (CH), 73.4 (CH), 72.5 (CH), 55.4 (CH_3), 43.3 (CH_2), 42.9 (CH_2), 33.4 (CH_2), 33.3 (CH_2), 31.6 (CH_2), 31.4 (CH_2), 23.9 (CH_2), 23.7 (CH_2), 22.3 (CH_3), 22.3 (CH_3), 21.5 (CH_3), 21.4 (CH_3); LRMS (GCEI) 8.27 min, *m/z* 292 (5%, $M^{+\cdot}$), 134 (100%); HRMS (EI) $C_{17}H_{24}O_4^{+\cdot}$ Calcd. 292.1675, found 292.1673.

1-(4-Methoxy-phenyl)-2-((2*S*,6*R*)-6-methyl-tetrahydro-pyran-2-yl)-ethanol (**8.30**)



At 0 °C to a solution of ketone **8.28** (12 mg, 0.05 mmol) in MeOH (1 mL) was added $NaBH_4$ (4 mg, 0.1 mmol). After 20 min the reaction was quenched by careful addition of 2M HCl (1 mL), H_2O (5 mL) and Et_2O (10 mL). The organic phase was separated and the aqueous phase extracted with Et_2O (2 x 10 mL). The combined organic phases were washed with $NaHCO_3$ (sat aq, 10 mL) then dried ($MgSO_4$) and concentrated *in vacuo* to give a colourless oil. Purification by column chromatography on silica gel (15% EtOAc/hexane → 30%) gave a 2:1 inseparable mixture of diastereoisomers of alcohol **8.30** (10 mg, 0.04 mmol, 85%) as a colourless oil: IR ν_{max} (neat) 3423 (s), 2932 (s), 1612 (s), 1512 (s), 1244 (s), 1174 (s), 1084 (s), 1035 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.30 (4H, d, J = 8.8 Hz, C**H** major/minor), 6.90 (2H, d, J = 8.8 Hz, C**H** minor), 6.88 (2H, d, J = 8.8 Hz, C**H** major), 4.98 (1H, br s, C**H**OH minor), 4.90 (1H, dd, J = 2.5, 10.0 Hz, C**H**OH major), 4.44 (1H, br, O**H** major), 3.90 (1H, br, O**H** minor), 3.81 (3H, s, OC**H**$_3$ minor), 3.80 (3H, s, OC**H**$_3$ major), 3.69 (1H, tt, J = 2.0, 10.8 Hz, OC**H**CH$_2$CHOH major), 3.60-3.49 (2H, m, OC**H**CH$_3$ major, OC**H**CH$_2$CHOH minor), 3.43 (1H, ddq, J = 2.0, 11.0, 6.2 Hz, OC**H**CH$_3$ minor), 1.99-1.17 (16H, m, C**H**$_2$ x 4 major/minor), 1.22 (3H, d, J = 6.2 Hz, C**H**$_3$CHO major), 1.21 (3H, d, J = 6.2 Hz, C**H**$_3$CHO minor); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 158.9 (C, major), 158.7 (C, minor), 137.1 (C, major/minor), 126.9 (CH, major), 126.8 (CH, minor), 113.8 (CH, major), 113.7 (CH, minor), 79.3 (CH, major), 75.8 (CH, minor), 74.4 (CH, major), 74.3 (CH, minor), 74.3 (CH, major), 71.4 (CH, minor), 55.4 (CH_3), 45.7 (CH_2, major), 44.0 (CH_2, minor), 33.2 (CH_2, major), 33.1 (CH_2, minor), 31.8 (CH_2, major), 30.9 (CH_2, minor), 23.6 (CH_2, major), 23.4 (CH_2, minor), 22.4 (CH_3, major), 22.3 (CH_3, minor); LRMS (GCEI) 8.26 min, *m/z* 250 (15%, $M^{+\cdot}$), 137 (100%); HRMS (ES^+) $C_{15}H_{22}O_3Na^+$ Calcd. 273.1461, found 273.1465.

Chapter 11

References

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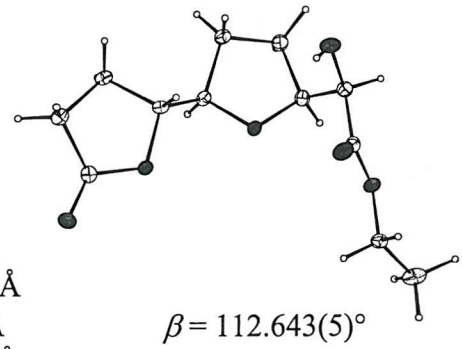
Chapter 12

Appendix

X-ray data for **4.11**

Table 1. Crystal data and structure refinement.



