UNIVERSITY OF SOUTHAMPTON

Oxidative Approaches to the Synthesis of *bis*-Tetrahydrofuran *Annonaceous* Acetogenins

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ABSTRACT

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OXIDATIVE APPROACHES TO THE SYNTHESIS OF *BIS*-TETRAHYDROFURAN *ANNONACEOUS* ACETOGENINS

by Geoffrey Douglas Head

Two *bis*-THF *Annonaceous* Acetogenin structures were synthesised, one of which corresponded to the cytotoxic antitumour compound membranacin **3.19**. Both derived from key epoxide intermediate **6.7**, which was synthesized *via* the chiral auxiliary directed oxidative cyclisation of 1,5,9-trienedioate **4.44** by potassium permanganate. The second THF ring was installed using a Sharpless asymmetric epoxidation and epoxide opening strategy. A number of intermediates were designed with the potential for future library synthesis of natural product analogues.

The combination of the permanganate oxidation and Kennedy's perrhenate cyclisation of *bis*-homoallylic alcohols was used to synthesise simple *bis*-THF model **7.2**. This combined strategy allows access to the acetogenin *bis*-THF core.

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Abbreviations

Ac	acetyl
acac	acetylacetonate
AD	asymmetric dihydroxylation
AIBN	2,2'-azo*bis*-*iso*-butyronitrile
app.	apparent
aq	aqueous
Ar	aryl
ATP	adenosine triphosphate
BINAL-H	binaphthylaluminium hydride
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad (spectral)
Bu	butyl
Bz	benzoyl
Calc.	calculated
CAN	cerium ammonium nitrate
CI	chemical ionisation
CSA	camphor sulfonic acid
d	doublet (spectral)
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DCC	*N,N*-dicyclohexylcarbodiimide
de	diastereomeric excess
DEAD	diethylazodicarboxylate
DET	diethyl tartrate
DIBAL-H	di-*iso*-butylaluminium hydride
DIPEA	di-*iso*-propylethylamine
DIPT	di-*iso*-propyl tartrate
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide

DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
ED_{50}	effective dose for 50% of assay
ee	enantiomeric excess
EI	electron impact
ES	electrospray
Et	ethyl
eq.	equivalent(s)
FT	Fourier Transform
hr	hour(s)
HMPA	hexamethylphosphoramide
HRMS	high-resolution mass spectrometry
IDCP	iodonium dicollidine perchlorate
IR	infrared
KAPA	potassium-3-aminopropylamide
LD_{50}	lethal dose for 50% of assay
LDA	lithium di-*iso*-propylamide
LRMS	low-resolution mass spectrometry
m	multiplet (spectral)
***m*-CPBA**	*m*-chloroperoxybenzoic acid
Me	methyl
Mes	2,4,6-trimethylbenzyl (mesityl)
MEM	(2-methoxyethoxy)methyl
min	minute(s)
MMPP	magnesium monoperoxyphthalate hexahydrate
MOM	methoxymethyl
m.p	melting point
Ms	methanesulfonyl (mesyl)
NADH	reduced nicotinamide adenine dinucleotide
NaHMDS	sodium hexamethyldisilazane
NMO	4-methylmorpholine *N*-oxide

NMP	*N*-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
Ph	phenyl
PNB	*p*-nitrobenzoyl
ppm	parts per million
PPTS	pyridinium *p*-toluene sulfonic acid
Pr	propyl
py	pyridine
q	quartet (spectral)
quin.	quintet (spectral)
s	singlet (spectral)
SAR	structure activity relationship
SEM	2-trimethylsilylethoxymethoxy
t	triplet (spectral)
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butylhydroperoxide
TBS	*tert*-butyldimethylsilyl
TBSOF	2-(*tert*-butyldimethylsiloxy)furan
TBSOP	*N*-(*tert*-butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)pyrrole
TBSOT	2-(*tert*-butyldimethylsiloxy)thiophene
Tf	trifluoromethanesulfony (triflyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl (tosyl)
UV	ultra violet

Chapter 1

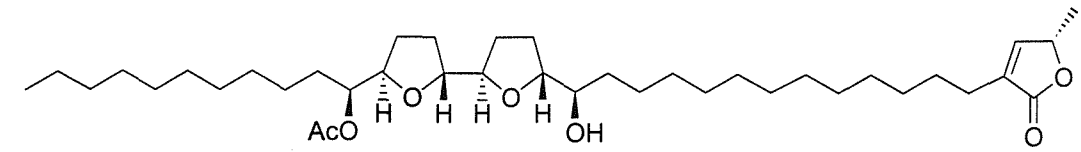
Annonaceous Acetogenins: Structure, Biological Activity and Synthesis

The following chapter summarises the structural and biological properties of the *Annonaceous* acetogenin natural products, and provides a summary of previous synthetic approaches.

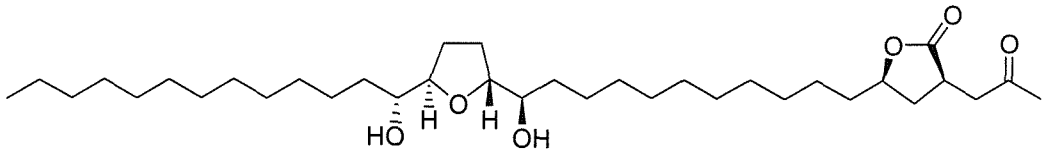
1.1 Introduction

The *Annonaceous* acetogenins are a class of natural products found only in a number of members of the plant family *Annonaceae*. Consisting of over 130 genera and 2300 species, this large group of tropical and subtropical plants and trees was until recently one of the least studied of the tropical plant families.[1] The first of the *Annonaceous* acetogenins, uvaricin **1.1**, was isolated as recently as 1982 and demonstrated potent *in vivo* antitumour properties against P-388 lymphocytic leukemia in mice.[2] The broad range of biological activity exhibited by these compounds has generated intensive interest in recent years, and they are now one of the most rapidly growing classes of natural products.[3-7]

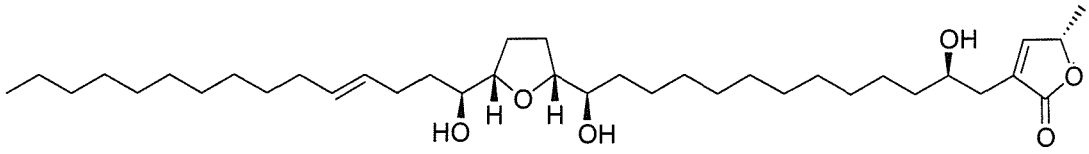
Structurally, the *Annonaceous* acetogenins are a series of C-35 / C-37 compounds derived from C-32 / C-34 long chain fatty acids, combined with a propan-2-ol moiety. They generally contain a long alkyl chain bearing a terminal, methyl-substituted α,β-unsaturated γ-lactone (butenolide), which in some cases may be replaced by a ketolactone. The carbon skeleton usually contains one, two or three tetrahydrofuran (THF) rings, and may also contain hydroxyl groups, ketones, acetates, epoxides, and unsaturation (Figure 1.1).[3] A number of acyclic or tetrahydropyran (THP) based examples have also been isolated and characterised.



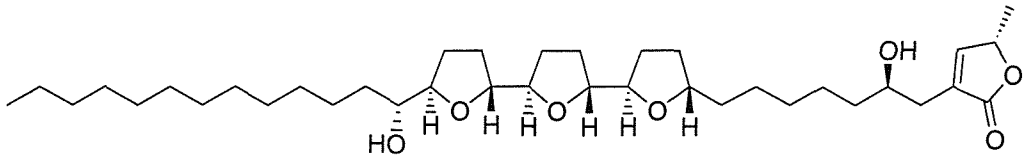
Uvaricin **1.1**



(2,4-*cis*)-Murisolinone **1.2**



Asiminenin **1.3**



Goniocin **1.4**

Figure 1.1 Some examples of *Annnonaceous* acetogenins

1.2 Structural Classification

The *Annonaceous* acetogenins may be classified in a number of ways, either by primarily considering the relative stereochemistry about the THF rings, or the number and arrangement of these subunits within the molecule. The former provides exact stereochemical detail, however requires the creation of many subclasses and therefore for the purposes of general discussion the latter method is more commonly employed. Thus, the structures may be divided into the following general classes; mono-THF **1.5**, adjacent bis-THF **1.6**, non adjacent bis-THF **1.7**, tris-THF **1.8**, non-THF ring **1.9**, and non-classical THP-based acetogenins **1.10**. Within these major classes exist many epimers and diastereoisomers, and also structures in which the lactone fragment is hydroxylated, reduced or rearranged (Figure 1.2).[3,4]

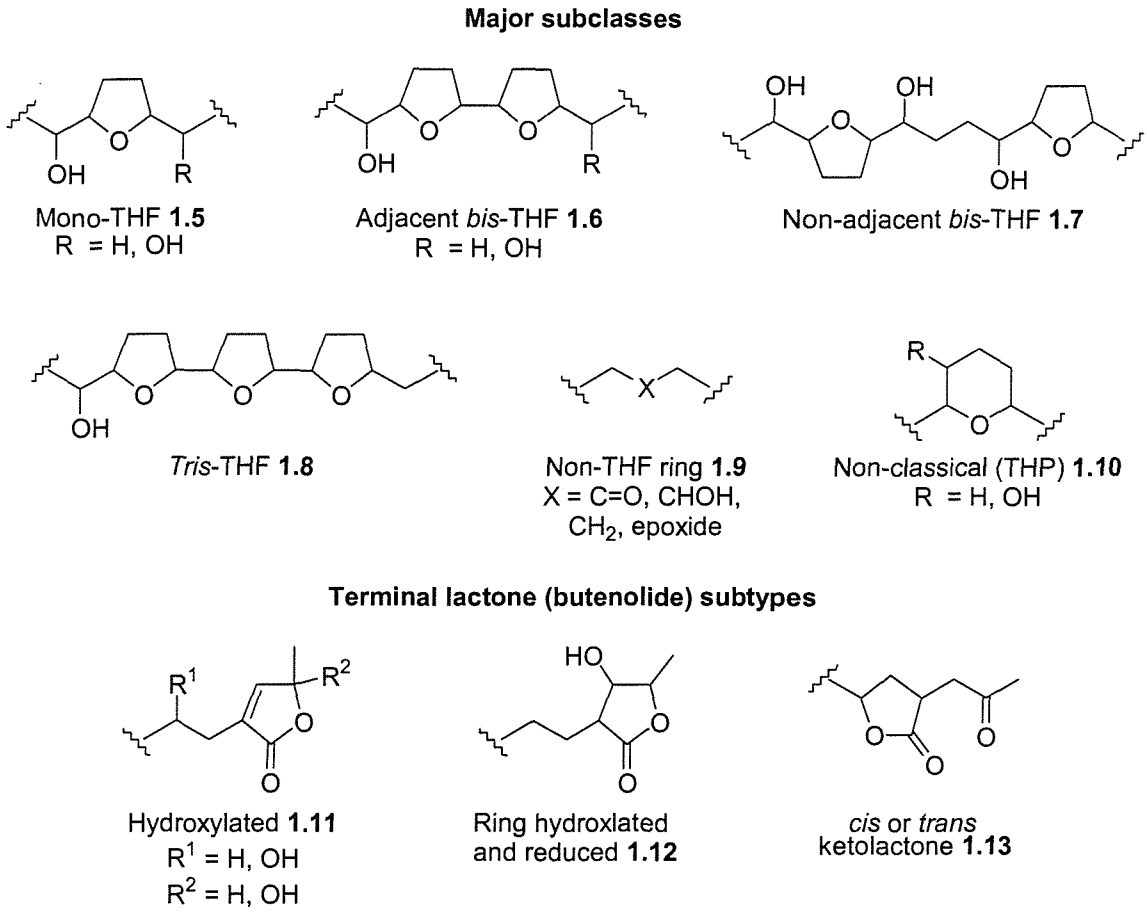


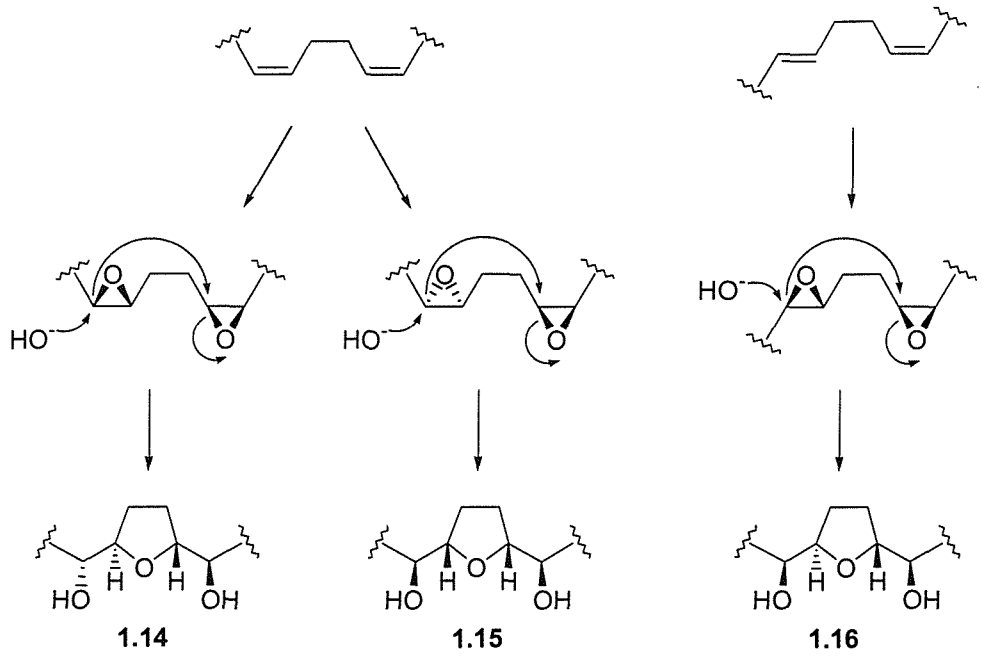
Figure 1.2 Major acetogenin structural classes

1.3 Biosynthesis

The degree and location of oxygenation of the *Annonaceous* acetogenins suggests that they are biosynthesised *via* a polyketide pathway, beginning with C-32 and C-34 unsaturated molecules containing 1,5-dienes, 1,5,9-trienes and 1,5,9,13-tetraenes. These precursors themselves may be built up using acetyl-CoA, malonyl-CoA and propanyl-CoA as for fatty acid biosynthesis. These polyenes are epoxidised and undergo cascade cyclisation initiated by nucleophilic attack from internal hydroxyl or external hydroxide to form the mono-THF, adjacent bis-THF and tris-THF acetogenins, with the cascade initiated at one end of the polyene.

In the case of mono-THF examples with two flanking hydroxyl groups, epoxidation of *cis-cis* or *cis-trans* dienes and attack by hydroxide gives access to a number of stereochemical

outcomes, such as *threo-trans-threo* annonacin type **1.14**, *threo-cis-threo cis*-annonacin type **1.15** and *erythro-trans-threo* annonacin-A type **1.16** (Scheme 1.1).

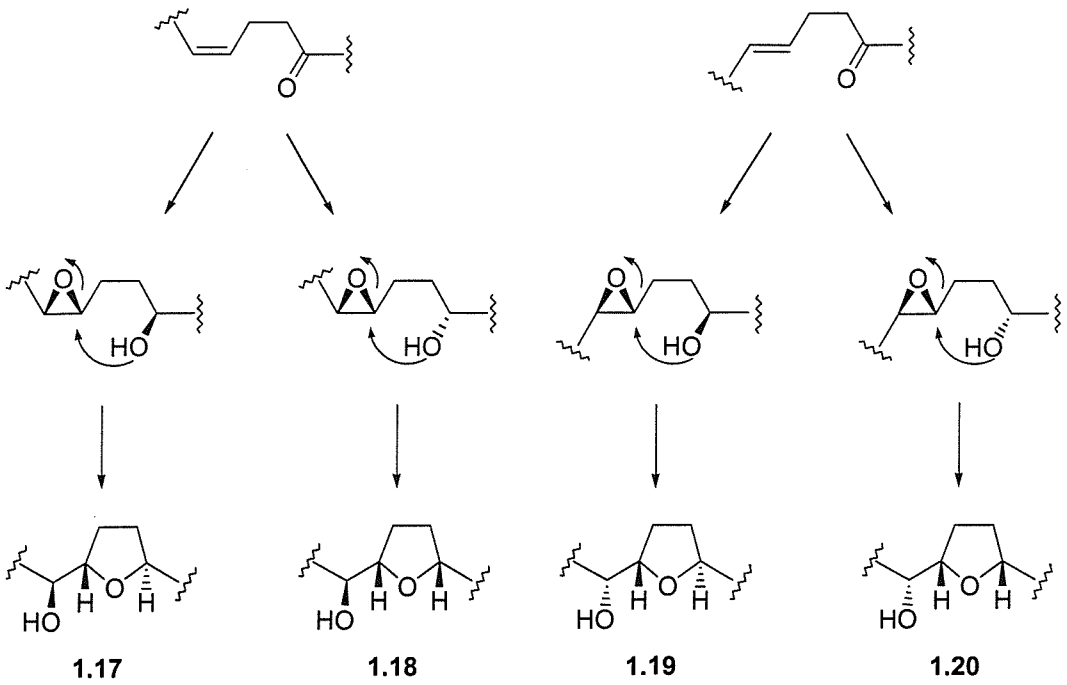


1.14 **1.15** **1.16**

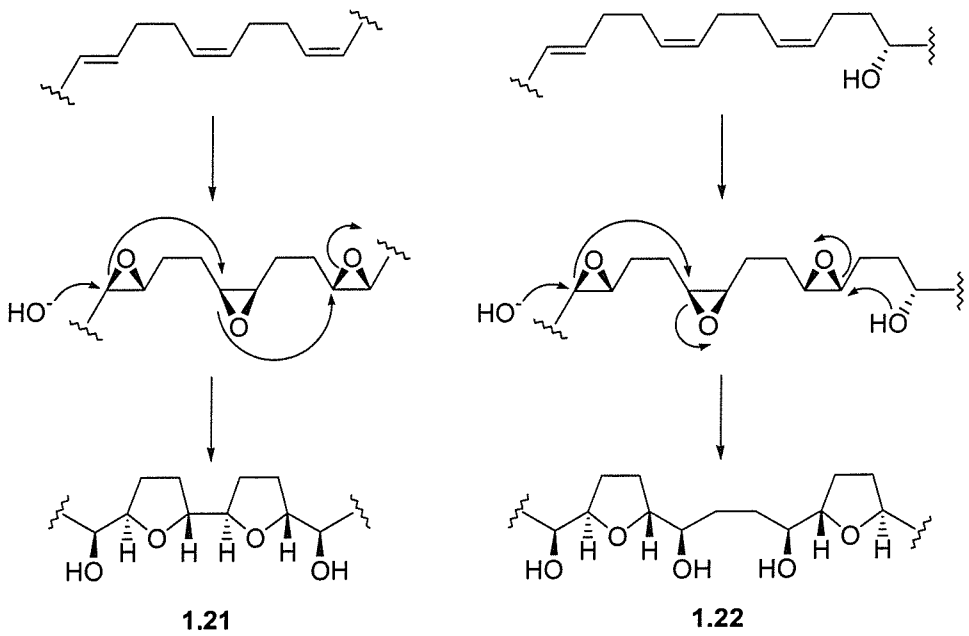
Scheme 1.1 Route to *mono*-THF's with two flanking hydroxyls

Mono-THF examples with a single flanking hydroxyl group are thought to derive from keto-*cis*- and keto-*trans*-alkenes *via* epoxidation, ketone reduction and nucleophilic attack by the internal hydroxy group. This route gives rise to *threo-trans* gigantetrocin-A type **1.17**, *threo-cis* muricatetrocin-A type **1.18**, *erythro-trans* muricatalin type **1.19** and *erythro-cis* type **1.20** (Scheme 1.2).

Adjacent *bis*-THF acetogenins **1.21** derive from epoxidation of 1,5,9-trienes, followed by tandem cyclisation initiated by the attack of hydroxide. Non-adjacent *bis*-THF examples **1.22** may be formed by simultaneous attack at both ends of a polyene (Scheme 1.3). In all cases the original double bond stereochemistries, as well as face of epoxidation, are responsible for the relative stereochemistry of the products.[4]

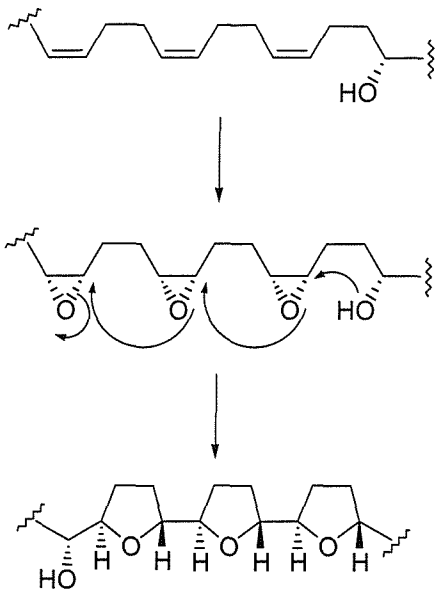


Scheme 1.2 Route to *mono*-THF's with one flanking hydroxyl



Scheme 1.3 Route to adjacent and non-adjacent *bis*-THF's

Hydroxy-*tris*-THF examples **1.23** derive from 13-hydroxy-1,5,9-trienes, *via* epoxidation and cascade cyclisation (Scheme **1.4**).

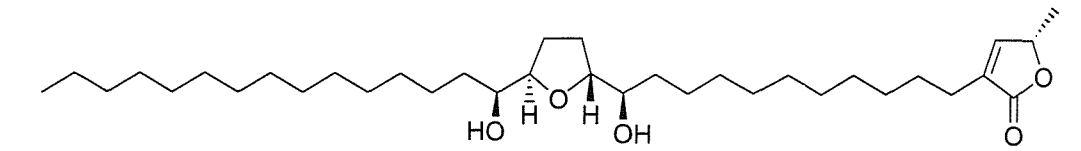


1.23

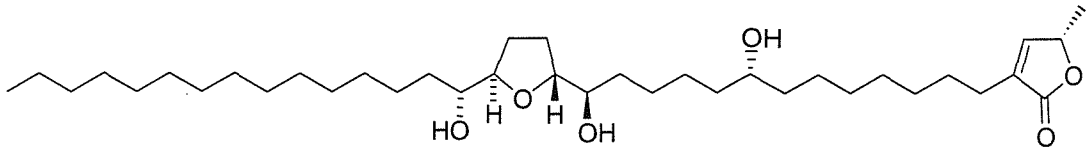
Scheme 1.4 Route to *tris*-THF's

1.4 Biological Activity

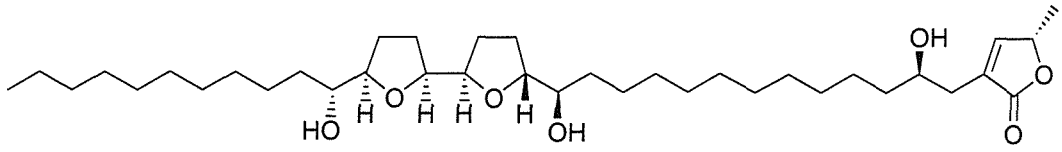
A variety of biological activities have been attributed to the *Annonaceous* acetogenins, including pesticidal,[8-10] insecticidal,[11-13] antiprotozoal and antimicrobial activity,[14] as well as antiparasitic and antifeedant properties.[15] Most notably, a number of examples exhibit highly selective cytotoxicity towards particular tumour cell lines.[16-19] This cytotoxicity generally increases from *mono*- to *bis*-THF compounds. For example, longicin **1.24** and longicoricin **1.25**, both *mono*-THF acetogenins, exhibit ED_{50} of 1.25×10^{-9} $g.mL^{-1}$ against human pancreatic carcinoma and 1×10^{-7} $g.mL^{-1}$ against human prostate adenocarcinoma respectively.[20,21] Adjacent *bis*-THF examples are commonly at least three orders of magnitude more potent. Trilobacin **1.26** exhibits $LD_{50} < 1 \times 10^{-12}$ $g.mL^{-1}$ in human colon carcinoma,[9] and (+)-parviflorin **1.27** exhibits LD_{50} of 1.3×10^{-15} $g.mL^{-1}$ for A-549 human lung carcinoma (Figure 1.3).[22,23] A number of *bis*-THF's are reported to be highly cytotoxic toward multidrug resistant mammalian cancers.[24-27]



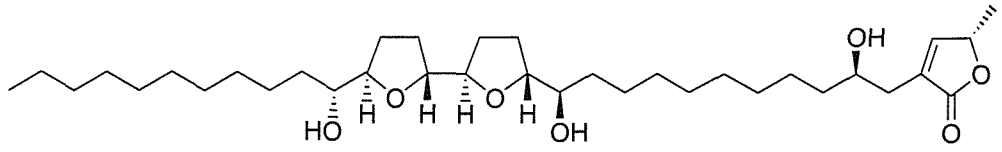
Longicin **1.24**



Longicoricin **1.25**



Trilobacin **1.26**



(+)-Parviflorin **1.27**

Figure 1.3 Cytotoxic antitumour acetogenins

The site of action of the *Annonaceous* acetogenins is within the mitochondria of cells. The major mechanism of action is inhibition of the reduced nicotinamide adenine dinucleotide, or NADH:ubiquinone oxidoreductase, also known as Complex I.[28-35] This large enzyme complex is involved in the transfer of electrons from NADH to O_2, and links electron transfer to the translocation of protons out of the mitochondrion. This process generates a transmembraneous electrochemical force which drives the production of adenosine triphosphate (ATP).[30] Inhibition of this process leads to depleted cellular ATP concentration and subsequent apoptosis, and this mechanism of action is particularly effective against cancerous cells, which have a higher demand for ATP than healthy cells.[36] A smaller number of acetogenins act at the ubiquinone-linked NADH oxidase found in the cytoplasmic membrane (lipid bilayer) of hepatocycles, which is involved in cellular growth and signal recognition.[25,28,37]

Inhibition studies have shown adjacent *bis*-THF compounds, particularly bullatacin, to be the most potent inhibitors of Complex-I yet described.[38] Structure-activity studies have

indicated that the potency depends approximately on the structure of the THF core such that adjacent *bis* > non-adjacent *bis* > *mono*.[38,39] Many examples are comparable to or more potent than well known Complex-I inhibitors such as rotenone and amytal.[40-44]

An alternative mechanism of action is as a poison of DNA topoisomerase I. This enzyme allows modification of the topological state of DNA by introduction of a transient protein-bridged break in a single strand, through which another strand may pass, and is an integral part of replication and transcription. This transient breakage of the DNA backbone is accompanied by the formation of a covalent enzyme-DNA complex.[45] Topoisomerase-I poisons act by stabilisation of the cleavable complex, and these drug stabilised complexes induce irreversible DNA strand breakage and cellular destruction.[46-48] An assay of an adjacent *bis*- and a *mono*-THF gave IC_{50} values of 8.25 and 9.84 μM respectively compared to 6.1 μM for etoposide, an antineoplastic agent and positive control.[28]

Such variety of biological activity and mechanism of action is the driving force for the intense interest in the discovery and synthesis of these natural products.

1.5 Synthesis of Adjacent *bis*-Tetrahydrofuran *Annonaceous* Acetogenins

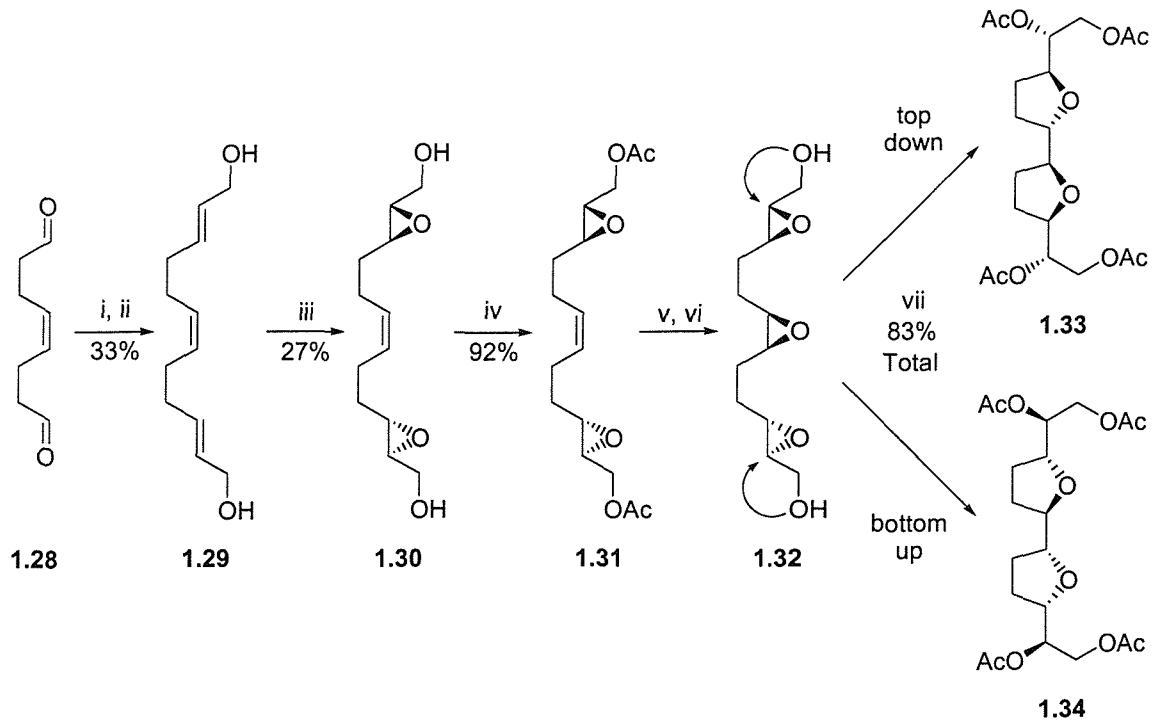
The following section summarises existing methodologies employed in the preparation of adjacent *bis*-tetrahydrofuran *Annonaceous* acetogenins. A number of review articles on this subject are available.[49-55]

1.5.1 Thomas R. Hoye *et al.*

1.5.1.1 Cascade Synthesis of *bis*-THF Core Fragments

The first reported synthetic approach to the core tetrahydrofuran structures of *Annonaceous* acetogenins was carried out by Hoye and Suhadolnik from 1985.[56] The approach was biomimetic, based upon an epoxide opening cascade strategy. Thus, double Horner-Emmons homologation of (*Z*)-oct-4-enedial **1.28** and reduction of the resulting diester afforded *bis*-allylic alcohol **1.29**. Sharpless asymmetric epoxidation and treatment with acetic anhydride gave *bis*-epoxide **1.31**.[57] Epoxidation with *m*-CPBA and basic treatment

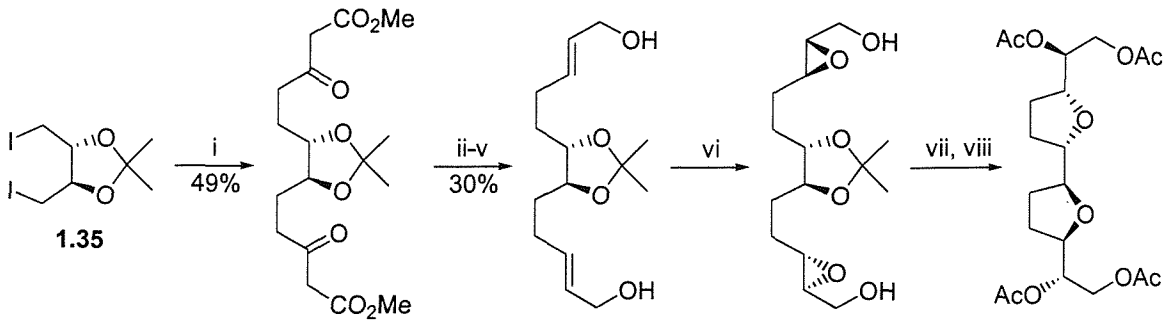
of the *tris*-epoxide resulted in deacylation and a rapid epoxide opening cascade initiated at one end of the molecule. The resulting terminal epoxides were hydrolysed under the reaction conditions, and the crude mixture acetylated affording *bis*-THF's **1.33** and **1.34** in a 1:1 ratio. The apparent racemisation is explained by the ability of the cascade to occur in a top-down or bottom-up fashion (Scheme 1.5).



Reagents and Conditions: (i) $(i\text{-PrO})_2P(O)CH_2CO_2Me$, NaH, Et_2O; (ii) DIBAL-H, Et_2O, 0 °C; (iii) $Ti(Oi\text{-Pr})_4$, (+)-DIPT, *t*-BuOOH, CH_2Cl_2, -20 °C; (iv) Ac_2O, py; (v) *m*-CPBA, CH_2Cl_2; (vi) 1N $NaOH_{(aq)}$, 50 °C; (vii) Ac_2O, py.

Scheme 1.5 Hoye's initial approach

The problem of racemisation was eliminated by the use of an inside-out epoxide opening route.[58] This began with 1,4-diiodide **1.35**, synthesised from L-(+)-diethyl tartrate. Treatment with the dianion of ethyl acetoacetate afforded *bis*-β-keto ester **1.36**. Borohydride reduction of the ketone, mesylation and elimination by base, followed by reduction of the resulting *bis*-ester afforded *bis*-allylic alcohol **1.37**. Asymmetric epoxidation gave bis-epoxide **1.38**, and subsequent treatment with protic acid resulted in acetonide removal and immediate, inside-out epoxide opening. Acylation of the crude residue afforded *bis*-THF tetraacetate **1.39** as a single diastereoisomer (Scheme 1.6)



1.35 **1.36** **1.37** **1.38** **1.39**

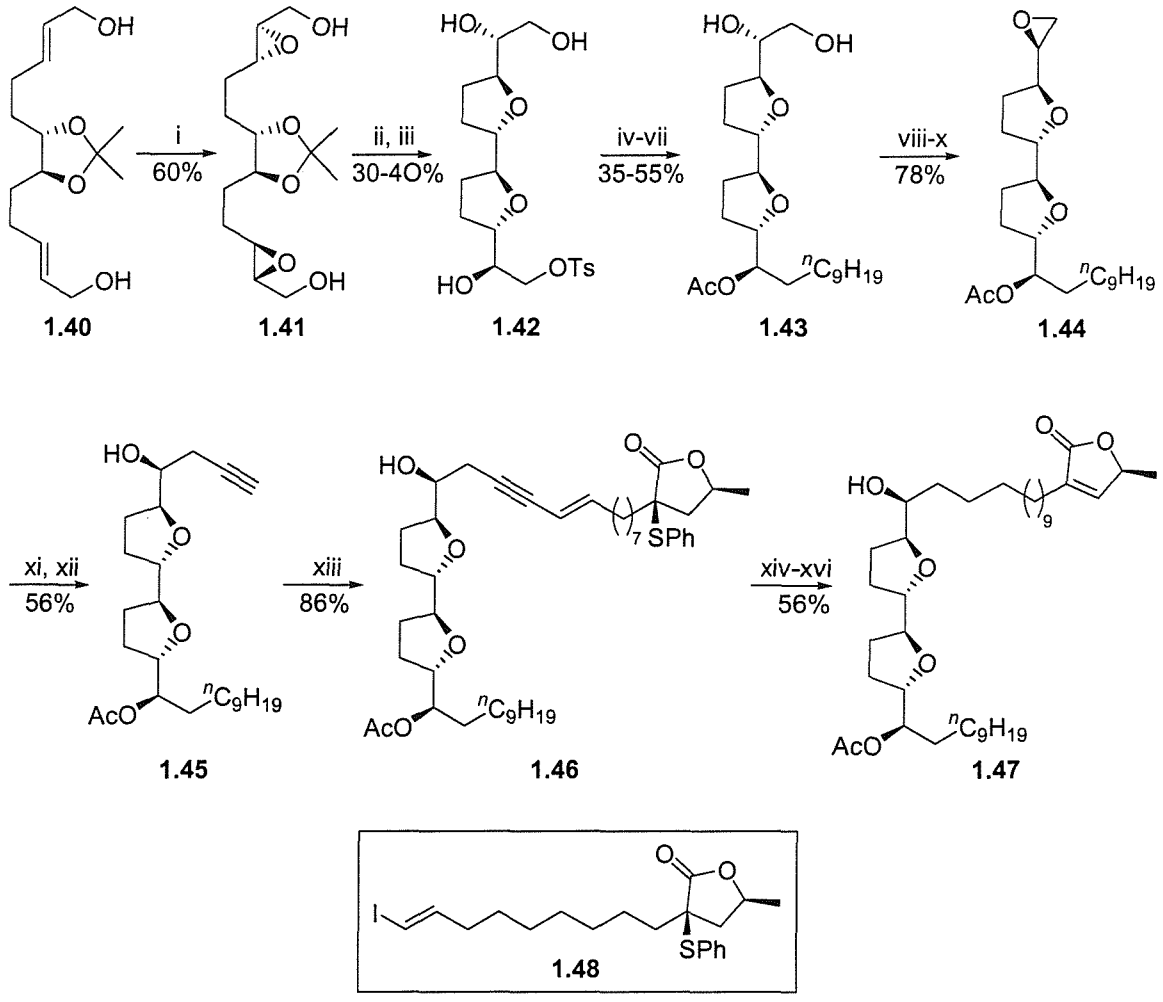
Reagents and Conditions: (i) $H_3CCOCH_2CO_2Et$, NaH, *n*-BuLi, THF; (ii) $NaBH_4$, MeOH, 0 °C; (iii) MsCl, Et_3N, CH_2Cl_2; (iv) DBU, CH_2Cl_2, 40 °C; (v) DIBAL-H, Et_2O, 0 °C; (vi) $Ti(O\textit{i}\text{-}Pr)_4$, L-(+)-DIPT, *t*-BuOOH, CH_2Cl_2, -20 °C; (vii) Amberlite-H, THF; (viii) Ac_2O, py.

Scheme 1.6 Hoye's inside-out epoxide opening approach

1.5.1.2 Total Synthesis of (+)-(15,16,19,20,23,24)-*hexepi*-Uvaricin 1.47

This initial investigation established methodology which led to the first total synthesis of (+)-(15,16,19,20,23,24)-*hexepi*-uvaricin **1.47**, confirming the proposed regiochemistry and relative stereochemistry of the natural product uvaricin **1.1**.[2] Asymmetric epoxidation of *bis*-allylic alcohol **1.40** using D-(-)-di*iso*propyl tartrate afforded *bis*-epoxide **1.41**. Desymmetrisation by mono-tosylation and acidic deprotection resulted in inside-out epoxide opening *bis*-THF product **1.42**. Coupling of the tosylate with excess lithium dinonylcuprate, acetonide formation of the vicinal diol, acetylation and acetonide removal installed the C24 acetate and C26-C34 sidechain of **1.43**.

Conversion to epoxide **1.44** was carried out with an inversion of configuration at C15, and epoxide opening by TMS protected lithium acetylide, followed by desilylation afforded alkyne **1.45**. The remainder of the carbon skeleton was added using chiral vinyl iodide **1.48**, *via* a palladium catalysed coupling reaction.[59] Enyne hydrogenation using Wilkinson's catalyst, oxidation of sulfide to sulfoxide and thermal elimination afforded the final product (Scheme 1.7).[60] Vinyl iodide **1.48** was prepared in three steps from 1-noyn-1-ol,[61] using a 4-methyl-2-phenylsulfenyl-γ-butyrolactone described by Iwai *et al.*[62]



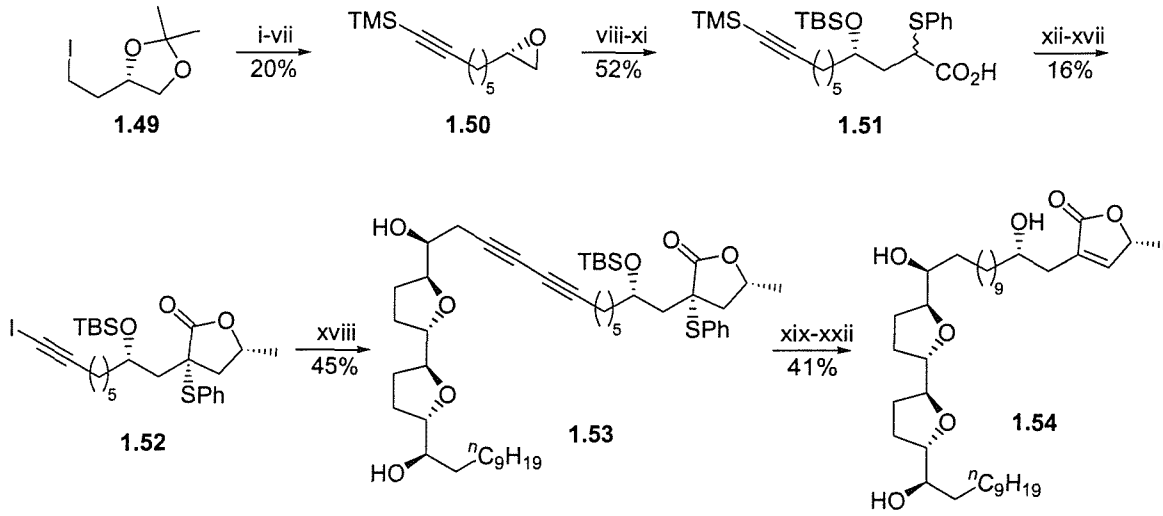
Reagents and Conditions: (i) Ti(*Oi*-Pr)$_4$, D-(-)-DIPT, *t*-BuOOH, CH_2Cl_2, -20 °C; (ii) TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C; (iii) Amberlyst-15, MeOH; (iv) (*n*-$C_9H_{19})_2$CuLi, THF, -10 °C; (v) $Me_2C(OMe)_2$, CSA, Me_2CO; (vi) Ac_2O, py; (vii) TsOH, MeOH; (viii) TBDPSCl, Et_3N, DMAP, CH_2Cl_2; (ix) TsCl, py, DMAP, CH_2Cl_2; (x) TBAF, THF; (xi) LiC≡CTMS, BF_3•Et_2O, THF, -78 °C; (xii) TBAF; (xiii) Iodide **1.48**, $Pd(PPh_3)_4$, CuI, Et_3N; (xiv) $Rh(PPh_3)_3Cl$, H_2; (xv) Oxone®, MeOH, H_2O, 0 °C; (xvi) PhMe, Δ.

Scheme 1.7 Hoye's total synthesis of (+)-(15,16,19,20,23,24)-*hexepi*-uvaricin

1.5.1.3 Total Synthesis of (-)-Bullatacin 1.54

At this point Hoye *et al.* studied the butenolide portion of 4-hydroxylated acetogenins,[63,64] culminating in the synthesis of (-)-bullatacin **1.54**, a 4-hydroxy-24-deacetyl analogue of (+)-(15,16,19,20,23,24)-*hexepi*-uvaricin. This was carried out by the coupling of deacetylated, previously described alkyne **1.45** with a new butenolide-bearing iodoalkyne fragment.[65] The synthesis of this fragment began by the conversion of iodide **1.49**,[66] over

seven steps, to epoxide **1.50**.[67] Reaction with dilithiated phenylthioacetic acid followed by silylation of the resulting hydroxyl group gave acid **1.51**. Dilithiation and treatment with (*R*)-propylene oxide followed by acid catalysed lactonisation and the replacement of the TMS group by iodide afforded coupling partner **1.52**. Palladium catalysed coupling to deacetyl-**1.45**,[68] diyne hydrogenation, sufide oxidation and thermal elimination were carried out as described previously. Final desilylation afforded enantiopure (-)-bullatacin **1.54** (Scheme 1.8).



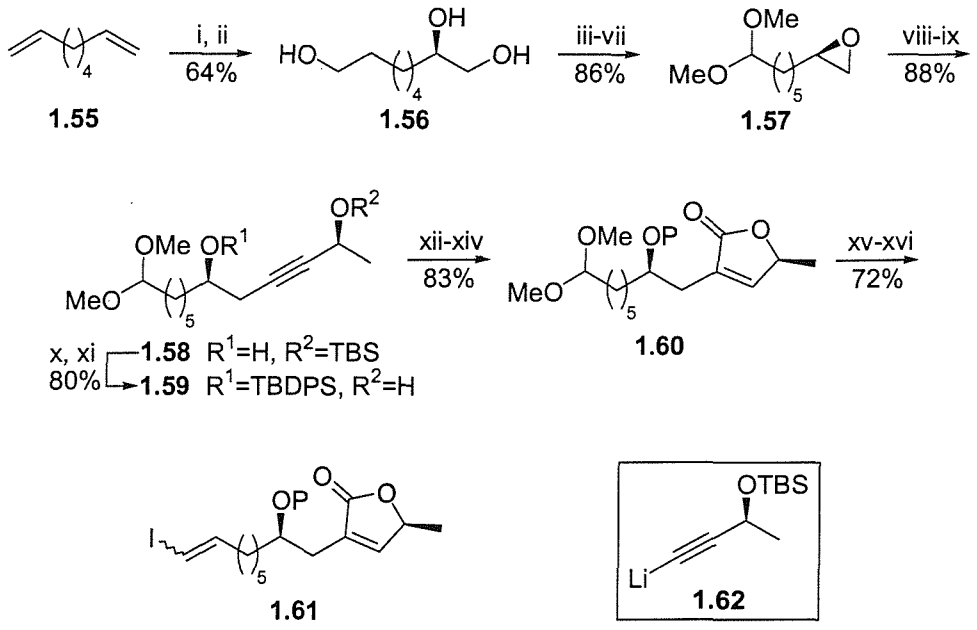
Reagents and Conditions: (i) *n*-PrC≡CLi; (ii) CSA, MeOH; (iii) KAPA, DAP; (iv) EtMgBr, TMSCl; (v) 10% HCl; (vi) TsCl, py, -10 °C; (vii) NaH, THF; (viii) $PhSCH{=}CO_2Li_2$; (ix) 10% citric acid; (x) TBSCl, imidazole; (xi) MeOH; (*xii*) LDA, 2 eq; (*xiii*) (*R*)-propylene oxide; (*xiv*) 10% citric acid; (xv) CSA, PhH, Δ; (xvi) MeOH, K_2CO_3; (xvii) I_2, morpholine; (xviii) Alkyne deacetyl-**1.45**, $Pd(PPh_3)_2Cl_2$, CuI, *i*-Pr_2NH, THF; (xix) $Rh(PPh_3)_3Cl$, H_2; (xx) Oxone®, MeOH, H_2O, 0 °C; (xxi) PhMe, Δ; (xxii) 5% HF, MeCN, THF.

Sceme 1.8 Hoye's synthesis of (-)-bullatacin

1.5.1.4 Total Synthesis of (+)-Acimicin 1.70

Hoye next turned his attention to the synthesis of (+)-asimicin **1.70**, using a new method of synthesis of the chiral butenolide fragment.[69] Thus, selective mono-hydroboration of 1,7-octadiene **1.55** followed by asymmetric dihydroxylation afforded triol **1.56** in high optical purity after recrystallisation.[70] This triol was processed in a five step, one pot sequence in high yield to epoxyacetal **1.57**, which was opened with optically pure lithium acetylide **1.62**,[63] affording homopropargylic alcohol **1.58**. Conversion to the TBDPS ether and removal of the TBS group afforded propargylic alcohol **1.59**. Red-Al reduction and treatment with iodine,[71] followed by carbonylation under Stille conditions gave butenolide

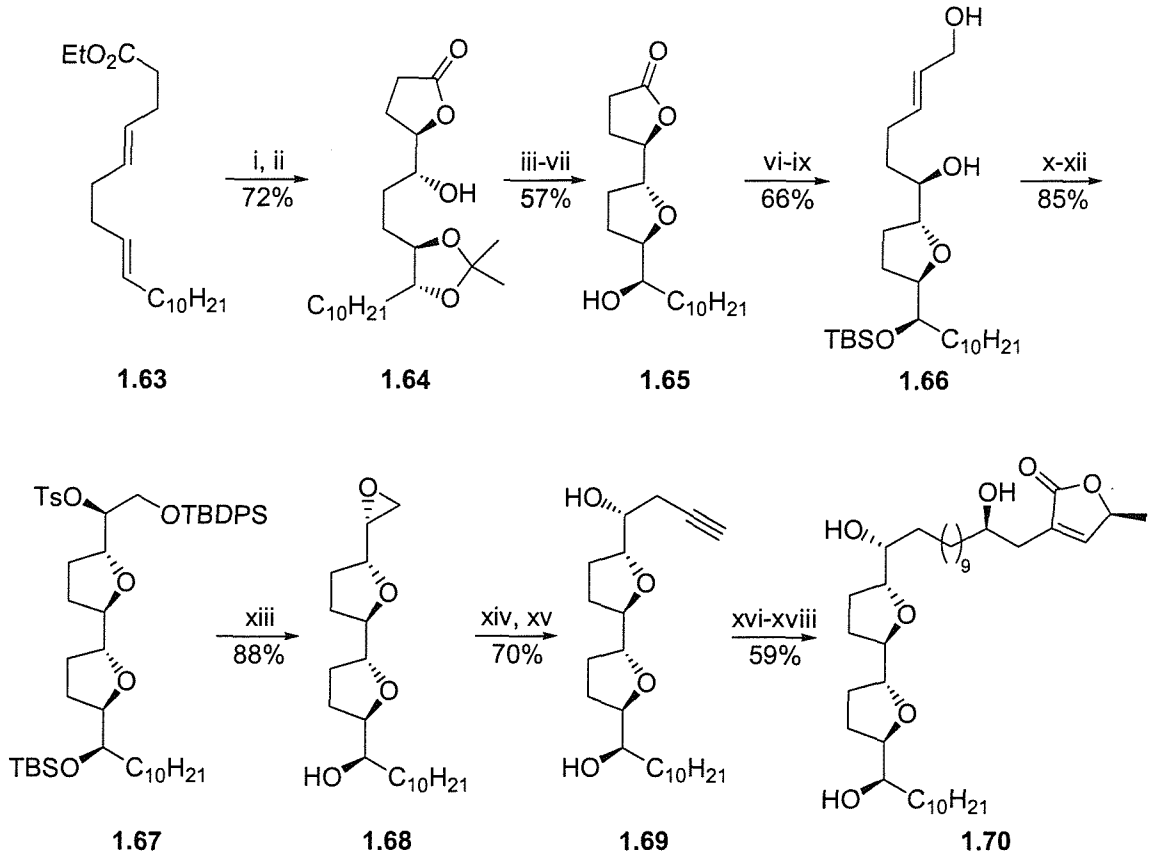
1.60.[72] Acetal hydrolysis and generation of the terminal vinyl iodide (4:1 *E*:*Z*) completed the butenolide subunit **1.61** in good yield (Scheme 1.9).[73]



Reagents and Conditions: (i) 9-BBN; (ii) AD-mix-β; (iii) $Me_2C(OMe)_2$, PPTS; (iv) TMSCl; (v) $(COCl)_2$, DMSO, Et_3N; (vi) TsOH, MeOH; (vii) K_2CO_3, MeOH; (viii) **1.62**, $BF_3{\bullet}Et_2O$; (ix) PPTS, MeOH; (x) TBDPSCl; (xi) PPTS, MeOH; (xii) RED-Al; (xiii) I_2; (xiv) $(Ph_3P)_2PdCl_2$, H_2NNH_2, K_2CO_3, THF, CO, 45 psi; (xv) TFA, H_2O, $CHCl_3$; (xvi) $CrCl_2$, CHI_3, dioxane, THF.

Scheme 1.9 An alternative butenolide fragment

The synthesis of the *bis*-THF fragment of (+)-asimicin initially followed the strategy used by Keinan *et al.* in the synthesis of *mono*-THF acetogenins.[74] Double asymmetric dihydroxylation of *E*,*E*-diene **1.63** and protection of the product as an acetonide gave lactone **1.64**. Tosylation and methanolysis gave an epoxide which underwent Lewis acid catalysed opening on hydrolytic workup, affording lactone **1.65**. Silylation, lactone reduction and homologation, followed by DIBAL reduction of the resulting ester gave allylic alcohol **1.66**. This substrate was subjected to Sharpless asymmetric epoxidation, the product of which was spontaneously opened forming the second THF ring. The primary hydroxy group was protected as the TBDPS ether and the secondary hydroxy group was converted to the tosylate **1.67**. Desilylation afforded epoxide **1.68**, and treatment with TMS protected lithium acetylide followed by deprotection gave terminal alkyne **1.69**. This fragment was coupled to vinyl iodide **1.61**, and subsequent enyne hydrogenation and desilylation afforded (+)-asimicin **1.70** (Scheme 1.10).



Reagents and Conditions: (i) AD-mix-β; (ii) $Me_2C(OMe)_2$, TsOH, Me_2CO; (iii) TsCl; (iv) K_2CO_3, MeOH; (v) 20 mol% $BF_3{\cdot}Et_2O$; (vi) TBSCl; (vii) DIBAL-H; (viii) $Ph_3P{=}CHCO_2Et$; (ix) DIBAL-H; (x) $Ti(O\textit{i}\text{-}Pr)_4$, L-(+)-DIPT, *t*-BuOOH, -20 °C; (xi) TBDPSCl; (xii) TsCl; (xiii) TBAF; (xiv) LiC≡CTMS, $BF_3{\cdot}Et_2O$; (xv) K_2CO_3, MeOH; (xvi) **1.61**, $Pd(Ph_3P)_2Cl_2$, CuI, Et_3N; (xvii) $Rh(PPh_3)_3Cl$, H_2; (xviii) AcCl, MeOH, Et_2O.

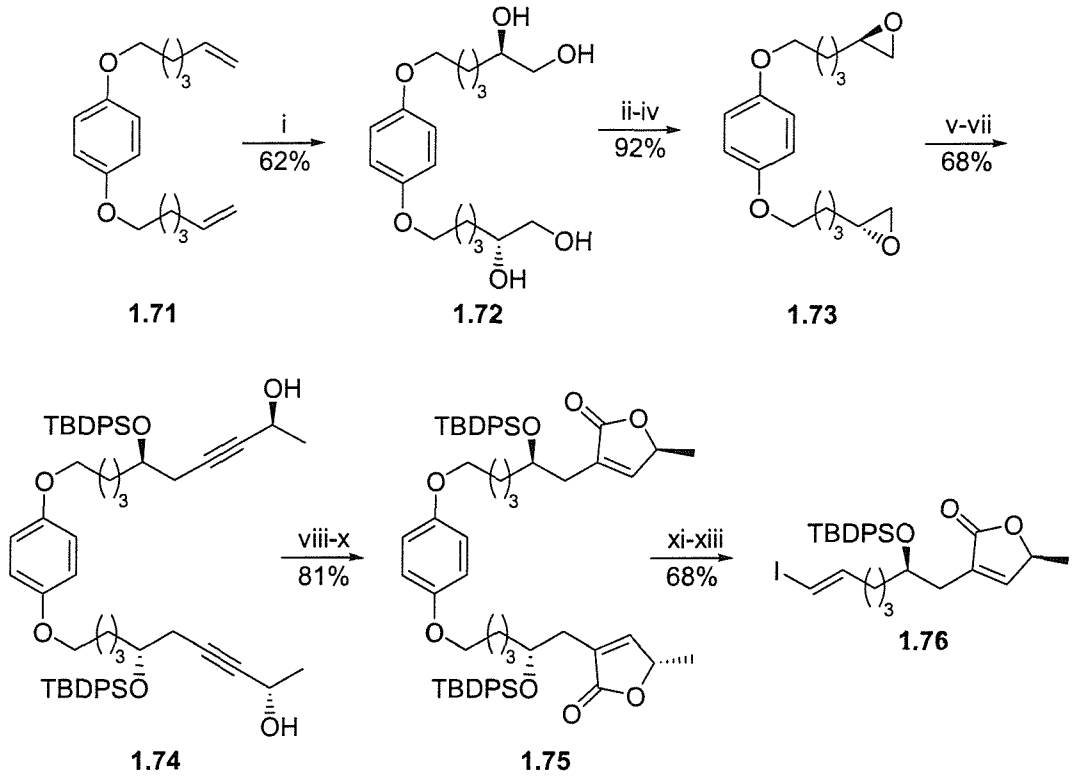
Scheme 1.10 Hoye's total synthesis of (+)-asimicin

1.5.1.5 Total Synthesis of (+)-Parviflorin 1.27

Using a revised approach to both the synthesis of the butenolide fragment and to de-symmetrisation of the *bis*-THF core, Hoye *et al.* described a fourteen step synthesis of (+)-parviflorin **1.27** which vastly improved upon their previous work.[22]

An improved route to the butenolide fragment began by the double asymmetric dihydroxylation of 1,4-*bis*(hexenyloxy)benzene **1.71**, affording tetraol **1.72** which, after recrystallisation, was enantiomerically pure. A one-pot reaction sequence gave *bis*-epoxide **1.73**,[75] which was opened with TBS protected lithium acetylide **1.62**. Silylation of the homopropargylic alcohol followed by selective removal of the TBS group gave propargylic

alcohol **1.74**. Red-Al reduction and treatment with iodine,[71] followed by carbonylation under Stille conditions afforded butenolide **1.75**.[72] Oxidative release using CAN, Swern oxidation and conversion to the terminal vinyl iodide (5:1 *E*:*Z*) completed the butenolide subunit **1.76** (Scheme 1.11).

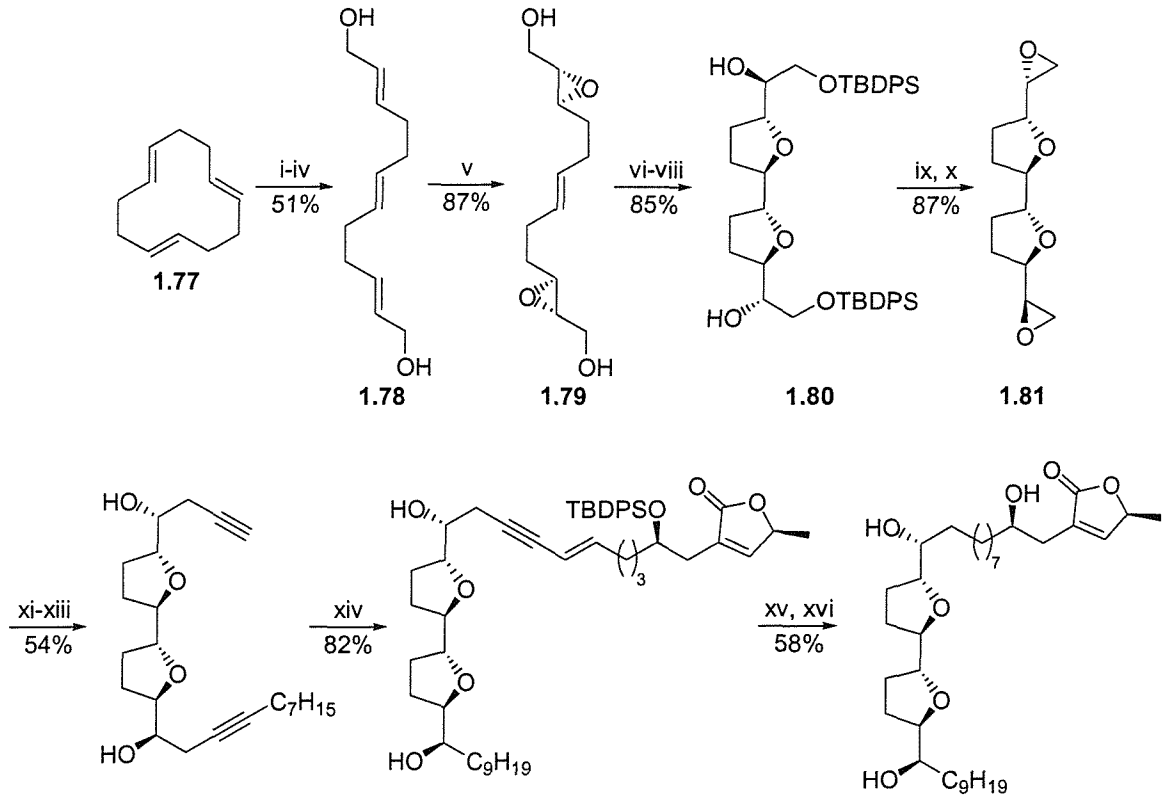


Reagents and Conditions: (i) AD-mix-β; (ii) $CH(OMe)_3$, PPTS; (iii) AcBr; (iv) K_2CO_3, MeOH; (v) **1.62**, $BF_3{\bullet}Et_2O$; (vi) TBDPSCl; (vii) PPTS, EtOH; (viii) RED-Al; (ix) I_2; (x) $(Ph_3P)_2PdCl_2$, H_2NNH_2, K_2CO_3, THF, CO, 45 psi; (xi) CAN; (xii) $(COCl)_2$, DMSO, Et_3N; (xiii) $CrCl_2$, CHI_3, dioxane, THF.

Scheme 1.11 Improved butenolide fragment synthesis

Construction of the *bis*-THF fragment began by the oxidation of two double bonds in *trans*, *trans*, *trans*-1,5,9-cyclododecatriene **1.77**, followed by oxidative cleavage to the *bis*-aldehyde, double Wittig homologation and reduction of the resulting ester to *bis*-allylic alcohol **1.78**. This intermediate was manipulated by the method of Taber *et al.*[76] Thus, asymmetric epoxidation gave *bis*-epoxide **1.79** in greater than 99% diastereomeric excess and 87% yield after recrystallisation.[77] Silylation, asymmetric dihydroxylation and treatment with trifluoroacetic acid afforded *bis*-THF **1.80**. Conversion to epoxide **1.81** with inversion of the carbinol centres was achieved by tosylation followed by desilyation. Careful treatment with lithium (trimethylsilyl)acetylide in the presence of boron trifluoride

etherate allowed de-symmetrisation. Treatment of the resulting *mono*-epoxide with excess 1-lithio-1-nonyne and removal of the TMS group afforded alkyne **1.82**. Palladium catalysed coupling of this alkyne with butenolide fragment **1.76**,[68] followed by hydrogenation and deprotection, completed the synthesis of (+)-parviflorin **1.27** (Scheme 1.12).



Reagents and Conditions: (i) OsO_4, NMO; (ii) KIO_4; (iii) $Ph_3P{=}CHCO_2Et$; (iv) DIBAL-H; (v) $Ti(O\textit{i}\text{-}Pr)_4$, L-(+)-DET, *t*-BuOOH, -20 °C; (vi) TBDPSCl, DMAP; (vii) AD-mix-*β*; (viii) TFA; (ix) TsCl; (x) TBAF; (xi) $LiC{\equiv}CTMS$, $BF_3{\bullet}Et_2O$; (xii) $n\text{-}C_7H_{15}C{\equiv}CLi$, $BF_3{\bullet}Et_2O$; (xiii) K_2CO_3, MeOH; (xiv) **1.76**, $Pd(Ph_3)_2Cl_2$, CuI, Et_3N; (xv) $Rh(PPh_3)_3Cl$, H_2; (xvi) AcCl, MeOH, Et_2O.

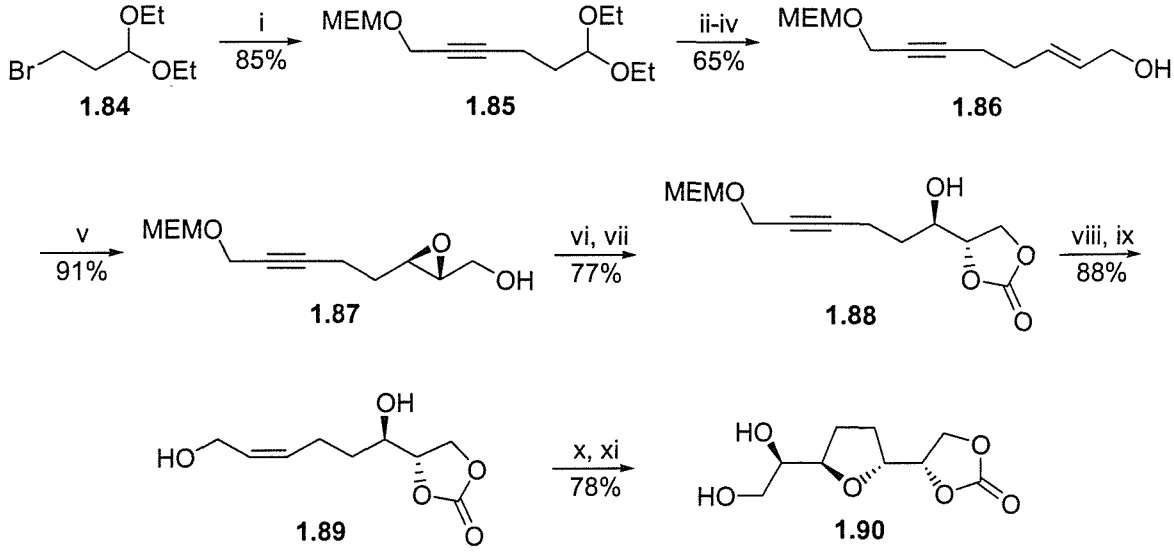
Scheme 1.12 Total synthesis of (+)-parviflorin

1.5.2 Hans-Dieter Scharf *et al.*

1.5.2.1 Epoxide Opening Approach to the THF Core

In order to facilitate the biological testing of acetogenin analogues, Scharf adopted an epoxide opening approach to the THF core in which each stereocentre could be varied to provide maximum diversity.[78] Thus, acetal protected 1-bromopropionaldehyde **1.84** was alkylated using lithiated, methoxyethoxymethyl protected propargylic alcohol. Removal of

the acetal, Horner-Emmons reaction of the aldehyde with triethyl phosphonoacetate and reduction of the resulting ester afforded allylic alcohol **1.86**. Sharpless asymmetric epoxidation installed the first two stereocentres with high selectivity, and epoxy alcohol **1.87** was converted to cyclic carbonate **1.88**.[79] Removal of the MEM protecting group and Lindlar reduction gave *cis*-allylic alcohol **1.89**. Asymmetric epoxidation and acidic workup gave fragment **1.90** in 19% overall yield. As is generally the case with the epoxidation of *cis*-allylic alcohols, the diastereoselectivity of this second epoxidation was in the region of 85:15 in favour of the illustrated product (Scheme 1.13).



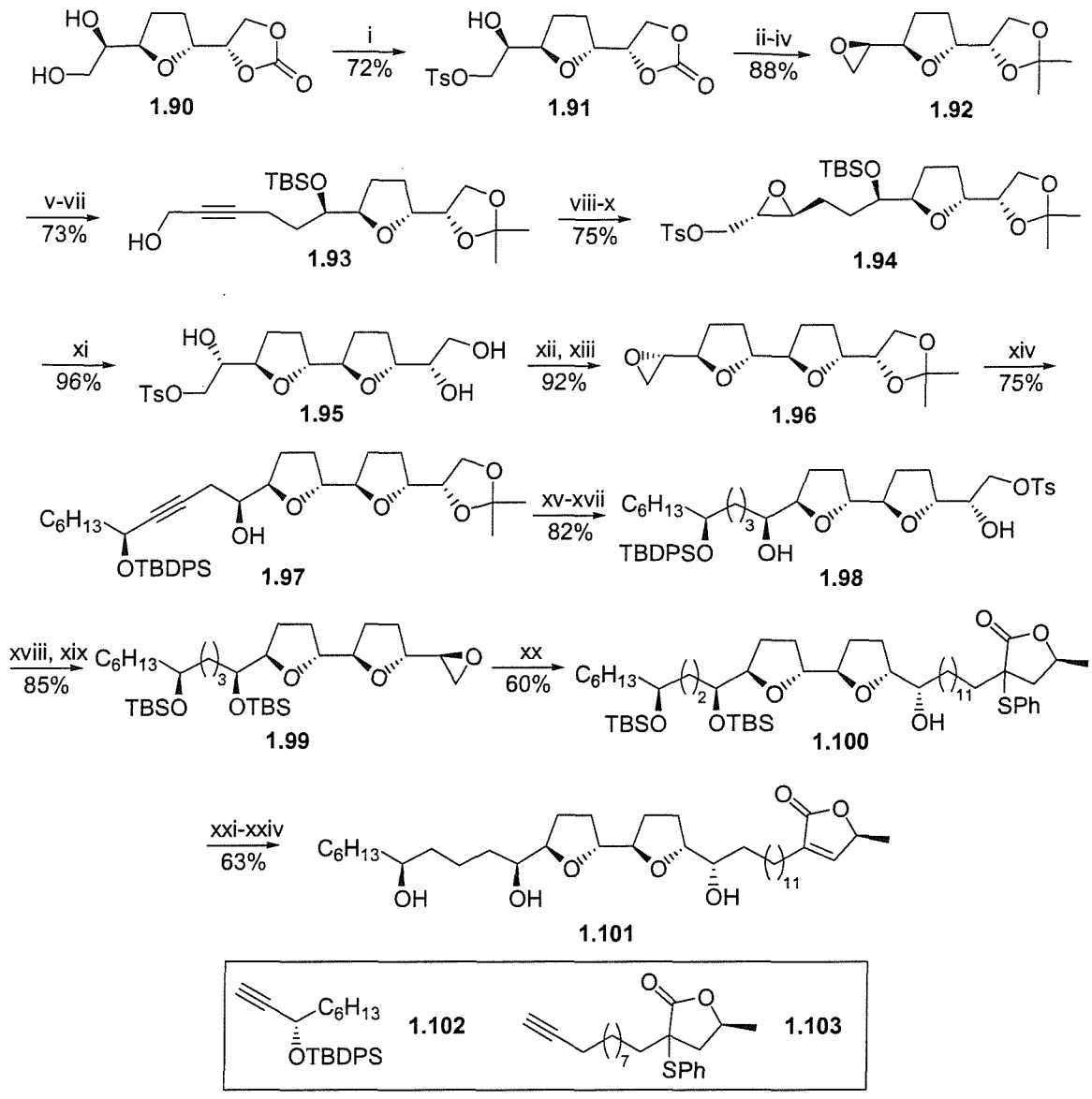
Reagents and Conditions: (i) LiC≡CCH$_2$OMEM, THF, DMPU, -60 °C; (ii) H$^+$, H$_2$O; (iii) LiBr, Et$_3$N, THF, (EtO)$_2$P(O)CH$_2$CO$_2$Et; (iv) DIBAL-H, CH$_2$Cl$_2$, -10 °C; (v) Ti(O*i*-Pr)$_4$, D-(-)-DIPT, *t*-BuOOH, -15 °C; (vi) PhNCO, Et$_3$N, CH$_2$Cl$_2$; (vii) SnCl$_4$, CH$_2$Cl$_2$, -20 °C; (viii) H$^+$, MeOH, 40 °C; (ix) H$_2$/Pd, CaCO$_3$, PbO; (x) Ti(O*i*-Pr)$_4$, D-(-)-DIPT, *t*-BuOOH, -15 °C; (xi) tartaric acid, H$_2$O.

Scheme 1.13 Scharf's synthesis of the THF core fragment

1.5.2.2 Synthesis of 15-*epi*-Annonin I, 1.101

Scharf then used THF intermediate **1.90** in the total synthesis of 15-*epi*-annonin I **1.101**.[80] Tosylation *via* dibutyltin stannylation afforded tosylate **1.91**.[81] Conversion to the epoxide, carbonate hydrolysis and acetal formation gave **1.92**. Opening of the epoxide with propargyl magnesium bromide, protection of the resulting alcohol as the TBS ether and hydroxymethylation with *t*-BuLi and paraformaldehyde afforded propargylic alcohol **1.93**. A *trans*-allylic alcohol was installed by Red-Al reduction, and asymmetric epoxidation and tosylation gave epoxide **1.94**. Desilylation and epoxide cascade was induced by treatment

with hexafluorosilicic acid. Protection of the resulting triol as the acetonide and treatment with base gave *bis*-THF epoxide **1.96** in excellent yield. Boron trifluoride mediated epoxide opening by lithiated alkyne **1.102** gave homopropargylic alcohol **1.97**. Hydrogenation, acetonide removal and primary tosylation afforded **1.98** which on treatment with TBAF underwent desilylation and epoxide formation. Both hydroxy groups were protected as TBS ethers affording epoxide **1.99**. Lactone-bearing lithiated alkyne **1.103** was then used in a second Boron trifluoride mediated epoxide opening. Hydrogenation, sulfide oxidation, thermal elimination and desilylation afforded 15-*epi*-annonin **1.101** (Scheme 1.14).



Reagents and Conditions: (i) $SnBu_2(OMe)_2$, TsCl, PhH; (ii) DBU, CH_2Cl_2; (iii) NaOMe, MeOH; (iv) $Me_2C(OMe)_2$, PPTS, Me_2CO; (v) Propargylmagnesium bromide, Et_2O, 0 °C; (vi) TBSOTf, py; (vii) *t*-BuLi, $(CH_2O)^n$, THF, -78 °C; (viii) Red-Al, Et_2O; (ix) $Ti(O\textit{i}\text{-}Pr)_4$, L-(+)-DIPT, *t*-BuOOH, CH_2Cl_2, -15 °C; (x) TsCl, Et_3N; (xi) H_2SiF_6, MeCN; (xii) $Me_2C(OMe)_2$, PPTS, Me_2CO; (xiii) K_2CO_3, MeOH; (xiv) **1.102**, *t*-BuLi, $BF_3{\bullet}Et_2O$, THF, -78 °C; (xv) Pd/C, H_2, EtOAc; (xvi) 80% AcOH; (xvii) $SnBu_2(OMe)_2$, TsCl, PhMe; (xviii) TBAF, THF; (xix) TBSCl, $AgNO_3$, py, THF; (xx) **1.103**, $BF_3{\bullet}Et_2O$, THF, -78 °C; (xxi) $(Ph_3P)_3RhCl$, H_2, PhH; (xxii) MMPP, H_2O, EtOH, $CHCl_3$; (xxiii) PhH, Δ; (xxiv) Lewatit-S100, MeOH.

