UNIVERSITY OF SOUTHAMPTON

Total synthesis of *cis*-sylvaticin and synthetic studies towards the synthesis of adjacent THF-THF and THF-THP *Annonaceous* acetogenins

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ABSTRACT

FACULTY OF ENGINEERING, SCIENCE AND MATHEMATICS

SCHOOL OF CHEMISTRY

Doctor of Philosophy

PART 1: TOTAL SYNTHESIS OF *CIS*-SYLVATICIN
PART 2: SYNTHETIC STUDIES TOWARDS ADJACENT THP-THF AND *BIS*-THF *ANNONACEOUS* ACETOGENINS

By Ian Spurr

The total synthesis of potent antitumour agent *cis*-sylvaticin (**1.100**) has been completed. Notable steps included the alcoholytic kinetic resolution of epoxide **2.2**, two permanganate promoted oxidative cyclisation reactions, a tethered RCM to unite the two major fragments and the use of P_4 phoshazene base to install the butenolide precursor.

Synthesis of adjacent THP-THF and *bis*-THF cores *via* cascade oxidative cyclisation reactions with permanganate is an attractive route to many *Annonaceous* acetogenins. Attempted synthesis of an adjacent THP-THF core and synthesis of an adjacent *bis*-THF core are discussed.

CONTENTS

Declaration

The research work described in this thesis was carried out by myself, At the University of Southampton, between October 2005 and November 2008. No part of this thesis has been submitted in any previous application for a higher degree.

Ian Spurr, June 2009

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A massive thank you must go to the people whom I worked with directly, these people are: Ali, Amanda, Amy, Clare, Fra, Iain, Joe, Louisa, Lynda, Nadeem, Nev, Rick, Sally, Sharif, Simon and Steve. For all the advice, the funny moments, the arguments, and for sharing the highs and the lows, thank you.

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Most importantly I would like to thank family and friends. The most important of these people are mum, dad and Tash. Mum and dad, you have always supported me through thick and thin, I hope this some how repays your

support. To Tash, thank you for your love and support you have shown me which has allowed me to complete another chapter of our life together.

Abbrreviations

9-BBN	9-Borabicyclo[3.3.1]nonane	**DMAP**	4-Dimethylaminopyridine
Ac	Acetyl	**DMDO**	Dimethyldioxirane
AD	Asymmetric dihydroxylation	**DME**	Dimethoxyethane
AIBN	2,2'-azoisobutyronitrile	**DMF**	*N*,*N*-dimethylformamide
aq	Aqueous	**DMPU**	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
ATP	Adenosine triphosphate	**DMS**	Dimethyl sulfide
BINAP	2,2'-*bis*(diphenylphosphino)-1,1'-binaphthyl	**DMSO**	Dimethyl sulfoxide
BINOL	1,1'-Bi-2-naphthol	***dr***	Diastereomeric excess
BOM	Benzyloxymethyl	***ee***	Enantiomeric excess
br	broad (NMR and IR)	**EI**	Electron ionisation
BST	Brine shrimp lethality test	***ent***	Enantiomer
Bu	Butyl	**equiv.**	Equivalent(s)
Bz	Benzyl	**ESI**	Electrospray ionisation
CAN	Ceric ammonium nitrate	**Et**	Ethyl
CM	Cross-metathesis	**FT**	Fourier transform
CSA	Camphorsulfonic acid	**GC**	Gas Chromatography
Cy	Cyclohexyl	**h**	Hour(s)
d	Doublet (NMR)	**HMDS**	Hexamethyldisilylamide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene	**HMPA**	Hexamethylphoshoric triamide
DCC	*N*,*N*'-Dicyclohexylcarbodiimide	**HPLC**	High pressure liquid chromatography
DCE	Dichloroethene	**HR**	High resolution
DCHT	Dicyclohexyl tartrate	**Hz**	Hertz
DDQ	2,3-dicyano-5,6-dichloroparabenzoquinone	***i***	*Iso*
DEAD	Diethyl azodicarboxylate	**IDCP**	iodonium dicollidine perchlorate
DET	Diethyl tartrate	**IMes**	1,3-dimesityl-2-imidazole
DHP	Dihydropyran	**IPA**	Isopropylalcohol
DHP	3,4-Dihydro-2*H*-pyran	***J***	Coupling constant
DIAD	Diisopropyl azodicarboxylate	**LDA**	Lithium diisopropylamide
DIBAL-H	Diisobutylaluminium hydride	**LR**	Low resolution
DIC	*N*,*N*'-Diisopropylcarbodiimide	**m**	Multiplet (NMR) or medium (IR)
DIPEA	Diisopropylethylamine	**M**	Mol dm^{-3}

***m*-CPBA**	*Meta*-chloroperbenzoic acid	**RCM**	Ring-closing methathesis
MDR	Multi-drug resistant	**rt**	Room temperature
Me	Methyl	***s***	*Sec*
MEM	Methoxyethoxymethyl ether	**s**	singlet (NMR) or strong (IR)
MOM	Methoxymethyl	**sat**	Saturated
MPLC	Medium pressure liquid chromatography	***t***	*Tert*
MPM	4-methoxyphenylmethyl	**t**	Triplet (NMR)
MS	Mass Spectrometry	**TBAB**	Tetrabutylammonium bromide
Ms	Methanesulfonyl, mesyl	**TBAF**	Tetrabutylammonium fluoride
n	normal	**TBDPS**	*Tert*-butyldiphenylsilyl
NADH	Nicotinamide adenine dinucleotide	**TBHP**	*tert*-Butyl hydroperoxide
NBS	*N*-Bromosuccinimide	**TBS**	*Tert*-butyldimethylsilyl
nbs	Nitrobenzenesulfonic acid	**TES**	Triethylsilyl
NMO	*N*-Methylmorpholine *N*-oxide	**Tf**	Trifluoromethanesulfonyl
NMP	*N*-methylpyrrolidone	**TFA**	Trifluoroacetic acid
NMR	Nuclear magnetic resonance	**THF**	Tetrahydrofuran
p	*Para*	**THP**	Tetrahydropyran
PCC	Pyridinium chlorochromate	**TIPS**	Triisopropylsilyl
Ph	Phenyl	**TLC**	Thin layer chromatography
Piv	Pivaloyl	**TMEDA**	*N*,*N*,*N*′,*N*′-Tetramethylethylenediamine
PMB	*Para*-methoxybenzyl	**TMS**	Trimethylsilyl
PMP	*Para*-methoxyphenol	**TPAP**	Tetrapropylammonium perruthenate
PNB	4-Nitrobenzoate	**Tr**	Triphenylmethane, trityl
ppm	Parts per million	**Ts**	Toluenesulfonyl, tosyl
PPTS	Pyridinium *para*-toluenesulfonate	**TTMS**	Tris(trimethylsilyl)silane
Pr	Propyl	**UV**	Ultraviolet
PTC	Phase transfer catalyst	**w**	weak (IR)
q	Quartet (NMR)	**xs**	excess
quin	Quintet (NMR)		

Chapter 1: Non Adjacent *bis*-THF and THF-THP *Annonaceous* Acetogenins

This chapter will give a brief overview of the isolation, structure and bioactivity of the *Annonaceous* acetogenin family of natural products. The focus will be on the non-adjacant *bis*-THF and non-classical non-adjacant THF-THP classes. The chapter will then give an in depth review of the total synthesis of these classes of *Annonaceous* acetogenins.

1.1 Introduction to Annonaceous Acetogenins

Annonaceous acetogenins are a group of natural products isolated from the *Annonaceous* tropical plant family (custard apple family, 130 genera and 2300 species).[1-9] The first *Annonaceous* acetogenin isolated and fully characterised was uvaricin in 1982.[10] Uvaricin's biological activity caused great interest in *Annonaceous* acetogenins, leading to the isolation of more than 400 acetogenins between 1982 and 2004.[2]

Structurally, *Annonaceous* acetogenins have unbranched C32/34 fatty acid chains typically with a terminal γ-lactone. Biogenesis of *Annonaceous* acetogenins appears to be through the polyketide pathway. The biosynthetic sequence postulated for the acetogenins starts by installing the terminal γ-lactone to a long chain unsaturated fatty acid (figure 1.1).

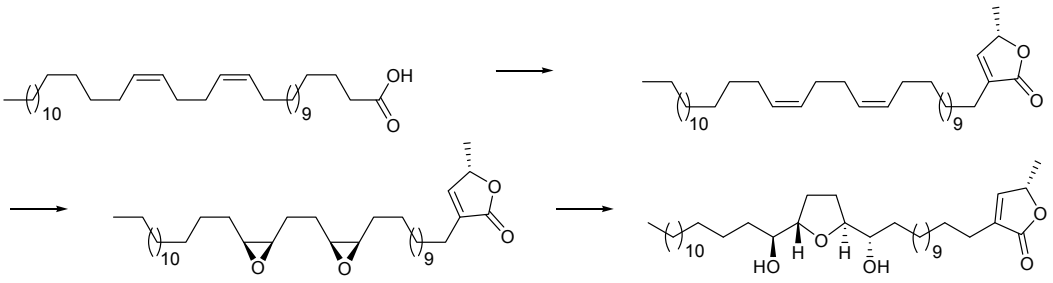


Figure 1.1 Postulated biosynthetic pathway for *Annonaceous* acetogenins.

The core unsaturated units are then partially or completely epoxidised followed by possible intermolecular or intramolecular ring opening and closing reactions, resulting in characteristic structural features such as THF, and THP diols. In

addition to these cyclic ethers, other functional groups found in *Annonaceous* acetogenins include epoxides, ketones, alkenes and alkynes.

Due to the large number of entries in this family of natural products a system of classification was introduced. The classification system groups acetogenins according to their core structures, the main classes are shown in figure 1.2.

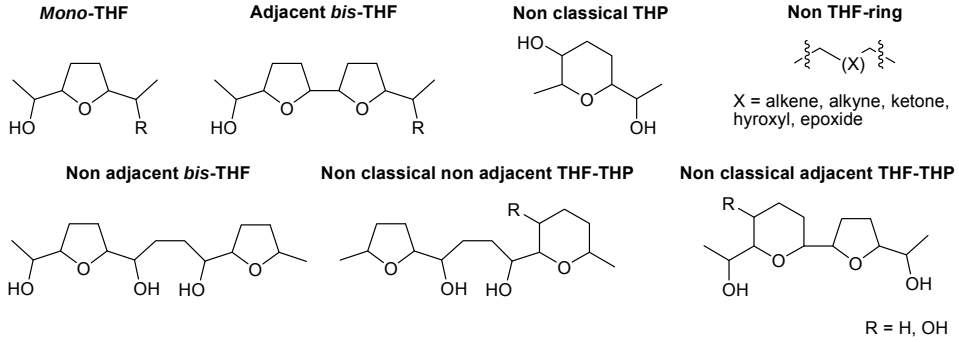


Figure 1.2 Annonaceous acetogenin core classes.

The core classes can be broken down into sub classes by the nature of the γ-lactone, but commonly a methyl substituted α,β-unsaturated γ-lactone (butenolide) is present with or without a hydroxyl group at C4 (figure 1.3).

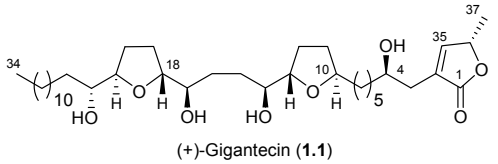


Figure 1.3 Structure of (+)-gigantecin (**1.1**).

Standardised numbering for *Annonaceous* acetogenins begins at the lactone carbonyl carbon, the numbering continues down the fatty acid backbone with the remaining lactone carbons numbered as shown.

1.2 Biological Activity

The *Annonaceous* acetogenins have many interesting biological effects, including *in vivo* antitumor, anti-parasitic, pesticidal, antimalarial and antibacterial activities.[2-9] Most notably *Annonaceous* acetogenins act as cytotoxic and anti-tumour agents. Interestingly this activity extends to multi-drug resistant (MDR) cancer cell lines.[11,12] The *Annonaceous* acetogenins trilobacin and asiminocin are amongst the most potent cytotoxic compounds known in several human

tumor cell lines (ED_{50} > 10^{-12} µg/mL).[13,14] The cytotoxic and anti-tumour properties are thought to be due to *Annonaceous* acetogenins being among the most potent known inhibitors of mitochondrial complex 1.[15-18]

Mitochondrial complex 1 has an important role in the mitochondrial electron transport chain. The electron transport chain supplies aerobic energy to cells by driving synthesis of ATP (figure 1.4).

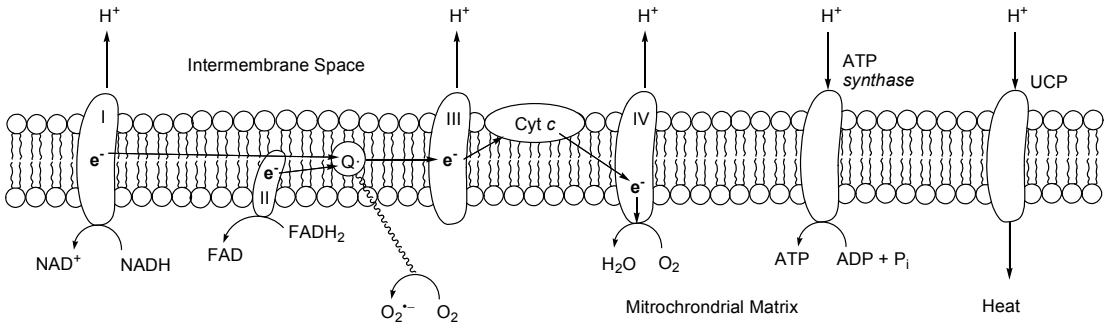


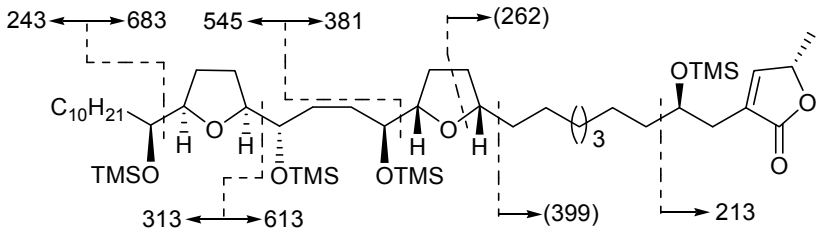
Figure 1.4 Mitochondrial electron transport chain.

The mitochondrial complex 1 site is responsible for oxidation of NADH. The resulting redox energy drives protons into mitochondrial intermembrane space, causing a battery effect which drives ATP production. Cancerous cells have a higher demand for ATP than non-cancerous cells, and this might explain why *Annonaceous* acetogenins are selectively cytotoxic for cancerous cells. The exact nature of the complex 1 inhibition caused by *Annonaceous* acetogenins is not fully understood. It is believed that *Annonaceous* acetogenins bind to either complex 1 or proximate hydrophilic lipid membranes, with the terminal α,β-unsaturated γ-lactone mimicking NADH and disturbing the mitochondrial electron transport chain. Although it is likely that cytotoxity in cancerous cells is related to complex 1 inhibition there has been no clear correlation found. This suggests *Annonaceous* acetogenins may also be involved in triggering further enzymatic pathways resulting in cell death.

Until the intricate nature of complex 1 and cell death pathways are fully understood, it will be difficult to fully assess the utility of *Annonaceous* acetogenins as candidates in drug research.

1.3 Isolation and Structural Assignment

Discussion will be focused on non-adjacent *bis*-THF and non-adjacent THF-THP acetogenins. *Annonaceous* acetogenins are soluble in organic solvents so they can be extracted from dried plant material. The same acetogenin can be isolated from different plant sources. For instance (+)-gigantecin (**1.1**) was isolated from two sources; the bark of *Goniothalamus giganteus* in southeast Asia and from the seeds of the Brazilian plant *Annona coriacea*.[19,20] A method of purification employed by McLaughlin was column chromatography with bioassay-guided fractionation (using brine shrimp lethality test) followed by HPLC.[21] Structural assignment is determined by various MS and NMR techniques. Molecular weight is established by ESI mass spectrometry, while THF/THP ring and hydroxyl positions on the alkyl chain are found by careful analysis of EI fragmentation mass spectrometry data (figure 1.5).[21]



* numbers in () denotes EIMS peak from un-derivatised *cis*-sylvaticin

Figure 1.5 EIMS fragmentation for derivatised and un-derivatised *cis*-sylvaticin.

Comparisons of NMR data from synthetic THF/THP cores with isolated acetogenins are used to determine relative stereochemistry.[22-26] An important observation from the ^{1}H NMR from *cis*-sylvaticin indicated that of the three flanking hydroxyls, two had a *threo* and one had an *erythro* relative configuration, although exact positions could not be assigned purely from the ^{1}H NMR of *cis*-sylvaticin (figure 1.6). The *threo* and *erythro* relative configuration could be concluded as it was known that carbinol peaks with a *threo* relative configuration come in the δ 3.4 – 3.6 ppm region, while carbinol peaks with an *erythro* relative configuration come at ~δ 3.8 ppm.[22]

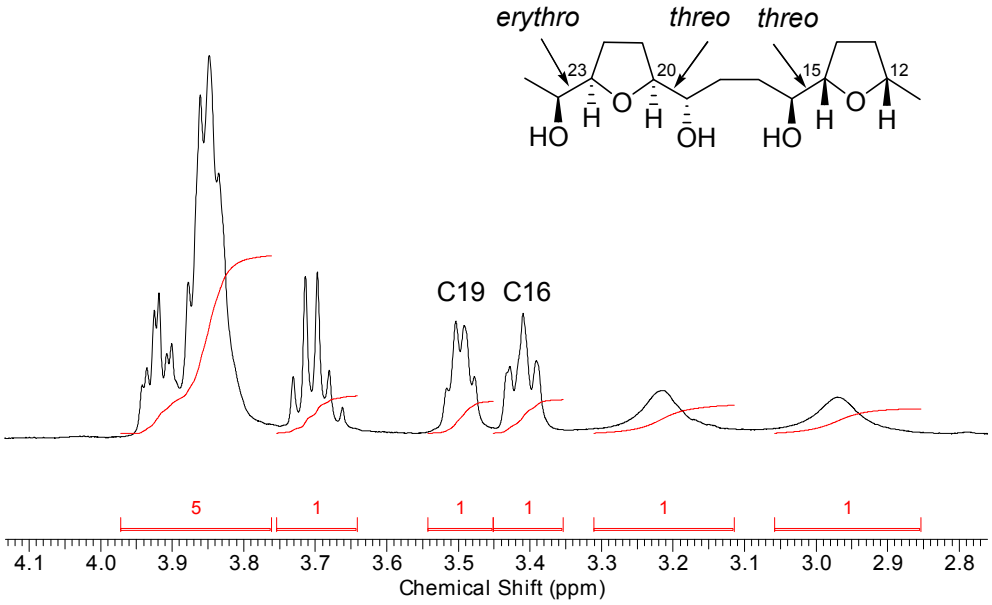


Figure 1.6 ^{1}H NMR for *cis*-sylvaticin.

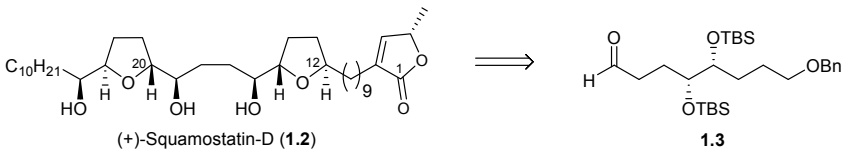
Absolute stereochemistry is the most difficult structural feature to verify, and total synthesis can be required to confirm absolute stereochemistry. In depth NMR studies of Mosher ester and acetal derivatives can be used to assign correctly absolute stereochemistry.[21,23,27] In the case of (+)-gigantecin (**1.1**) X-ray crystallography proved the relative and absolute stereochemistry.[20] However, this is unusual as *Annonaceous* acetogenins are characteristically waxy solids, which are unsuitable for X-ray analysis but derivatives can sometimes give crystals.

1.4 Synthesis of Non Adjacent *bis*-THF *Annonaceous* Acetogenins

In the following section the synthesis of the above mentioned sub-class of *Annonaceous* acetogenins will be discussed. It might be of interest to directly compare the syntheses of (+)-4-deoxygigantecin (**1.20**), (+)-gigantecin (**1.1**) and (+)-squamostatin-C (**1.79**). They each comprise of an identical non adjacent *bis*-THF core with respect to relative and absolute stereochemistry.

(+)-Squamostatin–D – Marshall (1998)

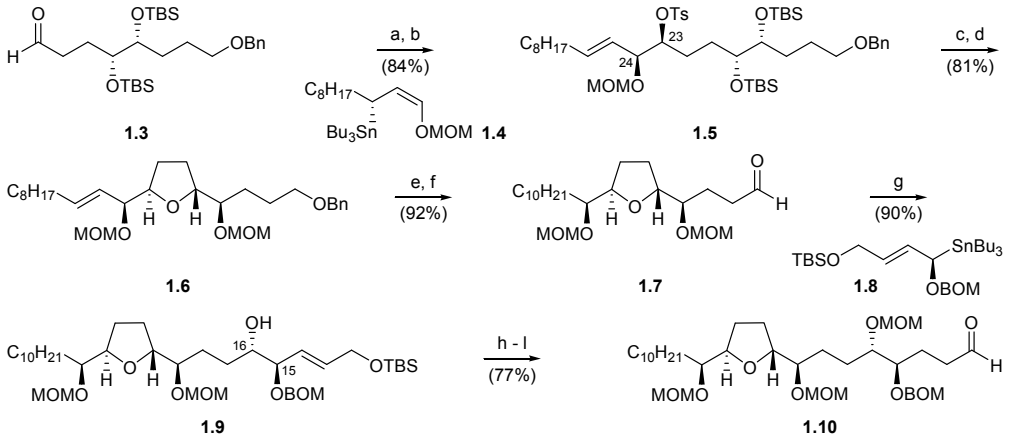
Marshall's approach uses a linear strategy in synthesising (+)-squamostatin-D (**1.2**), which relied on building up from known aldehyde **1.3** (scheme 1.1).[28]



Scheme 1.1 Retrosynthetic analysis employed by Marshall.

Key reactions in this approach utilise chemistry developed by Marshall using chiral γ-oxygenated allylic tin and indium reagents.[29] Aldehyde **1.3** is available from 1,4-butanediol in 7 steps in 50% yield.[30-32]

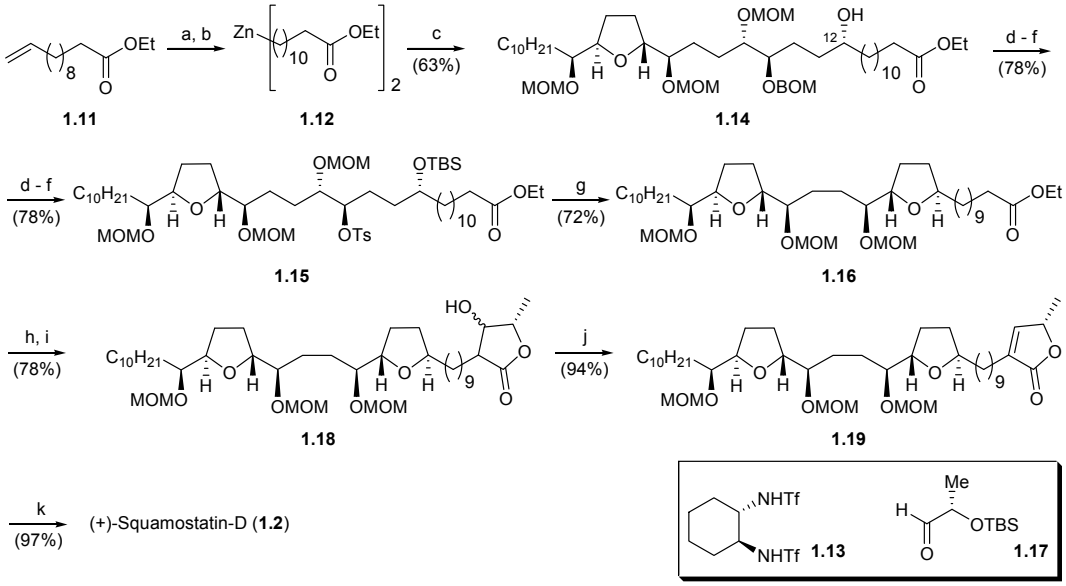
The synthesis began by addition of γ-oxygenated allylic tin reagent **1.4** to aldehyde **1.3**, this set up the *erythreo* configuration between C23 and C24 in (+)-squamostatin-D (**1.2**) (scheme 1.2). The resulting secondary alcohol which was isolated as a single isomer was converted to tosylate **1.5**. TBAF deprotection of silyl ethers **1.5** initiated cyclisation, with the resulting free hydroxyl protected as the MOM ether to give benzyl ether **1.6**. Debenzylation of **1.6** and oxidation of the alcohol gave aldehyde **1.7**, which set the stage for construction of the second THF ring.



Scheme 1.2 Synthesis of aldehyde **1.10**. *Reagents and conditions*: a) **1.4**, CH_2Cl_2, then BF_3•OEt_2; b) *p*-TsCl, pyridine; c) TBAF, THF; d) MOMCl, DIPEA, CH_2Cl_2; e) H_2/Pd-C, EtOH; f) Dess-Martin periodinane, CH_2Cl_2; g) $InCl_3$, EtOAc, then **1.8**; h) MOMCl, DIPEA, CH_2Cl_2; i) H_2/Rh-Al_2O_3, EtOAc; j) TBAF, THF; l) Dess-Martin periodinane, CH_2Cl_2.

A γ-oxygenated allylic indium reagent (derived from tin reagent **1.8**) addition to aldehyde **1.7** set up the *threo* configuration between C15 and C16. The resulting secondary alcohol **1.9** which was isolated as a single isomer was protected as the MOM ether, followed by reduction of the alkene, and then TBAF deprotection of the silyl ether gave a primary alcohol which was oxidised to give aldehyde **1.10**.

An enantioselective organozinc addition to aldehyde **1.10** permitted control of the C12 stereogenic carbinol (Scheme 1.3).



Scheme 1.3 Total synthesis of (+)-squamostatin-D (**1.2**). *Reagents and conditions*: a) Et_2BH; b) Et_2Zn; c) **1.13**, $Ti(O\text{-}iPr)_4$, MePh, Δ, then **1.10**; d) TBSCl, imidazole, DMF; e) H_2/Pd-C, EtOH; f) *p*-TsCl, pyridine; g) TBAF, THF; h) LDA, THF, then **1.17**; i) TBAF, THF; j) Tf_2O, Et_3N, CH_2Cl_2; k) HCl, THF, MeOH.

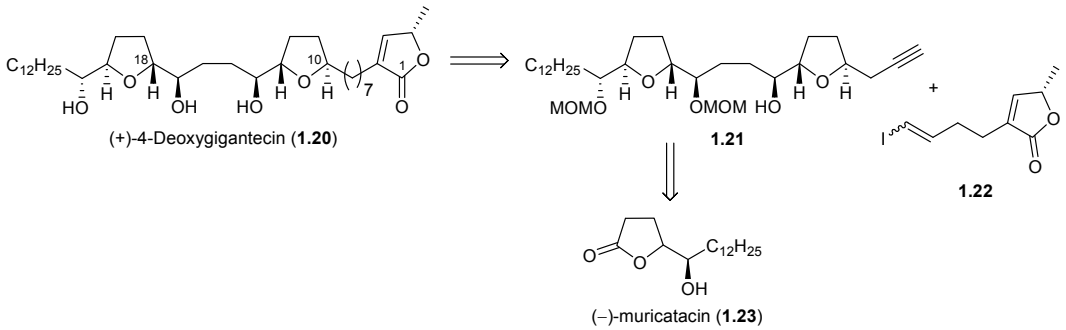
Following the Knochel protocol, addition of the zinc reagent **1.12** to aldehyde **1.10** selectively provided alcohol **1.14** with high stereoselectivity (*dr* > 95:5 by ^1H NMR).[33] Alcohol **1.14** was silylated, the BOM group was selectively removed with the resulting alcohol converted to tosylate **1.15**. TBAF desilylation of tosylate **1.15** resulted in cyclisation to give MOM ether **1.16**. The butenolide portion was installed using chemistry described by Wu.[34] The lithium enolate of ester **1.16** was reacted with aldehyde **1.17** to give an aldol product, which when desilylated delivered lactone **1.18**. Dehydration of lactone **1.18** was achieved with triflic anhydride and triethylamine to give butenolide **1.19** which was deprotected to give (+)-squamostatin-D (**1.2**). (+)-Squamostatin-D (**1.2**) was synthesised in 27 linear steps from 1,4-butanediol in a total yield of 5.5%.

Key aspects of Marshall's synthesis are:-

- Linear approach was adopted with the non-adjacent *bis*-THF core built up from aldehyde **1.3**.
- Use of reagent-based stereocontrol through additions of chiral non-racemic organometallics to aldehydes.[29]
- Formation of *trans*-THF rings by intramolecular nucleophilic substitution.
- Butenolide portion was installed by a modified aldol condensation.[34]

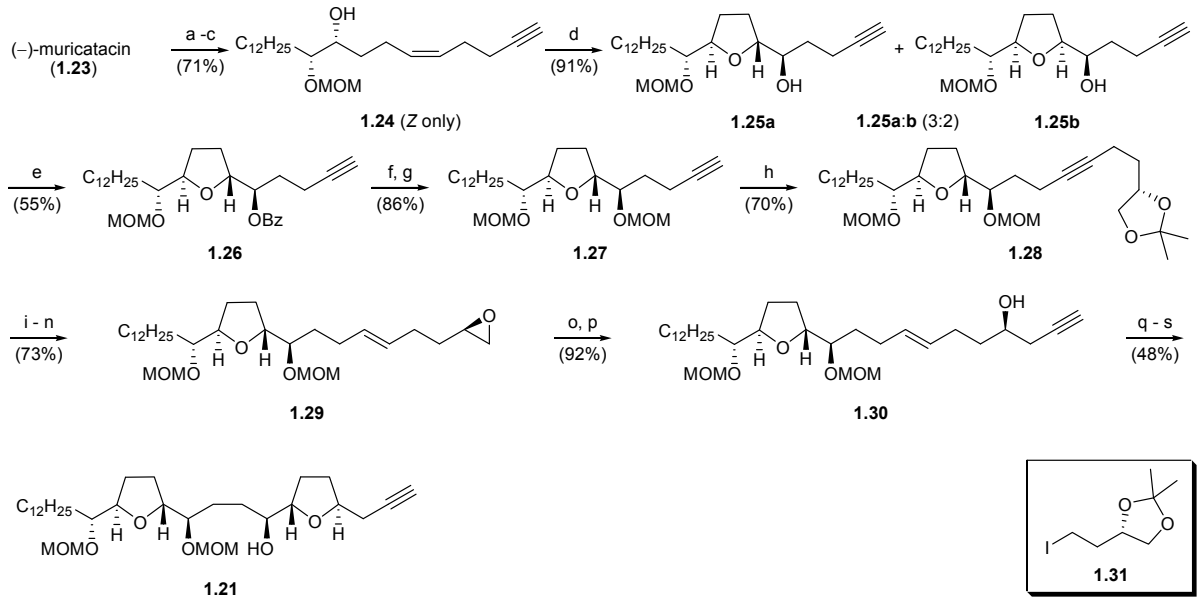
(+)-4-Deoxygigantecin – Makabe (1998)

The Makabe group synthesis of (+)-4-deoxygigantecin (**1.20**) couples 2 main fragments (scheme 1.4).[35] *Bis*-THF alkyne **1.21** was synthesised in a linear fashion from *mono*-THF acetogenin derivative (–)-muricatacin (**1.23**), avaliable in 7 steps from propargylic alcohol in a 27% yield.[36,37]



Scheme 1.4 Retrosynthetic analysis employed by Makabe.

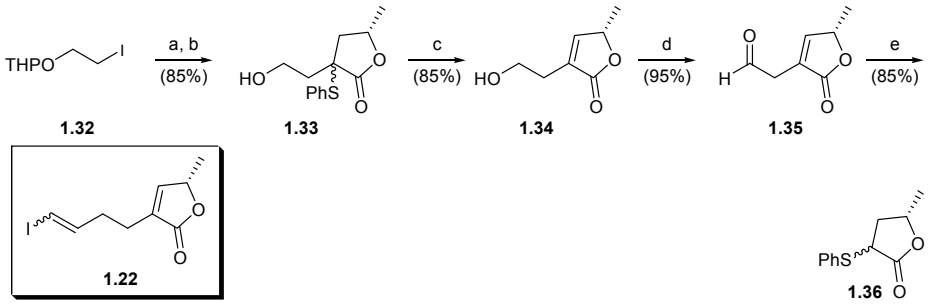
The synthesis starts with a MOM protection of (–)-muricatacin (**1.23**), then DIBAL-H reduction to give a lactol, which underwent a Wittig reaction delivering alkene **1.24** (scheme 1.5) as a single isomer.



Scheme 1.5 Synthesis of *bis*-THF alkyne **1.21**. *Reagents and conditions*: a) MOMCl, DIPEA, CH_2Cl_2; b) DIBAL-H, CH_2Cl_2; c) $HC{\equiv}C(CH_2)_3Ph_3P^+I^-$, NaOMe, DMF; d) *m*-CPBA, CH_2Cl_2; e) BzCl, pyridine; f) NaOH, MeOH; g) MOMCl, DIPEA, CH_2Cl_2; h) *n*-BuLi, THF, then **1.31**; i) Na/NH_3, *t*-BuOH, THF; j) 60% AcOH, Δ; l) TBSCl, Et_3N, DMAP, CH_2Cl_2; m) MsCl, Et_3N, CH_2Cl_2; n) TBAF, THF, then 10% NaOH; o) TMSC≡CH, *n*-BuLi, $BF_3{\bullet}Et_2O$, THF; p) TBAF, THF; q) MsCl, Et_3N, CH_2Cl_2; r) AD-mix-*α*, *t*-BuOH/H_2O; s) Triton B, MeOH.

Epoxidation of alkene **1.24** in a non-selective manner followed by cyclisation gave an inseparable mixture of THF products **1.25a**/**b** (**1.25a**:**1.25b** 3:2). Benzoylation of THF products **1.25a**/**b** then allowed separation to give benzoate **1.26** as a single diastereoisomer.[37] Debenzoylation followed by MOM protection gave alkyne **1.27**, which was alkylated with iodide **1.31** to give acetal **1.28**. A Birch reduction of alkyne **1.28**, followed by acid hydrolysis of the acetonide returned a terminal diol, which was converted to terminal epoxide **1.29** with inversion of stereochemistry. Epoxide **1.29** was then reacted with lithiated TMS acetylene in the presence of $BF_3{\bullet}OEt_2$, followed by TBAF desilylation to deliver alcohol **1.30**. Mesylation of alcohol **1.30**, then asymmetric dihydroxylation of the *E*-alkene followed by base induced cyclisation gave *bis*-THF alkyne **1.21**. Fragment **1.21** was synthesised in 25 steps from propargylic alcohol in 1.9% yield.

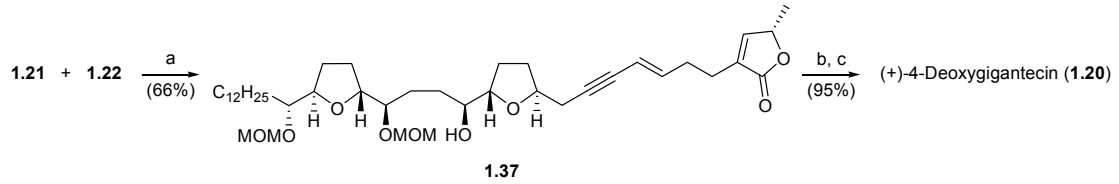
The synthesis of butenolide fragment **1.22** began by alkylation of lactone **1.36** with iodide **1.32** (scheme 1.6).[38] A THP deprotection of the resulting ether gave sulphide **1.33**.



Scheme 1.6 Synthesis of butenolide fragment **1.22** *Reagents and conditions*: a) **1.36**, NaHMDS, THF/HMPA, then **1.32**; b) *p*-TsOH, MeOH; c) *m*-CPBA, then Δ; d) Dess-Martin periodinane, $ClCH_2CH_2Cl$; e) $CrCl_2$, CHI_3, THF.

Oxidation of sulfide **1.33** to the sulfoxide then thermal elimination gave α,β-unsaturated γ-lactone **1.34**. Oxidation of primary alcohol **1.34** followed by a Takai olefination gave butenolide fragment **1.22**.[39] Fragment **1.22** was synthesised in 12 steps from ethyl (*S*)-lactate in a 14.6% yield.

Fragment **1.21** and **1.22** were successfully coupled using Sonogashira chemistry to give enyne **1.37** (scheme 1.7).[40]



Scheme 1.7 Total synthesis of (+)-4-deoxygigantecin (**1.20**). *Reagents and conditions*: a) $Pd(PPh_3)_4$, CuI, Et_3N, MePh; b) H_2, $Rh(PPh_3)_3Cl$, benzene; c) $BF_3{\bullet}OEt_2$, Me_2S.

Selective catalytic hydrogenation followed by global deprotection gave (+)-4-deoxygigantecin (**1.20**). (+)-4-Deoxygigantecin (**1.20**) was synthesised in 28 linear steps from propargylic alcohol in a total 1.2% yield.

Key aspects of Makabe synthesis are:-

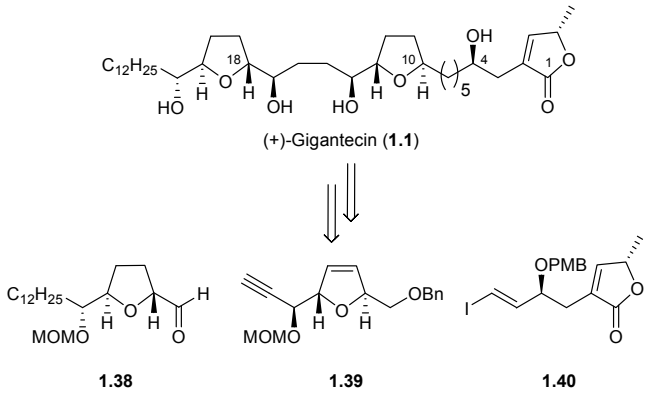
- The strategy involves a convergent 2 fragment approach with fragments **1.21** and **1.22** coupled using Sonogashira chemistry.[40]
- A linear approach to synthesising the non-adjacent *bis*-THF core, building up from (–)-muricatacin (**1.23**).[37]
- Established *trans*-THF rings nucleophilic by Williams-type substitution, C18-20 THF ring synthesised in a non-stereoselective fashion. Key stereochemistry for the C10-13 THF ring set-up by asymmetric dihydroxylation and Sharpless asymmetric epoxidation.
- Construction of the butenolide by alkylation of White's lactone **1.36**.[38]

(+)-Gigantecin

There have been two total syntheses of (+)-gigantecin (**1.1**) reported by the groups of Crimmins and Hoye.[41,42] These syntheses will be discussed in the ensuing section.

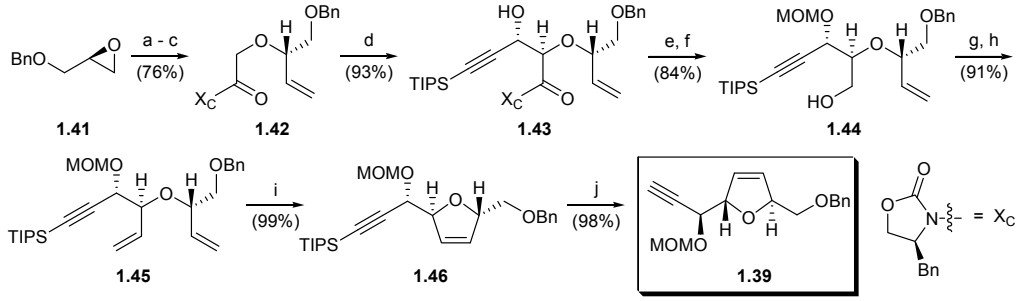
(+)-Gigantecin – Crimmins (2004)

Crimmins' synthesis of (+)-gigantecin (**1.1**) adopts a convergent 3 fragment approach (scheme 1.8).[41] Crimmins takes advantage of a Carreira type coupling of fragments **1.38** and **1.39** to construct the non-adjacent *bis*-THF core.



Scheme 1.8 Retrosynthetic analysis employed by Crimmins.

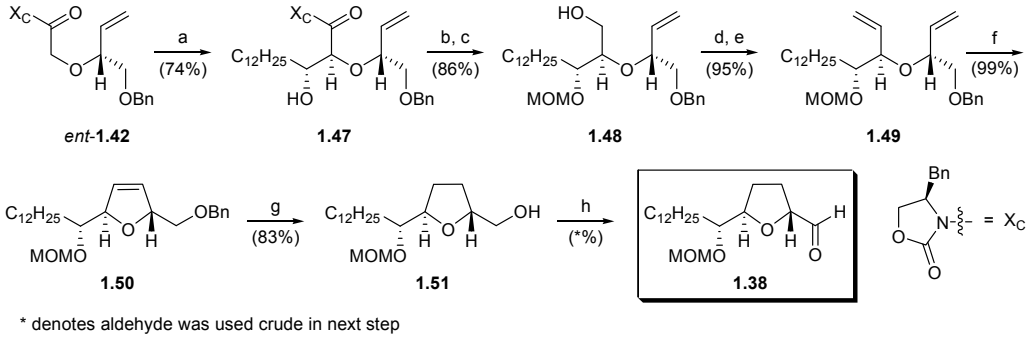
The key reaction in synthesising both THF fragments was chemistry developed by Crimmins, an extension of the asymmetric glycolate aldol reaction.[43] Fragment **1.39** required synthesis of glycolate **1.42**, which was achieved in 3 steps from (*S*)-benzyl glycidyl ether **1.41** (scheme 1.9).



Scheme 1.9 Synthesis of alkyne fragment **1.39**. *Reagents and conditions*: a) $Me_3S^+I^-$, *n*-BuLi, THF, –10 °C → 25 °C; b) NaH, $BrCH_2CO_2H$, THF; c) Me_3CCOCl, Et_3N, THF, –78 °C → 0 °C, (*S*)-lithio-4-benzyl-oxazolidin-2-one; d) $TiCl_4$, DIPEA, NMP, triisopropylsilanyl-propynal, CH_2Cl_2, –78 °C → –40 °C; e) $MeOCH_2Cl$, DIPEA, CH_2Cl_2, DMAP; f) $LiBH_4$, MeOH, Et_2O, 0 °C; g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; h) $Ph_3P{=}CH_2$, THF; i) $Cl_2(Cy_3P)(IMes)Ru{=}CHPh$ (5 mol %), CH_2Cl_2, 40 °C; j) TBAF, THF.

With glycolate **1.42** in hand and under their optimum conditions, the asymmetric glycolate aldol reaction with triisopropylsilanyl-propynal gave alcohol **1.43** with high selectivity (>20:1 major:all other isomers). Secondary alcohol **1.43** was protected as its MOM ether and the chiral auxiliary was reductively cleaved affording alcohol **1.44**. Swern oxidation of primary alcohol **1.44** followed by olefination returned diene **1.45**. RCM reaction was then carried out on diene **1.45** using second generation Grubbs catalyst which provided dihydrofuran **1.46**. The synthesis of fragment **1.39** was completed by desilylisation of alkyne **1.46**. Fragment **1.39** was synthesised in 10 steps from (*S*)-benzyl glycidyl ether **1.41** in 52% overall yield.