Identification code	01SOT170
Empirical formula	$C_{12}H_{18}O_6$
Formula weight	258.26
Temperature	120(2) K
Wavelength	0.71069 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 12.046(5) Å
	b = 7.916(5) Å β = 112.643(5)°
	c = 14.619(5) Å
Volume	1286.6(11) Å^3
Z	4
Density (calculated)	1.333 Mg / m^3
Absorption coefficient	0.107 mm^{-1}
F(000)	552
Crystal	Colourless Plate
Crystal size	0.20 × 0.15 × 0.03 mm^3
θ range for data collection	2.98 – 25.02°
Index ranges	$-14 \le h \le 14$, $-8 \le k \le 9$, $-15 \le l \le 15$
Reflections collected	7899
Independent reflections	2142 [R_{int} = 0.0572]
Completeness to θ = 25.02°	94.3 %
Max. and min. transmission	0.9968 and 0.9789
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2142 / 0 / 236
Goodness-of-fit on F^2	0.968
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0361, $wR2$ = 0.0795
R indices (all data)	$R1$ = 0.0647, $wR2$ = 0.0907
Extinction coefficient	0.012(2)
Largest diff. peak and hole	0.142 and –0.205 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were located from the difference map and fully refined.

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	1622(2)	6924(2)	8504(1)	23(1)	1
C2	2411(2)	6303(3)	7992(1)	26(1)	1
C3	1694(2)	6731(3)	6911(1)	25(1)	1
C4	398(2)	6664(3)	6845(1)	23(1)	1
C5	−432(2)	7869(3)	6100(1)	24(1)	1
C6	−593(2)	7494(3)	5039(1)	27(1)	1
C7	−1806(2)	8305(3)	4453(1)	27(1)	1
C8	−2506(2)	8083(2)	5129(1)	24(1)	1
C9	−3415(2)	6649(2)	4828(1)	25(1)	1
C10	−3821(2)	6256(2)	5662(1)	24(1)	1
C11	−4738(2)	7391(3)	6701(1)	26(1)	1
C12	−5539(2)	8849(3)	6671(2)	35(1)	1
O1	1878(1)	7204(2)	9373(1)	29(1)	1
O2	486(1)	7143(2)	7840(1)	25(1)	1
O3	−1622(1)	7727(2)	6105(1)	27(1)	1
O4	−2971(1)	5189(2)	4533(1)	32(1)	1
O5	−3671(1)	4916(2)	6087(1)	33(1)	1
O6	−4357(1)	7594(2)	5875(1)	26(1)	1

X-ray data for compound **5.7**

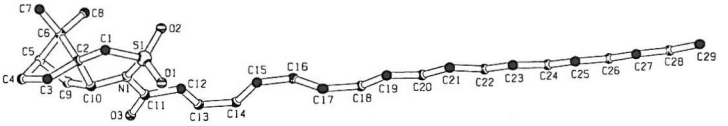


Table 1. Crystal data and structure refinement.

Identification code	**02sot035**	
Empirical formula	$C_{29}H_{49}NO_3S$	
Formula weight	491.75	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	$a = 7.8244(4)$ Å	$\alpha = 90°$
	$b = 9.0840(5)$ Å	$\beta = 90°$
	$c = 39.664(2)$ Å	$\gamma = 90°$
Volume	2819.2(3) $Å^3$	
Z	4	
Density (calculated)	1.159 Mg / m^3	
Absorption coefficient	0.144 mm^{-1}	
F(000)	1080	
Crystal	Plate; colourless	
Crystal size	0.20 × 0.12 × 0.03 mm^3	
θ range for data collection	2.30 – 27.43°	
Index ranges	$-7 \le h \le 9$, $-8 \le k \le 10$, $-48 \le l \le 45$	
Reflections collected	4080	
Independent reflections	2440 [$R_{int} = 0.0897$]	

Completeness to $\theta = 27.43°$	49.4 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9957 and 0.9718
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2440 / 0 / 312
Goodness-of-fit on F^2	0.969
Final R indices $[F^2 > 2\sigma(F^2)]$	$R1 = 0.0676$, $wR2 = 0.1587$
R indices (all data)	$R1 = 0.1137$, $wR2 = 0.1821$
Absolute structure parameter	0.3(2)
Extinction coefficient	0.0024(17)
Largest diff. peak and hole	0.343 and −0.331 e Å^{-3}

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Data collection and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Program used to solve structure**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Program used to refine structure**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).

Further information: http://www.soton.ac.uk/~xservice/strat.htm

Special details:

Racemic Twin (54 : 46 %). In the configuration shown in the figure C2 = S, C5 = R, C10 = R.

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	6815(10)	1477(8)	1620(2)	36(2)	1
C2	7750(10)	2494(7)	1856(2)	26(2)	1
C3	7637(10)	4159(8)	1786(2)	36(2)	1
C4	8381(10)	4841(8)	2113(2)	35(2)	1
C5	8798(10)	3511(8)	2336(2)	33(2)	1
C6	7333(10)	2442(8)	2243(2)	31(2)	1
C7	5516(10)	2998(9)	2326(2)	44(2)	1
C8	7484(10)	881(8)	2404(2)	37(2)	1
C9	10348(10)	2704(9)	2188(2)	31(2)	1
C10	9704(9)	2172(8)	1847(2)	26(2)	1
C11	11492(11)	−40(9)	1757(2)	28(2)	1
C12	11661(11)	−1553(8)	1641(2)	30(2)	1
C13	13194(11)	−2176(8)	1640(2)	33(2)	1
C14	13650(10)	−3712(8)	1532(2)	40(2)	1
C15	12266(10)	−4611(8)	1361(2)	38(2)	1
C16	12842(9)	−6188(8)	1306(2)	36(2)	1
C17	12938(10)	−6834(9)	1014(2)	42(2)	1
C18	13610(10)	−8400(8)	957(2)	34(2)	1
C19	12577(10)	−9314(8)	711(2)	35(2)	1
C20	13363(11)	−10817(8)	652(2)	35(2)	1
C21	12486(11)	−11730(8)	381(2)	42(2)	1