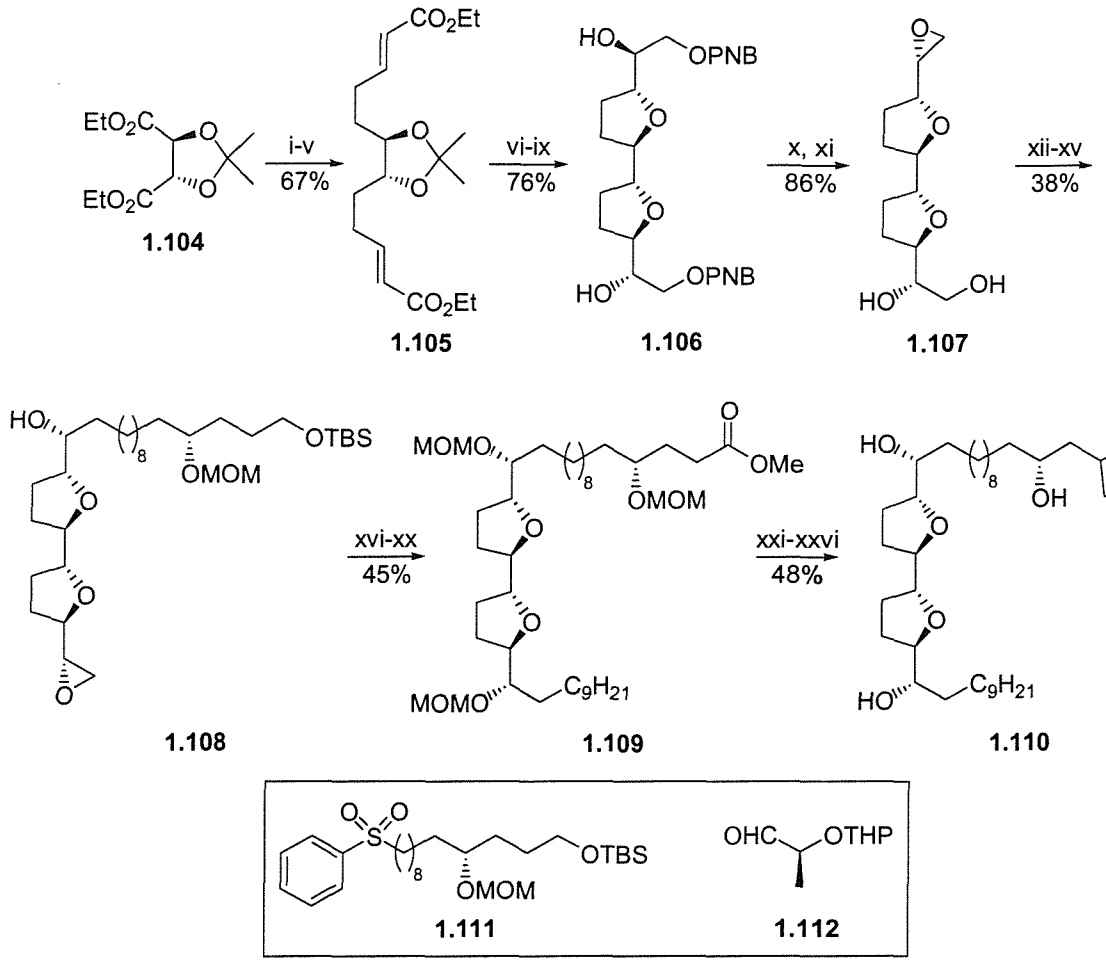
Scheme 1.14 Scharf's total synthesis of 15-*epi*-annonin

Scharf also carried out synthetic, nuclear magnetic resonance and circular dichroism studies of butenolide fragments as a method of elucidation of the butenolide stereochemistry in natural products.[82]

1.5.3 Shigeki Sasaki *et al*; Synthesis of (+)-Bullatacin 1.110

Using a method of *bis*-THF generation which paralleled that used by Hoye *et al.* in the synthesis of (+)-(15,16,19,20,23,24)-*hexepi*-uvaricin, Sasaki undertook the total synthesis of (+)-bullatacin. Thus, diethyl-2,3-*O*-*iso*propylidene-D-tartrate **1.104** underwent DIBAL-H reduction, Horner-Emmons olefination and hydrogenation. A second round of reduction and olefination afforded *bis*-ester **1.105**. Reduction of the esters, asymmetric epoxidation, *p*-nitrobenzoylation and treatment with acid afforded *bis*-THF **1.106**. *Mono*-mesylation and removal of the benzoyl esters resulted in the formation of epoxide **1.107**, which was opened by the lithium anion of sulfone **1.111**. Desulfonation of the product with sodium amalgam and treatment with toluenesulfonyl chloride followed by base gave epoxide **1.108**.

A Cu^{I}-mediated epoxide opening using *n*-nonylmagnesiumbromide and protection of the hydroxy groups was followed by desilylation, Jones oxidation and esterification with diazomethane, affording ester **1.109**. Aldol condensation with aldehyde **1.112** and removal of the THP protecting group resulted in lactonisation. Benzoylation and treatment with methanolic ammonia was required to cause elimination, thus constructing the butenolide portion. Removal of the MOM groups afforded (+)-bullatacin **1.110** (Scheme 1.15).



Reagents and Conditions: (i) DIBAL-H, $PhCH_3$, -78 °C; (ii) $(EtO)_2P(O)CH_2CO_2Et$, NaH, DME, -78 °C; (iii) Pd/C, H_2, EtOH; (iv) DIBAL-H, $PhCH_3$, -78 °C; (v) $(EtO)_2P(O)CH_2CO_2Et$, NaH, DME, -78 °C; (vi) DIBAL-H, $PhCH_3$, -78 °C; (vii) $Ti(O\textit{i}\text{-}Pr)_4$, L-(+)-DIPT, *t*-BuOOH, CH_2Cl_2, -30 °C; (viii) PNBCl, Et_3N, 0 °C; (ix) $BF_3{\bullet}Et_2O$, MeOH, CH_2Cl_2; (x) MsCl, Et_3N, THF, 0 °C; (xi) *n*-Bu_4NOH, THF, 0 °C; (xii) **1.111**, *n*-BuLi, DME; (xiii) Na-Hg, EtOH; (xiv) TsCl, py, -20 °C; (xv) K_2CO_3, EtOH, H_2O; (xvi) *n*-$C_9H_{21}MgBr$, CuBr, THF, 0 °C; (xvii) MOMCl, DIPEA, CH_2Cl_2, 0 °C; (xviii) TBAF, THF, 0 °C; (xix) CrO_3, H_2SO_4, Me_2CO, -20 °C; (xx) CH_2N_2, Et_2O, EtOAc; (xxi) LDA; (xxii) **1.112**, THF, -78 °C; (xxiii) CSA, MeOH, H_2O; (xxiv) BzCl, py, 0 °C; (xxv) NH_3, MeOH; (xxvi) $BF_3{\bullet}Et_2O$, DMS.

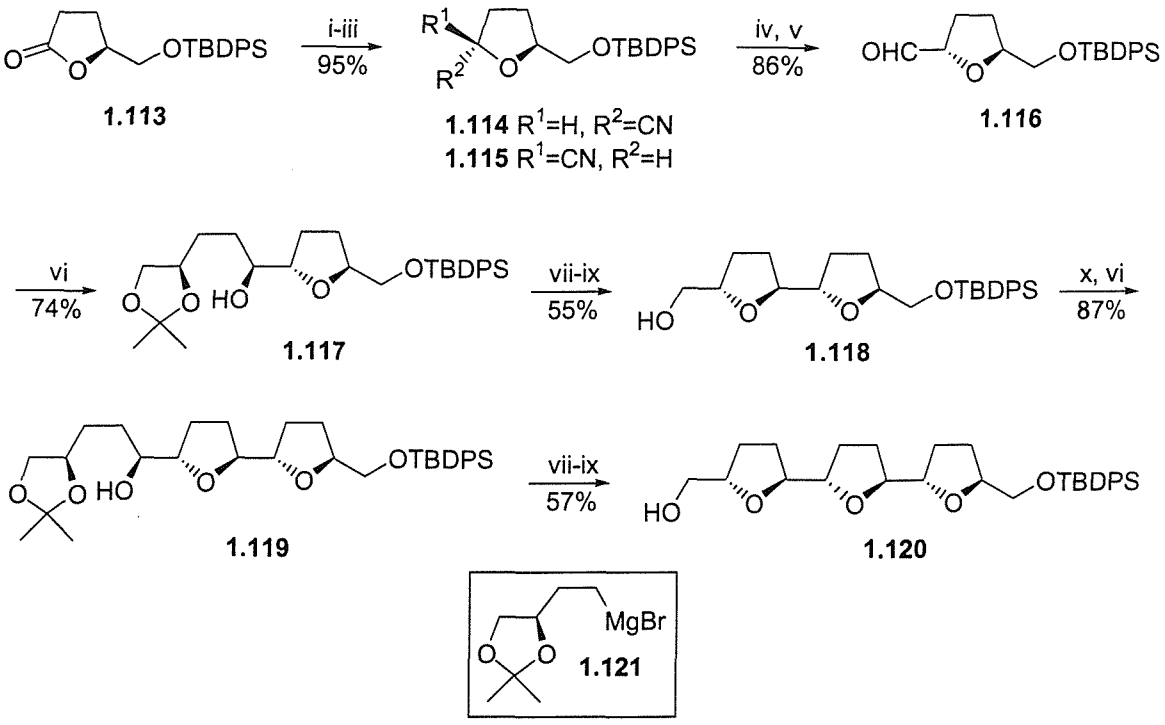
Scheme 1.15 Sasaki's synthesis of (+)-bullatacin

1.5.4 Ulrich Koert *et al.*

As part of an investigation of polyether helices with ion channel activity,[83] Koert *et al.* investigated the linear synthesis of 2,5-*trans*-linked oligo tetrahydrofurans based on the successive elaboration of a THF ring to a pre-existing chain of THF units.[84]

1.5.4.1 General Oligo-THF Synthesis

Their first approach was an iterative method of oligo THF extension. Thus, enantiomerically pure lactone **1.113**, obtained from glutamic acid,[85] was converted to separable epimeric nitriles **1.114** and **1.115** in a 5:2 ratio. The *trans*-nitrile was converted to the corresponding methyl ester, and DIBAL reduction gave aldehyde **1.116**. Reaction with Grignard **1.121** in the presence of Cu^{I} afforded alcohol **1.117**.[86] This was converted to *bis*-THF fragment **1.118** in four steps. Swern oxidation of the resulting primary alcohol and a further round of reactions gave *tris*-THF **1.120**, which could be further extended in an iterative process (Scheme 1.16). The preferred formation of **1.117** and **1.119** was as predicted by the Cram chelate model.[87]



Reagents and Conditions: (i) DIBAL-H, $PhCH_3$, -78 °C; (ii) Ac_2O, Et_3N; (iii) TMSCN, $BF_3{\bullet}Et_2O$, MeCN, -20 °C, collect **1.114**; (iv) NaOMe, MeOH; (v) DIBAL-H, CH_2Cl_2; (vi) **1.121**, $CuBr{\bullet}SMe_2$, Et_2O, -40 °C; (vii) $AcOH/H_2O$/THF, 9:2:1; (viii) $MesSO_2Cl$, py, CH_2Cl_2; (ix) K_2CO_3, MeCN then AcOH; (x) $(COCl)_2$, DMSO, Et_3N.

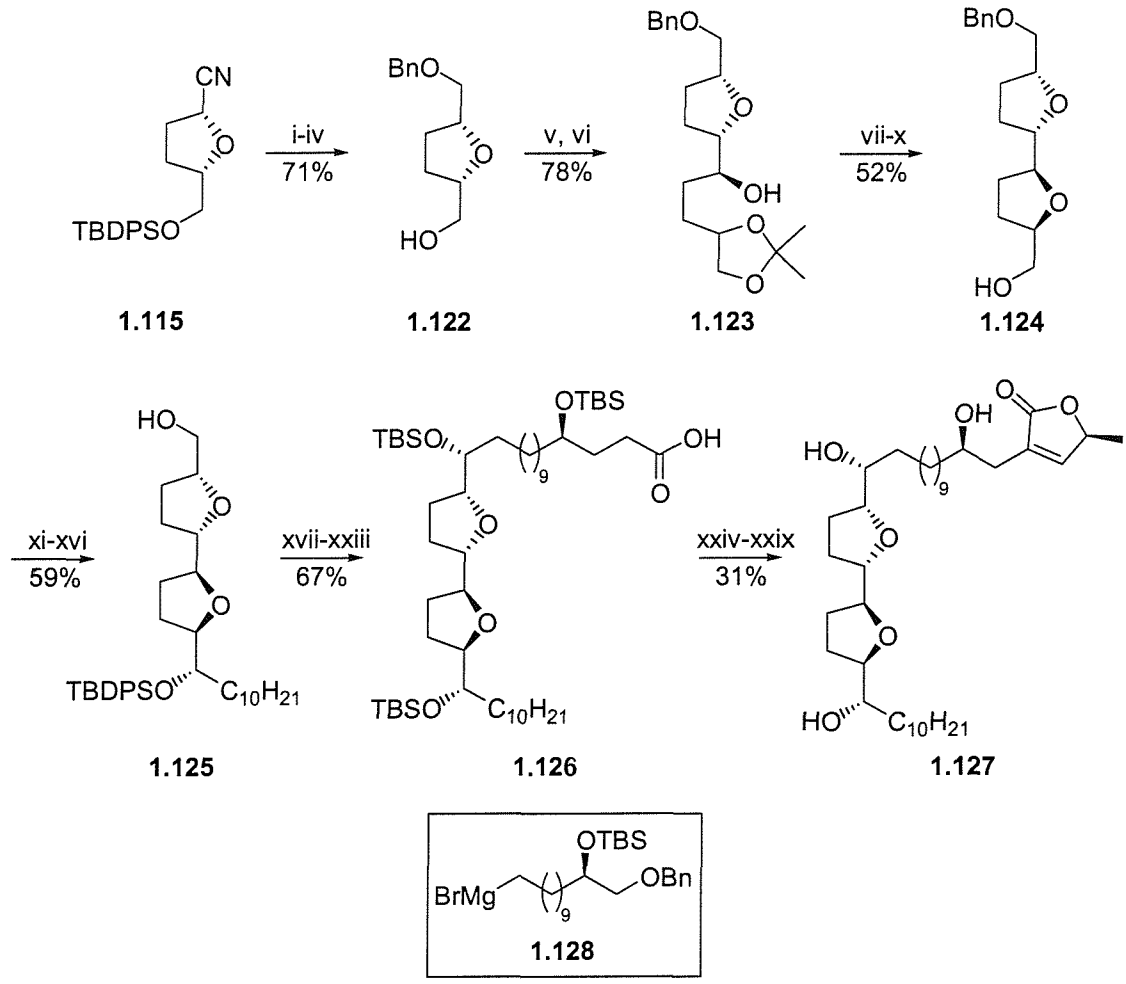
Scheme 1.16 Koert's iterative oligo-THF synthesis

1.5.4.2 Synthesis of (+)-Rolliniastatin I, 1.127

This methodology was then applied to the total synthesis of (+)-rolliniastatin I **1.127**.[88,89] Nitrile **1.115** was converted to the corresponding methyl ester, which was then reduced and benzylated. Desilyation gave alcohol **1.122**, which underwent Swern oxidation and Cu^I mediated Grignard reaction with *ent*-**1.121** affording acetonide **1.123**.[86] Removal of the acetonide and conversion to the epoxide, followed by acid-catalysed ring closure gave *bis*-THF moiety **1.124**. Swern oxidation, reaction with *n*-decylmagnesium bromide, a second Swern oxidation of the product and stereoselective reduction (82:18) was carried out, followed by silylation and debenzylation, affording alcohol **1.125**.

Installation of the butenolide-bearing sidechain was then addressed. Oxidation of **1.125** and treatment with Grignard reagent **1.128** afforded predominantly the *threo* product (95:5). Desilylation, reprotection as the *tris*-TBDMS ether and debenzylation was followed by

oxidation of the primary alcohol to acid **1.126**. Treatment of the dianion of this acid consecutively with diphenyl disulfide, (*S*)-propylene oxide and acid installed a phenyl sulfide substituted lactone as for Hoye *et al.* Oxidation, thermal elimination and desilylation afforded (+)-rolliniastatin I **1.127** (Scheme 1.17).

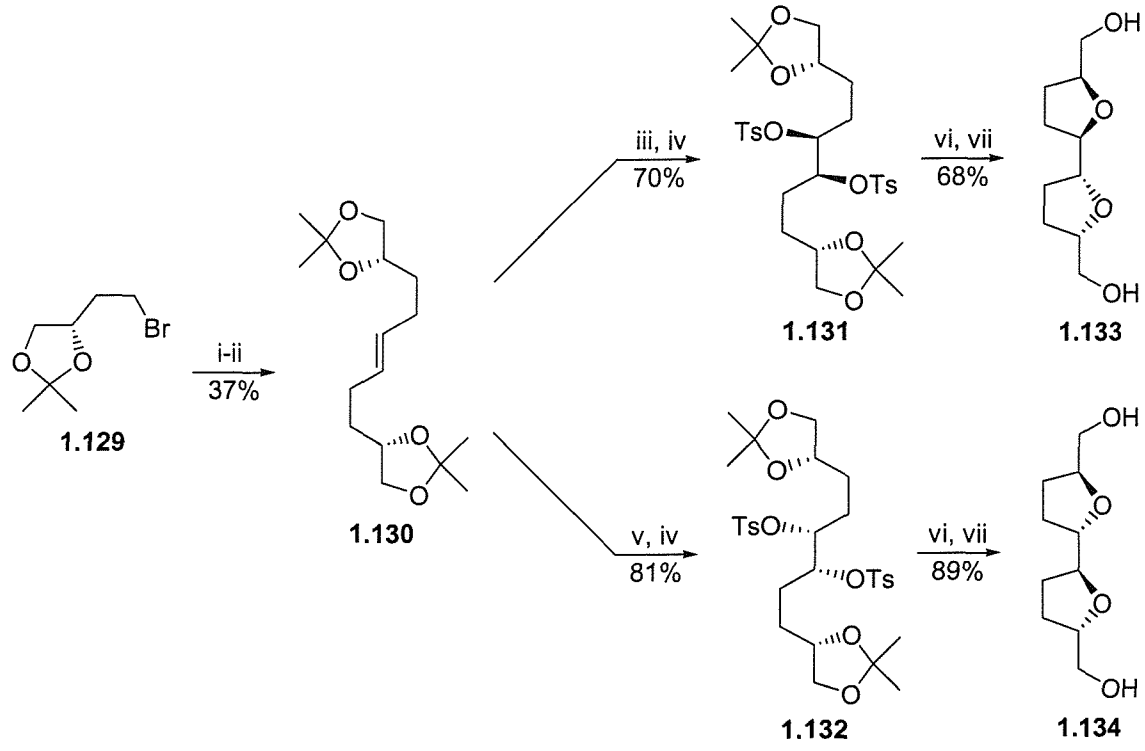


Reagents and Conditions: (i) NaOMe, MeOH; (ii) $LiAlH_4$, THF; (iii) BnBr, NaH; (iv) TBAF, THF; (v) Swern; (vi) *ent*-**1.121**, CuBr•SMe_2, Et_2O, -78 °C; (vii) AcOH, THF, H_2O; (viii) $MesSO_2Cl$, py, 0 °C; (ix) K_2CO_3, MeOH; (x) AcOH, CH_2Cl_2; (xi) Swern; (xii) *n*-$C_{10}H_{21}MgBr$; (xiii) Swern; (xiv) $Zn(BH_4)_2$, EtO_2, -78 °C; (xv) TBDPSCl; (xvi) Pd/C, H_2, THF; (xvii) Swern; (xviii) **1.128**, CuBr•SMe_2, Et_2O, -78 °C; (xix) TBAF; (xx) TBSCl; (xxi) Pd/C, H_2, THF; (xxii) Swern; (xxiii) $KMnO_4$, Na_2HPO_4; (xxiv) LDA, PhSSPh, 0 °C; (xxv) LDA, (*S*)-propylene oxide; (xxvi) TsOH; (xxvii) MMPP, THF, MeOH; (xxviii) $PhCH_3$, Δ; (xxix) HF, MeCN, THF.

Scheme 1.17 Koert's total synthesis of (+)-rolliniastatin I

1.5.4.3 Use of the Williamson Etherification Reaction

The second approach of Koert *et al.*[90] was the five membered ring selective Williamson annulation reaction of 4,5-dihydroxy tosylates.[91] Alkylation of lithium diacetylide using chiral bromide **1.129** and (*E*)-selective reduction of the alkyne afforded alkene **1.130**. Asymmetric dihydroxylation using AD-mix-α or AD-mix-β and treatment with excess toluenesulfonyl chloride gave ditosylates **1.131** and **1.132**. Deprotection of the diols and treatment with base resulted in double Williamson cyclisation of each, affording *bis*-THF diols **1.133** and **1.134** (Scheme 1.18).



Reagents and Conditions: (i) LiC≡CLi, TMEDA; (ii) Na, NH_3/THF 1:1, -30 °C; (iii) AD-mix-α, *t*-BuOH, H_2O, 0-20 °C; (iv) TsCl, py; (v) AD-mix-β, *t*-BuOH, H_2O, 0-20 °C; (vi) AcOH, H_2O, 40 °C; (vii) NaH, THF.

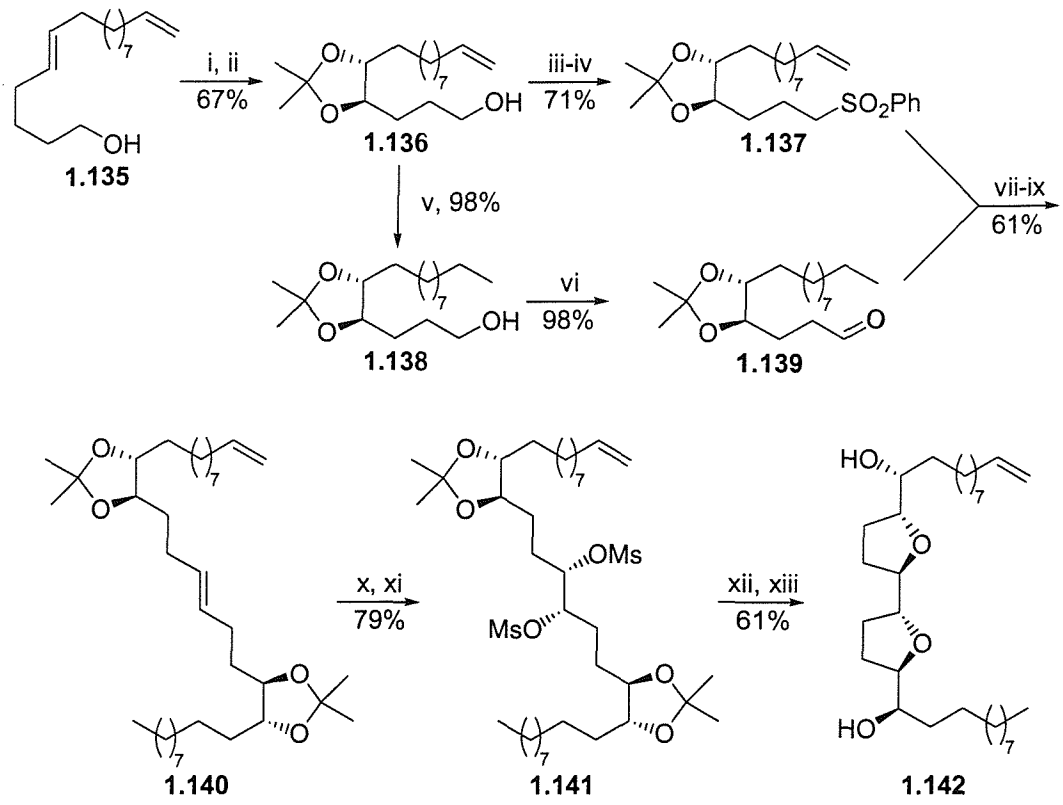
Scheme 1.18

In related research, Koert used both epoxide opening and multiple Williamson etherification reactions to construct molecules containing up to five adjacent 2,5-linked THF rings.[92,93]

1.5.5 Barry M. Trost *et al.*

Using a strategy based on asymmetric dihydroxylation chemistry, and which utilised the Williamson etherification protocol to install the *bis*-THF core, Trost carried out the total synthesis of (+)-parviflorin **1.27**.[94] The carbon skeleton was synthesised by the joining together of two almost identical building blocks by Julia olefination.[95] These were synthesised from dienol **1.135**,[96] which underwent asymmetric dihydroxylation and protection as the acetonide affording alcohol **1.136** (94% *ee*). The sulfone olefination partner **1.137** was obtained by conversion to the corresponding iodide followed by displacement by the sodium salt of benzenesulfinic acid.[97,98] Aldehyde partner **1.139** was obtained by hydrogenation of **1.136** followed by Dess-Martin oxidation.[99]

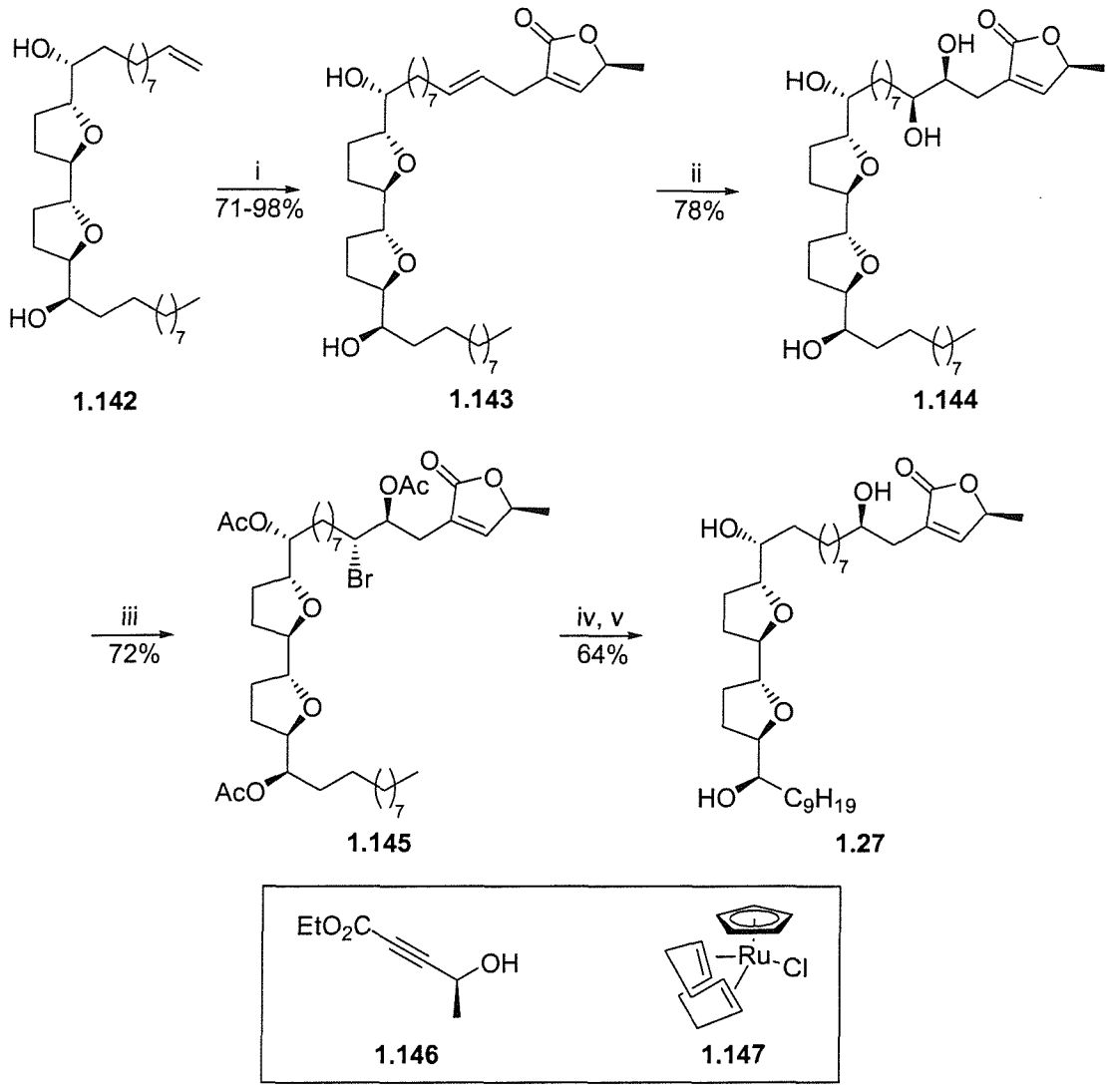
The aldehyde was then added to a cooled solution of the lithiated sulfone, and the reaction was quenched by the addition of benzoyl chloride. Treatment with sodium amalgam in the presence of a borate buffer gave alkyne **1.140** in an *E*:*Z* ratio of 3:1. Asymmetric dihydroxylation of the *E* isomer and treatment with methanesulfonyl chloride afforded *bis*-mesylate **1.141**. Acetonide removal and treatment of the crude product with base induced Williamson cyclisation, affording *bis*-THF **1.142** (Scheme 1.19).



Reagents and Conditions: (i) $K_3Fe(CN)_6$, $CH_3SO_2NH_2$, OsO_4, $(DHQD)_2PHAL$, *t*-BuOH, H_2O; (ii) $Me_2C(OMe)_2$, TsOH, PhH; (iii) Ph_3P, I_2, imidazole, THF; (iv) $PhSO_2Na$, DMF; (v) Pd/C, H_2, EtOH; (vi) DMP, CH_2Cl_2; (vii) *n*-BuLi, THF, -78 °C; (viii) PhCOCl; (ix) Na/Hg, H_3BO_3, EtOH; (x) $K_3Fe(CN)_6$, $CH_3SO_2NH_2$, OsO_4, $(DHQD)_2PHAL$, *t*-BuOH, H_2O; (xi) MsCl, py; (xii) Amberlyst-H, MeOH, 40 °C; (xiii) *t*-BuOK, THF.

Scheme 1.19

Alkene **1.142** underwent Trost's ruthenium catalysed Alder-ene reaction with alkyne **1.146** and catalyst **1.147**,[100] affording the unsaturated butenolide product **1.143** as a single epimer in good to excellent yield. The isolated double bond was dihydroxylated stereoselectively giving tetraol **1.144**. Chemoselective deoxygenation of the C-5 hydroxyl group was achieved upon treatment with acetyl bromide, by regioselective opening of the intermediate acetoxonium ion, affording bromoacetate **1.145**.[101] These conditions resulted in the acetylation of the other two hydroxy groups. Radical debromination and acidic hydrolysis completed the synthesis of (+)-parviflorin (Scheme 1.20).



Reagents and Conditions: (i) **1.146**, **1.147**, MeOH, 60 °C; (ii) $K_3Fe(CN)_6$, $CH_3SO_2NH_2$, OsO_4, $(DHQD)_2PHAL$, *t*-BuOH, H_2O; (iii) CH_3COBr, CH_2Cl_2; (iv) *n*-Bu_3SnH, AIBN, $PhCH_3$; (v) CH_3COCl, MeOH.

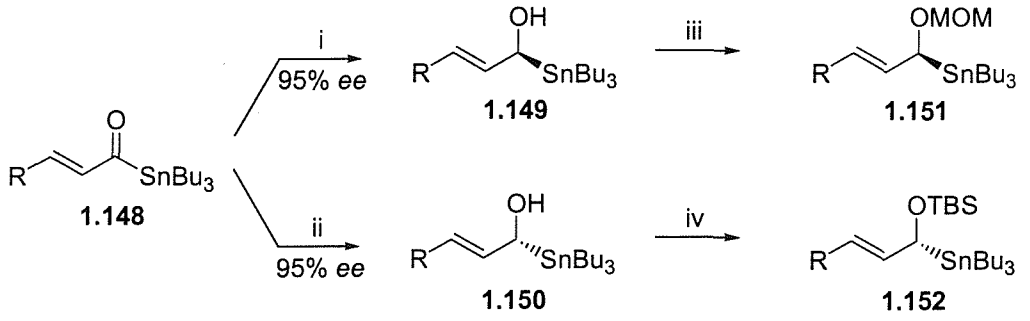
Scheme 1.20

1.5.6 James A. Marshall *et al.*

1.5.6.1 General 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,[102] which were prepared by the reduction of an acylstannane **1.148** by a chiral

hydride source, followed by the etherification of the resulting (*S*)- or (*R*)-hydroxy stannane **1.149** or **1.150** with a reactive halide or triflate (Scheme 1.21).

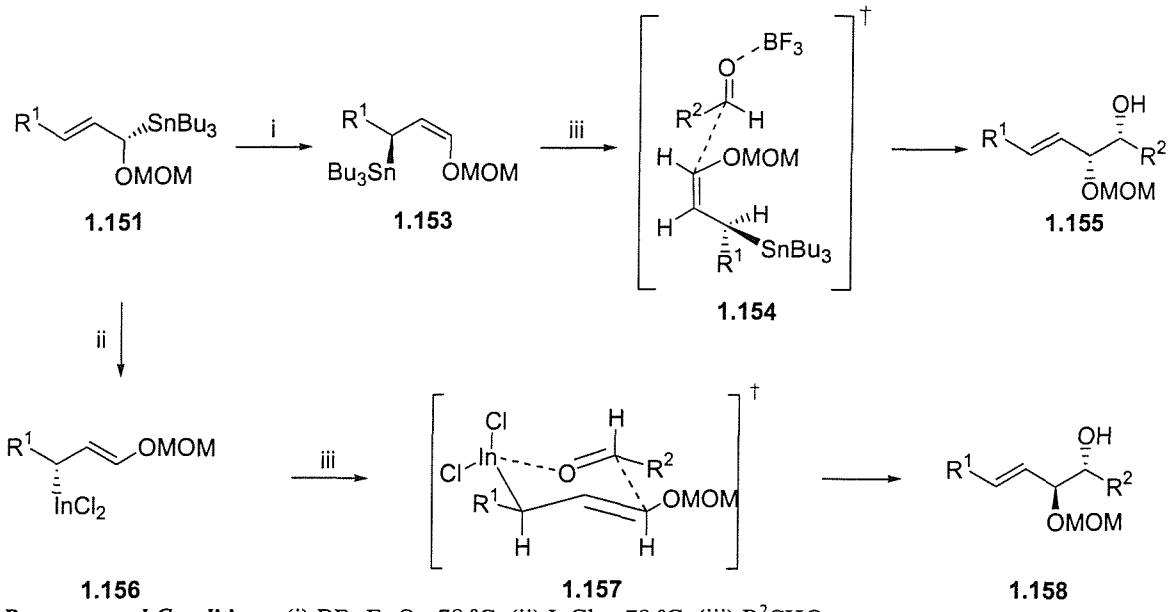


Reagents and Conditions: (i) (*R*)-(+)-BINAL-H, THF, -78 °C; (ii) (*S*)-(-)-BINAL-H, THF, -78 °C; (iii) MOMCl, DIPEA, CH_2Cl_2, 0 °C; (iv) TMSOTf, DIPEA, CH_2Cl_2, 0 °C.

Scheme 1.21 Synthesis of α-alkoxy chiral stannanes

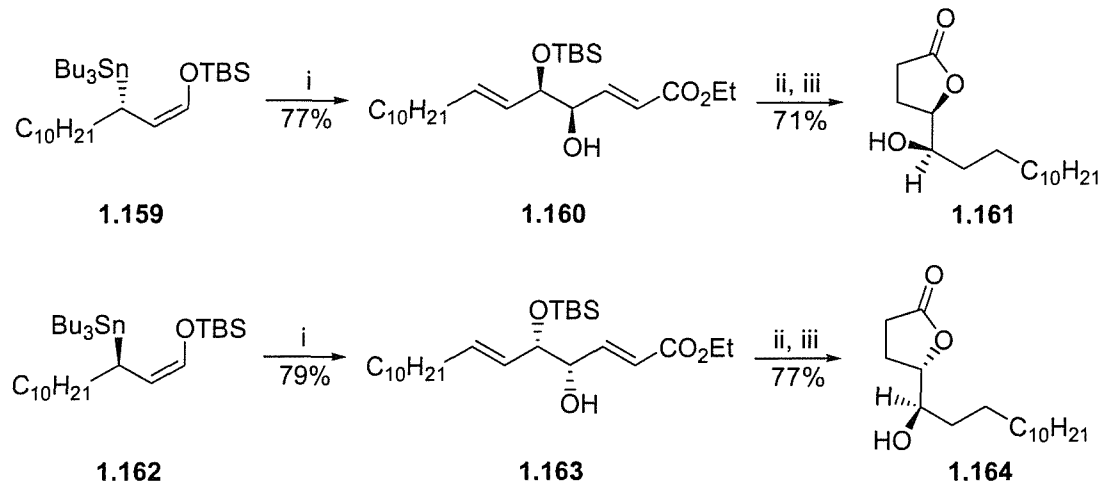
Upon treatment with a range of Lewis acids, α-alkoxy stannane **1.151** underwent stereospecific isomerisation to the γ-isomer **1.153** with inversion. Addition to aldehydes in the presence of Lewis acid afforded *mono*-protected *syn*-1,2-diols **1.155**, *via* an acyclic transition state **1.154**.[103] By contrast, pre-treatment of the stannane with indium trichloride and addition of aldehydes gave *mono*-protected *anti*- adducts **1.158**, *via* cyclic transition state **1.157** (Scheme 1.22).[104]

This methodology was applied to the synthesis of simple natural products (-)- and (+)-muricatacin, **1.161** and **1.164**.[105] Thus, reaction of two stannanes **1.159** and **1.162** with unsaturated aldehyde **1.165**, in the presence of boron trifluoride, gave adducts **1.160** and **1.163** in good yield and with high *syn*-selectivity. Hydrogenation and lactonisation of these intermediates afforded (-)- and (+)-muricatacin (Scheme 1.23).



Reagents and Conditions: (i) BF_3•Et_2O, -78 °C; (ii) $InCl_3$, -78 °C; (iii) R^2CHO.

Scheme 1.22 Isomerisation of α-alkoxy chiral stannanes and reaction with aldehydes



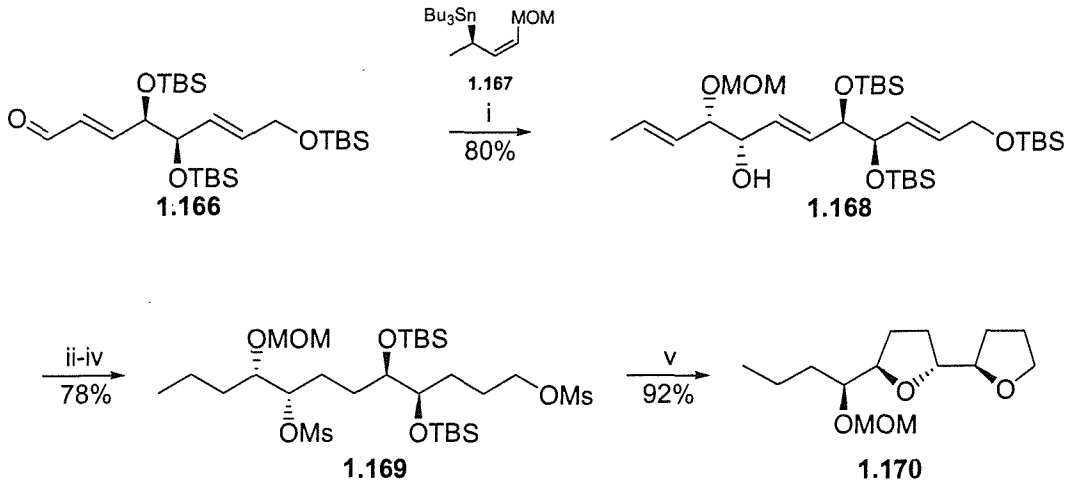
Reagents and Conditions: (i) *trans*-OHCCH=$CHCO_2Et$ (**1.165**), BF_3•Et_2O, -78 °C; (ii) Pd/C, H_2; (iii) HF, H_2O, THF.

Scheme 1.23 Synthesis of simple THF compounds using stannanes

1.5.6.2 Application of the Stannane Chemistry to *bis*-THF Synthesis

Marshall next applied his stannane chemistry to the synthesis of *bis*-THF containing molecules. Preparation of aldehyde **1.166** and reaction with stannane **1.167** gave alcohol **1.168**. Hydrogenation, selective removal of the allylic silyl ether and conversion to *bis*-

mesylate **1.169** provided a substrate which on desilylation underwent double Williamson cyclisation affording *bis*-THF **1.170** (Scheme 1.24).[53]

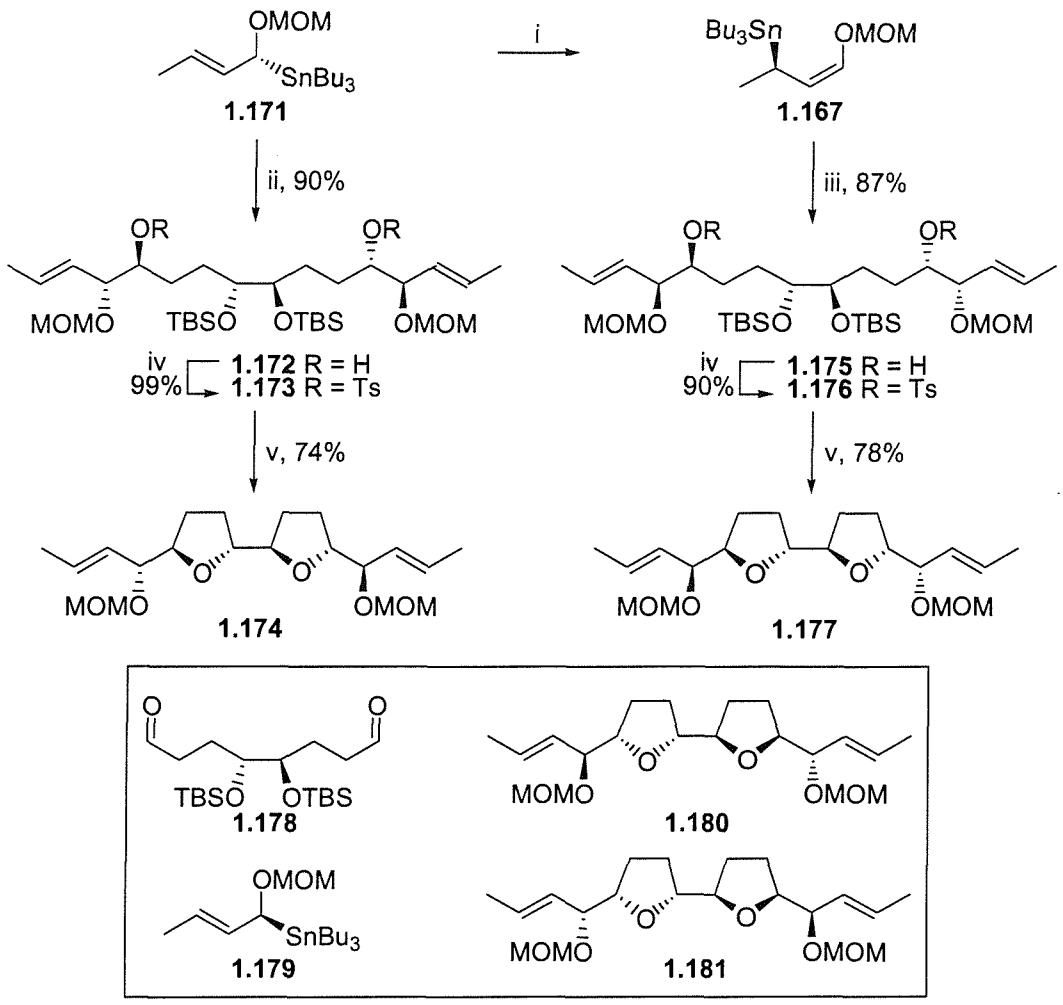


Reagents and Conditions: (i) **1.167**, $BF_3 \cdot Et_2O$; (ii) Pd/C, H_2; (iii) PPTS, MeOH; (iv) MsCl, py; (v) TBAF.

Scheme 1.24 Synthesis of a simple *bis*-THF fragment

A model study was also carried out using a bidirectional approach to synthesise *bis*-THF fragments with C_2 symmetry, a common feature of natural acetogenins. Stannane **1.171** was treated with either $InCl_3$ or Boron trifluoride etherate prior to treatment with *bis*-aldehyde **1.178**, affording predominantly the *bis-anti* and *bis-syn* alcohols **1.172** and **1.175** respectively in good yield. Tosylation of each and treatment with TBAF resulted in desilylation and double Williamson cyclisation affording *bis* THF's (*R,R,R,R,R,R*)-**1.174** and (*S,R,R,R,R,S*)-**1.177** respectively.[106]

Subjection of stannane **1.179** to identical reaction conditions resulted in the synthesis of (*S,S,R,R,S,S*)-**1.180** and (*R,S,R,R,S,R*)-**1.181** *via* the $InCl_3$ and Boron trifluoride etherate routes respectively (Scheme 1.25).

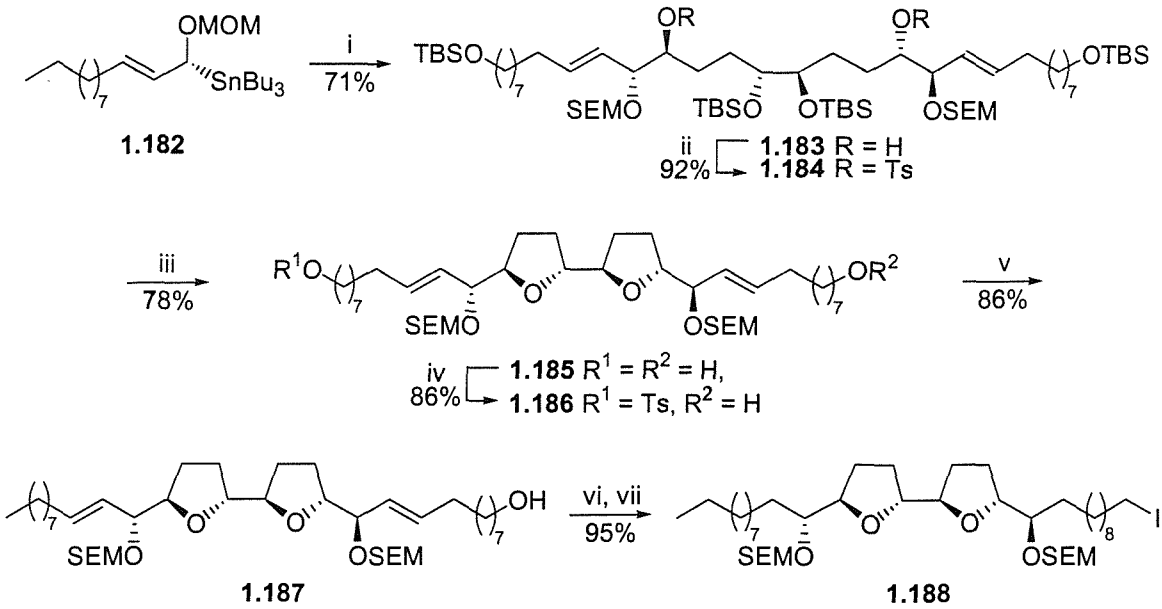


Reagents and Conditions: (i) $BF_3 \cdot Et_2O$; (ii) $InCl_3$, **1.178**, EtOAc; (iii) $BF_3 \cdot Et_2O$, **1.178**, CH_2Cl_2; (iv) TsCl; (v) TBAF, THF.

Scheme 1.25 A bidirectional approach to the C_2-symmetric *bis*-THF acetogenin core

1.5.6.3 Total Synthesis of (+)-Asimicin 1.70

Using the methodology described above for C_2 symmetric *bis*-THF's, Marshall undertook the total synthesis of (+)-asimicin **1.70**.[107] The indium mediated reaction between previously described aldehyde **1.178** and stannane **1.182** proceeded with high yield and selectivity affording diol **1.183**. Tosylation and desilylation resulted in double Williamson cyclisation affording *bis*-THF **1.185**, which was desymmetrised by the method of McDougal giving *mono*-tosylate **1.186**.[108] Reduction of the tosylate, ruthenium catalysed hydrogenation of the alkenes and treatment with iodine in the presence of triphenylphosphine afforded iodide **1.188** (Scheme 1.26).

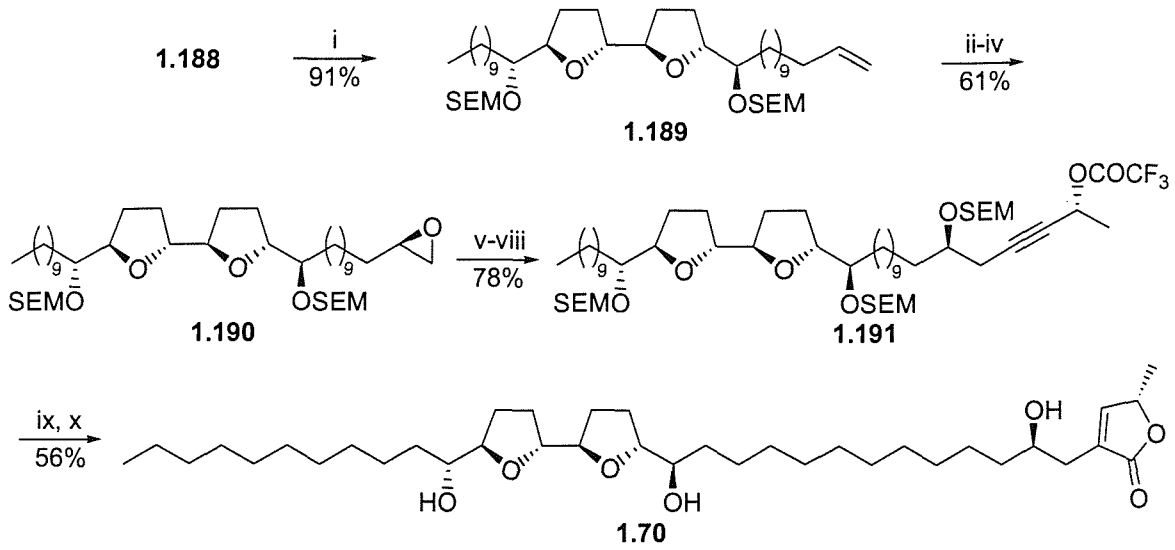


Reagents and Conditions: (i) **1.178**, $InCl_3$, EtOAc; (ii) TsCl, py; (iii) TBAF, THF; (iv) *n*-BuLi, THF then TsCl; (v) $LiBEt_3H$, THF; (vi) Rh/Al_2O_3, H_2, EtOAc; (vii) I_2, Ph_3P, imidazole, CH_2Cl_2.

Scheme 1.26 Synthesis of the THF core of (+)-asimicin

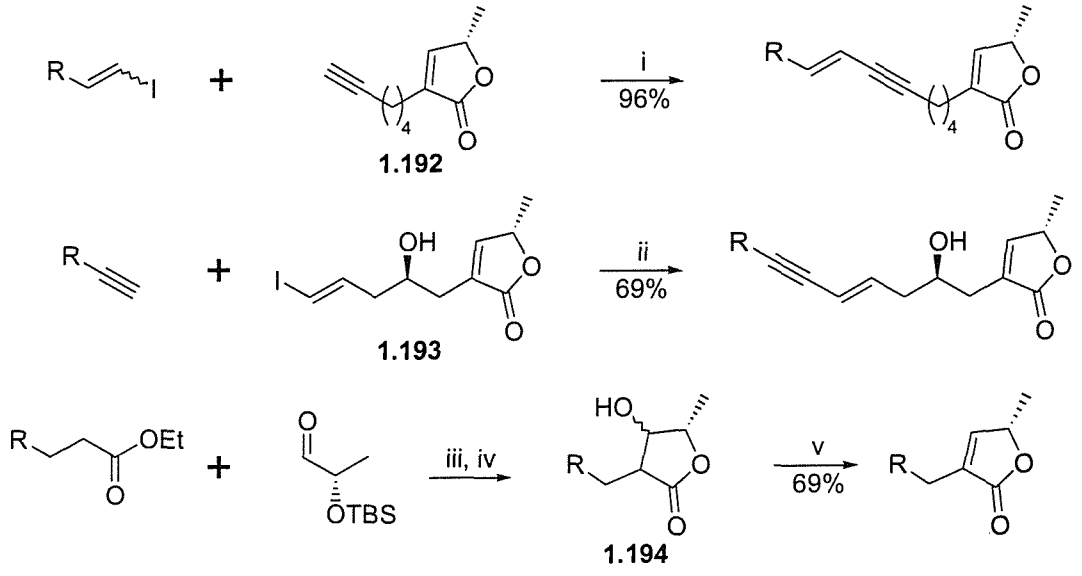
Coupling of iodide **1.188** with a higher order vinyl cuprate afforded olefin **1.189**, which was subjected to asymmetric dihydroxylation and conversion to epoxide **1.190**. Treatment with lithio-(*R*)-2-OTBS-3-butyne, protection of the resulting alcohol, desilylation and treatment with trifluoroacetic anhydride gave alkyne **1.191**. Addition of tetrakis-triphenylphosphine palladium under an atmosphere of carbon monoxide, followed by addition of silver nitrate supported on silica gel, resulted in formation of the butenolide headgroup. Removal of the protecting groups afforded (+)-asimicin **1.70** (Scheme 1.27).

Marshall has also published the total syntheses of a number of acetogenins based on the rearrangement of chiral α-alkoxy stannanes and their subsequent S_E2' addition to aldehydes, with some variation in the method of addition of the butenolide moiety. This took place by coupling of either butenolide-bearing terminal alkyne **1.192** with a terminal vinyl iodide, [109,110] or of butenolide-bearing vinyl iodide **1.193** with a terminal alkyne, followed by hydrogenation.[111] An alternative method was the aldol condensation of a terminal ethyl ester with the TBS ether of (*S*)-lactic acid. Desilylation gave γ-lactone adduct **1.194**, which on treatment with trifluoroacetic anhydride and base afforded the butenolide (Scheme 1.28).[112,113]



Reagents and Conditions: (i) $(HC{=}CH)_2Cu(CN)Li_2$, THF; (ii) $(DHQD)_2AQN$, $K_3Fe(CN)_6$, *t*-BuOH; (iii) 2,4,6-tri-*iso*-propyl benzenesulfonyl chloride, py; (iv) NaH, THF; (v) (*R*)-LiC≡CH(OTBS)CH_3, $BF_3{\bullet}Et_2O$, THF; (vi) SEMCl, DIPEA, CH_2Cl_2; (vii) TBAF, THF; (viii) $(CF_3CO)_2O$, 2,6-lutidine; (ix) 1% $Pd(Ph_3P)_4$, CO, THF, H_2O then $AgNO_3$, SiO_2; (x) PPTS, EtOH.

Scheme 1.27 Installation of the butenolide of (+)-asimicin



Reagents and Conditions: (i) $(Ph_3P)_2PdCl_2$, Et_2NH, CuI; (ii) $(Ph_3P)_2PdCl_2$, Et_3N, CuI; (iii) LDA; (iv) TBAF; (v) $(CF_3CO)_2O$, Et_3N.

Scheme 1.28 Alternative Marshall approaches to the butenolide

Bringing together a number of the most useful aspects of his methodology, Marshall also carried out a study into the versatile, modular synthesis of four *bis*-THF acetogenins from

seven fundamental subunits.[114] This study is not detailed herein as the fundamental ideas have been addressed previously.

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

The approach of Sinha *et al.* to the synthesis of *bis*-THF acetogenins is based primarily on a combination of the highly enantioselective Sharpless asymmetric dihydroxylation reaction and Kennedy's highly stereoselective rhenium based cyclisation of 5-hydroxy alkenes.[115-120] The starting materials for this approach are generally long chain unsaturated aliphatic molecules, commonly terminating at one end with an ester or synthetic equivalent. This methodology had previously been successfully applied to the synthesis of *mono*-THF acetogenins.[74]

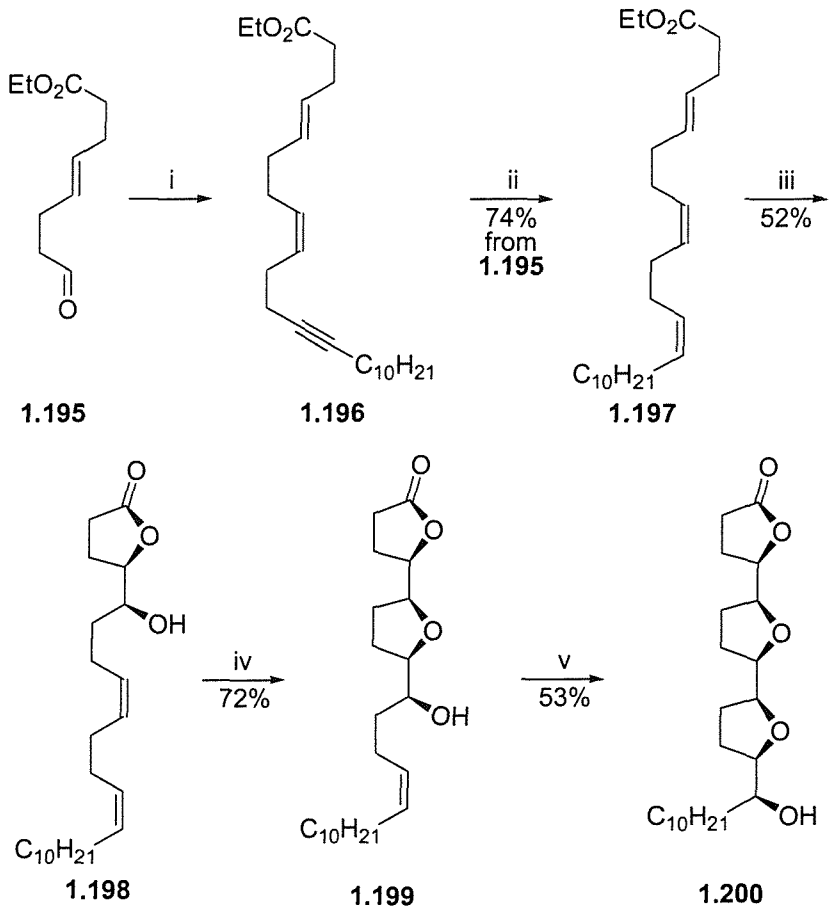
The use of Kennedy's cyclisation with rhenium was also investigated by Frank E. McDonald, who conducted studies directed at the synthesis of the tetrahydrofuran portions of *tris*-THF acetogenins.[121] Although McDonald's work is worthy of mention, this summary focuses on the synthesis of *bis*-THF compounds, and it is therefore not detailed

1.5.7.1 Initial Studies Using the Sharpless / Kennedy Approach

The initial aim was the synthesis of a polyene substrate on which to attempt the generation of a number of chiral centres in a single step *via* tandem oxidative cyclisation.[122] Thus, Wittig olefination of aldehyde **1.195** followed by hydrogenation over Lindlar's catalyst and dihydroxylation using AD-mix-β afforded hydroxylactone **1.198** as the major product. This differentiation is possible due to the significantly higher reactivity of AD reagents towards (*E*)-alkenes relative to (*Z*)-alkenes.[115]

Treatment of this intermediate with a mixture of Re_2O_7 and 2,6-lutidine gave cyclisation product **1.199**. When treated with the more reactive combination of Re_2O_7 and periodic acid a second cyclisation ocurred, affording *bis*-THF lactone **1.200** in moderate yield. It was found that both cyclisations could be effected in a single step by initial exposure of hydroxylactone **1.198** to these more reactive conditions, affording **1.200** in 25% yield and

installing four new stereocentres (Sceme 1.29). The ability to halt the reaction after the first cyclisation has obvious synthetic advantages.



Reagents and Conditions: (i) $C_{10}H_{12}C{\equiv}CCH_2CH_2CH{=}PPh_3$; (ii) H_2, Lindlar cat.; (iii) AD-mix-β; (iv) Re_2O_7, 2,6-lutidine; (v) Re_2O_7, H_5IO_6.

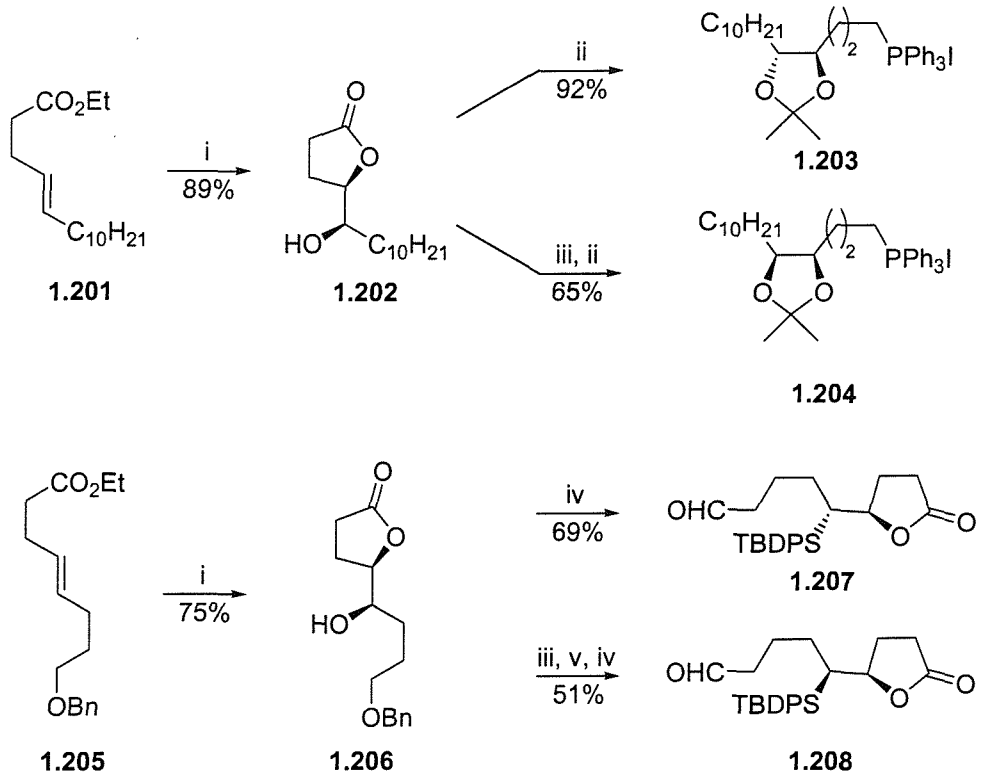
Scheme 1.29 Sinha's combined osmium – rhenium approach

1.5.7.2 Library Synthesis of bis-THF Fragments

Sinha and Keinan next demonstrated the use of their osmium – rhenium approach, in combination with the Mitsunobu inversion of alcohols,[123,124] to provide a number of intermediates which allowed the convergent synthesis of a library of *bis*-THF fragments. They then used one of these intermediates in the total synthesis of trilobacin **1.26**.[125]

This library synthesis began with two Wittig partners, a phosphonium salt and an aldehyde, each containing two stereogenic centres. In the structure of trilobacin **1.26** the phosphonium salt contains centres 23 and 24, and the aldehyde centres 15 and 16. Phosphonium salts

1.203 and **1.204** and aldehydes **1.207** and **1.208** were prepared by asymmetric dihydroxylation of alkenes **1.201** and **1.205** respectively. These intermediates were then either transformed directly to the corresponding phosphonium salt or aldehyde, or subjected to Mitsunobu inversion and then transformed. Illustrated below are some of the intermediates synthesised using only AD-mix-β (Scheme 1.30).

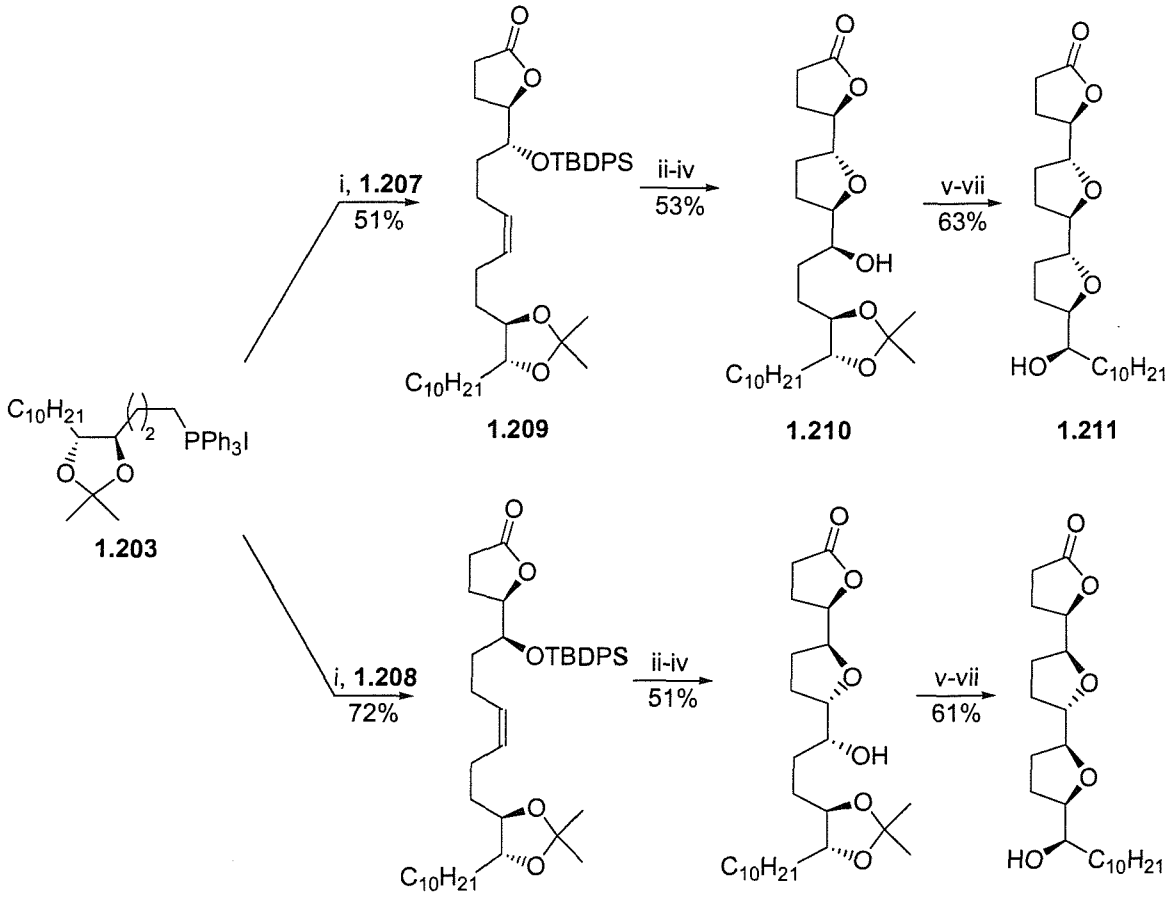


Reagents and Conditions: (i) (a) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH, H_2O, 0 °C; (b) KOH, H_2O, MeOH then 3N HCl; (c) TsOH, CH_2Cl_2; (ii) (a) $LiAlH_4$, Et_2O, THF, 0 °C; (b) TsOH, Me_2CO, Dean – Stark; (c) Ph_3P, I_2, imidazole, $PhCH_3$; (d) Ph_3P, $NaHCO_3$, CH_3CN; (iii) *p*-nitrobenzoic acid, Ph_3P, DEAD, PhH; (iv) (a) TBDPSCl, imidazole, DMF; (b) 10% Pd/C, MeOH, H_2; (c) PCC, CH_2Cl_2; (v) (a) KOH, H_2O, MeOH then 3N HCl; (b) TsOH, CH_2Cl_2.

Scheme 1.30 Synthesis of some library building blocks

Coupling together of these two phosphonium salts and two aldehydes provided four (*Z*)-alkenes, which were then subjected to the rhenium cyclisation affording the corresponding *trans*-substituted tetrahydrofurans. Illustrated below are the two products obtained by the reaction of phosphonium salt **1.203** with aldehydes **1.207** and **1.208** (Scheme 1.31). The products were desilylated and subjected to Kennedy cyclisation conditions, affording **1.209** and **1.212**. Mesylation and acetonide removal resulted in Williamson cyclisation to *bis*-THF lactones **1.211** and **1.214**. Sinha and Keinan synthesised four phosphonium salts and four

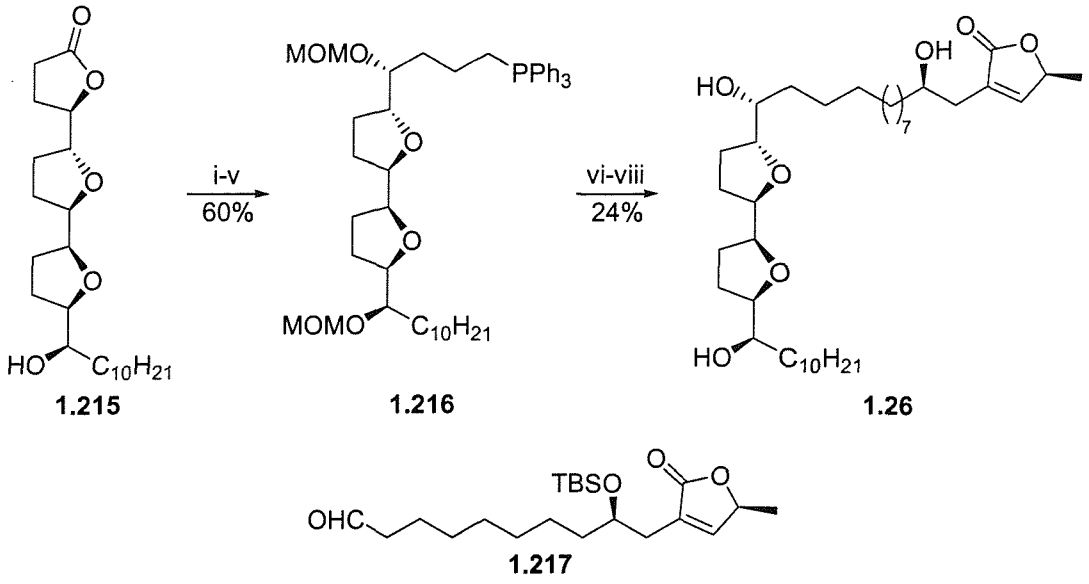
aldehydes, allowing the synthesis of sixteen possible Williamson cyclisation precursors of type **1.209**. Mitsunobu inversion of these alcohols prior to the final cyclisation would allow access to a total of thirty two *bis*-THF lactones.



Reagents and Conditions: (i) $KN(SiMe_3)_2$, THF, -78 °C, then aldehyde, THF, HMPA; (ii) TBAF, THF; (iii) Re_2O_7, 2,6-lutidine, CH_2Cl_2; (iv) $Me_2C(OMe)_2$, Me_2CO, TsOH; (v) MsCl, CH_2Cl_2; (vi) TsOH, MeOH, H_2O; (vii) py, 100 °C

Scheme 1.31 Examples of some library products

One member of this library, lactone **1.215**, was used in the synthesis of trilobacin **1.26**. Thus, $LiAlH_4$ reduction, formation of the TMS ether of the primary hydroxyl group and protection of the secondary hydroxyl as the MOM ether, followed by desilylation gave the primary alcohol. Conversion to the corresponding Wittig salt **1.216** *via* the iodide, coupling with aldehyde **1.217**, and subsequent hydrogenation and deprotection afforded the natural product (Scheme 1.32).



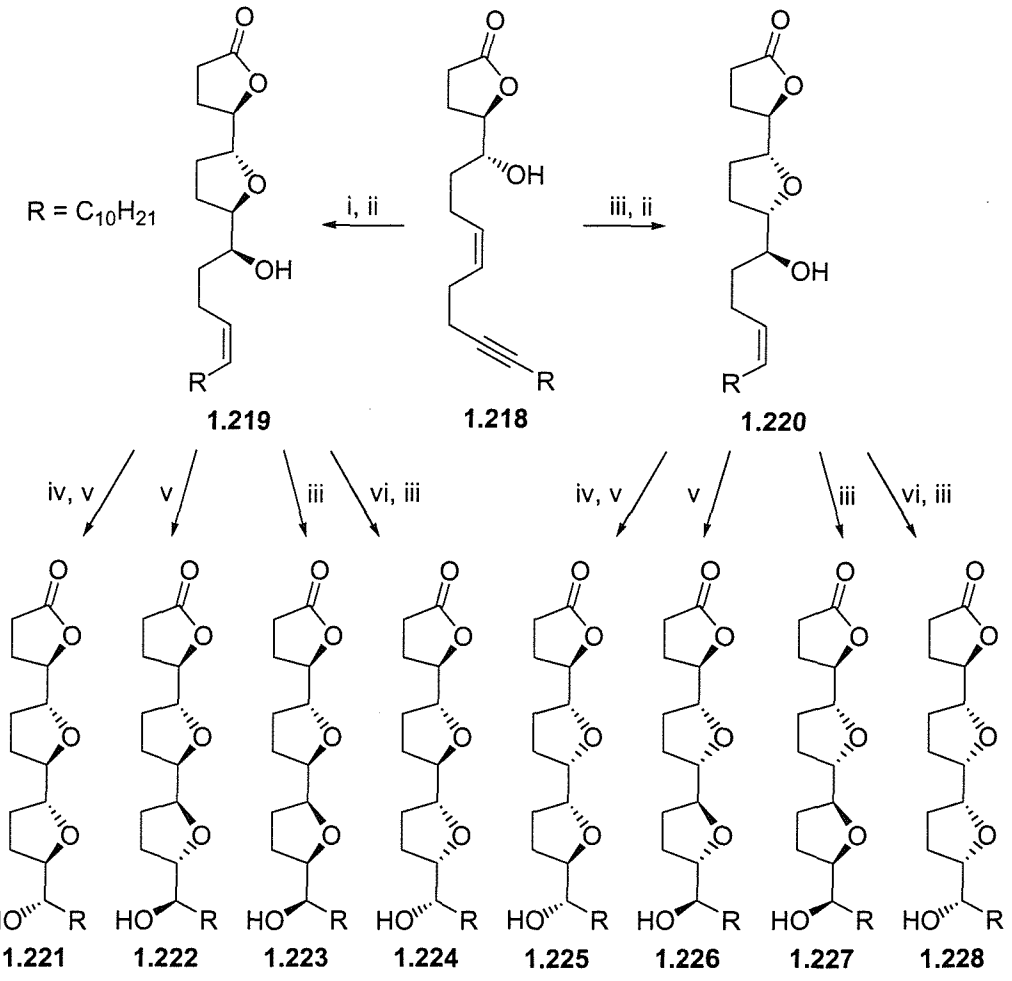
Reagents and Conditions: (i) $LiAlH_4$, Et_2O, THF, -78 °C; (ii) TMSCl, DIPEA, DMAP, CH_2Cl_2 then MOMCl; (iii) TBAF, THF; (iv) Ph_3P, I_2, imidazole, CH_2Cl_2; (v) Ph_3P, $NaHCO_3$, MeCN; (vi) *n*-BuLi, **1.217**, THF, 0 °C; (vii) $Rh(Ph_3P)_3Cl$, PhH, EtOH; (viii) AcCl, MeOH, Et_2O.

Scheme 1.32 Synthesis of trilobacin

An expanded library of sixty four *bis*-THF lactone building blocks was then constructed.[126] The approach was based on two complementary oxidative cyclisation procedures involving either Kennedy's rhenium cyclisation to give *trans*-THF products, or the use of $VO(acac)_2$ / TBHP to give *cis*-THF products.

A partial representation of this library (Scheme 1.33) originates from *cis*-alkene **1.218**, which itself was synthesised as for the conversion of ester **1.197** to lactone **1.198** (Scheme 1.29). Thus, **1.218** was one of four lactones resulting from four dienynes. Treatment of **1.218** with either Re_2O_7 or $VO(acac)_2$ gave *trans*- or *cis*-THF products **1.219** and **1.220** respectively. Lindlar reduction was followed by oxidative cyclisation by either strategy, or Mitsunobu inversion and then cyclisation affording eight *bis*-THF lactones **1.221-1.228** (Scheme 1.33). These lactones then underwent Mitsunobu inversion giving a total of sixteen products from **1.218**.

A modular synthesis of acetogenins asimicin and bullatacin was carried out, partly based on this approach.[127]



Reagents and Conditions: (i) Re_2O_7, 2,6-lutidine, CH_2Cl_2; (ii) $Pd/CaCO_3/Pb$, H_2, Et_3N, hexane; (iii) $VO(acac)_2$, *t*-BuOOH, CH_2Cl_2; (iv) (a) 4-nitrobenzoic acid, Ph_3P, DEAD, PhH; (b) $KOH_{(aq)}$, MeOH then 3N HCl; (c) TsOH, CH_2Cl_2; (v) Re_2O_7, H_5IO_6, CH_2Cl_2.

