UNIVERSITY OF SOUTHAMPTON

Faculty of Engineering, Science and Mathematics
School of Chemistry

The Total Synthesis of Membrarollin

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ABSTRACT

FACUTLY OF ENGINEERING, SCIENCE AND MATHEMATICS

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THE TOTAL SYNTHESIS OF MEMBRAROLLIN

by Claire-Louise Kay

A model adjacent *bis*-THF compound has been prepared with the installation of the first THF ring by a chiral auxiliary directed oxidative cyclisation of 1,5,9-dienyne **4.24** by potassium permanganate. The second THF ring was introduced by an acyl perrhenate cyclisation of hydroxy-alkene **4.28**. A crystal structure of the adjacent *bis*-THF product was obtained which showed the unexpected *trans* ring formed in the second cyclisation.

The central adjacent *bis*-THF core of the *Annonaceous* acetogenin membrarollin was established *via* a permanganate promoted selective oxidative cyclisation of 1,5,9-triene **5.26** followed by a base-induced cyclisation of cyclic sulphate **5.35**. Elaboration of the central core to terminal alkene **5.39** allowed the introduction of the butenolide fragment by Trost's ruthenium catalysed Alder-ene reaction. Selective alkene reduction completed the synthesis of membrarollin.

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Abbreviations

Ac	acetyl
acac	acetylacetonate
AD	asymmetric dihydroxylation
aq.	aqueous
Ar	aryl
ATP	adenosine triphosphate
BDA	2,3-butandiacetal
Bn	benzyl
brd	broad (spectral)
Bu	butyl
Bz	benzoyl
CAN	ceric ammonium nitrate
CI	chemical ionisation
CSA	camphorsulphonic acid
d	doublet (spectral)
Da	Dalton (spectral)
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
de	diastereomeric excess
DEF	*N*,*N*-diethylformamide
DET	diethyl tartrate
DHQ	dihydroquinine
DHQD	dihydroquinidine
$(DHQ)_2$-PHAL	hydroquinine 1,4-phthalazinediyl diether
$(DHQD)_2$-PHAL	hydroquinidine 1,4-phthalazinediyl diether
DIBAL-H	di*iso*-butylaluminium hydride
DMAP	4-(diemthylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMOP	dimethoxypropane
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone

DMSO	dimethyl sulphoxide
dr	diastereomeric ratio
ED_{50}	effective dose for 50% assay
EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
EI	electron impact
eq.	equivalents
ES	electrospray
Et	ethyl
FT	Fourier transform
GC	Gas chromatography
HMPA	hexamethylphosphoramide
HRMS	High resolution mass spectrometry
IC_{50}	inhibitory concentration for 50% assay
Ipc	*iso*-pinocamphenyl
IR	Infrared
KHMDS	potassium hexamethyldisilazane
LDA	lithium di*iso*-propylamide
LRMS	low resolution mass spectrometry
m	multiplet
***m*-CPBA**	*meta*-chloroperoxybenzoic acid
Me	methyl
min	minutes
MMPP	magnesium monoperoxyphthalate hexahydrate
MOM	methoxymethyl
Ms	methanesulphonyl
NADH	reduced nicotinamide adenine dinucleotide
NaHMDS	sodium hexamethyldisilazane
NMM	*N*-methylmorpholine
NMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
Ph	phenyl

PHAL	phthalazine linker
Piv	pivaloyl
ppm	parts per million
PYR	diphenylpyrimidine linker
RCM	ring closing metathesis
Rochelle's salt	sodium potassium tartrate
r.t.	room temperature
s	singlet (spectral)
SAR	structure activity relationship
t	triplet (spectral)
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
Tf	trifluoromethanesulphonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	*p*-toluenesulphonyl
UV	ultraviolet

Chapter One

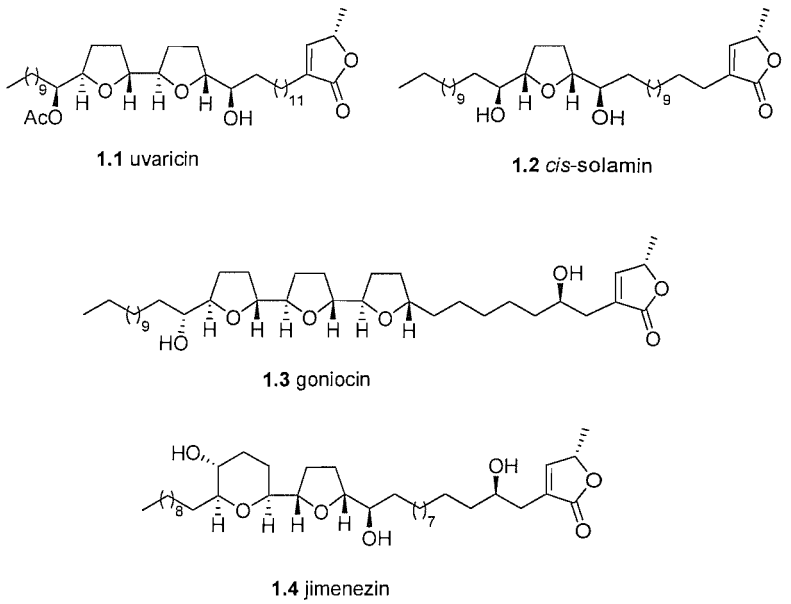
Structure, Biological Activity and Synthesis of *Annonaceous* Acetogenins

The following chapter summarises the general structure of *Annonaceous* acetogenins, their biological activity and recent syntheses of adjacent *bis*-tetrahydrofuran acetogenins.

1.1 General Introduction to Acetogenins

The *Annonaceous* acetogenins are a class of natural products that are only found in members of the plant family *Annonaceae*, the custard-apple. This family consists of over 130 genera and 2300 species but until relatively recently it was one of the least well known tropical plant families.[1] Interest in the family increased after the discovery in 1982 of the first acetogenin, uvaricin (**1.1**), from the roots of *uvaria accuminata*. It was found to demonstrate *in vivo* anti-tumour properties against P-388 lymphocytic leukaemia in mice.[2] The acetogenins exhibit a broad range of biological activities which has generated wide interest in the family, resulting in them becoming one of the most rapidly growing classes of natural products.[3]

Structurally, the 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 unit. They usually contain a long alkyl chain bearing a terminal methyl-substituted α,β-unsaturated γ-lactone ring (butenolide), which can sometimes be rearranged to a ketolactone.[3] The hydrocarbon chain usually contains one, two or three tetrahydrofuran (THF) rings and a number of oxygenated moieties (hydroxyls, acetoxyls, ketones or epoxides) and / or double bonds.[4] A number of tetrahydropyran (THP) containing products and acyclic compounds have also been found, although to a much lesser extent (figure 1.1).[5-8]



1.1 uvaricin

1.2 *cis*-solamin

1.3 goniocin

1.4 jimenezin

Figure 1.1: Some examples of *Annonaceous* acetogenins

1.2 Classification of Acetogenins

Acetogenins may be classified in a number of ways, either by the relative stereochemistry across the THF rings in the structure, or by the number and arrangement of the THF subunits within the molecule. Although the former leads to exact stereochemical detail, it requires the formation of several subclasses, whilst the latter is much simpler and more commonly employed. Therefore the acetogenins can be classified as *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 THP-ring **1.10** followed by sub-classification of the γ-lactone, substituted γ-lactone or ketolactone variations (figure 1.2).[3,9]

It is believed that acetogenins are derived from the polyketide pathway, with the THF, THP and epoxide ring fragments arising from the epoxidation and cyclisation of isolated double bonds.[9]

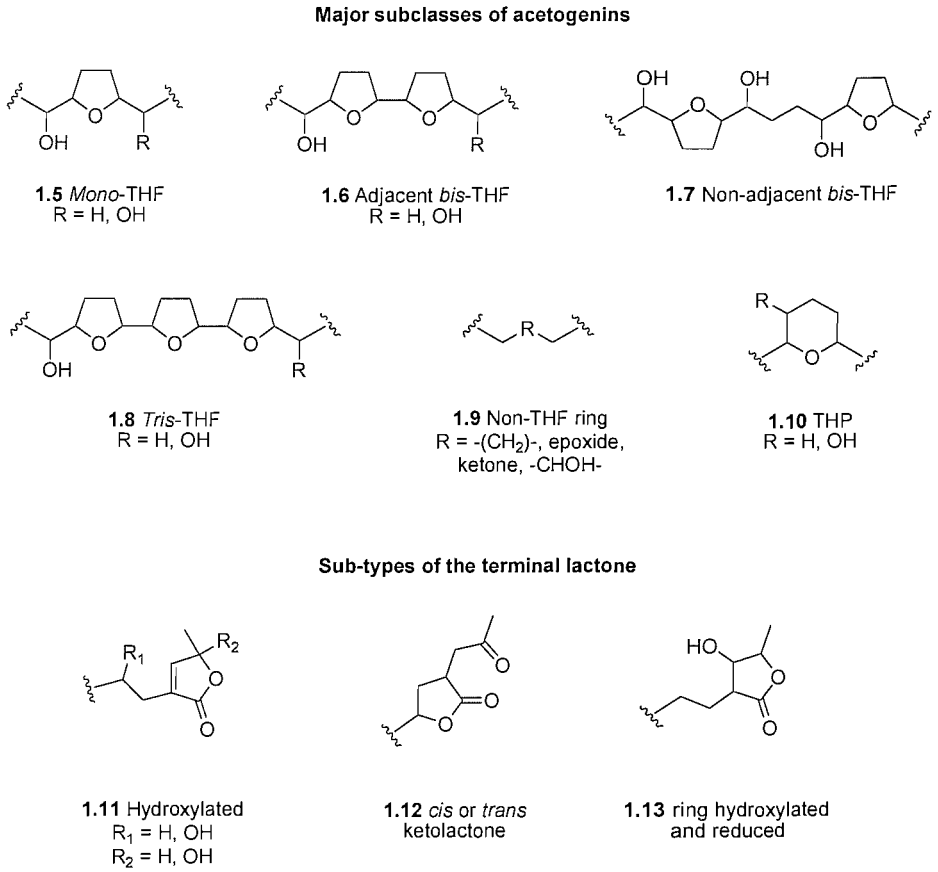
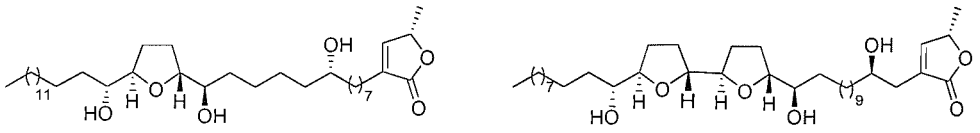


Figure 1.2: Core units of acetogenins

1.3 Biological Activity of Acetogenins

The extensive interest in the acetogenins as synthetic targets is due to their range of biological activities, including anti-malarial, anti-bacterial, anti-parasitic,[10] anti-feedant[11] and pesticidal.[12] More importantly, a number of acetogenins exhibit potent cytotoxicity against various tumour cell lines.[11,13] This cytotoxicity is generally lower for *mono*-THF acetogenins compared to the *bis*-THF compounds. For example longicoricin, a mono-THF acetogenin, shows an ED_{50} of $<1 \times 10^{-7}$ g / mL in human prostate adenocarcinoma[14] while adjacent *bis*-THF acetogenin trilobacin has an ED_{50} of $<1 \times 10^{-12}$ g / mL in human colon carcinoma (figure 1.3).[9] A number of *bis*-THF acetogenins have also shown cytotoxicity towards multi-drug resistant tumours.[12,15-17]



1.14 longicoricin **1.15** trilobacin

Figure 1.3: Examples of cytotoxic *Annonaceous* acetogenins

The site of action of acetogenins is thought to be within the mitochondria of cells. Acetogenins inhibit the reduced nicotinamide adenine dinucleotide, or NADH: ubiquinone oxidoreductase (complex I).[18-24] This complex catalyses the first step in the mitochondrial electron transport chain, by which electrons from the oxidation of NADH are used to convert oxygen to water. The energy from this process drives the production of adenosine triphosphate (ATP). Inhibition of this process results in depleted ATP levels and subsequent apoptosis.[25] It is this mechanism of action which is particularly effective against cancerous cells as they have a higher demand for ATP than healthy cells. Acetogenins are considered to be the most potent inhibitors of complex I yet described, with inhibition occurring in nanomolar concentrations for some acetogenins.[26,27]

Studies into the cytotoxicity of acetogenins have shown several structure-activity relationships (SARs):[18,27,28]

- Adjacent *bis*-THF acetogenins are the most potent, followed by non-adjacent *bis*-THF, mono-THF and non-ring THF compounds.
- The activity of the non-adjacent *bis*-THF compounds is dependant on the distance between the two THF rings, if the distance is large then *mono*-THF acetogenins become more active.
- The THP ring acetogenins are as active as the THF compounds and have the same mechanism of action.
- The terminal butenolide is crucial for activity.
- C_{35} acetogenins are more potent than the C_{37} equivalents.
- The alkyl spacer between the THF rings and the butenolide is crucial for activity, with 13 carbons being the optimum length.

The high cytotoxicity against cancerous cells and the range of biological activities possessed by the acetogenins have resulted in a vast interest in their isolation and synthesis.[29]

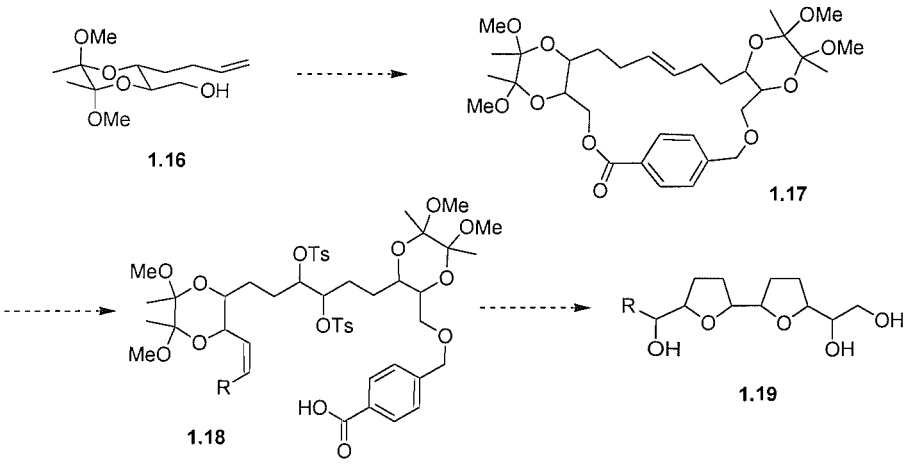
1.4 Synthesis of Adjacent *bis*-THF Acetogenins

A comprehensive summary of existing methodologies applied to the synthesis of adjacent *bis*-THF acetogenins up to 2003 has already been carried out.[30] The following section will summarise the syntheses of adjacent *bis*-THF acetogenins that have been reported from 2004 to date.

1.4.1 Steven V. Ley *et al.*

The recent approach of Ley *et al.* to the synthesis of adjacent *bis*-THF acetogenins has been based on an orthogonal and modular templating methodology. This was motivated by the desire to create a general route to a *bis*-THF core that could provide access to many members of the family.[31]

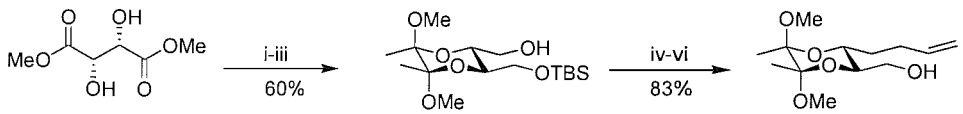
The overall strategy of Ley *et al.* depended on the preparation of a tether that could temporarily link two 2,3-butandiacetal (BDA) protected alkenol building blocks **1.16** (scheme 1.1). The tether could then induce stereocontrol during the ring-closing metathesis reaction (RCM) to give **1.17**.[32] Subsequent Sharpless asymmetric dihydroxylation, chemoselective cleavage of the tether and displacement of the desymmetrised *bis*-tosylate by the unmasked hydroxy groups would afford the *bis*-THF core **1.19**. This could, in principle, be of any desired stereochemical arrangement as it would be determined by the stereochemistry in the original alkenol building blocks.[33]



Scheme 1.1: Proposed synthetic route to adjacent *bis*-THF acetogenins

1.4.1.1 Total Synthesis of 10-Hydroxyasimicin

To date, the method has been successfully applied in the first total synthesis of 10-hydroxyasimicin (**1.41**),[31] an adjacent *bis*-THF acetogenin with a *threo*, *trans*, *threo*, *trans*, *threo* relative stereochemistry about the THF core. Synthesis of the required alkenol fragment (**1.22**) started with the conversion of (*S*,*S*)-dimethyl-D-tartrate (**1.20**) to the mono-protected diol **1.21** in three steps according to a procedure previously established by Ley *et al.*[33] (scheme 1.2). Tosylation of **1.21** followed by treatment with allylmagnesium bromide and subsequent deprotection afforded **1.22** in good yield.



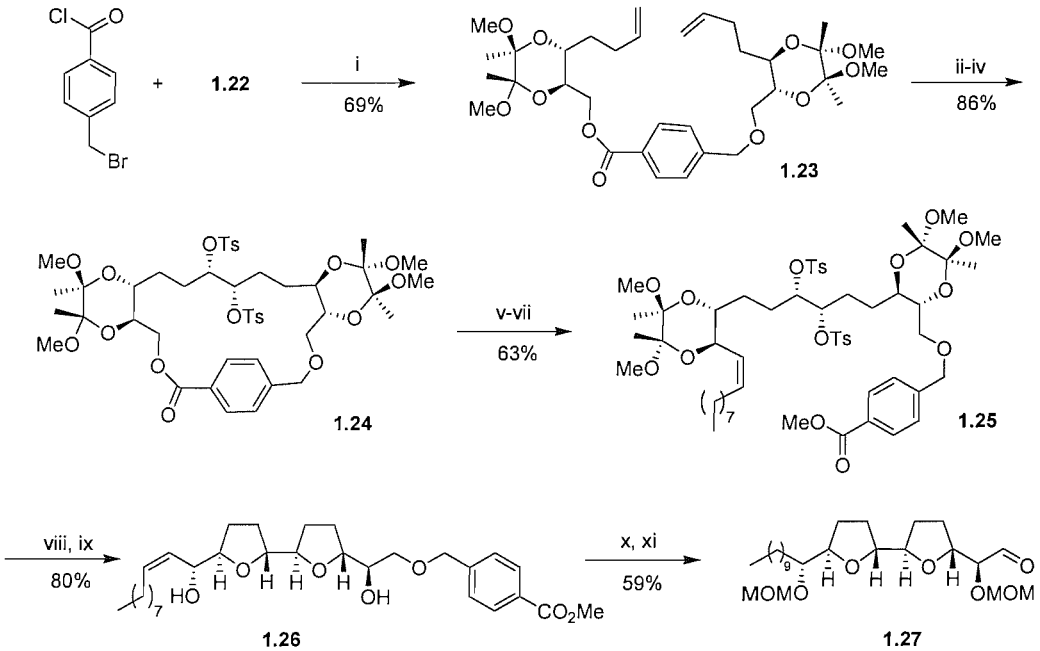
Reagents and conditions: (i) butane-2-3-dione, $CH(OMe)_3$, CSA, MeOH, reflux; (ii) $LiAlH_4$, THF, 0 °C to r.t.; (iii) NaH, TBSCl, THF, r.t.; (iv) NEt_3, TsCl, DMAP, CH_2Cl_2, r.t.; (v) CH_2=$CHCH_2MgBr$, CuBr, Et_2O, 0 °C; (vi) TBAF, THF, 0 °C.

Scheme 1.2: Synthesis of the alkenol fragment

The next stage in the synthesis was the coupling of the alkenol unit **1.22** to the tether which needed to fulfil a number of requirements. Once attached to the alkenol units, the tether needed to be able to adjust the conformation of the macrocycle to control the stereoselectivity during the RCM reaction.[32] The tether also needed to help to orientate the alkene moiety so that one face could be preferentially attacked during the

dihydroxylation.[34] Furthermore the tether would also act as a protecting group after cleavage of the macrocycle to enable desymmetrisation of the core, hence the tether was required to be dissymmetric to allow orthogonal cleavage after dihydroxylation. A dissymmetric tether would also allow two different alkenol units to be attached which would provide access to acetogenins with alternative stereochemistries in the THF core. Ley found that 4-bromomethylbenzoyl chloride fulfilled all of these requirements and produced the best results.

Thus, alkenol **1.22** was coupled with 4-bromomethylbenzoyl chloride to produce diene **1.23** (scheme 1.3). The intramolecular RCM was achieved using Grubbs' second-generation catalyst which was followed by Sharpless asymmetric dihydroxylation to afford the required (*S*,*S*)-product in a 16:1 diastereomeric ratio. Treatment with tosyl chloride afforded the ditosylated product **1.24** in a good yield.

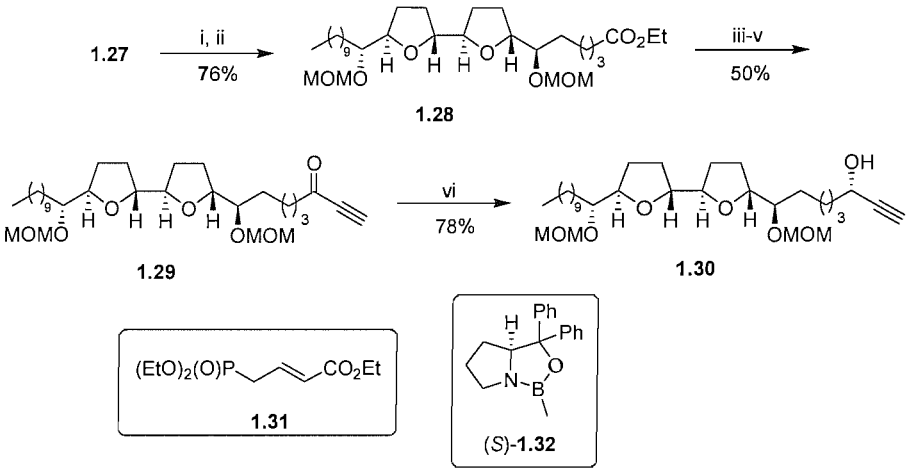


Reagents and conditions: (i) KHMDS, THF, −78 to 0 °C; (ii) 2nd generation Grubbs' catalyst, CH_2Cl_2, reflux; (iii) AD-mix α, $MeSO_2NH_2$, $NaHCO_3$, ^tBuOH, H_2O, 0 °C to r.t.; (iv) TsCl, pyridine, 0 °C to r.t.; (v) NaOMe, MeOH, r.t.; (vi) DMSO, $(COCl)_2$, CH_2Cl_2, NEt_3, −78 °C to r.t.; (vii) $CH_3(CH_2)_8PPh_3Br$, *n*-BuLi, THF, −78 to 0 °C; (viii) TFA, H_2O (repeat twice), r.t.; (ix) K_2CO_3, MeOH, reflux; (x) MOMCl, $^iPr_2NEt$, DMAP, CH_2Cl_2, 0 °C to r.t.; (xi) Pd / C, $HCO_2^-NH_4^+$, MeOH, reflux; (xii) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C to r.t.

Scheme 1.3: Synthesis of the *bis*-THF core

Macrocycle **1.24** was chemoselectively opened with sodium methoxide in methanol to afford the primary alcohol. Oxidation, followed by a Wittig olefination installed the required alkyl side chain. Removal of the BDA groups allowed a Williamson cyclisation to occur, forming the *bis*-THF core **1.26** of the natural product. Protection of the secondary alcohols, parallel deprotection of the benzyl group and alkene reduction followed by oxidation of the primary alcohol furnished fragment **1.27**.

A Horner-Wadsworth-Emmons type olefination was carried out on aldehyde **1.27** with phosphonate **1.31** to afford the *trans* diene, which was completely reduced with the Pearlman catalyst (scheme 1.4). The last stereocentre of the core was introduced *via* the formation of propargylic ketone **1.29**. A diastereoselective oxazaborolidine catalysed reduction gave the required alcohol **1.30** with a 44:1 diastereoisomeric ratio in favour of the desired isomer. This completed the synthesis of the core *bis*-THF fragment and was set up for the introduction of the butenolide portion by a Sonogashira coupling with **1.39**.

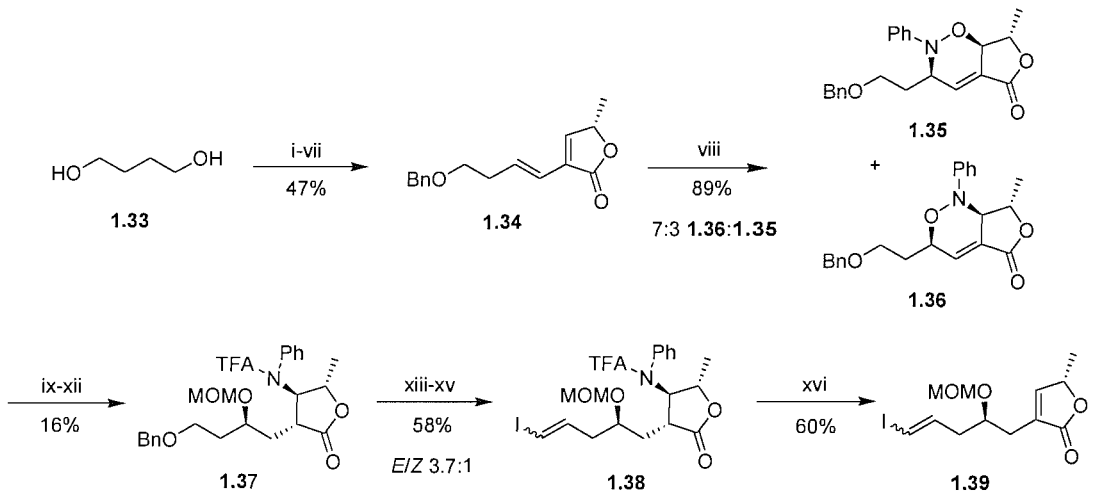


Reagents and conditions: (i) **1.31**, NaHMDS, THF, −78 °C to r.t.; (ii) $Pd(OH)_2$ / C, H_2, THF, r.t.; (iii) Me(MeO)NH.HCl, ^{i}PrMgCl, THF, −10 °C; (iv) trimethylsilylacetylene, *n*-BuLi, THF, −78 to 0 °C; (v) TBAF, THF, −20 °C; (vi) (*S*)-**1.32**, $BH_3 \cdot SMe_2$, THF, −35 °C.

Scheme 1.4: Completion of the *bis*-THF framework

The installation of the butenolide portion also required the insertion of two further stereocentres, with a 1,5 relationship to each other. Ley and co-workers had previously developed new methodology to achieve this in their synthesis of muricatetrocin C.[35,36] Following this previous synthesis, diene **1.34** was prepared in seven steps from 1,4-

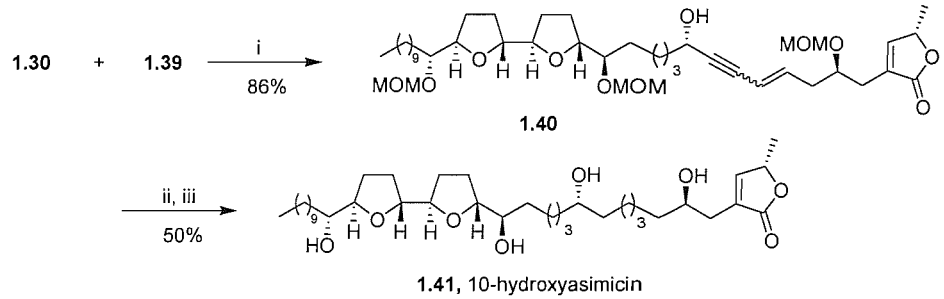
butanediol (scheme 1.5). The 1,5 stereochemical relationship was then inserted through a hetero-Diels-Alder reaction with nitrosobenzene, affording an inseparable mixture of regioisomers (7:3 **1.36**:**1.35**). Cleavage of the N-O bond was found to occur only with freshly prepared $[Mo(CO)_3(MeCN)_3]$ in water and subsequent MOM protection allowed the separation of regio- and stereoisomers by chromatography. Hydrogenation, protection of the amine as the trifluoroacetamide and debenzylation with the Pearlmann catalyst afforded the free alcohol which was oxidised with TPAP. Following the Takai procedure,[37] a one-carbon homologation furnished iodide **1.38**. Elimination of the trifluoroacetamide group was achieved with DBU in acetonitrile, affording butenolide fragment **1.39**.



Reagents and conditions: (i) NaH, BnBr, DMF, 20 °C; (ii) DMSO, $(COCl)_2$, CH_2Cl_2, NEt_3, −78 to 0 °C; (iii) (*tert*-butoxycarbonylmethylene)triphenylphosphorane, CH_2Cl_2, 0 to 20 °C; (iv) LDA, HMPA, THF, −78 °C then (*S*)-2-(*tert*-butyldimethylsiloxy)propanal, −78 to 0 °C; (v) MeOH, HCl, 20 °C; (vi) MsCl, NEt_3, CH_2Cl_2, 0 °C; (vii) I_2, irradiation; (viii) PhNO, MeOH, CH_2Cl_2, 0 °C; (ix) $[Mo(CO)_6]$, MeCN, reflux then **1.36**, H_2O, r.t.; (x) MOMCl, $^iPr_2NEt$, DMAP, CH_2Cl_2, 0 °C to r.t.; (xi) Pd / C, H_2, THF, r.t.; (xii) TFAA, $^iPr_2NEt$, CH_2Cl_2, 0 °C; (xiii) $Pd(OH)_2$ / C, H_2, MeOH, r.t.; (xiv) TPAP, NMO, NEt_3, CH_2Cl_2, r.t.; (xv) $CrCl_2$, CHI_3, THF, 0 °C to r.t.; (xvi) DBU, MeCN, −15 to −5 °C.

Scheme 1.5: Ley and co-workers synthesis of the butenolide fragment

The two fragments **1.30** and **1.39** were combined in a Sonogashira coupling furnishing **1.40** (scheme 1.6). A selective reduction of the enyne group with Wilkinson's catalyst and complete deprotection concluded the synthesis of 10-hydroxyasimicin **1.41** and showed the synthetic utility of Ley's template approach.

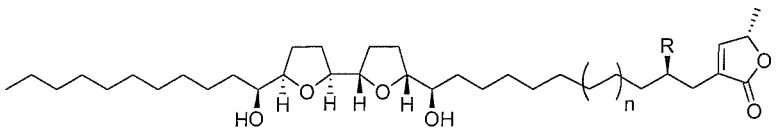


Reagents and conditions: (i) $[Pd(PPh_3)_2Cl_2]$, CuI, NEt_3, r.t.; (ii) $[Rh(PPh_3)_3Cl]$, H_2, benzene, EtOH, r.t.; (iii) $BF_3{\cdot}OEt_2$, Me_2S, r.t.

Scheme 1.6: Completion of the synthesis of 10-hydroxyasimicin

1.4.2 Eun Lee *et al.*

Lee *et al.* have concentrated their efforts on the synthesis of three adjacent *bis*-THF acetogenins; rolliniastatin 1 (**1.42**), rollimembrin (**1.43**) and membranacin (**1.44**) (figure 1.4). They belong to the most potent subgroup of *bis*-THF acetogenins, with a *threo*, *cis*, *threo*, *cis*, *erythro* relative configuration about the THF core.[38] Limited work has been carried out on this subgroup with only one reported synthesis of **1.42**[39] and **1.44**,[40] while the synthesis of **1.43** has not been reported.



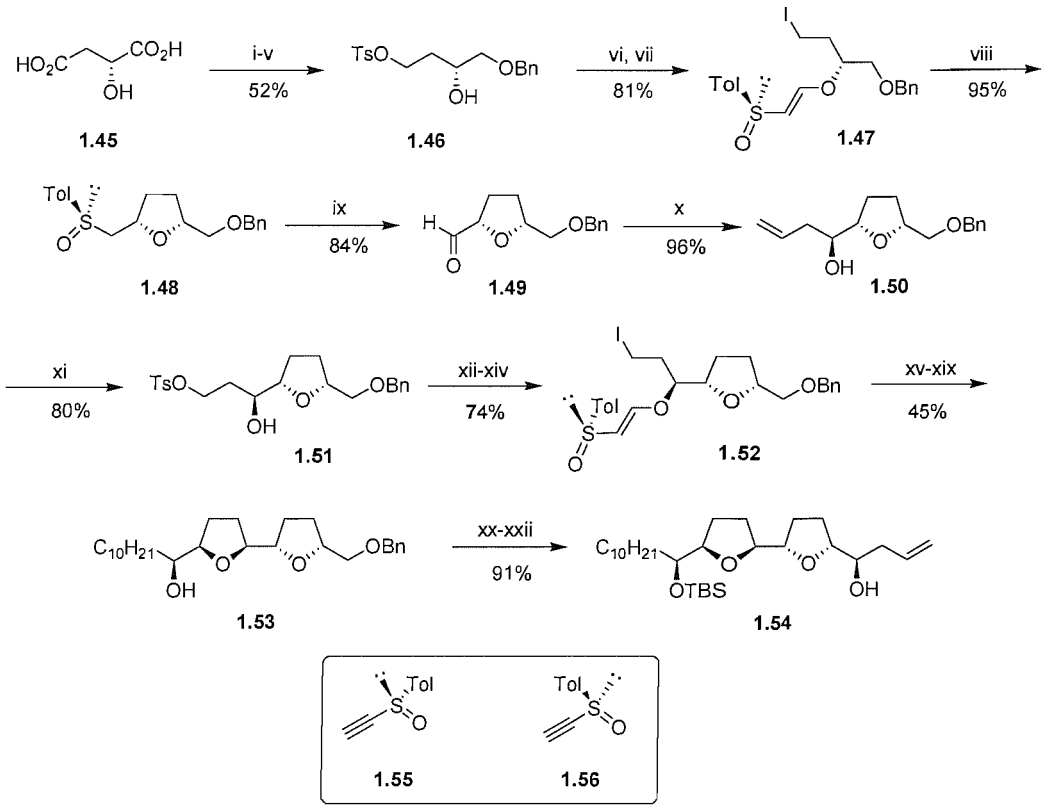
1.42 n=2, R=OH, rolliniastatin 1
1.43 n=1, R=OH, rollimembrin
1.44 n=2, R=H, membranacin

Figure 1.4: Acetogenins targeted by Lee *et al.*

The approach by Lee and co-workers has centred on a radical cyclisation of a β–alkoxyvinyl sulphoxide to insert the THF core. Lee recently showed that double stereocontrol in the radical cyclisation of β–alkoxyvinyl sulphoxides to tetrahydrofuranyl allyl carbinols could be achieved when coupled with subsequent Pummerer rearrangements and allylstannane reactions.[41] The synthesis of the three adjacent *bis*-THF acetogenins is the first application of this strategy in total synthesis.

1.4.2.1 Synthesis of Rolliniastatin 1, Rollimembrin and Membranacin

As all three of the target acetogenins contain the same stereochemical arrangement around the *bis*-THF core, it allows one core to be prepared with diversification to each product at a later stage of the synthesis. D-Malic acid (**1.45**) was converted to hydroxy tosylate **1.46** in five steps (scheme 1.7).[38,41] This was transformed into iodide **1.47** by reaction with ethynyl *p*-tolyl (*R*)-sulphoxide (**1.55**) in the presence of *N*-methylmorpholine, followed by nucleophilic substitution of the tosylate. **1.47** was set up for the radical cyclisation, which inserted the first THF ring with high stereoselectivity (*d.r.* = 99:1). A Pummerer rearrangement converted **1.48** into aldehyde **1.49** which, upon reaction with allyltributylstannane in the presence of magnesium bromide diethyletherate, proceeded stereoselectively (>99:1) furnishing allylic alcohol **1.50**. Oxidative cleavage of the double bond provided access to hydroxy tosylate **1.51** allowing the same sequence to be performed again, thus introducing the second THF ring. Further elaboration of **1.53** furnished the core *bis*-THF fragment (**1.54**) present in all three of the natural products.

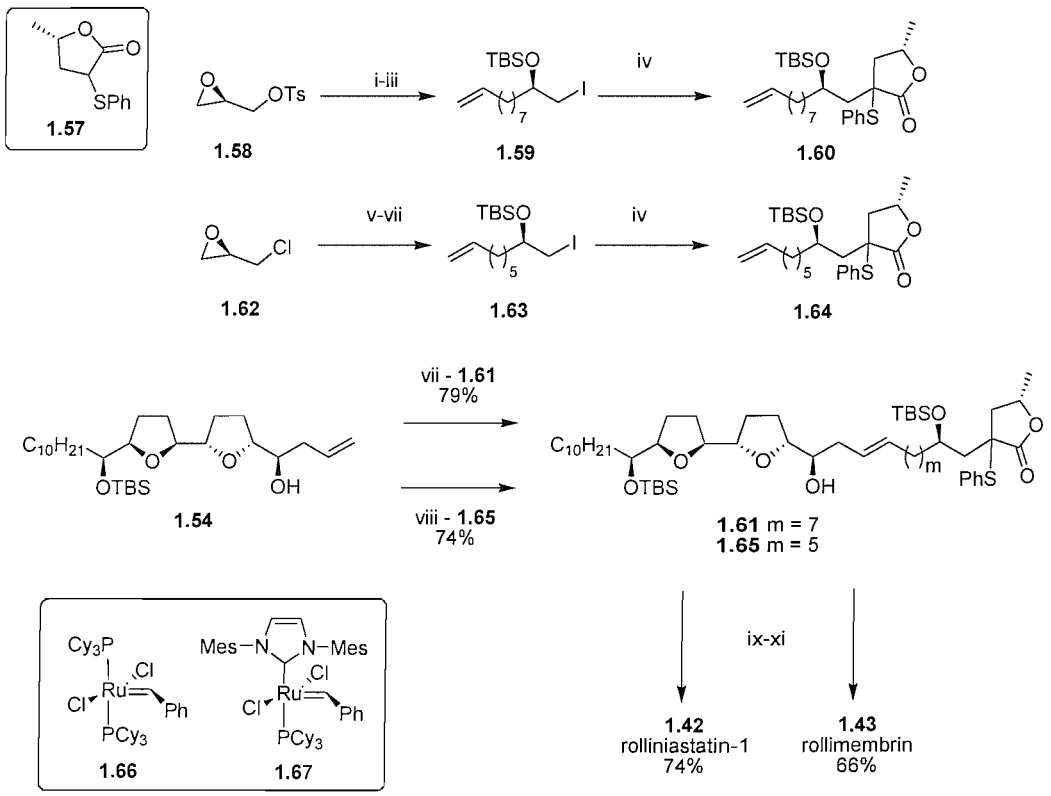


Reagents and conditions: (i) $BH_3 \cdot SMe_2$, $B(OMe)_3$, THF, r.t.; (ii) $PhCH(OMe)_2$, CSA, CH_2Cl_2, r.t.; (iii) BnBr, NaH, THF, r.t.; (iv) AcOH, H_2O, $NaIO_4$, MeOH, r.t.; (v) TsCl, NEt_3, CH_2Cl_2, r.t.; (vi) **1.55**, NMM, CH_2Cl_2, r.t.; (vii) NaI, acetone, reflux; (viii) *n*-Bu_3SnH, BEt_3, toluene, –20 °C; (ix) TFAA, pyridine, KOAc, MeCN, H_2O, r.t.; (x) $CH_2CHCH_2SnBu_3$, $MgBr_2 \cdot OEt_2$, CH_2Cl_2, r.t.; (xi) OsO_4, NMO, acetone, H_2O then $NaIO_4$, EtOH then $NaBH_4$, r.t.; (xii) *p*-TsOH, NEt_3, CH_2Cl_2, 0 °C; (xiii) **1.56**, NMM, CH_2Cl_2, 0 °C to r.t.; (xiv) NaI, acetone, reflux; (xv) *n*-Bu_3SnH, BEt_3, toluene, –20 °C; (xvi) TFAA, pyridine, KOAc, MeCN, H_2O, r.t.; (xvii) $C_{10}H_{21}MgBr$, Et_2O, –78 °C to r.t.; (xviii) DMSO, $(COCl)_2$, CH_2Cl_2, NEt_3, –78 °C to r.t.; (xix) L-selectride, THF, –78 °C; (xx) TBSCl, imidazole, CH_2Cl_2, DMF, r.t.; (xxi) H_2, Pd / C, EtOAc, r.t.; (xxii) DMSO, $(COCl)_2$, CH_2Cl_2, NEt_3, –78 °C to r.t.; (xxiii) $CH_2{=}CHCH_2SnBu_3$, $MgBr_2 \cdot OEt_2$, CH_2Cl_2, 0 °C to r.t.

Scheme 1.7: Formation of the *bis*-THF core

Lee proposed to complete the synthesis of all three of the natural products by a cross metathesis reaction of fragment **1.54** with an appropriate terminal olefin bearing the butenolide fragment. Rolliniastatin 1 (**1.42**) and rollimembrin (**1.43**) both required the butenolide fragment to contain a hydroxyl group with a 1,5-relationship to the methyl substituent, but with different alkyl chain lengths. The fragment required for

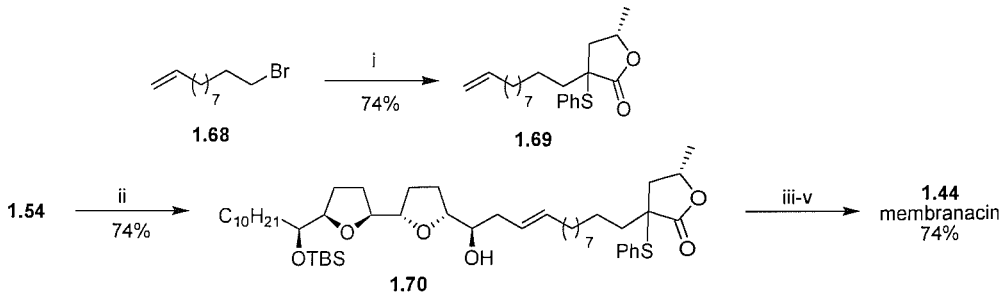
rolliniastatin 1 (**1.60**) was prepared from phenylthiolactone **1.57** and iodide **1.59** (scheme 1.8). The cross metathesis between **1.54** and **1.60** was carried out in the presence of the first generation Grubbs' catalyst (**1.66**), affording the product in 79% yield. The synthesis was completed *via* diimide reduction of the double bond, oxidation elimination of the phenylthio group and TBS deprotection. Terminal alkene **1.64** was also prepared and was coupled to **1.54** using Grubbs' second generation catalyst (**1.67**). Following the established three step sequence, **1.65** was converted to rollimembrin **1.43**.



Reagents and conditions: (i) CH_2=$CH(CH_2)_5CH_2MgBr$, Li_2CuCl_4, I_2, THF, −40 °C; (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; (iii) NaI, $NaHCO_3$, acetone, reflux; (iv) **1.57**, LDA, HMPA, THF, −78 °C to r.t.; (v) CH_2=$CH(CH_2)_3CH_2MgBr$, CuCN, THF, −40 °C; (vi) NaI, acetone, reflux; (vii) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; (vii) **1.60** (4 eq.), **1.66** (20 mol%), CH_2Cl_2, 45 °C; (viii) **1.64** (4 eq.), **1.67** (10 mol%), CH_2Cl_2, 45 °C; (ix) $TsNHNH_2$, NaOAc, DME, H_2O, reflux; (x) MMPP, THF, MeOH, 0 °C to r.t. then toluene, 90 °C; (xi) AcCl, MeOH, r.t.

Scheme 1.8: Completion of the synthesis of rolliniastatin 1 and rollimembrin

Terminal alkene **1.69** was prepared from phenylthiolactone **1.57** and bromide **1.68** and was used in the cross metathesis using Grubbs' second generation catalyst (**1.67**) (scheme 1.9). Application of the three step sequence completed the synthesis of the third natural product, membranacin **1.44**, and showed the synthetic versatility of Lee's methodology.



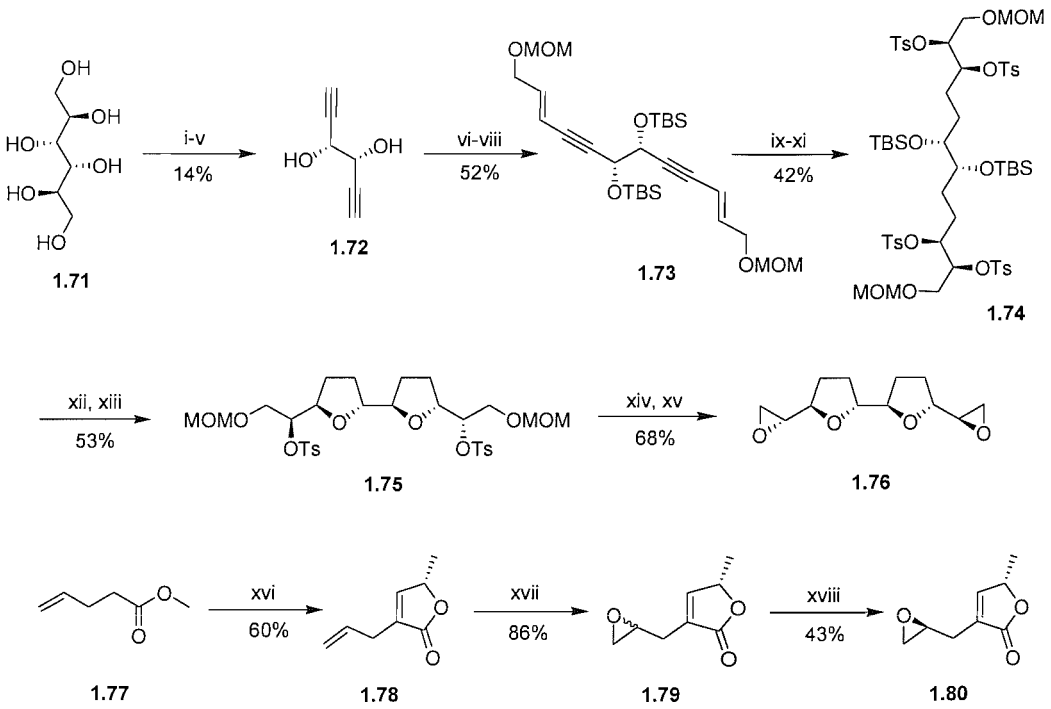
Reagents and conditions: (i) **1.57**, LDA, HMPA, THF, –78 °C to r.t.; (ii) **1.69** (4 eq.), **1.67** (10 mol%), CH_2Cl_2, 45 °C; (iii) $TsNHNH_2$, NaOAc, DME, H_2O, reflux; (iv) MMPP, THF, MeOH, 0 °C to r.t. then toluene, 90 °C; (v) AcCl, MeOH, r.t.

Scheme 1.9: Completion of the synthesis of membranacin

1.4.3 Zhu-Jun Yao *et al.*

Using a strategy based on iterative acetylene-epoxide coupling reactions and which utilised a Sharpless asymmetric dihydroxylation and intramolecular Williamson etherification to install the *bis*-THF core, Yao and co-workers have carried out the total synthesis of longimicin C **1.84**.[42]

Starting from D-mannitol **1.71**, conversion to alkyne-diol **1.72** was achieved in five steps (scheme 1.10). Both hydroxyl groups were protected as TBS ethers before a Sonogashira coupling afforded the symmetric *trans*-allylic alcohol **1.73**. After initial MOM ether protection, this intermediate was further elaborated by a Sharpless asymmetric dihydroxylation to introduce the additional oxygenated centres required. Hydrogenation of the alkyne moieties and removal of the silyl groups allowed an intramolecular Williamson reaction to occur, introducing the *bis*-THF core. **1.75** was converted to key epoxide intermediate **1.76** by removal of the MOM protection and base catalysed cyclisation.



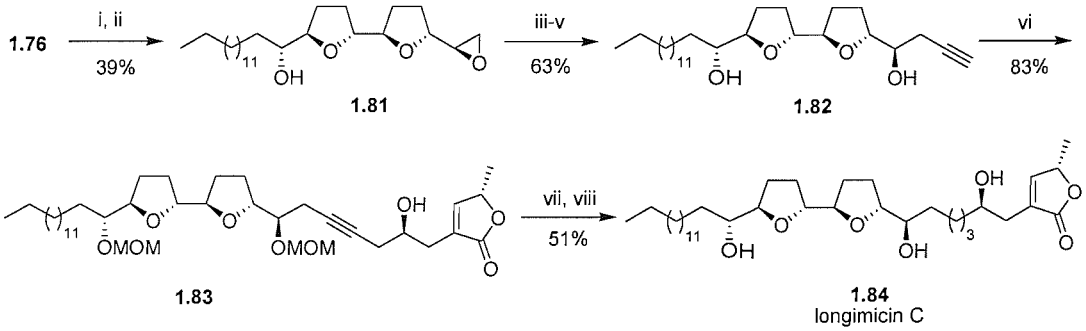
Reagents and conditions: (i) BzCl, pyridine; (ii) DMOP, *p*-TsOH·H_2O; (iii) K_2CO_3, MeOH, THF; (iv) PPh_3, CCl_4, K_2CO_3, $^iPr_2NEt$; (v) LDA, THF; (vi) TBSCl, imidazole, DMF; (vii) $BrCH{=}CHCH_2OH$, Et_2NH, $Pd(PPh)_2Cl_2$, CuI; (viii) MOMCl, $^iPr_2NEt$, CH_2Cl_2; (ix) $K_3Fe(CN)_6$, K_2CO_3, $K_2OsO_4{\cdot}2H_2O$, $(DHQ)_2$-PHAL, $MeSO_2NH_2$, ^{t}BuOH, H_2O; (x) PtO_2, H_2, MeOH; (xi) TsCl, DMAP, pyridine; (xii) TBAF, THF; (xiii) NaH, THF; (xiv) HCl, THF, MeOH; (xv) K_2CO_3, THF, MeOH; (xvi) (a) (*S*)-*O*-tetrahydropyranyl lactal, LDA, HMPA, THF, –78 °C; (b) 10% H_2SO_4, THF, r.t.; (c) TFAA, NEt_3, CH_2Cl_2; (xvii) *m*-CPBA, CH_2Cl_2, 0 °C; (xviii) (*S,S*)-salen-Co(OAc), H_2O.

Scheme 1.10: Formation of the *bis*-THF core and butenolide fragment

The butenolide fragment **1.80** was prepared in accordance with a method previously reported by Yao *et al.*,[43,44] with high optical purity of the epoxide being obtained by kinetic resolution with Jacobsen's catalyst, (*S,S*)-salen-Co(OAc) (scheme 1.10).

With all of the fragments assembled, the iterative acetylene-epoxide coupling strategy was implemented. Firstly, epoxide **1.76** was combined with one-half equivalent of tridec-1-yne in the presence of *n*-BuLi and $BF_3{\cdot}OEt_2$ (scheme 1.11). Reduction of the alkyne moiety was followed by the opening of the second epoxide with an excess of trimethylsilyl acetylene. Protection of the free hydroxyl groups and TMS deprotection allowed a third acetylene-epoxide coupling procedure to follow, installing the

butenolide segment. Selective reduction of the acetylene moiety of **1.83** and universal deprotection completed the total synthesis of longimicin C.



Reagents and conditions: (i) tridec-1-yne, *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, −78 °C; (ii) H_2, Pd / C, NEt_3, EtOAc, r.t.; (iii) TMSC≡CH, *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, −78 °C; (iv) MOMCl, $^iPr_2NEt$, CH_2Cl_2, r.t.; (v) TBAF, THF; (vi) **1.80**, *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, −78 °C; (vii) $TsNHNH_2$, NaOAc, DME, reflux; (viii) HCl, THF, MeOH.

Scheme 1.11: Completion of the synthesis of longmicin C

1.4.4 William R. Roush *et al.*

Work carried out within various groups has shown that the [3+2] annulation reaction of allylsilanes and aldehydes in the presence of Lewis acids is important for the synthesis of substituted tetrahydrofurans[45-49] and other five membered heterocycles.[50,51] Roush and co-workers have carried out extensive studies into these reactions and have demonstrated that β-silyoxy-substituted allylsilanes undergo [3+2] annulation reactions to produce either *trans* or *cis* THF rings.[52,53] Excellent stereoselectivity can be obtained depending on the nature of the Lewis acid employed in the reaction. It is predicted that the reaction progresses through the lowest energy *syn*-synclinical transition state available (figure 1.5).[54,55] For the non-chelate controlled reactions using $BF_3{\cdot}OEt_2$, this is believed to be transition state **1.85**, resulting in the *cis*-THF ring **1.86**. In the case of the chelate-controlled reactions, transition state **1.90** is expected to provide the lowest energy pathway, resulting in *trans*-THF **1.89**.

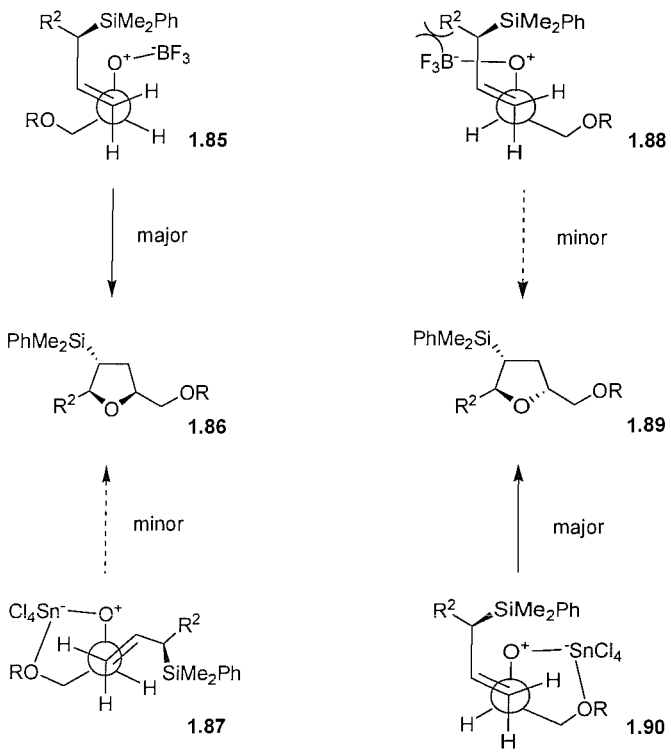


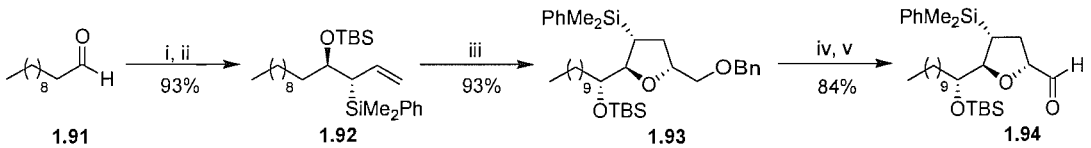
Figure 1.5: Transition states leading to *cis* and *trans* THF rings

Roush then studied the [3+2] annulation reaction as a method of forming an adjacent *bis*-THF core. He achieved this with two sequential annulation reactions, the second of which taking place on an aldehyde already containing the first THF ring. He found that by doing this he could access several different diastereomeric *bis*-THF structures through the use of different Lewis acid catalysts.[56]

1.4.4.1 Total Synthesis of Asimicin

Using the methodology described above, Roush completed the total synthesis of asimicin **1.104**,[57] an example of an adjacent *bis*-THF acetogenin where both THF rings are *trans*. Roush envisaged introducing both rings by chelate controlled [3+2] annulation reactions. Starting from commercially available undecanal **1.91**, allylsilane **1.92** was prepared in two steps (scheme 1.12). **1.92** was then subjected to the annulation reaction with α-benzyloxyacetaldehyde in the presence of $SnCl_4$, which afforded the *trans* THF ring **1.93** in good yield with a diastereoselectivity of >20:1.

1.93 was converted to the corresponding aldehyde by reductive removal of the benzyl group and subsequent oxidation of the primary alcohol.

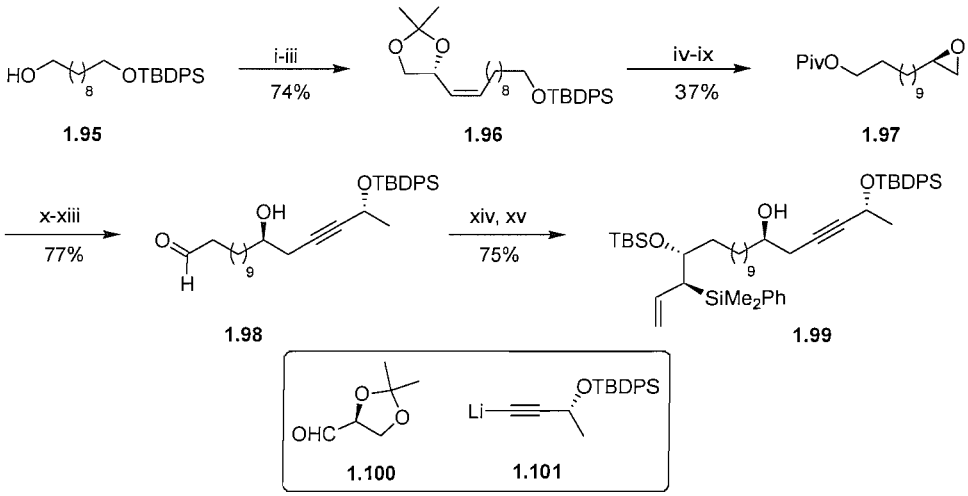


1.91 **1.92** **1.93** **1.94**

Reagents and conditions: (i) $PhMe_2SiCH{=}CHCH_2B(Ipc)_2$, $BF_3{\cdot}OEt_2$, hexane, THF, −78 °C; (ii) TBSCl, imidazole, DMF, 50 °C; (iii) α-benzyloxyacetaldehyde, $SnCl_4$, 4 Å sieves, CH_2Cl_2, −45 °C; (iv) $Pd(OH)_2$, H_2, r.t.; (v) SO_3·pyridine, DMSO, r.t.

Scheme 1.12: Formation of a THF ring by a [3+2] annulation reaction

Roush then planned to carry out the second annulation reaction using highly functionalised silane **1.99**. This contained functionality necessary for the installation of the butenolide fragment at the end of the synthesis. Thus the synthesis of silane **1.99** was initiated by the conversion of **1.95** to the iodide (scheme 1.13). Subsequent Wittig reaction with acetonide **1.100** afforded **1.96**. This was converted to epoxide **1.97** in a six step sequence. Reaction with acetylide **1.101**, protection of the secondary alcohol, reductive cleavage of the pivaloate group and oxidation of the primary alcohol provided aldehyde **1.98** which was converted to silane **1.99** in good yield.

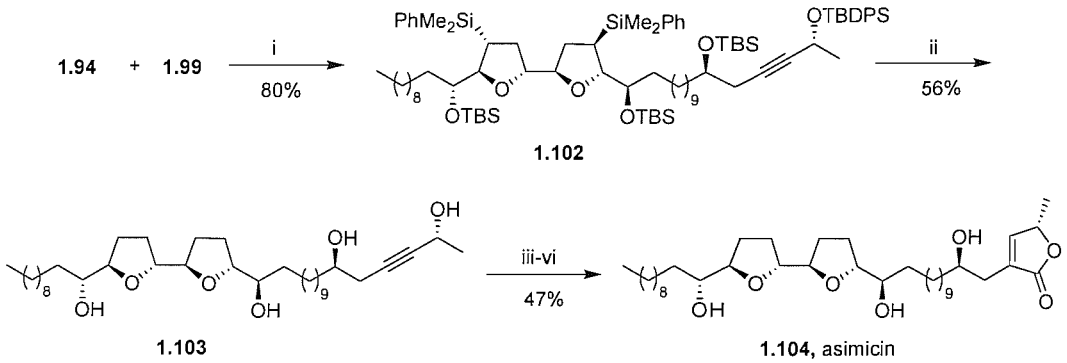


1.95 **1.96** **1.97** **1.98** **1.99** **1.100** **1.101**

Reagents and conditions: (i) PPh_3, I_2; (ii) PPh_3, MeCN; (iii) *n*-BuLi, **1.100**, THF; (iv) TBAF, THF; (v) Pd / C, H_2; (vi) PivCl, NEt_3; (vii) $FeCl_3$-SiO_2; (viii) Bu_2SnO, TsCl; (ix) K_2CO_3, MeOH, CH_2Cl_2, 0 °C; (x) **1.101**, $BF_3{\cdot}OEt_2$, THF, −78 °C; (xi) TBSCl, imidazole; (xii) DIBAL-H, −78 °C; (xiii) SO_3·pyridine, DMSO; (xiv) $PhMe_2SiCH{=}CHCH_2B(Ipc)_2$, $BF_3{\cdot}OEt_2$, −78 °C; (xv) TBSCl, imidazole, DEF, 50 °C.

Scheme 1.13: Synthesis of the functionalised silane

The second THF ring was inserted by a second [3+2] annulation between aldehyde **1.94** and silane **1.99** (scheme 1.14). The *bis*-THF product was obtained as a single diastereoisomer in good yield. The two silane groups and four TBS ethers were all removed following protiodesilylation conditions previously developed by Roush.[58] The butenolide fragment was then installed following a method developed by Marshall *et al.*[59,60] Thus, per-trifluoroacetylation of **1.103** followed by palladium catalysed hydroxycarbonylation, silver promoted cyclisation of the resulting allenyl carboxylic acid and deprotection of all of the trifluoroacetate esters completed the synthesis of asimicin **1.104**.



Reagents and conditions: (i) $SnCl_4$, 4 Å sieves, CH_2Cl_2, 0 °C; (ii) TBAF, THF, DMF, 90 °C; (iii) TFAA, lutidine, THF; (iv) $Pd(PPh_3)_4$, CO, THF, H_2O; (v) $AgNO_3$, silica gel; (vi) KCN, MeOH.

Scheme 1.14: Completion of the synthesis of asimicin

Roush has already extended this synthetic strategy to the synthesis of bullatacin, another adjacent *bis*-THF acetogenin.[61]

1.4.5 Subhash C. Sinha *et al.*

Sinha and co-workers have carried out extensive work in the area of acetogenin synthesis. Their approach has been primarily centred on the use of Kennedy's stereoselective rhenium based cyclisation of 5-hydroxy alkenes[62,63] and Sharpless' asymmetric dihydroxylation. Vanadium mediated epoxidations and Mitsunobu alcohol inversions have also been incorporated. This combination has allowed the total synthesis of many of the acetogenin family.[64-70]

More recently, Sinha has reported a bidirectional approach to the synthesis of a complete library of trilobacin analogues, a *bis*-THF acetogenin.[71] An adjacent *bis*-THF acetogenin can theoretically exist in sixty four diastereomeric forms due to the six stereogenic centres of the *bis*-THF core. Driven by a desire to fully understand the relationship between the stereochemistry of the *bis*-THF core and biological activity, Sinha and co-workers have begun the preparation of all sixty four isomers of trilobacin.

The approach taken by Sinha to achieve this was to prepare thirty six stereoisomeric bifunctional lactones (**1.107** or **1.107a**) which could be elaborated to all sixty four isomers (figure 1.6). Starting from diene-lactones **1.109**, five key reactions were used to introduce the *bis*-THF core in thirty six isomeric forms (twenty eight non-symmetrical and eight symmetrical). These were Shi *mono* and *bis*-epoxidations, rhenium oxide mediated *mono* and *bis*-oxidative cyclisations, Sharpless asymmetric dihydroxylations, Williamson etherifications and Mitsunobu inversion reactions.

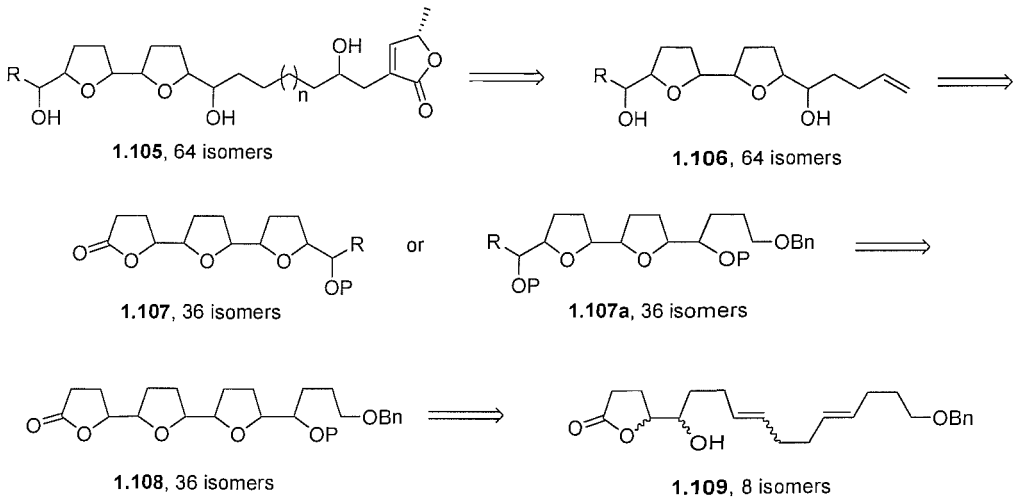
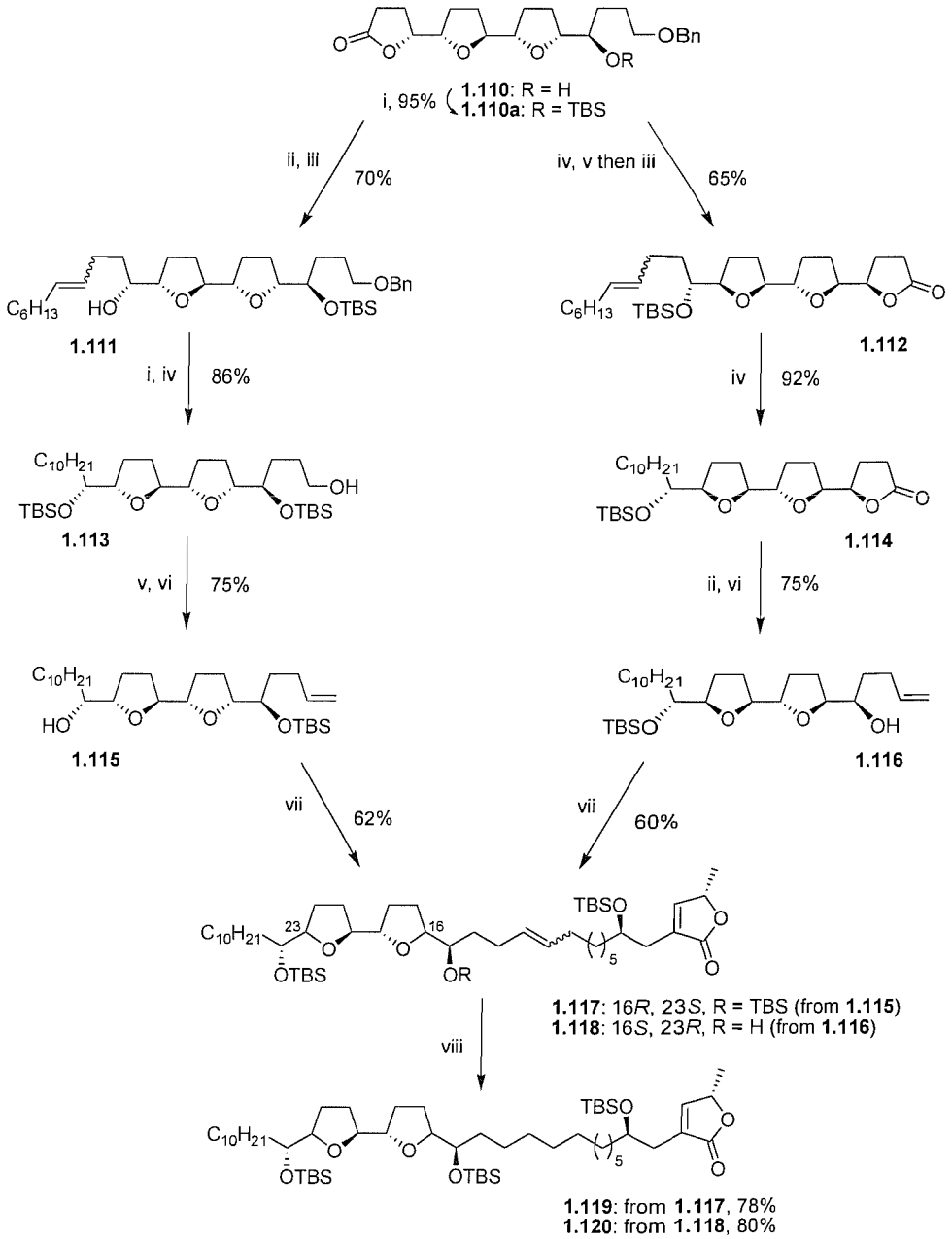


Figure 1.6: Partial retrosynthetic analysis of the adjacent *bis*-THF library

To show that each of the non-symmetrical lactones would give rise to two *bis*-THF acetogenin analogues, lactone **1.110** was converted into isomers **1.119** and **1.120** (scheme 1.15). After TBS protection of **1.110**, the alkyl chain was introduced at the two alternative ends affording **1.111** and **1.112**. Hydrogenation, followed by methylation of the aldehyde or lactol products furnished two diastereomeric alkenes **1.115** and **1.116**. A cross metathesis reaction using Grubbs' second generation catalyst was used to introduce the butenolide fragment and after deprotection and reduction, 19,23-*bis*-*epi*-

trilobacin **1.119** and 16,19-*bis*-*epi*-trilobacin **1.120** were obtained. The synthesis of all sixty four of the isomers is currently underway.



Reagents and conditions: (i) TBSOTf, lutidine, CH_2Cl_2; (ii) DIBAL-H, THF; (iii) $C_7H_{15}PPh_3I$, *n*-BuLi, THF; (iv) Pd / C, H_2, EtOAc; (v) TPAP, NMO, CH_2Cl_2; (vi) CH_3PPh_3I, *n*-BuLi, Et_2O; (vii) **1.67**, CH_2Cl_2, r.t. then 5% HF, MeCN; (viii) $TsNHNH_2$, NaOAc, MeCN, DME, H_2O.

Scheme 1.15: Synthesis of two trilobacin epimers

1.5 Conclusions

The many biological properties exhibited by the *Annonaceous* acetogenins, coupled with their synthetically challenging structures, have resulted in wide interest in the total synthesis of members of this family. The stereoselective construction of the tetrahydrofuran core of these natural products has been of particular interest, with a range of different strategies developed. This chapter has summarised recent developments in these strategies, particularly in application to the synthesis of adjacent *bis*-THF acetogenins.

Chapter Two

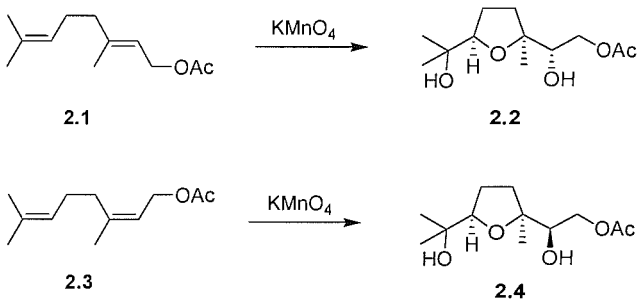
Synthetic Routes to 2,5-Disubstituted Tetrahydrofurans

Due to the prevelence of the tetrahydrofuran fragments in *Annonaceous* acetogenins, a number of synthetic approaches to their synthesis have been developed over the years. The previous chapter summarised the strategies applied to the synthesis of adjacent *bis*-tetrahydrofuran targets since 2004. The following chapter will look more broadly at the methods developed to prepare 2,5-disubstituted tetrahydrofurans from alkene precursors and their applications in synthesis.

2.1 Metal-oxo and Metal-peroxo Promoted Cyclisations

2.1.1 Permanganate Mediated Oxidative Cyclisations of 1,5-Dienes

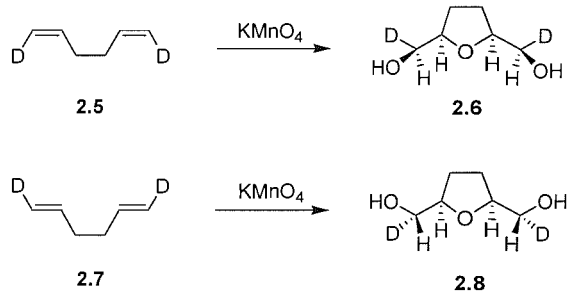
The permanganate oxidative cyclisation of 1,5-dienes to furnish tetrahydrofuran products was reported by Klein and Rojahn in 1965.[72] The reaction was found to proceed stereospecifically and only produced *cis*-2,5-disubstituted THFs. The permanganate oxidation of geranyl acetate (**2.1**) and neryl acetate (**2.3**) furnished *cis*-disubstituted THF diols **2.2** and **2.4** respectively (scheme 2.1).