C22	13357(11)	−13209(8)	319(2)	39(2)	1
C23	12623(11)	−14101(8)	30(2)	41(2)	1
C24	13451(11)	−15602(8)	−16(2)	32(2)	1
C25	12741(10)	−16465(7)	−308(2)	36(2)	1
C26	13533(10)	−18027(8)	−335(2)	36(2)	1
C27	12812(11)	−18936(8)	−618(2)	37(2)	1
C28	13568(11)	−20481(8)	−629(2)	40(2)	1
C29	12803(11)	−21471(8)	−892(2)	50(2)	1
N1	9856(8)	573(7)	1777(1)	31(2)	1
O1	8651(6)	−117(5)	1201(1)	41(1)	1
O2	7530(6)	−1388(5)	1699(1)	43(2)	1
O3	12719(6)	704(5)	1843(1)	30(1)	1
S1	8191(2)	−70(2)	1546(1)	34(1)	1

X-ray data for compound **7.35**

Table 1. Crystal data and structure refinement.

Identification code	**03sot046**
Empirical formula	$C_{20}H_{24}O_5$
Formula weight	344.39
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	*P*–1
Unit cell dimensions	a = 7.9840(2) Å α = 83.9370(10)°
	b = 10.2412(3) Å β = 72.6290(10)°
	c = 11.5363(3) Å γ = 74.108(2)°
Volume	865.55(4) Å^3
Z	2
Density (calculated)	1.321 Mg / m^3
Absorption coefficient	0.094 mm^{-1}
F(000)	368
Crystal	Block; colourless
Crystal size	0.36 × 0.20 × 0.20 mm^3
θ range for data collection	3.70 – 27.49°
Index ranges	$-10 \le h \le 10$, $-13 \le k \le 13$, $-14 \le l \le 14$
Reflections collected	15201
Independent reflections	3930 [R_{int} = 0.0438]
Completeness to θ = 27.49°	98.9 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9814 and 0.9669
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3930 / 0 / 229
Goodness-of-fit on F^2	0.990
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0403, *wR2* = 0.1083
R indices (all data)	*R1* = 0.0466, *wR2* = 0.1137
Extinction coefficient	0.027(8)

Largest diff. peak and hole	0.313 and −0.268 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details:

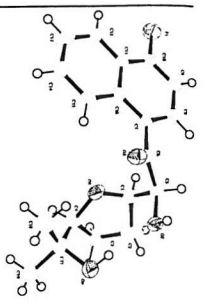
C13 = S, C14 = R, C17 = S.

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	138(2)	6312(1)	7628(1)	19(1)	1
C2	−1712(2)	7082(1)	7925(1)	20(1)	1
C3	−2758(2)	7374(1)	7078(1)	22(1)	1
C4	−4529(2)	8118(1)	7407(1)	28(1)	1
C5	−5363(2)	8611(1)	8600(1)	32(1)	1
C6	−4382(2)	8361(1)	9425(1)	31(1)	1
C7	−2543(2)	7615(1)	9113(1)	25(1)	1
C8	−1486(2)	7379(1)	9945(1)	30(1)	1
C9	293(2)	6670(1)	9642(1)	29(1)	1
C10	1120(2)	6124(1)	8471(1)	24(1)	1
C11	3982(2)	5172(2)	8910(1)	36(1)	1
C12	977(2)	5621(1)	6433(1)	18(1)	1
C13	2643(2)	5964(1)	5545(1)	19(1)	1
C14	2266(1)	7489(1)	5235(1)	18(1)	1
C15	3902(2)	7916(1)	4335(1)	24(1)	1
C16	3324(2)	8325(1)	3171(1)	22(1)	1
C17	1254(2)	8722(1)	3631(1)	17(1)	1
C18	252(2)	8551(1)	2732(1)	18(1)	1
C19	−1770(2)	8742(1)	3377(1)	24(1)	1
C20	535(2)	9578(1)	1683(1)	25(1)	1
O1	2861(1)	5344(1)	8111(1)	32(1)	1
O2	305(1)	4804(1)	6159(1)	24(1)	1
O3	3230(1)	5191(1)	4485(1)	25(1)	1
O4	827(1)	7831(1)	4668(1)	18(1)	1
O5	1000(1)	7239(1)	2202(1)	23(1)	1

X-ray data for compound **7.36**

Table 1. Crystal data and structure refinement.