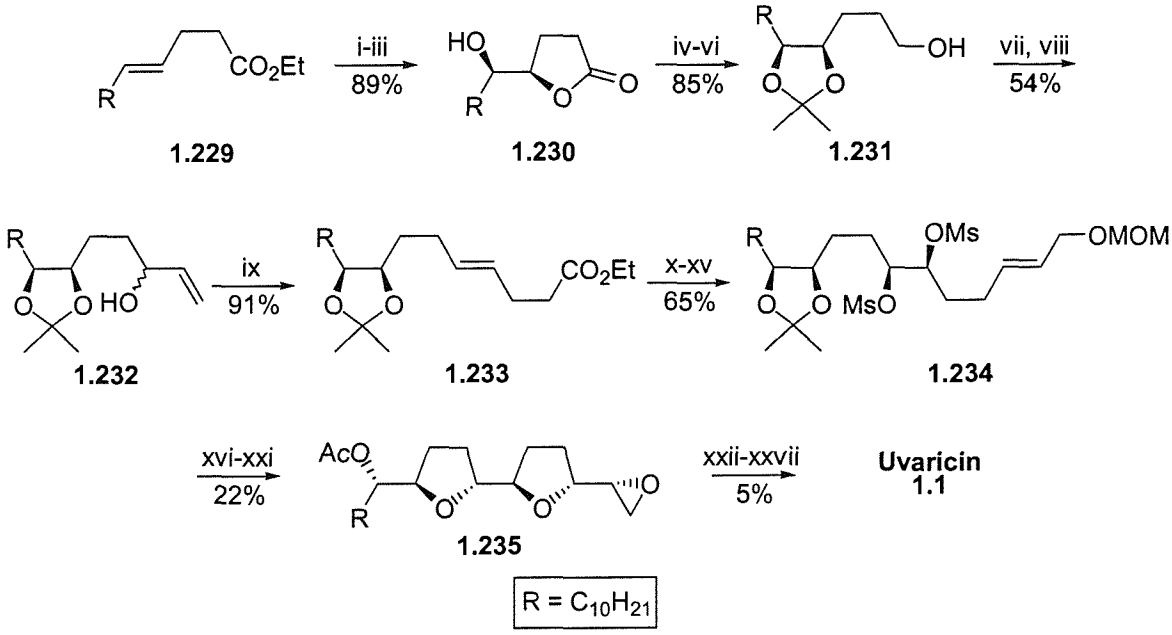
Scheme 1.33 Library synthesis using a combination of Re_2O_7 and $VO(acac)_2$ / *t*-BuOOH

1.5.7.3 Total Synthesis of Uvaricin 1.1

The total synthesis of uvaricin was achieved by Sinha and Keinan *via* an asymmetric dihydroxylation / Williamson annulation strategy.[128] Asymmetric dihydroxylation of alkene **1.229** gave *threo* hydroxy lactone **1.230**. Mitsunobu inversion of the alcohol followed by $LiAlH_4$ reduction of the benzyl ester and protection of the vicinal diol gave acetonide **1.231**. Oxidation by pyridimium chlorochromate and reaction of the resulting aldehyde with vinylmagnesium bromide afforded racemic alcohol **1.232**, which underwent Claisen-Johnson rearrangement to ester **1.233**.[129] This underwent DIBAL-H reduction, Horner-Emmons olefination with triethylphosphonoacetate, and DIBAL-H reduction of the ester.

Protection of the resulting allylic alcohol as the MOM ether, selective asymmetric dihydroxylation of the more electron rich, isolated alkene and mesylation afforded *bis*-mesylate **1.234**. Asymmetric epoxidation of the remaining double bond and treatment with toluenesulfonic acid resulted in diol deprotection and double cyclisation. Removal of the MOM ether using boron trifluoride etherate, processing of the resulting vicinal diol to the epoxide and protection of the remaining alcohol gave epoxide **1.235**.

This epoxide was opened using TMS-protected lithium acetylide, the product of which was desilylated affording the terminal alkyne. Palladium catalysed coupling with vinyl iodide **1.48**, hydrogenation, sulfide oxidation and thermal elimination afforded uvaricin **1.1** (Scheme 1.34). Squamotacin and trilobin, two other *bis*-THF acetogenins, were synthesised in a similar fashion.[130,131]

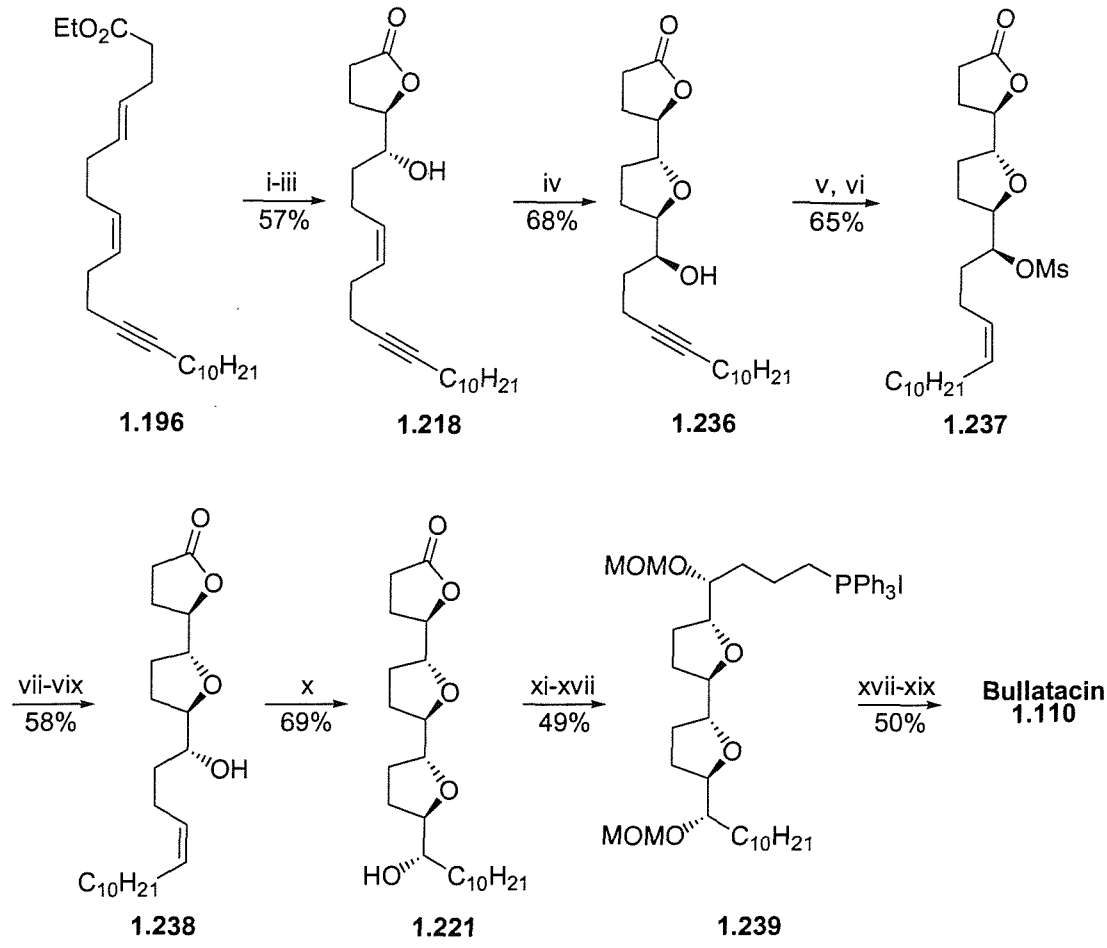


Reagents and Conditions: (i) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH, H_2O, 0 °C; (ii) KOH, H_2O, MeOH then 3N HCl; (iii) TsOH, CH_2Cl_2; (iv) 4-nitrobenzoic acid, Ph_3P, DEAD, PhH; (v) $LiAlH_4$, THF, Et_2O, 0 °C; (vi) Me_2CO, TsOH; (vii) PCC, CH_2Cl_2; (viii) Vinylmagnesium bromide, -30 °C; (ix) Triethyl orthoacetate, propionic acid, *p*-xylene; (x) DIBAL-H, THF, -78 °C; (xi) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, -78 °C; (xii) DIBAL-H, THF, -78 °C; (xiii) MOMCl, DIPEA, CH_2Cl_2; (xiv) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH, H_2O, 0 °C; (xv) MsCl, Et_3N, CH_2Cl_2, 0 °C; (xvi) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH, H_2O, 0 °C; (xvii) TsOH, MeOH; (xviii) $BF_3{\bullet}Et_2O$; (xix) TsCl, py, 0 °C; (xx) K_2CO_3, MeOH; (xxi) Ac_2O, py; (xxii) LiC≡CTMS, *n*-BuLi, THF, $BF_3{\bullet}Et_2O$; (xxiii) TBAF, THF; (xxiv) **1.48**, $Pd(Ph_3P)_4$, CuI, Et_3N; (xxv) $Rh(Ph_3P)_3Cl$, H_2, MeOH, PhH; (xxvi) *m*-CPBA, CH_2Cl_2; (xxvii) Δ, $PhCH_3$.

Scheme 1.34 Total synthesis of uvaricin

1.5.7.4 Total Synthesis of Asimicin and Bullatacin

Sinha and Keinan also carried out the total synthesis of acetogenins asimicin and bullatacin, using a combination of asymmetric epoxidation and the Kennedy cyclisation strategy.[132] The synthesis of bullatacin **1.110** is illustrated below (Scheme 1.35). Selective dihydroxylation of the *trans*-alkene of dienyne **1.196** gave hydroxy lactone **1.218**, which on treatment with pre-mixed Re_2O_7 and 2,6-lutidine cyclised to give THF lactone **1.236**. Lindlar reduction of the alkyne and mesylation afforded *cis*-alkene **1.237**. Displacement by cesium propionate followed by hydrolysis gave inverted alcohol **1.238**. A second Kennedy cyclisation, using the more reactive combination of Re_2O_7 and periodic acid, gave *bis*-THF lactone **1.221**. Protection of the hydroxyl groups as MOM ethers occurred during processing of the lactone moiety to phosphonium salt **1.239**, as described previously. Wittig reaction with aldehyde **1.227**, followed by reduction over Wilkinson's catalyst and final deprotection, afforded the natural product **1.110** in a total of nineteen steps from the dienyne.



Reagents and Conditions: (i) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH, H_2O, 0 °C; (ii) KOH, H_2O, MeOH then 3N HCl; (iii) TsOH, CH_2Cl_2; (iv) Re_2O_7, 2,6-lutidine, CH_2Cl_2; (v) 5% $Pd/CaCO_3/Pb$, H_2, Et_3N; (vi) MsCl, Et_3N, CH_2Cl_2, 0 °C; (vii) Cesium propionate, DMF, 100 °C; (viii) KOH, H_2O, MeOH then 3N HCl; (ix) TsOH, CH_2Cl_2; (x) Re_2O_7, H_5IO_6, CH_2Cl_2; (xi) $LiAlH_4$, Et_2O; (xii) TBSCl, DIPEA, DMAP, CH_2Cl_2; (xiii) MOMCl, DIPEA, 0 °C; (xiv) TBAF, THF; (xv) I_2, Ph_3P, imidazole, CH_2Cl_2; (xvi) Ph_3P, $NaHCO_3$, MeCN, 40 °C; (xvii) *n*-BuLi, THF, 0 °C, **1.217**; (xviii) $Rh(Ph_3P)_3Cl$, H_2, MeOH, PhH; (xix) AcCl, MeOH, CH_2Cl_2.

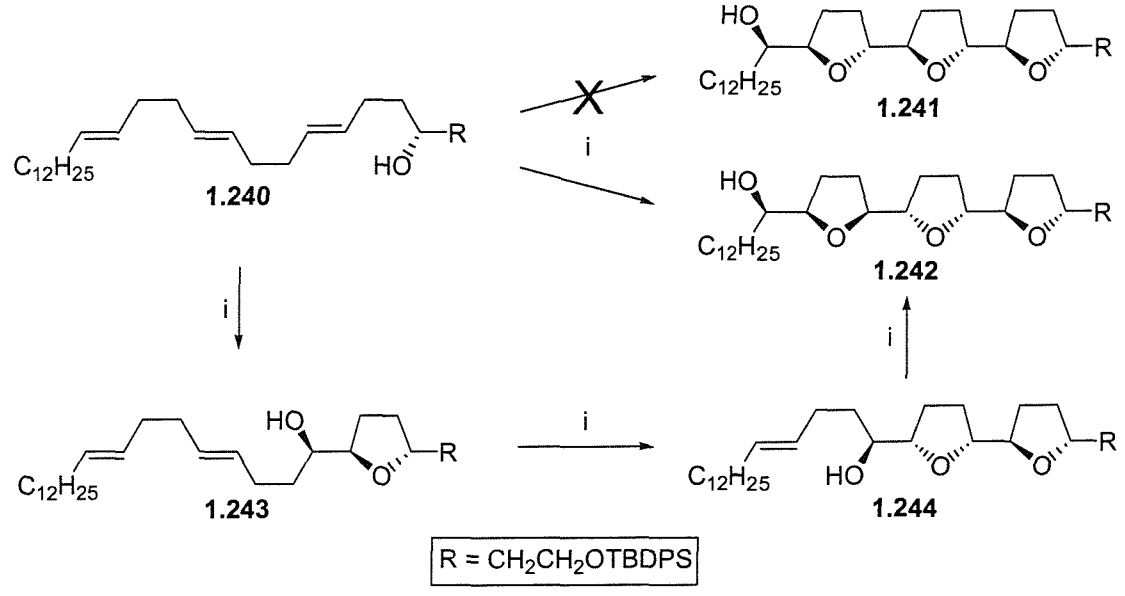
Scheme 1.35 Total synthesis of bullatacin

1.5.7.5 Rules of Stereoselectivity in the Rhenium (VII) Oxide Tandem Oxidative Polycyclisation Reaction

Kennedy's work on the monocyclisation reaction with simple *bis*-homoallylic alcohols suggested that the stereochemical outcome of the reaction resulted consistently in the formation of *trans*-THF products. This general rule was confirmed by the work of McDonald, and by Sinha and Keinan's library and natural product syntheses. More recently however, Sinha and Keinan carried out a triple oxidative cyclisation using trifluoroacetyl

perrhenate which gave a product with stereochemistry which was inconsistent with these findings.[133] It was expected that the reaction of triene **1.240** with trifluoroacetyl perrhenate would give all-*trans* product **1.241**, however the product obtained was *cis-cis-trans* **1.242** (Scheme 1.36).

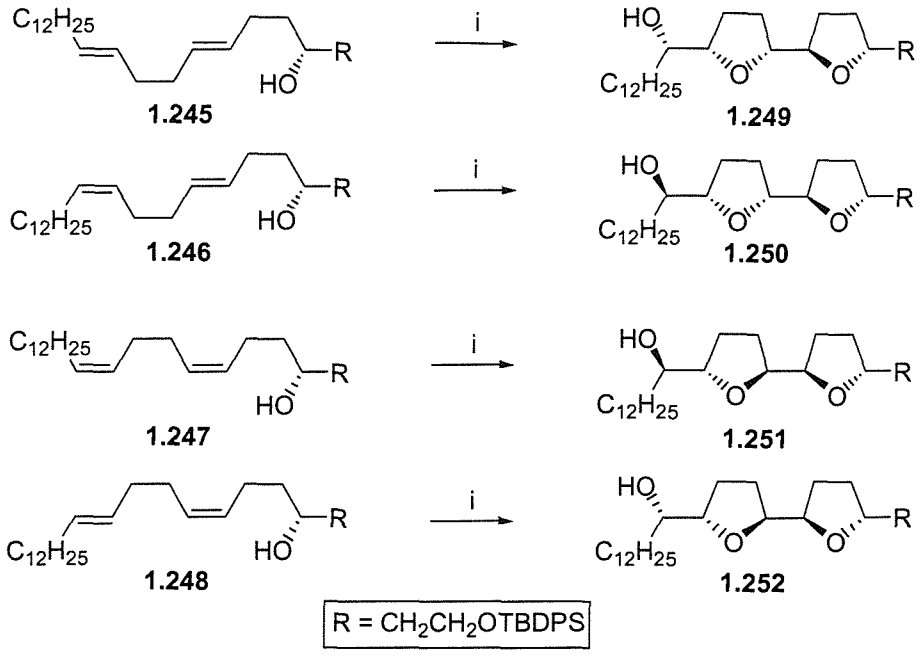
The relative and absolute stereochemistry of the triple cyclisation product was determined by conducting the reaction in a stepwise manner. Thus, the triene starting material underwent single cyclisation to **1.243**, which on treatment with further reagents was converted *via* **1.244** to the *cis-cis-trans* product. The structure of intermediates and final product was confirmed by a combination of Mosher's ester and long-range and through-space nuclear magnetic resonance studies. Preparation of **1.241** and **1.242** by independent asymmetric synthesis provided absolute confirmation of the *tris*-THF stereochemistry.[134]



Reagents and Conditions: (i) $CF_3CO_2ReO_3$, TFAA, CH_2Cl_2.

Scheme 1.36 Unexpected stereochemical outcome of the triple cyclisation

It was concluded from this study that the relative configuration of the THF ring formed during the cyclisation reaction is strongly dependent upon the configuration of the vicinal oxygen functions formed in the previous cyclisation, which itself arises from the double bond geometry of the polyene substrate. Four dienol substrates **1.245** – **1.248** were then prepared and treated with trifluoroacetyl perrhenate (Scheme 1.37).



Reagents and Conditions: (i) $CF_3CO_2ReO_3$, TFAA, CH_2Cl_2.

Scheme 1.37 Cyclisation of four dienols

On the basis of these and previous results, the following rules were proposed for a single step polycyclisation of polydisubstituted alkenols:

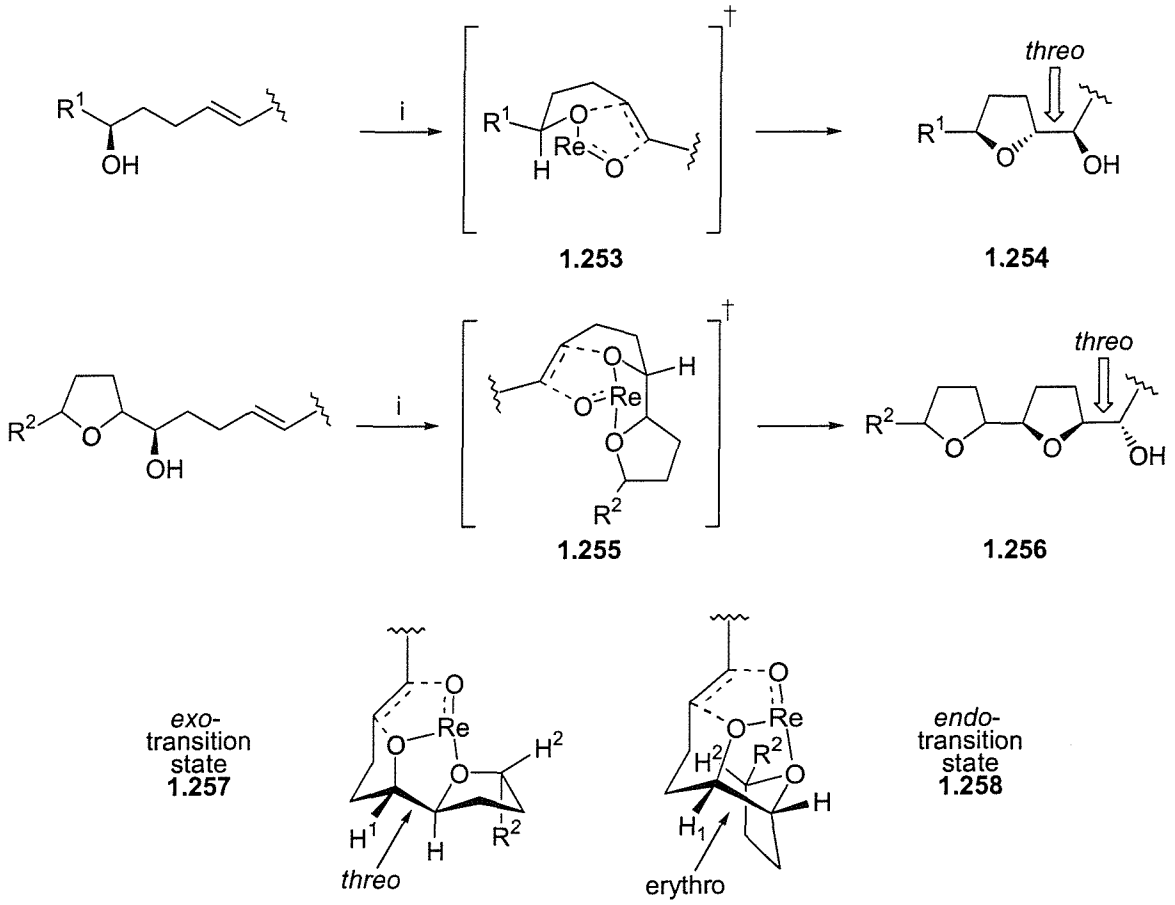
1. With a simple *bis*-homoallylic alcohol (where the hydroxyl group is the only strong coordination site for rhenium), the first THF ring is always produced with *trans*-configuration.
2. If the two vicinal oxygen functions formed in the first cyclisation have a *threo* relationship, the next cyclisation will produce a *cis*-THF ring.
3. If the two vicinal oxygen functions formed in the first cyclisation have an ery*thro* relationship, the next cyclisation will produce a *trans*-THF ring.

These rules reflect the marked change in the stereochemical course of the oxidative cyclisation from one substrate to the next. This might be explained by the ability of the newly formed THF ring to chelate the rhenium atom during the course of subsequent reactions. A transition state model was proposed to explain the experimental observations.

In the first cyclisation, the non-coordinating alkyl group will have a high preference to adopt a less sterically demanding *pseudo*-equatorial position in the proposed [3+2] transition state

1.253, resulting in a *trans*-THF. In cases where the R group possesses a potential coordination site for rhenium, the substrate may become a bidentate ligand. In this case, the preference for the coordinating group would be to adopt an energetically favoured pseudoaxial position **1.255**, resulting in the formation of a *cis*-THF product.

The coordinating ability of this bidentate ligand would depend on the relative configuration of the two oxygen functions. With a *threo* relationship the reaction can be seen to proceed *via* a favoured *exo*-type transition state **1.257**, but with an *erythro* relationship a disfavoured *endo*-type transition state **1.258** would be required. In this case, the non-chelated intermediate **1.253** would become more favourable (Sceme 1.38).



Reagents and Conditions: (i) $CF_3CO_2ReO_3$, TFAA, CH_2Cl_2.

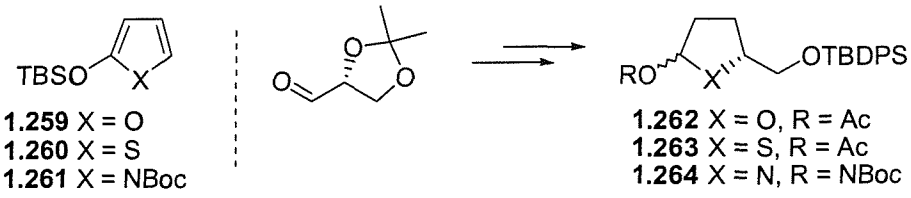
Scheme 1.38 Rhenium cyclisation transition states proposed by Sinha and Keinan

Later studies carried out by Morimoto and Iwai, using tertiary alcohols and trisubstituted double bonds, were in agreement with these basic rules.[135] Sinha and Keinan used their

rules to correctly predict the starting materials required to synthesise adjacent *tris*-THF acetogenins.[136]

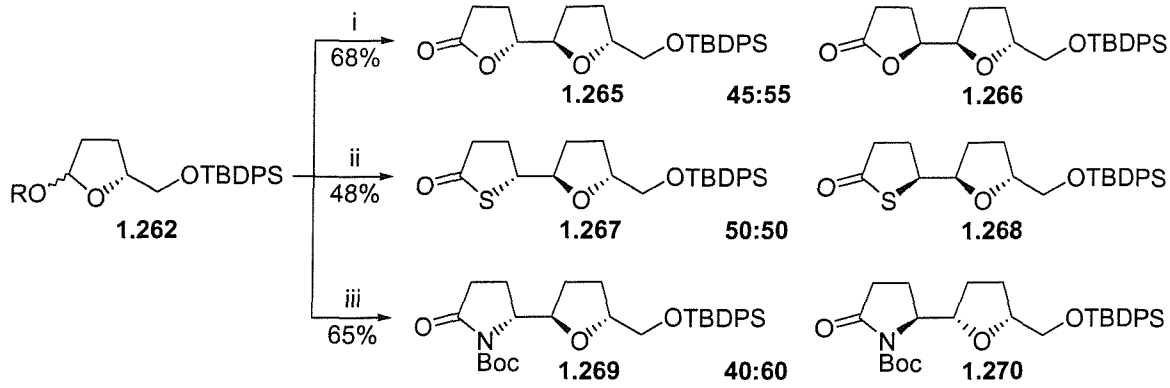
1.5.8 Giovanni Casiraghi and Franca Zanardi

Casiraghi and Zanardi carried out the synthesis of a series of oligo-THF fragments and their heteroatom analogues using a modular strategy.[137,138] This approach involved the stepwise addition of heterocycle units using silyloxy diene methodology.[139-144] The three building blocks on which this approach is based are the nucleophilic (acceptor) silyloxy dienes 2-(*tert*-butyldimethylsiloxy)furan (TBSOF) **1.259**, 2-(*tert*-butyldimethylsiloxy)thiophene (TBSOT) **1.260** and *N*-(*tert*-butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)pyrrole (TBSOP) **1.261**. The combinatorial coupling of these reagents with three electrophilic (donor) units **1.262-1.264** by sequential vinylogous couplings gave the project useful diversity (Scheme 1.39).[145]



Scheme 1.39 Casiraghi's acceptor and donor units

These units were used to construct dinuclear molecules using a method based on Lewis acid mediated Mukaiyama aldolisation.[146] For example the addition of **1.259** to **1.262** in the presence of TBSOTf followed by hydrogenation of the unsaturated lactone intermediate gave a separable 45:55 mixture of **1.265** and **1.266** in total yield of 68% over two steps. Using the three donors and three acceptors, eighteen dinuclear products were synthesised. The products of the reaction of donor **1.262** with the three silyloxy dienes are shown (Scheme 1.40).



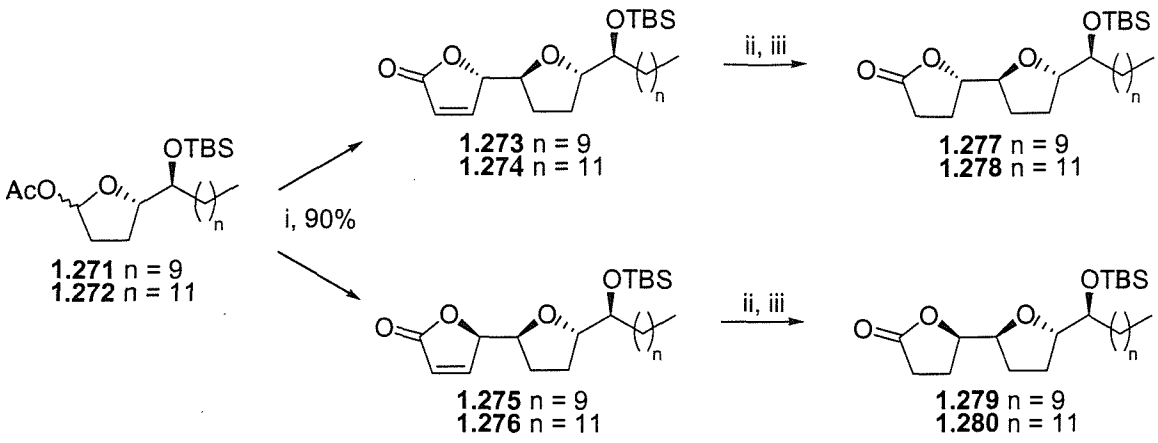
Reagents and Conditions: (i) **1.259**, TBSOTf, then hydrogenation; (ii) **1.260**, TBSOTf, then hydrogenation; (iii) **1.261**, TBSOTf, then hydrogenation.

Scheme 1.40 Products from the reaction between the oxygen donor and three acceptors

Reduction of the lactone products to the corresponding lactol and activation by conversion to the acetate or methoxy derivative provided substrates for the addition of a third heterocyclic unit. This therefore is a divergent strategy which would allow the rapid synthesis of libraries of oligo-THF moieties. Although the reaction gives product ratios in the region of 1:1, therefore requiring chromatography to separate diastereoisomers, it might be argued that this is a benefit in terms of the creation of molecular diversity.

1.5.9 Bruno Figadere *et al.*

Figadere *et al.* carried out the synthesis of chiral THF lactones with a single, long alkyl chain.[147] These corresponded to the central THF and sidechain parts of natural acetogenins. The approach involved the C-glycosylation of anomeric acetoxytetrahydrofurans with 2-(trimethylsilyloxy)furan, a direct analogy with the work of Casiraghi and Zanardi. Initially, L-glutamic acid was converted in seven steps to anomeric acetates **1.271** and **1.272**. Reaction of these acetates with 2-(trimethylsilyloxy)furan in the presence of catalytic trityl perchlorate gave, in both cases, a mixture of two products **1.273**:**1.275** and **1.274**:**1.276** in ratios of 2:3 (Scheme 1.41). Hydrogenation of the unsaturated products gave the THF lactone fragments **1.277-1.280**.

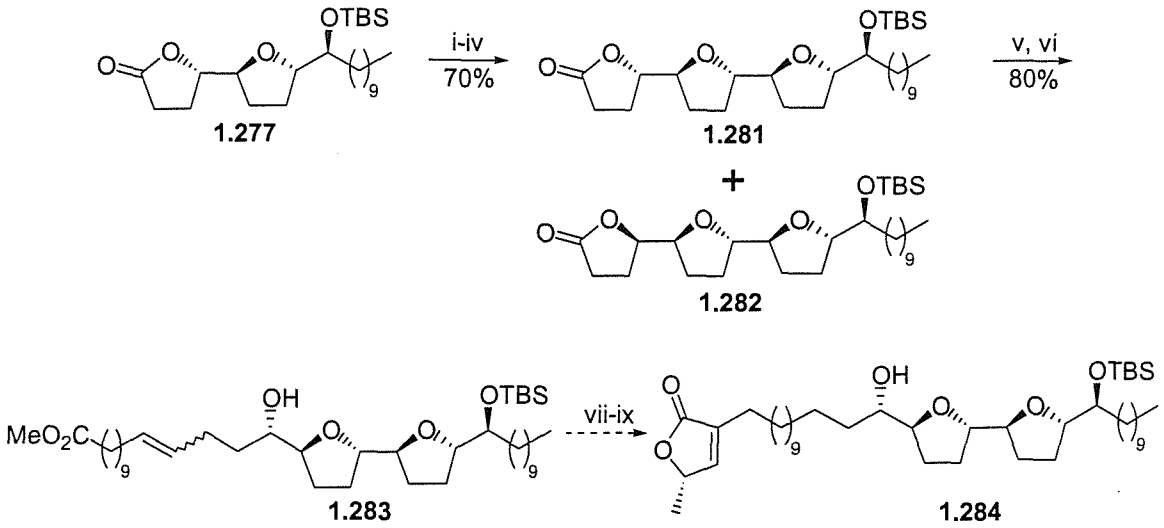


Reagents and Conditions: (i) 2-(trimethylsilyloxy)furan, $TrClO_4$, Et_2O, 0 °C; (ii) Pd/C, H_2, PhH; (iii) TBAF, THF.

Scheme 1.41 Figadere's synthesis of THF-lactone fragments

Figadere then demonstrated the stepwise nature of this approach, targeting intermediates in the synthesis of the acetogenin analogue (-)-desoxyasimicin.[148] Reduction of lactone **1.277**, activation of the resulting lactol as the acetate and treatment with 2-(trimethylsilyloxy)furan and catalytic trityl perchlorate, followed by reduction of the products gave separable *threo-trans-* and *erythro-trans-* lactones **1.281** and **1.282** in 70% yield over four steps and in a ratio of 2:3. This ratio was consistent with that obtained for the first glycosylation reaction (Scheme 1.42).

Reduction of **1.281** to the corresponding lactol followed by Wittig homologation gave alkene **1.283**. This was an intermediate which could be converted to (-)-desoxyasimicin **1.284** using methodology employed by Figadere in the synthesis of more simple non- or *mono*-THF acetogenins.[149] This protocol involved the treatment of ester **1.283** with lithium di*iso*propylamide followed by phenylselenium chloride. A second alkylation with (*S*)-proplylene oxide resulted in lactonisation, and treatment with hydrogen peroxide and acetic acid resulted in oxidation of selenium and *in-situ* elimination, forming the desired butenolide.



Reagents and Conditions: (i) DIBAL-H; (ii) Ac_2O, Et_3N; (iii) 2-(trimethylsilyloxy)furan, $TrClO_4$, Et_2O, 0 °C; (iv) Pd/C, H_2, PhH; (v) DIBAL-H; (vi) $Ph_3P{=}CH(CH_2)_9CO_2Me$; (vii) LDA then PhSeCl, THF, -78 °C; (viii) LDA then (*S*)-propylene oxide, THF, -78 °C; (ix) H_2O_2, AcOH.

Scheme 1.42 En-route to the total synthesis of (-)-desoxyasimicin

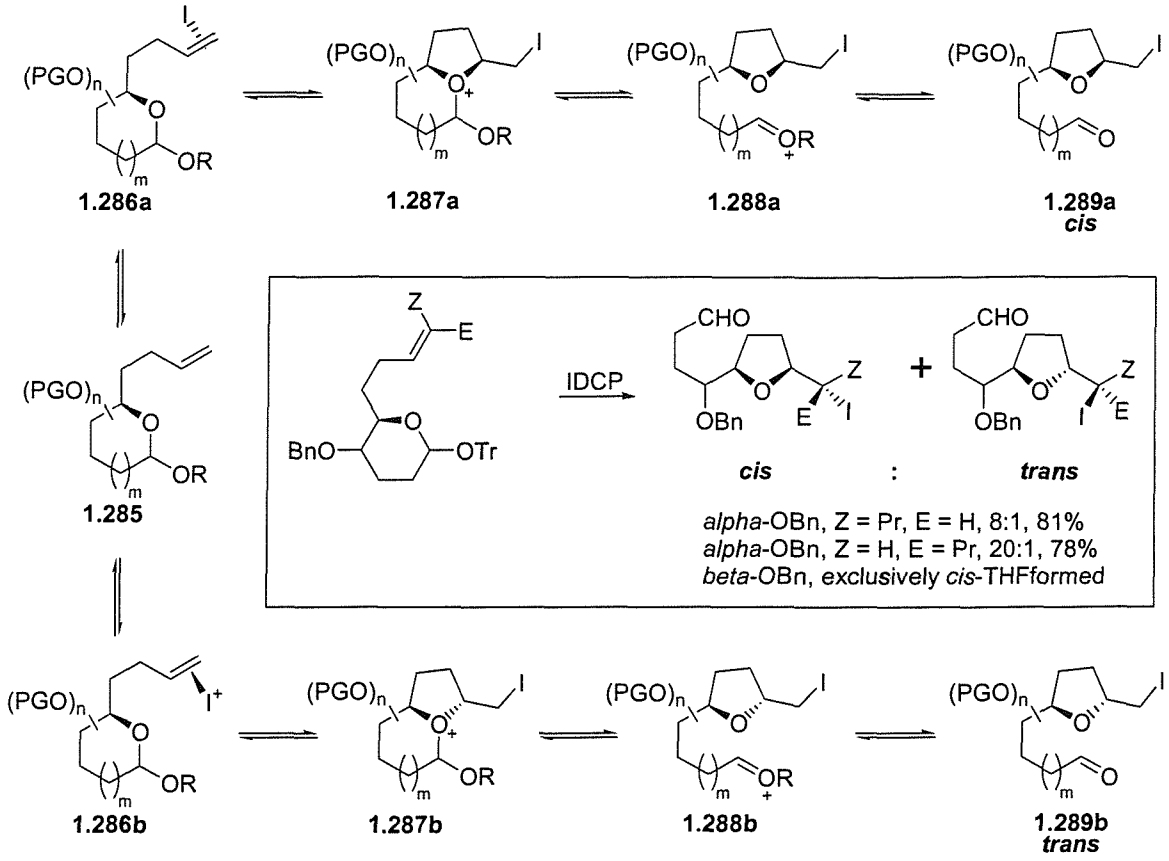
This approach is obviously suited to the construction of a number of acetogenin analogues by the use of starting materials of different alkyl chain length, and by the use of all product combinations of the glycosidation reactions. As for Casiraghi's work, the scope exists for the use of other heterocyclic building blocks.

1.5.10 David R. Mootoo *et al.*

1.5.10.1 A Monosaccharide-Based Approach to *cis*-2,5-Disubstituted THF's

Mootoo *et al.* described the halonium ion mediated transformation of monosaccharide alkenes **1.285** into tetrahydrofurans. The reaction is thought to proceed *via* the initial formation of an onium ion or charge transfer complex **1.286**, then to bicyclic THF-oxonium intermediate **1.287**, fragmentation of which leads to oxonium species **1.288**. On hydrolysis this gives THF aldehyde **1.289** (Scheme 1.43). The reaction is generally conducted in solution in wet dichloromethane with iodonium dicollidine perchlorate (IDCP) as the promoter. The bicyclic nature of the intermediate THF oxonium ion should lead to the transfer of chirality from the monosaccharide template to the newly formed THF ring.[150-154] As the synthetic modification of saccharides is a well studied area, Mootoo investigated

structural features within the saccharide which would lead with high stereoselectivity to 2,5-disubstituted THF's.[155]

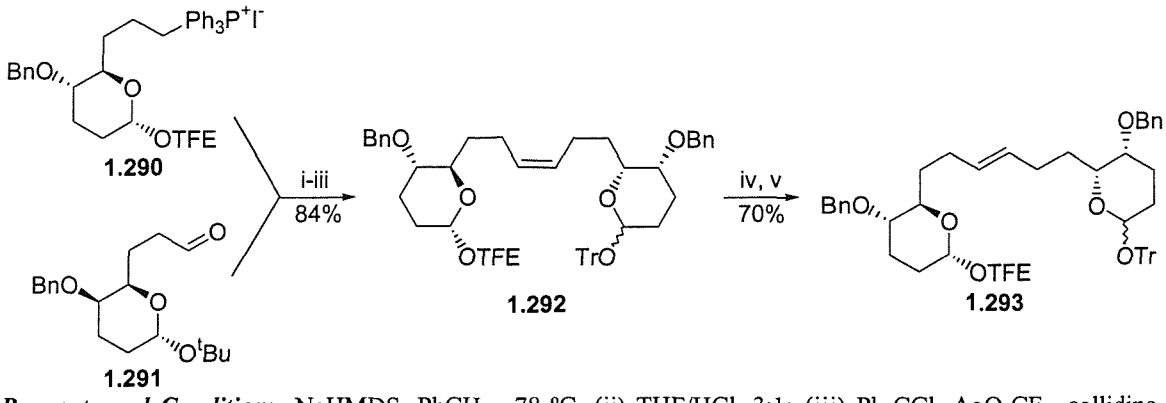


Scheme 1.43 Mechanism of haloetherification and examples of trityl glycoside selectivity

Initial studies involved 1:1 mixtures of α:β anomers of aglycones of similar size and different electronegativity, with a terminal alkene. When R = ethyl, the *cis*:*trans* ratio was 3:2. On changing from ethyl to trifluoroethyl this ratio remained unchanged, however reactivity decreased dramatically. More encouraging results were obtained by increasing the steric bulk of the aglycone. The tertiary butyl analogue gave a ratio of 3.5:1, and the trityl variant gave exclusively the *cis*-THF product in 81% yield.

The trityl glycosides of *cis*- and *trans*- alkenes were then investigated. It was found that *Z*-alkenes were inherently less *cis*-selective than the corresponding *E*-isomers in the case of the α -benzylate anomer. The β-benzylate anomer gave exclusively *cis*-THF products from both alkene geometries. (Scheme 1.43, inset).

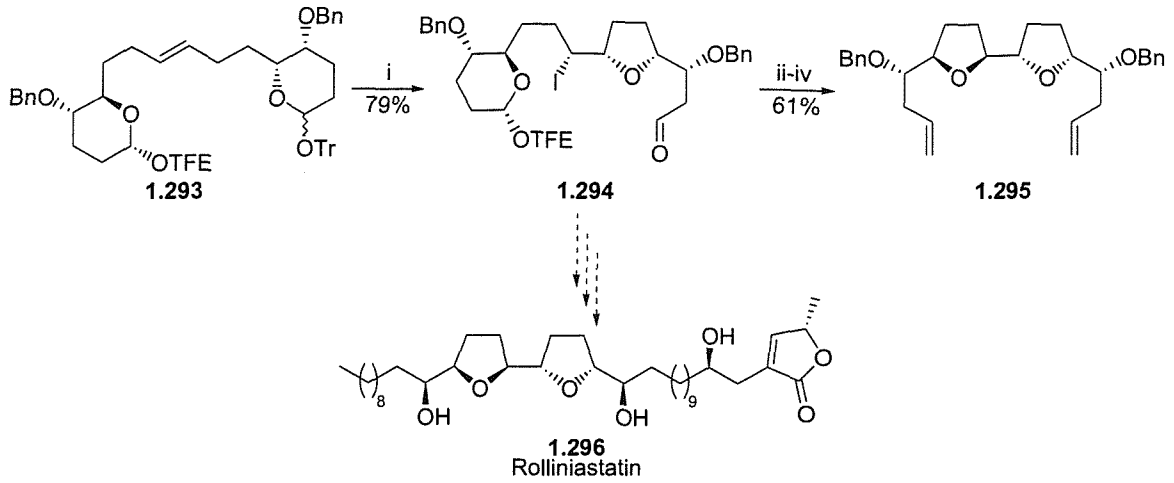
Mootoo next carried out the synthesis of the *bis*-THF core of acetogenin rolliniastatin **1.296**.[156,157] This approach was based on the *bis*-pyranoside-*E*-alkene **1.293** which was prepared by the Wittig coupling of two monosaccharide components **1.290** and **1.291**, followed by aglycone exchange and alkene isomerisation.[158] One monosaccharide had an activating, *cis*-directing trityl aglycone, the other a deactivating trifluoroethyl aglycone (Scheme 1.44).



Reagents and Conditions: NaHMDS, $PhCH_3$, -78 °C; (ii) THF/HCl, 3:1; (iii) Ph_3CCl, AgO_2CF_3, collidine, CH_2Cl_2; (iv) *m*-CPBA, CH_2Cl_2, phosphate buffer; (v) Ph_2PLi then MeI.

Scheme 1.44 Synthesis of the *bis*-pyranoside required for the rolliniastatin THF core

The conversion of this substrate to the required *bis*-THF fragment began with the haloetherification of the activated, stereodetermining pyranoside, affording halo-THF-trifluoroethyl pyranoside **1.294**. Wittig extension of the aldehyde and hydrolytic removal of the trifluoroethyl group gave a six-membered lactol. A second Wittig reaction formed the terminal alkene, and the resulting γ-hydroxy iodide underwent in-situ cyclisation affording *bis*-THF **1.295**. The use of two different Wittig partners would allow the installation of the sidechains of natural products such as rolliniastatin **1.296** (Scheme 1.45).

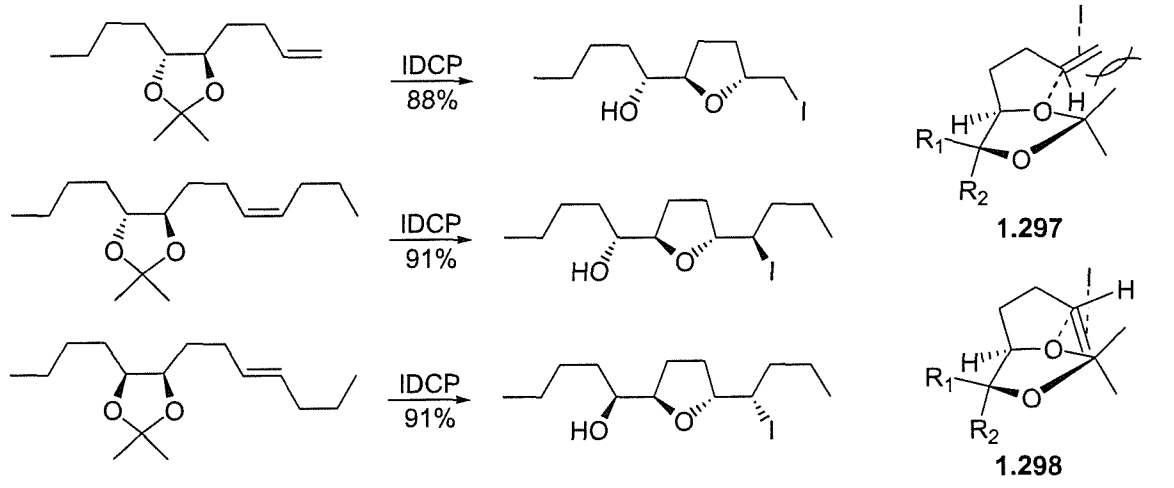


Reagents and Conditions: (i) IDCP, CH_2Cl_2, H_2O; (ii) $Ph_3P{=}CH_2$, THF; (iii) $BF_3{\bullet}Et_2O$, THF, H_2O; (iv) $Ph_3P{=}CH_2$, THF.

Scheme 1.45 Synthesis of the *bis*-THF core of rolliniastatin

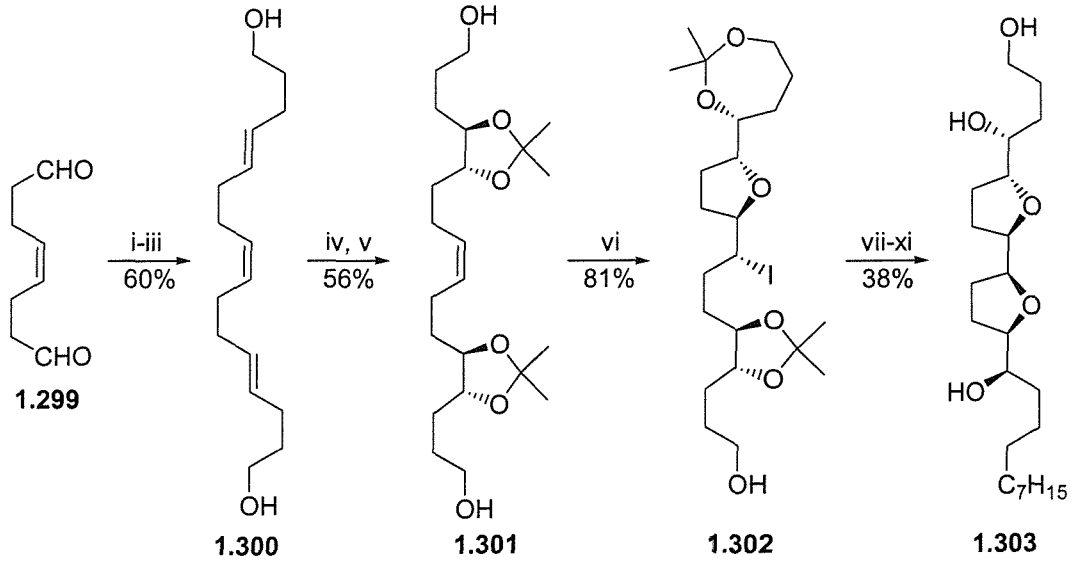
1.5.10.2 Acetal Templates for the Synthesis of *trans*-2,5-Disubstituted THF's

As a complement to their work with pyranoside alkenes, Mootoo *et al.* carried out the halocyclisation of 5,6-*O*-isopropylidene alkenes, resulting in the exclusive formation of *trans*-2,5-disubstituted THF's.[159] The high selectivity appears to be consistent with the formation of a THF-oxonium ion intermediate which, to form the *cis*-THF product, would have to adopt a geometry **1.297** in which high steric strain would be experienced between the acetonide methyl group and the aliphatic chain. Transition state **1.298** leads to the *trans*-fused product, and is sterically much more favourable (Scheme 1.46).



Scheme 1.46 Halocyclisation of 5,6-*O*-isopropylidene alkenes

Mootoo then used this reaction as the key step in a formal synthesis of trilobacin. Dialdehyde **1.299** was converted in three steps to *bis*-alcohol **1.300**. Asymmetric dihydroxylation of the *trans*-alkenes and acetal formation gave *bis*-acetonide **1.301** which underwent one-pot haloetherification and formation of a seven-membered acetal **1.302**. Oxidation of the primary alcohol and Wittig extension followed by acetal hydrolysis, base-mediated cyclisation and hydrogenation afforded triol **1.303**, a known intermediate in the synthesis of trilobacin (Scheme 1.47). This reaction sequence therefore represented a formal synthesis.



Reagents and Conditions: (i) Vinylmagnesuim bromide, THF; (ii) $CH_3C(OEt)_3$, $CH_3CH_2CO_2H$, 140 °C; (iii) DIBAL-H, CH_2Cl_2, -78 °C; (iv) AD-mix-β; (v) $Me_2C(OMe)_2$, CSA, DMF; (vi) IDCP, CH_2Cl_2, H_2O; (vii) Swern; (viii) $Ph_3P{=}CHC_6H_{13}$, THF; (ix) HCl, H_2SO_4; (x) py, 100 °C; (xi) Pd/C, H_2, EtOAc.

Scheme 1.47 Formal synthesis of trilobacin

This approach was also used by Mootoo in the synthesis of non-adjacent *bis*-THF acetogenins,[160] and as precursors to other oligo-THF compounds.[161,162]

1.6 Conclusions

The biological activities exhibited by the *Annonaceous* acetogenins have resulted in extensive synthetic study directed toward the tetrahydrofuran core domains, and toward total synthesis of the natural products and their analogues.

These approaches have utilised combinations of Sharpless asymmetric epoxidation and dihydroxylation with epoxide opening cascades, Williamson etherification annulations and Kennedy's cyclisation of hydroxy alkenes. The iterative annulation of pre-formed heterocyclic units, and haloetherification using monosaccharide templates has also been studied.

Although these approaches are varied and often complimentary, apart from Kennedy's cyclisation very little attention has been shown in the literature to the direct synthesis of the tetrahydrofuran domains of *bis*-THF acetogenins which rely on the oxidation of polyenes by transition metal oxo species.

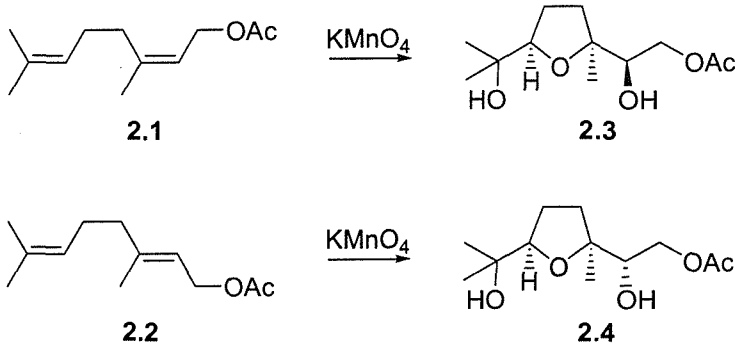
Chapter 2

Oxidative Cyclisation of 1,5-Dienes and *bis*-Homoallylic Alcohols by Transition Metal Oxidants

The following chapter will briefly summarise the synthesis of 2,5-disubstituted tetrahydrofurans from 1,5-dienes and *bis*-homoallylic alcohols *via* oxidative cyclisation using transition metal based oxidants. Brief mention was given in the previous chapter to the use of trifluoroacetyl perrhenate and vanadium (V) species by Sinha *et al.*

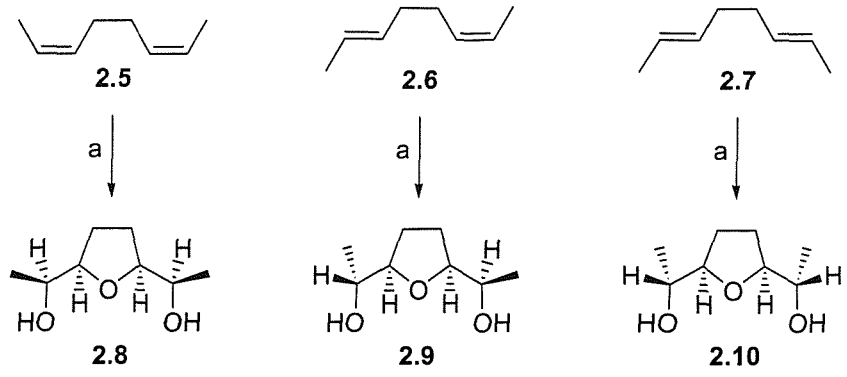
2.1 Permanganate Promoted Oxidative Cyclisation of 1,5-Dienes

The oxidative cyclisation of 1,5-dienes to tetrahydrofurans by potassium permanganate in slightly basic solution was first reported in 1965.[163] The tetrahydrofuran products of this oxidation were found to be exclusively *cis*-2,5-disubstituted. The oxidation of neryl acetate **2.1** and geranyl acetate **2.2** gave *cis*-2,5-*bis*-(hydroxymethyl)tetrahydrofurans (THF diols) **2.3** and **2.4** respectively (Scheme 2.1).



Scheme 2.1 Oxidative cyclisation of neryl and geranyl acetates by $KMnO_4$

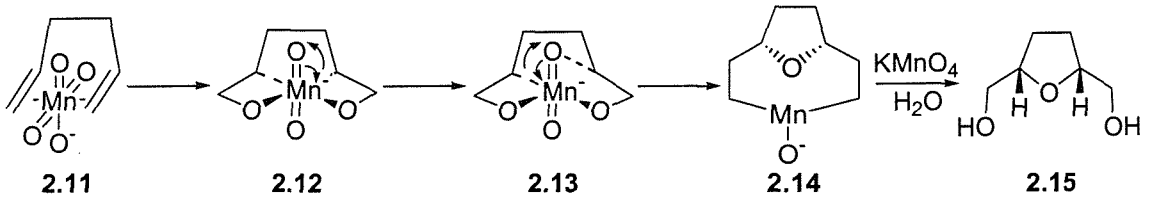
This work was re-examined fourteen years later by the groups of Baldwin and Walba, who recognised the synthetic utility of a reaction which introduces four new chiral centres stereoselectively in a single step. Walba investigated the stereochemical course of the reaction by carrying out the oxidation of isomeric dienes **2.5-2.7**, concluding that the stereochemistry of the hydroxymethyl groups in the predominant *cis*-THF products **2.8-2.10** are determined by the alkene geometry (Scheme 2.2).[164] Analysis by gas chromatography indicated the presence of the *trans*-THF products in approximately 3% abundance.



Reagents and Conditions: (i) $KMnO_4$, H_2O/Me_2CO, pH = 7.5, CO_2 ebulliation.

Scheme 2.2 Stereochemical investigation by Walba

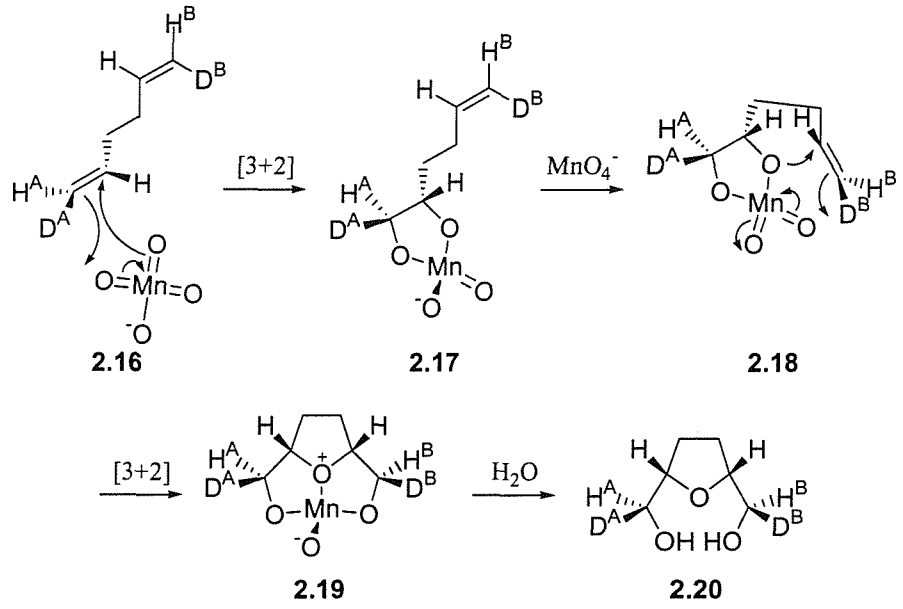
The mechanism suggested by Walba was based on earlier proposals from Sharpless concerning the oxidation of alkenes by transition metal oxo species.[165] The initial formation of a *bis*-π-complex **2.11** between the diene and permanganate ion is followed by two [2+2] cycloadditions (either concerted or stepwise) giving octahedral manganese (VII) intermediate **2.12**. Alkyl migration with retention followed by reductive elimination affords diester **2.14**, which is oxidised and hydrolysed affording *cis*-THF diol **2.15** (Scheme 2.3).



Scheme 2.3 Mechanism Proposed by Walba

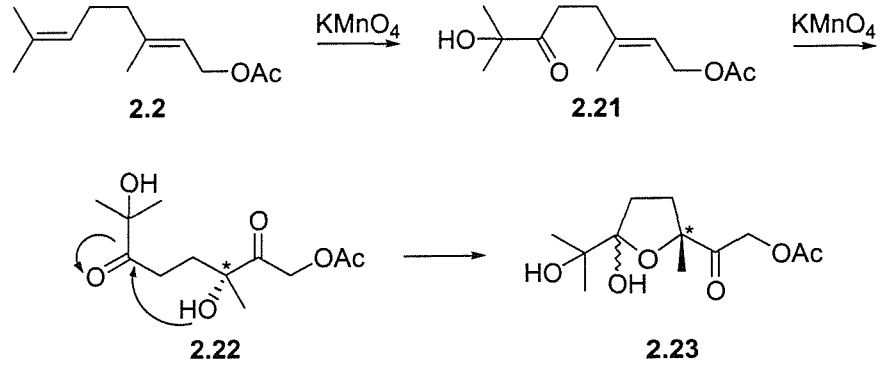
Baldwin's investigation involved the oxidative cyclisation of deuterated dienes of known geometry.[166] The mechanism which he proposed began with the [3+2] cycloaddition of permanganate to the first double bond, forming cyclic Mn^V ester **2.17**. This species is unreactive towards other double bonds,[167] and undergoes rapid oxidation by permanganate to Mn^{VI} ester **2.18**. This reactive intermediate undergoes a stereospecific intramolecular [3+2] cycloaddition to the second double bond, forming Mn^{IV} species **2.19**. Subsequent hydrolysis affords THF diol **2.20** with complete stereospecificity (Scheme 2.4). The mechanism is supported by evidence for the formation of cyclic Mn^V esters in reactions of isolated olefins with permanganate species.[168]

Studies by Wolfe *et al.* using ^{18}O labelled water showed incorporation into the THF diol, suggesting the involvement of five-coordinate manganese during the course of the reaction.[169]



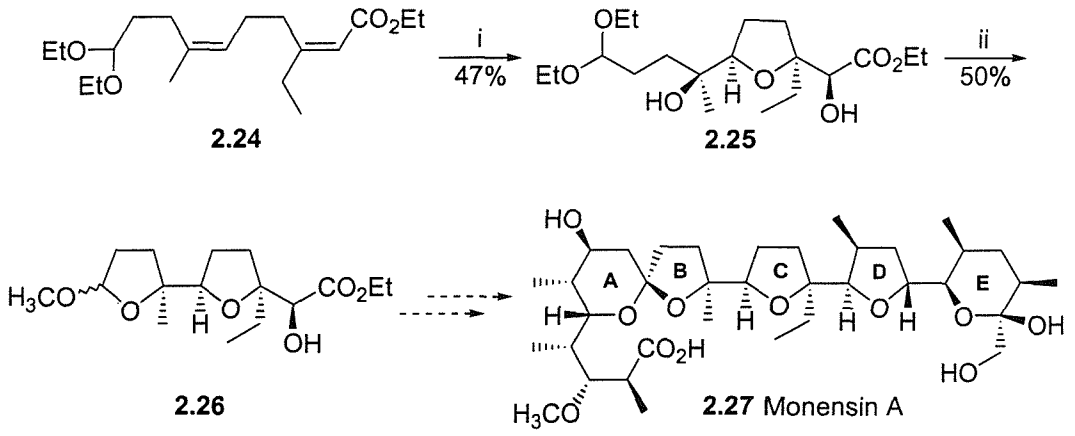
Scheme 2.4 Mechanism proposed by Baldwin

The yields observed for such reactions are often low, the reason for this being the formation of a number of side products which result from hydrolysis of intermediates such as Mn^V ester **2.17** prior to the second [3+2] cycloaddition. In the case of geranyl acetate **2.2** this results in the formation of α-hydroxy ketone **2.21**, which has been isolated from the reaction mixture. Oxidation of the remaining alkene forms a second hydroxyketone **2.22**, which undergoes cyclisation to lactol **2.23** (Scheme 2.5). Independent synthesis of **2.21** and exposure to the reaction conditions indeed afforded lactol **2.23**.[170] Buffering of the solution at pH 6.24 was found to give an optimum yield of desired THF-diol product of 59%.



Scheme 2.5 By-products from the oxidative cyclisation

Walba used the oxidative cyclisation to carry out the stereoselective (but racemic) synthesis of the B / C ring fragment of the monocarboxylic acid ionophore monensin **2.27**. This was achieved by the oxidation of diene **2.24** followed by treatment with trimethyl orthoformate and acid affording bicyclic **2.26** (Scheme 2.6).

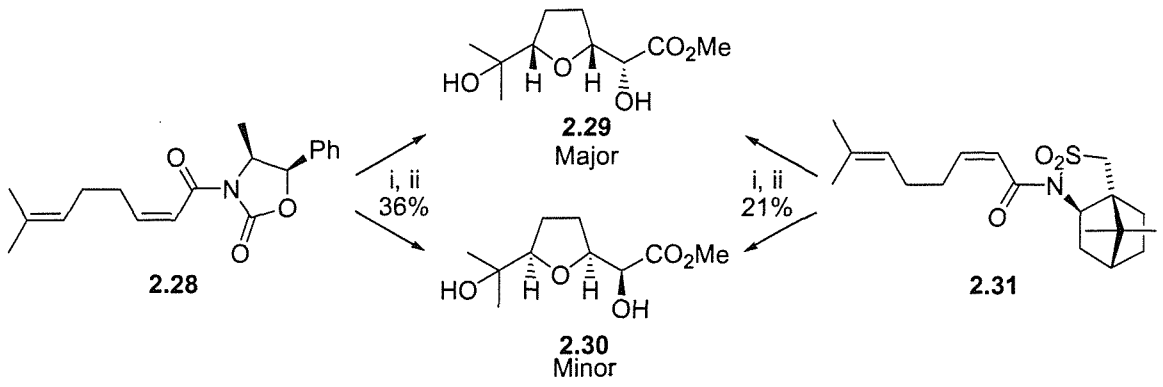


Reagents and Conditions: (i) $KMnO_4$, H_2O/Me_2CO, pH = 7.5, CO_2 ebulliation, -30 °C; (ii) $CH_3(OMe)_3$, TsOH, PhH.

Scheme 2.6

Walba then investigated the use of chiral auxiliaries to give regio- and facial selectivity to the oxidative cyclisation.[171] Alkenes which are conjugated to a carbonyl group are known to be more reactive to permanganate than isolated double bonds, and therefore the ideal method of attachment of a 1,5-diene to a chiral auxiliary was through an amide linkage. The use of Evan's oxazolidinone,[73,172-185] and Oppolzer's camphorsultam in asymmetric synthesis are well documented,[186-193] and Walba chose these for his diene oxidations.

The oxazolidinone gave selectivity of only 3:1 in the oxidative cyclisation of **2.28**, favouring major THF-diol **2.29** after transesterification. This resulted from initial addition of permanganate to the least hindered *Re*-face of the conjugated double bond, in which the carbonyl groups lie *anti* to each other. The relatively low selectivity was consistent with observations that Lewis acid chelation is required to obtain optimal results.[194] This problem was overcome by the use of the camphorsultam. Oxidation of dienoate **2.31** gave selectivity in excess of 9:1 in favour of **2.29** after transesterification (Scheme 2.7). Kocienski also used the camphorsultam for the oxidation of a 1,5-diene to provide a THF fragment in his elegant synthesis of the polyether anitibiotic salinomycin.[195]



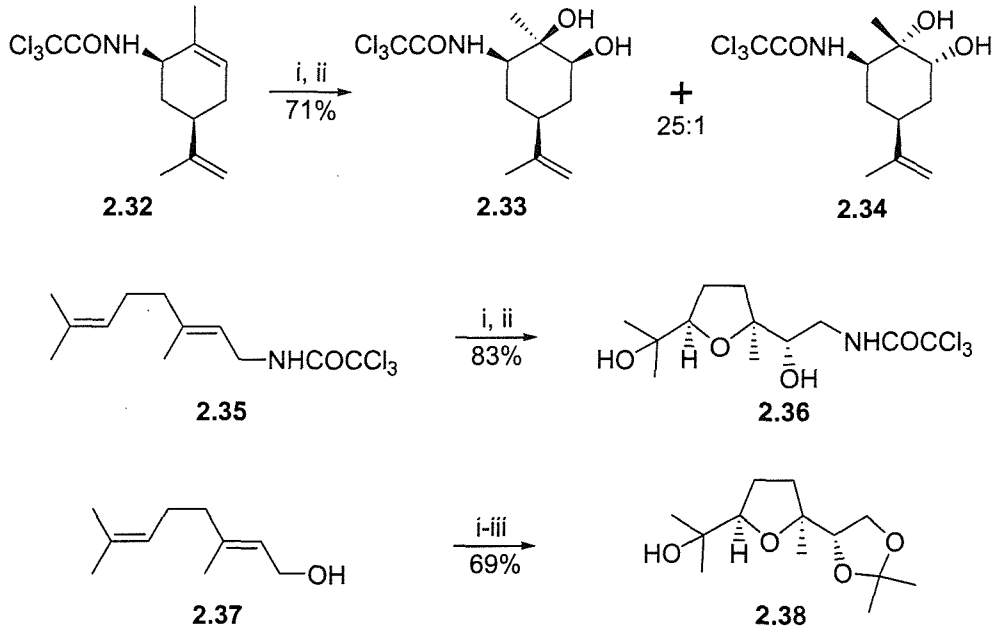
Reagents and Conditions: (i) $KMnO_4$, H_2O/Me_2CO, pH = 7.5, CO_2 ebulliation, -30 °C; (ii) CH_3OMgBr.

Scheme 2.7 Use of chiral auxiliaries in diene oxidation

2.2 Osmium Tetroxide Catalysed Oxidation of 1,5-Dienes

The treatment of 1,5-dienes with catalytic osmium tetroxide using sodium periodate as co-oxidant showed *cis*-selectivity for the THF cyclisation products. Oxidation of neryl and geranyl acetates afforded exclusively the *cis*-THF products as for the permanganate mediated cyclisation (Scheme 2.1) in yields of 53% and 55% for **2.3** and **2.4** respectively.[196]

Work by Donohoe *et al.* used a hydrogen bond acceptor combination of OsO_4 and TMEDA in the dihydroxylation of cyclic allylic alcohols and amides such as **2.32**, thus directing the reagent to one face of the alkene.[197] Directed oxidation of 1,5-diene substrates **2.35** and **2.37** afforded exclusively *cis*-THF products **2.36** and **2.38** in high yield (Scheme 2.8).

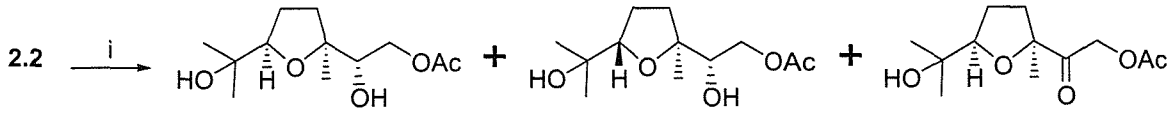


Reagents and Conditions: (i) OsO_4, TMEDA, CH_2Cl_2, -78 °C; (ii) MeOH, HCl; (iii) $Me_2C(OMe)_2$, TFA.

Scheme 2.8 Directed oxidation by OsO_4 / TMEDA

2.3 Oxidation of 1,5-Dienes by Ruthenium Tetroxide

As part of a project to improve the efficiency of ruthenium tetroxide as a catalytic alkene oxidant, Sharpless *et al.* found that oxidation of geranyl acetate gave a mixture of *cis*- and *trans*-THF products **2.4** and **2.39** in a ratio of 3:1, with a notable quantity of *cis*-2-keto derivative **2.40** also isolated.[198] The stereoselectivity and yield of the desired THF diol products was later improved, with reduction of the proportion of the *cis*-2-keto product, by Picialli *et al.* (Scheme 2.9).[199]

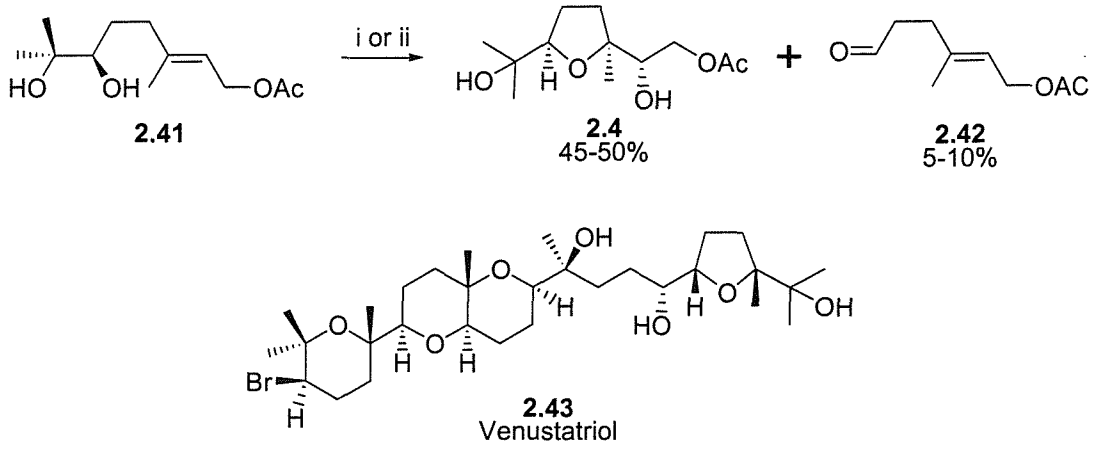


Reagents and Conditions: (i) Sharpless: 2.2 mol% $ReCl_3.(H_2O)_n$, 4.1 eq. $NaIO_4$, CCl_4, H_2O, MeCN, rt, 2 hr; Picialli: 4 mol% $RuO_2.2H_2O$, 4 eq. $NaIO_4$, EtOAc/CH_3CN/H_2O (3:3:1), rt, 4 min.

Scheme 2.9 Oxidative cyclisation by RuO_4

2.4 Chromium-Based Oxidants

Work by Walba *et al.* showed that the oxidative cyclisation of a 5,6-dihydroxyalkene such as geranyl acetate diol **2.41** by Collins reagent (CrO_3) resulted in the formation of *cis*-THF diol **2.4** in moderate yield, with small quantities of cleaved aldehyde **2.42**. Similar results were obtained using pyridinium chlorochromate, however bipyridinium chlorochromate gave only aldehyde **2.42** (Scheme 2.10).[200] Corey used pyridimium chlorochromate in a key cyclisation to form the THF region of the squalenoid, venustatriol **2.43**.[201]



Reagents and Conditions: (i) CrO_3, py; (ii) PCC.

Scheme 2.10 Collins oxidation of a 5,6-dihydroxyalkene

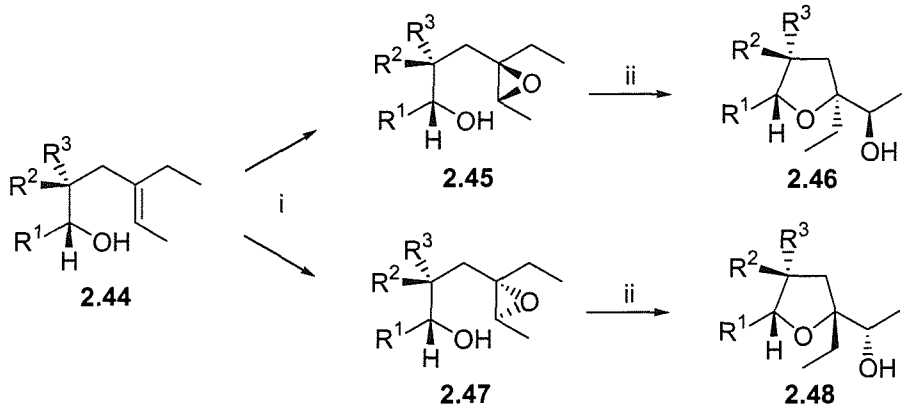
2.5 Oxidation of *bis*-Homoallylic Alcohols by $VO(acac)_2$ and *t*-BuOOH

The preparation of optically enriched tetrahydrofurans by treatment of γ,δ-unsaturated alcohols **2.44** with a mixture of $VO(acac)_2$ and *t*-butyl hydroperoxide was developed by Kishi *et al.*[202] and has been used in the synthesis of a number of natural products, an example of which is the bicyclic squalenoid (+)-eurylene (Scheme 2.11).[203] The alkene is epoxidised stereoselectively, and then undergoes cyclisation. A mechanism for the epoxidation was initially proposed by Sharpless.[204]

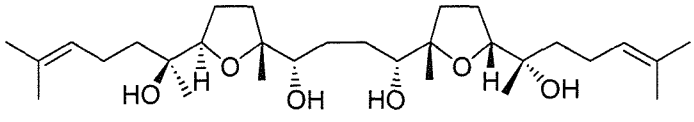
Prediction of the major THF diastereoisomer formed may be based on the following general principles:

1. When the γ,δ-unsaturated alcohol is substituted at the γ-position, the *trans*-THF is the major product.

2. When the γ,δ-unsaturated alcohol is substituted at the δ-position, the *cis*-THF is the major product.
3. The double bond geometry does not play a crucial role in the relative THF stereochemistry.



R^1 = *i*-Pr, R^2 = R^3 = H; **2.46**:**2.48** = 9:1
R^1 = *i*-Pr, R^2 = Me, R^3 = H; **2.46**:**2.48** = 6:1
R^1 = *i*-Pr, R^2 = H, R^3 = Me; **2.46**:**2.48** = >20:1



2.49 (+)-Eurylene

Reagents and Conditions: (i) $VO(acac)_2$, *t*-BuOOH, PhH; (ii) AcOH.

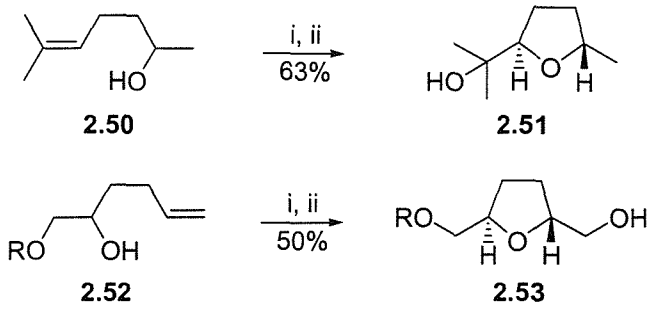
Scheme 2.11 $VO(acac)_2$ and *t*-BuOOH in the epoxidation of γ,δ-unsaturated alcohols

2.6 Oxidation of Homoallylic Alcohols by Rhenium Oxide

The use of rhenium oxide to promote the oxidative cyclisation of *bis*-homoallylic alcohols **2.50** and **2.52** to *trans*-2,5-disubstituted tetrahydrofurans **2.51** and **2.53** was first investigated by Kennedy.[116-119] The application of this work to acetogenin synthesis was discussed in detail previously (Chapter 1.5.7), and therefore only the early results are summarised below.

Treatment of a number of *bis*-homoallylic alcohols with rhenium (VII) oxide and 2,6-lutidine provided *trans*-2,5-disubstituted THF products (Scheme 2.12). Further studies involving acyl perrhenate reagents such as trifluoroacetyl trioxorhenium $(CF_3CO_2)ReO_3$ were conducted by McDonald and Towne.[205-210]

The coordination chemistry of oxorhenium compounds has been studied intensively by Herrmann *et al.* This included consideration of acyl perrhenates and methyl trioxorhenium, which catalyses a number of reactions of alkenes.[211-216]



2.50 **2.51**

2.52 **2.53**

Reagents and Conditions: (i) Re_2O_7, 2,6-lutidine, CH_2Cl_2; (ii) NaOOH.

Scheme 2.12 Kennedy's cyclisation

2.7 Conclusions

The oxidation of alkenes and hydroxy alkenes by transition metal oxide species is a powerful synthetic technique in the synthesis of 2,5-disubstituted tetrahydrofuran compounds. Particular transition metal reagents may be selected to provide access to both *cis*- and *trans*-THF's.