Fragment **1.38** was synthesised in an analogous manner to fragment **1.39** (scheme 1.10). Under the same conditions (scheme 1.9, steps a – c) glycolate *ent*-**1.42** was synthesised from (*R*)-benzyl glycidyl ether (*ent*-**1.41**). Under optimum conditions but with glycolate *ent*-**1.42** and tridecanal, the asymmetric glycolate aldol reaction delivered alcohol **1.47** with high selectivity (>15:1 major:all other isomers). Secondary alcohol **1.47** was protected as its MOM ether and the chiral auxiliary was reductively cleaved providing alcohol **1.48**. Swern oxidation of primary alcohol **1.48** followed by olefination gave diene **1.49**.

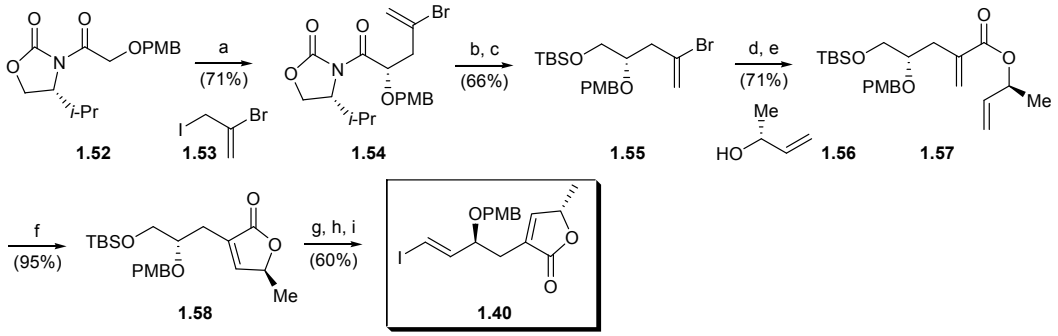


Scheme 1.10 Synthesis of alkyne fragment **1.38**. *Reagents and conditions*: a) $TiCl_4$, DIPEA, NMP, tridecanal, CH_2Cl_2, –78 °C → –40 °C; b) $MeOCH_2Cl$, DIPEA, CH_2Cl_2, DMAP; c) $LiBH_4$, MeOH, Et_2O, 0 °C; d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; e) $Ph_3P{=}CH_2$, THF; f) $Cl_2(Cy_3P)(IMes)Ru{=}CHPh$ (5 mol %), CH_2Cl_2, 40 °C; g) H_2, Pd/C, EtOH; h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2.

A RCM reaction was then performed using diene **1.49** and Grubbs catalyst (2^{nd} generation) which furnished dihydrofuran **1.50**. Under an atmosphere of hydrogen in the presence of Pd/C reduction of the alkene and debenzylation of dihydrofuran **1.50** was achieved yielding alcohol **1.51**. Swern oxidation on

primary alcohol **1.51** gave the crude fragment **1.38**. Fragment **1.38** was synthesised in 11 steps from (*R*)-benzyl glycidyl ether (*ent*-**1.5**) with 38% overall yield up to alcohol **1.51**.

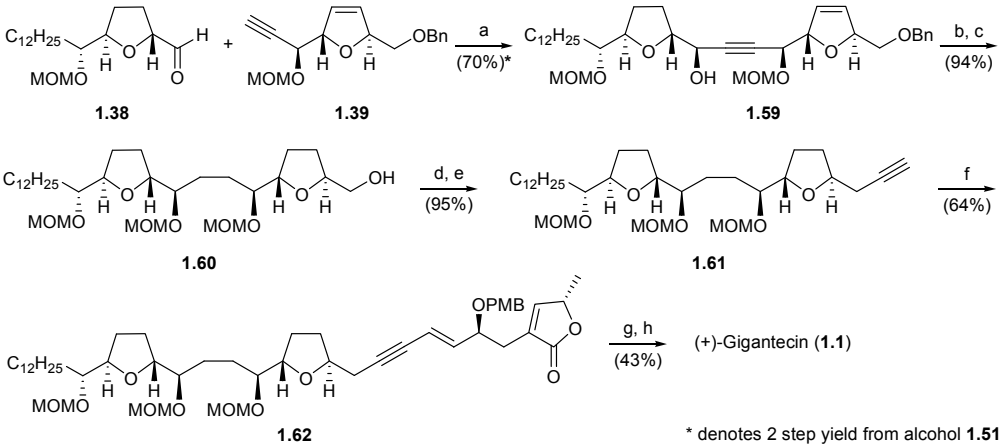
Fragment **1.40** synthesis began from glycolate **1.52**, which was synthesised in 2 steps from 4-methoxybenzyl alcohol in good yield (scheme 1.11). The key step involved a diastereoselective alkylation of the sodium enolate of glycolate **1.52**, which proceeded with high facial selectivity (dr >98:2).[44] Reductive cleavage of the chiral auxiliary from bromide **1.54** and subsequent silylation afforded vinyl bromide **1.55**.



Scheme 1.11 Synthesis of butenolide fragment **1.40**. *Reagents and conditions*: a) NaHMDS, THF, –78 °C → –45 °C, iodide **1.53**; b) $NaBH_4$, THF, H_2O; c) TBSCl, imidazole, CH_2Cl_2; d) *t*-BuLi, THF, –78 °C; CO_2; e) DEAD, Ph_3P, THF, alcohol **1.56**; f) $Cl_2(Cy_3P)(IMes)Ru{=}CHPh$ (6 mol %), CH_2Cl_2, 40 °C; g) 3HF•Et_3N, CH_3CN; h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; i) CHI_3, $CrCl_2$, THF.

Lithium-halogen exchange of bromide **1.55** followed by a quench with CO_2 gave an acrylic acid, which was used to invert secondary alcohol **1.56** using Mitsunobu conditions providing diene **1.57**.[45] RCM reaction on diene **1.57** with second generation Grubbs catalyst delivered butenolide **1.58**. Desilylation of butenolide **1.58**, oxidation of the corresponding primary alcohol gave an aldehyde which when submitted to Takai olefination conditions returning the desired butenolide fragment **1.40**.[39] Fragment **1.40** was synthesised in 11 steps from 4-methoxybenzyl alcohol.

With the 3 desired fragments in hand, the stage was set for the total synthesis (scheme 1.12). An asymmetric acetylide addition using protocol described by Carreira successful coupled aldehyde **1.38** and alkyne **1.39** delivering alcohol **1.59** as a single detectable stereoisomer.[46,47]



Scheme 1.12 Total synthesis of (+)-Gigantecin (**1.1**). *Reagents and conditions*: a) $Zn(OTf)_2$, (–)-*N*-methylephedrine, $PhCH_3$, **1.39** then **1.38**; b) $MeOCH_2Cl$, DIPEA, CH_2Cl_2, DMAP; c) H_2, Pd/C, EtOH; d) Tf_2O, Et_3N, CH_2Cl_2; e) Me_3SiCCH, *n*-BuLi, THF, HMPA, –78 °C, then MeOH, 25 °C; f) iodide **1.40**, $Pd(PPh_3)_4$, CuI, DIPEA, THF; g) H_2, $Rh(PPh_3)_3Cl$, C_6H_6, EtOH, LiI; h) BF_3•OEt_2, Me_2S, 0 °C.

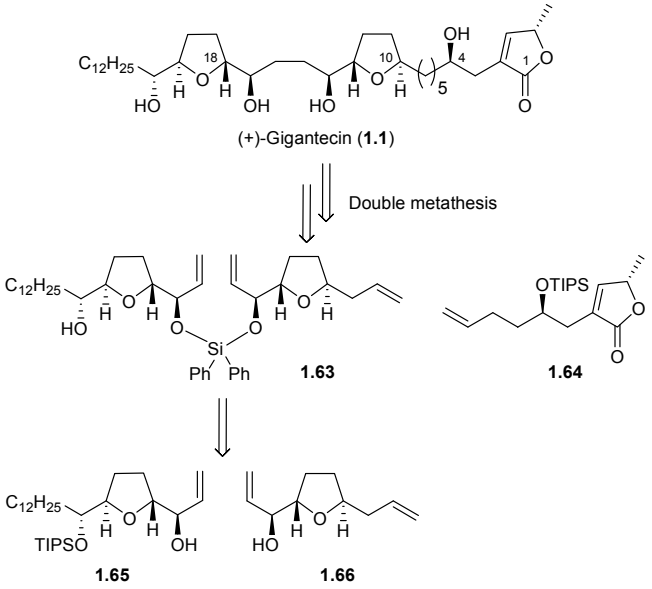
The secondary hydroxyl was protected as the MOM ether, then exposure to Pd/C under a hydrogen atmosphere achieved global reduction and debenzylation which gave primary alcohol **1.60**. Primary alcohol **1.60** was converted to a triflate which was alkylated delivering alkyne **1.61**. To this point a total of 16 linear steps were required from benzyl glycidyl ether, proceeding in 23.8% yield. Alkyne **1.61** was then successfully coupled with vinyl iodide **1.40** under Sonogashira conditions to afford enyne **1.62**.[40] Selective hydrogenation of enyne **1.62** followed by global deprotection provided (+)-gigantecin (**1.1**).[48] (+)-Gigantecin (**1.1**) was synthesised in 19 linear steps from benzyl glycidyl ether in a total yield of 6.5%.

Key aspects of Crimmins synthesis are:-

- Non-adjacent *bis*-THF core constructed by an asymmetric acetylide addition to aldehyde **1.38**.[46,47]
- *Trans*-THF ring stereochemistry was established using asymmetric glycolate aldol reaction.[43]
- Construction of the butenolide, with C4 hydroxyl stereochemistry set up by diastereoselective alkylation of glycolate **1.52**.[44]

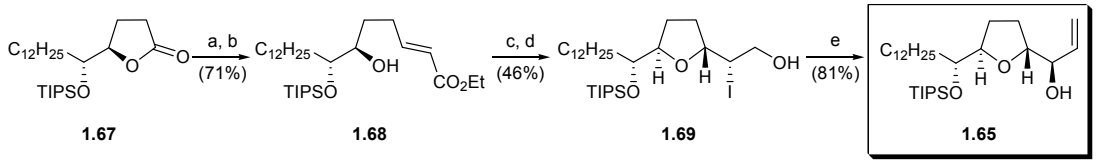
(+)-Gigantecin – Hoye (2006)

Hoye's approach to (+)-gigantecin (**1.1**) also exploited a convergent three fragment approach (scheme 1.13).[42] The key reaction is a one-pot double metathesis reaction, which was used to install the non-adjacent *bis*-THF core and couple the butenolide portion.



Scheme 1.13 Hoye's retrosynthetic analysis of (+)-gigantecin (**1.1**).

The synthesis of fragment **1.65** starts from lactone **1.67** (lactone **1.67** available in 4 steps from tridecanal in a 73% yield) (scheme 1.14).[49] DIBAL-H reduction of lactone **1.67** gave a lactol which underwent olenfination to give α,β-unsaturated ester **1.68**.

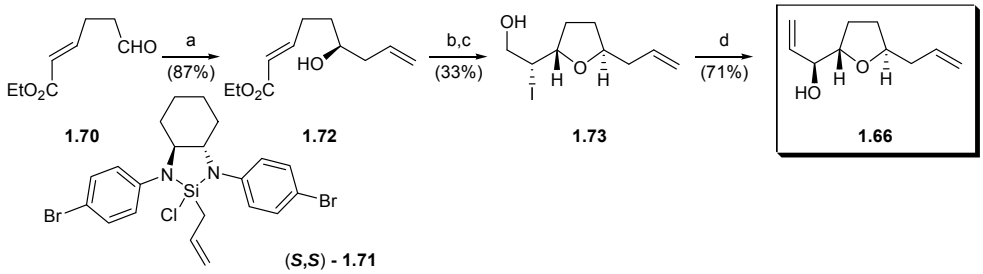


Scheme 1.14 Synthesis of THF fragment **1.65**. *Reagents and conditions*: a) DIBAL-H, PhMe, –78 °C; b) Ph_3PCHCO_2Et, PhMe, 60 °C; c) DIBAL-H, PhMe, 0 °C; d) I_2, K_2CO_3, THF, –78 °C; e) $Me_3S^+I^-$, *n*-BuLi, THF, –45 °C → rt.

Complete reduction of α,β-unsaturated ester **1.68** provided an allylic alcohol which was then submitted to iodoetherification, resulting in the iodohydrin **1.69** (*trans*:*cis* selectivity 4:1 with respect to THF ring). Iodohydrin **1.69** was then converted to the inverted allylic alcohol **1.65** with dimethylsulfonium methylide

($Me_2S{=}CH_2$).[50,51] Fragment **1.65** was synthesised in 9 steps from tridecanal in a total yield of 19.3%.

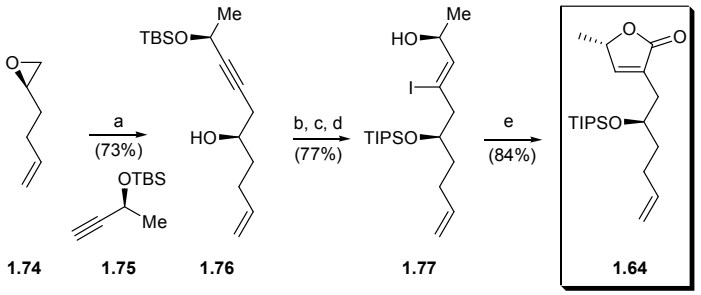
The synthesis of fragment **1.66** began with aldehyde **1.70** (aldehyde **1.70** available in 3 steps from γ-butyrolactone in a approximate 46% yield) (scheme 1.15).[52] A Leighton asymmetric allylation on aldehyde **1.70** gave ester **1.72** as a single isomer.[53]



Scheme 1.15 Synthesis of THF fragment **1.66**. *Reagents and conditions*: a) (***S,S***)**-1.71**, CH_2Cl_2, –20 °C; b) DIBAL-H, PhMe, 0 °C → rt; c) I_2, K_2CO_3, THF, –78 °C; d) $Me_3S^+I^-$, *n*-BuLi, THF, –45 °C → rt.

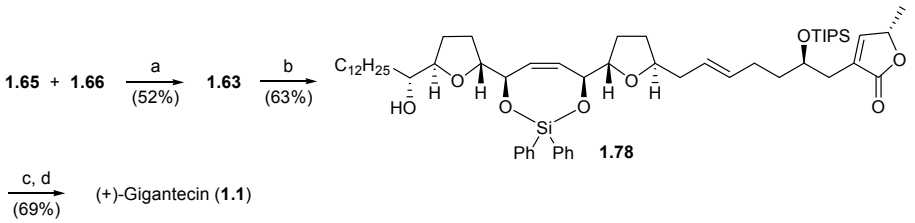
Reduction of ester **1.72** afforded an allylic alcohol which, underwent iodoetherification to give iodohydrin **1.73** as a single isomer. Iodohydrin **1.73** was then converted to the inverted allylic alcohol **1.66** with dimethylsulfonium methylide. Fragment **1.66** was synthesised in 7 steps from γ-butyrolactone in approximately 9.4% yield.

Butenolide fragment **1.64** was synthesised through modification of a known route (scheme 1.16).[54] Epoxide **1.74** (available in 1 step from racemic 1,2-epoxy-5-hexene) was opened with the lithiated alkyne **1.75** delivering alcohol **1.76**.[55]



Scheme 1.16 Synthesis of butenolide fragment **1.64**. *Reagents and conditions*: a) **1.75**, *n*-BuLi, $BF_3{\bullet}OEt_2$, THF, then **1.74**, –78 °C → rt; b) TIPSOTf, 2,6-lutidine, CH_2Cl_2, rt; c) PPTS, EtOH; d) (i) Red-Al, THF, 0 °C, (ii) EtOAc, 0 °C, (iii) I_2, –78 °C; e) CO (45 PSI), $Pd(PPh_3)_2Cl_2$, K_2CO_3, H_2NNH_2, THF, 40 °C.

From alcohol **1.76** protecting group manipulations followed by selective reduction and iodine treatment provided silyl ether **1.77**. A catalytic palladium-catalysed carbonylation on silyl ether **1.77** afforded butenolide fragment **1.64**. The butenolide fragment **1.64** was synthesised in 6 steps from racemic 1,2-epoxy-5-hexene in a total yield of 21%, with the 3 desired fragments in hand, the synthesis then entered the end game (scheme 1.17).



Scheme 1.17 Total synthesis of (+)-gigantecin (**1.1**). *Reagents and conditions*: a) **1.65** (1 equiv.), Ph_2SiCl_2, pyridine, PhMe, 0 °C → rt, then **1.66** (1 equiv.), pyridine, PhMe, 0 °C → rt; b) **1.64** (4 equiv.), $Cl_2(Cy_3P)(IMes)Ru{=}CHPh$ (20 mol %), CH_2Cl_2, 45 °C, syringe pump addition (9 h); c) $TsNHNH_2$, NaOAc, H_2O, DME, Δ; d) 5% HF/MeCN, CH_2Cl_2, rt.

Allylic alcohols **1.65** and **1.66** were successfully coupled with a diphenylsilyl tether which gave triene **1.63**. Double metathesis reaction successfully coupled triene **1.63** and butenolide fragment **1.64** to give lactone **1.78**. The key point from this reaction is that the CM between the type 1 alkene from triene **1.63** and butenolide fragment **1.64** takes place before the RCM reaction preventing by-product formation.[56] This is achieved by reacting triene **1.63** (1 equiv.) with butenolide fragment **1.64** (4 equiv.) with gradual addition of second generation Grubbs catalyst. Selective reduction of lactone **1.78** with diimide followed by global deprotection gave (+)-gigantecin (**1.1**). (+)-Gigantecin (**1.1**) was synthesised in 13 linear steps from tridecanal in a total yield of 4.4%.

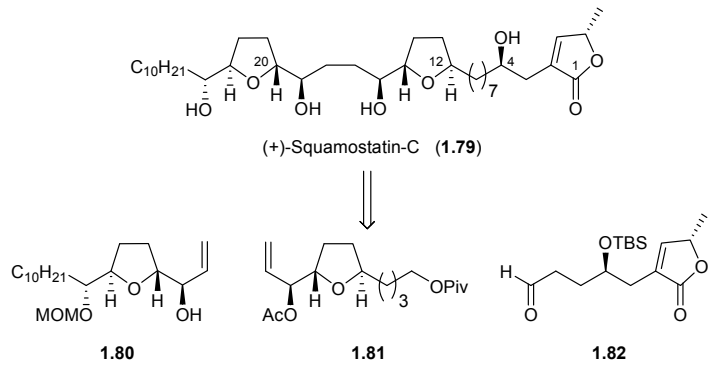
Key aspects of Hoye's synthesis are:-

- (+)-Gigantecin (**1.1**) is constructed by a one-pot double metathesis reaction. The non-adjacent *bis*-THF core is assembled by silicon tethered RCM, while the complete butenolide portion is coupled by CM.
- *Trans* selective iodoetherification reaction used to establish both *trans*-THF rings.

- Butenolide fragment with C4 hydroxyl synthesised through a modification of Hoye's earlier route.[54]

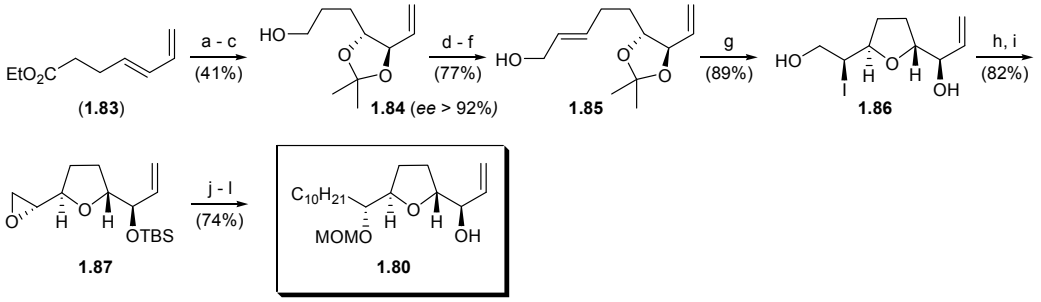
(+)-Squamostatin-C (Bullatanocin) – Mootoo (2004)

Mootoo's group synthesis of (+)-squamostatin-C (**1.79**) ultilised a CM approach requiring 3 main fragments (scheme 1.18).[57,58] The key reaction for installing the THF moiety in fragments **1.80** and **1.81** was iodoetherification, methodology developed by Mootoo.[59-62] The coupling strategy was to join firstly the two THF fragments **1.80** and **1.81** by cross-metathesis, and secondly to couple the butenolide fragment **1.82** by Wittig reaction.



Scheme 1.18 Retrosynthetic analysis employed by Mootoo.

Fragment **1.80** synthesis began with (*E*)-ethyl hepta-4,6-dienoate (**1.83**) which is synthesised in one step from 1,4-pentadien-3-ol by Claisen-Johnson rearrangement in a 73% yield (scheme 1.19).[63]

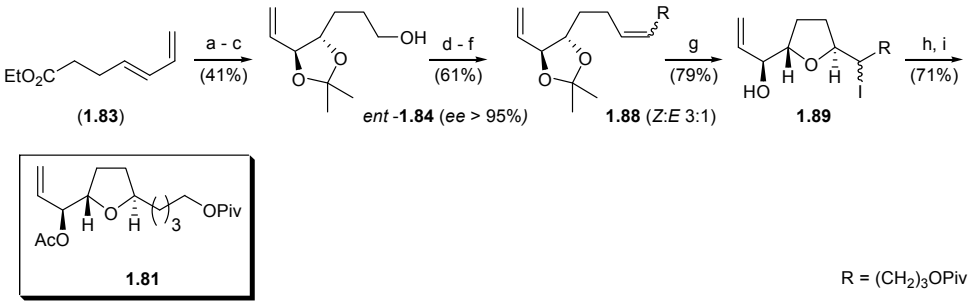


Scheme 1.19 Synthesis of THF fragment **1.80**. *Reagents and conditions*: a) AD-mix-*β*, *t*-BuOH-H_2O, $MeSO_2NH_2$; b) DIBAL-H, THF; c) $(MeO)_2CMe_2$, CSA, CH_2Cl_2; d) PCC, CH_2Cl_2; e) $Ph_3P{=}CHCO_2Me$; f) DIBAL-H, CH_2Cl_2; g) iodonium dicollidine perchlorate, MeCN; h) K_2CO_3, MeOH; i) TBSCl, imidazole, CH_2Cl_2; j) $CH_3(CH_2)_8MgBr$, CuBr, THF; k) MOMCl, DIPEA, CH_2Cl_2; l) TBAF, THF.

A poorly-regioselective asymmetric dihydroxylation on (*E*)-ethyl hepta-4,6-dienoate (**1.83**), then DIBAL-H reduction followed by acetal protection gave

alcohol **1.84** (*ee* > 92% by Mosher ester NMR analysis). Oxidation of primary alcohol **1.84** yielded an aldehyde which underwent Wittig olefination to deliver an α,β-unsaturated ester which was reduced with DIBAL-H to afford alcohol **1.85**. The alcohol **1.85** was set up for the key iodoetherfication reaction. Using iodonium dicollidine perchlorate (IDCP) in acetonitrile, gave THF iodohydrin **1.86** (single *trans* isomer). Iodohydrin **1.86** was closed to the epoxide under basic conditions and the free hydroxyl was silylated to give epoxide **1.87**. Cuprate addition to epoxide **1.87** installed the alkyl chain, followed by protection of the free hydroxyl as its MOM ether and desilylation gave fragment **1.80**. Fragment **1.80** was synthesised in 13 steps from 1,4-pentadien-3-ol in a 12.4% overall yield.

Fragment **1.81** synthesis began with (*E*)-ethyl hepta-4,6-dienoate (**1.83**) (scheme 1.20).

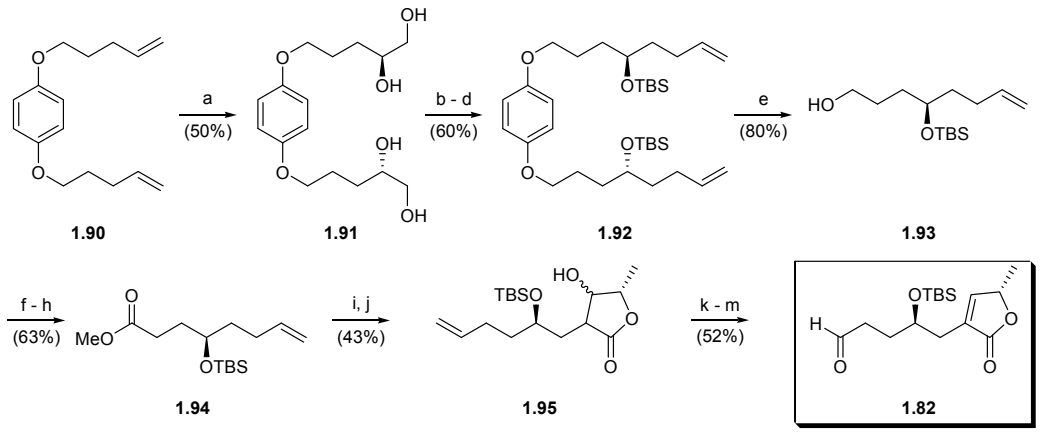


Scheme 1.20 Synthesis of THF fragment **1.81**. *Reagents and conditions*: a) AD-mix-*α*, *t*-BuOH-H_2O, $MeSONH_2$; b) DIBAL-H, THF; c) $(MeO)_2CMe_2$, CSA, CH_2Cl_2; d) Swern oxidation; e) $Ph_3P{=}CH(CH_2)_3OLi$, MePh; f) PivCl, pyridine, DMAP; g) iodonium dicollidine perchlorate, MeCN; h) Bu_3SnH, MePh, AIBN, Δ; i) Ac_2O, EtOAc, DMAP.

Primary alcohol *ent*-**1.84** was synthesised analogously to primary alcohol **1.84**, by switching to AD-mix-α for the dihydroxylation. Swern oxidation of alcohol *ent*-**1.84** followed by Wittig olefination of the corresponding aldehyde gave alkene **1.88** with low selectivity (*Z*:*E* 3:1). Submitting alkene **1.88** to their optimum iodoetherification conditions returned THF alcohol **1.89** as mixture of diastereoisomers (*dr trans*:*cis* 11:1 ^{1}H NMR from deiodonated derivative of alcohol **1.89**). A radical deiodonation of alcohol **1.89** followed by conversion of the free hydroxyl to acetate provided fragment **1.81**. Fragment **1.81** was synthesised in 10 steps from 1,4-pentadien-3-ol in a 10.2% yield.

Synthesis of butenolide fragment **1.82** began with diene **1.90** which is synthesised in 1 step from 6-iodo-1-hexene in 86% yield (scheme 1.21). A

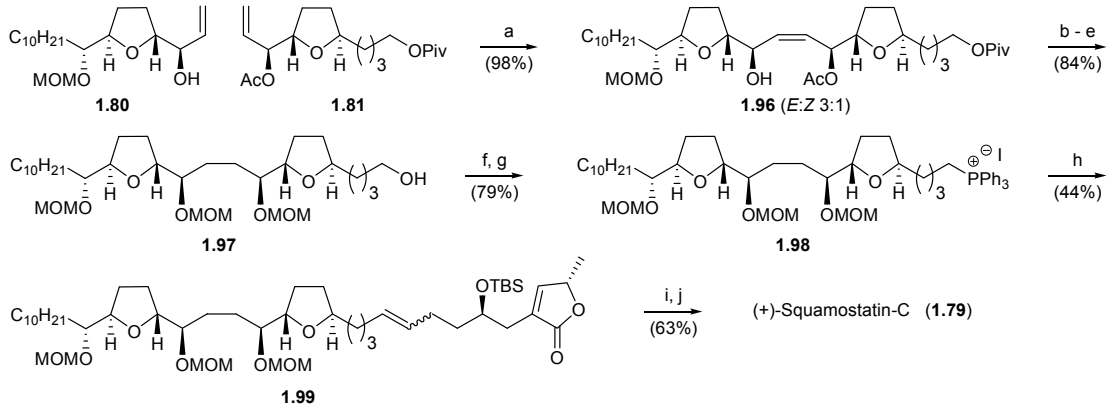
dihydroxylation of diene **1.90** followed by successive recrystallisation afforded tetraol **1.91** (*S*:*R* 20:1 by Mosher ester anaylsis).[64]



Scheme 1.21 Synthesis of butenolide portion **1.82**. *Reagents and conditions*: a) AD-mix-*α*; b) TsCl, pyridine; c) K_2CO_3, MeOH; d) allylMgBr, CuI; d) TBSCl, imidazole, CH_2Cl_2; e) CAN, CH_3CN-H_2O; f) PCC, CH_2Cl_2; g) $NaClO_2$, H_2O_2; h) MeOH, DCC, DMAP; i) LDA, THF, then (*S*)-2-(tetrahydropyran-2-yloxy)propanal; j) *p*-TsOH, MeOH; k) MsCl, Et_3N, CH_2Cl_2; l) AD-mix-*β*, *t*-BuOH-H_2O; m) $NaIO_4$, H_2O, CH_2Cl_2/acetone.

Conversion of tetraol **1.91** to *bis*-epoxide, then cuprate addition followed by silylation furnished silyl ether **1.92**. Removal of the phenol gave alcohol **1.93** which was oxidised in 2 steps to the carboxylic acid and converted to ester **1.94**. Using protocol described by Sinha and Keinan ester **1.94** was converted to butenolide fragment **1.82**.[65] Butenolide fragment **1.82** was synthesised in 14 steps from 6-iodo-1-hexene in a 2.9% yield.

To complete the synthesis, the key step was the CM reaction between alkenes **1.80** and **1.81** using Grubbs second generation catalyst (scheme 1.22).[56] The CM process relied on using an excess of allylic alcohol ester **1.81** with allylic alcohol **1.80**. The best results were obtained using 4:1 and 3:1 ratios of fragments **1.81** and **1.80** which gave 98% and 75% yields respectively, (based on fragment **1.80**).



Scheme 1.22 Total synthesis of (+)-squamostatin-C (**1.79**). *Reagents and conditions*: a) Method A: **1.80** (1 eq.), **1.81** (4 eq.), $Cl_2(Cy_3P)(IMes)Ru{=}CHPh$ (10 mol %), CH_2Cl_2, Δ, 18h, then $Cl_2(Cy_3P)(IMes)Ru{=}CHPh$ (10 mol %), rt, 4h; Method B: **1.80** (1 eq.), **1.81** (3 eq.), $Cl_2(Cy_3P)(IMes)Ru{=}CHPh$ (10 mol %), CH_2Cl_2, rt, 18h, then $Cl_2(Cy_3P)(IMes)Ru{=}CHPh$ (10 mol %), rt, 18h; b) H_2, Pd/C, EtOAc; c) K_2CO_3, MeOH; d) MOMCl, DIPEA, CH_2Cl_2; e) NaOMe, MeOH; f) Ph_3P, I_2, imidazole, benzene; g) Ph_3P, DIPEA, MeCN; h) **1.98**, *n*-BuLi, THF, then **1.82**; i) H_2, $Rh(PPh_3)_3Cl$; j) AcCl, MeOH-CH_2Cl_2.

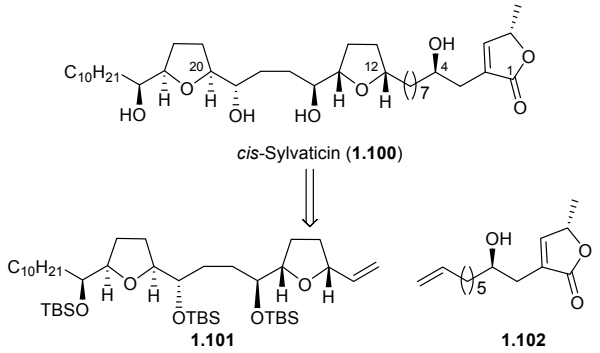
Hydrogenation of CM product **1.96**, selective hydrolysis of the acetate followed by global MOM protection, and then hydrolysis of the pivalate provided alcohol **1.97**. Wittig salt **1.98** was synthesised from alcohol **1.97** via the iodide. Wittig reaction with the butenolide fragment **1.82** afforded alkene **1.99**. Selective hydrogenation and deprotection gave (+)-squamostatin-C (**1.79**) in 23 steps from (*E*)-ethyl hepta-4,6-dienoate (**1.83**) in a total yield 2.2%.

Key aspects of Mootoo's synthesis are:-

- The non-adjacent *bis*-THF core was assembled by CM, while the butenolide portion was coupled by Wittig olenfination.
- Highly *trans* selective iodoetherification reaction used to establish both *trans*-THF rings.[59-62]
- Butenolide fragment with C4 hydroxyl synthesised through a modified route described by Sinha and Keinan.[64,65]

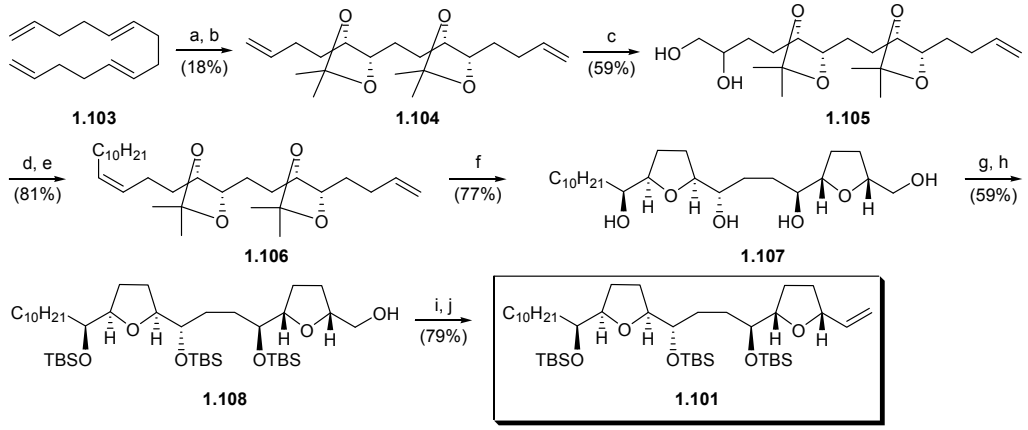
(+)-*cis*-Sylvaticin – Donohoe (2006)

The first total synthesis of *cis*-sylvaticin (**1.100**) was reported by Donohoe and the approach is based on a convergent coupling strategy with 2 main fragments (scheme 1.23).[66]



Scheme 1.23 Retrosynthetic analysis employed by Donohoe.

The key reaction in synthesising the non-adjacent bis-THF core (fragment **1.101**) was an osmium tetraoxide catalysed oxidative cyclisation reaction.[67] The synthesis of *bis*-THF fragment **1.101** began with commercially available tetradecatetraene **1.103** which is a mixture of isomers (*EE*, *EZ*, *ZZ*). Dihydroxylation of the tetraene followed by *in-situ* protection selectively gave diene **1.104** (*ee* > 98% through Mosher ester analysis, *dr* > 95:5), in modest yield (scheme 1.24).[68]

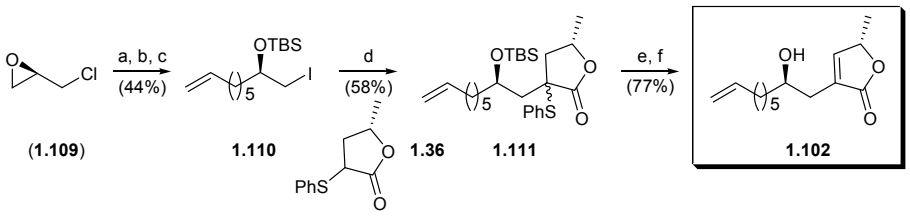


Scheme 1.24 Synthesis of *bis*-THF fragment **1.101**. *Reagents and conditions*: a) AD-mix-*α*; b) CH_2=CH(OMe)CH_3, CSA; c) AD-mix-*β*; d) $NaIO_4$; e) $C_{10}H_{21}CH{=}PPh_3$; f) OsO_4 (5 mol %), acetone, H_2O, Me_3NO (5 eq.), TFA, cinnamic acid; g) TBSOTf, 2,6-lutidine; h) TBAF (1 eq.); i) TPAP, NMO; j) $Ph_3P{=}CH_2$, THF.

mono–Dihydroxylation of diene **1.104** gave a diol **1.105** which was then submitted to periodate cleavage conditions, affording an aldehyde which

underwent olefination delivering diene **1.106**. With diene **1.106** in hand Donohoe was then set-up for the key oxidative cyclisation reaction. Under their optimum conditions diene **1.106** was converted to *bis*-THF **1.107** as a single diastereoisomer in high yield.[67] Global silylation of tetraol **1.107** followed by selective deprotection provided primary alcohol **1.108**. Oxidation of primary alcohol **1.108** to an aldehyde followed by Wittig olenfination gave fragment **1.101**. Fragment **1.101** was synthesised in 10 steps from tetradecatetraene **1.4** (*EE*, *EZ*, *ZZ*) in a total yield of 3.1%.

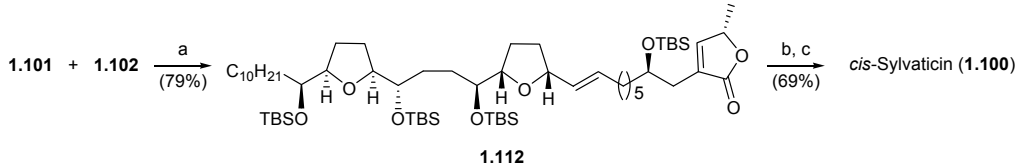
The synthesis of the butenolide fragment **1.102** began with (*R*)-epichlorohydrin (**1.109**) following work described by Lee (scheme 1.3).[69]



Scheme 1.25 Synthesis of butenolide fragment **1.102**. *Reagents and conditions*: a) $H_2C{=}CH(CH_2)_4MgBr$, CuCN; b) NaI; c) TBSOTf; d) **1.36**, LDA, HMPA, then **1.110**; e) *m*-CPBA, then Δ; f) AcCl, MeOH.

Cuprate addition to (*R*)-epichlorohydrin (**1.109**), followed by conversion of the chloride to the iodide then silylation of the secondary alcohol returned iodide **1.110**. The lithium enolate of lactone **1.36** was alkylated with iodide **1.110** to give sulfide **1.111**.[38] Sulfide **1.111** was oxidised to the sulfoxide, and subsequent thermal elimination followed by desilylation afforded the butenolide fragment **1.102**. The butenolide fragment **1.102** was synthesised in 6 steps from (*R*)-epichlorohydrin (**1.109**) in a total yield of 19.7%.

Fragments **1.101** and **1.102** were successfully coupled by CM to give silyl ether **1.112** (scheme 1.4).[56] Successful CM was achieved following Lee's protocol, by reacting fragment **1.101** (1 eq.) with an excess of fragment **1.102** (4 eq.) in the presence of second generation Grubbs catalyst.[69]



Scheme 1.26 Total synthesis of (+)-*cis*-sylvaticin (**1.100**). *Reagents and conditions*: a) **1.101** (1 eq.), **1.102** (4 eq.), $Cl_2(Cy_3P)(IMes)Ru{=}CHPh$ (10 mol %); b) $TsNHNH_2$, NaOAc; c) AcCl, MeOH.

Selective hydrogenation of silyl ether **1.112** followed by deprotection gave (+)-*cis*-sylvaticin (**1.100**). (+)-*cis*-Sylvaticin (**1.100**) was synthesised in 13 steps from tetradecatetraene **1.103** (*EE*, *EZ*, *ZZ*) in a total yield of 1.7%.

Key aspects of Donohoe's synthesis are:-

- Convergent 2 fragment approach, with fragment assembly carried out by CM.[56]
- The non-adjacent *bis*-THF core is constructed on tetraene alkyl skeleton.
- *cis*-THF rings assembled by osmium tetraoxide oxidative cyclisation.[67]
- Butenolide fragment with C4 hydroxyl synthesised through route described by Lee.[69]

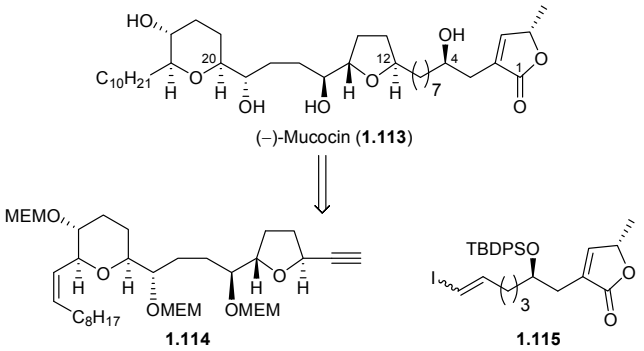
1.5 Synthesis of Non Adjacent THP/THF *Annonaceous* Acetogenins

In the following section the total synthesises of (–)-mucocin (**1.113**) will be discussed. (–)-Mucocin (**1.113**) belongs to the non adjacent THP/THF sub-class of *Annonaceous* acetogenins, which is structurally related to the non adjacent *bis*-THF sub-class. As a result, strategies used in the synthesis of (–)-mucocin (**1.113**) could be applied to non adjacent *bis*-THF *Annonaceous* acetogenins.

(–)-Mucocin

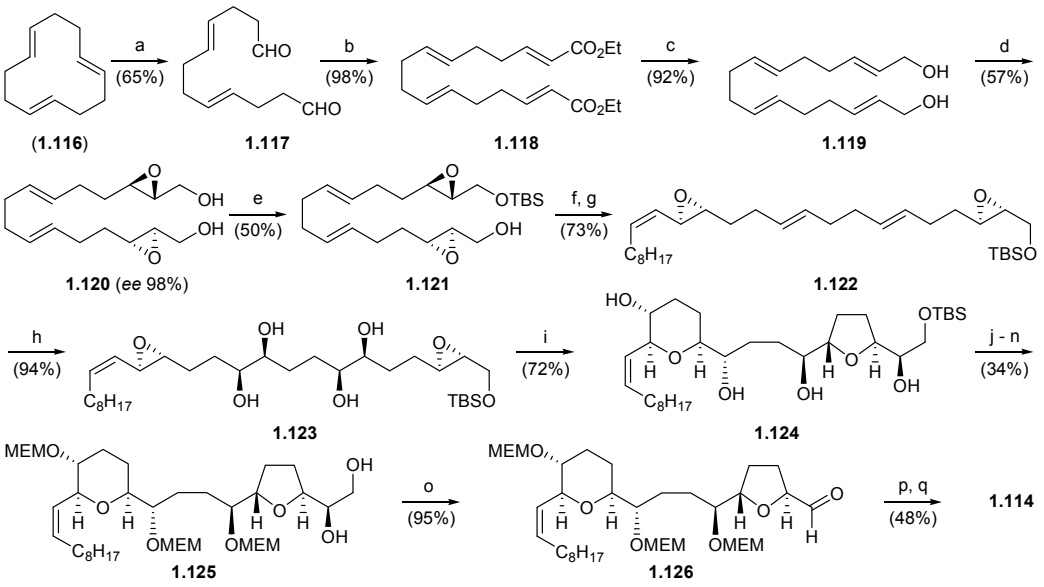
(–)-Mucocin – Sinha and Keinan (1998)

The first total synthesis by Sinha and Keinan group couples 2 main fragments **1.114** and **1.115** (scheme 1.27).



Scheme 1.27 Sinha and Keinan's retrosynthetic analysis of (–)-mucocin (**1.113**).