Identification code	**03sot060**	
Empirical formula	$C_{19}H_{21}FO_4$	
Formula weight	332.36	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Tetragonal	
Space group	$P4_32_12$	
Unit cell dimensions	$a = 8.5629(5)$ Å	$\alpha = 90°$
	$b = 8.5629(5)$ Å	$\beta = 90°$
	$c = 47.353(4)$ Å	$\gamma = 90°$
Volume	3472.1(4) Å^3	
Z	8	
Density (calculated)	1.272 Mg / m^3	
Absorption coefficient	0.095 mm^{-1}	
$F(000)$	1408	
Crystal	Shard; Colourless	
Crystal size	0.25 × 0.16 × 0.06 mm^3	
θ range for data collection	2.94 – 27.47°	
Index ranges	$-8 \le h \le 8$, $-9 \le k \le 9$, $-60 \le l \le 61$	
Reflections collected	11209	
Independent reflections	2735 [$R_{int} = 0.0907$]	
Completeness to $\theta = 27.47°$	76.1 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9943 and 0.9766	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2735 / 0 / 222	
Goodness-of-fit on F^2	0.970	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0598$, $wR2 = 0.1274$	
R indices (all data)	$R1 = 0.1321$, $wR2 = 0.1549$	
Absolute structure parameter	–0.7(19)	
Extinction coefficient	0.0075(13)	
Largest diff. peak and hole	0.996 and –0.215 e Å^{-3}	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. **A51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details:

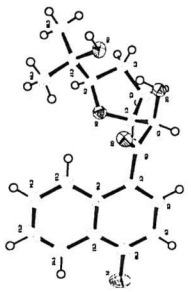
All hydrogen atoms were fixed.
The absolute structure could not be accurately determined.

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	3149(6)	8609(5)	−384(1)	39(1)	1
C2	3162(7)	10244(6)	−254(1)	56(2)	1
C3	4043(8)	11187(6)	−474(1)	68(2)	1
C4	5179(8)	10025(6)	−603(1)	59(2)	1
C5	3321(6)	7240(5)	−181(1)	33(1)	1
C6	3674(6)	5799(5)	−353(1)	31(1)	1
C7	2486(5)	5293(5)	−566(1)	27(1)	1
C8	937(6)	5365(5)	−501(1)	37(1)	1
C9	−221(6)	4814(5)	−687(1)	40(1)	1
C10	264(6)	4230(5)	−940(1)	36(1)	1
C11	1821(5)	4120(5)	−1027(1)	31(1)	1
C12	2247(6)	3502(6)	−1292(1)	40(1)	1
C13	3766(6)	3449(6)	−1366(1)	49(1)	1
C14	4928(6)	4041(6)	−1186(1)	45(1)	1
C15	4535(6)	4645(5)	−927(1)	35(1)	1
C16	2972(5)	4689(5)	−836(1)	29(1)	1
C17	6793(7)	9971(6)	−476(1)	54(2)	1
C18	7686(7)	8523(7)	−576(1)	83(2)	1
C19	7719(8)	11452(8)	−542(1)	94(3)	1
O1	4425(4)	8537(4)	−576(1)	45(1)	1
O2	4572(4)	7582(3)	8(1)	37(1)	1
O3	4891(4)	5082(4)	−321(1)	38(1)	1
O4	6708(4)	9906(4)	−172(1)	47(1)	1
F1	−864(3)	3694(3)	−1123(1)	52(1)	1

X-ray data for compound (*rac*)-**7.36**

Table 1. Crystal data and structure refinement.

Identification code	**03sot047**	
Empirical formula	$C_{19}H_{21}FO_4$	
Formula weight	332.36	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*C*2/*c*	
Unit cell dimensions	*a* = 18.9337(4) Å	$\alpha = 90°$
	b = 14.3837(3) Å	$\beta = 110.0380(10)°$
	c = 13.2136(3) Å	$\gamma = 90°$
Volume	3380.71(13) $Å^3$	
Z	8	
Density (calculated)	1.306 Mg / m^3	
Absorption coefficient	0.098 mm^{-1}	

F(000)	1408
Crystal	Slab; Colourless
Crystal size	0.35 × 0.30 × 0.06 mm^3
θ range for data collection	3.27 – 27.50°
Index ranges	$-24 \le h \le 24, -18 \le k \le 18, -16 \le l \le 17$
Reflections collected	20040
Independent reflections	3875 [$R_{int} = 0.0626$]
Completeness to $\theta = 27.50°$	99.6 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9942 and 0.9666
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3875 / 0 / 301
Goodness-of-fit on F^2	1.042
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0434$, $wR2 = 0.1014$
R indices (all data)	$R1 = 0.0705$, $wR2 = 0.1154$
Largest diff. peak and hole	0.168 and –0.280 e $Å^{-3}$

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details:

All hydrogen atoms found from the difference map.