There are many examples in the literature of the synthesis of acetogenins in which oxidation of alkenes by transition metals is employed. This commonly involves asymmetric epoxidation and dihydroxylation by osmium, with the products being used in epoxide-opening based strategies. The only commonly used direct THF forming reaction to be applied to *bis*-THF acetogenins is the Kennedy cyclisation.

Apart from some unexpected results as part of Sinha's work, the transition metal mediated formation of *cis*-tetrahydrofuran ring systems has not been investigated in detail in the context of acetogenin synthesis.

Chapter 3

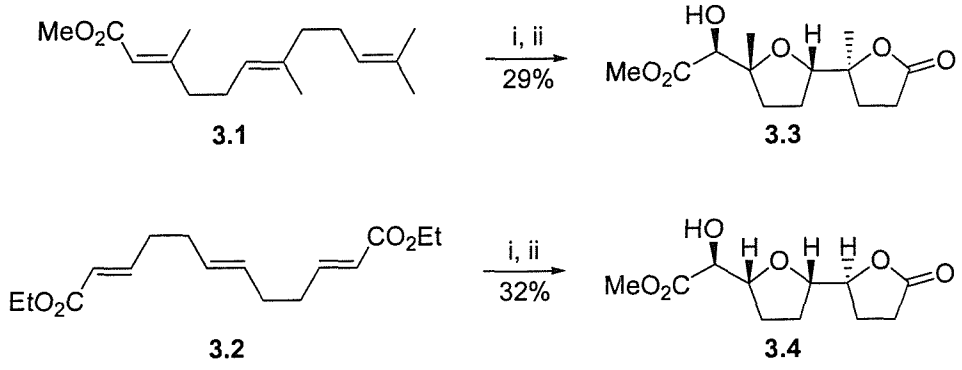
Southampton Approach to the *Annonaceous* Acetogenins

The previous chapters reviewed a number of synthetic approaches towards the *Annonaceous* acetogenins, as well as considering a number of general approaches to 2,5-disubstituted tetrahydrofurans using transition metal chemistry. The following chapter is a brief summary of work undertaken within our group, which was investigated concurrently with the research described in this thesis. It also provides an introduction to the work described herein.

3.1 The Oxidation of 1,5,9-Trienes by Potassium Permanganate

Early work within the group focused on the stereoselective synthesis of tetrahydrofuran-containing fragments *via* the oxidative cyclisation of 1,5,9-trienes by potassium permanganate. This approach was attractive as THF rings are key structural features of many natural products, and potassium permanganate is a relatively cheap and non-toxic reagent when compared with a number of other transition metal oxidants.

Initial studies into the oxidative cyclisation of 1,5,9-trienes such as methyl-(*E,E*)-farnesoate **3.1** and C_2-symmetrical triene **3.2** resulted in the formation of THF-lactone intermediates **3.3** and **3.4** respectively (Scheme 3.1).[217]

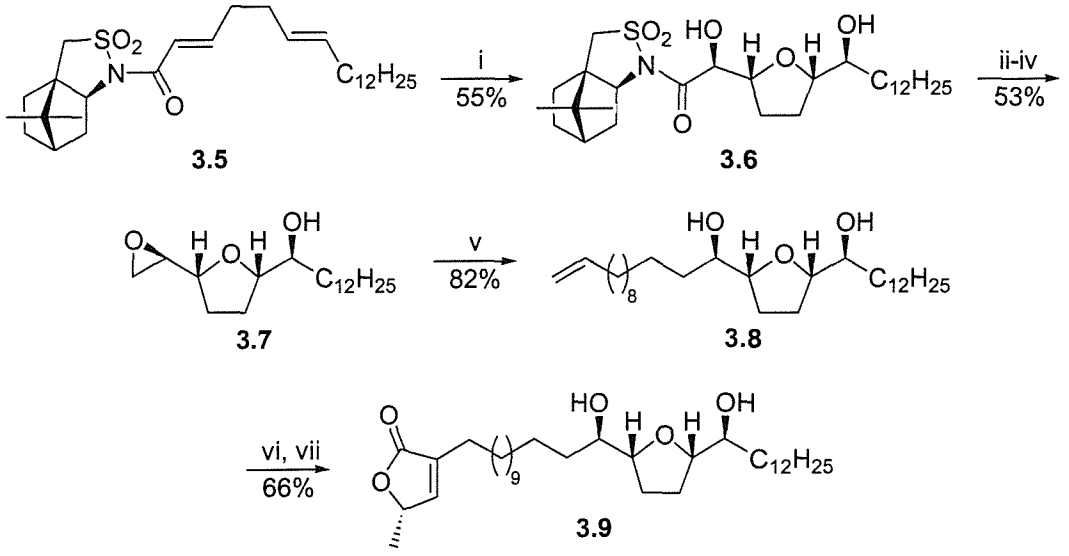


Reagents and Conditions: (i) $KMnO_4$, AcOH, phosphate buffer (pH 6.2), Me_2CO; (ii) $Pb(OAc)_4$, Na_2CO_3, CH_2Cl_2.

Scheme 3.1 Permanganate oxidation of 1,5,9-trienes

3.2 Synthesis of *cis*-Solamin, a *mono*-THF Acetogenin

The synthesis of *mono*-THF acetogenin *cis*-solamin **3.9** was carried out in a total of fourteen steps from inexpensive starting materials.[218] Key steps involved the oxidative cyclisation of sultam-diene **3.5**, affording predominantly the *cis*-THF product **3.6** (10:1 ratio based on crude proton NMR). Reduction with sodium borohydride, formation of the primary tosylate and treatment with base gave epoxide **3.7**. Opening of the epoxide *via* a copper-catalysed Grignard reaction provided a terminal alkene which allowed synthesis of the butenolide using Trost's Alder-ene reaction. Careful reduction using diimide afforded *cis*-solamin (Scheme **3.2**).



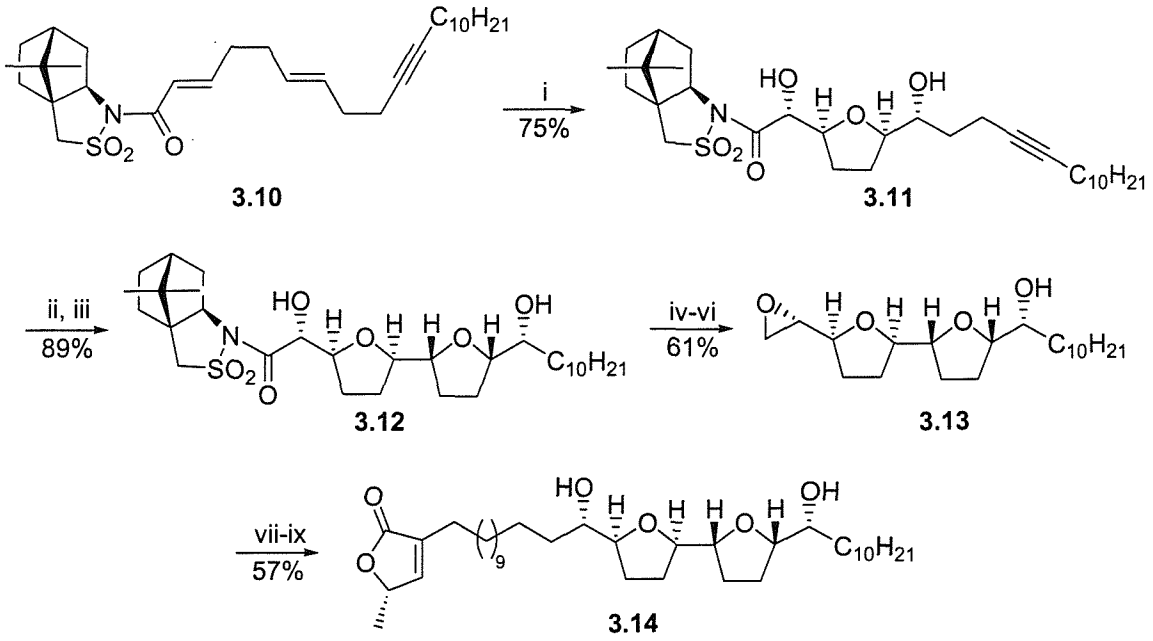
Reagents and Conditions: (i) $KMnO_4$ (2 eq.), AcOH, (8 eq.), adogen-464 (0.1 eq.), EtOAc, -30 °C to 0 °C; (ii) $NaBH_4$, THF, H_2O; (iii) TsCl, Et_3N, CH_2Cl_2; (iv) DBU, CH_2Cl_2; (v) CH_2=$CH(CH_2)_8MgBr$, CuI, THF, -60 °C; (vi) Propargylic alcohol **1.146**, catalyst **1.147**, MeOH, reflux; (vii) $TsNHNH_2$, NaOAc, THF, H_2O, reflux, 20 hr.

Scheme 3.2 Synthesis of *cis*-solamin

3.3 Synthesis of a *bis*-THF Acetogenin Analogue With Permanganate and Rhenium

The total synthesis of a *bis*-THF acetogenin analogue was carried out using a combination of the permanganate oxidative cyclisation of 1,5-dienes, and Kennedy's perrhenate cyclisation. The key steps in this synthesis involved the selective oxidation of the 1,5-diene part of sultam-dienyne **3.10** by potassium permanganate, affording *cis*-THF-diol **3.11** as the major diastereoisomer. Reduction of the alkyne to the *cis*-alkene and treatment with

trifluoroacetyl perrhenate resulted in formation of a second, *cis*-THF ring. Reductive removal of the sultam, primary tosylate formation and treatment with base afforded epoxide **3.13**. As for the synthesis of *cis*-solamin, the epoxide was opened by a cuprate bearing a terminal alkene. Trost's Alder-ene reaction and diimide reduction of the isolated double bond afforded *cis, cis, bis*-THF **3.14** (Scheme 3.3).



Reagents and Conditions: (i) $KMnO_4$ (1.1 eq.), acetone/AcOH 1:0.9, -30 °C to -15 °C, 25 min; (ii) $Pd/BaSO_4$, H_2, quinoline, hexane; (iii) Re_2O_7, TFAA, CH_2Cl_2; (iv) $NaBH_4$, THF, H_2O; (v) Bu_2SnO, PhH, reflux, 3 hr then TsCl, TBAB, 1 hr; (vi) DBU, CH_2Cl_2; (vii) $CH_2{=}CH(CH_2)_7MgBr$, CuI, THF, -60 °C; (viii) Propargylic alcohol **1.146**, catalyst **1.147**, MeOH, reflux; (ix) $TsNHNH_2$, NaOAc, THF, H_2O, reflux, 20 hr.

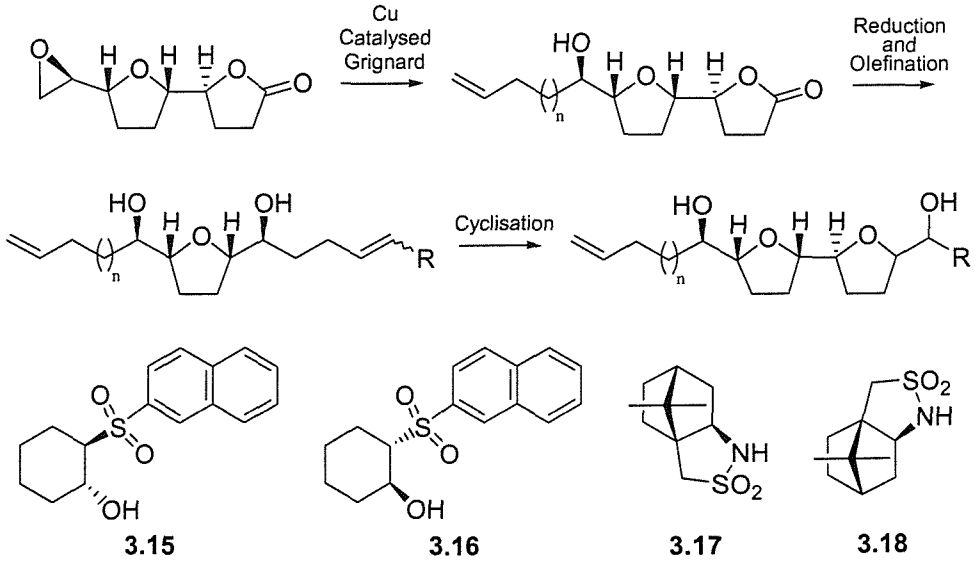
Scheme 3.3 Synthesis of a *cis, cis, bis*-THF acetogenin analogue

3.4 Proposed Work

Although the approaches to *cis*-solamin and *bis*-THF analogues summarised above were both efficient and diastereoselective, the incorporation of the aliphatic sidechain from the beginning of the synthesis was considered to be a limiting factor in terms of product diversity. The objective of this project was the asymmetric synthesis of a versatile key epoxy-THF-lactone intermediate, *via* the oxidative cyclisation of trienes (as for Scheme 3.1). The epoxide would allow for the addition of sidechains of various length, bearing a terminal alkene for later butenolide annulation using Trost's methodology. The lactone moiety would allow olefination *via* the corresponding lactol, thus forming a γ/δ-unsaturated

hydroxy product which could be used as a substrate for a second cyclisation (Scheme 3.4). We envisaged that the use of this methodology would provide a powerful approach to the synthesis of *bis*-THF acetogenin analogues.

We proposed to carry out initial studies into the permanganate mediated oxidation of a simple 1,5-diene model using Corey's hydroxy sulfone and Oppolzer's bornane-10,2-sultam chiral auxiliaries **3.15-3.18**.



Scheme 3.4 Proposed work

We proposed to target a natural product with the general structure of membranacin **3.19**, a *cis*, *cis-bis*-THF acetogenin.[35,219,220] Our versatile epoxide intermediate contains the stereochemistry of the left hand THF ring. Installation of a terminal alkene sidechain will leave the task of effecting formation of the right hand ring, either of membranacin or epimers such as **3.20-3.22**, and addition of the unsubstituted alkyl chain (Figure 3.5).

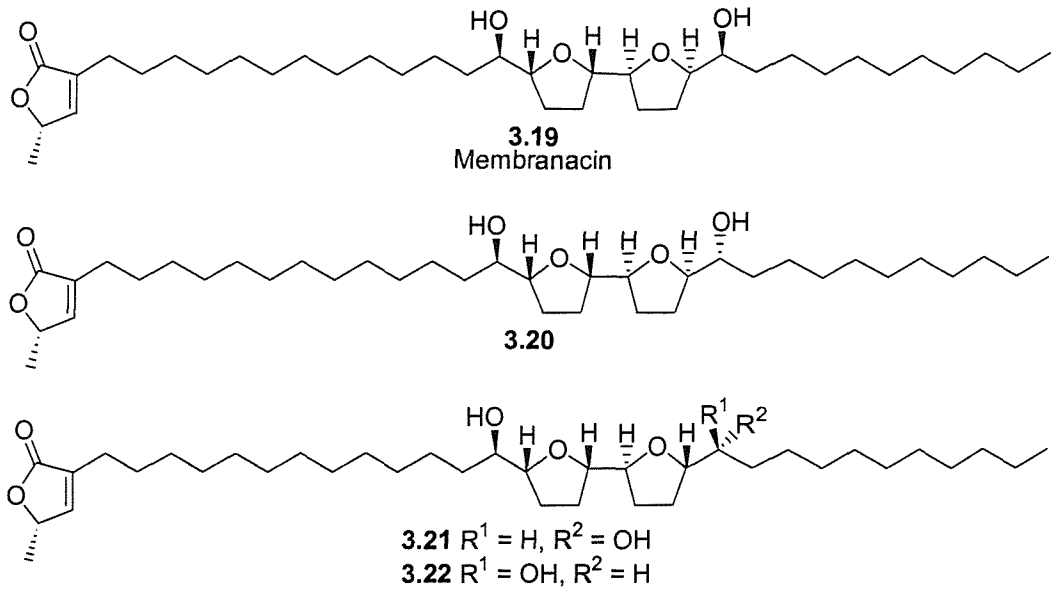


Figure 3.5 Membranacin and epimers

3.5 Conclusions

Previous work within our research group resulted in the efficient, diastereoselective synthesis of specific acetogenins and acetogenin analogues.

The following chapters will describe the research undertaken in an attempt to broaden this methodology by seeking complementary routes to acetogenin precursors.

Chapter 4

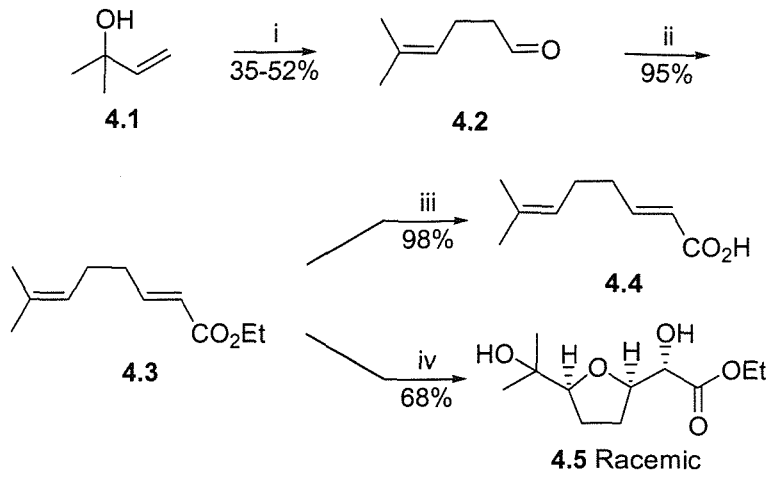
Synthesis and Asymmetric Oxidation of 1,5-Dienes and 1,5,9-Trienes

The following chapter describes the synthesis of a simple 1,5-dienoate substrate, its attachment to two chiral auxiliaries, and oxidative cyclisation by potassium permanganate. The synthesis and oxidative cyclisation of 1,5,9-triene substrates also discussed.

4.1 Synthesis and Oxidative Cyclisation of a Simple 1,5-Diene

The proposed use of chiral auxiliaries in the permanganate mediated oxidation of 1,5-dienes required the synthesis of a simple model substrate to which they could be attached. This model would allow a comparison of the effectiveness of the different chiral auxiliaries in directing the reaction of permanganate with the diene.

The model dienoate ester **4.3** was synthesised from inexpensive starting materials in two steps. Thus, 2-methyl-3-buten-1-ol **4.1** was heated in a sealed tube with ethyl vinyl ether and a catalytic quantity of phosphoric acid, affording aldehyde **4.2** in variable yield *via* a Claisen-Johnson rearrangement.[129] Wittig homologation using (carbethoxymethylene)-triphenylphosphorane afforded exclusively the *E*-α,β-unsaturated ester **4.3** (single isomer by ^{1}H NMR), which was hydrolysed to the corresponding carboxylic acid **4.4** required for coupling to chiral auxiliaries. Oxidation of dienoate **4.3** by potassium permanganate using previously optimised conditions afforded racemic *cis*-THF-diol **4.5** (Scheme 4.1).[170]

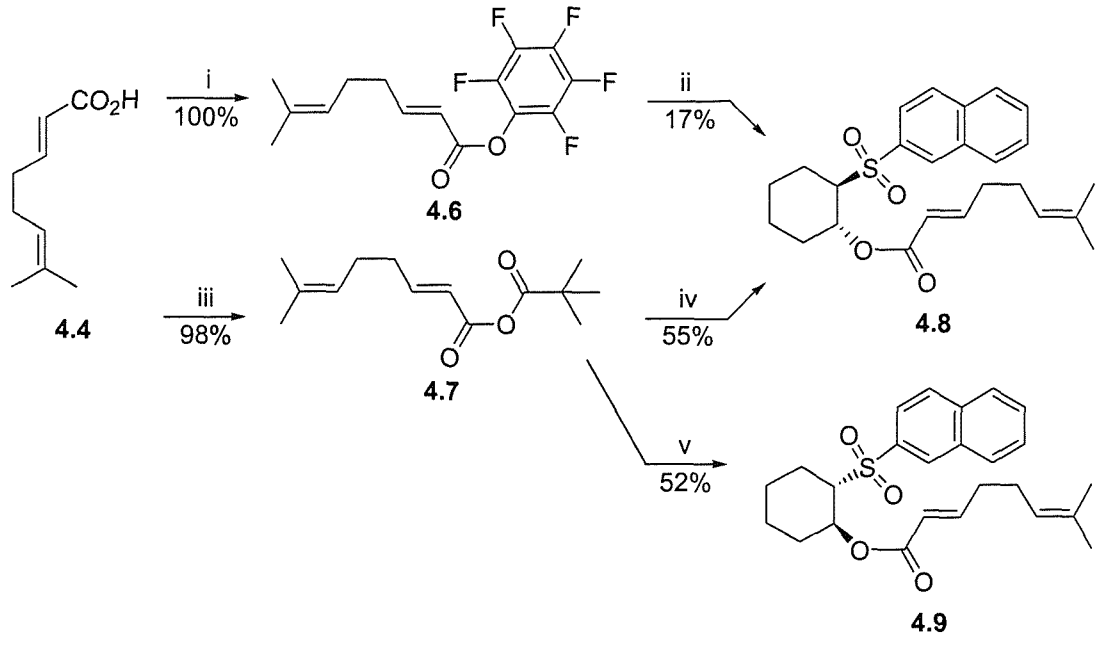


Reagents and Conditions: (i) Ethyl vinyl ether, H_3PO_4, 120 °C, 16 hr, then 2N HCl, Me_2CO, rt, 1 hr; (ii) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 14 hr; (iii) NaOH, $NaHCO_3$, MeOH, H_2O, reflux, 3 hr; (iv) 0.4M $KMnO_{4(aq)}$ (2 eq.), AcOH (2.8 eq.), pH 6.5, Me_2CO, -25 °C.

Scheme 4.1 Synthesis and oxidation of a simple 1,5-dienoate ester

4.2 Corey's Hydroxysulfone

Both enantiomers of the hydroxysulfone chiral auxiliary, **3.15** and **3.16**, were synthesised by the method of Corey and Sarakinos.[221] Initial attempts to couple **3.15** to dienoic acid **4.4** using three standard ester coupling reagents 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide, 2-chloro-1-methyl-pyridinium iodide and dicyclohexyl carbodiimide were unsuccessful, resulting in dimerisation of the acid to the anhydride. The acid was then converted to pentafluorophenyl ester **4.6** and unsymmetrical anhydride **4.7**, both of which reacted with the anion of **3.15** affording ester **4.8**. Due to the low yield obtained by the pentafluorophenyl ester method, **3.16** was attached to the acid *via* the anhydride affording ester **4.9** (Scheme 4.2).[193]

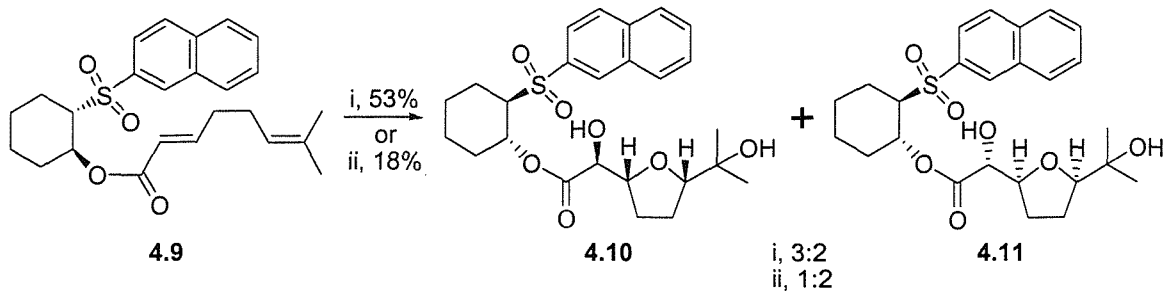


Reagents and Conditions: (i) C_6F_5OH, DCC, EtOAc, 16 hr; (ii) Sulfone **3.15**, *n*-Buli, THF, -78 °C, 1 hr; (iii) $(CH_3)_3CCOCl$, Et_3N, THF, 2 hr; (iv) Sulfone **3.15**, NaH, THF, -78 to 0 °C, 1 hr; (v) Sulfone **3.16**, NaH, THF, -78 to 0 °C, 1 hr.

Scheme 4.2 Coupling of chiral auxiliaries to a 1,5-dieneoic acid

Oxidative cyclisation of **4.9** by potassium permanganate in aqueous acetone afforded tetrahydrofuran diols **4.10** and **4.11** in 53% yield and a ratio of 3:2 (20% *de*) based on integration of discrete signals in the crude proton NMR spectrum. It was not ascertained which of the two diastereoisomers was the major product. When the reaction was conducted under phase transfer conditions, in methylene chloride with aqueous potassium permanganate and adogen-464 as a phase transfer catalyst, the yield dropped to 18%. Interestingly the product ratio was found to be 1:2 (33% *de*) in favour of the diastereoisomer which was the minor product in the aqueous acetone reaction (Scheme 4.3).

It was concluded that the combination of low yield for the formation of esters **4.8** and **4.9** and surprisingly low selectivity in the oxidative cyclisation meant that the use of this auxiliary was inpractical for acetogenin synthesis.



4.9 **4.10** **4.11**

Reagents and Conditions: (i) 0.4M $KMnO_{4(aq)}$ (2 eq.), AcOH (2.8 eq.), pH 6.5, Me_2CO, -25 °C, 15 min; (ii) 0.4M $KMnO_{4(aq)}$ (2 eq.), AcOH (2.8 eq.), pH 6.5, CH_2Cl_2, adogen-464, 0 °C, 20 min.

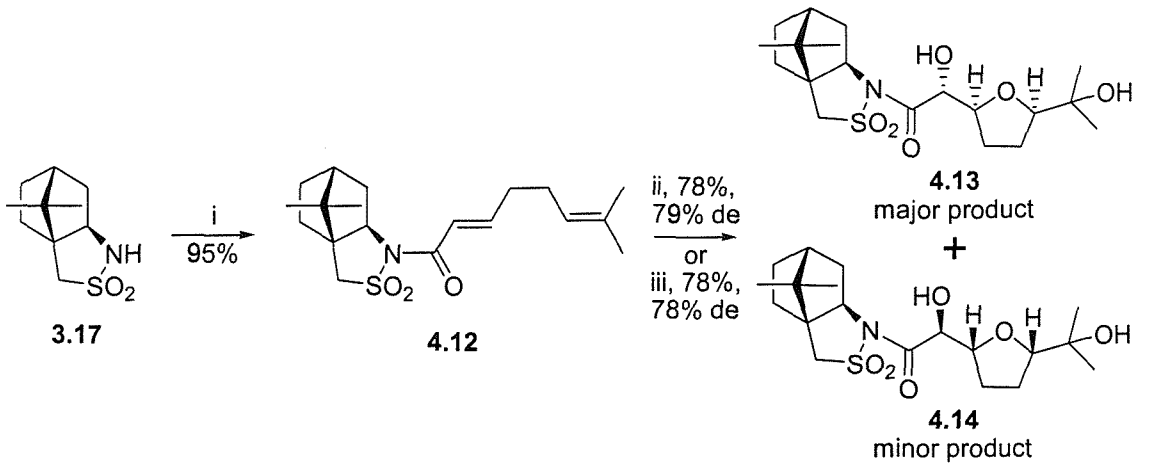
Scheme 4.3 Oxidative cyclisation directed by Corey's hydroxysulfone

4.3 Oppolzer's Sultam

Both enantiomers of Oppolzer's sultam were synthesised in four steps from the corresponding camphorsulfonic acids by the methods of Bartlett and Towson.[222-224] Deprotonation of **3.17** with *n*-butyllithium and addition of pentafluorophenyl ester **4.6** afforded sultam-diene **4.12**. The use of sodium hydride as base resulted in drastically reduced yields. Oxidative cyclisation was carried out both in aqueous acetone and under phase transfer conditions with solid potassium permanganate in methylene chloride with adogen-464. Both methods resulted in the formation of major and minor diastereoisomers **4.13** and **4.14** (Scheme 4.4).

The combined yields and diastereomeric excess for the two sets of conditions were identical within experimental error (75%, 79% *de.* for the reaction in aqueous acetone and 78%, 78% *de.* under phase transfer conditions). The ratios were estimated from integration of discrete signals in the crude proton NMR spectra, and were confirmed by isolated yields of the separable diastereoisomers.

The high yields obtained for both addition of the sultam to the diene component and oxidative cyclisation of the product, in combination with the good selectivity observed, confirmed this to be the best of the investigated chiral auxiliaries for our proposed asymmetric synthesis of acetogenin fragments.



Reagents and Conditions: (i) *n*-BuLi, THF, -78 °C, then **4.6**; (ii) 0.4M $KMnO_{4(aq)}$ (2 eq.), AcOH (2.8 eq.), pH 6.5, Me_2CO, -25 °C, 10 min; (iii) $KMnO_4$ (2 eq.), AcOH (2.8 eq.), CH_2Cl_2, adogen-464, 0 °C, 20 min.

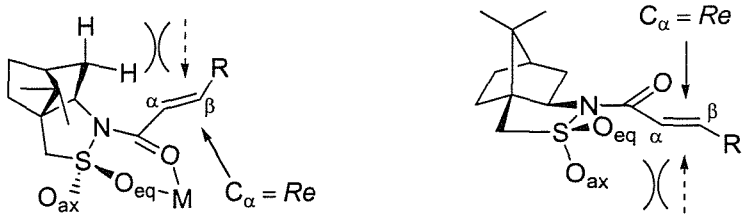
Scheme 4.4 Oxidative cyclisation directed by Oppolzer's sultam

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.[195] The selectivity may be explained by consideration of transition state models.[186,189,190] The following conditions must be fulfilled for face-selective reaction of the first double bond to occur:[225]

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 for steric reasons ($O < NR_2$).
2. The orientation of the carbonyl group must also 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 **4.15**, involving the *pseudo*-equatorial S-O bond. The upper face of the alkene is blocked by the camphor framework, and the reagent must attack from the lower C_α-*Re*-face.

In the absence of a chelating Lewis acid there is an *anti* relationship between C=O and SO_2, transition state **4.16**. 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_α-*Re*-face (Figure 4.1). The sultam therefore induces identical stereoselectivity whether or not Lewis acid chelation is available. In the oxidative cyclisation of 1,5-diene **4.12**, THF-diol **4.13** was the predicted product according to this model.



4.15 **4.16**

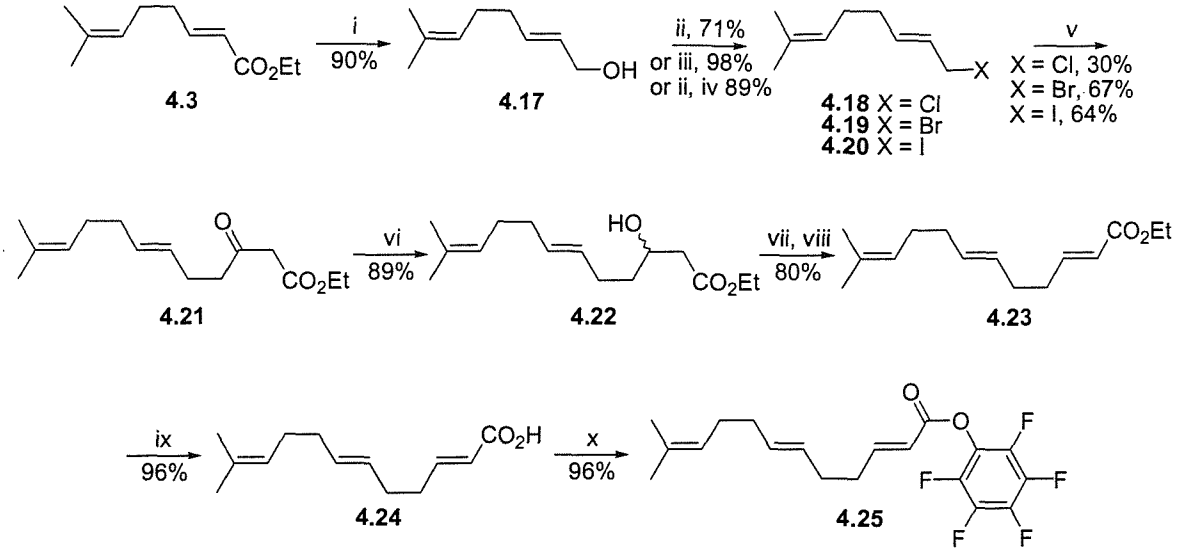
Figure 4.1 Transition state models for sultam selectivity.

4.4 Synthesis and Oxidation of a 1,5,9-Triene Substrate

The synthesis of a 1,5,9-triene began with the reduction of ester **4.3**. Conversion of the resulting alcohol to the allylic chloride **4.18** by treatment with methane sulfonyl chloride and lithium chloride,[226] to bromide **4.19** by treatment with triphenylphosphine and carbon tetrabromide,[227] and to iodide **4.20** by tretment of the chloride with sodium iodide in acetone was carried out.[228] In the case of the iodide, an inseparable impurity was formed during the course of the halide exchange, thought to be due to rearrangement of the trisubstituted double bond. The iodide itself was inherently unstable, and was used immediately after being passed through a short plug of silica.

Alkylation of these halides with the dianion of ethyl acetoacetate afforded β-ketoester **4.21**. The relative unreactivity of the chloride, and the presence of inseparable inpurity in the product of the iodide reaction, suggested that the use of bromide **4.19** would be best suited to large scale synthesis. This indeed proved to be the case, with good yields for multi-gram reactions. Borohydride reduction afforded β-hydroxy ester **4.22**, which was mesylated and

treated with base to afford exclusively *trans*-α/β-unsaturated ester **4.23**. Hydrolysis and esterification afforded pentafluorophenyl ester **4.25** (Scheme 4.5).



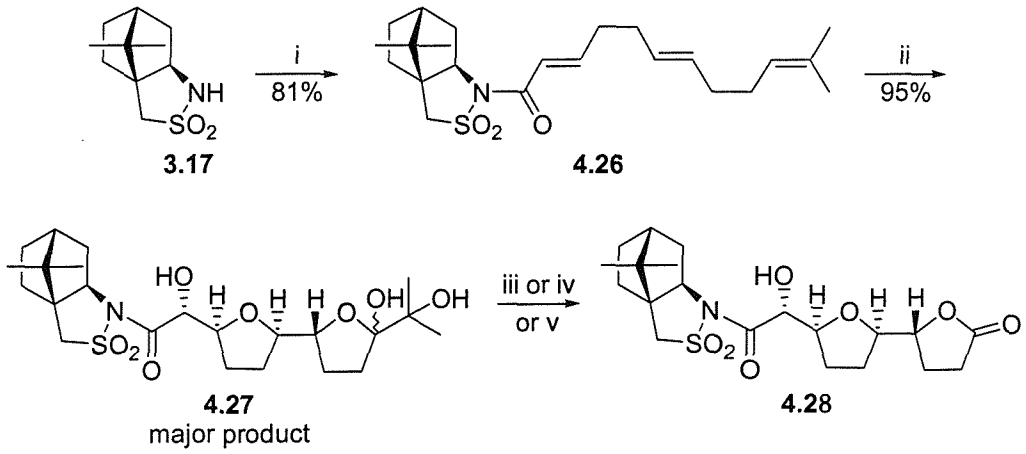
Reagents and Conditions: (i) DIBAL-H, CH_2Cl_2, -30 °C, 3 hr; (ii) 2,6-lutidine, MsCl, LiCl, DMF, 16 hr; (iii) Ph_3P, CBr_4, MeCN, dark, 0 °C, 2 hr; (iv) NaI, Me_2CO, reflux, dark, 18 hr; (v) Premixed $H_3CCOCH_2CO_2Et$, LDA, THF, -78 °C, 3 hr; (vi) $NaBH_4$, THF, H_2O, 0 °C, 1 hr; (vii) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1.5 hr; (viii) DBU, CH_2Cl_2, 0 °C, 1.5 hr; (ix) NaOH, $NaHCO_3$, MeOH, H_2O, reflux, 3 hr; (x) C_6F_5OH, DCC, EtOAc, 16 hr.

Scheme 4.5 1,5,9-triene synthesis

Addition of **4.25** to the anion of sultam **3.17** afforded triene **4.26**. Permanganate oxidation in aqueous acetone afforded lactol **4.27**. Oxidative cleavage using either lead (IV) acetate, sodium periodate with periodic acid or silica-supported sodium periodate afforded lactone **4.28** in low to moderate yield (Scheme 4.6). Purification of the lactol proved difficult, and generally had no beneficial effect on the yield over two steps, therefore the crude product from the cyclisation was generally passed through a short plug of silica gel to remove only the non-polar and TLC baseline impurities. In later experiments the silica-supported periodate method was adopted due to convenience, and the cyclisation product was used crude.

The reaction was also conducted under phase transfer conditions in methylene chloride with adogen-464. Treatment of the crude product with silica-supported sodium periodate afforded the lactone in 35% yield over two steps.

Analysis of the crude NMR spectra failed to show discrete signals on which an estimation of selectivity could be based, although it was assumed that it would be in agreement with results obtained for the oxidative cyclisation of diene **4.12**. The lactone product isolated after chromatography appeared to consist of a single diastereoisomer. The minor diastereoisomer was probably lost during the repeated chromatography which was necessary to obtain pure lactone product.



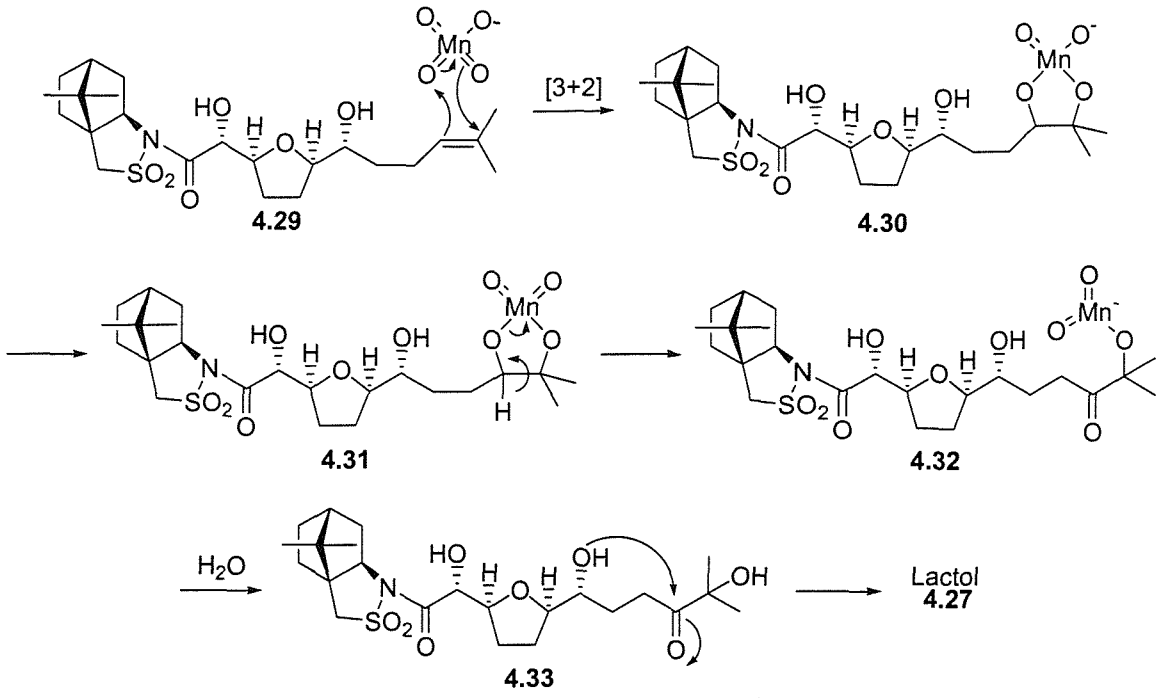
3.17 **4.26**

4.27 major product **4.28**

Results and Discussion: (i) *n*-BuLi, THF, -78 °C then **4.25**; (ii) $KMnO_4$, AcOH, phosphate buffer pH 6.5, Me_2CO, -25 °C, 10 min; (iii) $Pb(OAc)_4$, CH_2Cl_2, Na_2CO_3, 0 °C, 10 min, 19% two steps; (iv) $NaIO_4$, H_5IO_6, Me_2CO, water, 24 hr, 44% two steps; (v) $SiO_2/NaIO_4$, CH_2Cl_2, 35% two steps

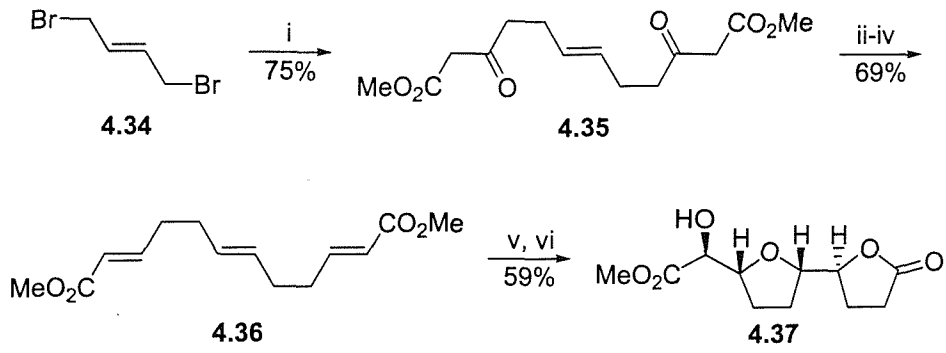
Scheme 4.6 1,5,9-triene oxidative cyclisation

The second cyclisation reaction occurs when permanganate undergoes cycloaddition to the trisubstituted double bond of **4.29**. Oxidation of Mn (V) ester **4.30**, rearrangement to ketone **4.32** and hydrolysis by water give hydroxy ketone **4.33**. Cyclisation affords lactol **4.27** (Scheme 4.7).



Scheme 4.7 Mechanism for the formation of the THF-lactol

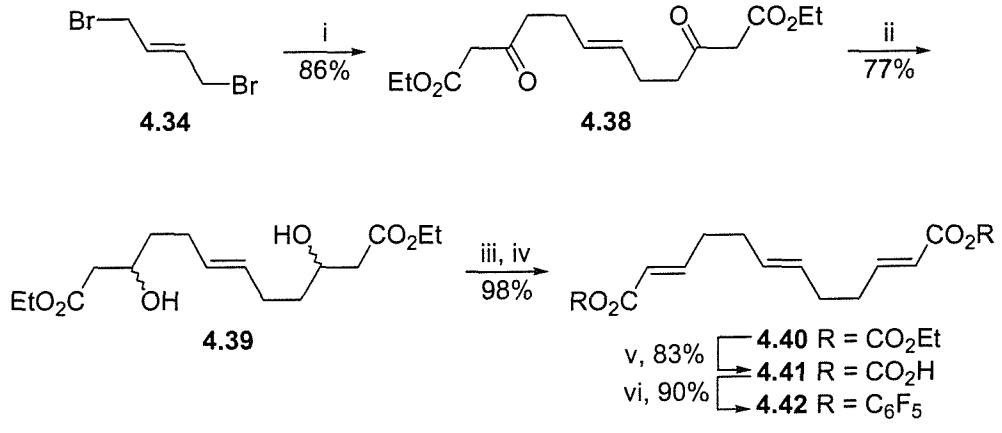
The average two-step yield for the formation of lactone **4.28** from the triene was 35%, and it was decided that a more concise route to a more reactive triene was required. It was thought that the oxidative cyclisation of a trienedioate ester such as **4.36** would give improved yields of lactone, due to the increased reactivity of the enoate alkene which would replace the trisubstituted double bond in our original substrate. Trienedioate ester **4.36** was synthesised by the method of Hoye *et al.*[22] Thus, 1,4-dibromo-2-butene **4.34** was alkylated with two equivalents of the dianion of methylacetoacetate affording *bis*-β-keto ester **4.35**. Reduction of the ketone, mesylation and elimination using DBU afforded **4.36** in 52% yield over four steps (Scheme 4.8).



Reagents and Conditions: (i) $H_3CCOCH_2CO_2Me$, LDA, THF, -50 °C; (ii) $NaBH_4$, THF, H_2O, -15 °C; (iii) MsCl, Et_3N, CH_2Cl_2, 0 °C; (iv) DBU, CH_2Cl_2, 0 °C; (v) $KMnO_4$ (2.6 eq), 5mol% Adogen-464, Me_2CO/AcOH 3:2, CH_2Cl_2, -25 °C; (vi) $NaIO_4/SiO_2$, CH_2Cl_2, 0 °C.

Scheme 4.8 Concise synthesis and oxidation of a trienedioate

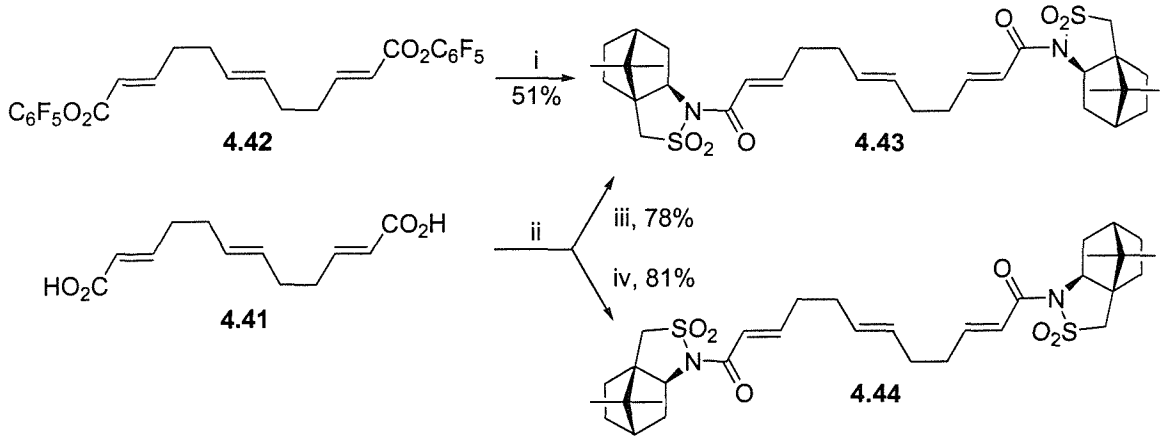
A different approach to the oxidative cyclisation reaction was also used. The use of acetone and acetic acid as solvent in a 3:2 ratio, with 5% adogen-464 to solubilise the permanganate, gave a relatively clean crude product which appeared to contain predominantly desired, racemic lactone **4.37**. Brief treatment with silica-supported $NaIO_4$ afforded the lactone in 59% yield. It was hoped that this trienedioate approach would lend itself to the use of the sultam. A large batch of triene was prepared, using identical conditions to those used for the synthesis of **4.36** but starting with ethyl acetoacetate. *Bis*-ethyl ester **4.40** was synthesised in 65% yield over four steps. Hydrolysis and esterification afforded *bis*-pentafluorophenyl ester **4.42** (Scheme 4.9).



Reagents and Conditions: (i) $H_3CCOCH_2CO_2Et$, LDA, THF, -50 °C; (ii) $NaBH_4$, THF, H_2O, -15 °C; (iii) MsCl, Et_3N, CH_2Cl_2, 0 °C; (iv) DBU, CH_2Cl_2, 0 °C; (v) NaOH, $NaHCO_3$, MeOH, H_2O, 80 °C; (vi) C_6F_5OH, DCC, EtOAc, 16 hr.

Scheme 4.9 Synthesis of a *bis*-pentafluorophenyl trienedioate

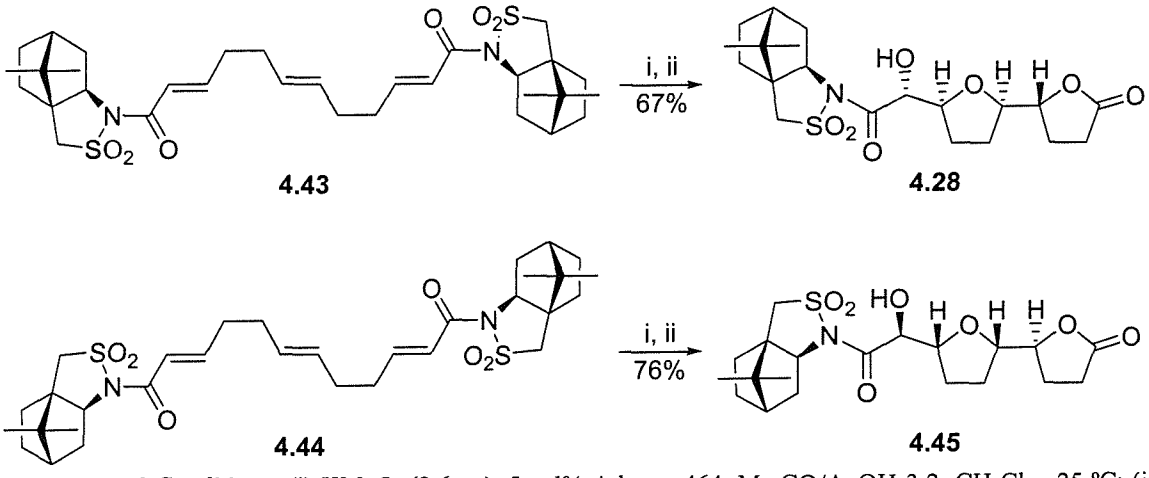
Treatment of **4.42** with the anion of sultam **3.17** gave *bis*-sultam triene **4.43** in a moderate yield of 51%. The yield was improved by conversion of acid **4.41** to the acid chloride, followed by addition of the anions of sultams **3.17** and **3.18**, affording **4.43** and **4.44** in high yield (Scheme 4.10).



***Reagents and Conditions*:** (i) Premixed **3.17**, *n*-BuLi, THF, -78 °C; (ii) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C; (iii) Premixed **3.17**, NaH, THF, 0 °C; (iv) Premixed **3.18**, NaH, THF, 0 °C.

Scheme 4.10 Synthesis of *bis*-sultam trienedioates

Oxidative cyclisation of **4.43** and **4.44** using 2.6 equivalents of potassium permanganate in a 3:2 mixture of acetone and acetic acid, with 5 mol% adogen-464 afforded lactones **4.28** and **4.45** respectively after periodate cleavage (Scheme 4.11). It was not possible to quantify the selectivity from the crude proton NMR, however the stated yields represent a single isolated diastereoisomer.



***Reagents and Conditions*:** (i) $KMnO_4$ (2.6 eq), 5mol% Adogen-464, Me_2CO/AcOH 3:2, CH_2Cl_2, -25 °C; (ii) $NaIO_4/SiO_2$, CH_2Cl_2, 0 °C.

Scheme 4.11 Oxidative cyclisation of *bis*-sultam trienedioates

4.5 Conclusions

A comparison of two chiral auxiliaries showed Oppolzer's sultam to induce good stereoselectivity in the oxidative cyclisation of 1,5-dienes. A concise synthetic route provided C_2 symmetrical 1,5,9-triene substrates which underwent oxidative cyclisation on treatment with potassium permanganate. The highest yields were obtained when a mixture of acetone and acetic acid was used as solvent, with the phase transfer reagent adogen-464 to aid solubility of the permanganate ion. This single synthetic step installed four new stereocentres with a good level of asymmetric induction.

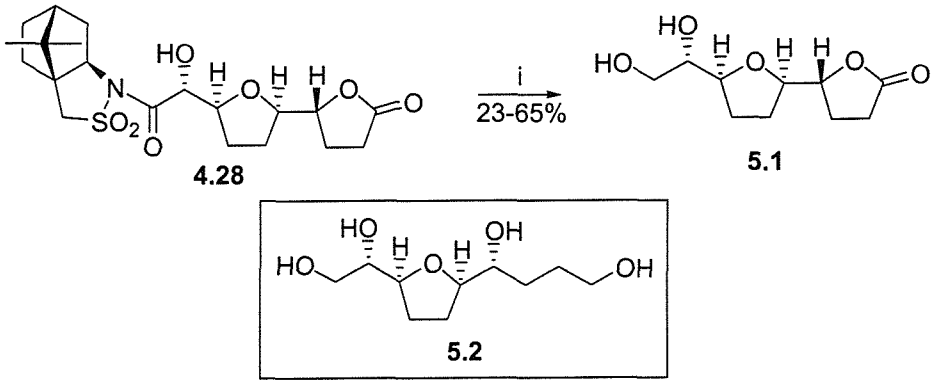
Chapter 5

Removal of the Sultam Chiral Auxiliary

5.1 The Initial Reductive Approach

Oppolzer's sultam is commonly removed by hydrolysis using lithium hydroxide, however this approach was not compatible with our substrates **4.28** and **4.45** due to hydrolysis of the lactone moiety. Precedent exists in the literature for the chemoselective reductive removal of an α-hydroxy sultam auxiliary in the presence of a lactone.[195] The method relied on the coordination of borane to the hydroxy group, and subsequent directed reduction using coordinated sodium borohydride. Lactone **4.28** was treated at -10 °C by the addition of borane dimethylsulfide complex, followed after two minutes by sodium borohydride and after ten minutes by a 9:1 mixture of methylene chloride and methanol. This gave diol **5.1** in yields ranging from 23-65%. In all cases sultam **3.17** was recovered quantitatively (Scheme 5.1). The polar by-products were never isolated, generally remaining in the aqueous phase. This observation was consistent with over-reduction of the lactone giving tetraol **5.2**, which one would expect to be soluble in water. The presence of this tetraol was confirmed by mass spectroscopy of the crude reaction mixture.

A number of other hydride sources were also investigated, with and without borane to direct them. These included lithium borohydride, lithium triethylborohydride, sodium cyanoborohydride and sodium triacetoxyborohydride, all of which failed to reduce the substrate chemoselectively.

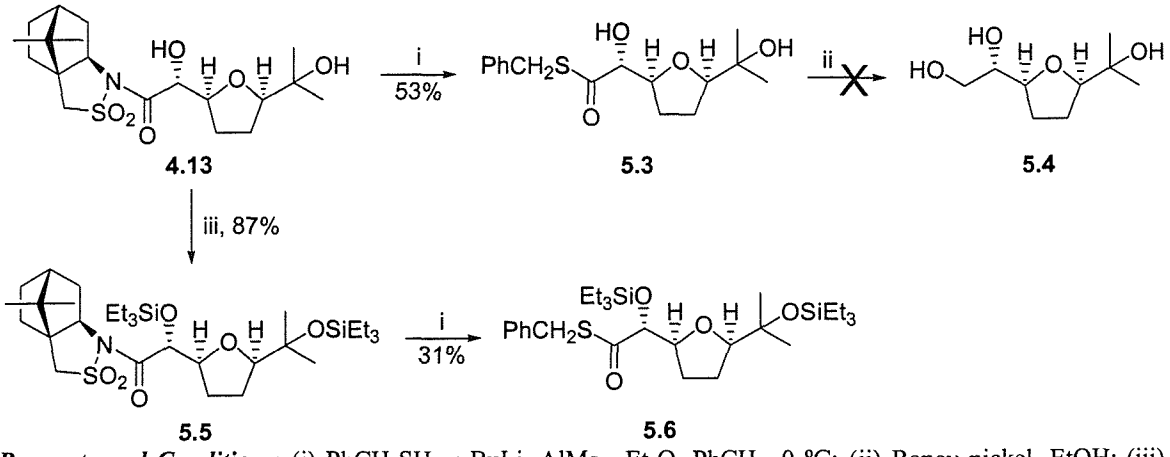


Reagents and Conditions: (i) BH_3•SMe_2, $NaBH_4$, THF, -10 °C, 10 min, then CH_2Cl_2/MeOH 9:1.

Scheme 5.1 Reductive removal of the sultam

5.2 Displacement Using a Sulfur-Based Nucleophile

The cleavage of sultam-based amides and conversion to *S*-benzyl esters was reported by Naito *et al.*[229] and later used by Oppolzer.[191] This was achieved by the action of the "ate" complex $PhCH_2SAlMe_3Li$, prepared *in situ* by the addition of trimethylaluminium to lithium benzylthiolate. The corresponding thioesters were obtained without racemisation at C_α. This methodology was used to effect the removal of the sultam from THF-diol **4.13**. The use of 1.5 equivalents of the "ate" complex gave thioester **5.3** in 53% yield. Treatment with Raney-Nickel afforded no desired triol **5.4**, and no recovered starting material. It was proposed that the polar triol product might have become bound to the Raney-Nickel surface. THF-diol was converted to *bis*-triethylsilyl ether **5.5** to reduce its polarity, however treatment of this compound with the "ate" complex gave thioester **5.6** in only 31% yield (Scheme 5.2).

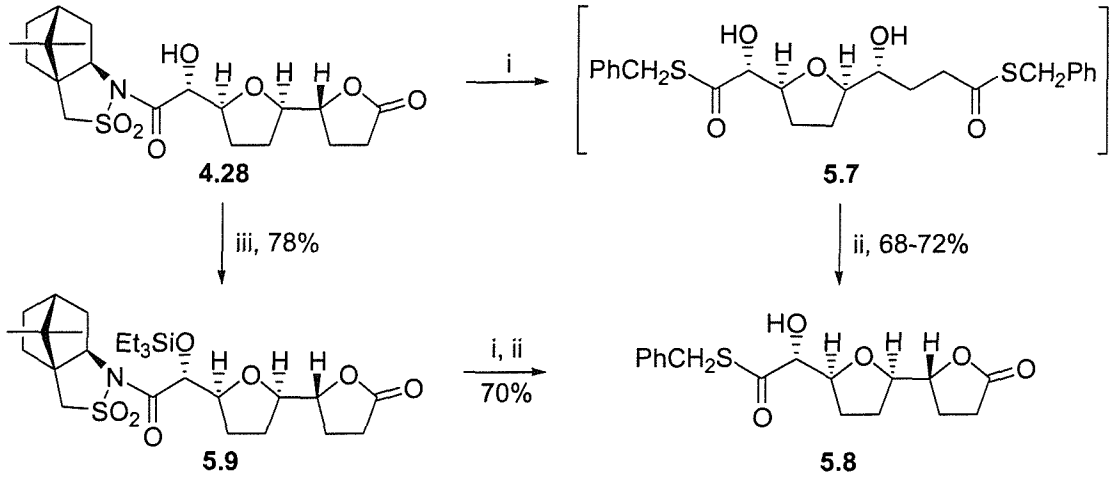


Reagents and Conditions: (i) $PhCH_2SH$, *n*-BuLi, $AlMe_3$, Et_2O, $PhCH_3$, 0 °C; (ii) Raney nickel, EtOH; (iii) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C.

Scheme 5.2 Thiol-based approach to sultam removal from the model THF-diol

After these initially disappointing results from the model substrate, it was decided at this point to attempt the removal of the sultam from lactone **4.28**. Three equivalents of the "ate" complex were used to account for the desired reaction, reversible opening of the lactone and possible deactivation by the hydroxyl group. Relactonisation was achieved by treatment with hydrochloric acid. Lactone **4.28** was also protected as the triethylsilyl ether, and on treatment with three equivalents of "ate" complex sultam displacement was accompanied by desilylation, affording **5.8** in good yield (Scheme 5.3). Unfortunately these encouraging

results were overshadowed when, on treatment of thioester **5.8** with either Raney-Nickel or other reducing agents, a complex mixture of products was obtained.



Reagents and Conditions: (i) $PhCH_2SH$, *n*-BuLi, $AlMe_3$, Et_2O, $PhCH_3$, 0 °C; (ii) 1M HCl; (iii) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C.

Scheme 5.3 Reaction of the THF-lactone with the "ate" complex

The results obtained from the use of the "ate" complex prompted a return to the investigation of reductive methods of sultam removal, particularly to the use of borane-directed borohydride reduction. It was thought that the inconsistency encountered earlier may have been due to the insolubilty of sodium borohydride in the reaction mixture, or to the relative times of reagent addition.

The reaction was repeated a number of times with slight variation to the conditions. The most consistent conditions, giving a repeatable yield of 50% of THF-diol **5.1**, required the addition of borane dimethylsulfide complex to the substrate at -20 °C. After stirring at this temperature for ten minutes the reaction was cooled to -78 °C and a solution of sodium borohydride in diglyme was added. After 1.5 hours a 10% solution of methanol in methylene chloride was added *via* syringe, and after thirty minutes the cold reaction mixture was filtered rapidly through silica gel.

5.3 Conclusions

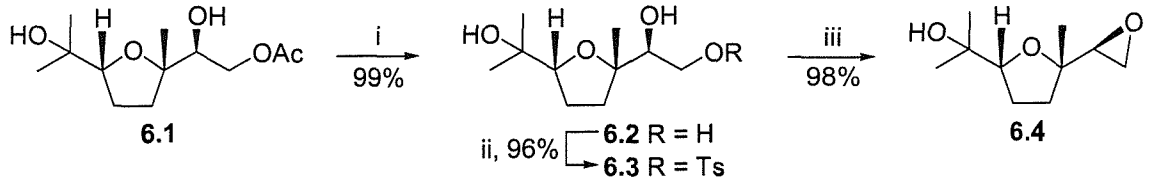
After extensive investigation into methods of sultam removal, the most consistent was found to be the rather capricious borane-directed borohydride reduction, with yields in the region of 50%.

Chapter 6

Synthesis of Acetogenin Analogues Using Oxidative Cyclisation Products

6.1 Conversion of Diol 5.1 to a Key Epoxide Intermediate

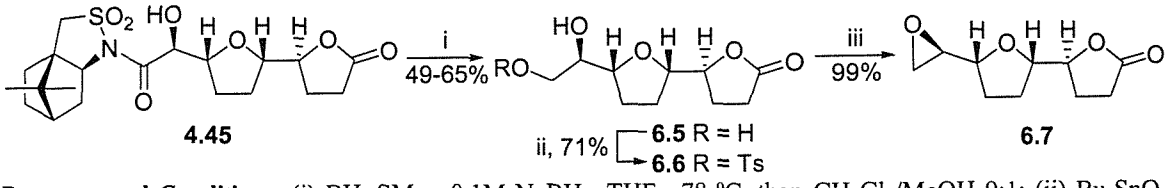
The conversion of the vicinal diol moiety of lactone **5.1** to the corresponding epoxide would provide us with a key intermediate in the synthesis of *Annonaceous* acetogenin analogues. The first step was the regiospecific tosylation of the primary alcohol. Precedent exists for the synthesis of primary tosylates from 1,2-diols upon treatment of cyclic stannylene intermediates with tosyl chloride and tetrabutylammonium bromide.[230] This was initially attempted using model diol **6.2**, obtained by hydrolysis of the racemic THF product of the oxidative cyclisation of geranyl acetate (kindly provided by a member of our research group).[170] The reaction was highly efficient, affording exclusively the primary tosylate. Conversion to the epoxide proceeded smoothly (Scheme 6.1).



Reagents and Conditions: (i) K_2CO_3, MeOH, 10 min; (ii) Bu_2SnO, PhH, reflux, 3 hr then TsCl, TBAB, 1 hr; (iii) DBU, CH_2Cl_2.

Scheme 6.1 Model study of epoxide formation

Although THF-lactone **4.28** was used for initial studies into the removal of the sultam, our targeted natural product analogues required the use of its enantiomer **4.45**. Removal of the sultam was followed by efficient conversion to the primary tosylate. Treatment with base afforded epoxide **6.7** in excellent yield (Scheme 6.2).

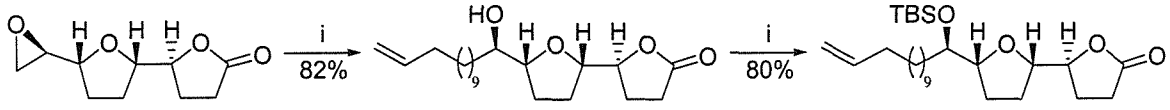


Reagents and Conditions: (i) $BH_3{\cdot}SMe_2$, 0.1M $NaBH_4$, THF, -78 °C, then CH_2Cl_2/MeOH 9:1; (ii) Bu_2SnO, TsCl, TBAB, PhH; (iii) DBU, CH_2Cl_2.

Scheme 6.2 Conversion of the lactone to our key epoxide intermediate

6.2 Elaboration of the Key Epoxide

The initial transformation of our key epoxide **6.7** was the installation of a sidechain, bearing a terminal alkene, which would eventually allow the annulation of the butenolide portion of our target molecules *via* Trost's Alder-ene reaction. This was achieved at reduced temperature in the presence of the lactone usung di-(undec-10-enyl)-cuprate, formed *in situ* from undec-10-enylmagnesiumbromide, affording alkene **6.8** in good yield. It was important for the attainment of good yields that the mixture of Grignard and copper iodide was not allowed to warm above -30 °C, in which case it became yellow in colour instead of the desired dark grey. The resulting hydroxyl group was protected as its *t*-butyldimethylsilyl ether **6.9** (Scheme 6.3).

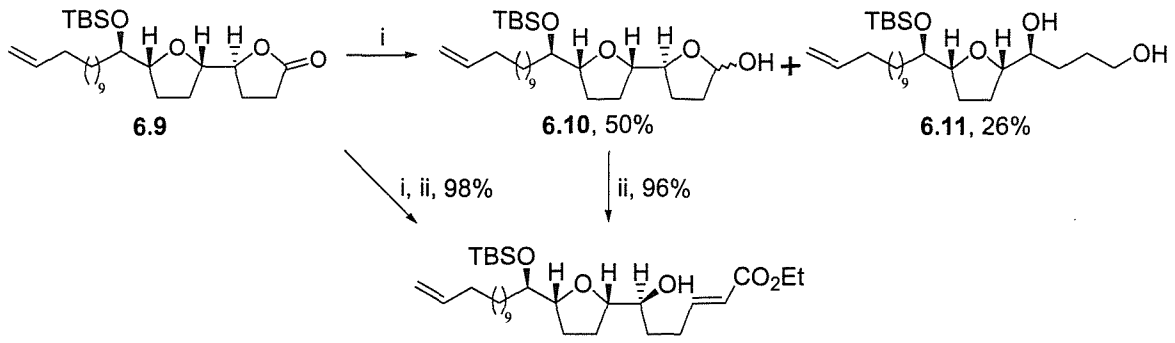


6.7 **6.8** **6.9**

Reagents and Conditions: (i) Undec-10-enylmagnesiumbromide, CuI, THF, -60 to -50 °C; (ii) TBSCl, imidazole, CH_2Cl_2, 18 hr.

Scheme 6.3 Opening of the lactone by a dialkylcuprate

The next aim was reduction of the lactone to the lactol, and homologation using Wittig chemistry. Reduction of the lactone by DIBAL-H appeared to proceed smoothly to a single product, however the product proved to be unstable to chromatograpy and a mixture of lactol **6.10** (as a 3:2 mixture of anomers) and ring-opened diol **6.11** was collected. Treatment of the lactol with (carbethoxymethylene)- triphenylphosphorane gave the desired, all-*trans* α/β-unsaturated ester **6.12**. Formation of the diol was avoided by quenching the reduction with water, filtration of the dried organic phase through celite and Wittig reaction of the crude lactol (Scheme 6.4).

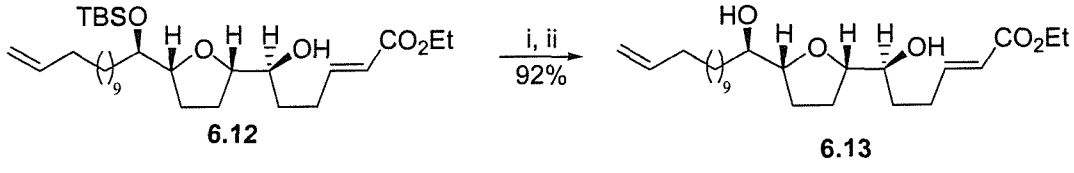


Reagents and Conditions: (i) DIBAL-H, THF, -78 °C, 2 hr; (ii) $Ph_3P{=}CHCO_2Et$, $PhCH_3$, 20 hr.

Scheme 6.4 Lactone reduction and olefination

6.3 An Attempt at the Kennedy Cyclisation

To obtain intermediates which could be used in the synthesis of *bis*-THF acetogenin analogues, the stereospecific formation of a second THF ring was required. As mentioned previously, γ/δ-unsaturated alkenes are substrates for Kennedy's rhenium-mediated oxidative cyclisation. The literature contained no examples of this reaction in which the alkene was adjacent to an ester, therefore the reaction was attempted using ester **6.12**. Unfortunately the only product isolated was alcohol **6.13**, due to desilylation of the starting material (Scheme 6.5). The presence of the ester probably rendered the cycloaddition of the rhenium reagent to the alkene electronically unfavourable, although the steric bulk of the carbonyl group may also be contributory. Desilylation was probably caused by the presence of trifluoroacetic acid.



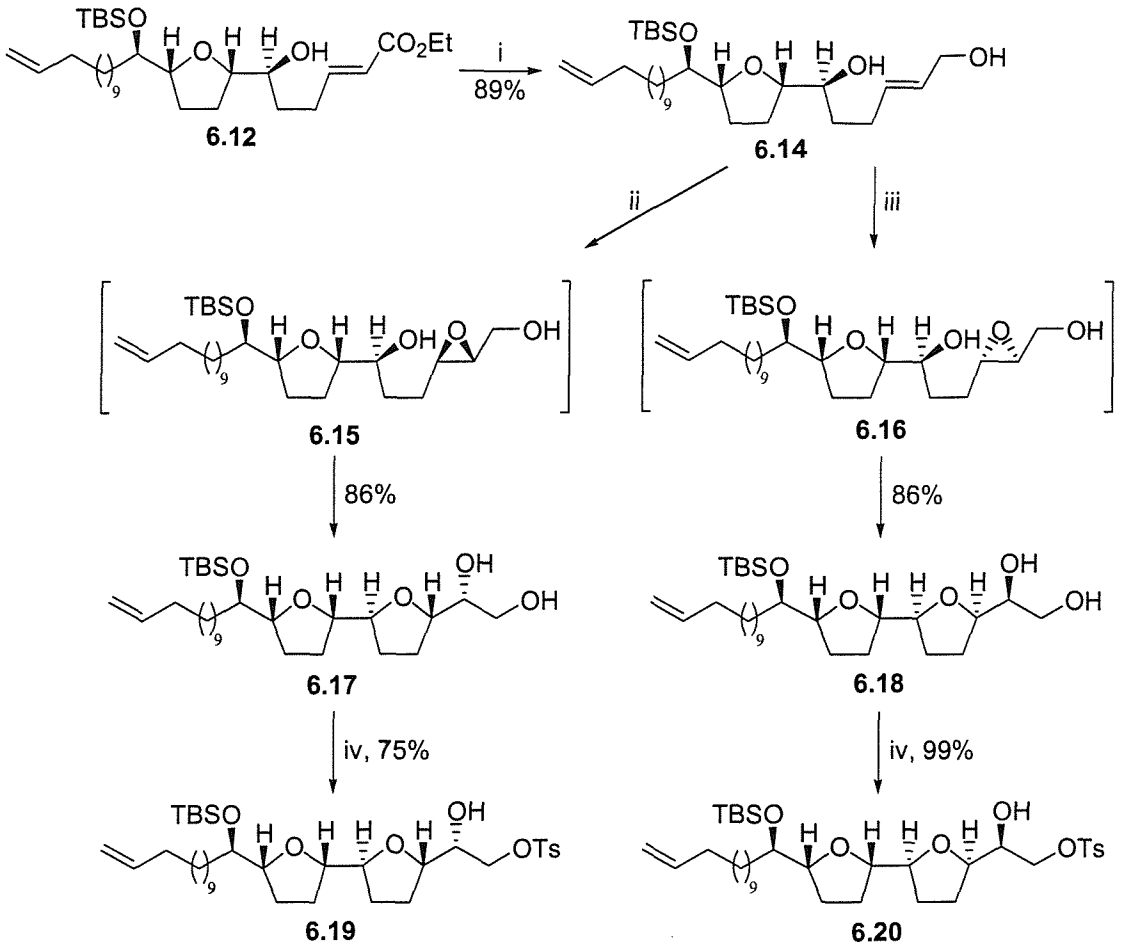
Reagents and Conditions: (i) Re_2O_7, TFAA, CH_2Cl_2; (ii) NaOOH.

Scheme 6.5 Attempted Kennedy cyclisation of the α/β-unsaturated ester

6.4 A Sharpless Asymmetric Epoxidation Approach to the Second Cyclisation

After the failure of the Kennedy cyclisation, it was decided that the second THF ring would be installed by reduction of ester **6.12** to the allylic alcohol, and Sharpless asymmetric epoxidation. In line with the work of Sinha and Keinan,[134] the resulting epoxide would be expected to undergo immediate opening by the γ-hydroxyl group, resulting in the formation of the THF ring. Thus, DIBAL-H reduction gave allylic alcohol **6.14** in very good yield. Initial attempts at epoxidation using D-(-)-diethyl tartrate, *t*-butyl hydroperoxide (TBHP) and catalytic titanium (IV) *iso*propoxide in the presence of molecular sieves resulted in the recovery of starting material.

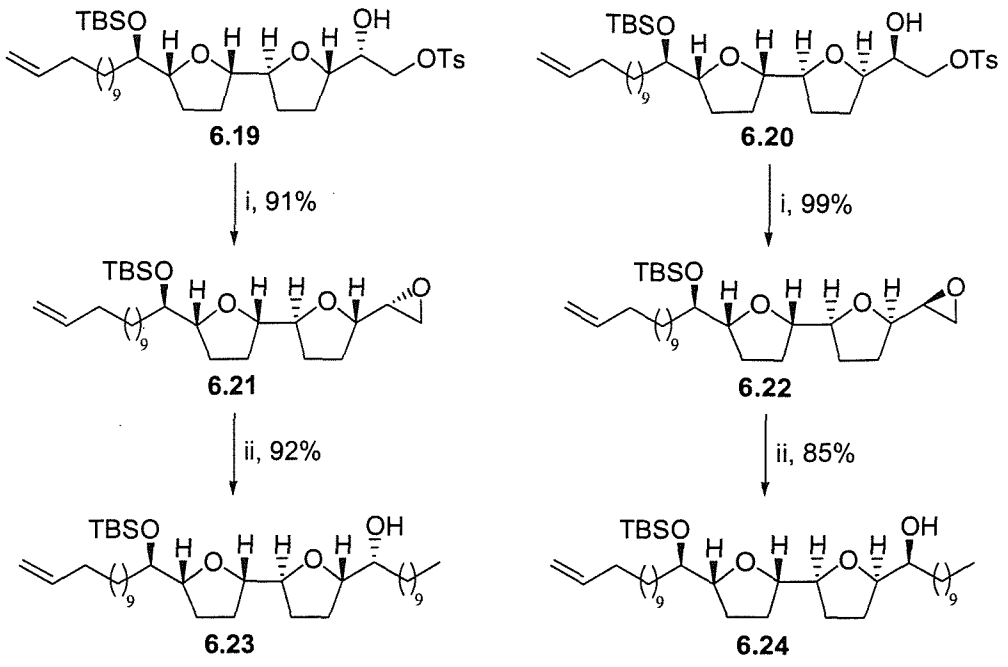
In order for the epoxidation to proceed, it was necessary to use 5.7 equivalents of the tartrate, 4.8 equivalents of titanium (IV) *iso*propoxide and 11.5 equivalents of TBHP. The reactions were conducted at -20 °C and generally took up to two days to reach completion. It was proposed that complexation of titanium by the existing THF moiety may have been responsible for the sluggish nature of the reactions. The reaction with D-(-)-diethyl tartrate afforded as the major product *cis-trans*-bis-THF diol **6.17**. This reaction also produced the *cis-cis-bis*-THF product **6.18**, although the two products were inseparable by chromatography. The ratio was found to be 15:1 (88% de.) in favour of the *trans*-THF after tosylation of the primary hydroxyl group *via* the cyclic stannylene and separation of the diastereoisomers. Reaction of **6.14** using L-(+)-diethyl tartrate afforded *cis*-THF **6.20** as the only product. Tosylation *via* the stannylene proceeded smoothly (Scheme 6.6).