Scheme 2.1: Permanganate oxidative cyclisation of geranyl and neryl acetate

The synthetic potential of this reaction was fully realised fourteen years later when it was re-examined by the groups of both Baldwin and Walba. Baldwin and co-workers studied the mechanism of the reaction using deuterated dienes (**2.5** and **2.7**) of known

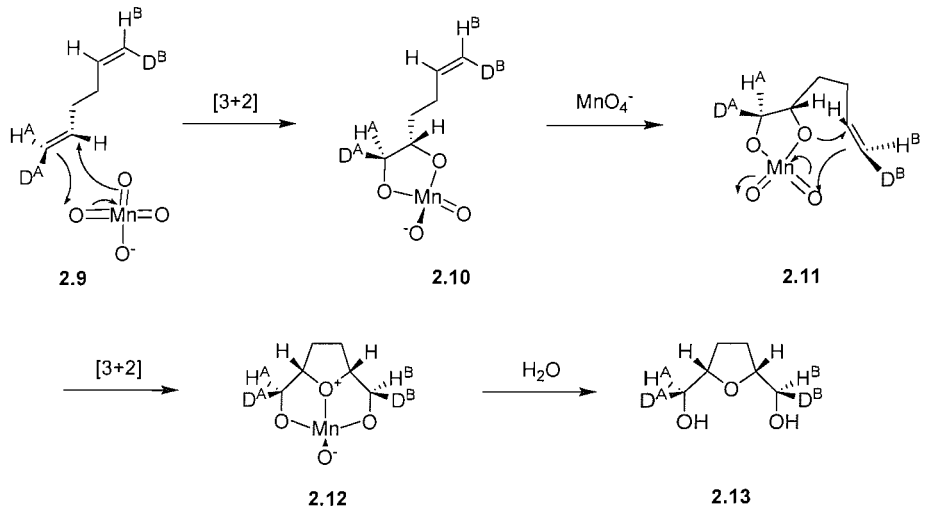
geometry (scheme 2.2). NMR analysis of the deuterated THF products (**2.6** and **2.8**) confirmed the *cis* selectivity of the reaction.[73]



2.5 **2.6** **2.7** **2.8**

Scheme 2.2: Stereochemical investigation by Baldwin

Baldwin proposed a mechanism to explain the selectivity of the reaction, which started with a [3+2] cycloaddition of permanganate onto one of the double bonds, forming Mn(V) ester **2.10** (scheme 2.3). This intermediate Mn(V) ester is unreactive to the remaining double bonds,[74] but undergoes rapid oxidation to Mn(VI) ester **2.11**. The resulting Mn(VI) diester can then undergo another [3+2] cycloaddition with the second double bond. Subsequent hydrolysis of the intermediate furnishes the THF product **2.13**. This mechanism is also supported by evidence of cyclic Mn(V) esters in reactions of isolated alkenes with permanganate.[75]

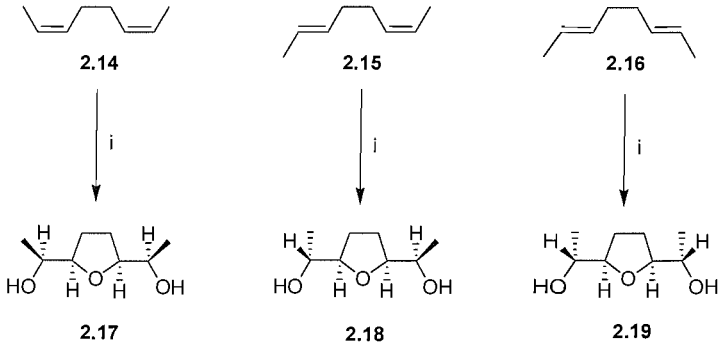


2.9 **2.10** **2.11** **2.12** **2.13**

Scheme 2.3: Baldwin's proposed mechanism

At the same time, Walba's group were investigating the stereoselectivity and mechanism of the reaction by carrying out the oxidation of dienes **2.14-2.16** (scheme 2.4). Gas chromatographic analysis of products **2.17-2.19** showed that the *cis*-THF ring

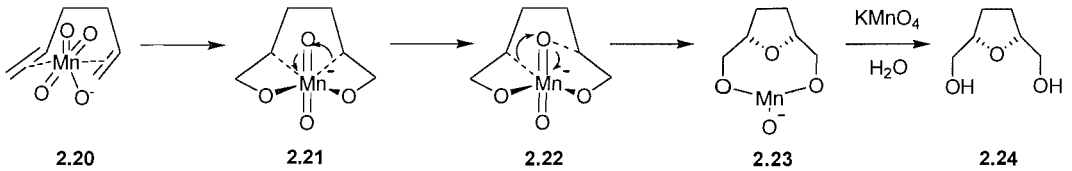
was obtained with approximately 97% stereoselectivity in all cases. Walba also concluded from this study that the stereochemistry of the THF product was dependant on the geometry of the diene precursor.[76]



Reagents and conditions: (i) $KMnO_4$, H_2O, acetone, pH = 7.5, CO_2, ebullition.

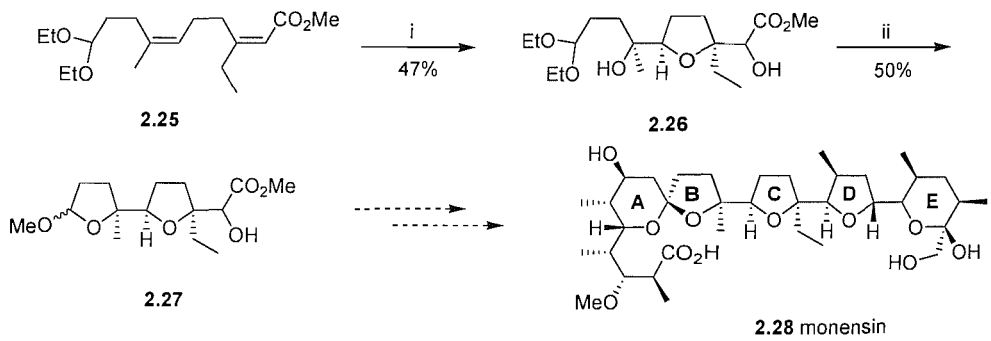
Scheme 2.4: Stereochemical investigation by Walba

Walba postulated a mechanism for the reaction which was based on earlier studies by Sharpless on the oxidation of alkenes by transition metal-oxo species.[77] It was suggested that initial formation of a *bis*-π-complex between the diene and permanganate is followed by two Sharpless type [2+2] additions producing the octahedral Mn(VII) intermediate **2.21** (scheme 2.5). Migration of the alkyl group with retention of configuration gives **2.22** which can undergo reductive elimination to Mn(III) diester **2.23**. Oxidation of the intermediate followed by hydrolysis yields the *cis*-THF product **2.24** with the correct relative stereochemistry. However, Baldwin's proposed mechanism is more widely accepted as a true representative of the reaction.



Scheme 2.5: Walba's proposed mechanism

Walba used the permanganate oxidative cyclisation in a racemic synthesis of the B / C ring portion of the natural product monensin **2.28**. This was achieved with the oxidative cyclisation of diene **2.25**, which following treatment with trimethyl orthoformate in the presence of acid, afforded **2.27** (scheme 2.6).[78]

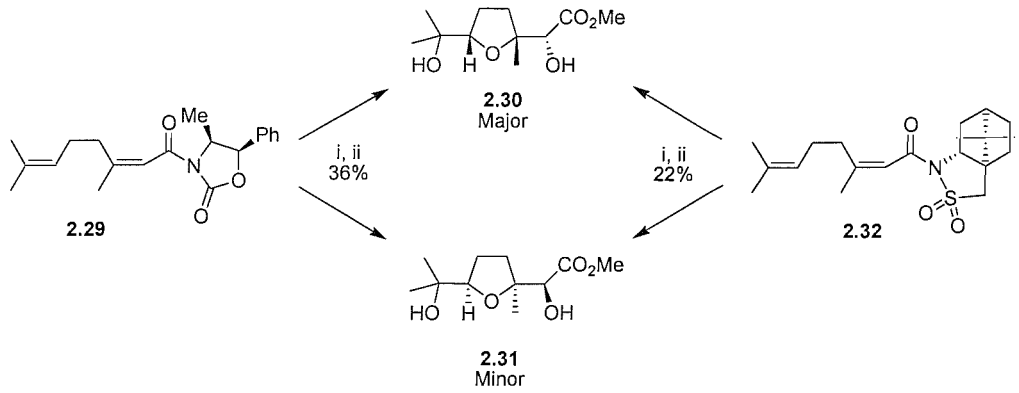


Reagents and conditions: (i) $KMnO_4$, H_2O, acetone, pH = 7.5, CO_2, ebullition, –30 °C; (ii) $Me(OMe)_3$, *p*-TsOH, benzene.

Scheme 2.6: Synthesis of B / C rings of monensin using permanganate

Walba then turned his attention to an enantioselective version of the permanganate oxidative cyclisation through the use of chiral auxiliaries. Alkenes that are conjugated to a carbonyl group are known to be more reactive to permanganate than isolated alkenes, allowing the attachment of a chiral auxiliary to a 1,5-diene through an amide link. Both Evans' oxazolidinone and Oppolzer's camphorsultam chiral auxiliaries were investigated as chiral directing groups in the oxidative cyclisations.[79]

The permanganate oxidation of **2.29** with Evans' auxiliary gave selectivity of only 3:1 in favour of isomer **2.30**, obtained after transesterification (scheme 2.7). The major isomer results from attack of the permanganate on the *Re* face of the conjugated double bond, which was explained by an *anti* arrangement of the carbonyl groups. The low selectivity was consistent with the observations made by Evans that Lewis acid catalysis is required to obtain high selectivity.[80] However, this low selectivity problem was solved through the use of Oppolzer's camphorsultam auxiliary. Oxidation of **2.32** resulted in the major isomer **2.30** in greater than 9:1 selectivity.



Reagents and conditions: (i) $KMnO_4$, H_2O, acetone, CO_2, ebullition, −30 °C; (ii) MeOMgBr.

Scheme 2.7: Use of chiral auxiliaries in the permanganate cyclisation

The stereochemistry of the major product induced by Oppolzer's camphorsultam chiral auxiliary can be explained by consideration of the transition states. The following conditions must be fulfilled for the face-selective reaction of the conjugated double bond to occur:[81]

- The reactive conformation of the CO-CC bond must be unambiguous. There are two possible conformations which allow the conjugation of the π- system, the *s-cis*-conformation is favoured due to steric reasons and also to the fact that *cis*-enolates of amides are more stable than *trans*-enolates.
- The carbonyl group must lie either parallel or anti-parallel to the N-S bond as other orientations are energetically less favourable.
- In the most favoured conformation, one face of the double bond needs to be blocked by the chiral auxiliary to force the permanganate to selectively react from the other face.

The carbonyl group of the camphorsultam auxiliary may have two different orientations depending on the reaction conditions. The addition of a Lewis acid with two co-ordination sites available results in both the carbonyl and SO_2 groups co-ordinating to it (**2.33**). The ring fragment of the auxiliary blocks the top face of the alkene, forcing the permanganate to attack from the lower *Re*-face (figure 2.1).

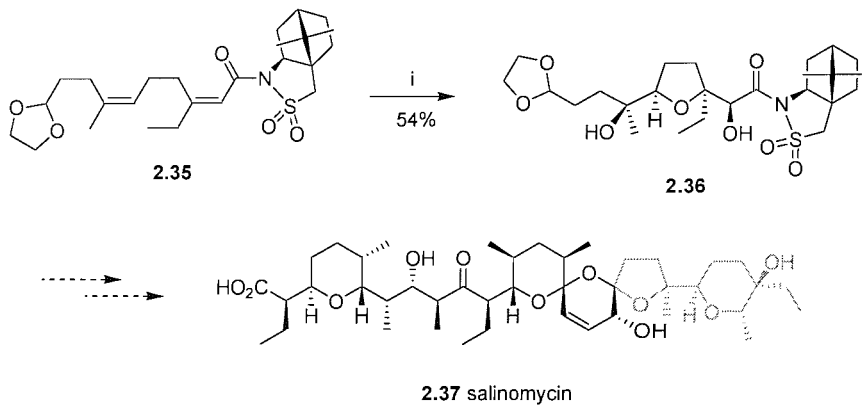
In the absence of a Lewis acid, the carbonyl and SO_2 groups prefer to adopt an *anti* relationship due to both steric and stereoelectronic reasons. In this case, the reactive

conformation resembles **2.34**, where the lower face is now blocked by the *pseudo*-axial oxygen atom of the SO_2 group. This favours reaction from the top *Re*-face resulting in the same product as from the Lewis acid case. The reverse absolute stereochemistry can be obtained by using the opposite enantiomer of the chiral auxiliary.

2.33 **2.34**

Figure 2.1: Models for camphorsultam selectivity

The first reported application of the permanganate oxidative cyclisation using the sultam auxiliary for asymmetric induction was by Kocienski *et al.* in their synthesis of salinomycin (**2.37**).[82,83] The permanganate cyclisation was carried out on sultam derivative **2.35**, furnishing the *cis*-THF ring of **2.36** in a moderate 54% yield with a 6:1 diastereomeric ratio of isomers.



2.35 **2.36**

2.37 salinomycin

Reagents and conditions: (i) $KMnO_4$, AcOH, NaOAc, acetone, H_2O, –35 °C.

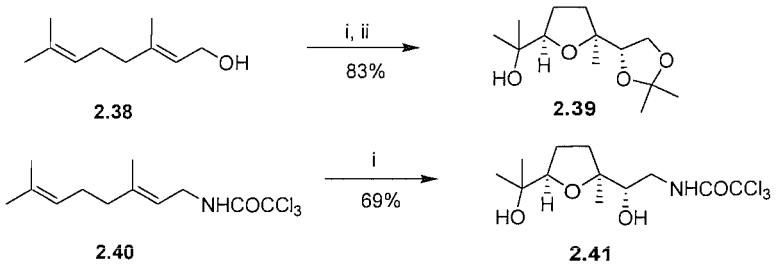
Scheme 2.8: Synthesis of THF fragment of salinomycin

2.1.2 Osmium Tetroxide Catalysed Oxidations

The preparation of 2,5-*cis*-disubstituted THF rings by an osmium tetroxide oxidative cyclisation of a 1,5-diene was first reported by Piccialli *et al.* in 1998.[84] The group showed that treatment of geranyl acetate (**2.1**) and neryl acetate (**2.3**) with catalytic

OsO_4, using sodium periodate as the co-oxidant, afforded exclusively the *cis*-THF products in yields of 55% and 53% of **2.2** and **2.4** respectively.

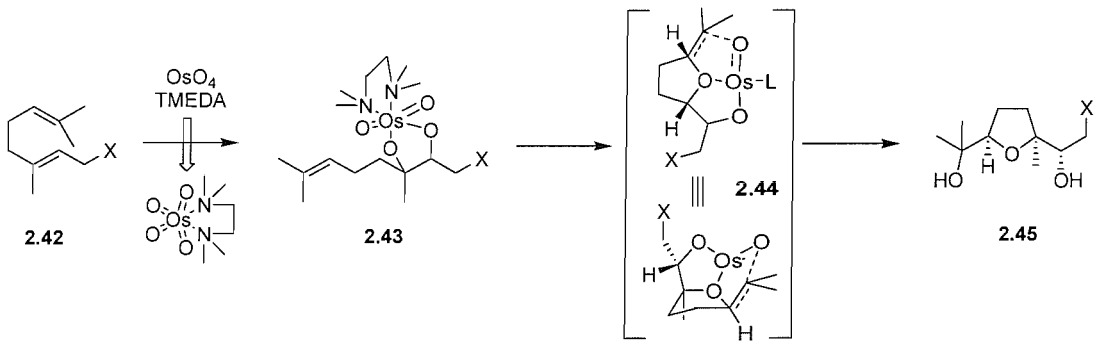
This methodology was further developed by Donohoe and co-workers, who combined osmium tetroxide with TMEDA to form a willing hydrogen bond acceptor reagent.[85] This was used to effect the oxidative cyclisation of a variety of substituted 1,5-dienes, furnishing the *cis*-THF products in good yields (scheme 2.9).



Reagents and conditions: (i) OsO_4 (1 eq.), TMEDA, CH_2Cl_2, −78 °C then MeOH, HCl, r.t.; (ii) $(MeO)_2CMe_2$, TFA.

Scheme 2.9: Osmium tetroxide oxidation of dienes

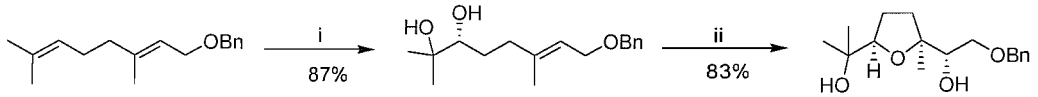
Donohoe *et al.* proposed a mechanism to account for the selectivity observed in the cyclisation reaction, which followed the one proposed by Baldwin *et al.*[73] in the permanganate cyclisation. The reaction is believed to start with a regioselective dihydroxylation of the polyene, which is controlled by hydrogen bonding (scheme 2.10). A [3+2] cycloaddition of the osmium onto the remaining double bond, followed by hydrolysis, produces the *cis*-THF product. It is thought that the addition of acid serves to promote whatever ligand exchange is necessary to allow the cyclisation to occur. Alternatively, the acid might protonate the oxo ligands, resulting in the metal becoming a better electrophile and more reactive in the cyclisation. The *cis* selectivity of the reaction is believed to arise from transition state **2.44**.



Scheme 2.10: Mechanism proposed by Donohoe

Despite the good yields obtained from the reaction, the use of stoichiometric quantities of osmium was a major drawback and so Donohoe sought a catalytic alternative. This was achieved using a combination of 5% OsO_4 and Me_3NO (4 eq.) with either CSA (6 eq.) or TFA (excess) to lower the pH. Under these revised conditions, the dihydroxylation / cyclisation reaction proceeded in higher yields than with stoichiometric osmium.[86]

The only drawback to the work that Donohoe *et al.* had carried out was that racemic mixtures were produced in the cyclisation. Attempts to introduce asymmetric induction into the reaction through the use of chiral amine ligands were unsuccessful, presumably due to the inability of the ligands to co-ordinate to the osmium in the acidic medium. However, Donohoe has found that vicinal diols derived from 1,5-dienes will cyclise to form THF rings when subjected to the osmium oxidative cyclisation conditions (scheme 2.11).[87] The diols can be obtained stereoselectively from the alkene precursor by using a Sharpless asymmetric dihydroxylation. The enantiomeric purity of the resulting diol was found to be completely transferred to the THF product after cyclisation.

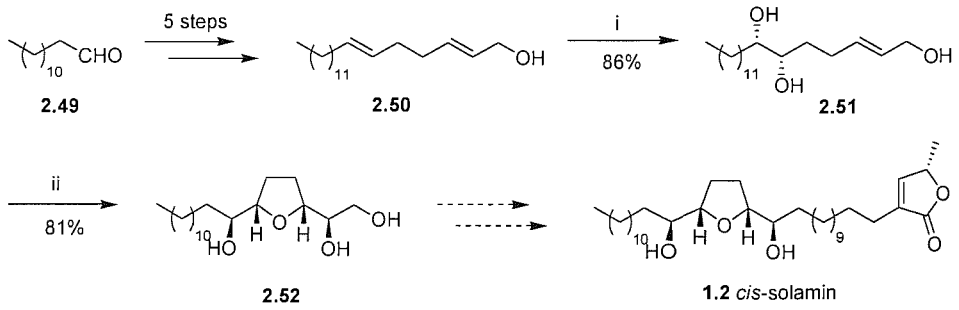


2.46 **2.47** (95% *ee*) **2.48** (95% *ee*)

Reagents and conditions: (i) AD-mix β; (ii) OsO_4 (5 mol%), Me_3NO, TFA, acetone, H_2O, r.t.

Scheme 2.11: Asymmetric osmium cyclisation

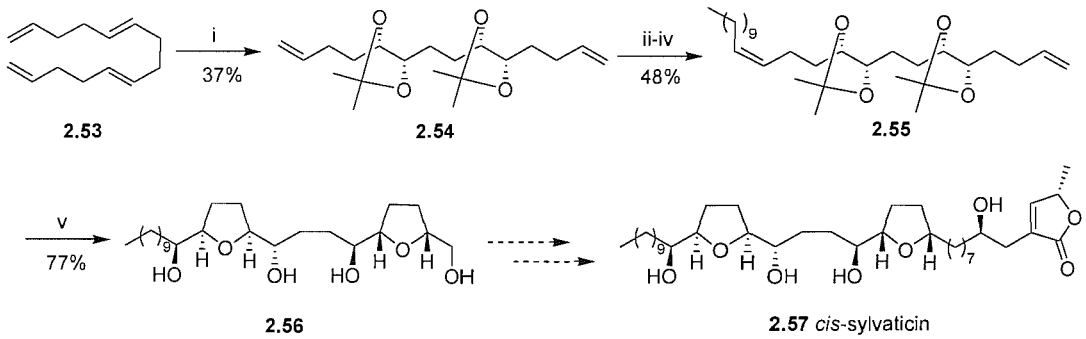
Donohoe has applied this new asymmetric strategy to the formal synthesis of *cis*-solamin (**1.2**).[87] A literature synthesis of alcohol **2.50** allowed a regioselective asymmetric dihydroxylation to be carried out, forming **2.51** in >90% *ee* (scheme 2.12). Subsequent osmium mediated oxidative cyclisation furnished the THF product **2.52** which was spectroscopically identical to that obtained by other groups.[88]



Reagents and conditions: (i) AD-mix α; (ii) OsO_4 (5 mol%), Me_3NO, TFA, isoprene, acetone, H_2O, r.t.

Scheme 2.12: Donohoe's synthesis of *cis*-solamin

The strategy has also recently been used in the first total synthesis of *cis*-sylvaticin (**2.57**), a non-adjacent *bis*-THF acetogenin.[89] Synthesis of *bis*-acetonide **2.55** allowed a double osmium catalysed oxidative cyclisation to occur, forming *bis*-THF **2.56** as a single diastereoisomer (scheme 2.13). The synthesis was completed by a cross metathesis reaction with the butenolide fragment prepared according to the method of Lee *et al.*[38]



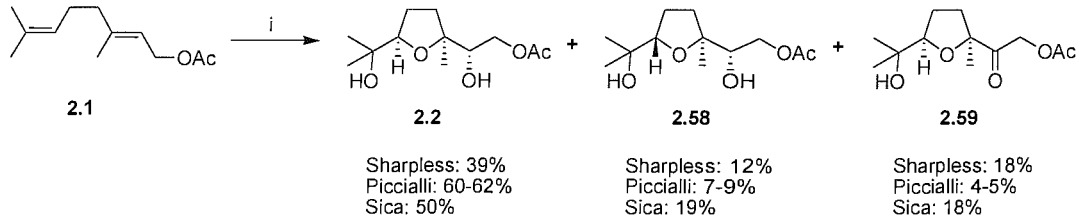
Reagents and conditions: (i) AD-mix α then CH_2=CH(OMe)Me, CSA; (ii) AD-mix β; (iii) $NaIO_4$; (iv) $C_{10}H_{21}CH$=PPh_3; (v) OsO_4 (5 mol%), Me_3NO, TFA, cinammic acid, acetone, H_2O.

Scheme 2.13: Donohoe's synthesis of *cis*-sylvaticin

2.1.3 Ruthenium Tetroxide Oxidation of Dienes

During a project that was aimed at improving the efficiency of ruthenium tetroxide as a catalytic alkene oxidant, Sharpless *et al.* found that the oxidation of geranyl acetate **2.1** afforded a mixture of THF products **2.2**, **2.58** and **2.59** (scheme 2.14).[90] The groups of

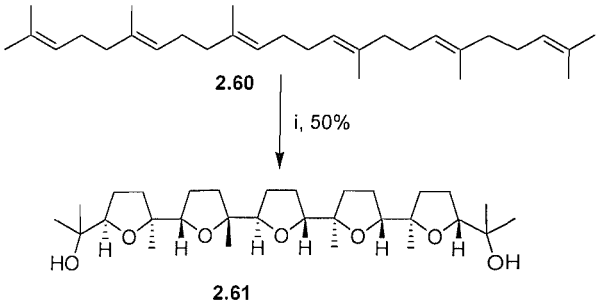
both Piccialli[91] and Sica[92] investigated this reaction further and both reported improved yields and selectivity for the *cis*-THF product **2.2**.



Reagents and conditions: (i) Sharpless: $RuCl_3.(H_2O)_n$ (2.2 mol%), $NaIO_4$ (4.1 eq.), CCl_4, MeCN, H_2O, r.t.; Piccialli: $RuO_2.2H_2O$ (4 mol%), $NaIO_4$ (4.0 eq.), EtOAc/MeCN/H_2O (3:3:1), r.t.; Sica: $RuO_2.2H_2O$ (20 mol%), $NaIO_4$ (2.5 eq.), EtOAc/acetone/H_2O (2:1:1), r.t.

Scheme 2.14: Ruthenium tetroxide oxidation of geranyl acetate

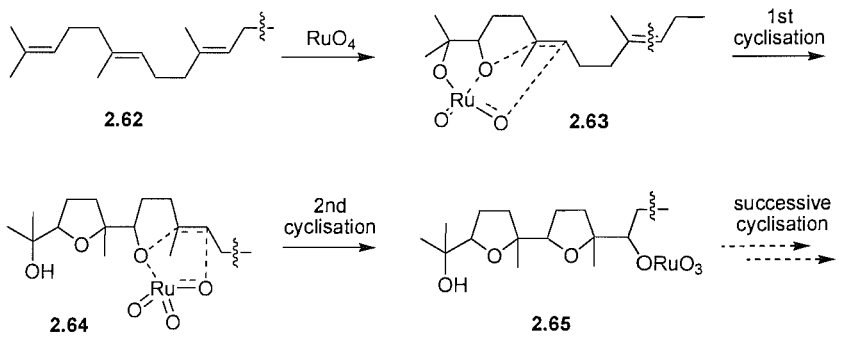
Piccialli *et al.* have also reported the construction of *bis*, *tris* and even *penta* adjacent THF units *via* a ruthenium tetroxide mediated cyclisation.[93,94] The oxidation of squalene **2.60** proceeded in an overall 50% yield, corresponding to 87% per cyclisation and the resulting *penta*-THF product **2.61** was determined to have a *cis*, *cis*, *trans*, *trans*, *trans* configuration of the THF rings (scheme 2.15).[95]



Reagents and conditions: (i) $RuO_2.2H_2O$ (20 mol%), $NaIO_4$ (8 eq.), MeCN/EtOAc/H_2O (3:3:1).

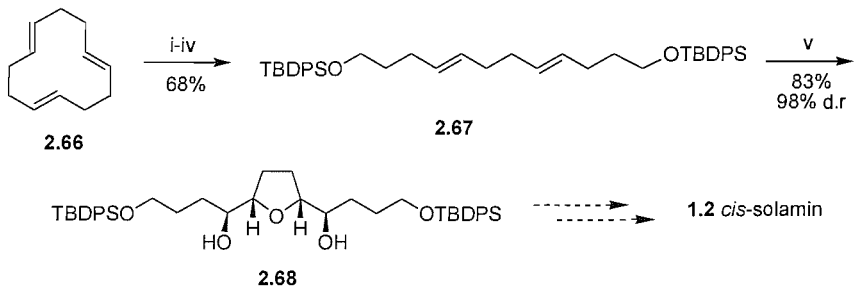
Scheme 2.15: Poly-cyclisation using ruthenium

A combination of studies carried out by Piccialli and co-workers led to a mechanistic hypothesis which predicted a cascade of ring closing steps.[93,95,96] It is believed that closure of each THF ring takes place *via* a *syn* addition of two oxygen atoms by a [3+2] cycloaddition of a O-Ru=O portion onto each double bond (scheme 2.16). The stereoselectivity of each cyclisation has been attributed to the steric constraint present in the cyclisation step. However, Piccialli has been unable to set general rules for the prediction of the stereochemical outcome of the reaction based on current findings.



Scheme 2.16: Mechanism proposed for the RuO_4 oxidative cyclisation

More recent investigations by Stark and co-workers have resulted in a greatly improved procedure for the cyclisation. They have found that the solvent composition is decisive in determining the stereoselectivity of the reaction. Their results have shown that changing the solvent system to 10 vol% of CH_2Cl_2 in THF results in the isolation of only the *cis*-THF ring in high yields, for most substrates.[97] These improved conditions have recently been exploited in the total synthesis of *cis*-solamin (**1.2**) with the insertion of the mono-THF core from a ruthenium tetroxide catalysed oxidative cyclisation of diene **2.67** (scheme 2.17).[98] The cyclisation product **2.68** was obtained as a single diastereoisomer in high yield.



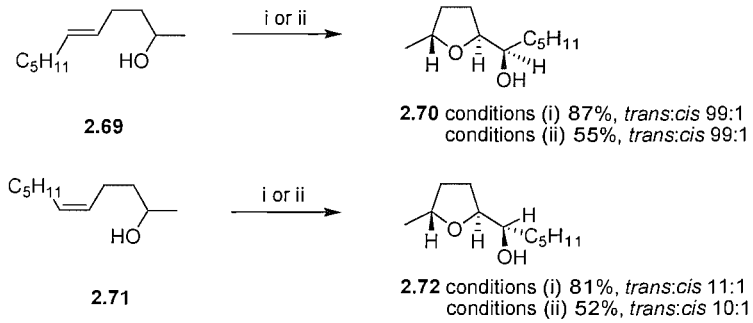
Reagents and conditions: (i) OsO_4, NMO, H_2O, CH_2Cl_2, r.t.; (ii) $NaIO_4$, CH_2Cl_2, H_2O, acetone; (iii) $NaBH_4$, MeOH, 0 °C; (iv) TBPDSCl, $^iPr_2NEt$, DMAP, CH_2Cl_2, 0 °C to r.t.; (v) $RuCl_3$ (0.2 mol%), $NaIO_4$ on wet silica, THF, 0 °C.

Scheme 2.17: Stark's synthesis of *cis*-solamin

2.1.4 Rhenium Oxide Mediated Oxidative Cyclisation of 5-Hydroxyalkenes

Kennedy *et al.* were the first group to investigate the use of rhenium oxide to promote the oxidative cyclisation of 5-hydroxyalkenes to THF products.[62,99] They found that

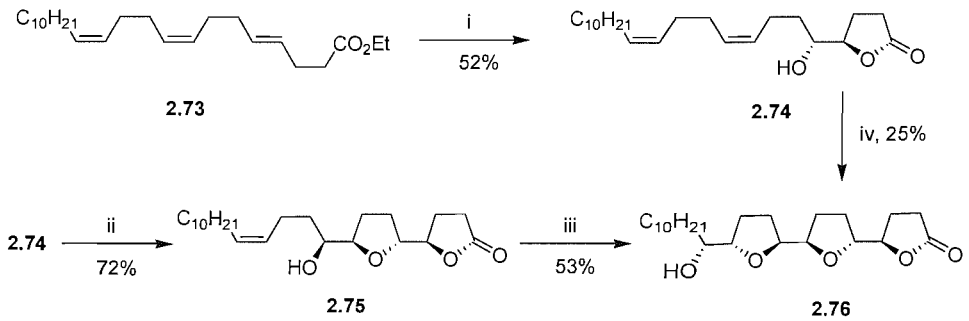
treatment of a range of hydroxyalkenes with rhenium(VII) oxide and 2,6-lutidine furnished *trans*-THF products in good yields (scheme 2.18). Further research found that using H_5IO_6 as a co-oxidant allowed a sub-stoichiometric 50 mol% of the rhenium species to be used, resulting in only slightly lower yields and selectivity.[63] McDonald and Towne have also reported the use of acyl perrhenate species such as trifluoroacetyl trioxorhenium as effective reagents for the cyclisation.[100]



Reagents and conditions: (i) Re_2O_7 (3.0 eq.), 2,6-lutidine (3.3 eq.), NaOOH, CH_2Cl_2, r.t.; (ii) Re_2O_7 (50 mol%), H_5IO_6 (1.3 eq.), ^tBuOOH, CH_2Cl_2, r.t.

Scheme 2.18: Rhenium cyclisation of 5-hydroxy alkenes

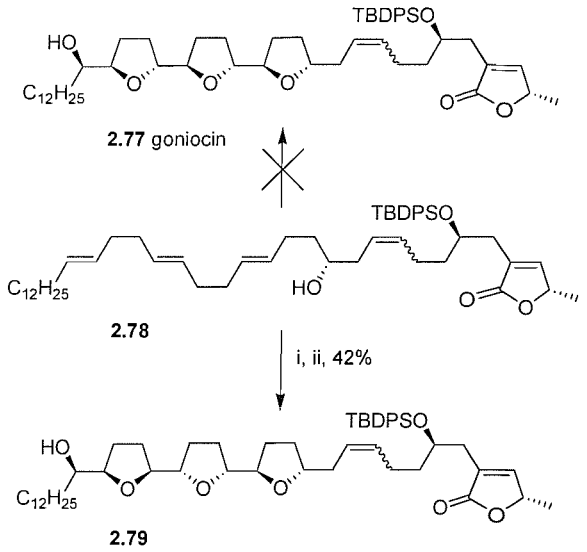
Sinha and co-workers then combined the stereoselectivity of the Kennedy cyclisation with the high enantioselectivity of the Sharpless asymmetric dihydroxylation to carry out an asymmetric polycyclisation of polyenes.[64] To demonstrate this strategy, Sinha prepared triene **2.73** which was then subjected to the asymmetric dihydroxylation conditions (scheme 2.19). The hydroxy lactone product **2.74** was then converted to bicyclic lactone **2.75** by a rhenium oxidative cyclisation. Sinha also found that treatment of **2.74** with the more reactive mixture of Re_2O_7 and H_5IO_6 furnished the *bis*-THF product **2.76** directly.



Reagents and conditions: (i) AD-mix β; (ii) Re_2O_7 (2 eq.), 2,6-lutidine (4 eq.), CH_2Cl_2, r.t.; (iii) Re_2O_7 (2 eq.), H_5IO_6 (3 eq.), CH_2Cl_2, r.t.; (iv) Re_2O_7 (3 eq.), H_5IO_6 (4 eq.), CH_2Cl_2, r.t.

Scheme 2.19: Poly-cyclisation of polyenes

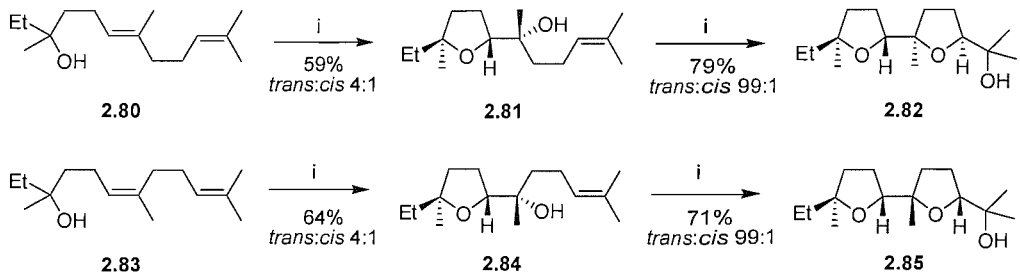
Sinha *et al.* then reported the synthesis of a *tris*-THF product from the rhenium oxide cyclisation of triene **2.78**, as part of their synthesis of goniocin (**2.77**).[67] However, the expected all *trans*-THF product was not obtained and NMR analysis indicated the product **2.79** had the *trans, cis, cis* stereochemistry **2.79**(scheme 2.20).



Reagents and conditions: (i) Re_2O_7, TFAA, THF, r.t. then **2.78**, TFAA, CH_2Cl_2, 0 °C to r.t.; (ii) H_2, Wilkinson's catalyst, benzene, EtOH, r.t. then 4% AcCl / MeOH, CH_2Cl_2, r.t.

Scheme 2.20: Sinha's synthesis of 17,18-*bis*-*epi*-goniocin

Morimoto also reported similar observations with the rhenium oxide oxidation of dienes **2.80** and **2.83** affording the *bis*-THF products **2.82** and **2.85** where the second ring was found to be *cis* in all cases (scheme 2.21).[101]

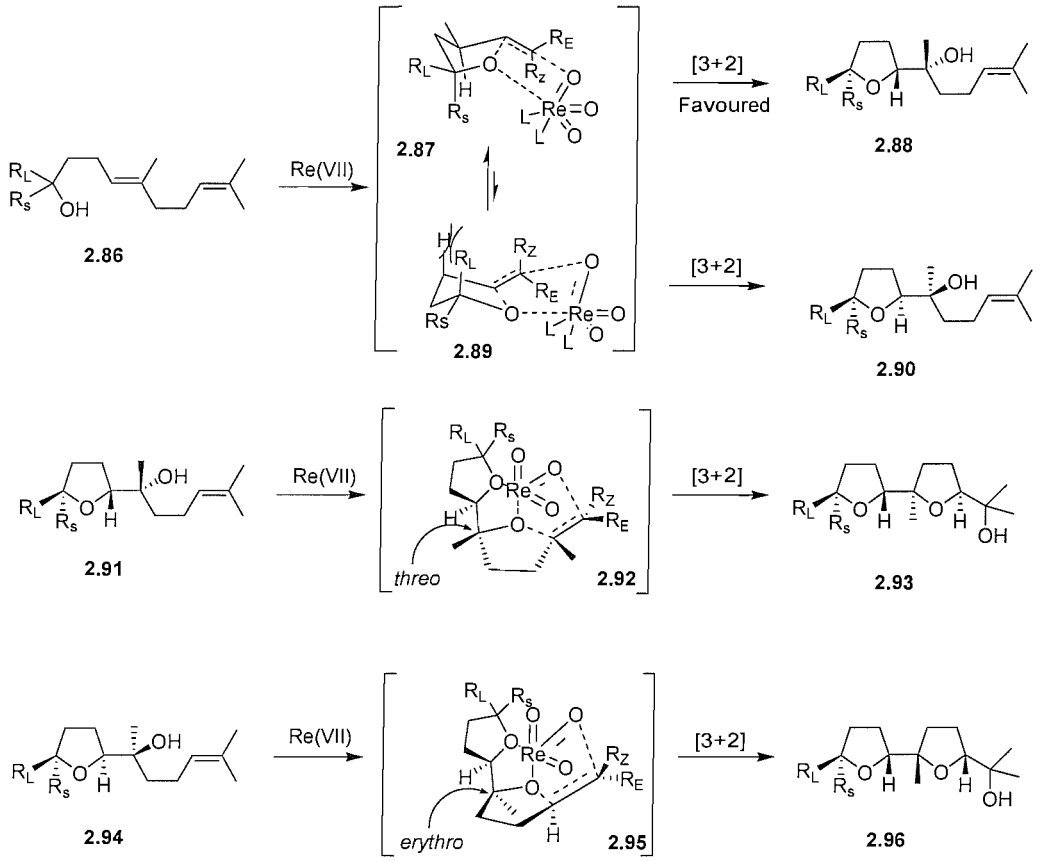


Reagents and conditions: (i) $(CF_3CO_2)ReO_3.2MeCN$ (4 eq.), CH_2Cl_2, 4 Å sieves, –45 °C.

Scheme 2.21: Morimoto's synthesis of adjacent *bis*-THF's using rhenium

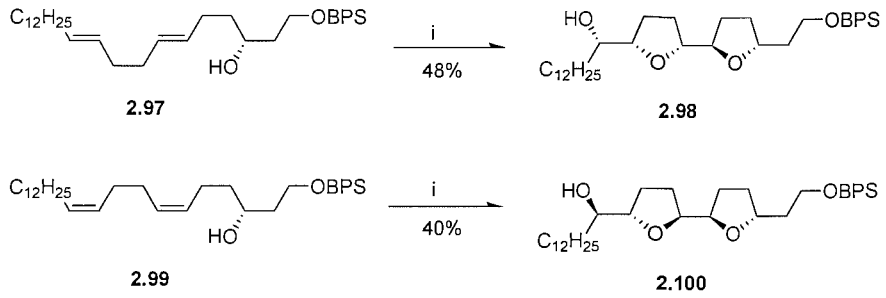
Morimoto postulated that the formation of a *trans*-THF from the cyclisation is determined by steric interactions in the chair-like transition state (scheme 2.22).[101,102] The *trans*-THF ring arises when the alkene and largest group are in the more preferred

pseudo-equatorial positions (**2.87**). Steric hindrance of the alkyl group and hydrogen in the transition state **2.89** prevent the *cis*-THF ring from forming. The reversal of selectivity in the second cyclisation is attributed to chelation of the first THF ring to the rhenium. The least strained approach of the alkene to the rhenium leads to the formation of the *cis*-THF ring.



Scheme 2.22: Investigation by Morimoto on the selectivity of the rhenium cyclisation

Further work carried out by Sinha *et al.* showed that the double rhenium cyclisation of diene **2.97** produced the *trans*, *cis-bis*-THF **2.98** whereas for **2.99**, the *trans*, *trans-bis*-THF **2.100** was the only product isolated (scheme 2.23).[103] These results suggested that Morimoto's explanation was not complete and other factors also influenced the cyclisation.



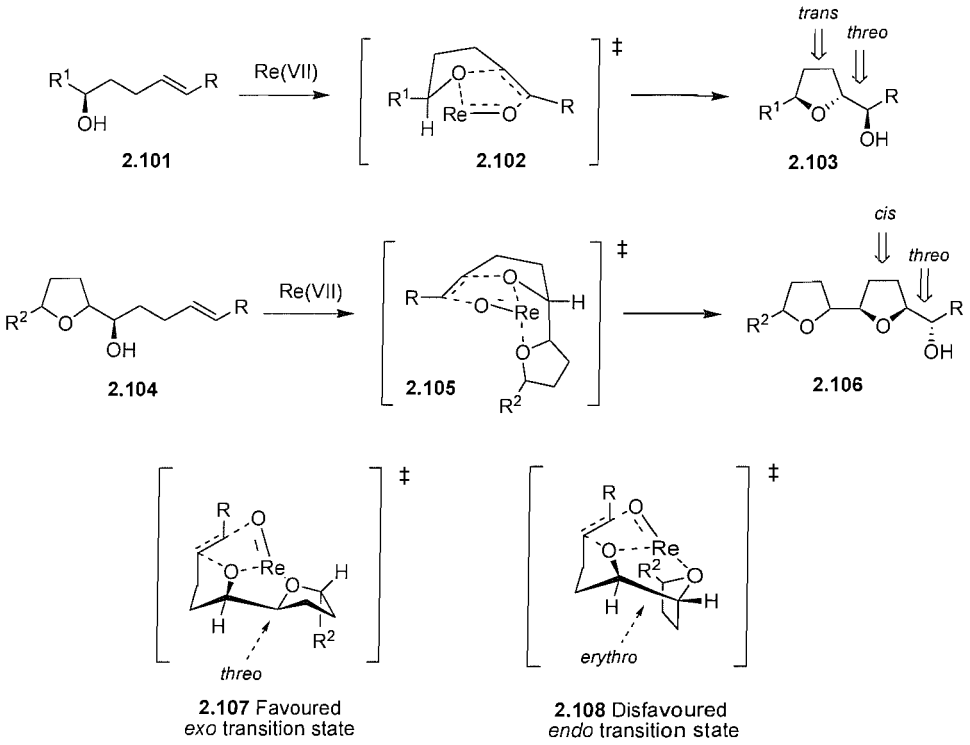
Reagents and conditions: (i) $(CF_3CO_2)ReO_3$ (2.5 eq.), TFAA (3.0 eq.), CH_2Cl_2.

Scheme 2.23: Sinha's synthesis of adjacent *bis*-THF's using rhenium

Sinha concluded that the relative configuration of the THF ring formed in the rhenium cyclisation depended on the configuration of the vicinal oxygen formed in the previous cyclisation, which itself arises from the original double bond geometry. On the basis of all of the results collected Sinha proposed the following set of rules for the prediction of stereochemical outcome of a single step polycyclisation of poly-disubstituted alkenols:[103,104]

- With a simple *bis*-homoallylic alcohol (where the hydroxyl is the only co-ordination site of rhenium), the first THF ring is always formed with a *trans* configuration.
- If the vicinal oxygen functions formed in the first cyclisation have a *threo* relationship, then the next cyclisation produces a *cis*-THF ring.
- If the vicinal oxygen functions formed in the first cyclisation have an *erythro* relationship, then the next cyclisation produces a *trans*-THF ring.

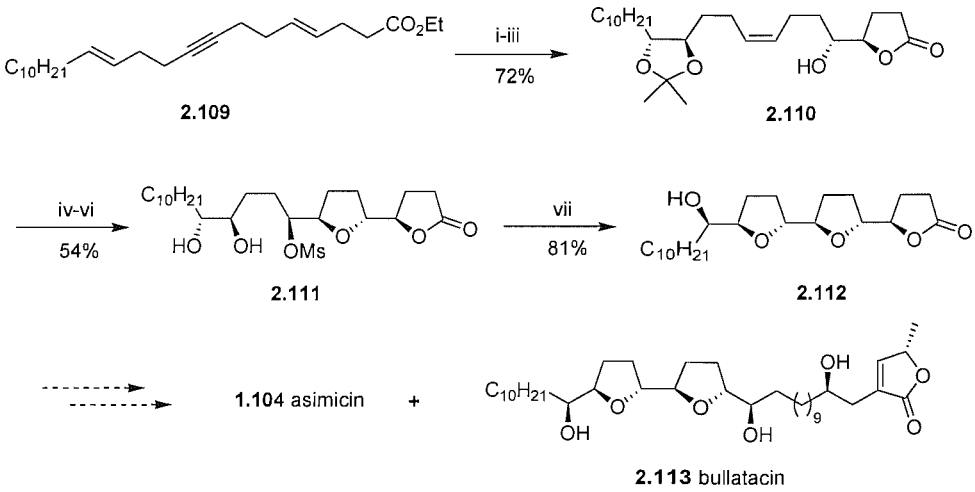
These rules reflect the change in the stereochemical course of the oxidative cyclisation from one substrate to the next and can be explained by the ability of the newly formed THF ring to chelate to the rhenium atom during subsequent cyclisations (scheme 2.24). Sinha proposed a transition state model to explain these observations. In the first cyclisation step, the non-coordinating alkyl chain has a high preference to take a less sterically demanding *pseudo*-equatorial position in the [3+2] transition state **2.102**, which leads to a *trans* THF ring. In cases where the chain possesses a potential co-ordination site the substrate may become a bidentate ligand to rhenium making the *pseudo*-axial position more favourable resulting in a *cis*-THF ring.



Scheme 2.24: Rhenium cyclisation transition states proposed by Sinha

The co-ordinating ability of the bidentate ligand would depend on the relative configuration of the two oxygen functions. With a *threo* relationship, the reaction would proceed through a sterically favoured *exo*-type transition state **2.107**. However, with an *erythro* relationship, the sterically disfavoured *endo* transition state **2.108** would be required making the non-chelated intermediate **2.102** more favourable.

Sinha and co-workers have applied these rules[70] along with a "naked" carbon skeleton strategy to the synthesis of two adjacent *bis*-THF acetogenins, asimicin **1.104** and bullatacin **2.113**.[105] Sharpless asymmetric dihydroxylation of skeleton **2.109** followed by acetonide formation and partial hydrogenation of the alkyne afforded **2.110** (scheme 2.25). Oxidative cyclisation with rhenium afforded the bicyclic lactone which was readily converted to the mesylate **2.111**. A Williamson-type etherification produced tricycle **2.112** which was then elaborated further to both asimicin **1.104** and bullatacin **2.113**.

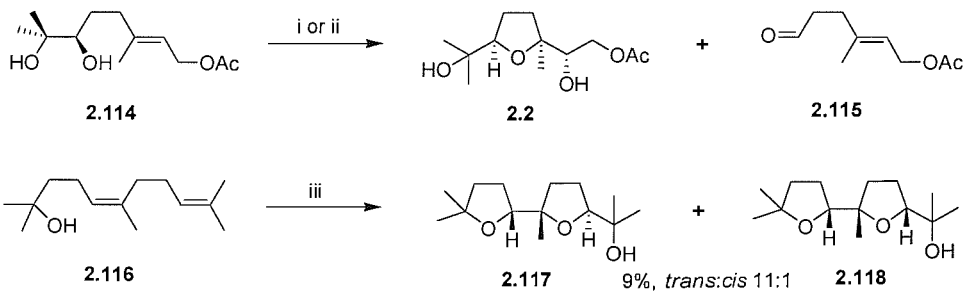


Reagents and conditions: (i) (a) AD-mix β, $MeSO_2NH_2$, ^tBuOH, H_2O, 0 °C; (b) KOH, MeOH, 60 °C then HCl; (c) *p*-TsOH, CH_2Cl_2; (ii) 2,2-dimethoxypropane, acetone, *p*-TsOH, 0 °C to r.t.; (iii) H_2, Pd / $CaCO_3$, hexane, cyclohexene, NEt_3, −10 °C; (iv) Re_2O_7, 2,6-lutidine, CH_2Cl_2, r.t.; (v) MsCl, NEt_3, CH_2Cl_2, 0 °C; (vi) *p*-TsOH, MeOH, H_2O, 60 °C; (vii) pyridine, 100 °C.

Scheme 2.25: Sinha's synthesis of bullatacin using rhenium

2.1.5 Chromium Promoted Cyclisations

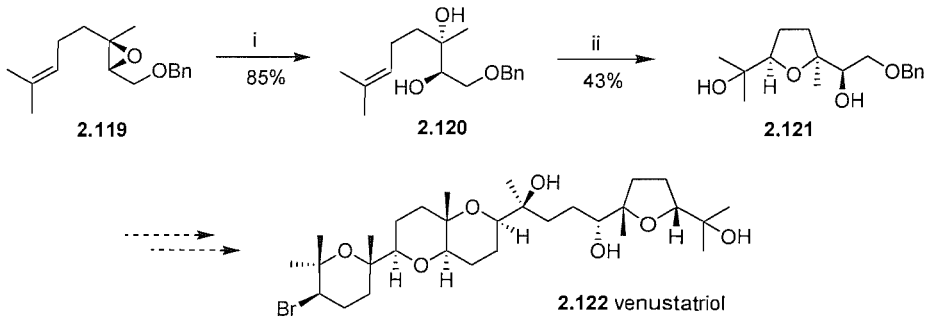
In 1982, Walba *et al.* reported that treatment of 5,6-hydroxyalkenes with Collins reagent (CrO_3) afforded *cis*-THF products.[106] Oxidation of geranyl acetate diol **2.114** was found to produce *cis*-THF **2.2** in moderate yield, with a small amount of aldehyde **2.115** observed (scheme 2.26). Further experiments showed that the use of pyridinium chlorochromate gave similar results, whereas the use of bipyridinium chlorochromate afforded aldehyde **2.115** as the major product. McDonald and co-workers have also reported polycyclisations of polyenes using pyridinium chlorochromate.[107]



Reagents and conditions: (i) CrO_3, pyridine; (ii) PCC; (iii) PCC (5 eq.), celite, AcOH, r.t.

Scheme 2.26: Chromium oxidation of hydroxyalkenes

A pyridinium chlorochromate oxidative cyclisation has been used by Corey *et al.*[108] to obtain the *cis*-THF ring of the natural product venustratriol **2.122**. Conversion of geraniol based epoxide **2.119** to the corresponding diol **2.120** allowed oxidative cyclisation with pyridinium chlorochromate to occur, furnishing THF diol **2.121** (scheme 2.27).



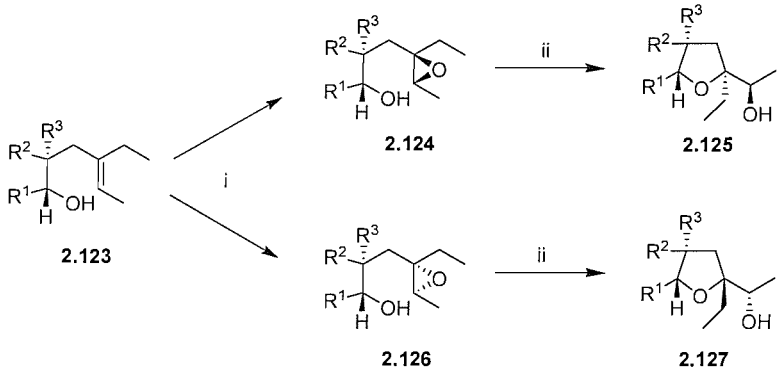
Reagents and conditions: (i) perchloric acid, THF, H_2O, r.t.; (ii) PCC (1.05 eq.), CH_2Cl_2, r.t.

Scheme 2.27: THF ring formation of venustatriol

2.2 Epoxidation-ring Closure Strategies on Hydroxyalkenes

2.2.1 Vanadium Catalysed Epoxidations

The stereocontrolled synthesis of THF rings *via* a vanadium catalysed epoxidation-cyclisation of γ,δ–unsaturated alcohols was pioneered by Kishi *et al.*[109] Treatment of a range of alcohols with a mixture of $VO(acac)_2$ and ^tBuOOH produced the corresponding *trans*-THF products with good selectivity (scheme 2.28).



R^1 = ^{i}Pr, R^2 = R^3 = H; **2.125**:**2.127** = 9:1
R^1 = ^{i}Pr, R^2 = H, R^3 = CH_3; **2.125**:**2.127** = 20:1
R^1 = *p*-$CH_3OC_6H_4$, R^2 = CH_3, R^3 = H; **2.125**:**2.127** = 8:1

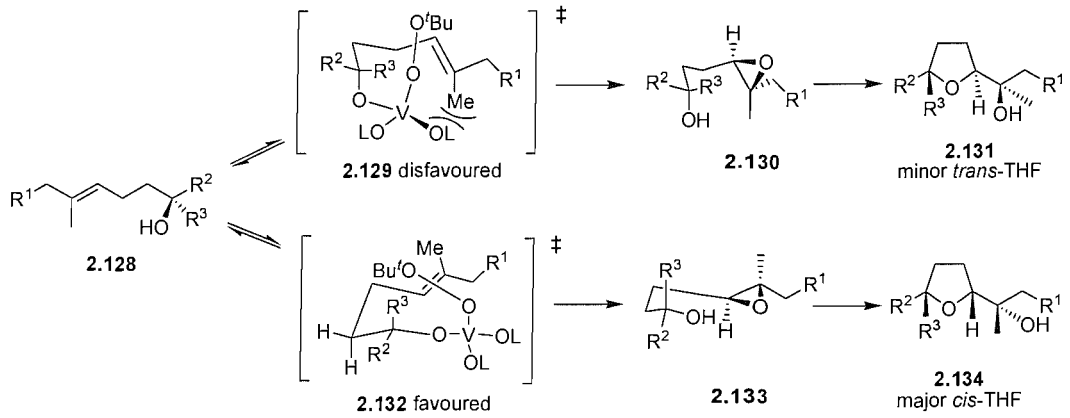
Reagents and conditions: (i) $VO(acac)_2$, ^{t}BuOOH, benzene, r.t.; (ii) AcOH.

Scheme 2.28: Vanadium epoxidation-cyclisations on hydroxyalkenes

Further work carried out by Shirahama and co-workers showed that the selectivity of the reaction in fact depended on the γ,δ–unsaturated alcohol precursor and that *cis*-THF rings could also be prepared. Based on their findings, Shirahama *et al.* presented a set of general principles that could be used to predict the major diastereoisomer from the reaction:[110,111]

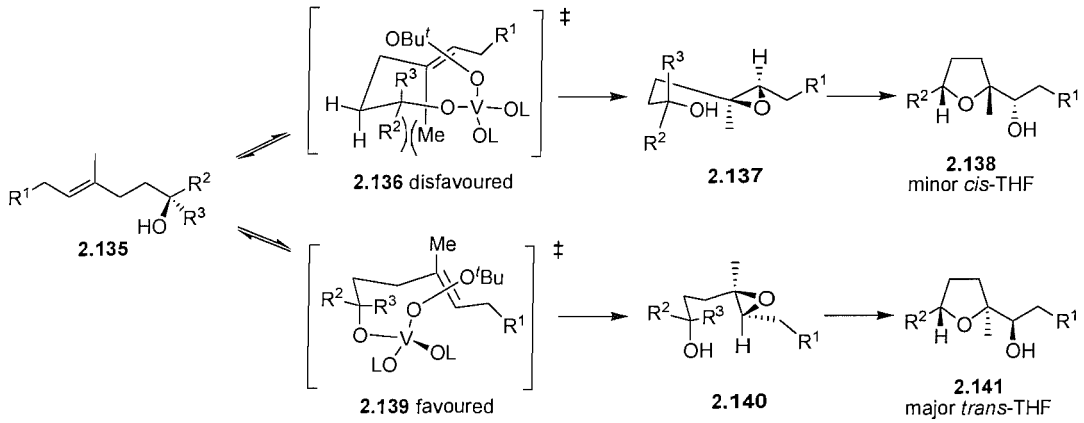
- When the γ,δ–unsaturated alcohol is substituted in the δ-position (type A), the *cis*-THF is the major product.
- When the γ,δ–unsaturated alcohol is substituted in the γ-position (type B), the *trans*-THF is the major product.
- The geometry of the double bond does not affect the stereoselectivity of the reaction.

It is thought that the selectivity of the reaction is affected by steric factors in the transition states. For type A precursors, transition state **2.129** which leads to the minor *trans*-THF can experience steric hindrance between the vinylic methyl group and the tertiary oxygen bound to the catalyst (scheme 2.29). Minimisation of this hindrance favours transition state **2.132**, resulting in the *cis* isomer.



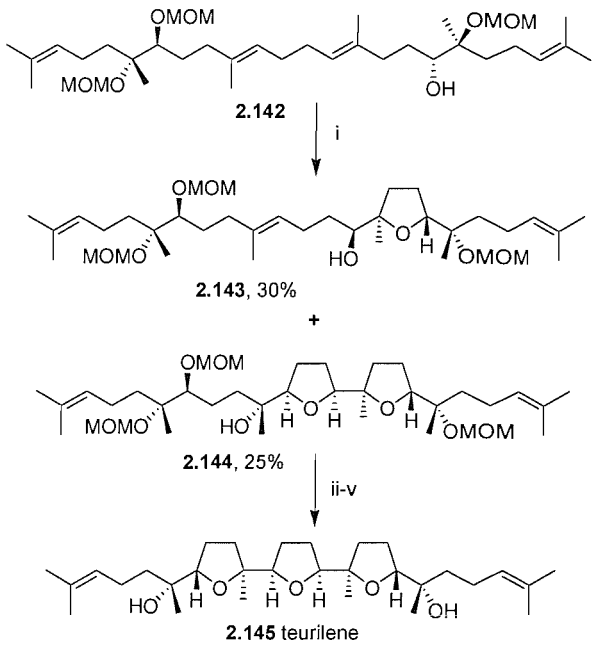
Scheme 2.29: Selectivity in type A systems

For type B precursors, transition state **2.136** which leads to the minor isomer, experiences steric compression due to the interaction between H, Me and R_2. This strain is minimised in transition state **2.139**, leading to the major *trans*-THF **2.141** (scheme 2.30).



Scheme 2.30: Selectivity in type B systems

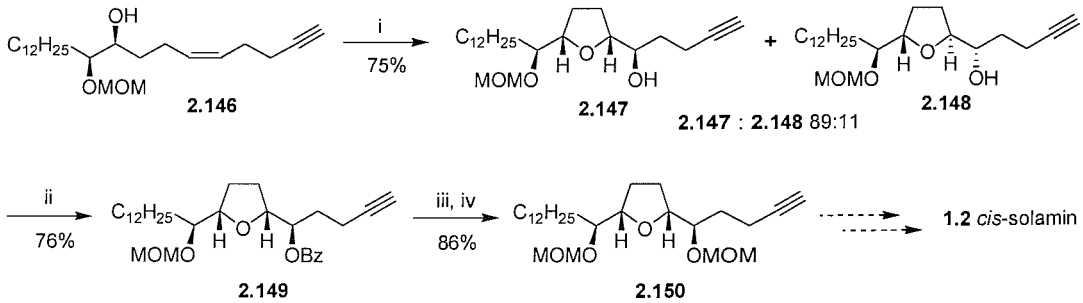
Shirahama has combined both type A and type B epoxidation-cyclisations in his stereoselective synthesis of teurilene **2.145**.[111] Treatment of tetraene **2.142** with $VO(acac)_2$ and ^tBuOOH allowed the sequential epoxidation-cyclisation affording the *bis*-THF product **2.144** in a single step (scheme 2.31). This was then converted to teurilene **2.145** through a series of known transformations.



Reagents and conditions: (i) $VO(acac)_2$, ^tBuOOH, AcOH, benzene, 47 °C; (ii) HCl, MeOH, r.t.; (iii) MsCl, NEt_3, CH_2Cl_2, –40 °C; (iv) K_2CO_3, MeOH, r.t.; (v) HCl, H_2O, Et_2O, r.t.

Scheme 2.31: Synthesis of teurilene using vanadium

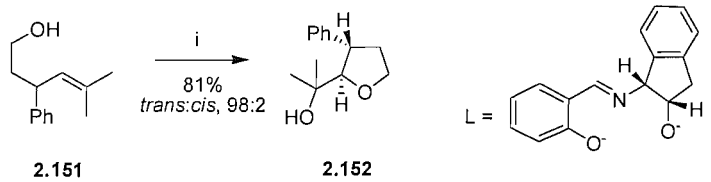
Vanadium catalysed epoxidations have also been applied to the synthesis of *mono*, *tris* and *penta* THF fragments for the use in total synthesis.[112] Makabe reported the vanadium catalysed epoxidation-cyclisation sequence of hydroxyalkene **2.146** which formed the key step of the total synthesis of *cis*-solamin **1.2** (scheme 2.32).[113]



Reagents and conditions: (i) $VO(acac)_2$, ^tBuOOH, 4 Å sieves, $(CH_2Cl)_2$; (ii) BnCl, pyridine then separation; (iii) NaOH, MeOH; (iv) MOMCl, $^iPr_2NEt$.

Scheme 2.32: Makabe's synthesis of *cis*-solamin

More recently, Hartung *et al.* have developed vanadium Schiff-base complexes with tridentate ligands that have been used to achieve the epoxidation-cyclisation sequence in good yields and high selectivity (scheme 2.33).[114,115]



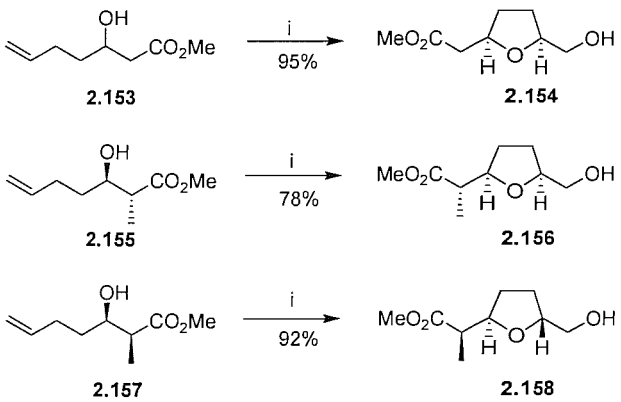
2.151 **2.152**

Reagents and conditions: (i) VO(OEt)L (10 mol%), ^{t}BuOOH, CH_2Cl_2, r.t.

Scheme 2.33: Vanadium cyclisation using Schiff-base complexes

2.2.2 *m*-CPBA Epoxidations

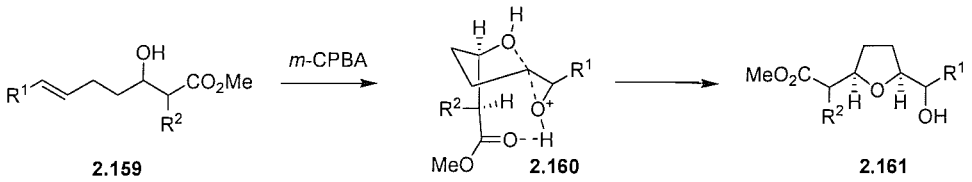
Iqbal and co-workers have reported the synthesis of a number of 2,5-disubstituted THF products from hydroxyester precursors *via* an *m*-CPBA epoxidation.[116] The mono-THF products were obtained in good yields and selectivity (scheme 2.34).



Reagents and conditions: (i) *m*-CPBA, CH_2Cl_2, 0 °C to r.t.

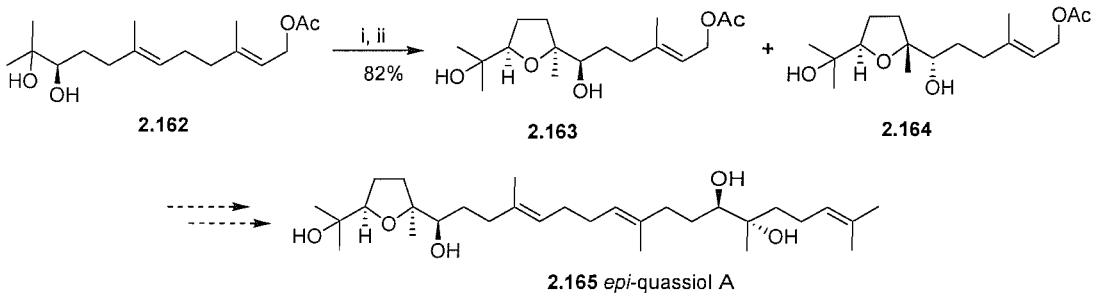
Scheme 2.34: *m*-CPBA epoxidation-cyclisations of hydroxyalkenes

The stereoselectivity obtained from the reactions is believed to be due to the involvement of the methoxycarbonyl group during the cyclisation. The electrophilic cyclisation of alcohols **2.153** and **2.155** is believed to proceed *via* transition state **2.160**. In this case the hydrogen bonding lowers the activation energy, resulting in the high selectivity for the *cis* product (scheme 2.35).[116] The *trans* selectivity observed for the cyclisation of **2.157** is believed to be due to the non-involvement of the ester group during the cyclisation.



Scheme 2.35: Selectivity in *m*-CPBA cyclisations

m-CPBA has been used in the total synthesis of a number of natural products but in a non-stereoselective manner.[117,118] Kodama *et al.* have reported the use of *m*-CPBA in their synthesis of *epi*-quassiol A **2.165**.[119] The epoxidation-cyclisation sequence on diene **2.162** afforded the two diastereomeric products in a 1:1 ratio (scheme 2.36).



Reagents and conditions: (i) *m*-CPBA, CH_2Cl_2; (ii) AcOH, CH_2Cl_2, r.t.

Scheme 2.36: Synthesis of *epi*-quassiol A

2.2.3 Chiral Ketones as Epoxidation Catalysts

The asymmetric epoxidation of alkenes by chiral dioxiranes generated *in situ* from potassium peroxomonosulphate and chiral ketones was first reported by Curci *et al.* (figure 2.2).[120]

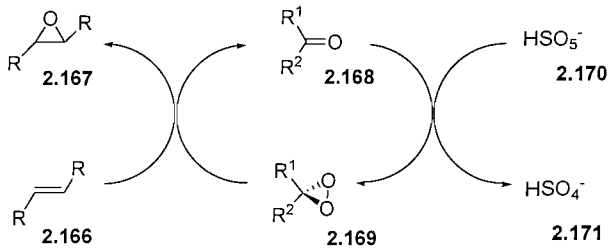
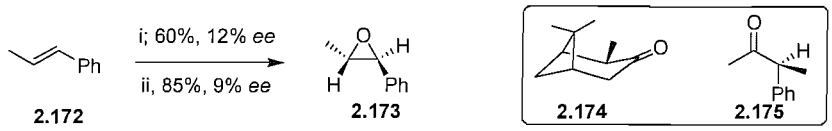


Figure 2.2: Epoxidation of alkenes using ketones

Chiral ketones **2.174** and **2.175** were initially used by Curci and were found to achieve the epoxidation of a range of alkenes in good yields (scheme 2.37).[120] However,

inconveniently long reaction times were required to achieve good substrate conversion and enantiomeric excesses were low, typically in the range of 6-12%.

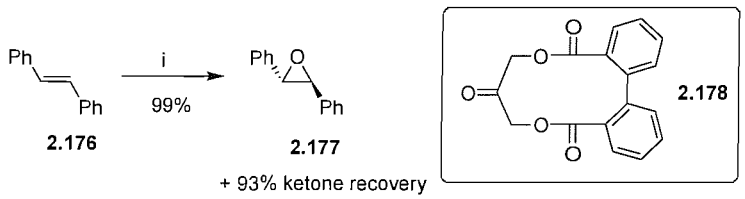


Reagents and conditions: (i) **2.174**, $KHSO_5$, CH_2Cl_2, H_2O, $Bu_4N^+HSO_4^-$ (pH 7-8), r.t.; (ii) **2.175**, $KHSO_5$, CH_2Cl_2, H_2O, $Bu_4N^+HSO_4^-$ (pH 7-8), r.t.

Scheme 2.37: Curci's epoxidation of alkenes

Further investigations by Curci *et al.* led to the conclusion that the low *ee* obtained from the reactions was due to *O*-transfer occurring from either of the two diastereotopic oxygen atoms of the peroxide O-O bond.[121] The development of chiral ketones containing structural features that would minimise the problem then became a priority.

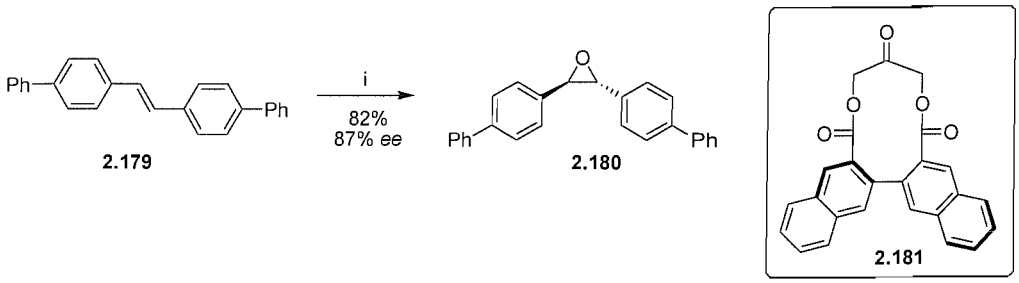
Yang and co-workers have concentrated on the development of ketones that have C_2 symmetrical and rigid conformations to overcome the low *ee*'s thus far obtained. Initial investigations found that ketone **2.178** showed unprecedented catalytic activity in the epoxidation of *trans*-stillbene.[122] The ketone was also recovered in high yield without the loss of catalytic activity (scheme 2.38).



Reagents and conditions: (i) **2.178**, $KHSO_5$, $NaHCO_3$, MeCN, Na_2EDTA, r.t.

Scheme 2.38: Yang's epoxidation of alkenes

The promising results obtained from the use of ketone **2.178** led to the development of chiral ketone **2.181** where the diphenic unit was replaced by a chiral binapthalene unit. The use of ketone **2.181** resulted in moderate to good enantioselectivity for the epoxidation of *trans* and trisubstituted alkenes. The epoxidation of **2.179** proceeded in 82% yield with 87% *ee* (scheme 2.39). However, ketone **2.181** was not as effective in the epoxidation of *cis* or terminal alkenes, with *ee* values being generally low (5-50%).[122]



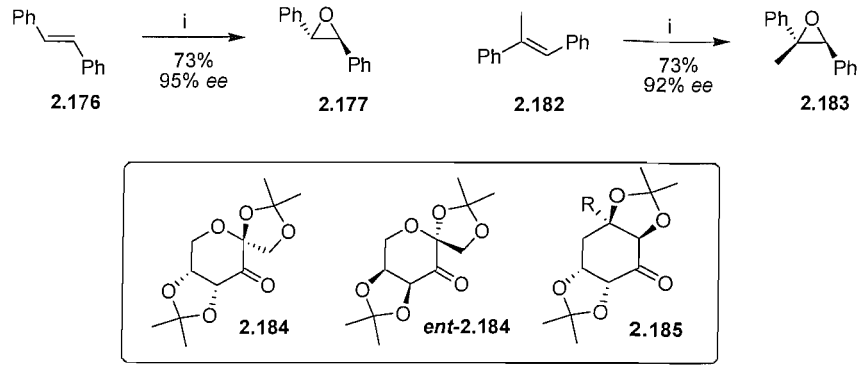
Reagents and conditions: (i) **2.184**, $KHSO_5$, $NaHCO_3$, MeCN, Na_2EDTA, r.t.