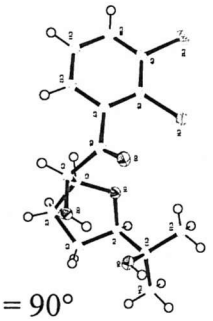
Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2$ × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	1751(1)	4079(1)	419(1)	31(1)	1
C2	2289(1)	4778(1)	203(1)	39(1)	1
C3	2258(1)	4561(1)	–936(1)	34(1)	1
C4	2057(1)	3530(1)	–1078(1)	32(1)	1
C5	946(1)	4429(1)	218(1)	28(1)	1
C6	477(1)	3596(1)	315(1)	26(1)	1
C7	709(1)	3083(1)	1359(1)	27(1)	1
C8	836(1)	3566(1)	2304(1)	32(1)	1
C9	995(1)	3103(1)	3295(1)	37(1)	1
C10	1023(1)	2162(1)	3297(1)	38(1)	1
C11	918(1)	1617(1)	2371(1)	33(1)	1
C12	966(1)	629(1)	2401(2)	42(1)	1
C13	890(1)	143(1)	1490(2)	45(1)	1
C14	762(1)	602(1)	510(2)	40(1)	1
C15	694(1)	1550(1)	446(1)	32(1)	1

C16	764(1)	2088(1)	1373(1)	28(1)	1
C17	1531(1)	3265(1)	−2204(1)	31(1)	1
C18	1946(1)	3384(1)	−3002(1)	43(1)	1
C19	1243(1)	2276(1)	−2238(2)	43(1)	1
O1	1698(1)	3316(1)	−302(1)	31(1)	1
O2	630(1)	4877(1)	−785(1)	31(1)	1
O3	−52(1)	3330(1)	−453(1)	33(1)	1
O4	905(1)	3903(1)	−2463(1)	32(1)	1
F1	1163(1)	1698(1)	4242(1)	54(1)	1

X-ray data for compound (*rac*)-**7.37**

Table 1. Crystal data and structure refinement.



Identification code	**03sot058**	
Empirical formula	$C_{15}H_{18}Cl_2O_4$	
Formula weight	333.19	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*C2/c*	
Unit cell dimensions	a = 18.1907(3) Å	α = 90°
	b = 13.6018(2) Å	β = 109.0270(10)°
	c = 13.5038(2) Å	γ = 90°
Volume	3158.65(8) Å^3	
Z	8	
Density (calculated)	1.401 Mg / m^3	
Absorption coefficient	0.423 mm^{-1}	
F(000)	1392	
Crystal	Shard; Colourless	
Crystal size	0.25 × 0.22 × 0.10 mm^3	
θ range for data collection	3.19 – 27.47°	
Index ranges	$-21 \le h \le 23$, $-16 \le k \le 17$, $-17 \le l \le 17$	
Reflections collected	22368	
Independent reflections	3621 [R_{int} = 0.0529]	
Completeness to θ = 27.47°	99.8 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9589 and 0.9016	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3621 / 0 / 262	
Goodness-of-fit on F^2	1.038	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0357, $wR2$ = 0.0832	
R indices (all data)	$R1$ = 0.0445, $wR2$ = 0.0883	
Largest diff. peak and hole	0.352 and −0.316 e Å^{-3}	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure**

solution: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details:

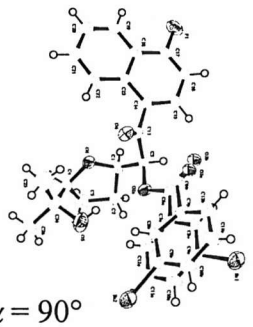
All hydrogen atoms found from the difference map.

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	1793(1)	4093(1)	5350(1)	18(1)	1
C2	2357(1)	4838(1)	5140(1)	22(1)	1
C3	2355(1)	4599(1)	4030(1)	20(1)	1
C4	2120(1)	3514(1)	3881(1)	18(1)	1
C5	960(1)	4459(1)	5159(1)	18(1)	1
C6	458(1)	3570(1)	5220(1)	17(1)	1
C7	688(1)	2988(1)	6223(1)	16(1)	1
C8	700(1)	1956(1)	6224(1)	18(1)	1
C9	882(1)	1455(1)	7174(1)	20(1)	1
C10	1036(1)	1962(1)	8113(1)	21(1)	1
C11	1024(1)	2977(1)	8115(1)	21(1)	1
C12	861(1)	3490(1)	7176(1)	20(1)	1
C13	1566(1)	3247(1)	2789(1)	18(1)	1
C14	1993(1)	3357(1)	1993(1)	25(1)	1
C15	1244(1)	2213(1)	2767(1)	25(1)	1
O1	1749(1)	3285(1)	4650(1)	19(1)	1
O2	644(1)	4951(1)	4191(1)	20(1)	1
O3	−101(1)	3329(1)	4482(1)	22(1)	1
O4	933(1)	3949(1)	2557(1)	20(1)	1
Cl1	499(1)	1291(1)	5073(1)	25(1)	1
Cl2	916(1)	180(1)	7205(1)	27(1)	1

X-ray data for compound **7.38**

Table 1. Crystal data and structure refinement.