Reagents and Conditions: (i) DIBAL-H, THF, -78 °C, 1 hr; (ii) D-(-)-DET, Ti(O*i*-Pr)$_4$, *t*-BuOOH, 4Å mol sieves, CH_2Cl_2, -20 °C, 48 hr, major product shown; (iii) L-(+)-DET, Ti(O*i*-Pr)$_4$, *t*-BuOOH, 4Å mol sieves, CH_2Cl_2, -20 °C, 48 hr; (iv) Bu_2SnO, TsCl, TBAB, PhH.

Scheme 6.6 Asymmetric epoxidation, cyclisation and tosylation

Both tosylates **6.19** and **6.20** were converted to the corresponding epoxides **6.21** and **6.22** by treatment with base. Installation of the unfunctionalised alkyl chain of the acetogenins was carried out by treatment of the epoxides with the cuprate derived from *n*-nonyl magnesium bromide (Scheme 6.7).



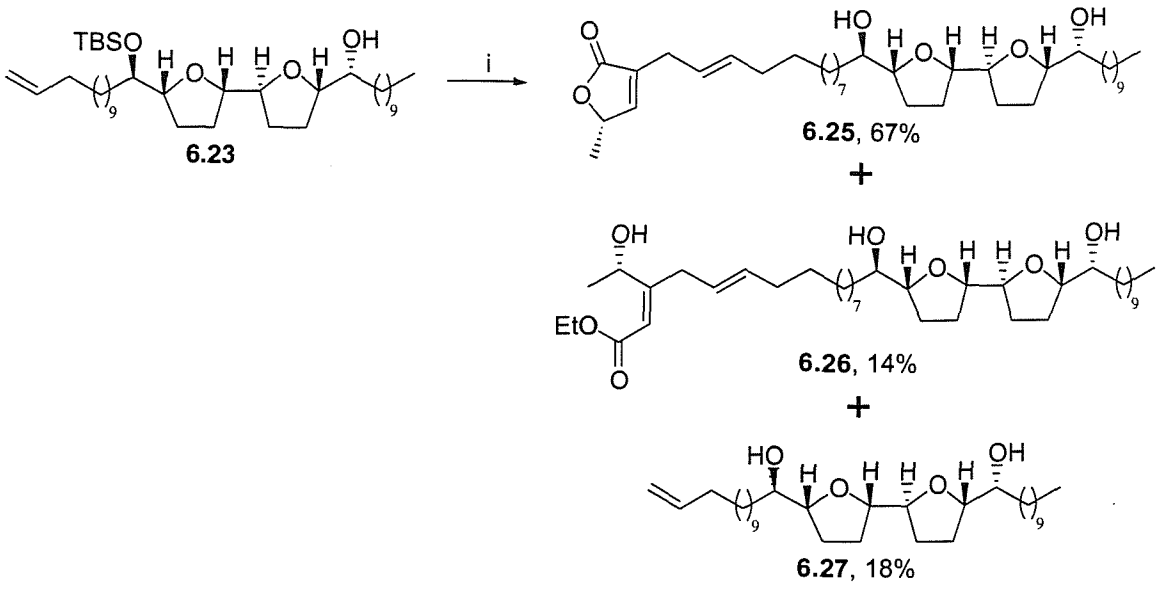
Reagents and Conditions: (i) DBU, CH_2Cl_2, 20 min; (ii) *n*-nonylmagnesiumbromide, CuI, THF, -60 to -50 °C.

Scheme 6.7 Installation of the acetogenin alkyl sidechain

6.5 Installation of the Butenolide and Completion of the Acetogenin Analogues

The chiral butenolide moiety present in all natural acetogenins was installed by the Alder-ene method of Trost *et al*, described previously (Chapter 1.5.5).[94,100,101] This involved the reaction of terminal alkenes **6.23** and **6.24** with non-racemic propargylic alcohol **1.146** and ruthenium catalyst **1.147**. These reactions required the use of 1.4 equivalents of alcohol and 5 mol% catalyst, and were carried out in methanol which was degassed with nitrogen or argon for at least twenty minutes to ensure good yields.

Alkene **6.23** was converted to the desired butenolide **6.25** and hydroxy-ester **6.26** in a ratio of 4.8:1. In both products the silyl ether protecting groups were conveniently cleaved, thus avoiding a separate deprotection step. Alkene **6.27** was also recoved, a result of starting material desilylation (Scheme 6.8).

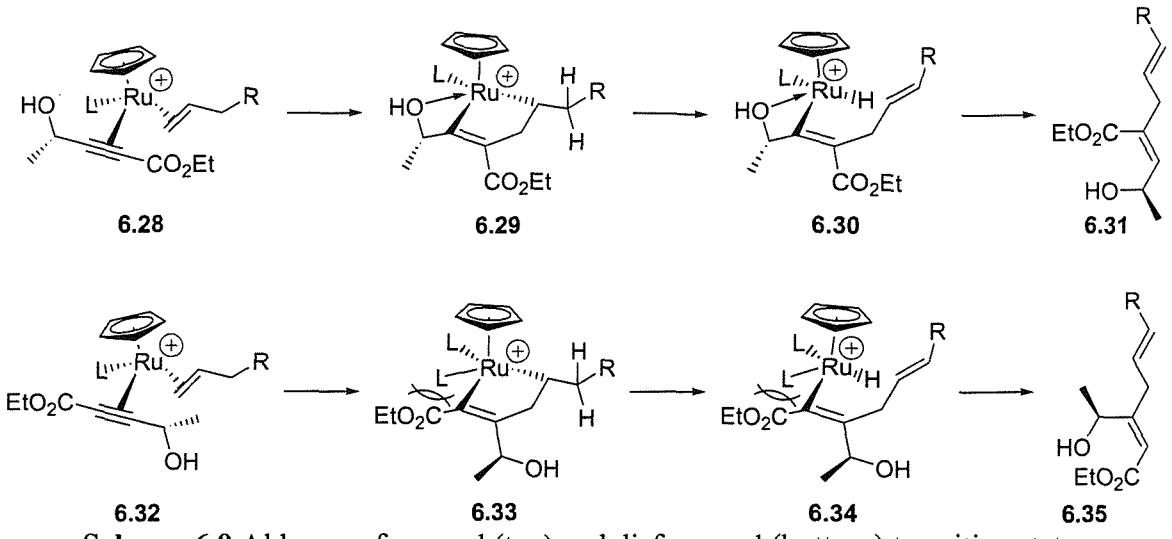


Reagents and Conditions: (i) Propargylic alcohol **1.146**, catalyst **1.147**, MeOH, reflux, 2.5 hr.

Scheme 6.8 Formation of the butenolide of the *cis, trans, bis*-THF acetogenin analogue

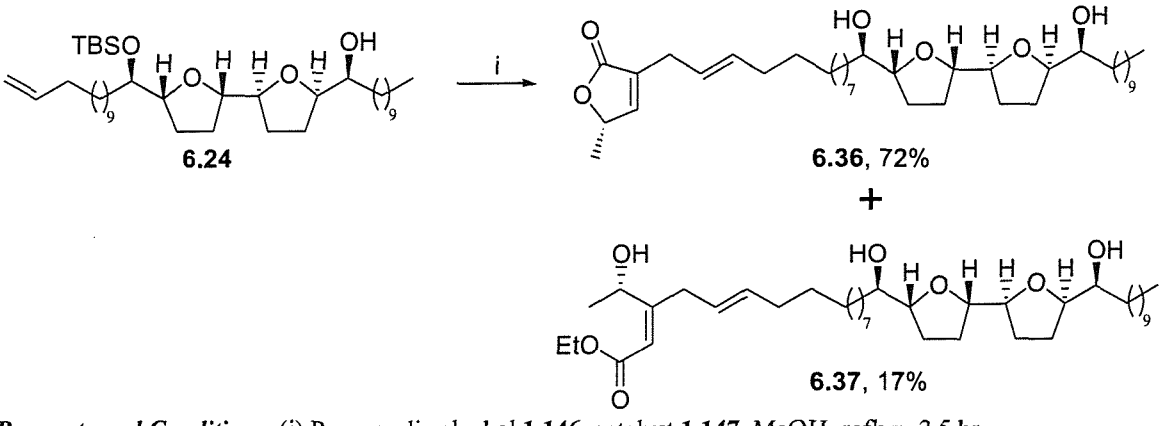
The reaction proceeds by coordination of the alkyne and alkene by the metal followed by metallacycle formation. The formation of the minor hydroxy-ester product is due to the passage of material through the disfavoured, sterically hindered transition state **6.33**, in which the ethyl ester and ruthenium ligand are in close proximity. In the corresponding transition state **6.29**, which leads to the desired butenolide product, a ligand is thought to be displaced by the hydroxy group of the substrate, thus stabilising the complex.

The metallacycle collapses *via* β-hydride elimination followed by reductive elimination, giving hydroxy-esters **6.31** and **6.35** (Scheme 6.9). Fortunately, subsequent lactonisation occured only in the case of **6.31**, affording the desired butenolide. This allowed chromatographic separation, which may not have been possible if both hydroxy-esters had undergone cyclisation.



Scheme 6.9 Alder-ene favoured (top) and disfavoured (bottom) transition states

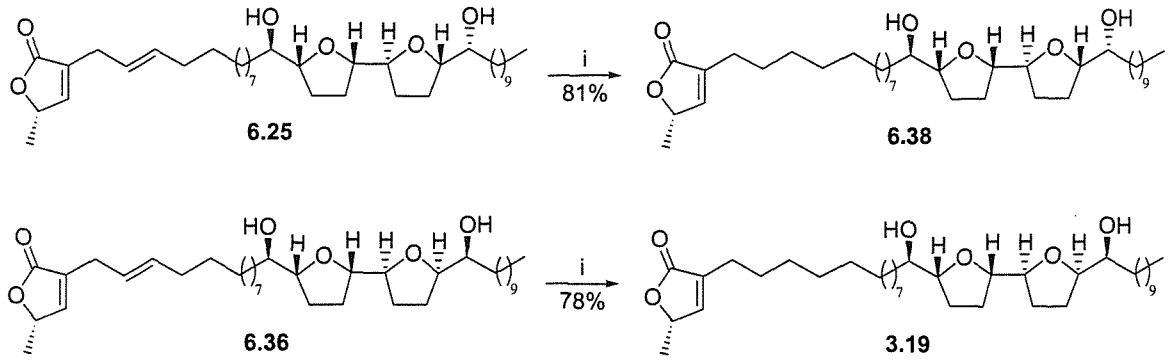
Alkene **6.24** was converted to the desired butenolide **6.36** and hydroxy-ester **6.37** in a ratio of 3.8:1 (Scheme 6.10). As was the case for the *cis, trans, bis*-THF example, the silyl ether was cleaved from both products.



Reagents and Conditions: (i) Propargylic alcohol **1.146**, catalyst **1.147**, MeOH, reflux, 2.5 hr.

Scheme 6.10 Formation of the butenolide of the *cis-cis-bis*-THF acetogenin analogue

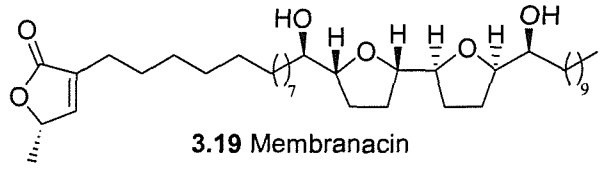
To complete the synthesis of the targeted acetogenin analogues, selective reduction of the isolated alkene in the presence of the butenolide was required. This was achieved for both **6.25** and **6.36** by diimide reduction, using ten equivalents of toluenesulfonyl hydrazide and sodium acetate in a mixture of tetrahydrofuran and water. No reduction of the conjugated double bond was noted in either case. Reduction of **6.36** afforded membranacin **3.19**. Reduction of **6.25** afforded membranacin epimer **6.38** (Scheme 6.11).



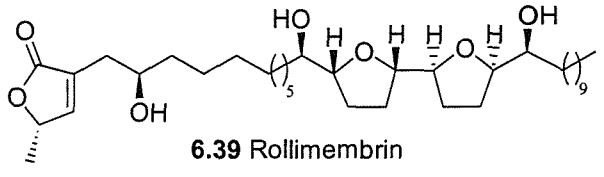
Reagents and Conditions: (i) $TsNHNH_2$, NaOAc, THF, H_2O, reflux, 20 hr.

Scheme 6.11 Diimide reduction and completion of acetogenin analogues

Both proton and carbon NMR data for the THF core portion of membranacin **3.19** was in close agreement with that for rollimembrin **6.39**, an analogue of membranacin with a shorter, hydroxylated alkyl chain on the butenolide side of the THF core (Figure 6.1). The distance of this hydroxyl group would not be expected to interfere with the chemical shifts of protons in the THF region.



3.19 Membranacin



6.39 Rollimembrin

Figure 6.1

6.6 Conclusions

The synthesis of a versatile epoxy-THF-lactone intermediate, and conversion to the useful α/β-unsaturated ester **6.12** was carried out. This ester did not react under the conditions of the Kennedy cyclisation, however a change in strategy and the use of the Sharpless asymmetric epoxidation reaction allowed entry to both a *cis*, *trans*, *bis*-THF and a *cis*, *cis*, *bis*-THF product. Elaboration of these products allowed the synthesis of the natural product membranacin and an epimer thereof.

Chapter 7

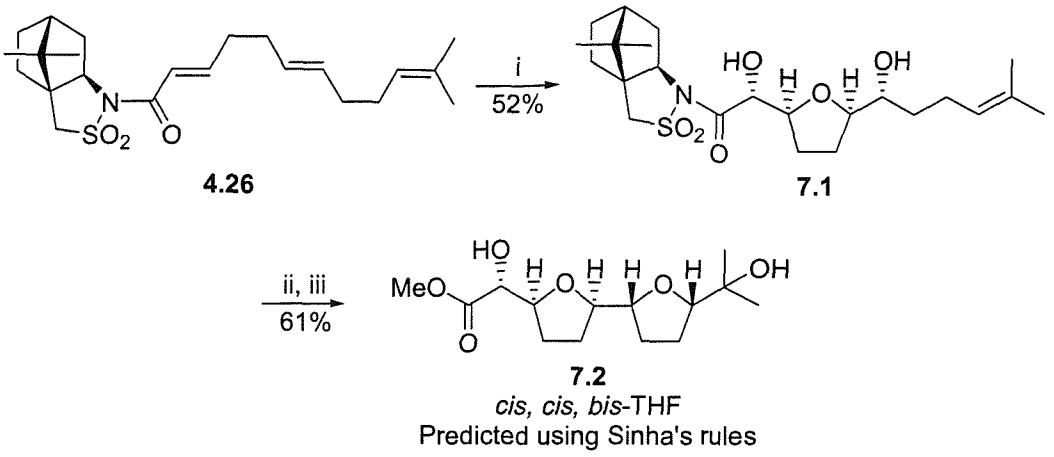
Other Approaches to THF Fragments

This chapter describes two short projects which were investigated to complement the work summarised in chapter six.

7.1 A Kennedy Cyclisation Experiment

In an attempt at combining the permanganate oxidative cyclisation of 1,5-dienes with Kennedy's rhenium cyclisation methodology, we attempted to arrest the reaction of 1,5,9-trienedioate **4.26** after the permanganate cyclisation of the 1,5-dienoate part. This would leave the trisubstituted double bond intact and provide **7.1**, a substrate for the Kennedy cyclisation. The THF oxygen atom and the hydroxy group which would participate in the next cyclisation have a *threo* relationship, and according to the rules proposed by Sinha and Keinan a Kennedy cyclisation should result in the formation of a second, *cis*-THF ring.

Oxidation of triene **4.26** using 1.8 equivalents of potassium permanganate in the 3:2 acetone / acetic acid solvent system afforded as the major product THF diol **7.1** in 52% yield. This was treated with trifluoroacetyl perrhenate at room temperature. Purification of the crude material on silica gel, eluting with methylene chloride / methanol 99:1, afforded transesterified product **7.2** (Scheme 7.1). Although the structure of the product was confirmed, we were unfortunately unable to confirm the stereochemistry of the cyclisation using the NMR data, and the material proved not to be crystalline. Insufficient time was available for further investigation of the stereochemistry of this product due to focus on the *bis*-THF acetogenin compounds, however other members of the group are currently undertaking work to clarify this issue.



***Reagents and Conditions*:** (i) $KMnO_4$ (1.8 eq.), 5mol% Adogen-464, Me_2CO/AcOH 3:2, CH_2Cl_2, -25 °C; (ii) Re_2O_7, TFAA, CH_2Cl_2; (iii) SiO_2, MeOH, CH_2Cl_2.

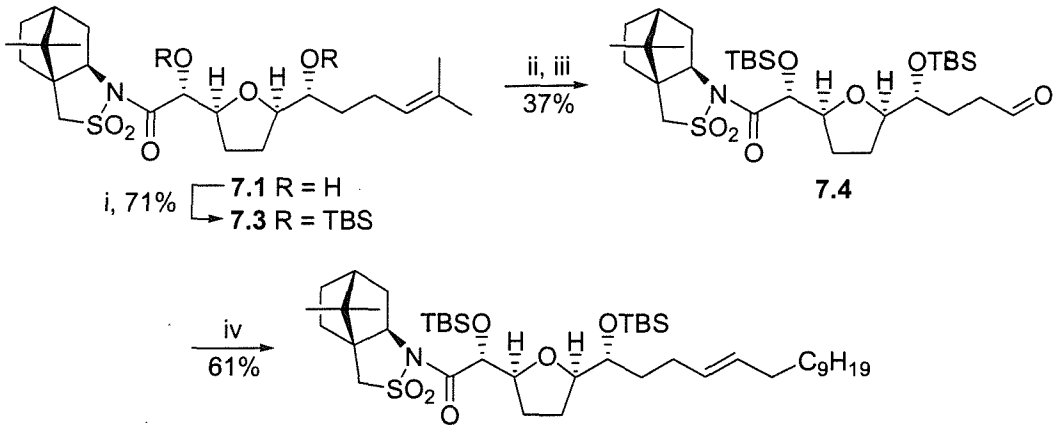
Scheme 7.1 Predicted outcome of a permanganate / rhenium approach to a *bis*-THF

7.2 An Alternative Approach to THF Analogues

To demonstate the versatility of THF-diol fragments, it was proposed that the trisubstituted double bond of THF-diol **7.1** could be cleaved to the aldehyde, providing an intermediate which would allow the addition of alkyl chains of various lengths by olefination chemistry. Reductive removal of the sultam and conversion to the epoxide would allow for the addition of alkyl chains at the other side of the molecule by copper-promoted Grignard chemistry.

Thus, protection of **7.1** as *bis*-silyl ether **7.3** and treatment with osmium tetroxide followed by sodium periodate cleavage afforded aldehyde **7.4**. This aldehyde underwent Kocienski-Julia olefination with sulfone **7.9**,[95,231,232] affording predominantly *trans*-alkene **7.5** (Scheme 7.2). The sulfone was synthesised from 1-*t*-butyl-1*H*-tetrazolyl-5-thiol **7.7**, which itself was synthesised from *t*-butyl*iso*thiocyanate **7.6** and sodium azide (Scheme 7.3).[233]

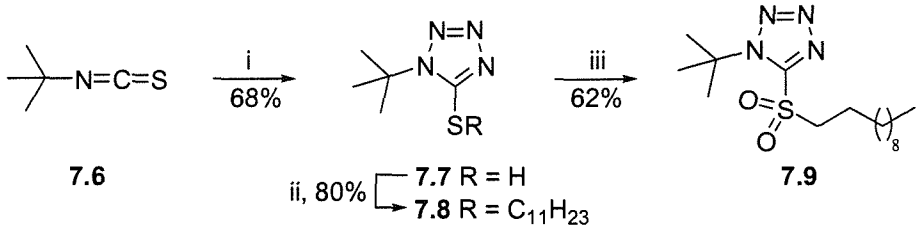
Although this work was pursued no further, it illustrates that, with optimisation of the alkene cleavage step, it is another potential route to acetogenin analogues.



7.5

***Reagents and Conditions*:** (i) TBSCl, imidazole, CH_2Cl_2; (ii) OsO_4, NMO, CH_2Cl_2; (iii) $NaIO_4$, CH_2Cl_2; (iv) Pre-mixed **7.9**, NaHMDS, DME.

Scheme 7.2 Alkene cleavage and olefination



7.6 **7.9**

***Reagents and Conditions*:** (i) NaN_3, 2-propanol, H_2O, reflux; (ii) KOH, 1-undecyl bromide, EtOH; (iii) AcOOH, CH_2Cl_2.

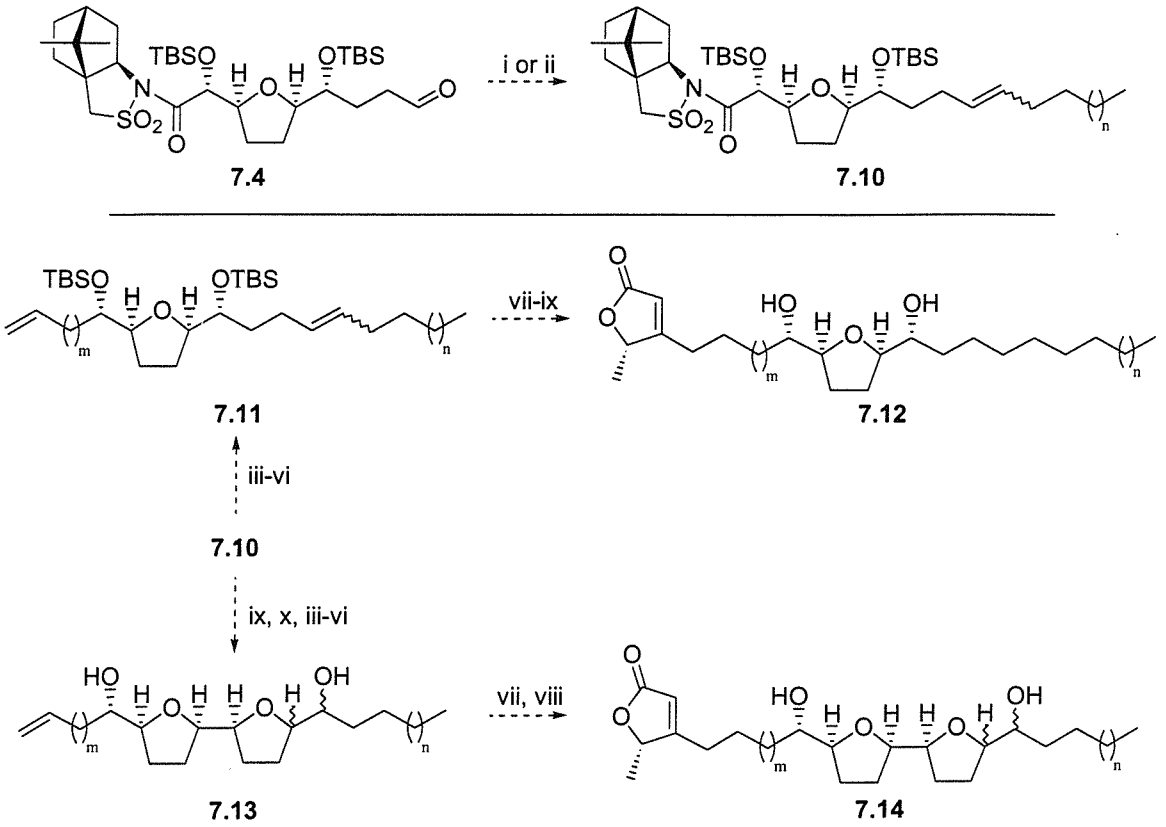
Scheme 7.3 Synthesis of the Kocienski-Julia olefination sulfone partner

7.3 Conclusions

Selective permanganate oxidative cyclisation of a 1,5-diene was carried out in the presence of an isolated, trisubstituted double bond. The product underwent Kennedy cyclisation affording a *bis*-THF product, although unambiguous assignment of the relative stereochemistry of the THF portion was not achieved due to time constraints.

The product of the permanganate reaction was also shown to be a versatile synthetic intermediate for acetogenin analogue synthesis. Aldehyde **7.4** might be used in the synthesis of *mono*- or *bis*-THF acetogenins. Installation of one sidechain by Kocienski-Julia olefination was demonstrated, affording the *trans*-alkene. Wittig olefination would install

the sidechain with *cis*-alkene geometry. Reduction of this alkene would provide access to *mono*-THF acetogenins, and oxidative cyclisation using transition metal oxidants would install a second THF ring. The relative stereochemistry of this second ring would be influenced by the choice of oxidant and double bond geometry. The butenolide bearing sidechain would then be installed as described previously (Scheme 7.4).



Reagents and Conditions: (i) Kocienski-Julia olefination for *trans* alkene; (ii) Wittig olefination for *cis*-alkene; (iii) $NaBH_4$, THF; (iv) Bu_2SnO, TsCl, PhH; (v) DBU, CH_2Cl_2; (vi) Alkylmagnesiumbromide, CuI, -60 to -50 °C; (vii) Propargylic alcohol **1.146**, catalyst **1.147**, MeOH, reflux, 2.5 hr; (viii) $TsNHNH_2$, NaOAc, THF, H_2O, reflux, 20 hr; (ix) TBAF, THF; (x) Oxidative cyclisation by transition metal oxidant.

Scheme 7.4

Chapter 8
Concluding Remarks

The following chapter summarises the key features of our approach to *bis*-2,5-disubstituted THF compounds and their use as synthetic precursors to the *Annonaceous* acetogenin membranacin and an unnatural epimer. The opportunities for future work in this area will also be discussed.

8.1 Our Approach Summarised

Initial studies to compare Corey's hydroxysulfone and Oppolzer's sultam chiral auxiliaries confirmed the sultam to be more effective at directing the oxidation of 1,5-dienes by potassium permanganate. The sultam directed the oxidative cyclisation of 1,5,9-trienes, installing four new stereocentres, affording useful, optically enriched THF-lactone intermediates **4.28** and **4.45** in very good yield. The use of a cheap and relatively environmentally friendly reagent such as permanganate is advantageous in comparison to other transition-metal based approaches to this synthetic transformation.

Removal of the sultam *via* a borane-directed borohydride reduction and processing of the resulting diol afforded versatile epoxide **6.7**. This intermediate was used in the synthesis of acetogenin membranacin **3.19** and its epimer **6.38** (Figure 8.1). Installation of the second THF ring of each example was achieved using the Sharpless asymmetric epoxidation reaction, a procedure demonstrated previously by Sinha *et al.*[132] The butenolide moiety was installed *via* Trost's Alder-ene reaction.[101] The use of epoxide **6.7** provides access to libraries of acetogenin analogues for structure-activity studies, as two alkyl chains of any length may be installed using copper-mediated Grignard chemistry.

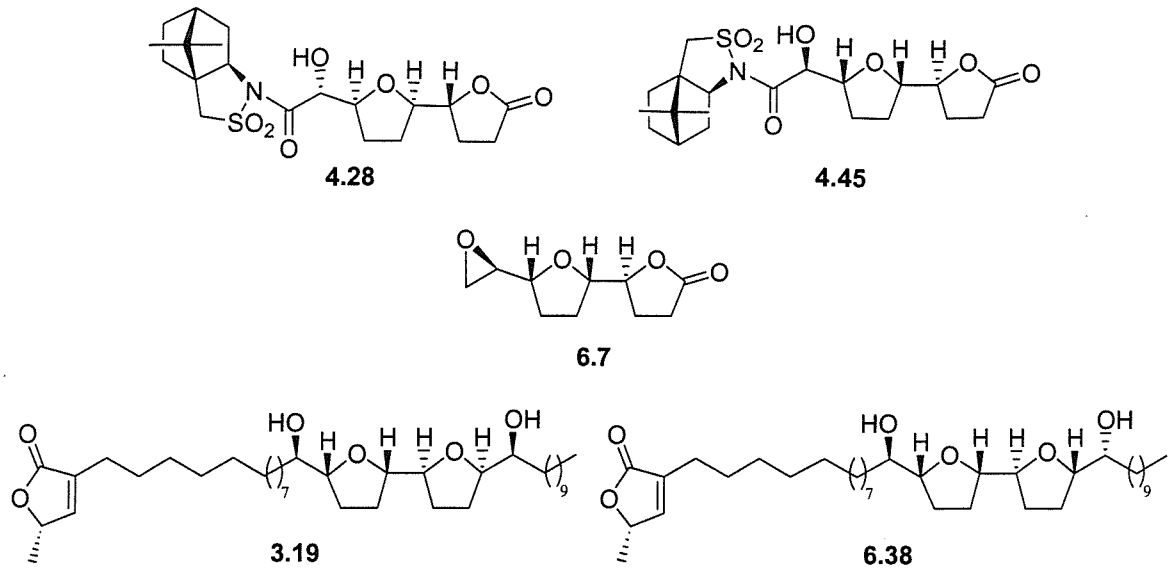
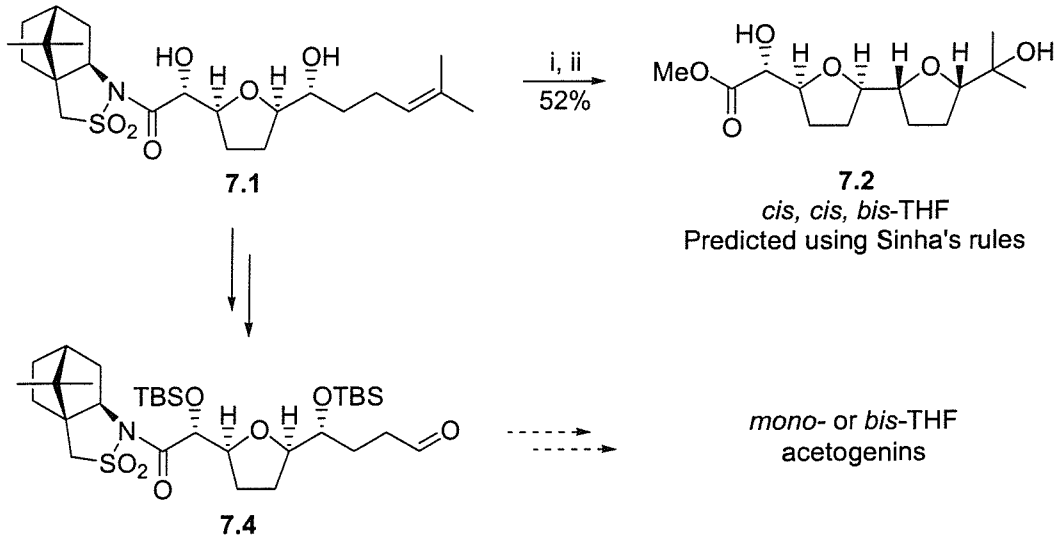


Figure 8.1

The selective oxidation of two double bonds of a 1,5,9-triene was also demonstrated. The product **7.1** was shown to be a substrate for Kennedy's perrhenate cyclisation, and also underwent oxidative cleavage to aldehyde **7.4**, a potential precursor to both *mono*- and *bis*-THF acetogenins (Scheme 8.1).

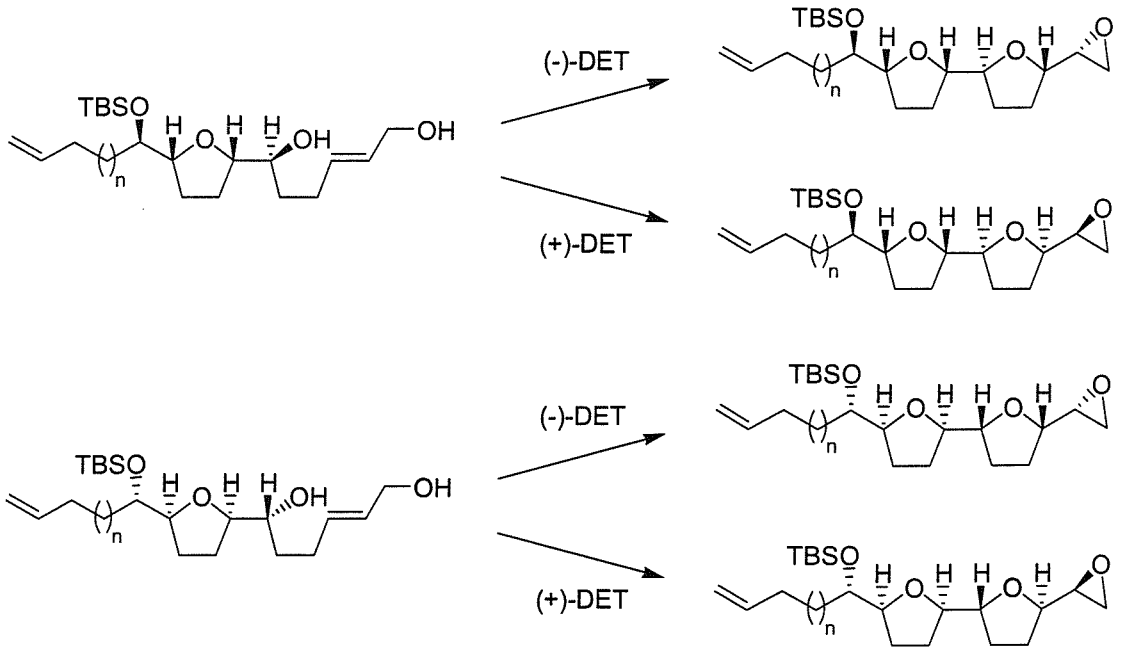


Reagents and Conditions: (i) Re_2O_7, TFAA, CH_2Cl_2; (ii) SiO_2, MeOH, CH_2Cl_2.

Scheme 8.1

8.2 Further Work

The methodology established in chapters four and six may be used to synthesise acetogenin analogues from symmetrical 1,5,9-trienes such as **4.43** and **4.44**. By using the two enantiomers of the sultam auxiliary for the permanganate cyclisation, in combination with the two enantiomers of diethyl tartrate in the Sharpless asymmetric epoxidation, four discrete *bis*-THF core fragments may be accessed (Scheme 8.2).



Scheme 8.2 Four *bis*-THF core fragments

Further variety may be introduced by the use of trienes with different combinations of double bond geometries. The scope for the introduction of alkyl sidechains *via* the copper-mediated Grignard reaction allows the possibility for library synthesis of many structural analogues, which could be used in SAR studies.

The selective oxidation of a 1,5,9-triene, leaving one double bond intact, also provides the potential for tandem oxidation sequences involving the use of permanganate followed by perrhenate.

The route which was studied in section 7.2 might also be investigated as a method of acetogenin analogue synthesis.

Chapter 9

Experimental Section

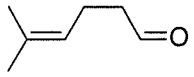
9.1 General Experimental

All air and / or moisture sensitive reactions were carried out under an inert atmosphere in oven dried glassware. Methylene chloride was dried by distillation from CaH_2, and tetrahydrofuran was distilled from sodium / benzophenone prior to use. Brine refers to a saturated aqueous solution of NaCl. All other solvents and reagents were purified, if required, by standard methods.[234] Reactions were monitored by TLC using aluminium-backed plates coated with silica gel 60 containing a fluorescence indicator active at 254 nm. The plates were visualised under UV light (254 nm) and by staining with cerium sulfate / ammonium molybdate in 2M $H_2SO_{4(aq)}$, 10% aqueous $KMnO_4$ or 20% phosphomolybdic acid in ethanol. Flash column chromatography was carried out using 40-63 μm silica gel (Merck). Column dimensions are quoted in mm (width x height). In the case of known compounds, the CAS registry number is present in square brackets.

^1H and ^{13}C NMR spectra were recorded on a Bruker AC300 or Bruker DPX400 spectrometer in deuterated chloroform with chloroform as the internal standard (^1H δ 7.26 ppm, ^{13}C δ 77.2 ppm. IR spectra are reported in wavenumbers (cm^{-1}) and were collected on a Nicolet Impact 400 instrument as neat liquids or solids. Melting points were obtained in open-ended capillary tubes using a Gallenkamp Electrothermal apparatus, and are uncorrected. Low resolution mass spectra were obtained on a Fisons VG platform single quadrupole mass spectrometer in either chemical ionisation or electron impact ionisation mode, or on a Micromass platform mass analyser with an electrospray ion source.

9.2 Experimental Details

5-Methyl-4-hexenal [764-32-9] (4.2)



4.2
$C_7H_{12}O$
112.16

The title compound was prepared according to the method of Johnson *et al.*[129] Thus, ethyl vinyl ether (100 mL, 956 mmol), 2-methyl-3-buten-1-ol (50 mL, 478 mmol) and phosphoric acid (0.5 mL) were heated at reflux under an atmosphere of N_2 at 120 °C in a thick-walled glass flask behind a blast shield for 16 hr, then allowed to cool to room temperature. The solution was diluted with acetone (150 mL) and 2N $HCl_{(aq)}$ (150 mL), and stirred at room temperature for 1 hr. The mixture was extracted with Et_2O (3 x 100 mL) and the organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by distillation (16 mbar, 52-56 °C) afforded the title compound **4.2** (27.4 g, 244 mmol, 51%) as a colourless oil. R_f = 0.30 (40% CH_2Cl_2/hexane).

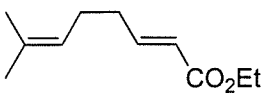
^{1}H NMR (300 MHz, $CDCl_3$) δ_H 9.76 (1H, s, **CH**O), 5.08 (1H, m, **CH**=C(CH_3)$_2$), 2.45 (2H, t, J = 7.4 Hz, **CH$_2$**CHO), 2.31 (2H, app. q, J = 7.4 Hz, **CH$_2$**CH$_2$CHO), 1.69 (3H, s, **CH$_3$**), 1.61 (3H, s, **CH$_3$**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ_C 202.9 (s, **C**HO), 133.3 (s, CH=**C**(CH_3)$_2$), 122.3 (d, **C**H=C(CH_3)$_2$), 44.1 (t, **CH$_2$**CHO), 25.8 (q, **CH$_3$**), 21.0 (t, **CH$_2$**CH$_2$CHO), 17.8 (q, **CH$_3$**) ppm.

FT-IR (film) ν_{max} 2969(m), 2915(m), 2853(w), 2720(w), 1725(s), 1445(m), 1410(w), 1377(m), 1111(w), 1058(m), 983(w), 828(m) cm^{-1}.

LRMS (CI) *m/z* 112 ([M+NH_4-H_2O]$^+$, 54%), 130 ([M+NH_4]$^+$, 13%), 94 ([M-H_2O]$^+$, 100%), 81 ([M-CH_2CHO]$^+$, 10%), 69 ([CH_2CH=C(CH_3)$_2$]$^+$, 46%), 58 ([CH_2CH_2CHO+H]$^+$, 22%) Da.

Ethyl-(*2E*)-7-methyl-2,6-octadienoate [74063-60-8] (4.3)



4.3
$C_{11}H_{18}O_2$
182.26

To a stirred solution of aldehyde **4.2** (27.4 g, 244 mmol) in CH_2Cl_2 (350 mL) at room temperature was added (carbethoxymethylene)triphenylphosphorane (85.8 g, 246 mmol), portionwise over a period of 10 min. The mixture was stirred for 14 hr and concentrated *in*

vacuo. The residue was triturated with pentane, and the resulting white solid was removed by filtration. Concentration of the filtrate *in vacuo* and purification of the residue by Kugelrohr bulb-to-bulb distillation (16 mbar, 60 °C) afforded the title compound **4.3** (42.4 g, 233 mmol, 95%) as a colourless oil. $R_f = 0.28$ (30% CH_2Cl_2/hexane).

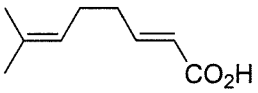
^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.97 (1H, dt, J = 16.2, 6.7 Hz, C**H**=CHCO$_2$Et), 5.82 (1H, dt, J = 16.2, 1.5 Hz, CH=C**H**CO$_2$Et), 5.10 (1H, m, C**H**=C(CH$_3$)$_2$), 4.18 (2H, q, J = 7.1 Hz, C**H**$_2$CH$_3$), 2.31-2.09 (4H, m, CHC**H**$_2$C**H**$_2$CH), 1.70 (3H, s, C**H**$_3$), 1.62 (3H, s, C**H**$_3$), 1.28 (3H, t, J = 7.1 Hz, CH$_2$C**H**$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ_C 166.9 (s, **C**O$_2$Et), 149.1 (d, **C**H=CHCO$_2$Et), 132.9 (s, CH=**C**(CH$_3$)$_2$), 123.0 (d, **C**H=C(CH$_3$)$_2$), 121.5 (d, CH=**C**HCO$_2$Et), 60.3 (t, O**C**H$_2$CH$_3$), 32.6 (t, **C**H$_2$CH=CHCO$_2$Et), 26.7 (t, **C**H$_2$CH$_2$CH=CHCO$_2$Et), 25.8 (q, **C**H$_3$), 17.9 (q, **C**H$_3$), 14.4 (q, OCH$_2$**C**H$_3$) ppm.

FT-IR (film) ν_{max} 2976(w), 2919(w), 1721(s), 1655(m), 1363(w), 1313(m), 1264(m), 1184(m), 1147(m), 1042(m), 976(m) cm^{-1}.

LRMS (CI) *m/z* 183 ([M+H]$^+$, 100%), 200 ([M+NH$_4$]$^+$, 23%), 139 (17%), 109 ([M-CH$_3$CH$_2$CO$_2$]$^+$, 32%), 81 ([M-CH$_2$CHO]$^+$, 10%), 69 ([CH$_2$CH=C(CH$_3$)$_2$]$^+$, 20%) Da.

(*2E*)-7-Methyl-2,6-octadienoic acid [84637-63-8] (4.4)



4.4
$C_9H_{14}O_2$
154.21

A solution of ester **4.3** (3.00 g, 16.5 mmol), NaOH (3.58 g, 89.5 mmol) and $NaHCO_3$ (0.69 g, 8.2 mmol) in MeOH (19 mL) and water (66 mL) was heated at reflux for 2 hr, allowed to cool to 0 °C, acidified with 2N $HCl_{(aq)}$ (10 mL) and extracted with Et_2O (3 x 80 mL). The combined organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to an oil which was purified by Kugelrohr bulb-to-bulb distillation (0.5 mbar, 90 °C) affording the title compound **4.4** (2.45 g, 16.2 mmol, 98%) as a colourless oil. R_f = 0.31 (30% EtOAc/hexane).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 11.44 (1H, br s, CO$_2$**H**), 7.10 (1H, dt, J = 15.4, 6.6 Hz, C**H**=CHCO$_2$H), 5.84 (1H, dt, J = 15.4, 1.5 Hz,

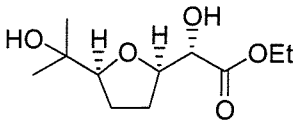
CH=C**H**CO_2H), 5.11 (1H, m, C**H**=C(CH_3)$_2$), 2.28 (2H, app. q, J = 6.6 Hz, C**H**$_2$CH=CHCO_2H), 2.17 (2H, app. q, J = 6.6 Hz, (C**H**$_2$CH=C(CH_3)$_2$), 1.71 (3H, s, C**H**$_3$), 1.61 (3H, s, C**H**$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ_C 172.4 (s, **C**O_2H), 152.2 (d, **C**H=CHCO_2H), 133.1 (s, CH=**C**(CH_3)$_2$), 122.8 (d, **C**H=C(CH_3)$_2$), 120.9 (d, CH=**C**HCO_2H), 32.7 (t, **C**H_2CH=CHCO_2H), 26.6 (t, **C**H_2CH=C(CH_3)$_2$), 25.8 (q, **C**H_3), 17.9 (q, **C**H_3) ppm.

FT-IR (film) ν_{max} 2971(w), 2919(w), 1696(s), 1650(m), 1420(m), 1287(m), 1218(m), 975(m), 935(m) cm^{-1}.

LRMS (CI) *m/z* 155 ([M+H]$^+$, 42%), 172 ([M+NH_4]$^+$, 32%), 139 ([M-H_3C]$^+$, 100%), 109 ([M-CO_2H]$^+$, 24%), 69 ([(H_3C)$_2$C=CHCH_2]$^+$, 26%) Da.

***Rac*-Ethyl-2-hydroxy-2-[5-(1-hydroxy-1-methylethyl)tetrahydro-2-furanyl]acetate (4.5)**



4.5
$C_{11}H_{20}O_5$
232.28

To a solution of ester **4.3** (500 mg, 2.70 mmol) in acetone (27 mL) with phosphate buffer (0.067M $KH_2PO_{4(aq)}$ / 0.067M $Na_2HPO_{4(aq)}$ 4:1, 1.8 mL) at –25 °C was added a mixture of 0.4M $KMnO_{4(aq)}$ (13.7 mL, 5.50 mmol) and AcOH (0.46 mL, 7.70 mmol) *via* dropping funnel over 10 min. The reaction was stirred at –25 °C for 5 min, poured onto ice (3 mL) and quenched by the dropwise addition of a saturated aqueous solution of $Na_2S_2O_5$ (40 mL). The solution was extracted with Et_2O (40 mL), then the aqueous phase was saturated with $NaCl_{(s)}$ and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phase was dried ($MgSO_4$) and concentrated *in vacuo*, and the residue was purified by flash column chromatography (silica gel 10 x 60 mm, 60% EtOAc/hexane) affording the title compound **4.5** (389 mg, 1.70 mmol, 62%) as a white solid. R_f = 0.21 (60% EtOAc/hexane).

m. p. 44-45 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.39 (1H, ddd, J = 7.5, 7.1, 2.3 Hz, C**H**CHOHCO_2Et), 4.28 (2H, q, J = 7.0 Hz, OC**H**$_2$CH_3), 4.10 (1H, d, J = 2.3 Hz, C**H**OHCO_2Et), 3.74 (1H, dd, J = 7.5, 7.0 Hz, C**H**COH(CH_3)$_2$), 3.15 (2H, br s, 2 x CHO**H**), 2.19-1.77 (4H, m, C**H**$_2$C**H**$_2$), 1.30 (3H, t, J = 7.0 Hz, OCH_2C**H**$_3$), 1.25 (3H, s, C**H**$_3$), 1.10 (3H, s, C**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 173.5 (s, **C**O_2Et), 86.7 (d, **C**HCOH$(CH_3)_2$) 80.0 (d, **C**HCHOHCO_2Et), 73.9 (d, **C**HOHCO_2Et), 72.0 (s, **C**OH$(CH_3)_2$), 61.8 (t, O**C**H_2CH$_3$), 28.2 (t, **C**H_2), 28.0 (q, **C**H_3), 26.3 (t, **C**H_2), 25.2 (q, **C**H_3), 14.3 (q, OCH_2**C**H_3) ppm.

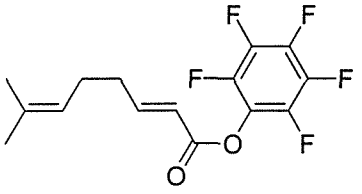
FT-IR (solid) ν_{max} 3452(w), 3329(w), 2976(w), 2929(w), 2868(w), 1737(s), 1475(w), 1445(w), 1388(w), 1362(w), 1332(w), 1236(m), 1195(m), 1127(s), 1071(m), 1024(m), 955(m), 723(m) cm^{-1}.

LRMS (ES^+) *m/z* 255 ($[M+Na]^+$, 100%), 250 ($[M+NH_4]^+$, 16%), 487 ($[2M+Na]^+$, 18%) Da.

HRMS (ES^+) $C_{11}H_{20}O_5Na$ Requires 255.1203; Found 255.1203 Da.

Elemental Calc. for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68%; Found: C, 56.85; H, 8.87%.

2,3,4,5,6-Pentafluorophenyl-(2*E*)-7-methyl-2,6-octadienoate (4.6)



4.6
$C_{15}H_{13}F_5O_2$
320.26

To a solution of acid **4.4** (1.28 g, 8.31 mmol) and pentafluorophenol (1.64 g, 8.90 mmol) in dry EtOAc (21 mL) at 0 °C under an atmosphere of N_2 was added DCC (1.84 g, 8.90 mmol) as a single batch. The reaction was allowed to warm to room temperature and stir for 18 hr. The mixture was filtered to remove the insoluble urea, and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (silica gel 35 x 120 mm, 8% EtOAc/hexane) afforded the title compound **4.6** (2.66 g, 8.30 mmol, 100%) as a white solid. R_f = 0.73 (40% EtOAc/hexane).

m.p. 29-30 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.31 (1H, dt, *J* = 15.4, 6.6 Hz, **CH**=CHCO_2Ar), 6.07 (1H, dt, *J* = 15.4, 1.5 Hz, CH=**CH**CO_2Ar), 5.18-5.09 (1H, m, **CH**=C$(CH_3)_2$), 2.43-2.32 (2H, m, **C**H_2CH=CHCO_2Ar), 2.29-2.18 (2H, m, **C**H_2CH=C$(CH_3)_2$), 1.73 (3H, s, **C**H_3), 1.63 (3H, s, **C**H_3) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ_C 162.2 (**C**O_2Ar), 155.2 (d, **C**H=CHCO_2Ar), 145.0-126.0 (m, 5 x F-coupled Ar**C**), 133.6 (s, CH=**C**$(CH_3)_2$), 122.5

(d, CH=**C**HCO$_2$Ar), 118.2 (d, **C**H=C(CH$_3$)$_2$), 33.1 (t, **C**H$_2$CH=CHCO$_2$Ar), 26.4 (t, **C**H$_2$CH=C(CH$_3$)$_2$), 25.8 (q, **C**H$_3$), 17.9 (q, **C**H$_3$) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ_F 9.14-8.88 (m), 3.32-3.27 (m), -0.75 to -1.00 (m) ppm.

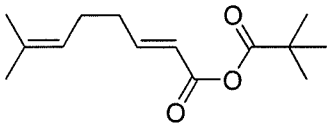
FT-IR (solid) ν_{max} 2974(w), 2917(w), 1765(m), 1654(w), 1519(s), 1290(w), 1213(w), 1145(w), 1119(m), 1074(w), 1024(m), 1004(s) cm^{-1}.

LRMS (EI) *m/z* 320 ([M]$^{\bullet+}$, 6%), 137 ([M-C_6F_5+H]$^{\bullet+}$, 81%), 109 ([M-C_6F_5OCO]$^{\bullet+}$, 18%), 69 ([CH$_2$CH=C(CH$_3$)$_2$]$^{\bullet+}$, 100%) Da.

HRMS (EI) $C_{15}H_{13}O_2F_5$ Requires 320.0836; Found 320.0844 Da

Elemental Calc. for $C_{15}H_{13}O_2F_5$: C, 56.26; H, 4.09%; Found: C, 56.13; H, 4.05%.

1,1-Dimethylpropanoic-(2*E*)-6-methyl-2,6-octadienoic anhydride (4.7)



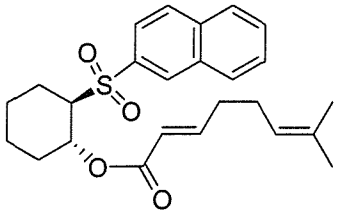
4.7
$C_{14}H_{22}O_3$
238.32

The title compound was prepared according to the method of Otaka *et al.*[193] Thus, to a solution of acid **4.4** (2.75 g, 17.8 mmol) in THF (69 mL) at –78 °C under an atmosphere of N_2 was added Et_3N (2.7 mL, 19.6 mmol) followed by trimethylacetyl chloride (2.4 mL, 19.6 mmol), both dropwise *via* syringe. The solution was stirred at this temperature for 1 hr then at 0 °C for 20 min, and was diluted with water (100 mL) and Et_2O (100 mL). The aqueous phase was extracted with Et_2O (2 x 50 mL) and the combined organic phase was washed with water (30 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 40 x 110 mm, 10% EtOAc/hexane) afforded the title compound **4.7** (4.15 g, 17.4 mmol, 98%) as a colourless oil. R_f = 0.68 (30% Et_2O/hexane).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.09 (1H, dt, *J* = 15.5, 6.6 Hz, C**H**=CHCO$_2$), 5.87 (1H, dt, *J* = 15.5, 1.5 Hz, CH=C**H**CO$_2$), 5.10 (1H, m, C**H**=C(CH$_3$)$_2$), 2.30 (2H, m, C**H**$_2$CH=C(CH$_3$)$_2$), 2.18 (2H, td, *J* = 8.1, 6.6 Hz, C**H**$_2$CH=CHCO$_2$), 1.70 (3H, s, C**H**$_3$), 1.61 (3H, s, C**H**$_3$), 1.39 (9H, s, CH=C(C**H**$_3$)$_2$) ppm.

^{13}C NMR	(75 MHz, $CDCl_3$) δ_C 174.3 (s, $CO_2COC(CH_3)_3$), 166.9 (s, $CO_2COC(CH_3)_3$), 153.9 (d, $CH=CHCO_2$), 133.4 (s, $CH=C(CH_3)_2$), 122.5 (d, $CH=C(CH_3)_2$), 120.9 (d, $CH_2CH=CHCO_2$), 40.1 (s, $COC(CH_3)_3$), 32.8 (t, $CH_2CH=CHCO_2$), 26.7 (q, $C(CH_3)_3$), 26.5 (t, $CH_2CH=C(CH_3)_2$) 25.8 (q, CH_3), 17.9 (q, CH_3), ppm.
FT-IR	(film) ν_{max} 2971(w), 2930(w), 2914(w), 1801(s), 1732(s), 1639(m), 1481(m), 1365(w), 1214(m), 1050(m), 1009(m) cm^{-1}.
LRMS	(CI) *m/z* 172 (5%), 154 (27%), 137 (100%), 95 (32%), 81 (16%), 69 ($[CH_2CH=C(CH_3)_2]^+$, 69%) Da.

(1*R*, 2*R*)-2-(2-Naphthylsulfonyl)cyclohexyl-(2*E*)-7-methyl-2,6-octadienoate (4.8)



4.8
$C_{25}H_{30}O_4S$
426.56

***Via* the mixed anhydride**

A solution of (-)-(1*R*, 2*R*)-2-(2-Naphthylsulfonyl)-1-cyclohexanol **3.15** (819 mg, 2.80 mmol) in THF (3.4 mL) at –78 °C under an atmosphere of N_2 was treated with a 60% suspension of sodium hydride in mineral oil (113 mg, 2.80 mmol). The mixture was stirred at this temperature for 10 min, at –30 °C for 10 min, and at room temperature for a further 10 min. The solution was then added dropwise *via* syringe to a solution of anhydride **4.7** (560 mg, 2.30 mmol) in THF (5.3 mL) at –78 °C. The reaction was stirred for 1 hr, warmed to 0 °C and quenched by the addition of a saturated aqueous solution of NH_4Cl (15 mL). The mixture was extracted with Et_2O (2 x 20 mL) and CH_2Cl_2 (3 x 30 mL), and the combined organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (10 mL) and brine (20 mL), then dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (silica gel 20 x 100 mm, 20-40% EtOAc/hexane) afforded the title compound **4.8** (543 mg, 1.27 mmol, 55%) as a colourless oil. R_f = 0.60 (60% EtOAc/hexane).

***Via* the pentafluorophenyl ester**

To a solution of (-)-(1*R*, 2*R*)-2-(2-Naphthylsulfonyl)-1-cyclohexanol 3.15 (725 mg, 2.50 mmol) in THF (10 mL) at –78 °C under an atmosphere of N_2 was added a 1.12M solution of

n-BuLi in hexanes (2.23 mL, 2.50 mmol). The solution was stirred for 30 min and a solution of pentafluorophenyl ester **4.6** (800 mg, 2.50 mmol) in THF (5 mL) was added via syringe. The reaction was allowed to warm to room temperature and was stirred for 16 hr, then was quenched by the addition of a saturated aqueous solution of NH_4Cl (15 mL) and extracted with Et_2O (3 x 30 mL). The combined organic phase was washed with water (30 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (silica gel 25 x 80 mm, 20-40% EtOAc/hexane) afforded the title compound **4.8** (180 mg, 0.42 mmol, 17%) as a colourless oil. R_f = 0.49 (40% EtOAc/hexane).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.40 (1H, d, J = 2.0 Hz, Ar**H**), 7.89-7.98 (3H, m, 3 x Ar**H**), 7.82 (1H, dd, J = 8.5, 2.0 Hz, Ar**H**), 7.64 (1H, ddd, J = 8.3, 7.0, 1.5 Hz Ar**H**), 7.60 (1H, ddd, J = 8.3, 6.8, 1.3 Hz Ar**H**), 6.45 (1H, dt, J = 15.8, 6.3 Hz, C**H**=CHCO$_2$), 5.10 (1H, app. td, J = 10.0, 5.0 Hz, C**H**O$_2$CCH=CH), 5.00-4.91 (2H, m, CH=C**H**CO$_2$ + C**H**=C(CH$_3$)$_2$), 3.42 (1H, ddd, J =12.3, 10.0, 4.0 Hz, C**H**SO$_2$Ar), 2.54-2.46 (1H, m), 2.19-2.11 (1H, m), 1.97-1.90 (1H, m), 1.89-1.67 (6H, m), 1.67 (3H, s, C**H**$_3$), 1.55 (3H, s, C**H**$_3$), 1.42-1.20 (3H, m) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ_C 164.9 (s, **C**O$_2$), 149.7 (d, **C**H=CHCO$_2$), 137.4 (s), 135.3 (s), 132.8 (s), 132.4 (s), 130.1 (d), 129.7 (d), 129.4 (d), 129.2 (d), 128.0 (d), 127.7 (d), 123.3 (d), 122.9 (d), 120.5 (d, CH=C**H**CO$_2$), 70.9 (d, **C**HO$_2$CCH=CH), 65.9 (d, **C**HSO$_2$Ar), 32.2 (t), 31.7 (t), 26.3 (t), 25.8 (q), 24.5 (t), 24.2 (t), 23.5 (t), 17.9 (q) ppm.

FT-IR (film) ν_{max} 3134(w), 3054(w), 2938(m), 2861(w), 1717(s), 1651(m), 1452(m), 1348(m), 1310(s), 1260(m), 1181(m), 1144(s), 1126(s), 1072(m), 1035(m), 854(w), 819(w), 760(w) cm^{-1}.

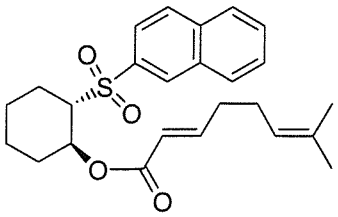
LRMS (ES$^+$) *m/z* 449 ([M+Na]$^+$, 42%), 490 ([M+Na+MeCN]$^+$, 100%), 875 ([2M+Na]$^+$, 68%), 1301 ([3M+Na]$^+$, 45%) Da.

HRMS (ES$^-$) $C_{25}H_{30}O_4SNa$ Requires 449.1757; Found 449.1747 Da.

Elemental Calc. for $C_{25}H_{30}O_4S$: C, 70.39; H, 7.09%; Found: C, 70.04; H, 7.18%.

$[\alpha]^{25}_D$ -35.3 (c. 0.68, $CHCl_3$).

(1*S*, 2*S*)-2-(2-Naphthylsulfonyl)cyclohexyl-(2*E*)-7-methyl-2,6-octadienoate (4.9)



4.8
$C_{25}H_{30}O_4S$
426.56

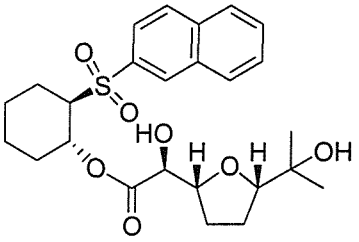
A solution of (+)-(1*S*, 2*S*)-2-(2-Naphthylsulfonyl)-1-cyclohexanol **3.16** (2.01 g, 6.92 mmol) in THF (8 mL) at –78 °C under an atmosphere of N_2 was treated with a 60% suspension of sodium hydride in mineral oil (0.28 g, 6.92 mmol). The mixture was stirred at this temperature for 10 min, then at 0 °C for 15 min and was added dropwise *via* syringe to a solution of anhydride **4.7** (1.50 g, 6.29 mmol) in THF (13 mL) at –78 °C. The solution was stirred for 1 hr, warmed to 0 °C and stirred for a further 1 hr, then quenched by the addition of a saturated aqueous solution of NH_4Cl (15 mL). The mixture was extracted with CH_2Cl_2 (3 x 80 mL), and the combined organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (10 mL) and brine (20 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 20 x 100 mm, 20-40% EtOAc/hexane) afforded the title compound **4.9** (1.40 g, 3.27 mmol, 52%) as a colourless oil. $R_f = 0.57$ (60% EtOAc/hexane).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.40 (1H, d, J = 2.0 Hz Ar**H**), 7.89-7.98 (3H, m, 3 x Ar**H**), 7.82 (1H, dd, J = 8.5, 2.0 Hz, Ar**H**), 7.64 (1H, ddd, J = 8.3, 7.0, 1.5 Hz Ar**H**), 7.60 (1H, ddd, J = 8.3, 6.8, 1.3 Hz Ar**H**), 6.45 (1H, dt, J = 15.8, 6.3 Hz, C**H**=CHCO$_2$), 5.10 (1H, app. td, J = 10.0, 5.0 Hz, C**H**O$_2$CCH=CH), 5.00-4.91 (2H, m, CH=C**H**CO$_2$ + C**H**=C(CH$_3$)$_2$), 3.42 (1H, ddd, J =12.3, 10.0, 4.0 Hz, C**H**SO$_2$Ar), 2.54-2.46 (1H, m), 2.19-2.11 (1H, m), 1.97-1.90 (1H, m), 1.89-1.67 (6H, m), 1.67 (3H, s, C**H**$_3$), 1.55 (3H, s, C**H**$_3$), 1.42-1.20 (3H, m) ppm.

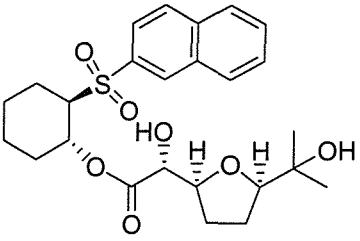
^{13}C NMR (75 MHz, $CDCl_3$) δ_C 164.9 (s, **C**O$_2$), 149.7 (d, **C**H=CHCO$_2$), 137.4 (s), 135.3 (s), 132.8 (s), 132.4 (s), 130.1 (d), 129.7 (d), 129.4 (d), 129.2 (d), 128.0 (d), 127.7 (d), 123.3 (d), 122.9 (d), 120.5 (d, CH=**C**HCO$_2$), 70.9 (d, **C**HO$_2$CCH=CH), 65.9 (d, **C**HSO$_2$Ar), 32.2 (t), 31.7 (t), 26.3 (t), 25.8 (q), 24.5 (t), 24.2 (t), 23.5 (t), 17.9 (q) ppm.

FT-IR	(film) ν_{max} 3130(w), 3054(w), 2937(m), 2861(w), 1717(s), 1651(m), 1452(m), 1348(m), 1310(s), 1260(m), 1181(m), 1144(s), 1126(s), 1072(m), 1035(m), 856(w), 819(w), 760(w) cm^{-1}.
LRMS	(ES^+) *m/z* 449 ($[M+Na]^+$, 32%), 490 ($[M+Na+MeCN]^+$, 100%), 875 ($[2M+Na]^+$, 80%), 1301 ($[3M+Na]^+$, 47%) Da.
HRMS	(ES^+) $C_{25}H_{30}O_4SNa$ Requires 449.1757; Found 449.1746 Da.
Elemental	Calc. for $C_{25}H_{30}O_4S$: C, 70.39; H, 7.09%; Found: C, 79.99; H, 7.02%.
$[\alpha]^{25}_D$	+37.0 (c. 0.81, $CHCl_3$).

(1*R*,2*R*)-2-(2-Naphthylsulfonyl)cyclohexyl-(2*S*)-2-hydroxy-2-[(2*S*,2*R*)-5-(1-hydroxy-1-methylethyl)-tetrahydro-2-furanyl]ethanoate (4.10) and (1*S*,2*S*)-2-(2-Naphthyl-sulfonyl)cyclohexyl-(2*R*)-2-hydroxy-2-[(2*R*,2*S*)-5-(1-hydroxy-1-methylethyl)-tetrahydro-2-furanyl]ethanoate (4.11)



4.10
$C_{25}H_{32}O_7S$
476.58

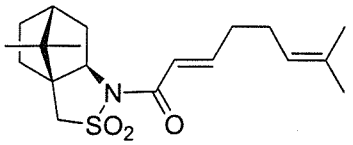


4.11
$C_{25}H_{32}O_7S$
476.58

To a stirred heterogeneous solution of diene **4.9** (300 mg, 0.70 mmol) and phosphate buffer (0.067 M $KH_2PO_{4(aq)}$ / 0.067 M $Na_2HPO_{4(aq)}$ 4:1, 0.49 mL) in acetone (7.0 mL) at –25 °C was added a mixture of 0.4M $KMnO_{4(aq)}$ (3.5 mL, 1.40 mmol) and AcOH (0.11 mL, 11.96 mmol) *via* dropping funnel over 10 min. The reaction was stirred at –25 °C for 10 min and quenched by the addition of an ice-cooled saturated aqueous solution of $Na_2S_2O_5$ (10 mL). The mixture was saturated with NaCl and extracted with Et_2O (30 mL) and CH_2Cl_2 (3 x 50 mL), and the combined organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 20 x 60 mm, 20-65% EtOAc/hexane) afforded an inseparable mixture of the title compounds **4.10** and **4.11** (177 mg, 0.37 mmol, 53%) as a white solid. Proton NMR indicated the presence of an optically enriched mixture of diastereoisomers in a ration of 1.5:1 based on the integral of two distinct signals at 3.65 and 3.79 ppm respectively. Although the diastereoisomers were inseparable by chromatography, the middle fractions, which were used for NMR of the purified mixture, contained a 1:1 mixture. The following data corresponds to that NMR sample. R_f = 0.17 (60% EtOAc/hexane).

m.p.	68-70 °C.
^{1}H NMR	(400 MHz, $CDCl_3$) δ_H 8.45 (1H, s, Ar**H**), 8.04-7.98 (2, m, Ar**H**), 7.94 (1H, d, J = 8.5 Hz, Ar**H**), 7.87 & 7.83 (1H, dd, J = 8.5, 1.8 Hz & dd, J = 8.5, 1.8 Hz, Ar**H**), 7.72-7.61 (2H, m, Ar**H**), 5.13 & 5.03 (1H, td, J = 10.0, 4.8 Hz & td, J = 9.5, 4.5 Hz, C**H**CO_2), 4.53 & 4.10 (1H, ddd, J = 6.8, 4.5, 2.0 Hz & td, J = 4.0, 2.0 Hz, C**H**CHOHCO_2), 4.08 & 3.53 (1H, d, J = 2.0 Hz & d, J = 2.0 Hz, CHC**H**OHCO_2), 3.79 & 3.66 (1H, app. t, J = 6.8 Hz & dd, J = 8.3, 6.3 Hz, C**H**COHC$(CH_3)_2$), 3.45-3.36 (1H, m, C**H**SO_2), 2.48 (2H, br s, 2 x CHO**H**), 2.28-1.58 (8H, m), 1.55-1.36 (2H, m), 1.35-1.18 (2H, m), 1.30 & 1.18 (3H, 2 x s, C$\mathbf{H}_3$), 1.13 & 1.06 (3H, 2 x s, C$\mathbf{H}_3$) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ_C 172.2 (s), 172.1 (s), 135.8 (s), 135.6 (s), 135.4 (s), 134.3 (s), 134.0 (s), 132.3 (s), 131.1 (d), 130.6 (d), 129.7 (d), 129.62 (d), 129.60 (d), 129.5 (d), 128.2 (d), 128.1 (d), 128.0 (d), 127.9 (d), 123.8 (d), 123.5 (d), 86.8 (d), 86.7 (d), 79.7 (d), 79.5 (d), 74.3 (d), 74.0 (d), 72.4 (d), 72.1 (s), 71.84 (d), 71.79 (d), 66.0 (d), 65.5 (d), 31.4 (t), 31.2 (t), 28.3 (q), 28.2 (t), 28.12 (t), 28.06 (q), 26.3 (q), 26.0 (q), 25.4 (t), 25.3 (t), 25.2 (t), 24.5 (t), 23.9 (t), 23.5 (t), 23.1 (t) ppm.
FT-IR	(solid) ν_{max} 3480(br), 3058(w), 2974(m), 2942(m), 2866(m), 1746(m), 1626(w), 1590(w), 1504(w), 1452(m), 1308(s), 1271(m), 1196(m), 1144(s), 1126(s), 1074(m), 1021(m), 953(m), 906(w), 869(w), 821(m), 735(m) cm^{-1}.
LRMS	(ES^+) *m/z* 499 ($[M+Na]^+$, 100%), 975 ($[2M+Na]^+$, 53%) Da.
HRMS	(ES^+) $C_{25}H_{32}O_7SNa$ Requires 499.1761; Found 499.1765 Da.
Elemental	Calc. for $C_{25}H_{32}O_7S$: C, 63.01; H, 6.77%; Found: C, 62.95; H, 6.73%.
$[\alpha]^{25}_D$	-42.6 (c. 1.65, $CHCl_3$).

(1*S*)-*N*-{(2*E*)-7-Methyl-2,6-octadienoyl}camphor-10,2-sultam (4.12)



4.12
$C_{19}H_{29}NO_3S$
351.51

To a solution of (1*S*)-(-)-2,10-camphorsultam **3.17** (1.72 g, 7.97 mmol) in THF (50 mL) at –78 °C under an atmosphere of N_2 was added a 2.36M solution of *n*-BuLi in hexanes (3.4 mL, 7.97 mmol), dropwise *via* syringe. After 10 min a solution of pentafluorophenyl ester **4.6** (2.43 g, 7.59 mmol) in THF (18 mL) was added dropwise, and the mixture was allowed to warm to –25 °C and stir for 10 min. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (30 mL) and extracted with Et_2O (3 x 50 mL), then the combined organic phase was washed with water (2 x 20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 45 x 200 mm, 4-10% EtOAc/hexane) afforded the title compound **4.12** (2.53 g, 7.21 mmol, 95%) as a white solid. R_f = 0.38 (20% EtOAc/hexane).

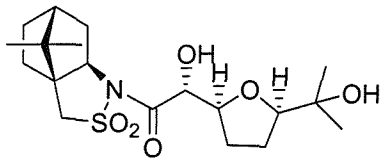
m.p. 74-76 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.08 (1H, dt, *J* = 15.1, 6.8 Hz, C**H**=CHCON), 6.56 (1H, dt, *J* = 15.1, 1.5 Hz, CH=C**H**CON), 5.10 (1H, m, C**H**=C(CH_3)$_2$), 3.93 (1H, dd, *J* = 7.5, 5.0 Hz, C**H**N), 3.51 & 3.44 (2 x 1H, 2 x d, *J* = 13.8 Hz, C**H**$_2$$SO_2$), 2.32-2.25 (2H, m, C**H**$_2$CH=CHCON), 2.21-2.05 (4H, m, C**H**$_2$CH=C(CH_3)$_2$ + C**H**$_2$CHN), 1.98-1.82 (3H, m, C**H**CH$_2$CHN + C**H**HCCH$_2$$SO_2$ + C**H**HCH$_2$CCH$_2$$SO_2$), 1.69 (3H, s, C**H**$_3$), 1.60 (3H, s, C**H**$_3$), 1.50-1.29 (2H, m, CH**H**CCH$_2$$SO_2$ + CH**H**CH$_2$CCH$_2$$SO_2$), 1.18 (3H, s, C**H**$_3$), 0.98 (3H, s, C**H**$_3$) ppm.

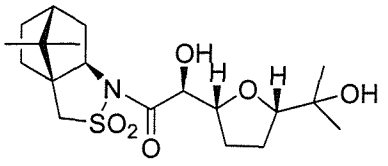
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 164.3 (s, **C**ON), 150.7 (d, **C**H=CHCON), 133.0 (s, CH=**C**(CH_3)$_2$), 123.0 (d, **C**H=C(CH_3)$_2$), 121.2 (CH=**C**HCON), 65.3 (d, **C**HN), 53.4 (t, **C**H$_2$$SO_2$), 48.6 & 48.0 (2 x s, **C**HCH$_2$CHN + **C**CH$_2$$SO_2$), 44.9 (d, **C**HCH$_2$CHN), 38.7 (t, **C**H$_2$CHN), 33.1 (t, **C**H$_2$CH=CHCON), 32.9 (t, **C**H$_2$CH$_2$CCH$_2$$SO_2$), 26.8 & 26.7 (2 x t, **C**H$_2$CCH$_2$$SO_2$ + **C**H$_2$CH=C(CH_3)$_2$), 25.8 (q, **C**H$_3$), 21.0 (q, **C**H$_3$), 20.1 (q, **C**H$_3$), 17.9 (q, **C**H$_3$), ppm.

FT-IR	(solid) ν_{max} 2959(w), 1678(m), 1640(m), 1370(w), 1330(s), 1238(m), 1214(m), 1134(s), 742(m), 729(s) cm^{-1}.
LRMS	(CI) *m/z* 352 ($[M+H]^+$, 65%), 369 ($[M+NH_4]^+$, 6%), 283 (26%), 176 (16%), 152 (20%), 135 (52%), 109 (29%), 93 (24%), 69 (100%), 55 (20%) Da.
HRMS	(ES^+) $C_{19}H_{29}NO_3SNa$ Requires 374.1760; Found 374.1760 Da.
Elemental	Calc. for $C_{19}H_{29}NO_3S$: C, 64.92; H, 8.32; N, 3.98%; Found: C, 64.68; H, 8.42; N, 3.83%.
$[\alpha]^{24}_D$	-80.3 (c. 0.35, $CHCl_3$).

(1*S*)-*N*-{(2S)-2-Hydroxy-2-[(2*S*,5*R*)-5-(1-hydroxy-1-methylethyl)-tetrahydro-2-furanyl]-ethanoyl}-camphor-10,2-sultam (4.13) and (1*S*)-*N*-{(2R)-2-Hydroxy-2-[(2*R*,5*S*)-5-(1-hydroxy-1-methylethyl)-tetrahydro-2-furanyl]-ethanoyl}-camphor-10,2-sultam (4.14)



4.13
$C_{19}H_{31}NO_6S$
401.52
Major Product



4.14
$C_{19}H_{31}NO_6S$
401.52
Minor Product

Aqueous Acetone Method

To a stirred heterogeneous solution of diene **4.12** (400 mg, 1.14 mmol) and phosphate buffer (0.067M $KH_2PO_{4(aq)}$ / 0.067M $Na_2HPO_{4(aq)}$ 4:1, 0.78 mL) in acetone (16 mL) at –25 °C was added a mixture of 0.4M $KMnO_{4(aq)}$ (5.69 mL, 2.28 mmol) and AcOH (0.18 mL, 3.19 mmol) *via* dropping funnel over 10 min. The reaction was stirred at –25 °C for 10 min and quenched by the addition of an ice-cooled saturated aqueous solution of $Na_2S_2O_5$ (10 mL). The mixture was saturated with NaCl and extracted with Et_2O (4 x 40 mL) then CH_2Cl_2 (3 x 30 mL), and the combined organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 10 x 80 mm, 30-60% EtOAc/hexane) afforded major diastereoisomer **4.13** (307 mg, 0.77 mmol, 67%) and minor diastereoisomer **4.14** (36 mg, 0.09 mmol, 8%) as white solids (total yield THF product 343

mg, 0.86 mmol, 75%). This corresponded to a product ratio of 8.5:1 (*de* = 79%). $R_{f, minor}$ = 0.35, $R_{f, major}$ = 0.27 (60% EtOAc/hexane).

Phase Transfer Method

To a solution of diene **4.12** (400 mg, 1.00 mmol), AcOH (0.73 mL, 12.74 mmol) and adogen-464 (65 mg, 0.01 mmol) in CH_2Cl_2 (16 mL) at –30 °C under an atmosphere of N_2 was added $KMnO_4$ (360 mg, 2.28 mmol) as a single batch, and the heterogeneous solution stirred for 2 hr. The reaction was quenched by addition to an ice-cooled saturated aqueous solution of $Na_2S_2O_5$ (20 mL) and the resulting yellow solution was extracted with EtOAc (3 x 50 mL) and CH_2Cl_2 (4 x 50 mL). The combined organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 12 x 50 mm, 5-35% EtOAc/hexane) afforded major diastereoisomer **4.13** (319 mg, 0.79 mmol, 70%) and minor diastereoisomer **4.14** (40 mg, 0.10 mmol, 8%) as white solids (total yield THF product 359 mg, 0.89 mmol, 78%). This corresponded to a product ratio of 8.5:1 (*de* = 78%). $R_{f, minor}$ = 0.35, $R_{f, major}$ = 0.27 (60% EtOAc/hexane).