The synthesis of fragment **1.114** began with (*E*,*E*,*E*)-cyclododecatriene (**1.116**) using a "naked alkyl skeleton approach" (where the non adjacent THF/THP core is built on a tetraene alkyl skeleton) (scheme 1.28).[70-72] Selective dihydroxylation followed by periodate cleavage furnished dialdehyde **1.117**. Double Horner-Wadsworth-Emmons olefination gave diester **1.118** which was reduced to diol **1.119**. Sharpless asymmetric epoxidation of diol **1.119** delivered *bis* epoxide **1.120** in 98% ee. Desymmetrisation of the *bis* epoxide **1.120** was achieved by a *mono* silylation which afforded alcohol **1.121**, oxidation of alcohol **1.121** and subsequent Wittig reaction gave alkene **1.122** (*Z* only). Selective double dihydroxylation of the central *E* alkene bonds gave tetraol **1.123** (*dr* not given).[73] With tetraol **1.123** in hand the stage was set for the key acid catalysed regioselective double cyclisation.[74,75] Under optimum condition the non-adjacent THP-THF core was constructed in one step from *bis*-epoxide **1.123** which provided ether **1.124**.

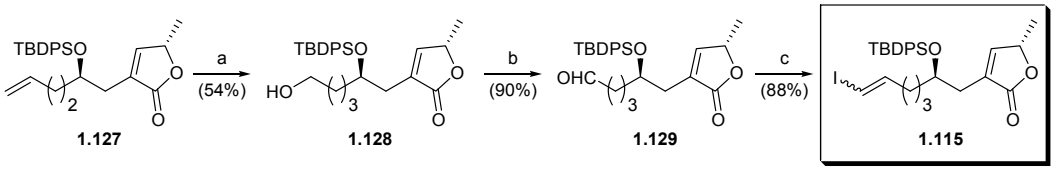


Scheme 1.28 Synthesis of alkyne **1.114**. *Reagents and conditions*: a) (i) OsO_4, acetone/H_2O; (ii) $NaIO_4$, CH_2Cl_2/acetone; b) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF; c) DIBAL-H, THF; d) Ti(O*i*-Pr)$_4$, (–)-DET, TBHP, CH_2Cl_2; e) TBSCl, imidazole, DMF; f) SO_3-pyridine, DMSO, Et_3N, CH_2Cl_2; g) $C_9H_{19}PPh_3Br$, KHMDS, HMPA/THF; h) AD-mix-α, $MeSO_2NH_2$, H_2O/*t*-BuOH; i) *p*-TsOH, CH_2Cl_2; j) TsOH, CH_2Cl_2/MeOH; k) *p*-TsOH, 2,2-dimethoxypropane, CH_2Cl_2; l) *p*-TsOH, MeOH/H_2O; m) MEM-Cl, DIPEA, CH_2Cl_2; n) AcOH/H_2O; o) $NaIO_4$, CH_2Cl_2/acetone; p) CBr_4, PPh_3, CH_2Cl_2; q) *n*-BuLi, THF;

A 5 step protecting group manipulation of tetraol **1.124** furnished diol **1.125** which was subject to an oxidative cleavage yielding aldehyde **1.126**. Using

Corey-Fuchs protocol aldehyde **1.126** was converted to fragment **1.114**.[76] Fragment **1.114** was synthesised in 18 steps from (*E*,*E*,*E*)-cyclododecatriene (**1.116**) in a total yield of 1.3%.

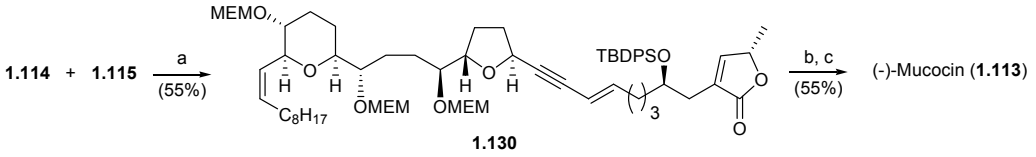
The synthesis of the butenolide fragment **1.115** began with alkene **1.127** (scheme 1.29). Alkene **1.127** had previously been synthesised by Sinha and Keinan from (*S*)-dihydro-5-(hydroxymethyl)furan-2(3*H*)-one in 9 steps in an approximate yield of 12%.[65]



Scheme 1.29 Synthesis of vinyl iodide **1.115**. *Reagents and conditions*: a) 9-BBN, THF; b) PCC, CH_2Cl_2; c) CHI_3, $CrCl_2$, THF.

A selective hydroboration of diene **1.127** followed by oxidation of alcohol **1.128** provided aldehyde **1.129**. Under Takai olefination conditions aldehyde **1.129** was converted to fragment **1.115**.[39]

Fragments **1.114** and **1.115** were successfully coupled using Sonogashira chemistry to give enyne **1.130** (scheme 1.30).[40] Selective hydrogenation and global deprotection gave (–)-mucocin (**1.113**). (–)-Mucocin (**1.113**) was synthesised in 21 steps from (*E*,*E*,*E*)-cyclododecatriene (**1.116**) in a total yield of 0.4%.



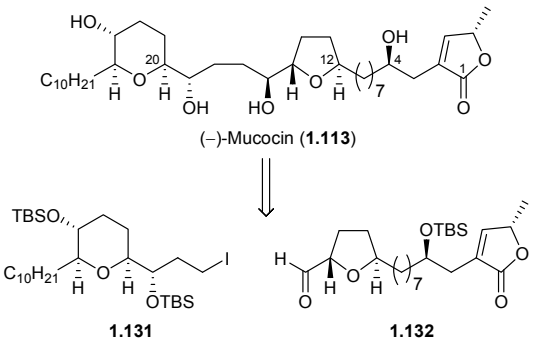
Scheme 1.30 Total synthesis of (–)-mucocin (**1.113**). *Reagents and conditions*: a) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, THF; b) H_2, $Rh(PPh_3)_3Cl$, benzene, EtOH; c) AcCl, $MeOH/CH_2Cl_2$.

Key aspects of Sinha's synthesis are:-

- Sonogashira coupling of 2 major fragments.[40]
- The non-adjacent THP-THF core constructed on a naked alkyl skeleton.[70-72]
- Established non-adjacent *cis*-THP-*trans*-THF core by intramolecular nucleophilic substitution, with key stereochemistry set-up by Sharpless asymmetric epoxidation and asymmetric dihydroxylation.[74,75]

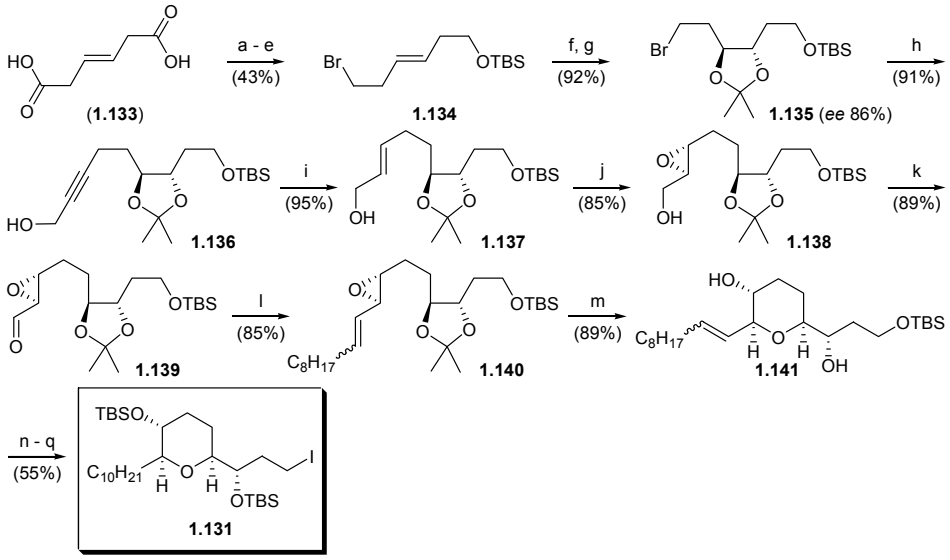
(–)-Mucocin – Koert (1999)

Koert group's synthesis of muconin (**1.113**) couples 2 main fragments **1.131** and **1.132** via enantioselective organometallic chemistry (scheme 1.31).[77,78]



Scheme 1.31 Koert's retrosynthetic analysis of (–)-mucocin (**1.113**).

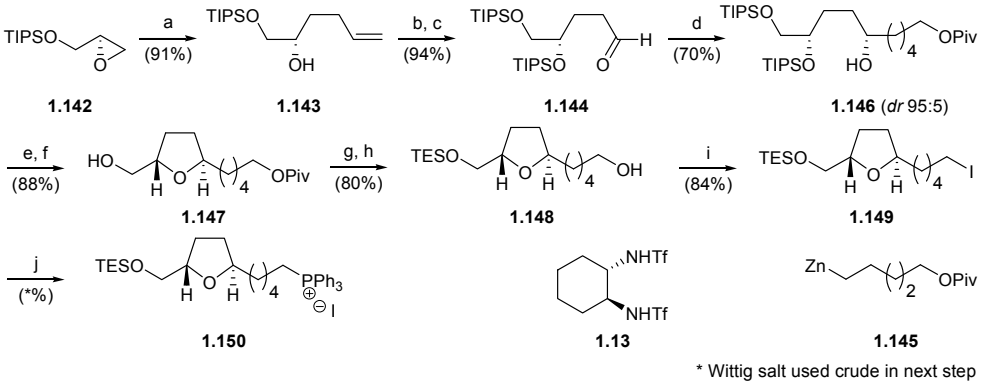
The synthesis of the THP fragment **1.131** began with (*E*)-dihydromuconic acid (**1.133**) (scheme 1.32), which was converted to its dimethyl ester, the diester was reduced to the diol where upon selective *mono* silylation was achieved, and the free hydroxyl was converted to a bromide to give alkene **1.134**.



Scheme 1.32 Synthesis of fragment **1.131**. *Reagents and conditions*: a) TMSCl, MeOH; b) $LiAlH_4$, THF; c) NaH, TBSCl, THF; d) *p*-TsCl, pyridine, CH_2Cl_2; e) LiBr, acetone; f) AD-mix-*α*, $MeSO_2NH_2$, H_2O/*t*-BuOH; g) *p*-TsOH (5 mol%), 2,2-dimethoxypropane, CH_2Cl_2; h) propargyl alcohol, *n*-BuLi, NH_3/THF/DMPU; i) Red-Al, THF; j) TBHP, (–)-DIPT, $Ti(O\textit{i}\text{-}Pr)_4$, CH_2Cl_2; k) Dess-Martin periodinane, pyridine, CH_2Cl_2; l) $H_{19}C_9PPh_3Br$, NaHMDS, THF; m) CSA, CH_2Cl_2/*i*-PrOH; n) H_2, 5% Pt/C, EtOAc; o) TBSOTf, 2,6-lutidine, CH_2Cl_2; p) CSA, CH_2Cl_2/MeOH; q) I_2, PPh_3, imidazole, CH_2Cl_2.

An asymmetric dihydroxylation of alkene **1.134** was followed by acetonide protection of the crude diol returning bromide **1.135** (*ee* 86%). Alkylation of lithiated propargylic alcohol with bromide **1.135** gave propargylic alcohol **1.136**. Propargylic alcohol **1.136** was reduced to allylic alcohol **1.137** which was submitted to Sharpless asymmetric epoxidation to afford alcohol **1.138** (*ee* for epoxidation > 98%). Dess-Martin oxidation of **1.138** followed by Wittig olefination successfully installed the alkyl chain to give alkene **1.140** (*E*:*Z* 1:1). Alkene **1.140** set the stage for the key THP forming reaction.[75] An acid deprotection then cyclisation favoured 6-*endo* cyclisation over 5-*exo* due to the stabilising effects of the alkene bond in the transition state providing THP diol **1.141**. Alkene **1.141** was reduced, global silylation then selective desilylation gave primary alcohol which was converted to the iodide, delivering fragment **1.131** in 17 steps from (*E*)-dihydromuconic acid (**1.133**) in 10.8% yield.

The synthesis of the fragment **1.132** began with TIPS protected (*R*)-glycidol **1.142** (scheme 1.33). Cuprate addition to glycidol **1.142** gave alcohol **1.143**. TIPS protection of alcohol **1.143** then ozonolysis of the terminal alkene furnished aldehyde **1.144**.

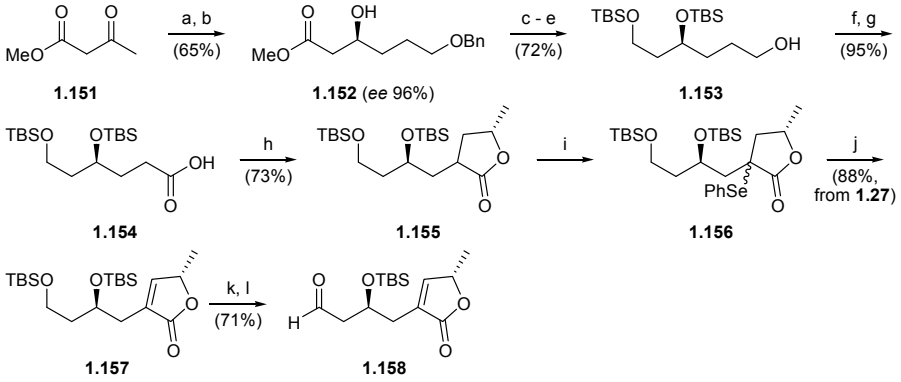


Scheme 1.33 Synthesis of Wittig salt **1.150**. *Reagents and conditions*: a) $H_2C{=}CHCH_2MgBr$, CuI, THF b) TIPSOTf, 2,6-lutidine, CH_2Cl_2; c) O_3, CH_2Cl_2, PPh_3; d) **1.145**, **1.13**, $Ti(O\textit{i}\text{-}Pr)_4$, xylenes, then **1.144**; e) *p*-TsCl, pyridine, CH_2Cl_2; f) TBAF, THF; g) TESCl, imidazole, CH_2Cl_2; h) DIBAL-H, THF; i) I_2, PPh_3, imidazole, CH_2Cl_2; j) PPh_3, CH_3CN/toluene.

Following Knochel's protocol, an asymmetric addition of diorganozinc reagent **1.145** to aldehyde **1.144** returned alcohol **1.146** (*dr* 95:5).[79] Tosylation of alcohol **1.146** followed by TBAF desilylation induced cyclisation which afforded THF alcohol **1.147** (*trans*:*cis* 95:5 due to diastereoselectivity from the diorganozinc addition). Protecting adjustment gave alcohol **1.148**, which was

subjected to iodination conditions to yield iodide **1.149**. Iodide **1.19** was then transformed to the Wittig salt **1.150** which was used crude in the next step.

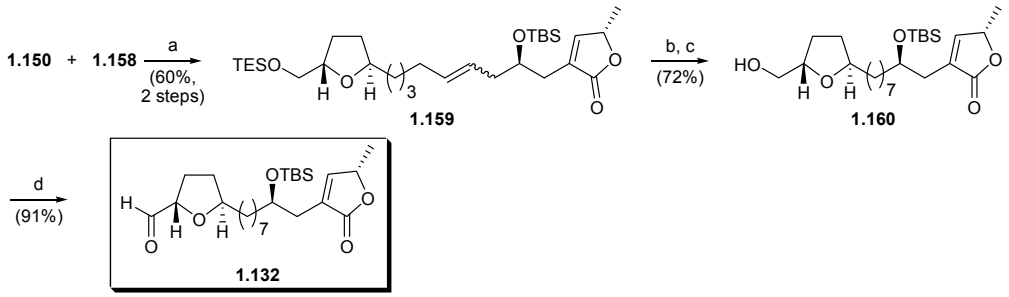
Synthesis of aldehyde **1.158** began with β-ketoester **1.151** (scheme 1.34). A selective alkylation of the β-ketoester **1.151** dianion followed by an enantioselective Noyori reduction of the ketone gave secondary alcohol **1.152** (ee = 96% by chiral HPLC).[80]



Scheme 1.34 Synthesis of butenolide aldehyde **1.158**. *Reagents and conditions*: a) NaH, *n*-BuLi, THF, then $Br(CH_2)_2OBn$; b) H_2, Ru(II)-(*S*)-(–)-BINAP; c) BH_3•SMe_2, THF; d) TBSCl, imidazole, DMAP, CH_2Cl_2; e) H_2, 10% Pd/C, EtOAc; f) Swern oxidation; g) $NaOCl_2$, NaH_2PO_4•$2H_2O$, methyl-2-butene, H_2O/*t*-BuOH; h) (i) LDA, THF, then (*S*)-(–)-propene oxide; (ii) PivCl, Et_3N, CH_2Cl_2; i) KHMDS, THF, PhSeCl; j) magnesium monoperoxyphthalate, THF/MeOH; k) CSA, CH_2Cl_2/MeOH; l) Dess-Martin periodinane, pyridine, CH_2Cl_2.

Reduction of ester **1.152** followed by global silylation then debenzylation gave alcohol **1.153**. A two step Swern/chlorite oxidation of alcohol **1.153** delivered carboxylic acid **1.154**.[81] The dianion of acid **1.154** was reacted with (*S*)-(–)-propene oxide to give a carboxylic acid, which was cyclised via a mixed anhydride species to give lactone **1.155**. The potassium enolate of lactone **1.155** was reacted with phenyl selenium chloride which provided selenoether **1.156**. Oxidisation to the selenoxide using magnesium monoperoxyphthalate led to rapid elimination and formation of the α,β-unsaturated lactone **1.157**. Selective primary desilylation and subsequent oxidation of the alcohol gave aldehyde **1.158**.

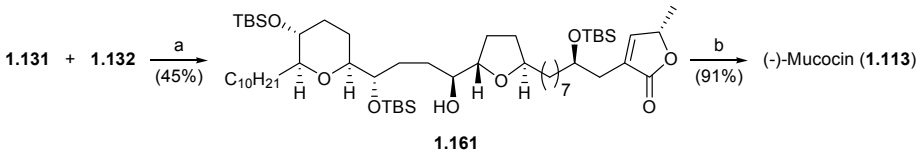
With Wittig salt **1.150** and aldehyde **1.158** in hand, successful coupling using NaHMDS afforded alkene **1.159** as a mixture *E*/*Z* isomers (scheme 1.35).



Scheme 1.35 Synthesis of fragment **1.132**. *Reagents and conditions*: a) **1.150**, NaHMDS, THF, then **1.158**; b) H_2, $Rh(PPh_3)_3Cl$, benzene; c) CSA, CH_2Cl_2/MeOH; d) Dess-Martin periodinane, pyridine, CH_2Cl_2.

Alkene **1.159** was selectively hydrogenated, and following desilylation delivered alcohol **1.160**, which was oxidised to the fragment **1.132** with Dess-Martin periodinane. Fragment **1.132** was synthesised in 17 steps from β-ketoester **1.151** in a total yield of 8.0%.

Koert employed a chelation-controlled Grignard addition to couple fragments **1.131** and **1.132** (scheme 1.36).



Scheme 1.36 Total synthesis of (–)-mucocin (**1.113**). *Reagents and conditions*: a) **1.131**, *t*-BuLi, Et_2O, then $MgBr_2 \bullet OEt_2$, then **1.132**; b) HF, CH_2Cl_2/MeCN.

The key for this was careful synthesis of a Grignard from iodide **1.131**, this was achieved by firstly iodide-lithium exchange with *t*-BuLi, followed by transmetallation with magnesium bromide which gave a Grignard reagent, addition of the Grignard to aldehyde **1.132** gave desired alcohol **1.161** (major:minor 4:1 by HPLC, separable by chromatography). Global desilylation of alcohol **1.161** gave (–)-mucocin (**1.113**) in 19 steps from β-ketoester **1.151** in a total yield of 3.3%.

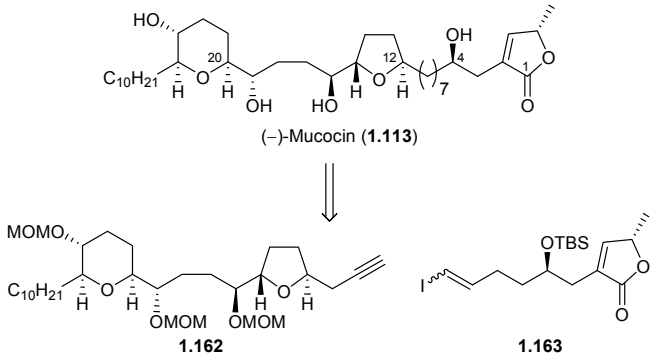
Key aspects of Koert's synthesis are:-

- Use of chelation controlled Grignard addition to couple 2 major fragments.
- *Trans*-THF ring established by nucleophilic substitution cyclisation, with key stereochemistry set-up by Sharpless asymmetric epoxidation and a Knochel asymmetric diorganozinc addition to aldehyde **1.114**.[79]

- *Cis*-THP ring established by selective 6-*endo* nucleophilic substitution cyclisation, with key stereochemistry set-up by asymmetric dihydroxylation and Sharpless asymmetric epoxidation.[75]
- C4 hydroxyl installed by enantioselective Noyori reduction.[80]

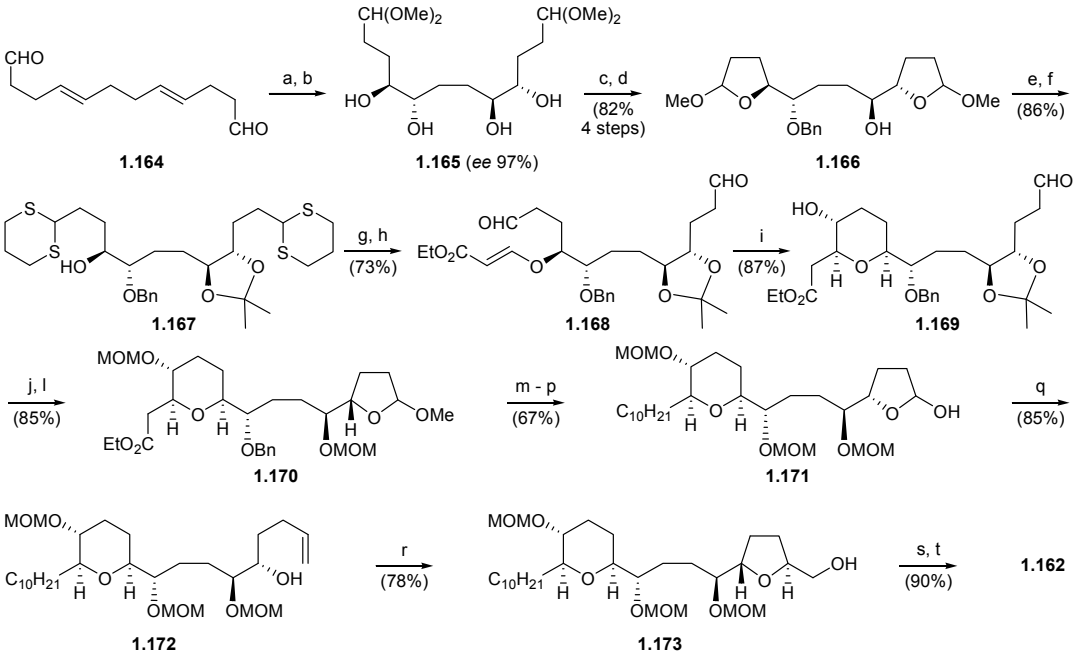
(–)-Mucocin – Nakata and Takahashi (2002)

Nakata's approach couples 2 main fragments **1.162** and **1.163**, requiring a linear synthesis of the non-adjacent THP-THF core (scheme 1.37).[82] A key reaction in their approach was a SmI_2 induced cyclisation developed by Nakata to install the *cis*-THP moiety.[83-87]



Scheme 1.37 Nakata's retrosynthetic analysis of (–)-mucocin (**1.113**).

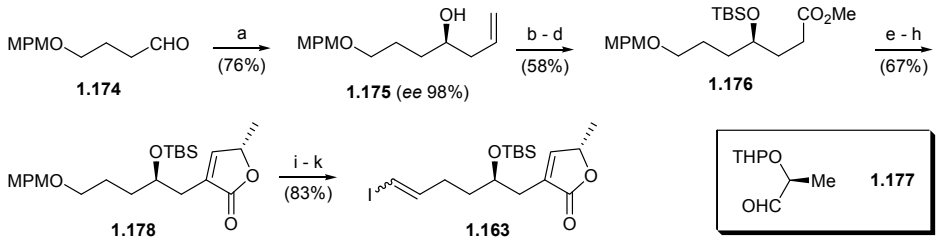
The synthesis of alkyne **1.162** began with dialdehyde **1.164** (available in one step from (*E*,*E*,*E*)-cyclododecatriene in 65% yield) (scheme 1.38).[88] Acetal protection of dialdehyde **1.164** followed by double asymmetric dihydroxylation gave tetraol **1.165** (*ee* = 97%, by ^{1}H NMR analysis of the Mosher ester derivative). Selective partial intramolecular acetal formation gave a *bis*-THF diol, where *mono* benzylation was used to effect desymmetrisation. Conversion of bis-acetal **1.166** to a *bis*-dithiane gave a 1,2-diol which was protected as its acetonide **1.167**.



Scheme 1.38 Synthesis of alkyne **1.162**. *Reagents and conditions*: a) $HC(OMe)_3$, CSA, MeOH; b) AD-mix-α, $MeSO_2NH_2$, H_2O/*t*-BuOH; c) CSA, MeOH; d) BnBr, NaH, THF; e) 1,3-propanedithiol, $Zn(OTf)_2$, DCE; f) $Me_2C(OMe)_2$, CSA, CH_2Cl_2; g) ethyl propiolate, *N*-methylmorpholine, CH_2Cl_2; h) CH_3I, $NaHCO_3$, $MeCN/H_2O$; i) SmI_2, MeOH, THF; j) $HC(OMe)_3$, CSA, MeOH; l) MOMBr, DIPEA, DCE; m) DIBAL-H, CH_2Cl_2, then $C_8H_{17}PPh_3Br$, *n*-BuLi, THF; n) 10% Pd/C, H_2, MeOH; o) MOMBr, DIPEA, DCE; p) $AcOH/H_2O$; q) CH_3PPh_3I, NaHMDS, THF; r) $[Co(modp)_2]$, O_2, *t*-BuO_2H, *i*-PrOH; s) Tf_2O, 2,6-lutidine, CH_2Cl_2; t) TMSC≡CLi, HMPA, THF, then K_2CO_3, MeOH.

Alcohol **1.167** was reacted with ethyl propiolate in a 1,4-addition to afford a *trans* α,β-unsaturated ester. Hydrolysis of the *bis*-dithiane gave key intermediate **1.168**. With intermediate **1.168** in hand, the molecule was set-up for the SmI_2 induced cyclisation. Under their optimum conditions intermediate **1.168** gave *cis*-THP alcohol **1.169** as the sole diastereoisomer. A selective partial intramolecular acetal formation gave a THP-THF alcohol, which was MOM-protected to furnish ester **1.170**. A three step protocol installed the alkyl chain, and subsequent acetal hydrolysis yielded lactol **1.171**. Wittig olefination of lactol **1.171** gave alkene **1.172** which set the scene for a cobalt oxidative cyclisation to install the *trans*-THF ring in alcohol **1.173**.[89] Conversion of alcohol **1.173** to a triflate then displacement with lithiated TMS acetylene followed by *in situ* desilylation gave fragment **1.162**. Fragment **1.162** was synthesised in 20 steps from (*E*,*E*,*E*)-cyclododecatriene (**1.116**) in a total yield of 9.9%.

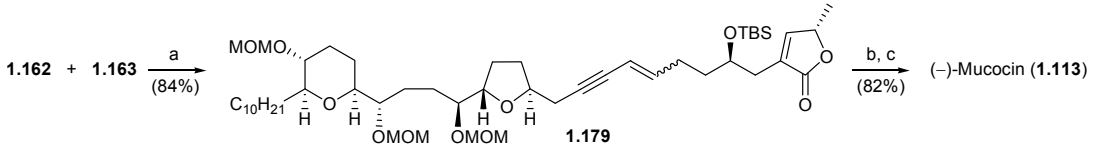
The synthesis of the butenolide fragment began with aldehyde **1.174** (available in 2 steps from 1,4-butanediol in 86% yield) (scheme 1.39).[90]



Scheme 1.39 Synthesis of vinyl iodide **1.163**. *Reagents and conditions*: a) (*S*)-BINOL, Ti(O*i*-Pr)$_4$, allyltributyltin,; b) TBSCl, imidazole, DMF; c) BH_3•THF, THF then NaOH, 30% H_2O_2; d) Jones reagent, acetone then CH_2N_2, Et_2O; e) LDA, THF, then **1.177**; f) CSA, MeOH/H_2O; g) MsCl, Et_3N, CH_2Cl_2; h) DBU, CH_2Cl_2; i) DDQ, CH_2Cl_2/phosphate buffer (pH 7.4); j) $(COCl)_2$, DMSO, CH_2Cl_2, then Et_3N; k) $CrCl_2$, CHI_3, THF.

An asymmetric allylation of aldehyde **1.174** gave alcohol **1.175** (ee > 98%).[91] Silylation followed by a three step hydroboration-oxidation-methylation procedure furnished ester **1.176**. The butenolide portion was installed using an adaptation of the chemistry described by Wu.[34] Hydroxyl deprotection, oxidation and Takai olefination delivered butenolide fragment **1.163**.[39] Butenolide fragment **1.163** was synthesised in 13 steps from 1,4-butanediol in a total yield of 21.1%.

Fragments **1.162** and **1.163** were coupled using Sonogashira chemistry to give enyne **1.179**, which was selectively hydrogenated and deprotected to afford (–)-mucocin (**1.113**) (scheme 1.40).[40]



Scheme 1.40 Total synthesis of (–)-mucocin (**1.113**). *Reagents and conditions*: a) $[PdCl_2(Ph_3P)_2]$, CuI, Et_3N; b) $(Ph_3P)_3RhCl$, H_2, benzene/EtOH; c) 10% HCl/MeOH, CH_2Cl_2.

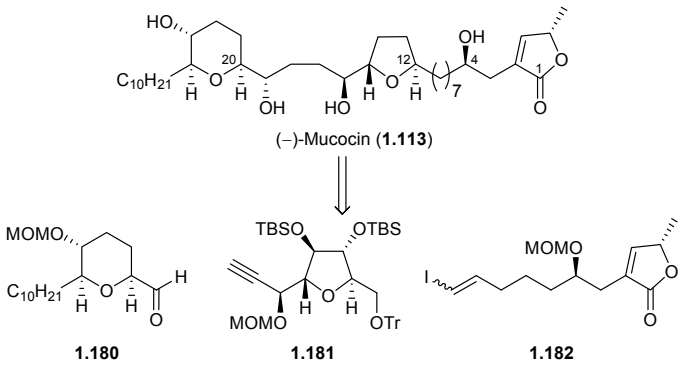
(–)-Mucocin (**1.113**) was synthesised in 23 steps from (*E*,*E*,*E*)-cyclododecatriene in a total yield of 6.8%.

Key aspects of Nakata's synthesis are:-

- Fragment coupling using Sonogashira chemistry.[40]
- *Cis*-THP ring established by SmI_2 induced cyclisation.[83-87]
- *Trans*-THF ring established by cobalt oxidative cyclisation.[89]
- C4 hydroxyl install by asymmetric allylation of aldehyde **1.174**.[91]

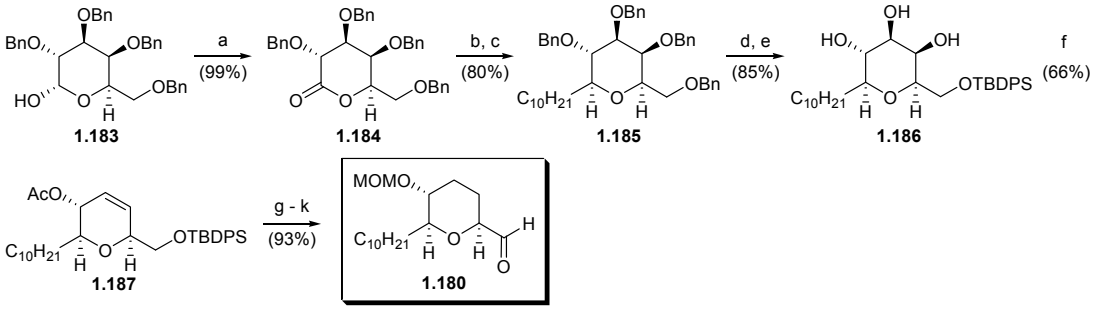
(–)-Mucocin – Takahashi (2002)

Takahashi's approach is based on a convergent coupling strategy with 3 main fragments, using the chiral pool as the source of the fragments (scheme 1.41).[48]



Scheme 1.41 Takahashi's retrosynthetic analysis of (–)-mucocin (**1.1**).

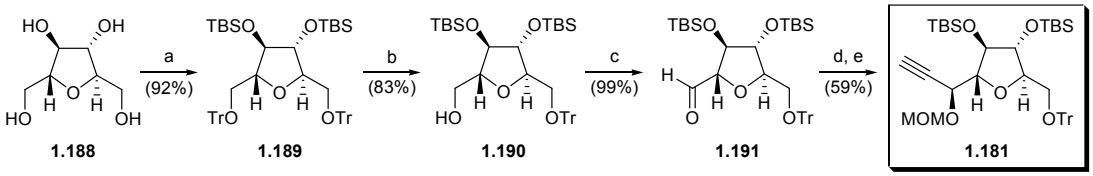
Synthesis of THP fragment **1.180** began with commercially available benzyl ether **1.183** (scheme 1.42). Swern oxidation followed by Grignard addition installed the alkyl chain, then a Lewis acid catalysed stereoselective reduction furnished *cis*-THP ether **1.185**.[92]



Scheme 1.42 Synthesis of THP fragment **1.180**. *Reagents and conditions*: a) Swern oxidation; b) decylmagnesium bromide, Et_2O; c) Et_3SiH, BF_3•Et_2O, CH_2Cl_2; d) 10% Pd/C, H_2, EtOAc-MeOH; e) TBDPSCl, imidazole, DMF; f) (i) $HC(OMe)_3$, CSA, CH_2Cl_2; (ii) Ac_2O, Δ; g) 10% Pd/C, H_2, EtOAc; h) NaOMe, MeOH; i) MOMCl, DIPEA, CH_2Cl_2; j) TBAF, THF; k) Swern oxidation.

Global debenzylation of ether **1.185** followed by a primary alcohol selective silylation gave silyl ether **1.186**. Triol **1.186** was selectively deoxygenated under Ando's conditions delivering acetate **1.187**.[93] Hydrogenation of alkene **1.187** followed by protecting group manipulations gave a primary alcohol, which under Swern conditions furnished desired THP fragment **1.180**. THP fragment **1.180** was synthesised in 12 steps from benzyl ether **1.183** in 41.3% yield.

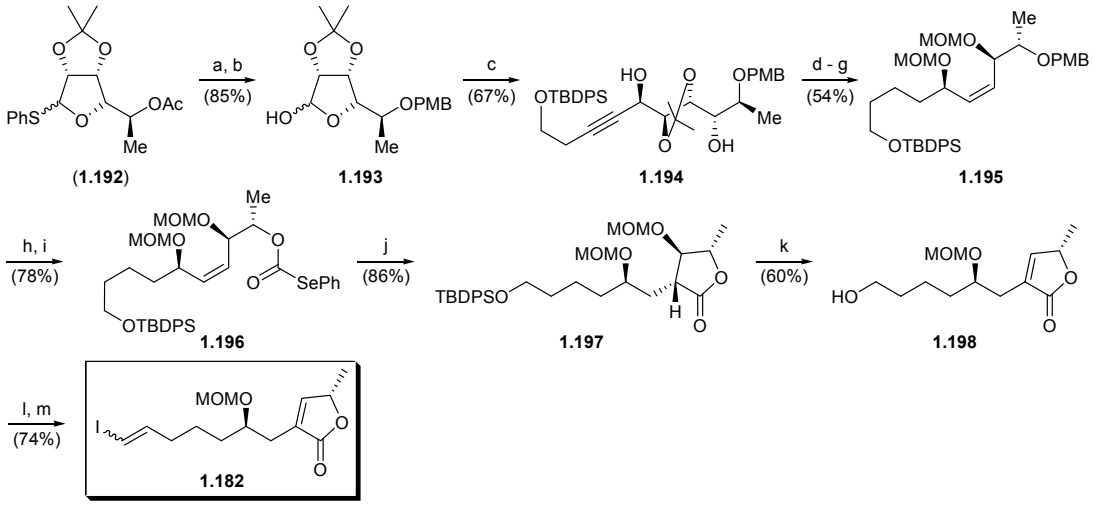
The synthesis of the THF fragment **1.181** began with commercially available 2,5-anhydro-*D*-mannitol (**1.188**) (scheme 1.43).



Scheme 1.43 Synthesis of THF fragment **1.181**. *Reagents and conditions*: a) TrCl, pyridine, then TBSCl, imidazole; b) Et_2AlCl, hexane; c) Swern oxidation; d) HC≡CMgCl, $ZnCl_2$, CH_2Cl_2/Et_2O/THF; e) MOMCl, DIPEA, CH_2Cl_2.

A one-pot procedure furnished protected 2,5-anhydro-*d*-mannitol **1.189**, then selective detritylation successfully effected desymmetrisation.[94] Swern oxidation of the resulting alcohol **1.190** followed by a stereoselective Grignard addition, then protection of the resulting alcohol as its MOM ether gave THF fragment **1.181**. The observed selectivity for the Grignard addition (93:7) may be explained by Felkin-Anh model but with possible competing chelation control. THF fragment **1.181** was synthesised in 5 steps from 2,5-anhydro-d-mannitol (**1.188**) in 44.6% yield.

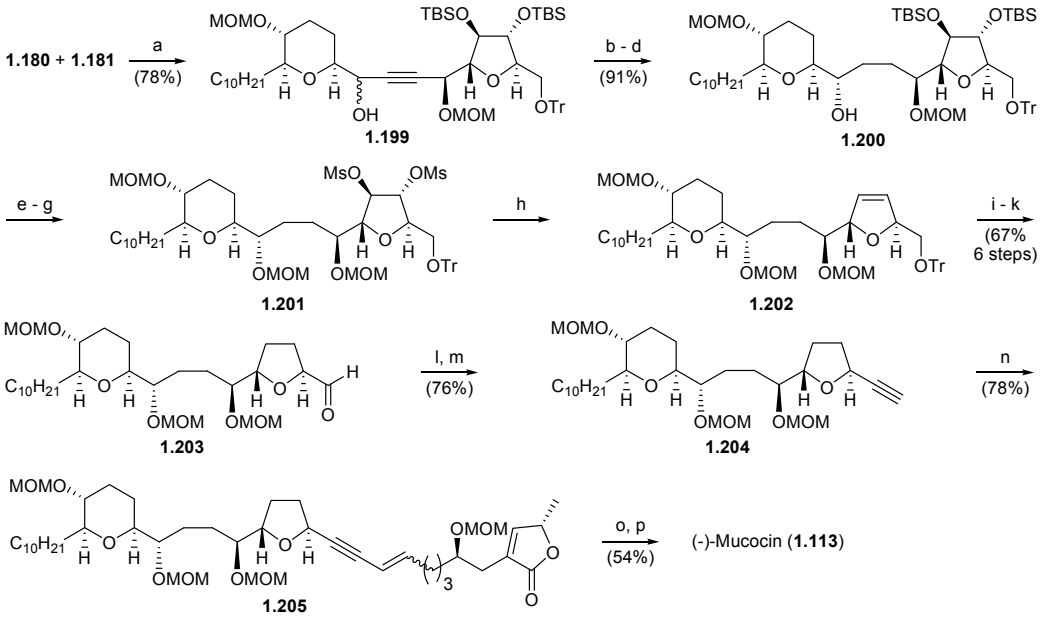
The synthesis of the butenolide fragment **1.182** began with phenyl 5-*O*-acetyl-2,3-*O*-isopropylidene-1-thio-*l*-rhamnofuranoside (**1.192**) (synthesised in 3 steps from *l*-rhamnose) (scheme 1.44).[95] Hydrolysis of acetate **1.192**, then PMB protection of the free hydroxyl followed by *in situ* treatment with NBS gave lactol **1.193**. Stereoselective addition of a lithiated alkyne to lactol **1.193** returned alcohol **1.194** (selectivity 6:1).



Scheme 1.44 Synthesis of butenolide fragment **1.182**. *Reagents and conditions*: a) NaOMe, MeOH; b) (i) PMBCl, NaH, TBAI, DMF; (ii) NBS, THF; c) $TBDPSOCH_2CH_2C{\equiv}CH$, *n*-BuLi, hexane/$Et_2O$ (3:1); d) MOMCl, DIPEA, CH_2Cl_2; e) 5% Rh/Al_2O_3, H_2, EtOAc; f) aq AcOH; g) (i) $HC(OMe)_3$, CSA, CH_2Cl_2; (ii) Ac_2O; h) DDQ, CH_2Cl_2; i) triphosgene, pyridine, CH_2Cl_2, then PhSeH, Et_3N; j) Bu_3SnH, AIBN, toluene; k) TBAF, AcOH, THF, then DBU, CH_3CN; l) Swern oxidation; m) CHI_3, $CrCl_2$, THF.

Protection of the free hydroxyls as their MOM ethers, reduction of the alkyne, then acetal hydrolysis followed by an Ando deoxygenation gave *Z*-alkene **1.195**.[93] A two step conversion of *Z*-alkene **1.195** furnished selenocarbonate **1.196**.[96] With selenocarbonate **1.196** in hand an acyl radical cyclisation selectively provided lactone **1.197**. Desilylation followed by treatment with DBU in acetonitrile afforded butenolide **1.198**. Swern oxidation followed by Takai olefination yielded the butenolide fragment **1.182**. Butenolide fragment **1.182** was synthesised in 18 steps from *l*-rhamnose.

The coupling of THF and THP fragments were achieved by reacting lithiated alkyne **1.180** with aldehyde **1.181**, giving a mixture of epimers in favour of the undesired enantiomer (scheme 1.45). Alkyne reduction, then alcohol oxidation followed by stereoselective hydride reduction delivered alcohol **1.200** with the correct stereochemistry (*dr* 24:1).



Scheme 1.45 Total synthesis of (–)-mucocin (**1.113**). *Reagents and conditions*: a) *n*-BuLi, $CeCl_3$, THF; b) 5% PtO_2, H_2, EtOAc; c) TPAP, NMO, CH_2Cl_2; d) L-selectride, THF; e) MOMCl, DIPEA, CH_2Cl_2; f) TBAF, THF; g) MsCl, Et_3N, CH_2Cl_2; h) Zn, NaI, DMF; i) 10% Pd/C, H_2, EtOAc; j) aq AcOH; k) Swern oxidation; l) Ph_3P, CBr_4, Et_3N, CH_2Cl_2, m) EtMgBr, THF; n) **1.182**, $(Ph_3P)_2PdCl_2$, CuI, Et_3N; o) $(Ph_3P)_3RhCl$, H_2, benzene/EtOH (6:1); p) BF_3•Et_2O, Me_2S.

Protecting group manipulations gave mesylate **1.201**, which underwent reductive elimination to afford alkene **1.202**.[97] Hydrogenation of alkene **1.202** followed by detritylation gave a primary alcohol that was oxidised to aldehyde **1.203**. Under Corey-Fuchs conditions, aldehyde **1.203** was converted to alkyne **1.204** which was used in a Sonogashira coupling with iodide **1.182**.[40,76] Finally a selective hydrogenolysis and global deprotection of enyne **1.205** gave (–)-mucocin (**1.113**) in 28 steps from benzyl ether **1.183** in a total yield of 6.3%.