Identification code	**03sot068**	
Empirical formula	$C_{26}H_{24}BrFO_5$	
Formula weight	515.36	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 12.2137(4) Å	α = 90°
	b = 7.3966(3) Å	β = 103.7100(10)°
	c = 12.9299(5) Å	γ = 90°

Volume	1134.80(7) Å^3
Z	2
Density (calculated)	1.508 Mg / m^3
Absorption coefficient	1.855 mm^{-1}
F(000)	528
Crystal	Slab; Colourless
Crystal size	0.10 × 0.06 × 0.02 mm^3
θ range for data collection	3.20 – 27.49°
Index ranges	$-15 \le h \le 15, -7 \le k \le 9, -16 \le l \le 16$
Reflections collected	11312
Independent reflections	4793 [R_{int} = 0.0754]
Completeness to θ = 27.49°	98.8 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9638 and 0.8362
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4793 / 19 / 329
Goodness-of-fit on F^2	1.044
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0589, $wR2$ = 0.1186
R indices (all data)	$R1$ = 0.0873, $wR2$ = 0.1310
Absolute structure parameter	–0.021(12)
Largest diff. peak and hole	0.620 and –0.533 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details:

All hydrogen atoms were fixed.
The 3-bromobenzoate group is disordered over two sites.

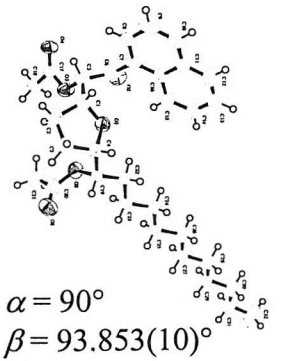
Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	1480(4)	–1862(6)	3467(4)	30(1)	1
C2	1047(4)	–3501(7)	2751(4)	37(1)	1
C3	1780(6)	–3417(8)	1951(5)	48(2)	1
C4	2012(5)	–1427(8)	1830(4)	36(1)	1
C5	605(4)	–862(6)	3921(4)	28(1)	1
C6A	–1282(5)	114(10)	3392(5)	28(2)	0.8692(12)
C7A	–2297(5)	345(9)	2489(5)	30(1)	0.8692(12)
C8A	–3231(4)	1126(9)	2719(4)	33(1)	0.8692(12)
C9A	–4193(5)	1398(9)	1912(5)	34(1)	0.8692(12)
C10A	–4242(5)	862(10)	889(5)	45(2)	0.8692(12)

C11A	−3314(6)	32(10)	663(5)	50(2)	0.8692(12)
C12A	−2332(5)	−245(9)	1461(5)	39(2)	0.8692(12)
Br1	−5473(1)	2486(1)	2237(1)	50(1)	0.8692(12)
O2A	−403(3)	−597(4)	3086(3)	33(1)	0.8692(12)
O3A	−1235(4)	544(8)	4292(3)	33(1)	0.8692(12)
C6B	−1250(30)	470(100)	3750(30)	28(2)	0.1308(12)
C7B	−2330(20)	590(70)	2900(20)	30(1)	0.1308(12)
C8B	−2370(20)	480(60)	1840(20)	33(1)	0.1308(12)
C9B	−3400(20)	870(60)	1110(14)	34(1)	0.1308(12)
C10B	−4320(30)	1520(80)	1430(20)	45(2)	0.1308(12)
C11B	−4200(30)	1920(60)	2480(20)	50(2)	0.1308(12)
C12B	−3220(30)	1450(60)	3230(20)	39(2)	0.1308(12)
Br2	−3623(3)	343(7)	−360(4)	50(1)	0.1308(12)
O2B	−403(3)	−597(4)	3086(3)	33(1)	0.1308(12)
O3B	−1070(40)	630(70)	4670(30)	33(1)	0.1308(12)
C13	1089(4)	974(6)	4348(4)	27(1)	1
C14	1888(4)	942(6)	5424(4)	29(1)	1
C15	1517(4)	149(7)	6239(4)	32(1)	1
C16	2193(5)	176(8)	7286(4)	38(1)	1
C17	3223(4)	935(8)	7458(4)	38(1)	1
C18	3672(4)	1732(6)	6665(4)	34(1)	1
C19	4768(3)	2473(9)	6874(4)	39(1)	1
C20	5148(4)	3309(8)	6093(5)	45(1)	1
C21	4456(4)	3388(7)	5047(4)	41(1)	1
C22	3406(4)	2645(8)	4813(3)	34(1)	1
C23	2975(4)	1776(6)	5614(4)	27(1)	1
C24	1286(4)	−359(8)	914(5)	48(2)	1
C25	1572(7)	1579(11)	993(7)	88(3)	1
C26	1399(6)	−1077(12)	−152(5)	76(2)	1
O1	1937(3)	−615(5)	2824(3)	33(1)	1
O4	849(2)	2335(5)	3824(2)	37(1)	1
O5	127(3)	−622(7)	929(3)	59(1)	1
F1	3879(3)	947(5)	8468(2)	56(1)	1

X-ray data for compound (*rac*)-**7.48**

Table 1. Crystal data and structure refinement.