Major Diastereoisomer 4.13

m.p 67-69 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.64 (1H, ddd, *J* = 6.0, 5.8, 2.5 Hz, C**H**CHOHCON), 4.56 (1H, dd, *J* = 6.8, 2.5 Hz, C**H**OHCON), 4.24 (1H, d, *J* = 6.8 Hz, CHO**H**), 3.96 (1H, dd, *J* = 8.0, 5.3 Hz, C**H**N), 3.78 (1H, dd, *J* = 8.3, 6.5 Hz, C**H**COH$(CH_3)_2$), 3.52 & 3.44 (2 x 1H, 2 x d, *J* = 13.6 Hz, C**H**$_2SO_2$), 2.96 (1H, br s, CO**H**$(CH_3)_2$), 2.29-2.18 (1H, m, C**H**HCH$_2$CCH$_2SO_2$), 2.09-1.62 (7H, m, CHC**H**$_2$C**H**$_2$CH + C**H**$_2$CHN + C**H**CH$_2$CHN), 1.40-1.12 (3H, m, C**H**$_2$CCH$_2SO_2$ + CH**H**CH$_2$CCH$_2SO_2$), 1.29 (3H, s, C**H**$_3$), 1.15 (3H, s, C**H**$_3$), 1.12 (3H, s, C**H**$_3$), (3H, s, C**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 172.2 (s, **C**ON), 87.0 (d, **C**HCOH$(CH_3)_2$), 78.7 (d, **C**HCHOHCON), 74.5 (d, **C**HOHCON), 72.1 (s, **C**OH$(CH_3)_2$), 66.1 (d, **C**HN), 53.3 (t, **C**H$_2SO_2$), 49.3 (s), 48.1 (s), 44.8 (d, **C**HCH$_2$CHN), 38.6 (t, COCHOHCH**C**H$_2$), 33.2 (t), 29.1 (t), 28.5 (q), 26.6 (t), 26.4 (t), 25.2 (q), 21.1 (q), 20.1 (q) ppm.

FT-IR	(solid) ν_{max} 3457(br), 2963(w), 2881(w), 1686(m), 1457(w), 1413(w), 1375(m), 1330(s), 1269(s), 1236(s), 1218(s), 1166(s), 1108(s), 1078(s), 990(m), 953(m), 735(m) cm^{-1}.
LRMS	(ES^+) *m/z* 402 ($[M+H]^+$, 8%), 424 ($[M+Na]^+$, 78%), 803 ($[2M+H]^+$, 100%), 825 ($[2M+Na]^+$, 5%) Da.
HRMS	(ES^+) $C_{19}H_{31}NO_6SNa$ Requires 424.1762; Found 424.1762 Da.
Elemental	Calc. for $C_{19}H_{31}NO_6S$: C, 56.84; H, 7.78; N, 3.49%; Found: C, 56.48; H, 7.45; N, 3.47%.
$[\alpha]^{25}_D$	-37.8 (c. 0.63, $CHCl_3$).

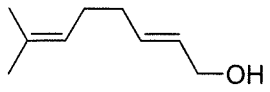
Minor Diastereoisomer 4.14

m.p	68-70 °C.
^{1}H NMR	(400 MHz, $CDCl_3$) δ_H 4.69 (1H, dd, *J* = 9.8, 2.3 Hz, C**H**OHCON), 4.55 (1H, ddd, *J* = 7.3, 3.0, 2.3 Hz, C**H**CHOHCON), 3.96 (1H, dd, *J* = 6.8, 5.8 Hz, C**H**N), 3.87 (1H, d, *J* = 9.8 Hz, CHO**H**), 3.69 (1H, dd, *J* = 8.5, 6.8 Hz, C**H**COH$(CH_3)_2$), 3.51 & 3.45 (2 x 1H, 2 x d, *J* = 13.8 Hz, C$\mathbf{H}_2SO_2$), 2.76 (1H, br s, CO**H**$(CH_3)_2$), 2.25-1.61 (8H, m, CH**H**$CH_2CCH_2SO_2$ + CH$\mathbf{H}_2$C$\mathbf{H}_2$CH + C$\mathbf{H}_2$CHN + C**H**CH_2CHN), 1.42-1.21 (3H, m, C$\mathbf{H}_2CCH_2SO_2$ + CH**H**$CH_2CCH_2SO_2$), 1.23 (3H, s, C$\mathbf{H}_3$), 1.17 (3H, s, C$\mathbf{H}_3$), 1.10 (3H, s, C$\mathbf{H}_3$), 0.98 (3H, s, C$\mathbf{H}_3$) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ_C 173.6 (s, **C**ON), 86.9 (d, **C**HCOH$(CH_3)_2$), 80.3 (d, **C**HCHOHCON), 75.5 (d, **C**HOHCON), 71.9 (s, **C**OH$(CH_3)_2$), 65.2 (d, **C**HN), 53.3 (t, **C**H_2SO_2), 49.3 (s), 48.2 (s), 44.8 (d, **C**HCH_2CHN), 37.9 (t, COCH(OH)CH**C**H_2), 32.9 (t), 28.7 (t), 28.6 (q), 26.8 (t), 26.5 (t), 25.0 (q), 20.7 (q), 20.2 (q) ppm.
FT-IR	(solid) ν_{max} 3458(br), 2963(m), 2881(m), 1686(s), 1458(m), 1375(m), 1330(s), 1270(m), 1238(m), 1218(m), 1166(s), 1135(m), 1108(m), 1078(m), 991(m), 953(m), 735(m) cm^{-1}.
LRMS	(ES^+) *m/z* 419 ($[M+NH_4]^+$, 100%), 402 ($[M+H]^+$, 28%), 424 ($[M+Na]^+$, 22%), 820 ($[2M+NH_4]^+$, 26%), 825 ($[2M+Na]^+$, 5%) Da.
HRMS	(ES^+) $C_{19}H_{31}NO_6SNa$ Requires 424.1764; Found 424.1759 Da.

Elemental Calc. for $C_{19}H_{31}NO_6S$: C, 56.84; H, 7.78; N, 3.49%; Found: C, 56.80; H, 7.85; N, 3.37%.

$[\alpha]^{25}_D$ -119.8 (c. 0.52, $CHCl_3$).

(2*E*)-7-Methyl-2,6-octadien-1-ol [58167-00-3] (4.17)



4.17
$C_9H_{16}O$
140.23

To a solution of ester **4.3** (26.4 g, 145 mmol) in CH_2Cl_2 (600 mL) at –30 °C under an atmosphere of Ar was added a 1M solution of di-*iso*-butyl aluminium hydride in hexanes (290 mL, 290 mmol) *via* dropping funnel over a period of 3 hr. The reaction was stirred for a further 1 hr at –30 °C, then was warmed to 0 °C and quenched by the addition of MeOH (340 mL), water (340 mL) and 2N $HCl_{(aq)}$ (200 mL). The aqueous phase was extracted with Et_2O (3 x 400 mL) and the organic phase was washed with 2N $HCl_{(aq)}$ (100 mL), a saturated aqueous solution of $NaHCO_3$ (100 mL) and brine (100 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by flash column chromatography (silica gel 80 x 160 mm, 20-50% EtOAc/hexane) afforded the title compound **4.17** (16.2 g, 115 mmol, 80%) as a colourless oil. R_f = 0.16 (10% EtOAc/hexane).

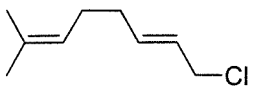
^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.78 (2H, m, C**H**=C**H**CH_2OH), 5.12 (1H, app. tt, J = 6.7, 1.5 Hz, C**H**=$C(CH_3)_2$), 4.10 (2H, d, J = 5.2 Hz, C**H**$_2$OH), 2.11-2.04 (4H, m, CHC**H**$_2$C**H**$_2$CH), 1.70 (3H, s, C**H**$_3$), 1.60 (3H, s, C**H**$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ_C 133.2 (d, **C**H=$CHCH_2OH$), 132.1 (s, CH=**C**$(CH_3)_2$), 129.2 (d, CH=**C**HCH_2OH), 123.9 (d, **C**H=$C(CH_3)_2$), 64.0 (t, **C**H_2OH), 32.6 (t, **C**H_2CH=$CHCH_2OH$), 27.8 (t, **C**H_2CH=$C(CH_3)_2$), 25.8 (q, **C**H_3), 17.9 (q, **C**H_3) ppm.

FT-IR (film) ν_{max} 3333(br), 2969(w), 2917(m), 2850(w), 1441(m), 1375(m), 1224(w), 1093(m), 1003(s), 968(s), 835(m), 733(m) cm^{-1}.

LRMS (CI) *m/z* 140 ($[M+NH_4-H_2O]^+$, 84%), 158 ($[M+NH_4]^+$, 60%), 123 ($[M-OH]^+$, 100%), 109 (28%), 69 (68%), 58 (18%) Da.

(2*E*)-1-Chloro-7-methyl-2,6-octadiene (4.18)



4.18
$C_9H_{15}Cl$
158.72

The title compound was prepared according to the method Collington *et al.*[226] Thus, to a solution of alcohol **4.17** (12.5 g, 89 mmol), 2,6-lutidine (11.4 mL, 98 mmol) and oven-dried LiCl (4.2 g, 98 mmol) in dry DMF (125 mL) at 0 °C under an atmosphere of N_2 was added methanesulfonyl chloride (8.3 mL, 107 mmol), dropwise *via* syringe. The mixture was stirred at 0 °C for 1 hr, then at room temperature for 2 hr, at which point further LiCl (0.2 g, 5 mmol) was added as a single batch. After stirring for 2.5 hr at room temperature, the mixture was diluted with Et_2O (100 mL) and washed with water (100 mL), 2N $HCl_{(aq)}$ (100 mL), and brine (100 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by short-path distillation under reduced pressure (17 mbar, 95 °C) afforded the title compound **4.19** (10.1 g, 64 mmol, 71%) as a colourless oil. R_f = 0.66 (10% EtOAc/hexane).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.79 (1H, dt, J = 14.7, 6.3 Hz, C**H**=CHCH$_2$Cl), 5.63 (1H, dt, J = 14.7, 6.6 Hz, CH=C**H**CH$_2$Cl), 5.11 (1H, app. tq, J = 5.2, 1.5 Hz, C**H**=C(CH$_3$)$_2$), 4.05 (2H, d, J = 6.6 Hz, C**H**$_2$Cl), 2.12-2.05 (4H, m, CHC**H**$_2$C**H**$_2$CH), 1.70 (3H, s, C**H**$_3$), 1.62 (3H, s, C**H**$_3$) ppm.

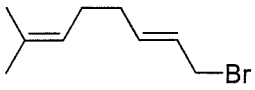
^{13}C NMR (75 MHz, $CDCl_3$) δ_C 136.0 (d, **C**H=CHCH$_2$Cl), 132.4 (s, CH=**C**(CH$_3$)$_2$), 126.2 (d, CH=**C**HCH$_2$Cl), 123.6 (d, **C**H=C(CH$_3$)$_2$), 45.7 (t, **C**H$_2$Cl), 32.4 (t, **C**H$_2$CH=CHCH$_2$Cl), 27.6 (t, **C**H$_2$CH=C(CH$_3$)$_2$), 25.8 (q, **C**H$_3$), 17.9 (q, **C**H$_3$) ppm.

FT-IR (film) ν_{max} 2959(m), 2926(m), 2855(w), 1730(w), 1663(w), 1441(m), 1375(m), 1251(m), 965(s), 684(s) cm^{-1}.

LRMS (CI) *m/z* 158 ([M]$^+$, 5%), 176 ([M+NH$_4$]$^+$, 2%), 123 ([M-Cl]$^+$, 95%), 109 (27%), 91 (12%), 81 (25%), 69 (100%), 58 (23%) Da.

HRMS (ES$^+$) $C_{19}H_{15}ClNa$ Requires 158.0862; Found 158.0871 Da.

(2*E*)-1-Bromo-7-methyl-2,6-octadiene [58135-14-1] (4.19)



4.19
$C_9H_{15}Br$
203.12

The title compound was prepared according to the method Collington *et al.*[227] Thus, to a solution of alcohol **4.17** (4.00 g, 28.53 mmol) in MeCN (150 mL) at 0 °C under an atmosphere of N_2 was added CBr_4 (9.99 g, 29.95 mmol) as a single batch followed by PPh_3 (7.86 g, 29.95 mmol), *via* solid addition screw over a period of 10 min. The reaction vessel was enclosed in aluminium foil to exclude light at all times. The mixture was stirred at 0 °C for 1 hr, then further CBr_4 (0.47 g, 1.43 mmol) followed by PPh_3 (0.37 g, 1.43 mmol) was added. After 1 hr, the solution was concentrated *in vacuo*, the residue was triturated with pentane (2 x 30 mL), the solid removed by filtration and the filtrate concentrated *in vacuo*. Purification of the residue by flash column chromatography (silica gel 30 x 80 mm, 5-15% EtOAc/hexane) afforded the title compound **4.19** (5.67 g, 27.89 mmol, 98%) as a colourless oil. $R_f = 0.75$ (20% EtOAc/hexane).

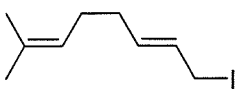
^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.88-5.64 (2H, m, C**H**=C**H**CH_2Br), 5.09 (1H, m, C**H**=$C(CH_3)_2$), 4.05 (2H, d, J = 6.6 Hz, CH_2**Br**), 2.11-2.02 (4H, m, CH_2CH_2), 1.71 (3H, s, CH_3), 1.61 (3H, s, CH_3) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ_C 136.4 (d, **C**H=$CHCH_2Br$), 132.4 (s, CH=**C**$(CH_3)_2$), 126.6 (d, CH=**C**HCH_2Br), 123.5 (d, **C**H=$C(CH_3)_2$), 33.8 (t, CH_2Br), 32.4 (t, **C**H_2CH=$CHCH_2Br$), 27.5 (t, **C**H_2CH=$C(CH_3)_2$), 25.9 (q, **C**H_3), 17.9 (q, **C**H_3) ppm.

FT-IR (film) ν_{max} 2960(m), 2922(m), 2851(w), 1654(w), 1446(m), 1370(m), 1203(m), 966(s) cm^{-1}.

LRMS (CI) *m/z* 123 ($[M-Br]^+$, 69%), 107 (28%), 91 (22%), 79 (36%), 69 (100%), 54 (46%) Da.

(2*E*)-1-Iodo-7-methyl-2,6-octadiene (4.20)



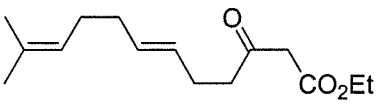
4.20
$C_9H_{15}I$
250.12

The title compound was prepared according to the method D'Aniello *et al.*[228] Thus, to a suspension of oven-dried NaI (22.4 g, 150 mmol) in dry acetone (60 mL) under an atmosphere of N_2 was added a solution of chloride **4.18** (9.5 g, 60 mmol) in dry acetone (40

mL). The mixture was heated at reflux for 3.5 hr, diluted with CH_2Cl_2 (200 mL) and washed with water (2 x 50 mL) and a saturated aqueous solution of $Na_2S_2O_3$ (20 mL). The organic phase was concentrated *in vacuo* to a brown liquid which was passed through a plug of silica gel (60 x 50 mm, 10% EtOAc/hexane) affording the title compound **4.20** (13.3 g, 53.1 mmol, 89%) as an orange oil. R_f = 0.66 (10% EtOAc/hexane). The compound was used immediately without further purification or characterisation due to a tendency towards decomposition. An impurity, thought to be due to double bond isomerisation, was present in the proton NMR spectrum. The data reported below corresponds to the desired product only.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.77-5.69 (2H, m, C**H**=C**H**), 5.10 (1H, m, C**H**=C$(CH_3)_2$), 3.89 (2H, m, C$\mathbf{H}_2$I), 2.08-1.92 (4H, m, C$\mathbf{H}_2$C$\mathbf{H}_2$), 1.71 (3H, s, C$\mathbf{H}_3$), 1.61 (3H, s, C$\mathbf{H}_3$) ppm.

Ethyl-(6*E*)-11-methyl-3-oxo-6,10-dodecadienoate (4.21)



4.21
$C_{15}H_{24}O_3$
252.35

To a solution of di-*iso*-propylamine (1.50 mL, 10.67 mmol) in THF (13 mL) at –78 °C under an atmosphere of N_2 was added, dropwise *via* syringe, a 1.36M solution of *n*-BuLi (7.84 mL, 10.67 mmol). The solution was allowed to warm to 0 °C and stir for 10 min, then was re-cooled to –78 °C and treated by the dropwise addition of ethyl acetoacetate (0.68 mL, 5.34 mmol). The yellow solution was allowed to warm to 0 °C and stir for 1.5 hr. The resulting orange solution was cooled to –78 °C, and a solution of bromide **4.19** (0.96 g, 4.85 mmol) in THF (6 mL) was added *via* syringe. The solution was stirred for 1 hr at –78 °C, allowed to warm to room temperature, and was quenched by the addition of water (10 mL) and 2N $HCl_{(aq)}$ (10 mL). The mixture was extracted with Et_2O (3 x 40 mL), and the combined organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 25 x 80 mm, 5-10% EtOAc/hexane) afforded the title compound **4.21** (0.82 g, 3.23 mmol, 67%) as a slightly yellow oil. R_f = 0.33 (20% EtOAc/hexane).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.49-5.25 (2H, m, CH_2C**H**=C**H**CH_2), 5.07 (1H, m, C**H**=C$(CH_3)_2$), 4.12 (2H, q, J = 7.4 Hz, OC$\mathbf{H}_2$CH_3), 3.36 (2H, s, C$\mathbf{H}_2$CO_2Et), 2.60 (2H, t, J = 7.4 Hz, CH_2C$\mathbf{H}_2$CO), 2.30 (2H, m,

CH_2CH_2CO), 2.10-1.98 (4H, m, $CHCH_2CH_2CH$), 1.61 (3H, s, CH_3), 1.51 (3H, s, CH_3), 1.29 (3H, t, J = 7.4 Hz, OCH_2CH_3) ppm.

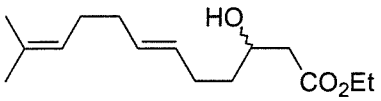
^{13}C NMR (75 MHz, $CDCl_3$) δ_C 202.4 (s, C=O), 178.1 (s, CO_2Et), 131.5 (s, $CH=C(CH_3)_2$), 131.4 (d, $CH=C(CH_3)_2$), 128.0 (d, CH=CH), 123.9 (d, CH=CH), 61.3 (t, OCH_2CH_3), 49.4 (t, CH_2CO_2Et), 42.8 (t, CH_2CH_2CO), 32.7 (t, CH_2CH_2CO), 29.2 (t, $CHCH_2CH_2CH$), 26.5 (t, $CHCH_2CH_2CH$), 25.6 (q, CH_3), 17.7 (q, CH_3), 14.1 (q, OCH_2CH_3) ppm.

FT-IR (film) ν_{max} 2917(w), 1747(s), 1719(s), 1654(w), 1437(m), 1370(m), 1323(m), 1234(s), 1035(s), 968(m) cm^{-1}.

LRMS (ES^+) *m/z* 275 ($[M+Na]^+$, 100%), 291 ($[M+K]^+$, 33%) Da.

HRMS (ES^+) $C_{15}H_{24}O_3Na$ Requires 275.1617; Found 275.1617 Da.

Ethyl-(6*E*)-3-hydroxy-11-methyl-6,10-dodecadienoate (4.22)



4.22
$C_{15}H_{26}O_3$
254.60

To a solution of β-keto ester **4.21** (1.00 g, 3.96 mmol) in THF (30 mL) at –15 °C under an atmosphere of N_2 was added $NaBH_4$ (0.15 g, 3.96 mmol) in 10 batches of approximately equal size at intervals of 4 min. Upon complete reduction, the reaction was quenched by the addition of water (10 mL) and extracted with Et_2O (4 x 50 mL), and the combined organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 25 x 80 mm, 10-20% EtOAc/hexane) afforded the title compound **4.22** (0.89 g, 3.49 mmol, 89%) as a colourless oil. R_f = 0.50 (40% EtOAc/hexane).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.48-5.34 (2H, m, CH=CH), 5.18-5.13 (1H, m, $CH=C(CH_3)_2$), 4.18 (2H, q, J = 6.6 Hz, OCH_2CH_3), 4.09-3.96 (1H, dtd, J = 8.5, 4.8, 3.3 Hz, CHOH), 2.93 (1H, br s, CHOH), 2.49 (1H, dd, J = 16.4, 3.3 Hz, $CHHCO_2Et$), 2.39 (1H, dd, J = 16.4, 8.5 Hz, $CHHCO_2Et$), 2.24-1.92 (6H, m, $CH_2CH_2CH=CHCH_2$) 1.68 (3H, s, CH_3), 1.59 (3H, s, 3H, CH_3), 1.59-1.40 (2H, m, CH_2CH_2CHOH), 1.27 (3H, t, J = 6.6 Hz, OCH_2CH_3) ppm.

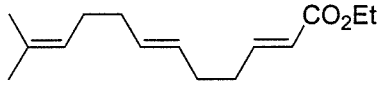
^{13}C NMR (75 MHz, $CDCl_3$) δ_C 173.2 (s, **C**O_2Et), 131.8 (s, CH=**C**$(CH_3)_2$), 131.1, 129.6, 124.2 (3 x d, **C**H=C$(CH_3)_2$ + **C**H=CH), 67.6 (d, **C**HOH), 60.8 (t, O**C**H_2CH_3), 41.4 (**C**H_2CO_2Et), 36.4 (t, CH_2**C**H_2CHOH), 32.9, 28.7, 28.2 (3 x t, **C**H_2**C**H_2CH=CH**C**H_2), 25.9 (q, **C**H_3), 17.9 (q, **C**H_3), 14.3 (q, OCH$_2$**C**H_3) ppm.

FT-IR (film) ν_{max} 3432(br), 2974(w), 2926(m), 2855(w), 1734(s), 1451(m), 1380(m), 1304(m), 1187(m), 1096(m), 1030(m), 968(m) cm^{-1}.

LRMS (CI) *m/z* 255 ($[M+H]^+$, 100%), 272 ($[M+NH_4]^+$, 4%), 237 ($[M-OH]^+$, 57%), 191 (34%), 167 (64%), 149 (68%), 123 (38%), 97 (34%), 69 (83%), 58 (18%) Da.

HRMS (ES^+) $C_{15}H_{26}O_3Na$ Requires 277.1774; Found 277.1770 Da.

Ethyl-(2*E*,6*E*)-11-methyl-2,6,10-dodecatrienoate (4.23)



4.23
$C_{15}H_{24}O_2$
236.35

To a solution of β-hydroxy ester **4.22** (4.62 g, 18.16 mmol) in CH_2Cl_2 (150 mL) at 0 °C under an atmosphere of N_2 was added MsCl (1.55 mL, 19.98 mmol) followed by Et_3N (3.04 mL, 21.79 mmol), both dropwise *via* syringe. The mixture was stirred at this temperature for 1.5 hr and washed with water (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL), and the combined organic phase dried ($MgSO_4$) and concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 (150 mL), cooled to 0 °C, and treated by the dropwise addition of DBU (2.69 mL, 17.99 mmol). The mixture was stirred at this temperature for 30 min and treated by the addition of further DBU (0.30 mL, 0.20 mmol), then was allowed to warm to room temperature and stir for 1 hr. The reaction was quenched by the addition of a 10% w/v aqueous solution of citric acid (100 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 60 x 120 mm, 4% EtOAc/hexane) afforded the title compound **4.23** (3.48 g, 14.71 mmol, 81%) as a slightly yellow oil. R_f = 0.71 (40% EtOAc/hexane).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.96 (1H, dt, *J* = 15.4, 6.6 Hz, C**H**=CHCO$_2$Et), 5.82 (1H, dt, *J* = 15.4, 1.5 Hz, CH=C**H**CO$_2$Et), 5.52-5.33 (2H, m, CH$_2$C**H**=C**H**CH$_2$), 5.15-5.06 (1H, m, C**H**=C$(CH_3)_2$), 4.18 (2H, q, *J* =

6.6 Hz, OCH_2CH_3), 2.33-2.12 (4H, m, $CH_2CH_2CH{=}CHCO_2Et$), 2.08-1.97 (4H, m, $CH_2CH_2CH{=}C(CH_3)_2$), 1.69 (3H, s, CH_3), 1.60 (3H, s, CH_3), 1.29 (3H, t, J = 6.6 Hz, OCH_2CH_3) ppm.

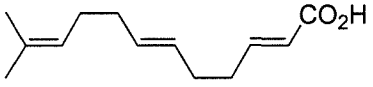
^{13}C NMR (75 MHz, $CDCl_3$) δ_C 166.8 (s, CO_2Et), 148.8 (d, $CH{=}CHCO_2Et$), 131.8 (s, $CH{=}C(CH_3)_2$), 131.5 (d), 128.7 (d), 124.1 (d), 121.6 (d), 60.3 (t, OCH_2CH_3), 32.9 (t), 32.4 (t), 31.1 (t), 28.2 (t), 25.8 (q), 17.9 (q), 14.4 (q, OCH_2CH_3) ppm.

FT-IR (film) ν_{max} 2974(w), 2926(w), 1722(s), 1659(m), 1451(w), 1370(w), 1309(m), 1265(m), 1197(m), 1175(m), 1046(m), 969(m), 843(m) cm^{-1}.

LRMS (EI) *m/z* 237 ($[M+H]^{\bullet+}$, 13%), 254 ($[M+NH_4]^{\bullet+}$, 5%), 191 (8%), 163 (32%), 114 (14%), 69 ($[CH_2CH{=}C(CH_3)_2]^{\bullet+}$, 100%), 53 (18%) Da.

HRMS (EI) $C_{15}H_{24}O_2$ Requires 236.1777; Found 236.1783 Da.

(2*E*,6*E*)-11-Methyl-2,6,10-dodecatrienoic acid (4.24)



4.24
$C_{13}H_{20}O_2$
208.30

A stirred heterogeneous solution of trienoate ester **4.23** (1.00 g, 4.23 mmol), NaOH (0.91 g, 22.85 mmol) and $NaHCO_3$ (0.18 g, 2.12 mmol) in MeOH (5 mL) and water (18 mL) was heated at reflux for 3 hr. The solution was cooled to 0 °C and extracted with Et_2O (3 x 60 mL). The aqueous layer was acidified to pH 1 with 2N $HCl_{(aq)}$ and extracted with Et_2O (3 x 40 mL). This second combined organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by Kugelrohr bulb to bulb distillation (0.5 mbar, 160 °C) afforded the title compound **4.24** (0.85 g, 4.07 mmol, 96%) as a colourless oil. R_f = 0.56 (60% EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 11.00 (1H, br s, CO_2H), 7.09 (1H, dt, J = 15.8, 6.8 Hz, $CH{=}CHCO_2H$), 5.84 (1H, dt, J = 15.8, 1.5 Hz, $CH{=}CHCO_2H$), 5.53-5.36 (2H, m, $CH_2CH{=}CHCH_2$), 5.14-5.08 (1H, m, $CH{=}C(CH_3)_2$), 2.34-2.26 (2H, m, $CH_2CH{=}CHCO_2H$), 2.21-2.14 (2H, m, $CH_2CH_2CH{=}CHCO_2H$), 2.10-1.97 (4H, m, $CH_2CH_2CH{=}C(CH_3)_2$), 1.69 (3H, s, CH_3), 1.60 (3H, s, CH_3) ppm.

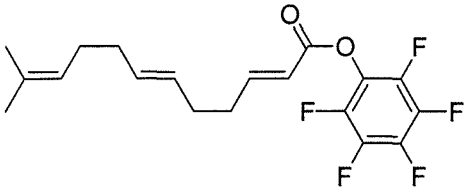
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 172.2 (s, **C**O_2H), 151.9 (d, **C**H=CHCO$_2$H), 131.9 (s, CH=**C**(CH$_3$)$_2$), 131.8 (d, CH=**C**HCO$_2$H), 128.6 (d), 124.2 (d), 121.1 (d), 32.9 (t), 32.5 (t), 31.0 (t), 28.2 (t), 25.8 (q), 17.9 (q) ppm.

FT-IR (film) ν_{max} 2966(m), 2916(m), 2852(m), 2671(w), 2548(w), 1698(s), 1651(s), 1420(m), 1376(w), 1286(m), 1232(w), 968(m) cm^{-1}.

LRMS (ES$^-$) *m/z* 207 ([M-H]$^-$, 100%) Da.

HRMS (ES$^-$) $C_{13}H_{19}O_2$ Requires 207.1390; Found 207.1392 Da.

2,3,4,5,6-Pentafluorophenyl-(2*E*,6*E*)-11-methyl-2,6,10-dodecatrienoate (4.25)



4.25
$C_{19}H_{19}F_5O_2$
374.35

To a solution of acid **4.24** (1.71 g, 8.22 mmol) and pentafluorophenol (1.50 g, 8.15 mmol) in dry EtOAc (23 mL) at 0 °C under an atmosphere of N_2 was added DCC (1.68 g, 8.15 mmol) as a single batch. The reaction was allowed to warm to room temperature and stir for 15 hr, then the mixture was diluted with hexane (30 mL) and filtered to remove the insoluble urea. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 40 x 120 mm, 5% EtOAc/hexane) affording the title compound **4.25** (2.96 g, 7.90 mmol, 96%) as a colourless oil. R_f = 0.75 (40% EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.30 (1H, dt, *J* = 15.8, 6.8 Hz, C**H**=CHCO$_2$Ar), 6.07 (1H, dt, *J* = 15.8, 1.8 Hz, CH=C**H**CO$_2$Ar), 5.57-5.38 (2H, m, CH$_2$C**H**=C**H**CH$_2$), 5.16-5.09 (1H, m, C**H**=C(CH$_3$)$_2$), 2.44-2.36 (2H, m, C**H**$_2$CH=CHCO$_2$Ar), 2.28-2.20 (2H, m, C**H**$_2$CH$_2$CH=CHCO$_2$Ar), 2.11-1.98 (4H, m, C**H**$_2$C**H**$_2$CH=C(CH$_3$)$_2$), 1.70 (3H, s, C**H**$_3$), 1.61 (3H, s, C**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 162.3 (s, **C**O_2Ar), 154.9 (d, **C**H=CHCO$_2$Ar), 144.0-136.0 (m, 5 x F-coupled Ar**C**), 132.2 (d, CH=**C**HCO$_2$Ar), 132.1 (s, CH=**C**(CH$_3$)$_2$), 128.3 (d), 124.2 (d), 118.5 (d), 34.0 (t), 33.0 (t), 31.0 (t), 28.3 (t), 25.9 (q), 18.0 (q) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ_F 9.16-8.90 (m), 3.31-3.26 (m), -0.73 to -1.00 (m) ppm.

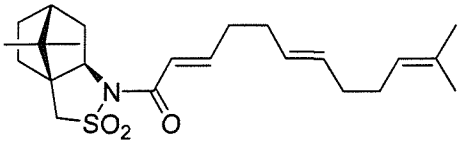
FT-IR (film) ν_{max} 2941(w), 1768(m), 1645(w), 1519(s), 1209(w), 1120(m), 1030(m), 1004(s), 741(m), 689(m) cm^{-1}.

LRMS (EI) *m/z* 374 ($[M]^{\bullet+}$, 10%), 191 ($[M\text{-}C_6F_5O]^{\bullet+}$, 20%), 69 ($[CH_2CH{=}C(CH_3)_2]^{\bullet+}$, 100%) Da.

HRMS (EI) $C_{19}H_{19}O_2F_5$ Requires 374.1304; Found 374.1305 Da.

Elemental Calc. for $C_{19}H_{19}O_2F_5$: C, 74.96; H, 9.68%; Found: C, 74.87; H, 9.79%.

(1*S*)-*N*-[(2*E*,6*E*)-11-Methyl-2,6,10-dodecatrienoyl] -10,2-Camphorsultam (4.26)



4.26
$C_{23}H_{35}NO_3S$
405.60

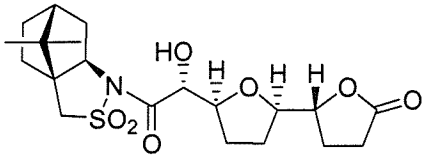
To a solution of (1*S*)-(-)-10,2-camphorsultam **3.17** (1.62 g, 7.51 mmol) in THF (18 mL) at –78 °C under an atmosphere of N_2 was added a 1.46M solution of *n*-BuLi in hexanes (5.15 mL, 7.51 mmol), dropwise *via* syringe. The solution was allowed to warm to –30 °C over a period of 1 hr and stir for 10 min, then was cooled to –50 °C. A solution of pentafluorophenyl ester **4.25** (2.81 g, 7.51 mmol) in THF (15 mL) was added, dropwise *via* syringe. The mixture was allowed to warm to –25 °C, then was stirred for 30 min and quenched by the addition of a saturated aqueous solution of NH_4Cl (20 mL). The mixture was extracted with Et_2O (3 x 50 mL), then the combined organic phase was washed with 2N $HCl_{(aq)}$ (2 x 30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 50 x 95 mm, 5-10% EtOAc/hexane) afforded the title compound **4.26** (2.46 g, 6.06 mmol, 81%) as a white solid. R_f = 0.63 (40% EtOAc/hexane).

m.p. 54-56 °C (EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.09 (1H, dt, *J* = 15.4, 7.4 Hz, C**H**=CHCON), 6.57 (1H, dt, *J* = 15.4, 1.5 Hz, CH=C**H**CON), 5.57-5.32 (2H, m, CH_2C**H**=C**H**CH_2), 5.11 (1H, m, C**H**=$C(CH_3)_2$), 3.93 (1H, dd, *J* = 7.4, 5.9 Hz, C**H**N), 3.54 & 3.45 (2 x 1H, 2 x d, *J* = 13.9 Hz, CH_2SO_2), 2.35-2.28 (2H, m, CH_2CH=CHCON), 2.30-1.58 (11H, m, $CH_2CH{=}C(CH_3)_2$ + $CH_2CH{=}CHCH_2$ + $CHCH_2CHN$ + CH_2CHN +

	CHHCCH$_2$SO$_2$ + CHHCH$_2$CCH$_2$SO$_2$), 1.70 (3H, s, CH$_3$), 1.60 (3H, s, CH$_3$), 1.56-1.30 (2H, m, CHHCCH$_2$SO$_2$ + CHHCCH$_2$SO$_2$), 1.19 (3H, s, CH$_3$), 1.00 (3H, s, CH$_3$) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ_C 164.4 (s, CON), 150.6 (d, CH=CHCON), 131.9 (s, CH=C(CH$_3$)$_2$), 131.7 (d, CH$_2$CH=CHCH$_2$), 128.8 (d, CH$_2$CH=CHCH$_2$), 124.4 (d, CH=C(CH$_3$)$_2$), 121.3 (d, CH=CHCON), 65.5 (d, CHN), 53.5 (t, CH$_2$SO$_2$), 48.7 & 48.1 (2 x s, CHC(CH$_3$)$_2$ + CCH$_2$SO$_2$), 45.0 (d, CHCH$_2$CHN), 38.8 (t, CH$_2$), 33.2 (t, CH$_2$), 33.0 (t, CH$_2$), 32.8 (t, CH$_2$), 31.3 (t, CH$_2$), 28.3 (t, CH$_2$), 26.8 (t, CH$_2$), 26.0 (q, CH$_3$), 21.1 (q, CH$_3$), 20.2 (q, CH$_3$), 18.0 (q, CH$_3$) ppm.
FT-IR	(film) ν_{max} 2941(m), 2683(m), 1635(m), 1332(s), 1237(m), 1218(m), 1134(s), 1119(m), 969(m), 761(w) cm^{-1}.
LRMS	(CI) *m/z* 406 ([M+H]$^+$, 22%), 283 (33%), 216 (8%), 152 ([M-sultam]$^+$, 15%), 135 (48%), 109 (30%), 93 (37%), 69 (100%) Da.
HRMS	(ES$^+$) $C_{23}H_{35}NO_3SNa$ Requires 428.2230; Found 428.2228 Da.
Elemental	Calc. for $C_{23}H_{35}NO_3S$: C, 68.11; H, 8.70; N, 3.43%; Found: C, 67.88; H, 8.92; N, 3.37%.
$[\alpha]^{24}_D$	-67.4 (c. 0.64, $CDCl_3$).

(1*S*)-*N*-{(*R*)-2-Hydroxy-2-((2*S*,5*R*)-5-((*R*)-5-oxo-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)ethanoyl}-camphor-10,2-sultam (4.28)



4.28
$C_{20}H_{29}NO_7S$
427.51

Aqueous Acetone Method

To a stirred heterogeneous solution of triene **4.26** (2.00 g, 4.93 mmol) and phosphate buffer (0.067M $KH_2PO_{4(aq)}$ / 0.067M $Na_2HPO_{4(aq)}$ 4:1, 6.6 mL) in acetone (80 mL) at –25 °C was added a mixture of 0.4M $KMnO_{4(aq)}$ (37.0 mL, 14.79 mmol) and AcOH (1.2 mL, 20.71 mmol) *via* dropping funnel over 10 min. The reaction was stirred at –25 °C for 10 min and quenched by addition to an ice-cooled saturated aqueous solution of $Na_2S_2O_5$ (100 mL). The mixture was saturated with NaCl and extracted with EtOAc (3 x 150 mL) and CH_2Cl_2 (5 x 50 mL), then the combined organic phase was dried ($MgSO_4$) and concentrated *in*

vacuo. The residue was taken up in CH_2Cl_2 (20 mL), SiO_2-supported $NaIO_4$ (1.00 g) was added and the solution was stirred at room temperature for 5 hr. The solid was removed by filtration then washed with $CHCl_3$ (2 x 10 mL) and CH_2Cl_2 (2 x 10 mL), and the filtrate was concentrated *in vacuo*. Purification by flash column chromatography (silica gel 25 x 45 mm, 20-35% EtOAc/hexane) afforded the title compound **4.28** (0.76 g, 1.79 mmol, 35%) as a white foamy solid. $R_f = 0.29$ (70% EtOAc/toluene).

Phase Transfer Method

To a solution of triene **4.26** (500 mg, 1.23 mmol), adogen-464 (57 mg, 0.12 mmol) and AcOH (0.79 mL, 13.81 mmol) in CH_2Cl_2 (15 mL) at –35 °C under an atmosphere of N_2 was added powdered $KMnO_4$ (574 mg, 3.64 mmol) as a single batch. The reaction was stirred for 2 hr and quenched by addition to an ice-cooled saturated aqueous solution of $Na_2S_2O_5$ (50 mL). The solution was extracted with EtOAc (3 x 30 mL) and CH_2Cl_2 (3 x 30 mL) and the combined organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 (7 mL), and SiO_2-supported $NaIO_4$ (980 mg) was added as a single batch. The suspension was stirred at room temperature for 5 hr, the solid was removed by filtration and washed with CH_2Cl_2 (3 x 30 mL) and $CHCl_3$ (3 x 20 mL), and the filtrate was concentrated *in vacuo*. Purification by flash column chromatography (silica gel 25 x 35 mm, 10-30% EtOAc/hexane) afforded the title compound **4.28** (184 mg, 0.04 mmol, 35%) as a white foamy solid. $R_f = 0.28$ (70% EtOAc/toluene).

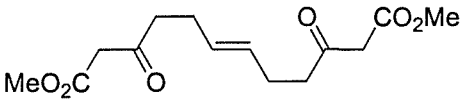
Acetone/Acetic Acid Method

To a solution of *bis*-sultam trienedioate **4.43** (1.00 g, 1.62 mmol) and adogen-464 (0.04 g, 0.08 mmol) in acetone (23 mL) and AcOH (15 mL) at –25 °C under an atmosphere of N_2 was added $KMnO_4$ (0.66 g, 4.20 mmol) in three batches at intervals of 30 seconds. The reaction was stirred for 1 hr and was quenched by pouring into an ice-cooled saturated aqueous solution of $Na_2S_2O_5$ (50 mL). The solution was extracted with EtOAc (3 x 70 mL) and CH_2Cl_2 (3 x 50 mL) and the combined organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 (16 mL), and SiO_2-supported $NaIO_4$ (3.23g) was added as a single batch. The suspension was stirred at room temperature for 40 min, the solid removed by filtration and washed with CH_2Cl_2 (3 x 30 mL) and $CHCl_3$ (3 x 15 mL), and the filtrate concentrated *in vacuo*. Purification by fiash column chromatography (silica gel 30 x 45 mm, 10-30% EtOAc/hexane) afforded the title

compound **4.28** (0.46 g, 1.08 mmol, 67%) as a white foamy solid. R_f = 0.26 (70% EtOAc/toluene).

m.p.	69-71 °C.
^{1}H NMR	(400 MHz, $CDCl_3$) δ_H 4.58-4.48 (3H, m, C**H**OC=O + C**H**OHCON + C**H**CHOHCON), 4.01 (1H, td, *J* = 7.3, 3.0 Hz, C**H**CHOC=O), 3.93 (1H, dd, *J* = 7.8, 5.0 Hz, C**H**N), 3.51 & 3.43 (2 x 1H, 2 x d, *J* = 13.8 Hz, C**H**$_2$SO$_2$), 3.24 (1H, br d, *J* = 7.8 Hz, CHO**H**), 2.73 (1H, ddd, *J* = 17.6, 10.0, 7.3 Hz, C**H**HC=O), 2.43 (1H, ddd, *J* = 17.6, 10.0, 6.3 Hz, CH**H**C=O), 2.33-1.80 (10H, m), 1.50-1.30 (3H, m), 1.14 (3H, s, C**H**$_3$), 0.97 (3H, s, C**H**$_3$) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ_C 178.1 (s), 170.8 (s), 81.8 (d), 80.5 (d), 78.9 (d), 72.7 (d), 65.8 (d), 53.1 (t), 49.4 (s), 48.2 (s), 44.7 (d), 38.3 (t), 33.1 (t), 28.4 (t), 28.1 (t), 27.5 (t), 26.7 (t), 24.9 (t), 21.0 (q), 20.2 (q) ppm.
FT-IR	(film) ν_{max} 3507(br), 2959(m), 2833(m), 1771(s), 1693(s), 1459(w), 1414(m), 1331(s), 1270(s), 1218(m), 1167(s), 1136(s), 1109(m), 1063(m), 989(w), 734(m), 701(w) cm^{-1}.
LRMS	(ES$^+$) *m/z* 445 ([M+NH$_4$]$^+$, 100%), 450 ([M+Na]$^+$, 38%), 466 ([M+K]$^+$, 86%), 872 ([2M+NH$_4$]$^+$, 12%), 877 ([2M+Na]$^+$, 10%), 893 ([2M+K]$^+$, 16%) Da.
HRMS	(ES$^+$) $C_{20}H_{29}NO_7SNa$ Requires 450.1557; Found 450.1563 Da.
Elemental	Calc. for $C_{20}H_{29}NO_7S$: C, 56.19; H, 6.84; N, 3.27%; Found: C, 55.96; H, 6.96; N, 3.13%.
$[\alpha]^{23}_D$	-40.5 (c. 0.24, $CHCl_3$).

Dimethyl-(6*E*)-3,10-dioxododec-6-enedioate [107093-52-7] (4.35)



4.35
$C_{14}H_{20}O_6$
284.30

The title compound was prepared according to the method Hoye *et al.*[22] Thus, to a solution of di-*iso*-propylamine (13.4 mL, 96 mmol) in dry THF (80 mL) at –55 °C under an atmosphere of N_2 was added, dropwise *via* syringe, a 2.28M solution of *n*-BuLi in hexanes (42.1 mL, 96 mmol). The solution was warmed to 0 °C, stirred for 10 min, then cooled to –60 °C and treated with methyl acetoacetate (5.2 mL, 48 mmol), also added dropwise. The

yellow solution was allowed to warm to 0 °C and stir for 1.5 hr. The resulting orange solution was cooled to –50 °C, and a solution of 1,4-dibromo-2-butene **4.34** (5.00 g, 23 mmol) in dry THF (25 mL) was added dropwise *via* syringe. The solution was stirred for 30 min at –50 °C, allowed to warm to 0 °C, and was quenched by the addition of a saturated aqueous solution of NH_4Cl (35 mL). The mixture was extracted with Et_2O (3 x 60 mL), and the combined organic phase was washed with 2N $HCl_{(aq)}$ (2 x 50 mL) and brine (50 mL) then dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 50 x 130 mm, 5-35% EtOAc/hexane) afforded the title compound **4.35** (5.00 g, 18 mmol, 75%) as a pale yellow solid. R_f = 0.60 (20% EtOAc/hexane).

m.p. 28-30 °C (EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.25 (2H, tt, J = 3.5, 1.5 Hz, C**H**=C**H**), 3.74 (6H, s, OC**H**$_3$), 3.44 (4H, s, C**H**$_2$CO$_2$CH$_3$), 2.59 (4H, t, J = 7.3 Hz, CH$_2$C**H**$_2$C=O), 2.27 (4H, tdd, J = 7.3, 3.5, 1.5 Hz, C**H**$_2$CH=CHC**H**$_2$) ppm.

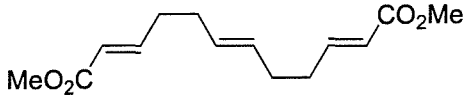
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 202.2 (s, CH$_2$**C**OCH$_2$), 167.8 (s, **C**O$_2$CH$_3$), 129.6 (d, **C**H=**C**H), 52.6 (q, OCH$_3$), 49.3 (t, **C**H$_2$CO$_2$CH$_3$), 42.9 (t, CH$_2$**C**H$_2$C=O), 26.6 (t, **C**H$_2$CH=CH**C**H$_2$) ppm.

FT-IR (film) ν_{max} 2992(w), 2954(w), 2846(w), 1744(s), 1714(s), 1626(w), 1437(m), 1407(m), 1320(m), 1266(m), 1197(m), 1148(m), 973(w) cm^{-1}.

LRMS (ES$^+$) *m/z* 285 ([M+H]$^+$, 72%), 302 ([M+NH$_4$]$^+$, 100%), 307 ([M+Na]$^+$, 71%) Da.

HRMS (ES$^+$) *m/z* $C_{14}H_{20}O_6Na$ Requires 307.1152; Found 307.1151 Da.

Dimethyl-(2*E*,6*E*,10*E*)-3,10-dodeca-2,6,10-trienedioate [107093-49-2] (4.36)



4.36
$C_{14}H_{20}O_4$
252.31

The title compound was prepared according to the method Hoye *et al.*[22] Thus, to a solution of *bis*-β-keto ester **4.35** (5.00 g, 17.6 mmol) in THF (135 mL) and water (7 mL) at –15 °C was added $NaBH_4$ (0.67 g, 17.6 mmol) in ten batches over a period of 10 min. The reaction was monitored by TLC, and $NaBH_4$ was added in small batches (0.05 g) until the starting

material was consumed. The mixture was quenched by the addition of 2N $HCl_{(aq)}$ (200 mL) and extracted with Et_2O (3 x 150 mL), then the combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 (135 mL) and at 0 °C under an atmosphere of N_2 MsCl (2.6 mL, 33.4 mmol) and Et_3N (4.9 mL, 35.1 mmol) were added dropwise *via* syringe. The reaction was stirred for 1 hr then washed with H_2O (100 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic phase was concentrated *in vacuo* to a volume of ~135 mL, cooled to 0 °C under an atmosphere of N_2, and DBU (5.0 mL, 33.6 mmol) was added dropwise *via* syringe. After stirring for 1 hr the reaction was quenched by the addition of 2N $HCl_{(aq)}$ (200 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 40 x 100 mm, 5-10% EtOAc/hexane) afforded the title compound **4.36** (2.67 g, 10.6 mmol, 69%) as a pale yellow solid. $R_{f,\ \beta\text{-hydroxy ketone}} = 0.17$, $R_{f,\ trienedioate} = 0.64$ (60% EtOAc/hexane).

m.p. 30-32 °C (EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.94 (2H, dt, J = 15.6, 6.8 Hz, C**H**=CHCO$_2$CH$_3$), 5.82, (2H, dt, J = 15.6, 1.5 Hz, CH=C**H**CO$_2$CH$_3$), 5.44 (2H, tt, J = 3.5, 2.0 Hz, C**H**=C**H**), 3.72 (6H, s, CO$_2$C**H**$_3$), 2.31-2.23 (4H, m, C**H**$_2$CH=CHCO$_2$CH$_3$), 2.22-2.11 (4H, m, CH$_2$CH=CHC**H**$_2$) ppm.

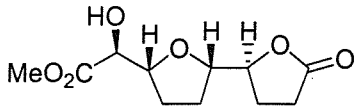
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 167.3 (s, **C**O$_2$CH$_3$), 148.9 (d, **C**H=CHCO$_2$CH$_3$), 130.1 (d, CH=**C**HCO$_2$CH$_3$), 121.5 (d, **C**H=**C**H), 51.6 (q, CO$_2$**C**H$_3$), 32.3 (t, **C**H$_2$CH=CH**C**H$_2$), 31.1 (t, **C**H$_2$CH=CHCO$_2$CH$_3$) ppm.

FT-IR (film) ν_{max} 2953(w), 2887(w), 2842(w), 1709(s), 1656(m), 1437(m), 1336(m), 1290(w), 1235(w), 1212(m), 1158(m), 1088(w), 1025(w), 1007(w), 981(w), 914(w), 861(w), 723(w) cm^{-1}.

LRMS (ES$^+$) *m/z* 253 ([M+H]$^+$, 100%), 270 ([M+NH$_4$]$^+$, 83%) Da.

HRMS (ES$^+$) *m/z* $C_{14}H_{20}O_4Na$ Requires 275.1254; Found 275.1253 Da.

***Rac*-(*S*)-Methyl-2-hydroxy-2-((2*R*,5*S*)-5-((*S*)-5-oxo-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)acetate (4.37)**



4.37
$C_{11}H_{16}O_6$
244.24

To a solution of trienedioate **4.36** (500 mg, 1.98 mmol) and adogen-464 (45 mg, 0.10 mmol) in acetone (28 mL) and AcOH (18 mL) at –26 °C under an atmosphere of N_2 was added powdered $KMnO_4$ (814 mg, 5.15 mmol) and the solution stirred for 45 min. The reaction was quenched by dropwise addition to an ice-cooled saturated aqueous solution of $Na_2S_2O_5$ (70 mL). The mixture was extracted with EtOAc (5 x 60 mL) and CH_2Cl_2 (4 x 70 mL) and the combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 30 x 50 mm, 5-35% EtOAc/hexane) afforded the title compound **4.37** (288 mg, 1.78 mmol, 59%) as a white solid. R_f = 0.23 (60% EtOAc/hexane).

m.p. 67-69 °C (EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.52 (1H, ddd, *J* = 8.0, 5.0, 3.0 Hz, C**H**OC=O), 4.28 (1H, m, C**H**CH(OH)CO), 4.11 (1H, br d, *J* = 2.5 Hz, C**H**OH), 3.99 (1H, ddd, *J* = 7.3, 6.8, 3.0 Hz, C**H**CHOC=O), 3.80 (3H, s, $CO_2C\mathbf{H}_3$), 2.86 (1H, br s, CHO**H**), 2.60 (1H, ddd, *J* = 17.6, 10.3, 7.5 Hz, C**H**HCO), 2.43 (1H, ddd, *J* = 17.6, 10.0, 5.8 Hz, CH**H**CO), 2.28 (1H, dddd, *J* = 12.6, 10.0, 8.0, 7.3 Hz, CH**H**CH_2CO), 2.20-2.09 (2H, m, C**H**HCH_2CO + CH(OH)CHC**H**H), 2.08-1.90 (3H, m, CH(OH)CHCH**H** + CH(OH)$CHCH_2C\mathbf{H}_2$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 177.8 (s), 173.1 (s), 81.9 (d, **C**HCHCO), 80.6 d, **C**HCHOH), 80.3 (d, **C**HCO), 77.4 (d, **C**HOH), 52.7 (q, $\mathbf{C}H_3$), 28.2 (t, $\mathbf{C}H_2$CO), 27.7 (t), 27.4 (t), 24.7 (t, $\mathbf{C}H_2CH_2$CO) ppm.

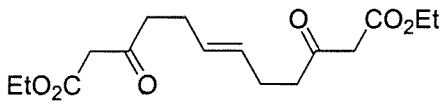
FT-IR (film) ν_{max} 3506(br), 2954(m), 2879(w), 1770(s), 1746(s), 1460(m), 1440(m), 1270(m), 1185(s), 1127(s), 1082(m), 1024(m), 930(w) cm^{-1}.

LRMS (ES^+) *m/z* 262 ($[M+NH_4]^+$, 100%), 506 ($[2M+NH_4]^+$, 37%), 511 ($[2M+Na]^+$, 4%) Da.

HRMS (ES^+) $C_{11}H_{16}O_6Na$ Requires 267.0839; Found 267.0839 Da.

Elemental Calc. for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60%; Found: C, 54.09; H, 6.70%.

Diethyl-(6*E*)-3,10-dioxododec-6-enedioate [207684-25-1] (4.38)



4.38
$C_{16}H_{24}O_6$
312.36

The title compound was prepared according to the method Hoye *et al.*[22] To a solution of di-*iso*-propylamine (94 mL, 671 mmol) in THF (560 mL) at –55 °C under an atmosphere of N_2 was added, dropwise *via* syringe, a 2.19M solution of *n*-BuLi in hexanes (307 mL, 671 mmol). The solution was warmed to 0 °C, stirred for 10 min, re-cooled to –60 °C and treated with ethyl acetoacetate (43 mL, 335 mmol), also added dropwise. The yellow solution was allowed to warm to 0 °C and stir for 1.5 hr. The resulting orange solution was cooled to –50 °C, and a solution of 1,4-dibromo-2-butene **4.34** (35.00 g, 164 mmol) in THF (180 mL) was added *via* syringe. The solution was stirred for 30 min at –50 °C, allowed to warm to 0 °C, and was quenched by the addition of a saturated aqueous solution of NH_4Cl (200 mL). The mixture was extracted with Et_2O (3 x 250 mL), and the combined organic phase was washed with 2N $HCl_{(aq)}$ (2 x 100 mL) and brine (150 mL) then dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 70 x 170 mm, 5-35% EtOAc/hexane) afforded the title compound **4.38** (43.96 g, 141 mmol, 86%) as a pale yellow oil. $R_f = 0.66$ (Et_2O).

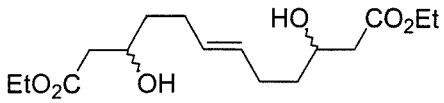
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.43 (2H, tt, J = 3.5, 1.5 Hz, C**H**=C**H**), 4.19 (4H, q, J = 7.3 Hz, OC**H**$_2$CH$_3$), 3.41 (4H, s, C**H**$_2$CO$_2$Et), 2.58 (4H, t, J = 7.3 Hz, CH$_2$C**H**$_2$C=O), 2.30-2.22 (4H, m, C**H**$_2$CH=CHC**H**$_2$), 1.28 (6H, t, J = 7.3 Hz, OCH$_2$C**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 202.3 (s, CH$_2$**C**OCH$_2$), 167.3 (s, **C**O$_2$Et), 129.5 (d, **C**H=**C**H), 61.5 (t, O**C**H$_2$CH$_3$), 49.5 (t, **C**H$_2$CO$_2$Et), 42.7 (t, CH$_2$**C**H$_2$CO), 26.5 (t, **C**H$_2$CH=CH**C**H$_2$), 14.3 (q, OCH$_2$**C**H$_3$) ppm.

FT-IR (film) ν_{max} 2983(w), 2936(w), 1743(s), 1714(s), 1444(w), 1410(m), 1368(m), 1316(m), 1249(m), 1184(m), 1096(m), 1033(m), 971(w) cm^{-1}.

LRMS (ES$^+$) *m/z* 335 ([M+Na]$^+$, 100%), 351 ([M+K]$^+$, 4%), 647 ([2M+Na]$^+$, 83%) Da.

Diethyl-(6*E*)-3,10-dihydroxydodec-6-enedioate (4.39)



4.39
$C_{16}H_{28}O_6$
316.39

To a solution of *bis*-β-keto ester **4.38** (42.8 g, 137 mmol) in THF (1050 mL) and water (50 mL) at –15 °C was added $NaBH_4$ (5.2 g, 137 mmol) in twenty batches over a period of 2 hr. The reaction was quenched by the addition of 2N $HCl_{(aq)}$ (300 mL), extracted with Et_2O (4 x 400 mL) and the combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 100 x 130 mm, 70-100% Et_2O/hexane) afforded the title compound **4.39** (33.6 g, 106 mmol, 77%) as a pale yellow oil. $R_f = 0.34$ (Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.46 (2H, tt, J = 3.5, 1.5 Hz, C**H**=C**H**), 4.17 (4H, q, J = 7.3 Hz, OC**H**$_2$CH$_3$), 4.00 (2H, ttd, J = 8.3, 4.8, 3.5 Hz, C**H**OH), 2.95 (2H, br s, CHO**H**), 2.49 (2H, dd, J = 16.3, 3.3 Hz, C**H**HCO$_2$Et), 2.41 (2H, dd, J = 16.3, 8.8 Hz, CH**H**CO$_2$Et), 2.20-2.12 (4H, m, C**H**$_2$CH=CHC**H**$_2$), 1.62-1.39 (4H, m, CH$_2$C**H**$_2$CHOH), 1.27 (6H, t, J = 7.3 Hz, OCH$_2$C**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 173.1 (s, **C**O$_2$Et), 130.3 (d, **C**H=**C**H), 67.6 (d, **C**HOH), 60.8 (t, O**C**H$_2$CH$_3$), 41.5 (t, **C**H$_2$CO$_2$Et), 36.3 (t, CH**C**H$_2$CHOH), 28.7 (t, **C**H$_2$CH=CH), 14.3 (q, OCH$_2$**C**H$_3$) ppm.

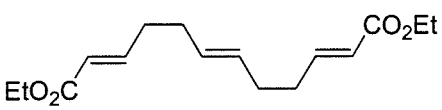
FT-IR (film) ν_{max} 3449(br), 2981(m), 2934(s), 2850(m), 1732(s), 1446(s), 1405(m), 1373(s), 1300(s), 1183(s), 1091(s), 1029(s), 970(m) cm^{-1}.

LRMS (ES$^+$) *m/z* 334 ([M+NH$_4$]$^+$, 100%), 317 ([M+H]$^+$, 58%), 650 ([2M+NH$_4$]$^+$, 26%) Da.

HRMS (ES$^+$) *m/z* $C_{26}H_{28}O_6Na$ Requires 339.1778; Found 339.1777 Da.

Elemental Calc. for $C_{26}H_{28}O_6$: C, 60.74; H, 8.92%; Found: C, 60.48; H, 9.01%.

Diethyl-(2*E*,6*E*,10*E*)-3,10-dodeca-2,6,10-trienedioate [197968-20-0] (4.40)



4.40
$C_{16}H_{24}O_4$
280.36

To a solution of *bis*-β-hydroxy ester **4.39** (28.6 g, 90 mmol) in CH_2Cl_2 (815 mL) at 0 °C under an atmosphere of N_2 was added MsCl (14.7 mL, 190 mmol) followed by Et_3N (27.7 mL, 199 mmol), both dropwise *via* syringe. The reaction was stirred for 1.5 hr then washed

with H_2O (300 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 100 mL) and the combined organic phase was concentrated *in vacuo* to a volume of ~800 mL, cooled to 0 °C and DBU (27.1 mL, 181 mmol) was added dropwise *via* syringe. The orange solution was stirred for 20 min and further DBU (2.0 mL, 13 mmol) was added. After 30 min the reaction was quenched by the addition of a 10% w/v aqueous solution of citric acid (100 mL) followed by 2N $HCl_{(aq)}$ (250 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 200 mL) and the combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 100 x 150 mm, 5% EtOAc/hexane) afforded the title compound **4.40** (24.8 g, 88 mmol, 98%) as a pale yellow oil. R_f = 0.79 (Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.94 (2H, dt, *J* = 15.6, 6.8 Hz, C**H**=CHCO$_2$Et), 5.82, (2H, dt, *J* = 15.6, 1.5 Hz, CH=C**H**CO$_2$Et), 5.44 (2H, dt, *J* = 3.5, 1.8 Hz, C**H**=C**H**), 4.19 (4H, q, *J* = 7.3 Hz, OC**H**$_2$CH$_3$), 2.30-2.22 (4H, app. qd, *J* = 6.8, 1.5 Hz, C**H**$_2$CH=CHCO$_2$Et), 2.19-2.12 (4H, m, CH$_2$CH=CHC**H**$_2$), 1.27 (6H, t, *J* = 7.3 Hz, OCH$_2$C**H**$_3$) ppm.

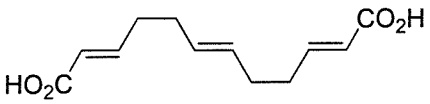
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 166.8 (s, **C**O$_2$Et), 148.5 (d, **C**H=CHCO$_2$Et), 130.0 (d, CH=**C**HCO$_2$Et), 121.8 (d, **C**H=**C**H), 60.3 (t, O**C**H$_2$CH$_3$), 32.3 (**C**H$_2$CH=CH**C**H$_2$), 31.1 (t, **C**H$_2$CH=CHCO$_2$Et), 14.3 (q, OCH$_2$**C**H$_3$) ppm.

FT-IR (film) ν_{max} 2982(m), 2934(m), 2848(w), 1720(m), 1655(s), 1446(m), 1367(m), 1313(s), 1268(s), 1200(s), 1179(s), 1096(m), 1043(s), 974(s), 853(m) cm^{-1}.

LRMS (ES$^+$) *m/z* 281 ([M+H]$^+$, 100%) 298 ([M+NH$_4$]$^+$, 40%), 578 ([2M+NH$_4$]$^+$, 15%), 583 ([2M+Na]$^+$, 8%) Da.

HRMS (ES$^+$) *m/z* $C_{16}H_{24}O_4Na$ Requires 303.1567; Found 303.1567 Da.

(2*E*,6*E*,10*E*)-Dodeca-2,6,10-trienedioic acid (4.41)



4.41
$C_{12}H_{16}O_4$
224.25

A stirred heterogeneous solution of *bis*-ester **4.40** (24.8 g, 88 mmol), NaOH (38.2 g, 955 mmol), and $NaHCO_3$ (7.5 g, 88 mmol) in MeOH (206 mL) and water (710 mL) was heated at reflux for 3 hr. The solution was allowed to cool to room temperature and was extracted

with CH_2Cl_2 (2 x 150 mL). The aqueous phase was cooled to 0 °C and acidified to pH 3 with a 10% w/v aqueous solution of citric acid, then to pH 1 with 2N $HCl_{(aq)}$. After slow stirring for 10 min the precipitate was collected by filtration and washed with ice-cooled Et_2O (~100 mL). Drying *in vacuo* over P_2O_5 afforded the title compound **4.41** (16.5 g, 74 mmol, 83%) as a white solid. R_f = 0.26, streaked (90:10:0.01 CH_2Cl_2:MeOH:AcOH).

m.p. 234-237 °C.

^{1}H NMR (400 MHz, DMSO) δ_H 12.15 (2H, br s, CO_2**H**), 6.84 (2H, dt, *J* = 15.6, 6.8 Hz, C**H**=CHCO$_2$H), 5.80, (2H, dt, *J* = 15.6, 1.5 Hz, CH=C**H**CO$_2$H), 5.48 (2H, tt, *J* = 3.5, 1.3 Hz CH_2C**H**=C**H**CH_2), 2.26 (4H, app. q, *J* = 6.8 Hz, C**H**$_2$CH=CHCO$_2$H), 2.18-2.11 (4H, m, C**H**$_2$CH=CHC**H**$_2$) ppm.

^{13}C NMR (100 MHz, DMSO) δ_C 167.5 (s, **C**O$_2$H), 148.6 (d, **C**H=CHCO$_2$H), 130.1 (d, CH_2**C**H=**C**HCH_2), 122.6 (d, CH=**C**HCO$_2$H), 31.8 (t, **C**H$_2$), 30.9 (t, **C**H$_2$) ppm.

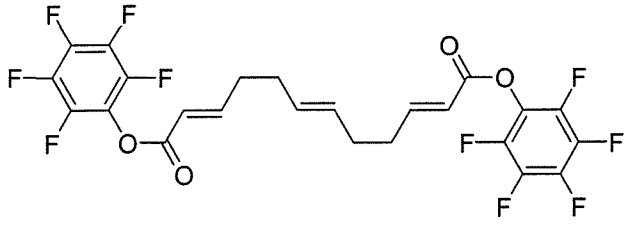
FT-IR (solid) ν_{max} 3415(br), 2909(w), 1691(s), 1647(w), 1425(w), 1321(m), 1250(w), 1214(w), 1039(w), 972(m), 856(w) cm^{-1}.

LRMS (ES$^-$) *m/z* 223.1 ([M-H]$^-$, 100%), 337.1 ([M-H+TFA], 12%), 447.1 ([2M-H]$^-$, 22%) Da.

HRMS (ES$^-$) $C_{12}H_{14}O_4$ Requires 223.0975; Found 223.0970 Da.

Elemental Calc. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19%; Found: C, 64.47; H, 7.32%.

(2*E*,6*E*,10*E*)-*bis*-(Perfluorophenyl)-dodeca-2,6,10-trienedioate (4.42)



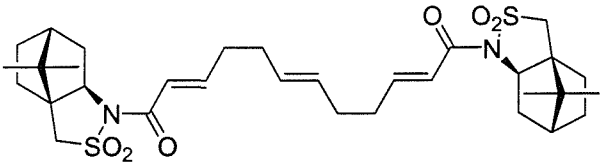
4.42
$C_{24}H_{14}F_{10}O_4$
556.35

To a heterogeneous solution of *bis*-acid **4.41** (150 mg, 0.67 mmol) and pentafluorophenol (241 mg, 1.31 mmol) in dry EtOAc (4.0 mL) at room temperature under an atmosphere of N_2 was added DCC (273 mg, 1.32 mmol) as a single batch and the reaction allowed to stir for 20 hr. The solid urea was removed by filtration and the filtrate was concentrated *in vacuo*. Purification by flash column chromatography (silica gel 12 x 120 mm, 4%

EtOAc/hexane) afforded the title compound **4.42** (335 mg, 0.60 mmol, 90%) as a white crystalline solid. R_f = 0.93 (60% EtOAc/hexane).

m.p.	62-63 °C.
^{1}H NMR	(400 MHz, $CDCl_3$) δ_H 7.28 (2H, dt, J = 15.5, 6.8 Hz, C**H**=CHCO$_2$Ar), 6.08 (2H, dt, J = 15.5, 1.5 Hz, CH=C**H**CO$_2$Ar), 5.52 (2H, tt, J = 3.8, 1.5 Hz, CH$_2$C**H**=C**H**CH$_2$), 2.42 (4H, app. q, J = 7.0 Hz, C**H**$_2$CH=CHCO$_2$Ar), 2.31-2.24 (4H, m, C**H**$_2$CH=CHC**H**$_2$) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ_C 162.2 (s, **C**O$_2$Ar), 154.5 (d, **C**H=CHCO$_2$Ar), 144-136 (m, 5 x F-coupled Ar**C**), 130.2 (d, CH$_2$C**H**=C**H**CH$_2$), 118.7 (d, CH=C**H**CO$_2$Ar), 32.7 (t), 30.9 (t) ppm.
^{19}F NMR	(282 MHz, $CDCl_3$) δ_F 9.15-8.89 (m), 3.33-3.27 (m), -0.75 to -1.0 (m) ppm.
FT-IR	(solid) ν_{max} 2907(w), 2848(w), 1756(s), 1648(m), 1518(s), 1334(w), 1175(w), 1131(m), 993(s), 968(m), 920(w), 851(w) cm^{-1}.
LRMS	(EI) *m/z* 373 ([M-C$_6$F$_5$O]$^{\bullet+}$, 100%), 189 (19%), 133 (20%), 68 (47%), 41 (11%) Da.
HRMS	(EI) [M-C$_6$F$_5$O]$^{\bullet+}$ Requires 373.0863; Found 373.0865 Da.
Elemental	Calc. for $C_{24}H_{14}F_{10}O_4$: C, 51.81; H, 2.54%; Found: C, 52.19; H, 2.59%.

(1*S*)-*N*-[(2*E*,6*E*,10*E*)-3,10-Dodeca-2,6,10-trienedioate]-*bis*-camphor-10,2-sultam (4.43)



4.43
$C_{32}H_{46}N_2O_6S_2$
618.85

***Via* the Pentafluorophenyl Ester**

To a solution of (1*S*)-(-)-camphorsultam **3.17** (81 mg, 0.38 mmol) in THF (3 mL) at –78 °C under an atmosphere of N_2 was added a 2.05M solution of *n*-BuLi in hexanes (0.19 mL, 0.38 mmol), dropwise *via* syringe. The solution was allowed to warm to –40 °C and stir for 20 min, then a solution of *bis*-pentafluorophenyl ester **4.42** (100 mg, 0.18 mmol) in THF (1.5 mL) was added dropwise *via* syringe. The mixture was allowed to warm to –20 °C and stir for 45 min, then was quenched by the addition of a saturated aqueous solution of NH_4Cl (10 mL). The mixture was extracted with Et_2O (3 x 40 mL) and EtOAc (30 mL), then the

combined organic phase was washed with 2N $HCl_{(aq)}$ (2 x 30 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 12 x 80 mm, 2-35% EtOAc/hexane) afforded the title compound **4.43** (57 mg, 0.09 mmol, 51%) as a white solid. R_f = 0.54 (60% EtOAc/hexane).

***Via* the Acid Chloride**

To a heterogeneous solution of *bis*-acid **4.41** (75 mg, 0.33 mmol) and oxalyl chloride (0.06 mL, 0.74 mmol) in CH_2Cl_2 (2 mL) at 0 °C under an atmosphere of N_2 was added dry DMF (2 drops) and the solution allowed to warm to room temperature and stir for 4.5 hr. The solvent was removed *in vacuo* and the residue was taken up in CH_2Cl_2 (2 mL). Concurrently, 60% sodium hydride in mineral oil (29 mg, 0.74 mmol) was added to a solution of (1*S*)-(-)-camphorsultam **3.17** (158 mg, 0.74 mmol) in THF (3 mL) at –78 °C under an atmosphere of N_2. The mixture was allowed to warm to –25 °C and stir for 10 min, and the solution of acid chloride was added *via* canula. The reaction was warmed to 0 °C, stirred for 30 min and was quenched by the addition of a saturated aqueous solution of NH_4Cl (10 mL). The solution was extracted with Et_2O (3 x 30 mL) and EtOAc (40 mL), and the combined organic phase was washed with water (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 12 x 90 mm, 5-30% EtOAc/hexane) afforded the title compound **4.43** (161 mg, 0.26 mmol, 78%) as a white solid. Rf=0.54 (60% EtOAc/hexane).

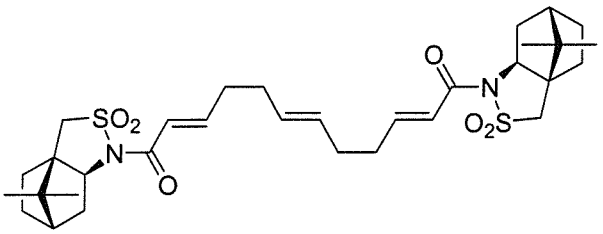
m.p. 172-174 °C (EtOAc/Hexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.06 (2H, dt, J = 15.1, 7.0 Hz, C**H**=CHCON), 6.55 (2H, dt, J = 15.1, 1.5 Hz, CH=C**H**CON), 5.45 (2H, tt, J = 3.5, 1.5 Hz, CH_2C**H**=C**H**CH_2), 3.93 (2H, dd, J = 7.5, 5.0 Hz, C**H**N), 3.51 & 3.44 (2 x 1H, 2 x d, J = 13.8 Hz, CH_2SO_2), 2.31 (4H, app. qd, J = 7.0, 1.5 Hz, CH_2CH=CHCON), 2.23-2.04 (8H, m, CH_2CH=CHC**H**$_2$ + CH_2CHN), 1.97-1.82 (6H, m, C**H**CH_2CHN) + C**H**HCCH_2SO_2 + C**H**HCH_2CCH_2SO_2), 1.47-1.30 (4H, m, CH**H**CCH_2SO_2 + CH**H**CH_2CCH_2SO_2), 1.17 (3H, s, CH_3), 0.97 (3H, s, CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 164.3 (s, **C**ON), 150.2 (d, **C**H=CHCON), 130.0 (d, CH_2**C**H=**C**HCH_2), 121.3 (d, CH=**C**HCON), 65.3 (d, **C**HN), 53.3 (t, **C**H_2SO_2), 48.6 & 48.0 (2 x s, **C**$(CH_3)_2$ + **C**CH_2SO_2), 44.9 (d,

	CHCH$_2$CHN), 38.7 (t, **C**H$_2$CHN), 33.0 (t, **C**H$_2$CH$_2$CCH$_2$SO$_2$), 32.5 (t, **C**H$_2$CH=CHCON), 31.0 (t, **C**H$_2$CH=CH**C**H$_2$), 26.7 (t, **C**H$_2$CCH$_2$SO$_2$), 21.0 (q, **C**H$_3$), 20.1 (q, **C**H$_3$) ppm.
FT-IR	(solid) ν_{max} 2959(m), 2880(w), 1681(s), 1638(s), 1455(w), 1414(w), 1373(m), 1330(s), 1282(m), 1236(s), 1217(s), 1165(m), 1134(s), 1048(m), 995(m), 971(m), 913(w), 731(s) cm^{-1}.
LRMS	(ES$^+$) *m/z* 641 ([M+Na]$^+$, 100%), 619 ([M+H]$^+$, 13%), 1259 ([2M+Na]$^+$, 17%) Da.
HRMS	(ES$^+$) $C_{32}H_{46}N_2O_6S_2Na$ Requires 641.2689; Found 641.2698 Da.
Elemental	Calc. for $C_{32}H_{46}N_2O_6S_2$: C, 62.11; H, 7.49; N, 4.52%; Found: C, 62.28; H, 7.55; N, 4.63%.
$[\alpha]^{24}_D$	-84.2 (c. 0.51, $CHCl_3$).

(1*R*)-*N*-[(2*E*,6*E*,10*E*)-3,10-Dodeca-2,6,10-trienedioate]-*bis*-camphor-10,2-sultam (4.44)



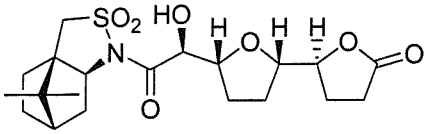
4.44
$C_{32}H_{46}N_2O_6S_2$
618.85

To a heterogeneous solution of *bis*-acid **4.41** (0.50 g, 2.30 mmol) and oxalyl chloride (0.49 mL, 5.57 mmol) in CH_2Cl_2 (13 mL) at 0 °C under an atmosphere of N_2 was added dry DMF (2 drops) and the solution allowed to warm to room temperature and stir for 4 hr. The solvent was removed *in vacuo* and the residue was taken up in CH_2Cl_2 (13 mL). Concurrently, 60% sodium hydride in mineral oil (0.22 g, 5.56 mmol) was added to a solution of (1*R*)-(+)-camphorsultam **3.18** (1.14g, 5.29 mmol) in THF (12 mL) at 0 °C under an atmosphere of N_2. The mixture was stirred for 40 min, and the solution of acid chloride was added *via* canula. The reaction was stirred for 40 min and quenched by the addition of a saturated aqueous solution of NH_4Cl (50 mL), then extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phase was dried (Na_2SO_4), concentrated *in vacuo* and purified by flash column chromatography (silica gel 15 x 90 mm, 5-30% EtOAc/hexane) affording the title compound **4.44** (1.15 g, 1.86 mmol, 81%) as a white solid. R_f = 0.54 (60% EtOAc/hexane).

m.p. 173-175 °C (EtOAc/hexane).