Scheme 2.39: Yang's second generation epoxidation

Shi and co-workers have also investigated the dioxirane mediated epoxidation of alkenes, and have concentrated on the synthesis and application of ketones containing the following general features:[123,124]

- The stereogenic centres are close to the reacting centre to allow efficient stereochemical communication between the substrate and catalyst.
- The presence of fused ring(s) or a quaternary centre α to the carbonyl group to minimise epimerisation of the stereogenic centres.
- One face of the catalyst is sterically blocked to limit the approach of the alkene to the dioxirane.
- Inductively electron-withdrawing substituents to activate the carbonyl.

Shi and co-workers have developed a number of chiral ketones that fulfil the above criteria in an attempt to improve enantioselectivity in the epoxidation reaction. Ketone **2.184** and its enantiomer ***ent*-2.184** have been found to catalyse the epoxidation of *trans* and trisubstituted alkenes resulting in good yields and high enantioselectivity (scheme 2.40).[123] Attempts at improving the yields through longer reaction times resulted in lower *ee*, believed to be due to the decomposition of the ketone under the reaction conditions.

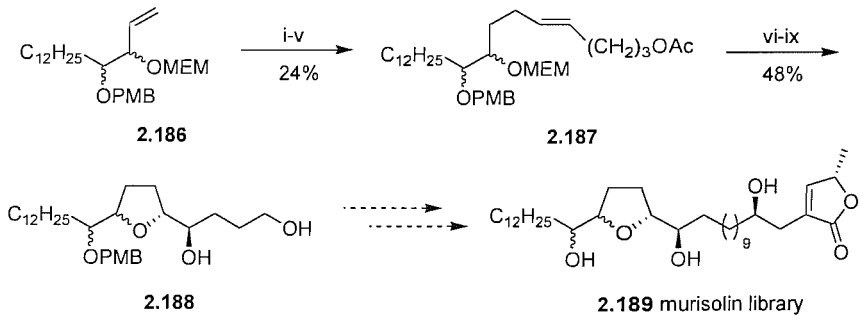


Reagents and conditions: (i) **2.84** (3 eq.), $KHSO_5$, $NaHCO_3$, MeCN, Na_2EDTA, 0 °C.

Scheme 2.40: Shi's epoxidation of alkenes

Shi *et al.* have also developed a series of ketones based on the general structure **2.185**. These catalysts are more stable than **2.184** and a smaller quantity is required in the reaction. The epoxidation of *cis* and terminal alkenes is also higher but it is less selective for both *trans* and trisubstituted alkenes.[125]

Curran *et al.* have recently used both enantiomers of Shi's epoxidation catalyst (**2.184** and ***ent*-2.184**) to insert the mono-THF core of (+)-murisolin in their synthesis of a complete library of stereoisomers (scheme 2.41).[126] The catalysts have also be used by Sinha and co-workers to carry out mono and *bis* epoxidations in their synthesis of a complete library of trilobacin analogues (see section 1.4.4).[71]



Reagents and conditions: (i) BH_3, H_2O_2; (ii) PPh_3, I_2; (iii) $ICH{=}CH(CH_2)_3OTBS$, *t*-BuLi, $ZnCl_2$, $Pd(PPh_3)_4$; (iv) TBAF; (v) AcCl; (vi) **2.184**, Oxone; (vii) CSA; (viii) Mitsunobu; (ix) NaOH.

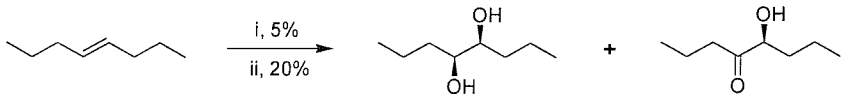
Scheme 2.41: Curran's synthesis of murisolin

2.3 Dihydroxylation-Cyclisation Strategies

2.3.1 The Osmium Mediated Dihydroxylation Reaction

The *cis*-dihydroxylation of alkenes to the corresponding 1,2-diols using osmium tetroxide is a powerful transformation and has received much attention over the years. The following section will therefore summarise the work carried out in this area, highlighting the major developments.

The combination of osmium tetroxide and pyridine has been shown to affect the dihydroxylation of alkenes in moderate yields. However stoichiometric quantities of osmium were required for this which, due to the expense of osmium, was undesirable. This has therefore led to a wide interest in the development of alternative procedures using catalytic osmium and stoichiometric amounts of co-oxidants. Two early examples of catalytic systems were presented by Hoffmann[127] and Milas.[128] The former used metal chlorates as the stoichiometric oxidant whilst Milas used a combination of hydrogen peroxide and *tert*-butanol. Although both these methods allowed the use of catalytic osmium, low yields due to the formation of over-oxidised by-products such as **2.192** presented a big problem (scheme 2.42).

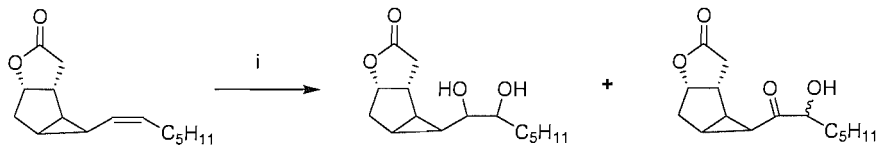


2.190 **2.191** **2.192**

Reagents and conditions: (i) Hoffmann: $KClO_3$, OsO_4 (0.2 mol%), dioxane, H_2O, 50 °C; (ii) Milas: OsO_4 (0.2 mol%), H_2O_2, ^tBuOH.

Scheme 2.42: Dihydroxylation of an alkene using osmium

Around the mid-seventies interest once again increased and the groups of both VanRheenen and Sharpless investigated the reaction with the aim of increasing yields through the reduction of unwanted by-products. VanRheenen and co-workers found that the combination of hydrogen peroxide and NMO allowed 1 mol% of osmium tetroxide to be used to effect the dihydroxylation of alkene **2.193** without any of the over-oxidised product **2.195** being produced (scheme 2.43).[129]



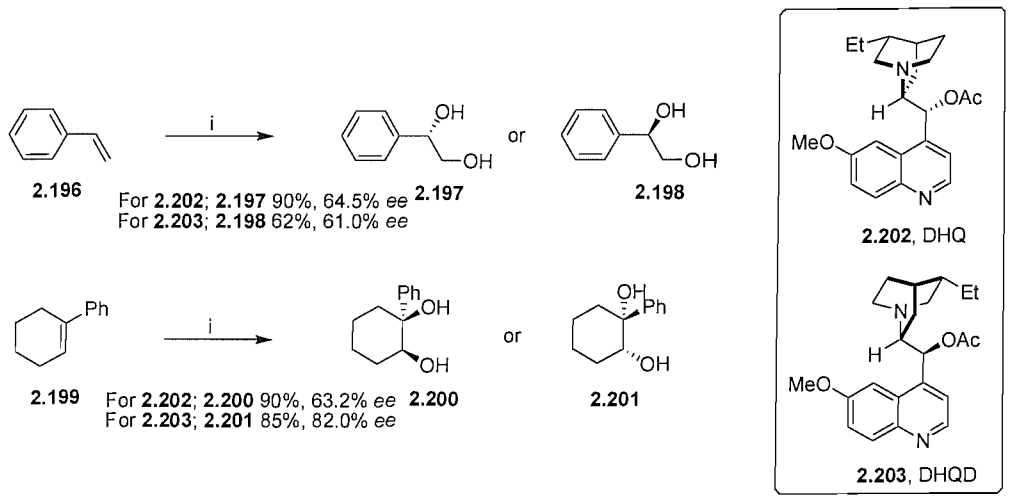
2.193 **2.194**, 95% **2.195**, 0%

Reagents and conditions: (i) OsO_4 (1 mol%), NMO (1 eq.), ^tBuOH, H_2O.

Scheme 2.43: VanRheenen's dihydroxylation using osmium

Sharpless *et al.* concentrated on the suppression of the over oxidised by-products through alkaline reaction conditions.[127] They found that using Et_4NOH with *tert*-butyl hydroperoxide and catalytic osmium allowed the rapid hydrolytic removal of the diol from osmium before the over oxidation could occur. This method proved to be successful in most cases, apart from base sensitive compounds. This limitation was overcome by replacing Et_4NOH with Et_4NOAc and changing the solvent system to acetone.[130] Despite these developments, the pyridine and stoichiometric osmium combination remained the most reliable method.

Sharpless and co-workers also began to look at the possibility of an asymmetric version of the dihydroxylation reaction. It was already known that pyridine accelerated the reaction and it was thought that this was due to co-ordination of pyridine to the metal centre. Sharpless therefore reasoned that using a chiral, pyridine based ligand might induce chirality into the product. Griffith and co-workers had previously observed that tertiary alkyl bridgehead amines formed stable complexes with osmium.[131] Cinchona alkaloid derivatives **2.202** and **2.203** were originally tested in the stoichiometric dihydroxylation and were found to achieve moderate enantiomeric excesses (scheme 2.44).[132] However, introduction of these chiral ligands into the catalytic reaction resulted in much lower selectivity.



Reagents and conditions: (i) OsO_4 (1.1 eq.), **2.202** or **2.203** (1.1 eq.), toluene, r.t.

Scheme 2.44: Sharpless' asymmetric dihydroxylation

Several years later Sharpless and co-workers made a significant breakthrough in the catalytic asymmetric reaction conditions when they realised that in fact two catalytic cycles occurred during the reaction (figure 2.3).[133] The second catalytic cycle is believed to be as efficient as the first cycle but has little or no enantioselectivity. Complex **2.206** occupies the pivotal position between the two cycles and so the properties of this complex determine which route is taken. Sharpless found that the slow addition of the alkene precursor allowed the hydrolysis of complex **2.206** to occur before it was trapped by more of the alkene and forced to proceed through the second cycle, resulting in improved selectivity.

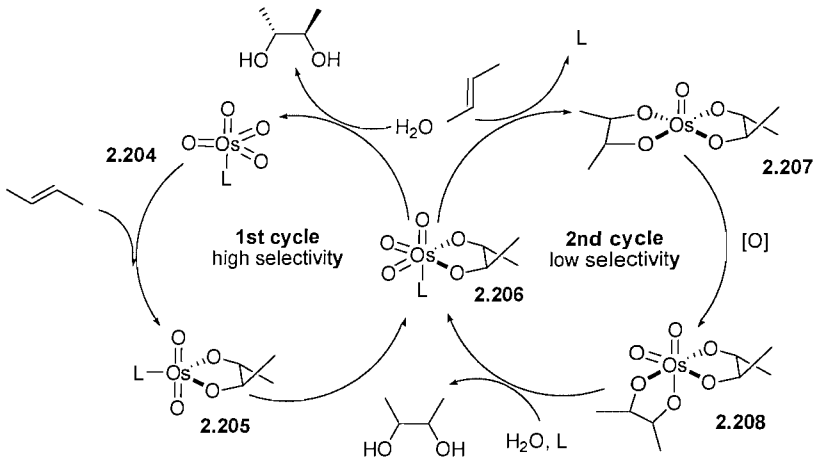


Figure 2.3: Proposed catalytic cycles with NMO as the co-oxidant

The selectivity of the reaction was further improved when Sharpless found that the second cycle could be completely eliminated by changing the co-oxidant from NMO to $K_3Fe(CN)_6$[134] and carrying out the reaction in a two-phase solvent system. Under these conditions there is no oxidant other than osmium in the organic layer. This allows osmate ester **2.209** to undergo hydrolysis to release the diol and ligands to the organic layer and osmium to the aqueous layer for re-oxidation (figure 2.4).[135] This resulted in increased enantioselectivity in the dihydroxylation of the alkenes previously tested.[136]

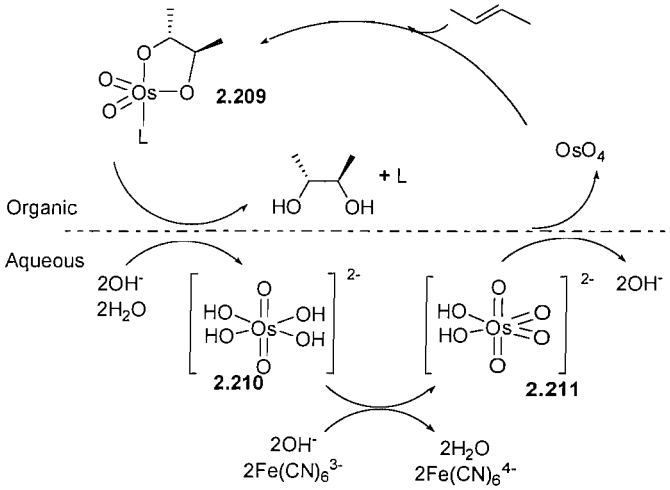
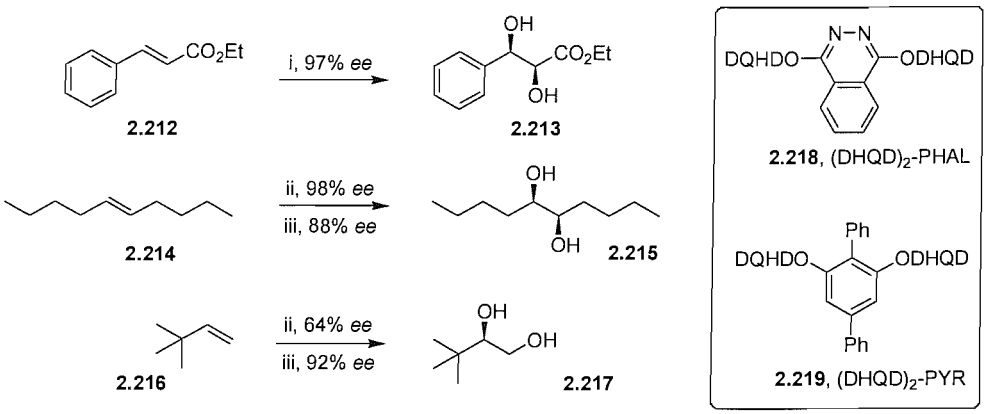


Figure 2.4: Proposed catalytic cycle with $K_3Fe(CN)_6$ as the co-oxidant

Two further improvements for the asymmetric dihydroxylation reaction were then discovered by the group of Sharpless. Firstly, the addition of organic sulphonamides to the reaction mixture was found to accelerate the hydrolysis of osmate ester **2.209** resulting in shorter reaction times.[135] Secondly Sharpless and co-workers found that the use of ligands with two of the cinchona alkaloid units attached to a heterocyclic spacer resulted in an increase in the enantioselectivity and scope of the reaction.[137] The phthalazine linker (PHAL) is generally used for *trans* disubstituted and trisubstituted alkenes whilst the diphenylpyrimidine linker (PYR) has been shown to give superior results for previously problematic terminal alkenes (scheme 2.45).[138]

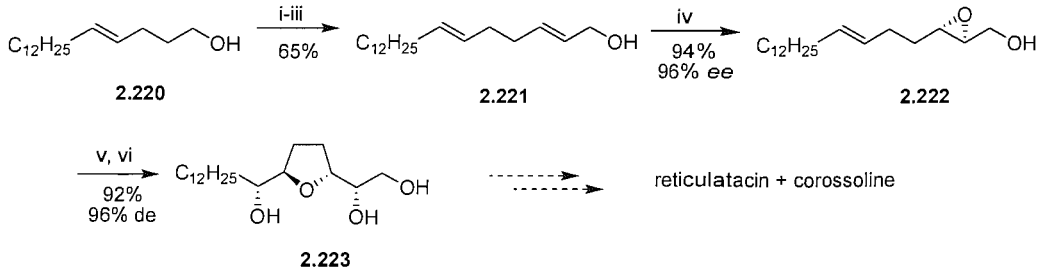


Reagents and conditions: (i) AD-mix β, $MeSO_2NH_2$, ^tBuOH, H_2O, 0 °C; (ii) OsO_4 (1 mol%), **2.218** (1 mol%), $K_3Fe(CN)_6$ (3 eq.), K_2CO_3, ^tBuOH, H_2O, 0 °C; (iii) OsO_4 (1 mol%), **2.219** (1 mol%), $K_3Fe(CN)_6$ (3 eq.), K_2CO_3, ^tBuOH, H_2O, 0 °C.

Scheme 2.45: Asymmetric dihydroxylation reaction

A number of other groups have developed bidentate chiral ligands for the asymmetric dihydroxylation reaction achieving moderate to high asymmetric induction.[139,140] However stoichiometric quantities of both osmium and the ligand are generally required resulting in Sharpless' conditions being the most widely used to carry out the transformation. Experimental procedures using Sharpless asymmetric dihydroxylation procedure have been further simplified with the development of an AD-mix formulation consisting of the standard reactants.[137,141] This simplifies performing the reaction on a millimolar scale where only trace amounts of the osmium source and ligands are required.

Due to the synthetic utility of chiral 1,2-diol units, the Sharpless asymmetric dihydroxylation has been used extensively. Makabe *et al.* employed the asymmetric dihydroxylation for the construction of the mono-THF core of two acetogenins; reticulatacin[142] and corossoline.[143] Alcohol **2.220** was converted to corresponding epoxide **2.222** using Sharpless asymmetric epoxidation conditions (scheme 2.46). Subsequent dihydroxylation followed by acid-catalysed ring closure introduced the mono-THF core with high asymmetric induction.

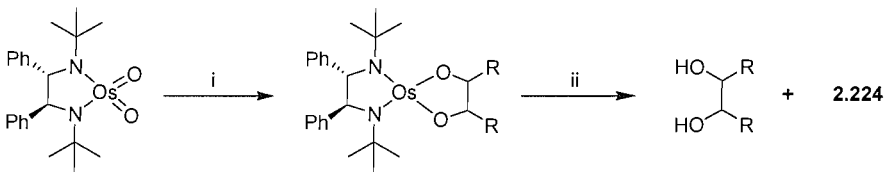


2.220 **2.221** **2.222** **2.223**

Reagents and conditions: (i) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2; (ii) triethyl phosphonoacetate, NaH, THF; (iii) DIBAL-H, CH_2Cl_2; (iv) $Ti(O^iPr)_4$, L-(+)-DET, ^{t}BuOOH, CH_2Cl_2; (v) AD-mix β, ^{t}BuOH, H_2O; (vi) CSA, CH_2Cl_2.

Scheme 2.46: Makabe's synthesis of reticulatacin and corossoline

More recent efforts in this area have concentrated on the synthesis of new osmium-based reagents for the dihydroxylation reaction so as to avoid the expense and toxicity of osmium tetroxide. Donohoe *et al.* have reported the *syn*-dihydroxylation of alkenes using osmium complex **2.224**.[144] Moderate yields of the diol products have been obtained with high recovery of the osmium complex (scheme 2.47). However, attempts at incorporating **2.224** in a catalytic dihydroxylation cycle have been unsuccessful and Sharpless' dihydroxylation conditions remain unsurpassed.



2.224 **2.225a-b** **2.226a-b**

2.225a: R = Ph ; **2.226a**: 87%, 88% recovered **2.224**
2.225b: R = Pr ; **2.226b**: 91%, 94% recovered **2.224**

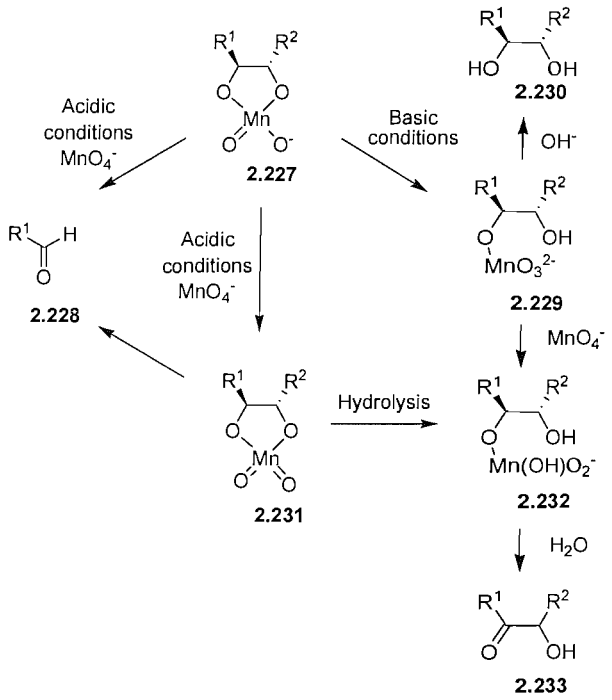
Reagents and conditions: (i) ^{t}BuOOH, CH_2Cl_2; (ii) acetone, H_2O, 60 °C.

Scheme 2.47: Donohoe's approach to the osmium dihydroxylation

2.3.2 Permanganate Mediated Dihydroxylation Reaction

Permanganate has also been shown to effect the *syn*-dihydroxylation of alkenes with both of the oxygen atoms being transferred directly from the MnO_4^- ion.[145] An initial [3+2] cycloaddition between the alkene and permanganate results in manganate ester **2.227**. What happens at this point is highly dependant on the reaction conditions. Under highly basic conditions **2.227** can undergo hydrolysis to Mn(V) intermediate **2.229**

which can be converted to either diol **2.230** or oxidised to Mn(VI) ester **2.232**. Both of these processes occur rapidly but the diol dominates when the hydroxide content is high. Ester **2.232** can rearrange to form hydroxyketone **2.233**. Alternatively under acidic conditions **2.227** can be oxidised to diester **2.231** which can undergo cleavage resulting in aldehyde **2.228** or alternatively hydrolysis affording hydroxyketone **2.233** (scheme 2.48).

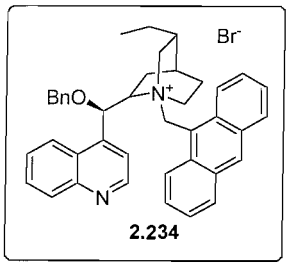


Scheme 2.48: Product of permanganate dihydroxylation under different conditions

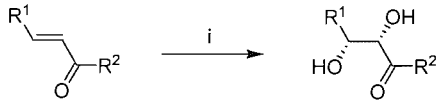
Early examples of the dihydroxylation reaction used aqueous permanganate in polar solvents but yields were often very low. However, the addition of phase transfer catalysts was found to greatly improve these yields. In 1972, Weber showed that benzyltriethylammonium chloride was an effective phase transfer catalyst when it was used in the conversion of cyclooctene to the diol product.[146]

More recently our group has shown that permanganate can be used to achieve the asymmetric dihydroxylation of enones using a chiral phase transfer reagent.[147] Quaternary ammonium salt **2.234** was chosen as the phase transfer reagent as it had previously been used to good effect in the oxidative cyclisation of 1,5-dienes.[148] Initial results found moderate yields and good selectivities were obtained for a number of

alkenes (scheme 2.49). However, a major drawback was the relatively large quantities of **2.234** that were required.



2.234



2.235a-c **2.236a-c**

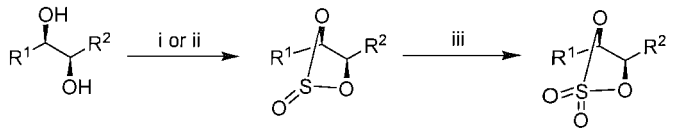
2.235a: $R^1 = {}^n$Bu, $R^2 = p$-BrC_6H_4 ; **2.236a**: 52%, 77%*ee*
2.235b: $R^1 = {}^n$Bu, $R^2 = p$-$OMeC_6H_4$; **2.236b**: 34%, 80%*ee*
2.235c: $R^1 = {}^i$Pr, R^2 = Ph ; **2.236c**: 28%, 67%*ee*

Reagents and conditions: (i) **2.234** (1 eq.), $KMnO_4$ (1.5 eq.), CH_2Cl_2, −60 °C.

Scheme 2.49: Permanganate phase transfer dihydroxylation

2.3.3 Activation of Vicinal Diols as Cyclic Sulphites and Sulphates to Provide Epoxide-like Synthons

Optically active epoxides are important as organic building blocks due to their synthetic versatility. The useful properties of epoxides are shared by cyclic sulphites and sulphates with the latter being more reactive than their epoxide equivalents.[149,150] Cyclic sulphites can be readily prepared from chiral diol precursors obtained from a Sharpless asymmetric dihydroxylation, by reaction with thionyl chloride in the presence of an amine base. Oxidation of the crude sulphite intermediate provides access to the cyclic sulphate (scheme 2.50).



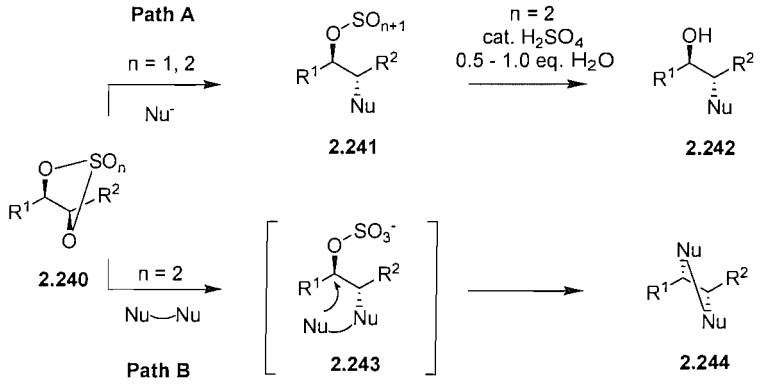
2.237 **2.238** **2.239**

Reagents and conditions: (i) $SOCl_2$, CCl_4, reflux; (ii) $SOCl_2$, NEt_3, CH_2Cl_2, 0 °C; (iii) $NaIO_4$, $RuCl_3$, CCl_4, CH_3CN, H_2O, 0 °C to r.t.

Scheme 2.50: Preparation of cyclic sulphites and sulphates from 1,2-diols

Analogous to epoxides, cyclic sulphites and sulphates can be opened by the nucleophilic attack in either inter- or intramolecular fashion at either carbon centre with inversion of configuration. With cyclic sulphates the product is a sulphate monoester (**2.241**) which can be hydrolysed to the free alcohol under mild acidic conditions (path

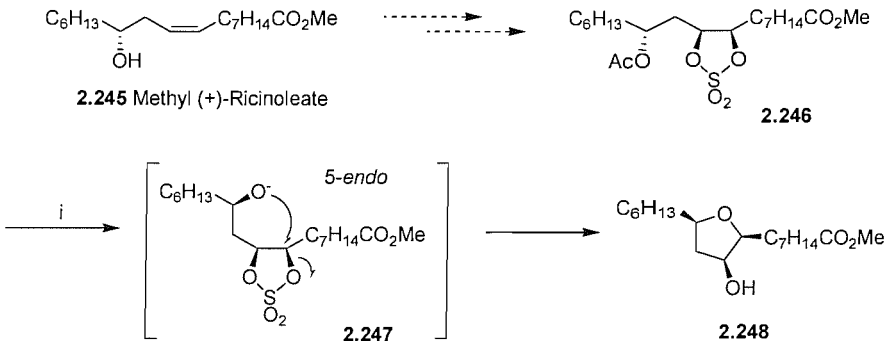
a, scheme 2.51). Alternatively the sulphate can act as a leaving group allowing a second substitution (path b, scheme 2.51).



Scheme 2.51: Nucleophilic opening of cyclic sulphates

Cyclic sulphites react in a similar manner but the additional hydrolysis step is not required. However, in contrast to cyclic sulphates, cyclic sulphites are kinetically labile at the sulphur centre which can lead to unwanted side reactions. In addition the carbon centre is less reactive than in cyclic sulphates, which often results in the need for more powerful nucleophiles.[151]

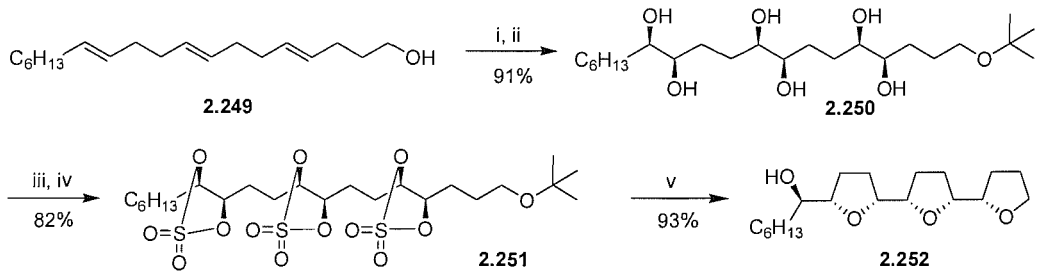
The intramolecular nucleophilic opening of hydroxy cyclic sulphates has been reported as a method of preparing optically active THF fragments.[135,150] Sharpless *et al.* have reported the synthesis of mono-THF **2.248** using a combination of an asymmetric dihydroxylation and cyclic sulphate formation. Starting from methyl (+)-ricinoleate **2.245**, the THF ring was inserted by a 5-*endo* nucleophilic opening of the hydroxy cyclic sulphate formed *in situ* by saponification of the acetate (scheme 2.52).[152]



Reagents and conditions: (i) NaOEt, EtOH, r.t.

Scheme 2.52: THF ring formation from cyclic sulphate opening

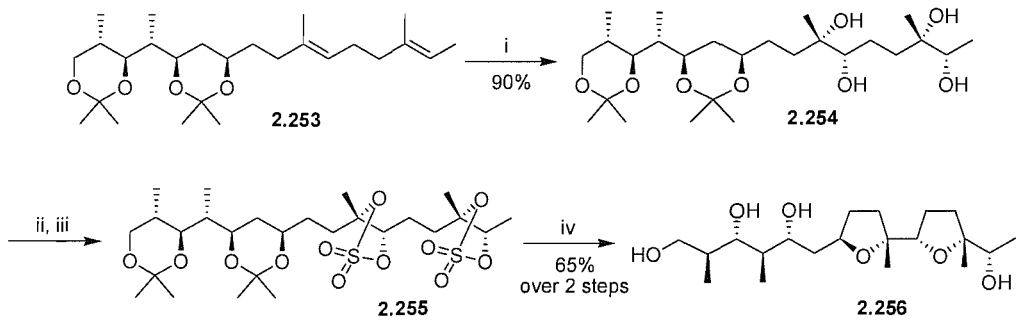
Rychnovsky and co-workers have reported examples of the formation of poly-THF products resulting from the cascade cyclisations of cyclic sulphates derived from optically pure polyols.[153] Triene **2.249** was subjected to Sharpless asymmetric dihydroxylation conditions affording hexol **2.250** as a single isomer (scheme 2.53). Conversion to *tris*-THF **2.252** proceeded *via* the poly-cyclisation of *tris*-sulphate **2.251**, with the sulphate ester formed from each cyclisation presumably hydrolysed under the reaction conditions.



Reagents and conditions: (i) Isobutylene, amberlyst-15; (ii) AD- mix β; (iii) $SOIm_2$, THF; (iv) $RuCl_3$, $NaIO_4$; (v) MeCN, H_2O, reflux.

Scheme 2.53: Cascade opening of cyclic sulphates

Rychnovsky has applied these findings to the synthesis of the C_{17}-C_{32} fragment of ionomycin.[153] Diene **2.253** was converted to tetraol **2.254** by an asymmetric dihydroxylation reaction. *Bis*-cyclic sulphate formation followed by cyclisation furnished the required *bis*-THF fragment **2.256** (scheme 2.54).



Reagents and conditions: (i) AD-mix α; (ii) $SOCl_2$, NEt_3; (iii) $RuCl_3$, $NaIO_4$; (iv) MeCN, H_2O, reflux.

Scheme 2.54: *Bis*-THF formation from cyclic sulphates

2.3.4 Halohydrin Esters as a Route to Epoxides

Chiral 1,2-diols can be converted to the corresponding epoxides with overall retention of configuration *via* the formation of halohydrin esters (figure 2.5). The halohydrin intermediate is formed on the 1,2-diol with inversion of configuration and subsequent base-mediated cyclisation to form the epoxide also proceeds with inversion, leading to overall retention. The advantage of this strategy is that the regioselectivity of the halohydrin formation is trivial as both regioisomers form the same epoxide upon cyclisation.

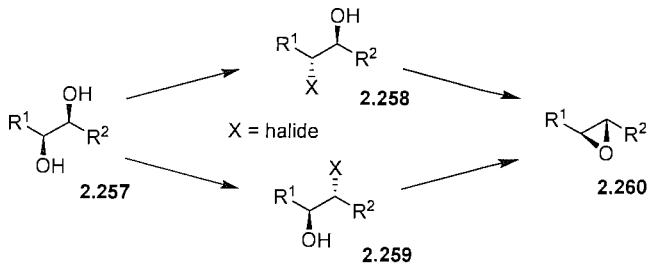
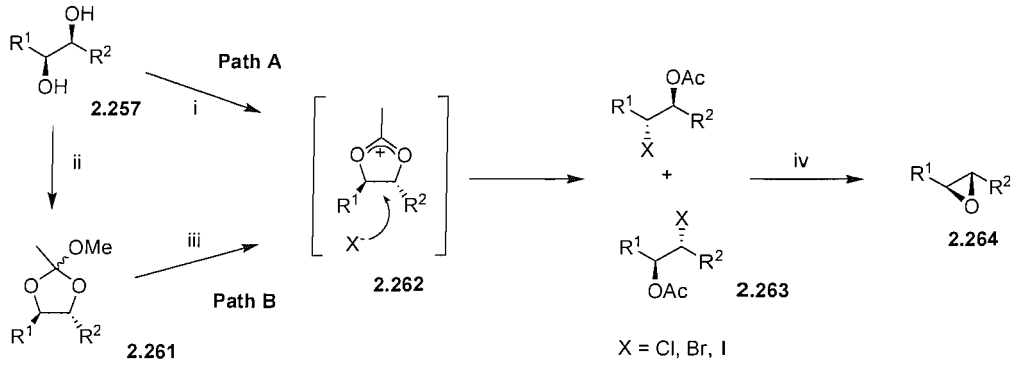


Figure 2.5: Conversion of 1,2-diols into epoxides through halohydrin esters

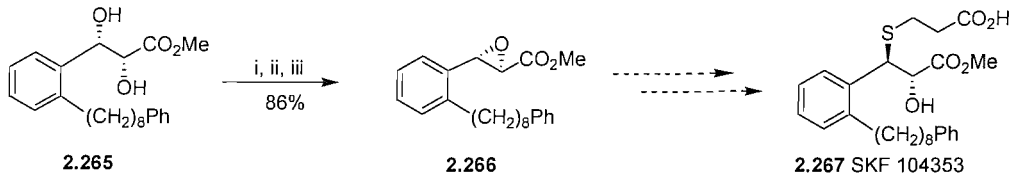
A large variety of reagents and conditions have been reported in the literature for the conversion of 1,2-diols into these halohydrin esters and they all depend on the nucleophilic opening of a 1,3-dioxolan-2-ylium cation intermediate (**2.262**, scheme 2.55). In 1958, Baganz and Domaschke reported the formation of halohydrin formates, obtained from the treatment of cyclic orthoformates with neat acetyl bromide or chloride under refluxing conditions.[154] Newman later showed that the same transformation could be achieved by treatment with neat trityl chloride[155] or trimethylsilyl chloride.[156]



Reagents and conditions: (i) HBr, AcOH; (ii) $MeC(OMe)_3$, *p*-TsOH; (iii) AcX or Me_3SiX; (iv) base, MeOH.

Scheme 2.55: Halohydrin ester formation

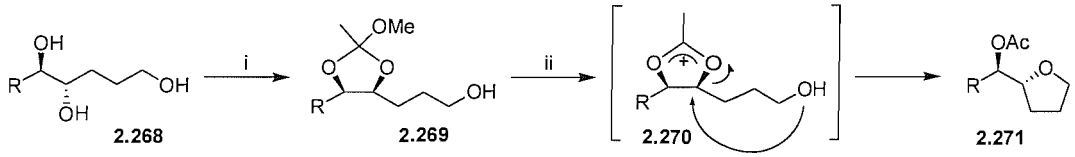
Further investigations carried out by Kolb *et al.* found that the formation of the ortho ester intermediate, subsequent opening and base-catalysed cyclisation to the epoxide could be carried out as a "one-pot" procedure.[157] The work-up between the steps was simple evaporation of the volatiles before re-dissolving in the appropriate solvent for the next stage. All of the reagents used were cheap and readily available. This simplified procedure has been shown to tolerate a wide range of functionality and has been applied in the synthesis of the leukotriene antagonist SKF 104353 (**2.267**, scheme 2.56).



Reagents and conditions: (i) $MeC(OMe)_3$, *p*-TsOH, r.t.; (ii) Me_3SiCl, r.t. to 40 °C; (iii) K_2CO_3, MeOH, −17 °C.

Scheme 2.56: Halohydrin esters in synthesis

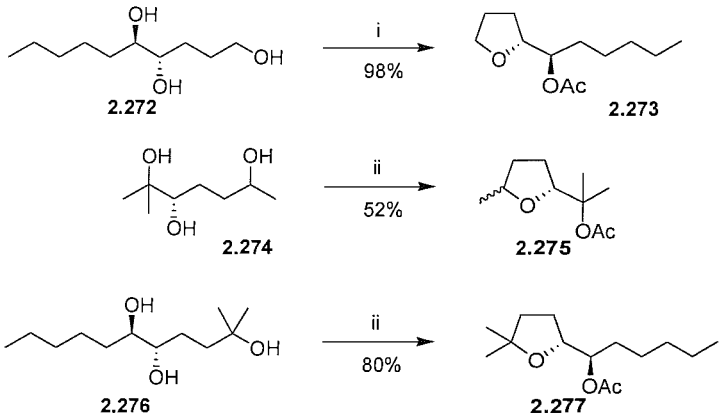
More recent work in this area by Zheng *et al.*[158] has resulted in the development of a one-pot method to access cyclic ethers from 1,2,*n*-triols by the generation of a cyclic ortho ester intermediate **2.269** (scheme 2.57). Ionisation of **2.269** with a Lewis acid results in a reactive acetoxonium species **2.270** which can form the cyclised ether after an intramolecular nucleophilic displacement with the pendant hydroxyl. A range of Lewis acids have been screened, with $BF_3{\cdot}OEt_2$ found to be the most effective.



Reagents and conditions: (i) $MeC(OMe)_3$, *p*-TsOH, CH_2Cl_2, r.t.; (ii) Lewis acid.

Scheme 2.57: THF formation from ortho ester intermediates

Primary, secondary and tertiary hydroxyls have all been found to carry out the intramolecular displacement, resulting in cyclic ethers in good yields (scheme 2.58). This work is however, a relatively recent discovery and has not been applied in synthesis thus far.



Reagents and conditions: (i) $MeC(OMe)_3$, $BF_3{\cdot}OEt_2$, CH_2Cl_2; (ii) $MeC(OMe)_3$, *p*-TsOH, CH_2Cl_2.

Scheme 2.58: THF formation from ortho ester intermediates

2.4 Conclusions

Due to the increasing abundance of tetrahydrofuran rings in biologically active natural products, different routes to their synthesis have become more desirable. This chapter has summarised a range of methods to achieve the THF ring formation starting from alkenes or hydroxyalkenes.

Chapter Three

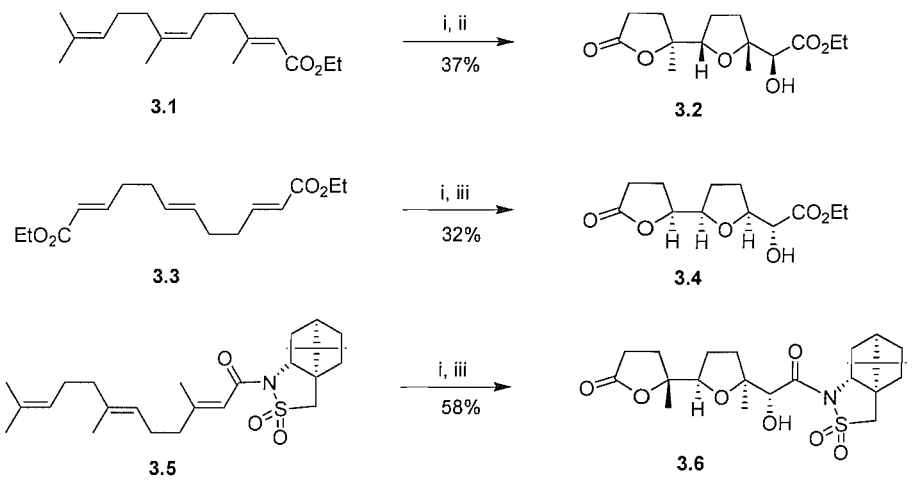
The Southampton Approach to the *Annonaceous* Acetogenins

The previous chapters summarised recent approaches to the synthesis of *Annonaceous* acetogenins in addition to general methods for the construction of 2,5-disubstituted tetrahydrofuran units. The following chapter will review work undertaken within our group which was carried out prior to the research described in this thesis.

3.1 The Potassium Permanganate Mediated Oxidative Cyclisation of Polyenes

Early investigations within the group concentrated on the stereoselective synthesis of tetrahydrofuran containing building blocks by a potassium permanganate mediated oxidative cyclisation of 1,5,9-trienes. This approach was attractive due to the low cost of potassium permanganate and the low toxicity of the reaction co-product, MnO_2, in comparison with other reagents capable of effecting the transformation.

Initial work concentrated on the oxidative cyclisation of 1,5,9-trienes such as **3.1** and **3.3**, with a two step process providing access to THF-lactone products **3.2** and **3.4** (scheme 3.1).[159,160] An enantioselective version of the cyclisation was achieved by the introduction of the camphorsultam chiral auxiliary to the triene skeleton.[79] Oxidative cyclisation of triene **3.5** proceeded with high diastereoselectivity, yielding the THF-lactone product **3.6** in moderate yield.



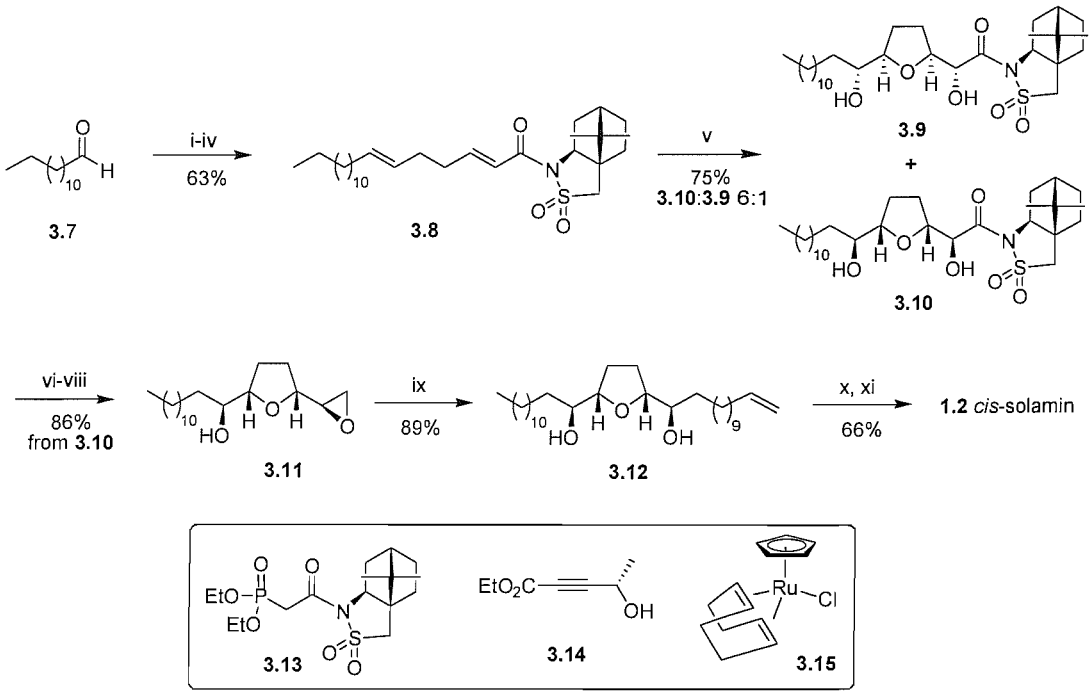
Reagents and conditions: (i) $KMnO_4$, AcOH, phosphate buffer, acetone; (ii) $Pb(OAc)_4$, CH_2Cl_2, Na_2CO_3; (iii) $NaIO_4$, acetone, H_2O.

Scheme 3.1: Potassium permanganate oxidation of 1,5,9-trienes

3.2 Application of the Oxidative Cyclisation to *Annonaceous* Acetogenin Synthesis

The methodology established within the group was then applied to the synthesis of acetogenin natural products. The first target of interest was *cis*-solamin (**1.2**), an example of a mono-THF acetogenin.

Starting from commercially available aldehyde **3.7** diene **3.8**, required for the key cyclisation step, was prepared in four steps (scheme 3.2). The camphorsultam chiral auxiliary was incorporated into the structure through a Horner-Wadsworth-Emmons type olefination using phosphonate **3.13** already containing the auxiliary. Optimisation of the cyclisation conditions using potassium permanganate (1.3 eq.) in an acetone / acetic acid solvent mixture resulted in good yields and a diastereomeric ratio of 6:1 in favour of the desired isomer **3.10**. Removal of the chiral auxiliary, formation of the primary tosylate and subsequent treatment with base afforded epoxide **3.11**. Opening of the epoxide *via* a copper catalysed Grignard reaction furnished terminal alkene **3.12** which allowed the introduction of the butenolide fragment by Trost's Alder-ene reaction. Reduction by diimide afforded *cis*-solamin **1.2** in eleven steps overall.[88,161]



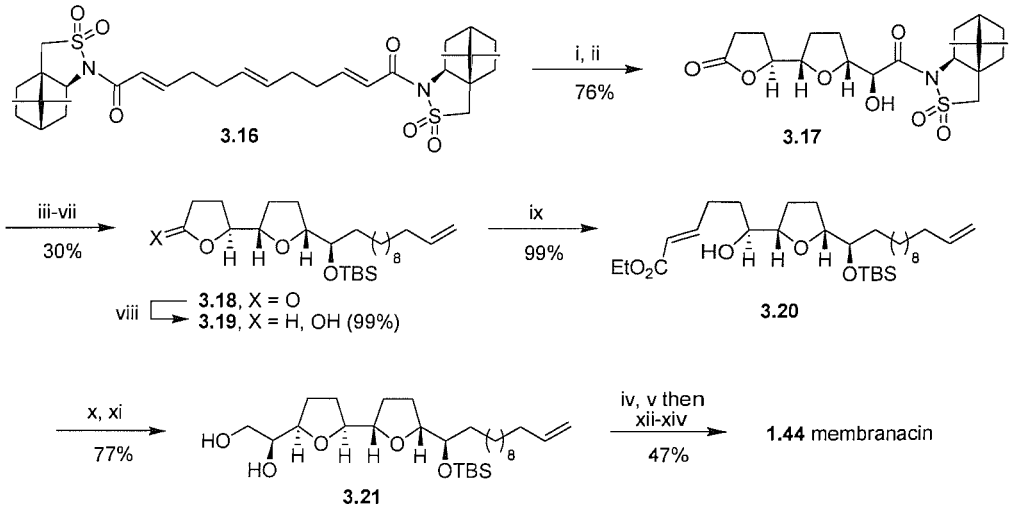
Reagents and conditions: (i) CH_2=CHMgBr, THF; (ii) $MeC(OEt)_3$, xylene, reflux; (iii) DIBAL-H, toluene, –60 °C; (iv) **3.13**, NaH, 0 °C to r.t.; (v) $KMnO_4$, acetone : AcOH (3:2); (vi) $NaBH_4$, THF, H_2O; (vii) Bu_2SnO, benzene then TsCl, TBAB; (viii) DBU, CH_2Cl_2; (ix) CH_2=$CH(CH_2)_9MgBr$, CuI, THF, –60 to –20 °C; (x) **3.14**, **3.15**, MeOH, reflux; (xi) $TsNHNH_2$, NaOAc, THF, H_2O, 60 °C.

Scheme 3.2: Synthesis of *cis*-solamin

Contemporaneously, other group members were investigating the incorporation of the permanganate oxidative cyclisation into the synthesis of adjacent *bis*-THF acetogenins. The strategy of this work was based on the synthesis of versatile THF-lactone intermediates such as **3.6** from triene precursors, which could be elaborated to several acetogenin natural products. Membranacin **1.44** was chosen as a target to assess this strategy.

The required triene starting material **3.16** was prepared using previously established procedures. Permanganate oxidation followed by periodate cleavage afforded the desired THF-lactone product **3.17** as a single isolated diastereoisomer in high yield (scheme 3.3). Reduction of the chiral auxiliary followed by conversion to the epoxide allowed the copper catalysed insertion of the terminal alkene side chain. The lactone ring was then reduced to the corresponding lactol which underwent *trans* selective

olefination producing ester **3.20**. Reduction to the allylic alcohol allowed a Sharpless asymmetric epoxidation and *in situ* ring closure to provide the *bis*-THF core **3.21**. Repeating the earlier steps for the cuprate addition allowed a second side chain to be installed. The butenolide fragment was introduced following the same procedures used in the synthesis of *cis*-solamin, completing the synthesis of membranacin **1.44**.[40]



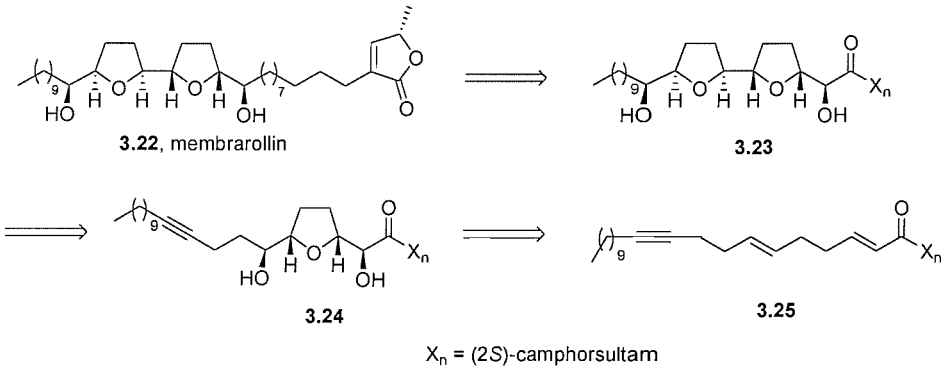
Reagents and conditions: (i) $KMnO_4$ (2.6 eq.), adogen-464 (5 mol%), acetone : AcOH (3:2); (ii) $NaIO_4$, SiO_2, CH_2Cl_2; (iii) $BH_3{\cdot}SMe_2$, $NaBH_4$, THF then CH_2Cl_2, MeOH; (iv) Bu_2SnO, TsCl, TBAB, benzene; (v) DBU, CH_2Cl_2; (vi) undec-10-yl-MgBr, CuI, THF, −50 °C; (vii) TBSCl, imidazole; (viii) DIBAL-H, THF; (ix) $Ph_3P{=}CHCO_2Et$, toluene; (x) DIBAL-H, THF; (xi) L-(+)-DET, $Ti(O^iPr)_4$, ^{t}BuOOH, 4 Å sieves, CH_2Cl_2; (xii) $CH_3(CH_2)_8MgBr$, CuI, THF; (xiii) **3.14**, **3.15**, MeOH, reflux; (xiv) $TsNHNH_2$, NaOAc, THF, H_2O, reflux.

Scheme 3.3: Synthesis of membranacin

3.3 Introduction to the Proposed Work

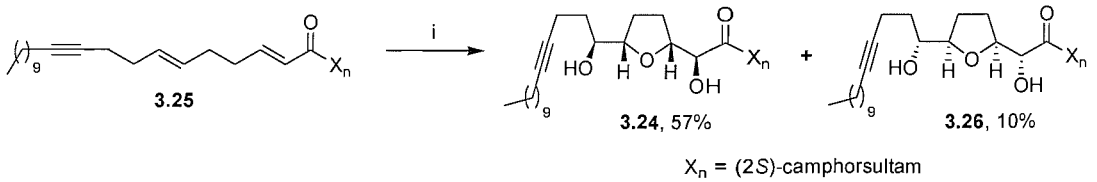
An alternative approach to the synthesis of adjacent *bis*-THF acetogenins was also investigated based on two sequential oxidative cyclisations. Membrarollin **3.22** was isolated from the seeds of *Rollinia membranacea* and is a member of the small family of adjacent *bis*-THF acetogenins with a *threo*, *cis*, *threo*, *cis*, *erythro* relative configuration about the *bis*-THF core.[162] Membrarollin was found to be a very potent inhibitor of NADH oxidase activity with IC_{50} values < 0.3 nM and was therefore chosen as the target for this strategy.

Retrosynthetic analysis of the target suggested that mono-THF **3.24**, obtained from a permanganate oxidative cyclisation of dienyne **3.25**, could be elaborated to the *bis*-THF **3.23** by partial reduction followed by a second directed oxidative cyclisation (scheme 3.4). The stereochemistry of the second THF ring could then in theory be controlled through the choice of metal-oxo or peroxo mediated cyclisation and the alkene geometry.



Scheme 3.4: Retrosynthetic analysis of the target molecule

Dienyne **3.25** was prepared from a commercially available alkyne following previously established procedures. The permanganate oxidative cyclisation was found to proceed selectively, furnishing the mono-THF product **3.24** in moderate yield (*d.r.* 6:1 from NMR of crude reaction mixture). Most importantly, products arising from the oxidation of the alkyne were not evident (scheme 3.5).



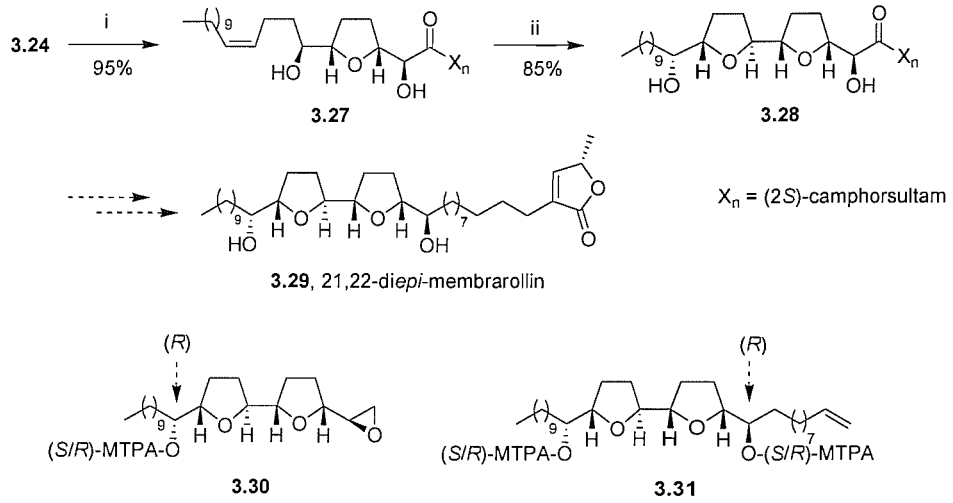
Reagents and conditions: (i) $KMnO_4$, acetone : AcOH (1:1).

Scheme 3.5: Oxidative cyclisation of a 1,5,9-dienyne

At this point attention turned to the construction of the second THF ring. Research carried out by Sinha and co-workers had shown that both *cis* and *trans* THF rings could be constructed from hydroxy alkene precursors using a rhenium oxide species and they proposed a set of rules to predict the stereochemical outcome (see section 2.1.4).[103,104] The vicinal oxygen functions in **3.24** have a *threo* relationship and so according to the rules set out by Sinha, a rhenium oxide cyclisation would produce a *cis* THF ring. This would insert the required stereochemical arrangement for the second ring of

membrarollin, with the relative stereochemistry of the final hydroxyl group being determined by the alkene geometry.

Semi-hydrogenation and subsequent acyl perrhenate promoted oxidative cyclisation reactions converted mono-THF **3.24** to *bis*-THF **3.28** where the second THF ring was suggested to have *trans* configuration of the two substituents (scheme 3.6). The stereochemistry of the *bis*-THF unit was assigned from the ^{1}H NMR spectra of the (*R*) and (*S*)-Mosher ester derivatives **3.30** and **3.31**. The same series of steps used previously within the group were applied to *bis*-THF **3.28**, completing the synthesis of 21,22-di*epi*-membrarollin **3.29**.[163]



Reagents and conditions: (i) H_2, Pd / $BaSO_4$, quinoline, hexane; (ii) Re_2O_7, TFAA, THF.

Scheme 3.6: Completion of the synthesis of 21,22-di*epi*-membrarollin

As the formation of the unexpected *trans* THF ring from the rhenium oxide cyclisation was in contradiction to the rules set out by Sinha and co-workers proof of this result was required. Therefore the first objective of this project was to acquire a crystal structure of a *bis*-THF product thereby obtaining unambiguous proof of the *trans*-THF. It was anticipated that this would be achieved by the preparation of a short chain model *bis*-THF compound following the same route as for 21,22-di*epi*-membrarollin **3.29**. Next we planned to investigate the stereochemical outcome of alternative cyclisation methods, with a view to obtaining the required absolute stereochemistry for membrarollin **3.22**. The final aim of the project was to complete the total synthesis of membrarollin **3.22**.

3.4 Conclusions

Previous work within the group has resulted in the selective synthesis of both mono and adjacent *bis*-THF acetogenins and acetogenin analogues. The following chapters will describe the research carried out to discover alternative, more efficient routes to adjacent *bis*-THF acetogenins.

Chapter Four

Synthesis of the Model Adjacent *bis*-THF Compound

The following chapter describes the synthesis of a model adjacent *bis*-THF compound prepared by two selective oxidative cyclisation reactions using potassium permanganate and rhenium heptoxide. A discussion of the resulting stereochemistry is included.

4.1 Our Initial Route to a Model Adjacent *bis*-THF System

The proposed work required the preparation of a simple, short chained 1,5,9-dienynoate substrate which could undergo oxidative cyclisation reactions with both potassium permanganate and rhenium heptoxide to afford the required adjacent *bis*-THF compound **4.2** (figure 4.1). The model 1,5,9-dienynoate **4.1** was anticipated to be prepared by methodology used previously within the Brown group (see section 3.3).

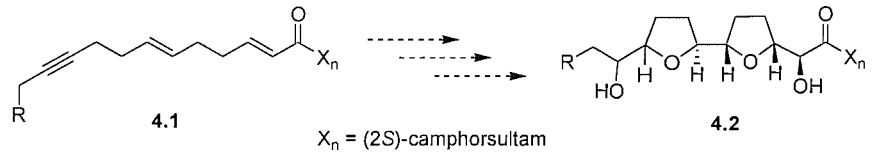
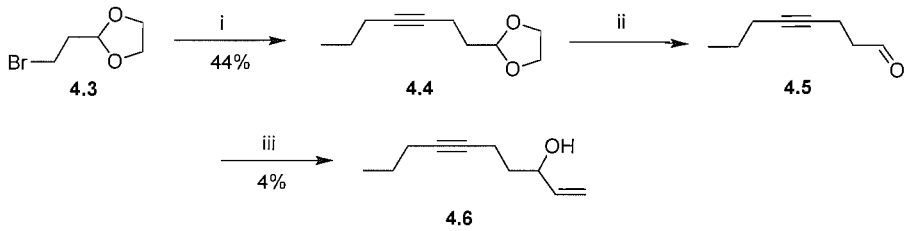


Figure 4.1: Proposed direction to the *bis*-THF model compound

Pent-1-yne was found to be a cheap, readily available starting material and was converted to acetal **4.4** by reaction with commercial alkyl bromide **4.3** (scheme 4.1). Although the unreacted alkyl bromide **4.3** was found to be inseparable from the acetal product (**4.4**), both by chromatography and distillation, this problem was overcome by using 0.98 eq. of **4.3**, to afford the required acetal **4.4** in a moderate 44% yield. It was then hoped that **4.4** would undergo a straightforward deprotection to its corresponding aldehyde **4.5**, but this reaction proved to be more difficult than originally anticipated.



Reagents and conditions: (i) Pent-1-yne, *n*-BuLi, DMPU, THF, −78 °C to r.t.; (ii) CAN (2.5 eq.), MeCN, H_2O, 70 °C; (iii) CH_2=CHMgBr, Et_2O, −40 °C.

Scheme 4.1: Synthesis of alcohol **4.6**

The use of both stoichiometric and catalytic CAN have been reported as efficient methods of removing both acetal and ketal protecting groups.[164] Firstly, following the method of Marko *et al.*,[165] acetal **4.4** was dissolved in a degassed mixture of acetonitrile and borate buffer (Merck, pH 8) before being treated with 3-4 mol% CAN. The mixture was heated to 70 °C and monitored by GC over several hours but was found never to reach completion.

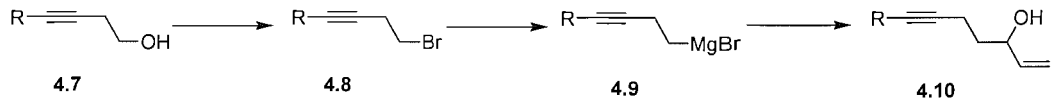
The use of stoichiometric quantities of CAN was then investigated by following the method of Ates *et al.*[166] A solution of acetal **4.4** in acetonitrile was pre-heated to 70 °C before treatment with 2.5 eq. CAN in water. The initial orange solution turned to pale yellow over 5 minutes, at which point the reaction was stopped. Crude ^{1}H NMR showed the desired product (loss of CH peak at δ 4.98 ppm and appearance of the aldehydic CH at δ 9.72 ppm) but the resulting aldehyde was found to be extremely volatile. Therefore when the reaction was repeated, the crude material was used directly in the subsequent Grignard addition to afford alcohol **4.6** in a poor 4% yield over the two steps (scheme 4.1). Attempts to improve the yield by trying different solvents (ether or THF) and the reverse addition of the crude aldehyde to the Grignard reagent proved unsuccessful.

Considering that the acetal deprotection was thought to be the problematic step in the sequence, more classical acid deprotection conditions were investigated. Treatment of **4.4** with 5% HCl in a 1:1 acetone / water mixture following the method of Carballeira *et al.*[167] was found to give incomplete deprotection. Harsher conditions were applied by repeating the experiment with a 1:1 mix of 2 M HCl / acetone, and although crude

NMR showed complete conversion for this reaction, the addition of the Grignard reagent did not produce a significant yield of alcohol **4.6**.

4.2 Alternative Approaches to the Alcohol

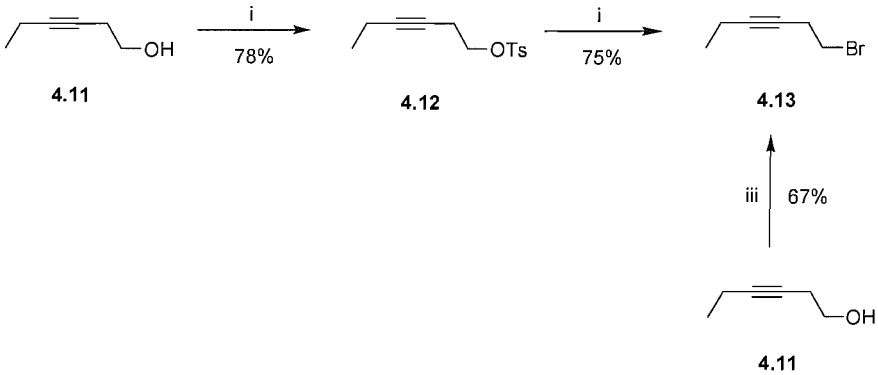
Due to the problems experienced with the acetal deprotection described above, alternative routes to the alcohol were explored. The first approach considered was to prepare bromide **4.8**, which upon conversion to the corresponding Grignard could then react with acrolein to afford alcohol **4.10** (scheme 4.2).



4.7 **4.8** **4.9** **4.10**

Scheme 4.2 Proposed alternative route to the desired alcohol

Thus in applying this new approach to the model system, commercially available 3-hexyn-1-ol (**4.11**) was converted to bromide **4.13**. This was achieved first by activating the alcohol into its tosylate,[168] which then underwent nucleophilic displacement with LiBr providing **4.13** in 59% over two steps (scheme 4.3).[169] Alternatively, **4.13** could be prepared directly from the alcohol following the methods of Zoretic and Khanapure in an improved 67% yield.[170,171]



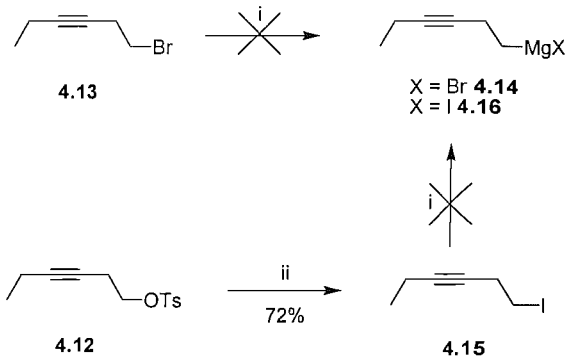
4.11 **4.12** **4.13** **4.11**

Reagents and conditions: (i) TsCl, NEt_3, CH_2Cl_2, 0 °C to r.t.; (ii) LiBr, acetone, reflux; (iii) PPh_3, CBr_4, CH_2Cl_2, 0 °C to r.t.

Scheme 4.3: Preparation of bromide **4.13**

Attempts at converting bromide **4.13** into the Grignard reagent **4.14** using both I_2 and TMSCl to activate the magnesium were unsuccessful (scheme 4.4). Formation of the

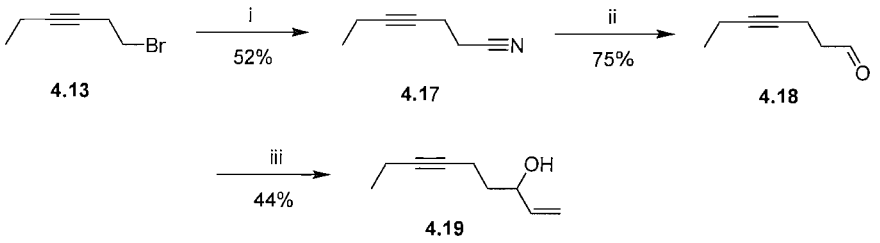
equivalent Grignard **4.16** from the more reactive iodide **4.15** was also attempted, but again resulted in failure. In both cases the starting material decomposed.



Reagents and conditions: (i) Mg turnings, I_2 or TMSCl, THF, reflux; (ii) LiI, acetone, reflux.

Scheme 4.4: Attempts at the formation of a Grignard reagent

A different strategy to the alcohol had to be considered. Inspired by similar work undertaken by Mori *et al.*,[172] bromide **4.13** was converted to nitrile **4.17**, reduced to its corresponding aldehyde **4.18**,[173] and lastly reacted with vinylmagnesium bromide to provide alcohol **4.19** in a moderate 44% yield (scheme 4.5).



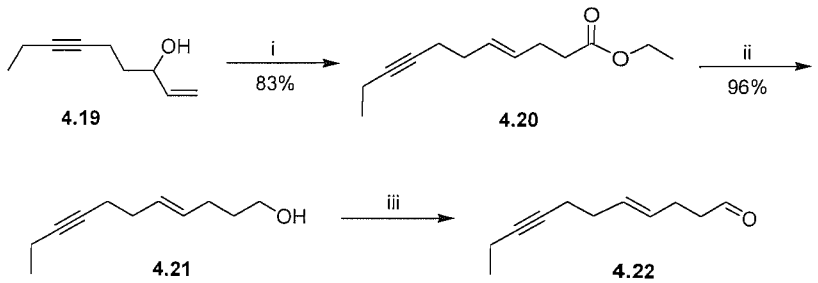
Reagents and conditions: (i) NaCN, DMF, 0 °C to r.t.; (ii) DIBAL-H, CH_2Cl_2, −78 to −60 °C; (iii) CH_2=CHMgBr, Et_2O, −50 °C.

Scheme 4.5: Improved synthesis of alcohol **4.19**

4.3 Elaboration of Alcohol 4.19

With alcohol **4.19** in hand, the preparation of the model compound could now proceed *via* the proposed route. **4.19** was converted to ester **4.20** in 83% yield *via* a Claisen-Johnson rearrangement, following the method of Avedissian *et al.* (scheme 4.6).[105] This is an example of a [3,3]-sigmatropic rearrangement and results in the exclusive introduction of a *trans*-1,2-disubstituted double bond due to the alkyl chain adopting a favoured equatorial position in the chair-like transition state.

Ester **4.20** was reduced to alcohol **4.21**, which then required oxidation to the corresponding aldehyde **4.22** in preparation for a Horner-Wadsworth-Emmons type olefination to insert the second *trans* double bond (scheme 4.6). Several different oxidation conditions were employed and the results are summarised in table 4.1.



Reagents and conditions: (i) $MeC(OEt)_3$, propionic acid, reflux; (ii) $LiAlH_4$, THF, −30 °C to r.t.; (iii) for conditions see table 4.1.

Scheme 4.6: Preparation of aldehyde **4.22**

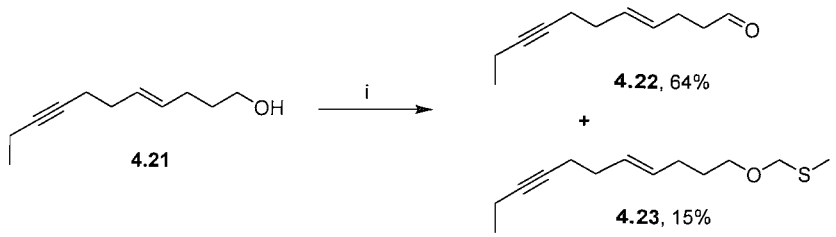
Table 4.1: Conditions explored for the oxidation of alcohol **4.21**

Entry	Reagents	Solvent	Temperature	Isolated Yield
1	TPAP, NMO[174]	CH_2Cl_2	r.t.	54%
2	PCC	CH_2Cl_2	r.t.	0%[a]
3	NaOCl, TEMPO, NaBr[175]	CH_2Cl_2, H_2O	0 °C	0%[a]
4	$(COCl)_2$, NEt_3[176]	DMSO	−78 to −60 °C	60%
5	SO_3·pyridine complex	DMSO	r.t.	64%[b]
6	DMP	CH_2Cl_2	0 °C to r.t.	94%

[a] Decomposition of the starting material was observed; [b] Additional 15% yield of by-product **4.23**.

A variety of classical and non-classical conditions were employed to oxidise alcohol **4.21** with a simple Dess-Martin oxidation[177-179] (entry 6) providing the most promising reaction conditions for future scale-up. Indeed the excellent yield of 94% proved to be reproducible on a large scale. It is worth mentioning that before these conditions were found, the best yield had been obtained with a modification of the Swern oxidation using sulphur trioxide-pyridine complex (entry 5).[180] On a small scale the product was obtained in a satisfactory 64% yield with a 15% yield of by-product **4.23** (scheme 4.7). However, upon scale-up (from mg to g scale) the yield of this reaction decreased to a

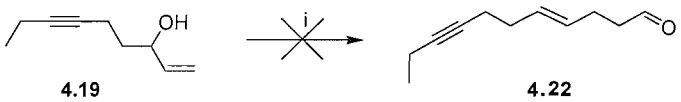
disappointing 46%, thus justifying the use of the Dess-Martin procedure as an efficient route to the aldehyde.



Reagents and conditions: (i) SO_3·pyridine complex, DMSO, r.t.

Scheme 4.7: SO_3·pyridine oxidation of alcohol **4.21**

Another reaction worthy of note is the attempted direct conversion of allylic alcohol **4.19** to obtain aldehyde **4.22** in one step (scheme 4.8). It has been reported in the literature that such aldehydes could be prepared directly from their allylic alcohol precursor, generating the *trans* double bond in the required position and thus reducing the total number of steps required.[181] However when the method of Zhang *et al.*[182] was followed, crude ^{1}H NMR analysis showed no evidence of the aldehyde within the complex mixture of products.



Reagents and conditions: (i) $Hg(OAc)_2$, butyl vinyl ether, 95 °C.