Identification code	**03sot021**	
Empirical formula	$C_{32}H_{44}O_6$	
Formula weight	524.67	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*C*2/*c*	
Unit cell dimensions	$a = 49.711(16)$ Å	$\alpha = 90°$
	$b = 7.9573(19)$ Å	$\beta = 93.853(10)°$
	$c = 15.281(5)$ Å	$\gamma = 90°$
Volume	6031(3) Å^3	

Z	8
Density (calculated)	1.156 Mg / m^3
Absorption coefficient	0.078 mm^{-1}
F(000)	2272
Crystal	Plate; Colourless
Crystal size	0.34 × 0.16 × 0.03 mm^3
θ range for data collection	2.93 – 27.39°
Index ranges	$-47 \le h \le 64$, $-9 \le k \le 8$, $-19 \le l \le 18$
Reflections collected	9690
Independent reflections	4180 [$R_{int} = 0.1533$]
Completeness to $\theta = 27.39°$	61.0 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9977 and 0.9739
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4180 / 0 / 346
Goodness-of-fit on F^2	0.898
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0811$, $wR2 = 0.1196$
R indices (all data)	$R1 = 0.3297$, $wR2 = 0.1752$
Largest diff. peak and hole	0.197 and –0.205 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details:

All hydrogen atoms were fixed.

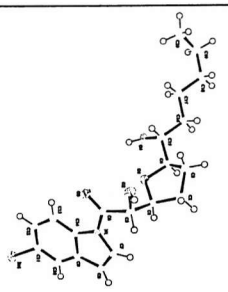
Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	5667(2)	2201(9)	5104(5)	55(2)	1
C2	5434(1)	1067(10)	4788(5)	62(2)	1
C3	5580(1)	–507(8)	4515(4)	58(2)	1
C4	5855(2)	150(9)	4247(5)	53(2)	1
C5	5607(2)	4077(10)	5137(5)	55(2)	1
C6	5867(2)	5050(10)	5188(7)	56(2)	1
C7	6063(2)	4654(8)	5947(7)	51(2)	1
C8	5979(2)	4672(7)	6786(8)	54(2)	1
C9	6160(2)	4360(8)	7519(6)	66(3)	1
C10	6427(2)	4018(9)	7381(6)	70(3)	1
C11	6522(2)	3995(9)	6530(7)	57(2)	1
C12	6794(2)	3629(9)	6398(7)	75(3)	1
C13	6886(2)	3560(9)	5578(8)	81(3)	1

C14	6702(2)	3847(9)	4867(6)	67(2)	1
C15	6436(2)	4211(8)	4954(6)	55(2)	1
C16	6337(2)	4316(8)	5797(6)	48(2)	1
C17	5258(2)	5745(10)	4453(6)	49(2)	1
C18	5111(1)	6066(8)	3583(4)	56(2)	1
C19	5891(1)	12(8)	3263(5)	47(2)	1
C20	5487(2)	137(13)	2285(6)	59(2)	1
C21	5292(1)	1380(10)	1864(5)	84(3)	1
C22	6156(1)	692(8)	2995(5)	51(2)	1
C23	6197(1)	541(8)	2007(5)	53(2)	1
C24	6484(1)	988(8)	1791(5)	58(2)	1
C25	6529(1)	905(8)	825(5)	54(2)	1
C26	6820(1)	1244(9)	627(5)	70(2)	1
C27	6860(1)	1200(8)	−357(5)	58(2)	1
C28	7153(2)	1349(9)	−570(5)	68(2)	1
C29	7188(1)	1447(9)	−1543(5)	68(3)	1
C30	7474(2)	1485(9)	−1804(5)	77(3)	1
C31	7497(2)	1548(9)	−2794(5)	84(3)	1
C32	7778(2)	1545(10)	−3111(5)	103(3)	1
O1	5869(1)	1910(5)	4496(3)	50(1)	1
O2	5919(1)	6087(6)	4637(3)	63(2)	1
O3	5450(1)	4549(6)	4359(3)	57(2)	1
O4	5221(1)	6390(6)	5141(3)	55(2)	1
O5	5675(1)	962(6)	2796(3)	56(1)	1
O6	5483(1)	−1364(7)	2185(3)	72(2)	1

X-ray data for compound **7.92**

Table 1. Crystal data and structure refinement.



Identification code	**03sot101**	
Empirical formula	$C_{20}H_{26}BrNO_4$	
Formula weight	424.33	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	*Pbca*	
Unit cell dimensions	$a = 13.5119(4)$ Å	$\alpha = 90°$
	$b = 7.9111(2)$ Å	$\beta = 90°$
	$c = 35.2505(12)$ Å	$\gamma = 90°$
Volume	3768.07(19) Å^3	
Z	8	
Density (calculated)	1.496 Mg / m^3	
Absorption coefficient	2.207 mm^{-1}	
F(000)	1760	
Crystal	Plate; Colourless	
Crystal size	0.30 × 0.10 × 0.01 mm^3	
θ range for data collection	3.02 – 27.48°	
Index ranges	$-16 \le h \le 17$, $-10 \le k \le 9$, $-45 \le l \le 45$	
Reflections collected	18389	

Independent reflections	4046 [R_{int} = 0.1258]
Completeness to θ = 27.48°	93.6 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9783 and 0.5573
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4046 / 0 / 239
Goodness-of-fit on F^2	1.025
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0626, $wR2$ = 0.1265
R indices (all data)	$R1$ = 0.1079, $wR2$ = 0.1451
Extinction coefficient	0.0026(4)
Largest diff. peak and hole	0.582 and –0.673 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. **A51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details:

All hydrogen atoms were fixed.
The crystal system is not chiral.