^{1}H NMR	(400 MHz, $CDCl_3$) δ_H 7.06 (2H, dt, J = 15.1, 7.0 Hz, C**H**=CHCON), 6.56 (2H, dt, J = 15.1, 1.5 Hz, CH=C**H**CON), 5.45 (2H, tt, J = 3.5, 1.5 Hz CH_2CH=C**H**CH_2), 3.93 (2H, dd, J = 7.5, 5.0 Hz, C**H**N), 3.51 & 3.44 (2 x 1H, 2 x d, J = 13.8 Hz, CH_2SO_2), 2.31 (4H, app. qd, J = 7.0, 1.5 Hz, CH_2CH=CHCON), 2.23-2.04 (8H, m, CH_2CH=$CHCH_2$ + CH_2CHN), 1.97-1.81 (6H, m, C**H**CH_2CHN + C**H**HCCH_2SO_2 + C**H**H$CH_2CCH_2SO_2$), 1.47-1.30 (4H, m, CH**H**CCH_2SO_2 + CH**H**$CH_2CCH_2SO_2$), 1.16 (3H, s, CH_3), 0.98 (3H, s, CH_3) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ_C 164.3 (s, **C**ON), 150.2 (d, **C**H=CHCON), 130.0 (d, CH**C**H=**C**HCH_2), 121.3 (d, CH=**C**HCON), 65.3 (d, **C**HN), 53.3 (t, CH_2SO_2), 48.6 & 48.0 (2 x s, CH**C**$(CH_3)_2$ + **C**CH_2SO_2), 44.9 (d, **C**HCH_2CHN), 38.7 (t, CH_2CHN), 33.0 (t, $CH_2CH_2CCH_2SO_2$), 32.5 (t, CH_2CH=CHCON), 31.0 (t, CH_2CH=CHCH_2), 26.7 (t, $CH_2CCH_2SO_2$), 21.0 (q, CH_3), 20.1 (q, CH_3) ppm.
FT-IR	(solid) ν_{max} 2960(s), 1682(s), 1639(m), 1456(w), 1414(w), 1374(m), 1331(s), 1217(s), 1166(s), 1134(s), 1063(m), 972(m), 813(m), 732(s) cm^{-1}.
LRMS	(ES^+) *m/z* 641 ($[M+Na]^+$, 100%), 619 ($[M+H]^+$, 6%), 1259 ($[2M+Na]^+$, 5%) Da.
HRMS	(ES^+) $C_{32}H_{46}N_2O_6S_2Na$ Requires 641.2689; Found 641.2696 Da.
Elemental	Calc. for $C_{32}H_{46}N_2O_6S_2$: C, 62.11; H, 7.49; N, 4.52%; Found: C, 62.23; H, 7.52; N, 4.54%.
$[\alpha]^{24}_D$	+82.3 (c. 0.47, $CHCl_3$).

(1*R*)-*N*-[(*S*)-Methyl-2-hydroxy-2-((2*R*,5*S*)-5-((*S*)-5-oxo-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)ethanoyl]-camphor-10,2-sultam (4.45)



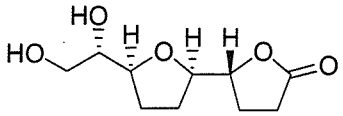
4.45
$C_{20}H_{29}NO_7S$
427.51

To a solution of *bis*-sultam trienedioate **4.44** (1.00 g, 1.62 mmol) and adogen-464 (0.04 g, 0.08 mmol) in acetone (23 mL) and AcOH (15 mL) at –25 °C under an atmosphere of N_2 was added powdered $KMnO_4$ (0.66 g, 4.20 mmol) in three batches at intervals of 30

seconds. The reaction was stirred for 1 hr and was quenched by pouring into an ice-cooled saturated aqueous solution of $Na_2S_2O_5$ (50 mL). The solution was extracted with EtOAc (3 x 70 mL) and CH_2Cl_2 (3 x 50 mL) and the combined organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 (16 mL), and SiO_2-supported $NaIO_4$ (3.23g) was added as a single batch. The suspension was stirred at room temperature for 40 min, the solid removed by filtration and washed with CH_2Cl_2 (3 x 30 mL) and $CHCl_3$ (3 x 15 mL), and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (silica gel 20 x 30 mm, 10-30% EtOAc/hexane) afforded the title compound **4.45** (0.52 g, 1.23 mmol, 76%) as a white foamy solid. R_f = 0.26 (70% EtOAc/toluene).

m.p.	69-71 °C.
^{1}H NMR	(400 MHz, $CDCl_3$) δ_H 4.55-4.45 (3H, m, C**H**OC=O + C**H**OHCON + C**H**CHOHCON), 3.99 (1H, dt, *J* = 7.0, 3.3 Hz, C**H**CHOC=O), 3.92 (1H, dd, *J* = 7.8, 5.0 Hz, C**H**N), 3.50 & 3.42 (2 x 1H, 2 x d, *J* = 13.8 Hz, C**H**$_2$SO$_2$), 3.25 (1H, br d, *J* = 9.3 Hz, CHO**H**), 2.70 (1H, ddd, *J* = 17.6, 10.0, 7.0 Hz, C**H**HC=O), 2.43 (1H, ddd, *J* = 17.6, 10.0, 6.2 Hz, CH**H**C=O), 2.37-1.79 (10H, m), 1.49-1.19 (3H, m), 1.12 (3H, s, C**H**$_3$), 0.95 (3H, s, C**H**$_3$) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ_C 178.0 (s), 170.8 (s), 81.8 (d), 80.5 (d), 78.9 (d), 72.7 (d), 65.7 (d), 53.0 (t), 49.3 (s), 48.1 (s), 44.7 (d), 38.3 (t), 33.0 (t), 28.3 (t), 28.0 (t), 27.4 (t), 26.6 (t), 24.8 (t), 20.9 (q), 20.1 (q) ppm.
FT-IR	(film) ν_{max} 3492(br), 2958(w), 2879(w), 1774(s), 1692(s), 1460(w), 1413(w), 1330(s), 1270(m), 1218(m), 1167(m), 1136(s), 1109(m), 1063(m), 988(w), 760(w), 734(w) cm^{-1}.
LRMS	(ES$^+$) *m/z* 450 ([M+Na]$^+$, 100%) Da.
HRMS	(ES$^+$) $C_{20}H_{29}NO_7SNa$ Requires 450.1557; Found 450.1571 Da.
Elemental	Calc. for $C_{20}H_{29}NO_7S$: C, 56.19; H, 6.84; N, 3.27%; Found: C, 56.01; H, 6.91; N, 3.17%.
$[\alpha]^{24}_D$	+63.3 (c. 0.35, $CHCl_3$).

(2*R*,2`*R*,5`*S*)-5`-[(1*S*)-1,2-Dihydroxyethyl]-hexahydro-2-2`-bifuran-5-(2*H*)-one (5.1)



5.1
$C_{10}H_{16}O_5$
216.23

To a solution of THF-lactone **4.28** (70 mg, 0.16 mmol) in THF (1.6 mL) at –10 °C under an atmosphere of N_2 was added a 2M solution of $BH_3{\cdot}SMe_2$ in THF (123 μL, 0.25 mmol) followed after 10 min by $NaBH_4$ (6 mg, 0.15 mmol). The reaction was stirred for 1.5 hr and 10% MeOH/CH_2Cl_2 (2 mL) was added *via* syringe. The reaction was stirred for a further 10 min, quenched with 2N $HCl_{(aq)}$ (1 ml), diluted with CH_2Cl_2 (10 mL) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue purified by flash column chromatography (silica gel 20 x 25 mm, 0-5% MeOH/CH_2Cl_2) affording the title compound **5.1** (23 mg, 0.11 mmol, 65%) as a colourless oil. R_f = 0.25 (10% MeOH/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.51 (1H, ddd, *J* = 7.5, 5.5, 3.5 Hz, C**H**OC=O), 4.06-3.99 (2H, m), 3.73-3.54 (3H, m), 2.68 (1H, ddd, *J* = 17.6, 10.0, 6.5 Hz, C**H**HC=O), 2.50 (1H, ddd, *J* = 17.6, 10.0, 6.5 Hz, CH**H**C=O), 2.34-2.22 (2H, m, C**H**HCH$_2$C=O + CHO**H**), 2.17 (1H, ddd, *J* = 13.1, 10.1, 6.0, CH**H**CH$_2$C=O), 2.11-1.80 (4H, m, CHC**H**$_2$C**H**$_2$CH) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 177.8 (s), 81.3 (d), 81.2 (d), 81.1 (d), 74.0 (d), 65.6 (t), 28.5 (t), 28.0 (t), 27.7 (t), 24.7 (t) ppm.

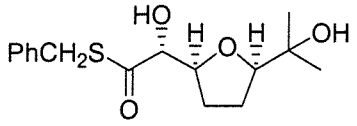
FT-IR (film) ν_{max} 3398(br), 2946(w), 2881(w), 1767(s), 1459(w), 1418(w), 1342(w), 1294(w), 1227(m), 1188(m), 1067(m), 1016(m), 944(w), 896(w), 869(w), 812(w) cm^{-1}.

LRMS (ES$^+$) *m/z* 239 ([M+Na]$^+$, 100%) Da.

HRMS (ES$^+$) $C_{10}H_{16}O_5Na$ Requires 239.0890; Found 239.0890 Da.

$[\alpha]^{24}_D$ -27.3 (c. 0.89, $CDCl_3$).

(2*S*)-2-Hydroxy-[(2*S*,2*R*)-5-(1-hydroxy-1-methylethyl)-tetrahydrofuran-2-yl]-thioacetic acid *S*-benzyl ester (5.3)



5.3
$C_{16}H_{22}O_4S$
310.41

The title compound was prepared according to the method of Oppolzer *et al.*[191] To a solution of benzyl mercaptan (58 μL, 0.560 mmol) in dry Et_2O (3.5 mL) at 0 °C under an atmosphere of N_2 was added a 2.36M solution of *n*-BuLi in hexanes (0.24 mL, 0.560 mmol), dropwise *via* syringe. The yellow solution was stirred for 5 min and treated by the dropwise addition of a 2M solution of $AlMe_3$ in hexanes (0.28 mL, 0.560 mmol). The now colourless solution was stirred for 30 min and treated by the dropwise addition of a solution of diol **4.13** (150 mg, 0.374 mmol) in dry toluene (4.8 mL), and the reaction was stirred for 1 hr. The mixture was diluted with Et_2O (5 mL) and quenched by the addition of 2N $HCl_{(aq)}$ (1 mL). The aqueous phase was extracted with Et_2O (4 x 10 mL), and the combined organic phase was washed with 1M $NaOH_{(aq)}$ (5 mL) and a saturated aqueous solution of $NaHCO_3$ (10 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, 12 x 55 mm, 20-100% EtOAc/hexane) afforded the title compound **5.3** (136 mg, 0.437 mmol, 78%) as a white solid. R_f = 0.38 (60% EtOAc/hexane).

m.p. 96-98 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.33-7.20 (5H, m, Ar**H**), 4.58 (1H, ddd, *J* = 6.9, 5.0, 2.0 Hz, C**H**CHOH), 4.19 (1H, d, *J* = 13.6 Hz, SC**H**HAr), 4.13 (1H, d, *J* = 13.6 Hz, SCH**H**Ar), 4.12 (1H, d, *J* = 2.0 Hz, C**H**OH), 3.78 (1H, t, *J* = 7.5 Hz, C**H**COH$(CH_3)_2$), 2.20-2.00 (3H, m), 1.87 (1H, ddd, *J* = 12.1, 8.0, 7.5 Hz, C**H**HCHCOH$(CH_3)_2$), 1.27 (3H, s, C**H**$_3$), 1.14 (3H, s, C**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 203.5 (s), 137.7 (s), 129.0 (d), 128.7 (d), 127.4 (d), 86.5 (d), 81.0 (d), 80.5 (d), 72.9 (s), 32.9 (t), 28.7 (t), 28.1 (q), 26.2 (t), 26.1 (q) ppm.

FT-IR (film) ν_{max} 3292(br), 2970(w), 1681(s), 1495(w), 1454(w), 1379(w), 1340(w), 1296(w), 1162(m), 1127(m), 1072(s), 951(m), 702(m) cm^{-1}.

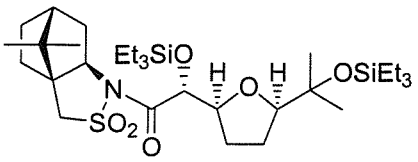
LRMS (ES^+) *m/z* 333 ($[M+Na]^+$, 100%), 643 ($[2M+Na]^+$, 13%) Da.

HRMS (ES^+) $C_{16}H_{22}O_4SNa$ Requires 333.1124; Found 333.1128 Da.

Elemental Calc. for $C_{16}H_{22}O_4S$: C, 61.91; H, 7.14%; Found: C, 61.81; H, 7.15%.

$[\alpha]^{24}_D$ +93.9 (c. 0.26, $CHCl_3$).

(1*S*)-*N*-{(2*R*)-2-Triethylsilyloxy-2-[(2*R*,5*S*)-5-(1-triethylsilyloxy-1-methylethyl)-tetrahydro-2-furanyl]-ethanoyl}-camphor-10,2-sultam (5.5)



5.5
$C_{31}H_{59}NO_6SSi_2$
630.05

To a solution of diol **4.13** (192 mg, 0.48 mmol) in dry CH_2Cl_2 (4.3 mL) at 0 °C under an atmosphere of N_2 was added 2,6-lutidine (0.12 mL, 1.00 mmol) followed by triethylsilyltrifluoromethanesulfonate (0.22 mL, 0.98 mmol), and the solution stirred for 40 min. The reaction mixture was then washed twice with a 10% v/w aqueous solution of citric acid (2 x 5 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 30 x 50 mm, 15% EtOAc/hexane) afforded the title compound **5.5** (261 mg, 0.41 mmol, 87%) as a white solid. R_f = 0.84 (60% EtOAc/hexane).

m.p. 124-126 °C.

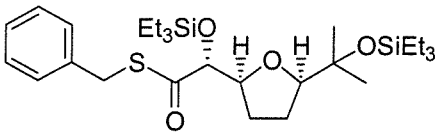
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.64 (1H, d, J = 6.8 Hz, C**H**OSiEt$_3$), 4.11 (1H, ddd, J = 9.3, 6.8, 6.3 Hz, C**H**CHOSiEt$_3$), 3.89 (1H, dd, J = 7.8, 5.3 Hz, C**H**N), 3.68 (1H, t, J = 7.3 Hz, C**H**C(CH$_3$)$_2$), 3.51 & 3.43 (2 x 1H, 2 x d, J = 13.6 Hz, C**H**$_2$SO$_2$), 2.20-2.03 (2H, m), 1.98-1.70 (5H, m), 1.66-1.53 (2H, m), 1.46-1.30 (2H, m), 1.28 (3H, s, C**H**$_3$), 1.18 (6H, s, 2 x C**H**$_3$), 1.00-0.85 (21H, m, C**H**$_3$ + 2 x SiCH$_2$C**H**$_3$), 0.70 (6H, q, J = 8.28 Hz, SiC**H**$_2$CH$_3$), 0.58 (6H, q, J = 8.03 Hz, SiC**H**$_2$CH$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.5 (s), 87.3 (d), 81.7 (d), 77.8 (d), 74.8 (s), 65.8 (d), 53.7 (t), 48.9 (s), 48.2 (s), 45.1 (d), 38.8 (t), 33.5 (t), 29.0 (q), 27.7 (t), 26.9 (t), 26.6 (t), 24.7 (q), 21.2 (q), 20.4 (q), 7.6 (q), 7.3 (q), 5.3 (t) ppm.

FT-IR (film) ν_{max} 2955(s), 2911(m), 2876(m), 1691(s), 1458(w), 1394(w), 1329(s), 1237(m), 1172(m), 1135(m), 1106(m), 1082(s), 1062(m), 1012(w), 985(w), 743(s), 728(s) cm^{-1}.

LRMS	(ES^+) *m/z* 652 ($[M+Na]^+$, 100%) Da.
HRMS	(ES^+) $C_{31}H_{59}NO_6SSi_2Na$ Requires 652.3493; Found 652.3486 Da.
Elemental	Calc. for $C_{31}H_{59}NO_7SSi_2$: C, 59.10; H, 9.44; N, 2.22%; Found: C, 58.82; H, 9.514; N, 1.99%.
$[\alpha]^{24}_D$	-27.8 (c. 0.27, $CDCl_3$).

(*R*)-S-Benzyl-2-(triethylsilyloxy)-2-((2*S*,2*R*)-5-(2-triethylsilyloxy))propan-2-yl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)ethanethioate 5.6



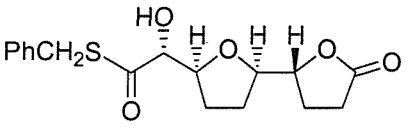
5.6
$C_{28}H_{50}O_4SSi_2$
538.93

To a solution of benzyl mercaptan (19 μL, 0.164 mmol) in dry Et_2O (1.2 mL) at 0 °C under an atmosphere of N_2 was added a 2.15M solution of *n*-BuLi in hexanes (76 μL, 0.164 mmol), dropwise *via* syringe. The yellow solution was stirred for 5 min and treated by the dropwise addition of a 2M solution of $AlMe_3$ in hexanes (82 μL, 0.164 mmol). The now colourless solution was stirred for 30 min and treated by the dropwise addition of a solution of *bis*-silyl ether **5.5** (69 mg, 0.109 mmol) in dry toluene (2.0 mL), then stirred for 2 hr. The reaction was diluted with Et_2O (5 mL) and quenched by the addition of an aqueous solution of $NaHSO_4$ (1 g in 200 mL, 10 mL used). The mixture was extracted with EtOAc (3 x 30 mL) and the combined organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (2 x 20 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 10 x 60 mm, 5-40% EtOAc/hexane) afforded the title compound **5.6** (18 mg, 0.033 mmol, 31%) as a colourless oil.

^{1}H NMR	(300MHz, $CDCl_3$) δ_H 7.33-7.19 (5H, m, Ar**H**), 4.17 (1H, d, J = 5.0 Hz, C**H**($OSiEt_3$)), 4.09 & 4.04 (2 x 1H, 2 x d, J = 13.8 Hz, C**H**$_2SO_2$), 3.95 (1H, ddd, J = 7.2, 7.1, 5.0 Hz, C**H**CH($OSiEt_3$)), 3.67 (1H, app. t, J = 6.8 Hz, C**H**C($OSiEt_3$)$(CH_3)_2$), 1.92-1.67 (4H, m, 2 x C**H**$_2$C**H**$_2$), 1.22 (3H, s, C**H**$_3$), 1.14 (3H, s, C**H**$_3$), 1.10-0.88 (18H, m, SiCH$_2$C**H**$_3$), 0.71-0.50 (12H, m, SiC**H**$_2$CH$_3$) ppm.
FT-IR	(film) ν_{max} 2970(w), 2957(s), 2871(m), 1685(s), 1499(w), 1451(w), 1382(w), 1346(w), 1294(w), 1167(m), 1127(m), 1073(s), 947(m), 740(s), 703(m) cm^{-1}.

LRMS	(ES$^+$) *m/z* 539 ([M+H]$^+$, 5%), 561 ([M+Na]$^+$, 100%) Da.
Elemental	Calc. for $C_{28}H_{50}O_4SSi_2$: C, 62.40; H, 9.35%; Found: C, 62.80; H, 9.01%.
$[\alpha]^{24}_D$	+84.3 (c. 0.15, $CHCl_3$).

(*R*)-*S*-Benzyl-2-hydroxy-2-((2*S*,5*R*)-5-((*R*)-5-oxo-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)ethanethioate (5.8)



5.8
$C_{17}H_{20}O_5S$
336.40

The title compound was prepared according to the method of Oppolzer *et al.*[191] To a solution of benzyl mercaptan (78 μL, 0.660 mmol) in dry Et_2O (2.0 mL) at 0 °C under an atmosphere of N_2 was added a 1.40M solution of *n*-BuLi in hexanes (0.47 mL, 0.660 mmol), dropwise *via* syringe. The yellow solution was stirred for 5 min and treated by the dropwise addition of a 2M solution of $AlMe_3$ in hexanes (0.33 mL, 0.660 mmol). The now colourless solution was stirred for 30 min and treated by the dropwise addition of a solution of lactone **4.28** (94 mg, 0.220 mmol) in dry toluene (3.0 mL), then stirred for a further 1.25 hr. The reaction was quenched by the addition of 0.5N $HCl_{(aq)}$ (2 mL), was stirred at room temperature for 1 hr, and the organic phase was shaken vigorously with 1N $HCl_{(aq)}$ (2 x 10 mL). The aqueous phase was extracted with Et_2O (2 x 20 mL) and EtOAc (2 x 20 mL), and the organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, 10-60% EtOAc/hexane) afforded the title compound **5.8** (53 mg, 0.158 mmol, 72%) as a white solid. R_f = 0.38 (60% EtOAc/hexane).

m.p.	78-80 °C.
^{1}H NMR	(400 MHz, $CDCl_3$) δ_H 7.30-7.16 (5H, m, Ar**H**), 4.48 (1H, ddd, *J* = 8.0, 5.5, 2.5 Hz, C**H**OH), 4.39 (1H, app. td, *J* = 6.0, 2.5 Hz, C**H**OC=O), 4.16 (1H, d, *J* = 15.1 Hz, SC**H**HAr), 4.12 (1H, dd, *J* = 9.5, 2.5 Hz, C**H**CHOH), 4.08 (1H, d, *J* = 15.1 Hz, SCH**H**Ar), 3.95 (1H, td, *J* = 7.0, 2.5 Hz, C**H**CHOC=O), 3.02 (1H, d, *J* = 8.0 Hz, CHO**H**), 2.42 (1H, ddd, *J* = 17.6, 10.5, 7.0 Hz, C**H**HC=O), 2.34 (1H, ddd, *J* = 17.6, 9.5, 6.0 Hz, CH**H**C=O), 2.27-1.90 (6H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 202.1 (s), 177.7 (s), 137.7 (s), 129.0 (d), 128.7 (d), 127.4 (d), 81.5 (d), 80.7 (d), 80.1 (d), 79.4 (d), 32.8 (t), 28.2 (t), 27.7 (t), 27.5 (t), 24.8 (t) ppm.

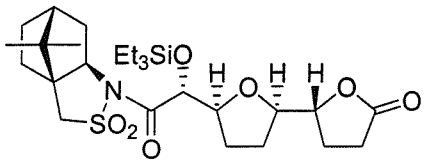
FT-IR (film) ν_{max} 3480(br), 2950(w), 2879(w), 1771(s), 1681(s), 1495(w), 1454(w), 1183(m), 1128(m), 1072(m), 983(w), 925(w), 813(w), 731(m), 704(m) cm^{-1}.

LRMS (ES^+) *m/z* 354 ($[M+NH_4]^+$, 100%), 359 ($[M+Na]^+$, 7%), 690 ($[2M+NH_4]^+$, 68%), 695 ($[2M+Na]^+$, 20%) Da.

HRMS (ES^+) $C_{17}H_{20}O_5SNa$ Requires 359.0923; Found 359.0920 Da.

$[\alpha]^{25}_D$ +51.2 (c. 0.58, $CDCl_3$).

(1*S*)-*N*-{(*R*)-2-Triethylsilyloxy-2-((2*S*,5*R*)-5-((*R*)-5-oxo-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)ethanoyl}-camphor-10,2-sultam (5.9)



5.9
$C_{26}H_{43}NO_7SSi$
541.77

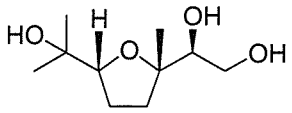
To a solution of lactone **4.28** (303 mg, 0.71 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C under an atmosphere of N_2 was added 2,6-lutidine (0.09 mL, 0.74 mmol) followed by triethylsilyltrifluoromethanesulfonate (0.16 mL, 0.73 mmol), and the solution stirred for 20 min. The reaction was quenched by the addition of a 10% v/w aqueous solution of citric acid (10 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phase was washed with 1N HCl (2 x 10 mL) and a saturated aqueous solution of $NaHCO_3$ (2 x 20 mL), then dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 30 x 50 mm, 10-40% EtOAc/hexane) afforded the title compound **5.9** (301 mg, 0.56 mmol, 78%) as a white solid. R_f = 0.55 (70% EtOAc/hexane).

m.p. 64-65 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.72 (1H, d, *J* = 7.8 Hz, C**H**OSiEt$_3$), 4.50 (1H, td, *J* =7.0, 3.8 Hz, C**H**OC=O), 4.27 (1H, m, C**H**CHOSiEt$_3$), 4.00 (1H, dd, *J* = 7.5, 5.5 Hz, C**H**N), 3.94 (1H, td, *J* = 7.6, 3.8 Hz, C**H**CHOC=O), 3.48 (2H, s, C**H**$_2$SO$_2$), 2.70 (1H, ddd, *J* = 17.3, 9.5, 6.5 Hz, C**H**HC=O), 2.41 (1H, ddd, *J* = 17.3, 9.5, 8.9 Hz, CH**H**C=O), 2.30-2.01 (5H, m), 1.95-1.76 (6H, m), 1.55-1.28 (2H, m), 1.14 (3H, s,

	CH_3), 0.95 (3H, s, CH_3), 0.91 (9H, t, J = 7.8 Hz, $SiCH_2CH_3$), 0.63 (6H, q, J = 7.8 Hz, $SiCH_2CH_3$) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ_C 177.8 (s), 169.9 (s), 81.2 (d), 80.8 (d), 80.5 (d), 72.7 (d), 65.6 (d), 53.2 (t), 48.6 (s), 47.8 (s), 44.9 (d), 38.5 (t), 32.8 (t), 28.5 (t), 27.0 (t), 26.8 (t), 26.4 (t), 24.3 (t), 21.0 (q), 20.0 (q), 6.8 (q), 4.8 (t) ppm.
FT-IR	(film) ν_{max} 2960(s), 2912(s), 2879(s), 1776(s), 1697(s), 1455(m), 1413(m), 1333(s), 1266(s), 1233(s), 1218(s), 1160(s), 1136(s), 1058(m), 1011(m), 735(s) cm^{-1}.
LRMS	(ES^+) *m/z* 564 ($[M+Na]^+$, 100%), 559 ($[M+NH_4]^+$, 78%), 580 ($[M+K]^+$, 7%), 1100 ($[2M+NH_4]^+$, 25%), 1105 ($[2M+Na]^+$, 47%) Da.
HRMS	(ES^+) $C_{26}H_{43}NO_7SSiNa$ Requires 564.2421; Found 564.2429 Da.
Elemental	Calc. for $C_{26}H_{43}NO_7SSi$: C, 57.64; H, 8.00; N, 2.58%; Found: C, 57.57; H, 8.04; N, 2.35%.
$[\alpha]^{25}_D$	-32.4 (c. 0.38, $CHCl_3$).

***Rac*-(1*S*)-1-[(2*S*,5*R*)-5-(1-Hydroxy-1-methylethyl)-2-methyltetrahydrofuran-2-yl]-ethane-1,2-diol (6.2)**



6.2
$C_{10}H_{20}O_4$
204.26

To a solution of acetate **6.1** (550 mg, 2.23 mmol) in MeOH (12 mL) at 0 °C was added K_2CO_3 (15 mg, 0.11 mmol) and the heterogeneous solution stirred for 2 hr. The K_2CO_3 was removed by filtration and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (silica gel 30 x 40 mm, 0-10% MeOH/CH_2Cl_2) afforded the title compound **6.2** (449 mg, 2.20 mmol, 99%) as a white solid. R_f = 0.33 (10% MeOH/CH_2Cl_2).

m.p.	97-99 °C (MeOH).
^{1}H NMR	(400 MHz, $CDCl_3$) δ_H 3.86 (1H, t, J = 7.3 Hz, C**H**COH$(CH_3)_2$), 3.79 (1H, dd, J = 11.3, 6.5 Hz, C**H**HOH), 3.71 (1H, dd, J = 11.3, 3.0 Hz, CH**H**OH), 3.53 (1H, dd, J = 6.5, 3.0 Hz, C**H**OHCH$_2$OH), 3.26 (3H, br s, 3 x CHO**H**), 2.23 (1H, ddd, J = 12.3, 9.0, 5.3 Hz, C**H**HCCH$_3$), 2.01 (1H, dddd, J = 12.3, 9.0, 7.8, 7.3 Hz, C**H**HCH$_2$CCH$_3$), 1.90 (1H, dddd, J = 12.3, 8.5, 7.3, 5.3 Hz, CH**H**CH$_2$CCH$_3$), 1.66 (1H, ddd,

J = 12.3, 8.5, 7.8 Hz, CH**H**CCH$_3$), 1.27 (3H, s, C**H**$_3$), 1.20 (3H, s, C**H**$_3$), 1.12 (3H, s, C**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 86.0 (d, **C**HCOH(CH$_3$)$_2$), 85.4 (s, CH$_2$**C**CH$_3$), 76.8 (d, **C**HOHCH$_2$OH), 72.1 (s, **C**OH(CH$_3$)$_2$), 63.8 (t, **C**H$_2$OH), 35.9 (t, **C**H$_2$CCH$_3$), 27.0 (q, **C**H$_3$), 26.6 (t, **C**H$_2$CH$_2$CCH$_3$), 25.7 (q, **C**H$_3$), 23.8 (q, **C**H$_3$) ppm.

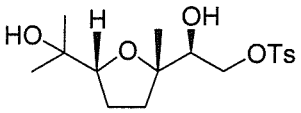
FT-IR (film) ν_{max} 3376(br), 2972(s), 2879(m), 1457(w), 1379(m), 1182(m), 1082(s), 1058(s), 1025(s), 951(m) cm^{-1}.

LRMS (ES$^+$) *m/z* 227 ([M+Na]$^+$, 100%), 431 ([2M+Na]$^+$, 11%) Da.

HRMS (ES$^+$) *m/z* $C_{10}H_{20}O_4Na$ Requires 227.1254; Found 227.1254 Da.

Elemental Calc. for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87%; Found: C, 58.90; H, 9.89%.

Rac-(2_S_)-2-Hydroxy-2-[(2_S_,5_R_)-5-(1-hydroxy-1-methylethyl)-2-methyltetrahydrofuran-2-yl]-ethyl-4-methylbenzenesufonate (6.3)



6.3
$C_{17}H_{26}O_6S$
358.45

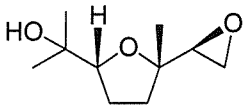
The title compound was prepared according to the method of Hu *et al.*[230] Thus, to a solution of diol **6.2** (336 mg, 1.65 mmol) in C_6H_6 (15 mL) were added Bu_2SnO (492 mg, 1.97 mmol) and oven-dried molecular sieves (100 mg) and the heterogeneous solution stirred at reflux under an atmosphere of N_2 for 2.5 hr. The reaction was allowed to cool to room temperature and TsCl (330 mg, 1.73 mmol) and TBAB (530 mg, 1.65 mmol) were added. The mixture was stirred for 1 hr, the sieves were removed by filtration and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (silica gel 20 x 50 mm, 5-25% EtOAc/hexane) afforded the title compound **6.3** (564 mg, 1.57 mmol, 96%) as a white solid. R_f = 0.78 (10% MeOH/CH_2Cl_2).

m.p. 81-83 °C (MeOH/hexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.82 (2H, d, J = 8.0 Hz, 2 x Ar**H**), 7.36 (2H, d, J = 8.0 Hz, 2 x Ar**H**), 4.28 (1H, dd, J = 10.3, 3.4 Hz, C**H**HOTs), 4.06 (1H, dd, J = 10.3, 8.0 Hz, CH**H**OTs), 3.82 (1H, t, J = 7.3 Hz, C**H**COH(CH$_3$)$_2$), 3.75-3.69 (1H, m, C**H**OHCH$_2$OTs), 3.24 (1H, d, J = 5.0 Hz, CHO**H**), 2.45 (3H, s, ArC**H**$_3$), 2.40 (1H, br s, CO**H**(CH$_3$)$_2$), 2.20 (1H, ddd, J = 12.3, 9.0, 5.5 Hz, C**H**HCCH$_3$), 2.03-1.85 (2H, m,

	$CHHCCH_3$ + $CHHCH_2CCH_3$), 1.64 (1H, m, $CHHCH_2CCH_3$), 1.20 (3H, s, CH_3), 1.16 (3H, s, CH_3), 1.09 (3H, s, CH_3) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ_C 145.1 (s, ArCCH_3), 133.0 (s, ArCSO_2), 130.1 (2 x d, ArCH), 128.2 (2 x d, ArCH), 85.9 (d, $CHCOH(CH_3)_2$), 84.1 (s, CH_2CCH_3), 74.9 (d, $CHOHCH_2OTs$), 72.1 (s, $COH(CH_3)_2$), 71.7 (t, CH_2OTs), 35.7 (t, $CH_2CH_2CCH_3$), 27.8 (q, CH_3), 26.6 (t, CH_2CCH_3), 25.5 (q, CH_3), 23.7 (q, CH_3), 21.8 (q, ArCH_3) ppm.
FT-IR	(film) ν_{max} 3373(br), 2973(m), 2926(w), 2874(w), 1598(w), 1451(w), 1359(s), 1189(s), 1176(s), 1097(m), 970(s), 917(m), 837(m), 815(m), 772(w) cm^{-1}.
LRMS	(ES^+) *m/z* 381 ($[M+Na]^+$, 92%), 739 ($[2M+Na]^+$, 100%) Da.
HRMS	(ES^+) *m/z* $C_{17}H_{26}O_6SNa$ Requires 381.1342; Found 381.1346 Da.
Elemental	Calc. for $C_{17}H_{26}O_6S$: C, 56.96; H, 7.31%; Found: C, 56.68; H, 7.39%.

***Rac*-2-{(2*R*,5*S*)-5-Methyl-5-[(2*S*)-oxiran-2-yl]-tetrahydrofuran-2-yl}-propan-2-ol (6.4)**



6.4
$C_{10}H_{18}O_3$
186.25

To a solution of tosylate **6.3** (427 mg, 1.19 mmol) in CH_2Cl_2 (15 mL) at 0 °C under an atmosphere of N_2 was added DBU (218 mg, 1.43 mmol) and the reaction stirred for 10 min. Further DBU (30 mg, 0.20 mmol) was added and the reaction was stirred for a further 10 min, then quenched by the addition of a 10% v/w aqueous solution of citric acid (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 20 x 35 mm, 0-20% EtOAc/hexane) afforded the title compound **6.4** (217 mg, 1.17 mmol, 96%) as a colourless oil. R_f = 0.31 (40% EtOAc/hexane).

^{1}H NMR	(400 MHz, $CDCl_3$) δ_H 3.84 (1H, t, *J* = 7.0 Hz, $CHCOH(CH_3)_2$), 3.50 (1H, br s, CHOH), 2.99 (1H, dd, *J* = 4.3, 3.0 Hz, epoxide CH), 2.86 (1H, dd, *J* = 5.3, 3.0 Hz, epoxide CHH), 2.72 (1H, dd, *J* = 5.3, 4.3 Hz, epoxide CHH), 2.22 (1H, ddd, *J* = 11.8, 8.5, 5.3 Hz, $CHHCCH_3$), 2.13-2.03 (1H, m, $CHHCH_2CCH_3$), 1.95-1.75 (2H, m, $CHHCCH_3$ + $CHHCH_2CCH_3$), 1.28 (3H, s, CH_3), 1.20 (3H, s, CH_3), 1.06 (3H, s, CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 86.8 (d, **C**HCOH$(CH_3)_2$), 79.5 (s, CH_2**C**CH_3), 71.5 (s, **C**OH$(CH_3)_2$), 58.2 (d, epoxide **C**H), 44.0 (t, epoxide CH_2), 36.6 (t, **C**H_2CCH_3), 28.3 (q, **C**H_3), 26.1 (t, **C**$H_2CH_2CCH_3$), 25.3 (q, **C**H_3), 24.8 (q, **C**H_3) ppm.

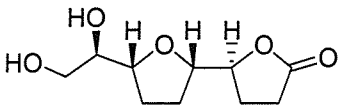
FT-IR (film) ν_{max} 3451(br), 2975(s), 2926(m), 2874(m), 1469(m), 1375(m), 1266(m), 1181(m), 1120(m), 1077(s), 1053(s), 1033(s), 951(m), 892(s) cm^{-1}.

LRMS (ES^+) *m/z* 209 ($[M+Na]^+$, 100%), 395 ($[2M+Na]^+$, 57%) Da.

HRMS (ES^+) *m/z* $C_{20}H_{36}O_6Na$ Requires 395.2404; Found 395.2403 Da.

Elemental Calc. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74%; Found: C, 64.41; H, 9.61%.

(2*S*, 2`*S*, 5`*R*)-5`-[(1*R*)-1,2-Dihydroxyethyl]-hexahydro-2-2`-bifuran-5-(2*H*)-one (6.5)



6.5
$C_{10}H_{16}O_5$
216.23

To a solution of lactone **4.45** (198 mg, 0.46 mmol) in THF (5 mL) at –20 °C under an atmosphere of N_2 was added a 2M solution of $BH_3{\cdot}SMe_2$ in THF (0.35 mL, 0.70 mmol). The mixture was stirred for 10 min, cooled to –78 °C and a 0.1M solution of $NaBH_4$ in diglyme (2.45 mL, 0.23 mmol) was added *via* syringe. The reaction was stirred for 1.5 hr, 10% MeOH/CH_2Cl_2 (2 mL) was added, and after stirring for a further 30 min the solution was passed through a plug of silica gel (12 x 30 mm, 10% MeOH/CH_2Cl_2). The solvent was removed *in vacuo* and the residue purified by flash column chromatography (silica gel 12 x 30 mm, 0-5% MeOH/CH_2Cl_2) affording the title compound **6.5** (49 mg, 0.23 mmol, 49%) as a colourless oil. R_f = 0.24 (10% MeOH/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.51 (1H, ddd, *J* = 7.5, 5.5, 3.5 Hz, **CH**OC=O), 4.06-3.99 (2H, m), 3.73-3.54 (3H, m), 2.68 (1H, ddd, *J* = 17.6, 10.0, 6.5 Hz, C**H**HC=O), 2.50 (1H, ddd, *J* = 17.6, 10.0, 6.5 Hz, CH**H**C=O), 2.34-2.22 (2H, m, C**H**HCH$_2$C=O + O**H**), 2.17 (1H, ddd, *J* = 13.1, 10.1, 6.0, CH**H**CH$_2$C=O), 2.10-1.80 (4H, m, CHC**H**$_2$C**H**$_2$CH) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 177.8 (s), 81.3 (d), 81.2 (d), 81.1 (d), 74.0 (d), 65.6 (t), 28.5 (t), 28.0 (t), 27.7 (t), 24.7 (t) ppm.

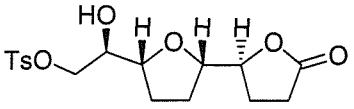
FT-IR (film) ν_{max} 3398(br), 2947(w), 2886(w), 1767(s), 1463(w), 1418(w), 1342(w), 1293(w), 1188(m), 1127(m), 1067(m), 1015(m), 944(w), 895(w), 814(w) cm^{-1}.

LRMS (ES^+) *m/z* 239 ($[M+Na]^+$, 100%) Da.

HRMS (ES^+) $C_{10}H_{16}O_5Na$ Requires 239.0890; Found 239.0890 Da.

$[\alpha]^{24}_D$ +26.4 (c. 0.21, $CDCl_3$).

(2*R*)-2-Hydroxy-2-[(2*S*,2*S*`,5*S*)-5`-oxooctahydro-2-2`-bifuran-5-yl]-ethyl-4-methylbenzenesulfonate (6.6)



6.6
$C_{17}H_{22}O_7S$
370.42

The title compound was prepared according to the method of Hu *et al.*[230] Thus, to a solution of diol **6.5** (389 mg, 1.80 mmol) in C_6H_6 (22 mL) was added Bu_2SnO (537 mg, 2.16 mmol) and the heterogeneous solution stirred at reflux under an atmosphere of N_2 for 3.5 hr. The reaction was allowed to cool to room temperature and TsCl (360 mg, 1.89 mmol) was added. The mixture was stirred for 2 hr, the sieves were removed by filtration and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (silica gel 15 x 30 mm, 0-2% MeOH/CH_2Cl_2) afforded the title compound **6.6** (473 mg, 1.28 mmol, 71%) as an off-white solid. R_f = 0.46 (10% MeOH/CH_2Cl_2).

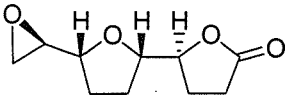
m.p. 99-101 °C (MeOH/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.81 (2H, d, *J* = 7.8 Hz, 2 x Ar**H**), 7.36 (2H, d, *J* = 7.8 Hz, 2 x Ar**H**), 4.50 (1H, ddd, *J* = 7.8, 5.8, 5.5 Hz, C**H**OC=O), 4.07-3.97 (4H, m, C**H**$_2$OTs + C**H**OHCH$_2$OTs + C**H**CHOHCH$_2$OTs), 3.71 (1H, dtd, *J* = 7.0, 5.5, 4.0 Hz, C**H**CHOC=O), 2.58 (1H, ddd, *J* = 17.8, 10.0, 6.5 Hz, C**H**HC=O), 2.46 (1H, ddd, *J* = 17.8, 10.0, 6.8 Hz, CH**H**C=O), 2.45 (3H, s, ArC**H**$_3$), 2.28 (1H, dddd, *J* = 12.8, 10.0, 7.8, 6.5 Hz, C**H**HCH$_2$C=O), 2.26 (1H, d, *J* = 7.3 Hz, CHO**H**), 2.16 (1H, dddd, *J* = 12.8, 10.0, 7.0, 5.8 Hz, CH**H**CH$_2$C=O), 2.06-1.86 (4H, m, CHC**H**$_2$C**H**$_2$CH) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 177.6 (s), 145.2 (s), 132.8 (s), 130.1 (2 x d), 128.2 (2 x d), 81.3 (d), 80.7 (d), 79.5 (d), 71.5 (d), 70.9 (t), 28.4 (t), 28.0 (t), 27.5 (t), 24.8 (q), 21.8 (t) ppm.

FT-IR	(film) ν_{max} 2950(w), 2923(w), 2851(w), 1772(s), 1455(w), 1357(m), 1175(s), 1166(s), 1098(w), 1019(w), 975(m), 950(m), 815(m) cm^{-1}.
LRMS	(ES^+) *m/z* 388 ($[M+NH_4]^+$, 100%), 758 ($[2M+NH_4]^+$, 27%) Da.
HRMS	(ES^+) $C_{17}H_{22}O_7SNa$ Requires 393.0978; Found 393.0944 Da.
Elemental	Calc. for $C_{17}H_{22}O_7S$: C, 55.12; H, 5.99%; Found: C, 54.86; H, 5.92%.
$[\alpha]^{24}_D$	+8.5 (c. 0.35, $CDCl_3$).

(2*S*,2`*S*,5`*S*)-5`-[(2*R*)-Oxiran-2-yl]-hexahydro-2-2`-bifuran-5-(2*H*)-one (6.7)



6.7
$C_{10}H_{14}O_4$
198.21

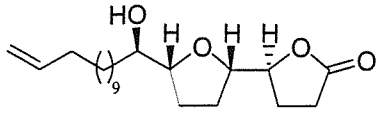
To a solution of tosylate **6.6** (460 mg, 1.24 mmol) in CH_2Cl_2 (20 mL) at room temperature was added a solution of DBU (199 mg, 1.30 mmol) in CH_2Cl_2 (2 mL) and the reaction stirred for 30 min then quenched by the addition of a 10% v/w aqueous solution of citric acid (5 mL). The aqueous phase was extracted with EtOAc (3 x 30 mL) and the combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 12 x 35 mm, 0-2% MeOH/CH_2Cl_2) afforded the title compound **6.7** (245 mg, 1.24 mmol, 99%) as an off-white solid. R_f = 0.45 (5% MeOH/CH_2Cl_2). The crystal structure for this epoxide is contained in the appendix at the rear of this thesis.

m.p.	107-108 °C (MeOH/CH_2Cl_2).
^{1}H NMR	(400 MHz, $CDCl_3$) δ_H 4.50 (1H, ddd, *J* = 7.8, 5.5, 3.0 Hz, C**H**OC=O), 4.07 (1H, ddd, *J* = 7.3, 6.5, 3.0 Hz, C**H**CHOC=O), 3.73 (1H, m, C**H**), 2.94 (1H, ddd, *J* = 5.8, 4.0, 3.0 Hz, epoxide C**H**), 2.75 (1H, dd, *J* = 5.0, 4.0 Hz, epoxide CH**H**), 2.70 (1H, ddd, *J* = 17.6, 10.0, 7.0 Hz, CHHC=O), 2.61 (1H, dd, *J* = 5.0, 3.0 Hz, epoxide CH**H**), 2.46 (1H, ddd, *J* = 17.6, 9.5, 7.0 Hz, CH**H**C=O), 2.33-2.18 (2H, m, CH_2CH_2C=O), 2.05-1.88 (4H, m, CHCH_2CH_2CH) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ_C 177.8 (s, **C**=O), 81.5 (d, **C**HCHOC=O), 81.3 (d, **C**HOC=O), 81.0 (d, **C**H), 53.8 (d, epoxide **C**H), 44.0 (t, epoxide **C**H_2), 28.5 (t), 28.4 (t), 27.8 (t), 24.4 (t, **C**H_2CH_2C=O) ppm.
FT-IR	(film) ν_{max} 2916(m), 1770(s), 1257(m), 1180(m), 1072(m), 1023(m), 925(w), 893(w) cm^{-1}.
LRMS	(ES^+) *m/z* 216 ($[M+NH_4]^+$, 100%), 199 ($[M+H]^+$, 10%) Da.

Elemental Calc. for $C_{10}H_{14}O_4$: C, 60.54; H, 7.12%; Found: C, 60.65; H, 7.20%.

$[\alpha]^{24}_D$ +24.8 (c. 0.25, $CDCl_3$).

(*S*)-5-((2*S*,5*R*)-5-((*R*)-1-Hydroxytridec-12-enyl)-tetrahydrofuran-2-yl)-dihydrofuran-2-(3*H*)-one (6.8)



6.8
$C_{21}H_{36}O_4$
352.49

Magnesium turnings (457 mg, 18.8 mmol) were heated at ~400 °C under an atmosphere of Ar for 5 min then allowed to cool to room temperature. THF (50 mL) and I_2 (1 crystal) were added, followed by the dropwise addition of 11-bromo-1-undecene (0.30 mL, 1.4 mmol). The solution was heated at reflux for 10 min, further 11-bromo-1-undecene (3.13 mL, 14.3 mmol) was added and the solution was heated at reflux for 20 min and then stirred at room temperature for 1 hr. Titration of this solution using excess I_2 and $Na_2S_2O_3$ gave its average concentration as 0.33M. An aliquot of this solution (8.72 mL, 2.87 mmol) was added to a suspension of CuI (273 mg, 1.44 mmol) in THF (15 mL) at –60 °C under an atmosphere of Ar. The solution was allowed to warm to –25 °C and stir for 20 min, then was cooled to –60 °C, and a solution of epoxide **6.7** (237 mg, 1.20 mmol) in THF (3 mL) was added *via* syringe. The solution was allowed to warm to –50 °C and stir for 10 min, then was quenched by the addition of a saturated aqueous solution of NH_4Cl (10 mL) followed by water (10 mL). The mixture was extracted with EtOAc (3 x 40 mL) and CH_2Cl_2 (2 x 40 mL), and the combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 25 x 40 mm, 5-30% EtOAc/hexane) afforded the title compound **6.8** (346 mg, 0.98 mmol, 82%) as a white, waxy solid. R_f = 0.29 (70% EtOAc/hexane).

m.p. 47-49 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.81 (1H, ddt, J = 17.1, 10.3, 6.5 Hz, H_2C=C**H**), 4.99 (1H, ddt, J = 17.1, 2.3, 1.8 Hz, **H**HC=CH), 4.93 (1H, ddt, J = 10.3, 2.3, 1.3 Hz, H**H**C=CH), 4.50 (1H, ddd, J = 8.3, 5.5, 3.0 Hz, C**H**OC=O), 4.02 (1H, ddd, J = 7.0, 6.8, 3.0 Hz, C**H**CHOC=O), 3.81 (1H, ddd, J = 7.5, 6.5, 6.0 Hz, CH_2CHOHC**H**), 3.41 (1H, ddd, J = 11.3, 6.5, 5.8 Hz, CH_2C**H**OHCH), 2.64 (1H, ddd, J = 17.8, 10.0, 7.0 Hz, C**H**HC=O), 2.48 (1H, ddd, J = 17.8, 10.0, 6.8 Hz,

CHHC=O), 2.29 (1H, dddd, J = 12.6, 10.0, 8.3, 6.8 Hz, CHHCH$_2$C=O), 2.20 (1H, dddd, J = 12.6, 10.0, 7.0, 5.5 Hz, CHHCH$_2$C=O), 2.10-1.86 (6H, m), 1.76 (1H, m), 1.57-1.18 (17H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 177.7 (s), 139.4 (d), 114.2 (t), 83.8 (d), 81.1 (d), 81.0 (d), 74.6 (d), 34.0 (t), 33.9 (t), 29.9 (t), 29.8 (t), 29.7 (t), 29.3 (t), 29.1 (t), 28.5 (t), 28.1 (t), 27.9 (t), 25.8 (t), 24.7 (t) ppm.

FT-IR (film) ν_{max} 2926(s), 2854(m), 1781(s), 1463(w), 1255(w), 1170(w), 1103(m), 1077(m), 835(m), 775(m) cm^{-1}.

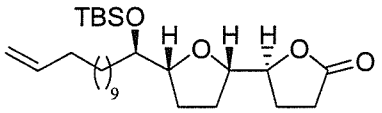
LRMS (ES$^+$) *m/z* 370 ([M+NH$_4$]$^+$, 81%), 375 ([M+Na]$^+$, 11%), 722 ([2M+NH$_4$]$^+$, 100%), 727 ([2M+Na]$^+$, 32%) Da.

HRMS (ES$^+$) $C_{21}H_{36}O_4Na$ Requires 375.2506; Found 375.2509 Da.

Elemental Calc. for $C_{21}H_{36}O_4$: C, 71.55; H, 10.29; Found: C, 71.42; H, 9.98%.

$[\alpha]^{23}_D$ +21.4 (c. 0.28, $CDCl_3$).

(*S*)-5-((2*S*,5*R*)-5-((*R*)-1-(*tert*-Butyldimethylsilyloxy)tridec-12-enyl)-tetrahydrofuran-2-yl)-dihydrofuran-2-(3*H*)-one (6.9)



6.9
$C_{27}H_{50}O_4Si$
466.78

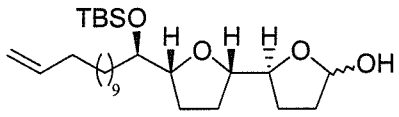
To a solution of alcohol **6.8** (198 mg, 0.56 mmol) and TBSCl (169 mg, 1.13 mmol) in CH_2Cl_2 (4 mL) at room temperature was added imidazole (76 mg, 1.13 mmol), and the cloudy solution stirred at room temperature for 72 hr. The reaction was quenched by the addition of water (4 mL) and extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 12 x 30 mm, 5% EtOAc/hexane) afforded the title compound **6.9** (216 mg, 0.46 mmol, 82%) as a white, waxy solid. R_f = 0.47 (40% EtOAc/hexane).

m.p. 39-41 °C (EtOAc/hexane).

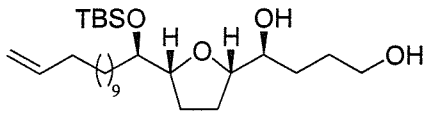
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.82 (1H, ddt, J = 17.1, 10.3, 6.8 Hz, H$_2$C=CH), 4.99 (1H, ddt, J = 17.1, 2.3, 1.8 Hz, HHC=CH), 4.93 (1H, ddt, J = 10.3, 2.3, 1.3 Hz, HHC=CH), 4.50 (1H, ddd, J = 7.8, 6.5, 3.3 Hz, CHOC=O), 3.96 (1H, ddd, J = 7.8, 6.5, 3.3 Hz, CHCHOC=O), 3.85 (1H, app. dt, J = 8.3, 6.0 Hz, CH$_2$CH(OSiR$_3$)CH), 3.63 (1H,

	ddd, J = 6.8, 6.0, 3.5 Hz, $CH_2CH(OSiR_3)CH$), 2.61 (1H, ddd, J = 17.6, 10.0, 6.3 Hz, CHHC=O), 2.47 (1H, ddd, J = 17.6, 9.5, 8.0 Hz, CHHC=O), 2.26-2.11 (2H, m, CH_2CH_2CO), 2.01-1.58 (6H, m, H_2C=CHCH_2 + CHCH_2CH_2CH), 1.48-1.11 (18H, m, $(CH_2)_9$), 0.91 (9H, s, SiC(CH_3)$_3$), 0.09 (3H, s, SiCH_3), 0.08 (3H, s, SiCH_3) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ_C 177.4 (s), 139.5 (d), 114.2 (t), 83.5 (d), 81.4 (d), 80.3 (d), 74.7 (d), 34.0 (t), 33.1 (t), 30.0 (t), 29.81 (t), 29.77 (t), 29.7 (t), 29.3 (t), 29.2 (t), 28.6 (t), 27.7 (t), 27.1 (t), 26.1 (q), 25.5 (t), 24.3 (s), 18.4 (t), -4.1 (q), -4.4 (q) ppm.
FT-IR	(film) ν_{max} 2926(s), 2854(s), 1782(s), 1462(w), 1252(m), 1169(m), 1101(m), 1071(m), 908(w), 835(s), 775(s) cm^{-1}.
LRMS	(ES$^+$) *m/z* 489 ([M+Na]$^+$, 100%), 484 ([M+NH_4]$^+$, 61%), 467 ([M+H]$^+$, 42%) Da.
HRMS	(ES$^+$) $C_{27}H_{50}O_4SiNa$ Requires 489.3371; Found 489.3367 Da.
Elemental	Calc. for $C_{27}H_{50}O_4Si$: C, 69.48; H, 10.80%; Found: C, 69.23; H, 10.54%.
$[\alpha]^{25}_D$	+19.1 (c. 0.46, $CDCl_3$).

(*S*)-5-((2*S*,5*R*)-5-((*R*)-1-(*tert*-Butyldimethylsilyloxy)tridec-12-enyl)-tetrahydrofuran-2-yl)-dihydrofuran-2-ol (6.10) and
(*S*)-1-((2*S*,5*R*)-5-((*R*)-1-(*tert*-Butyldimethylsilyloxy)tridec-12-enyl)-tetrahydrofuran-2-yl)-butane-1,4-diol (6.11)



6.10
$C_{27}H_{52}O_4Si$
468.76



6.11
$C_{27}H_{54}O_4Si$
470.80

To a solution of lactone **6.9** (151 mg, 0.323 mmol) in THF (4.0 mL) at –78 °C under an atmosphere of N_2 was added a 1M solution of DIBAL-H in hexanes (0.42 mL, 0.420 mmol) and the solution allowed to stir for 2 hr. The reaction was diluted with Et_2O (3 mL) and quenched by the addition of 1M $HCl_{(aq)}$ (2 mL), then extracted with EtOAc (3 x 25 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash

column chromatography (silica gel 12 x 30 mm, 5-10% EtOAc/hexane) afforded anomeric lactol **6.10** (76 mg, 0.165 mmol, 50%) as a colourless oil, and diol **6.11** (40 mg, 0.084 mmol, 26%) as a pale yellow oil. $R_{f,\ lactol} = 0.47$, $R_{f,\ diol} = 0.19$ (40% EtOAc/toluene).

Lactol 6.10

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.82 (1H, ddt, J = 17.1, 10.3, 6.8 Hz, H_2C=C**H**), 5.60 & 5.44 (1H total, 2 x m, anomeric C**H**OH), 5.00 (1H, ddt, J = 17.1, 2.3, 1.8 Hz, **H**HC=CH), 4.93 (1H, ddt, J = 10.3, 2.3, 1.3 Hz, H**H**C=CH), 4.19 & 4.10 (1H total, 2 x m, C**H**OCHOH), 3.99-3.66 (3H, m), 3.54 (1H, d, J = 6.5 Hz, CHO**H**), 2.16-1.74 (10H, m), 1.68-1.50 (2H, m), 1.44-1.20 (16H, m), 0.91 & 0.90 (total 9H, 2 x s, 2:1, SiC(C**H**$_3$)$_3$), 0.08 & 0.07 (2 x 6H, 2 x s, 2:1, Si(C**H**$_3$)$_2$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 139.6 (d), 114.4 (t), 99.4 (t), 99.1 (t), 82.5 (d), 82.3 (d), 82.0 (d), 81.8 (d), 81.6 (d), 81.0 (d), 74.3 (d), 74.2 (d), 34.8 (t), 34.1 (t), 33.5 (t), 33.3 (t), 32.0 (t), 30.2 (t), 30.1 (t), 30.0 (t), 29.91 (t), 29.89 (t), 29.87 (t), 29.8 (t), 28.1 (t), 27.0 (t), 26.3 (t), 26.24 (t), 26.22 (q), 25.9 (t), 25.8 (t), 18.5 (s), -4.0 (q), -4.2 (q) ppm.

FT-IR (film) ν_{max} 2945(s), 2857(s), 1590(w), 1462(m), 1359(m), 1318(w), 1257(m), 1179 (m), 1060(m), 911(m), 835(m) cm^{-1}.

LRMS (ES^+) *m/z* 491 ($[M+Na]^+$, 100%), 959 ($[2M+Na]^+$, 13%) Da.

HRMS (ES^+) $C_{27}H_{52}O_4SiNa$ Requires 491.3527; Found 491.3531 Da.

Elemental Calc. for $C_{27}H_{52}O_4Si$: C, 69.18; H, 11.18%; Found: C, 68.93; H, 11.21%.

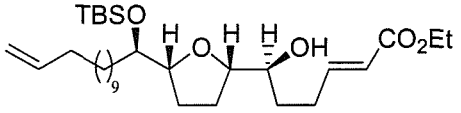
$[\alpha]^{24}_D$ +21.5 (c. 0.72, $CDCl_3$).

Diol 6.11

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.82 (1H, ddt, J = 17.1, 10.3, 6.8 Hz, H_2C=C**H**), 5.00 (1H, ddt, J = 17.1, 2.3, 1.5 Hz, **H**HC=CH), 4.93 (1H, ddt, J = 10.3, 2.3, 1.3 Hz, H**H**C=CH), 3.96 (1H, app. td, J = 7.0, 3.8 Hz), 3.73-3.55 (3H, m), 3.42 (1H, ddd, J = 8.8, 5.0, 3.0 Hz), 3.13 (1H, br s, O**H**), 2.67 (1H, br s, O**H**), 2.08-2.01 (2H, m), 1.99-1.39 (10H, m), 1.38-1.14 (16H, m), 0.91 (9H, s, SiC(C**H**$_3$)$_3$), 0.08 (6H, s, Si(C**H**$_3$)$_2$) ppm.

^{13}C NMR	(100 MHz, $CDCl_3$) δ_C 139.5 (d), 114.4 (t), 82.4 (d), 81.6 (d), 74.8 (d), 74.7 (d), 63.3 (t), 34.5 (t), 34.1 (t), 31.9 (t), 30.1 (t), 30.0 (t), 29.89 (t), 29.85 (t), 29.8 (t), 29.4 (t), 29.2 (t), 28.6 (t), 27.7 (t), 26.2 (q), 25.7 (t), 18.5 (s), -4.0 (q), -4.2 (q) ppm.
FT-IR	(film) ν_{max} 3384(br), 2926(s), 2855(s), 1463(w), 1360(w), 1253(m), 1078(m), 909(m), 836(m), 775(m) cm^{-1}.
LRMS	(ES^+) *m/z* 471 ($[M+H]^+$, 100%), 493 ($[M+Na]^+$, 86%), 963 ($[2M+Na]^+$, 27%), 958 ($[2M+NH_4]^+$, 16%), 941 ($[2M+H]^+$, 10%) Da.
HRMS	(ES^+) $C_{27}H_{54}O_4SiNa$ Requires 493.3683; Found 493.3676 Da.
Elemental	Calc. for $C_{27}H_{54}O_4Si$: C, 68.88; H, 11.56%; Found: C, 68.41; H, 11.61%.
$[\alpha]^{25}_D$	-6.6 (c. 0.32, $CDCl_3$).

(*S*,*E*)-Ethyl-6-((2*S*,5*R*)-5-((*R*)-1-(*tert*-butyldimethylsilyloxy)tridec-12-enyl)-tetrahydrofuran-2-yl)-6 hydroxyhex-2-enoate (6.12)



6.12
$C_{31}H_{58}O_5Si$
538.88

From lactol 6.10

To a solution of lactol **6.10** (19 mg, 0.041 mmol) in toluene (2.0 mL) at room temperature under an atmosphere of N_2 was added (carbethoxymethylene)triphenylphosphorane (22 mg, 0.061 mmol) and the solution stirred at room temperature for 16 hr. Further phosphorane (22mg, 0.061 mmol) was added and the reaction stirred for a further 5 hr, then the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel 8 x 40 mm, 5% EtOAc/hexane) afforded the title compound **6.12** (21 mg, 0.039 mmol, 96%) as a colourless oil. R_f = 0.66 (40% EtOAc/hexane).

From Lactone 6.9 Without Lactol Isolation

To a solution of lactone **6.9** (0.734 g, 1.57 mmol) in THF (30 mL) at –78 °C under an atmosphere of N_2 was added a 1M solution of DIBAL-H in hexanes (2.14 mL, 2.14 mmol). The solution was stirred for 1 hr, then diluted with CH_2Cl_2 (25 mL) and quenched with water (5 mL). The mixture was filtered through cellite and the organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was taken up in toluene (25 mL),

(carbethoxymethylene)triphenylphosphorane (3.000 g, 8.21 mmol) was added and the solution stirred for 16 hr. Removal of the solvent *in vacuo* and purification by flash column chromatography (silica gel 20 x 55 mm, 5% EtOAc/hexane) afforded the title compound **6.12** (0.834 g, 1.55 mmol, 96%) as a colourless oil. R_f = 0.66 (40% EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.00 (1H, dt, J = 15.8, 6.8 Hz, C**H**=CHCO$_2$Et), 5.85 (1H, dt, J = 15.8, 1.8 Hz, CH=C**H**CO$_2$Et), 5.82 (1H, ddt, J = 17.1, 10.3, 6.5 Hz, H$_2$C=C**H**), 5.00 (1H, ddt, J = 17.1, 2.3, 1.5 Hz, **H**HC=CH), 4.93 (1H, ddt, J = 10.3, 2.3, 1.3 Hz, H**H**C=CH), 4.18 (2H, q, J = 7.0 Hz, OC**H**$_2$CH$_3$), 3.95 (1H, app. td, J = 7.0, 3.5 Hz, CH$_2$CH(OSiR$_3$)C**H**), 3.80 (1H, m, C**H**CHOH), 3.58 (1H, ddd, J = 6.8, 5.8, 3.5 Hz, CH$_2$C**H**(OSiR$_3$)CH), 3.39 (1H, m, C**H**OH), 2.80 (1H, d, J = 6.3 Hz, CHO**H**), 2.46 (1H, m), 2.30 (1H, m), 2.04 (1H, m), 1.85 (1H, m), 1.81-1.76 (3H, m), 1.75-1.45 (3H, m), 1.40-1.18 (21H, m), 0.91 (9H, s, SiC(C**H**$_3$)$_3$), 0.08 (6H, s, Si(C**H**$_3$)$_2$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 167.0 (s), 149.4 (d), 139.5 (d), 121.7 (d), 114.4 (t), 82.1 (d), 81.5 (d), 74.9 (d), 73.6 (d), 60.4 (t), 34.6 (t), 34.1 (t), 33.2 (t), 30.2 (t), 29.91 (t), 29.86 (t), 29.8 (t), 29.4 (t), 29.2 (t), 28.8 (t), 28.6 (t), 27.7 (t), 26.2 (q), 25.7 (t), 18.5 (s), 14.6 (q), -4.0 (q), -4.2 (q) ppm.

FT-IR (film) ν_{max} 2927(s), 2855(s), 1722(s), 1655(w), 1463(w), 1257(m), 1194(m), 1072(m), 1046(m), 836(m), 775(m) cm^{-1}.

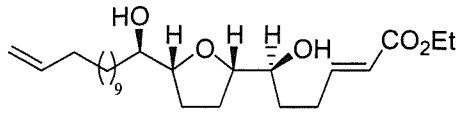
LRMS (ES$^+$) *m/z* 561 ([M+Na]$^+$, 100%), 1099 ([2M+Na]$^+$, 49%) Da.

HRMS (ES$^+$) $C_{31}H_{58}O_5SiNa$ Requires 561.3946; Found 561.3958 Da.

Elemental Calc. for $C_{31}H_{58}O_5Si$: C, 69.10; H, 10.85%; Found: C, 69.19; H, 11.21%.

$[\alpha]^{25}_D$ -11.3 (c. 0.17, $CDCl_3$).

(*S*,*E*)-Ethyl-6-hydroxy-6-((2*S*,5*R*)-5-((*R*)-1-hydroxytridec-12-enyl)-tetrahydrofuran-2-yl)-hex-2-enoate (6.13)



6.13
$C_{25}H_{44}O_5$
424.62

To a suspension of Re_2O_7 (123 mg, 0.255 mmol) in THF (2 mL) at room temperature under an atmosphere of N_2 was added freshly distilled TFAA (0.045 mL, 0.321 mmol) and the suspension stirred for 1.5 hr. The solvent was removed *in vacuo*, and the dark blue residue washed with freshly distilled hexane (2 x 2 mL) and solvated with CH_2Cl_2 (2 mL). TFAA (0.045 mL, 0.321 mmol) was added *via* syringe, followed by a solution of ester **6.12** (50 mg, 0.095 mmol) in CH_2Cl_2 (1.5 mL). The suspension was stirred for 2 hr during which the colour changed from dark blue to purple and then to black, and the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (1.5 mL) and 30% aqueous H_2O_2 (2 mL). The mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 12 x 40 mm, 10-40% EtOAc/hexane) afforded the title compound **6.13** (37 mg, 0.087 mmol, 92%) as a white solid. R_f = 0.21 (40% EtOAc/hexane).

m.p 27-29^{O}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.99 (1H, dt, J = 15.6, 7.0 Hz, C**H**=CHCO$_2$Et), 5.86 (1H, dt, J = 15.6, 1.8 Hz, CH=C**H**CO$_2$Et), 5.82 (1H, ddt, J = 17.1, 10.0, 6.5 Hz, H$_2$C=C**H**), 4.99 (1H, ddt, J = 17.1, 2.3, 1.5 Hz, **H**HC=CH), 4.93 (1H, ddt, J = 10.4, 2.3, 1.3 Hz, H**H**C=CH), 4.19 (2H, q, J = 7.3 Hz, OC**H**$_2$CH$_3$), 3.87-3.79 (2H, m, C**H**OC**H**), 3.47-3.41 (2H, m, C**H**OHCHOCHC**H**OH), 2.50-4.88 (9H, m), 1.85-1.20 (24H, m) ppm.

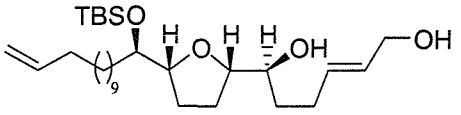
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 166.9 (s), 148.8 (d), 139.4 (d), 121.9 (d), 114.3 (t), 82.9 (d), 82.7 (d), 74.5 (d), 73.6 (d), 60.4 (t), 34.3 (t), 34.0 (t), 32.6 (t), 29.85 (t), 29.77 (t), 29.7 (t), 29.3 (t), 29.1 (t), 28.5 (t), 28.30 (t), 28.25 (t), 25.9 (t), 14.5 (q) ppm.

FT-IR (film) ν_{max} 3425(br), 2925(s), 2854(m), 1720(m), 1654(m), 1465(w), 1441(m), 1368(m), 1268(m), 1197(m), 1044(m), 979(m), 910(m), 737(m) cm^{-1}.

LRMS (ES$^+$) *m/z* 447 ([M+Na]$^+$, 100%), 871 ([2M+Na]$^+$, 30%) Da.

HRMS	(ES$^+$) $C_{25}H_{44}O_5Na$ Requires 447.3081; Found 447.3084 Da.
Elemental	Calc. for $C_{25}H_{44}O_5$: C, 70.72; H, 10.44%; Found: C, 70.76; H, 10.72%.
$[\alpha]^{24}_D$	-2.2 (c. 0.49, $CDCl_3$).

(*S*,*E*)-6-((2*S*,5*R*)-5-((*R*)-1-(*tert*-Butyldimethylsilyloxy)tridec-12-enyl)-tetrahydrofuran-2-yl)hex-2-ene-1,6-diol (6.14)



6.14
$C_{29}H_{56}O_4Si$
496.85

To a solution of ester **6.12** (112 mg, 0.21 mmol) in THF (5 mL) at –78 °C under an atmosphere of N_2 was added a 1M solution of DIBAL-H in hexanes (0.52 mL, 0.52 mmol) and the solution strirred for 30 min. Further DIBAL-H (0.52 mL, 0.52 mmol) was then added and the reaction stirred for 20 min and quenched by the addition of water (3 mL). The mixture was extracted with Et_2O (3 x 10 mL), and the combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 12 x 30 mm, 5-20% EtOAc/hexane) afforded the title compound **6.14** (92 mg, 0.19 mmol, 89%) as a colourless oil. R_f = 0.40 (40% EtOAc/hexane).

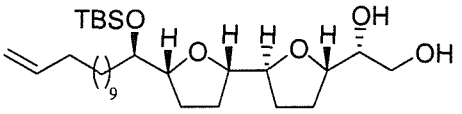
^{1}H NMR	(400 MHz, $CDCl_3$) δ_H 5.82 (1H, ddt, *J* = 17.1, 10.3, 6.8 Hz, H_2C=C**H**), 5.75-5.63 (2H, m, C**H**=C**H**CH_2OH), 4.99 (1H, ddt, *J* = 17.1, 2.3, 1.5 Hz, **H**HC=CH), 4.93 (1H, ddt, *J* = 10.3, 2.3, 1.3 Hz, H**H**C=CH), 4.09 (2H, d, *J* = 5.0 Hz, C**H**$_2$OH), 3.93 (1H, app. td, *J* = 7.0, 3.8 Hz, CH_2CH(OSiR_3)C**H**), 3.79 (1H, m, C**H**CHOH), 3.59 (1H, app. td, *J* = 6.0, 3.8 Hz, CH_2C**H**(OSiR_3)CH), 3.39 (1H, m, C**H**OH), 2.28 (1H, m), 2.15 (1H, m), 2.08-2.00 (2H, m), 1.95-1.73 (5H, m), 1.68-1.49 (3H, m), 1.47-1.23 (17H, m), 0.91 (9H, s, SiC(C**H**$_3$)$_3$), 0.08 (6H, s, Si(C**H**$_3$)$_2$) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ_C 139.5 (d), 133.3 (d), 129.5 (d), 114.4 (t), 82.3 (d), 81.7 (d), 74.9 (d), 73.9 (d), 64.0 (t), 34.4 (t), 34.2 (t), 34.1 (t), 30.1 (t), 29.9 (t), 29.85 (t), 29.76 (t), 29.4 (t), 29.2 (t), 28.7 (t), 28.5 (t), 27.7 (t), 26.2 (q), 25.7 (t), 18.5 (s), -4.0 (q), -4.2 (q) ppm.
FT-IR	(film) ν_{max} 3366(br), 2926(s), 2854(m), 1460(w), 1253(m), 1083(m), 997(m), 968(m), 902(m), 835(m), 775(m) cm^{-1}.

LRMS (ES$^+$) *m/z* 519 ([M+Na]$^+$, 100%), 514 ([M+NH$_4$]$^+$, 74%), 497 ([M+H]$^+$, 28%), 1010 ([2M+NH$_4$]$^+$, 5%), 1015 ([2M+Na]$^+$, 3%) Da.

HRMS (ES$^+$) $C_{29}H_{56}O_4SiNa$ Requires 519.3840; Found 519.3840 Da.

$[\alpha]^{25}_D$ -9.7 (c. 0.21, $CDCl_3$).

(*R*)-1-((2*S*,5*S*)-5-((2*S*,5*R*)-5-((*R*)-1-*tert*-Butyldimethylsilyloxy)tridec-12-enyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)ethane-1,2-diol (6.17)



6.17
$C_{29}H_{56}O_5Si$
512.84

The title compound was prepared according to the method Sinha *et al.*[132] Thus, to a solution of alcohol **6.14** (209 mg, 0.421 mmol) in CH_2Cl_2 (6 mL) at –20 °C under an atmosphere of N_2 were added powdered 4Å molecular sieves (200 mg), D-(-)-diethyl tartrate (0.42 mL, 2.415 mmol) and Ti(O*i*-Pr)$_4$ (0.60 mL, 2.013 mmol), and the mixture stirred for 30 min. A 5M solution of *t*-BuOOH in *n*-C_9H_{20} (0.80 mL, 4.830 mmol) was added *via* syringe and the reaction was stirred for a further 48 hr at –20 °C then quenched by the addition of water (2 mL) and 1M $NaOH_{(aq)}$ (3 mL). After stirring vigorously for 20 min the mixture was filtered through celite and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (silica gel 15 x 85 mm, 10-25% EtOAc/hexane) afforded the title compound **6.17** (185 mg, 0.361 mmol, 86%) as a colourless oil. The product was an inseparable mixture of major (**6.17**) and minor (**6.18**) diastereoisomers, the ratio of which was obtained after later tosylation. All signals are reported in the carbon NMR. R_f = 0.32 (60% EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.82 (1H, ddt, *J* = 17.1, 10.3, 6.8 Hz, H_2C=C**H**), 4.99 (1H, ddt, *J* = 17.1, 2.3, 1.5 Hz, **H**HC=CH), 4.93 (1H, ddt, *J* = 10.3, 2.3, 1.3 Hz, H**H**C=CH), 4.03-3.58 (8H, m), 2.17 (2H, br s, 2 x CHO**H** + CH_2O**H**), 2.10-1.59 (10H, m), 1.55-1.18 (18H, m), 0.89 (9H, s, SiC(C**H**$_3$)$_3$), 0.07 (3H, s, SiC**H**$_3$), 0.06 (3H, s, SiC**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 139.4 (d), 114.2 (t), 82.44 (d), 82.38 (d), 82.3 (d), 81.8 (d), 81.2 (d), 80.7 (d), 74.4 (d), 74.3 (d), 73.1 (d), 73.0 (d), 72.2 (d), 64.1 (t), 63.9 (t), 34.0 (t), 32.6 (t), 32.2 (t), 30.08 (t), 30.05 (t), 29.84 (t), 29.78 (t), 29.76 (t), 29.7 (t), 29.3 (t), 29.1 (t), 28.8 (t),

28.5 (t), 28.3 (t), 28.2 (t), 27.2 (t), 26.6 (t), 26.4 (t), 26.1 (q), 26.02 (t), 25.96 (t), 25.8 (t), 25.1 (t), 18.4 (s), 14.3 (s), -4.1 (q), -4.4 (q) ppm.

FT-IR (film) ν_{max} 3380(br), 2925(m), 2854(m), 1462(w), 1250(w), 1061(s), 939(m), 835(s), 775(s), 721(w) cm^{-1}.

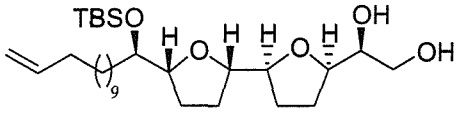
LRMS (ES^+) *m/z* 535 ($[M+Na]^+$, 100%), 530 ($[M+NH_4]^+$, 22%), 551 ($[M+K]^+$, 15%), 1042 ($[2M+NH_4]^+$, 3%), 1047 ($[2M+Na]^+$, 8%) Da.