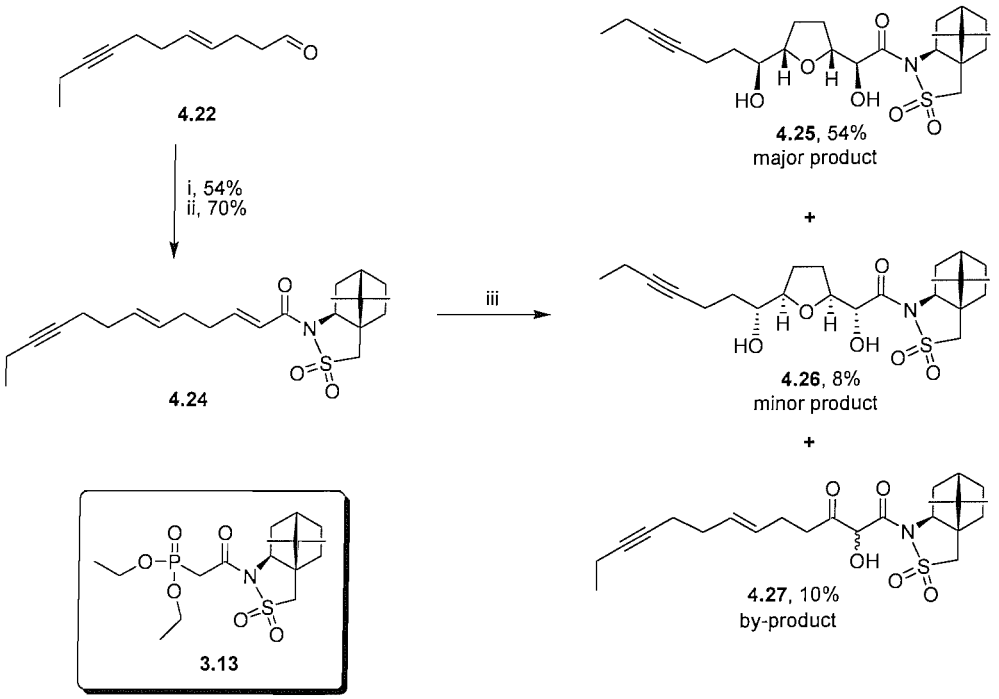
Scheme 4.8: Attempted direct conversion of alcohol **4.19** to **4.22**

4.4 Synthesis and Oxidative Cyclisation of the 1,5,9-Dienyne

The second *trans* double bond was introduced into the system by a Horner-Wadsworth-Emmons type olefination on aldehyde **4.22**. Oppolzer's sultam chiral auxiliary, required for the asymmetric induction in the ensuing cyclisation reaction (see section 2.1.1), was also incorporated at this point. This was achieved through the preparation of phosphonate reagent **3.13** from commercially available (2*R*)-camphorsulphonic acid following the methods of Bartlett, Towson and Oppolzer.[183-186]

Slow addition of aldehyde **4.22** to a stirred solution of deprotonated phosphonate **3.13** afforded dienyne **4.24** in a moderate 54% yield (98:2 *trans*:*cis*, scheme 4.9). The low

yield was believed to be due to a lack of solubility of NaH in CH_2Cl_2 and so the solvent was changed to THF, resulting in a much improved 70% yield, albeit with a slightly diminished *trans* selectivity (12:1 *trans*:*cis*).

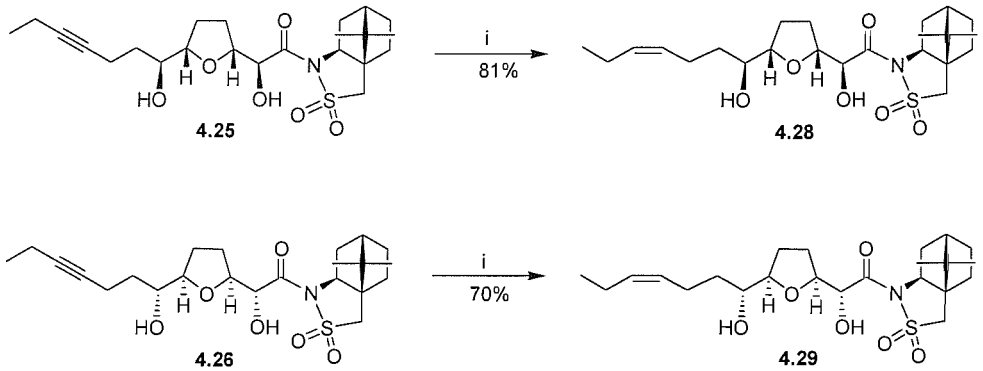


Reagents and conditions: (i) **3.13**, NaH, CH_2Cl_2, r.t.; (ii) **3.13**, NaH, THF, r.t.; (iii) $KMnO_4$, acetone, AcOH, −30 to −20 °C.

Scheme 4.9: 1,5,9-Dienyne synthesis and oxidative cyclisation

Dienyne **4.24** was treated with $KMnO_4$ under conditions previously optimised within the group for the oxidative cyclisation; thus **4.24** was dissolved in a 3:2 mixture of acetone : AcOH and once cooled to −30 °C, 1.3 eq. $KMnO_4$ was added. This afforded three products including the major and minor mono-THF diastereoisomers **4.25** and **4.26** obtained from attack of permanganate from either the α- or β-faces of the enoyl double bond. Analysis of the crude NMR spectrum showed a 6:1 ratio of major : minor isomers, which was further confirmed by the isolated yields of 54% and 8% respectively. The third product obtained from the reaction was the hydroxyketone by-product **4.27**, formed from oxidation of the most electron deficient double bond without cyclisation. There were no identified products arising from the oxidation of the alkyne moiety.

The alkyne in both the major and minor diastereoisomers **4.25** and **4.26** was further elaborated to the corresponding *cis* alkene by semi-hydrogenation, affording mono-THFs **4.28** and **4.29** (scheme 4.10).

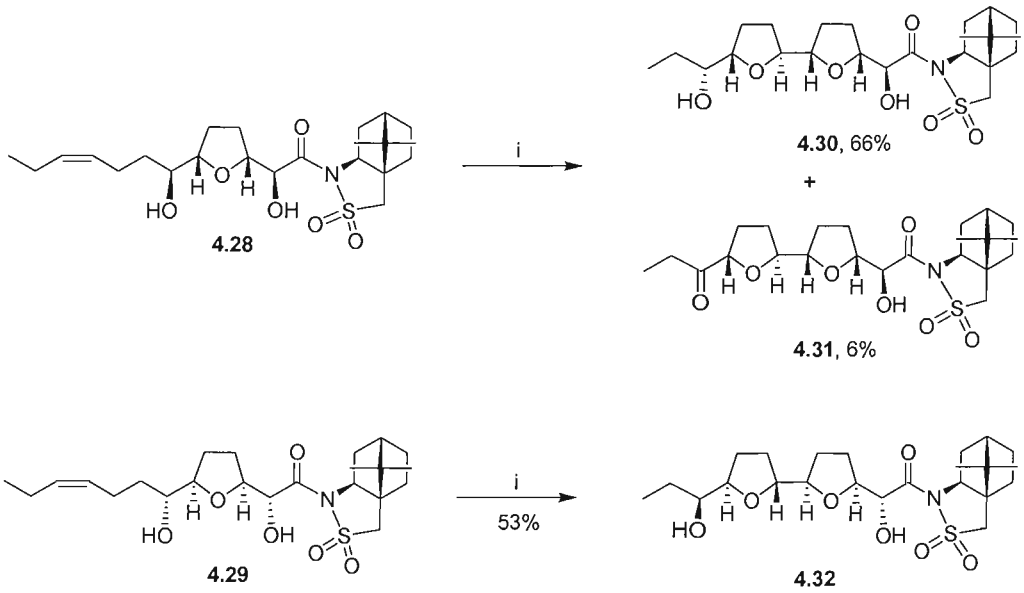


Reagents and conditions: (i) H_2, Pd / $CaCO_3$, quinoline, EtOAc, r.t.

Scheme 4.10: Semi-hydrogenation of the mono-THF products

4.5 Formation of the Target Adjacent *bis*-THF Model Compound

Mono-THF alkene **4.28** underwent an acyl-perrhenate promoted hydroxyl-directed oxidative cyclisation following the method of D'Souza *et al.*[70] and Sinha *et al.*[67] to afford the single diastereomeric *bis*-THF **4.30** in a respectable yield (scheme 4.11). A small amount of the over-oxidised by-product **4.31** was also obtained. *Bis*-THF **4.30** was expected to have the absolute stereochemistry shown based on the predictions of the Mosher's ester work previously carried out within the group.[163] It was hoped that a crystal structure of **4.30** would unambiguously prove the absolute stereochemistry but unfortunately **4.30** did not form crystals suitable for X-ray diffraction.



Reagents and conditions: (i) Re_2O_7, TFAA, THF, hexane, CH_2Cl_2, r.t.

Scheme 4.11: Insertion of the adjacent *bis*-THF core

Unable to prove the stereochemistry of *bis*-THF **4.30**, our attention then turned to indirectly extracting this stereochemical information from the original minor isomer **4.26**, obtained from the permanganate oxidative cyclisation (scheme 4.9). After reducing this diastereoisomer to the *cis* alkene (**4.29**, scheme 4.10) and subjecting this compound to the same cyclisation with rhenium heptoxide, *bis*-THF **4.32** was isolated (scheme 4.11). Although the yield for **4.32** was only a moderate 53%, to our delight this compound was a crystalline solid. This was then used to generate a crystal structure (figure 4.2) which clearly shows the *cis*-THF ring formed from the permanganate cyclisation, and more importantly the *trans*-THF ring formed from the acyl-perrhenate cyclisation.

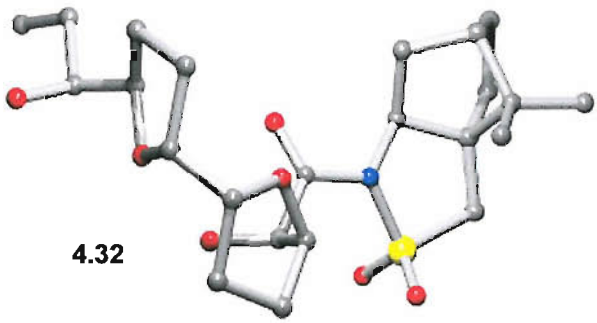
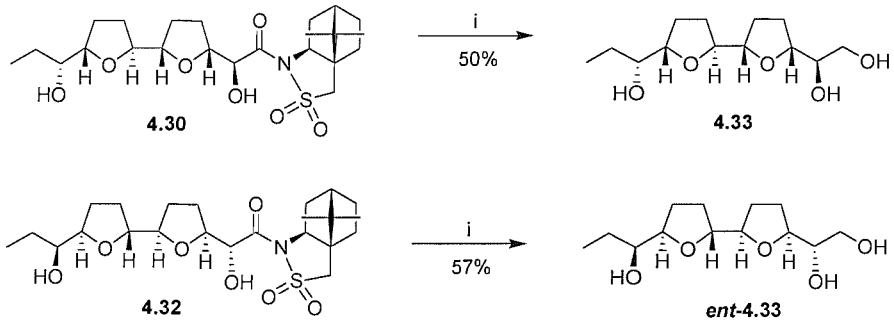


Figure 4.2: Crystal structure of adjacent *bis*-THF compound **4.32**

Aware that the crystal structure was generated from the minor isomer of the permanganate cyclisation it was accepted that this result did not provide unambiguous proof that the *trans*-THF was formed from the major isomer. Yet if the *trans*-THF was formed in both cases then we know that **4.30** and **4.32** would be diastereoisomers due to the presence of the chiral auxiliary. This leads to the conclusion that removal of the auxiliary should then lead to the formation of enantiomers. Thus, following the method of Cecil *et al.*,[88] **4.30** and **4.32** were both treated with $NaBH_4$ in a THF / H_2O mixture to produce compounds **4.33** and ***ent*-4.33** (scheme 4.12). Compounds **4.33** and ***ent*-4.33** had identical physical properties by analysis of ^1H, ^{13}C NMR, IR and mass spectra, the only difference being their α_D values which were equal and opposite within experimental error. This confirmed that the two molecules were in fact enantiomeric and so the stereochemistry of compound **4.30** was indirectly confirmed with a very high level of certainty.



Reagents and conditions: (i) $NaBH_4$, THF / H_2O (2:1), 0 °C to r.t.

Scheme 4.12: Reductive removal of the chiral auxiliary

The rules set out in the literature by Sinha and Keinan state that 'if the two vicinal oxygen functions formed in the first cyclisation have a *threo* relationship, the next cyclisation will produce a *cis*-THF ring'.[103,104] The results discussed above show that although the two vicinal oxygen functions from the first cyclisation had a *threo* relationship, the acyl-perrhenate cyclisation produced the unexpected *trans*-THF ring. The observed stereoselectivity can be rationalised by applying a chair-like transition state **4.34** for the cyclisation (figure 4.2). The alternative transition state **4.35**, which would lead to the formation of a *cis*-THF ring, is presumed to be dis-favoured due to steric interactions between the hydroxy substituent on the first THF ring and the metal-oxo complex. It should however, be noted that the rules set out in the literature originated from systems where the first THF ring was always *trans*.

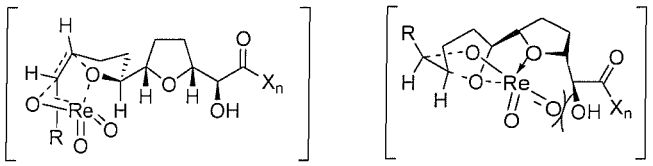
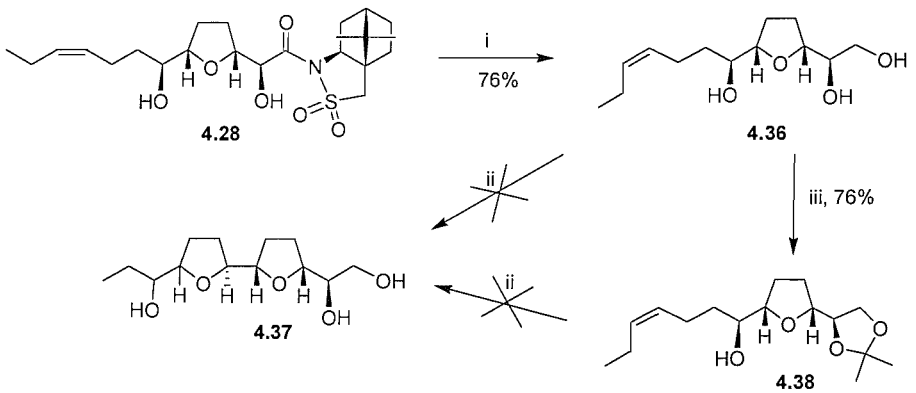


Figure 4.2: Possible transition states for the acyl-perrhenate cyclisation

As the model compound **4.30** provided unambiguous proof of the formation of the *trans*-THF from the rhenium cyclisation on **4.28**, further investigations into the stereochemical outcome of this reaction were carried out. Compound **4.28** contained the sultam chiral auxiliary and it was not known what effect, if any, this had on the rhenium cyclisation. Therefore the auxiliary was removed by reduction with borohydride and the resulting triol **4.36** was subjected to the same conditions for the rhenium cyclisation (scheme 4.13). The expected *bis*-THF product (**4.37**) did not form and only the starting material was isolated. Triol **4.36** was protected as the acetal (**4.38**) and again subjected to the rhenium cyclisation conditions. The cyclisation did not occur but the reaction conditions did remove the acetal protecting group returning triol **4.36**.



Reagents and conditions: (i) $NaBH_4$, THF / H_2O (2:1), 0 °C to r.t.; (ii) Re_2O_7, TFAA, THF, hexane, CH_2Cl_2, r.t.; (iii) 2,2-dimethoxypropane, *p*-TsOH, r.t.

Scheme 4.13

4.6 Alternative Methods of Introducing the *bis*-THF Core

At this point, alternatives to the rhenium cyclisation were examined. One possible method of introducing the second THF ring would be to carry out an epoxidation on the alkene followed by ring closure using the flanking hydroxyl of the mono-THF (figure

4.3). In order to explore this idea and obtain the correct absolute stereochemistry for the natural product, a *trans* double bond would be required. Therefore different methods for the *trans* selective reduction of alkynes were explored.

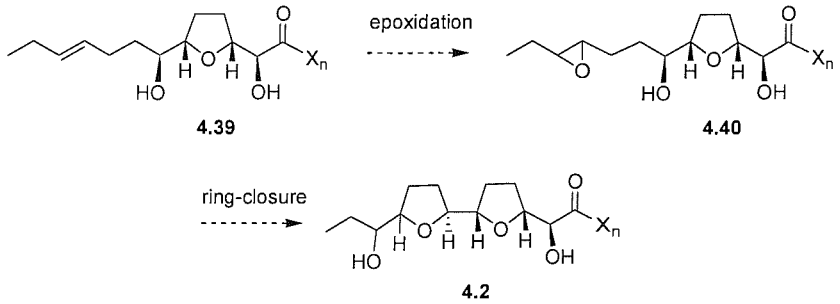
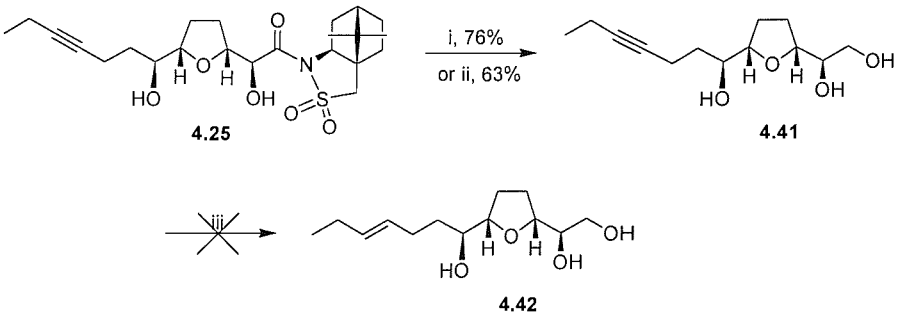


Figure 4.3: Proposed alternatives to form the *bis*-THF core

Firstly, mono-THF **4.25** was converted to the corresponding triol **4.41** before attempting a reduction with $LiAlH_4$, following the method of Frank *et al.* (scheme 4.14).[187] Unfortunately on this occasion the alkyne moiety was not reduced. It had been anticipated that the reaction would proceed through the co-ordination of the $LiAlH_4$ to the hydroxyl group that would then deliver the hydride source to the alkyne, but here it seems likely that the 1,2-diol also co-ordinated to $LiAlH_4$ preventing the reaction from proceeding.

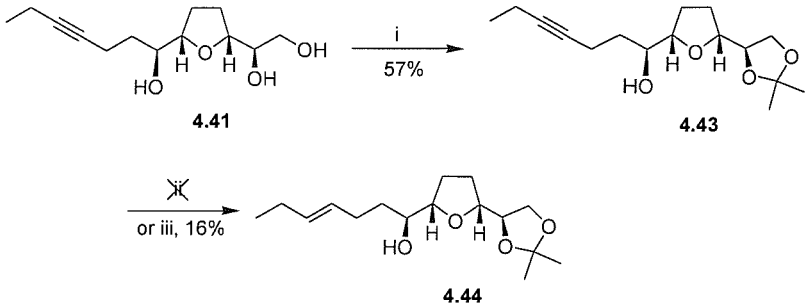


Reagents and conditions; (i) $NaBH_4$, THF / H_2O (3:1), r.t.; (ii) $LiAlH_4$ (2.2 eq.), THF, reflux; (iii) $LiAlH_4$ (1.2 eq.), THF, reflux.

Scheme 4.14: Attempted *trans* selective reduction of the alkyne

The 1,2-diol unit was therefore protected as the acetal **4.43** in an attempt to hinder the chelation described, and again treated with $LiAlH_4$. Once more the alkyne was not reduced and the starting material was recovered (scheme 4.15). A more classical Birch reduction was then applied using sodium and liquid ammonia. Initially, the reduction

was carried out on the protected 1,2-diol **4.43** and despite the very low 16% yield, the alkyne was completely reduced.

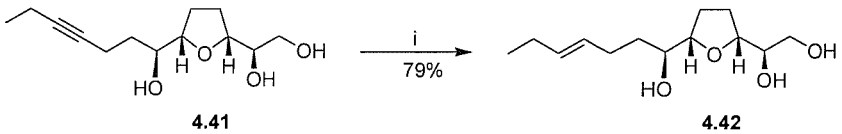


4.41 4.43 4.44

Reagents and conditions: (i) 2,2-dimethoxypropane, *p*-TsOH, r.t.; (ii) $LiAlH_4$ (1.2 eq.), THF, reflux; (iii) Na, NH_3, THF, –78 to –60 °C.

Scheme 4.15: Attempted reduction of the alkyne

The Birch reduction was then performed on triol **4.41**, and although after 5 hours only 50% of the starting alkyne had been consumed, leaving the reaction mixture for a further 6 ½ hours resulted in the complete reduction to the desired *trans* alkene in a respectable 79% yield (scheme 4.16). This reaction was carried out successfully on a small scale (0.2 mmol) but unfortunately due to human error, the small amount of sample **4.42** was lost. The reaction did however show that the alkyne could be selectively reduced to the corresponding *trans* alkene using the Birch reduction providing confidence in applying these conditions to further analogues of these compounds.



4.41 4.42

Reagents and conditions: (i) Na, NH_3, THF, –78 to –60 °C.

Scheme 4.16: Birch reduction of triol **4.41**

Due to a lack of material with which to proceed and to the low yields and volatility of the compounds at the start of the model compound synthesis, it was decided to concentrate on the synthesis of the natural product series. The results of this study will be discussed in chapter 5.

4.7 Conclusions

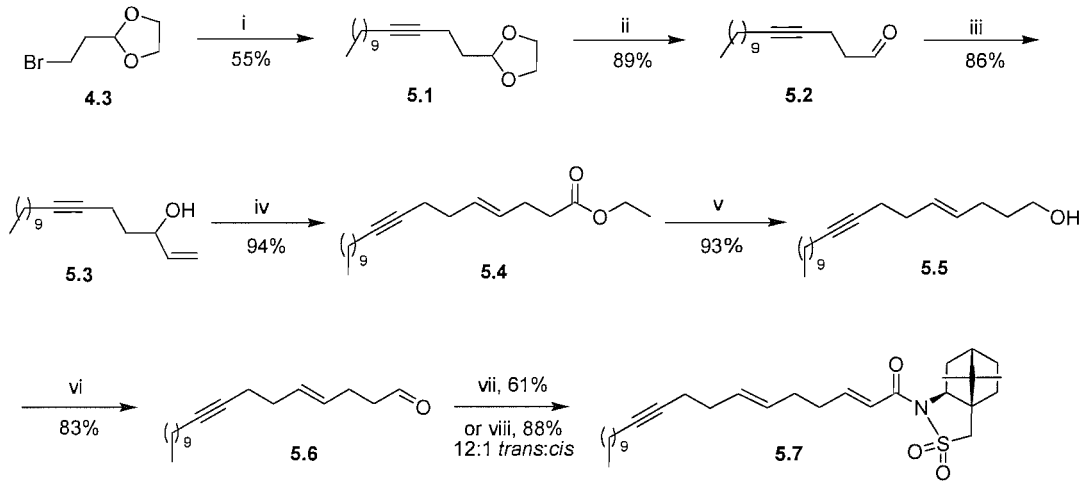
The synthesis of a model adjacent *bis*-THF compound was achieved in good yields by incorporating the *bis*-THF core from highly diastereoselective potassium permanganate and rhenium heptoxide cyclisations, providing an adjacent *bis*-THF with the *threo*, *cis*, *threo*, *trans*, *erythro* stereochemistry. A crystal structure was obtained for the *bis*-THF product, which provided unambiguous proof of the *trans*-THF ring stereochemistry formed from the rhenium cyclisation.

Chapter Five

Synthesis of the Natural Product Membrarollin

5.1 Synthesis of the mono-THF alkyne

From previous work within the group and on the model compound (**4.25**), mono-THF **3.24** was established to be a key intermediate. Therefore the synthesis of **3.24** was undertaken in accordance with a synthetic route previously established within the Brown group.[163] Thus, starting from commercially available dodecyne and bromide **4.3**, acetal **5.1** was prepared according to the method of Carballeira in 55% yield (scheme 5.1).[167] The removal of the acetal protecting group was higher yielding in comparison with that of the model compound (see section 4.1), probably due to the lower volatility of the aldehyde product. Aldehyde **5.2** was obtained in a good 89% yield and was converted to aldehyde **5.6** by Grignard addition, Claisen-Johnson rearrangement, reduction and re-oxidation in 62% yield over the 4 steps.

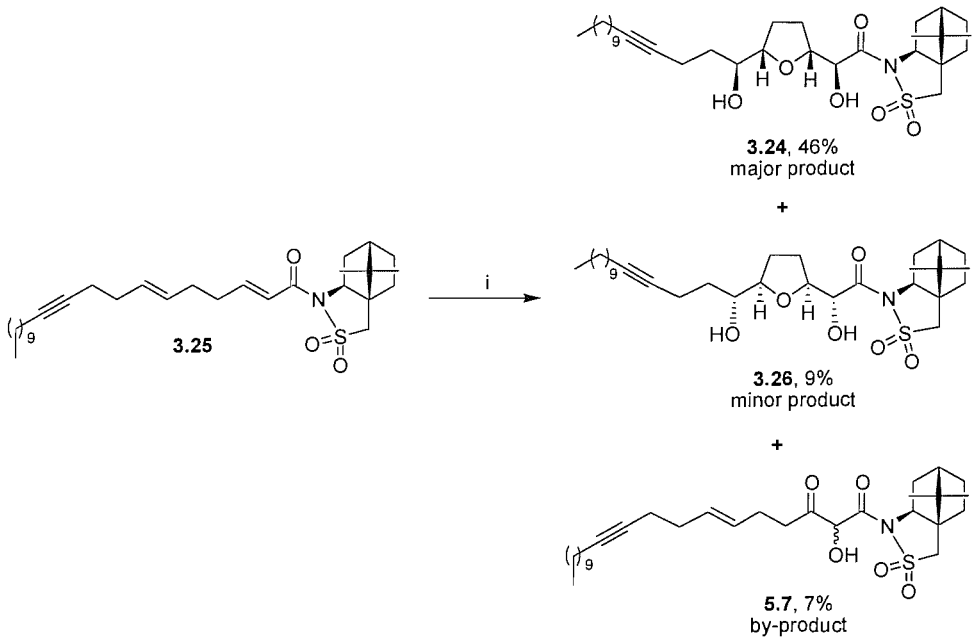


Reagents and conditions: (i) Dodec-1-yne, *n*-BuLi, DMPU, THF, −78 °C to r.t.; (ii) AcOH / H_2O (4:1), 95 °C; (iii) CH_2=CHMgBr, THF, −40 to −30 °C; (iv) $MeC(OEt)_3$, propionic acid, reflux; (v) $LiAlH_4$, THF, 0 °C to r.t.; (vi) DMP, CH_2Cl_2, 0 °C to r.t.; (vii) **3.13**, NaH, THF, r.t.; (viii) **3.13**, $^iPrNEt_2$, LiCl, MeCN, THF, r.t.

Scheme 5.1: Synthesis of the 1,5,9-dienyne

Aldehyde **5.6** was converted to 1,5,9-dienyne **3.25** by a Horner-Wadsworth-Emmons type olefination using phosphonate **3.13** (scheme 5.1). The studies on the model compound indicated that carrying out the reaction in THF and using NaH as the base produced the best yields. When these conditions were applied to aldehyde **5.6**, the *trans* olefin was obtained in 61% yield. Blanchette *et al.* carried out such olefination reactions with acetonitrile as the solvent and using DIPEA, in combination with lithium chloride, as the base.[188] When these revised conditions were applied to aldehyde **5.6** it was found that a small amount of THF was required to solubilise the aldehyde, but the desired 1,5,9-dienyne **3.25** was obtained in an excellent 88% yield. A small amount of the *cis* isomer was also formed (20:1 *trans*:*cis*), but was removed during chromatography.

The previously employed conditions for the potassium permanganate oxidative cyclisation were applied to dienyne **3.25** affording the three expected products (scheme 5.2). A slightly lower 5:1 diastereomeric ratio of the major : minor isomers was obtained, with a combined yield of the two isomers of 55% (in comparison to 62% for the model compound).

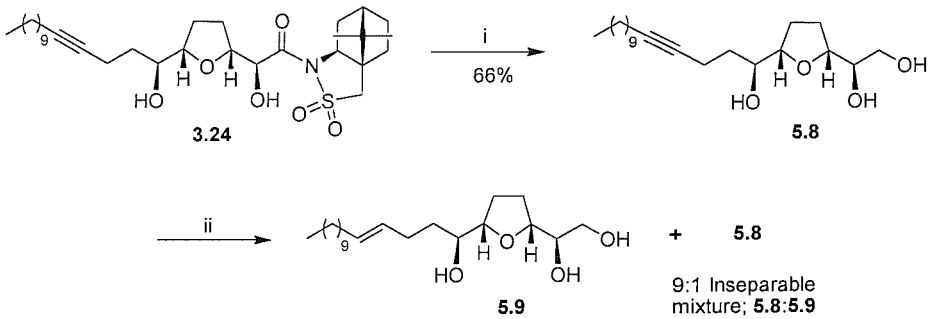


Reagents and conditions: (i) $KMnO_4$, acetone, AcOH, −30 to −20 °C.

Scheme 5.2: Oxidative cyclisation of the 1,5,9-dienyne

5.2 *Trans* selective reduction of the alkyne

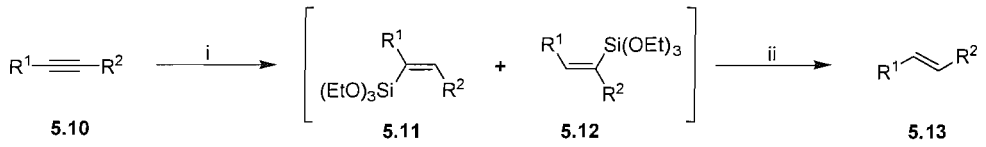
With the key mono-THF **3.24** intermediate in hand, the corresponding *trans* alkene was required for the introduction of the second THF ring with the correct absolute stereochemistry for the natural product *via* an epoxidation-ring closure mechanism. Work carried out on the model compound indicated that a Birch reduction of the alkyne was the most effective method to obtain the *trans* alkene. Mono-THF **3.24** was therefore converted to triol **5.8** which was subjected to the conditions previously used for the Birch reduction (scheme 5.3). However, even after performing the reaction in refluxing ammonia (reaction temperature –40 °C) and using lithium metal instead of sodium, a 9:1 inseparable mixture of the starting material and product was obtained. One possible theory to explain the incomplete reduction is the formation of a micelles type structure in the reaction mixture. As triol **5.8** has a long, hydrophobic chain and a hydrophilic end there could be the potential to form micelles which would protect the triple bond from the reducing environment.



Reagents and conditions: (i) $NaBH_4$, THF / H_2O (2:1), 0 °C to r.t.; (ii) Li, NH_3, THF, –78 to –40 °C.

Scheme 5.3: Birch reduction of the alkyne

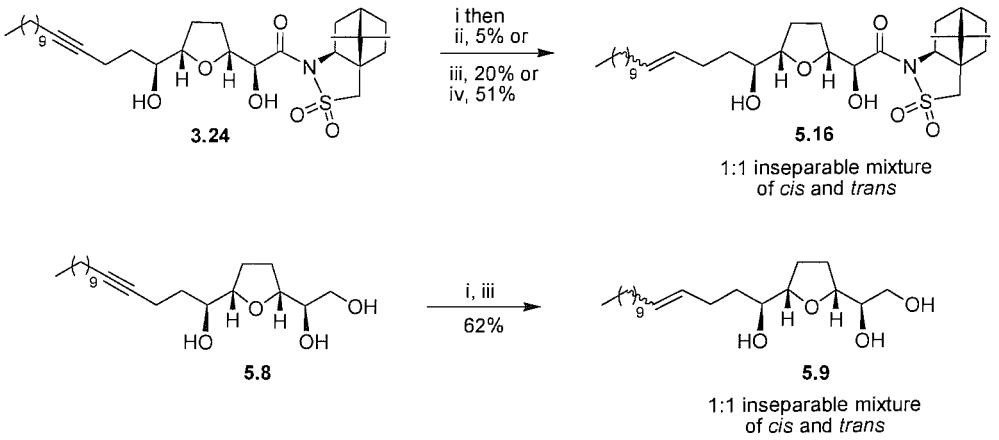
An alternative *trans* selective reduction which utilises a ruthenium catalyst to carry out a *trans* selective hydrosilylation of alkynes has been developed by Trost *et al.*[189] (scheme 5.4). Proto-desilylation of the intermediate (**5.11** and **5.12**) has the overall effect of a *trans* reduction. The catalyst employed by Trost was $[Cp^*Ru(MeCN)_3]PF_6$ (**5.14**) and has been found to be effective on a range of substrates, affording the desired products in good yields.



Reagents and conditions: (i) $(EtO)_3SiH$, **5.14**, CH_2Cl_2 r.t.; (ii) CuI, TBAF, THF, r.t.

Scheme 5.4: Trost's ruthenium catalysed *trans* selective reduction

The catalyst used by Trost and co-workers was not commercially available so the related complex $[CpRu(MeCN)_3]PF_6$ (**5.15**), already available in the laboratory, was used to effect the hydrosilylation of mono-THF **3.24** (scheme 5.5). The reaction was followed by TLC and after 1 hour, two new products had formed. Two products were expected from the first step as two regioisomers of the silylated product could form, both of which would give the same *trans* alkene after proto-desilylation. Two different conditions were reported by Trost for the desilylation, both using copper(I) iodide and TBAF but in different quantities.[190] Initially catalytic copper(I) iodide (0.1 eq.) and 2 eq. TBAF were used, but the desired *trans* alkene product **5.16** was obtained as a 1:1 inseparable mixture of *cis* and *trans* isomers in a poor 5% yield. The milder conditions for desilylation using stoichiometric quantities of copper(I) iodide (1.5 eq.) with 3 eq. TBAF were then employed and although the yield improved to 20%, a 1:1 mixture was again obtained.



Reagents and conditions: (i) $(EtO)_3SiH$, **5.15**, CH_2Cl_2, r.t.; (ii) CuI (0.1 eq.), TBAF (2.0 eq.), THF, r.t.; (iii) CuI (1.5 eq.), TBAF (3.0 eq.), THF, r.t.; (iv) AgF (2.0 eq.), MeOH, r.t.

Scheme 5.5: Application of Trost's methodology to the alkyne

The same conditions were also applied to triol **5.8** in case the chiral auxiliary was affecting the selectivity, but again a mixture of isomers was obtained (although in a much improved 62% yield, scheme 5.5).

It was unclear at this stage if the problem was with the first hydrosilylation step or with the subsequent desilylation. Alternative methods for the desilylation were researched, and according to Lacombe *et al.*, the use of silver(I) fluoride in aqueous methanol would effect the desilylation under significantly milder conditions.[191] These alternative conditions were tried on mono-THF **3.24** and although the yield more than doubled, a mixture of isomers was still obtained (scheme 5.5, step iv). This resulted in the conclusion that the problem was in fact due to the first hydrosilylation step being less selective. This is believed to be due to the use of the less sterically demanding Cp ligand on the catalyst rather than the Cp^* ligand that Trost had used. The synthesis of catalyst **5.14** was not facile and with no guarantee that it would selectively hydrosilylate mono-THF **3.24**, an alternative, more reliable method of introducing the required *trans* double bond was pursued.

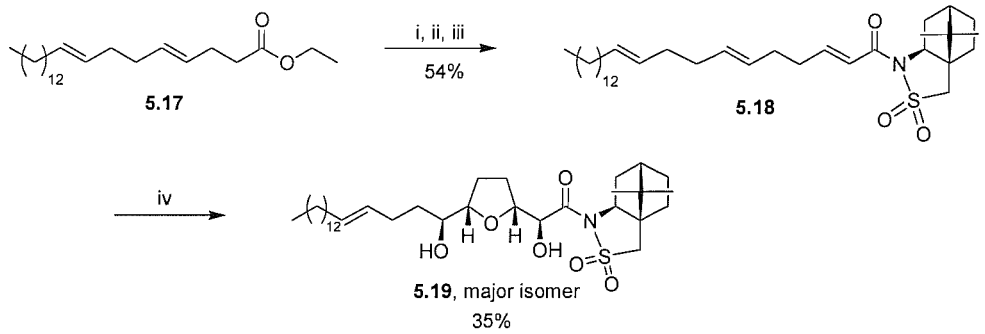
5.3 Second generation approach to the required *trans* mono-THF alkene

5.3.1 Evaluation of the proposed route

The reason for the presence of the alkyne moiety in mono-THF **3.24** was to allow a point of diversification later in the synthesis, so with the *trans* reduction proving problematic, it was decided to introduce the double bond at an earlier stage. The only problem that could be foreseen from this was having to carry out the permanganate oxidative cyclisation on a 1,5,9-triene with the desired product being the result of oxidation on two of the three double bonds.

To test the new route, a model 1,5,9-triene **5.18**, obtained by reduction, oxidation and olefination of ester **5.17** (I acknowledge Sherif Fouda for the preparation of **5.17**), was subjected to the permanganate cyclisation (scheme 5.6). The desired mono-THF **5.19** was obtained and although the yield of the major isomer was only 35%, no other by-

products were formed in the reaction. This observation suggested that the new route could be a successful way to obtain the *trans* mono-THF alkene **5.16**.

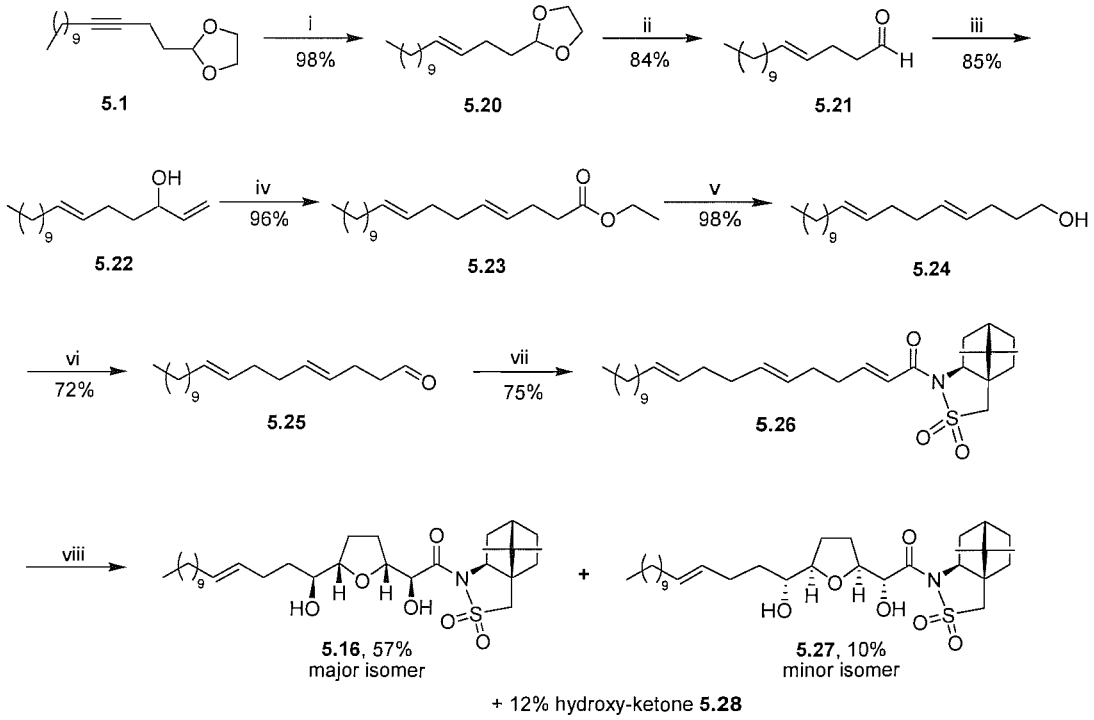


Reagents and conditions: (i) $LiAlH_4$, THF, 0 °C to r.t.; (ii) DMP, CH_2Cl_2, 0 °C to r.t.; (iii) **3.13**, ^{i}PrNEt, LiCl, MeCN, THF, r.t.; (iv) $KMnO_4$, acetone, AcOH, −30 to −20 °C.

Scheme 5.6: Evaluation of the proposed route

5.3.2 Application of the new route to the natural product synthesis

The alkyne in acetal **5.1** was converted to the *trans* alkene by a Birch reduction and proceeded very smoothly, resulting in quantitative yields (scheme 5.7). The *trans* double bond was then carried through the synthesis to the 1,5,9-triene following the same route that had been used for the alkyne. The conditions for the permanganate mediated oxidative cyclisation were then applied to triene **5.26**. The major diastereoisomer **5.16** was obtained in a very good 57% yield, which is higher than the yield obtained with the corresponding alkyne. No by-products from the oxidation of the third double bond were observed. One point worthy of note was the effect of concentration on the yield of the reaction. The optimum yield was obtained when the reaction was carried out at a dilute concentration of 0.02 M with a 4:1 ratio of acetone: acetic acid. When the concentration was doubled to a still relatively dilute 0.04 M, the combined yield of the two diastereoisomers drastically reduced to 35%. Carrying out the reaction at a concentration of 0.02 M was found to produce consistently good yields, including on a multi-gram scale.



Reagents and conditions: (i) Li, NH_3, ^{t}BuOH, THF, −78 to −40 °C; (ii) AcOH / H_2O (4:1), 95 °C; (iii) CH_2=CHMgBr, THF, −40 to −30 °C; (iv) $MeC(OEt)_3$, propionic acid, reflux; (v) $LiAlH_4$, THF, 0 °C to r.t.; (vi) DMP, CH_2Cl_2, 0 °C to r.t.; (vii) **3.13**, ^{i}PrNEt, LiCl, MeCN, THF, r.t.; (viii) $KMnO_4$, acetone, AcOH, −30 to −20 °C.

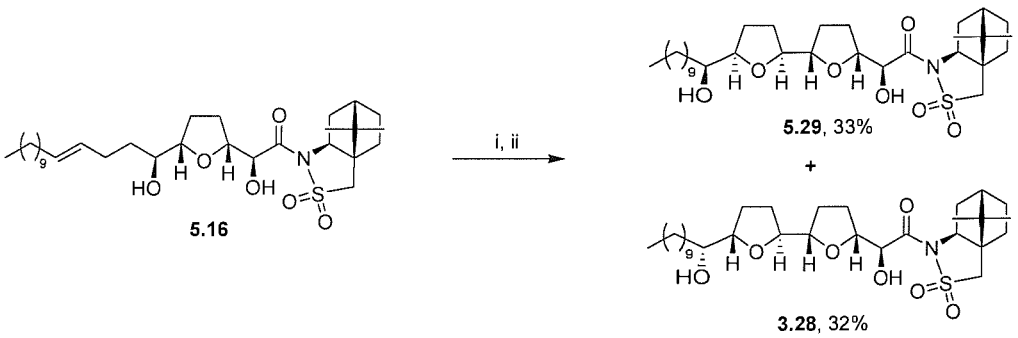
Scheme 5.7: Synthesis and oxidative cyclisation of the 1,5,9-triene

5.4 Insertion of the *bis*-THF core of membrarollin

5.4.1 Non-stereoselective *m*-CPBA epoxidation

With the key mono-THF alkene **5.16** in hand, the system was ready to insert the second THF ring by an epoxidation-ring closure mechanism. This was firstly achieved in a non-stereoselective manner following the method of Johnson *et al.* using *m*-CPBA to generate the epoxide.[192] The crude mixture of epoxide diastereoisomers was treated with acid which induced the ring closure from the flanking hydroxyl of the first THF ring (scheme 5.8). The overall result was the formation of two diastereoisomers **5.29** and **3.28**, one of which had the correct absolute stereochemistry for the natural product

and the other with the expected stereochemistry shown. This should correlate with the product of the rhenium heptoxide cyclisation on the *cis* alkene (see section 6.2 for a full discussion on this).



Reagents and conditions: (i) *m*-CPBA, CH_2Cl_2, r.t.; (ii) CSA, CH_2Cl_2, r.t.

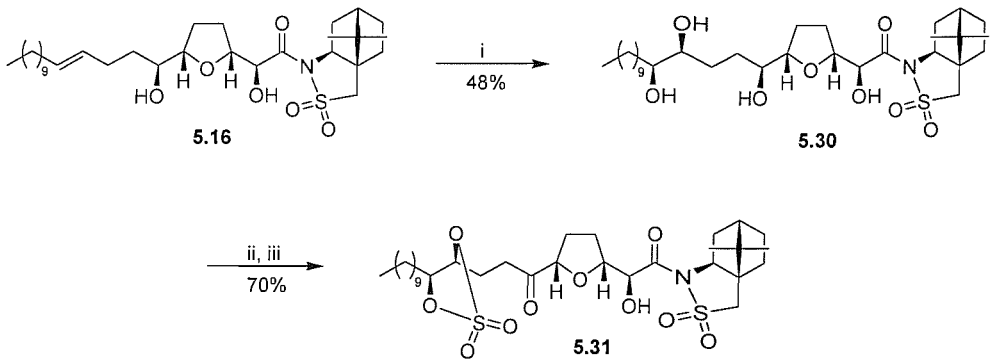
Scheme 5.8: Installation of the adjacent *bis*-THF core

Although this was a non-stereoselective synthesis of the *bis*-THF core, it was important to carry out as it provided two reference compounds for assistance with future work, and **5.29** could be used to complete an unselective total synthesis of membrarollin if required.

5.4.2 Stereoselective dihydroxylation strategy

It was proposed that the second THF ring of membrarollin could be constructed stereoselectively by a Sharpless asymmetric dihydroxylation on the *trans* alkene of mono-THF **5.16**, followed by the formation of a cyclic sulphate. Nucleophilic attack of the flanking hydroxyl inserted by the permanganate cyclisation would allow the formation of the THF ring with the required stereochemistry, by inversion of configuration at the reacting carbon centre.

Mono-THF **5.16** was converted to tetraol **5.30** using AD-mix α following the methods of Sharpless *et al.*[137] and Fernandes *et al.*[193] (scheme 5.9). Although the reaction proceeded smoothly by TLC and by inspection of the NMR produced only the desired diastereoisomer, the product was only isolated in a moderate 48% yield. Attempts at improving this were unsuccessful. The low yield was believed to be due to the polarity of the product formed, causing loss during work-up or purification.



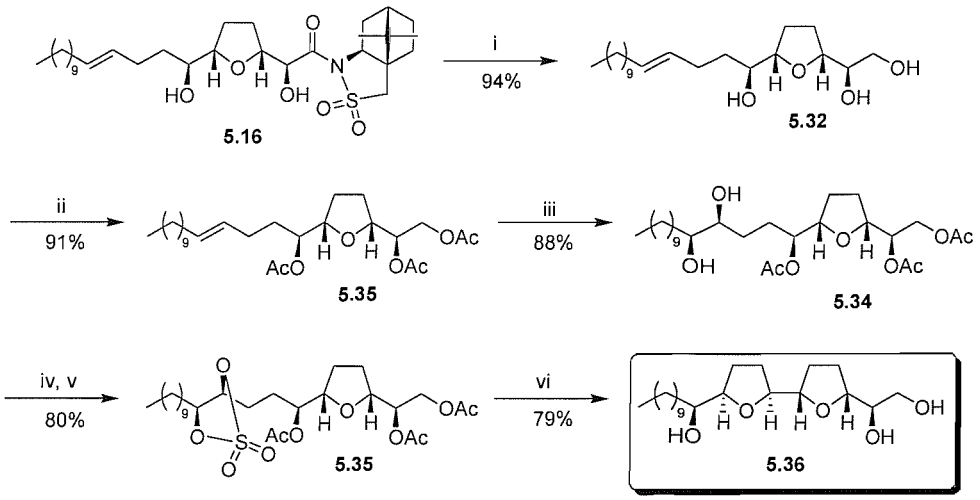
Reagents and conditions: (i) AD-mix α, $MeSO_2NH_2$, ^tBuOH, H_2O, 0 °C to r.t.; (ii) $SOCl_2$, pyridine, CH_2Cl_2, r.t.; (iii) $RuCl_3.H_2O$, $NaIO_4$, MeCN, H_2O, r.t.

Scheme 5.9: Application of the cyclic sulphate strategy

The 1,2-diol unit of tetraol **5.30** was expected to be converted to the corresponding cyclic sulphate (**5.31**) following the method of Byun *et al.*[150] Although the cyclic sulphate formed on the 1,2-diol unit, the hydroxyl group that would eventually form part of the second THF ring was also oxidised in the presence of ruthenium tetroxide (scheme 5.9). It was believed that if the free hydroxyls were protected then the formation of the cyclic sulphate could still be a viable route to the natural product.

The borohydride reduction of the chiral auxiliary to produce the free triol had in the past been rather capricious, with yields ranging from 80% down to 40-50%. Further investigation into the reaction resulted in a modified method similar to that employed by Kudyba *et al.*[194] Only 1.1 eq. of sodium borohydride were used instead of the 4 eq. used previously, and the quantity of water used was reduced from a 1:3 mixture with THF to quantities in the μL range. This new method resulted in consistently high yields (>90%) on both small and multi-gram scales.

The new borohydride reduction was applied to mono-THF **5.16** and the resulting triol **5.32** was *tris*-acetylated in one step in an excellent 91% yield (scheme 5.10). Asymmetric dihydroxylation of this intermediate proceeded in a much higher 88% yield, with inspection of the NMR again only showing one diastereoisomer (**5.34**). The higher yield for this reaction was believed to be due to the lower polarity of the diol product, in comparison to the tetraol prepared earlier. The two step transformation of the diol unit into the cyclic sulphate also progressed smoothly in 80% yield.



Reagents and conditions: (i) $NaBH_4$, THF, H_2O, r.t.; (ii) Ac_2O, pyridine, 95 °C, (iii) AD-mix α, $MeSO_2NH_2$, ^tBuOH, H_2O, 0 °C to r.t.; (iv) $SOCl_2$, pyridine, CH_2Cl_2, r.t.; (v) $RuCl_3.H_2O$, $NaIO_4$, MeCN, H_2O, r.t.; (vi) K_2CO_3, MeOH, r.t., then H_2SO_4, 0 °C to r.t.

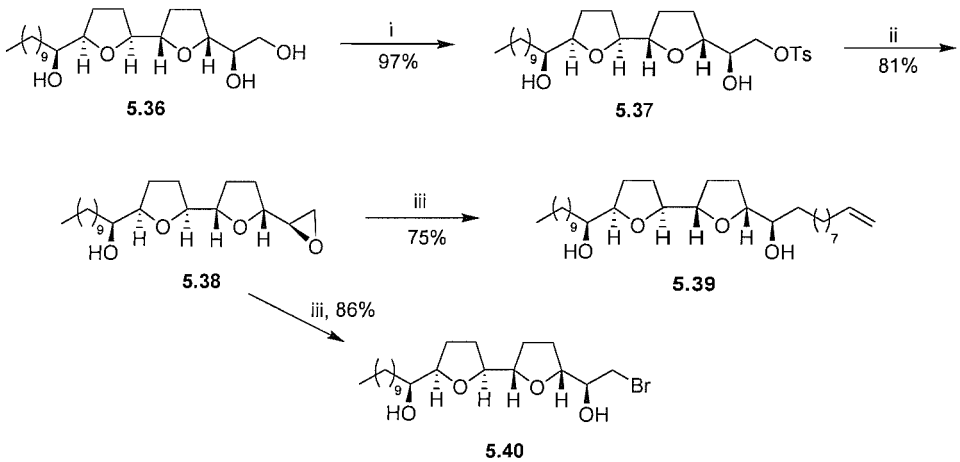
Scheme 5.10: Introduction of the adjacent *bis*-THF core

It was then hoped that saponification of the acetate groups followed by nucleophilic attack of the hydroxy anion onto the cyclic sulphate, with inversion of configuration at the reacting centre, would lead to the formation of the desired THF ring. Treatment of cyclic sulphate **5.35** with potassium carbonate in methanol furnished the sulphate monoester. The first attempt at removing the sulphate group followed the method of Friedrich *et al.*,[195] whereby the reaction mixture was treated with 20 mol% of sulphuric acid and water. This gave the desired *bis*-THF triol **5.36** in 29% yield. It was thought that as the first step had proceeded cleanly, the low yield must have been due to incomplete cleavage of the sulphate group. Different conditions were applied to the sulphate intermediate; both TFA and 2 M HCl were found to cleave the sulphate but were very slow (incomplete cleavage after 48 hours). Further investigation into the use of sulphuric acid found that excess acid and longer reaction times were required. Addition of concentrated sulphuric acid to the reaction mixture after the first step had gone to completion (as determined by TLC) and allowing the acidic mixture to stir for 16 hours produced the desired *bis*-THF triol **5.36** in a respectable 79% yield.

With the synthesis of the adjacent *bis*-THF core of the natural product membrarollin achieved, the completion of the synthesis could now be carried out following a number of established steps.

5.5 Elaboration of the *bis*-THF triol

The first step to complete the synthesis of the natural product membrarollin was the regiospecific tosylation of the primary alcohol of triol **5.36**. This was achieved through the formation of a cyclic stannylene intermediate following the method of Hu *et al.*,[196] which upon treatment with tosyl chloride and tetrabutylammonium bromide afforded the primary tosylate **5.37** in quantitative yields (scheme 5.11). Conversion to the corresponding epoxide was achieved by treatment with potassium carbonate in methanol.



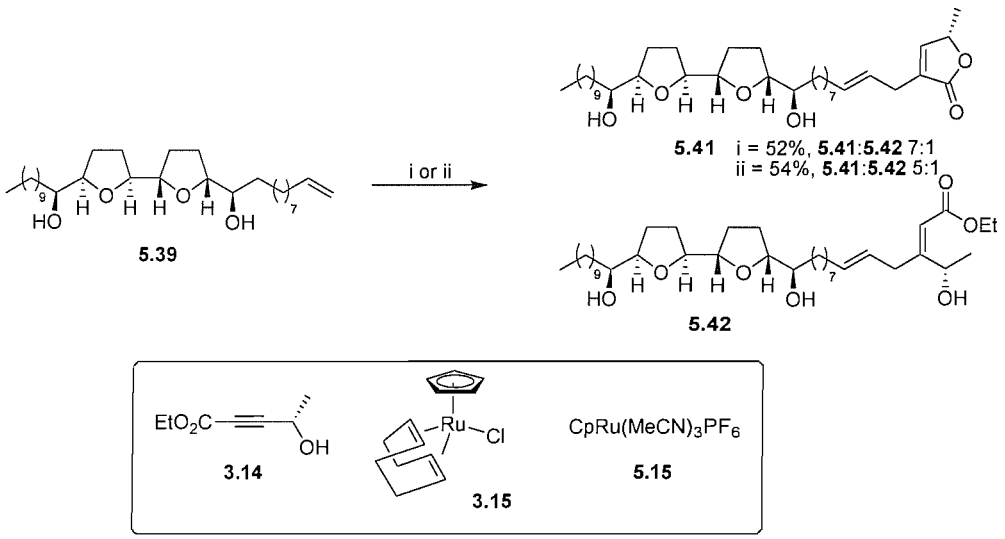
Reagents and conditions: (i) Bu_2SnO, benzene, reflux then TsCl, TBAB, r.t.; (ii) K_2CO_3, MeOH, r.t.; (iii) bromonon-1-ene, Mg, I_2, reflux, then CuBr, THF, −60 to −30 °C.

Scheme 5.11: Introduction of the side chain

Installation of the side chain bearing a terminal alkene was achieved using di-(non-8-enyl)-cuprate, formed *in situ* from non-8-enylmagnesium bromide in a good 75% yield (scheme 5.11). It was found that the ratio of the pre-formed Grignard reagent and copper source was vital to the outcome of the reaction. When a 1.3:1 ratio of Grignard: copper was used an 86% yield of bromide **5.40** was obtained. However, when the ratio was changed to 4:1, the desired alkyl side chain was introduced.

5.6 Installation of the butenolide fragment and completion of the synthesis

With the terminal alkene in place the butenolide fragment could be introduced by Trost's Alder-ene reaction. Following the conditions of Trost *et al.*,[197] terminal alkene **5.39**, propargylic alcohol **3.14** and ruthenium catalyst **3.15** were refluxed in methanol for 4 hours (scheme 5.12). This afforded the desired butenolide **5.41** in 52% yield. Inspection of the crude NMR showed a 7:1 ratio of the product to the hydroxy-ester by-product **5.42**. However due to the small scale of the reaction, the by-product was not isolated after chromatography.



Reagents and conditions: (i) catalyst **3.15**, propargylic alcohol **3.14**, MeOH, reflux; (ii) catalyst **5.15**, propargylic alcohol **3.14**, DMF, r.t.

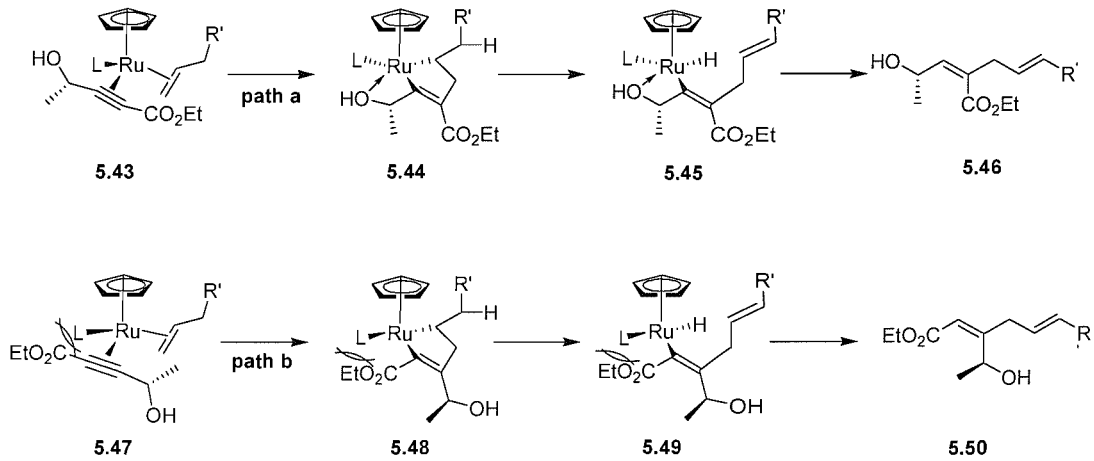
Scheme 5.12: Formation of the butenolide fragment

As the yield for the butenolide formation was lower than desired, alternative conditions were applied. Following the method of Goksel *et al.*,[198] alkene **5.39**, alcohol **3.14** and commercially available catalyst **5.15** were combined in DMF at r.t. for 2 hours (scheme 5.12). This provided the product in a very slightly improved 54% yield, with a 5:1 ratio of product: by-product. Once again the by-product was not isolated after chromatography.

The Alder-ene reaction works by the co-ordination of both the terminal alkene and the alkyne portion of the propargylic alcohol to the metal centre, followed by metallacycle formation (scheme 5.13). It has been proposed that the major hydroxy-ester product

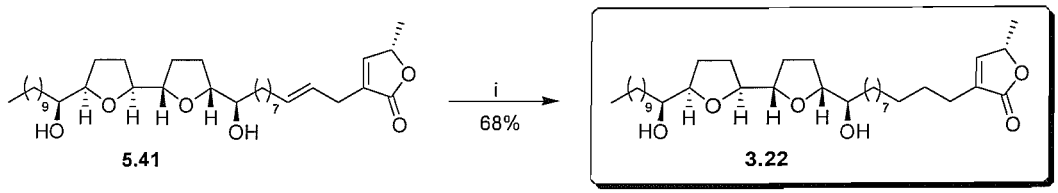
5.46 arises through reaction pathway a, and the minor product **5.50** through the sterically hindered transition state required for pathway b. In path a, a ligand is believed to be displaced from the metal centre by the hydroxyl group of the alcohol, further stabilising the complex.

Collapse of the metallacycle *via* β–hydride elimination and reductive elimination afford hydroxy-esters **5.46** and **5.50**. Spontaneous lactonisation to form the butenolide portion only occurs for major hydroxy-ester **5.46**, allowing separation of the two products.



Scheme 5.13: Alder-ene transition states

In order to complete the synthesis, the isolated double bond was selectively reduced by diimide affording membrarollin **3.22** (scheme 5.14).



Reagents and conditions: (i) $TsNHNH_2$, NaOAc, THF, H_2O, reflux.

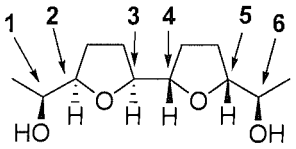
Scheme 5.14: Diimide reduction and completion of the synthesis

5.7 Comparison of NMR signals in natural and synthetic membrarollin

A natural sample of membrarollin was isolated from the seeds of *Rollinia membranacea* by Gonzalez *et al.*[162] The absolute stereochemistry was determined by comparison of the methine bearing oxygenated signals in the proton and carbon NMR

data to those of three other acetogenins with identical systems: rollimembrin **1.43**,[24] membranacin **1.44**[199] and rolliniastatin 1 **1.42**.[10] The NMR data of the oxygenated methine signals obtained from the natural sample and from the synthetic sample prepared during this research are summarised in table 5.1.

Table 5.1: Significant signals in the NMR of natural and synthetic membrarollin



adjacent *bis*-THF core of membrarollin

Position	Proton Shifts [a]		Carbon Shifts [b]	
	Natural [c]	Synthetic [c]	Natural	Synthetic
1	3.85, m	3.88-3.80, m	71.91	71.84
2	3.90, m	3.94-3.89, m	83.02	83.03
3	3.87, m	3.89, m	80.99	80.99
4	3.87, m	3.89, m	81.10	81.12
5	3.81, m	3.88-3.80, m	83.02	82.89
6	3.40, dt	3.44-3.38, m	74.00	74.03

[a] Proton NMR calibrated to 7.26 ppm; [b] Carbon NMR calibrated to 77.0 ppm; [c] multiplicity of proton signals is defined as m = multiplet and dt = doublet of triplets.

The oxygenated methine signals in the ^{1}H NMR appear as multiplets and therefore can not be used to confirm the structure of the synthetic sample of membrarollin. However the equivalent signals in the ^{13}C NMR are diagnostic of the relative stereochemistry of the *bis*-THF core. The signals in the synthetic sample were in close agreement not only with the signals for the natural sample but also the equivalent signals from the three other acetogenins with the same system. This leads to the conclusion that the synthetically prepared sample had the same stereochemistry as the isolated product, making this the first total synthesis of the natural product membrarollin.

5.8 Conclusions

The adjacent *bis*-THF core of membrarollin **3.22** was constructed by a potassium permanganate oxidative cyclisation of a 1,5,9-triene followed by Sharpless asymmetric dihydroxylation, formation of a cyclic sulphate and base-induced cyclisation. Elaboration of the *bis*-THF triol completed the synthesis of the natural product in 18 steps in an overall 2% yield. Analytical data obtained were in close agreement to that reported in the literature.

Chapter Six

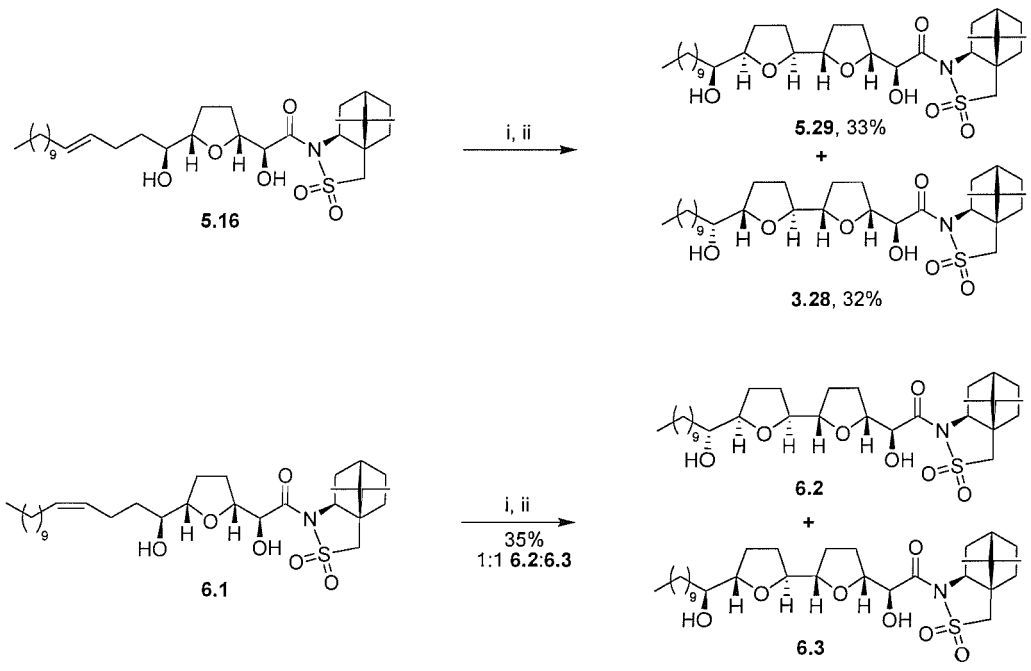
Other Approaches to Adjacent *bis*-THF Fragments

The previous chapter described the synthesis of the adjacent *bis*-THF acetogenin membrarollin. The following chapter discusses alternative methods of introducing the adjacent *bis*-THF core that were investigated to complement the work summarised in chapter five.

6.1 Epoxidation-cyclisation strategies on hydroxy alkenes

6.1.1 Non-stereoselective *m*-CPBA epoxidation

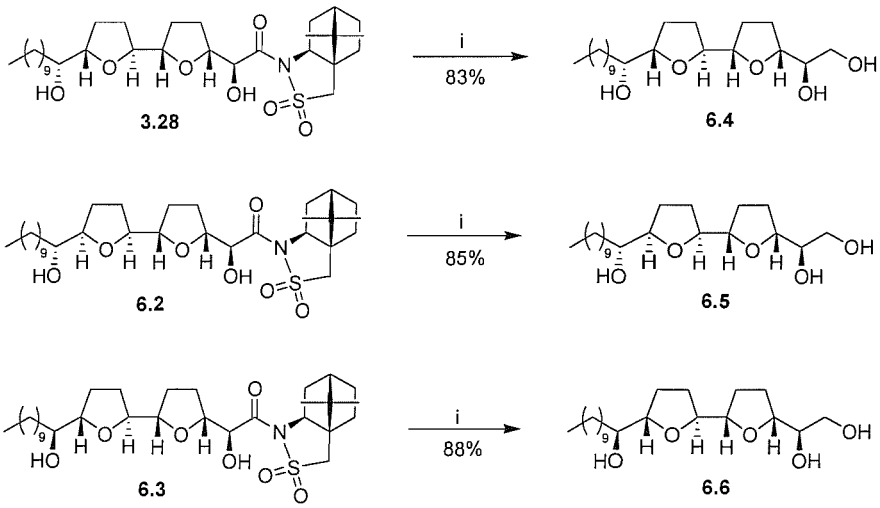
An *m*-CPBA epoxidation and acid catalysed cyclisation of both the *trans* (**5.16**) and *cis* (**6.1**, I acknowledge Yulai Hu for the preparation of **6.1**) mono-THF alkenes afforded the four possible diastereomeric products, **3.28**, **5.29**, **6.2** and **6.3** (scheme 6.1).



Reagents and conditions: (i) *m*-CPBA, CH_2Cl_2, r.t.; (ii) CSA, CH_2Cl_2, r.t.

Scheme 6.1: Installation of the *bis*-THF core *via* an *m*-CPBA epoxidation

The chiral auxiliary was removed from isomers **3.28**, **6.2** and **6.3** affording the corresponding diastereomeric triols **6.4**, **6.5** and **6.6** (scheme 6.2). Combining the data from these triols with the fourth possible isomer **5.36** (the data obtained from the cyclic sulphate cyclisation corresponded with that obtained from the removal of the auxiliary from **5.29**) allowed the comparison of the signals in the NMR to products obtained from alternative methods of introducing the second THF ring which helped with stereochemical assignments.



Reagents and conditions: (i) $NaBH_4$ (1.1 eq.), THF, H_2O, r.t.

Scheme 6.2: Reductive removal of the chiral auxiliary

6.1.2 Stereoselective epoxidation

Ketone **2.184** and its enantiomer ***ent*-2.184** have been used by Shi *et al.* in the stereoselective epoxidation of alkenes, resulting in moderate yields and high enantiomeric excesses (figure 6.1).[124]

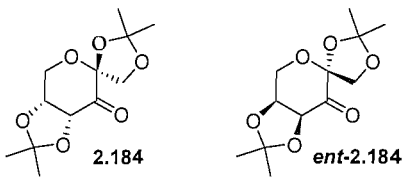
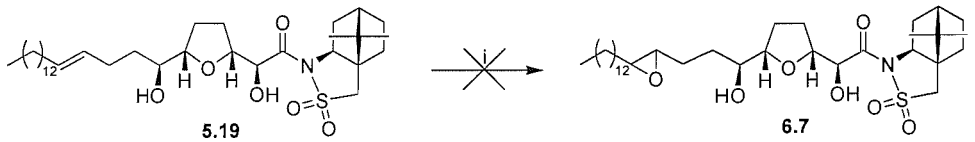


Figure 6.1: Chiral ketones used for stereoselective epoxidations

The effects of pH, solvent and temperature on the epoxidation reaction have been studied in detail by Shi and co-workers and following a general method, the

epoxidation of the model mono-THF **5.19** was attempted (scheme 6.4). Although the starting material was consumed in the reaction, once isolated the product formed was found not to be the desired epoxide as the double bond remained intact. The product was unable to be identified, and due to time constraints this method could not be investigated further.

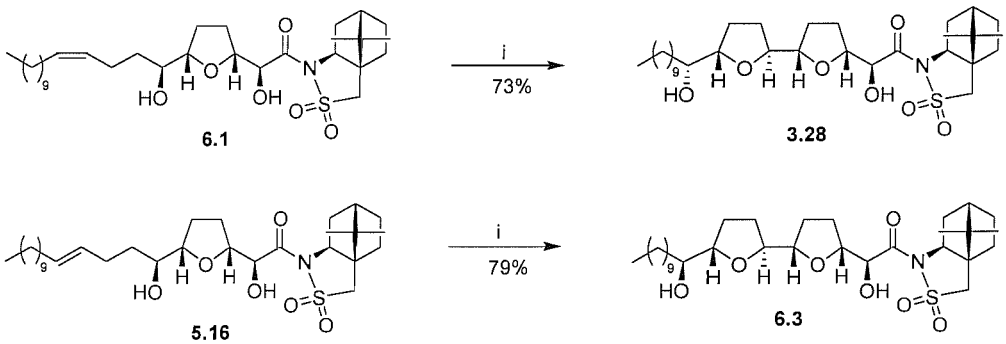


Reagents and conditions: (i) ***ent*-2.184**, K_2CO_3-AcOH buffer, Bu_4NHSO_4, Oxone, Na_2EDTA, KOH, 2,2-dimethoxypropane, MeCN.

Scheme 6.4: Attempted Shi epoxidation

6.2 Metal-oxo cyclisations on hydroxy alkenes

The introduction of the second THF ring by an acyl-perrhenate promoted cyclisation on the *cis* alkene of the model compound has been shown to afford a *trans* THF ring (see section 4.5). The rhenium heptoxide cyclisation was also carried out on the *cis* (**6.1**) and *trans* (**5.16**) olefins, affording diastereoisomers **3.28** and **6.3** respectively (scheme 6.5). The analytical data for **3.28** corresponded with one of the products obtained from the *m*-CPBA epoxidation-cyclisation on the *trans* alkene as expected.



Reagents and conditions: (i) Re_2O_7, TFAA, THF, hexane, CH_2Cl_2, r.t.

Scheme 6.5: Installation of the *bis*-THF core *via* acyl perrhenate cyclisations

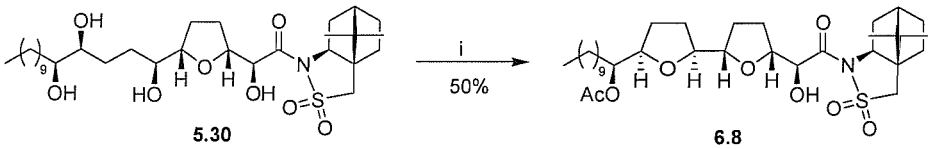
The stereochemistry of the product obtained from the *trans* alkene was predicted, using the rules set out by Sinha,[103] to have a *trans* THF ring with a *threo* relationship between the THF oxygen and the flanking hydroxyl. This was confirmed when the NMR data

was found to match with one of the products from the *m*-CPBA epoxidation-cyclisation on the *cis* alkene.

6.3 Dihydroxylation-cyclisation strategies on hydroxy alkenes

The synthetic utility of chiral 1,2-diols has already been exploited in the synthesis of membrarollin through the formation of a cyclic sulphate (see section 5.4.2). 1,2-Diols can also be transformed to the corresponding chiral epoxides by the formation of halohydrin esters, or they can be directly converted to the THF ring by cyclisation of the ortho ester intermediate. It was believed that either of these methods could be used to introduce the second THF ring of the *bis*-THF core of membrarollin.

Initially it was intended to form the halohydrin ester intermediate from mono-THF tetraol **5.30** which could then be converted to the epoxide following the one-pot method of Kolb *et al.*[157] Subsequent acid-catalysed ring closure would provide the *bis*-THF in a stereoselective fashion. However when **5.30** was treated with a small excess of trimethylorthoacetate and catalytic *p*-TsOH, it was found that the mono-acetate *bis*-THF **6.8** was formed directly, in a promising 50% yield (scheme 6.6). Efforts at improving this yield further were unsuccessful.