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	4592(3)	3620(5)	1554(1)	20(1)	1
C2	5087(3)	4125(6)	1175(1)	24(1)	1
C3	4756(3)	2745(6)	901(1)	26(1)	1
C4	4558(3)	1265(5)	1163(1)	19(1)	1
C5	3840(3)	4917(6)	1698(1)	21(1)	1
C6	3249(3)	4185(6)	2029(1)	19(1)	1
C7	4697(3)	4566(6)	2468(1)	21(1)	1
C8	4907(3)	4187(6)	2832(1)	21(1)	1
C9	4059(3)	3362(5)	2993(1)	19(1)	1
C10	3836(3)	2787(5)	3358(1)	21(1)	1
C11	2892(3)	2166(6)	3423(1)	20(1)	1
C12	2185(3)	2073(6)	3137(1)	22(1)	1
C13	2390(3)	2617(6)	2776(1)	21(1)	1
C14	3331(3)	3274(5)	2703(1)	19(1)	1
C15	3889(3)	–108(6)	1015(1)	20(1)	1
C16	4336(3)	–1013(6)	675(1)	22(1)	1
C17	3670(3)	–2347(6)	501(1)	26(1)	1
C18	4062(4)	–3027(6)	126(1)	33(1)	1
C19	3445(4)	–4432(7)	–49(2)	36(1)	1
C20	2380(4)	–3935(6)	–132(2)	36(1)	1

N1	3735(2)	4003(5)	2375(1)	19(1)	1
O1	4098(2)	2051(4)	1488(1)	21(1)	1
O2	3171(2)	5343(4)	1406(1)	23(1)	1
O3	2392(2)	3741(4)	1993(1)	27(1)	1
O4	3695(2)	−1319(4)	1307(1)	20(1)	1
Br1	2544(1)	1433(1)	3919(1)	26(1)	1

X-ray data for compound (*rac*)-**8.19**

Table 1. Crystal data and structure refinement.

Identification code	**03SOT0094**
Empirical formula	$C_{15}H_{20}O_5$
Formula weight	280.31
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 8.8996(3) Å
	b = 14.8744(5) Å β = 92.199(2)°
	c = 10.3684(4) Å
Volume	1371.52(8) Å^3
Z	4
Density (calculated)	1.358 Mg / m^3
Absorption coefficient	0.101 mm^{-1}
F(000)	600
Crystal	Colourless Needle
Crystal size	0.10 × 0.05 × 0.03 mm^3
θ range for data collection	3.26 – 25.02°
Index ranges	$-10 \le h \le 10$, $-17 \le k \le 17$, $-12 \le l \le 12$
Reflections collected	4741
Independent reflections	2424 [R_{int} = 0.0232]
Completeness to θ = 25.02°	99.8 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9970 and 0.9899
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2424 / 0 / 185
Goodness-of-fit on F^2	1.039
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0332, $wR2$ = 0.0813
R indices (all data)	$R1$ = 0.0522, $wR2$ = 0.0886
Extinction coefficient	0.0062(18)
Largest diff. peak and hole	0.171 and –0.174 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure**

solution: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A46 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

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

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	7763(2)	1695(1)	7929(1)	27(1)	1
C2	6292(2)	2063(1)	8375(1)	24(1)	1
C3	6424(2)	2590(1)	9619(1)	27(1)	1
C4	4870(2)	2899(1)	9994(2)	29(1)	1
C5	3839(2)	2090(1)	10080(1)	29(1)	1
C6	3808(2)	1566(1)	8824(1)	24(1)	1
C7	2876(2)	704(1)	8867(1)	26(1)	1
C8	2988(2)	168(1)	7615(2)	27(1)	1
C9	2258(2)	518(1)	6412(1)	24(1)	1
C10	1159(2)	1187(1)	6407(2)	26(1)	1
C11	474(2)	1479(1)	5274(1)	28(1)	1
C12	873(2)	1111(1)	4106(1)	26(1)	1
C13	1977(2)	452(1)	4081(2)	29(1)	1
C14	2648(2)	159(1)	5232(2)	29(1)	1
C15	419(2)	1044(1)	1821(2)	37(1)	1
O1	8547(1)	1154(1)	8861(1)	34(1)	1
O2	5295(1)	1305(1)	8495(1)	23(1)	1
O3	3332(1)	154(1)	9928(1)	32(1)	1
O4	3693(1)	−535(1)	7646(1)	37(1)	1
O5	129(1)	1445(1)	3039(1)	35(1)	1