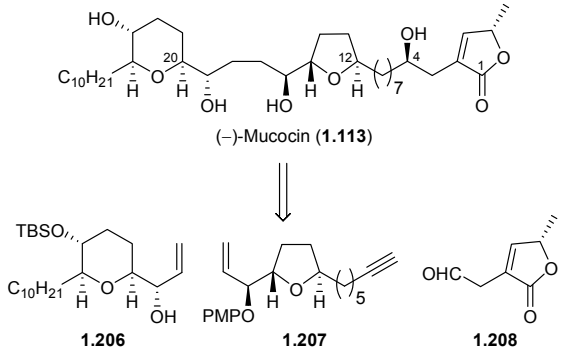
Key aspects of Takahashi's synthesis are:-

- 3 fragments synthesised using chiron approach.
- Non-adjacent THP-THF core constructed by acetylide addition to aldehyde **1.180**.
- *Cis*-THP ring stereochemistry delivered from chiral starting material except C24 position which was installed by stereoselective reduction.[92]
- *Trans*-THF stereochemistry delivered from chiral starting material, with C16 stereochemistry installed by chelation controlled Grignard addition.

- C4 hydroxyl stereochemistry installed by substrate controlled acetylide addition to lactol **1.193**.

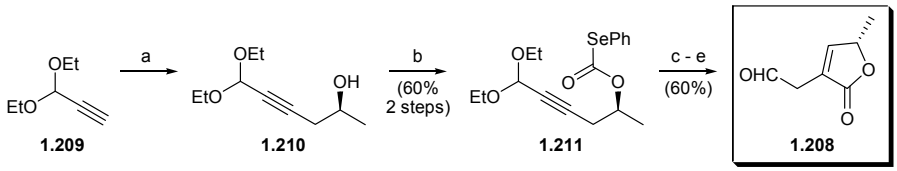
(–)-Mucocin – Evans (2003)

Evans' group employs a highly convergent coupling strategy with 3 main fragments (scheme 1.46).



Scheme 1.46 Evans retrosynthetic analysis for (–)-mucocin (**1.113**).

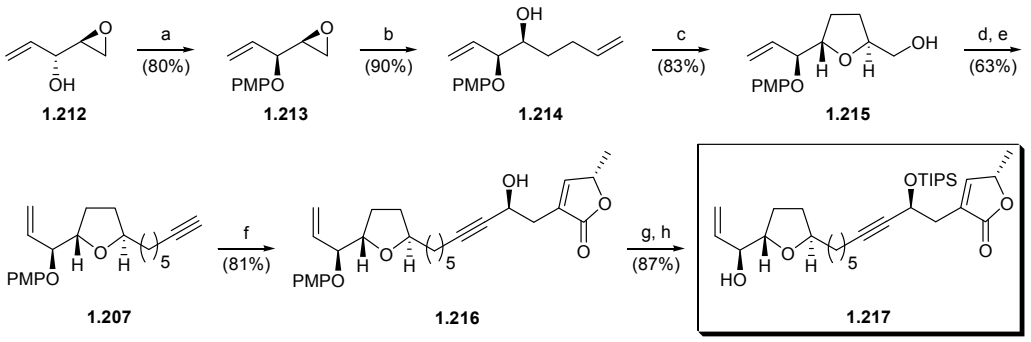
The synthesis of the aldehyde fragment **1.208** started with a regioselective opening of (*S*)-propylene oxide with lithiated alkyne **1.209**, affording alcohol **1.210** (scheme 1.47).



Scheme 1.47 Synthesis of butenolide aldehyde **1.208**. *Reagents and conditions* a) (*S*)-propylene oxide, *n*-BuLi, HMPA, THF; b) $COCl_2$, Et_3N, benzene, then PhSeH, pyridine, THF/benzene; c) *n*-Bu_3SnH, AIBN, benzene, Δ; d) $RhH(CO)(PPh_3)_3$, benzene; e) HCOOH, pentane.

Alcohol **1.210** was converted to the selenocarbonate **1.211**, and then under free radical conditions a γ-lactone was formed. A ruthenium catalysed isomerisation followed by acid hydrolysis gave desired aldehyde **1.208** in 5 steps from alkyne **1.209** in 36% yield.

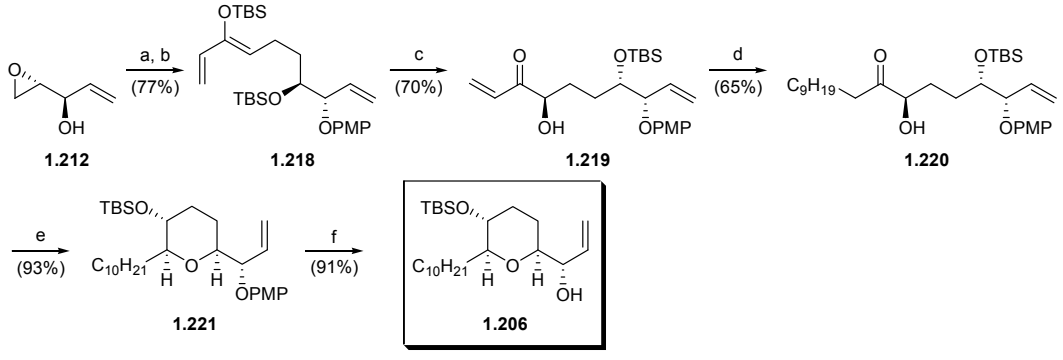
The synthesis of the THF fragment **1.217** began with alcohol **1.212** (available in one step from 1,4-pentadien-3-ol in a 45% yield) (scheme 1.48).



Scheme 1.48 Synthesis of THF fragment **1.217**. *Reagents and conditions*: a) *p*-$MeOC_6H_4OH$, DIAD, PPh_3, THF; b) CH_2=$CHCH_2MgBr$, CuCN, Et_2O; c) $Co(modp)_2$, O_2, *t*-BuOOH, *i*-PrOH; d) Tf_2O, Et_3N, CH_2Cl_2; e) $TMSC{\equiv}C(CH_2)_4MgBr$, CuI, THF, then MeOH, TBAF; f) **1.207** (6 equiv.), Et_2Zn, PhMe, Δ, then (*R*)-BINOL (1 equiv.), $Ti(Oi\text{-}Pr)_4$, THF, then **1.208** (1 equiv.); g) TIPSOTf, pyridine, DMAP; h) $(NH_4)_2Ce(NO_3)_6$, $MeCN/H_2O$.

Mitsunobu inversion of alcohol **1.212** with *p*-methoxyphenol gave epoxide **1.213**, followed by a regioselective cuprate opening delivered alcohol **1.214**. Cobalt mediated oxidative cyclisation returned THF alcohol **1.215** (*dr* ≥ 19:1).[89] Conversion of alcohol **1.215** to a triflate then displacement with a cuprate followed by *in situ* desilylation afforded alkyne **1.207**. An asymmetric addition of alkyne **1.207** to aldehyde **1.208** furnished alcohol **1.216** (*dr* = 20:1 by HPLC).[98-100] Protecting group manipulations then gave allylic alcohol **1.217** in 9 steps from 1,4-pentadien-3-ol in 11.9% yield.

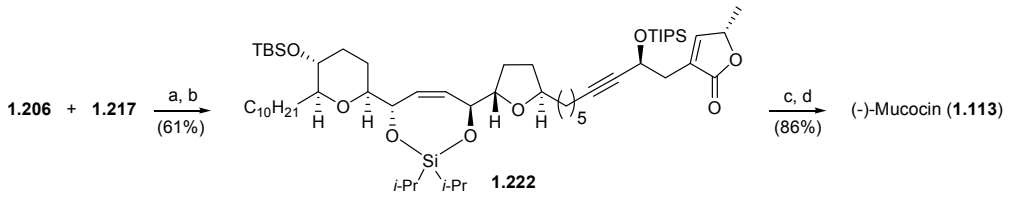
The synthesis of the THP fragment **1.206** also began with alcohol **1.212** (scheme 1.49). A Mitsunobu inversion of alcohol **1.212** with *p*-methoxyphenol, then a regioselective opening with the lithium homoenolate of TBS protected divinyl alcohol, followed by *in situ* silylation gave triene **1.218**.



Scheme 1.49 Synthesis of THP fragment **1.206**. *Reagents and conditions*: a) *p*-$MeOC_6H_4OH$, DIAD, PPh_3, THF; b) $(CH_2{=}CH)_2CHOTBS$, *s*-BuLi, THF, then TBSOTf, 2,6-lutidine; c) AD-mix-α, *t*-$BuOH/H_2O$, $MeSO_2NH_2$; d) *n*-octylMgBr, CuCN, THF; e) $BiBr_3$, *t*-$BuMe_2SiH$, MeCN, then 2,6-lutidine, TBSOTf; f) $(NH_4)_2Ce(NO_3)_6$, $MeCN/H_2O$.

Asymmetric dihydroxylation furnished ketone **1.219** (*dr* 99:1).[101] A copper-mediated 1,4-addition installed the alkyl chain which gave ketone **1.220**. With ketone **1.220** in hand Evans was set up for the key THP forming reaction, a catalytic bismuth reductive etherification reaction. Under their optimum conditions ketone **1.220** was converted to a *cis*-THP alcohol which was silylated *in situ* furnishing silyl ether **1.221** (*dr* ≥ 19:1 by NMR).[102,103] Deprotection of the methyl phenyl ether gave THP fragment **1.206** in 7 steps from 1,4-pentadien-3-ol in 13.3% yield.

Central to Evans' approach was to link temporarily fragments **1.206** and **1.217** by a silicon tether which would allow RCM. Fragments **1.206** and **1.217** were efficiently coupled with a diisopropylsilyl tether (scheme 1.50).



Scheme 1.50 Total synthesis of (–)-mucocin (**1.1**). *Reagents and conditions*: a) **1.206**, *i*-Pr_2SiCl_2 (xs), CH_2Cl_2, imidazole, then **1.217**, imidazole; b) Grubbs' first generation catalyst (1.8 equiv), 1,2-DCE, Δ; c) HF/MeCN, CH_2Cl_2; d) $TsNHNH_2$, NaOAc, 1,2-DME/H_2O, Δ.

RCM reaction of the tethered diene with Grubbs' first generation catalyst (1.8 equiv) returned silyl ether **1.222**. A global desilylation and selective hydrogenolysis gave (–)-mucocin (**1.113**) in 13 steps from 1,4-pentadien-3-ol in 6.2% yield.

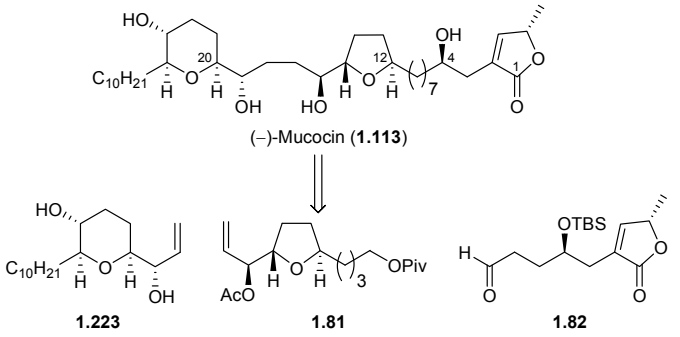
Key aspects of Evans synthesis are:-

- The non-adjacent THP-THF core constructed by silicon tethered RCM.
- C*is*-THP ring constructed by catalytic bismuth reductive etherification.[102,103]
- *Trans*-THF ring constructed by diastereoselective cobalt oxidative cyclisation.[89]
- C4 hydroxyl installed by an asymmetric acetylide addition.[98-100]

(–)-Mucocin – Mootoo (2005)

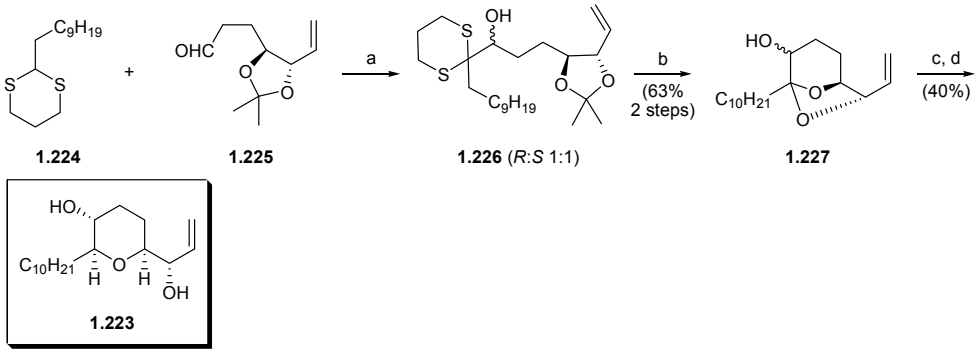
Mootoo's synthesis constructs mucocin (**1.113**) from 3 main fragments (scheme 1.51).[104] Mootoo uses a coupling strategy similar to his earlier successful total synthesis of squamostatin-C (**1.79**), with synthesis of fragments

1.81 and **1.82** previously published. THF fragment **1.81** was synthesised in 10 steps from 1,4-pentadien-3-ol in a 10.2% yield.[57] Butenolide fragment **1.82** was synthesised in 13 steps from 6-iodo-1-hexene in a 2.9% yield.[58]



Scheme 1.51 Mootoo's retrosynthetic analysis of (–)-mucocin (**1.113**).

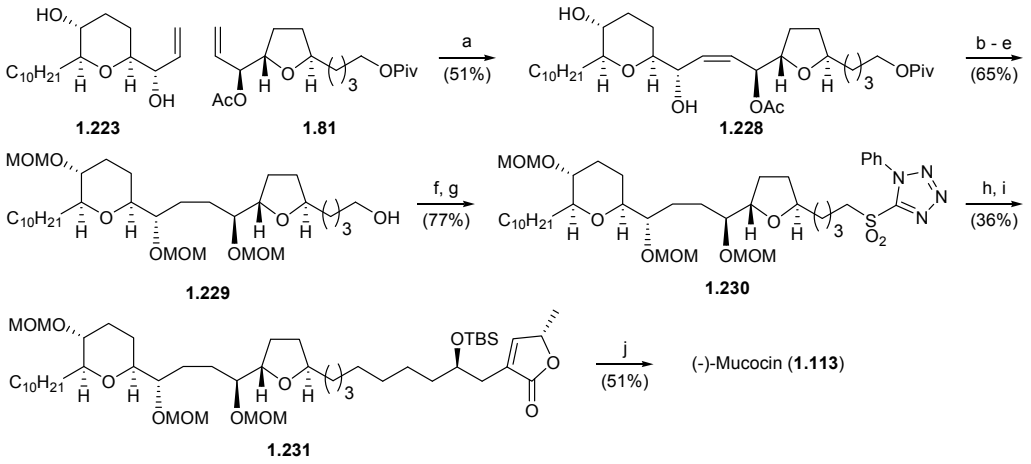
The synthesis of THP fragment **1.223** began with aldehyde **1.225** (scheme 1.52).[57] Addition of lithiated dithiane **1.224** to aldehyde **1.225** gave acetal **1.226** as an inseparable of epimers.



Scheme 1.52 Synthesis of THP fragment **1.223**. *Reagents and conditions*: a) **1.224**, *n*-BuLi, THF then **1.225**; b) $Hg(ClO_4)_2$, THF; c) column chromatography; d) Et_3SiH, BF_3•OEt_2, CH_2Cl_2.

Acetal **1.226** was exposed to mercury(ii)perchlorate which caused acetal exchange affording bicyclic acetal **1.227**, the alcohol epimers were separated using column chromatography to give the desired *R* alcohol. Reductive acetal cleavage furnished the desired fragment **1.223** as a single isomer. The THP fragment **1.223** was synthesised in 8 steps from 1,4-pentadien-3-ol in 6.7% yield.

A key aspect of Mootoo's approach was to couple fragments **1.223** and **1.81** by CM, using similar conditions used to assemble squamostatin-C.[57] Allylic alcohol fragment **1.223** and a three-fold excess of acetate **1.81** were coupled in the presence Grubbs 2nd generation catalyst (scheme 1.53).



Scheme 1.53 Total synthesis of (–)-mucocin (**1.113**). *Reagents and conditions*: a) **1.223** (1 equiv.), **1.81** (3 equiv.), $Cl_2(Cy_3P)(IMes)Ru{=}CHPh$ (10 mol %), CH_2Cl_2, rt, 18h, then $Cl_2(Cy_3P)(IMes)Ru{=}CHPh$ (10 mol %), rt, 18h; b) H_2, Pd/C, EtOAc; c) K_2CO_3, MeOH; d) MOMCl, DIPEA, CH_2Cl_2; e) NaOMe, MeOH; f) Ph_3P, DIAD, 1-phenyl-1*H*-tetrazole-5-thiol, THF; g) *m*-CPBA, $NaHCO_3$, CH_2Cl_2; h) **1.230**, LiHMDS, THF, then **1.82**; i) H_2, $Rh(Ph_3P)_3Cl$, benzene–EtOH; j) 5% AcCl, MeOH/CH_2Cl_2.

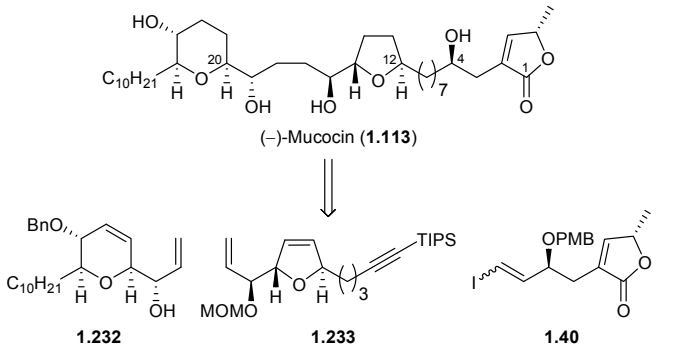
With CM product **1.228** in hand, hydrogenolysis and protecting group manipulations delivered alcohol **1.229**. Mootoo planned to couple the butenolide fragment **1.82** by Julia-Kocienski olefination. Therefore alcohol **1.229** was converted to sulfone **1.230** under classical conditions.[105] Lithiated sulfone **1.230** was then reacted with an excess of aldehyde **1.82** followed by a selective hydrogenolysis which returned MOM ether **1.231**. Finally a global deprotection gave (–)-mucocin (**1.113**) in 20 steps from 1,4-pentadien-3-ol in 0.5% yield.

Key aspects of Mootoo's synthesis are:-

- The non-adjacent THP-THF core constructed by CM.[56]
- *Cis*-THP ring established by reductive acetal cleavage.
- *Trans*-THF ring established by *trans*-selective iodoetherification reaction.[59-62]
- Butenolide portion installed by Julia-Kocienski olefination.

(–)-Mucocin – Crimmins (2006)

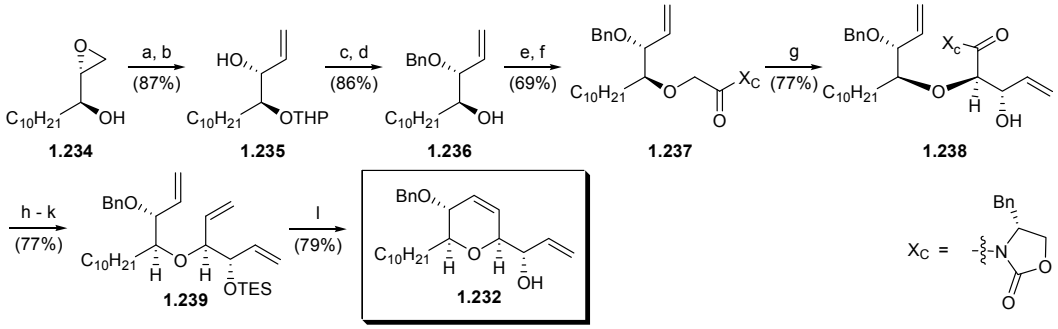
Crimmins' approach was based on a convergent coupling strategy with 3 main fragments (scheme 1.54).



Scheme 1.54 Crimmins group's retrosynthetic analysis of (–)-mucocin (**1.113**).

The THP and THF fragments **1.232** and **1.233** were synthesised using glycolate aldol-RCM chemistry similar to that used by Crimmins in the total synthesis of (+)-gigantecin (**1.1**).[43] Vinyl iodide **1.40** was a known compound from the (+)-gigantecin (**1.1**) synthesis.[43]

The synthesis of allylic alcohol **1.232** started with known alcohol **1.234** (available in two steps from undecanal in 48% yield) (scheme 1.55).[106,107]

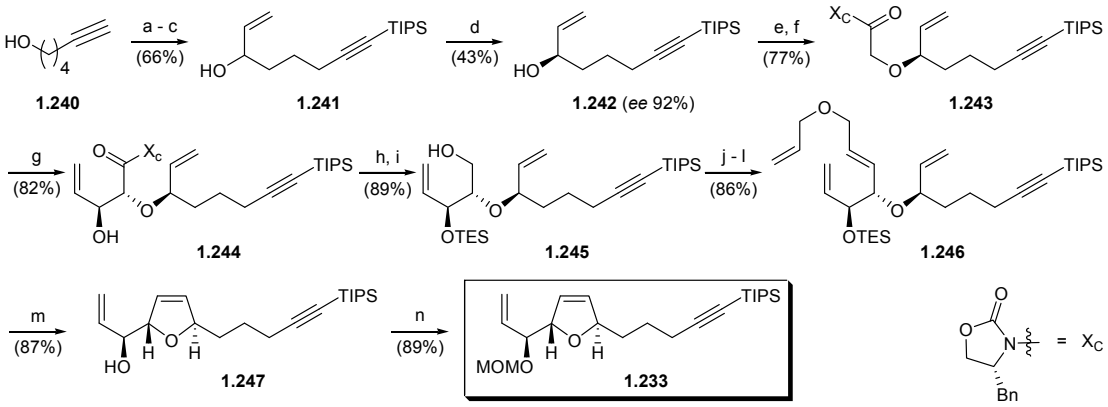


Scheme 1.55 Synthesis of THP fragment **1.232**. *Reagents and conditions*: a) DHP, PPTS, CH_2Cl_2; b) $Me_3S^+I^-$, *n*-BuLi, THF; c) NaH, BnBr, TBAI, THF; d) *p*-TsOH, MeOH, CH_2Cl_2; e) $BrCH_2CO_2H$, NaH, THF; f) Me_3CCOCl, Et_3N, THF, then (*R*)-lithio-4-benzyl-oxazolidin-2-one; g) $TiCl_4$, DIPEA, NMP, acrolein, CH_2Cl_2; h) TESOTf, 2,6-lutidine, CH_2Cl_2; i) $LiBH_4$, MeOH, Et_2O; j) Swern oxidation; k) Ph_3PCH_3Br, KO*t*-Bu, THF; l) $Cl_2(Cy_3P)(IMes)Ru{=}CHPh$ (10 mol %), benzene, then *p*-TsOH, MeOH.

Alcohol **1.234** was protected as its THP ether then exposured to $Me_2S{=}CH_2$ affording allylic alcohol **1.235**. Protection group manipulations gave benzyl ether **1.236**. The sodium alkoxide of allylic alcohol **1.236** was alkylated with sodium bromoacetate, then converted to a mixed anhydride and reacted with lithiated oxazolidinone to afford glycolate **1.237**. Under their optimum aldol conditions, reaction between glycolate **1.237** and acrolein gave *syn*-aldol product **1.238** (*dr* 11:1).[43] Silylation of the free hydroxyl, reductive cleavage of the glycolate, Swern oxidation of the resulting primary alcohol then Wittig olefination gave diene **1.239**.

RCM using Grubbs 2nd generation catalyst with acidic work up regioselectivity gave THP fragment **1.232** in 14 steps from undecanal in a 11.6% yield.[108]

The synthesis of the THF fragment **1.233** began with alcohol **1.240** (scheme 1.56). Silylation of alkyne **1.240**, Swern oxidation of the primary alcohol followed by treatment with vinyl Grignard yielded racemic alcohol **1.241**.

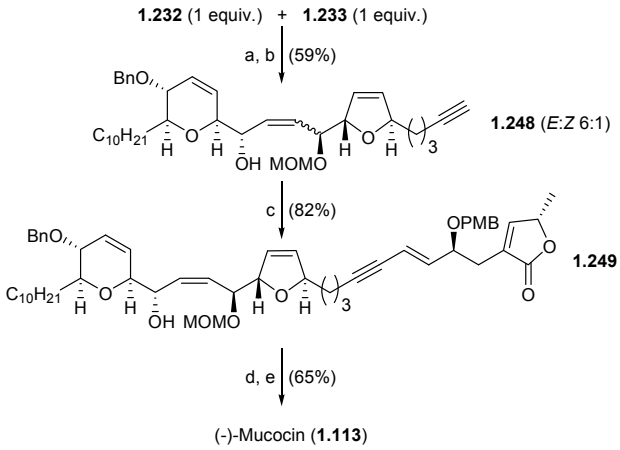


Scheme 1.56 Synthesis of THF fragment **1.233**. *Reagents and conditions*: a) EtMgCl, TIPSCl, THF; b) Swern oxidation; c) CH_2=CHMgBr, THF; d) Ti(O*i*-Pr)$_4$, (+)-DCHT, *t*-BuOOH, CH_2Cl_2; e) $BrCH_2CO_2H$, NaH, THF; f) Me_3CCOCl, Et_3N, THF, then (*R*)-lithio-4-benzyl-oxazolidin-2-one; g) $TiCl_4$, DIPEA, NMP, acrolein, CH_2Cl_2; h) TESOTf, 2,6-lutidine, CH_2Cl_2; i) $LiBH_4$, MeOH, Et_2O; j) Swern oxidation then Ph_3P=$CHCO_2Me$; k) DIBAL-H, Et_2O; l) allyl bromide, NaH, THF; m) $Cl_2(Cy_3P)(IMes)Ru$=CHPh (10 mol %), benzene, then *p*-TsOH, MeOH; n) MOMCl, DIPEA, DMAP, CH_2Cl_2.

Sharpless kinetic resolution on secondary alcohol **1.241** delivered the *R* alcohol **1.242** (ee 92%, HPLC of glycolate **1.243**).[109] As previously described, alcohol **1.242** was converted to glycolate **1.243**. Again under their optimum aldol conditions, reaction between glycolate **1.243** and acrolein provided *syn*-aldol product **1.244** (*dr* 4:1). Silylation and reductive cleavage of the glycolate returned alcohol **1.245**. To overcome selectivity problems in the forthcoming RCM step, Hoye's "activation" strategy was employed.[110] The strategy required a three-step conversion of alcohol **1.245** to tetraene **1.246**. With tetraene **1.246** in hand ruthenium carbene insertion could be controlled, therefore exposure of tetraene **1.246** to Grubbs 2nd generation catalyst followed by acidic work up, gave alcohol **1.247** in excellent yield. A MOM protection of alcohol **1.247** then provided THF fragment **1.233** in 14 steps from alcohol **1.240** in 3.3% overall yield.

The steric hindrance of the MOM ether group deactivated allylic alcohol **1.233** to metathesis relative to allylic alcohol **1.323**. The differences in reactivity

allowed successful CM coupling using Hoveyda-Grubbs catalyst (scheme 1.57).[56]



Scheme 1.57 Total synthesis of (–)-mucocin (**1.113**). *Reagents and conditions*: a) Hoveyda-Grubbs catalyst (10 mol %), CH_2Cl_2; b) TBAF, THF; c) **1.40**, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N; d) $TsNHNH_2$, NaOAc, 1,2-DME/H_2O, Δ; e) BF_3•OEt_2, Me_2S.

The CM product was desilylated delivering alkyne **1.248** which was used in a Sonogashira coupling with iodide **1.40** to secure enyne **1.249**.[40] Selective global hydrogenation and deprotection gave (–)-mucocin (**1.113**) in 19 linear steps from alcohol **1.240** in 1.0% yield.

Key aspects of Crimmins' synthesis are:-

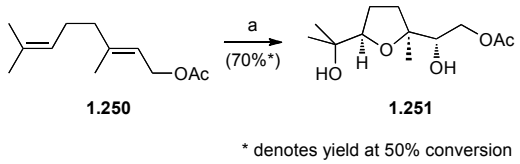
- The non-adjacent THP-THF core constructed by CM.[56]
- C*is*-THP and *trans*-THF rings constructed by glycolate aldol-RCM chemistry.[43]
- Butenolide portion installed by Sonogashira coupling.[40]

Conclusion

The *Annonaceous* acetogenins family of natural products have sparked great interest both biologically and synthetically. There is still much to be learnt about their inhibitive effects of mitochondrial complex 1, and selective cytotoxicity in cancerous cells that might lead to significant advances in therapeutics. Synthetically *Annonaceous* acetogenins have also attracted very substantial interest. The synthesis of the non-adjacent *bis*-THF and non-adjacent THP-THF classes still represents a considerable challenge. Multiple chiral centres and introduction of the THF-THF/THP-THF core has inspired the synthetic chemist to invent a plethora of adaptable and imaginative solutions.

1.6 Permanganate Oxidative Cyclisation of 1,5-dienes

Permangante oxidative cyclisation of 1,5-dienes is now an established method to synthesize *cis*-2,5-*bis*(hydroxyalkyl) tetrahydrofurans (THF diols). The following section will give a brief introduction to the reaction and highlight some key discoveries. Klein and Rojan made the first significant observation in 1965.[111] They described the oxidation of various 1,5-dienes by potassium permanganate. Importantly, for the first time the products from the permangante oxidation were structurally assigned as THF diols, which were obtained in a stereospecific manner (scheme 1.58).

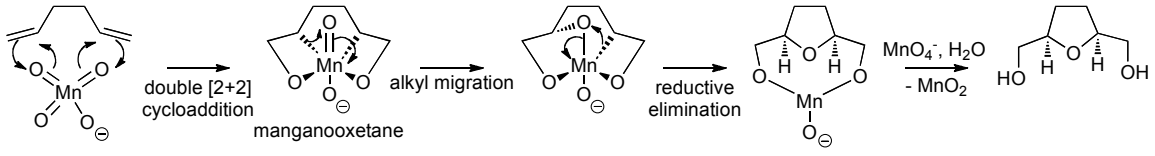


1.250 **1.251**

* denotes yield at 50% conversion

Scheme 1.58 Oxidative cyclisation of 1,5-dienes by Klein and Rojan. *Reagents and conditions:* a) $KMnO_4$ (1.5 equiv), 10% aq acetone, CO_2 stream, 0 °C.

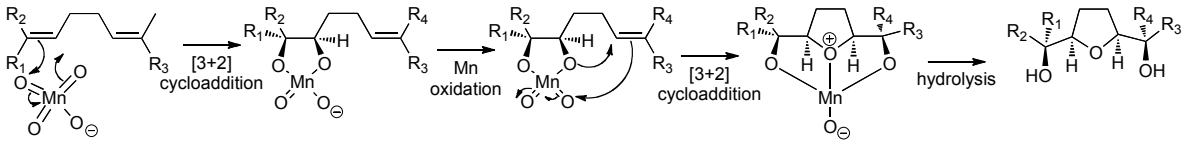
There was no significant work until 1979, where independent work by Baldwin and Walba discussed mechanistic aspects of the permanganate oxidative cyclisation of 1,5-dienes.[112,113] Both supported the observations made by Klein and Rojan with respect to the stereospecific nature of permanganate oxidative cyclisation, delivering *cis*-2,5-*bis*(hydroxyalkyl) tetrahydrofurans. Baldwin oxidised deuterium labelled (*E*,*E*) and (*E*,*Z*)-hexa-1,5-dienes, and Walba oxidised the three isomeric forms of octa-2,6-diene. While, both agreed on the stereospecifically of the reaction, their proposed mechanisms for the reaction differed. Walba preferred to describe the permanganate oxidative cyclisation reaction going through a 'Sharpless type' mechanism with organometallic intermediates (scheme 1.59).



Scheme 1.59 Walba's proposed mechanism.

Walba argued a double [2+2] cycloaddition gave a manganooxetane intermediate, where alkyl migration with retention of configuration and reductive

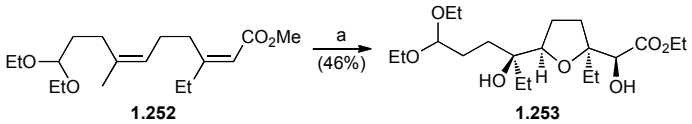
elimination gave a *cis*-THF diol. Baldwin's mechanism began with a [3+2] cycloaddition producing a manganese(v) species. Subsequent oxidisation to manganese(vi), and a further [3+2] cycloaddition would deliver a manganese diester, which is hydrolysised returning a *cis*-THF diol (scheme 1.60).



Scheme 1.60 Baldwin's proposed mechanism.

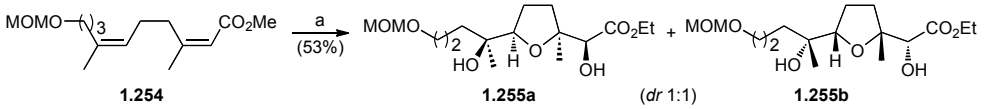
The Baldwin mechanism is more reasonable based on related osmium tetroxide and ruthenium tetroxide chemistry, and is supported by density functional theory calculations.[114-120]

The first synthetic application was by Walba and Edwards in their synthesis of ionophore monesin.[121] Oxidative cyclisation of diene **1.252** gave a racemic mixture of *cis*-THF diols **1.253** (scheme 1.61).



Scheme 1.61 Synthesis of THF diol **1.253**. *Reagents and conditions*: a) $KMnO_4$, 10% aq acetone, CO_2 stream, –30 °C.

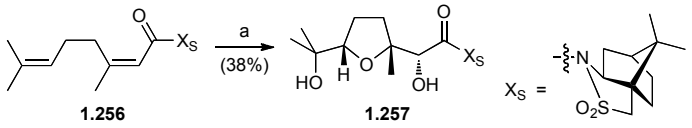
Initial problems with the work up of the reaction were overcome which returned diol **1.253** in reasonable yield. Spino and Weiler continued research in their synthesis of ionomycin.[122] Diene **1.254** was cyclised using similar conditions to Walba (scheme 1.62).



Scheme 1.62 Synthesis of THF diols **1.255a**/**b**. *Reagents and conditions*: a) $KMnO_4$, 10% aq acetone, CO_2 stream, –25 °C.

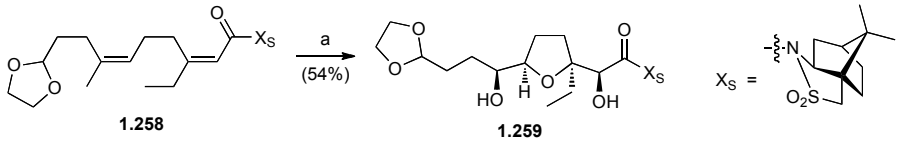
THF diols **1.255a**/**b** were returned as a racemic mixture. Separation of the diastereoisomers was achieved by derivatisation with (*S*)-(+)-*O*-acetyl mandelic acid. Although permanganate oxidative cyclisation of 1,5-dienes had been shown to successfully return *cis*-THF diols, there had been no way to control absolute stereochemistry. This was overcome by Walba, oxidative cyclisation of a 1,5-

diene **1.256** functionised with Oppolzer's camphor sultam returned THF diol **1.257** as the major diastereoisomer in reasonable yield and good diastereoselectivity (*dr* > 9:1) (scheme 1.63).[123]



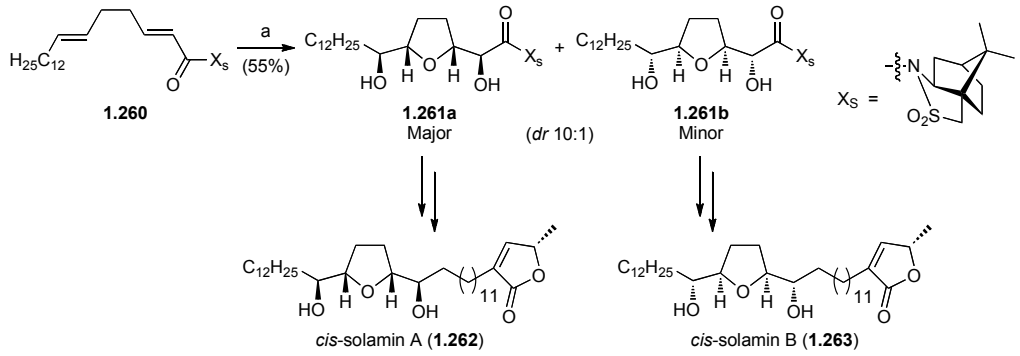
Scheme 1.63 Asymmetric oxidative cyclisation of 1,5-dienes. *Reagents and conditions*: a) $KMnO_4$, 10% aq acetone, CO_2 stream, –30 °C.

Facial selectivity originates from initial attack of permanganate at the electron deficient alkene, where the approach of permanganate is governed by the proximal camphor sultam auxiliary. The facial selectivity matched the observations made by Oppolzer in the osmylation of sultam-functionalized enoates.[124] Kocienski and Brown applied this strategy to their synthesis of a salinomycin fragment, which required intermediate **1.259**.[125,126] Oxidative cyclisation of diene **1.258** delivered THF diol **1.259** as an inseparable mixture of diastereoisomers (*dr* 6:1) (scheme 1.64).



Scheme 1.64 Synthesis of THF diol **1.259**. *Reagents and conditions*: a) $KMnO_4$, acetate buffer (pH = 6), acetone/HOAc/H_2O, –35 °C.

Significantly, previously well-established reaction conditions for the oxidative cyclisation were in their case problematic. This lead to optimisation of reaction conditions where they believe pH was playing a significant role. Brown continued research in stereo-controlled permanganate oxidative cyclisation of 1,5-dienes with his own group. A classic example of the work is shown in the total synthesis of *cis*-solamin (scheme 1.65).[127-129] Brown continued to use the camphor sultam auxiliary to gain stereo-control. Oxidative cyclisation of un-branched 1,5-diene **1.260** gave THF diol **1.261a** as the major product in good diastereoselectivity, which correctly set up 4 stereocentres in one synthetic step.



Scheme 1.65 Synthesis of THF diol **1.261a**. *Reagents and conditions*: a) $KMnO_4$ (1.4 equiv), AcOH (8 equiv), Adogen 464 (0.1 equiv), EtOAc, −30 to 0 °C.

From THF diol intermediates **1.261a**/**b** the total synthesis of *cis*-solamin A (**1.262**) and *cis*-solamin B (**1.263**) were completed. Subsequent chiral HPLC studies confirmed that naturally isolated *cis*-solamin was a mixture of *cis*-solamin A (**1.262**) and *cis*-solamin B (**1.263**).[129] The key contributions by the Brown group have been optimisation of reaction conditions and extension of synthetic applications. Interestingly, Brown had also published an asymmetric permanganate oxidative cyclisation, where an achiral diene was oxidised by permanganate in the presence of a chiral phase transfer catalyst, which induced good levels of enantioselectivity in the THF diol product.[130]

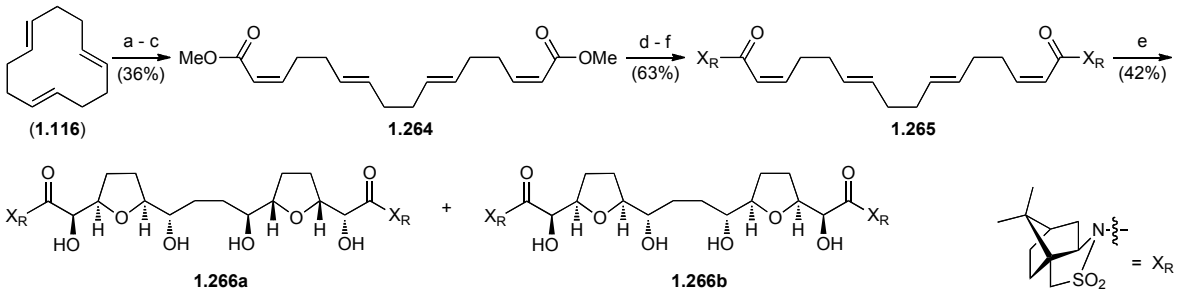
1.7 Southampton Approach to (+)-*cis*-Sylvaticin

Brown had already shown the application of stereo-controlled permanganate oxidative cyclisation of 1,5-dienoyl systems in the synthesis of *cis*-THF *Annonaceous* acetogenin natural products. To date membranacin (adjacent *bis*-THF), membrarollin (adjacent *bis*-THF) and *cis*-solamin (*mono*-THF) have been synthesised using this methodology.[128,131-133] A synthesis of *cis*-sylvaticin (**1.100**) where stereo-controlled permanganate oxidative cyclisation of 1,5-dienes was a key step, would extend the utility of the reaction, while also posing fresh challenges with construction of the non-adjacent *bis*-THF core and installation of the C4 hydroxyl.

Double Oxidative Cyclisation Approach

Initial activity from the Brown lab came from Dr Riaz Bhunnoo, who used a naked skeleton approach to install the non-adjacent *bis*-THF core. The synthesis

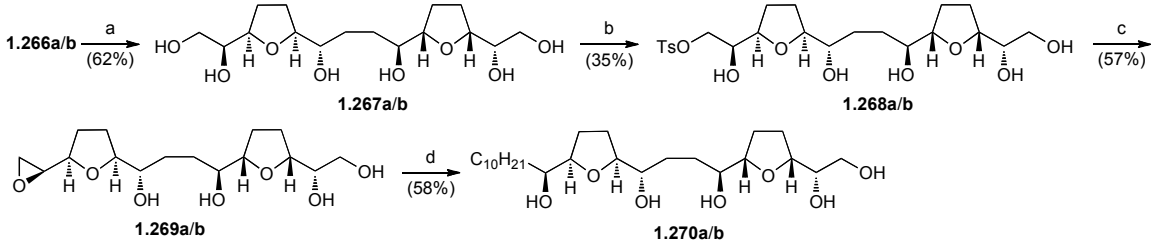
began with (*E*,*E*,*E*)-cyclododecatriene (**1.116**), a selective *mono*-dihydroxylation, periodate cleavage then double *cis*-selective olefination delivered diester **1.264** (scheme 1.66).[54]



Scheme 1.66 Synthesis of *bis*-THF tetraols **1.266a/b**. *Reagents and conditions*: a) OsO_4, NMO, H_2O, CH_2Cl_2; b) $NaIO_4$-SiO_2, H_2O, CH_2Cl_2; c) $(PhO)_2POCH_2COOMe$, KHMDS, 18-crown-6, THF; d) NaOH, $NaHCO_3$, MeOH/H_2O (1:3), then citric acid (aq), HCl (aq); e) $(COCl)_2$, DMF, CH_2Cl_2; f) (1*S*,2*R*)-camphorsultam, NaH, toluene; e) $NaMnO_4$, AcOH/acetone/buffer.

Hydrolysis of diester **1.264**, followed by acid chloride formation then coupling with the sodium salt of (1*S*,2*R*)-camphorsultam furnished tetraene **1.265**. With tetraene **1.265** in hand, the key double permanganate oxidative cyclisation reaction provided tetraols **1.266a**/**b** as an inseparable mixture of isomers (**1.266a**:**1.266b** 3:1). In the oxidative cyclisation step, seven of the desired stereocentres had been correctly installed giving a C_2 symmetric intermediate **1.266a** in 7 steps in 7.1% yield.

Two approaches were attempted to desymmetrise intermediate **1.266a**. Tetraols **1.266a**/**b** were reductively cleaved which gave hexaols **1.267a**/**b**, a selective *mono*-tosylation followed by ring closing substitution successfully gave desymmetrised epoxides **1.269a**/**b** (scheme 1.67).