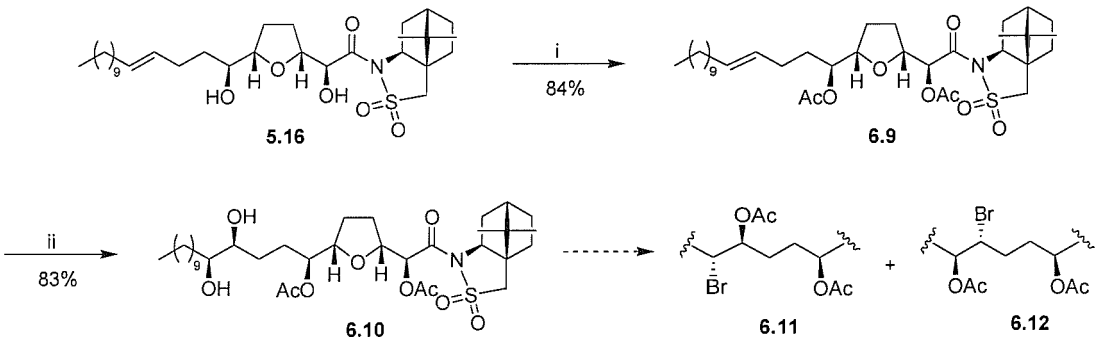


Reagents and conditions: (i) $MeC(OMe)_3$, *p*-TsOH, CH_2Cl_2, r.t.

Scheme 6.6: Installation of the *bis*-THF core *via* an ortho ester intermediate

The result of the direct cyclisation was in line with the work carried out by Zheng and co-workers[158] and only required removal of the acetate group to provide access to the *bis*-THF core of membrarollin. Attempts at removing both the acetate group and chiral auxiliary in one step with sodium borohydride in THF or potassium carbonate in methanol caused the decomposition of the starting material. Due to a lack of material and time this could not be further investigated.

As the yield for both the dihydroxylation and THF ring formation were too low to be incorporated into the total synthesis, an alternative approach using this methodology was considered. It was believed that the yield for the dihydroxylation was low due to the polarity of the tetraol product. Therefore mono-THF **5.16** was *bis*-acetylated and subsequent dihydroxylation of **6.9** proceeded in a much improved 83% yield (scheme 6.7).

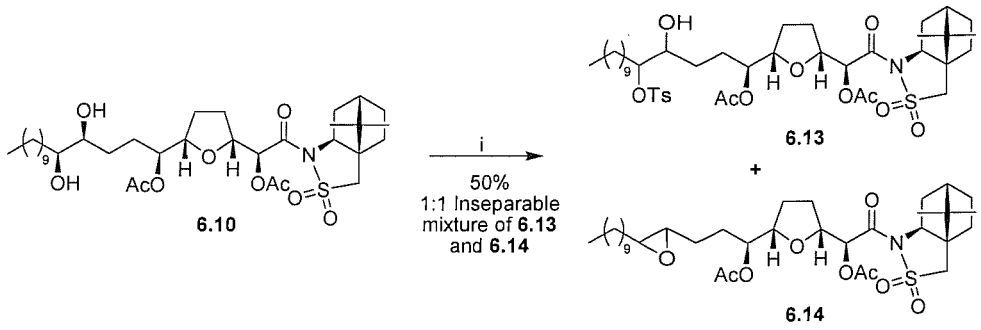


Reagents and conditions: (i) Ac_2O, pyridine, reflux; (ii) AD-mix α, $MeSO_2NH_2$, ^tBuOH, H_2O, 0 °C to r.t.

Scheme 6.7: Proposed halohydrin ester route

It was hoped that combining diol **6.10** with trimethylorthoacetate would form the cyclic ortho ester intermediate which could be converted to the corresponding halohydrin esters (**6.11** and **6.12**). Further treatment of the halohydrin esters with potassium carbonate would remove all three acetate groups and would allow the formation of the second THF ring.

However when the first step was attempted three new products were formed during the reaction. Interestingly, as the reaction time was increased, the least polar of these products by TLC increased in intensity. After heating the mixture to reflux it was found that this was the only product of the reaction. After chromatographic purification, what was thought to be a single product was actually found to be an inseparable mixture of two compounds. The major compound was tosylate **6.13**, presumably formed from the opening of the cyclic ortho ester intermediate with the *p*-TsOH in the reaction mixture (scheme 6.8). The second compound was found to be epoxide **6.14**. Only a small amount of these two compounds was isolated, with the rest of the material believed to have decomposed during the reaction.

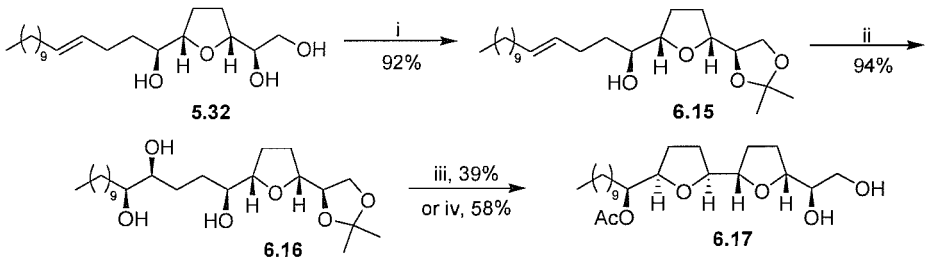


Reagents and conditions: (i) $MeC(OMe)_3$, *p*-TsOH, CH_2Cl_2, reflux.

Scheme 6.8: Attempted halohydrin ester formation

6.4 Second generation approach of the dihydroxylation-cyclisation strategy

As the dihydroxylation-cyclisation strategy on mono-THF **5.16** had produced a promising result but with a low yield, a second generation approach was devised. The 1,2-diol unit of triol **5.32** was converted to acetal **6.15** before dihydroxylation in an excellent 94% yield (scheme 6.9). It was then hoped that subjecting triol **6.16** to the conditions of Zheng and co-workers would allow the direct cyclisation to the *bis*-THF. In the event the reaction conditions not only caused the desired cyclisation to take place, but also removed the acetal group. *Bis*-THF **6.17** was initially produced in 39% yield. Increasing the amount of trimethylorthoacetate from 1.2 eq. to 2 eq. increased the yield to a more respectable 58%. An NMR sample of the product from this reaction was spiked with a sample of the triol prepared by the cyclic sulphate route. Only one set of methine signals was observed in the ^{13}C NMR spectrum indicating that the same *bis*-THF diastereoisomer was produced in both cyclisation approaches.

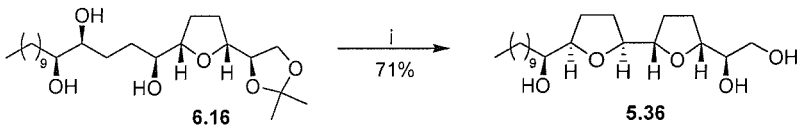


Reagents and conditions: (i) 2,2-dimethoxypropane, *p*-TsOH, r.t.; (ii) AD-mix α, $MeSO_2NH_2$, ^tBuOH, H_2O, 0 °C to r.t.; (iii) $MeC(OMe)_3$ (1.2 eq.), $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C to r.t.; (iv) $MeC(OMe)_3$ (2.0 eq.), $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C to r.t.

Scheme 6.9: Installation of the *bis*-THF core *via* an ortho ester intermediate

The yield of the cyclisation was still a lot lower than desired and needed to be improved if this were to be a viable route to the *bis*-THF triol **5.36**. Closer inspection of the ^{1}H NMR of the crude reaction mixture showed a second acetate peak. This was believed to be due to the presence of a *bis*-acetate product in the reaction mixture which had not been isolated. If this were the case then it might account for the low yield.

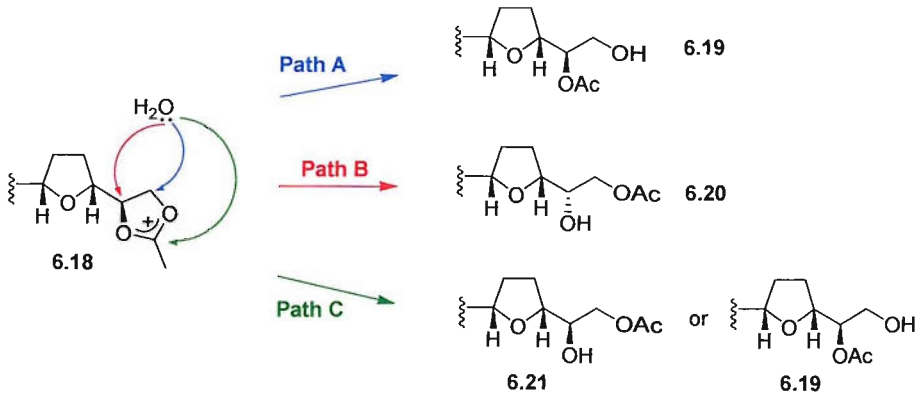
The reaction was carried out again but the crude reaction mixture was treated with potassium carbonate and methanol. The *bis*-THF triol **5.36** was furnished in a good 71% yield (scheme 6.10). The relatively high yield over the two steps suggested that the cyclisation reaction was proceeding well, but that a mixture of products was being obtained. Carrying out the acetate cleavage on the reaction mixture to give the desired *bis*-THF as the major product inferred that the other products formed in the cyclisation were indeed *bis*-acetate derivatives of **5.36**.



Reagents and conditions: (i) $MeC(OMe)_3$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C then K_2CO_3, MeOH, r.t.

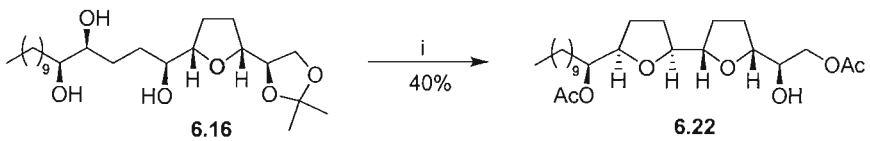
Scheme 6.10: Formation of the *bis*-THF core *via* an ortho ester intermediate

There are three possible mechanistic routes to account for the formation of the *bis*-acetate (scheme 6.11). In all three routes, a second ortho ester intermediate forms on the 1,2-diol unit after the acetal group has been removed. Path A shows attack of water at the least hindered end of the 1,2-diol leading to the primary alcohol in **6.19**. Path B occurs when the water attacks at the more hindered end leading to the secondary alcohol **6.20**. This however leads to inversion of configuration at the hydroxy centre. Path C occurs when the water attacks at the ortho ester centre. This could form two different hydroxy acetates **6.21** and **6.19**, both of which would have retention of configuration.



Scheme 6.11: Possible mechanistic routes for the *bis*-acetate formation

The results of the first spiked NMR suggested that the reaction proceeded *via* path A or C where the product has retention of configuration. In order to determine which one of these paths was correct and to further our understanding of the reaction, the *bis*-acetate needed to be isolated. The reaction was carried out again and once the cyclisation and acetal removal had been found to have gone to completion, further trimethylorthoacetate and $BF_3{\cdot}OEt_2$ were added (scheme 6.12). This resulted in a complex mixture of spots by TLC, but pure *bis*-acetate **6.22** was isolated from the mixture. The second acetate group was determined to be on the primary alcohol suggesting that the reaction proceeded *via* path C.



Reagents and conditions: (i) $MeC(OMe)_3$ (2 eq.), $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C to r.t., 22 hours then further $MeC(OMe)_3$ (1.2 eq.), $BF_3{\cdot}OEt_2$.

Scheme 6.12: Formation of the *bis*-acetate

As a final confirmation of this the two acetate groups were removed from **6.22** and the NMR sample of the resulting product was spiked with a sample of triol **5.36** prepared from the cyclic sulphate. The resulting NMR again showed one set of signals, suggesting that the two individual NMR samples had the same absolute stereochemistry and that the formation of the *bis*-acetate by-product proceeded *via* pathway C.

Although this route requires further investigation so that the yield for the THF formation can be improved, it is already showing potential as an alternative to the

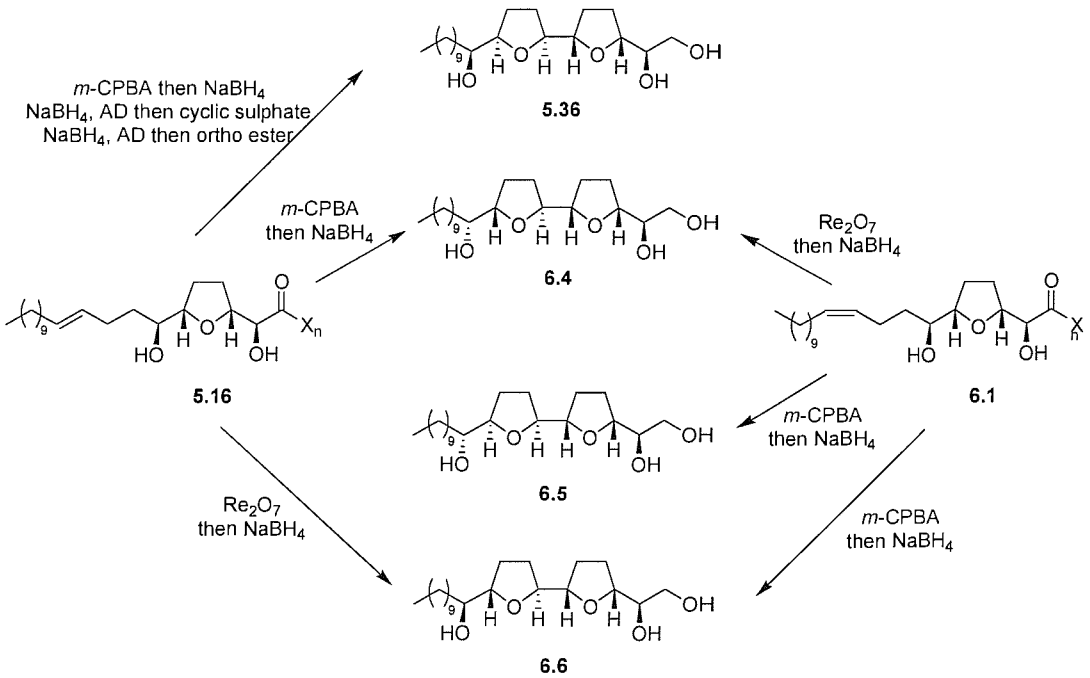
cyclic sulphate route. The formation of *bis*-THF triol **5.36** *via* the cyclic sulphate proceeded in four steps and a 51% yield. The formation of the ortho ester intermediate allowed the formation of the *bis*-THF triol **5.36** in only three steps in an improved 61% yield. Incorporation of this method into the total synthesis of membrarollin would not only increase the current overall yield, but would have the potential for further improvements.

6.5 Conclusions

Four of the six stereocentres of the adjacent *bis*-THF core were inserted by a permanganate mediated oxidative cyclisation. The remaining two stereocentres were introduced in all four possible arrangements by an unselective epoxidation reaction. Acid-catalysed cyclisation of the resulting mixtures of diastereoisomeric epoxides ultimately led to all four possible diastereoisomers at the adjacent THF oxygen and hydroxyl groups in the resulting *bis*-THFs.

A new method for the introduction of THF rings from hydroxy alkenes *via* an ortho ester intermediate was investigated. The yields for the initial THF formation were lower than desired but further examination into the mechanism of the reaction has led to much improved yields with the potential for further development.

Scheme 6.13 summarises the stereochemical outcomes of the different oxidative cyclisation methods investigated in this research. When the *bis*-THF products were obtained from more than one route, comparison of the analytical data found them to be identical. The structure of *bis*-THF **6.4** was also confirmed by Moshers ester derivatives and from the work carried out on the model compound (as described in chapter 4).


m-CPBA then NaBH4
NaBH4, AD then cyclic sulphate
NaBH4, AD then ortho ester
m-CPBA then NaBH4
Re2O7 then NaBH4
m-CPBA then NaBH4
Re2O7 then NaBH4
m-CPBA then NaBH4
5.36
6.4
5.16
6.1
6.5
6.6

Scheme 6.13

Chapter Seven

Concluding Remarks and Future Work

Sequential permanganate and acyl perrhenate oxidative cyclisations were carried out on a model system producing an adjacent *bis*-THF compound. A crystal structure was obtained from the minor diastereoisomer **4.32** which showed the *cis*-THF ring formed from the permanganate cyclisation and the *trans*-THF ring inserted by the perrhenate cyclisation (figure 7.1). This result was in contrast with the stereoselectivity rules set out by Sinha but was rationalised through transition state models.

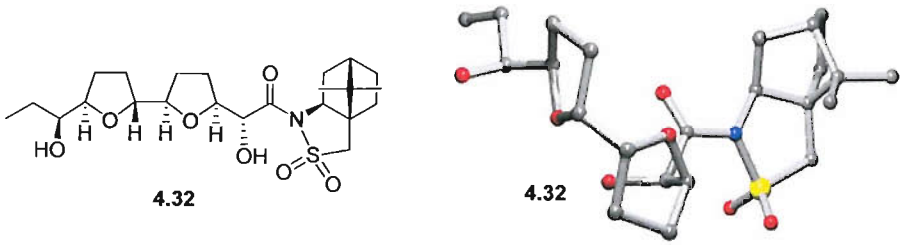


Figure 7.1: Crystal structure of *bis*-THF **4.32**

The synthetic route towards membrarollin **3.22** relied upon the selective oxidative cyclisation of two of the double bonds of 1,5,9-triene **5.26** by permanganate. Installation of the second THF ring was achieved using the Sharpless asymmetric dihydroxylation reaction followed by a base induced cyclisation of a cyclic sulphate derivative. Elaboration of *bis*-THF **5.36** allowed the butenolide fragment to be installed using Trost's ruthenium catalysed Alder-ene reaction. Selective reduction of the disubstituted alkene in the presence of the butenolide completed the total synthesis of membrarollin **3.22** in 18 steps overall (figure 7.2).

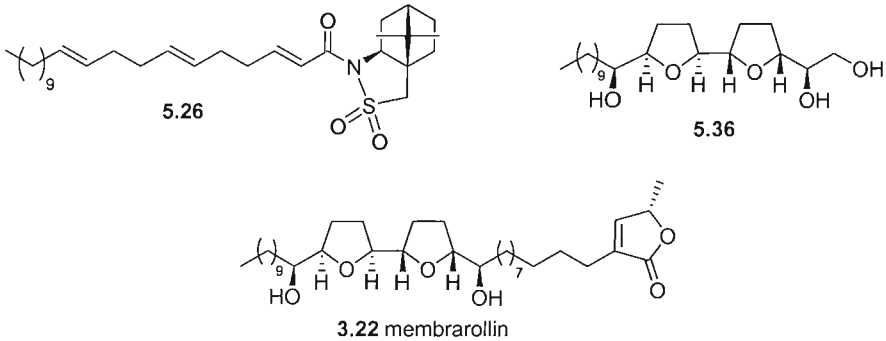
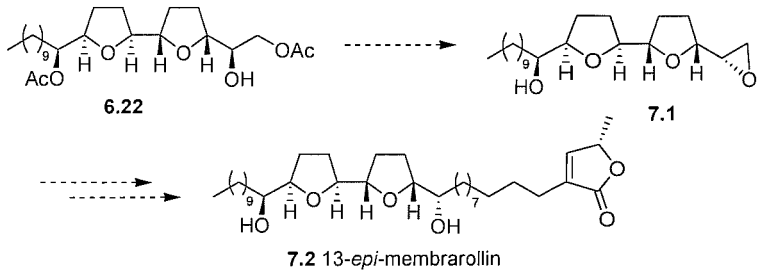


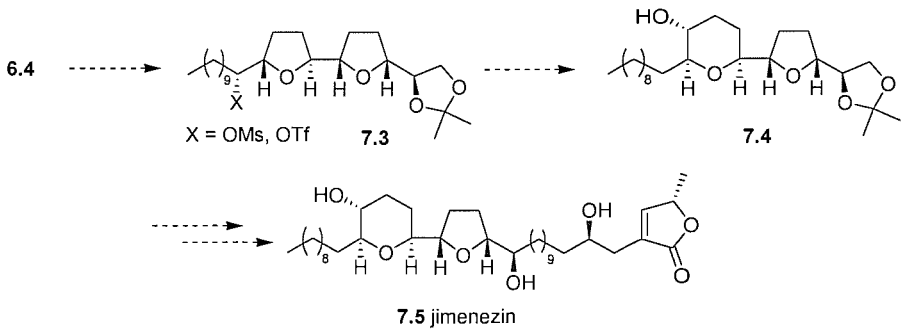
Figure 7.2

Investigations into alternative methods of introducing the second THF ring led to the discovery of a novel cyclisation to form the *bis*-THF system *via* an ortho ester intermediate. Application of this methodology allowed *bis*-THF **5.36** to be formed in good yield and fewer steps than the original cyclic sulphate method. Due to time constraints this method could not be optimised but there is a possibility that the yield could be improved even further. The ortho ester cyclisation did produce significant quantities of *bis*-acetate **6.22** which could be used in the synthesis of analogues of membrarollin. If complete conversion to *bis*-acetate **6.22** were achieved then this could be converted to diastereomeric epoxide **7.1** which could be further elaborated to 13-*epi*-membrarollin **7.2** (scheme 7.1).



Scheme 7.1

We were also intrigued by the possibility that the adjacent *bis*-THF core of membrarollin could be rearranged to an adjacent THP-THF core which could then be used in the synthesis of acetogenins such as jimenezin **7.5**. Several groups have reported the expansion of THF rings to the THP equivalents through the formation of either the mesylate or triflate on the flanking hydroxyl group followed by a silver mediated expansion.[83,200-203] Protection of the 1,2-diol unit of triol **6.4** would allow the conversion of the remaining alcohol to a suitable leaving group. Silver promoted ring expansion would then access the THP-THF core (scheme 7.2).



Scheme 7.2

Chapter Eight

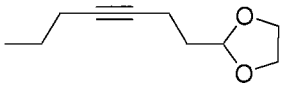
Experimental Section

8.1 General Experimental

All air and/or moisture sensitive reactions were carried out in oven-dried glassware under an inert atmosphere. Tetrahydrofuran and diethyl ether were distilled over sodium and benzophenone. Triethylamine and dichloromethane were distilled over calcium hydride. All other solvents and reagents were purified, if required, by standard methods.[204] TLC was carried out with Merck Kieselgel silica gel 60 F_{254}, visualised by UV illumination or staining with $KMnO_4$ or ceric ammonium molybdate. Flash column chromatography was carried out using Merck Kieselgel 60 silica gel. Column dimensions refer to width x height (in mm) of silica gel. Preparative HPLC was carried out on a Kontron 420 Master system using a normal phase Bio-sil silica column (22 x 250 mm), eluting with an EtOAc / hexane mixture. Infrared spectra are reported in wavenumbers (cm^{-1}) and were recorded on a Nicolet 380 fitted Diamond platform. Absorptions are described as strong (s), medium (m), weak (w) or broad (brd). Proton and carbon NMR spectra were recorded in solution on a Bruker AC300 and AV300 (at 300 and 75 MHz respectively) or on a Bruker DPX400 (at 400 and 100 MHz respectively). Fluorine and phosphorus NMR spectra were recorded in solution on a Bruker AV300 (282 and 121 MHz respectively). Chemical shifts are reported using the δ scale, relative to chloroform as the internal reference (δ 7.27 ppm ^{1}H, δ 77.36 ppm ^{13}C). Proton spectra are described using the following abbreviations; s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sext (sextet) and brd (broad). The following abbreviations are used in the case of carbon spectra; s (quaternary), d (methine), t (methylene), q (methyl). Electron impact and chemical ionisation mass spectra were obtained using a Fisons VG platform single quadropole mass spectrometer. Electrospray mass spectra were obtained using a Micromass platform mass analyser with an electrospray ion source. Relative intensities are reported in brackets after m/z. Melting points were obtained using a Gallenkamp Electrothermal apparatus and are uncorrected.

8.2 Experimental Details

2-Hept-3-ynyl-1,3-dioxolane (4.4)



$C_{10}H_{16}O_2$

M.W. = 168.23 g/mol

To a solution of 1-pentyne (500 mg, 7.34 mmol) in THF (10 mL) at –78 °C was added *n*-BuLi (3.05 mL, 7.19 mmol, 2.4 M solution in THF). The mixture was stirred for 10 minutes before the addition of DMPU (1.78 mL, 14.68 mmol) and 2-(2-bromoethyl)-1,3-dioxolane (0.84 mL, 7.19 mmol). The mixture was warmed to 0 °C after 30 min, stirred for 3 hours then warmed to r.t. and stirred for a further 17 hours. The mixture was quenched with H_2O (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (silica gel, 50 x 210 mm, 15% Et_2O / hexane) afforded the title compound **4.4** (543 mg, 3.23 mmol, 44%) as a colourless oil.

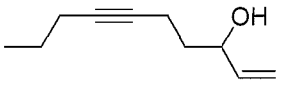
FT-IR ν_{max} (neat) 2961 (m), 2934 (m), 2874 (m), 2337 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 (1H, t, J = 4.8 Hz, C**H**), 3.99-3.91 (2H, m, 2 x OC**H**H), 3.91-3.83 (2H, m, 2 x OCH**H**), 2.30 (2H, tt, J = 7.4, 2.4 Hz, C**H$_2$**CH$_2$CH), 2.12 (2H, tt, J = 7.4, 2.4 Hz, CH$_3$CH$_2$C**H$_2$**), 1.85 (2H, td, J = 7.4, 4.8 Hz, C**H$_2$**CH), 1.50 (2H, sext, J = 7.4 Hz, CH$_3$C**H$_2$**), 0.97 (3H, t, J = 7.4 Hz, C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 103.51 (d, **C**H), 80.50 (s, **C**C), 79.15 (s, C**C**), 65.02 (t, 2 x O**C**H$_2$), 33.57 (t, **C**H$_2$CH), 22.55 (t, CH$_3$**C**H$_2$), 20.85 (t, CH$_3$CH$_2$**C**H$_2$), 13.85 (t, **C**H$_2$CH$_2$CH), 13.55 (q, **C**H$_3$) ppm.

LRMS (CI) Retention time = 7.38 min, *m/z* 186 (10%) $[M+NH_4]^+$, 169 (100%) $[M+H]^+$, 139 (8%) $[M-C_2H_5]^+$, 73 (32%) Da.

Dec-1-en-6-yn-3-ol (4.6)



$C_{10}H_{16}O$

M.W. = 152.12 g/mol

A solution of acetal **4.4** (0.20 g, 1.19 mmol) in MeCN (3 mL) was heated to 70 °C before the addition of CAN (1.63 g, 2.97 mmol) in H_2O (5 mL). Over a period of 5 minutes the dark orange solution changed to a pale yellow solution and the mixture was quenched by the addition of H_2O (5 mL). The aqueous phase was extracted with Et_2O (4 x 3 mL) and the combined organic phases were dried ($MgSO_4$). Crude NMR analysis showed the presence of an aldehydic proton and the crude material was taken through to the next stage. Thus crude oct-4-ynal **4.5** in Et_2O was cooled to −78 °C before the dropwise addition of vinylmagnesium bromide (3.57 mL, 3.57 mmol). The mixture was allowed to warm to r.t. over 12 hours before quenching with a sat. aq. NH_4Cl (8 mL) and H_2O (5 mL). The aqueous phase was extracted with Et_2O (4 x 10 mL), the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to an orange oil. Purification by column chromatography (silica gel, 20 x 100 mm, 20% EtOAc / hexane) afforded the title compound **4.6** (0.007 g, 0.04 mmol, 4%) as a colourless oil.

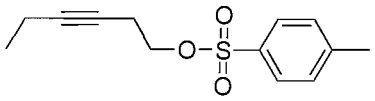
FT-IR ν_{max} (neat) 3368 (brd, w), 2962 (m), 2931 (m), 2871 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (1H, ddd, *J* = 17.2, 10.5, 6.3 Hz, C**H**CH_2), 5.28 (1H, dt, *J* = 17.2, 1.5 Hz, CHC**H**H *trans* to CH), 5.14 (1H, dt, *J* = 10.5, 1.5 Hz, CHCH**H** *cis* to CH), 4.32-4.25 (1H, m, C**H**OH), 2.38-2.20 (2H, m, C**H$_2$**CH_2CHOH), 2.13 (2H, tt, *J* = 7.3, 2.4 Hz, CH_3CH_2C**H$_2$**), 1.77-1.66 (2H, m, C**H$_2$**CHOH), 1.51 (2H, sext, *J* = 7.3 Hz, CH_3C**H$_2$**), 1.26 (1H, brd s, O**H**), 0.98 (3H, t, *J* = 7.3 Hz, C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.70 (d, **C**HCH_2), 114.95 (t, CH**C**H_2), 81.22 (s, **C**C), 79.60 (s, C**C**), 72.37 (d, **C**HOH), 36.10 (t, **C**H_2CHOH), 22.59 (t, CH_3**C**H_2), 20.89 (t, CH_3CH_2**C**H_2), 15.21 (t, **C**H_2CH_2CHOH), 13.61 (q, **C**H_3) ppm.

LRMS (CI) Retention time = 6.97 min, *m/z* 170 (34%) $[M+NH_4]^+$, 153 (100%) $[M+H]^+$, 135 (44%) $[M-OH]^+$ Da.

Hex-3-ynyl 4-methylbenzenesulphonate (4.12)



$C_{13}H_{16}O_3S$

M.W. = 252.33 g/mol

To a solution of 3-hexyn-1-ol (1.98 g, 0.02 mol) in CH_2Cl_2 (30 mL) at 0 °C was added NEt_3 (3.06 g, 0.03 mol) and the resulting mixture stirred for 10 min. A solution of TsCl (5.77 g, 0.03 mol) in CH_2Cl_2 (30 mL) was added dropwise over 15 minutes and the solution was warmed to r.t. after 1 hour and stirred for a further 2 hours. The mixture was quenched by the addition of H_2O (45 mL) and extracted with Et_2O (4 x 25 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to a colourless oil. Purification by column chromatography (silica gel, 80 x 110 mm, 10% EtOAc / hexane) afforded the title compound **4.12** (3.95 g, 0.016 mol, 78%) as a colourless oil.

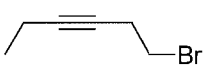
FT-IR ν_{max} (neat) 2978 (w), 1598 (w), 1360 (m), 1176 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (2H, d, J = 8.4 Hz, Ar-**H**), 7.36 (2H, d, J = 8.4 Hz, Ar-**H**), 4.07 (2H, t, J = 7.3 Hz, C**H$_2$**O), 2.52 (2H, tt, J = 7.3, 2.5 Hz, C**H$_2$**CH$_2$O), 2.46 (3H, s, Ar-C**H$_3$**), 2.10 (2H, qt, J = 7.5, 2.5 Hz, CH$_3$C**H$_2$**), 1.08 (3H, t, J = 7.5 Hz, C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.94 (s, **C**CH$_3$), 133.26 (s, SO$_2$**C**), 129.97 (d, 2 x Ar-**C**), 128.10 (d, 2 x Ar-**C**), 84.39 (s, **C**C), 73.39 (s, C**C**), 68.42 (t, **C**H$_2$O), 21.76 (q, **C**CH$_3$), 19.86 (t, **C**H$_2$CH$_2$O), 14.05 (q, **C**H$_3$), 12.41 (t, CH$_3$**C**H$_2$) ppm.

LRMS (EI) Retention time = 9.68 min, *m/z* 252 (2%) $[M]^{+\cdot}$, 155 (72%), 91 (100%) Da.

1-Bromohex-3-yne (4.13)



C_6H_9Br

M.W. = 161.05 g/mol

To a solution of 3-hexyn-1-ol (2.00 g, 20.38 mmol) and PPh_3 (8.02 g, 30.57 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added a solution of CBr_4 (10.14 g, 30.57 mmol) in CH_2Cl_2 (65 mL) dropwise over 30 min. The resulting orange solution was stirred for 1 hour,

concentrated *in vacuo* to an orange oil which was triturated with hexane (50 mL) to remove triphenylphosphine oxide. The organic phases were concentrated *in vacuo* to a colourless oil. Purification by column chromatography (silica gel, 50 x 110 mm, hexane) afforded the title compound **4.13** (2.21 g, 13.74 mmol, 67%) as a colourless oil.

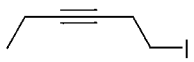
FT-IR ν_{max} (neat) 2974 (m), 2922 (m), 2343 (w), 1211 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.42 (2H, t, J = 7.4 Hz, CH_2Br), 2.71 (2H, tt, J = 7.4, 2.4 Hz, CH_2CH_2Br), 2.17 (2H, qt, J = 7.5, 2.4 Hz, CH_3CH_2), 1.13 (3H, t, J = 7.5 Hz, CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 84.13 (s, **C**C), 76.37 (s, C**C**), 30.44 (t, **C**H_2Br), 23.48 (t, **C**H_2CH_2Br), 14.15 (q, **C**H_3), 12.51 (t, CH_3**C**H_2) ppm.

LRMS (CI) Retention time = 5.59 min, *m/z* 162 and 160 (2%) $[M+H]^+$ (1:1 ratio), 81 (100%) $[M-Br]^+$ Da.

1-Iodohex-3-yne (4.15)



C_6H_9I

M.W. = 207.97 g/mol

To a solution of tosylate **4.12** (500 mg, 1.98 mmol) in acetone (15 mL) was added NaI (594 mg, 3.96 mmol) and the mixture heated to reflux for 4 ½ hours. The mixture was cooled, H_2O (15 mL) added and extracted with Et_2O (3 x 15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to an orange oil. Purification by column chromatography (silica gel, 20 x 60 mm, hexane) afforded the title compound **4.15** (296 mg, 1.42 mmol, 72%) as a colourless oil.

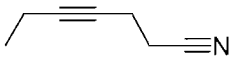
FT-IR ν_{max} (neat) 2974 (m), 2935 (w), 2919 (w), 2876 (w), 1171 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.21 (2H, t, J = 7.4 Hz, CH_2I), 2.73 (2H, tt, J = 7.4, 2.3 Hz, CH_2CH_2I), 2.16 (2H, qt, J = 7.5, 2.3 Hz, CH_3CH_2), 1.14 (3H, t, J = 7.5 Hz, CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 84.04 (s, **C**C), 78.30 (s, C**C**), 24.28 (t, **C**$H_2$$CH_2$I), 14.14 (q, **C**$H_3$), 12.56 (t, CH_3**C**H_2), 2.74 (t, **C**H_2I) ppm.

LRMS (EI) Retention time = 6.27 min, *m/z* 208 (4%) $[M]^{+\cdot}$, 127 (12%) $[M\text{-}C_6H_9]^+$, 81 (100%) $[M\text{-}I]^+$ Da.

Hept-4-ynenitrile (4.17)



C_7H_9N

M.W. = 107.15 g/mol

To a solution of NaCN (959 mg, 19.56 mmol) in DMF (25 mL) at 0 °C was added a solution of bromide **4.13** (900 mg, 5.59 mmol) in DMF (2 mL). The resulting orange solution was warmed to r.t. after 1 hour and stirred for a further 17 hours. The mixture was quenched by pouring the dark orange solution onto ice-water (30 mL) and extracting with Et_2O (3 x 30 mL). The combined organic phases were washed with H_2O (3 x 30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to an orange oil. Purification by column chromatography (silica gel, 40 x 100 mm, 10% Et_2O / hexane) afforded the title compound **4.17** (310 mg, 2.90 mmol, 52%) as a colourless oil.

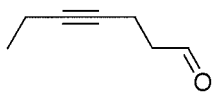
FT-IR ν_{max} (neat) 2979 (m), 2938 (w), 2879 (w), 2251 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.53-2.50 (4H, brd m, C**H$_2$**C**H$_2$**CN), 2.18 (2H, qt, *J* = 7.5, 2.5 Hz, CH_3C**H$_2$**), 1.13 (3H, t, *J* = 7.5 Hz, C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 118.65 (s, **C**N), 84.93 (s, **C**C), 75.11 (s, C**C**), 18.11 (t, **C**H_2), 16.28 (t, **C**H_2), 14.05 (q, **C**H_3), 12.43 (t, CH_3**C**H_2) ppm.

LRMS (CI) Retention time = 6.11 min, *m/z* 125 (12%) $[M+NH_4]^+$, 108 (24%) $[M+H]^+$, 106 (100%), 81 (36%) $[M\text{-}CN]^+$, 67 (59%) $[M\text{-}CH_2CN]^+$ Da.

Hept-4-ynal (4.18)



$C_7H_{10}O$

M.W. = 110.16 g/mol

To a solution of nitrile **4.17** (200 mg, 1.87 mmol) in CH_2Cl_2 (8 mL) at –78 °C was added DIBAL-H (2.8 mL, 2.80 mmol, 1 M solution in hexane) and the resulting mixture was stirred for 1 ½ hours. The reaction was quenched by pouring the mixture onto sat. aq. Rochelle's salt (25 mL) and stirring for 3 hours. The aqueous phase was extracted with Et_2O (3 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to a colourless oil. Purification by column chromatography (silica gel, 40 x 90 mm, 10% Et_2O / pentane) afforded the title compound **4.18** (145 mg, 1.41 mmol, 75%) as a yellow oil.

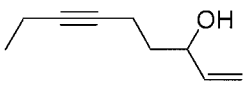
FT-IR ν_{max} (neat) 2976 (m), 2919 (w), 2841 (w), 2729 (w), 2363 (w), 1726 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (1H, t, J = 1.3 Hz, C(O)**H**), 2.65-2.58 (2H, m, C**H$_2$**C(O)H), 2.52-2.45 (2H, m, C**H$_2$**CH$_2$C(O)H), 2.14 (2H, qt, J = 7.5, 2.5 Hz, CH$_3$C**H$_2$**), 1.11 (3H, t, J = 7.5 Hz, C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 201.20 (d, **C**(O)H), 83.07 (s, **C**C), 77.26 (s, C**C**), 43.12 (t, **C**H$_2$C(O)H), 14.25 (q, **C**H$_3$), 12.47 (t, CH$_3$**C**H$_2$), 12.30 (t, **C**H$_2$CH$_2$C(O)H) ppm.

LRMS (CI) Retention time = 5.48 min, *m/z* 128 (3%) $[M+NH_4]^+$, 111 (5%) $[M+H]^+$, 110 (15%), 95 (100%) $[M-CH_3]^+$ Da.

Non-1-en-6-yn-3-ol (4.19)



$C_9H_{14}O$

M.W. = 138.21 g/mol

To a solution of aldehyde **4.18** (228 mg, 2.07 mmol) in Et_2O (10 mL) at –50 °C was added vinylmagnesium bromide (6.21 mL, 6.21 mmol, 1 M solution in THF) dropwise. The resulting mixture was stirred for 2 hours before quenching with H_2O (10 mL) and extracting with Et_2O (3 x 10 mL). The combined organic phases were washed with

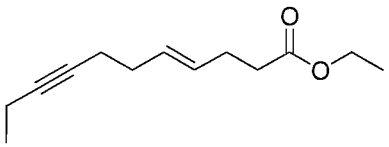
brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (silica gel, 40 x 100 mm, 30% Et_2O / pentane) afforded the title compound **4.19** (125 mg, 0.91 mmol, 44%) as a yellow oil.

FT-IR ν_{max} (neat) 3359 (brd, m), 2976 (m), 2921 (m), 2850 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (1H, ddd, J = 17.2, 10.4, 6.0 Hz, **CH**CH_2), 5.28 (1H, dt, J = 17.2, 1.5 Hz, CHC**H**H *trans* to CH), 5.14 (1H, dt, J = 10.4, 1.5 Hz, CHCH**H** *cis* to CH), 4.33-4.24 (1H, m, C**H**OH), 2.37-2.22 (2H, m, **CH_2**CH_2CHOH), 2.17 (2H, qt, J = 7.4, 2.4 Hz, CH_3**CH_2**), 1.83 (1H, brd d, J = 4.3 Hz, O**H**), 1.75-1.66 (2H, m, **CH_2**CHOH), 1.13 (3H, t, J = 7.4 Hz, **CH_3**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.70 (d, **C**HCH_2), 114.94 (t, $CHCH_2$), 82.74 (s, **C**C), 78.82 (s, C**C**), 72.35 (d, **C**HOH), 36.15 (t, **C**H_2CHOH), 15.18 (t, **C**H_2CH_2CHOH), 14.40 (q, **C**H_3), 12.54 (t, CH_3**C**H_2) ppm.

(4*E*)-Ethyl undec-4-en-8-ynoate (4.20)



$C_{13}H_{20}O_2$

M.W. = 208.30 g/mol

A mixture of alcohol **4.19** (0.40 g, 2.92 mmol), propionic acid (0.02 g, 0.29 mmol) and triethylorthoacetate (2.84 g, 17.50 mmol) were heated to reflux for 4 hours. The mixture was cooled to r.t. before H_2O (8 mL) was added and extracted with EtOAc (4 x 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (silica gel, 30 x 100 mm, 10% Et_2O / hexane) afforded the title compound **4.20** (0.51 g, 2.44 mmol, 83%) as a colourless oil.

FT-IR ν_{max} (neat) 2977 (m), 2919 (m), 2851 (w), 1736 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57-5.43 (2H, m, C**H**C**H**), 4.14 (2H, q, J = 7.1 Hz, OC**H_2**), 2.40-2.27 (4H, m, 2 x C**H_2**), 2.20-2.12 (6H, m, 3

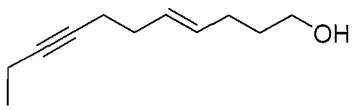
x CH_2), 1.26 (3H, t, J = 7.1 Hz, OCH_2CH_3), 1.12 (3H, t, J = 7.4 Hz, CH_3CH_2) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.30 (s, **C**O), 130.12 (d, **C**HCH), 129.41 (d, CH**C**H), 82.22 (s, **C**C), 79.00 (s, C**C**), 60.38 (t, OCH_2), 34.46 (t, CH_2), 32.35 (t, CHCHCH_2), 28.04 (t, CH_2CHCH), 19.27 (t, CH_2), 14.49 (q, CH_3), 14.40 (q, CH_3), 12.55 (t, CH_3CH_2) ppm.

LRMS (ES^+) *m/z* 231 (100%) $[M+Na]^+$ Da.

HRMS (EI) for $C_{13}H_{20}O_2$, calculated 208.1463, found 208.1462 Da.

(4*E*)-Undec-4-en-8-yn-1-ol (4.21)



$C_{11}H_{18}O$

M.W. = 166.26 g/mol

To a solution of ester **4.20** (0.51 g, 2.45 mmol) in THF (15 mL) at –30 °C was added $LiAlH_4$ (2.45 mL, 2.45 mmol, 1 M solution in THF) and the resulting cloudy solution was warmed to r.t. over 30 min and stirred for a further 30 min. The mixture was quenched by the addition of H_2O (0.1 mL) followed by 15% aq. NaOH (0.1 mL) and H_2O (0.3 mL). The white precipitate was removed by filtration and the organic phase concentrated *in vacuo* to a colourless oil. Purification by column chromatography (silica gel, 30 x 100 mm, 25% EtOAc / hexane) afforded the title compound **4.21** (0.39 g, 2.35 mmol, 96%) as a colourless oil.

FT-IR ν_{max} (neat) 3323 (brd m), 2975 (m), 2935 (s), 2848 (m) cm^{-1}.

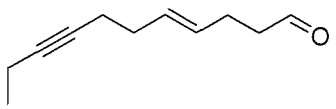
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.53-5.45 (2H, m, C**H**C**H**), 3.70-3.62 (2H, m, CH_2OH), 2.24-2.06 (8H, m, 4 x CH_2), 1.65 (2H, tt, J = 6.7, 6.5 Hz, CH_2CH_2OH), 1.28 (1H, t, J = 5.3 Hz, O**H**), 1.12 (3H, t, J = 7.4 Hz, CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 130.90 (d, **C**HCH), 129.57 (d, CH**C**H), 82.23 (s, **C**C), 79.10 (s, C**C**), 62.68 (t, CH_2OH), 32.49 (t, CH_2), 32.36 (t, CH_2), 29.06 (t, $CH_2CH_2CH_2$OH), 19.34 (t, CH_2), 14.48 (q, CH_3), 12.55 (t, CH_3CH_2) ppm.

LRMS (CI) Retention time = 7.71 min, *m/z* 184 (6%) $[M+NH_4]^+$, 149 (8%), 135 (18%) $[M-CH_2OH]^+$, 91 (26%), 81 (100%) $[C_6H_9]^+$ Da.

HRMS (EI) for $C_{11}H_{18}O$, calculated 166.13577, found 166.13601 Da.

(4*E*)-Undec-4-en-8-ynal (4.22)



$C_{11}H_{16}O$

M.W. = 164.24 g/mol

To a solution of alcohol **4.21** (3.0 g, 18 mmol) in CH_2Cl_2 (120 mL) at 0 °C was added a solution of DMP (9.18 g, 22 mmol) in CH_2Cl_2 (40 mL). The cloudy white solution was warmed to r.t. after 5 min and was stirred at this temperature for a further 5 hours. Pentane (30 mL) was added and the white precipitate removed by filtration through silica, washing with Et_2O / pentane (20%, 200 mL). The organic phases were concentrated *in vacuo* affording the title compound **4.22** (2.79 g, 17 mmol, 94%) as a colourless oil which required no further purification.

FT-IR ν_{max} (neat) 2976 (w), 2914 (w), 2844 (w), 1726 (s) cm^{-1}.

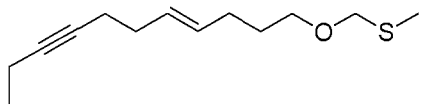
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (1H, t, *J* = 1.8 Hz, C(O)**H**), 5.58-5.44 (2H, m, C**H**C**H**), 2.54-2.47 (2H, m, C**H$_2$**C(O)H), 2.39-2.32 (2H, m, C**H$_2$**CH$_2$C(O)H), 2.22-2.12 (6H, m, CH$_3$C**H$_2$**CCC**H$_2$**CH$_2$), 1.12 (3H, t, *J* = 7.4 Hz, C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 202.35 (d, **C**(O)H), 130.39 (d, **C**HCH), 129.11 (d, CH**C**H), 82.31 (s, **C**C), 78.91 (s, C**C**), 43.57 (t, **C**H$_2$C(O)H), 32.27 (t, **C**H$_2$), 25.30 (t, **C**H$_2$CH$_2$C(O)H), 19.21 (t, **C**H$_2$), 14.49 (q, **C**H$_3$), 12.54 (t, CH$_3$**C**H$_2$) ppm.

LRMS (ES$^+$) *m/z* 187 (100%) $[M+Na]^+$ Da.

HRMS (EI) for $C_{11}H_{16}O$, calculated 164.1201, found 164.1203 Da.

(((4*E*)-Undec-4-en-8-ynyloxy)methyl) methyl sulphane (4.23)



$C_{13}H_{22}OS$

M.W. = 226.38 g/mol

To a solution of alcohol **4.21** (100 mg, 0.60 mmol) in DMSO (3 mL) at r.t. was added NEt_3 (0.55 mL, 3.98 mmol) followed by SO_3·pyridine complex (574 mg, 3.61 mmol). The resulting solution was stirred for 1 hour before quenching with 10% aq. $KHSO_4$ (7 mL). The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. The title compound **4.23** was separated from aldehyde **4.22** by column chromatography (silica gel, 10 x 130 mm, 5% Et_2O / pentane) and was obtained as a colourless oil (20 mg, 0.09 mmol, 15%).

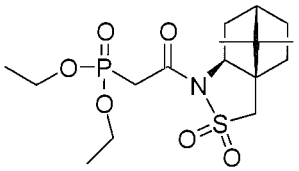
FT-IR ν_{max} (neat) 2972 (w), 2919 (m), 1089 (s), 1072 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51-5.46 (2H, m, **CHCH**), 4.63 (2H, s, OCH_2S), 3.53 (2H, t, J = 6.7 Hz, CH_2O), 2.24-2.05 (11H, m, 4 x CH_2 and SCH_3), 1.67 (2H, quin, J = 6.7 Hz, CH_2CH_2O), 1.12 (3H, t, J = 7.4 Hz, CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 130.71 (d, **C**HCH), 129.48 (d, CH**C**H), 82.15 (s, **C**C), 79.15 (s, C**C**), 75.35 (t, OCH_2S), 67.70 (t, CH_2O), 32.43 (t, CH_2), 29.34 (t, CH_2), 29.28 (t, CH_2), 19.38 (t, CH_2), 14.51 (q, CH_3), 14.07 (q, SCH_3), 12.56 (t, CH_3CH_2) ppm.

LRMS (CI) Retention time = 8.65 min *m/z* 244 (42%) $[M+NH_4]^+$, 227 (64%) $[M+H]^+$, 179 (96%), 161 (60%), 119 (50%), 78 (100%), 61 (66%) Da.

Diethyl 2-oxo-2-*N*-((2*S*)-camphor-10,2-sultam)-ethyl phosphonate (3.13)



$C_{16}H_{28}NO_6PS$

M.W. = 393.44 g/mol

The title compound **3.13** was prepared according to a modified method by Oppolzer *et al.*[186] To a solution of (2*S*)-camphor sultam (12.92 g, 60 mmol) in CH_2Cl_2 (250 mL) was added NaH (3.12 g, 78 mmol) portionwise over 5 min. The resulting grey cloudy solution was stirred for 40 min then cooled to –60 °C before the dropwise addition of chloroacetyl chloride (8.19 g, 72 mmol). The mixture was warmed to r.t. over 1 ½ hours and was stirred for a further 4 ½ hours before quenching with H_2O (50 mL) and sat. aq. NH_4Cl (30 mL). The aqueous phase was extracted with CH_2Cl_2 (4 x 100 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to an off-white solid. The crude solid was combined with $P(OEt)_3$ (9.29 g, 56 mmol) and the mixture was heated to 150 °C for 2 hours. The resulting mixture was cooled to r.t. and directly purified by column chromatography (silica gel, 80 x 80 mm, 30-100% EtOAc / hexane). Further purification by Kugelrohr bulb-to-bulb distillation (100 °C, 0.2 mbar) afforded the title compound **3.13** (15.51 g, 39 mmol, 65%) as a thick yellow oil. Spectroscopic data was in agreement with the literature.[88]

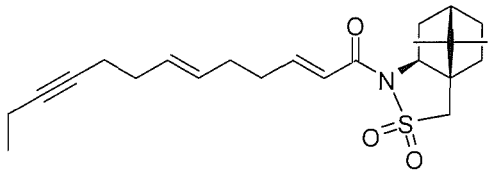
FT-IR ν_{max} (neat) 2963 (w), 1692 (m), 1329 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.25-4.11 (4H, m, 2 x $POCH_2$), 3.90 (1H, dd, J = 7.6, 4.9 Hz, NCH), 3.58 (1H, dd, J = 20.3, 15.4 Hz, P(O)CHHCO), 3.52 (1H, d, J = 13.8 Hz, $CHHSO_2$), 3.44 (1H, d, J = 13.8 Hz, $CHHSO_2$), 3.21 (1H, dd, J = 22.4, 15.4 Hz, P(O)CHHCO), 2.21-2.03 (2H, m, $NCHCH_2$), 1.98-1.83 (3H, m, $NCHCH_2CHCHHCHH$), 1.46-1.36 (2H, m, $NCHCH_2CHCHHCHH$), 1.34 (6H, td, J = 7.0, 2.8 Hz, 2 x $POCH_2CH_3$), 1.19 (3H, s, CH_3), 0.98 (3H, s, CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.74 (s, doublet, J_{P-C} = 6.8 Hz, CO), 65.43 (d, NCH), 62.96 (t, doublet, J_{P-C} = 6.8 Hz, $POCH_2$), 62.67 (t, doublet, J_{P-C} = 6.8 Hz, $POCH_2$), 53.05 (t, CH_2SO_2), 48.46 (s,

	C$(CH_3)_2$), 47.97 (s, **C**CH_2SO_2), 44.78 (d, NCHCH_2**C**H), 38.35 (t, NCH**C**H_2), 35.15 (t, doublet, $J_{P\text{-}C}$ = 136.2 Hz, P(O)**C**H_2CO), 32.95 (t, **C**H_2), 26.62 (t, **C**H_2), 20.85 (q, **C**H_3), 20.04 (q, **C**H_3), 16.50 (q, doublet, $J_{P\text{-}C}$ = 5.8 Hz, POCH$_2$**C**H_3), 16.44 (q, d, J = 5.8 Hz, POCH$_2$**C**H_3) ppm.
^{31}P NMR	(121 MHz, $CDCl_3$) δ 19.87 (**P**) ppm.
LRMS	(ES$^+$) *m/z* 809 (49%) $[2M+Na]^+$, 416 (100%) $[M+Na]^+$ Da.

(2*S*)-*N*-((2*E*,6*E*)-Trideca-2,6-dien-10-ynoyl)-camphor-10,2-sultam (4.24)



$C_{23}H_{33}NO_3S$

M.W. = 403.58 g/mol

To a solution of phosphonate **3.13** (902 mg, 2.29 mmol) in THF (25 mL) was added NaH (92 mg, 2.29 mmol) in one portion. The resulting cloudy grey mixture was stirred for 1 hour before the dropwise addition of aldehyde **4.22** (359 mg, 2.18 mmol) in THF (3 mL). The solution was stirred for a further 6 ½ hours before quenching with sat. aq. NH_4Cl (30 mL). The aqueous phase was extracted with EtOAc (3 x 30 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (silica gel, 50 x 150 mm, 10% EtOAc / hexane) afforded the title compound **4.24** (620 mg, 1.54 mmol, 70%) as a white crystalline solid.

$[\alpha]^{20}_D$	+67.05 (*c* 0.56, $CHCl_3$).
M.p	76-78 °C.
FT-IR	ν_{max} (neat) 2958 (m), 2917 (m), 2845 (w), 1680 (s), 1638 (s), 1326 (s) cm^{-1}.
^{1}H NMR	(400 MHz, $CDCl_3$) δ 7.08 (1H, dt, J = 15.1, 6.8 Hz, **CH**CHCO), 6.57 (1H, dt, J = 15.1, 1.5 Hz, **CH**CO), 5.57-5.41 (2H, m, **CHCH**), 3.93 (1H, dd, J = 7.5, 5.0 Hz, NC**H**), 3.51 (1H, d, J = 13.8 Hz, C**H**HSO$_2$), 3.44 (1H, d, J = 13.8 Hz, CH**H**SO$_2$), 2.37-2.28 (2H, m, C**H**$_2$CHCHCO), 2.23-2.05 (10H, m, 4 x C**H**$_2$ and NCHC**H**$_2$), 1.98-1.84 (3H, m, NCHCH$_2$C**H**C**H**HC**H**H), 1.47-

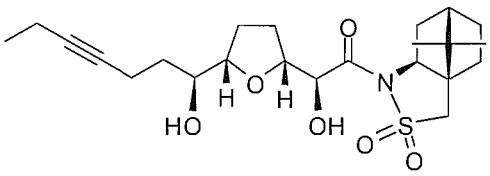
1.32 (2H, m, $NCHCH_2CHCH\mathbf{H}CH\mathbf{H}$), 1.18 (3H, s, $CC\mathbf{H_3}$), 1.12 (3H, t, J = 7.5 Hz, $C\mathbf{H_3}$), 0.98 (3H, s, $CC\mathbf{H_3}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.24 (s, **C**O), 150.20 (d, **C**HCHCO), 130.19 (d, **C**HCH), 129.68 (d, CH**C**H), 121.28 (d, **C**HCO), 82.17 (s, **C**C), 79.08 (s, C**C**), 65.31 (d, N**C**H), 53.32 (t, $\mathbf{C}H_2SO_2$), 48.58 (s, $\mathbf{C}(CH_3)_2$), 47.93 (s, $\mathbf{C}CH_2SO_2$), 44.88 (d, $NCHCH_2\mathbf{C}H$), 38.67 (t, $\mathbf{C}H_2$), 33.02 (t, $NCH\mathbf{C}H_2$), 32.58 (t, $\mathbf{C}H_2$), 32.36 (t, $\mathbf{C}H_2$), 31.04 (t, $\mathbf{C}H_2$), 26.65 (t, $\mathbf{C}H_2$), 20.99 (q, $C\mathbf{C}H_3$), 20.04 (q, $C\mathbf{C}H_3$), 19.27 (t, $\mathbf{C}H_2$), 14.50 (q, $\mathbf{C}H_3$), 12.55 (t, $CH_3\mathbf{C}H_2$) ppm.

LRMS (ES^+) *m/z* 829 (63%) $[2M+Na]^+$, 426 (100%) $[M+Na]^+$, 404 (15%) $[M+H]^+$ Da.

HRMS (ES^+) for $C_{23}H_{34}NO_3S^+$, calculated 404.2254, found 404.2256 Da.

(2*S*)-*N*-((2*S*)-2-Hydroxy-2-((2*R*,5*S*)-5-((1*S*)-1-hydroxyhept-4-ynyl)-tetrahydrofuran-2-yl)ethanoyl)-camphor-10,2-sultam (4.25)



$C_{23}H_{35}NO_6S$

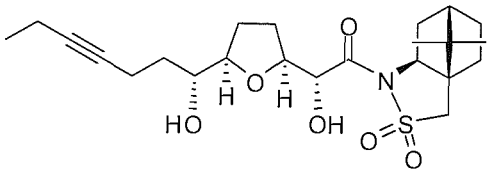
M.W. = 453.59 g/mol

To a solution of dienyne **4.24** (106 mg, 0.26 mmol) in acetone (3 mL) and AcOH (2 mL) at –30 °C was added $KMnO_4$ (54 mg, 0.34 mmol). The solution immediately turned purple which changed to brown over 5 min. The mixture was stirred between –30 °C and –20 °C for 40 min before quenching with sat. aq. $Na_2S_2O_5$ (8 mL). The aqueous phase was extracted with EtOAc (4 x 8 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to a thick yellow oil. Purification by column chromatography (silica gel, 20 x 130 mm, 30% EtOAc / hexane) afforded three different fractions. The major diastereoisomer **4.25** (title compound) (64 mg, 0.14 mmol, 54%) was obtained as a white crystalline solid, the minor diastereoisomer **4.26** (10 mg, 0.02 mmol, 8%) as a colourless oil and the hydroxy-ketone by-product **4.27**, an inseparable mixture of diastereoisomers, (11 mg, 0.03 mmol, 10%) as a yellow oil.

Data for major diastereoisomer (4.25)

$[\alpha]^{20}_D$	+24.54 (*c* 0.54, $CHCl_3$).
FT-IR	ν_{max} (neat) 3444 (brd, w), 2956 (m), 2882 (m), 1688 (m), 1328 (s) cm^{-1}.
^{1}H NMR	(400 MHz, $CDCl_3$) δ 4.61-4.53 (2H, m, C**H**C**H**(OH)CO), 3.96 (1H, dd, *J* = 7.8, 4.9 Hz, NC**H**), 3.89 (1H, td, *J* = 7.0, 4.2 Hz, C**H**), 3.62 (1H, dt, *J* = 9.0, 3.8 Hz, C**H**OH), 3.52 (1H, d, *J* = 13.7 Hz, C**H**HSO_2), 3.45 (1H, d, *J* = 13.7 Hz, CH**H**SO_2), 2.36-2.20 (3H, m, $CH_3CH_2CCC\mathbf{H_2}$ and NCHC**H**H), 2.15 (2H, qt, *J* = 7.6, 2.2 Hz, $CH_3C\mathbf{H_2}$), 2.12-2.03 (3H, m, $C\mathbf{H_2}$ THF and NCHCH**H**), 1.98-1.84 (5H, m, $C\mathbf{H_2}$ THF and NCHCH_2C**H**C**H**HC**H**H), 1.77-1.59 (2H, m, $C\mathbf{H_2}$CHOH), 1.47-1.30 (2H, m, NCHCH_2CHCH**H**CH**H**), 1.16 (3H, s, CC$\mathbf{H_3}$), 1.11 (3H, t, *J* = 7.6 Hz, $C\mathbf{H_3}$), 0.98 (3H, s, CC$\mathbf{H_3}$) ppm. Hydroxyl proton signals not observed.
^{13}C NMR	(100 MHz, $CDCl_3$) δ 171.82 (s, **C**O), 83.04 (d, **C**H), 82.40 (s, **C**C), 79.03 (s, C**C**), 78.80 (d, **C**H), 73.67 (d, **C**H), 72.99 (d, **C**HOH), 65.95 (d, N**C**H), 53.18 (t, **C**H_2SO_2), 49.18 (s, **C**$(CH_3)_2$), 48.01 (s, **C**CH_2SO_2), 44.70 (d, NCHCH_2**C**H), 38.38 (t, NCH**C**H_2), 34.03 (t, **C**H_2CH(OH)), 33.04 (t, **C**H_2), 28.44 (t, **C**H_2 THF), 28.26 (t, **C**H_2 THF), 26.52 (t, **C**H_2), 20.96 (q, C**C**H_3), 20.02 (q, C**C**H_3), 15.49 (t, **C**H_2), 14.43 (q, **C**H_3), 12.55 (t, CH_3**C**H_2) ppm.
LRMS	(ES^+) *m/z* 929 (20%) $[2M+Na]^+$, 476 (100%) $[M+Na]^+$ Da.
HRMS	(ES^+) for $C_{23}H_{36}NO_6S^+$, calculated 454.2258, found 454.2257 Da.

Data for minor diastereoisomer: (2*S*)-*N*-((2*R*)-2-Hydroxy-2-((2*S*,5*R*)-5-((1*R*)-1-hydroxyhept-4-ynyl)-tetrahydrofuran-2-yl)ethanoyl)-camphor-10,2-sultam (4.26)

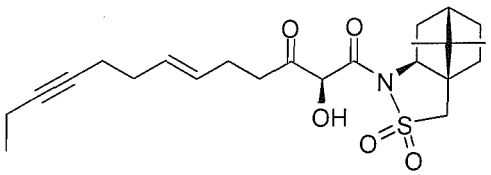


$C_{23}H_{35}NO_6S$

M.W. = 453.59 g/mol

$[\alpha]^{20}_D$	+98.05 (*c* 0.52, $CHCl_3$).
FT-IR	ν_{max} (neat) 3454 (brd, w), 2955 (m), 2879 (m), 1692 (m), 1329 (s) cm^{-1}.
^{1}H NMR	(400 MHz, $CDCl_3$) δ 4.68 (1H, dd, *J* = 8.7, 1.9 Hz, C**H**), 4.50 (1H, ddd, *J* = 7.4, 5.1, 2.0 Hz, C**H**OH), 3.96 (1H, t, *J* = 6.3 Hz, NC**H**), 3.80 (1H, td, *J* = 7.0, 4.5 Hz, C**H**), 3.62 (1H, d, *J* = 8.8 Hz, C**H**OH), 3.57 (2H, brd s, 2 x O**H**), 3.50 (1H, d, *J* = 13.7 Hz, C**H**HSO$_2$), 3.45 (1H, d, *J* = 13.7 Hz, CH**H**SO$_2$), 2.35-2.28 (2H, m, C**H$_2$**CH$_2$CHOH), 2.24-2.11 (2H, m, CH$_3$C**H$_2$**), 2.10-2.01 (4H, m, NCHC**H$_2$** and C**H$_2$** THF), 2.00-1.85 (5H, m, C**H$_2$** THF and NCHCH$_2$C**H**C**H**HC**H**H), 1.69-1.53 (2H, m, C**H$_2$**CHOH), 1.51-1.32 (2H, m, NCHCH$_2$CHCH**H**CH**H**), 1.16 (3H, s, CC**H$_3$**), 1.12 (3H, t, *J* = 7.5 Hz, C**H$_3$**), 0.98 (3H, s, CC**H$_3$**) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ 173.21 (s, **C**O), 83.00 (d, **C**H), 82.29 (s, CH$_3$CH$_2$**C**C), 80.39 (d, **C**HOH), 79.04 (s, CH$_3$CH$_2$C**C**), 74.25 (d, **C**H), 72.78 (d, **C**HOH), 65.08 (d, N**C**H), 53.12 (t, **C**H$_2$SO$_2$), 49.19 (s, **C**(CH$_3$)$_2$), 48.08 (s, **C**CH$_2$SO$_2$), 44.62 (d, NCHCH$_2$**C**H), 37.80 (t, NCH**C**H$_2$), 34.10 (t, **C**H$_2$CHOH), 32.74 (t, **C**H$_2$), 28.30 (t, **C**H$_2$ THF), 27.90 (t, **C**H$_2$ THF), 26.69 (t, **C**H$_2$), 20.52 (q, C**C**H$_3$), 20.06 (q, C**C**H$_3$), 15.44 (t, **C**H$_2$CH$_2$CHOH), 14.46 (q, **C**H$_3$), 12.56 (t, CH$_3$**C**H$_2$) ppm.
LRMS	(ES$^+$) *m/z* 476 (100%) [M+Na]$^+$ Da.

Data for hydroxy-ketone by-product: (2*S*)-*N*-((2*S*,6*E*)-2-Hydroxy-3-oxotridec-6-en-10-ynoyl)-camphor-10,2-sultam (4.27)



$C_{23}H_{33}NO_5S$

M.W. = 435.58 g/mol

+ diastereoisomer

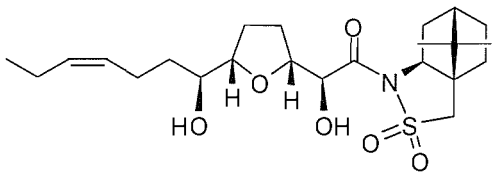
$[\alpha]^{20}_D$	+73.52 (*c* 0.46, $CHCl_3$).
FT-IR	ν_{max} (neat) 3455 (brd w), 2963 (m), 2917 (m), 1726 (s), 1689 (s), 1331 (s) cm^{-1}.
^{1}H NMR	(400 MHz, $CDCl_3$) δ 5.56-5.37 (2H, m, C**H**C**H**), 5.24 (1H, s, C**H**OH), 3.95 (1H, dd, *J* = 7.5, 5.0 Hz, NC**H**), 3.52 (1H, d, *J* = 13.8 Hz, C**H**HSO$_2$), 3.47 (1H, d, *J* = 13.8 Hz, CH**H**SO$_2$), 2.81 (1H, dt, *J* = 18.1, 7.4 Hz, C**H**HCO), 2.66 (1H, dt, *J* = 17.8, 7.4 Hz, CH**H**CO), 2.38-2.26 (2H, m, C**H$_2$**CH$_2$CO), 2.22-2.02 (8H, m, CH$_3$C**H$_2$**CCC**H$_2$**C**H$_2$** and NCHC**H$_2$**), 1.99-1.85 (3H, m, NCHCH$_2$C**H**C**H**HC**H**H), 1.53-1.31 (2H, m, NCHCH$_2$CHCH**H**CH**H**), 1.16 (3H, s, CC**H$_3$**), 1.11 (3H, t, *J* = 7.2 Hz, C**H$_3$**), 0.99 (3H, s, CC**H$_3$**) ppm. Hydroxyl proton signal not observed.
^{13}C NMR	(100 MHz, $CDCl_3$) δ 203.23 (s, CH$_2$**C**O), 168.31 (s, **C**(O)N), 130.20 (d, **C**HCH), 129.01 (d, CH**C**H), 82.20 (s, CH$_3$CH$_2$**C**C), 79.00 (s, CH$_3$CH$_2$C**C**), 76.59 (d, **C**HOH), 65.20 (d, N**C**H), 52.98 (t, **C**H$_2$SO$_2$), 49.21 (s, **C**(CH$_3$)$_2$), 48.03 (s, **C**CH$_2$SO$_2$), 44.70 (d, NCHCH$_2$**C**H), 39.26 (t, **C**H$_2$CO), 37.90 (t, **C**H$_2$), 32.94 (t, **C**H$_2$), 32.34 (t, **C**H$_2$), 26.56 (t, **C**H$_2$CH$_2$CO), 26.15 (t, **C**H$_2$), 20.55 (q, **C**CH$_3$), 20.06 (q, **C**CH$_3$), 19.21 (t, **C**H$_2$), 14.47 (q, **C**H$_3$), 12.53 (t, CH$_3$**C**H$_2$) ppm.
LRMS	(ES$^+$) *m/z* 458 (100%) [M+Na]$^+$ Da.
HRMS	(ES$^+$) for $C_{23}H_{34}NO_6S^+$, calculated 436.2152, found 436.2154 Da.

Selected data for minor diastereoisomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16 (1H, s, C(O)C**H**(OH)CO), 3.57 (1H, d, J = 13.8 Hz, C**H**HSO$_2$), 3.49 (1H, d, J = 13.8 Hz, CH**H**SO$_2$), 1.18 (3H, s, CC**H$_3$**), 0.99 (3H, s, CC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 203.69 (s, CH_2**C**O), 167.67 (s, **C**(O)N), 130.33 (d, **C**HCH), 76.03 (d, **C**HOH), 65.47 (d, N**C**H), 53.06 (t, **C**H$_2$SO$_2$), 49.16 (s, **C**(CH$_3$)$_2$), 44.84 (d, NCHCH$_2$**C**H), 39.30 (t, **C**H$_2$CO), 38.70 (t, **C**H$_2$), 33.01 (t, **C**H$_2$), 32.30 (t, **C**H$_2$), 26.49 (t, **C**H$_2$CH$_2$CO), 26.26 (t, **C**H$_2$), 21.02 (q, C**C**H$_3$), 19.98 (q, C**C**H$_3$) ppm.

(2*S*)-*N*-((2*S*)-2-Hydroxy-2-((2*R*,5*S*)-5-((1*S*,4*Z*)-1-hydroxyhept-4-enyl)-tetrahydrofuran-2-yl)ethanoyl)-camphor-10,2-sultam (4.28)



$C_{23}H_{37}NO_6S$

M.W. = 455.61 g/mol

To a solution of mono-THF **4.25** (85 mg, 0.19 mmol) in EtOAc (5 mL) was added Pd / $CaCO_3$ (40 mg, 19 μmol) followed by quinoline (2 drops). The resulting black mixture was evacuated, placed under an atmosphere of hydrogen and was stirred for 16 hours. The mixture was filtered, the black residue washed with EtOAc (3 mL) and the organic phase washed with 2 M HCl (3 x 5 mL) and brine (5 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to afford the title compound **4.28** (70 mg, 0.15 mmol, 81%) as a colourless sticky oil which required no further purification.

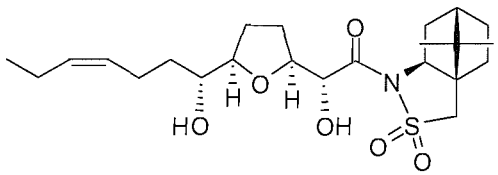
$[\alpha]^{20}_D$ +31.16 (*c* 0.65, $CHCl_3$).

FT-IR ν_{max} (neat) 3434 (brd w), 2959 (m), 2876 (m), 1687 (s), 1328 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43-5.27 (2H, m, C**H**C**H**), 4.60-4.52 (2H, m, C**H**C**H**(OH)CO), 3.96 (1H, dd, J = 7.8, 5.3 Hz, NC**H**), 3.86 (1H, td, J = 7.3, 4.5 Hz, C**H**), 3.52 (1H, d, J = 13.8 Hz, C**H**HSO$_2$), 3.51-3.46 (1H, m, C**H**OH), 3.44 (1H, d, J = 13.8 Hz,

	CH**H**SO_2), 2.29-2.14 (3H, m, $C\mathbf{H_2}CH_2CHOH$ and NCHC**H**H), 2.14-2.00 (5H, m, $CH_3C\mathbf{H_2}$, $C\mathbf{H_2}$ THF and NCHCH**H**), 1.97-1.82 (5H, m, $C\mathbf{H_2}$ THF and $NCHCH_2C\mathbf{H}C\mathbf{H}HC\mathbf{H}H$), 1.64-1.30 (4H, m, $C\mathbf{H_2}CHOH$ and $NCHCH_2CHCH\mathbf{H}CH\mathbf{H}$), 1.16 (3H, s, $CC\mathbf{H_3}$), 0.97 (3H, s, $CC\mathbf{H_3}$), 0.96 (3H, t, J = 7.5 Hz, $C\mathbf{H_3}$) ppm. Hydroxyl proton signals not observed.
^{13}C NMR	(100 MHz, $CDCl_3$) δ 171.79 (s, **C**O), 132.43 (d, **C**HCH), 128.63 (d, CH**C**H), 83.25 (d, **C**H), 78.74 (d, **C**HCH(OH)CO), 73.64 (d, **C**HOH), 73.55 (d, **C**HOH), 65.92 (d, N**C**H), 53.16 (t, $\mathbf{C}H_2SO_2$), 49.17 (s, $\mathbf{C}(CH_3)_2$), 48.00 (s, $\mathbf{C}CH_2SO_2$), 44.67 (d, $NCHCH_2\mathbf{C}H$), 38.36 (t, $NCH\mathbf{C}H_2$), 34.63 (t, $\mathbf{C}H_2CHOH$), 33.01 (t, $\mathbf{C}H_2$), 28.44 (t, $\mathbf{C}H_2$ THF), 28.29 (t, $\mathbf{C}H_2$ THF), 26.50 (t, $\mathbf{C}H_2$), 23.53 (t, $\mathbf{C}H_2CH_2CHOH$), 20.94 (q, $C\mathbf{C}H_3$), 20.64 (t, $CH_3\mathbf{C}H_2$), 19.99 (q, $C\mathbf{C}H_3$), 14.45 (q, $\mathbf{C}H_3$) ppm.
LRMS	(ES^+) *m/z* 933 (10%) $[2M+Na]^+$, 478 (100%) $[M+Na]^+$ Da.
HRMS	(ES^+) for $C_{23}H_{37}NO_6SNa^+$, calculated 478.2234, found 478.2232 Da.