HRMS (ES^+) $C_{29}H_{56}O_5SiNa$ Requires 535.3789; Found 535.3796 Da.

Elemental Calc. for $C_{29}H_{56}O_5Si$: C, 67.92; H, 11.01%; Found: C, 67.98; H, 11.02%.

$[\alpha]^{23}_D$ +15.0 (c. 0.32, $CDCl_3$).

(*S*)-1-((2*R*,5*S*)-5-((2*S*,5*R*)-5-((*R*)-1-*tert*-Butyldimethylsilyloxy)tridec-12-enyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)ethane-1,2-diol (6.18)



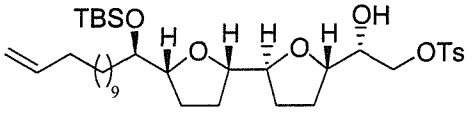
6.18
$C_{29}H_{56}O_5Si$
512.84

The title compound was prepared according to the method Sinha *et al.*[132] Thus, to a solution of alcohol **6.14** (221 mg, 0.444 mmol) in CH_2Cl_2 (6 mL) at –20 °C under an atmosphere of N_2 were added powdered 4Å molecular sieves (200 mg), L-(+)-diethyl tartrate (0.42 mL, 2.415 mmol) and Ti(O*i*-Pr)$_4$ (0.60 mL, 2.013 mmol), and the mixture stirred for 30 min. A 5M solution of *t*-BuOOH in *n*-C_9H_{20} (0.80 mL, 4.830 mmol) was added *via* syringe and the reaction was stirred for a further 48 hr at –20 °C then quenched by the addition of H_2O (2 mL) and 1M $NaOH_{(aq)}$ (3 mL). After stirring vigorously for 20 min the mixture was filtered through celite and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (silica gel 15 x 80 mm, 10-25% EtOAc/hexane) afforded the title compound **6.18** (196 mg, 0.382 mmol, 86%) as a colourless oil. The product was obtained as a single diastereoisomer. R_f = 0.32 (60% EtOAc/hexane).

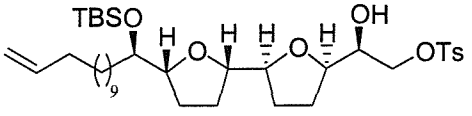
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.82 (1H, ddt, *J* = 17.1, 10.3, 6.5 Hz, H_2C=C**H**), 4.99 (1H, ddt, *J* = 17.1, 2.0, 1.5 Hz, **H**HC=CH), 4.93 (1H, ddt, *J* = 10.3, 2.0, 1.3 Hz, H**H**C=CH), 4.01-3.56 (8H, m), 2.97 (1H, d, *J* = 4.0 Hz, CHO**H**), 2.23 (1H, dd, *J* = 7.5, 4.5 Hz, CH_2O**H**), 2.08-2.01 (2H, m), 2.00-1.73 (6H, m), 1.71-1.23 (20H, m), 0.89 (9H, s, SiC(C**H**$_3$)$_3$), 0.075 (3H, s, SiC**H**$_3$), 0.70 (3H, s, SiC**H**$_3$) ppm.

^{13}C NMR	(100 MHz, $CDCl_3$) δ_C 139.5 (d), 114.3 (t), 82.3 (d), 81.8 (d), 81.2 (d, 2 x **C**H), 74.4 (d), 73.2 (d), 64.0 (t), 34.0 (t), 32.6 (t), 30.1 (t), 29.84 (t), 29.77 (t), 29.7 (t), 29.3 (t), 29.1 (t), 28.5 (t), 28.3 (t), 26.6 (t), 26.14 (q), 26.06 (t), 26.0 (t), 18.4 (s), -4.2 (q), -4.3 (q) ppm.
FT-IR	(film) ν_{max} 3550(br), 2925(s), 2854(m), 1641(w), 1462(m), 1061(s), 1006(m), 939(m), 908(m), 835(s), 775(s), 721(w) cm^{-1}.
LRMS	(ES^+) *m/z* 530 ($[M+NH_4]^+$, 100%), 535 ($[M+Na]^+$, 96%) Da.
HRMS	(ES^+) $C_{29}H_{56}O_5SiNa$ Requires 535.3789; Found 535.3796 Da.
$[\alpha]^{23}_D$	+18.1 (c = 0.54, $CDCl_3$).

(*R*)-2-((2*S*,5*S*)-5-((2*S*,5*R*)-5-((*R*)-1-*tert*-Butyldimethylsilyloxy)tridec-12-enyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)-2-hydroxyethyl-4-methylbenzenesulfonate (6.19) and
(*S*)-2-((2*R*,5*S*)-5-((2*S*,5*R*)-5-((*R*)-1-*tert*-Butyldimethylsilyloxy)tridec-12-enyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)-2-hydroxyethyl-4-methylbenzenesulfonate (6.20)



6.19
$C_{25}H_{62}O_7SSi$
667.03
Major Product



6.20
$C_{25}H_{62}O_7SSi$
667.03
Minor Product

The title compounds were prepared according to the method Hu *et al.*[230] Thus, to a solution of diol **6.17** (enriched, inseparable mixture of diastereoisomers, 196 mg, 0.382 mmol) in C_6H_6 (19 mL) under an atmosphere of N_2 was added Bu_2SnO (124 mg, 0.497 mmol) and the heterogeneous solution stirred at reflux for 3.5 hr then allowed to cool to room temperature. TsCl (80 mg, 0.420 mmol) was added followed after 2 hr by TBAB (5 mg, 0.016 mmol) and the reaction stirred for 18 hr. Concentration *in vacuo* and purification of the residue by flash column chromatography (silica gel 30 x 80 mm, 5% EtOAc/hexane) afforded major diastereoisomer **6.19** (178 mg, 0.267 mmol, 70%) and minor diastereoisomer **6.20** (12 mg, 0.018 mmol, 5%) as pale yellow oils (total yield 190 mg, 0.285 mmol, 75%). This

corresponded to an epoxidation product ratio of 15:1 (*de* = 86%). $R_{f,\ minor} = 0.72$, $R_{f,\ major} = 0.75$ (60% EtOAc/hexane).

Major Product 6.19

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.80 (2H, d, *J* = 8.3 Hz, Ar**H**), 7.35 (2H, d, *J* = 8.3 Hz, Ar**H**), 5.82 (1H, ddt, *J* = 17.1, 10.3, 6.8 Hz, H_2C=C**H**), 5.00 (1H, ddt, *J* = 17.1, 3.3, 1.8 Hz, **H**HC=CH), 4.93 (1H, ddt, *J* = 10.3, 3.3, 1.3 Hz, H**H**C=CH), 4.19 (1H, dd, *J* = 10.3, 3.3 Hz, C**H**HOTs), 4.00 (1H, dd, *J* = 10.3, 6.8 Hz, C**H**HOTs), 3.96-3.86 (4H, m), 3.75-3.62 (2H, m), 2.45 (3H, s, $ArCH_3$), 2.33 (1H, br s, O**H**), 2.11-1.58 (10H, m), 1.54-1.20 (18H, m), 0.88 (9H, s, $SiC(CH_3)_3$), 0.06 (6H, s, $Si(CH_3)_2$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 145.1 (s), 139.5 (d), 133.0 (s), 130.1 (2 x d), 129.2 (2 x d), 114.3 (t), 82.54 (d), 82.47 (d), 82.3 (d), 79.3 (d), 74.4 (d), 71.7 (t), 70.9 (d), 34.0 (t), 32.2 (t), 30.1 (t), 29.9 (t), 29.8 (t), 29.7 (t), 29.3 (t), 29.1 (t), 28.6 (t), 28.2 (t), 27.2 (t), 26.4 (t), 26.1 (q), 26.0 (t), 21.8 (q), 18.4 (s), -4.1 (q), -4.4 (q) ppm.

FT-IR (film) ν_{max} 2925(s), 2853(m), 1598(w), 1462(m), 1360(m), 1252(m), 1191(m), 1177(s), 1097(m), 1067(m), 978(m), 908(m), 835(s), 813(m), 776(m) cm^{-1}.

LRMS (ES^+) *m/z* 684 ($[M+NH_4]^+$, 100%), 689 ($[M+Na]^+$, 98%), 705 ($[M+K]^+$, 73%) Da.

HRMS (ES^+) $C_{36}H_{62}O_7SSiNa$ Requires 689.3878; Found 689.3888 Da.

Elemental Calc. for $C_{36}H_{62}O_7SSi$: C, 64.82; H, 9.37%; Found: C, 65.12; H, 9.73%.

$[\alpha]^{23}_D$ +16.0 (c. 0.42, $CDCl_3$).

Minor Product 6.20

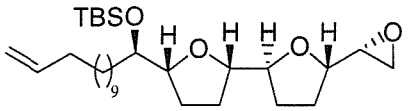
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.80 (2H, d, *J* = 8.5 Hz, Ar**H**), 7.35 (2H, d, *J* = 8.5 Hz, Ar**H**), 5.82 (1H, ddt, *J* = 17.1, 10.3, 6.8 Hz, H_2C=C**H**), 5.00 (1H, ddt, *J* = 17.1, 3.3, 1.8 Hz, **H**HC=CH), 4.93 (1H, ddt, *J* = 10.3, 3.3, 1.3 Hz, H**H**C=CH), 4.11 (1H, dd, *J* = 10.0, 4.5 Hz, C**H**HOTs), 4.01 (1H, dd, *J* = 10.0, 6.0 Hz, C**H**HOTs), 3.97-3.91 (2H, m), 3.90-

	3.84 (2H, m), 3.72 (1H, m), 3.64 (1H, m), 2.88 (1H, br s, OH), 2.45 (3H, s, $ArCH_3$), 2.09-2.01 (2H, m), 1.98-1.21 (26H, m), 0.88 (9H, s, $SiC(CH_3)_3$), 0.06 (6H, s, $Si(CH_3)_2$) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ_C 145.1 (s), 139.5 (d), 133.0 (s), 130.1 (2 x d), 128.2 (2 x d), 114.3 (t), 82.3 (d), 81.7 (d), 81.5 (d), 79.7 (d), 74.3 (d), 71.3 (t), 70.9 (d), 34.0 (t), 32.6 (t), 30.1 (t), 29.84 (t), 29.77 (t), 29.7 (t), 29.3 (t), 29.2 (t), 28.3 (t), 28.2 (t), 26.6 (t), 26.1 (t), 25.9 (q), 25.8 (t), 21.8 (q), 18.4 (s), -4.2 (q), -4.4 (q) ppm.
FT-IR	(film) ν_{max} 3439(br), 2954(m), 2926(s), 2854(m), 1598(w), 1462(m), 1361(m), 1291(w), 1253(m), 1190(m), 1177(s), 1071(m), 974(m), 909(m), 836(s), 814(m), 776(m) cm^{-1}.
LRMS	(ES^+) *m/z* 689 ($[M+Na]^+$, 100%), 684 ($[M+NH_4]^+$, 25%), 705 ($[M+K]^+$, 52%), 1355 ($[2M+Na]^+$, 3%) Da.
HRMS	(ES^+) $C_{36}H_{62}O_7SSiNa$ Requires 689.3878; Found 689.3882 Da.
$[\alpha]^{23}_D$	+7.12 (c. 0.85, $CDCl_3$).

(*S*)-2-((2*R*,5*S*)-5-((2*S*,5*R*)-5-((*R*)-1-*tert*-Butyldimethylsilyloxy)tridec-12-enyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)-2-hydroxyethyl-4-methylbenzenesulfonate (6.20)

The title compound was prepared according to the method Hu *et al.*[230] Thus, to a solution of diol **6.18** (196 mg, 0.382 mmol) in C_6H_6 (19 mL) under an atmosphere of N_2 was added Bu_2SnO (124 mg, 0.497 mmol) and the heterogeneous solution stirred at reflux for 3.5 hr then allowed to cool to room temperature. TsCl (80 mg, 0.420 mmol) was added and the reaction stirred for 5 hr. Concentration *in vacuo* and purification of the residue by flash column chromatography (silica gel 25 x 75 mm, 5% EtOAc/hexane) afforded the title compound **6.20** (252 mg, 0.378 mmol, 99%) as a pale yellow oil. R_f = 0.72 (60% EtOAc/hexane). The data for this product is stated above.

***tert*-Butyldimethyl((*R*)-1-((2*S*,5*S*)-5-((2*S*,5*S*)-5-((*R*)-oxiran-2-yl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)tridec-12-enyloxy)silane (6.21)**



6.21
$C_{29}H_{54}O_4Si$
494.83

To a solution of tosylate **6.19** (411 mg, 0.62 mmol) in CH_2Cl_2 (30 mL) at room temperature under an atmosphere of N_2 was added a solution of DBU (188 mg, 1.23 mmol) in CH_2Cl_2 (2 mL) and the mixture stirred for 10 min. Further DBU (188 mg, 1.23 mmol) was added and the reaction stirred for a further 20 min, then quenched by the addition of a 10% v/w aqueous solution of citric acid (25 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL) and EtOAc (2 x 30 mL) and the combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 15 x 90 mm, 5-20% EtOAc/hexane) afforded the title compound **6.21** (276 mg, 0.56 mmol, 91%) as a colourless oil. R_f = 0.80 (60% EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.82 (1H, ddt, J = 17.1, 10.3, 6.5 Hz, H_2C=C**H**), 5.00 (1H, ddt, J = 17.1, 2.0, 1.5 Hz, **H**HC=CH), 4.93 (1H, ddt, J = 10.3, 2.0, 1.3 Hz, H**H**C=CH), 4.03-3.83 (3H, m), 3.81-3.68 (2H, m), 3.02 (1H, ddd, J = 5.3, 4.0, 2.8 Hz, epoxide C**H**), 2.79 (1H, dd, J = 5.0, 4.0 Hz, epoxide C**H**H), 2.58 (1H, dd, J = 5.0, 2.8 Hz, epoxide CH**H**), 2.12-1.97 (4H, m), 1.88-1.62 (6H, m), 1.60-1.16 (18H, m), 0.88 (9H, s, SiC(CH_3)$_3$), 0.05 (6H, s, Si(CH_3)$_2$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 139.5 (d), 114.3 (t), 82.3 (d), 82.2 (d), 79.8 (d), 77.5 (d), 74.2 (d), 53.5 (d), 46.0 (t), 34.0 (t), 31.9 (t), 30.1 (t), 29.9 (t), 29.78 (t), 29.77 (t), 29.7 (t), 29.3 (t), 29.1 (t), 28.4 (t), 28.3 (t), 28.2 (t), 26.2 (t), 26.1 (q), 18.3 (s), -4.1 (q), -4.4 (q) ppm.

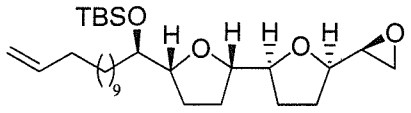
FT-IR (film) ν_{max} 2926(s), 2854(s), 1635(w), 1460(w), 1247(w), 1076(w), 902(w), 835(m), 775(m) cm^{-1}.

LRMS (ES$^+$) *m/z* 517 ([M+Na]$^+$, 100%), 512 ([M+NH_4]$^+$, 62%), 1006 ([2M+NH_4]$^+$, 42%) Da.

HRMS (ES$^+$) $C_{29}H_{54}O_4SiNa$ Requires 517.3684; Found 517.3695 Da.

$[\alpha]^{23}_D$ +14.6 (c. 0.37, $CDCl_3$).

***tert*-Butyldimethyl((*R*)-1-((2*S*,5*S*)-5-((2*S*,5*R*)-5-((*S*)-oxiran-2-yl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)tridec-12-enyloxy)silane (6.22)**



6.22
$C_{29}H_{54}O_4Si$
494.83

To a solution of tosylate **6.20** (252 mg, 0.38 mmol) in CH_2Cl_2 (30 mL) at room temperature under an atmosphere of N_2 was added a solution of DBU (188 mg, 1.23 mmol) in CH_2Cl_2 (2 mL) and the mixture stirred for 10 min. Further DBU (188 mg, 1.23 mmol) was added and the reaction stirred for a further 20 min then quenched by the addition of a 10% v/w aqueous solution of citric acid (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 12 x 80 mm, 5-25% EtOAc/hexane) afforded the title compound **6.22** (185 mg, 0.38 mmol, 99%) as a colourless oil. R_f = 0.80 (60% EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.82 (1H, ddt, J = 17.1, 10.0, 6.5 Hz, H_2C=C**H**), 5.00 (1H, ddt, J = 17.1, 2.0, 1.5 Hz, **H**HC=CH), 4.93 (1H, m, H**H**C=CH), 4.04-3.68 (5H, m), 3.00 (1H, ddd, J = 5.5, 4.0, 3.0 Hz, epoxide C**H**), 2.80 (1H, m, epoxide C**H**H), 2.62 (1H, dd, J = 5.0, 3.0 Hz, epoxide CH**H**), 2.10-1.77 (8H, m), 1.74-1.51 (2H, m), 1.59-1.18 (18H, m), 0.88 (9H, s, SiC(CH_3)$_3$), 0.054 (3H, s, SiCH_3), 0.047 (3H, s, SiCH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 139.4 (d), 114.2 (t), 82.7 (d), 82.4 (d), 82.3 (d), 80.1 (d), 74.1 (d), 53.5 (d), 46.5 (t), 34.0 (t), 31.7 (t), 30.1 (t), 29.84 (t), 29.77 (t), 29.75 (t), 29.7 (t), 29.3 (t), 29.1 (t), 28.3 (t), 28.1 (t), 27.8 (t), 26.2 (q), 26.1 (t), 18.3 (s), -4.1 (q), -4.4 (q) ppm.

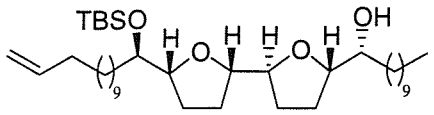
FT-IR (film) ν_{max} 2926(s), 2854(s), 1635(w), 1460(w), 1247(w), 1076(w), 902(w), 835(m), 775(m) cm^{-1}.

LRMS (ES$^+$) *m/z* 512 ([M+NH_4]$^+$, 100%), 517 ([M+Na]$^+$, 46%), 1006 ([2M+NH_4]$^+$, 18%) Da.

HRMS (ES$^+$) $C_{29}H_{54}O_4SiNa$ Requires 517.3684; Found 517.3686 Da.

$[\alpha]^{23}_D$ +13.1 (c. 0.37, $CDCl_3$).

(*R*)-1-((2*S*,5*S*)-5-((2*S*,5*R*)-5-((*R*)-1-*tert*-Butyldimethylsilyloxy)tridec-12-enyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)undec-1-ol (6.23)



6.23
$C_{38}H_{74}O_4Si$
623.08

Magnesium turnings (457 mg, 18.8 mmol) were heated at ~400 °C under an atmosphere of Ar for 5 min then allowed to cool to room temperature. THF (50 mL) and a single crystal of I_2 were added, followed by 9-bromononane (0.30 mL, 1.5 mmol), dropwise *via* syringe. The yellow solution was heated at reflux for 10 min until it became colourless, and the remaining 1-bromononane (2.69 mL, 14.1 mmol) was added *via* syringe. The solution was heated at reflux for 20 min and at room temperature for 1 hr. The grignard solution was filtered under an atmosphere of Ar and titrated using excess I_2 and $Na_2S_2O_3$, giving an average concentration of 0.40M. An aliquot of this solution (13.6 mL, 3.27 mmol) was then added *via* syringe to a suspension of CuI (312 mg, 1.64 mmol) in THF (30 mL) at –60 °C under an atmosphere of Ar. The mixture was allowed to warm to –25 °C over a period of 30 min, and was stirred for a further 15 min until dark grey in colour. The reaction mixture was cooled to –60 °C and a solution of epoxide **6.21** (270 mg, 0.55 mmol) in THF (10 mL) was added *via* syringe. After stirring for 20 min the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (20 mL) followed by water (10 mL), and extracted with Et_2O (3 x 30 mL) and EtOAc (2 x 30 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, 5-10% EtOAc/hexane) afforded the title compound **6.23** (312 mg, 0.50 mmol, 92%) as a colourless oil. R_f = 0.85 (60% EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.82 (1H, ddt, J = 17.1, 10.3, 6.5 Hz, H_2C=C**H**), 5.00 (1H, ddt, J = 17.1, 2.0, 1.5 Hz, **H**HC=CH), 4.93 (1H, ddt, J = 10.3, 2.0, 1.2 Hz, H**H**C=CH), 3.98-3.84 (4H, m), 3.79-3.69 (2H, m), 2.14 (1H, br s, CHO**H**), 2.10-1.76 (8H, m), 1.71-1.19 (41H, m), 0.88 (9H, s, SiC($C\mathbf{H}_3$)$_3$), 0.054 (3H, s, Si$C\mathbf{H}_3$), 0.047 (3H, s, Si$C\mathbf{H}_3$) ppm.

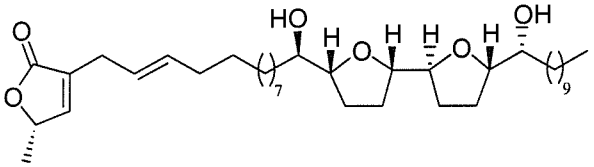
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 139.5 (d), 114.3 (t), 82.80 (d), 82.77 (d), 82.5 (d), 82.3 (d), 74.2 (d), 71.5 (d), 34.0 (t), 32.6 (t), 32.1 (t), 31.9 (t), 30.0 (t), 29.91 (t), 29.88 (t), 29.81 (t), 29.76 (t), 29.7 (t), 29.5 (t), 29.4

	(t), 29.2 (t), 29.1 (t), 28.2 (t), 26.3 (t), 26.22 (t), 26.17 (t), 26.1 (q), 24.7 (t), 22.9 (t), 18.4 (s), 14.3 (q), -4.1 (q), -4.4 (q) ppm.
FT-IR	(film) ν_{max} 3483(br), 2926(s), 2854(s), 1464(w), 1360(w), 1252(w), 1110(w), 1075(m), 909(w), 836(m), 776(m), 721(w) cm^{-1}.
LRMS	(ES^+) *m/z* 640 ($[M+NH_4]^+$, 100%), 645 ($[M+Na]^+$, 40%), 661 ($[M+K]^+$, 12%) Da.
HRMS	(ES^+) $C_{38}H_{74}O_4SiNa$ Requires 645.5248; Found 645.5246 Da.
Elemental	Calc. for $C_{38}H_{74}O_4Si$: C, 73.25; H, 11.97%; Found: C, 72.86; H, 11.78%.
$[\alpha]^{23}_D$	+12.5 (c. 0.26, $CDCl_3$).

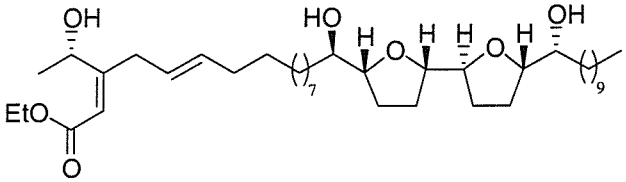
(*S*)-3-(*R*,*E*)13-Hydroxy-13-((2*R*,5*S*)-5-((2*S*,5*S*)-5-((*R*)-1-hydroxyundecyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)tridec-2-enyl)-5-methylfuran-2(5*H*)-one (6.25),

(*R*,2*Z*,5*E*)-Ethyl-16-Hydroxy-3-((*S*)-1-hydroxyethyl)-16-((2*R*,5*S*)-5-((2*S*,5*S*)-5-((*R*)-1-hydroxyundecyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)hexadeca-2,5-dienoate (6.26) and

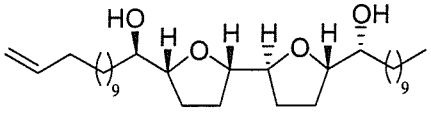
(*R*)-1-((2*R*,5*S*)-5-((2*S*,5*S*)-5-((*R*)-1-Hydroxyundecyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)tridec-12-en-1-ol) (6.27)



6.25
$C_{37}H_{64}O_6$
604.91



6.26
$C_{39}H_{70}O_7$
650.98



6.27
$C_{32}H_{60}O_4$
508.83

A solution of terminal alkene **6.23** (23.7 mg, 0.038 mmol) and hydroxy-alkyne **1.146** (7.6 mg, 0.053 mmol) in MeOH (2 mL) was degassed with N_2 for 20 min. Ruthenium catalyst **1.147** (0.6 mg, 0.002 mmol) was added and the orange solution heated at 70 °C under an

atmosphere of N_2 for 18 hr. The solution was allowed to cool to room temperature, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (silica gel 15 x 120 mm, 1-2% MeOH/CH_2Cl_2). This afforded butenolide **6.25** (15.5 mg, 0.026 mmol, 67%), hydroxy-ester **6.26** (3.8 mg, 0.005 mmol, 14%), and desilylated starting material, alkene **6.27** (4.0 mg, 0.008 mmol, 18%) as pale yellow oils. The ratio of butenolide to hydroxy ester was 4.8:1. $R_{f,\ 6.25}$ = 0.71, $R_{f,\ 6.26}$ = 0.51, $R_{f,\ 6.27}$ = 0.44 (5% MeOH/CH_2Cl_2).

Butenolide 6.25

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.99 (1H, app q, J = 1.5 Hz, $OCH(CH_3)C\mathbf{H}$=), 5.62-5.53 (1H, m, $=CCH_2C\mathbf{H}$=CH), 5.51-5.42 (1H, m, $=CCH_2CH$=C**H**), 5.04-4.97 (1H, m, O**C**H(CH_3)CH=), 3.99-3.80 (5H, m), 3.41-3.34 (1H, m), 2.96 (2H, dd, J = 6.5, 1.0 Hz, $=CC\mathbf{H}_2CH$=CH), 2.07-1.66 (12H, m), 1.55-1.18 (38H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 173.7 (s), 149.5 (d), 134.3 (d), 133.8 (s), 124.5 (d), 83.1 (d), 83.0 (d), 82.4 (d), 82.0 (d), 77.8 (d), 74.8 (d), 71.8 (d), 34.5 (t), 32.8 (t), 32.7 (t), 32.1 (t), 29.92 (t), 29.88 (t), 29.82 (t), 29.80 (t), 29.75 (t), 29.65 (t), 29.5 (t), 29.4 (t), 28.62 (t), 28.59 (t), 28.4 (t), 26.2 (t), 26.0 (t), 25.1 (t), 22.9 (t), 19.3 (q), 14.2 (q) ppm.

FT-IR (film) ν_{max} 3439(br), 2925(s), 2852(m), 1758(m), 1660(w), 1373(w), 1318(w), 1261(w), 1190(w), 1077(m), 1023(m), 968(w), 945(w), 875(w), 802(w), 732(m) cm^{-1}.

LRMS (ES^+) *m/z* 627 ($[M+Na]^+$, 100%), 622 ($[M+NH_4]^+$, 78%) Da.

HRMS (ES^+) $C_{37}H_{64}O_6Na$ Requires 627.4595; Found 627.4608 Da.

$[\alpha]^{24}_D$ +9.0 (c. 0.51, $CDCl_3$).

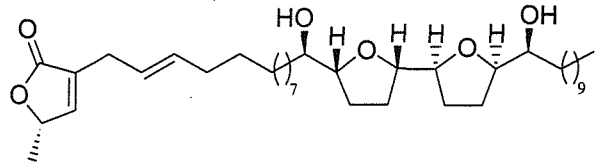
Hydroxy-ester 6.26

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.01 (1H, s, $=C\mathbf{H}CO_2Et$), 5.57-5.48 (1H, m, $=CCH_2C\mathbf{H}$=CH), 5.47-5.39 (1H, m, $=CCH_2CH$=C**H**), 4.34 (1H, app q, J = 6.5 Hz, C**H**OHCH_3), 4.18 (2H, q, J = 7.0 Hz, $OC\mathbf{H}_2CH_3$), 4.00-3.80 (5H, m), 3.56 (1H, ddd, J = 13.6, 6.0, 1.0 Hz, $=CC\mathbf{H}HCH$=CH), 3.42-3.35 (1H, m), 3.17 (1H, dd, J = 13.6, 7.0 Hz,

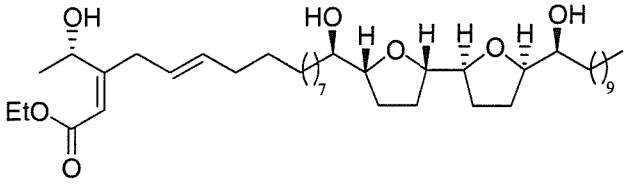
	=CCH**H**CH=CH), 2.85 (2H, br s, 2 x CH**OH**), 2.11-1.71 (12H, m), 1.68-1.19 (42H, m) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ_C 163.5 (s), 162.1 (s), 133.2 (d), 126.8 (d), 114.3 (d), 83.2 (d), 82.9 (d), 82.3 (d), 82.0 (d), 74.8 (d), 71.8 (d), 70.9 (d), 60.0 (t), 34.5 (t), 32.9 (t), 32.8 (t), 32.7 (t), 32.1 (t), 29.9 (t), 29.81 (t), 29.76 (t), 29.72 (t), 29.68 (t), 29.59 (t), 29.56 (t), 29.5 (t), 29.4 (t), 29.3 (t), 28.6 (t), 28.4 (t), 26.2 (t), 26.0 (t), 25.1 (t), 22.9 (q), 22.5 (t), 14.5 (q), 14.3 (q) ppm.
FT-IR	(film) ν_{max} 3432(br), 2924(s), 2853(s), 1716(m), 1647(w), 1460(m), 1368(m), 1261(m), 1176(m), 1153(m), 1060(m), 970(w), 878(w), 804(w), 732(w) cm^{-1}.
LRMS	(ES^+) *m/z* 673 ($[M+Na]^+$, 100%), 668 ($[M+NH_4]^+$, 42%) Da.
HRMS	(ES^+) $C_{39}H_{70}O_7Na$ Requires 673.5014; Found 673.5022 Da.
$[\alpha]^{24}_D$	+20.2 (c. 0.29, $CDCl_3$).
Alkene 6.27	
^{1}H NMR	(400 MHz, $CDCl_3$) δ_H 5.82 (1H, ddt, *J* = 17.1, 10.5, 6.5 Hz, H_2C=C**H**), 5.00 (1H, ddt, *J* = 17.1, 2.0, 1.5 Hz, **H**HC=CH), 4.93 (1H, ddt, *J* = 10.5, 2.0, 1.0 Hz, H**H**C=CH), 4.00-3.80 (5H, m), 3.42-3.35 (1H, m), 2.10-1.20 (49H, m) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ_C 139.3 (d), 114.2 (t), 83.0 (d), 82.8 (d), 82.2 (d), 81.9 (d), 74.7 (d), 71.7 (d), 34.5 (t), 33.9 (t), 32.7 (t), 32.0 (t), 30.4 (t), 29.83 (t), 29.78 (t), 29.72 (t), 29.70 (t), 29.65 (t), 29.58 (t), 29.4 (t), 29.3 (t), 28.5 (t), 28.3 (t), 26.1 (t), 26.0 (t), 25.0 (t), 22.8 (t), 14.2 (q) ppm.
FT-IR	(film) ν_{max} 3446(br), 2924(s), 2853(s), 1640(w), 1464(w), 1376(w), 1261(w), 1065(m), 952(w), 909(w), 874(w), 803(w), 721(w) cm^{-1}.
LRMS	(ES^+) *m/z* 531 ($[M+Na]^+$, 100%), 526 ($[M+NH_4]^+$, 37%), 547 ($[M+K]^+$, 5%), 1039 ($[2M+Na]^+$, 18%) Da.
HRMS	(ES^+) $C_{32}H_{60}O_4Na$ Requires 531.4384; Found 531.4381 Da.
$[\alpha]^{24}_D$	+25.6 (c. 0.21, $CDCl_3$).

(*S*)-3-(*R*,*E*)13-Hydroxy-13-((2*R*,5*S*)-5-((2*S*,5*R*)-5-((*S*)-1-hydroxyundecyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)tridec-2-enyl)-5-methylfuran-2(5*H*)-one (6.36) and

(*R*,2*Z*,5*E*)-Ethyl-16-hydroxy-3-((*S*)-1-hydroxyethyl)-16-((2*R*,5*S*)-5-((2*S*,5*R*)-5-((*S*)-1-hydroxyundecyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)hexadeca-2,5-dienoate (6.37)



6.36
$C_{37}H_{64}O_6$
604.91



6.37
$C_{39}H_{70}O_7$
650.98

A solution of terminal alkene **6.24** (51.5 mg, 0.083 mmol) and hydroxy-alkyne **1.146** (16.4 mg, 0.116 mmol) in MeOH (6 mL) was degassed with N_2 for 20 min. Ruthenium catalyst **1.147** (1.3 mg, 0.004 mmol) was added and the orange solution heated at 70 °C under an atmosphere of N_2 for 18 hr. The solution was allowed to cool to room temperature, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (silica gel 15 x 130 mm, 1-2% MeOH/CH_2Cl_2). This afforded butenolide **6.36** (36.0 mg, 0.059 mmol, 72%) and hydroxy-ester **6.37** (10.1 mg, 0.015 mmol, 19%) as pale yellow oils. The ratio of butenolide to hydroxy ester was 3.8:1. $R_{f,\,6.36}$ = 0.53, $R_{f,\,6.37}$ = 0.45 (5% MeOH/CH_2Cl_2).

Butenolide 6.36

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.00 (1H, app q, J = 1.5 Hz, OCH(CH_3)C**H**=), 5.62-5.53 (1H, m, =CCH_2C**H**=CH), 5.51-5.41 (1H, m, =CCH_2CH=C**H**), 5.00 (1H, app q, J = 1.5 Hz, OC**H**(CH_3)CH=), 3.96-3.80 (5H, m), 3.44-3.34 (1H, m), 2.96 (2H, app d, J = 6.5 Hz, =C**H**$_2$CH=CH), 2.85 (2H, br s, 2 x CHO**H**), 2.18-1.70 (12H, m), 1.55-1.18 (38H, m) ppm.

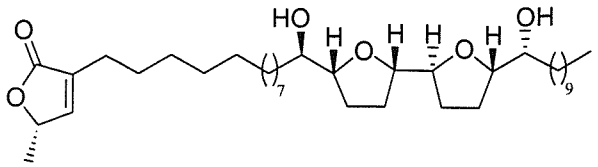
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 173.7 (s), 149.5 (d), 134.4 (d), 133.8 (s), 123.3 (d), 83.2 (d), 83.1 (d), 81.3 (d), 81.1 (d), 77.7 (d), 74.2 (d), 72.2 (d), 34.5 (t), 33.0 (t), 32.7 (t), 32.1 (t), 30.5 (t), 29.9 (t), 29.80 (t), 29.76

	(t), 29.6 (t), 29.5 (t), 29.4 (t), 29.0 (t), 28.7 (t), 28.6 (t), 28.1 (t), 26.2 (t), 26.0 (t), 24.0 (t), 22.9 (t), 19.3 (q), 14.3 (q) ppm.
FT-IR	(film) ν_{max} 3441(br), 2923(s), 2852(s), 1758(m), 1465(w), 1370(w), 1318(w), 1261(w), 1191(w), 1081(m), 1023(m), 968(w), 862(w), 802(w), 733(w) cm^{-1}.
LRMS	(ES^+) *m/z* 627 ($[M+Na]^+$, 100%), 622 ($[M+NH_4]^+$, 45%) Da.
HRMS	(ES^+) $C_{37}H_{64}O_6Na$ Requires 627.4595; Found 627.4600 Da.
$[\alpha]^{24}_D$	+9.6 (c. 0.18, $CDCl_3$).

Hydroxy-ester 6.37

^{1}H NMR	(400 MHz, $CDCl_3$) δ_H 6.00 (1H, s, =C**H**CO_2Et), 5.57-5.48 (1H, m, =CCH_2C**H**=CH), 5.47-5.38 (1H, m, =CCH_2CH=C**H**), 4.35 (1H, app dq, *J* = 6.5, 1.0 Hz, C**H**OHCH_3), 4.18 (2H, q, *J* = 7.0 Hz, O**C**H_2CH_3), 3.95-3.82 (5H, m), 3.56 (1H, dd, *J* = 13.6, 6.0 Hz, =CC**H**HCH=CH), 3.45-3.38 (1H, m), 3.07 (1H, dd, *J* = 13.6, 7.0 Hz, =CCH**H**CH=CH), 2.90 (2H, br s, 2 x CHO**H**), 2.05-1.73 (12H, m), 1.57-1.20 (42H, m) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ_C 166.8 (s), 163.5 (s), 133.2 (d), 126.8 (d), 114.3 (d), 83.3 (d), 83.1 (d), 81.3 (d), 81.2 (d), 74.2 (d), 72.2 (d), 70.9 (d), 60.0 (t), 34.5 (t), 34.4 (t), 33.0 (t), 32.9 (t), 32.6 (t), 32.1 (t), 30.5 (t), 29.9 (t), 29.82 (t), 29.77 (t), 29.69 (t), 29.66 (t), 29.57 (t), 29.55 (t), 29.5 (t), 29.2 (t), 29.0 (t), 28.6 (t), 28.1 (t), 26.2 (t), 26.0 (t), 23.9 (t), 22.9 (t), 22.5 (q), 14.5 (q), 14.3 (q) ppm.
FT-IR	(film) ν_{max} 3455(br), 2955(m), 2923(s), 2853(m), 1736(m), 1718(m), 1458(w), 1366(m), 1260(w), 1230(w), 1152(w), 1092(w), 1047(w), 800(w) cm^{-1}.
LRMS	(ES^+) *m/z* 673 ($[M+Na]^+$, 100%), 668 ($[M+NH_4]^+$, 53%) Da.
HRMS	(ES^+) $C_{39}H_{70}O_7Na$ Requires 673.5014; Found 673.5029 Da.
$[\alpha]^{24}_D$	+17.3 (c. 0.52, $CDCl_3$).

(*S*)-3-((*R*)-13-Hydroxy-13-((2*R*,5*S*)-5-((2*S*,5*S*)-5-((*R*)-1-hydroxyundecyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)tridecyl)-5-methylfuran-2-(5*H*)-one (6.38)



6.38
$C_{37}H_{66}O_6$
606.92

To a solution of butenolide **6.25** (15.5 mg, 0.026 mmol) and toluenesulfonyl hydrazide (38.2 mg, 0.205 mmol) in THF (2 mL) was added a solution of NaOAc (16.2 mg, 0.205 mmol) in water (2 mL), and the reaction heated at 70 °C for 20 hr. The mixture was allowed to cool to room temperature, diluted with water (5 mL) and extracted with Et_2O (2 x 15 mL) and EtOAc (3 x 15 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 15 x 100 mm, 1-2% MeOH/ CH_2Cl_2) afforded the title compound (12.6 mg, 0.021 mmol, 81%) as a white solid. R_f = 0.51 (5% MeOH/CH_2Cl_2).

m.p 38-39 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.99 (1H, app q, J = 1.5 Hz, OCH(CH_3)C**H**=), 5.00 (1H, app qq, J = 6.5, 1.5 Hz, OC**H**(CH_3)CH=), 3.99-3.81 (5H, m), 3.42-3.35 (1H, m), 2.27 (2H, app. tt, J = 7.8, 1.5 Hz, =CC**H**$_2$$CH_2$), 2.13-1.71 (12H, m), 1.61-1.20 (44H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.1 (s), 149.0 (d), 134.6 (s), 83.1 (d), 83.0 (d), 82.3 (d), 82.0 (d), 78.0 (d), 74.8 (d), 71.8 (d), 34.5 (t), 32.8 (t), 32.1 (t), 29.94 (t), 29.89 (t), 29.81 (t), 29.76 (t), 29.71 (t), 29.53 (t), 29.51 (t), 29.4 (t), 28.6 (t), 28.4 (t), 27.6 (t), 26.2 (t), 26.0 (t), 25.4 (t), 25.1 (t), 22.9 (t), 19.4 (q), 14.3 (q) ppm.

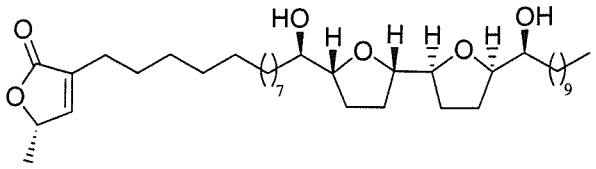
FT-IR (film) ν_{max} 3402(br), 2923(s), 2852(m), 1758(s), 1465(m), 1317(m), 1261(m), 1069(s), 1027(s), 952(m), 875(m), 804(m), 732(m) cm^{-1}.

LRMS (ES$^+$) *m/z* 629 ([M+Na]$^+$, 100%), 624 ([M+NH$_4$]$^+$, 32%) Da.

HRMS (ES$^+$) $C_{37}H_{66}O_6Na$ Requires 629.4751; Found 629.4759 Da.

$[\alpha]^{24}_D$ +8.5 (c. 0.35, $CDCl_3$).

(*S*)-3-((*R*)-13-Hydroxy-13-((2*R*,5*S*)-5-((2*S*,5*R*)-5-((*S*)-1-hydroxyundecyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)tridecyl)-5-methylfuran-2-(5*H*)-one (3.19)



3.19
$C_{37}H_{66}O_6$
606.92

To a solution of butenolide **6.36** (33 mg, 0.055 mmol) and toluenesulfonyl hydrazide (102 mg, 0.546 mmol) in THF (4 mL) was added a solution of NaOAc (45 mg, 0.546 mmol) in water (4 mL), and the reaction heated at 70 °C for 20 hr. The mixture was allowed to cool to room temperature, diluted with water and extracted with Et_2O (2 x 15 mL) and EtOAc (3 x 15 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 15 x 100 mm, 1-2% MeOH/CH_2Cl_2) afforded the title compound (26 mg, 0.055 mmol, 78%) as a white solid. R_f = 0.51 (5% MeOH/CH_2Cl_2).

m.p 37-38 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.99 (1H, app q, J = 1.5 Hz, OCH(CH_3)C**H**=), 4.99 (1H, app qq, J = 6.5, 1.5 Hz, OC**H**(CH_3)CH=), 3.96-3.70 (5H, m), 3.45-3.38 (1H, m), 2.31 (2H, br s, 2 x CHO**H**), 2.27 (2H, app tt, J = 7.8, 1.5 Hz, =CC**H**$_2$CH$_2$), 2.10-1.71 (10H, m), 1.61-1.20 (44H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.0 (s), 149.0 (d), 134.6 (s), 83.2 (d), 83.1 (d), 81.3 (d), 81.2 (d), 77.6 (d), 74.2 (d), 72.2 (d), 34.5 (t), 33.0 (t), 32.1 (t), 29.9 (t), 29.81 (t), 29.76 (t), 29.7 (t), 29.52 (t), 29.50 (t), 29.4 (t), 29.0 (t), 28.6 (t), 28.1 (t), 27.6 (t), 26.2 (t), 26.0 (t), 24.0 (t), 22.9 (t), 19.4 (q), 14.3 (q) ppm.

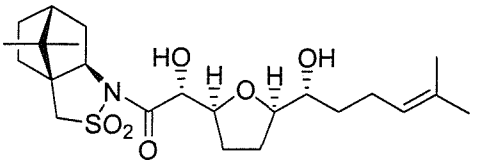
FT-IR (film) ν_{max} 3444(br), 2924(s), 2852(s), 1757(s), 1464(m), 1373(w), 1318(w), 1261(w), 1069(m), 1028(m), 954(w), 873(w), 802(m), 722(w) cm^{-1}.

LRMS (ES$^+$) *m/z* 629 ([M+Na]$^+$, 100%), 624 ([M+NH$_4$]$^+$, 5%) Da.

HRMS (ES$^+$) $C_{37}H_{66}O_6Na$ Requires 629.4752; Found 629.4748 Da.

$[\alpha]^{24}_D$ +14.7 (c. 0.32, $CDCl_3$).

(1*S*)-*N*-{(*R*)-2-Hydroxy-2-((2*S*,5*R*)-5-((*R*)-1-hydroxy)-5methylhex-4-enyl)-tetrahydrofuran-2-yl)ethanoyl}-camphor-10,2-sultam (7.1)



7.1
$C_{23}H_{37}NO_6S$
455.61

To a solution of triene **4.26** (400 mg, 0.99 mmol), and adogen-464 (2 drops) in acetone (14 mL) and AcOH (9 mL) at –25 °C under an atmosphere of N_2 was added powdered $KMnO_4$ (280 mg, 1.78 mmol) in three batches at intervals of 30 seconds. The reaction was stirred for 1 hr and quenched by pouring into an ice-cooled saturated aqueous solution of $Na_2S_2O_5$ (50 mL). The solution was extracted with EtOAc (3 x 20 mL) and CH_2Cl_2 (3 x 20 mL) and the combined organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 20 x 30 mm, 10-30% EtOAc/hexane) afforded the title compound **7.2** (237 mg, 0.52 mmol, 52%) as a white solid. R_f = 0.53 (60% EtOAc/hexane).

m.p. 48-50 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.14-5.08 (1H, m, C**H**=C(CH_3)$_2$), 4.59-4.52 (2H, m, C**H**C**H**OHCON), 4.03 (1H, br d, J = 8.5 Hz, CHO**H**), 3.95 (1H, dd, J = 7.5, 5.0 Hz, C**H**N), 3.85 (1H, td, J = 7.5, 4.5 Hz, CHC**H**OHCH$_2$), 3.51 & 3.44 (2 x 1H, 2 x d, J = 13.6 Hz, C**H**$_2$SO$_2$), 3.46 (1H, td, J = 13.1, 4.5 Hz, C**H**CHOHCH$_2$), 2.91 (1H, br s, CHO**H**), 2.30-1.80 (8H, m), 1.68 (3H, s, C**H**$_3$), 1.61 (3H, s, C**H**$_3$), 1.60-1.16 (7H, m), 1.15 (3H, s, C**H**$_3$), 0.97 (3H, s, C**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 171.8 (s), 132.2 (s), 124.2 (d), 83.3 (d), 78.8 (d), 73.7 (d), 73.6 (d), 65.9 (d), 53.2 (t), 49.2 (s), 48.0 (s), 44.7 (d), 38.4 (t), 34.7 (t), 33.0 (t), 28.5 (t), 28.3 (t), 26.5 (t), 25.9 (q), 24.4 (t), 21.0 (q), 20.0 (q), 17.9 (q) ppm.

FT-IR (film) ν_{max} 3462(br), 2959(m), 2916(s), 2849(w), 1690(m), 1456(w), 1413(w), 1376(m), 1376(w), 1333(s), 1218(m), 1167(m), 1136(s), 1111(m), 1069(m), 990(w), 763(m) cm^{-1}.

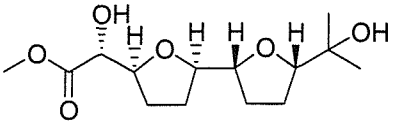
LRMS (ES$^+$) *m/z* 478 ([M+Na]$^+$, 100%), 933 ([2M+Na]$^+$, 25%) Da.

HRMS (ES$^+$) $C_{23}H_{37}NO_6SNa$ Requires 478.2234; Found 478.2234 Da.

Elemental Calc. for $C_{23}H_{37}NO_6S$: C, 60.63; H, 8.16; N, 3.07%; Found: C, 60.73; H, 8.16; N, 2.87%.

$[\alpha]^{24}_D$ -25.5 (c. 0.64, $CHCl_3$).

(*R*)-Methyl-2-hydroxy-2-((2*S*,5*R*)-5-((2*R*,5*S*)-5-(2-hydroxypropan-2-yl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)acetate (7.2)



7.2
$C_{14}H_{24}O_6$
288.34

To a suspension of Re_2O_7 (238 mg, 0.49 mmol) in THF (4 mL) at room temperature under an atmosphere of N_2 was added TFAA (0.09 mL, 0.62 mmol), and the mixture stirred for 1.5 hr. The solvent was removed *in vacuo* and the residue was washed with freshly distilled hexane (2 x 1 mL) and then taken up in CH_2Cl_2 (4 mL). To the dark blue suspension was added TFAA (0.09 mL, 0.62 mmol) followed by a solution of alkene **7.1** (83 mg, 0.18 mmol) in CH_2Cl_2 (2 mL), resulting in an immediate colour change to purple. The mixture was stirred for 20 min, during which the colour changed to black. The reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (4 mL) and a 30% aqueous solution of H_2O_2 (4 mL), and extracted with CH_2Cl_2 (3 x 20 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, 12 x 50 mm, 1-2% MeOH/CH_2Cl_2) resulted in transesterification to the methyl ester, affording title compound **7.2** (32 mg, 0.11 mmol, 61%) as a colourless oil. $R_f = 0.20$ (10% MeOH/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.50 (1H, ddd, J = 8.0, 3.0, 2.0 Hz), 4.07-3.97 (4H, m), 3.78 (3H, s), 2.25-2.04 (4H, m), 2.00-1.85 (6H, m), 1.31 (3H, s), 1.15 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 173.5 (s), 86.7 (d), 81.8 (d), 81.3 (d), 80.6 (d), 75.4 (d), 71.5 (s), 52.2 (q), 29.7 (t), 29.0 (t), 28.9 (t), 27.9 (q), 27.1 (t), 24.2 (q) ppm.

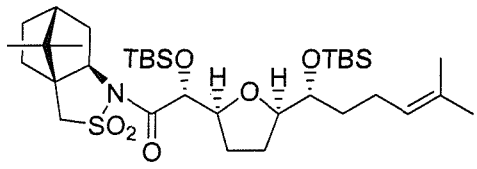
FT-IR (film) ν_{max} 3400(br), 2972(m), 2874(w), 1752(s), 1462(m), 1441(m), 1268(m), 1195(m), 1178(s), 1128(s), 1104(s), 1061(s), 949(m), 881(m), 798(m), 760(m) cm^{-1}.

LRMS (ES^+) *m/z* 311 ($[M+Na]^+$, 100%), 306 ($[M+NH_4]^+$, 35%), 327 ($[M+K]^+$, 7%), 594 ($[2M+NH_4]^+$, 8%), 594 ($[2M+Na]^+$, 35%) Da.

HRMS (ES$^+$) $C_{14}H_{24}O_6Na$ Requires 311.1465; Found 311.1466 Da.

$[\alpha]^{24}_D$ +42.0 (c. 0.49, $CHCl_3$).

(1*S*)-*N*-{(*R*)-2-(*tert*-Butyldimethylsilyloxy)-2-((2*S*,5*R*)-5-((*R*)-1-(*tert*-butyldimethylsilyloxy)-5methylhex-4-enyl)-tetrahydrofuran-2-yl)ethanoyl}-camphor-10,2-sultam (7.3)



7.3
$C_{35}H_{65}NO_6SSi$
684.16

To a solution of diol **7.1** (0.30 g, 0.67 mmol) and TBSCl (1.00 g, 6.67 mmol) in CH_2Cl_2 (8 mL) at room temperature under an atmosphere of N_2 was added imidazole (0.91 g, 13.34 mmol) as a single batch. The reaction was stirred for 30 hr, quenched with water (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, 20 x 50 mm, 5% EtOAc/hexane) afforded the title compound **7.3** (0.36 g, 0.53 mmol, 79%) as a white solid. R_f = 0.66 (40% EtOAc/hexane).

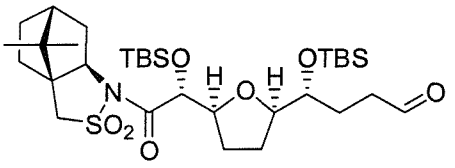
m.p. 154-156 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.17-5.09 (1H, m, C**H**=C(CH_3)$_2$), 4.66 (1H, d, J = 6.3 Hz, C**H**(OSiR_3)CON), 4.21 (1H, app. q, J = 6.3 Hz, C**H**CH(OSiR_3)CON), 3.94-3.87 (2H, m, C**H**N + C**H**CH(OSiR_3)CH_2), 3.77-3.70 (1H, m, C**H**(OSiR_3)CH_2), 3.49 & 3.42 (2 x 1H, 2 x d, J = 13.6 Hz, C**H**$_2$$SO_2$), 2.22-2.03 (3H, m), 2.00-1.69 (9H, m), 1.68 (3H, s, C**H**$_3$), 1.60 (3H, s, C**H**$_3$), 1.47-1.29 (3H, m), 1.16 (3H, s, C**H**$_3$), 0.96 (3H, s, C**H**$_3$), 0.89 (9H, s, SiC(C**H**$_3$)$_3$), 0.87 (9H, s, SiC(C**H**$_3$)$_3$), 0.14 (3H, s, SiC**H**$_3$), 0.12 (3H, s, SiC**H**$_3$), 0.06 (3H, s, SiC**H**$_3$), 0.05 (3H, s, SiC**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.1 (s), 131.3 (s), 124.9 (d), 82.0 (d), 80.3 (d), 74.9 (d), 73.1 (d), 65.6 (d), 53.4 (t), 48.6 (s), 47.9 (s), 44.7 (d), 38.6 (t), 33.2 (t), 32.3 (t), 27.5 (t), 26.6 (t), 26.1 (q), 26.0 (t), 25.9 (q), 24.8 (t), 21.1 (q), 20.1 (q), 18.4 (s), 18.3 (s), 17.9 (q), -4.2 (q), -4.37 (q), -4.42 (q), -4.7 (q) ppm.

FT-IR	(film) ν_{max} 2955(m), 2928(m), 2884(m), 2856(m), 1699(m), 1471(w), 1463(w), 1389(w), 1337(w), 1251(w), 1215(w), 1166(w), 1135(m), 1081(m), 982(w), 837(s), 774(m) cm^{-1}.
LRMS	(ES^+) *m/z* 706 ($[M+Na]^+$, 100%), 701 ($[M+NH_4]^+$, 76%), 1389 ($[2M+Na]^+$, 6%) Da.
HRMS	(ES^+) $C_{35}H_{65}NO_6SSi_2Na$ Requires 706.3963; Found 706.3979 Da.
Elemental	Calc. for $C_{35}H_{65}NO_6SSi_2$: C, 61.45; H, 9.58; N, 2.05%; Found: C, 61.23; H, 9.80; N, 1.91%.
$[\alpha]^{24}_D$	-13.8 (c. 0.16, $CHCl_3$).

(1*S*)-*N*-{(*R*)-2-(*tert*-Butyldimethylsilyloxy)-2-((2*S*,5*R*)-5-((*R*)-1-*tert*-butyldimethylsilyloxy)-4-oxobutyl)tetrahydrofuran-2-yl)ethanoyl}-camphor-10,2-sultam (7.4)



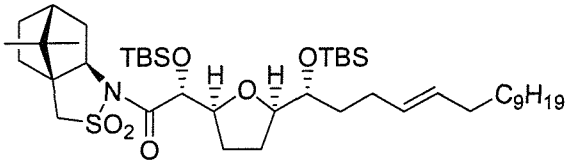
7.4
$C_{32}H_{59}NO_7SSi_2$
658.06

To a solution of alkene **7.3** (50 mg, 0.073 mmol) in CH_2Cl_2 (2 mL) at room temperature were added a 2.5% w/w solution of OsO_4 in 2-methyl-2-propanol (10 mg) and NMO (17 mg, 0.146 mmol) and the solution stirred for 8 hr. The mixture was quenched with a 10% w/v aqueous solution of $NaHSO_3$ (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 (2 mL) and SiO_2-supported $NaIO_4$ (500 mg) was added. After 3 hr the solution was filtered, the filtrate concentrated *in vacuo* and the residue purified by flash column chromatography (silica gel, 20 x 50 mm, 5% EtOAc/hexane) affording the title compound **7.4** (18 mg, 0.027 mmol, 37%) as a white solid. R_f = 0.66 (40% EtOAc/hexane).

m.p.	158-160 °C.
^{1}H NMR	(400 MHz, $CDCl_3$) δ_H 9.77 (1H, t, *J* = 13.6 Hz, C**H**O), 4.70 (1H, d, *J* = 5.5 Hz, C**H**(OSiR$_3$)CON), 4.27 (1H, app. q, *J* = 5.5 Hz, C**H**CH(OSiR$_3$)CON), 3.94-3.88 (2H, m, C**H**N + C**H**CH(OSiR$_3$)CH$_2$), 3.84-3.78 (1H, m, C**H**(OSiR$_3$)CH$_2$), 3.49 & 3.43 (2 x 1H, 2 x d, *J* = 13.6 Hz, C**H**$_2$SO$_2$), 2.55-2.41 (2H, m, C**H**$_2$CHO), 2.12-1.58 (10H, m), 1.46-1.25 (3H, m), 1.15 (3H, s, C**H**$_3$), 0.97 (3H, s, C**H**$_3$), 0.88 (18H, s,

	2 x $SiC(CH_3)_3$), 0.13 (3H, s, $SiCH_3$), 0.10 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ_C 203.2 (d), 169.9 (s), 82.0 (d), 80.2 (d), 74.4 (d), 72.4 (d), 65.7 (d), 53.4 (t), 48.7 (s), 47.9 (s), 44.7 (d), 40.8 (t), 38.6 (t), 33.1 (t), 27.4 (t), 26.6 (t), 26.0 (q), 25.7 (t), 24.7 (t), 21.0 (q), 20.1 (q), 18.4 (s), 18.2 (s), -4.2 (q), -4.48 (q), -4.51 (q), -4.6 (q) ppm.
FT-IR	(film) ν_{max} 2954(m), 2926(m), 2885(m), 2855(m), 1724(m), 1701(m), 1471(w), 1390(w), 1334(m), 1252(m), 1216(m), 1134(s), 1005(s), 838(s), 778(m) cm^{-1}.
LRMS	(ES^+) *m/z* 680 ($[M+Na]^+$, 100%), 675 ($[M+NH_4]^+$, 4%), 696 ($[M+K]^+$, 14%) Da.
HRMS	(ES^+) $C_{32}H_{59}NO_7SSi_2Na$ Requires 680.3443; Found 680.3452 Da.
Elemental	Calc. for $C_{32}H_{59}NO_7SSi_2$: C, 58.41; H, 9.04; N, 2.13%; Found: C, 58.56; H, 8.84; N, 1.88%.
$[\alpha]^{24}_D$	-10.8 (c. 0.64, $CHCl_3$).

(1*S*)-*N*-{(*R*)-2-(*tert*-Butyldimethylsilyloxy)-2-((2*S*,5*R*)-5-((*R*,*E*)-1-*tert*-butyldimethylsilyloxy)pentadec-4-enyl)-tetrahydrofuran-2-yl)}-camphor-10,2-sultam (7.5)



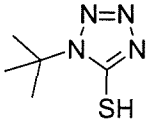
7.5
$C_{43}H_{81}NO_6SSi$
796.34

The title compound was prepared according to the method Kocienski *et al.*[232] Thus, to a solution of sulfone **7.9** (25 mg, 0.072 mmol) in DME (2 mL) at –60 °C under an atmosphere of N_2 was added a 1M solution of NaHMDS in hexanes (0.07 mL, 0.070 mmol) over 5 min, and the reaction was stirred for 45 min. A solution of aldehyde **7.4** (43 mg, 0.065 mmol) in DME (1 mL) was added and the mixture was stirred at –55 °C for 1 hr then at room temperature for 18 hr. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (5 mL) and extracted with Et_2O (2 x 10 mL) and EtOAc (2 x 10 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to a residue which was purified by flash column chromatography (silica gel, 10 x 60 mm, 5% EtOAc/hexane)

affording the title compound **7.5** (31 mg, 0.039 mmol, 60%) as a white solid. R_f = 0.69 (40% EtOAc/hexane).

m.p	173-175 °C.
^{1}H NMR	(400 MHz, $CDCl_3$) δ_H 5.47-5.33 (2H, m, C**H**=C**H**), 4.52 (1H, d, J = 6.0 Hz, C**H**(OSiR$_3$)CON), 4.25-4.18 (1H, m), 3.94-3.87 (2H, m), 3.78-3.71 (1H, m), 3.49 & 3.42 (2 x 1H, 2 x d, J = 14.1 Hz, C**H**$_2$SO$_2$), 2.55-2.41 (2H, m, C**H**$_2$CHO), 2.22-1.22 (33H, m), 1.16 (3H, s, C**H**$_3$), 0.97 (3H, s, C**H**$_3$), 0.92-0.87 (21H, m, 2 x SiC(C**H**$_3$)$_3$ + CH$_2$C**H**$_3$), 0.15 (3H, s, SiC**H**$_3$), 0.13 (3H, s, SiC**H**$_3$), 0.06 (3H, s, SiC**H**$_3$), 0.05 (3H, s, SiC**H**$_3$) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ_C 170.1 (s), 130.7 (d), 130.3 (d), 81.9 (d), 80.3 (d), 75.0 (d), 72.8 (d), 65.6 (d), 53.4 (t), 48.7 (s), 47.9 (s), 44.7 (d), 38.6 (t), 33.2 (t), 32.9 (t), 32.1 (t), 29.9 (t), 29.8 (t), 29.59 (t), 29.56 (t), 29.5 (t), 29.2 (t), 27.5 (t), 26.7 (t), 26.1 (q), 26.0 (t), 22.9 (t), 21.1 (q), 20.1 (t), 18.5 (s), 18.3 (s), 14.3 (q), -4.2 (q), -4.29 (q), -4.31 (q), -4.7 (q) ppm.
FT-IR	(film) ν_{max} 2959(m), 2925(m), 2854(m), 1701(s), 1459(m), 1338(s), 1252(s), 1215(s), 1165(m), 1135(s), 1081(s), 837(s), 779(s), 734(m) cm^{-1}.
LRMS	(ES$^+$) *m/z* 818 ([M+Na]$^+$, 100%), 813 ([M+NH$_4$]$^+$, 19%), 834 ([M+K]$^+$, 4%) Da.
HRMS	(ES$^+$) $C_{43}H_{81}NO_6SSi_2Na$ Requires 818.5215; Found 818.5226 Da.
[α]$^{24}_D$	-16.9 (c. 0.28, $CHCl_3$).

1-*tert*-Butyl-1*H*-tetrazole-5-thiol (7.7)



7.7
$C_5H_{10}N_4S$
158.23

The title compound was prepared according to the method Quast *et al.*[233] Thus, a solution of NaN_3 (2.82 g, 43.4 mmol) in water (13.6 mL) was heated at reflux for 1.5 hr, and a solution of *t*-butyl-*iso*-thiocyanate (5.00 g, 43.4 mmol) in 2-propanol (10.6 mL) was added. The mixture was heated at reflux for 16 hr, then was cooled to 0 °C and quenched by the careful dropwise addition of concentrated HCl (6.4 mL). The 2-propanol was removed *in*

vacuo and the resulting white solid was collected by filtration, recrystallised from cyclohexane and dried *in vacuo* over P_2O_5 affording the title compound **7.7** (4.44 g, 29.3 mmol, 68%) as an off-white solid. $R_f = 0.12$ (20% EtOAc/hexane).

m.p. 92-94 °C (EtOH).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 14.60 (1H, br s, **SH**), 1.86 (9H, s, $(CH_3)_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 163.1(s, **C**SH), 63.8 (s, **C**$(CH_3)_3$), 27.9 (q, $(CH_3)_3$ ppm.

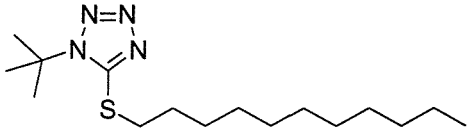
FT-IR (solid) ν_{max} 3056(m), 2983(s), 2914(s), 2784(s), 2745(m), 2610(m), 2575(w), 2541(w), 1513(s), 1479(w), 1406(w), 1369(m), 1363(m), 1335(s), 1304(s), 1236(w), 1213(m), 1095(m), 1065(m), 1029(m), 993(w), 805(m) cm^{-1}.

LRMS (CI) *m/z* 159 ($[M+H]^+$, 24%), 127 (32%), 99 (100%), 57 (11%) Da.

HRMS (EI) $C_5H_{10}N_4S$ Requires 158.0626; Found 158.0624 Da.

Elemental Calc. for $C_5H_{10}N_4S$: C, 37.96; H, 6.37; N, 35.39%; Found: C, 37.74; H, 6.50; N, 35.22%.

1-*tert*-Butyl-5-(undecylthio)-1*H*-tetrazole (7.8)



7.8
$C_{16}H_{32}N_4S$
312.53

The title compound was prepared according to the method Kocienski *et al.*[232] Thus, to a solution of thiol **7.7** (1.50 g, 9.48 mmol) in EtOH (95 mL) was added ground KOH (0.75 g, 13.36 mmol) followed after 30 min by 1-bromoundecane (2.33 mL, 9.32 mmol), and the solution stirred at room temperature for 60 hr. SiO_2 (5 g) was added, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (silica gel, 35 x 150 mm, 5% EtOAc/hexane) affording the title compound **7.8** (2.37 g, 7.59 mmol, 80%) as a white solid. $R_f = 0.50$ (20% EtOAc/hexane).

m.p. 60-62 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.37 (2H, t, J = 7.3 Hz, S**CH$_2$**), 1.80 (2H, app. quin, J = 7.3 Hz, SCH_2**CH$_2$**), 1.71 (9H, s, C$(CH_3)_3$), 1.48-1.40 (2H,

m, CH_2CH_3), 1.38-1.21 (14H, m, $(CH_2)_7$), 0.88 (3H, t, J = 7.0 Hz, CH_2CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 153.0 (s), 61.0 (s), 34.1 (t), 32.1 (t), 29.74 (t), 29.71 (t), 29.6 (t), 29.5 (t), 29.2 (t), 28.9 (q), 23.3 (t), 14.7 (q) ppm.

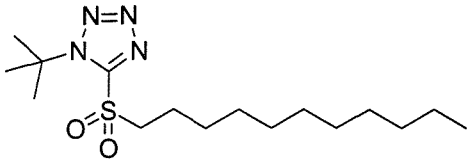
FT-IR (solid) ν_{max} 2983(m), 2918(s), 2852(m), 1470(w), 1388(s), 1360(m), 1286(m), 1224(m), 1138(m), 1101(m) cm^{-1}.

LRMS (ES^+) *m/z* 335 ($[M+Na]^+$, 100%), 647 ($[2M+Na]^+$, 98%) Da.

HRMS (ES^+) $C_{32}H_{64}N_8S_2Na$ Requires 647.4588; Found 647.4589 Da.

Elemental Calc. for $C_{16}H_{32}N_4S$: C, 61.49; H, 10.32; N, 17.92%; Found: C, 61.22; H, 10.19; N, 17.63%.

1-*tert*-Butyl-5-(undecylsulfonyl)-1*H*-tetrazole (7.9)



7.9
$C_{16}H_{32}N_4O_2S$
344.53

To a heterogeneous solution of thioether **7.8** (2.78 g, 8.9 mmol) and $NaHCO_3$ (3.73 g, 44.5 mmol) in CH_2Cl_2 (38 mL) was added 50% *m*-CPBA (7.67 g, 22.2 mmol) in ten batches over a period of 10 min. The reaction was stirred at room temperature for 14 hr, diluted with CH_2Cl_2 (60 mL) and quenched by the addition of saturated aqueous solutions of $Na_2S_2O_5$ (75 mL) then $NaHCO_3$ (75 mL). The mixture was extracted with CH_2Cl_2 (2 x 75 mL) and the combined organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (3 x 75 mL) and brine (70 mL), then dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel 30 x 210 mm, 5% EtOAc/hexane) afforded the title compound **7.9** (1.91 g, 5.5 mmol, 62%) as a white solid. R_f = 0.55 (20% EtOAc/hexane).

m.p. 65-67 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.83-3.80 (2H, m, SO_2CH_2), 2.25-1.89 (2H, m, $SO_2CH_2CH_2$), 1.86 (9H, s, $(CH_3)_3$), 1.55-1.48 (2H, m, CH_2CH_3), 1.40-1.23 (14H, m, $(CH_2)_7$), 0.89 (3H, t, J = 7.03 Hz, CH_2CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 154.2 (s, CSO_2), 65.6 (s, $C(CH_3)_3$), 56.9 (t, SO_2CH_2), 32.1 (t, $SO_2CH_2CH_2$), 29.8 (q, $C(CH_3)_3$), 29.7 (t), 29.6 (t), 29.5 (t), 29.4 (t), 29.1 (t), 28.4 (t), 22.8 (t), 22.3 (t), 14.3 (q, CH_2CH_3) ppm.

FT-IR	(solid) ν_{max} 2925(s), 2855(s), 1466(w), 1376(m), 1337(s), 1245(w), 1210(m), 1159(s), 1123(m) cm^{-1}.
LRMS	(ES^+) *m/z* 367 ($[M+Na]^+$, 100%) Da.
HRMS	(ES^+) $C_{32}H_{64}N_8O_4S_2Na$ Requires 711.4384; Found 711.4397 Da.
Elemental	Calc. for $C_{16}H_{32}N_4S$: C, 55.78; H, 9.36; N, 16.25%; Found: C, 55.56; H, 9.51; N, 16.32%.

Chapter 10

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Appendices

Crystal Structure Data for Epoxide 6.7

Table 1. Crystal data and structure refinement.

Identification code	**03sot0105**	
Empirical formula	$C_{10}H_{14}O_4$	
Formula weight	198.21	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 10.3413(4) Å	α = 90°
	b = 9.5255(3) Å	β = 90°
	c = 9.6037(3) Å	γ = 90°
Volume	946.02(6) Å^3	
Z	4	
Density (calculated)	1.392 Mg / m^3	
Absorption coefficient	0.107 mm^{-1}	
F(000)	424	
Crystal	Slab; Colourless	
Crystal size	0.22 × 0.18 × 0.05 mm^3	
θ range for data collection	3.01 – 27.47°	
Index ranges	$-13 \le h \le 13$, $-12 \le k \le 12$, $-11 \le l \le 12$	
Reflections collected	10543	
Independent reflections	2156 [R_{int} = 0.0657]	
Completeness to θ = 27.47°	98.9 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9947 and 0.9768	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2156 / 0 / 128	
Goodness-of-fit on F^2	1.064	
Final R indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0367, *wR2* = 0.0887	
R indices (all data)	*R1* = 0.0396, *wR2* = 0.0909	
Absolute structure parameter	0.0(11)	
Extinction coefficient	0.032(7)	
Largest diff. peak and hole	0.299 and –0.155 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.
It was not possible to determine the absolute structure.
The relative structure is *S, S, R, R* (C4, C5, C8, C9).

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	9711(2)	2113(2)	1427(2)	32(1)	1
C2	10802(2)	1080(2)	1257(2)	33(1)	1
C3	11323(2)	901(2)	2732(2)	23(1)	1
C4	10168(1)	1305(2)	3637(2)	20(1)	1
C5	10533(1)	2041(2)	4969(2)	20(1)	1
C6	11375(1)	1094(2)	5894(2)	23(1)	1
C7	10860(2)	1360(2)	7362(2)	23(1)	1
C8	9438(2)	1727(1)	7112(2)	21(1)	1
C9	8601(2)	445(2)	7143(2)	26(1)	1
C10	7901(2)	66(2)	8410(2)	31(1)	1
O1	9397(1)	2263(1)	2775(1)	24(1)	1
O2	9137(2)	2761(2)	529(1)	53(1)	1
O3	9389(1)	2382(1)	5766(1)	25(1)	1
O4	7222(1)	674(1)	7236(1)	35(1)	1

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

C1–O2	1.215(2)	C6–C7	1.529(2)
C1–O1	1.343(2)	C6–H6A	0.9900
C1–C2	1.505(3)	C6–H6B	0.9900
C2–C3	1.525(2)	C7–C8	1.531(2)
C2–H2A	0.9900	C7–H7A	0.9900
C2–H2B	0.9900	C7–H7B	0.9900
C3–C4	1.527(2)	C8–O3	1.4365(18)
C3–H3A	0.9900	C8–C9	1.497(2)
C3–H3B	0.9900	C8–H8	1.0000
C4–O1	1.4676(17)	C9–O4	1.4450(19)
C4–C5	1.507(2)	C9–C10	1.461(2)
C4–H4	1.0000	C9–H9	1.0000
C5–O3	1.4463(17)	C10–O4	1.449(2)
C5–C6	1.536(2)	C10–H10A	0.9900
C5–H5	1.0000	C10–H10B	0.9900
O2–C1–O1	120.78(17)	O3–C5–C4	110.43(12)
O2–C1–C2	128.40(16)	O3–C5–C6	106.85(11)
O1–C1–C2	110.82(13)	C4–C5–C6	111.03(12)
C1–C2–C3	103.71(13)	O3–C5–H5	109.5
C1–C2–H2A	111.0	C4–C5–H5	109.5
C3–C2–H2A	111.0	C6–C5–H5	109.5
C1–C2–H2B	111.0	C7–C6–C5	103.78(12)
C3–C2–H2B	111.0	C7–C6–H6A	111.0
H2A–C2–H2B	109.0	C5–C6–H6A	111.0
C2–C3–C4	102.96(13)	C7–C6–H6B	111.0
C2–C3–H3A	111.2	C5–C6–H6B	111.0
C4–C3–H3A	111.2	H6A–C6–H6B	109.0
C2–C3–H3B	111.2	C6–C7–C8	103.16(12)
C4–C3–H3B	111.2	C6–C7–H7A	111.1
H3A–C3–H3B	109.1	C8–C7–H7A	111.1
O1–C4–C5	108.98(11)	C6–C7–H7B	111.1
O1–C4–C3	105.09(12)	C8–C7–H7B	111.1
C5–C4–C3	113.86(12)	H7A–C7–H7B	109.1
O1–C4–H4	109.6	O3–C8–C9	110.61(13)
C5–C4–H4	109.6	O3–C8–C7	105.91(12)
C3–C4–H4	109.6	C9–C8–C7	111.49(13)

O3–C8–H8	109.6
C9–C8–H8	109.6
C7–C8–H8	109.6
O4–C9–C10	59.82(10)
O4–C9–C8	116.62(13)
C10–C9–C8	120.27(15)
O4–C9–H9	116.1
C10–C9–H9	116.1
C8–C9–H9	116.1
O4–C10–C9	59.56(10)
O4–C10–H10A	117.8
C9–C10–H10A	117.8
O4–C10–H10B	117.8
C9–C10–H10B	117.8
H10A–C10–H10B	115.0
C1–O1–C4	110.25(12)
C8–O3–C5	110.47(10)
C9–O4–C10	60.62(11)

Symmetry transformations used to generate equivalent atoms:

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

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	52(1)	24(1)	20(1)	−2(1)	−8(1)	7(1)
C2	50(1)	29(1)	20(1)	−3(1)	2(1)	8(1)
C3	26(1)	22(1)	22(1)	−1(1)	4(1)	0(1)
C4	21(1)	18(1)	20(1)	2(1)	−3(1)	1(1)
C5	20(1)	21(1)	20(1)	0(1)	3(1)	1(1)
C6	21(1)	26(1)	21(1)	1(1)	−2(1)	3(1)
C7	24(1)	25(1)	20(1)	0(1)	−3(1)	−2(1)
C8	24(1)	22(1)	18(1)	2(1)	0(1)	2(1)
C9	22(1)	25(1)	30(1)	2(1)	−4(1)	1(1)
C10	23(1)	32(1)	37(1)	12(1)	−3(1)	0(1)
O1	30(1)	22(1)	20(1)	0(1)	−5(1)	6(1)
O2	96(1)	38(1)	24(1)	−2(1)	−14(1)	30(1)
O3	26(1)	29(1)	20(1)	5(1)	4(1)	9(1)
O4	22(1)	35(1)	47(1)	14(1)	−9(1)	−1(1)

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

Atom	x	y	z	U_{eq}	*S.o.f.*
H2A	11476	1455	627	40	1
H2B	10483	176	881	40	1
H3A	12067	1532	2903	28	1
H3B	11591	−81	2905	28	1
H4	9648	447	3857	23	1
H5	11016	2922	4746	24	1
H6A	11275	95	5631	27	1
H6B	12299	1356	5822	27	1
H7A	11323	2148	7813	27	1
H7B	10945	512	7951	27	1
H8	9139	2406	7838	25	1
H9	8884	−354	6540	31	1
H10A	7766	−944	8604	37	1
H10B	8030	660	9244	37	1

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