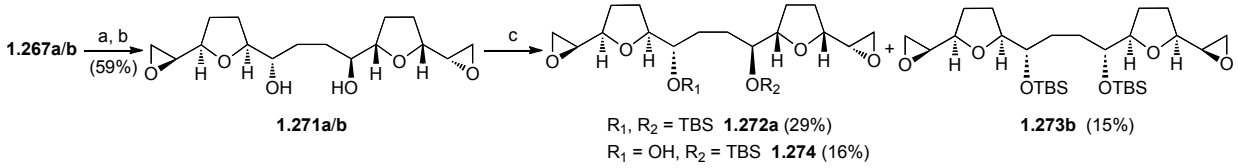


Scheme 1.67 Synthesis of *bis*-THF pentols **1.270a/b**. *Reagents and conditions*: a) $LiBH_4$, THF; b) Bu_2SnO, dioxane, Δ, then TsCl; c) DBU, CH_2Cl_2; d) nonylmagnesium bromide, CuI, THF.

Cuprate addition to epoxide **1.269a**/**b** installed the alkyl chain. Pentaol **1.270a**/**b** was submitted to a one-off periodate cleavage followed by olefination. By TLC and crude ^1H NMR results were encouraging, but due to the lack of material no

firm conclusion could be obtained. Although desymmetrisation was successful the route was hampered by poor yields and an inability to separate diastereoisomers.

A second approach was therefore investigated. Hexaols **1.267a**/**b** were selectively *bis*-tosylated followed by ring closing substitution delivering *bis*-epoxides **1.271a**/**b** (scheme 1.68).



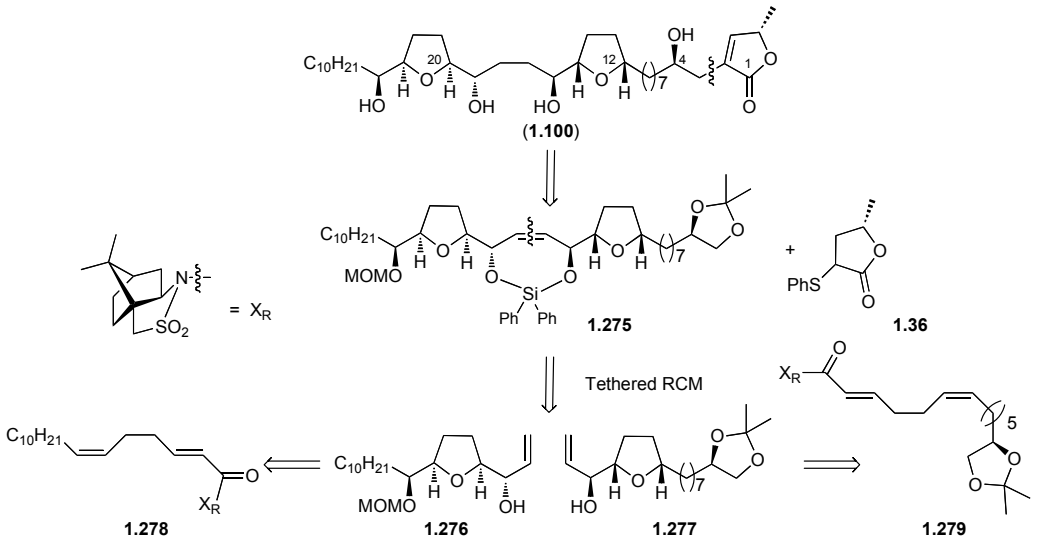
Scheme 1.68 Synthesis of *bis*-THF silyl ether **1.272a**. *Reagents and conditions*: a) Bu_2SnO, dioxane, Δ, then TsCl; b) DBU, CH_2Cl_2; c) 2,6-lutidine, TBSOTf, CH_2Cl_2.

Silylation of *bis*-epoxides **1.271a**/**b** gave a mixture of products, but allowed separation of diastereoisomers by column chromatography. A one-off cuprate addition to *bis*-epoxide **1.272a** caused decomposition of material. Due to lack of material it was not possible to explore the cuprate addition further.

The double permanganate oxidative cyclisation approach was attractive due to the relatively short access to complex hexaols **1.267a**/**b**. However, the approach was hampered by low yields and desymmetrisation problems, so it was deemed more profitable to explore a THF fragment coupling strategy.

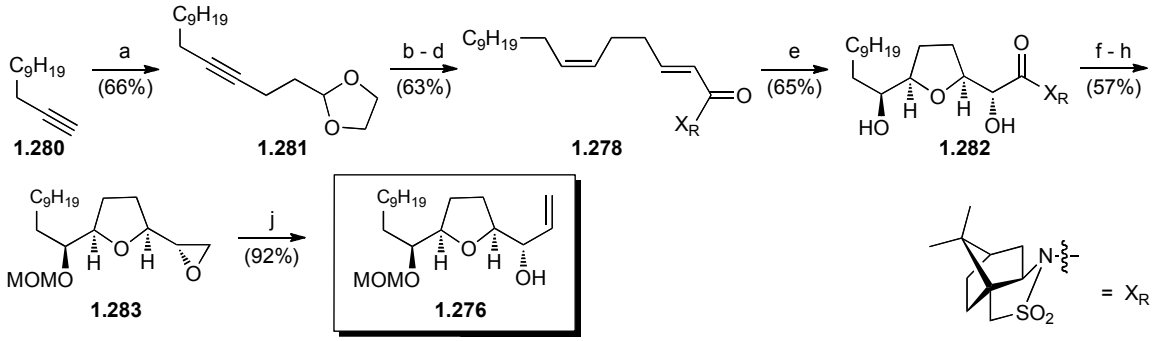
Tethered RCM Approach

The tethered RCM approach required synthesis of 3 main fragments **1.276**, **1.277** and **1.36**. The 2 THF fragments **1.276** and **1.277** would be synthesised from suitable 1,5-diene precursors by permanganate oxidative cyclisation. The key coupling reaction would be a silicon tethered RCM reaction described by Evans (scheme 1.69).[98]



Scheme 1.69 Retrosynthetic analysis of *cis*-sylvaticin.

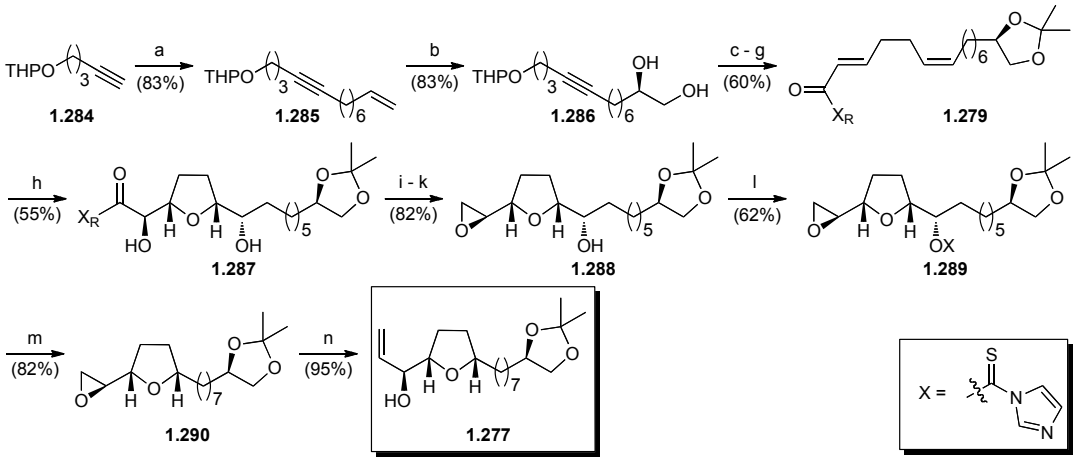
Work on this strategy was started by Dr Stephen Kemp. Fragment **1.276** synthesis began by alkylation of alkyne **1.280** (scheme 1.70). The resulting alkyne **1.281** was partially reduced, followed by hydrolysis of the acetal and olefination with camphorsultam phosphonates delivering 1,5-diene **1.278**.



Scheme 1.70 Synthesis of fragment **1.276**. *Reagents and conditions*: a) *n*-BuLi, HMPA, THF, then 2-(2-bromoethyl)-1,3-dioxolane; b) H_2, Lindlar catalyst, quinoline, hexane; c) AcOH/H_2O 4:1, Δ; d) $(EtO)_2POCH_2COX_R$, Et_3N, LiCl, MeCN; e) $KMnO_4$, AcOH/acetone (2:3); f) $NaBH_4$, THF/H_20 (3:1); g) (i) Bn_2SnO, benzene, Δ; (ii) TsCl, TBAB; h) DBU, CH_2Cl_2; i) MOMCl, DIPEA, CH_2Cl_2; j) $Me_3S^+I^-$, *n*-BuLi, THF.

Oxidative cyclisation of 1,5-dienoyl **1.278** with permanganate gave THF diol **1.282** as the major diastereoisomer (*dr* 9:1 by crude ^{1}H NMR). THF diol **1.282** was reductively cleaved, and a selective *mono*-tosylation allowed ring closing substitution followed by protection of the alcohol as its MOM ether **1.283**. Epoxide **1.283** was converted to fragment **1.276** using the trimethylsulfonium ylide.

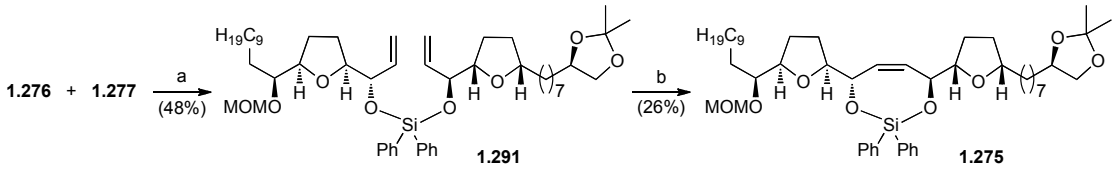
Fragment **1.277** synthesis began by alkylation of alkyne **1.284** with 8-bromo-oct-1-ene. A Sharpless dihydroxylation on alkene **1.285** installed the C4 hydroxyl (*ee* ≈ 80%) (scheme 1.71).



Scheme 1.71 Synthesis of fragment **1.277**. *Reagents and conditions*: a) *n*-BuLi, HMPA, THF, 8-bromooct-1-ene; b) AD-mix-*β*, *t*-BuOH/H_2O; c) MeOH, *p*-TsOH; d) acetone, *p*-TsOH; e) H_2, Lindlar catalyst, quinoline; f) Dess-Martin periodinane, CH_2Cl_2; g) $(EtO)_2POCH_2COX_R$, Et_3N, LiCl, MeCN; h) $KMnO_4$, AcOH/acetone (2:3); i) $NaBH_4$, THF/H_20 (3:1); j) Bn_2SnO, benzene, Δ, then TsCl, TBAB; k) DBU, CH_2Cl_2; l) thiocarbonyldiimidazole, DMAP, CH_2Cl_2; m) $(n\text{-}Bu_4N)_2S_2O_8$, HCO_2Na, Na_2CO_3, DMF; n) $Me_3S^+I^-$, *n*-BuLi, THF.

The THP group was removed, 1,2-diol **1.286** was protected as its acetonide, followed by Lindlar reduction of the alkyne, subsequent Dess-Martin oxidation and olefination furnished 1,5-dienoyl **1.279**. Oxidative cyclisation of 1,5-dienoyl sultam **1.279** with permanganate gave THF diol **1.287** as the major diastereoisomer (*dr* 9:1). THF diol **1.287** was reductively cleaved, then selective *mono*-tosylation allowed ring closing substitution delivering alcohol **1.288**. A radical deoxygenation via the thiocarbonyl imidazole derivative **1.289** gave epoxide **1.290**. Epoxide **1.290** was converted to fragment **1.277**.

Fragments **1.276** and **1.277** were coupled using a diphenylsilyl tether (scheme 1.72). RCM reaction using Grubbs 2nd generation catalyst gave the desired RCM product **1.275** in poor yield.



Scheme 1.72 Synthesis of alkene **1.275**. *Reagents and conditions*: a) **1.276**, Ph_2SiCl_2, DIPEA, CH_2Cl_2, then **1.277**, DIPEA, DMAP; b) Grubbs 2nd generation catalyst (20 mol %), C_6D_6, 100 °C.

The THF fragment coupling approach was highly attractive, and excellent progress had been made but there were a number of problems with the synthesis. The synthesis of fragment **1.277** was long at 14 steps and the thiocarbonyl imidazole formation/radical deoxygenation protocol was unreliable. Installation of the C4 hydroxyl by asymmetric dihydroxylation of terminal alkene **1.285** proceeded with poor stereoselectivity. In addition protection of the terminal 1,2-diol as an acetonide caused concern for later stage protecting group manipulations. Finally, for the THF fragment coupling approach to be viable an improvement to the tethering-RCM chemistry was required.

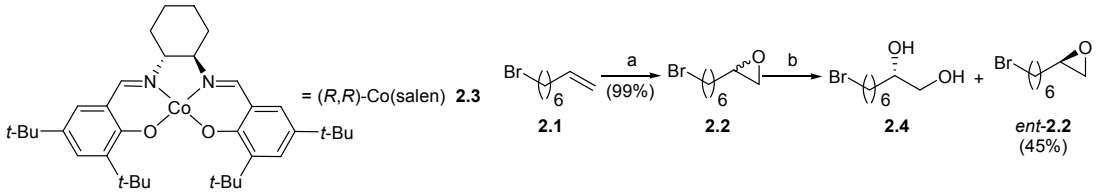
Chapter 2: Results and Discussion

2.1 Kinetic Resolution Chemistry

Hydrolytic Kinetic Resolution

Investigations into the optimisation of Dr Kemp's proposed synthesis of *cis*-sylvaticin (**1.100**) required an improved method for installing the C4 hydroxyl. In the original work a Sharpless asymmetric dihydroxylation on terminal alkene **1.285** installed the C4 hydroxyl, but with disappointing *ee*. Also the resulting 1,2-diol required additional steps for orthogonal protection. Initial work focused on the hydrolytic kinetic resolution (HKR) chemistry of terminal epoxides described by Jacobsen.[134]

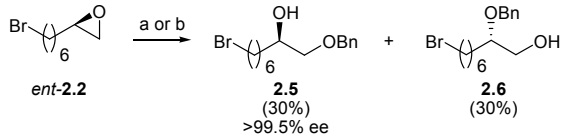
Bromo-olefin **2.1** was used as it had the appropriate alkyl spacer, while the bromide gave a suitable handle for extension. Following the Haufe procedure, epoxidation of commercially available olefin **2.1** gave racemic epoxide **2.2** (scheme 2.1).[135] With racemic epoxide **2.2** in hand the HKR chemistry was studied.



Scheme 2.1 Synthesis of enantio-enriched epoxide *ent*-**2.2**. *Reagents and conditions*: a) *m*-CPBA, CH_2Cl_2, 0 °C → rt; b) (i) (*R*,*R*)-Co(salen) **2.3** 0.5 mol %, AcOH, CH_2Cl_2, (ii) **2.2**, IPA, H_2O (0.55 equiv.).

Commercially available (*R*,*R*)-Co(salen) **2.3** was oxidised by air in the presence of acetic acid which gave the active Co(III)-OAc catalyst. Exposure of racemic epoxide **2.2** to the Co(III)-OAc catalyst in the presence of H_2O (0.55 equiv.) gave epoxide *ent*-**2.2** (*ee* determined in next step, the sense of the enantioselectivity was assumed to follow well established literature precedent).[134] Our plan was to carry out a regioselective opening of epoxide *ent*-**2.2** with benzyl alcohol. This would successfully unmask the C4 hydroxyl while affording orthogonal protection the 1° alcohol. Under Lewis acid conditions epoxide *ent*-**2.2** was opened with

benzyl alcohol which gave the desired benzyl ether **2.5** (*ee* >99% by HPLC) in poor regioselectively (1:1) and only moderate yield (scheme 2.2).



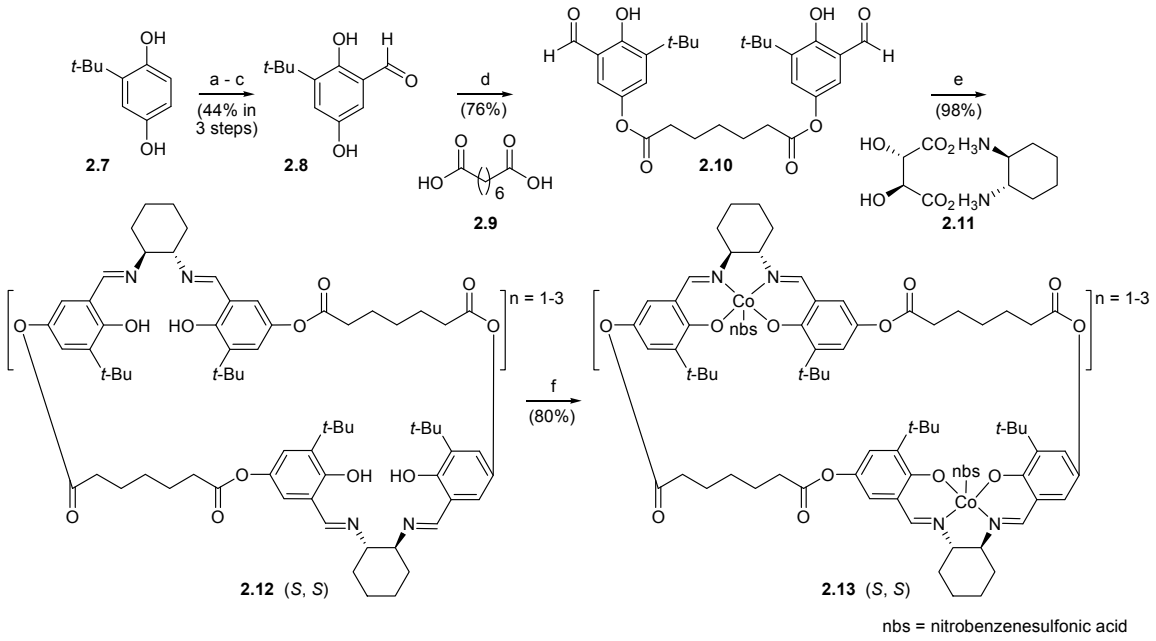
ent-**2.2** **2.5** (30%) >99.5% ee **2.6** (30%)

Scheme 2.2 Synthesis of benzyl ether **2.5**. *Reagents and conditions*: a) BF_3•OEt_2, BnOH, CH_2Cl_2, –70 °C → rt; b) $ClRh(Ph_3P)_3$, benzaldehyde, Et_3N, $B(Et)_3$.

Opening of epoxide *ent*-**2.2** with the alkoxide of benzyl alcohol was attempted but no reaction was witnessed. The regioselectivity was a major problem as regioisomers **2.5**, **2.6** and benzyl alcohol were difficult to separate by MPLC. A ruthenium catalysed reductive coupling described by Jamison was investigated.[136] Following the Jamison procedure epoxide *ent*-**2.2** was coupled with benzaldehyde to give benzyl ether **2.5** (*ee* not determined) in disappointing yield (45%) but with excellent regioselectivity (>95:5 by ^{1}H NMR). Benzyl ether **2.5** was an extremely attractive intermediate which would be required on a 10 to 20 gram scale, but the current route would be impractical due to the cost of the starting olefin **2.1** and inefficient opening of epoxide *ent*-**2.2**.

Oligomeric Co(salen) Catalyst

Further work by Jacobsen had shown kinetic resolution chemistry with an oligomeric Co(salen) catalyst **2.13**.[137,138] The more active oligomeric Co(salen) catalyst **2.13** had allowed direct opening of 2-butyloxirane with benzyl alcohol during the kinetic resolution.[138] Following the Jacobsen procedure the synthesis of the oligomeric Co(salen) catalyst **2.13** began with a selective *mono*-TIPS protection of *bis*-phenol **2.7** (scheme 2.3).[138]



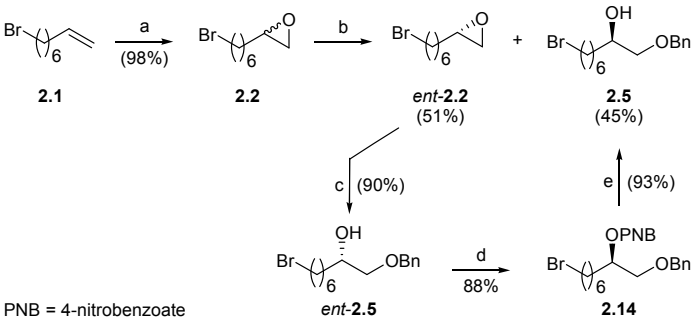
Scheme 2.3 Synthesis of oligomeric (*S*,*S*)-Co(salen) catalyst **2.13**. *Reagents and conditions*: a) TIPSCl, DMAP, imidazole, CH_2Cl_2; b) $SnCl_4$, 2,6-lutidine, paraformaldehyde, toluene; c) TBAF, THF; d) **2.9**, DIC, DMAP, CH_2Cl_2, DMF, 0 °C → rt; e) **2.11**, K_2CO_3, THF/water, Δ; f) (i) $Co(OAc)_2$, MeOH/toluene; (ii) nbs•H_2O, CH_2Cl_2.

The resulting TIPS ether was acetylated under Lewis acid conditions which was followed by desilylation to furnish aldehyde **2.8**. 2 Equivalents of aldehyde **2.8** were successfully coupled with *bis*-acid **2.9** selectively yielding *bis*-aldehyde **2.10**. Imide formation between (*S*,*S*) *bis*-ammonium salt **2.11** and *bis*-aldehyde **2.10** gave (*S*,*S*) oligomeric salen ligand **2.12**. Insertion of Co(II) into (*S*,*S*) oligomeric salen ligand **2.12** followed by oxidation by air in the presence of nitrobenzenesulfonic acid gave (*S*,*S*) oligomeric Co(salen) catalyst **2.13**. Either enantiomer of *bis*-ammonium salt **2.11** may be used which gave an analogous route to both (*S*,*S*) and (*R*,*R*) versions of the oligomeric Co(salen) catalyst. With the desired enantiomers of oligomeric Co(salen) in hand the modified kinetic resolution studies were commenced.

Modified Kinetic Resolution

Bromo-olefin **2.1** was epoxidised but this time a catalytic rhenium method was preferred to *m*-CPBA (scheme 2.3).[139,140] Experimental observations suggested the presence of benzoic acid gave disappointing results in the subsequent kinetic resolution step. Presumably this was due to catalyst deactivation through ion exchange, as the negative counterion in the active

cobalt catalyst has been shown to affect kinetic resolution.[138] The advantage of the rhenium method is the by-product from epoxidation is H_2O rather than benzoic acid.



Scheme 2.4 Synthesis of chiral building block **2.5**. *Reagents and conditions*: a) $MeReO_3$ 0.5 mol %, pyrazole, 30% H_2O_2 aq, CH_2Cl_2, rt, 24h; b) (*S*,*S*) **2.13** 0.25 mol %, BnOH (0.45 equiv.), MeCN, 4 °C, 16h; c) (*R*,*R*) **2.13** 0.25 mol %, BnOH (0.9 equiv.), MeCN, 4 °C, 16h; d) Ph_3P, DIAD, *p*-nitrobenzoic acid, THF; e) NaOH, MeOH.

When epoxide **2.2** was exposed to benzyl alcohol (0.45 eq.) in the presence of (*S*,*S*) oligomeric Co(salen) catalyst **2.13** the desired benzyl ether **2.5** was delivered in excellent yield (*ee* >99% by chiral HPLC, the sense of the enantioselectivity was assumed to follow well established literature precedent).[138] The un-reacted epoxide *ent*-**2.2** which was recovered presumably in high enantioselectivity, was then opened with benzyl alcohol (0.9 eq.) in the presence of the (*R*,*R*) oligomeric Co(salen) catalyst **2.13** gave benzyl ether *ent*-**2.5** (*ee* > 99% by chiral HPLC). Benzyl ether *ent*-**2.5** was converted to the desired chiral building block **2.5** via an efficient Mitsunobu-hydrolysis procedure.[45]

For the first time there was an extremely efficient route for chiral building block **2.5** (84% yield from alkene **2.1**, 5 steps). More importantly the C4 hydroxyl of *cis*-sylvaticin had been installed with excellent enantioselectivity, plus the terminal diol had been orthogonally protected with a robust benzyl group.

Conclusion

- HKR route gave the desired chiral building block **2.5** in excellent *ee* but was impractical due to low yields and poor regiocontrol in the epoxide opening.
- An efficient alcoholytic kinetic resolution approach to chiral building block **2.5** was achieved installing the C4 hydroxyl group with excellent

enantioselectiviy (*ee* > 99%), while orthogonally protecting the terminal diol.

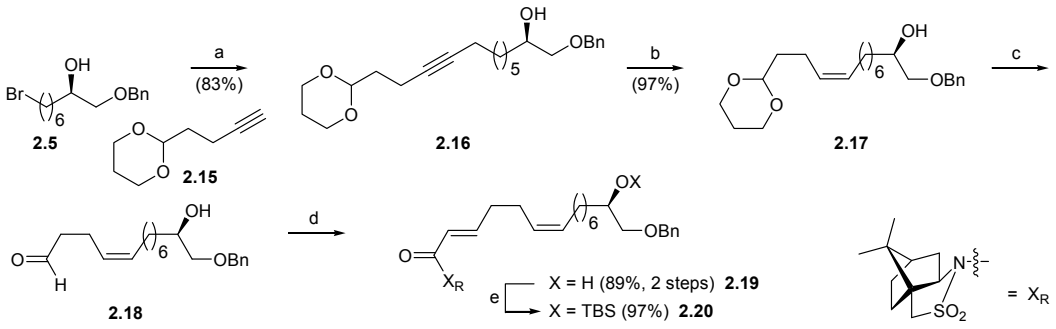
With the C4 hydroxyl and terminal diol protection issues addressed attention was focused on synthesis of a *cis*-sylvaticin C3-C17 THF fragment.

2.2 Synthesis of *cis*-Sylvaticin C3-C17 THF Fragment

Oxidative Cyclisation Precursor

Within the group synthesis of *cis*-THF diols through oxidative cyclisation of 1,5-diene systems with permanganate is well established.[128,131,133] Initial goals were to convert chiral building block **2.5** to a suitable 1,5-diene for oxidative cyclisation.

The synthesis began by alkylation of a 2-fold excess of lithiated alkyne **2.15** with chiral building block **2.5** (scheme 2.5). Alkylation was achieved in good yield when HMPA was used as a co-solvent. Partial reduction of alkyne **2.16** under an atmosphere of hydrogen in the presence of Lindlar catalyst gave *cis*-alkene **2.17**. Overexposure of the product to the reduction reaction conditions surprisingly gave what appeared to be isomerisation of the alkene bond, so care was taken to control the reaction time.



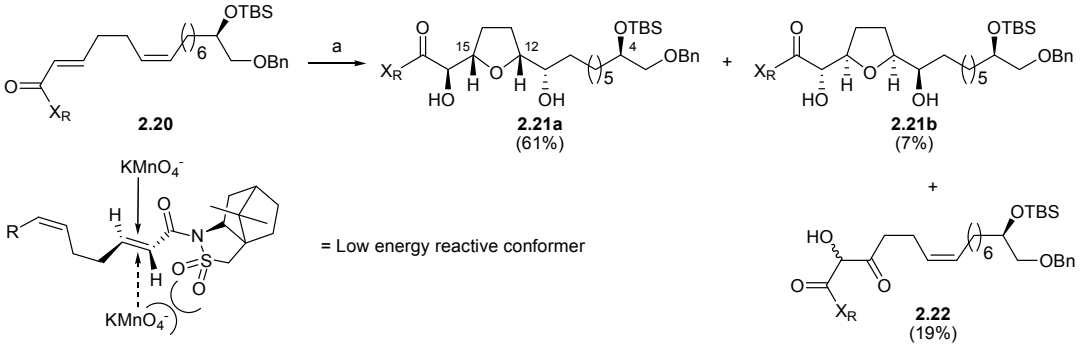
Scheme 2.5 Synthesis of 1,5-diene **2.20**. *Reagents and conditions*: a) **2.15** (2 equiv.), *n*-BuLi, HMPA, THF, then **2.5**; b) H_2, Lindlar catalyst, quinoline, hexane; c) H_2SO_4:dioxane:H_2O (1:49.5:49.5), Δ; d) $(EtO)_2POCH_2COX_R$, DIPEA, LiCl, MeCN; e) TBSOTf, 2,6-lutidine, CH_2Cl_2.

Acid hydrolysis of acetal **2.17** gave aldehyde **2.18** which was used crude in the next step. Initial attempts at hydrolysis of acetal **2.17** using aqueous acetic acid caused un-wanted acetylation. Olefination of crude aldehyde **2.18** with Oppolzer's camphorsultam phosphonate under mild conditions described by Blanchette *et al.* gave diene **2.19** in excellent yield.[141,142] Intermediate **2.19**

presented an opportunity to protect the C4 hydroxyl, which was effected by silylation with TBSOTf to yield the oxidative cyclisation precursor **2.20**.

Permanganate Oxidative Cyclisation

Permanganate oxidative cyclisation of diene **2.20** in a mixture of acetone and acetic acid delivered 3 main products (scheme 2.6).



Scheme 2.6 Oxidative cyclisation of diene **2.20**. *Reagents and conditions*: a) $KMnO_4$ (1.3 equiv), AcOH/acetone (1:4), –40 °C.

The major distereoisomer was isolated in very good yield with the C12, C15, and C16 stereocentres correctly installed. The distereoselectivity was 9:1 in favour of the desired stereoisomer **2.21a**.

A possible mechanism for the oxidative cyclisation of 1,5 dienes by permanganate was proposed by Baldwin (figure 1).[112] Firstly the permanganate ion attacks the most electron deficient alkene in a [3+2] cycloaddition.

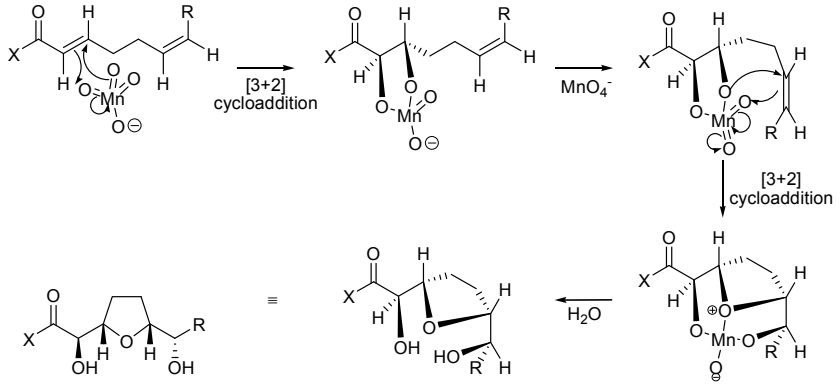


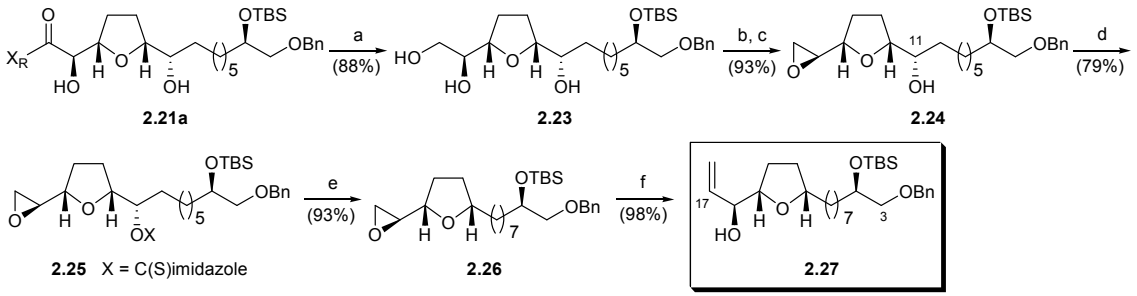
Figure 2.1 Baldwin's proposed oxidative cyclisation mechanism.

An excess of permanganate is thought to be required to oxidise the Mn(V) ion to the Mn(VI) ion where by a further [3+2] cycloaddition gives a manganese diester with addition of oxygen to one face of the diene. Hydrolysis of the manganese diester delivers the *cis*-THF diol.

It would seem likely that the distereoselectivity seen in the oxidative cyclisation of diene **2.20** is a case of preferential attack of the permanganate ion to one face of diene **2.20** governed by the proximate camphorsultam auxiliary. Under non-chelating conditions the diene may have a low energy reactive conformation shown in scheme 2.6. The low energy conformation shown has the favourable s-*cis*-arrangement between the C=O and C=C bonds, also dipolar interactions are minimised between SO_2 and the carbonyl. In this conformation attack of permanganate from the bottom face is hindered by the sulfonyl oxygen making attack from the top face preferential.

Completing the C3-C17 THF Fragment

With major THF diol diastereoisomer **2.21a** in hand, reductive cleavage in wet THF gave triol **2.23** (scheme 2.7). Selective *mono* tosylation of triol **2.23** via the dibutylstannylene acetal derivative, followed by base mediated ring closing substitution gave epoxide **2.24**.[143] This was an ideal time to remove the free hydroxyl from the C11 position. A radical deoxygenation via the thiocarbonylimidazole derivative **2.25** was planned. Previous work by Dr Kemp had found analogous chemistry to be unreliable. In the present case, formation of the thiocarbonylimidazole derivative **2.25** proceeded very cleanly and in reproducibly good yield.



Scheme 2.7 Synthesis of THF fragment **2.27**. *Reagents and conditions*: a) $NaBH_4$, THF/H_2O; b) (i) Bn_2SnO, benzene, Δ; (ii) TsCl, TBAB, 0 °C; c) K_2CO_3, MeOH; d) thiocarbonyldiimidazole, DMAP, CH_2Cl_2; e) TTMS, AIBN, toluene, 80 °C; f) $Me_3S^+I^-$, *n*-BuLi, THF.

Submission of thiocarbonate **2.25** to radical conditions resulted in highly efficient deoxygenation providing epoxide **2.26** in excellent yield. Fears over the sensitivity of an epoxide in the radical deoxygenation were unfounded and large amounts of thiocarbonate **2.25** were deoxygenated reliably. To complete the

synthesis terminal epoxide **2.26** was converted to allylic alcohol fragment **2.27** using the trimethylsulfonium ylide.

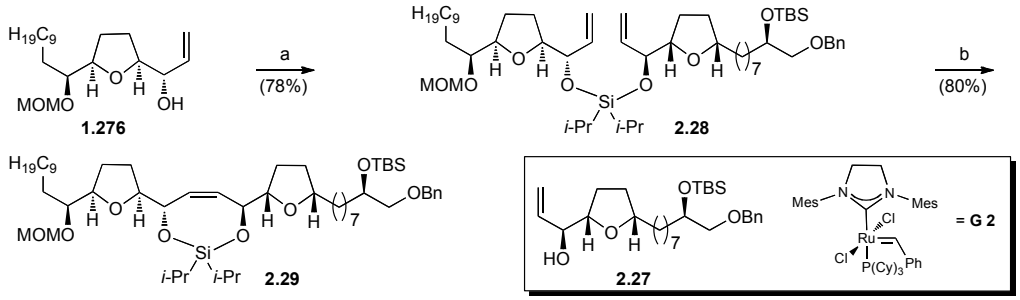
Conclusion

- Chiral building block **2.5** was efficiently converted to permanganate oxidative cyclisation precursor **2.20**.
- Stereochemistry at C12, C15 and C16 correctly installed by stereocontrolled permanganate oxidative cyclisation of 1,5-diene **2.20**.
- THF diol **2.21a** was converted to allylic alcohol fragment **2.27**, a key step was a radical deoxygenation at C11 position.
- Allylic alcohol fragment **2.27** was synthesised in 17 steps and a total yield of 20%, allowing for the first time synthesis of relatively large amounts of the fragment.

2.3 Total Synthesis of *cis*-Sylvaticin

Tethered RCM

Central to our approach was adaptation of the work by the Evans group, where they utilised a silicon tethered RCM of two hetero-allylic alcohol fragments in their synthesis of mucocin (**1.113**).[98] Initial tethering experiments within our laboratory with suitable allylic alcohol fragments **1.276** and **1.277** showed the reaction to be unreliable and proceeded in generally poor yield. Extensive research by Dr L. Brown coupled the allylic alcohol fragments **1.276** and **2.27** with a diisopropylsilyl tether in reliably good yield (scheme 2.8). An important experimental observation was that the initial coupling between fragment **1.276** and diisopropylsilane dichloride was carried out at high concentration. This appeared to reduce the formation of hydrolysis and homodimerisation by-products. Also, rigorously anhydrous conditions were necessary for high yields that included azeotropic drying of fragments **1.276** and **2.27** with benzene.



Scheme 2.8 Synthesis of RCM product **2.29**. *Reagents and conditions*: a) *i*-Pr_2SiCl_2, imidazole, CH_2Cl_2, then **2.27**; b) **G2** (10 mol %), toluene, 75 °C.

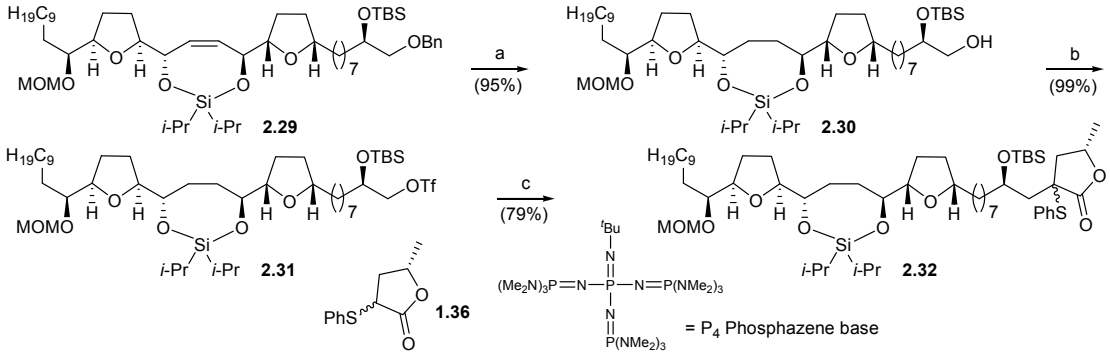
Early work by Dr S. Kemp and Dr L. Brown had shown the RCM reaction of dienes **1.291** and **2.28** to be sluggish, requiring microwave heating at 100 °C and relatively high loading of Grubbs 2nd generation catalyst. Catalyst loading was 20 mol % which was either added in 3 batches (10, 5 and 5 mol %) or 1 batch (20 mol %). The RCM reactions did appear to be clean by TLC but attempts to optimise the reactions returned the RCM products in disappointing yields (25 – 50 %) and with poor mass recovery.

At this stage, no improvement to the diene **2.28** synthsis was possible so to improve the RCM reaction focus turned to the RCM catalyst. For an efficient catalytic metathesis, rate of metathesis should be greater than the rate of catalyst decomposition. A decomposition pathway for Grubbs 2nd generation catalyst is formation of a bimetallic hydride species, which has been shown to isomerise alkenes.[144] It would seem logical to suggest that catalyst decomposition to a destructive bimetallic hydride species may be a problem, although no direct evidence for the decomposition of the catalyst or diene **2.28** was collected. To suppress formation of the bimetallic species, Grubbs 2nd generation catalyst concentrations and reaction temperatures were decreased. Under optimal conditions Grubbs 2nd generation catalyst was added in 2 mol % batches, up to a total catalyst loading of 10 mol % returning RCM product **2.29** in very good yield with recovery of starting diene **2.28** (10%). Various ruthenium 1st and 2nd generation metathesis catalysts were tried and under the batch-wise addition conditions Grubbs 2nd generation catalyst was found to be the best performing catalyst in terms of conversion. Under optimum conditions a direct comparison between Grubbs 2nd generation catalyst and Grubbs-Hoyveda, showed Grubbs 2nd generation catalyst to give significantly higher conversions than Grubbs-Hoyveda. With the higher activation energy of Grubbs-Hoyveda catalyst, higher

reaction temperatures and longer reaction times may have returned higher conversion for the RCM reaction.

End Game

The key decision to use benzyl alcohol in the kinetic resolution step was paying dividends, as debenzylation and reduction of the alkene could be done in one step (scheme 2.9). Exposure of RCM product **2.29** to a hydrogen atmosphere in the presence of a 5% Pd/C Degussa type catalyst delivered alcohol **2.30** in excellent yield, with rate of debenzylation appearing to be greater than the rate of alkene reduction by TLC. Importantly, the 5% Pd/C Degussa type catalyst is activated towards *O*-debenzylations. Initially, using a standard bench 5% Pd/C catalyst selective reduction of the alkene was observed. Then debenzylation was achieved under a hydrogen atmosphere in the presence of $Pd(OH)_2/C$. Attempts at a one step reduction/debenzylation of RCM product **2.29** using $Pd(OH)_2/C$ failed to give any reaction.

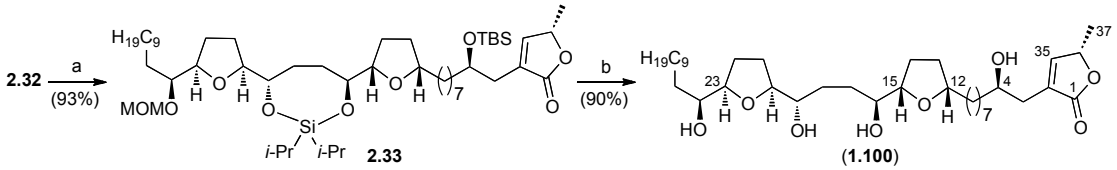


Scheme 2.9 Synthesis of lactone **2.32**. *Reagents and conditions*: a) H_2, 5% Pd/C Degussa type E101 NO/W (15 Mol %), EtOAc; b) Tf_2O, 2,6-lutidine, CH_2Cl_2; c) **1.36**, P_4-phosphazene base, THF, –78 °C, then **2.31**.

With all but one of the hydroxyls in THF ether **2.30** robustly protected, the free hydroxyl was then converted to triflate **2.31** which was used directly to alkylate lactone **1.36**. Triflation of alcohol **2.30** proceeded in excellent yield but required freshly distilled triflic anhydride. Our plan was to alkylate White's lactone **1.36** with triflate **2.31** which would install the terminal lactone.[38] This is a common step in many *Annonaceous* acetogenin syntheses and is often reported in disappointing yield especially for complex examples analogous to triflate **2.31** which has a C4 hydroxyl.[66,145] Previous work from Dr L. Brown had shown alkylation of the potassium enolate of lactone **1.36** with triflate **2.31** to be

extremely unreliable and poor yielding. The alkylation was slow but increasing the temperature caused decomposition of the enolate releasing thiophenoxide which reacted with triflate **2.31** to give a thioether by-product. Successful alkylation was accomplished by deprotonation of lactone **1.36** with strong non-nucleophilic nitrogen P_4 phosphazene base. As the P_4 phosphazene base has no counter ion, deprotonation of lactone **1.36** produces a 'naked' and reactive enolate. Experimental observations would agree with this as addition of triflate **2.31** to P_4 phosphazene deprotonated lactone **1.36** at –78 °C provides the alkylated product **2.32** as a mixture of diastereoisomers (*dr* 1:1) in good yield within 5 minutes. Importantly, P_4 phosphazene base-mediated alkylation of lactone **1.36** with precious triflate **2.31** was also highly reproducible.

With sulfide **2.32** in hand, an oxidation gave a sulfoxide intermediate which readily underwent thermal elimination to afford α,β-unsaturated lactone **2.33** in excellent yield (scheme 2.10). Classically this type of elimination reaction requires significant heating, but for this example elimination occurred on removal of solvent on the rotary evaporator at ~ 40 °C.