(2*S*)-*N*-((2*R*)-2-Hydroxy-2-((2*S*,5*R*)-5-((1*R*,4*Z*)-1-hydroxyhept-4-enyl)-tetrahydrofuran-2-yl)ethanoyl)-camphor-10,2-sultam (4.29)



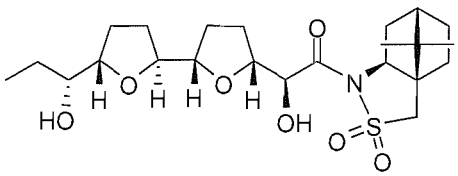
$C_{23}H_{37}NO_6S$

M.W. = 455.61 g/mol

To a solution of mono-THF **4.26** (540 mg, 1.19 mmol) in EtOAc (30 mL) was added Pd / $CaCO_3$ (253 mg, 0.12 mmol) followed by quinoline (5 drops). The resulting black mixture was evacuated, placed under an atmosphere of hydrogen and stirred for 16 hours. The mixture was filtered, the black residue washed with EtOAc (20 mL) and the organic phase washed with 2 M HCl (3 x 15 mL) and brine (20 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (silica gel, 30 x 120 mm, 30% EtOAc / hexane) afforded the title compound **4.29** (381 mg, 0.84 mmol, 70%) as a thick colourless oil.

$[\alpha]^{24}_D$	+120.18 (*c* 0.55, $CHCl_3$).
FT-IR	ν_{max} (neat) 3485 (brd, w), 2957 (m), 2877 (m), 1690 (m), 1327 (s) cm^{-1}.
^{1}H NMR	(400 MHz, $CDCl_3$) δ 5.44-5.27 (2H, m, C**H**C**H**), 4.68 (1H, d, *J* = 2.0 Hz, C**H**(OH)CO), 4.50 (1H, ddd, *J* = 7.4, 5.0, 2.0 Hz, C**H**CH(OH)CO), 3.96 (1H, app t, *J* = 6.2 Hz, NC**H**), 3.78 (1H, td, *J* = 7.3, 4.5 Hz, C**H**), 3.50 (1H, d, *J* = 13.8 Hz, C**H**HSO_2), 3.45 (1H, d, *J* = 13.8 Hz, CH**H**SO_2), 3.44 (1H, td, *J* = 8.5, 4.4 Hz, C**H**OH), 2.27-1.85 (13H, m, 2 x C**H$_2$** THF, $CH_3C\mathbf{H_2}CHCHC\mathbf{H_2}$ and NCHC**H$_2$**C**H**CH**H**C**H**H), 1.57-1.32 (4H, m, C**H$_2$**CHOH and NCHC**H$_2$**CHCH**H**C**H**H), 1.15 (3H, s, CC**H$_3$**), 0.98 (3H, s, CC**H$_3$**), 0.96 (3H, t, *J* = 7.5 Hz, C**H$_3$**) ppm. Hydroxyl proton signals not observed.
^{13}C NMR	(100 MHz, $CDCl_3$) δ 173.25 (s, **C**O), 132.41 (d, **C**HCH), 128.63 (d, CH**C**H), 83.11 (d, **C**H), 80.32 (d, **C**HCH(OH)CO), 74.31 (d, **C**H(OH)CO), 73.31 (d, **C**HOH), 65.05 (d, N**C**H), 53.09 (t, **C**H$_2$$SO_2$), 49.17 (s, **C**(CH$_3$)$_2$), 48.05 (s, **C**CH$_2$$SO_2$), 44.59 (d, NCHCH$_2$**C**H), 37.75 (t, NCH**C**H$_2$), 34.74 (t, **C**H$_2$CHOH), 32.71 (t, **C**H$_2$), 28.32 (t, **C**H$_2$ THF), 27.89 (t, **C**H$_2$ THF), 26.67 (t, **C**H$_2$), 23.48 (t, $CH_3CH_2CHC\mathbf{H}CH_2$), 20.62 (t, $CH_3\mathbf{C}H_2$), 20.49 (q, C**C**H$_3$), 20.04 (q, C**C**H$_3$), 14.48 (q, **C**H$_3$) ppm.
LRMS	(ES$^+$) *m/z* 478 (100%) $[M+Na]^+$ Da.

(2*S*)-*N*-((2*S*)-2-Hydroxy-2-((2*R*,5*S*)-5-((2*S*,5*S*)-5-((1*R*)-1-hydroxypropyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)ethanoyl)-camphor-10,2-sultam (4.30)



$C_{23}H_{37}NO_7S$

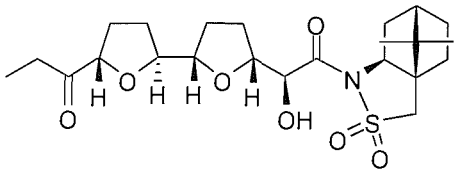
M.W. = 471.61 g/mol

To a solution of Re_2O_7 (638 mg, 1.32 mmol) in THF (8 mL) was added TFAA (0.25 mL, 369 mg, 1.76 mmol) and the resulting pale yellow solution was stirred for 1 hour, over which time it changed colour to pale black. The THF was removed *in vacuo* at 0 °C and the deep purple residue was washed with freshly distilled hexane (4 x 4 mL).

The purple residue was dissolved in CH_2Cl_2 (20 mL) before the dropwise addition of hydroxy olefin **4.28** (200 mg, 0.44 mmol) in CH_2Cl_2 (5 mL). The resulting black solution was stirred for 1 hour before quenching with sat. aq. $KHSO_4$ (10 mL) and H_2O (10 mL). The aqueous phase was extracted with EtOAc (4 x 20 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to an orange oil. Purification by column chromatography (silica gel, 30 x 120 mm, 60% EtOAc / hexane) afforded the title compound **4.30** (137 mg, 0.29 mmol, 66%) as a yellow solid and the over-oxidised by-product **4.31** (12 mg, 0.03 mmol, 6%) as a colourless gum.

$[\alpha]^{24}_D$	+28.78 (*c* 0.45, $CHCl_3$).
FT-IR	ν_{max} (neat) 3400 (brd, w), 2959 (m), 2878 (m), 1692 (m), 1457 (s), 1328 (s) cm^{-1}.
^{1}H NMR	(400 MHz, $CDCl_3$) δ 4.68-4.62 (1H, m, C**H**CH(OH)CO), 4.51 (2H, appt qd, *J* = 10.0, 2.3 Hz, C**H**(OH)CO and O**H**), 4.14 (1H, td, *J* = 7.3, 4.1 Hz, $CH_3CH_2CH(OH)C\mathbf{H}$), 4.02-3.92 (4H, m, **CHCH**, NC**H** and O**H**), 3.76 (1H, dt, *J* = 8.3, 4.1 Hz, $CH_3CH_2C\mathbf{H}OH$), 3.50 (1H, d, *J* = 13.7 Hz, C**H**HSO_2), 3.42 (1H, d, *J* = 13.7 Hz, CH**H**SO_2), 2.24-1.83 (13H, 4 x $C\mathbf{H_2}$ THF and $NCHC\mathbf{H_2}C\mathbf{H}C\mathbf{H}HC\mathbf{H}H$), 1.52-1.30 (4H, m, $CH_3C\mathbf{H_2}$ and $NCHCH_2CHC\mathbf{H}\mathbf{H}C\mathbf{H}\mathbf{H}$), 1.17 (3H, s, $CC\mathbf{H_3}$), 0.99 (3H, t, *J* = 7.3 Hz, $C\mathbf{H_3}$), 0.97 (3H, s, $CC\mathbf{H_3}$) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ 172.02 (s, **C**O), 82.83 (d, $CH_3CH_2CH(OH)\mathbf{C}H$), 81.62 (d, **C**H), 81.58 (d, **C**H), 78.92 (d, **C**HCH(OH)CO), 74.72 (d, **C**H(OH)CO), 73.43 (d, **C**HOH), 66.10 (d, N**C**H), 53.39 (t, $\mathbf{C}H_2SO_2$), 48.92 (s, $\mathbf{C}(CH_3)_2$), 47.91 (s, $\mathbf{C}CH_2SO_2$), 44.93 (d, $NCHCH_2\mathbf{C}H$), 38.61 (t, $NCH\mathbf{C}H_2$), 33.27 (t, $\mathbf{C}H_2$), 29.40 (t, $\mathbf{C}H_2$ THF), 28.93 (t, $\mathbf{C}H_2$ THF), 28.66 (t, $\mathbf{C}H_2$ THF), 26.50 (t, $\mathbf{C}H_2$), 25.62 (t, $\mathbf{C}H_2$), 25.26 (t, $\mathbf{C}H_2$ THF), 21.17 (q, $C\mathbf{C}H_3$), 20.04 (q, $C\mathbf{C}H_3$), 10.54 (q, $\mathbf{C}H_3$) ppm.
LRMS	(ES^+) *m/z* 494 (100%) $[M+Na]^+$ Da.
HRMS	(ES^+) for $C_{23}H_{38}NO_7S^+$, calculated 472.2364, found 472.2363 Da.

(2*S*)-*N*-((2*S*)-2-Hydroxy-2-((2*R*,5*S*)-5-((2*S*,5*S*)-5-(1-oxopropyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)ethanoyl)-camphor-10,2-sultam (4.31)



$C_{23}H_{35}NO_7S$

M.W. = 469.59 g/mol

FT-IR ν_{max} (neat) 3390 (brd, w), 2959 (m), 2878 (m), 1782 (w), 1697 (s), 1329 (s) cm^{-1}.

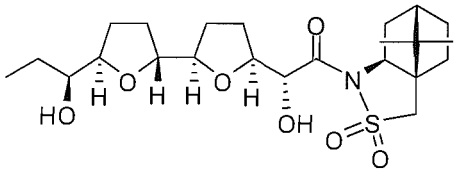
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71-4.63 (2H, m, C**H**CH(OH)CO and C(O)C**H**), 4.45 (2H, appt qd, *J* = 10.4, 2.3 Hz, C**H**(O**H**)CO), 4.16-4.09 (1H, m, C**H**), 4.05-3.99 (1H, m, C**H**), 3.97 (1H, dd, *J* = 7.9, 5.0 Hz, NC**H**), 3.51 (1H, d, *J* = 13.7 Hz, C**H**HSO$_2$), 3.42 (1H, d, *J* = 13.7 Hz, CH**H**SO$_2$), 2.70-2.49 (2H, m, CH$_3$C**H$_2$**), 2.34-1.81 (13H, m, 4 x C**H$_2$** THF and NCHC**H$_2$**C**H**C**H**HC**H**H), 1.46-1.33 (2H, m, NCHCH$_2$CHCH**H**CH**H**), 1.17 (3H, s, CC**H$_3$**), 1.06 (3H, t, *J* = 7.3 Hz, C**H$_3$**), 0.98 (3H, s, CC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 212.92 (s, CH_2**C**O), 172.18 (s, CH(OH)**C**O), 83.81 (d, CH_2C(O)**C**H), 82.13 (d, **C**H), 81.34 (d, **C**H), 79.14 (d, **C**HCH(OH)CO), 74.82 (d, **C**H(OH)CO), 66.22 (d, N**C**H), 53.46 (t, **C**H$_2$SO$_2$), 48.95 (s, **C**(CH$_3$)$_2$), 47.93 (s, **C**CH$_2$SO$_2$), 44.94 (d, NCHCH$_2$**C**H), 38.67 (t, NCH**C**H$_2$), 33.29 (t, **C**H$_2$), 31.86 (t, CH$_3$**C**H$_2$), 29.09 (t, **C**H$_2$ THF), 28.87 (t, **C**H$_2$ THF), 28.63 (t, **C**H$_2$ THF), 28.60 (t, **C**H$_2$), 26.51 (t, **C**H$_2$ THF), 21.14 (q, C**C**H$_3$), 20.04 (q, C**C**H$_3$), 7.34 (q, **C**H$_3$) ppm.

LRMS (ES$^+$) *m/z* 492 (100%) [M+Na]$^+$ Da.

HRMS (ES$^+$) for $C_{23}H_{36}NO_7S^+$, calculated 470.2207, found 470.2219 Da.

(2*S*)-*N*-((2*R*)-2-Hydroxy-2-((2*S*,5*R*)-5-((2*R*,5*R*)-5-((1*S*)-1-hydroxypropyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)ethanoyl)-camphor-10,2-sultam (4.32)



$C_{23}H_{37}NO_7S$

M.W. = 471.61 g/mol

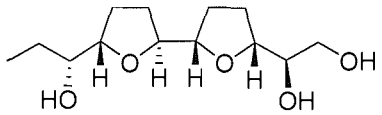
To a solution of Re_2O_7 (319 mg, 0.66 mmol) in THF (5 mL) was added TFAA (0.12 mL, 184 mg, 0.88 mmol) and the resulting pale yellow solution was stirred for 1 hour, over which time it changed colour to pale black. The THF was removed *in vacuo* at 0 °C and the deep purple residue was washed with freshly distilled hexane (3 x 4 mL). The purple residue was dissolved in CH_2Cl_2 (10 mL) before the dropwise addition of hydroxyalkene **4.29** (100 mg, 0.22 mmol) in CH_2Cl_2 (2 mL). The resulting black solution was stirred for 1 ½ hours before quenching with sat. aq. $KHSO_4$ (5 mL) and H_2O (5 mL). The aqueous phase was extracted with EtOAc (4 x 10 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to a brown oil. Purification by column chromatography (silica gel, 20 x 120 mm, 40% EtOAc / hexane) afforded the title compound **4.32** (55 mg, 0.12 mmol, 53%) as a white solid which was recrystallised from Et_2O.

M.p	162-164 °C.
$[\alpha]^{24}_D$	+126.20 (*c* 0.36, $CHCl_3$).
FT-IR	ν_{max} (neat) 3386 (brd, w), 2958 (m), 2877 (m), 1706 (m), 1324 (s) cm^{-1}.
^{1}H NMR	(400 MHz, $CDCl_3$) δ 4.61 (1H, brd s, C**H**(OH)CO), 4.55 (1H, dd, *J* = 7.0, 3.0 Hz, C**H**CH(OH)CO), 4.28-4.22 (1H, m, $CH_3CH_2CH(OH)C\mathbf{H}$), 4.02-3.89 (3H, m, C**H**C**H** and NC**H**), 3.77 (1H, dt, *J* = 8.5, 4.1 Hz, $CH_3CH_2C\mathbf{H}OH$), 3.48 (1H, d, *J* = 13.6 Hz, C**H**HSO$_2$), 3.44 (1H, d, *J* = 13.6 Hz, CH**H**SO$_2$), 2.20-1.81 (13H, m, 4 x C**H$_2$** THF and NCHC**H$_2$**C**H**C**H**H**H**C**H**H**), 1.56-1.31 (4H, m, $CH_3C\mathbf{H_2}$ and $NCHCH_2CHCH\mathbf{H}CH\mathbf{H}$), 1.17 (3H, s, CC**H$_3$**), 1.02 (3H, t, *J* = 7.4 Hz, C**H$_3$**), 0.97 (3H, s, CC**H$_3$**) ppm. Hydroxyl proton signals not observed.

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.47 (s, **C**O), 82.72 (d, **C**H), 81.51 (d, **C**HCH), 81.35 (d, CH**C**H), 80.53 (d, **C**HCH(OH)CO), 75.89 (d, **C**H(OH)CO), 73.60 (d, CH_3CH_2**C**HOH), 64.94 (d, N**C**H), 53.04 (t, **C**H_2SO_2), 48.97 (s, **C**$(CH_3)_2$), 47.98 (s, **C**CH_2SO_2), 44.54 (d, NCHCH$_2$**C**H), 37.84 (d, NCH**C**H_2), 32.65 (t, **C**H_2), 29.33 (t, **C**H_2 THF), 28.98 (t, **C**H_2 THF), 28.43 (t, **C**H_2 THF), 26.67 (t, **C**H_2), 25.66 (t, CH_3**C**H_2), 25.39 (t, **C**H_2 THF), 20.66 (q, C**C**H_3), 20.02 (q, C**C**H_3), 10.51 (q, **C**H_3) ppm.

LRMS (ES^+) *m/z* 494 (100%) $[M+Na]^+$ Da.

(1*R*)-1-((2*R*,5*S*)-5-((2*S*,5*S*)-5-((1*R*)-1-Hydroxypropyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)-ethane-1,2-diol (4.33)



$C_{13}H_{24}O_5$

M.W. = 260.33 g/mol

To a solution of *bis*-THF **4.30** (97 mg, 0.20 mmol) in THF (4 mL) and H_2O (2 mL) at 0 °C was added $NaBH_4$ (31 mg, 0.82 mmol). The resulting mixture was warmed to r.t. after 10 min and stirred for a further 3 hours. The mixture was quenched with sat. aq. NH_4Cl (2 mL) and H_2O (2 mL) and extracted with EtOAc (8 x 5 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to a white solid. Purification by column chromatography (silica gel, 10 x 90 mm, 5-10% MeOH / CH_2Cl_2) afforded the title compound **4.33** (26 mg, 0.10 mmol, 50%) as a colourless oil.

$[\alpha]^{25}_D$ −13.88 (*c* 0.40, $CHCl_3$).

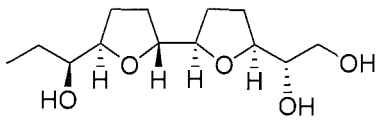
FT-IR ν_{max} (neat) 3395 (brd, m), 2966 (m), 2925 (m), 2872 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11-4.05 (1H, m, CHCH(OH)CH_2OH), 4.01-3.87 (3H, m, 3 x C**H**), 3.78-3.71 (1H, m, C**H**OH), 3.70-3.64 (2H, m, C**H$_2$**OH), 3.57-3.50 (1H, m, C**H**(OH)CH_2OH), 2.72 (2H, brd s, 2 x O**H**), 2.55 (1H, brd s, O**H**), 2.07-1.67 (8H, m, 4 x C**H$_2$** THF), 1.47-1.35 (2H, m, CH_3C**H$_2$**), 0.99 (3H, t, *J* = 7.4 Hz, C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 83.06 (d, CH(OH)**C**H), 82.42 (d, **C**H), 82.19 (d, **C**H), 81.11 (d, **C**HCH(OH)CH_2OH), 74.45 (d,

	CH(OH)CH_2OH), 73.56 (d, **C**HOH), 65.43 (t, **C**H_2OH), 29.58 (t, **C**H_2 THF), 28.62 (t, **C**H_2 THF), 28.47 (t, **C**H_2 THF), 25.90 (t, CH_3**C**H_2), 25.24 (t, **C**H_2 THF), 10.79 (q, **C**H_3) ppm.
LRMS	(ES^+) *m/z* 283 (100%) $[M+Na]^+$ Da.
HRMS	(ES^+) for $C_{13}H_{25}O_5^+$, calculated 261.1696, found 261.1697 Da.

(1*S*)-1-((2*S*,5*R*)-5-((2*R*,5*R*)-5-((1*S*)-1-Hydroxypropyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)-ethane-1,2-diol (*ent*-4.33)



$C_{13}H_{24}O_5$

M.W. = 260.33 g/mol

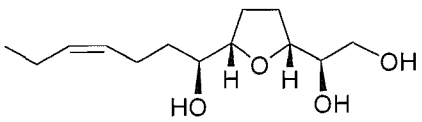
To a solution of *bis*-THF **4.32** (49 mg, 0.10 mmol) in THF (2 mL) and H_2O (1 mL) at 0 °C was added $NaBH_4$ (16 mg, 0.42 mmol). The resulting mixture was warmed to r.t. after 10 min and was stirred for a further 3 hours. The mixture was quenched with sat. aq. NH_4Cl (1 mL) and H_2O (1 mL) and extracted with EtOAc (8 x 3 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to a white solid. Purification by column chromatography (silica gel, 5 x 90 mm, 5-10% MeOH / CH_2Cl_2) afforded the title compound ***ent*-4.33** (15 mg, 0.06 mmol, 57%) as a colourless oil.

$[\alpha]^{27}_D$	+18.52 (*c* 0.44, $CHCl_3$).
FT-IR	ν_{max} (neat) 3375 (brd, m), 2962 (m), 2921 (m), 2868 (m) cm^{-1}.
^{1}H NMR	(400 MHz, $CDCl_3$) δ 4.10-4.04 (1H, m, **CH**CH(OH)CH_2OH), 4.00-3.86 (3H, m, 3 x **CH**), 3.77-3.71 (1H, m, **CH**OH), 3.68 (2H, d, *J* = 4.8 Hz, **CH_2**OH), 3.56-3.50 (1H, m, **CH**(OH)CH_2OH), 2.78 (2H, brd s, 2 x **OH**), 2.68 (1H, brd s, **OH**), 2.07-1.66 (8H, m, 4 x **CH_2** THF), 1.46-1.35 (2H, m, CH_3**CH_2**), 0.98 (3H, t, *J* = 7.4 Hz, **CH_3**) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ 83.05 (d, CH(OH)**C**H), 82.45 (d, **C**H), 82.21 (d, **C**H), 81.10 (d, **C**HCH(OH)CH_2OH), 74.45 (d, **C**H(OH)CH_2OH), 73.53 (d, **C**HOH), 65.38 (t, **C**H_2OH), 29.57 (t, **C**H_2 THF), 28.59 (t, **C**H_2 THF), 28.43 (t, **C**H_2 THF), 25.89 (t, CH_3**C**H_2), 25.20 (t, **C**H_2 THF), 10.79 (q, **C**H_3) ppm.

LRMS (ES$^+$) *m/z* 283 (100%) $[M+Na]^+$ Da.

HRMS (ES$^+$) for $C_{13}H_{25}O_5^+$, calculated 261.1696, found 261.1699 Da.

(1*R*)-1-((2*R*,5*S*)-5-((1*S*,4*Z*)-1-Hydroxyhept-4-enyl)-tetrahydrofuran-2-yl)-ethane-1,2-diol (4.36)



$C_{13}H_{24}O_4$

M.W. = 244.33 g/mol

To a solution of mono-THF alkene **4.28** (99 mg, 0.22 mmol) in THF (3 mL) and H_2O (1.5 mL) at 0 °C was added $NaBH_4$ (33 mg, 0.87 mmol). The resulting mixture was warmed to r.t. after 10 min and was stirred for a further 1 hour before quenching with 2 M HCl (3 mL). The aqueous phase was extracted with EtOAc (5 x 5 mL) and the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo* to a colourless oil. Purification by column chromatography (silica gel, 10 x 14 mm, 5% MeOH / CH_2Cl_2) afforded the title compound **4.36** (41 mg, 0.17 mmol, 76%) as a colourless oil.

$[\alpha]^{20}_D$ -13.59 (*c* 0.66, $CHCl_3$).

FT-IR ν_{max} (neat) 3330 (brd, m), 2958 (m), 2931 (m), 2870 (m) cm^{-1}.

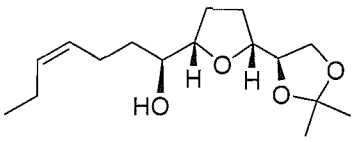
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46-5.28 (2H, m, C**H**C**H**), 4.06-3.99 (1H, m, C**H**CH(OH)CH_2OH), 3.91-3.83 (1H, m, C**H**), 3.71 (2H, brd d, *J* = 4.0 Hz, C**H$_2$**OH), 3.62-3.55 (1H, m, C**H**(OH)CH_2OH), 3.48 (1H, dt, *J* = 8.4, 4.5 Hz, C**H**OH), 2.30-1.77 (8H, m, $CH_3CH_2CHCHCH_2$ and 2 x C**H$_2$** THF), 1.67-1.43 (2H, m, C**H$_2$**CHOH), 0.97 (3H, t, *J* = 7.6 Hz, C**H$_3$**) ppm. Hydroxyl proton signals not observed.

^{13}C NMR (100 MHz, $CDCl_3$) δ 132.62 (d, **C**HCH), 128.50 (d, CH**C**H), 82.97 (d, **C**H), 80.55 (d, **C**HCH(OH)CH_2OH), 73.98 (d, **C**HOH), 73.81 (d, **C**HOH), 65.22 (t, **C**H_2OH), 34.47 (t, **C**H_2CHOH), 28.16 (t, **C**H_2 THF), 28.13 (t, **C**H_2 THF), 23.52 (t, **C**H_2CH_2CHOH), 20.67 (t, CH_3**C**H_2), 14.45 (q, **C**H_3) ppm.

LRMS (ES$^+$) *m/z* 267 (100%) $[M+Na]^+$ Da.

HRMS (ES$^+$) for $C_{13}H_{24}O_4SNa^+$, calculated 267.1567, found 267.1565 Da.

(1*S*,4*Z*)-1-((2*S*,5*R*)-5-((4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-tetrahydrofuran-2-yl)-hept-4-en-1-ol (4.38)



$C_{16}H_{28}O_4$
M.W. = 284.39 g/mol

To a solution of mono-THF **4.36** (210 mg, 0.86 mmol) in 2,2-dimethoxypropane (7 mL) was added *p*-TsOH (50 mg). The colourless solution was allowed to stir for 15 hours before diluting with EtOAc (10 mL) and washing with sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to a colourless oil. Purification by column chromatography (silica gel, 20 x 100 mm, 20% EtOAc / hexane) afforded the title compound **4.38** (186 mg, 0.65 mmol, 76%) as a colourless oil.

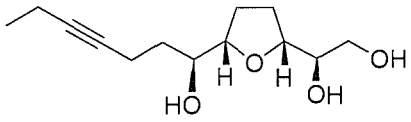
FT-IR ν_{max} (neat) 3473 (brd, w), 2962 (m), 2935 (m), 2875 (m) cm^{-1}.

^{1}H NMR (400 MHz, C_6H_6) δ 5.53-5.42 (2H, m, C**H**C**H**), 3.81-3.59 (5H, m, C**H**$_2$OC(CH$_3$)$_2$ and 3 x C**H**), 3.46-3.32 (1H, m, C**H**), 2.44-2.25 (2H, m, CHC**H**$_2$), 2.15-2.04 (2H, m, CH$_3$C**H**$_2$), 1.77-1.60 (3H, C**H**HCHOH and C**H**$_2$ THF), 1.57-1.40 (3H, m, CH**H**CHOH and C**H**$_2$ THF), 1.47 (3H, s, CC**H**$_3$), 1.27 (3H, s, CC**H**$_3$), 0.95 (3H, t, *J* = 7.5 Hz, C**H**$_3$) ppm. Hydroxyl proton signal not observed.

^{13}C NMR (100 MHz, C_6H_6) δ 132.28 (d, **C**HCH), 129.35 (d, CH**C**H), 109.49 (s, **C**(CH$_3$)$_2$), 83.03 (d, **C**H), 78.45 (d, **C**H), 77.90 (d, **C**H), 73.85 (d, **C**H), 66.32 (t, **C**H$_2$OC(CH$_3$)$_2$), 35.12 (t, **C**H$_2$CHOH), 28.49 (t, **C**H$_2$ THF), 28.21 (t, **C**H$_2$ THF), 26.67 (q, C**C**H$_3$), 25.71 (q, C**C**H$_3$), 23.95 (t, **C**H$_2$), 20.94 (t, CH$_3$**C**H$_2$), 14.63 (q, **C**H$_3$) ppm.

LRMS (ES$^+$) *m/z* 307 (100%) [M+Na]$^+$ Da.

(1*R*)-1-((2*R*,5*S*)-5-((1*S*)-1-Hydroxyhept-4-ynyl)-tetrahydrofuran-2-yl)-ethane-1,2-diol (4.41)



$C_{13}H_{22}O_4$

M.W. = 242.31 g/mol

To a solution of mono-THF alkyne **4.25** (377 mg, 0.83 mmol) in THF (12 mL) and H_2O (6 mL) at 0 °C was added $NaBH_4$ (126 mg, 3.32 mmol). The resulting solution was warmed to r.t. after 10 min and was stirred for a further 1 hour before quenching with 2 M HCl (5 mL). The aqueous phase was extracted with EtOAc (6 x 10 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to an orange oil. Purification by column chromatography (silica gel, 40 x 120 mm, 5% MeOH / CH_2Cl_2) afforded the title compound **4.41** (156 mg, 0.64 mmol, 76%) as a colourless gum.

FT-IR ν_{max} (neat) 3373 (brd, s), 2969 (m), 2920 (s), 2875 (m) cm^{-1}.

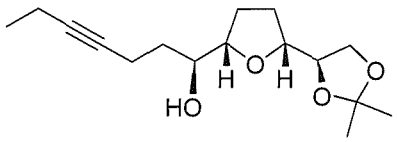
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 (1H, td, *J* = 6.6, 3.8 Hz, C**H**CH(OH)CH_2OH), 3.92 (1H, td, *J* = 6.8, 4.1 Hz, C**H**), 3.73 (2H, d, *J* = 4.8 Hz, C**H_2**OH), 3.66 (1H, dt, *J* = 9.0, 4.0 Hz, C**H**OH), 3.63-3.58 (1H, m, C**H**OH), 2.34 (2H, tt, *J* = 6.5, 2.5 Hz, C**H_2**CH_2CHOH), 2.16 (2H, qd, *J* = 7.5, 2.5 Hz, CH_3C**H_2**), 2.04-1.90 (4H, m, 2 x C**H_2** THF), 1.78-1.60 (2H, m, C**H_2**CHOH), 1.12 (3H, t, *J* = 7.5 Hz, C**H_3**) ppm. Hydroxyl proton signals not observed.

^{13}C NMR (100 MHz, $CDCl_3$) δ 82.81 (d, CH(OH)**C**H), 80.58 (d, **C**HCH(OH)CH_2OH), 78.94 (s, CH_3CH_2**C**C), 77.35 (s, CH_3CH_2C**C**), 73.96 (d, **C**HOH), 73.27 (d, **C**HOH), 65.29 (t, **C**H_2OH), 33.78 (t, **C**H_2CHOH), 28.17 (t, **C**H_2 THF), 28.11 (t, **C**H_2 THF), 15.49 (t, **C**H_2CH_2CHOH), 14.42 (q, **C**H_3), 12.54 (t, CH_3**C**H_2) ppm.

LRMS (ES^+) *m/z* 265 (100%) $[M+Na]^+$ Da.

HRMS (ES^+) for $C_{13}H_{22}O_4Na^+$, calculated 265.1410, found 265.1407 Da.

(1*S*)-1-((2*S*,5*R*)-5-((4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-tetrahydrofuran-2-yl)-hept-4-yn-1-ol (4.43)



$C_{16}H_{26}O_4$

M.W. = 282.38 g/mol

To a solution of triol **4.41** (60 mg, 0.25 mmol) in 2,2-dimethoxypropane (3 mL) was added *p*-TsOH (15 mg) and the resulting mixture was stirred for 17 hours. The solution was diluted with EtOAc (5 mL) and washed with sat. aq. $NaHCO_3$ (5 mL) and brine (2 x 5 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* affording the title compound **4.43** (40 mg, 0.14 mmol, 57%) as a colourless oil which required no further purification.

FT-IR ν_{max} (neat) 3374 (brd, m), 2920 (m), 2874 (m), 1061 (s) cm^{-1}.

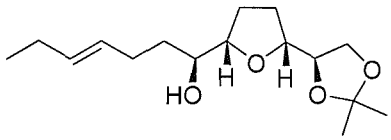
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11 (1H, ddd, *J* = 7.8, 6.5, 4.5 Hz, C**H**OC$(CH_3)_2$), 4.04-3.96 (2H, m, **CH** and CH**H**OC$(CH_3)_2$), 3.93-3.88 (1H, m, C**H**), 3.78 (1H, t, *J* = 7.8 Hz, CH**H**OC$(CH_3)_2$), 3.57 (1H, dt, *J* = 9.3, 4.3 Hz, C**H**OH), 2.40-2.25 (2H, m, C**H$_2$**CH_2CHOH), 2.15 (2H, qt, *J* = 7.5, 2.4 Hz, CH_3C**H$_2$**), 2.04-1.78 (4H, m, 2 x C**H$_2$** THF), 1.75-1.58 (2H, m, C**H$_2$**CHOH), 1.45 (3H, s, CC**H$_3$**), 1.38 (3H, s, CC**H$_3$**), 1.11 (3H, t, *J* = 7.5 Hz, C**H$_3$**) ppm. Hydroxyl proton signal not observed.

^{13}C NMR (100 MHz, $CDCl_3$) δ 109.74 (s, **C**$(CH_3)_2$), 82.71 (d, CH(OH)**C**H), 82.14 (s, CH_3CH_2**C**C), 79.18 (d, **C**H), 79.12 (s, CH_3CH_2C**C**), 78.15 (d, **C**HOC$(CH_3)_2$), 73.29 (d, **C**HOH), 66.29 (t, **C**H_2OC$(CH_3)_2$), 33.78 (t, **C**H_2CHOH), 28.24 (t, **C**H_2 THF), 28.16 (**C**H_2 THF), 26.56 (q, C**C**H_3), 25.62 (q, C**C**H_3), 15.35 (t, **C**H_2CH_2CHOH), 14.47 (q, **C**H_3), 12.56 (t, CH_3**C**H_2) ppm.

LRMS (ES^+) *m/z* 305 (20%) $[M+Na]^+$, 300 (55%) $[M+NH_4]^+$, 283 (100%) $[M+H]^+$, 265 (55%), 243 (50%) Da.

HRMS (ES^+) for $C_{16}H_{26}O_4Na^+$, calculated 305.1723, found 305.1727 Da.

(1*S*,4*E*)-1-((2*S*,5*R*)-5-((4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-tetrahydrofuran-2-yl)-hept-4-en-1-ol (4.44)



$C_{16}H_{28}O_4$

M.W. = 284.39 g/mol

Ammonia (5 mL) was condensed at −78 °C before the addition of sodium (30 mg, 1.30 g-atom) in small pieces and the solution turned a deep blue colour. Mono-THF acetal **4.43** (50 mg, 0.18 mmol) in THF (2 mL) was added dropwise and the resulting mixture was stirred at −78 °C for 3 ½ hours before warming to r.t. to allow the ammonia to evaporate. The residue was quenched with sat. aq. NH_4Cl (4 mL) and extracted with EtOAc (4 x 5 mL). The combined organic phases were washed with 2 M HCl (10 mL), sat. aq. $NaHCO_3$ (10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to a colourless oil. Purification by column chromatography (silica gel, 10 x 100 mm, 20% EtOAc / hexane) afforded the title compound **4.44** (8 mg, 0.03 mmol, 16%) as a colourless oil.

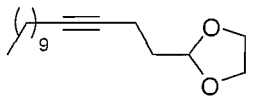
FT-IR ν_{max} (neat) 3471 (brd, w), 2983 (m), 2963 (m), 2936 (m), 2874 (m) cm^{-1}.

^{1}H NMR (400 MHz, C_6H_6) δ 5.59-5.45 (2H, m, C**H**C**H**), 3.82-3.59 (5H, m, C**H**$_2$OC(CH$_3$)$_2$ and 3 x C**H**), 3.45-3.38 (1H, m, C**H**), 2.45-2.35 (1H, m, CHC**H**H), 2.31-2.20 (1H, m, CHCH**H**), 2.02-1.93 (2H, m, CH$_3$C**H**$_2$), 1.80-1.62 (3H, m, C**H**HCHOH and C**H**$_2$ THF), 1.59-1.40 (3H, m, CH**H**CHOH and C**H**$_2$ THF), 1.47 (3H, s, CC**H**$_3$), 1.28 (3H, s, CC**H**$_3$), 0.95 (3H, t, J = 7.4 Hz, C**H**$_3$) ppm. Hydroxyl proton signal not observed.

^{13}C NMR (100 MHz, C_6H_6) δ 132.47 (d, **C**HCH), 129.54 (d, CH**C**H), 109.49 (s, **C**(CH$_3$)$_2$), 83.01 (d, **C**H), 78.45 (d, **C**H), 77.91 (d, **C**H), 73.85 (d, **C**H), 66.32 (t, **C**H$_2$OC(CH$_3$)$_2$), 35.09 (t, **C**H$_2$CHOH), 29.36 (t, **C**H$_2$CH$_2$CHOH), 28.46 (t, **C**H$_2$ THF), 28.22 (t, **C**H$_2$ THF), 26.67 (q, C**C**H$_3$), 26.09 (t, CH$_3$**C**H$_2$), 25.71 (q, C**C**H$_3$), 14.23 (q, **C**H$_3$) ppm.

LRMS (ES$^+$) *m/z* 307 (100%) [M+Na]$^+$ Da.

2-(Tetradec-3-ynyl)-1,3-dioxolane (5.1)



$C_{17}H_{30}O_2$

M.W. = 266.42 g/mol

The title compound **5.1** was prepared according to the method described by Carballeira *et al.*[167] To a solution of dodecyne (6.0 g, 36 mmol) in THF (75 mL) at −78 °C was added *n*-BuLi (14.43 mL, 36 mmol, 2.5 M solution in THF) and the resulting mixture was allowed to warm to −50 °C over 1 hour. HMPA (12.93 g, 72 mmol) was added followed by 2,2-bromoethyl-1,3-dioxolane (6.5 g, 36 mmol) and the resulting yellow solution was warmed to r.t. over 2 hours and stirred for a further 3 hours. The mixture was quenched by the addition of sat. aq. NH_4Cl (25 mL) and H_2O (20 mL). The aqueous phase was extracted with EtOAc (4 x 20 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to an orange liquid. Purification by column chromatography (silica gel, 50 x 140 mm, 0-5% Et_2O / hexane) afforded the title compound **5.1** (5.3 g, 20 mmol, 55%) as a colourless oil. Spectroscopic data was in agreement with the literature.[167]

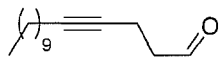
FT-IR ν_{max} (neat) 2951 (m), 2924 (s), 2853 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 (1H, t, J = 4.8 Hz, C**H**), 4.01-3.82 (4H, m, 2 x O**C**$\mathbf{H_2}$), 2.30 (2H, tt, J = 7.4, 2.5 Hz, C$\mathbf{H_2}$$CH_2$CH), 2.13 (2H, tt, J = 7.0, 2.5 Hz, C$\mathbf{H_2}$CC), 1.85 (2H, td, J = 7.4, 4.8 Hz, C$\mathbf{H_2}$CH), 1.52-1.42 (2H, m, C$\mathbf{H_2}$$CH_2$CC), 1.40-1.21 (14H, m, 7 x C$\mathbf{H_2}$), 0.89 (3H, t, J = 7.0 Hz, C$\mathbf{H_3}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 103.79 (d, **C**H), 80.99 (s, **C**C), 79.23 (s, **C**C), 65.28 (t, 2 x O$\mathbf{C}$$H_2$), 33.82 (t, **C**$H_2$CH), 32.26 (t, **C**$H_2$), 29.94 (t, **C**$H_2$), 29.91 (t, **C**$H_2$), 29.68 (t, **C**$H_2$), 29.52 (t, **C**$H_2$), 29.43 (t, **C**$H_2$), 29.23 (t, **C**$H_2$), 23.03 (t, **C**$H_2$), 19.10 (t, CC**C**$H_2$), 14.45 (q, **C**$H_3$), 14.13 (t, **C**$H_2$$CH_2$CC) ppm.

LRMS (CI) Retention time = 9.28 min, *m/z* 284 (20%) $[M+NH_4]^+$, 267 (100%) $[M+H]^+$, 205 (22%), 73 (60%) Da.

Pentadec-4-ynal (5.2)



$C_{15}H_{26}O$

M.W. = 222.37 g/mol

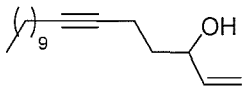
A solution of acetal **5.1** (6.0 g, 23.0 mmol), AcOH (192 mL) and H_2O (48 mL) was heated to 95 °C for 5 ½ hours, cooled to r.t. and diluted with EtOAc (100 mL). The aqueous phase was extracted with further portions of EtOAc (3 x 100 mL) and the combined organic phases washed with brine (2 x 100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to an orange liquid. Purification by column chromatography (silica gel, 50 x 130 mm, 0-3% Et_2O / hexane) afforded the title compound **5.2** (4.5 g, 20.4 mmol, 89%) as a colourless oil.

FT-IR ν_{max} (neat) 2924 (s), 2854 (s), 1728 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (1H, t, J = 1.4 Hz, C(O)**H**), 2.65-2.59 (2H, m, C**H$_2$**C(O)H), 2.52-2.46 (2H, m, C**H$_2$**C**H$_2$**C(O)H), 2.13 (2H, tt, J = 7.2, 2.4 Hz, C**H$_2$**C), 1.51-1.42 (2H, m, C**H$_2$**C**H$_2$**C), 1.39-1.20 (14H, m, 7 x C**H$_2$**), 0.89 (3H, t, J = 6.8 Hz, C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 201.46 (d, **C**(O)H), 82.02 (s, **C**C), 78.87 (s, C**C**), 43.37 (t, **C**H$_2$C(O)H), 32.26 (t, **C**H$_2$), 29.93 (t, **C**H$_2$), 29.88 (t, **C**H$_2$), 29.67 (t, **C**H$_2$), 29.49 (t, **C**H$_2$), 29.28 (t, **C**H$_2$), 29.21 (t, **C**H$_2$), 23.03 (t, **C**H$_2$), 19.02 (t, **C**H$_2$CC), 14.46 (q, **C**H$_3$), 12.56 (t, **C**H$_2$CH$_2$C(O)H) ppm.

Heptadec-1-en-6-yn-3-ol (5.3)



$C_{17}H_{30}O$

M.W. = 250.42 g/mol

The title compound **5.3** was prepared according to the method described by Avedissian *et al.*[69] THF (45 mL) was cooled to –40 °C before the addition of vinylmagnesium bromide (8.1 mL, 8.10 mmol, 1 M solution in THF) followed by aldehyde **5.2** (600 mg, 2.70 mmol). The resulting yellow solution was allowed to stir between –40 and –30 °C for 3 hours before quenching with sat. aq. NH_4Cl (15 mL). The aqueous phase was extracted with EtOAc (4 x 25 mL) and the combined organic phases washed with brine

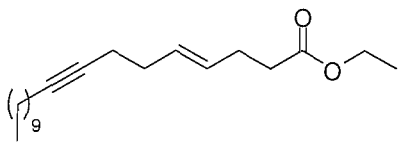
(50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to an orange liquid. Purification by column chromatography (silica gel, 40 x 110 mm, 5% EtOAc / hexane) afforded the title compound **5.3** (579 mg, 2.31 mmol, 86%) as a colourless oil. Spectroscopic data was in agreement with the literature.[69]

FT-IR ν_{max} (neat) 3346 (brd, w), 2923 (s), 2853 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (1H, ddd, *J* = 17.3, 10.5, 6.0 Hz, C**H**CH_2), 5.28 (1H, dt, *J* = 17.3, 1.5 Hz, CHC**H**H *trans* to CH), 5.14 (1H, dt, *J* = 10.5, 1.5 Hz, CHCH**H** *cis* to CH), 4.32-4.25 (1H, m, C**H**OH), 2.38-2.20 (2H, m, C**H$_2$**CH_2CHOH), 2.15 (2H, tt, *J* = 7.0, 2.5 Hz, C**H$_2$**CC), 1.75-1.66 (2H, m, C**H$_2$**CHOH), 1.53-1.43 (2H, m, C**H$_2$**CH_2CC), 1.41-1.22 (14H, m, 7 x C**H$_2$**), 0.89 (3H, t, *J* = 6.9 Hz, C**H$_3$**) ppm. Hydroxyl proton signal not observed.

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.91 (d, **C**HCH_2), 115.14 (t, CH**C**H_2), 81.63 (s, **C**C), 79.63 (s, C**C**), 72.57 (d, **C**HOH), 36.30 (t, **C**H_2CHOH), 32.25 (t, **C**H_2), 29.93 (t, **C**H_2), 29.89 (t, **C**H_2), 29.66 (t, **C**H_2), 29.51 (t, **C**H_2), 29.42 (t, **C**H_2), 29.24 (t, **C**H_2), 23.02 (t, **C**H_2), 19.08 (t, **C**H_2CC), 15.42 (t, **C**H_2CH_2CHOH), 14.44 (q, **C**H_3) ppm.

(4*E*)-Ethyl nonadec-4-en-8-ynoate (5.4)



$C_{21}H_{36}O_2$

M.W. = 320.51 g/mol

The title compound **5.4** was prepared according to the method described by Avedissian *et al.*[69] Alcohol **5.3** (650 mg, 2.59 mmol), propionic acid (19 mg, 0.26 mmol) and triethylorthoacetate (2.9 mL, 15.57 mmol) were combined and heated to reflux for 6 hours. The resulting mixture was cooled to r.t., diluted with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to a yellow liquid. Purification by column chromatography (silica gel, 40 x 110 mm, 5% Et_2O / hexane) afforded the title compound **5.4** (783 mg,

2.44 mmol, 94%) as a colourless oil. Spectroscopic data was in agreement with the literature.[69]

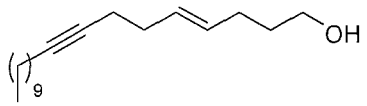
FT-IR ν_{max} (neat) 2917 (s), 2844 (m), 1736 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57-5.43 (2H, m, C**H**C**H**), 4.14 (2H, q, *J* = 7.1 Hz, O**CH_2**CH_3), 2.41-2.27 (4H, m, **CH_2CH_2**CO), 2.20-2.10 (6H, m, **CH_2**CCC**H_2CH_2**CH), 1.52-1.43 (2H, m, **CH_2**CH_2CC), 1.43-1.26 (14H, m, 7 x **CH_2**), 1.26 (3H, t, *J* = 7.1 Hz, OCH_2**CH_3**), 0.89 (3H, t, *J* = 6.9 Hz, **CH_3**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.53 (s, **C**O), 130.37 (d, **C**HCH), 129.58 (d, CH**C**H), 81.10 (s, **C**C), 79.84 (s, C**C**), 60.60 (t, O**C**H_2CH_3), 34.66 (t, **C**H_2), 32.61 (t, **C**H_2), 32.27 (t, **C**H_2), 29.95 (t, **C**H_2), 29.92 (t, **C**H_2), 29.68 (t, **C**H_2), 29.52 (t, **C**H_2), 29.50 (t, **C**H_2), 29.24 (t, **C**H_2), 28.25 (t, **C**H_2), 23.03 (t, **C**H_2), 19.53 (t, **C**H_2), 19.10 (t, **C**H_2), 14.61 (q, **C**H_3), 14.46 (q, **C**H_3) ppm.

LRMS (ES^+) *m/z* 343 (100%) $[M+Na]^+$ Da.

(4*E*)-Nonadec-4-en-8-yn-1-ol (5.5)



$C_{19}H_{34}O$

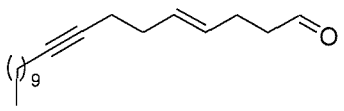
M.W. = 278.47 g/mol

To a solution of ester **5.4** (769 mg, 2.40 mmol) in THF (15 mL) at 0 °C was added $LiAlH_4$ (178 mg, 4.71 mmol) and the resulting grey mixture was warmed to r.t. over 1 hour then stirred at this temperature for a further 3 hours. The mixture was quenched with H_2O (0.2 mL), 15% aq. NaOH (0.2 mL) and H_2O (0.6 mL) and allowed to stir for 30 min. The white precipitate was removed by filtration through celite, washing with EtOAc (2 x 20 mL). The combined organics were concentrated *in vacuo* to a colourless oil. Purification by column chromatography (silica gel, 30 x 120 mm, 5% EtOAc / hexane) afforded the title compound **5.5** (621 mg, 2.23 mmol, 93%) as a colourless oil. Spectroscopic data was in agreement with the literature.[69]

FT-IR ν_{max} (neat) 3338 (brd, w), 2923 (s), 2852 (m) cm^{-1}.

^{1}H NMR	(400 MHz, $CDCl_3$) δ 5.56-5.44 (2H, m, C**H**C**H**), 3.67 (2H, t, J = 6.7 Hz, C$\mathbf{H_2}$OH), 2.23-2.07 (8H, m, 4 x C$\mathbf{H_2}$), 1.65 (2H, quin, J = 6.7 Hz, C$\mathbf{H_2}$CH$_2$OH), 1.52-1.43 (2H, m, C$\mathbf{H_2}$CH$_2$CC), 1.41-1.20 (14H, m, 7 x C$\mathbf{H_2}$), 0.89 (3H, t, J = 6.9 Hz, C$\mathbf{H_3}$) ppm. Hydroxyl proton signal not observed.
^{13}C NMR	(100 MHz, $CDCl_3$) δ 131.06 (d, **C**HCH), 129.80 (d, CH**C**H), 81.12 (s, **C**C), 79.93 (s, C**C**), 62.88 (t, **C**H$_2$OH), 32.67 (t, **C**H$_2$), 32.62 (t, **C**H$_2$), 32.27 (t, **C**H$_2$), 29.95 (t, **C**H$_2$), 29.92 (t, **C**H$_2$), 29.68 (t, **C**H$_2$), 29.53 (t, **C**H$_2$), 29.50 (t, **C**H$_2$), 29.27 (t, **C**H$_2$), 29.23 (t, **C**H$_2$), 23.03 (t, **C**H$_2$), 19.58 (t, CC**C**H$_2$), 19.10 (t, **C**H$_2$CC), 14.47 (q, **C**H$_3$) ppm.
LRMS	(ES$^+$) *m/z* 301 (100%) $[M+Na]^+$ Da.

(4*E*)-Nonadec-4-en-8-ynal (5.6)



$C_{19}H_{32}O$

M.W. = 276.45 g/mol

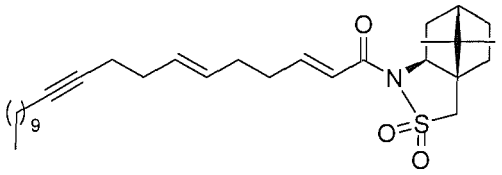
To a solution of alcohol **5.5** (215 mg, 0.77 mmol) in CH_2Cl_2 at 0 °C was added DMP (425 mg, 1.00 mmol) and the resulting cloudy white solution was stirred for 30 min before warming to r.t. and stirred for a further 2 ½ hours. Pentane (5 mL) was added and the mixture filtered through a plug of silica gel (30 x 30 mm) washing with Et_2O / pentane (5%, 40 mL). The combined organics were concentrated *in vacuo* to a colourless oil. Purification by column chromatography (silica gel, 20 x 120 mm, 5% Et_2O / hexane) afforded the title compound **5.6** (176 mg, 0.64 mmol, 83%) as a colourless oil.

FT-IR	ν_{max} (neat) 2921 (m), 2850 (m), 2713 (m), 1725 (s) cm^{-1}.
^{1}H NMR	(400 MHz, $CDCl_3$) δ 9.78 (1H, t, J = 1.6 Hz, C(O)**H**), 5.59-5.44 (2H, m, C**H**C**H**), 2.51 (2H, td, J = 6.9, 1.6 Hz, C$\mathbf{H_2}$C(O)H), 2.40-2.32 (2H, m, C$\mathbf{H_2}$CH$_2$C(O)H), 2.23-2.10 (6H, m, C$\mathbf{H_2}$CCC$\mathbf{H_2}$C$\mathbf{H_2}$), 1.52-1.43 (2H, m, C$\mathbf{H_2}$CH$_2$CC), 1.41-1.23 (14H, m, 7 x C$\mathbf{H_2}$), 0.89 (3H, t, J = 6.9 Hz, C$\mathbf{H_3}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 202.52 (s, **C**(O)H), 130.64 (d, **C**HCH), 129.29 (d, CH**C**H), 81.18 (s, **C**C), 79.76 (s, C**C**), 43.78 (t, **C**H_2C(O)H), 32.53 (t, **C**H_2), 32.27 (t, **C**H_2), 29.95 (t, **C**H_2), 29.93 (t, **C**H_2), 29.68 (t, **C**H_2), 29.53 (t, **C**H_2), 29.50 (t, **C**H_2), 29.23 (t, **C**H_2), 25.51 (t, **C**$H_2$$CH_2$C(O)H), 23.03 (t, CH_3**C**H_2), 19.47 (t, CC**C**H_2), 19.09 (t, **C**H_2CC), 14.46 (q, **C**H_3) ppm.

LRMS (EI) *m/z* 276 (12%) $[M]^{+\cdot}$, 135 (15%), 79 (58%) Da.

(2*S*)-*N*-((2*E*,6*E*)-Henicosa-2,6-dien-10-ynoyl)-camphor-10,2-sultam (3.25)



$C_{31}H_{49}NO_3S$

M.W. = 515.79 g/mol

To a solution of phosphonate **3.13** (5.89 g, 15.0 mmol) in MeCN (70 mL) was added LiCl (0.63 g, 15.0 mmol) and the suspension was stirred for 10 min before the addition of $^{i}Pr_2NEt$ (2.6 mL, 15.0 mmol) and the pale yellow solution was stirred for a further 10 min. Aldehyde **5.6** (2.95 g, 10.7 mmol) in THF (10 mL) was added dropwise to the reaction mixture and the resulting mixture was stirred for 25 hours. The mixture was quenched with sat. aq. NH_4Cl (20 mL) and H_2O (15 mL) and extracted with EtOAc (4 x 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (silica gel, 80 x 120 mm, 5-30% EtOAc / hexane) afforded the title compound **3.25** (4.86 g, 9.4 mmol, 88%) as a thick colourless gum.

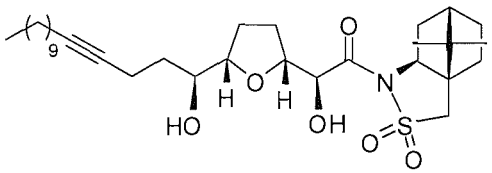
$[\alpha]^{27}_D$ +54.02 (*c* 0.56, $CHCl_3$).

FT-IR ν_{max} (neat) 2923 (m), 2852 (m), 1684 (m), 1641 (m), 1331 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (1H, dt, *J* = 15.1, 6.9 Hz, CHCHCO), 6.57 (1H, dt, *J* = 15.1, 1.6 Hz, **CH**CO), 5.56-5.41 (2H, m, **CHCH**), 3.93 (1H, dd, *J* = 7.7, 5.0 Hz, NC**H**), 3.51 (1H, d, *J* = 13.8 Hz, C**H**HSO_2), 3.44 (1H, d, *J* = 13.8 Hz, CH**H**SO_2), 2.37-2.29 (2H, m, C**H**$_2$CHCHCO), 2.22-2.06 (10H, m, 4 x C**H**$_2$ and NCHC**H**$_2$), 1.98-1.85 (3H, m, NCHCH_2C**H**C**H**HC**H**H), 1.52-

	1.33 (4H, m, CH_2CH_2CC and $NCHCH_2CHCHHCHH$), 1.33-1.21 (14H, m, 7 x CH_2), 1.18 (3H, s, CCH_3), 0.98 (3H, s, CCH_3), 0.89 (3H, t, J = 6.9 Hz, CH_3) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ 164.43 (s, **C**O), 150.43 (d, **C**HCHCO), 130.43 (d, **C**HCH), 129.85 (d, CH**C**H), 121.46 (d, **C**HCO), 81.03 (s, **C**C), 79.91 (s, C**C**), 65.51 (d, N**C**H), 53.52 (t, CH_2SO_2), 48.78 (s, $C(CH_3)_2$), 48.13 (s, CCH_2SO_2), 45.07 (d, $NCHCH_2CH$), 38.87 (t, CH_2), 33.22 (t, CH_2), 32.79 (t, CH_2), 32.63 (t, CH_2), 32.25 (t, CH_2), 31.25 (t, CH_2), 29.94 (t, CH_2), 29.91 (t, CH_2), 29.67 (t, CH_2), 29.52 (t, CH_2), 29.50 (t, CH_2), 29.23 (t, CH_2), 26.85 (t, CH_2), 23.02 (t, CH_3CH_2), 21.20 (q, CCH_3), 20.25 (q, CCH_3), 19.52 (t, $CCCH_2$), 19.10 (t, CH_2CC), 14.46 (q, CH_3) ppm.
LRMS	(ES^+) *m/z* 538 (100%) $[M+Na]^+$ Da.

(2*S*)-*N*-((2*S*)-2-Hydroxy-2-((2*R*,5*S*)-5-((1*S*)-1-hydroxypentadec-4-ynyl)-tetrahydrofuran-2-yl)ethanoyl)-camphor-10,2-sultam (3.24)



$C_{31}H_{51}NO_6S$

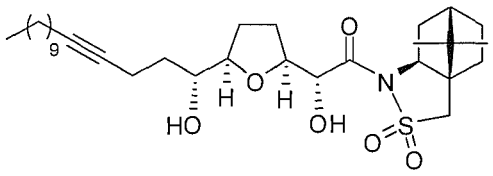
M.W. = 565.80 g/mol

To a solution of dienyne **3.25** (3.48 g, 6.7 mmol) in acetone (45 mL) and AcOH (30 mL) at –30 °C was added $KMnO_4$ (1.39 g, 8.8 mmol). The solution immediately turned purple which changed to brown over ca. 5 min. The mixture was stirred between –30 and –20 °C for 1 hour before quenching with sat. aq. $Na_2S_2O_5$ (15 mL) and H_2O (15 mL). The aqueous phase was extracted with EtOAc (4 x 30 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (silica gel, 50 x 140 mm, 20-50% EtOAc / hexane) afforded three different fractions. The major diastereoisomer **3.24** (title compound) (1.76 g, 3.1 mmol, 46%) was obtained as a thick colourless gum, the minor diastereoisomer **3.26** (0.34 g, 0.6 mmol, 9%) as a colourless gum and the hydroxy-ketone by-product **5.7**, an inseparable mixture of diastereoisomers, (0.25 g, 0.5 mmol, 7%) as a yellow oil.

Data for major diastereoisomer (3.24)

$[\alpha]^{27}_D$	+12.05 (*c* 0.56, $CHCl_3$).
FT-IR	ν_{max} (neat) 3461 (brd, w), 2926 (s), 2848 (m), 1687 (m), 1332 (m) cm^{-1}.
^{1}H NMR	(400 MHz, $CDCl_3$) δ 4.60 (1H, td, *J* = 6.7, 2.7 Hz, C**H**), 4.59-4.54 (1H, m, C**H**), 3.97 (1H, dd, *J* = 8.0, 5.0 Hz, NC**H**), 3.96-3.93 (1H, brd s, O**H**), 3.90 (1H, td, *J* = 7.0, 4.0 Hz, C**H**CH(OH)CO), 3.66-3.59 (1H, m, C**H**OH), 3.52 (1H, d, *J* = 13.8 Hz, C**H**HSO_2), 3.45 (1H, d, *J* = 13.8 Hz, CH**H**SO_2), 2.84 (1H, brd d, *J* = 6.0 Hz, O**H**), 2.36-2.30 (2H, m, C$\mathbf{H_2}CH_2$CHOH), 2.29-2.21 (1H, m, NCHC**H**H), 2.17-2.03 (5H, m, C$\mathbf{H_2}$CC, C$\mathbf{H_2}$ THF and NCHCH**H**), 1.99-1.86 (5H, m, C$\mathbf{H_2}$ THF and NCHCH_2C**H**C**H**HC**H**H), 1.78-1.60 (2H, m, C$\mathbf{H_2}$CHOH), 1.52-1.40 (2H, m, C$\mathbf{H_2}CH_2$CC), 1.40-1.22 (16H, m, 7 x C$\mathbf{H_2}$ and NCHCH_2CHCH**H**CH**H**), 1.16 (3H, s, CC$\mathbf{H_3}$), 0.98 (3H, s, CC$\mathbf{H_3}$), 0.89 (3H, t, *J* = 6.7 Hz, C$\mathbf{H_3}$) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ 172.05 (s, **C**O), 83.21 (d, **C**HCH(OH)CO), 81.31 (s, **C**C), 79.81 (s, C**C**), 79.02 (d, **C**H(OH)CO), 73.93 (d, **C**H), 73.21 (d, **C**HOH), 66.17 (d, N**C**H), 53.41 (t, **C**H_2SO_2), 49.41 (s, **C**$(CH_3)_2$), 48.25 (s, **C**CH_2SO_2), 44.91 (d, NCHCH_2**C**H), 38.60 (t, NCH**C**H_2), 34.35 (t, **C**H_2CHOH), 33.26 (t, **C**H_2), 32.27 (t, **C**H_2), 29.96 (t, **C**H_2), 29.92 (t, **C**H_2), 29.68 (t, **C**H_2), 29.53 (t, **C**H_2), 29.48 (t, **C**H_2), 29.28 (t, **C**H_2), 28.67 (t, **C**H_2), 28.52 (t, **C**H_2), 26.75 (t, **C**H_2), 23.03 (t, CH_3**C**H_2), 21.18 (q, C**C**H_3), 20.24 (q, C**C**H_3), 19.12 (t, **C**H_2CC), 15.76 (t, **C**H_2CH_2CHOH), 14.46 (q, **C**H_3) ppm.
LRMS	(ES^+) *m/z* 588 (100%) $[M+Na]^+$ Da.
HRMS	(ES^+) for $C_{31}H_{51}NO_6SNa^+$, calculated 588.3329, found 588.3331 Da.

Data for minor diastereoisomer: (2*S*)-*N*-((2*R*)-2-Hydroxy-2-((2*S*,5*R*)-5-((1*R*)-1-hydroxypentadec-4-ynyl)-tetrahydrofuran-2-yl)ethanoyl)-camphor-10,2-sultam (3.26)

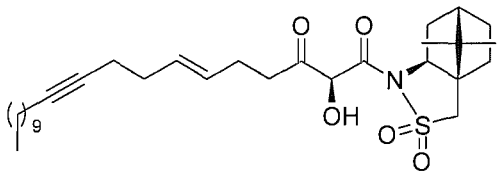


$C_{31}H_{51}NO_6S$

M.W. = 565.80 g/mol

$[\alpha]^{27}_D$	+90.12 (*c* 0.41, $CHCl_3$).
FT-IR	ν_{max} (neat) 3493 (brd w), 2954 (m), 2927 (s), 2848 (m), 1695 (w), 1333 (m) cm^{-1}.
^{1}H NMR	(400 MHz, $CDCl_3$) δ 4.68 (1H, brd s, C**H**(OH)CO) 4.50 (1H, ddd, *J* = 7.5, 5.3, 2.2 Hz, C**H**CH(OH)CO), 3.96 (1H, app t, *J* = 6.3 Hz, NC**H**), 3.80 (1H, td, *J* = 7.1, 4.4 Hz, C**H**O), 3.57 (1H, dt, *J* = 8.0, 4.5 Hz, C**H**OH), 3.50 (1H, d, *J* = 13.8 Hz, C**H**HSO$_2$), 3.45 (1H, d, *J* = 13.8 Hz, CH**H**SO$_2$), 2.38-2.26 (2H, m, C**H$_2$**CH$_2$CHOH), 2.24-2.01 (6H, m, C**H$_2$**CC, C**H$_2$** THF and NCHC**H$_2$**), 2.00-1.85 (5H, m, C**H$_2$** THF and NCHCH$_2$C**H**C**H**HC**H**H), 1.66-1.57 (2H, m, C**H$_2$**CHOH), 1.52-1.42 (2H, m, C**H$_2$**CH$_2$CC), 1.41-1.20 (16H, m, C 7 x C**H$_2$** and NCHCH$_2$CHCH**H**CH**H**), 1.15 (3H, s, CC**H$_3$**), 0.98 (3H, s, CC**H$_3$**), 0.89 (3H, t, *J* = 6.8 Hz, C**H$_3$**) ppm. Hydroxyl proton signals not observed.
^{13}C NMR	(100 MHz, $CDCl_3$) δ 173.42 (s, **C**O), 83.18 (d, **C**H), 81.14 (s, **C**C), 80.59 (d, **C**HCH(OH)CO), 79.83 (s, C**C**), 74.45 (d, **C**H(OH)CO), 72.96 (d, **C**HOH), 65.28 (d, N**C**H), 53.32 (t, **C**H$_2$SO$_2$), 49.39 (s, **C**(CH$_3$)$_2$), 48.28 (s, **C**CH$_2$SO$_2$), 44.81 (d, NCHCH$_2$**C**H), 37.99 (t, NCH**C**H$_2$), 34.37 (t, **C**H$_2$), 32.93 (t, **C**H$_2$), 32.26 (t, **C**H$_2$), 29.95 (t, **C**H$_2$), 29.91 (t, **C**H$_2$), 29.67 (t, **C**H$_2$), 29.52 (t, **C**H$_2$), 29.48 (t, **C**H$_2$), 29.25 (t, **C**H$_2$), 28.50 (t, **C**H$_2$ THF), 28.10 (t, **C**H$_2$ THF), 26.89 (t, **C**H$_2$), 23.02 (t, CH$_3$**C**H$_2$), 20.72 (q, C**C**H$_3$), 20.26 (q, C**C**H$_3$), 19.11 (t, **C**H$_2$CC), 15.68 (t, **C**H$_2$CH$_2$CHOH), 14.45 (q, **C**H$_3$) ppm.
LRMS	(ES$^+$) *m/z* 588 (100%) [M+Na]$^+$ Da.

Data for hydroxy-ketone by-product: (2*S*)-*N*-((2*S*,6*E*)-2-Hydroxy-3-oxo-6-henicosa-10-ynoyl)-camphor-10,2-sultam (5.7)



$C_{31}H_{49}NO_5S$

M.W. = 547.79 g/mol

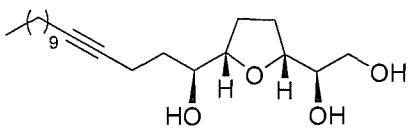
+ diastereoisomer

$[\alpha]^{27}_D$	+61.55 (*c* 0.55, $CHCl_3$).
FT-IR	ν_{max} (neat) 3465 (brd w), 2923 (s), 2848 (m), 1728 (m), 1689 (m), 1336 (s) cm^{-1}.
^{1}H NMR	(400 MHz, $CDCl_3$) δ 5.57-5.38 (2H, m, C**H**C**H**), 5.24 (1H, brd s, C**H**OH), 3.96 (1H, dd, *J* = 7.8, 5.0 Hz, NC**H**), 3.91 (1H, brd s, O**H**), 3.53 (1H, d, *J* = 13.8 Hz, C**H**HSO$_2$), 3.48 (1H, d, *J* = 13.8 Hz, CH**H**SO$_2$), 2.82 (1H, dt, *J* = 17.9, 7.5 Hz, C**H**HCO), 2.66 (1H, dt, *J* = 17.9, 7.5 Hz, CH**H**CO), 2.39-2.27 (2H, m, C**H$_2$**CH$_2$CO), 2.21-2.04 (8H, m, 3 x C**H$_2$** and NCHC**H$_2$**), 2.01-1.86 (3H, m, NCHCH$_2$C**H**C**H**HC**H**H), 1.52-1.42 (2H, m, CCCH$_2$C**H$_2$**), 1.41-1.22 (16H, m, 7 x C**H$_2$** and NCHCH$_2$CHCH**H**CH**H**), 1.16 (3H, s, CC**H$_3$**), 1.00 (3H, s, CC**H$_3$**), 0.89 (3H, t, *J* = 6.6 Hz, C**H$_3$**) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ 203.43 (s, CH$_2$**C**O), 168.53 (s, **C**(O)N), 130.48 (d, **C**HCH), 129.19 (d, CH**C**H), 81.07 (s, **C**C), 79.84 (s, C**C**), 76.80 (d, **C**HOH), 65.42 (d, N**C**H), 53.21 (t, **C**H$_2$SO$_2$), 49.44 (s, **C**(CH$_3$)$_2$), 48.26 (s, **C**CH$_2$SO$_2$), 44.92 (d, NCHCH$_2$**C**H), 39.49 (t, **C**H$_2$CO), 38.12 (t, NCH**C**H$_2$), 33.17 (t, **C**H$_2$), 32.64 (t, **C**H$_2$), 32.26 (t, **C**H$_2$), 29.94 (t, **C**H$_2$), 29.91 (t, **C**H$_2$), 29.67 (t, **C**H$_2$), 29.52 (t, 2 x **C**H$_2$), 29.23 (t, **C**H$_2$), 26.79 (t, **C**H$_2$), 26.38 (t, **C**H$_2$CH$_2$CO), 23.02 (t, CH$_3$**C**H$_2$), 20.77 (q, C**C**H$_3$), 20.29 (q, C**C**H$_3$), 19.48 (t, **C**H$_2$CC), 19.10 (t, CC**C**H$_2$), 14.46 (q, **C**H$_3$) ppm.
LRMS	(ES$^+$) *m/z* 570 (100%) [M+Na]$^+$, 160 (80%) Da.
HRMS	(ES$^+$) for $C_{31}H_{49}NO_5SNa^+$, calculated 570.3229, found 570.3223 Da.

Selected data for minor diastereoisomer:

^{1}H NMR	(400 MHz, $CDCl_3$) δ 5.16 (1H, s, C**H**OH), 3.58 (1H, d, J = 13.8 Hz, C**H**HSO$_2$), 3.49 (1H, d, J = 13.8 Hz, CH**H**SO$_2$), 2.91 (1H, dt, J = 17.8, 7.3 Hz, C**H**HCO), 1.19 (3H, s, CC**H$_3$**), 1.01 (3H, s, CC**H$_3$**) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ 203.88 (s, CH_2**C**O), 180.93 (s, **C**(O)N), 76.24 (d, **C**HOH), 65.69 (d, N**C**H), 53.29 (t, **C**H$_2$SO$_2$), 45.03 (d, NCHCH$_2$**C**H), 33.24 (t, **C**H$_2$), 20.21 (q, **C**CH$_3$) ppm.

(1*R*)-1-((2*R*,5*S*)-5-((1*S*)-1-Hydroxypentadec-4-ynyl)-tetrahydrofuran-2-yl)-ethane-1,2-diol (5.8)



$C_{21}H_{38}O_4$

M.W. = 354.52 g/mol

To a solution of mono-THF **3.24** (1.15 g, 2.03 mmol) in THF (30 mL) and H_2O (15 mL) at 0 °C was added $NaBH_4$ (0.31 g, 8.13 mmol). The resulting mixture was warmed to r.t. after 15 min and was stirred for a further 1 hour. The THF was removed *in vacuo* to a white suspension and the aqueous phase extracted with EtOAc (5 x 10 mL). The combined organic phases were concentrated *in vacuo* to a white solid. Purification by column chromatography (silica gel, 30 x 120 mm, 5% MeOH / CH_2Cl_2) afforded the title compound **5.8** (0.47 g, 1.34 mmol, 66%) as a colourless oil.

$[\alpha]^{27}_D$	–20.56 (*c* 0.54, $CHCl_3$).
FT-IR	ν_{max} (neat) 3353 (brd, w), 2921 (s), 2852 (s) cm^{-1}.
^{1}H NMR	(400 MHz, $CDCl_3$) δ 4.07-3.95 (1H, brd m, C**H**), 3.94-3.86 (1H, m, C**H**), 3.71 (2H, d, J = 4.7 Hz, C**H$_2$**OH), 3.64 (1H, dt, J = 9.0, 4.3 Hz, C**H**OH), 3.60 (1H, app q, J = 4.7 Hz, C**H**(OH)CH$_2$OH), 2.37-2.28 (2H, m, C**H$_2$**CH$_2$CHOH), 2.14 (2H, tt, J = 7.3, 2.4 Hz, C**H$_2$**CC), 2.03-1.88 (4H, m, 2 x C**H$_2$** THF), 1.77-1.60 (2H, m, C**H$_2$**CHOH), 1.52-1.43 (2H, m, C**H$_2$**CH$_2$CC), 1.40-1.23 (14H, m,

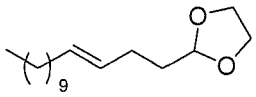
7 x CH_2), 0.89 (3H, t, J = 6.9 Hz, CH_3) ppm. Hydroxyl proton signals not observed.