Scheme 2.10 Synthesis of *cis*-sylvaticin (**1.100**). *Reagents and conditions*: a) *m*-CPBA, CH_2Cl_2; b) AcCl, MeOH, CH_2Cl_2.

The final step was an acidic global deprotection which delivered *cis*-sylvaticn (**1.100**) in excellent yield. Spectroscopic data were in agreement with that published (table 2.1).[66] Noteably, 200 milligrams of this complex natural product was synthesised through the above route, which is testament to its efficiency.

Carbon	Natural[21] Chemical shift (ppm) (125MHz, $CDCl_3$)	Donohoe[66] Chemical shift (ppm) (125MHz, $CDCl_3$)	Our Synthetic Chemical shift (ppm) (100MHz, $CDCl_3$)
1	174.63	174.62	174.55
35	151.81	151.82	151.74
2	131.18	131.17	131.15
23	82.99	82.99	82.96
20	82.45	82.44	82.41
15	82.08	82.09	82.12
12	80.05	80.05	79.99
36	77.97	77.99	77.92
16	74.89	74.88	74.76

19	74.23	74.22	74.13
24	72.51	72.47	72.41
4	69.91	69.91	69.86
5	37.38	37.38	37.37
11	35.93	35.93	35.91
3	33.32	33.32	33.29
25	33.08	33.06	33.09
37	19.11	19.12	19.08
34	14.06	14.12	14.07

Table 2.1 Comparision of carbon NMR data from our synthetic sample of *cis*-sylvaticin (**1.110**) with Donohoe's synthetic and natural isolated samples. Carbons 6-10, 13, 14, 17, 18, 21, 22 and 26–33 fall in the range 22.7–31.0 ppm and are unassigned.

Conclusion

- A total synthesis of *cis*-sylvaticin (**1.100**) was completed in 24 steps and in 7.8% yield.
- The efficency of the synthesis was demonstrated through the production of more than 200 mg of *cis*-sylvaticin (**1.100**).

Notable steps included the alcoholytic kinetic resolution of epoxide **2.2**, two permanganate promoted oxidative cyclisation reactions, a tethered RCM to unite the two major fragments and the use of P_4 phoshazene base to install the butenolide precursor.

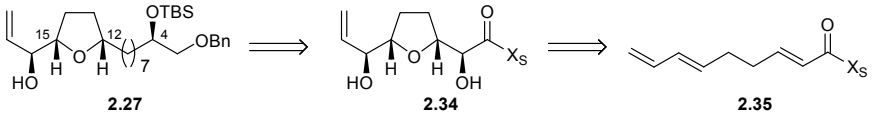
2.4 Abandoned Routes to a *cis*-Sylvaticin C3-C17 THF Fragment

A number of other approaches to the *mono* THF fragments were also investigated. For various reasons each of these routes were ultimately abandoned. Nonetheless, some important insight into oxidative cyclisation reactions was gained and these studies will be summerised in the ensuing sections.

Terminal Enyne/Diene Approach

Early strategies in the synthesis of a C3-C17 *cis*-sylvaticin fragment via permanganate oxidative cyclisation of 1,5-diene systems, required reductive cleavage of the chiral auxiliary after the oxidative cyclisation providing a terminal diol which was converted to an allylic alcohol in 3 steps (see scheme 2.7, steps

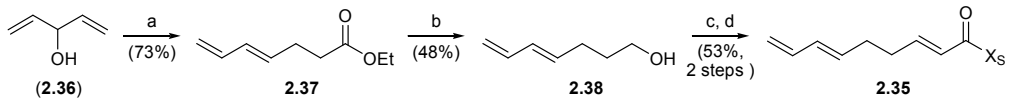
b, c and f). This approach was attractive due to high yields, but would require a radical deoxygenation at the C11 position. At the time, the radical deoxygenation reaction had proved to be somewhat capricious, althought this issue was later solved in our total synthesis. An alternative approach to the allylic alcohol fragment **2.27** was planned where oxidative cyclisation of triene **2.35** would give THF diol **2.34** more directly (scheme 2.11).



Scheme 2.11 Retrosynthetic analysis of C3-C17 fragment **2.27**.

With the allylic alcohol in place it was hoped that THF diol **2.34** could be converted to a suitable C3-C17 fragment without the need for a radical deoxygenation. Permanganate oxidative cyclisation of a 1,5,7-triene would also be novel, and the effect of the terminal diene would be intriguing.

The synthesis of triene **2.35** began by Claisen-Johnson rearrangement of commercially available penta-1,4-dien-3-ol (**2.36**) delivering ester **2.37** in good yield (*E* isomer only observed) (scheme 2.12).[63,146]

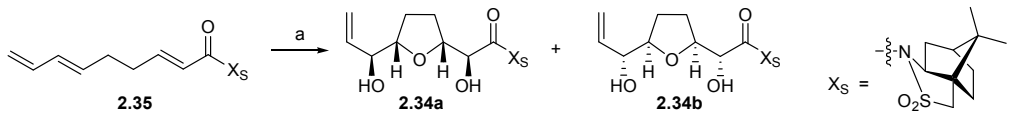


Scheme 2.12 Synthesis of triene **2.35**. *Reagents and conditions*: a) triethyl orthoacetate, propionic acid, Δ; b) $LiAlH_4$, THF, 0 °C; c) DMSO, $(COCl)_2$, Et_3N, THF, –60 °C; d) $(EtO)_2POCH_2COX_S$, DIPEA, LiCl, MeCN.

Lithium aluminium hydride reduction of ester **2.37** returned alcohol **2.38** in modest yield. Swern oxidation gave a volatile aldehyde that underwent Horner-Wadsworth-Emmons olefination under mild conditions providing triene **2.35** in reasonable yield.[142] The high volatility of triene **2.35** precursors was a problem throughout this route.

Permanganate oxidative cyclisation of triene **2.35** was studied (scheme 2.13). Under typical conditions (table 2.1, entry 1), the oxidative cyclisation reaction proceeded cleanly providing THF diols **2.34a**/**b** as an inseparable mixture of distereoisomers (*dr* un-determined, typical *dr* 9:1) in poor yield. Along with poor yields there was poor mass recovery with no evidence of by-products.

It seemed logical to assume over oxidation had occurred generating highly polar water soluble intermediates and volatile by-products.



Scheme 2.13 Synthesis of THF diols **2.34a**/**b**. *Reagents and conditions*: a) see table 2.1.

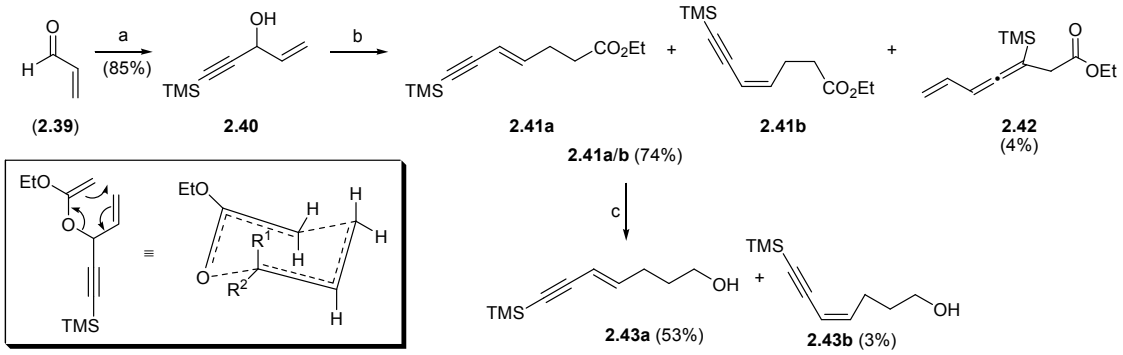
Entry	$KMnO_4$ (eq)	PTC[a]	Solvent	Time (min)	Temp. (°C)	Yield[b]
1	1.3	N	Acetone/AcOH (3:2)	60	–30	22%
2	1	N	Acetone/AcOH (3:2)	30	–30	17%
3	0.8	N	Acetone/AcOH (3:2)	30	–30	11%
4	1	Y	Acetone/AcOH (3:2)	30	–40	9%
5	1.4	N	Acetone/AcOH (3:2)	60	–30	8%
6	1.3	Y	CH_2Cl_2	30	–30	12%
7	1.3	Y	CF_3CH_2OH	30	–30	0%[c]
8	1.3	Y	*t*-BuOH	30	30	0%[c]
9	0.8	Y	Et_2O/H_2O	75	–60	0%[c]
10	0.8 → 1.5	Y	EtOAc	145	–40	0%

Table 2.2 Results for the oxidative cyclisation of triene **2.35** (see Scheme 2.13). [a] PTC used was adogen 464 (40 mol %); [b] Combined yield of THF diols **2.34a** and **2.34b**; [c] Starting material recovered.

Initial attempts at optimisation focused on reducing the number of equivalents of permanganate and reaction times (table 2.1, entry 2,3), but this failed to give any advantage. Switching solvent systems and using a phase transfer catalyst was also disappointing. It was clear that the conjugated terminal alkene was causing significant problems in the oxidative cyclisation reaction, and optimisation to a suitable level would be a challenge. A solution was to substitute the terminal alkene for an alkyne. Results from our lab and the literature had shown the rate of reaction of permanganate with alkynes to be slower than alkenes.[132,147]

The modified strategy began by lithiated TMS acetylene 1,2-addition to acrolein (**2.39**) furnishing allylic alcohol **2.40** (scheme 2.14).[148] Allylic alcohol **2.40** was submitted to Claisen-Johnson rearrangement delivering esters **2.41a**/**b** (*E*:*Z* 18:1) and allene **2.42**. Previous Claisen-Johnson rearrangement of allylic alcohol **2.36** gave the *E* isomer only, Claisen-Johnson rearrangement of allylic alcohol **2.40** delivered a mixture of *E*:*Z* isomers. The lower stereoselectivity can be explained if you consider the reaction transition state. The Claisen-Johnson

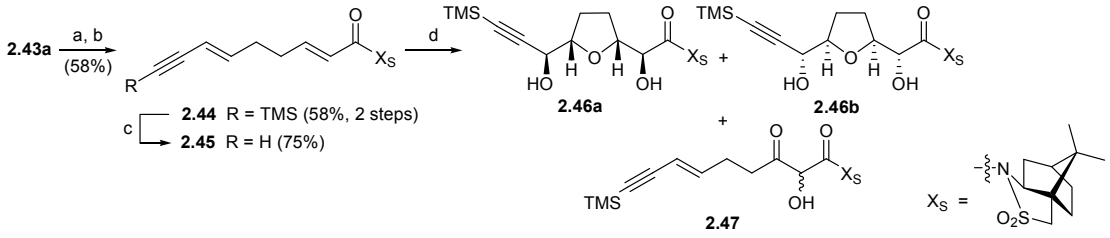
rearrangement proceeds through a six member transition state. For allylic alcohol **2.36** the sterically more demanding vinyl group would not favour the R^1 position in the transition state due unfavourable 1,3-diaxial interactions preventing *Z* alkene formation. For allylic alcohol **2.40**, the less sterically demanding alkynyl group may occupy the R^1 position as there are reduced 1,3-diaxial interactions allowing formation of the *Z* isomer.



Scheme 2.14 Synthesis of alcohol **2.43a**. *Reagents and conditions*: a) TMS acetylene, *n*-BuLi, THF, then **2.39**; b) triethyl orthoacetate, propionic acid, Δ; c) DIBAL-H, THF, –50 °C.

Esters **2.41a**/**b** were obtained as an inseparable mixture by distillation, DIBAL-H reduction afforded alcohols **2.43a** and **2.43b** allowing separation by chromatography.

Swern oxidation of alcohol **2.43a** gave an aldehyde which underwent Horner-Wadsworth-Emmons olefination to provide dienyne **2.44** in reasonable yield (scheme 2.15). Desilylation of dienyne **2.44** afforded dienyne **2.45**, which required addition of acetic acid to prevent decomposition. With dienyne's **2.44** and **2.45** in hand, their permanganate oxidative cyclisation was studied (table 2.2 and 2.3).



Scheme 2.15 Oxidative cyclisation of dienyne systems. *Reagents and conditions*: a) DMSO, $(COCl)_2$, Et_3N, THF, –60 °C; b) $(EtO)_2POCH_2COX_S$, DIPEA, LiCl, MeCN; c) TBAF, AcOH, THF; d) see table 2.2 and 2.3.

Under typical conditions (table 2.2, entry 1), the oxidative cyclisation of dienyne **2.44** afforded THF diols **2.46a**/**b** as an inseparable mixture of distereoisomers (*dr*

9:1 ^{13}C NMR) in disappointing yield and mass recovery. Attempted optimisation focused on altering the co-solvent ratios and reaction times. No advantage was seen over the original conditions, but in general the yield of hydroxyl ketone **2.47** was observed to be increased by decreasing the ratio of acetic acid. Oxidative cyclisation of dienyne **2.45** with the TMS group removed did not give any improvement (table 2.2, entry 10).

Entry	R	Solvent	Time (min)	Yield 2.46a/b	Yield 2.47
1	TMS	Acetone/AcOH (3:2) [a]	30	41%	1%
2	TMS	Acetone/AcOH (4:1) [a]	30	33%	31%
3	TMS	Acetone/AcOH (3:2) [a]	15	39%	1%
4	TMS	Acetone/AcOH (3:2) [a]	5	17%	1%
5	TMS	Acetone/AcOH (6:5) [a]	10	33%	1%
6	TMS	Aq Acetone [b]	10	0%	27%
7	TMS	Acetone/AcOH (3:2) [a]	60	32%	9%
8	TMS	Acetone/AcOH (3:2) [a]	15	32%	24%
9	TMS	Acetone/AcOH (3:2) [a]	15	27%	22%
10	H	Acetone/AcOH (3:2) [a]	30	37%	1%

Table 2.3 Results for the oxidative cyclisation of dienyne **2.44** and **2.45** (see scheme 2.15). [a] $KMnO_4$ (1.3 eq.), –30 °C; [b] AcOH (5eq.) with phosphate buffer.

Oxidative cyclisation of dienyne **2.44** was also attempted under PTC conditions (table 2.3). Oxidative cyclisation under bi-phasic conditions in dichloromethane (table 2.3 entry 1) gave THF diols **2.46a**/**b** in poor yield.

Entry	Solvent	AcOH (eq.)	Temp. (°C)	Yield 2.46a/b	Yield 2.47
1	CH_2Cl_2 [a]	6	0	7%	18%
2	Diethyl ether [a]	6	–50 → 25	1%	1%
3	Diethyl ether [a,b]	6	–50 → 25	1%	14%
4	Diethyl ether [a]	35	–50 → 25	10%	16%

Table 2.4 Results for the solid-liquid phase transfer catalysed oxidative cyclisation of dienyne **2.44**. [a] adogen 464 (40 mol %), $KMnO_4$ (2 eq.), 60 min; [b] H_2O (10µL) added.

Attempts at bi-phasic oxidative cyclisation in diethyl ether initially resulted in minimal consumption of dieyne **2.44**, adding water or increased acetic acid gave

complete consumption of starting material but returned THF diols **2.46a**/**b** in poor yield.

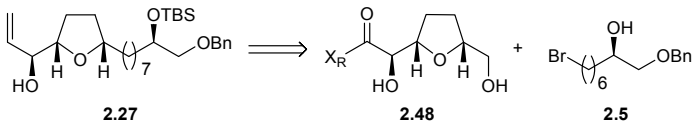
To summarise, the triene/dienyne approach gave swift access to valuable intermediates. Unfortunately the approach suffered from poor yields for the oxidative cyclisation step and the resulting diastereoisomers could not be separated by MPLC. The oxidative cyclisation reaction of triene **2.35** and dienyne **2.44** saw complete consumption of starting material in short reaction times but with poor mass recovery. The terminal alkene or alkyne prevented efficient oxidative cyclisation. It would seem logical to assume the major competing reactions were over oxidation with possible oxidative cleavage, providing a mixture of highly polar or volatile intermediates which were removed from the organic layer upon work up. Switching from a terminal alkene to a terminal alkyne did result in significant improvement in the oxidative cyclisation reaction yields. As previously stated permanganate has been shown to react with alkynes slower than alkenes, this effect has been shown to be important in the oxidative cyclisation of 1,5,7-triene relative to 1,5,7-dienynes. Optimisation of the oxidative cyclisation of triene **2.35** and dienyne **2.44** to a suitable level appeared unlikely, therefore this approach was considered impractical for the application towards a total synthesis of *cis*-sylvaticin.

Conclusion

- Oxidative cyclisation of 1,5,7-triene **2.35** gave desired THF diols **2.34a**/**b** but in poor yield.
- Oxidative cyclisation of dieneyne **2.44** provided desired THF diols **2.46a**/**b**, showing improved efficiency relative to the triene oxidations.
- Due to poor yields in the permanganate oxidative cyclisation of 1,5,7-triene **2.35** and dieneyne **2.44**, neither were considered viable intermediates for the synthesis of *cis*-sylvaticin.

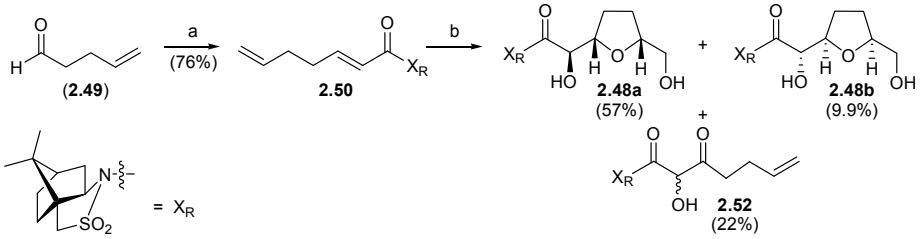
Convergent Route

A new convergent route was planned for the synthesis of THF fragment **2.27**, which entailed synthesising two main fragments **2.48** and **2.5** (scheme 2.16).



Scheme 2.16 Retrosynthetic analysis of THF fragment **2.27**.

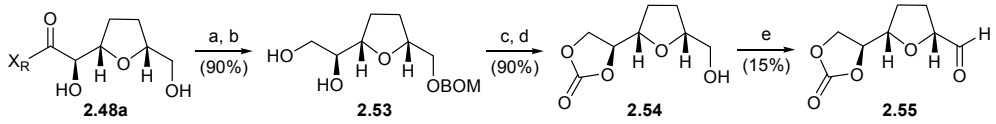
Work on this approach was going to be carried out in collaboration with Dr L Brown. The synthesis began by olefination of commercially available pent-4-enal (**2.49**) under mild conditions furnishing dienoyl **2.50** in good yield (scheme 2.17). The stage was set for the oxidative cyclisation reaction.



Scheme 2.17 Synthesis of THF diol **2.48a**. *Reagents and conditions*: a) $(EtO)_2POCH_2COX_R$, DIPEA, LiCl, MeCN; b) $KMnO_4$ (1.3 equiv), AcOH/acetone (2:3), –40 °C.

Pleasingly the oxidative cyclisation reaction of diene **2.50** gave THF diol **2.48a** in good yield and diastereoselectivity (6:1). Elaboration of THF diol **2.48a** was explored by Dr L Brown.

Elaboration of THF diol **2.48a** by Dr L Brown began with a selective *mono* protection of the primary hydroxyl as its BOM ether, followed by a reductive cleavage to remove the chiral auxiliary affording diol **2.53** (scheme 2.18).



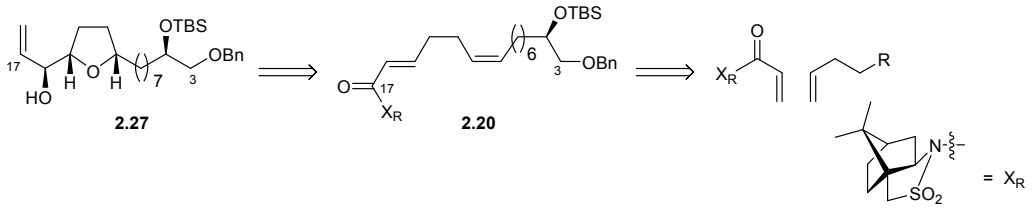
Scheme 2.18 Synthesis of aldehyde **2.55**. *Reagents and conditions*: a) BOMCl; b) $NaBH_4$, THF/H_2O; c) phosgene, CH_2Cl_2; d) H_2, Pd/C; e) Dess-Martin periodinane, CH_2Cl_2.

Conversion of diol **2.53** to a carbonate followed by cleavage of the BOM group delivered alcohol **2.54**. The carbonate protection was chosen as it could be removed under basic conditions. It was hoped oxidation of alcohol **2.54** would give an aldehyde coupling partner. Unfortunately oxidation of alcohol **2.54** gave aldehyde **2.55** in poor yield. The oxidation was observed to initially proceed smoothly by TLC, but the product was unstable and decomposed. Efficient oxidation of a related THF system was shown by Donohoe.[66] In our case presence of the carbonate was thought to be responsible for the decomposition

of aldehyde **2.55**. A modified protection group strategy was anticipated to overcome the un-reliable oxidation, but with the discovery of the efficient synthesis of benzyl ether **2.5** focus shifted to the route to THF fragment **2.27** that was ultimately successful.

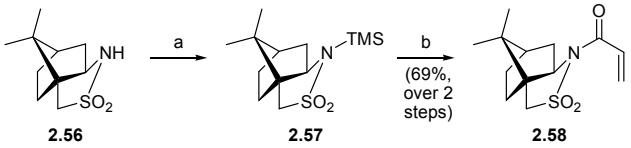
A Cross-Metathesis Approach to Diene Fragments

Synthesis of fragment **2.27** via functionalised diene **2.20** was a desirable route. It was recognised that the *trans* enoyl system **2.20** could be constructed by cross-metathesis (CM) reaction (Scheme 2.19).



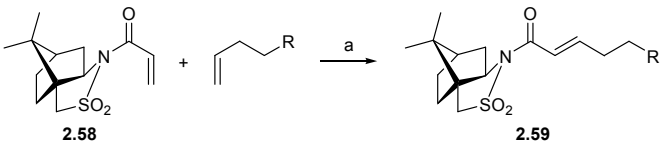
Scheme 2.19 Retrosynthetic analysis of THF fragment **2.27**.

Grubbs *et al* had shown α,β-unsaturated amides and terminal olefins to be excellent CM partners.[149] Synthesis of *N*-propenoyl sultam **2.56** was carried out following work described by Kocienski *et al* (scheme 2.20).[150] Direct addition of (2*R*) camphor sultam **2.56** to acryloyl chloride provides the desired enoyl **2.58**, but due to the enoyl sultam **2.58** having excellent Michael acceptor ability, further 1,4-addition with (2*R*) camphor sultam **2.56** occurs returning enoyl sultam **2.58** in poor yield.



Scheme 2.20 Synthesis of *N*-propenoyl sultam **2.58**. *Reagents and conditions*: a) TMSCl, Et_3N, benzene, MeCN; b) acryloyl chloride, $CuCl_2$, benzene, Δ, 16 h.

Kocienski's method prevented 1,4-addition by-product formation by firstly silylating (2*R*) camphor sultam **2.56**, followed by a copper mediated *in situ* desilylation and acylation returning *N*-propenoyl sultam **2.58** in good yield. With *N*-propenoyl sultam **2.58** in hand, CM with various terminal olefins was studied (scheme 2.21).



Scheme 2.21 Cross metatheses of *N*-propenoyl sultam **2.58** with terminal olefins. *Reagents and conditions*: a) Grubbs 2nd generation catalyst (5 mol %), CH_2Cl_2.

There were attempts to couple three terminal alkenes with *N*-propenoyl sultam **2.58** by CM (entry 1-3, table 2.4), of these the best in terms of yield was silyl protected 4-penten-1-ol (entry 3, table 2.4).

Entry	R	Equiv. of terminal alkene	Conditions	Yield
1	CHO	1.25	40°C, 16 h	0%
2	CH_2OH	1.25	40°C, 16 h	≈5% [a]
3	CH_2OTBS	1.25	40°C, 16 h	43%
4	CH_2OTBS	1.25	100°C, 1 h [b]	43%
5	CH_2OTBS	2	100°C, 1 h [b]	55%
6	CH_2OTBS	0.5	100°C, 1 h [b]	89%

Table 2.5 CM of N-propenoyl sultam **2.58** with terminal olefins. [a] Yield estimated from the crude ^{1}H NMR spectrum [b] Microwave heating.

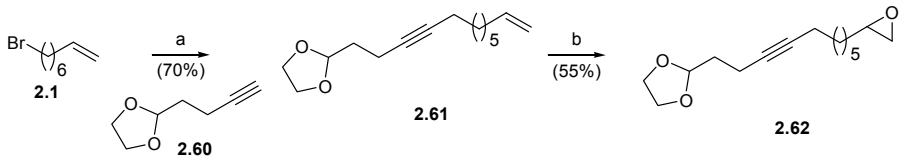
Interestingly, a comparison between thermal heating and microwave heating (entry 3-4, table 2.4) showed no advantage with respect to yield of the product but did reduced reaction time considerably. Under optimum conditions a 2 fold excess of *N*-propenoyl sultam **2.58** was reacted with silyl protected 4-penten-1-ol (entry 6, table 2.4) which returned the CM product in excellent yield and *E* selectivity.

Attempts at CM between *N*-propenoyl sultam **2.58** and a functionalised 1,5-diene system returning a suitable permanganate oxidative cyclisation precursor were unsuccessful. However, all of these reactions required significant amounts of the Grubbs 2nd generation catalyst, even at 5 mol % loadings. Due to concerns relating to the economic viability of a CM so early in the synthesis, further studies were aborted.

Enyne Epoxidation and Kinetic Resolution

Initially, the alkylation of chiral building block **2.5** with terminal alkyne **2.15** gave some problems, which were later overcome. Therefore a modified route

which could still utilise the kinetic resolution chemistry was sought. Alkylation of bromide **2.1** with terminal alkyne **2.60** gave enyne **2.61** in reasonable yield (scheme 2.22)



Scheme 2.22 Synthesis of epoxide **2.62**. *Reagents and conditions*: a) **2.60**, *n*-BuLi, HMPA, THF, then **2.1**; b) 0.068M DMDO in acetone.

Next the epoxidation of enyne **2.61** was examined, using a dimethyldioxirane (DMDO) solution to deliver epoxide **2.62** in disappointing yield. Epoxidation of enyne **2.61** with *m*-CPBA or DMDO returned two major by-products. Spectroscopic data suggested that the by-products were a α,β-unsaturated ketone and a ketone with a non-conjugated alkene. Independent work by Curci *et al* and Murray *et al* had shown alkynes to be oxidised by DMDO.[151,152] They both postulated one π-bond of an alkyne would form an unstable oxirene. Two postulated pathways are shown which give products consistent with the spectroscopic data (figure 2.2).

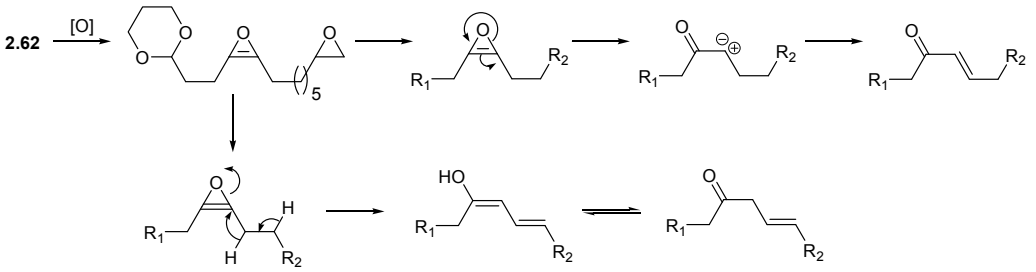


Figure 2.7 Proposed decomposition pathways.

With epoxidation of enyne **2.61** proceeding with un-wanted oxidation of the alkyne, further optimisation was required. Work published by Mizuno *et al* reported a polyoxovanadometalate catalysed hydrogen peroxide epoxidation.[153,154] Interestingly the procedure was selective to terminal olefins over substituted olefins due to steric constraints of the polyoxovanadometalate catalyst. The polyoxovanadometalate catalyst ($[(C_4H_9)_4N]_4[\gamma$-1,2-$H_2SiV_2W_{10}O_{40}]\cdot H_2O$) was synthesised in 3 steps from commercial available sodium metasilicate and sodium tungstate. (Equations **1**-**3**).

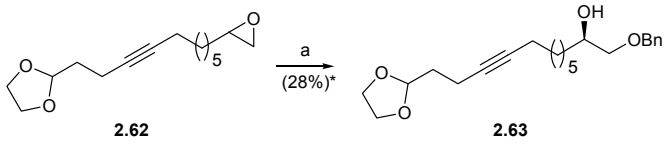
$$11[WO_4]^{2-} + [SiO_3]^{2-} + 16H^+ + 8K^+ + 6H_20 \rightarrow K_8[\beta_2\text{-}SiW_{11}O_{39}]\cdot 14H_2O \quad (\mathbf{1})$$

$$[\beta_2\text{-}SiW_{11}O_{39}]^{8-} + 2CO_3^{2-} + 8K^+ + 13H_2O \rightarrow K_8[\gamma\text{-}SiW_{10}O_{36}]\cdot 12H_2O + 2HCO_3^- + [WO_4]^{2-} \quad (\mathbf{2})$$

$$[\gamma\text{-}SiW_{10}O_{36}]^{8-} + 2[VO_3]^- + 4[(C_4H_9)_4N]^+ + 6H^+ \rightarrow [(C_4H_9)_4N]_4[\gamma\text{-}1,2\text{-}H_2SiV_2W_{10}O_{40}]\cdot H_2O + H_2O \quad (\mathbf{3})$$

Epoxidation of enyne **2.61** with the catalytic polyoxovanadometalate ($[(C_4H_9)_4N]_4[\gamma\text{-}1,2\text{-}H_2SiV_2W_{10}O_{40}]\cdot H_2O$) did prevent the formation of by-products which were seen during DMDO and *m*-CPBA epoxidations. Unfortunately mass recovery was disappointing. Using 10 mol % polyoxovanadometalate and hydrogen peroxide (2 equiv), epoxide **2.62** was obtained in poor yield (30%) with recovery of starting olefin **2.61** (20%).

The stage was set for the kinetic resolution of epoxide **2.62**. Under analogous conditions to epoxide **2.2**, kinetic resolution of epoxide **2.62** gave benzyl ether **2.63** in poor yield (*ee* not determined) and recovered epoxide **2.62** (58%) (scheme 2.23).



2.62 **2.63**

* denotes yield is with respect to starting epoxide used, maximum yield is 45%.

Scheme 2.23 Synthesis of benzyl ether **2.63**. *Reagents and conditions*: a) (*S*,*S*) **2.13** 0.25 mol %, BnOH (0.45 equiv.), MeCN, 4 °C, 16h.

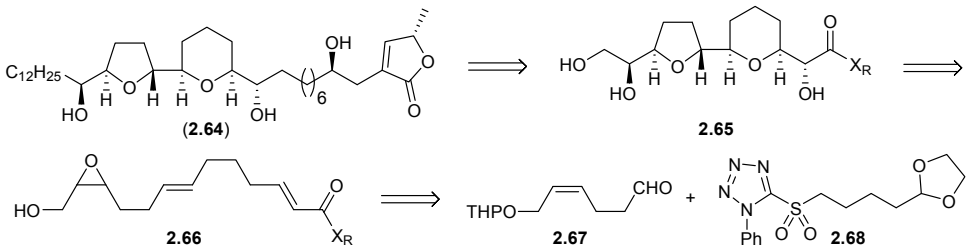
Kinetic resolution of epoxide **2.62** proceeded with poor mass recovery in comparison to epoxide **2.2**. No by-products were detected from the reaction so it is un-clear why mass recovery was poor. The presence of the alkyne and/or acetal would probably be an important factor to consider.

2.5 Approaches to Adjacent THP/THF and *bis*-THF *Annonaceous* Acetogenins via Cascade Oxidative Cyclisation Reactions

A new approach in the synthesis of adjacent THP/THF and *bis*-THF *Annonaceous* acetogenins would be cascade oxidative cyclisation reaction with permanganate. The primary goal from this work was to construct valuable intermediates for the synthesis of (+)-muconin (**2.64**). The following section will discuss studies towards cascade oxidative cyclisation reactions.

Synthesis of Adjacent THP/THF *Annonaceous* Acetogenin Core

Synthesis of *cis*-THP diols by oxidative cyclisation of 1,6-dienes had been achieved by Brown and Cecil.[155] Yields and diastereoselectivities of *cis*-THP diols from oxidative cyclisation of 1,6-dienes were observed to be lower than for the analogous 1,5-dienes oxidative cyclisations providing *cis*-THF diols. Despite these limitations, oxidative cyclisation of 1,6-dienes is still a promising avenue for stereoselective synthesis of *cis*-THP diols. It was hoped that the *cis*-THP core of (+)-muconin (**2.64**) could be synthesised by oxidative cyclisation of 1,6-diene **2.66** (scheme 2.24).[156]



Scheme 2.24 Retrosynthetic analysis of (+)-muconin (**2.64**).

Our retrosynthetic analysis entailed construction of the central *E*-alkene by Julia-Kocienski olefination, between aldehyde **2.67** and sulfone **2.68**.

It was hoped that a permanganate oxidative cyclisation reaction of 1,6-diene **2.66** would give a *cis*-THP diol, which under acidic conditions would provide triol **2.65** via an intramolecular cyclisation (figure 2.3).

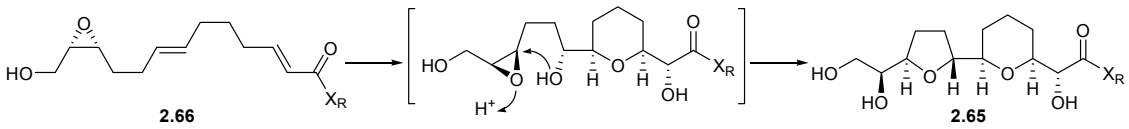
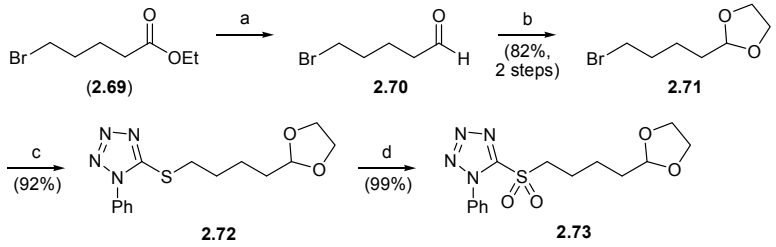


Figure 2.3 Cascade oxidative cyclisation approach.

It is anticipated that triol **2.65** would be a valuable intermediate in the synthesis of (+)-mucocin (**2.64**).

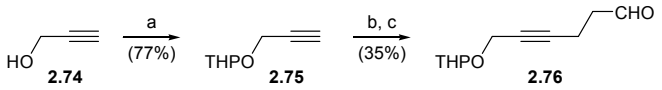
Following work described by Maier, DIBAL-H reduction of ethyl 5-bromopentanoate (**2.69**) providing aldehyde **2.70**, which was converted to acetal **2.71** in excellent yield (scheme 2.25).[157]



Scheme 2.25 Synthesis of sulfone **2.73**. *Reagents and conditions:* a) DIBAL-H, toluene, –78 °C; b) ethylene glycol, *p*-TsOH, benzene, Δ; c) 1-phenyl-1H-tetrazole-5-thiol, K_2CO_3, acetone; d) $[NH_4]_6Mo_7O_{24}•4H_2O$, 30% H_2O_2, EtOH.

Under classical conditions nucleophilic substitution of bromide **2.71** with 1-phenyl-1H-tetrazole-5-thiol followed by oxidation of sulfide **2.72** furnished sulfone **2.73**.[105]

The synthesis of two aldehydes that could be used in the Julia-Kocienski olefination reaction was explored. Synthesis of aldehyde **2.76** began by protection of propargylic alcohol as its tetrahydropyranyl ether **2.75** (scheme 2.26).

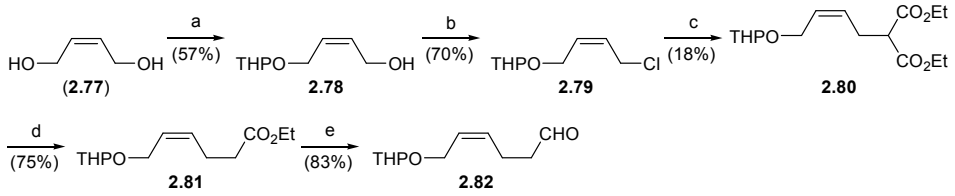


Scheme 2.26 Synthesis of aldehyde **2.76**. *Reagents and conditions*: a) DHP, PPTS, CH_2Cl_2; b) *n*-BuLi, THF, –10 °C, then CuI•0.75 DMS, TMSI, –78 °C, then acrolein; c) K_2CO_3, MeOH, 0 °C.

Under conditions described by Herczegh, 1,4-addition of terminal alkyne **2.75** to acrolein gave a silyl enol ether, which under basic conditions, furnished aldehyde **2.76** in poor yield.[158]

Synthesis of aldehyde **2.82** began by *mono*-protection of *cis*-butene-1,4-diol (**2.77**) as its tetrahydropyranyl ether **2.78** (scheme 2.27). Alcohol **2.78** was

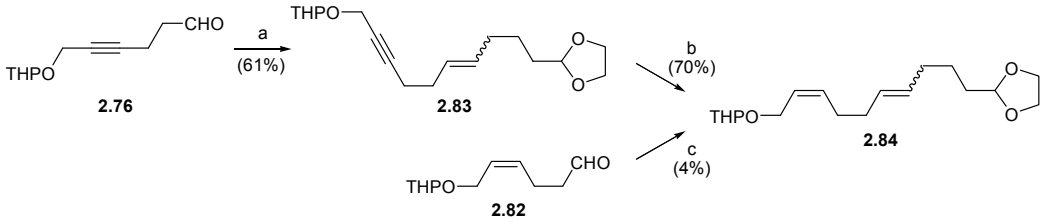
converted to chloride **2.79** which was used to alkylate diethyl malonate delivering malonate **2.80** but in rather poor yield.



Scheme 2.27 Synthesis of aldehyde **2.82**. *Reagents and conditions*: a) DHP, *p*-TsOH, CH_2Cl_2/THF (2:5); b) MsCl, DIPEA, CH_2Cl_2; c) diethyl malonate, NaH 60%, DMF, then **2.79**; d) KOAc, DMSO/H_2O (75:1) Δ; e) DIBAL-H, toluene, –78 °C.

Malonate **2.80** was submitted to Krapcho decarboxylation which returned ester **2.81**, whereupon partial reduction with DIBAL-H gave aldehyde **2.82**.[159]

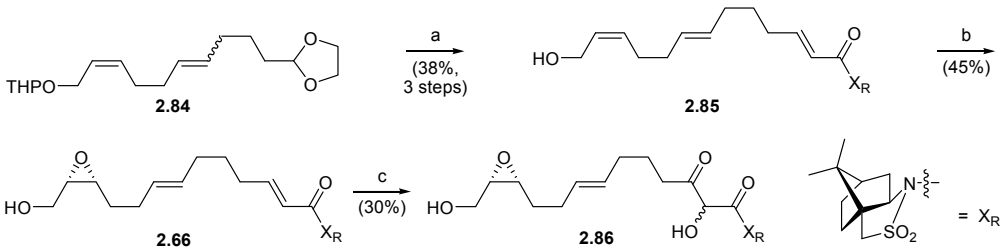
With aldehydes **2.76**, **2.82** and sulfone **2.73** in hand the Julia-Kocienski olefination was studied (scheme 2.28). The Julia-Kocienski olefination classically gives *E* alkenes. Selectivity for *E* alkenes in Julia-Kocienski olefinations can be increased by carrying out the reaction in polar solvents and using a base with a large counter-cation.[105] Initially, Julia-Kocienski olefination between **2.73** and **2.76** in THF using KHMDS as the base gave alkene **2.83** as inseparable mixture of isomers in reasonable yield but poor selectively (*E*:*Z* 5:1).



Scheme 2.28 Synthesis of diene **2.84**. *Reagents and conditions*: a) **2.73**, KHMDS, DME, –55 °C, then **2.76**; b) H_2, Lindlar catalyst, quinoline, hexane; c) **2.73**, KHMDS, DME, –55 °C, then **2.82**.

Repeating the Julia-Kocienski olefination between **2.73** and **2.76** in a more polar solvent such as DME gave an improvement in selectivity (*E*:*Z* 6:1). With alkyne **2.83** in hand partial reduction gave diene **2.84** in respectable yield. Unfortunately repeating this reaction on a larger scale gave an inseparable mixture of over-reduced and isomerised material. Julia-Kocienski olefination between **2.73** and **2.82** under optimal conditions with respect to *E* selectivity gave diene **2.84** in very poor yield (*E* selectivity un-determined).

Deprotection of allylic alcohol **2.84**, followed by hydrolysis of the acetal gave an aldehyde which underwent olefination returning triene **2.85** in reasonable yield (scheme 2.29).[142]



Scheme 2.29 Synthesis of hydroxyl ketone **2.86**. *Reagents and conditions*: a (i) *p*-TsOH, MeOH; (ii) H_2SO_4:dioxane:H_2O (1:49.5:49.5), Δ; (iii) $(EtO)_2POCH_2COX_R$, DIPEA, LiCl, MeCN; b) DET-(+), Ti(O*i*-Pr)$_4$, *t*-BuOOH, CH_2Cl_2; c) $KMnO_4$ (1.3 equiv), AcOH/acetone (1:3), –40 °C.

Sharpless asymmetric epoxidation of allylic alcohol **2.85** afforded epoxide **2.66** in disappointing yield (*ee* not determined, typical *ee* for *cis* allylic alcohol is between 85 – 90%).[160] Attempted oxidative cyclisation of 1,6-dienoyl **2.66** failed to give the desired adjacent THF/THP core **2.65**. In fact, the main product from the attempted oxidative cyclisation was hydroxyl ketone **2.86**. It was clear that synthesis of a *cis*-THP diol by permanganate oxidative cyclisation would require optimisation. Due to time and material constraints the permanganate oxidative cyclisation of 1,6-diene **2.66** was not studied further. To test the cascade oxidative cyclisation approach, efforts were concentrated on synthesis of *bis*-THF structures. The main advantage was that key oxidative cyclisation reaction of a 1,5-diene system was expected to proceed with greater efficiency.

Conclusion

- A triene was successfully constructed using Julia-Kocienski olefination, albeit in disappointing *E* selectivity.
- Attempted cascade oxidative cyclisation of 1,6-diene **2.66** was unsuccessful in delivering an adjacent THP-THF core.

Synthesis of Adjacent *bis*-THF *Annonaceous* Acetogenin Core

There are over 100 examples of *Annonaceous* acetogenins with adjacent *bis*-THF cores.[2] Our cascade oxidative cyclisation approach would give relatively short access to triol **2.90** (figure 2.4).

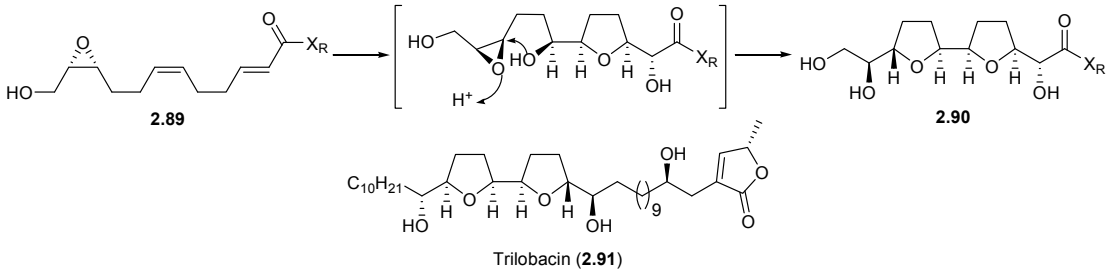
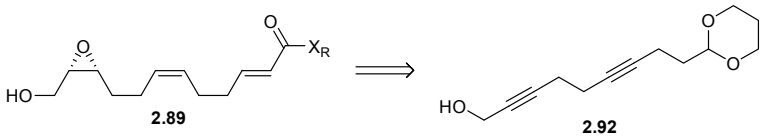


Figure 2.4 Cascade oxidative cyclisation approach.

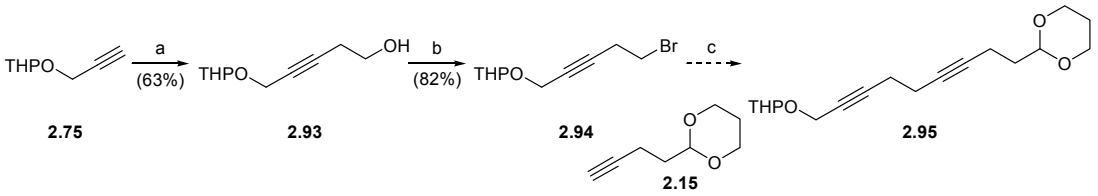
Triol **2.90** has a *bis*-THF core with identical relative stereochemistry to trilobacin (**2.91**).[161,162] Successful cascade oxidative cyclisation of modified diene systems would give intermediates with relative and absolute stereochemistry matching many adjacent *bis*-THF *Annonaceous* acetogenins.

Our plan was to synthesis diene **2.89** via a 1,5-hexadienyne intermediate **2.92** (scheme 2.30).



Scheme 2.30 Retrosynthetic analysis of dienoyl **2.89**.

Initial work focused on building a 1,5-hexadienyne by alkylation. Lithiated alkyne **2.75** in a THF/HMPA co-solvent opened ethylene oxide in reasonable yield (scheme 2.31).

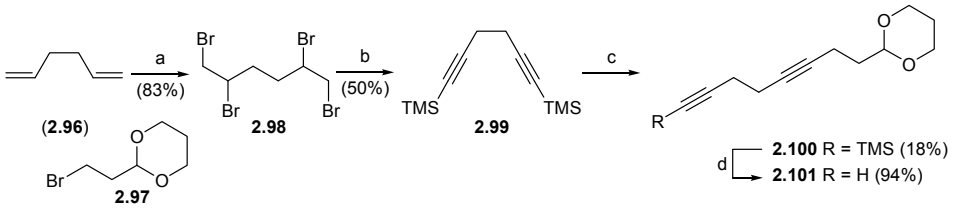


Scheme 2.31 Synthesis of bromide **2.94**. *Reagents and conditions*: a) *n*-BuLi, HMPA, THF/Et_2O (1:2), then ethylene oxide; b) CBr_4, PPh_3, pyridine, CH_2Cl_2; c) **2.15**, *n*-BuLi, HMPA, THF, then **2.94**.

Free hydroxyl **2.93** was efficiently converted to its corresponding bromide **2.94** which set the scene for alkylation. Unfortunately, attempted alkylation of lithiated alkyne **2.15** with bromide **2.94** failed to give acetal **2.95**. The favoured pathway was elimination of HBr resulting in a conjugated enyne, a pathway that would be difficult to suppress. Therefore, an alternative route was explored.

Bromination of 1,5-hexadiene (**2.96**) delivered tetrabromide **2.98** in good yield (scheme 2.32). Treatment of tetrabromide **2.98** with LDA (6 equiv.) would

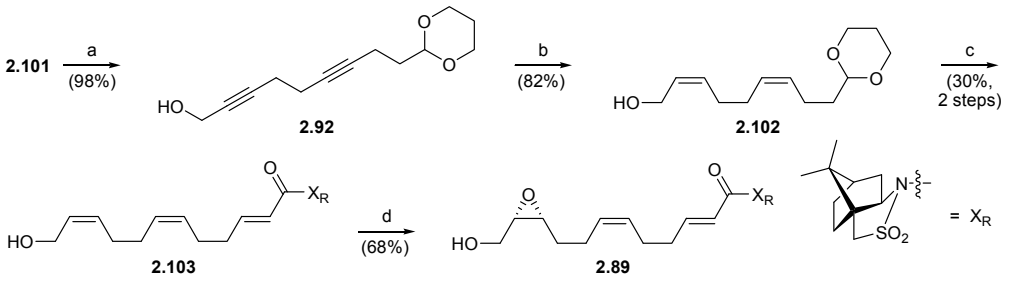
return lithiated 1,5-hexadienyne, allowing electrophile trapping. Initial experiments focussed on protonation of the expected dianion intermediate, but subsequent purification of 1,5-hexadienyne was unsuccessful. Secondly, *mono* alkylation was attempted using bromide **2.97** (1 equiv.) as the trapping electrophile which would provide alkyne **2.101**. Unfortunately alkylation was unsuccessful with HBr elimination from electrophile **2.97** a preferred pathway. Successful trapping was eventually achieved using TMSCl as the electrophile affording silane **2.99** in reasonable yield.



Scheme 2.32 Synthesis of acetal **2.101**. *Reagents and conditions*: a) Br_2, CH_2Cl_2; b) LDA, THF, –78 °C, then TMSCl; c) MeLi•LiBr, THF, –78 °C, then HMPA, **2.97**; d) K_2CO_3, MeOH.

Desymmetrisation of silane **2.99** was accomplished by selective desilylation, using MeLi•LiBr complex (1.5 equiv.) followed by alkylation with bromide **2.97** to provide silyl alkyne **2.100** in poor yield.[163] Efficient desilylation of silane **2.100** returned alkyne **2.101**.

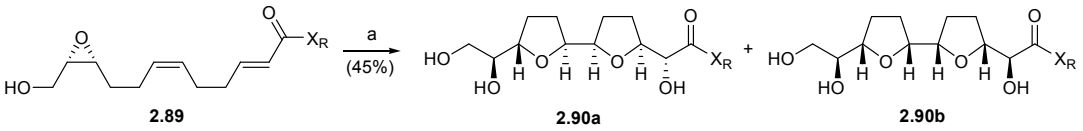
Mono lithiated alkyne **2.101** was reacted with an excess of paraformaldehyde affording propargylic alcohol **2.92** in excellent yield (scheme 2.33). Partial reduction of dialkyne **2.92** under a hydrogen atmosphere using Lindlar catalyst gave *Z*,*Z* diene **2.102** in reasonable yield. Unfortunately, repeating this reaction on a larger scale successfully reduced the alkyne bonds but caused isomerisation of the alkenes to give a mixture of isomeric dienes.



Scheme 2.33 Synthesis of dienoyl **2.89**. *Reagents and conditions*: a) *n*-BuLi, THF, –78 °C, then paraformaldehyde; b) H_2, Lindlar catalyst, quinoline, EtOAc; c) (i) H_2SO_4:dioxane:H_2O (1:49.5:49.5), Δ; (ii) $(EtO)_2POCH_2COX_R$, DIPEA, LiCl, MeCN; d) DET-(+), Ti(O*i*-Pr)$_4$, *t*-BuOOH, CH_2Cl_2.

Acid hydrolysis of acetal **2.102** provided an aldehyde which under went HWE olefination returning triene **2.103** in disappointing yield.[142] Allylic alcohol **2.103** was submitted to Sharpless asymmetric epoxidation furnishing epoxide **2.89** in satisfactory yield (*ee* not determined, typical *ee* for *cis* allylic alcohol is between 85 – 90%).[160]

With epoxydiene **2.89** in hand the key cascade oxidative cyclisation was studied (scheme 2.34). Oxidative cyclisation of epoxydiene **2.89** would give 2 possible diastereoisomers from attack of permanganate from either face. Therefore triols **2.90a**/**b** would be the expected major products from cascade oxidative cyclisation if you do not consider the epoxide isomers.



2.89 **2.90a** **2.90b**

Scheme 2.34 Synthesis of triol **2.90a**/**b**. *Reagents and conditions*: a) $KMnO_4$ (1.3 equiv), AcOH/acetone (1:3), –40 °C.

A one-off oxidative cyclisation of epoxydiene **2.89** gave triols **2.90a**/**b** in a combined yield of 45%. Diastereoselectivity for the reaction is undetermined, with relative and absolute stereochemistry tentatively assigned. Due to time and material constraints no further study was possible, but the cascade oxidative cyclisation concept appears to provide a viable route to adjacent *bis*-THF core motifs.

Conclusion

- Silane **2.99** was successfully desymmetrised by a selective desilylation-alkylation procedure.
- Cascade oxidative cyclisation of diene **2.89** was achieved delivering adjacent *bis*-THF triols **2.90a**/**b**.

Future work

Initially, the cascade oxidative cyclisation of epoxydiene **2.89** would need to be repeated on a larger scale, so diastereoselectivities and ring stereochemistry could be confirmed. A problem with the routes shown in section 2.5 is the Sharpless asymmetric epoxidation of the *cis*-allylic alcohols, as typical enantioselectivity's are between 80-90%.[160] A possible solution would be to

follow work by Yamamoto, where a vanadium asymmetric epoxidation of *cis*-homoallylic alcohols proceeds with excellent enantioselectivity.[164]

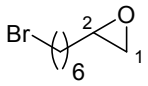
A more ambitious plan assuming that all aspects of the permanganate cascade oxidative cyclisation are satisfactory would be to again apply it to the synthesis of (+)-muconin (**2.64**). A study of the oxidative cyclisation of 1,6-dienes with permanganate would be required to improve our knowledge of the reaction. Armed with this extra knowledge, it would be hoped that cascade oxidative cyclisation of a suitable diene epoxide with permanganate would give the adjacent THP-THF core, with relative and absolute stereochemistry identical to (+)-muconin (**2.64**). From this point no major obstacles are foreseen in the total synthesis of (+)-muconin (**2.64**).

Chapter 3: Experimental

General procedures

All reactions which were air and/or moisture sensitive were run under an inert atmosphere of either argon or nitrogen using oven-dried glassware. THF was distilled over Na/benzophenone, dichloromethane was distilled over CaH_2, benzene and toluene were distilled over sodium prior to use. All other solvents and reagents were purified according to standard procedures.[165] Thin-layer chromatography was carried out on Merck silica gel aluminium-backed plates with a fluoresence indicator (254 nm). Visualisation of TLC plates was carried out by UV light, then by either a cerium sulphate/ammonium molybdate or $KMnO_4$ stain. Flash chromatography was preformed with 35–70 μm silica gel (Fisher Davisil). Infrared spectra were recorded using a FTIR spectrometer fitted with an ATR accessory. Absorption peaks were recorded in cm^{-1} and were described as strong (s), medium (m), weak (w) or broad (br). ^1H NMR and ^{13}C NMR were recorded using a Bruker AC300 or AV300 (at 300 and 75 MHz) or a Bruker DPX400 (400 and 100 MHz) in $CDCl_3$ with chloroform (7.27 ppm ^1H, 77.0 ppm ^{13}C) or in C_6D_6 with benzene (7.16 ppm ^1H, 128.4 ppm ^{13}C) or $(CD_3)_2SO$ with DMSO (2.50 ppm ^1H, 39.5 ppm ^{13}C) as an internal reference. Chemical shifts δ are given in ppm; multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad); coupling constants, *J*, are reported in Hz. Proton assignments have been made using a combination of 1D and 2D experiments. Low resolution mass spectra using electrospray ionisation (ESI) were recorded on a Fisons VG platform single quadrupole mass spectrometer. Chiral analytical HPLC was preformed on a HP1090 series LC system with Chiralcel OD-H column with 254 nm detection, eluting with IPA/hexane mixtures.

2-(6-Bromohexyl)oxirane (**2.2**)



$C_8H_{15}BrO$
Exact Mass: 206.0306
Mol. Wt.: 207.1081

At room temperature under an atmosphere of N_2, to a vigorously stirred solution of 8-bromooct-1-ene (9.49 g, 0.0497 mol), pyrazole (0.46 g, 5.96 mmol) and methyltrioxorhenium (61.9 mg, 0.248 mmol) in CH_2Cl_2 (23.5 mL) was added dropwise 30% H_2O_2 aq (8.45 g, 0.0746 mol), the reaction was stirred for 24 hours. MnO_2 was carefully added and reaction was diluted with CH_2Cl_2 (75 mL) and water (75 mL), the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 75 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to afford a colourless oil. Purification on SiO_2 (8 x 4 cm) eluting with hexane/Et_2O (9:1) gave 2-(6-bromohexyl)oxirane (**2.2**) (10.1 g, 0.0493 mol, 98%) as a colourless oil.

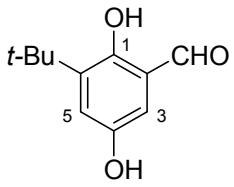
Spectroscopic characterisation agreed with that published.[135]

IR ν_{max} (neat) cm^{-1} 3044 (w), 2931 (s), 2857 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.40 (2H, t, *J* = 6.8 Hz, **C8**), 2.94 – 2.83 (1H, m, **C2**), 2.74 (1H, dd, *J* = 5.0, 4.0 Hz, **C1**), 2.46 (1H, dd, *J* = 5.0, 2.7 Hz, **C1**), 1.85 (2H, tt, *J* = 7.0, 6.8 Hz, **C7**), 1.59 – 1.31 (8H, m, **C3** – **C6**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 52.4 (CH_1), 47.2 (CH_2), 34.0 (CH_2), 32.8 (CH_2), 32.5 (CH_2), 28.7 (CH_2), 28.2 (CH_2), 26.0 (CH_2).

3-*tert*-Butyl-2,5-dihydroxybenzaldehyde (**2.8**)



$C_{11}H_{14}O_3$
Exact Mass: 194.0943
Mol. Wt.: 194.2271

At room temperature under an atmosphere of N_2, to a stirred solution of *tert*-butyl hydroquinone (50 g, 0.300 mol), DMAP (4.41 g, 0.036 mol) and imidazole (25.6 g, 0.380 mol) in CH_2Cl_2 (300 mL) was added dropwise TIPSCl (59.3 g, 65.8 mL, 0.308 mol). The reaction was stirred for 3 hours and poured into NH_4Cl (sat aq, 300 mL). The organic layer was separated, washed with brine, dried over

($MgSO_4$) and concentrated *in vacuo* to afford 2-(1,1-dimethylethyl)-4-(triisopropylsilyloxy)phenol as a viscous yellow oil.

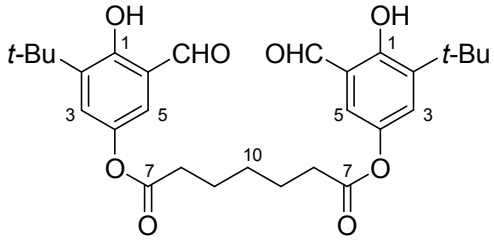
At 0 °C under an atmosphere of N_2, to a stirred solution of crude 2-(1,1-dimethylethyl)-4-(triisopropylsilyloxy)phenol, toluene (700 mL) and 2,6-lutidine (57.3 mL, 0.492 mol) was added $SnCl_4$ (14.2 mL, 0.120 mol) dropwise. The reaction was warmed to room temperature and stirred for 20 minutes then paraformaldehyde (55 g, 1.83 mol) was added. The reaction was heated at 100 °C for 12 hours then cooled to room temperature. 1M HCl (500 mL) was added and the mixture was filtered through a pad of Celite. The collected solids were washed with EtOAc (500 mL). The filtrates were combined, washed with brine, dried over ($MgSO_4$) and concentrated *in vacuo* to afford a dark oil which was dissolved in THF (800 mL). Under an atmosphere of N_2, the solution was cooled to –78 °C and 1M TBAF in THF (360 mL, 0.36 mol) was added. The reaction was warmed to room temperature and stirred for 2 hours. The reaction was diluted with water (800 mL) and EtOAc (800 mL). The organic layer was separated, washed with brine, dried over ($MgSO_4$) and concentrated *in vacuo* to afford a dark solid. The dark solid was suspended in CH_2Cl_2, filtered and washed with cold CH_2Cl_2 providing 3-*tert*-butyl-2,5-dihydroxybenzaldehyde (**2.8**) (34.9 g, 0.18 mol, 60% yield, over 3 steps) as a yellow powder.
Spectroscopic characterisation agreed with that published.[138]

IR ν_{max} (neat) cm^{-1} 3329 (s), 2960 (m), 1645 (s), 1587 (s), 1297 (s).

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.37 – 11.14 (1H, m, **OH**), 9.97 – 9.77 (1H, m, **CHO**), 9.26 (1H, m, **OH**), 7.04 (1H, m, **C3**), 6.95 (1H, m, **C5**), 1.34 (9H, s, ***t*-Bu**).

^{13}C NMR (75 MHz, DMSO-d_6) δ 198.2 (CH_1), 153.0 (C), 149.6 (C), 138.4 (C), 122.8 (CH_1), 120.7 (C), 115.3 (CH_1), 34.4 (C), 29.0 (CH_3).

bis(3-*tert*-Butyl-5-formyl-4-hydroxyphenyl) heptanedioate (**2.10**)



$C_{29}H_{36}O_8$
Exact Mass: 512.241
Mol. Wt.: 512.5913

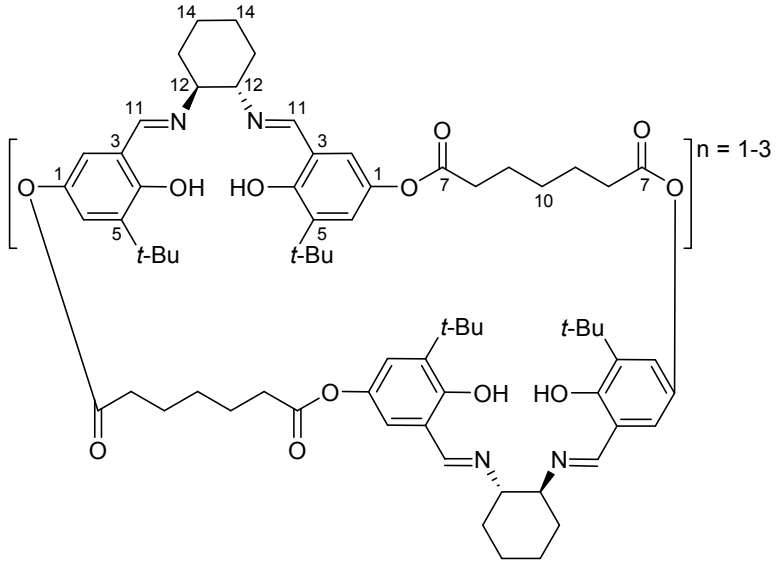
At 0 °C under an atmosphere of N_2, to a stirred solution of 3-*tert*-butyl-2,5-dihydroxybenzaldehyde (**2.8**) (5.57 g, 28.7 mmol), DMAP (0.34 g, 2.8 mmol), pimelic acid (2.24 g, 14 mmol) in CH_2Cl_2 (27 mL) and DMF (2 mL) was added 1,3-diisopropylcarbodiimide (4.60 mL, 29.4 mmol). The reaction was stirred at 0 °C for 5 minutes and at room temperature for 2 hours. The reaction was diluted with CH_2Cl_2 (150 mL), and washed with 0.1 M HCl (150 mL) and brine (150 mL). The organic phase were dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was suspended in hexanes (200 mL), filtered and washed with 2% K_2CO_3 (4 x aq 50 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to provide *bis*(3-*tert*-butyl-5-formyl-4-hydroxyphenyl) heptanedioate (**2.10**) (7.11 g, 13.9 mmol, 99%) as a yellow oil.
Spectroscopic characterisation agreed with that published.[138]

IR ν_{max} (neat) cm^{-1} 2958 (m), 1755 (s), 1652 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.71 (2H, s, **OH**), 9.81 (2H, s, **CHO**), 7.21 (2H, d, *J* = 2.8 Hz, **C5**), 7.18 (2H, d, *J* = 2.8 Hz, **C3**), 2.63 (4H, t, *J* = 7.5 Hz, **C8**), 1.85 (4H, quin, *J* = 7.5 Hz, **C9**), 1.64 – 1.51 (2H, m, **C10**), 1.44 – 1.36 (18H, s, ***t*-Bu**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 196.5 (CH_1), 172.4 (C), 159.1 (C), 142.5 (C), 140.3 (C), 128.1 (CH_1), 123.3 (CH_1), 120.2 (C), 35.2 (C), 34.1 (CH_2), 29.2 (CH_3), 28.6 (CH_2), 24.6 (CH_2).

Oligomeric salen ligand 2.12



Under an atmosphere of N_2, a solution of (*S,S*)-1,2-diammoniumcyclohexanemono-(–)-tartrate salt (1.75 g, 6.59 mmol), K_2CO_3 (1.84 g, 13.32 mmol) in THF (22 mL) and water (8.2 mL) were heated to reflux. Dialdehyde **2.10** (3.41 g, 6.66 mmol) in THF (22 mL) was added and the reaction was stirred at reflux for 2 hours, then cooled to room temperature and diluted with EtOAc (100 mL). The organic layer was separated, washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to afford oligomeric salen ligand **2.12** (3.88 g, 99%) as a yellow solid.

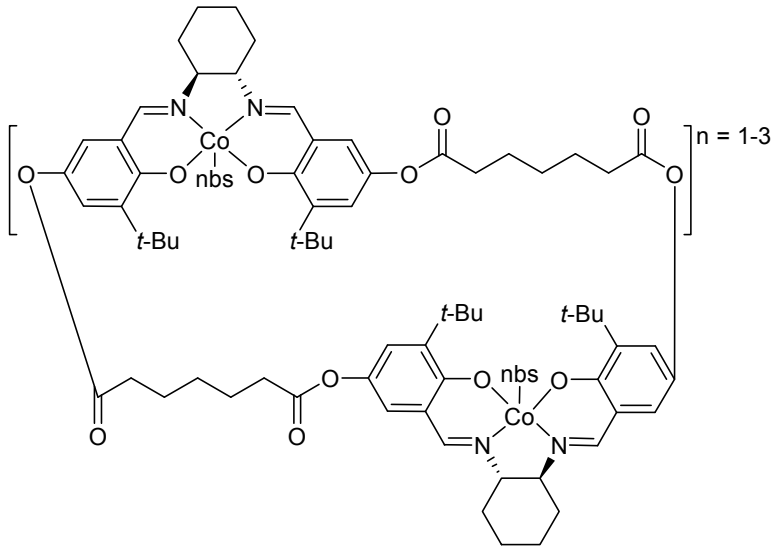
Spectroscopic characterisation agreed with that published.[138]

IR ν_{max} (neat) cm^{-1} 2931 (s), 2860 (s), 1755 (s), 1632 (s), 1593 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ 13.77 (2H, br s, **OH**), 8.24 (2H, s, **C11**), 6.94 (2H, d, *J* = 2.7 Hz, **C2**), 6.78 (2H, d, *J* = 2.7 Hz, **C4**), 3.32 (2H, m, **C12**), 2.54 (4H, t, *J* = 7.4 Hz, **C8**), 2.02 – 1.62 (8H, m, **C9** and **C13**), 1.62 – 1.23 (24H, m, **C10**, **C14** and ***t*-Bu**).

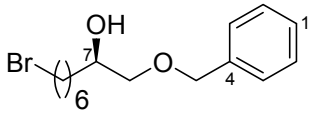
^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6 (C), 164.9 (CH_1), 158.2 (C), 141.7 (C), 138.8 (C), 123.1 (CH_1), 121.5 (CH_1), 118.3 (C), 72.4 (CH_1), 35.1 (C), 34.2 (CH_2), 33.2 (CH_2), 29.3 (CH_3), 28.7 (CH_2), 24.7 (CH_2), 24.4 (CH_2).

Oligomeric Co(salen) catalyst 2.13



At room temperature under an atmosphere of N_2, to a stirred degassed solution of oligomeric salen ligand **2.10** (0.390 g, 0.66 mmol) in toluene (7 mL) was added a degassed solution of $Co(OAc)_2 \bullet 2H_2O$ (0.329 g, 1.32 mmol) in MeOH (7 mL) *via* canula. The reaction was stirred for 30 minutes where 3-nitrobenzenesulfonic acid *mono* hydrate (0.291 g, 1.32 mmol) in CH_2Cl_2 (10 mL) were added. The reaction was stirred open to the air for 2 hours. The reaction was concentrated *in vacuo* to afford a brown residue which was suspended in CH_2Cl_2. The suspension was filtered through a pad of celite to remove excess $Co(OAc)_2$ and the celite was washed with CH_2Cl_2 (500 mL). The filtrate was concentrated *in vacuo* to afford the oligomeric Co(salen) catalyst **2.13** (474 mg, 0.528 mmol, 80%) as a black solid which was used crude in the next step.

(*R*)-1-(Benzyloxy)-8-bromooctan-2-ol (**2.5**)



$C_{15}H_{23}BrO_2$
Exact Mass: 314.0881
Mol. Wt.: 315.2459

At 0 °C under an atmosphere of Ar, to a stirred solution of 2-(6-bromohexyl)oxirane (9.5 g, 0.0458 mol) and oligomeric Co(salen) (*S,S*) **2.13** (106 mg, 0.118 mmol) in MeCN (3.5 mL) was added dropwise benzyl alcohol (2.14 mL, 0.0206 mol), the reaction was stirred for 24 hours. The reaction was filtered through a plug of silica with Et_2O (300 mL) and concentrated *in vacuo* to afford an orange oil. Purification on SiO_2 (8 x 10 cm) eluting with hexane/Et_2O (4:1)

then hexane/Et_2O (0:1) gave enantiometrically enriched (*S*)-2-(6-bromohexyl)oxirane (**2.2**) (4.82 g, 0.0233 mol) as a colourless oil and (*R*)-1-(benzyloxy)-8-bromooctan-2-ol (**2.5**) (6.5 g, 0.0206 mol, 99%) as a orange oil.

$[\alpha]^{25}_D$ –1.1 ($CHCl_3$, *c* 1.4).

IR ν_{max} (neat) cm^{-1} 3447 (br), 2931 (m), 2856 (m).

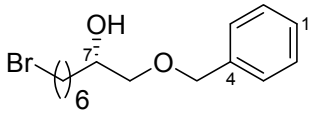
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.20 (5H, m, **C1**, **C2** and **C3**), 4.57 (2H, s, **C5**), 3.87 – 3.76 (1H, m, **C7**), 3.51 (1H, dd, *J* = 9.4, 3.1 Hz, **C6**(1H)), 3.41 (2H, t, *J* = 6.8 Hz, **C13**), 3.34 (1H, dd, *J* = 9.4, 7.9 Hz, **C6**(1H)), 2.37 (1H, d, *J* = 2.9 Hz, **OH**), 1.86 (2H, br p, *J* = 7.1 Hz, **C12**), 1.51 – 1.31 (8H, m, **C8** – **C11**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.12 (C), 128.6 (CH_1), 128.0 (CH_1), 127.9 (CH_1), 74.8 (CH_2), 73.5 (CH_2), 70.5 (CH_1), 34.0 (CH_2), 33.2 (CH_2), 32.9 (CH_2), 28.9 (CH_2), 28.2 (CH_2), 25.5 (CH_2).

LRMS ESI+ 337 $[M+Na]^+$ (100%), 339 $[M+Na]^+$ (83%).

HRMS ESI+ $[M+Na]^+$ calculated = 337.0774, $[M+Na]^+$ found = 337.0770.

(*S*)-1-(Benzyloxy)-8-bromooctan-2-ol (*ent*-**2.5**)

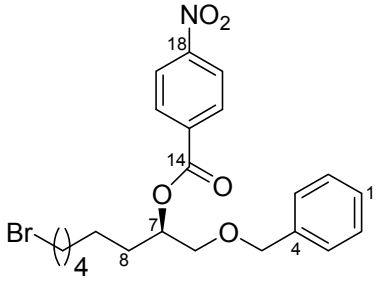


$C_{15}H_{23}BrO_2$
Exact Mass: 314.0881
Mol. Wt.: 315.2459

At 0 °C under an atmosphere of Ar, to a stirred solution of enantiometrically enriched (*S*)-2-(6-bromohexyl)oxirane (4.75 g, 0.0229 mol) and oligomeric Co(salen) (*R,R*) (51 mg, 0.057 mmol) in MeCN (1.75 mL) was added dropwise benzyl alcohol (2.14 mL, 0.0206 mol), the reaction was stirred for 24 hours. The reaction was filtered through a plug of silica with Et_2O (250 mL) and concentrated *in vacuo* to afford an orange oil. Purification on SiO_2 (11 x 5 cm) eluting with hexane/Et_2O (4:1) then hexane/Et_2O (1:3) gave 2-(6-bromohexyl)oxirane (**2.2**) (0.375 g, 1.81 mmol, 8%) as a colourless oil and (*S*)-1-(benzyloxy)-8-bromooctan-2-ol (*ent*-**2.5**) (6.47 g, 0.0206 mol, 99%) as an orange oil.
Spectroscopic characterisation for benzyl ether *ent*-**2.5** identical to benzyl ether **2.5** except for the shown data.

$[\alpha]^{25}_{D}$ +4.4 ($CHCl_3$, *c* 0.94).

(*R*)-1-(Benzyloxy)-8-bromooctan-2-yl 4-nitrobenzoate (**2.14**)



$C_{22}H_{26}BrNO_5$
Exact Mass: 463.0994
Mol. Wt.: 464.3495

At –30 °C under an atmosphere of N_2, to a stirred solution of (*S*)-1-(benzyloxy)-8-bromooctan-2-ol (*ent*-**2.5**) (6.90 g, 0.0219 mol), triphenyl phosphine (11.8 g, 0.0449 mol) and 4-nitrobenzoic acid (12.8 g, 0.0767 mol) in dry THF (74 mL) was added dropwise DIAD 95% (9.08 mL, 0.0438 mol). The reaction was allowed to warm to room temperature over 2 hours and stirred for a further 2 hours. The reaction was concentrated *in vacuo* to afford a yellow oil. Purification on SiO_2 (10 x 10 cm) eluting with hexane/Et_2O (9:1 → 4:1) gave (*R*)-1-(benzyloxy)-8-bromooctan-2-yl 4-nitrobenzoate (**2.14**) (8.83 g, 0.019 mol, 87%) as a pale yellow oil.

$[\alpha]^{29}_{D}$ +11.6 ($CHCl_3$, *c* 1.13).

IR ν_{max} (neat) cm^{-1} 2933 (m), 2858 (m), 1721 (s), 1526 (s), 1348 (m), 1271 (s).

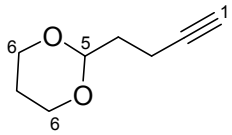
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (2H, d with fine splitting, *J* = 9.0 Hz, **C17**), 8.15 (2H, d with fine splitting, *J* = 9.0 Hz, **C16**), 7.37 – 7.23 (5H, m, **C1** – **C3**), 5.35 (1H, br p, *J* = 5.3 Hz, **C7**), 4.61 (1H, d, *J* = 12.3 Hz, **C5**), 4.53 (1H, d, *J* = 12.3 Hz, **C5**), 3.67 (2H, d, *J* = 4.9 Hz, **C6**), 3.39 (2H, t, *J* = 6.8 Hz, **C13**), 1.81 (4H, m, **C8** and **C12**), 1.43 (6H, m, **C9** – **C11**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7 (C), 150.9 (C), 138.2 (C), 136.2 (C), 131.1 (CH_1), 128.7 (CH_1), 128.1 (CH_1), 127.9 (CH_1), 123.8 (CH_1) 74.9 (CH_1), 73.5 (CH_2) 71.3 (CH_2), 34.1 (CH_2) 32.9 (CH_2) 31.1 (CH_2), 28.9 (CH_2), 28.3 (CH_2), 25.4 (CH_2).

LRMS ESI+ 488 $[M+Na]^+$ (100%), 486 $[M+Na]^+$ (93%).

HRMS ESI+ $[M+Na]^+$ calculated = 486.0887, $[M+Na]^+$ found = 486.0884.

2-(But-3-ynyl)-1,3-dioxane (**2.15**)



$C_8H_{12}O_2$
Exact Mass: 140.0837
Mol. Wt.: 140.1797

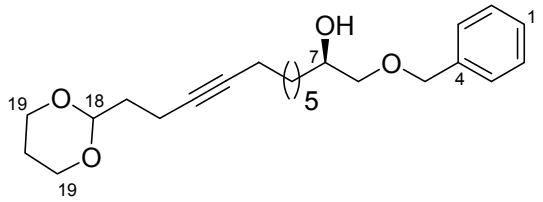
At 0 °C under an atmosphere of N_2, to a stirred solution of 2-(2-bromoethyl)-1,3-dioxane (33.4 mL, 0.245 mol), distilled TMEDA (33.5 mL, 0.49 mol) in dry THF (500 mL) was added portionwise lithium acetylide ethylene diamine complex 90% (50 g, 0.49 mol) followed by dropwise addition of HMPA (42.6 mL, 0.245 mol), the reaction was allowed to warm to room temperature and stirred for 24 hours (Reaction monitored by GC). Reaction was slowly poured into NH_4Cl (sat aq, 400 mL), the organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 200 mL). The combined organic phases were washed with water (300 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to afford crude brown oil. Purification by distillation under reduced pressure (59–61 °C, 9 mbar) gave 2-(but-3-ynyl)-1,3-dioxane (**2.15**) as a colourless oil (25.0g, 0.179 mol, 73%).

IR ν_{max} (neat) cm^{-1} 3291 (m), 2966 (s), 2852 (s), 2118 (w), 1135 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.66 (1H, t, *J* = 5.2 Hz, **C5**), 4.11 (2H, dd, *J* = 10.6, 5.1 Hz, **C6^{eq}**), 3.78 (2H, m, **C6^{ax}**), 2.30 (2H, td, *J* = 7.4, 2.6 Hz, **C3**), 2.07 (1H, dtt, *J* = 13.4, 12.5, 5.1 Hz, **C7^{ax}**), 1.94 (1H, t, *J* = 2.6 Hz, **C1**), 1.81 (2H, td, *J* = 7.4, 5.2 Hz, **C4**), 1.35 (1H, d with fine splitting, *J* = 13.4 Hz, **C7^{eq}**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 100.6 (CH_1), 83.8 (CH_1) 68.3 (C), 66.9 (CH_2) 33.8 (CH_2), 25.8 (CH_2) 13.2 (CH_2).

(*R*)-1-(Benzyloxy)-12-(1,3-dioxan-2-yl)dodec-9-yn-2-ol (**2.16**)



$C_{23}H_{34}O_4$
Exact Mass: 374.2457
Mol. Wt.: 374.5137

At –78 °C under an atmosphere of Ar, to a stirred solution of 2-(but-3-ynyl)-1,3-dioxane (**2.15**) (4.83 g, 0.0345 mol) in dry THF (42 mL) was added 2.11M *n*-BuLi

in hexane (15.9 mL, 0.0336 mol). After stirring for 15 minutes, HMPA (11.7 mL, 0.0672 mmol) was added dropwise. After stirring for 30 minutes, bromide **2.5** (5.3 g, 0.0168 mol) was added dropwise. The reaction was allowed to warm to room temperature and stirred for 90 minutes. The reaction was slowly poured into NH_4Cl (sat aq, 50 mL), the organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 50 mL) and CH_2Cl_2 (1 x 50 mL). The combined organic phases were concentrated *in vacuo* to give a yellow oil. The yellow oil was dissolved in Et_2O (150 mL) and washed with water (3 x 150 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil. Purification on SiO_2 (15 x 8 cm) eluting with hexane/Et_2O (1:0 → 0:1) gave (*R*)-1-(benzyloxy)-12-(1,3-dioxan-2-yl)dodec-9-yn-2-ol (**2.16**) (5.20 g, 0.0139 mol, 83%) as a colourless oil.

$[\alpha]^{28}_D$ –2.5 ($CHCl_3$, *c* 1.6).

IR ν_{max} (neat) cm^{-1} 3470 (br), 2932 (s), 2856 (s), 2025 (w), 1135 (s).

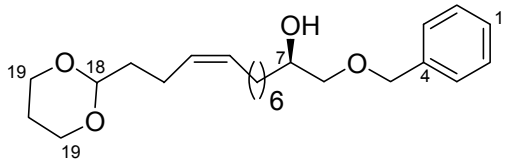
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.16 (5H, m, **C1, C2** and **C3**), 4.64 (1H, t, *J* = 5.2 Hz, **C18**), 4.56 (2H, s, **C5**), 4.09 (2H, dd, *J* = 10.6, 5.0 Hz, **C19^{eq}**), 3.88 – 3.69 (3H, m, **C7** and **C19^{ax}**), 3.51 (1H, dd, *J* = 9.4, 3.2 Hz, **C6**(1H)), 3.33 (1H, dd, *J* = 9.4, 7.9 Hz, **C6**(1H)), 2.33 (1H, br s, **OH**), 2.25 (2H, tt, *J* = 7.2, 2.2 Hz, **C16**), 2.18 – 1.98 (3H, m, **C13** and **C20^{ax}**), 1.77 (2H, td, *J* = 7.2, 5.2 Hz, **C17**), 1.55 – 1.22 (11H, m, **C8** – **C12** and **C20^{eq}**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2 (C), 128.6 (CH_1), 127.9 (CH_1), 127.9 (CH_1), 101.2 (CH_1), 80.5 (C), 79.4 (C), 74.8 (CH_2), 73.5 (CH_2), 70.6 (CH_1), 67.1 (CH_2), 34.7 (CH_2), 33.3 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 26.0 (CH_2), 25.6 (CH_2), 18.9 (CH_2), 13.8 (CH_2).

LRMS ESI+ 397 $[M+Na]^+$ (100%).

HRMS ESI+ $[M+Na]^+$ calculated = 397.2349, $[M+Na]^+$ found = 397.2351.

(*R*,*Z*)-1-(Benzyloxy)-12-(1,3-dioxan-2-yl)dodec-9-en-2-ol (**2.17**)



$C_{23}H_{36}O_4$
Exact Mass: 376.2614
Mol. Wt.: 376.5295

Under an atmosphere of H_2, a solution of (*R*)-1-(benzyloxy)-12-(1,3-dioxan-2-yl)dodec-9-yn-2-ol (**2.16**) (5.63 g, 15.1 mmol), Lindlar catalyst (Pd 5%, calcium carbonate poisoned with Pb) (0.96 g, 0.452 mol) in hexane (150 mL) was stirred for 4 hours. The reaction was filtered through celite and washed through with EtOAc (300 mL). The filtrate was dried ($MgSO_4$) and concentrated *in vacuo* to afford a pale yellow oil. Purification on SiO_2 (7 x 7 cm) eluting with hexane/Et_2O (1:1) gave (*R*,*Z*)-1-(benzyloxy)-12-(1,3-dioxan-2-yl)dodec-9-en-2-ol (**2.17**) (5.48 g, 14.6 mol, 97%) as a colourless oil.

$[\alpha]^{25}_D$ –2.2 ($CHCl_3$, *c* 1.08).

IR ν_{max} (neat) cm^{-1} 3472 (br), 2925 (s), 2852 (s), 1653 (w), 1136 (s), 1085 (s);

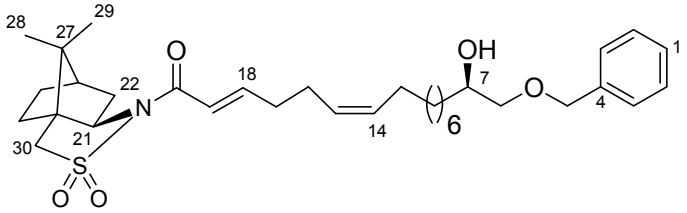
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.22 (5H, m, **C1, C2** and **C3**), 5.49 – 5.22 (2H, m, **C14** and **C15**), 4.56 (2H, s, **C5**), 4.51 (1H, t, *J* = 5.3 Hz, **C18**), 4.11 (2H, dd with fine splitting, *J* = 10.6, 5.0 Hz, **C19^{eq}**), 3.89 – 3.67 (3H, m, **C7** and **C19^{ax}**), 3.51 (1H, dd, *J* = 9.4, 3.0 Hz, **C6**(1H)), 3.32 (1H, dd, *J* = 9.4, 8.0 Hz, **C6**(1H)), 2.42 (1H, d, *J* = 3.2 Hz, **OH**), 2.22 – 1.90 (5H, m, **C13**, **C16** and **C20^{ax}**), 1.71 – 1.55 (2H, m, **C17**), 1.53 – 1.15 (11H, m, **C8** – **C12** and **C20^{eq}**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2 (C), 130.8 (CH_1), 128.9 (CH_1), 128.6 (CH_1), 127.9 (CH_1), 102.0 (CH_1), 74.9 (CH_2), 73.5 (CH_2), 70.6 (CH_1), 67.1 (CH_2), 35.2 (CH_2), 33.3 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 27.3 (CH_2), 26.0 (CH_2), 25.6 (CH_2), 22.0 (CH_2).

LRMS ESI+ 399 $[M+Na]^+$ (100%).

HRMS ESI+ $[M+Na]^+$ calculated = 399.2506, $[M+Na]^+$ found = 399.2496.

(2*E*,6*Z*)-(R)-15-Benzyloxy-1-((*R*)-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-14-hydroxy-pentadeca-2,6-dien-1-one (**2.19**)



$C_{32}H_{47}NO_5S$
Exact Mass: 557.3175
Mol. Wt.: 557.7843

To a solution of (*R*,*Z*)-1-(benzyloxy)-12-(1,3-dioxan-2-yl)dodec-9-en-2-ol (**2.17**) (5.48 g, 14.6 mmol) in 1,4-dioxane: water: conc. H_2SO_4 (49.5: 49.5: 1) (550 mL) was refluxed for 6 hours. The reaction was diluted with Et_2O (300 mL) and washed with water (100 mL), $NaHCO_3$ (sat aq, 2 x 100 mL) and brine (100 mL). The organic layer were dried (Na_2SO_4) and concentrated *in vacuo* to afford a pale yellow oil which was used crude in the next step.

Under an atmosphere of N_2, to a stirred solution of (1*S*,2*R*)-camphorsultam phosphonate (6.9 g, 17.5 mmol) in dry acetonitrile (60 mL) was added dried lithium chloride (170 °C/ 0.035 mbar overnight) (0.74 g, 17.5 mmol). After stirring for 15 minutes, dry DIPEA (3.1 mL, 17.5 mmol) was added. After stirring for 10 minutes, crude (*R*,*Z*)-13-(benzyloxy)-12-hydroxytridec-4-enal in dry acetonitrile (5 mL) was then added. The reaction was left to stir for 20 hours. The reaction was diluted with water (50 mL) and brine (50 mL) then extracted with Et_2O (3 x 100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give an orange oil. Purification on SiO_2 (10 x 10 cm) eluting with Et_2O/hexane (3:2 → 4:1) gave diene **2.19** (8.14 g, 13.0 mmol, 89% over 2 steps) as a colourless oil.

[α]$^{26.5}_D$ –52.7 ($CHCl_3$, *c* 1.4).