^{13}C NMR (100 MHz, $CDCl_3$) δ 83.00 (d, **C**H), 81.56 (s, **C**C), 80.79 (d, **C**H), 79.71 (s, C**C**), 74.16 (d, **C**H(OH)CH_2OH), 73.48 (d, **C**HOH), 65.51 (t, **C**H_2OH), 34.03 (t, **C**H_2CHOH), 32.25 (t, **C**H_2), 29.95 (t, **C**H_2), 29.91 (t, **C**H_2), 29.67 (t, **C**H_2), 29.52 (t, **C**H_2), 29.45 (t, **C**H_2), 29.27 (t, **C**H_2), 28.39 (t, **C**H_2 THF), 28.32 (t, **C**H_2 THF), 23.02 (t, CH_3**C**H_2), 19.10 (t, **C**H_2CC), 15.75 (t, **C**H_2CH_2CHOH), 14.45 (q, **C**H_3) ppm.

LRMS (ES^+) *m/z* 377 (100%) $[M+Na]^+$ Da.

HRMS (ES^+) for $C_{21}H_{39}O_4^+$, calculated 355.2842, found 355.2845 Da.

2-((3*E*)-Tetradec-3-enyl)-1,3-dioxolane (5.20)



$C_{17}H_{32}O_2$

M.W. = 268.58 g/mol

Ammonia (200 mL) was condensed at –78 °C then allowed to warm to –50 °C before the addition of acetal **5.1** (4.64 g, 17 mmol) in a mixture of THF (15 mL) and ^{t}BuOH (5.11 g, 69 mmol). The mixture was cooled to –60 °C before lithium (0.48 g, 69 g-atom) was added over 10 min and the solution turned a deep blue colour. The mixture was allowed to stir between –50 and –40 °C for 2 hours before warming to r.t. to allow the ammonia to evaporate. The residue was diluted with Et_2O (50 mL), quenched with sat. aq. NH_4Cl (20 mL) and H_2O (20 mL) and the aqueous phase extracted with further portions of Et_2O (3 x 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* affording the title compound **5.20** (4.57 g, 17 mmol, 98%) as a colourless liquid which required no further purification.

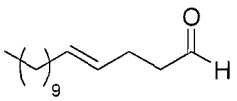
FT-IR ν_{max} (neat) 2954 (m), 2917 (s), 2852 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51-5.37 (2H, m, C**H**C**H**), 4.87 (1H, t, J = 4.9 Hz, C**H**), 4.02-3.92 (2H, m, 2 x OC**H**H), 3.90-3.81 (2H, m, 2 x OCH**H**), 2.16-2.09 (2H, m, C**H**$_2$CH_2CH), 2.01-1.94 (2H, m, CHCHC**H**$_2$), 1.76-1.69 (2H, m, C**H**$_2$CH), 1.38-1.20 (16H, m, 8 x C**H**$_2$), 0.89 (3H, t, J = 6.8 Hz, C**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 131.45 (d, **C**HCH), 129.32 (d, CH**C**H), 104.55 (d, **C**HO), 65.21 (t, 2 x O**C**H_2), 34.23 (t, **C**H_2CHO), 32.90 (t, CHCH**C**H_2), 32.27 (t, **C**H_2), 29.98 (t, **C**H_2), 29.89 (t, **C**H_2), 29.87 (t, **C**H_2), 29.69 (t, **C**H_2), 29.51 (t, 2 x **C**H_2), 27.47 (t, **C**H_2CH_2CHO), 23.03 (t, CH_3**C**H_2), 14.46 (q, **C**H_3) ppm.

LRMS (EI) Relative intensity = 9.17 min, *m/z* 268 (4%) $[M]^{+\cdot}$, 207 (13%), 99 (89%), 73 (100%) Da.

(4*E*)-Pentadec-4-enal (5.21)



$C_{15}H_{28}O$

M.W. = 224.39 g/mol

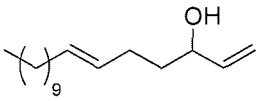
A solution of acetal **5.20** (18.0 g, 69 mmol), AcOH (290 mL) and H_2O (72 mL) was heated to 95 °C for 5 ½ hours, cooled to r.t. and diluted with EtOAc (150 mL). The aqueous phase was extracted with further portions of EtOAc (3 x 150 mL) and the combined organic phases washed with brine (2 x 50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (silica gel, 80 x 100 mm, 0-5% Et_2O / hexane) afforded the title compound **5.21** (13.0 g, 58 mmol, 84%) as a colourless oil. Spectroscopic data was in agreement with the literature.[69]

FT-IR ν_{max} (neat) 2922 (s), 2852 (m), 2714 (w), 1728 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (1H, t, J = 1.8 Hz, C(O)**H**), 5.53-5.36 (2H, m, C**HCH**), 2.52-2.46 (2H, m, C**H$_2$**C(O)H), 2.38-2.30 (2H, m, C**H$_2$**CH_2C(O)H), 2.01-1.94 (2H, m, C**H$_2$**CHCH), 1.97-1.22 (16H, m, 8 x C**H$_2$**), 0.89 (3H, t, J = 6.9 Hz, C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 202.72 (s, **C**(O)H), 132.50 (d, **C**HCH), 127.93 (d, CH**C**H), 43.90 (t, **C**H_2C(O)H), 32.83 (t, **C**H_2CHCH), 32.26 (t, **C**H_2), 29.97 (t, 2 x **C**H_2), 29.83 (t, **C**H_2), 29.77 (t, **C**H_2), 29.68 (t, **C**H_2), 29.50 (t, **C**H_2), 25.55 (t, **C**H_2CH_2C(O)H), 23.02 (t, CH_3**C**H_2), 14.44 (q, **C**H_3) ppm.

(6*E*)-Heptadeca-1,6-dien-3-ol (5.22)



$C_{17}H_{32}O$

M.W. = 252.44 g/mol

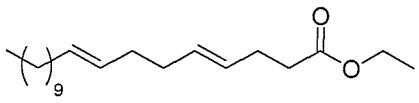
THF (300 mL) was cooled to –40 °C before the addition of vinylmagnesium bromide (173 mL, 0.170 mol, 1 M solution in THF) followed by aldehyde **5.21** (13.0 g, 0.058 mol). The resulting orange solution was warmed to –20 °C over 3 hours before quenching with sat. aq. NH_4Cl (40 mL) and H_2O (50 mL). The aqueous phase was extracted with Et_2O (3 x 50 mL), the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to a yellow liquid. Purification by column chromatography (silica gel, 80 x 10 mm, 5-20% EtOAc / hexane) afforded the title compound **5.22** (12.4 g, 0.049 mol, 85%) as a colourless liquid. Spectroscopic data was in agreement with the literature.[205]

FT-IR ν_{max} (neat) 3345 (brd, w), 2922 (s), 2852 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (1H, ddd, *J* = 17.0, 10.5, 6.3 Hz, C**H**CH_2), 5.51-5.37 (2H, m, CH**CH**), 5.24 (1H, dt, *J* = 17.0, 1.4 Hz, CHC**H**H *trans* to CH), 5.12 (1H, dt, *J* = 10.5, 1.4 Hz, CHCH**H** *cis* to CH), 4.18-4.10 (1H, m, C**H**OH), 2.14-2.06 (2H, m, C$\mathbf{H_2}CH_2CHOH$), 2.02-1.95 (2H, m, C$\mathbf{H_2}$CHCH), 1.64-1.55 (2H, m, C$\mathbf{H_2}$CHOH), 1.51 (1H, d, *J* = 4.5 Hz, O**H**), 1.39-1.20 (16H, m, 8 x C$\mathbf{H_2}$), 0.89 (3H, t, *J* = 6.9 Hz, C$\mathbf{H_3}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.48 (d, **C**HCH_2), 131.69 (d, **C**HCH), 129.70 (d, CH**C**H), 114.91 (t, CH**C**H_2), 73.07 (d, **C**HOH), 37.15 (t, **C**H_2CHOH), 32.92 (t, **C**H_2CHCH), 32.26 (t, **C**H_2), 29.98 (t, 2 x **C**H_2), 29.92 (t, **C**H_2), 29.86 (t, **C**H_2), 29.69 (t, **C**H_2), 29.52 (t, **C**H_2), 28.85 (t, **C**H_2CH_2CHOH), 23.03 (t, CH_3**C**H_2), 14.45 (q, **C**H_3) ppm.

(4*E*,8*E*)-Ethyl nonadeca-4,8-dienoate (5.23)



$C_{21}H_{38}O_2$

M.W. = 322.53 g/mol

Alcohol **5.22** (12.4 g, 0.049 mol), propionic acid (0.4 mL, 0.005 mol) and triethylorthoacetate (55 mL, 0.294 mmol) were heated to reflux for 6 hours. The mixture was cooled to r.t., diluted with H_2O (40 mL) and extracted with EtOAc (4 x 50 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* affording the title compound **5.23** (15.1 g, 0.047 mol, 96%) as a yellow liquid which required no further purification. Spectroscopic data was in agreement with the literature.[205]

FT-IR ν_{max} (neat) 2923 (s), 2853 (m), 1739 (s) cm^{-1}.

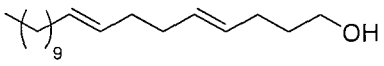
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49-5.36 (4H, m, 2 x C**H**C**H**), 4.14 (2H, q, J = 7.1 Hz, OC**H**$_2$CH$_3$), 2.39-2.27 (4H, m, C**H**$_2$C**H**$_2$CO), 2.06-1.94 (6H, m, C**H**$_2$CHCHC**H**$_2$C**H**$_2$), 1.39-1.20 (19H, m, 8 x C**H**$_2$ and OCH$_2$C**H**$_3$), 0.89 (3H, t, J = 6.9 Hz, C**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.57 (s, **C**O), 131.52 (d, **C**HCH), 131.23 (d, CH**C**H), 129.79 (d, **C**HCH), 128.63 (d, CH**C**H), 60.55 (t, O**C**H$_2$CH$_3$), 34.77 (t, **C**H$_2$), 32.99 (t, **C**H$_2$), 32.92 (t, **C**H$_2$), 32.89 (t, **C**H$_2$), 32.27 (t, **C**H$_2$), 29.99 (t, 2 x **C**H$_2$), 29.87 (t, 2 x **C**H$_2$), 29.69 (t, **C**H$_2$), 29.51 (t, **C**H$_2$), 28.29 (t, **C**H$_2$), 23.03 (t, CH$_3$**C**H$_2$), 14.61 (q, **C**H$_3$), 14.45 (q, **C**H$_3$) ppm.

LRMS (ES$^+$) *m/z* 323 (84%) $[M+H]^+$, 277 (52%) $[M-OCH_2CH_3]^+$, 234 (32%), 141 (98%), 67 (100%) Da.

HRMS (EI) for $C_{21}H_{38}O_2$, calculated 322.28718, found 322.28669 Da.

(4*E*,8*E*)-Nonadeca-4,8-dien-1-ol (5.24)



$C_{19}H_{36}O$

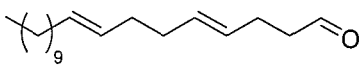
M.W. = 280.49 g/mol

To a solution of ester **5.23** (15.1 g, 47 mmol) in THF (230 mL) at 0 °C was added $LiAlH_4$ (2.7 g, 70 mmol). The resulting grey solution was stirred for 1 hour, warmed to

r.t. and was stirred for a further 2 hours. The reaction was quenched with H_2O (3.2 mL), 15% aq. NaOH (3.2 mL) and H_2O (9.6 mL) and stirred for 1 hour. The white precipitate was removed by filtration through celite and washed with EtOAc (100 mL). The organic phases were concentrated *in vacuo* affording the title compound **5.24** (13.1 g, 46 mmol, 98%) as a colourless liquid which required no further purification.

FT-IR	ν_{max} (neat) 3328 (brd, w), 2922 (s), 2852 (m) cm^{-1}.
^{1}H NMR	(400 MHz, $CDCl_3$) δ 5.48-5.37 (4H, m, 2 x C**H**C**H**), 3.66 (2H, t, J = 6.5 Hz, C**H$_2$**OH), 2.13-2.02 (6H, m, C**H$_2$**C**H$_2$**CHCHC**H$_2$**), 2.01-1.94 (2H, m, C**H$_2$**CHCH), 1.69-1.60 (2H, m, C**H$_2$**CH$_2$OH), 1.39-1.20 (16H, m, 8 x C**H$_2$**), 0.89 (3H, t, J = 6.9 Hz, C**H$_3$**) ppm. Hydroxyl proton signal not observed.
^{13}C NMR	(100 MHz, $CDCl_3$) δ 131.23 (d, **C**HCH), 130.98 (d, CH**C**H), 130.06 (d, **C**HCH), 129.87 (d, CH**C**H), 62.94 (t, **C**H$_2$OH), 33.03 (t, **C**H$_2$CH), 32.99 (t, **C**H$_2$CH), 32.93 (t, **C**H$_2$CH), 32.80 (t, **C**H$_2$CH$_2$OH), 32.27 (t, **C**H$_2$), 29.99 (t, 2 x **C**H$_2$), 29.97 (t, **C**H$_2$), 29.88 (t, **C**H$_2$), 29.69 (t, **C**H$_2$), 29.51 (t, **C**H$_2$), 29.27 (t, **C**H$_2$), 23.03 (t, CH$_3$**C**H$_2$), 14.45 (q, **C**H$_3$) ppm.
LRMS	(EI) *m/z* 280 (100%) $[M]^{+\cdot}$, 81 (100%) Da.
HRMS	(EI) for $C_{19}H_{36}O$, calculated 280.27662, found 280.27642 Da.

(4*E*,8*E*)-Nonadeca-4,8-dienal (5.25)



$C_{19}H_{34}O$

M.W. = 278.47 g/mol

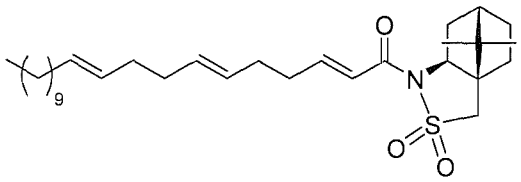
To a solution of alcohol **5.24** (13.1 g, 0.046 mol) in CH_2Cl_2 (200 mL) at 0 °C was added DMP (25.5 g, 0.060 mol) in batches over 5 min. The resulting cloudy white solution was stirred for 30 min before warming to r.t. and stirred for a further 3 hours. The mixture was filtered through a plug of silica gel (80 x 80 mm) and washed with Et_2O / pentane (10%, 500 mL). The combined organic phases were concentrated *in vacuo* to a cream oil. Purification by column chromatography (silica gel, 80 x 100 mm, 5% Et_2O / hexane) afforded the title compound **5.25** (9.2 g, 0.030 mol, 72%) as a colourless oil.

FT-IR ν_{max} (neat) 2923 (s), 2852 (m), 1729 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (1H, t, J = 1.8 Hz, C(O)**H**), 5.53-5.33 (4H, m, 2 x C**H**C**H**), 2.52-2.46 (2H, m, C**H$_2$**C(O)H), 2.38-2.30 (2H, m, C**H$_2$**CH$_2$C(O)H), 2.07-2.02 (4H, m, 2 x C**H$_2$**), 2.01-1.94 (2H, m, C**H$_2$**), 1.39-1.21 (16H, m, 8 x C**H$_2$**), 0.89 (3H, t, J = 6.9 Hz, C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 202.68 (s, **C**(O)H), 131.82 (d, **C**HCH), 131.34 (d, CH**C**H), 129.70 (d, **C**HCH), 128.31 (d, CH**C**H), 43.86 (t, **C**H$_2$C(O)H), 32.93 (t, CH**C**H$_2$), 32.92 (t, CH**C**H$_2$), 32.83 (t, **C**H$_2$CH), 32.27 (t, **C**H$_2$), 30.00 (t, 2 x **C**H$_2$), 29.96 (t, **C**H$_2$), 29.87 (t, **C**H$_2$), 29.69 (t, **C**H$_2$), 29.51 (t, **C**H$_2$), 25.54 (t, **C**H$_2$CH$_2$C(O)H), 23.03 (t, CH$_3$**C**H$_2$), 14.45 (q, **C**H$_3$) ppm.

(2*S*)-*N*-((2*E*,6*E*,10*E*)-Henicosa-2,6,10-trienoyl)-camphor-10,2-sultam (5.26)



$C_{31}H_{51}NO_3S$

M.W. = 517.81 g/mol

To a solution of phosphonate **3.13** (13.0 g, 0.03 mol) in MeCN (150 mL) was added LiCl (1.4 g, 0.03 mol) and the suspension was stirred for 10 min before the addition of ^{i}Pr$_2$NEt (5.8 mL, 0.03 mol) and the pale yellow solution was stirred for a further 10 min. Aldehyde **5.25** (9.2 g, 0.03 mol) in THF (35 mL) was added dropwise to the mixture and the resulting solution was stirred for 22 hours. The mixture was quenched with sat. aq. NH_4Cl (50 mL) and H_2O (30 mL) and extracted with EtOAc (4 x 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to an orange oil. Purification by column chromatography (silica gel, 80 x 120 mm, 5-30% EtOAc / hexane) afforded the title compound **5.26** (11.6 g, 0.02 mol, 75%) as a white solid.

M.p 30-32 °C

$[\alpha]^{27}_D$ +59.92 (*c* 0.65, $CHCl_3$).

FT-IR ν_{max} (neat) 2955 (m), 2922 (s), 2852 (m), 1683 (m), 1640 (m), 1332 (s) cm^{-1}.

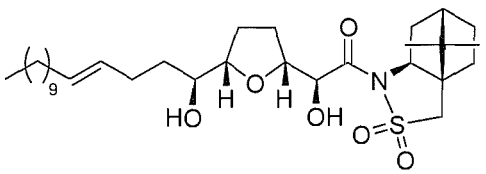
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (1H, dt, J = 15.1, 6.9 Hz, C**H**CHCO), 6.57 (1H, dt, J = 15.1, 1.5 Hz, C**H**CO), 5.52-5.33 (4H, m, 2 x C**H**C**H**), 3.94 (1H, dd, J = 7.5, 5.0 Hz, NC**H**), 3.51 (1H, d, J = 13.7 Hz, C**H**HSO$_2$), 3.44 (1H, d, J = 13.7 Hz, CH**H**SO$_2$), 2.36-2.28 (2H, m, C**H$_2$**CHCHCO), 2.21-1.85 (13H, m, 4 x C**H$_2$** and NCHC**H$_2$**C**H**C**H**HC**H**H), 1.47-1.21 (18H, m, 8 x C**H$_2$** and NCHCH$_2$CHC**H**HC**H**H), 1.19 (3H, s, CC**H$_3$**), 0.98 (3H, s, CC**H$_3$**), 0.89 (3H, t, J = 6.9 Hz, C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.47 (s, **C**O), 150.59 (d, **C**HCHCO), 131.63 (d, **C**HCH), 131.19 (d, CH**C**H), 129.89 (d, **C**HCH), 128.92 (d, CH**C**H), 121.43 (d, **C**HCO), 65.54 (d, N**C**H), 53.54 (t, **C**H$_2$SO$_2$), 48.80 (s, **C**(CH$_3$)$_2$), 48.15 (s, **C**CH$_2$SO$_2$), 45.10 (d, NCHCH$_2$**C**H), 38.89 (t, NCH**C**H$_2$), 33.25 (t, **C**H$_2$), 33.03 (t, **C**H$_2$), 32.93 (t, 2 x **C**H$_2$), 32.91 (t, 2 x **C**H$_2$), 32.28 (t, **C**H$_2$), 31.31 (t, **C**H$_2$), 29.99 (t, 2 x **C**H$_2$), 29.89 (t, **C**H$_2$), 29.70 (t, **C**H$_2$), 29.53 (t, **C**H$_2$), 26.87 (t, **C**H$_2$), 23.04 (t, CH$_3$**C**H$_2$), 21.22 (q, **C**CH$_3$), 20.26 (q, **C**CH$_3$), 14.47 (q, **C**H$_3$) ppm.

LRMS (ES$^+$) *m/z* 540 (100%) [M+Na]$^+$ Da.

HRMS (ES$^+$) for $C_{31}H_{51}NO_3SNa^+$, calculated 540.3482, found 540.3495 Da.

(2*S*)-*N*-((2*S*)-2-Hydroxy-2-((2*R*,5*S*)-5-((1*S*,4*E*)-1-hydroxypentadec-4-enyl)-tetrahydrofuran-2-yl)ethanoyl)-camphor-10,2-sultam (5.16)



$C_{31}H_{53}NO_6S$

M.W. = 567.82 g/mol

To a solution of triene **5.26** (980 mg, 1.89 mmol) in acetone (64 mL) and AcOH (16 mL) at –30 °C was added $KMnO_4$ (389 mg, 2.46 mmol). The solution immediately turned purple which changed to brown over ca. 5 min. The mixture was stirred between –30 and –20 °C for 2 hours before quenching with sat. aq. $Na_2S_2O_5$ (8 mL) and H_2O (8

mL).The aqueous phase was extracted with EtOAc (4 x 15 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (silica gel, 50 x 140 mm, 20-40% EtOAc / hexane) afforded three different fractions. The major diastereoisomer **5.16** (title compound) (611 mg, 1.08 mmol, 57%) was obtained as a thick colourless gum, the minor diastereoisomer **5.27** (103 mg, 0.18 mmol, 10%) as a cream solid and the hydroxy-ketone by-product **5.28**, an inseparable mixture of diastereoisomers (124 mg, 0.23 mmol, 12%) as a yellow oil.

Data for major diastereoisomer (5.16)

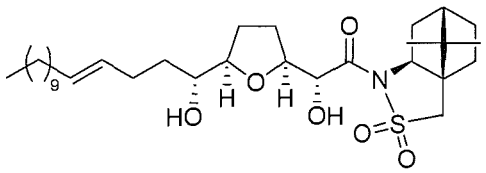
$[\alpha]^{26}_D$	+27.60 (*c* 0.75, $CHCl_3$).
FT-IR	ν_{max} (neat) 3458 (brd, w), 2956 (m), 2923 (s), 2853 (m), 1696 (m), 1333 (s) cm^{-1}.
^{1}H NMR	(400 MHz, $CDCl_3$) δ 5.50-5.36 (2H, m, C**H**C**H**), 4.62-4.52 (2H, m, C**H** and C**H**(OH)CO), 3.97 (1H, dd, *J* = 7.8, 4.9 Hz, NC**H**), 3.96-3.91 (1H, m, C**H**), 3.88 (1H, dt, *J* = 7.3, 4.2 Hz, C**H**), 3.52 (1H, d, *J* = 13.7 Hz, C**H**HSO$_2$), 3.51-3.44 (2H, m, 2 x O**H**), 3.45 (1H, d, *J* = 13.7 Hz, CH**H**SO$_2$), 2.30-2.15 (1H, m, NCHC**H**H), 2.15-2.01 (8H, m, C**H$_2$**CHCHC**H$_2$**, C**H$_2$** THF and NCHCH**H**C**H**), 2.01-1.82 (6H, m, C**H$_2$**CHOH, C**H$_2$** THF and NCHCH$_2$CHC**H**HC**H**H), 1.66-1.41 (2H, m, NCHCH$_2$CHCH**H**CH**H**), 1.40-1.22 (16H, m, 8 x C**H$_2$**), 1.17 (3H, s, CC**H$_3$**), 0.98 (3H, s, CC**H$_3$**), 0.89 (3H, t, *J* = 6.9 Hz, C**H$_3$**) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ 172.06 (s, **C**O), 131.53 (d, **C**HCH), 129.83 (d, CH**C**H), 83.40 (d, **C**HCH(OH)CO), 79.01 (d, **C**H(OH)CO), 74.01 (d, **C**H), 73.74 (d, **C**H), 66.18 (d, N**C**H), 53.42 (t, **C**H$_2$SO$_2$), 49.40 (s, **C**(CH$_3$)$_2$), 48.25 (s, **C**CH$_2$SO$_2$), 44.92 (d, NCHCH$_2$**C**H), 38.60 (t, NCH**C**H$_2$), 34.85 (t, **C**H$_2$), 33.27 (t, **C**H$_2$), 32.95 (t, **C**H$_2$), 32.28 (t, **C**H$_2$), 30.00 (t, 2 x **C**H$_2$), 29.95 (t, **C**H$_2$), 29.88 (t, **C**H$_2$), 29.70 (t, **C**H$_2$), 29.55 (t, **C**H$_2$), 29.16 (t, **C**H$_2$), 28.72 (t, **C**H$_2$), 28.57 (t, **C**H$_2$), 26.75 (t, **C**H$_2$), 23.04 (t,

CH_3CH_2), 21.20 (q, CCH_3), 20.24 (q, CCH_3), 14.47 (q, CH_3) ppm.

LRMS (ES^+) *m/z* 590 (100%) $[M+Na]^+$ Da.

HRMS (ES^+) for $C_{31}H_{53}NO_6SNa^+$, calculated 590.3486, found 590.3503 Da.

(2*S*)-*N*-((2*R*)-2-Hydroxy-2-((2*S*,5*R*)-5-((1*R*,4*E*)-1-hydroxypentadec-4-enyl)-tetrahydrofuran-2-yl)ethanoyl)-camphor-10,2-sultam (5.27)



$C_{31}H_{53}NO_6S$

M.W. = 567.82 g/mol

$[\alpha]^{26}_D$ +84.75 (*c* 1.20, $CHCl_3$).

FT-IR ν_{max} (neat) 3482 (brd, w), 2956 (m), 2922 (s), 2853 (m), 1693 (m), 1331 (s) cm^{-1}.

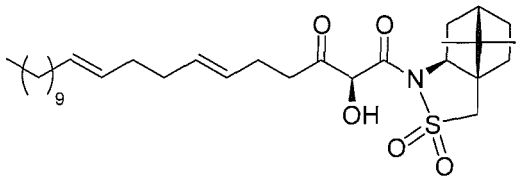
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49-5.35 (2H, m, C**H**C**H**), 4.68 (1H, d, *J* = 2.3 Hz, C**H**(OH)CO), 4.50 (1H, ddd, *J* = 7.4, 4.9, 2.3 Hz, C**H**CH(OH)CO), 3.96 (1H, app t, *J* = 6.1 Hz, NC**H**), 3.77 (1H, td, *J* = 7.3, 4.5 Hz, C**H**), 3.51-3.42 (1H, m, C**H**OH), 3.50 (1H, d, *J* = 13.7 Hz, C**H**HSO_2), 3.45 (1H, d, *J* = 13.7 Hz, CH**H**SO_2), 2.24-1.84 (13H, m, $CH_2CHCHCH_2$, 2 x CH_2 THF and NCHC**H**$_2$C**H**C**H**HC**H**H), 1.57-1.43 (2H, m, CH_2CHOH), 1.42-1.20 (18H, m, 8 x CH_2 and $NCHCH_2CHCHHCHH$), 1.16 (3H, s, CCH_3), 0.98 (3H, s, CCH_3), 0.89 (3H, t, *J* = 6.9 Hz, CH_3) ppm. Hydroxyl proton signals not observed.

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.46 (s, **C**O), 131.42 (d, **C**HCH), 129.88 (d, CH**C**H), 83.33 (d, **C**H), 80.52 (**C**HCH(OH)CO), 74.55 (d, **C**H(OH)CO), 73.40 (d, **C**HOH), 65.28 (d, N**C**H), 53.32 (t, CH_2SO_2), 49.39 (s, $C(CH_3)_2$), 48.28 (s, CCH_2SO_2), 44.82 (d, $NCHCH_2CH$), 37.98 (t, CH_2), 34.89 (t, CH_2CHOH), 32.93 (t, 2 x CH_2), 32.26 (t, CH_2), 29.99 (t, 2 x CH_2), 29.97 (t, CH_2), 29.88 (t, CH_2), 29.69 (t, CH_2), 29.53 (t, CH_2), 29.02 (t, CH_2), 28.51 (t,

CH_2), 28.10 (t, CH_2), 26.89 (t, CH_2), 23.03 (t, CH_3CH_2), 20.72 (q, CCH_3), 20.27 (q, CCH_3), 14.45 (q, CH_3) ppm.

LRMS (ES^+) *m/z* 590 (100%) $[M+Na]^+$ Da.

(2*S*)-*N*-((2*S*,6*E*,10*E*)-2-Hydroxy-3-oxohenicosa-6,10-dienoyl)-camphor-10,2-sultam (5.28)



$C_{31}H_{51}NO_5S$

M.W. = 549.80 g/mol

+diastereoisomer

$[\alpha]^{27}_D$ +58.33 (*c* 1.10, $CHCl_3$).

FT-IR ν_{max} (neat) 3458 (brd, w), 2956 (m), 2923 (s), 2853 (m), 1729 (s), 1690 (m), 1336 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50-5.33 (4H, m, 2 x **CH**CH), 5.24 (1H, brd s, **CH**OH), 3.96 (1H, dd, *J* = 7.5, 5.0 Hz, NC**H**), 3.53 (1H, d, *J* = 13.8 Hz, C**H**HSO$_2$), 3.48 (1H, d, *J* = 13.8 Hz, CH**H**SO$_2$), 2.81 (1H, dt, *J* = 17.8, 7.5 Hz, C**H**HCO), 2.65 (1H, dt, *J* = 17.8, 7.5 Hz, CH**H**CO), 2.45-2.26 (3H, m, C**H$_2$**CH$_2$CO and O**H**), 2.17-1.87 (9H, m, 4 x C**H$_2$** and NCHCH$_2$C**H**), 1.54-1.22 (20H, m, 8 x C**H$_2$** and NCHCH$_2$CHC**H$_2$**C**H$_2$**), 1.17 (3H, s, CC**H$_3$**), 0.99 (3H, s, CC**H$_3$**), 0.89 (3H, t, *J* = 6.9 Hz, C**H$_3$**) ppm.

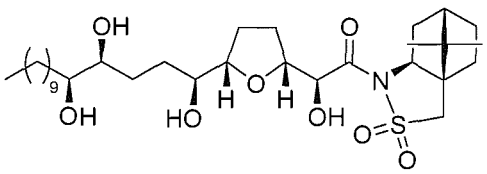
^{13}C NMR (100 MHz, $CDCl_3$) δ 203.50 (s, CH_2**C**O), 168.55 (s, **C**(O)N), 131.63 (d, **C**HCH), 131.22 (d, CH**C**H), 129.79 (d, **C**HCH), 128.23 (d, CH**C**H), 76.84 (d, **C**HOH), 65.43 (d, N**C**H), 53.22 (t, **C**H$_2$SO$_2$), 49.42 (s, **C**(CH$_3$)$_2$), 48.26 (s, **C**CH$_2$SO$_2$), 44.93 (d, NCHCH$_2$**C**H), 39.59 (t, **C**H$_2$CO), 38.13 (t, NCH**C**H$_2$), 34.17 (t, **C**H$_2$), 33.17 (t, **C**H$_2$), 33.00 (t, **C**H$_2$), 32.96 (t, **C**H$_2$), 32.93 (t, **C**H$_2$), 32.86 (t, **C**H$_2$), 32.27 (t, **C**H$_2$), 29.99 (t, **C**H$_2$), 29.87 (t, **C**H$_2$), 29.69 (t, **C**H$_2$), 29.53 (t, **C**H$_2$), 26.78 (t, **C**H$_2$), 26.42 (t, **C**H$_2$), 23.03 (t, CH$_3$**C**H$_2$), 20.80 (q, C**C**H$_3$), 20.28 (q, C**C**H$_3$), 14.45 (q, **C**H$_3$) ppm.

LRMS	(ES$^+$) *m/z* 572 (100%) $[M+Na]^+$, 567 (60%) $[M+NH_4]^+$ Da.
HRMS	(ES$^+$) for $C_{31}H_{51}NO_5SNa^+$, calculated 572.3380, found 572.3393 Da.

Selected data for minor diastereoisomer:

^{1}H NMR	(400 MHz, $CDCl_3$) δ 5.17 (1H, s, C**H**OH), 3.58 (1H, d, *J* = 14.0 Hz, C**H**HSO$_2$), 3.49 (1H, d, *J* = 14.0 Hz, CH**H**SO$_2$), 2.94 (1H, dt, *J* = 18.3, 7.5 Hz, C**H**HCO), 2.85 (1H, dt, *J* = 18.3, 7.5 Hz, CH**H**CO), 0.98 (3H, s, CC**H$_3$**) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ 178.06 (s, **C**(O)N), 131.86 (d, C**H**CH), 131.29 (d, CHC**H**), 129.74 (d, C**H**CH), 127.85 (d, CHC**H**), 64.23 (d, N**C**H), 52.23 (t, **C**H$_2$SO$_2$), 51.25 (s, **C**(CH$_3$)$_2$), 48.54 (s, **C**CH$_2$SO$_2$), 27.93 (t, **C**H$_2$), 25.92 (t, **C**H$_2$) ppm.

(2*S*)-*N*-((2*S*)-2-Hydroxy-2-((2*R*,5*S*)-5-((1*S*,4*S*,5*S*)-1,4,5-trihydroxypentadecyl)-tetrahydrofuran-2-yl)ethanoyl)-camphor-10,2-sultam (5.30)



$C_{31}H_{55}NO_8S$

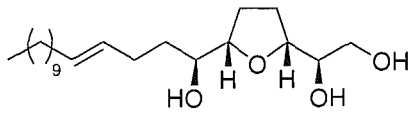
M.W. = 601.83 g/mol

To an orange bi-phasic mixture of H_2O (2.5 mL), ^{t}BuOH (2.5 mL), AD-mix α (250 mg) and $MeSO_2NH_2$ (17 mg, 0.18 mmol) at 0 °C was added mono-THF **5.16** (100 mg, 0.18 mmol) in Et_2O (0.5 mL) and ^{t}BuOH (0.5 mL). The resulting orange mixture was warmed to r.t. after 1 hour and was stirred for a further 5 ½ hours before it was quenched with Na_2SO_3 (250 mg) and stirred for 30 min. The aqueous phase was extracted with EtOAc (5 x 5mL) and the combined organic phases were washed with 2 M KOH (10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to a colourless gum. Purification by column chromatography (silica gel, 20 x 60 mm, 60-100% EtOAc / hexane and 5% MeOH / CH_2Cl_2) afforded the title compound **5.30** (52 mg, 0.09 mmol, 48%) as a colourless oil.

$[\alpha]^{29}_D$	+42.09 (*c* 0.80, $CHCl_3$).

FT-IR	ν_{max} (neat) 3384 (brd, w), 2922 (s), 2851 (m), 1671 (s), 1360 (m) cm^{-1}.
^{1}H NMR	(400 MHz, $CDCl_3$) δ 6.06 (1H, d, *J* = 8.0 Hz, O**H**), 4.90 (1H, d, *J* = 8.4 Hz, C**H**(OH)CO), 4.52 (1H, td, *J* = 8.4, 5.0 Hz, C**H**CH(OH)CO), 3.98 (1H, td, *J* = 7.2, 4.0 Hz, C**H**(OH)CHOH), 3.83 (1H, td, *J* = 8.5, 4.5 Hz, NC**H**), 3.58 (1H, d, *J* = 15.5 Hz, C**H**HSO_2), 3.50-3.37 (3H, m, CH(OH)C**H**OH and C**H**(OH)C**H**), 3.30 (1H, d, *J* = 15.5 Hz, CH**H**SO_2), 2.28-2.15 (1H, m, C**H**H THF), 2.13-1.87 (6H, m, C**H$_2$**CH(OH)CH(OH), C**H$_2$** THF and NCHC**H**HCHC**H**H), 1.84-1.58 (6H, m, C**H$_2$**, CH**H** THF and NCHCH**H**C**H**CH**H**), 1.54-1.21 (20H, m, 9 x C**H$_2$** and NCHCH_2CHCH_2C**H$_2$**), 0.98 (3H, s, CC**H$_3$**), 0.90 (3H, s, CC**H$_3$**), 0.88 (3H, t, *J* = 7.0 Hz, C**H$_3$**) ppm. Three hydroxyl proton signals not observed.
^{13}C NMR	(100 MHz, $CDCl_3$) δ 168.90 (s, **C**O), 83.87 (d, **C**HOH), 78.01 (d, **C**H(OH)CO), 76.98 (d, **C**HCH(OH)CO), 74.96 (d, **C**H), 74.60 (d, **C**H), 73.41 (d, **C**H), 58.67 (d, N**C**H), 54.02 (t, **C**H_2SO_2), 51.12 (s, **C**$(CH_3)_2$), 49.96 (s, **C**CH_2SO_2), 44.52 (d, NCHCH_2**C**H), 39.82 (t, NCH**C**H_2), 34.00 (t, **C**H_2), 33.11 (t, **C**H_2), 32.24 (t, 2 x **C**H_2), 31.16 (t, **C**H_2), 30.64 (t, **C**H_2), 30.07 (t, **C**H_2), 29.96 (t, 2 x **C**H_2), 29.66 (t, **C**H_2), 28.64 (t, **C**H_2), 27.60 (t, **C**H_2), 27.16 (t, **C**H_2), 26.09 (t, **C**H_2), 23.00 (t, CH_3**C**H_2), 20.97 (q, C**C**H_3), 20.42 (q, C**C**H_3), 14.43 (q, **C**H_3) ppm.
LRMS	(ES^+) *m/z* 624 (100%) $[M+Na]^+$ Da.
HRMS	(ES^+) for $C_{31}H_{55}NO_8SNa^+$, calculated 624.3540, found 624.3542 Da.

(1*R*)-1-((2*R*,5*S*)-5-((1*S*,4*E*)-1-Hydroxypentadec-4-enyl)-tetrahydrofuran-2-yl)-ethane-1,2-diol (5.32)



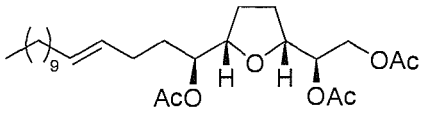
$C_{21}H_{40}O_4$

M.W. = 356.54 g/mol

To a solution of mono-THF **5.16** (1.00 g, 1.76 mmol) in THF (25 mL) and H_2O (25 μL) was added $NaBH_4$ (0.07 g, 1.94 mmol). The resulting mixture was stirred for 3 hours before quenching with H_2O (10 mL). The aqueous phase was extracted with EtOAc (3 x 100 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to a cream oil. Purification by column chromatography (silica gel, 50 x 50 mm, 5% MeOH / CH_2Cl_2) afforded the title compound **5.32** (0.59 g, 1.65 mmol, 94%) as a colourless oil.

$[\alpha]^{27}_D$	−10.11 (*c* 0.44, $CHCl_3$).
FT-IR	ν_{max} (neat) 3360 (brd, w), 2956 (m), 2923 (s), 2853 (m) cm^{-1}.
^{1}H NMR	(400 MHz, $CDCl_3$) δ 5.52-5.36 (2H, m, C**H**C**H**), 4.05 (1H, td, *J* = 6.8, 3.9 Hz, C**H**CH(OH)CH_2OH), 3.89 (1H, td, *J* = 6.8, 4.5 Hz, C**H**), 3.75-3.69 (2H, brd t, *J* = 4.3 Hz, C**H$_2$**OH), 3.62-3.57 (1H, m, C**H**(OH)CH_2OH), 3.53-3.47 (1H, m, C**H**OH), 3.13 (1H, brd s, O**H**), 2.53 (1H, brd s, O**H**), 2.42 (1H, brd s, O**H**), 2.26-2.05 (2H, m, C**H$_2$**CH_2CHOH), 2.03-1.85 (6H, m, C**H$_2$**CHCH and 2 x C**H$_2$** THF), 1.66-1.48 (2H, m, C**H$_2$**CHOH), 1.38-1.22 (16H, m, 8 x C**H$_2$**), 0.89 (3H, t, *J* = 6.9 Hz, C**H$_3$**) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ 131.79 (d, **C**HCH), 129.72 (d, CH**C**H), 83.15 (d, **C**H), 80.84 (d, **C**HCH(OH)CH_2OH), 74.09 (d, **C**HOH), 73.99 (d, **C**HOH), 65.53 (t, **C**H_2OH), 34.63 (t, **C**H_2CHOH), 32.93 (t, **C**$H_2$$CH_2$CHOH), 32.27 (t, **C**$H_2$), 30.00 (t, 2 x **C**$H_2$), 29.92 (t, **C**$H_2$), 29.87 (t, **C**$H_2$), 29.70 (t, **C**$H_2$), 29.55 (t, **C**$H_2$), 29.20 (t, **C**$H_2$CHCH), 28.42 (t, **C**$H_2$ THF), 28.36 (t, **C**H_2 THF), 23.04 (t, CH_3**C**H_2), 14.46 (q, **C**H_3) ppm.
LRMS	(ES$^+$) *m/z* 735 (30%) $[2M+Na]^+$, 379 (100%) $[M+Na]^+$ Da.
HRMS	(ES$^+$) for $C_{21}H_{40}O_4Na^+$, calculated 379.2819, found 379.2813 Da.

(1*R*)-2-Acetyloxy-1-((2*R*,5*S*)-5-((1*S*,4*E*)-1-acetyloxypentadec-4-enyl)-tetrahyrdofuran-2-yl)-ethyl ethanoate (5.33)



$C_{27}H_{46}O_7$

M.W. = 482.65 g/mol

To a solution of triol **5.32** (0.59 g, 1.65 mmol) and Ac_2O (50 mL) was added pyridine (0.53 mL, 6.59 mmol) and the resulting mixture was heated to 95 °C for 15 hours. The orange solution was cooled to r.t., concentrated *in vacuo* to an orange oil which was dissolved in EtOAc (20 mL) and washed with H_2O (10 mL) and brine (10 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to an oil. Purification by column chromatography (silica gel, 30 x 50 mm, 20% EtOAc / hexane) afforded the title compound **5.33** (0.73 g, 1.50 mmol, 91%) as a colourless oil.

$[\alpha]^{27}_D$ +7.08 (*c* 0.36, $CHCl_3$).

FT-IR ν_{max} (neat) 2954 (w), 2924 (m), 2854 (w), 1743 (s) cm^{-1}.

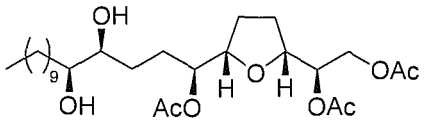
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47-5.32 (2H, m, C**H**C**H**), 5.12 (1H, ddd, *J* = 7.3, 4.9, 3.6 Hz, C**H**(OAc)CH_2OAc), 4.92 (1H, td, *J* = 6.4, 5.3 Hz, C**H**OAc), 4.37 (1H, dd, *J* = 12.0, 3.6 Hz, C**H**HOAc), 4.13-4.07 (1H, m, C**H**), 4.11 (1H, dd, *J* = 12.0, 7.3 Hz, CH**H**OAc), 3.98 (1H, td, *J* = 6.7, 5.2 Hz, C**H**), 2.11 (3H, s, C(O)C**H**$_3$), 2.08 (3H, s, C(O)C**H**$_3$), 2.06-1.88 (6H, m, C**H**$_2$CHCHC**H**$_2$ and C**H**$_2$ THF), 2.05 (3H, s, C(O)C**H**$_3$), 1.76-1.58 (4H, m, C**H**$_2$CHOAc and C**H**$_2$ THF), 1.36-1.22 (16H, m, 8 x C**H**$_2$), 0.89 (3H, t, *J* = 6.8 Hz, C**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.05 (s, **C**(O)CH_3), 170.95 (s, **C**(O)CH_3), 170.75 (s, **C**(O)CH_3), 131.76 (d, **C**HCH), 129.18 (d, CH**C**H), 80.45 (d, **C**H), 77.79 (d, **C**H), 75.01 (d, **C**HOAc), 73.11 (d, **C**H(OAc)CH_2OAc), 63.65 (t, **C**H_2OAc), 32.93 (t, **C**H_2CHCH), 32.27 (t, **C**H_2), 31.22 (t, **C**H_2CHOAc), 29.99 (t, 2 x **C**H_2), 29.89 (t, **C**H_2), 29.87 (t, **C**H_2), 29.69 (t, **C**H_2), 29.55 (t, **C**H_2), 28.77 (t, **C**H_2), 28.04 (t, **C**H_2 THF), 27.99 (t, **C**H_2 THF), 23.03 (t, CH_3**C**H_2), 21.44 (q, C(O)**C**H_3), 21.31 (q, C(O)**C**H_3), 21.11 (q, C(O)**C**H_3), 14.45 (q, **C**H_3), ppm.

LRMS (ES$^+$) *m/z* 987 (40%) $[2M+Na]^+$, 505 (100%) $[M+Na]^+$ Da.

HRMS (ES$^+$) for $C_{27}H_{47}O_7^+$, calculated 483.3317, found 483.3321 Da.

(1*R*)-2-Acetyloxy-1-((2*R*,5*S*)-5-((1*S*,4*S*,5*S*)-1-acetyloxy-4,5-dihydroxypentadecyl)-tetrahydrofuran-2-yl)-ethyl ethanoate (5.34)



$C_{27}H_{48}O_9$

M.W. = 516.66 g/mol

To an orange bi-phasic mixture of H_2O (30 mL), ^{t}BuOH (30 mL), AD-mix α (5.60 g) and $MeSO_2NH_2$ (0.14 g, 1.50 mmol) at 0 °C was added mono-THF **5.33** (0.73 g, 1.50 mmol) in Et_2O (2 mL) and ^{t}BuOH (2 mL). The resulting orange mixture was warmed to r.t. after 1 hour and was stirred at this temperature for a further 18 hours. Further AD-mix α (0.50 g) was added and the mixture was stirred for a further 2 hours before it was quenched with Na_2SO_3 (6.00 g) and stirred for 30 min. H_2O (10 mL) was added and extracted with EtOAc (5 x 20 mL). The combined organic phases were washed with 2 M KOH (2 x 20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to an orange oil. Purification by column chromatography (silica gel, 40 x 50 mm, 60-80% EtOAc / hexane) afforded the title compound **5.34** (0.68 g, 1.32 mmol, 88%) as a colourless oil.

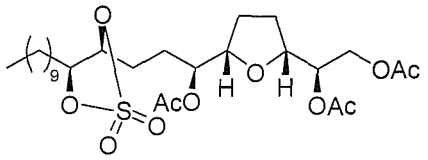
$[\alpha]^{27}_D$ −6.38 (*c* 0.40, $CHCl_3$).

FT-IR ν_{max} (neat) 3462 (brd, w), 2955 (w), 2924 (m), 2854 (m), 1741 (s), 1371 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13 (1H, ddd, *J* = 7.3, 5.5, 3.5 Hz, C**H**(OAc)CH_2OAc), 4.96 (1H, dt, *J* = 7.4, 5.4 Hz, C**H**OAc), 4.36 (1H, dd, *J* = 11.8, 3.5 Hz, C**H**HOAc), 4.14-4.08 (1H, m, C**H**), 4.10 (1H, dd, *J* = 11.8, 7.3 Hz, CH**H**OAc), 4.04-3.98 (1H, m, C**H**), 3.47-3.36 (2H, m, C**H**(OH)C**H**OH), 2.12 (3H, s, C(O)C**H**$_3$), 2.10 (3H, s, C(O)C**H**$_3$), 2.10-1.90 (2H, m, C**H**$_2$ THF), 2.05 (3H, s, C(O)C**H**$_3$), 1.79-1.66 (4H, m, C**H**$_2$CHOAc and C**H**$_2$ THF), 1.57-1.41 (4H, m C**H**$_2$CH(OH)CH(OH)C**H**$_2$), 1.39-1.20 (16H, m, 8 x C**H**$_2$), 0.89 (3H, t, *J* = 6.9 Hz, C**H**$_3$) ppm. Hydroxyl proton signals not observed.

^{13}C NMR	(100 MHz, $CDCl_3$) δ 171.13 (s, **C**(O)CH_3), 171.07 (s, **C**(O)CH_3), 170.88 (s, **C**(O)CH_3), 80.47 (d, **C**H), 77.91 (d, **C**H), 75.04 (d, **C**HOAc), 74.88 (d, **C**HOH), 74.16 (d, **C**HOH), 73.24 (d, **C**H(OAc)CH_2OAc), 63.59 (t, **C**H_2OAc), 33.97 (t, CH(OH)**C**H_2), 32.26 (t, **C**H_2), 30.04 (t, **C**H_2), 29.96 (t, 2 x **C**H_2), 29.68 (t, 2 x **C**H_2), 29.46 (t, **C**H_2), 28.06 (t, **C**H_2 THF), 27.97 (t, **C**H_2 THF), 27.11 (t, **C**H_2), 26.02 (t, **C**H_2), 23.03 (t, CH_3**C**H_2), 21.45 (q, C(O)**C**H_3), 21.34 (q, C(O)**C**H_3), 21.11 (q, C(O)**C**H_3), 14.45 (q, **C**H_3) ppm.
LRMS	(ES^+) *m/z* 539 (100%) $[M+Na]^+$ Da.
HRMS	(ES^+) for $C_{27}H_{48}O_9Na^+$, calculated 539.3190, found 539.3182 Da.

(1*R*)-2-Acetyloxy-1-((2*R*,5*S*)-5-((1*S*)-1-acetyloxy-3-((4*S*,5*S*)-5-decyl-2,2-dioxo-1,3,2-dioxathiolan-4-yl)propyl)-tetrahydrofuran-2-yl)-ethyl ethanoate (5.35)



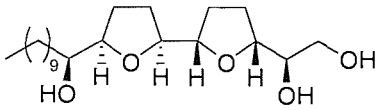
$C_{27}H_{46}O_{11}S$
M.W. = 578.71 g/mol

To a solution of diol **5.34** (0.67 g, 1.30 mmol) in CH_2Cl_2 (10 mL) was added pyridine (0.31 mL, 3.90 mmol) followed by $SOCl_2$ (0.14 mL, 1.95 mmol) and the resulting mixture was stirred for 1 hour. Further $SOCl_2$ (0.14 mL, 1.95 mmol) was added and the mixture was allowed to stir for 30 min before quenching with H_2O (5 mL). The aqueous phase was extracted with EtOAc (4 x 10 mL), the combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to an orange oil. Purification by column chromatography (silica gel, 30 x 60 mm) eluting with EtOAc / hexane (20-40%) afforded the cyclic sulphite which was used directly in the next reaction. Thus, to a solution of the crude cyclic sulphite in MeCN (25 mL) was added $NaIO_4$ (0.42 g, 1.95 mmol) and $RuCl_3.H_2O$ (0.04 g, 0.19 mmol) in H_2O (5 mL). The resulting dark green solution was stirred for 1 hour before EtOAc (15 mL) was added. The dark green precipitate was removed by filtration, the organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to a green oil. Purification by column chromatography (silica

gel, 30 x 60 mm, 40% EtOAc / hexane) afforded the title compound **5.35** (0.60 g, 1.04 mmol, 80%) as a colourless oil.

$[\alpha]^{26}_{D}$	−21.31 (*c* 0.80, $CHCl_3$).
FT-IR	ν_{max} (neat) 2953 (w), 2926 (m), 2855 (w), 1741 (s), 1375 (m), 1236 (s), 1209 (s) cm^{-1}.
^{1}H NMR	(400 MHz, $CDCl_3$) δ 5.15 (1H, ddd, *J* = 7.3, 5.1, 3.6 Hz, C**H**(OAc)CH_2OAc), 4.99-4.93 (1H, m, C**H**OAc), 4.65 (1H, td, *J* = 8.6, 2.6 Hz, C**H**OSO_2), 4.54 (1H, td, *J* = 8.6, 3.4 Hz, C**H**OSO_2), 4.35 (1H, dd, *J* = 12.0, 3.6 Hz, C**H**HOAc), 4.14-4.07 (1H, m, C**H**), 4.09 (1H, dd, *J* = 12.0, 7.3 Hz, CH**H**OAc), 4.00 (1H, td, *J* = 6.8, 5.1 Hz, C**H**), 2.12 (3H, s, C(O)C**H$_3$**), 2.12 (3H, s, C(O)C**H$_3$**), 2.06 (3H, s, C(O)C**H$_3$**), 2.03-1.93 (2H, m, C**H$_2$** THF), 1.92-1.63 (8H, m, 3 x C**H$_2$** and C**H$_2$** THF), 1.50-1.20 (16H, m, 8 x C**H$_2$**), 0.89 (3H, t, *J* = 6.9 Hz, C**H$_3$**) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ 171.19 (s, **C**(O)CH_3), 171.02 (s, **C**(O)CH_3), 170.71 (s, **C**(O)CH_3), 87.81 (d, **C**HOSO_2), 86.86 (d, **C**HOSO_2), 80.28 (d, **C**H), 78.06 (d, **C**H), 73.83 (d, **C**HOAc), 73.04 (d, **C**H(OAc)CH_2OAc), 63.56 (t, **C**H_2OAc), 32.23 (t, **C**H_2), 32.16 (t, **C**H_2), 29.87 (t, **C**H_2), 29.80 (t, **C**H_2), 29.63 (t, 2 x **C**H_2), 29.41 (t, **C**H_2), 28.28 (t, **C**H_2), 28.05 (t, **C**H_2), 28.00 (t, **C**H_2), 26.98 (t, **C**H_2), 25.53 (t, **C**H_2), 23.01 (t, CH_3**C**H_2), 21.34 (q, C(O)**C**H_3), 21.31 (q, C(O)**C**H_3), 21.10 (q, C(O)**C**H_3), 14.45 (q, **C**H_3) ppm.
LRMS	(ES^+) *m/z* 601 (100%) $[M+Na]^+$ Da.
HRMS	(ES^+) for $C_{27}H_{46}O_{11}SNa^+$, calculated 601.2653, found 601.2647 Da.

(1*R*)-1-((2*R*,5*S*)-5-((2*S*,5*R*)-5-((1*S*)-1-Hydroxyundecyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)-ethane-1,2-diol (5.36)



$C_{21}H_{40}O_5$

M.W. = 372.54 g/mol

Method A:

To a solution of cyclic sulphate **5.35** (440 mg, 0.76 mmol) in MeOH (32 mL) was added K_2CO_3 (315 mg, 2.28 mmol) and the resulting yellow solution was allowed to stir for 1 hour. The reaction mixture was cooled to 0 °C before H_2SO_4 (2.6 mL) was added. The resulting mixture was allowed to stir for 16 hours before neutralising with 2 M KOH (50 mL). The aqueous phase was extracted with EtOAc (5 x 50 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to an orange oil. Purification by column chromatography (silica gel, 30 x 60 mm, 5% MeOH / CH_2Cl_2) afforded the title compound **5.36** (224 mg, 0.60 mmol, 79%) as a colourless gum.

Method B:

To a solution of mono-THF acetal **6.16** (57 mg, 0.13 mmol) and trimethylorthoacetate (19 mg, 0.16 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added $BF_3{\cdot}OEt_2$ (2 mg, 0.01 mmol) and the resulting mixture was warmed to r.t. after 1 hour and stirred for a further 35 hours. Acetone (1 mL) was added and the mixture was concentrated *in vacuo* to a colourless oil. The crude oil was re-dissolved in MeOH (3 mL) before K_2CO_3 (74 mg, 0.52 mmol) was added and the mixture was allowed to stir for 4 hours before concentrating *in vacuo* to a white solid. Purification by column chromatography (silica gel, 20 x 50 mm, 5% MeOH / CH_2Cl_2) afforded the title compound **5.36** (34 mg, 0.09 mmol, 71%) as a colourless gum.

$[\alpha]^{27}_D$	+0.62 (*c* 1.05, $CHCl_3$).
FT-IR	ν_{max} (neat) 3404 (brd, m), 2923 (s), 2853 (s) cm^{-1}.
^{1}H NMR	(400 MHz, $CDCl_3$) δ 4.14 (1H, td, *J* = 6.0, 3.1 Hz, C**H**CH(OH)CH_2OH), 4.03-3.97 (1H, m, C**H**), 3.93-3.83 (3H, m, C**H**OH and 2 x C**H**), 3.79-3.66 (3H, m, C**H**$_2$OH and O**H**), 3.57-3.50 (1H, m, C**H**(OH)CH_2OH), 3.33 (1H, brd s, O**H**), 2.85 (1H,

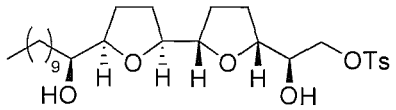
dd, J = 8.0, 4.0 Hz, OH), 2.06-1.71 (8H, m, 4 x CH_2 THF), 1.41-1.23 (18H, m, 9 x CH_2), 0.89 (3H, t, J = 6.9 Hz, CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 83.51 (d, CH), 81.95 (d, $CHCH(OH)CH_2OH$), 81.28 (d, CH), 81.11 (d, CH), 73.84 (d, $CH(OH)CH_2OH$), 71.87 (d, CH), 66.08 (t, CH_2OH), 33.47 (t, CH_2), 32.26 (t, CH_2), 30.06 (t, CH_2), 29.97 (t, 2 x CH_2), 29.93 (t, CH_2), 29.69 (t, CH_2), 29.00 (t, CH_2 THF), 28.78 (t, CH_2 THF), 28.65 (t, CH_2 THF), 26.39 (t, CH_2), 23.75 (t, CH_2), 23.03 (t, CH_3CH_2), 14.46 (q, CH_3) ppm.

LRMS (ES^+) *m/z* 395 (100%) $[M+Na]^+$, 373 (55%) $[M+H]^+$ Da.

HRMS (ES^+) for $C_{21}H_{40}O_5Na^+$, calculated 395.2768, found 395.2762 Da.

(2*R*)-2-((2*R*,5*S*)-5-((2*S*,5*R*)-((1*S*)-1-Hydroxyundecyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)-2-hydroxyethyl-4-methylbenzenesulphonate (5.37)



$C_{28}H_{46}O_7S$

M.W. = 526.73 g/mol

To a solution of triol **5.36** (197 mg, 0.53 mmol) in benzene (12 mL) was added Bu_2SnO (158 mg, 0.63 mmol) and the resulting mixture was heated to reflux for 3 hours. The cloudy white solution was then cooled to r.t. before TsCl (111 mg, 0.58 mmol) and TBAB (85 mg, 0.26 mmol) were added. The mixture was allowed to stir for 1 ½ hours then concentrated *in vacuo* to a white oil. Purification by column chromatography (silica gel, 30 x 60 mm, 40-60% EtOAc / hexane) afforded the title compound **5.37** (272 mg, 0.52 mmol, 97%) as a colourless gum.

$[\alpha]^{27}_D$ +0.15 (*c* 0.68, $CHCl_3$).

FT-IR ν_{max} (neat) 3411 (brd, w), 2923 (m), 2853 (m), 1189 (m), 1176 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (2H, d, J = 8.1 Hz, Ar-H), 7.34 (2H, d, J = 8.1 Hz, Ar-H), 4.08 (2H, dd, J = 6.3, 1.8 Hz, CH_2OSO_2), 4.07-4.01 (1H, m, CHCHOH), 3.92 (1H, td, J = 6.8, 3.8 Hz, CHCH), 3.87-3.78 (3H, m, CH(OH)CH and CHCH), 3.74-3.67

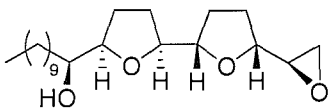
(1H, m, C**H**(OH)CH_2OSO_2), 3.45 (1H, s, O**H**), 3.43 (1H, s, O**H**), 2.45 (3H, s, CCH_3), 2.02-1.70 (8H, m, 4 x CH_2 THF), 1.53-1.21 (18H, m, 9 x CH_2), 0.89 (3H, t, J = 6.9 Hz, CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.10 (s, SO_2C), 133.32 (s, CCH_3), 130.16 (d, 2 x Ar-CH), 128.37 (d, 2 x Ar-C), 83.40 (d, CH), 81.40 (d, CH), 80.94 (d, CH), 78.92 (d, CHCHOH), 72.04 (d, CH), 71.77 (d, CH(OH)CH_2OSO_2), 71.50 (t, CH_2SO_2), 33.50 (t, CH_2), 32.25 (t, CH_2), 30.02 (t, CH_2), 29.96 (t, 2 x CH_2), 29.91 (t, CH_2), 29.67 (t, CH_2), 28.90 (t, CH_2 THF), 28.73 (t, CH_2 THF), 28.06 (t, CH_2 THF), 26.29 (t, CH_2), 24.05 (t, CH_2 THF), 23.02 (t, CH_3CH_2), 21.97 (q, CCH_3), 14.45 (q, CH_3) ppm.

LRMS (ES^+) *m/z* 549 (100%) $[M+Na]^+$, 527 (50%) $[M+H]^+$ Da.

HRMS (ES^+) for $C_{28}H_{46}O_7SNa^+$, calculated 549.2856, found 549.2846 Da.

(1*S*)-1-((1*R*,5*S*)-5-((2*S*,5*R*)-5-((1*R*)-Oxiran-2-yl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)-undecan-1-ol (5.38)



$C_{21}H_{38}O_4$

M.W. = 354.52 g/mol

To a solution of tosylate **5.37** (202 mg, 0.38 mmol) in MeOH (14 mL) was added K_2CO_3 (58 mg, 0.42 mmol) and the resulting cloudy mixture was stirred for 2 hours then concentrated *in vacuo* to a white solid. Purification by column chromatography (silica gel, 20 x 60 mm, 40% EtOAc / hexane) afforded the title compound **5.38** (109 mg, 0.31 mmol, 81%) as a colourless gum.

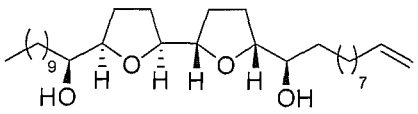
$[\alpha]^{27}_D$ +1.67 (*c* 0.30, $CHCl_3$).

FT-IR ν_{max} (neat) 3477 (brd, w), 2923 (s), 2853 (m), 1466 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95-3.83 (5H, m, C**H**(OH)C**H**, C**H**CH and C**H**CH(O)CH_2), 3.03 (1H, dd, J = 7.8, 3.5 Hz, C**H**(O)CH_2), 2.75 (2H, d, J = 3.5 Hz, CH(O)C**H$_2$**), 2.07-1.70 (8H, m, 4 x CH_2 THF), 1.53-1.21 (18H, m, 9 x C**H$_2$**), 0.89 (3H, t, J = 6.9 Hz, C**H$_3$**) ppm. Hydroxyl proton signal not observed.

^{13}C NMR	(100 MHz, $CDCl_3$) δ 83.19 (d, **C**H), 81.97 (d, **C**H), 81.40 (d, **C**H), 78.93 (d, **C**H), 72.13 (d, **C**HCH(O)CH_2), 54.03 (d, **C**H(O)CH_2), 44.43 (t, CH(O)**C**H_2), 33.09 (t, **C**H_2), 32.26 (t, **C**H_2), 30.09 (t, **C**H_2), 29.97 (t, 2 x **C**H_2), 29.92 (t, **C**H_2), 29.68 (t, **C**H_2), 28.81 (t, **C**H_2 THF), 28.73 (t, **C**H_2 THF), 28.48 (t, **C**H_2 THF), 26.40 (t, **C**H_2), 24.05 (t, **C**H_2 THF), 23.03 (t, CH_3**C**H_2), 14.45 (q, **C**H_3) ppm.
LRMS	(ES^+) *m/z* 377 (50%) $[M+Na]^+$, 372 (100%) $[M+NH_4]^+$, 337 (80%), 319 (25%) Da.
HRMS	(ES^+) for $C_{21}H_{38}O_4Na^+$, calculated 377.2662, found 377.2661 Da.

(1*R*)-1-((2*R*,5*S*)-5-((2*S*,5*R*)-5-((1*S*)-1-Hydroxyundecyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)-undec-10-en-1-ol (5.39)



$C_{30}H_{56}O_4$

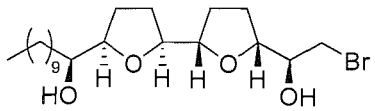
M.W. = 480.76 g/mol

Magnesium turnings (95 mg, 3.90 mmol) were heated to ca. 400 °C for 10 min then allowed to cool to r.t. THF (9 mL) and I_2 (1 crystal) were added followed by the dropwise addition of 1-bromononene (50 mg, 0.24 mmol). The resulting orange solution was heated to reflux until the orange colour disappeared (ca. 5 min) and the remaining 1-bromononene (500 mg, 2.44 mmol) was added. The mixture was heated to reflux for a further 1 hour. Titration of this solution using I_2 gave an average concentration of 0.28 M. An aliquot of this solution (2.5 mL, 0.69 mmol) was added to a suspension of CuBr (25 mg, 0.17 mmol) in THF (3 mL) at −60 °C and the resulting grey solution was warmed to −30 °C over 1 hour. The mixture was allowed to stir at this temperature for a further 30 min. The reaction mixture was then cooled back to −60 °C before epoxide **5.38** (41 mg, 0.12 mmol) in THF (1 mL) was added dropwise. The resulting mixture was warmed to −40 °C over 1 hour before quenching with sat. aq. NH_4Cl (3 mL) and NH_3 (1 mL). The aqueous phase was extracted with EtOAc (4 x 5 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 10 x 40 mm, 20-40% EtOAc /

hexane) afforded the title compound **5.39** (42 mg, 0.09 mmol, 75%) as a colourless gum.

$[\alpha]^{27}_D$	+15.85 (*c* 0.65, $CHCl_3$).
FT-IR	ν_{max} (neat) 3437 (brd, w), 2922 (s), 2852 (s) cm^{-1}.
^{1}H NMR	(400 MHz, $CDCl_3$) δ 5.81 (1H, ddt, *J* = 17.1, 10.3, 6.7 Hz, C**H**CH_2), 4.99 (1H, dq, *J* = 17.1, 1.8 Hz, CHC**H**H *trans* to CH), 4.93 (1H, ddt, *J* = 10.3, 2.3, 1.2 Hz, CHCH**H** *cis* to CH), 3.95-3.80 (5H, m, C**H**(OH)C**H**, C**H**C**H** and C**H**CHOH), 3.46-3.37 (1H, m, C**H**OH), 2.93 (1H, brd s, O**H**), 2.83 (1H, brd d, *J* = 5.0 Hz, O**H**), 2.08-2.01 (2H, m, C$\mathbf{H_2}$CHC$\mathbf{H_2}$), 2.01-1.74 (8H, m, 4 x C$\mathbf{H_2}$ THF), 1.54-1.42 (2H, m, CH(OH)C$\mathbf{H_2}$), 1.42-1.21 (30H, m, 15 x C$\mathbf{H_2}$), 0.89 (3H, t, *J* = 6.9 Hz, C$\mathbf{H_3}$) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ 139.59 (d, **C**HCH_2), 114.41 (t, CH**C**H_2), 83.42 (d, **C**H), 83.27 (d, **C**H), 81.47 (d, **C**H), 81.32 (d, **C**H), 74.37 (d, **C**HOH), 72.30 (d, **C**HCHOH), 34.63 (t, **C**H_2), 34.15 (t, **C**H_2CHCH_2), 33.16 (t, **C**H_2), 32.25 (t, **C**H_2), 30.05 (t, **C**H_2), 30.03 (t, **C**H_2), 29.97 (t, 2 x **C**H_2), 29.92 (t, **C**H_2), 29.90 (t, **C**H_2), 29.80 (t, **C**H_2), 29.68 (t, **C**H_2), 29.48 (t, **C**H_2), 29.28 (t, **C**H_2), 29.11 (t, **C**H_2), 28.79 (t, **C**H_2), 28.26 (t, **C**H_2), 26.37 (t, **C**H_2), 26.13 (t, **C**H_2), 24.12 (t, **C**H_2 THF), 23.02 (t, CH_3**C**H_2), 14.44 (q, **C**H_3) ppm.
LRMS	(ES$^+$) *m/z* 503 (95%) $[M+Na]^+$, 481 (100%) $[M+H]^+$ Da.
HRMS	(ES$^+$) for $C_{30}H_{56}O_4Na^+$, calculated 503.4071, found 503.4073 Da.

(1*S*)-1((2*R*,5*S*)-5-((2*S*,5*R*)-5-((1*S*)-2-Bromo-1-hydroxyethyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)-undecan-1-ol (5.40)



$C_{21}H_{39}BrO_4$

M.W. = 435.44 g/mol

Magnesium turnings (32 mg, 1.34 mmol) were heated to ca. 400 °C for 10 min then allowed to cool to r.t. THF (4 mL) and I_2 (1 crystal) were added followed by the

dropwise addition of 1-bromononene (30 mg, 0.15 mmol). The resulting orange solution was heated to reflux until the orange colour disappeared (ca. 5 min) and the remaining 1-bromononene (200 mg, 0.97 mmol) was added. The mixture was heated to reflux for a further 1 hour. Titration of this solution using I_2 gave an average concentration of 0.1 M. An aliquot of this solution (1.8 mL, 0.18 mmol) was added to a suspension of CuBr (20 mg, 0.14 mmol) in THF (2 mL) at –60 °C and the resulting grey solution was warmed to –30 °C over 30 min. The mixture was allowed to stir at this temperature for a further 30 min. The black reaction mixture was then cooled to –60 °C before epoxide **5.38** (20 mg, 0.06 mmol) in THF (1 mL) was added dropwise. The resulting mixture was warmed to –20 °C over 2 hours before quenching with sat. aq. NH_4Cl (3 mL) and NH_3 (1 mL). The aqueous phase was extracted with EtOAc (4 x 5 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 15 x 40 mm, 20-30% EtOAc / hexane) afforded the title compound **5.40** (21 mg, 0.05 mmol, 86%) as a colourless gum.

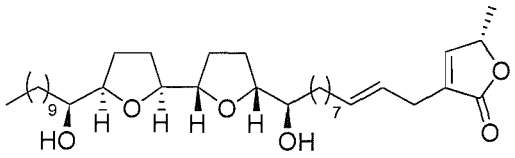
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28-4.22 (1H, m, C**H**CH(OH)CH_2Br), 3.98 (1H, td, *J* = 6.9, 4.0 Hz, C**H**CH), 3.91-3.83 (3H, m, C**H**(OH)C**H** and CHC**H**), 3.69 (1H, td, *J* = 6.4, 2.7 Hz, C**H**(OH)CH_2Br), 3.50 (1H, dd, *J* = 10.1, 6.4 Hz, C**H**HBr), 3.44 (1H, dd, *J* = 10.1, 6.4 Hz, CH**H**Br), 2.09-1.72 (8H, m, 4 x C**H$_2$** THF), 1.54-1.22 (18H, m, 9 x C**H$_2$**), 0.88 (3H, t, *J* = 6.9 Hz, C**H$_3$**) ppm. Hydroxyl proton signals not observed.

^{13}C NMR (100 MHz, $CDCl_3$) δ 83.48 (d, **C**H), 81.36 (d, **C**HCH), 81.08 (d, CH**C**H), 79.61 (d, **C**HCH(OH)CH_2Br), 74.07 (d, **C**H(OH)CH_2Br), 72.11 (d, **C**H), 35.20 (t, **C**H_2Br), 33.41 (t, **C**H_2), 32.25 (t, **C**H_2), 30.01 (t, **C**H_2), 29.95 (t, 2 x **C**H_2), 29.90 (t, **C**H_2), 29.67 (t, **C**H_2), 28.96 (t, **C**H_2 THF), 28.81 (t, **C**H_2 THF), 28.41 (t, **C**H_2 THF), 26.33 (t, **C**H_2), 24.10 (t, **C**H_2 THF), 23.02 (t, CH_3**C**H_2), 14.45 (q, **C**H_3) ppm.

LRMS (ES^+) *m/z* 459 and 457 (100%) $[M+Na]^+$, 437 and 435 (75%) $[M+H]^+$, 419 and 417 (5%), 401 and 399 (15%) Da.

HRMS (ES$^+$) for $C_{21}H_{39}BrO_4Na^+$, calculated 457.1924, found 457.1914 Da.

(5*S*)-3-((11*R*,2*E*)-11-Hydroxy-11-((2*R*,5*S*)-5-(2*S*,5*R*)-5-((1*S*)-1-hydroxyundecyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)undec-2-enyl)-5-methylfuran-2(5*H*)-one (5.41)



$C_{35}H_{60}O_6$
M.W. = 576.86 g/mol

Method A:

To a solution of terminal alkene **5.39** (14 mg, 30 μmol) and propargylic alcohol **3.14** (5 mg, 36 μmol) in degassed MeOH (2 mL) was added a solution of CpRu(COD)Cl (**3.15**) (2 mg, 6 μmol) in degassed MeOH (0.5 mL). The resulting orange mixture was heated to reflux for 4 hours before cooling to r.t. and concentrating *in vacuo* to a brown oil. Purification by column chromatography (silica gel, 10 x 40 mm, 1% MeOH / CH_2Cl_2) afforded the title compound **5.41** (9 mg, 10 μmol, 52%) as an orange oil.

Method B:

To a solution of terminal alkene **5.39** (42 mg, 90 μmol) and propargylic alcohol **3.14** (14 mg, 96 μmol) in DMF (2 mL) was added $[CpRu(MeCN)_3]PF_6$ (**5.15**, 4 mg, 9 μmol). The resulting orange mixture was allowed to stir for 2 hours then filtered through a plug of silica (20 x 40 mm) eluting with EtOAc / hexane (60%). Purification by column chromatography (silica gel, 20 x 50 mm, 1-2% MeOH / CH_2Cl_2) afforded the title compound **5.41** (28 mg, 49 μmol, 55%) as an orange oil.

$[\alpha]^{27}_D$ +19.55 (*c* 0.45, $CHCl_3$).

FT-IR ν_{max} (neat) 3448 (brd, w), 2923 (s), 2853 (s), 1757 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (1H, q, *J* = 1.9 Hz, CC**H**CH(CH$_3$)), 5.58 (1H, dt, *J* = 15.1, 6.5 Hz, C**H**CH), 5.46 (1H, dtt, *J* = 15.3, 6.5, 1.3 Hz, CHC**H**), 5.01 (1H, qq, *J* = 6.4, 1.9 Hz, C**H**CH$_3$), 3.95-3.81 (5H, m, C**H**(OH)C**H**, C**H**CH and C**H**CHOH), 3.42

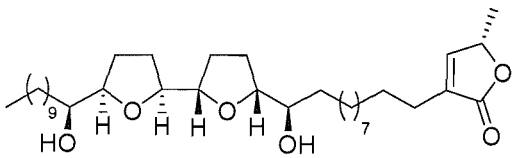
(1H, dt, J = 7.5, 4.2 Hz, C**H**OH), 2.96 (2H, d, J = 6.5 Hz, CHCHC**H**$_2$CCH), 2.86 (2H, brd s, 2 x O**H**), 2.07-1.99 (2H, m, C**H**$_2$CHCH), 1.99-1.71 (8H, m, 4 x C**H**$_2$ THF), 1.55-1.43 (2H, m, CH(OH)C**H**$_2$), 1.42 (3H, d, J = 6.4 Hz, CH(C**H**$_3$)), 1.39-1.20 (28H, m, 14 x C**H**$_2$), 0.89 (3H, t, J = 6.9 Hz, C**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.82 (s, **C**O), 149.70 (d, **C**CH), 134.51 (d, **C**HCH), 133.94 (s, **C**CH), 124.65 (d, CH**C**H), 83.41 (d, **C**H), 83.24 (d, **C**H), 81.47 (d, **C**H), 81.30 (d, **C**H), 77.92 (d, **C**H(CH$_3$)), 74.38 (d, **C**HOH), 72.33 (d, **C**HCHOH), 34.66 (t, **C**H$_2$), 33.17 (t, **C**H$_2$), 32.81 (t, **C**H$_2$), 32.26 (t, **C**H$_2$), 30.06 (t, **C**H$_2$), 30.00 (t, **C**H$_2$), 29.97 (t, 2 x **C**H$_2$), 29.93 (t, **C**H$_2$), 29.78 (t, **C**H$_2$), 29.68 (t, **C**H$_2$), 29.64 (t, **C**H$_2$), 29.47 (t, **C**H$_2$), 29.13 (t, **C**H$_2$), 28.81 (t, **C**H$_2$), 28.78 (t, **C**H$_2$), 28.27 (t, **C**H$_2$), 26.37 (t, **C**H$_2$), 26.14 (t, **C**H$_2$), 24.11 (t, **C**H$_2$), 23.03 (t, CH$_3$**C**H$_2$), 19.51 (q, CH(**C**H$_3$)), 14.45 (q, **C**H$_3$) ppm.

LRMS (ES$^+$) *m/z* 1175 (35%) [2M+Na]$^+$, 599 (100%) [M+Na]$^+$, 594 (35%) [M+NH$_4$]$^+$ Da.

HRMS (ES$^+$) for $C_{35}H_{60}O_6Na^+$, calculated 599.4282, found 599.4286 Da.

(5*S*)-3-((11*R*)-11-Hydroxy-11-((2*R*,5*S*)-5-(2*S*,5*R*)-5-((1*S*)-1-hydroxyundecyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)undecyl)-5-methylfuran-2(5*H*)-one (3.22)



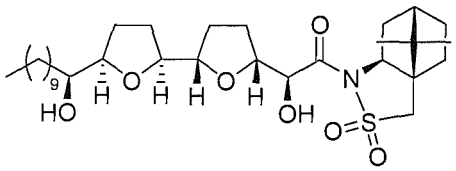
$C_{35}H_{62}O_6$
M.W. = 578.87 g/mol

To a solution of *bis*-THF **5.41** (28 mg, 49 μmol) and $TsNHNH_2$ (91 mg, 490 μmol) in THF (4 mL) was added a solution of NaOAc (40 mg, 490 μmol) in H_2O (4 mL). The resulting mixture was heated to reflux for 29 hours before further $TsNHNH_2$ (45 mg, 245 μmol) and NaOAc (20 mg, 245 μmol) were added. The mixture was heated to reflux for a further 18 hours then cooled to r.t. and diluted with H_2O (2 mL). The aqueous phase was extracted with Et_2O (5 x 4 mL) and the combined organic phases

were dried (Na_2SO_4) and concentrated *in vacuo* to a colourless oil. Purification by column chromatography (silica gel, 10 x 50 mm, 0-1% MeOH / CH_2Cl_2) afforded the title compound **3.22** (19 mg, 33 μmol, 68%) as a colourless oil.

$[\alpha]^{27}_D$	+23.54 (*c* 0.95, $CHCl_3$).
FT-IR	ν_{max} (neat) 3444 (brd, w), 2924 (s), 2853 (m), 1757 (m) cm^{-1}.
^{1}H NMR	(400 MHz, $CDCl_3$) δ 3.99 (1H, appt q, *J* = 1.7 Hz, CC**H**CH(CH_3)), 4.99 (1H, qq, *J* = 6.8, 1.7 Hz, C**H**CH_3), 3.95-3.81 (5H, m, C**H**(OH)C**H**, C**H**C**H** and C**H**CHOH), 3.45-3.39 (1H, m, C**H**OH), 2.89 (2H, brd m, 2 x O**H**), 2.27 (2H, tt, *J* = 7.8, 1.6 Hz, C**H$_2$**CCH), 2.01-1.72 (8H, m, 4 x C**H$_2$** THF), 1.60-1.39 (4H, m, CH(OH)C**H$_2$** and C**H$_2$**CH_2CCH), 1.41 (3H, d, *J* = 6.8 Hz, CHC**H$_3$**), 1.38-1.22 (32H, m, 16 x C**H$_2$**), 0.89 (3H, t, *J* = 6.9 Hz, C**H$_3$**) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ 174.21 (s, **C**O), 149.15 (d, **C**CH), 134.73 (s, **C**CH), 83.42 (d, **C**H), 83.26 (d, **C**H), 81.48 (d, **C**HCH), 81.32 (d, CH**C**H), 77.56 (d, **C**HCH_3), 74.38 (d, **C**HOHCH_2), 72.32 (d, CH_2**C**HOH), 34.66 (t, **C**H_2), 33.17 (t, **C**H_2), 32.27 (t, **C**H_2), 30.06 (t, **C**H_2), 30.04 (t, **C**H_2), 29.97 (t, 2 x **C**H_2), 29.93 (t, 2 x **C**H_2), 29.91 (t, **C**H_2), 29.84 (t, **C**H_2), 29.67 (t, **C**H_2), 29.65 (t, **C**H_2), 29.52 (t, **C**H_2), 29.13 (t, **C**H_2), 28.81 (t, **C**H_2 THF), 28.27 (t, **C**H_2 THF), 27.76 (t, **C**H_2 THF), 26.38 (t, **C**H_2), 26.15 (t, **C**H_2), 25.54 (t, **C**H_2), 24.12 (t, **C**H_2 THF), 23.03 (t, CH_3**C**H_2), 19.58 (q, CH**C**H_3), 14.46 (q, **C**H_3) ppm.
LRMS	(ES$^+$) *m/z* 601 (100%) $[M+Na]^+$, 579 (95%) $[M+H]^+$, 381 (35%), 162 (75%) Da.
HRMS	(ES$^+$) for $C_{35}H_{62}O_6Na^+$, calculated 601.4439, found 601.4422 Da.

(2*S*)-*N*-((2*S*)-2-Hydroxy-2-((2*R*,5*S*)-5-((2*S*,5*R*)-5-((1*S*)-1-hydroxyundecyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)ethanoyl)-camphor-10,2-sultam (5.29)



$C_{31}H_{53}NO_7S$

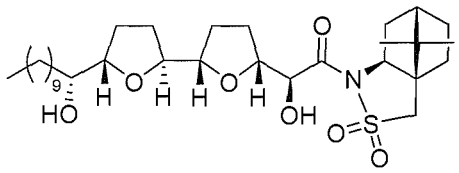
M.W. = 583.82 g/mol

To a solution of mono-THF **5.16** (88 mg, 0.16 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added *m*-CPBA (70 mg, 0.31 mmol) and the resulting mixture was stirred for 1 hour. The cloudy solution was diluted with CH_2Cl_2 (5 mL) and washed with sat. aq. $NaHCO_3$ (5 mL) and H_2O (2 x 5 mL). The organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to a colourless gum. The gum was re-dissolved in CH_2Cl_2 (5 mL) before CSA (9 mg, 0.04 mmol) was added and stirred for 1 hour. The resulting mixture was diluted with CH_2Cl_2 (5 mL) and washed with sat. aq. $NaHCO_3$ (5 mL) and H_2O (2 x 5 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to a colourless gum. Purification by column chromatography (silica gel, 20 x 60 mm, 50% EtOAc / hexane) afforded two diastereoisomers. The title compound **5.29** (31 mg, 0.05 mmol, 33%) was obtained as a colourless oil and **3.28** (30 mg, 0.05 mmol, 32%) as a cream oil (data corresponded with that obtained from the Re_2O_7 cyclisation on the *cis* alkene).

$[\alpha]^{27}_D$	+21.38 (*c* 0.94, $CHCl_3$).
FT-IR	ν_{max} (neat) 3503 (brd, w), 2956 (m), 2925 (s), 2854 (m), 1695 (m) cm^{-1}.
^{1}H NMR	(400 MHz, $CDCl_3$) δ 4.89 (1H, d, *J* = 10.3 Hz, O**H**), 4.70-4.65 (1H, m, C**H**CH(OH)CO), 4.58 (1H, brd d, *J* = 8.3 Hz, C**H**(OH)CO), 4.09-4.03 (1H, m, C**H**), 3.96-3.89 (4H, m, C**H**(OH)C**H**, NC**H** and O**H**), 3.83 (1H, ddd, *J* = 8.7, 5.9, 2.4 Hz, C**H**), 3.49 (1H, d, *J* = 13.8 Hz, C**H**HSO$_2$), 3.42 (1H, d, *J* = 13.8 Hz, CH**H**SO$_2$), 2.34-2.24 (1H, m, NCHC**H**H), 2.19-2.02 (7H, m, 3 x C**H$_2$** THF and NCHCH**H**), 1.99-1.69 (9H, m, C**H$_2$**CHOH, C**H$_2$** THF and NCHCH$_2$C**H**C**H$_2$**C**H$_2$**), 1.45-1.21 (16H, m, 8 x C**H$_2$**), 1.15 (3H, s, CC**H$_3$**), 0.96 (3H, s, CC**H$_3$**), 0.89 (3H, t, *J* = 6.8 Hz, C**H$_3$**) ppm.

^{13}C NMR	(100 MHz, $CDCl_3$) δ 172.28 (s, **C**O), 83.38 (d, CH(OH)**C**H), 80.98 (**C**H), 80.73 (d, **C**H), 78.64 (d, **C**HCH(OH)CO), 74.52 (d, **C**H(OH)CO), 71.83 (d, **C**HOH), 66.22 (d, N**C**H), 53.37 (t, **C**H_2SO_2), 49.29 (s, **C**$(CH_3)_2$), 48.19 (s, **C**CH_2SO_2), 44.91 (d, NCHCH$_2$**C**H), 38.64 (t, NCH**C**H_2), 33.74 (t, **C**H_2), 33.36 (t, **C**H_2), 32.26 (t, **C**H_2), 30.09 (t, **C**H_2), 29.98 (t, 2 x **C**H_2), 29.95 (t, **C**H_2), 29.69 (t, **C**H_2), 29.40 (t, **C**H_2), 29.24 (t, **C**H_2), 28.94 (t, **C**H_2), 26.72 (t, **C**H_2), 26.43 (t, **C**H_2), 23.90 (t, **C**H_2), 23.02 (t, CH_3**C**H_2), 21.26 (q, C**C**H_3), 20.26 (q, C**C**H_3), 14.45 (q, **C**H_3) ppm.
LRMS	(ES$^+$) *m/z* 606 (100%) $[M+Na]^+$ Da.
HRMS	(ES$^+$) for $C_{31}H_{53}NO_7SNa^+$, calculated 606.3435, found 606.3425 Da.

(2*S*)-*N*-((2*S*)-2-Hydroxy-2-((2*R*,5*S*)-5-((2*S*,5*S*)-5-((1*R*)-1-hydroxyundecyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)ethanoyl)-camphor-10,2-sultam (3.28)



$C_{31}H_{53}NO_7S$

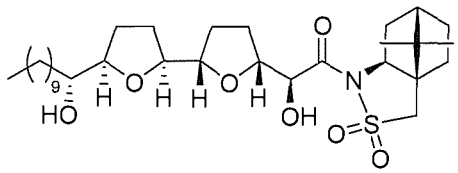
M.W. = 583.82 g/mol

To a solution of Re_2O_7 (768 mg, 1.58 mmol) in THF (10 mL) was added TFAA (0.3 mL, 2.11 mmol) and the resulting pale blue solution was stirred for 1 hour, over which time it changed colour to pale black. The THF was removed *in vacuo* at 0 °C and the purple residue was washed with freshly distilled hexane (3 x 5 mL). The purple residue was dissolved in CH_2Cl_2 (15 mL) before the dropwise addition of mono-THF **6.1** (300 mg, 0.53 mmol) in CH_2Cl_2 (2 mL). The resulting black solution was stirred for 1 ½ hours before quenching with sat. aq. $KHSO_4$ (10 mL) and H_2O (5 mL). The aqueous phase was extracted with EtOAc (4 x 20 mL) and the combined organics were dried (Na_2SO_4) and concentrated *in vacuo* to a black oil. Purification by column chromatography (silica gel, 30 x 80 mm, 40-60% EtOAc / hexane) afforded the title compound **3.28** (226 mg, 0.39 mmol, 73%) as a colourless oil.

$[\alpha]^{27}_D$	+22.79 (*c* 0.34, $CHCl_3$).

FT-IR	ν_{max} (neat) 3426 (brd, w), 2923 (s), 2854 (m), 1696 (m) cm^{-1}.
^{1}H NMR	(400 MHz, $CDCl_3$) δ 4.67-4.62 (1H, m, C**H**CH(OH)CO), 4.50 (1H, d, J = 2.3 Hz, C**H**(OH)CO), 4.16-4.09 (1H, m, C**H**), 4.03-3.93 (3H, m, C**H**C**H** and NC**H**), 3.88-3.82 (1H, m, C**H**OH), 3.51 (1H, d, J = 13.7 Hz, C**H**HSO$_2$), 3.42 (1H, d, J = 13.7 Hz, CH**H**SO$_2$), 2.26-2.16 (1H, m, NCHC**H**H), 2.15-1.83 (12H, m, 4 x C**H$_2$** THF and NCHCH**H**C**H**C**H**HC**H**H), 1.56-1.22 (20H, m, 9 x C**H$_2$** and NCHCH$_2$CHCH**H**CH**H**), 1.17 (3H, s, CC**H$_3$**), 0.98 (3H, s, CC**H$_3$**), 0.89 (3H, t, J = 6.9 Hz, C**H$_3$**) ppm. Hydroxyl proton signals not observed.
^{13}C NMR	(100 MHz, $CDCl_3$) δ 172.31 (s, **C**O), 83.28 (d, **C**H), 81.90 (d, **C**H), 81.87 (d, **C**H), 79.11 (d, **C**HCH(OH)CO), 74.70 (d, **C**H(OH)CO), 71.99 (d, **C**HOH), 66.29 (d, N**C**H), 53.58 (t, **C**H$_2$SO$_2$), 49.15 (s, **C**(CH$_3$)$_3$), 48.13 (s, **C**CH$_2$SO$_2$), 45.12 (d, NCHCH$_2$**C**H), 38.81 (t, NCH**C**H$_2$), 33.47 (t, **C**H$_2$), 32.73 (t, **C**H$_2$), 32.27 (t, **C**H$_2$), 30.07 (t, **C**H$_2$), 29.98 (t, **C**H$_2$), 29.95 (t, **C**H$_2$), 29.69 (t, **C**H$_2$), 29.61 (t, **C**H$_2$), 29.10 (t, **C**H$_2$), 28.83 (t, **C**H$_2$), 26.71 (t, **C**H$_2$), 26.37 (t, **C**H$_2$), 25.28 (t, **C**H$_2$), 23.02 (t, **C**H$_2$), 21.37 (t, CH$_3$**C**H$_2$), 20.25 (q, C**C**H$_3$), 14.54 (q, C**C**H$_3$), 14.45 (q, **C**H$_3$) ppm.
LRMS	(ES$^+$) *m/z* 606 (100%) [M+Na]$^+$ Da.

(2*S*)-*N*-((2*S*)-2-Hydroxy-2-((2*R*,5*S*)-5-((2*S*,5*R*)-5-((1*R*)-1-hydroxyundecyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)ethanoyl)-camphor-10,2-sultam (6.2)



$C_{31}H_{53}NO_7S$

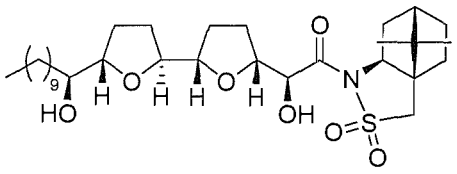
M.W. = 583.82 g/mol

To a solution of mono-THF **6.1**(261 mg, 0.46 mmol) in CH_2Cl_2 (10 mL) was added *m*-CPBA (309 mg, 1.38 mmol) and the resulting mixture was stirred for 2 hours. The cloudy solution was diluted with CH_2Cl_2 (10 mL) and washed with sat. aq. $NaHCO_3$ (3 x 5 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to a colourless gum. The gum was re-dissolved in CH_2Cl_2 (15 mL) before CSA (53 mg,

0.23 mmol) was added and stirred for 15 hours. The resulting mixture was diluted with CH_2Cl_2 (10 mL) and washed with sat. aq. $NaHCO_3$ (2 x 5 mL), 2 M HCl (5 mL) then brine (10 mL). The organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to a colourless gum. Purification by column chromatography (silica gel, 30 x 80 mm, 40% EtOAc / hexane) afforded a mixture of the two diastereoisomers (130 mg, 0.22 mmol, 48%). Further purification by preparative HPLC afforded the title compound **6.2** (23 mg, 0.04 mmol, 9%) as a colourless oil and a mixture of **6.2** and **6.3** (65 mg, 0.11 mmol, 24%) as a colourless oil.

$[\alpha]^{27}_D$	+36.25 (*c* 0.36, $CHCl_3$).
FT-IR	ν_{max} (neat) 3486 (brd, w), 2922 (m), 2853 (m), 1693 (m), 1330 (s) cm^{-1}.
^{1}H NMR	(400 MHz, $CDCl_3$) δ 4.62-4.57 (1H, m, C**H**CH(OH)CO), 4.55 (1H, brd d, *J* = 2.0 Hz, C**H**(OH)CO), 3.98 (1H, td, *J* = 7.0, 3.0 Hz, C**H**), 3.95 (1H, dd, *J* = 7.8, 5.0 Hz, NC**H**), 3.88 (1H, td, *J* = 7.0, 3.3 Hz, C**H**), 3.86-3.81 (1H, m, CH(OH)C**H**), 3.52-3.46 (1H, m, C**H**OH), 3.50 (1H, d, *J* = 13.8 Hz, C**H**HSO$_2$), 3.42 (1H, d, *J* = 13.8 Hz, CH**H**SO$_2$), 2.29-2.20 (1H, m, NCHC**H**H), 2.14-2.00 (3H, C**H$_2$** THF and NCHCH**H**), 1.97-1.82 (7H, m, 3 x C**H$_2$** THF and NCHCH$_2$C**H**), 1.59-1.38 (6H, m, C**H$_2$**CHOH and NCHCH$_2$CHC**H$_2$**C**H$_2$**), 1.38-1.21 (16H, m, 8 x C**H$_2$**), 1.16 (3H, s, CC**H$_3$**), 0.97 (3H, s, CC**H$_3$**), 0.88 (3H, t, *J* = 6.9 Hz, C**H$_3$**) ppm. Hydroxyl proton signals not observed.
^{13}C NMR	(100 MHz, $CDCl_3$) δ 171.97 (s, **C**O), 83.17 (d, CH(OH)**C**H), 81.30 (d, **C**HCH), 80.94 (d, CH**C**H), 78.66 (d, **C**HCH(OH)CO), 73.96 (d, 2 x **C**HOH), 66.14 (d, N**C**H), 53.39 (t, **C**H$_2$SO$_2$), 49.26 (s, **C**(CH$_3$)$_2$), 48.18 (s, **C**CH$_2$SO$_2$), 44.95 (d, NCHCH$_2$**C**H), 38.63 (t, NCH**C**H$_2$), 34.48 (t, **C**H$_2$), 33.34 (t, **C**H$_2$), 32.26 (t, **C**H$_2$), 30.05 (t, 2 x **C**H$_2$), 30.01 (t, 2 x **C**H$_2$), 29.70 (t, **C**H$_2$), 28.92 (t, **C**H$_2$ THF), 28.74 (t, 2 x **C**H$_2$ THF), 28.07 (t, **C**H$_2$ THF), 26.72 (t, **C**H$_2$), 26.26 (t, **C**H$_2$), 23.02 (t, CH$_3$**C**H$_2$), 21.26 (q, C**C**H$_3$), 20.24 (q, C**C**H$_3$), 14.44 (q, **C**H$_3$) ppm.
LRMS	(ES$^+$) *m/z* 606 (100%) [M+Na]$^+$, 584 (15%) [M+H]$^+$ Da.

(2*S*)-*N*-((2*S*)-2-Hydroxy-2-((2*R*,5*S*)-5-((2*S*,5*S*)-5-((1*S*)-1-hydroxyundecyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)ethanoyl)-camphor-10,2-sultam (6.3)



$C_{31}H_{53}NO_7S$

M.W. = 583.82 g/mol

To a solution of Re_2O_7 (179 mg, 0.37 mmol) in THF (3 mL) was added TFAA (0.07 mL, 0.49 mmol) and the resulting pale blue solution was stirred for 1 hour, over which time it changed colour to pale black. The THF was removed *in vacuo* at 0 °C and the purple residue was washed with freshly distilled hexane (3 x 3 mL). The purple residue was dissolved in CH_2Cl_2 (5 mL) before the dropwise addition of mono-THF **5.16** (70 mg, 0.12 mmol) in CH_2Cl_2 (3 mL). The resulting black solution was stirred for 1 hour before quenching with sat. aq. $KHSO_4$ (5 mL). The aqueous phase was extracted with EtOAc (4 x 10 mL) and the combined organics dried (Na_2SO_4) and concentrated *in vacuo* to a black oil. Purification by column chromatography (silica gel, 20 x 80 mm, 50% EtOAc / hexane) afforded the title compound **6.3** (55 mg, 0.09 mmol, 79%) as a colourless oil.

$[\alpha]^{27}_D$ -10.11 (*c* 0.44, $CHCl_3$).

FT-IR ν_{max} (neat) 3446 (brd, w), 2922 (s), 2853 (m), 1693 (s), 1330 (s) cm^{-1}.

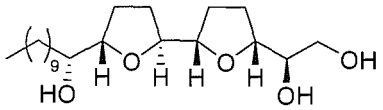
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67-4.61 (1H, m, C**H**CH(OH)CO), 4.51-4.47 (1H, m, C**H**(OH)CO), 4.04 (1H, dt, *J* = 8.5, 6.3 Hz, CH(OH)C**H**), 4.02-3.91 (3H, m, C**H**C**H** and NC**H**), 3.50 (1H, d, *J* = 13.7 Hz, C**H**HSO$_2$), 3.44-3.36 (1H, m, C**H**OH), 3.42 (1H, d, *J* = 13.7 Hz, CH**H**SO$_2$), 2.25-2.16 (1H, m, NCHC**H**H), 2.14-1.82 (11H, m, 3 x C**H$_2$** THF, C**H**H THF and NCHCH**H**C**H**C**H**HC**H**H), 1.73-1.62 (1H, m, CH**H** THF), 1.46-1.20 (20H, m, 9 x C**H$_2$** and NCHCH$_2$CHCH**H**CH**H**), 1.17 (3H, s, CC**H$_3$**), 0.97 (3H, s, CC**H$_3$**), 0.88 (3H, t, *J* = 6.9 Hz, C**H$_3$**) ppm. Hydroxyl proton signals not observed.

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.19 (s, **C**O), 83.58 (d, CH(OH)**C**H), 81.63 (d, **C**H), 81.16 (d, **C**H), 79.11 (d, **C**HCH(OH)CO), 74.70

(d, **C**H(OH)CO), 74.25 (d, **C**HOH), 66.25 (d, N**C**H), 53.54 (t, **C**H_2SO_2), 49.13 (s, **C**$(CH_3)_2$), 48.11 (s, **C**CH_2SO_2), 45.10 (d, NCHCH$_2$**C**H), 38.79 (t, NCH**C**H_2), 33.92 (t, **C**H_2CHOH), 33.42 (t, **C**H_2), 32.24 (t, 2 x **C**H_2), 30.03 (t, **C**H_2), 29.97 (t, 2 x **C**H_2), 29.66 (t, 2 x **C**H_2), 29.06 (t, **C**H_2), 28.80 (t, 2 x **C**H_2), 26.69 (t, **C**H_2 THF), 25.95 (t, **C**H_2), 23.00 (t, CH_3**C**H_2), 21.36 (q, C**C**H_3), 20.22 (q, C**C**H_3), 14.43 (q, **C**H_3) ppm.

LRMS (ES$^+$) *m/z* 606 (100%) $[M+Na]^+$ Da.

(1*R*)-1-((2*R*,5*S*)-5-((2*S*,5*S*)-5-((1*R*)-1-Hydroxyundecyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)-ethane-1,2-diol (6.4)



$C_{21}H_{40}O_5$

M.W. = 372.54 g/mol

To a solution of mono-THF **3.28** (219 mg, 0.38 mmol) in THF (3 mL) and H_2O (20 μL) was added $NaBH_4$ (16 mg, 0.41 mmol). The resulting mixture was stirred for 4 hours before quenching with H_2O (3 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to a cream oil. Purification by column chromatography (silica gel, 20 x 50 mm, 5-10% MeOH / CH_2Cl_2) afforded the title compound **6.4** (117 mg, 0.31 mmol, 83%) as a colourless gum.

$[\alpha]^{27}_D$ −8.54 (*c* 0.24, $CHCl_3$).

FT-IR ν_{max} (neat) 3402 (brd, m), 2923 (s), 2853 (m) cm^{-1}.

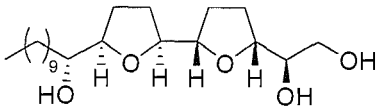
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13-4.07 (1H, m, C**H**CH(OH)CH_2OH), 4.00-3.88 (3H, m, CH(OH)C**H** and C**H**C**H**), 3.86-3.80 (1H, m, C**H**OH), 3.69 (2H, d, *J* = 4.0 Hz, C**H$_2$**OH), 3.57-3.51 (1H, m, C**H**(OH)CH_2OH), 2.57 (1H, brd s, O**H**), 2.29 (2H, brd s, 2 x O**H**), 2.06-1.70 (8H, m, 4 x C**H$_2$** THF), 1.40-1.22 (18H, m, 9 x C**H$_2$**), 0.89 (3H, t, *J* = 6.7 Hz, C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 83.35 (d, CH(OH)**C**H), 82.38 (d, **C**H), 82.15 (d, **C**H), 81.11 (d, **C**HCH(OH)CH_2OH), 74.38 (d, **C**H(OH)CH_2OH), 72.05 (d, **C**HOH), 65.54 (t, **C**H_2OH), 32.86 (t,

CH_2), 32.26 (t, CH_2), 30.03 (t, CH_2), 29.96 (t, 2 x CH_2), 29.91 (t, CH_2), 29.68 (t, CH_2), 29.62 (t, CH_2 THF), 28.66 (t, CH_2 THF), 28.56 (t, CH_2 THF), 26.36 (t, CH_2), 25.23 (t, CH_2), 23.03 (t, CH_3CH_2), 14.45 (q, CH_3) ppm.

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

(1*R*)-1-((2*R*,5*S*)-5-((2*S*,5*R*)-5-((1*R*)-1-Hydroxyundecyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)-ethane-1,2-diol (6.5)



$C_{21}H_{40}O_5$

M.W. = 372.54 g/mol

To a solution of mono-THF **6.2** (22 mg, 0.04 mmol) in THF (2 mL) and H_2O (3 μL) was added $NaBH_4$ (2 mg, 0.04 mmol). The resulting mixture was stirred for 2 hours before quenching with H_2O (2 mL). The aqueous phase was extracted with EtOAc (5 x 5 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to a cream oil. Purification by column chromatography (silica gel, 10 x 40 mm, 5% MeOH / CH_2Cl_2) afforded the title compound **6.5** (12 mg, 0.03 mmol, 85%) as a colourless oil.

$[\alpha]^{27}_D$ +0.77 (*c* 0.65, $CHCl_3$).

FT-IR ν_{max} (neat) 3387 (brd, w), 2922 (s), 2853 (m) cm^{-1}.

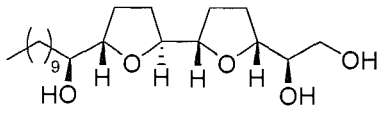
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11-4.04 (1H, m, C**H**CH(OH)CH_2OH), 3.96-3.86 (2H, m, C**H**C**H**), 3.86-3.79 (1H, m, CH(OH)C**H**), 3.72-3.67 (2H, brd m, C**H**$_2$OH), 3.56 (1H, appt q, *J* = 4.4 Hz, C**H**(OH)CH_2OH), 3.45-3.39 (1H, m, C**H**OH), 2.91 (3H, brd s, 3 x O**H**), 2.03-1.87 (6H, m, 3 x C**H**$_2$ THF), 1.87-1.74 (2H, m, C**H**$_2$ THF), 1.56-1.41 (2H, m, C**H**$_2$CHOH), 1.37-1.20 (16H, m, 8 x CH_2), 0.88 (3H, t, *J* = 6.8 Hz, C**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 83.20 (d, CH(OH)**C**H), 81.60 (d, **C**H), 81.37 (d, **C**H), 81.26 (d, **C**H), 74.12 (d, **C**HOH), 73.90 (d, **C**HOH), 65.61 (t, CH_2OH), 34.63 (t, CH_2CHOH), 32.26 (t, CH_2), 30.07 (t, CH_2), 29.97 (t, 2 x CH_2), 29.68 (t, 2 x CH_2), 28.64 (t, CH_2 THF), 28.62 (t, CH_2 THF), 28.38 (t, CH_2 THF),

28.10 (t, **C**H_2 THF), 26.18 (t, **C**H_2), 23.02 (t,CH_3**C**H_2), 14.44 (q, **C**H_3) ppm.

LRMS (ES^+) *m/z* 767 (40%) $[2M+Na]^+$, 395 (100%) $[M+Na]^+$, 390 (40%) $[M+NH_4]^+$, 373 (30%) $[M+H]^+$ Da.

(1*R*)-1-((2*R*,5*S*)-5-((2*S*,5*S*)-5-((1*S*)-1-Hydroxyundecyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)-ethane-1,2-diol (6.6)



$C_{21}H_{40}O_5$

M.W. = 372.54 g/mol

To a solution of mono-THF **6.3** (62 mg, 0.11 mmol) in THF (3 mL) and H_2O (10 μL) was added $NaBH_4$ (4 mg, 0.12 mmol). The resulting mixture was stirred for 2 hours before quenching with H_2O (3 mL). The aqueous phase was extracted with EtOAc (4 x 10 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to a cream oil. Purification by column chromatography (silica gel, 20 x 50 mm, 5% MeOH / CH_2Cl_2) afforded the title compound **6.6** (36 mg, 0.10 mmol, 88%) as a colourless gum.

$[\alpha]^{27}_D$ −12.93 (*c* 0.29, $CHCl_3$).

FT-IR ν_{max} (neat) 3405 (brd, w), 2922 (s), 2853 (m) cm^{-1}.

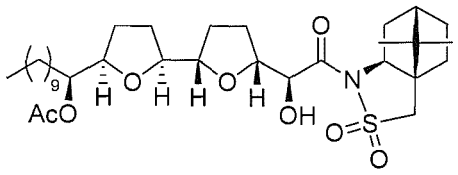
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (1H, ddd, *J* = 7.0, 5.3, 3.3 Hz, **CH**CH(OH)CH_2OH), 3.98-3.91 (2H, m, **CHCH**), 3.89 (1H, dt, *J* = 8.3, 6.0 Hz, CH(OH)**CH**), 3.72-3.64 (2H, m, **CH_2**OH), 3.57-3.50 (1H, m, **CH**(OH)CH_2OH), 3.45-3.36 (2H, m, **CHOH** and **OH**), 2.51 (1H, brd s, **OH**), 2.30 (1H, brd s, **OH**), 2.07-1.89 (6H, m, 3 x **CH_2** THF), 1.87-1.66 (2H, m, **CH_2** THF), 1.46-1.39 (2H, m, **CH_2**CHOH), 1.34-1.22 (16H, m, 8 x **CH_2**), 0.89 (3H, t, *J* = 6.9 Hz, **CH_3**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 83.64 (d, CH(OH)**C**H), 81.73 (d, **C**HCH), 81.61 (d, CH**C**H), 81.07 (d, **C**HCH(OH)CH_2OH), 74.34 (d, **C**HOH), 74.20 (d, **C**HOH), 65.64 (t, **C**H_2OH), 33.94 (t, **C**H_2), 32.27 (t, **C**H_2), 30.04 (t, 2 x **C**H_2), 29.97 (t, 2 x **C**H_2), 29.69 (t, 2

x CH_2), 28.80 (t, CH_2 THF), 28.76 (t, CH_2 THF), 28.65 (t, CH_2 THF), 26.01 (t, CH_2), 23.03 (t, CH_3CH_2), 14.46 (q, CH_3) ppm.

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

(2*S*)-*N*-((2*S*)-2-Hydroxy-2-((2*R*,5*S*)-5-((2*S*,5*R*)-5-((1*S*)-1-acetyloxyundecyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)ethanoyl)-camphor-10,2-sultam (6.8)



$C_{33}H_{55}NO_8S$

M.W. = 625.86 g/mol

To a solution of tetraol **5.30** (52 mg, 0.09 mmol) in CH_2Cl_2 (2 mL) was added *p*-TsOH (2 mg) followed by $MeC(OMe)_3$ (14 μL, 0.11 mmol). The resulting colourless solution was stirred for 1 hour then concentrated *in vacuo* to a pale yellow oil. Purification by column chromatography (silica gel, 10 x 50 mm, 50% EtOAc / hexane) afforded the title compound **6.8** (27 mg, 0.04 mmol, 50%) as a colourless oil.

$[\alpha]^{30}_D$ +43.27 (*c* 0.26, $CHCl_3$).

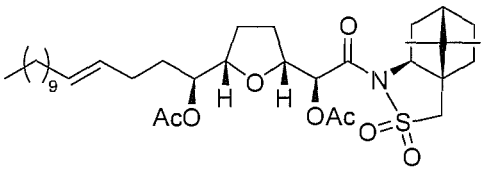
FT-IR ν_{max} (neat) 3221 (brd, w), 2955 (m), 2924 (m), 2854 (m), 1732 (m), 1671 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (1H, brd s, O**H**), 4.96 (1H, d, *J* = 7.7 Hz, C**H**(OH)CO), 4.85 (1H, ddd, *J* = 8.0, 6.9, 4.0 Hz, C**H**OAc), 4.40 (1H, q, *J* = 7.7 Hz, **C**HCH(OH)CO), 4.02 (1H, td, *J* = 6.9, 4.4 Hz, C**H**), 3.96 (3H, m, CH(OAc)C**H**, C**H** and NC**H**), 3.56 (1H, d, *J* = 15.3 Hz, C**H**HSO$_2$), 3.28 (1H, d, *J* = 15.3 Hz, CH**H**SO$_2$), 2.18-2.00 (1H, m, NCHC**H**H), 2.05 (3H, s, C(O)C**H**$_3$), 2.00-1.53 (14H, m, C**H**$_2$CHOAc, 4 x C**H**$_2$ THF and NCHCH**H**C**H**C**H**HC**H**H), 1.35-1.20 (18H, m, 8 x C**H**$_2$ and NCHCH$_2$CHCH**H**CH**H**), 0.98 (3H, s, CC**H**$_3$), 0.89 (3H, s, CC**H**$_3$), 0.88 (3H, t, *J* = 7.0 Hz, C**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.78 (s, **C**(O)CH$_3$), 168.78 (s, **C**O), 81.89 (d, **C**H), 81.43 (d, **C**H), 80.52 (d, **C**H), 78.14 (d, **C**H(OH)CO), 77.55 (d, **C**HCH(OH)CO), 76.10 (d, **C**HOAc), 58.30 (d, N**C**H), 54.01 (t, **C**H$_2$SO$_2$), 51.15 (s, **C**(CH$_3$)$_2$), 49.82 (s,

	CCH_2SO_2), 44.63 (d, NCHCH$_2$C**H**), 39.92 (NCH**C**H$_2$), 32.76 (t, **C**H$_2$), 32.23 (t, **C**H$_2$), 31.64 (t, **C**H$_2$), 29.99 (t, **C**H$_2$), 29.92 (t, 2 x **C**H$_2$), 29.65 (t, 2 x **C**H$_2$), 28.68 (t, **C**H$_2$), 28.32 (t, **C**H$_2$), 27.91 (t, **C**H$_2$), 27.12 (t, **C**H$_2$), 27.09 (t, **C**H$_2$), 25.34 (t, **C**H$_2$), 23.00 (t, CH$_3$**C**H$_2$), 21.50 (q, C(O)**C**H$_3$), 21.01 (q, C**C**H$_3$), 20.58 (q, C**C**H$_3$), 14.44 (q, **C**H$_3$) ppm.
LRMS	(ES$^+$) *m/z* 648 (100%) [M+Na]$^+$ Da.
HRMS	(ES$^+$) for $C_{33}H_{56}NO_8S^+$, calculated 626.3721, found 626.3722 Da.

(2*S*)-*N*-((2*S*)-2-Acetyloxy-2-((2*R*,5*S*)-5-((1*S*,4*E*)-1-acetyloxypentadec-4-enyl)-tetrahydrofuran-2-yl)ethanoyl)-camphor-10,2-sultam (6.9)



$C_{35}H_{57}NO_8S$

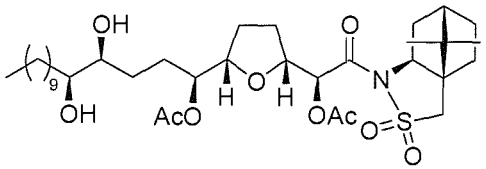
M.W. = 651.89 g/mol

To a solution of mono-THF **5.16** (300 mg, 0.53 mmol) in Ac_2O (18 mL) was added pyridine (128 μL, 1.58 mmol) and the resulting mixture was heated to reflux for 3 ½ hours. The mixture was cooled to r.t. and concentrated *in vacuo* to an orange oil which was re-dissolved in EtOAc (20 mL) and washed with H_2O (2 x 10 mL) then brine (2 x 10 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to an orange oil. Purification by column chromatography (silica gel, 30 x 60 mm, 25-30% EtOAc / hexane) afforded the title compound **6.9** (289 mg, 0.44 mmol, 84%) as a yellow oil.

$[\alpha]^{27}_D$	+13.51 (*c* 0.39, $CHCl_3$).
FT-IR	ν_{max} (neat) 2956 (m), 2924 (s), 2852 (m), 1740 (s), 1234 (s) cm^{-1}.
^{1}H NMR	(400 MHz, $CDCl_3$) δ 5.46-5.32 (2H, m, C**H**C**H**), 5.30 (1H, d, *J* = 5.1 Hz, C**H**(OAc)CO), 4.92 (1H, dt, *J* = 8.8, 4.8 Hz, C**H**OAc), 4.54 (1H, td, *J* = 6.7, 5.1 Hz, C**H**CH(OAc)CO), 4.03 (1H, td, *J* = 7.0, 4.8 Hz, C**H**), 3.96 (1H, dd, *J* = 7.8, 5.0 Hz, NC**H**), 3.49 (1H, d, *J* = 13.8 Hz, C**H**HSO$_2$), 3.42 (1H, d, *J* = 13.8 Hz, CH**H**SO$_2$), 2.25-2.16 (1H, m, NCHC**H**H), 2.11 (3H, s, C(O)C**H**$_3$), 2.08 (3H,

	s, C(O)CH_3), 2.07-1.82 (10H, m, $CH_2CHCHCH_2$, 2 x CH_2 THF and NCHCH**HCH**), 1.81-1.58 (2H, m, CH_2CHOAc), 1.46-1.22 (20H, m, 8 x CH_2 and $NCHCH_2CHCH_2CH_2$), 1.21 (3H, s, CCH_3), 0.97 (3H, s, CCH_3), 0.87 (3H, t, J = 6.8 Hz, CH_3) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ 171.13 (s, **C**(O)CH_3), 170.45 (s, **C**(O)CH_3), 167.21 (s, **C**O), 131.48 (d, **C**HCH), 129.36 (d, CH**C**H), 80.65 (d, **C**H), 77.45 (d, **C**HCH(OAc)), 74.80 (d, **C**HOAc), 74.45 (d, **C**H(OAc)CO), 66.03 (d, N**C**H), 53.39 (t, CH_2SO_2), 49.18 (s, $C(CH_3)_2$), 48.12 (s, CCH_2SO_2), 44.99 (d, $NCHCH_2CH$), 38.49 (t, $NCHCH_2$), 33.26 (t, CH_2), 32.90 (t, CH_2), 32.22 (t, CH_2), 30.93 (t, CH_2), 29.94 (t, 2 x CH_2), 29.86 (t, CH_2), 29.83 (t, CH_2), 29.64 (t, CH_2), 29.51 (t, CH_2), 28.80 (t, CH_2), 27.96 (t, CH_2), 27.56 (t, CH_2), 26.72 (t, CH_2), 22.99 (t, CH_3CH_2), 21.44 (q, C(O)CH_3), 20.91 (q, CH_3), 20.86 (q, CH_3), 20.29 (q, CCH_3), 14.41 (q, CH_3) ppm.
LRMS	(ES$^+$) *m/z* 674 (100%) $[M+Na]^+$, 669 (20%) $[M+NH_4]^+$ Da.
HRMS	(ES$^+$) for $C_{35}H_{57}NO_8SNa^+$, calculated 674.3697, found 674.3713 Da.

(2*S*)-*N*-((2*S*)-2-Acetyloxy-2-((2*R*,5*S*)-5-((1*S*,4*S*,5*S*)-1-acetyloxy-4,5-dihydroxypentadecyl)-tetrahydrofuran-2-yl)ethanoyl)-camphor-10,2-sultam (6.10)



$C_{35}H_{59}NO_{10}S$

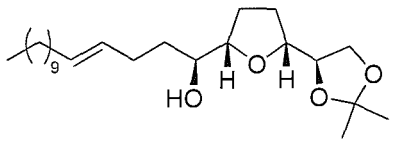
M.W. = 685.90 g/mol

To an orange bi-phasic mixture of H_2O (9 mL), ^{t}BuOH (9 mL), AD-mix α (850 mg) and $MeSO_2NH_2$ (39 mg, 0.41 mmol) at 0 °C was added mono-THF **6.9** (266 mg, 0.41 mmol) in Et_2O (3 mL) and ^{t}BuOH (3 mL). The resulting orange mixture was allowed to stir for 15 hours before it was quenched with Na_2SO_3 (850 mg) and stirred for a further 30 min. H_2O (10 mL) was added and the aqueous phase extracted with EtOAc (4 x 30 mL). The combined organic phases were washed with 2 M KOH (2 x 30 mL), dried (Na_2SO_4) and concentrated *in vacuo* to an orange oil. Purification by column

chromatography (silica gel, 30 x 60 mm, 60-70% EtOAc / hexane) afforded the title compound **6.10** (233 mg, 0.34 mmol, 83%) as a colourless oil.

$[\alpha]^{27}_D$	+3.52 (*c* 0.36, $CHCl_3$).
FT-IR	ν_{max} (neat) 3468 (brd, w), 2955 (w), 2923 (m), 2854 (w), 1736 (m), 1693 (m), 1233 (s) cm^{-1}.
^{1}H NMR	(400 MHz, $CDCl_3$) δ 5.37 (1H, d, *J* = 4.9 Hz, C**H**(OAc)CO), 4.97 (1H, dt, *J* = 8.5, 4.5 Hz, C**H**OAc), 4.58 (1H, td, *J* = 6.7, 4.9 Hz, C**H**CH(OAc)CO), 4.06 (1H, td, *J* = 6.9, 4.5 Hz, C**H**), 3.96 (1H, dd, *J* = 7.8, 5.0 Hz, NC**H**), 3.51 (1H, d, *J* = 13.8 Hz, C**H**HSO_2), 3.47-3.36 (2H, m, C**H**(OH)C**H**OH), 3.43 (1H, d, *J* = 13.8 Hz, CH**H**SO_2), 2.66 (1H, brd s, O**H**), 2.35 (1H, brd s, O**H**), 2.26-2.17 (1H, m, NCHC**H**H), 2.13 (3H, s, C(O)C**H**$_3$), 2.11-1.77 (6H, m, 2 x C**H**$_2$ THF and NCHCH**H**C**H**), 2.09 (3H, s, C(O)C**H**$_3$), 1.77-1.66 (2H, m, C**H**$_2$CHOAc), 1.55-1.23 (24H, m, 10 x C**H**$_2$ and NCHCH_2CHC**H**$_2$C**H**$_2$), 1.21 (3H, s, CC**H**$_3$), 0.97 (3H, s, CC**H**$_3$), 0.88 (3H, t, *J* = 6.8 Hz, C**H**$_3$) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ 171.20 (s, **C**(O)CH_3), 170.52 (s, **C**(O)CH_3), 167.18 (s, **C**O), 80.57 (d, **C**H), 77.26 (d, **C**HCH(OAc)), 74.65 (d, 2 x **C**HOH), 74.38 (d, **C**HOAc), 73.99 (d, **C**H(OAc)CO), 66.03 (d, N**C**H), 53.40 (t, **C**H_2SO_2), 49.32 (s, **C**$(CH_3)_2$), 48.19 (s, **C**CH_2SO_2), 44.93 (d, NCHCH_2**C**H), 38.41 (t, NCH**C**H_2), 33.89 (t, **C**H_2), 33.23 (t, **C**H_2), 32.24 (t, **C**H_2), 30.09 (t, **C**H_2), 29.97 (t, 3 x **C**H_2), 29.66 (t, **C**H_2), 29.62 (t, **C**H_2), 28.07 (t, **C**H_2), 27.15 (t, **C**H_2), 26.73 (t, **C**H_2), 26.26 (t, **C**H_2), 26.07 (t, **C**H_2), 23.00 (t, CH_3**C**H_2), 21.46 (q, C(O)**C**H_3), 20.88 (q, **C**H_3), 20.83 (q, **C**H_3), 20.29 (q, C**C**H_3), 14.44 (q, **C**H_3) ppm.
LRMS	(ES^+) *m/z* 708 (100%) $[M+Na]^+$, 703 (30%) $[M+NH_4]^+$, 686 (10%) $[M+H]^+$ Da.
HRMS	(ES^+) for $C_{35}H_{59}NO_{10}SNa^+$, calculated 708.3752, found 708.3746 Da.

(1*S*,4*E*)-1-((2*S*,5*R*,)-5-((4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-tetrahydrofuran-2-yl)-pentadec-4-en-1-ol (6.15)



$C_{24}H_{44}O_4$

M.W. = 396.61 g/mol

To a solution of triol **5.32** (326 mg, 0.91 mmol) in 2,2-dimethoxypropane (15 mL) was added *p*-TsOH (20 mg) and the resulting mixture was stirred for 2 ½ hours. The solution was diluted with EtOAc (30 mL) and washed with H_2O (10 mL), sat. aq. $NaHCO_3$ (2 x 10 mL) and brine (20 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to a colourless oil. Purification by column chromatography (silica gel, 40 x 90 mm, 20% EtOAc / hexane) afforded the title compound **6.15** (333 mg, 0.84 mmol, 92%) as a colourless oil.

$[\alpha]^{27}_D$ +1.30 (*c* 0.39, $CHCl_3$).

FT-IR ν_{max} (neat) 3476 (brd, w), 2923 (s), 2853 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.45 (1H, dt, *J* = 15.3, 5.6 Hz, C**H**CH), 5.40 (1H, dt, *J* = 15.3, 5.6 Hz, CHC**H**), 4.11 (1H, ddd, *J* = 7.6, 6.5, 4.8 Hz, C**H**OC(CH_3)$_2$), 4.02-3.95 (1H, m, C**H**), 4.01 (1H, t, *J* = 7.6 Hz, C**H**HOC(CH_3)$_2$), 3.91-3.85 (1H, m, C**H**), 3.78 (1H, t, *J* = 7.6 Hz, CH**H**OC(CH_3)$_2$), 3.46-3.39 (1H, m, C**H**OH), 2.60 (1H, d, *J* = 6.5 Hz, O**H**), 2.26-2.04 (2H, m, CHCHC**H$_2$**), 2.02-1.89 (4H, m, C**H$_2$**CHCH and C**H$_2$** THF), 1.86-1.76 (2H, m, C**H$_2$** THF), 1.63-1.48 (2H, m, C**H$_2$**CHOH), 1.45 (3H, s, CC**H$_3$**), 1.38 (3H, s, CC**H$_3$**), 1.36-1.22 (16H, m, 8 x C**H$_2$**), 0.89 (3H, t, *J* = 6.9 Hz, C**H$_3$**) ppm.

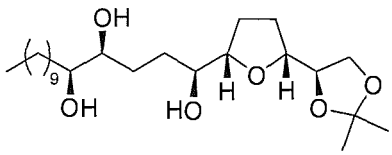
^{13}C NMR (100 MHz, $CDCl_3$) δ 131.38 (d, **C**HCH), 129.96 (d, CH**C**H), 109.96 (s, **C**(CH_3)$_2$), 83.16 (d, **C**H), 79.42 (d, **C**H), 78.39 (d, **C**HOC(CH_3)$_2$), 74.11 (d, **C**HOH), 66.51 (t, **C**H_2OC(CH_3)$_2$), 34.49 (t, **C**H_2CHOH), 32.94 (t, **C**H_2), 32.27 (t, **C**H_2), 30.00 (t, 2 x **C**H_2), 29.96 (t, **C**H_2), 29.88 (t, **C**H_2), 29.70 (t, **C**H_2), 29.54 (t, **C**H_2), 29.06 (t, **C**H_2), 28.49 (t, **C**H_2 THF), 28.35 (t, **C**H_2 THF),

26.79 (q, C$\mathbf{C}$H$_3$), 25.85 (q, C$\mathbf{C}$H$_3$), 23.04 (t, CH$_3\mathbf{C}$H$_2$), 14.46 (q, $\mathbf{C}$H$_3$) ppm.

LRMS (ES$^+$) *m/z* 419 (100%) [M+Na]$^+$, 414 (20%) [M+NH$_4$]$^+$ Da.

HRMS (ES$^+$) for $C_{24}H_{44}O_4Na^+$, calculated 419.3132, found 419.3132 Da.

(1*S*,4*S*,5*S*)-1-((2*S*,5*R*,)-5-((4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-tetrahydrofuran-2-yl)-4,5-dihydroxypentadecan-1-ol (6.16)



$C_{24}H_{46}O_6$

M.W. = 430.62 g/mol

To an orange bi-phasic mixture of H_2O (10 mL), ^{t}BuOH (10 mL), AD-mix α (2.00 g) and $MeSO_2NH_2$ (0.08 g, 0.84 mmol) at 0 °C was added mono-THF **6.15** (0.33 g, 0.84 mmol) in Et_2O (3 mL) and ^{t}BuOH (3 mL). The resulting orange mixture was allowed to stir for 15 hours before it was quenched with Na_2SO_3 (2.00 g) and stirred for a further 30 min. H_2O (15 mL) was added and the aqueous phase extracted with EtOAc (4 x 20 mL). The combined organic phases were washed with 2 M KOH (3 x 15 mL), dried (Na_2SO_4) and concentrated *in vacuo* to an orange oil. Purification by column chromatography (silica gel, 40 x 80 mm, 5% MeOH / CH_2Cl_2) afforded the title compound **6.16** (0.34 g, 0.79 mmol, 94%) as a colourless oil.

$[\alpha]^{27}_D$ +1.44 (*c* 0.52, $CHCl_3$).

FT-IR ν_{max} (neat) 3408 (brd, w), 2922 (s), 2853 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (1H, ddd, *J* = 7.5, 6.3, 4.5, C$\mathbf{H}$OC(CH$_3$)$_2$), 4.03-3.97 (1H, m, C$\mathbf{H}$CHOC(CH$_3$)$_2$), 4.01 (1H, t, *J* = 7.5 Hz, C$\mathbf{H}$HOC(CH$_3$)$_2$), 3.92-3.86 (1H, m, C$\mathbf{H}$), 3.78 (1H, t, *J* = 7.5 Hz, CH$\mathbf{H}$OC(CH$_3$)$_2$), 3.53 (1H, brd s, O$\mathbf{H}$), 3.51-3.37 (3H, m, C$\mathbf{H}$(OH)C$\mathbf{H}$OH and C$\mathbf{H}$OH), 3.19 (1H, brd s, O$\mathbf{H}$), 2.29 (1H, d, *J* = 4.8 Hz, O$\mathbf{H}$), 2.03-1.92 (2H, m, C$\mathbf{H}_2$ THF), 1.86-1.78 (2H, m, C$\mathbf{H}_2$ THF), 1.77-1.57 (4H, m, C$\mathbf{H}_2$CH(OH)CH(OH)C$\mathbf{H}_2$), 1.54-1.42 (2H, m, C$\mathbf{H}_2$CHOH), 1.46

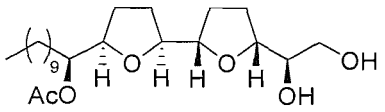
(3H, s, CCH_3), 1.38 (3H, s, CCH_3), 1.34-1.21 (16H, m, 8 x CH_2), 0.89 (3H, t, J = 6.9 Hz, CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 110.01 (s, $C(CH_3)_2$), 83.27 (d, CH), 79.50 (d, CH), 78.33 (d, $CHOC(CH_3)_2$), 75.14 (d, 2 x CHOH), 74.69 (d, CHOH), 66.51 (t, $CH_2OC(CH_3)_2$), 34.09 (t, CH_2), 32.27 (t, CH_2), 31.14 (t, CH_2), 31.07 (t, CH_2), 30.09 (t, CH_2), 29.97 (t, 3 x CH_2), 29.68 (t, CH_2), 28.52 (t, CH_2 THF), 28.31 (t, CH_2 THF), 26.81 (t, CH_2), 26.10 (q, CCH_3), 25.81 (q, CCH_3), 23.03 (t, CH_3CH_2), 14.46 (q, CH_3) ppm.

LRMS (ES^+) *m/z* 453 (100%) $[M+Na]^+$, 431 (15%) $[M+H]^+$ Da.

HRMS (ES^+) for $C_{24}H_{46}O_6Na^+$, calculated 453.3187, found 453.3180 Da.

(1*R*)-1-((2*R*,5*S*)-5-((2*S*,5*R*)-5-((1*S*)-1-Acetyloxyundecyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)-ethane-1,2-diol (6.17)



$C_{23}H_{42}O_6$

M.W. = 414.58 g/mol

To a solution of mono-THF acetal **6.16** (48 mg, 0.11 mmol) and $MeC(OMe)_3$ (27 mg, 0.22 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added $BF_3{\cdot}OEt_2$ (8 mg, 0.06 mmol). The resulting mixture was warmed to r.t. after 1 hour and was allowed to stir for a further 4 hours. Acetone (3 mL) was added and the mixture concentrated *in vacuo* to a colourless oil. Purification by column chromatography (silica gel, 20 x 60 mm, 30-100% EtOAc / hexane) afforded the title compound **6.17** (26 mg, 0.06 mmol, 58%) as a colourless oil.

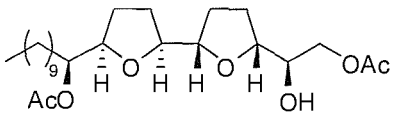
$[\alpha]^{31}_D$ +2.10 (*c* 0.50, $CHCl_3$).

FT-IR ν_{max} (neat) 3424 (brd, w), 2923 (s), 2854 (m), 1737 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99 (1H, ddd, J = 8.5, 5.3, 4.3 Hz, CHOAc), 4.02 (1H, ddd, J = 7.6, 5.8, 4.3 Hz, $CHCH(OH)CH_2OH$), 3.94 (1H, q, J = 6.4 Hz, CH), 3.85 (2H, sext, J = 5.9 Hz, CHCH), 3.67 (2H, brd d, J = 4.8 Hz, CH_2OH), 3.54 (1H, q, J = 4.8 Hz, CHOH), 3.08 (1H, brd s, OH), 2.47 (1H, brd s, OH), 2.07 (3H, s, $C(O)CH_3$), 2.01-1.51 (8H, m, 4 x CH_2

	THF), 1.36-1.20 (18H, m, 9 x CH_2), 0.89 (3H, t, J = 6.8 Hz, CH_3) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ 171.18 (s, CO), 82.00 (d, CH), 81.85 (d, CH), 80.98 (d, CH), 80.96 (d, CH), 75.18 (d, CHOAc), 73.95 (d, CHOH), 65.21 (t, CH_2OH), 32.26 (t, CH_2), 31.69 (t, CH_2), 29.95 (t, CH_2), 29.92 (t, CH_2), 29.87 (t, 2 x CH_2), 29.67 (t, CH_2), 28.49 (t, CH_2), 28.17 (t, CH_2), 28.12 (t, CH_2), 27.28 (t, CH_2), 25.69 (t, CH_2), 23.02 (t, CH_3CH_2), 21.55 (q, $C(O)CH_3$), 14.45 (q, CH_3) ppm.
LRMS	(ES$^+$) *m/z* 437 (100%) $[M+Na]^+$, 432 (20%) $[M+NH_4]^+$ Da.
HRMS	(ES$^+$) for $C_{23}H_{42}O_6Na^+$, calculated 437.2874, found 437.2869 Da.

(1*S*)-1-((2*R*,5*S*)-5-((2*S*,5*R*)-5-((1*R*)-2-Acetyloxy-1-hydroxyethyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)-undecyl-1-acetate (6.22)



$C_{25}H_{44}O_7$

M.W. = 456.62 g/mol

To a solution of mono-THF acetal **6.16** (92 mg, 0.21 mmol) and $MeC(OMe)_3$ (25 mg, 0.21 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added $BF_3{\cdot}OEt_2$ (15 mg, 0.11 mmol). The resulting mixture was warmed to r.t. after 15 min and stirred for a further 15 hours. Further $MeC(OMe)_3$ (25 mg, 0.21 mmol) and $BF_3{\cdot}OEt_2$ (15 mg, 0.11 mmol) were added and the mixture was stirred for a further 7 hours before concentrating *in vacuo* to a yellow oil. The crude mono-acetate was re-dissolved in CH_2Cl_2 (3 mL) and $MeC(OMe)_3$ (31 mg, 0.26 mmol) and $BF_3{\cdot}OEt_2$ (15 mg, 0.11 mmol) were added. The resulting mixture was allowed to stir for 1 ½ hours before quenching with H_2O (3 mL) and stirring for 30 min. The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (silica gel, 20 x 60 mm, 30-50% EtOAc / hexane) afforded the title compound **6.22** (38 mg, 0.08 mmol, 40%) as a colourless oil.

$[\alpha]^{29}_D$	+1.84 (*c* 0.74, $CHCl_3$).

FT-IR	ν_{max} (neat) 3464 (brd, w), 2924 (m), 2854 (m), 1739 (s) cm^{-1}.
^{1}H NMR	(400 MHz, $CDCl_3$) δ 4.96 (1H, ddd, *J* = 8.3, 5.5, 4.5 Hz, C**H**OAc), 4.16 (1H, dd, *J* = 11.4, 4.9 Hz, C**H**HOAc), 4.11 (1H, dd, *J* = 11.4, 6.4 Hz, CH**H**OAc), 3.98 (1H, ddd, *J* = 7.2, 5.9, 4.2 Hz, C**H**CHOH), 3.95-3.86 (2H, m, CH(OAc)C**H** and C**H**CH), 3.86-3.80 (1H, m, CHC**H**), 3.71-3.64 (1H, m, C**H**OH), 2.97 (1H, d, *J* = 7.3 Hz, O**H**), 2.09 (3H, s, C(O)C**H$_3$**), 2.06 (3H, s, C(O)C**H$_3$**), 2.02-1.68 (8H, m, 4 x C**H$_2$** THF), 1.65-1.52 (2H, m, C**H$_2$**CHOAc), 1.36-1.20 (16H, m, 8 x C**H$_2$**), 0.88 (3H, t, *J* = 6.9 Hz, C**H$_3$**) ppm.
^{13}C NMR	(100 MHz, $CDCl_3$) δ 171.37 (s, **C**O), 171.03 (s, **C**O), 81.84 (d, **C**HCH), 81.69 (d, CH**C**H), 80.87 (CH(OAc)C**H**), 79.61 (d, **C**HCHOH), 75.13 (d, **C**HOAc), 72.38 (d, **C**HOH), 66.56 (t, **C**H$_2$OAc), 32.24 (t, **C**H$_2$), 31.62 (t, **C**H$_2$CHOAc), 29.94 (t, **C**H$_2$), 29.91 (t, **C**H$_2$), 29.87 (t, 2 x **C**H$_2$), 29.66 (t, **C**H$_2$), 28.55 (t, **C**H$_2$ THF), 28.15 (t, **C**H$_2$ THF), 28.02 (t, **C**H$_2$ THF), 27.29 (t, **C**H$_2$ THF), 25.68 (t, **C**H$_2$), 23.01 (t, CH$_3$**C**H$_2$), 21.55 (q, C(O)**C**H$_3$), 21.26 (q, C(O)**C**H$_3$), 14.44 (q, **C**H$_3$) ppm.
LRMS	(ES$^+$) *m/z* 479 (100%) $[M+Na]^+$, 474 (20%) $[M+NH_4]^+$ Da.
HRMS	(ES$^+$) for $C_{25}H_{44}O_7Na^+$, calculated 479.2979, found 479.2977 Da.

Chapter Nine

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Appendices

Crystal structure data for *bis*-THF 4.32

Table 1: Crystal data and structure refinement details.

Identification code	**2005sot1325 (CK4277/85)**
Empirical formula	$C_{23}H_{37}NO_7S$
Formula weight	471.60
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 9.3028(2) Å
	b = 11.6999(3) Å
	c = 21.3740(4) Å
Volume	2326.39(9) Å^3
Z	4
Density (calculated)	1.346 Mg / m^3
Absorption coefficient	0.183 mm^{-1}
F(000)	1016
Crystal	Block; Colourless
Crystal size	0.1 × 0.1 × 0.02 mm^3
θ range for data collection	2.96 – 27.48°
Index ranges	$-11 \le h \le 12$, $-15 \le k \le 15$, $-22 \le l \le 27$
Reflections collected	22557
Independent reflections	5324 [R_{int} = 0.0644]
Completeness to θ = 27.48°	99.8 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9963 and 0.9719
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5324 / 0 / 295
Goodness-of-fit on F^2	1.042

Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0458, $wR2$ = 0.0917
R indices (all data)	$R1$ = 0.0663, $wR2$ = 0.1007
Absolute structure parameter	–0.02(7)
Extinction coefficient	0.0096(9)
Largest diff. peak and hole	0.296 and –0.326 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **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 placed in idealised positions and refined using a riding model.

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

Atom	x	y	z	U_{eq}	$S.o.f.$
C1	2553(3)	14701(2)	10081(1)	33(1)	1
C2	3305(3)	13579(2)	10238(1)	29(1)	1
C3	2281(3)	12564(2)	10239(1)	25(1)	1
C4	3086(2)	11446(2)	10219(1)	23(1)	1
C5	3976(2)	11151(2)	10792(1)	25(1)	1
C6	4024(3)	9853(2)	10769(1)	26(1)	1
C7	2543(3)	9537(2)	10514(1)	25(1)	1
C8	2522(2)	8485(2)	10100(1)	24(1)	1
C9	1058(3)	8158(2)	9845(1)	28(1)	1

C10	1404(3)	7656(2)	9203(1)	27(1)	1
C11	2730(3)	8327(2)	8996(1)	23(1)	1
C12	2378(2)	9389(2)	8599(1)	21(1)	1
C13	3779(3)	9975(2)	8414(1)	21(1)	1
C14	5949(2)	9978(2)	7736(1)	21(1)	1
C15	7144(2)	10023(2)	8237(1)	28(1)	1
C16	8378(3)	9397(2)	7914(1)	30(1)	1
C17	8850(3)	10118(2)	7352(1)	35(1)	1
C18	7651(3)	9919(2)	6861(1)	28(1)	1
C20	7607(2)	8378(2)	7606(1)	26(1)	1
C21	8573(3)	7644(2)	7186(1)	41(1)	1
C22	6869(3)	7555(2)	8067(1)	36(1)	1
C23	5351(2)	8633(2)	6867(1)	26(1)	1
C29	6578(2)	9179(2)	7229(1)	21(1)	1
N1	4573(2)	9462(2)	7936(1)	19(1)	1
O1	1378(2)	12541(2)	10784(1)	31(1)	1
O2	2064(2)	10520(1)	10161(1)	25(1)	1
O3	3433(2)	8686(1)	9563(1)	23(1)	1
O4	1447(2)	10159(1)	8902(1)	24(1)	1
O5	4256(2)	10811(1)	8683(1)	25(1)	1
O6	3208(2)	7713(1)	7539(1)	31(1)	1
O7	2792(2)	9566(2)	7040(1)	30(1)	1
S1	3768(1)	8784(1)	7330(1)	21(1)	1

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

C1-C2	1.525(4)	C13-O5	1.218(3)
C2-C3	1.522(3)	C13-N1	1.395(3)
C3-O1	1.436(3)	C14-N1	1.479(3)
C3-C4	1.508(3)	C14-C15	1.546(3)
C4-O2	1.447(3)	C14-C29	1.546(3)
C4-C5	1.519(3)	C15-C16	1.526(3)

C5-C6	1.520(4)	C16-C17	1.532(4)
C6-C7	1.527(3)	C16-C20	1.540(4)
C7-O2	1.446(3)	C17-C18	1.549(4)
C7-C8	1.517(3)	C18-C29	1.537(3)
C8-O3	1.444(3)	C20-C21	1.533(3)
C8-C9	1.516(3)	C20-C22	1.540(3)
C9-C10	1.527(3)	C20-C29	1.564(3)
C10-C11	1.527(3)	C23-C29	1.519(3)
C11-O3	1.440(3)	C23-S1	1.782(2)
C11-C12	1.540(3)	N1-S1	1.6950(19)
C12-O4	1.408(3)	O6-S1	1.4284(17)
C12-C13	1.525(3)	O7-S1	1.4298(17)

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	35(2)	29(2)	34(1)	3(1)	−3(1)	−4(1)
C2	25(1)	30(2)	31(1)	4(1)	−1(1)	−3(1)
C3	27(1)	26(1)	23(1)	1(1)	−2(1)	2(1)
C4	22(1)	23(1)	23(1)	1(1)	0(1)	−1(1)
C5	21(1)	32(1)	22(1)	−1(1)	1(1)	1(1)
C6	26(1)	29(1)	23(1)	3(1)	−1(1)	4(1)
C7	24(1)	25(1)	25(1)	6(1)	0(1)	4(1)
C8	23(1)	23(1)	26(1)	3(1)	6(1)	−1(1)
C9	24(1)	27(1)	34(1)	2(1)	4(1)	−3(1)
C10	28(1)	21(1)	32(1)	3(1)	3(1)	−4(1)
C11	24(1)	22(1)	22(1)	−2(1)	2(1)	1(1)
C12	20(1)	22(1)	22(1)	−1(1)	0(1)	0(1)
C13	24(1)	19(1)	19(1)	2(1)	−2(1)	3(1)

C14	20(1)	21(1)	23(1)	0(1)	0(1)	−2(1)
C15	22(1)	37(2)	24(1)	−4(1)	1(1)	−7(1)
C16	20(1)	43(2)	27(1)	−1(1)	−3(1)	−1(1)
C17	25(1)	40(2)	41(1)	−8(1)	9(1)	−7(1)
C18	28(1)	28(1)	27(1)	1(1)	6(1)	−4(1)
C20	23(1)	28(1)	29(1)	3(1)	−2(1)	4(1)
C21	36(2)	36(2)	51(2)	−3(1)	9(1)	10(1)
C22	36(2)	31(2)	42(2)	12(1)	−1(1)	7(1)
C23	26(1)	33(2)	20(1)	−6(1)	1(1)	0(1)
C29	23(1)	22(1)	18(1)	0(1)	2(1)	0(1)
N1	18(1)	21(1)	19(1)	−2(1)	−1(1)	−2(1)
O1	31(1)	28(1)	34(1)	0(1)	10(1)	4(1)
O2	25(1)	21(1)	27(1)	−2(1)	−6(1)	2(1)
O3	21(1)	27(1)	21(1)	1(1)	1(1)	0(1)
O4	21(1)	27(1)	24(1)	0(1)	2(1)	3(1)
O5	28(1)	22(1)	26(1)	−5(1)	2(1)	−4(1)
O6	34(1)	23(1)	35(1)	−4(1)	1(1)	−8(1)
O7	29(1)	32(1)	28(1)	−2(1)	−10(1)	8(1)
S1	21(1)	22(1)	21(1)	−4(1)	−3(1)	0(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.*
H1A	2278	14702	9639	49	1
H1B	3207	15341	10163	49	1
H1C	1691	14782	10341	49	1
H2A	4076	13440	9928	34	1
H2B	3760	13645	10655	34	1
H3	1655	12615	9860	30	1

H4	3728	11443	9843	27	1
H5A	3506	11424	11180	30	1
H5B	4952	11483	10765	30	1
H6A	4176	9526	11191	31	1
H6B	4796	9583	10487	31	1
H7	1872	9414	10874	30	1
H8	2918	7825	10341	29	1
H9A	426	8835	9808	34	1
H9B	586	7584	10117	34	1
H10A	596	7772	8908	33	1
H10B	1617	6829	9233	33	1
H11	3386	7812	8755	27	1
H12	1894	9124	8207	25	1
H14	5779	10758	7558	25	1
H15A	7410	10821	8339	34	1
H15B	6846	9625	8625	34	1
H16	9181	9176	8201	36	1
H17A	9793	9858	7191	42	1
H17B	8918	10936	7466	42	1
H18A	7210	10649	6727	33	1
H18B	8022	9510	6489	33	1
H21A	9185	8142	6931	61	1
H21B	7974	7170	6912	61	1
H21C	9177	7151	7447	61	1
H22A	7600	7166	8320	54	1
H22B	6312	6987	7833	54	1
H22C	6226	7988	8342	54	1
H23A	5556	7815	6790	32	1
H23B	5225	9019	6459	32	1
H1	972	13178	10827	47	1
H94	1752	10289	9265	36	1

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*DHA*)
O1–H1···O5^{i}	0.84	2.25	2.985(2)	146.8
O4–H94···O2	0.84	1.96	2.783(2)	168.4

Symmetry transformations used to generate equivalent atoms:

(i) x–1/2,–y+5/2,–z+2