IR ν_{max} (neat) cm^{-1} 3481 (br), 2928 (s), 2855 (s), 1682 (s), 1638 (s).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.25 (5H, m, **C1** – **C3**), 7.08 (1H, dt, *J* = 15.1, 6.9 Hz, **C18**), 6.58 (1H, d, *J* = 15.1 Hz, **C19**), 5.46 – 5.30 (2H, m, **C14** and **C15**), 4.56 (2H, s, **C5**), 3.93 (1H, dd, *J* = 7.5, 5.1 Hz, **C21**), 3.86 – 3.77 (1H, m, **C7**), 3.52 (1H, dd, *J* = 9.4, 3.1 Hz, **C6**(1H)), 3.50 (1H, d, *J* = 13.8 Hz, **C30**(1H)), 3.43

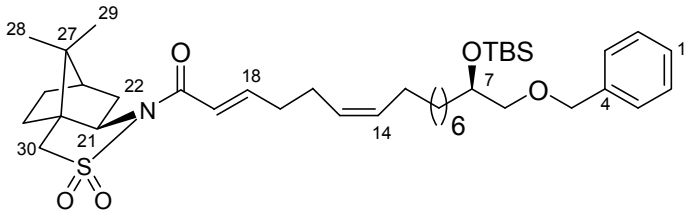
(1H, d, *J* = 13.8 Hz, **C30**(1H)), 3.34 (1H, dd, *J* = 9.4, 7.8 Hz, **C6**(1H)), 2.37 – 2.26 (3H, m, **C17** and **OH**), 2.25 – 2.16 (2H, m, **C16**), 2.15 – 2.06 (2H, m, **C22**), 2.05 – 1.94 (2H, m, **C13**), 1.95 – 1.83 (3H, m, **C23** and **C24**(1H) and **C25**(1H)), 1.52 – 1.24 (12H, m, **C8 – C12, C24**(1H) and **C25**(1H)), 1.18 (3H, s, **C29**), 0.98 (3H, s, **C28**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2 (C), 150.3 (CH_1), 138.3 (C), 131.4 (CH_1), 128.6 (CH_1), 127.9 (CH_1), 127.9 (CH_1), 121.3 (CH_1), 74.9 (CH_2), 73.5 (CH_2), 70.6 (CH_1), 65.3 (CH_1), 53.3 (CH_2), 48.6 (C), 48.0 (C), 44.9 (CH_1), 38.7 (CH_2), 33.4 (CH_2), 33.0 (CH_2), 32.8 (CH_2), 29.7 (CH_2), 29.3 (CH_2), 27.4 (CH_2), 26.7 (CH_2), 26.0 (CH_2), 25.6 (CH_2), 21.0 (CH_3), 20.1 (CH_3).

LRMS 580.4 $[M+Na]^+$ (100%).

HRMS ESI+ $[M+Na]^+$ calculated = 580.3067, $[M+Na]^+$ found = 580.3058.

(2*E*,6*Z*)-(*R*)-15-Benzyloxy-14-(*tert*-butyl-dimethyl-silanyloxy)-1-((*R*)-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-pentadeca-2,6-dien-1-one (**2.20**)



$C_{38}H_{61}NO_5SSi$
Exact Mass: 671.404
Mol. Wt.: 672.0451

At –10 °C under an atmosphere of N_2, to a stirred solution of alcohol **2.19** (5.00 g, 8.98 mmol) and 2,6-lutidine (3.66 mL, 31.43 mmol) in dry CH_2Cl_2 (30 mL) was added TBSOTf (4.14 mL, 17.96 mmol). The reaction was stirred for 20 minutes then warmed to room temperature for 15 minutes. The reaction was diluted with NH_4Cl (sat aq, 50 mL), the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were washed with $NaHCO_3$ (sat aq, 50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification on SiO_2 (5 x 10 cm) eluting with Et_2O/hexane (1:9) gave diene **2.20** (5.84 g, 8.71 mmol, 97%) as a colourless oil.

$[\alpha]^{28}_D$ –38.3 ($CHCl_3$, *c* 1.28).

IR ν_{max} (neat) cm^{-1} 2927 (s), 2854 (s), 1683 (s), 1639 (s).

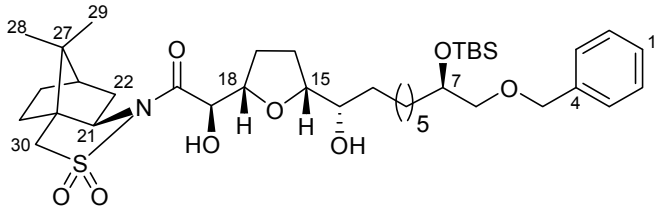
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.17 (5H, m, **C1** – **C3**), 7.02 (1H, dt, *J* = 15.1, 6.9 Hz, **C18**), 6.52 (1H, d, *J* = 15.1 Hz, **C19**), 5.44 – 5.20 (2H, m, **C14** and **C15**), 4.46 (2H, s, **C5**), 3.86 (1H, dd, *J* = 7.7, 5.0 Hz, **C21**), 3.80 – 3.72 (1H, br p, **C7**), 3.43 (1H, d, *J* = 13.7 Hz, **C30**(1H)), 3.36 (1H, d, *J* = 13.7 Hz, **C30**(1H)), 3.34 (1H, dd, *J* = 9.6, 6.0 Hz, **C6**(1H)), 3.31 (1H, dd, *J* = 9.6, 5.4 Hz, **C6**(1H)), 2.29 – 2.20 (2H, m, **C17**), 2.18 – 2.13 (2H, m, **C16**), 2.12 – 2.01 (2H, m, **C22**), 2.01 – 1.89 (2H, m, **C13**), 1.88 – 1.77 (3H, m, **C23** and **C24**(1H) and **C25**(1H)), 1.53 – 1.43 (1H, m, **C8**(1H)), 1.43 – 1.18 (11H, m, **C9** –**C12, C8**(1H), **C24**(1H) and **C25**(1H)), 1.12 (3H, s, **C29**), 0.91 (3H, s, **C28**), 0.83 (9H, s, **TBS**), 0.00 (3H, s, **TBS**), -0.01 (3H, s, **TBS**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3 (C), 150.4 (CH_1), 138.8 (C), 131.5 (CH_1), 128.5 (CH_1), 127.9 (CH_1), 127.8 (CH_1), 127.6 (CH_1), 121.3 (CH_1), 75.1 (CH_2), 73.5 (CH_2), 71.8 (CH_1), 65.4 (CH_1), 53.4 (CH_2), 48.6 (C), 48.0 (C), 44.9 (CH_1), 38.7 (CH_2), 34.9 (CH_2), 33.1 (CH_2), 32.8 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 27.5 (CH_2), 26.7 (CH_2), 26.1 (CH_1), 26.0 (CH_2), 25.4 (CH_2), 21.1 (CH_3), 20.1 (CH_3), 18.4 (C), -4.1 (CH_3), -4.5 (CH_3).

LRMS ESI+ 694.6 $[M+Na]^+$ (100%), 689.6 $[M+NH_4]^+$ (67%).

HRMS ESI+ $[M+Na]^+$ calculated = 694.3932, $[M+Na]^+$ found = 694.3915.

(*R*)-2-((2*S*,5*R*)-5-[(1*S*,8*R*)-9-Benzyloxy-8-(*tert*-butyl-dimethyl-silanyloxy)-1-hydroxy-nonyl]-tetrahydro-furan-2-yl)-1-((*R*)-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-hydroxy-ethanone (**2.21a**)



$C_{38}H_{63}NO_8SSi$
Exact Mass: 721.4044
Mol. Wt.: 722.0592

At –40 °C under an atmosphere of N_2, to a stirred solution of diene **2.20** (2.95 g, 4.4 mmol) in acetone/acetic acid (3:1 220 mL) was added powdered $KMnO_4$ (0.9 g, 5.72 mmol). The reaction was warmed to –30 °C over 40 minutes, the reaction

was quenched by addition of $Na_2S_2O_5$ (sat aq, 20 mL) and neutralised by addition of $NaHCO_3$ (sat aq, 100 mL). The organic layer was separated. The aqueous layer was re-extracted with EtOAc (3 x 150 mL) and CH_2Cl_2 (1 x 100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification on SiO_2 (5 x 15 cm) eluting with EtOAc/hexane (1:4 → 3:7) gave 3 main fractions: THF diol **2.21a** (1.94 g, 2.7 mmol, 61%) as a colourless oil, THF diol **2.21b** (0.22 g, 0.31 mmol, 7%) as a colourless oil and hydroxyl ketone **2.22** (0.59 g, 0.84 mmol, 19%) as a pale yellow oil.
Spectroscopic characterisation for THF diol **2.21a**.

$[\alpha]^{27}_D$ –15.6 ($CHCl_3$, *c* 1.5);

IR ν_{max} (neat) cm^{-1} 3467 (br), 2929 (s), 2855 (s), 1690 (s);

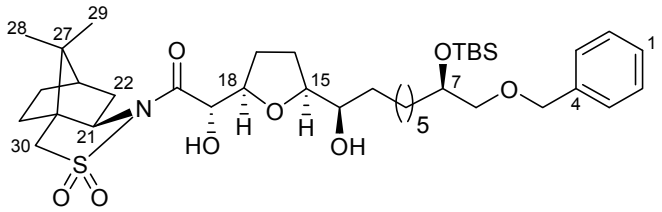
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.21 (5H, m, **C1** – **C3**), 4.65 – 4.61 (1H, ddd, *J* = 6.2, 5.7, 2.0 Hz, **C18**), 4.60 – 4.57 (1H, br d, *J* = 2.0 Hz, **C19**), 4.53 (2H, apparent s, **C5**), 4.14 (1H, br. s, **OH**), 3.99 – 3.90 (3H, m, **C14**, **C15** and **C21**), 3.86 – 3.76 (1H, dq, *J* = 6.4, 5.3 Hz, **C7**), 3.52 (1H, d, *J* = 13.8 Hz, **C30**(1H)), 3.45 (1H, d, *J* = 13.8 Hz, **C30**(1H)), 3.40 (1H, dd, *J* = 9.7, 5.3 Hz, **C6**(1H)), 3.37 (1H, dd, *J* = 9.7, 5.3 Hz, **C6**(1H)), 3.12 (1H, br d, *J* = 4.1 Hz, **OH**), 2.31 – 2.22 (1H, m, **C22**(1H)), 2.15 – 1.98 (4H, m, **C17**, **C16**(1H) and **C22**(1H)), 1.98 – 1.83 (3H, m, **C23**, **C24**(1H) and **C25**(1H)), 1.80 – 1.70 (1H, m, **C16**(1H)), 1.60 – 1.22 (12H, m, **C8** – **C13**, **C24**(1H) and **C25**(1H)), 1.16 (3H, s, **C29**), 0.97 (3H, s, **C28**), 0.89 (9H, s, **TBS**), 0.06 (3H, s, **TBS**), 0.05 (3H, s, **TBS**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0 (C), 138.7 (C), 128.5 (CH_1), 127.8 (CH_1), 127.6 (CH_1), 83.6 (CH_1), 78.3 (CH_1), 75.1 (CH_2), 74.3 (CH_1), 73.5 (CH_2), 72.2 (CH_1), 71.7 (CH_1), 66.0 (CH_1), 53.2 (CH_2), 49.2 (C), 48.1 (C), 44.7 (CH_1), 38.4 (CH_2), 34.9 (CH_2), 33.0 (CH_2), 32.8 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.0 (CH_2), 26.6 (CH_2), 26.2 (CH_2), 26.1 (CH_3), 25.4 (CH_2), 24.2 (CH_2), 20.9 (CH_3), 20.1 (CH_3), 18.4 (C), -4.2 (CH_3), -4.5 (CH_3).

LRMS ESI+ 745 $[M+Na]^+$ (100%).

HRMS ESI+ $[M+Na]^+$ calculated = 744.3936, $[M+Na]^+$ found = 744.3925.

(*S*)-2-((2*R*,5*S*)-5-[(1*R*,8*R*)-9-Benzyloxy-8-(*tert*-butyl-dimethyl-silanyloxy)-1-hydroxy-nonyl]-tetrahydro-furan-2-yl)-1-((*R*)-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-hydroxy-ethanone (**2.21b**)



$C_{38}H_{63}NO_8SSi$
Exact Mass: 721.4044
Mol. Wt.: 722.0592

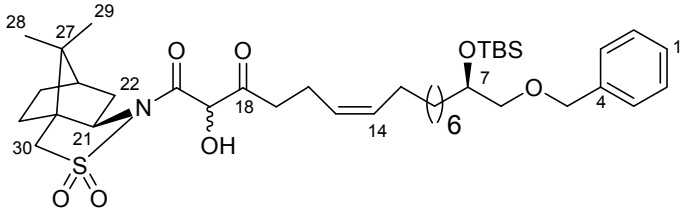
[α]$^{28}_D$ –59.0 ($CHCl_3$, *c* 0.93).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.24 (5H, m, **C1** – **C3**), 4.69 (1H, br s, **OH**), 4.53 (2H, apparent s, **C5**), 4.54 – 4.46 (2H, m, **C18** and **C19**), 3.95 (1H, dd, *J* = 7.3, 5.0 Hz, **C21**), 3.89 – 3.78 (3H, m, **C7**, **C14** and **C15**), 3.50 (1H, d, *J* = 13.8 Hz, **C30**(1H)), 3.45 (1H, d, *J* = 13.8 Hz, **C30**(1H)), 3.42 – 3.33 (2H, m, **C6**), 2.92 (1H, br s, **OH**), 2.23 – 2.13 (1H, m, **C22**(1H)), 2.12 – 2.00 (4H, m, **C17**, **C16**(1H) and **C22**(1H)), 1.96 – 1.85 (3H, m, **C23**, **C24**(1H) and **C25**(1H)), 1.79 – 1.22 (13H, m, **C8** – **C13**, **C16**(1H), **C24**(1H) and **C25**(1H)), 1.17 (3H, s, **C29**), 0.98 (3H, s, **C28**), 0.89 (9H, s, **TBS**), 0.06 (3H, s, **TBS**), 0.05 (3H, s, **TBS**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1 (C), 138.5 (C), 128.3 (CH_1), 127.6 (CH_1), 127.4 (CH_1), 83.4 (CH_1), 79.7 (CH_1), 74.9 (CH_2), 74.9 (CH_1), 73.3 (CH_2), 72.2 (CH_1), 71.5 (CH_1), 64.9 (CH_1), 53.0 (CH_2), 49.0 (C), 47.9 (C), 44.5 (CH_1), 37.7 (CH_2), 34.7 (CH_2), 32.6 (CH_2), 32.6 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 28.6 (CH_2), 26.6 (CH_2), 26.0 (CH_2), 25.9 (CH_3), 25.2 (CH_2), 24.3 (CH_2), 20.5 (CH_3), 19.9 (CH_3), 18.2 (C), -4.3 (CH_3), -4.7 (CH_3).

LRMS ESI+ 745 $[M+Na]^+$ (100%).

(*Z*)-(*R*)-15-Benzyloxy-14-(*tert*-butyl-dimethyl-silanyloxy)-1-((*R*)-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-hydroxy-pentadec-6-ene-1,3-dione (**2.22**)



$C_{38}H_{61}NO_7SSi$
Exact Mass: 703.3938
Mol. Wt.: 704.0439

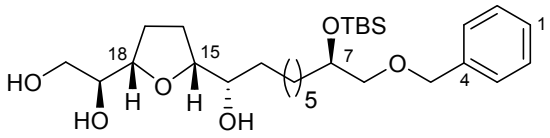
Spectroscopic characterisation for hydroxy ketone **2.22** isolated as a mixture of stereoisomers.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.24 (5H, m, **C1** – **C3**), 5.54 – 5.16 (3H, m, **C5**, **C14** and **C15**), 4.53 (2H, apparent s, **C5**), 4.22 – 4.06 + 3.95 (1H, m $_{4.22-4.06}$, $dd_{3.95}$, $J_{3.95}$ = 7.4, 5.2 Hz, **C21**), 3.82 (1H, m, **C7**), 3.61 – 3.33 + 3.18 – 3.06 (4H, 2 x m, **C6** and **C30**), 2.94 – 2.48 + 2.48 – 1.77 (12H, 2 x m, **C13**, **C17**, **C16**, **C22**, **C23**, **C24**(1H) and **C25**(1H)), 1.75 – 1.23 (12H, m, **C8**–**C12**, **C24**(1H) and **C25**(1H)), 1.22 + 1.16 + 1.14 (3H, 3 x s, **C29**), 1.07 + 0.98 + 0.94 (3H, 3 x s, **C28**), 0.89 (9H, s, **TBS**), 0.06 (3H, s, **TBS**), 0.05 (3H, s, **TBS**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2 (C), 178.0 (C), 138.5 + 138.4 (C), 131.7 + 131.5 (CH_1), 128.2 (CH_1), 127.5 (CH_1), 127.4 (CH_1), 127.0 (CH_1), 76.4 (CH_1), 74.8 + 74.8 (CH_2), 73.2 (CH_2), 71.5 (CH_1), 65.0 + 62.8 (CH_1), 52.8 + 50.3 (CH_2), 49.5 + 47.9 (C), 47.9 + 47.4 (C), 44.7 + 44.5 (CH_1), 39.3 (CH_2), 37.7 (CH_2), 36.1 (CH_2), 34.7 (CH_2), 34.6 (CH_2), 34.0 (CH_2), 32.7 (CH_2), 31.8 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 27.1 (CH_2), 26.8 (CH_2), 26.4 (CH_2), 25.9 (CH_3), 25.5 (CH_2), 25.1 (CH_2), 25.1 (CH_2), 22.5 (CH_2), 20.4 (CH_3), 19.9 (CH_3), 18.2 (C), -4.4 (CH_3), -4.8 (CH_3), Peaks between 39.3 – 22.5 except 25.9 represent 11 CH_2, extra peaks are assumed to come from stereoisomers.

LRMS ESI+ 746 $[M+Na]^+$ (100%).

(*S*)-1-((2*S*,5*R*)-5-[(1*S*,8*R*)-9-Benzyloxy-8-(*tert*-butyl-dimethyl-silanyloxy)-1-hydroxy-nonyl]-tetrahydro-furan-2-yl)-ethane-1,2-diol (2.23)



$C_{28}H_{50}O_6Si$
Exact Mass: 510.3377
Mol. Wt.: 510.7785

At 0 °C to a stirred solution of THF diol **2.21a** (2.7 g, 3.74 mmol), water (140 µL) in THF (33 mL) was added $NaBH_4$ (157 mg, 4.11 mmol). The reaction was allowed to warm to room temperature and stirred for 1 hour. The reaction was diluted with EtOAc (50 mL) and water (50 mL), the organic layer was separated and the aqueous layer was re-extracted with EtOAc (3 x 70 mL) and CH_2Cl_2 (70 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford a cloudy oil. Purification on SiO_2 (8 x 4 cm) eluting with EtOAc/methanol (1:0 → 9:1) gave triol **2.23** (1.68 g, 3.29 mol, 88%) as a colourless oil.

$[\alpha]^{27}_D$ +20.1 ($CHCl_3$, *c* 1).

IR ν_{max} (neat) cm^{-1} 3362 (br), 2928 (s), 2855 (s), 1098 (s), 1073 (s).

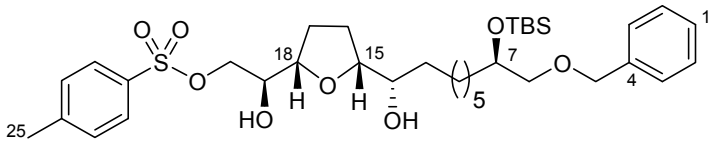
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.24 (5H, m, **C1** – **C3**), 4.53 (2H, s, **C5**), 4.07 – 3.99 (1H, td, *J* = 6.5, 3.3 Hz, **C18**), 3.97 – 3.90 (1H, td, *J* = 7.2, 2.6 Hz, **C15**), 3.90 – 3.84 (1H, m, **C14**), 3.85 – 3.78 (1H, m, **C7**), 3.74 – 3.68 (2H, m, **C20**), 3.63 – 3.56 (1H, m, **C19**), 3.40 (1H, dd, *J* = 9.7, 5.7 Hz, **C6**(1H)), 3.37 (1H, dd, *J* = 9.7, 5.4 Hz, **C6**(1H)), 3.20 (1H, broad s, **OH**), 2.94 (1H, broad s, **OH**) 2.08 – 1.92 (3H, m, **C17**(2H) and **C16**(1H)), 1.83 – 1.74 (1H, m, **C16**(1H)), 1.49 – 1.26 (12H, m, **C8** – **C13**), 0.89 (9H, s, **TBS**), 0.06 (3H, s, **TBS**), 0.05 (3H, s, **TBS**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7 (C), 128.5 (CH_1), 127.8 (CH_1), 127.6 (CH_1), 83.3 (CH_1), 80.3 (CH_1), 75.0 (CH_2), 74.0 (CH_1), 73.5 (CH_2), 72.5 (CH_1), 71.7 (CH_1), 65.5 (CH_2), 34.9 (CH_2), 33.4 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 28.7 (CH_2), 26.1 (CH_3), 25.4 (CH_2), 24.0 (CH_2), 18.4 (C), -4.2 (CH_3), -4.5 (CH_3).

LRMS ESI+ 533 $[M+Na]^+$ (100%).

HRMS ESI+ $[M+Na]^+$ calculated = 533.3269, $[M+Na]^+$ found = 533.3263.

Toluene-4-sulfonic acid (*S*)-2-((2*S*,5*R*)-5-[(1*S*,8*R*)-9-benzyloxy-8-(*tert*-butyl-dimethyl-silanyloxy)-1-hydroxy-nonyl]-tetrahydro-furan-2-yl)-2-hydroxy-ethyl ester



$C_{35}H_{56}O_8SSi$
Exact Mass: 664.3465
Mol. Wt.: 664.9648

Under an atmosphere of N_2, a solution of triol **2.23** (1.525 g, 2.99 mmol) and Bu_2SnO (0.893 g, 3.59 mmol) in dry benzene (50 mL) was refluxed for 3.5 hours using Dean-Stark apparatus. The reaction was cooled to 10 °C, then TsCl (0.627 g, 3.29 mmol) and TBAB (0.48 g, 1.5 mmol) were added. The reaction was gradually warmed to room temperature over 1 hour then stirred for a further 1 hour. The reaction was diluted with EtOAc (50 mL) and water (50 mL), the organic layer was separated and washed with $NaHCO_3$ (sat aq, 50 mL), brine (50 mL) and water (50 mL). The aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford a cloudy white oil. Purification on SiO_2 (5 x 12 cm) eluting with EtOAc/hexane (1:9 → 7:3) gave the tosylate (1.89 g, 2.84 mmol, 95%) as a colourless oil.

$[\alpha]^{27}_D$ +16.4 ($CHCl_3$, *c* 1.65).

IR ν_{max} (neat) cm^{-1} 3365 (br), 2928 (s), 2855 (s), 1598 (w), 1135 (s).

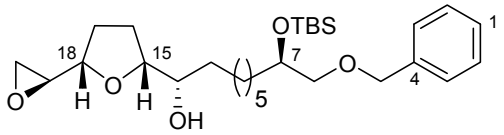
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (2H, d, *J* = 8.4 Hz, **Tosylate**), 7.40 – 7.26 (7H, m, **C1** – **C3** and **Tosylate**), 4.53 (2H, apparent s, **C5**), 4.13 (1H, dd, *J* = 10.3, 5.4 Hz, **C20**(1H)), 4.09 (1H, dd, *J* = 10.3, 6.7 Hz, **C20**(1H)), 4.05 – 4.00 (1H, ddd, *J* = 7.2, 6.0, 2.6 Hz, **C18**), 3.94 – 3.88 (1H, ddd, *J* = 6.9, 6.6, 2.6 Hz **C15**), 3.87 – 3.79 (2H, m, **C7** and **C14**), 3.79 – 3.72 (1H, m, **C19**), 3.40 (1H, dd, *J* = 9.7, 5.7 Hz, **C6**(1H)), 3.36 (1H, dd, *J* = 9.7, 5.4 Hz, **C6**(1H)), 3.23 – 3.19 (1H, d, *J* = 2.9 Hz, **OH**), 2.46 (3H, s, **Tosylate**), 2.42 – 2.39 (1H, d, *J* = 2.9 Hz, **OH**), 2.06 – 1.93 (3H, m, **C17**(2H) and **C16**(1H)), 1.84 – 1.73 (1H, m, **C16**(1H)), 1.59 – 1.22 (12H, m, **C8** – **C13**), 0.89 (9H, s, **TBS**), 0.06 (3H, s, **TBS**), 0.05 (3H, s, **TBS**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1 (C), 138.7 (C), 133.0 (C), 130.1 (CH_1), 128.5 (CH_1), 128.2 (CH_1), 127.8 (CH_1), 127.6 (CH_1), 83.3 (CH_1), 78.2 (CH_1), 75.0 (CH_2), 73.5 (CH_2), 72.9 (CH_1), 72.0 (CH_1), 71.9 (CH_2), 71.7 (CH_1), 34.9 (CH_2), 33.5 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 28.6 (CH_2), 26.1 (CH_3), 26.1 (CH_2), 25.3 (CH_2), 24.2 (CH_2), 21.8 (CH_1), 18.4 (C), -4.1 (CH_3), -4.5 (CH_3).

LRMS ESI+ 687.5 $[M+Na]^+$ (100%).

HRMS ESI+ $[M+Na]^+$ calculated = 687.3357, $[M+Na]^+$ found = 687.3368.

(1*S*,8*R*)-9-Benzyloxy-8-(*tert*-butyl-dimethyl-silanyloxy)-1-((2*R*,5*S*)-(*S*)-5-oxiranyl-tetrahydro-furan-2-yl)-nonan-1-ol (**2.24**)



$C_{28}H_{48}O_5Si$
Exact Mass: 492.3271
Mol. Wt.: 492.7632

At 0 °C under an atmosphere of N_2, to a stirred solution of tosylate (1.88 g, 2.83 mmol) in dry methanol (40 mL) was added dry K_2CO_3 (0.43 g, 3.12 mmol). The reaction was stirred for 2 hours then warmed to room temperature for 30 minutes, then the reaction was concentrated *in vacuo* to afford cloudy white oil. Purification on SiO_2 (4 x 11 cm) eluting with EtOAc/hexane (1:1) gave epoxide **2.24** (1.36 g, 2.77 mmol, 98%) as a colourless oil.

$[\alpha]^{29}_D$ +16.7 ($CHCl_3$, *c* 0.91).

IR ν_{max} (neat) cm^{-1} 3454 (br), 2927 (s), 2854 (s).

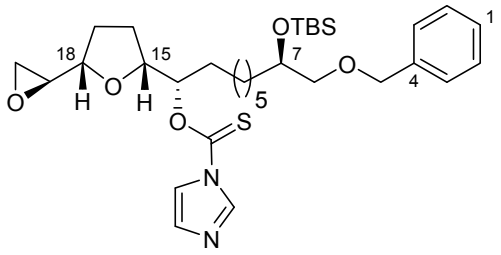
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.24 (5H, m, **C1, C2** and **C3**), 4.53 (2H, s, **C5**), 4.09 (1H, ddd, *J* = 7.8, 5.4, 2.8 Hz, **C18**), 3.96 – 3.89 (1H, m, **C15**), 3.85 – 3.77 (2H, m, **C7** and **C14**), 3.40 (1H, dd, *J* = 9.5, 5.7 Hz, **C6**), 3.36 (1H, dd, *J* = 9.5, 5.3 Hz, **C6**), 3.12 (1H, br s, **OH**), 3.04 (1H, dt, *J* = 4.2, 2.8 Hz, **C19**), 2.85 (1H, dd, *J* = 5.2, 2.8 Hz, **C20**(1H)), 2.77 (1H, dd, *J* = 5.2, 4.2 Hz, **C20**(1H)), 2.18 – 2.08 (1H, m, **C17**(1H)), 2.08 – 1.97 (2H, m, **C16**(1H) and **C17**(1H)), 1.86 – 1.74 (1H, m, **C16**(1H)), 1.60 – 1.23 (12H, m, **C8** – **C13**), 0.90 (9H, s, **TBS**), 0.06 (3H, s, **TBS**), 0.05 (3H, s, **TBS**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7 (C), 128.4 (CH_1), 127.8 (CH_1), 127.6 (CH_1), 83.9 (CH_1), 76.3 (CH_1), 75.1 (CH_2), 73.5 (CH_2), 72.5 (CH_1), 71.7 (CH_1), 54.8 (CH_1), 44.3 (CH_2), 34.9 (CH_2), 33.2 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 26.2 (CH_2), 26.1 (CH_3), 25.4 (CH_2), 24.0 (CH_2), 18.4 (C), -4.2 (CH_3), -4.5 (CH_3).

LRMS ESI+ 515.4 $[M+Na]^+$ (100%).

HRMS ESI+ $[M+Na]^+$ calculated = 515.3163, $[M+Na]^+$ found = 515.3157.

Imidazole-1-carbothioic acid *O*-[(1*S*,8*R*)-9-benzyloxy-8-(*tert*-butyl-dimethyl-silanyloxy)-1-((2*R*,5*S*)-(*S*)-5-oxiranyl-tetrahydro-furan-2-yl)-nonyl] ester (**2.25**)



$C_{32}H_{50}N_2O_5SSi$
Exact Mass: 602.321
Mol. Wt.: 602.9003

Under an atmosphere of N_2, a solution of alcohol **2.24** (0.21 g, 0.427 mmol), thioylcarbonyl diimidazole 95% (0.24 g, 1.28 mmol) and DMAP (17.2 mg, 0.141 mmol) in dry CH_2Cl_2 (3.75 mL) was stirred for 18 hours. The reaction was concentrated *in vacuo* to afford yellow oil. Purification on SiO_2 (10 x 3 cm) eluting with EtOAc/hexane (2:3) gave epoxide **2.25** (200 mg, 0.333 mol, 78%) as a colourless oil.

$[\alpha]^{27}_D$ +0.6 ($CHCl_3$, *c* 1.05).

IR ν_{max} (neat) cm^{-1} 2928 (s), 2855 (s).

^{1}H NMR (400 MHz, C_6D_6) δ 8.40 (1H, s, **Imidazole**), 7.51 (1H, t, *J* = 1.5 Hz, **Imidazole**), 7.31 (2H, br d, *J* = 7.5 Hz, **C3**), 7.22 – 7.17 (2H, m, **C2**), 7.13 – 7.08 (1H, m, **C1**), 6.96 (1H, dd, *J* = 1.5, 0.8 Hz, **Imidazole**), 5.80 (1H, dt, *J* = 7.7, 5.0 Hz, **C14**), 4.39 (1H, d, *J* = 12.2 Hz, **C5**(1H)), 4.35 (1H, d, *J* = 12.2 Hz, **C5**(1H)), 3.94 – 3.83 (1H, m, **C7**), 3.76 (1H, m, **C15**), 3.56 (1H, td, *J* = 6.5, 4.0 Hz, **C18**), 3.39 (1H, dd, *J* = 9.4, 6.2 Hz, **C6**(1H)), 3.32 (1H, dd, *J* = 9.4, 5.0 Hz, **C6**(1H)), 2.50 (1H, td, *J* = 4.0, 2.6 Hz, **C19**), 2.37 (1H, dd, *J* = 5.6, 2.6 Hz, **C20**(1H)), 2.20

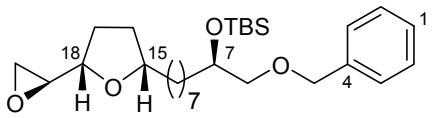
(1H, dd, *J* = 5.6, 4.0 Hz, **C20**(1H)), 1.68 – 1.60 (2H, m, **C13**), 1.57 – 1.49 (4H, m, **C8**, **C16**(1H) and **C17**(1H)), 1.48 (2H, m, **C16**(1H) and **C17**(1H)), 1.34 – 1.17 (8H, m, **C9** – **C12**), 1.02 (9H, s, **TBS**), 0.15 (3H, s, **TBS**), 0.14 (3H, s, **TBS**).

^{13}C NMR (100 MHz, C_6D_6) δ 185.24 (C), 139.48 (C), 137.15 (CH), 131.93 (CH), 128.92 (CH), 128.68 (CH), 128.19 (CH), 128.08 (CH), 118.83 (CH), 84.87 (CH), 80.55 (CH), 78.74 (CH), 75.75 (CH_2), 73.84 (CH_2), 72.38 (CH), 53.75 (CH), 43.66 (CH_2), 35.48 (CH_2), 31.25 (CH_2), 30.26 (CH_2), 30.19 (CH_2), 28.65 (CH_2), 27.61 (CH_2), 26.57 (CH_3), 25.91 (CH_2), 25.65 (CH_2), 18.84 (C), -3.60 (CH_3), -4.15 (CH_3).

LRMS ESI+ 603.5 [M+H] (100%), 625.5 $[M+Na]^+$ (75%).

HRMS ESI+ $[M+Na]^+$ calculated = 603.3282, $[M+Na]^+$ found = 603.3277.

[(*R*)-1-Benzyloxymethyl-8-((2*S*,5*S*)-(*S*)-5-oxiranyl-tetrahydro-furan-2-yl)-octyloxy]-*tert*-butyl-dimethyl-silane (**2.26**)



$C_{28}H_{48}O_4Si$
Exact Mass: 476.3322
Mol. Wt.: 476.7638

Under an atmosphere of N_2, a solution of epoxide **2.25** (187 mg, 0.31 mmol), tris(trimethylsilyl)silane (0.38 mL, 1.24 mmol) in dry degassed toluene (7 mL) was added AIBN (13 mg, 0.078 mmol) in dry degassed toluene (1.2 mL). The reaction was heated to 80 °C for 25 minutes then poured into $NaHCO_3$ (sat aq, 10 mL) and diluted with EtOAc (10 mL). The organic layer was separated and washed with brine (5 mL) and water (5 mL). The aqueous layer was re-extracted with EtOAc (3 x 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford a pale oil. Purification on SiO_2 (10 x 3 cm) eluting with EtOAc/hexane (0:1 → 3:17) gave epoxide **2.26** (137 mg, 0.288 mmol, 93%) as a colourless oil.

$[\alpha]^{27}_D$ +13.8 ($CHCl_3$, *c* 1.08).

IR ν_{max} (neat) cm^{-1} 2927 (s), 2854 (s).

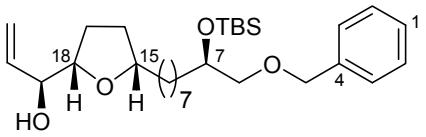
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.25 (5H, m, **C1, C2** and **C3**), 4.53 (2H, s, **C5**), 3.91 – 3.74 (3H, m, **C7**, **C15** and **C18**), 3.41 (1H, dd, *J* = 9.7, 5.7 Hz, **C6**(1H)), 3.37 (1H, dd, *J* = 9.7, 5.4 Hz, **C6**(1H)), 2.97 (1H, ddd, *J* = 5.0, 4.1, 2.7 Hz, **C19**), 2.74 (1H, dd, *J* = 5.3, 4.1 Hz, **C20**(1H)), 2.67 (1H, dd, *J* = 5.3, 2.7 Hz, **C20**(1H)), 2.06 – 1.90 (2H, m, **C16**(1H) and **C17**(1H)), 1.90 – 1.81 (1H, m, **C17**(1H)), 1.67 – 1.35 (5H, m, **C8**, **C14** and **C16**(1H)), 1.35 – 1.23 (10H, br s, **C9** – **C13**), 0.89 (9H, s, **TBS**), 0.06 (3H, s, **TBS**), 0.05 (3H, s, **TBS**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7 (C), 128.5 (CH_1), 127.8 (CH_1), 127.6 (CH_1), 80.7 (CH_1), 78.7 (CH_1), 75.1 (CH_2), 73.5 (CH_2), 71.8 (CH_1), 54.4 (CH_1), 44.1 (CH_2), 35.8 (CH_2), 34.9 (CH_2), 31.3 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 28.6 (CH_2), 26.4 (CH_2), 26.1 (CH_3), 25.4 (CH_2), 18.4 (C), -4.1 (CH_3), -4.5 (CH_3).

LRMS ESI+ 499.4 $[M+Na]^+$ (100%), 494.5 $[M+NH_4]$ (49%).

HRMS ESI+ $[M+Na]^+$ calculated = 499.3214, $[M+Na]^+$ found = 499.3211.

(*S*)-1-((2*S*,5*S*)-5-[(*R*)-9-Benzyloxy-8-(*tert*-butyl-dimethyl-silanyloxy)-nonyl]-tetrahydro-furan-2-yl)-prop-2-en-1-ol (**2.27**)



$C_{29}H_{50}O_4Si$
Exact Mass: 490.3478
Mol. Wt.: 490.7904

At –10 °C under an atmosphere of N_2, to a stirred solution of $Me_3S^+I^-$ (0.551 g, 2.7 mmol) in dry THF (10 mL) was added 2.13M *n*-BuLi in hexane (1.3 mL, 2.7 mmol). The reaction was stirred for 30 minutes then epoxide **2.26** (130 mg, 0.273 mmol) in dry THF (0.25 mL) was added dropwise. The reaction was warmed to room temperature and stirred for 4 hours. The reaction was diluted with EtOAc (20 mL) and water (20 mL), the organic layer was separated and washed with brine (10 mL). The aqueous layer was re-extracted with EtOAc (2 x 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow liquid. Purification on SiO_2 (3 x 8 cm) eluting with EtOAc/hexane (3:17) gave allylic alcohol **2.27** (130 mg, 2.65 mmol, 98%) as a colourless oil.

$[\alpha]^{29}_D$ +6.78 ($CHCl_3$, *c* 0.87).

IR ν_{max} (neat) cm^{-1} 3449 (br), 2928 (s), 2855 (s), 1739 (w), 1103 (s).

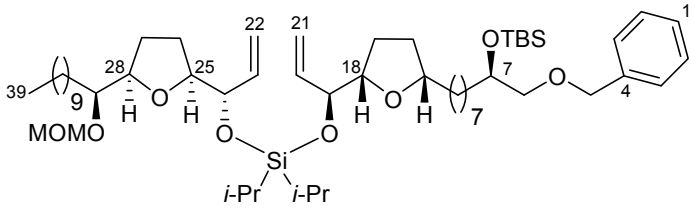
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (5H, m, **C1, C2** and **C3**), 5.85 (1H, ddd, *J* = 17.2, 10.7, 6.0 Hz, **C20**), 5.36 (1H, dt, *J* = 17.2, 1.5 Hz, **C21^{trans}**), 5.21 (1H, dt, *J* = 10.7, 1.5 Hz, **C21^{cis}**), 4.53 (2H, s, **C5**), 3.95 – 3.86 (2H, m, **C15** and **C19**), 3.86 – 3.74 (2H, m, **C7** and **C18**), 3.40 (1H, dd, *J* = 9.7, 5.7 Hz, **C6**(1H)), 3.36 (1H, dd, *J* = 9.7, 5.4 Hz, **C6**(1H)), 2.52 (1H, d, *J* = 4.0 Hz, **OH**), 2.05 – 1.83 (2H, m, **C16**(1H) and **C17**(1H)), 1.79 – 1.68 (1H, m, **C17**(1H)), 1.67 – 1.24 (15H, m, **C8** – **C14** and **C16**(1H)), 0.89 (9H, s, **TBS**), 0.06 (3H, s, **TBS**), 0.06 (3H, s, **TBS**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8 (CH_1), 137.6 (CH_1), 128.5 (CH_1), 127.8 (CH_1), 127.6 (CH_1), 116.9 (CH_2), 81.9 (CH_1), 80.5 (CH_1), 76.1 (CH_1), 75.1 (CH_2), 73.5 (CH_2), 71.8 (CH_2), 36.2 (CH_2), 34.9 (CH_2), 31.4 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 27.7 (CH_2), 26.4 (CH_2), 26.1 (CH_3), 25.4 (CH_2), 18.4 (C), -4.1 (CH_3), -4.5 (CH_3).

LRMS ESI+ 513 $[M+Na]^+$ (100%).

HRMS ESI+ $[M+Na]^+$ calculated = 513.3371, $[M+Na]^+$ found = 513.3360.

(2*S*,5*R*)-2-((*S*)-1-(((*S*)-1-((2*S*,5*S*)-5-((*R*)-9-(Benzyloxy)-8-(*tert*-butyldimethylsilyloxy)nonyl)-tetrahydrofuran-2-yl)allyloxy)diisopropylsilyloxy)allyl)-5-((*S*)-1-(methoxymethyoxy)undecyl)-tetrahydrofuran (2.28)



$C_{55}H_{100}O_8Si_2$
Exact Mass: 944.6957
Mol. Wt.: 945.5487

At room temperature under an atmosphere of N_2, to a stirred solution of allylic alcohol **1.262** (0.50 g, 1.02 mmol) in dry CH_2Cl_2 (2 mL) was added imidazole (0.35 g, 5.10 mmol) followed by *i*-Pr_2SiCl_2 (184 µL, 1.02 mmol). The reaction was stirred for 20 minutes and then the allylic alcohol **2.27** (0.35 g, 1.02 mol) in dry CH_2Cl_2 (0.4 mL) was added dropwise. The reaction was stirred for 3 hours and then purification directly on SiO_2 (3 x 14 cm) eluting with EtOAc/hexane (0:1 → 3:22) gave diene **2.28** (0.74g, 0.79 mmol, 78%, (95% based on recovered **1.262**)) as a colourless oil.

$[\alpha]^{28}_{D}$ –33.6 ($CHCl_3$, c 1.33).

IR ν_{max} (neat) cm^{-1} 2925 (s), 2854 (s), 1739 (w), 1465 (s), 1362 (m), 1251 (s), 1101 (s).

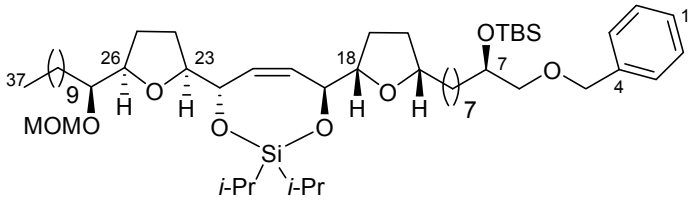
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.21 (5H, m, **C1, C2** and **C3**), 5.89 (2H, 2 x ddd, *J* = 17.0, 10.6, 5.4 Hz, **C20** and **C23**), 5.32 (2H, finely split d, *J* = 17.0, **C21^{trans}** (1H) and **C22 ^{trans}** (1H)), 5.22 – 5.10 (2H, finely split d, *J* = 10.6, **C21^{cis}** (1H) and **C22 ^{cis}** (1H)), 4.77 (1H, d, *J* = 6.7 Hz, **MOMO**), 4.64 (1H, d, *J* = 6.7 Hz, **MOMO**), 4.53 (2H, apparent s, **C5**), 4.52 – 4.43 (2H, m, **C19** and **C24**), 4.03 – 3.91 (2H, m, **C18** and **C25**), 3.86 – 3.75 (3H, m, **C7, C15** and **C28**), 3.65 – 3.58 (1H, m, **C29**), 3.43 – 3.34 (5H, m, **MOMO** and **C6**), 1.90 – 1.65 (7H, m, **C16**(1H), **C17**, **C26** and **C27**), 1.65 – 1.19 (33H, m, **C8** – **C14**, **C16**(1H) and **C30** – **C38**), 1.09 – 0.99 (14H, m, ***i*-Pr$_2$Si**), 0.89 (12H, s, **C39** and **TBS**), 0.06 (3H, s, **TBS**), 0.06 (3H, s, **TBS**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6 (C), 137.3 (CH_1), 137.2 (CH_1), 128.3 (CH_1), 127.6 (CH_1), 127.4 (CH_1), 115.7 (CH_2), 115.5 (CH_2), 96.8 (CH_2), 82.1 (CH_1), 81.7 (CH_1), 81.6 (CH_1), 80.1 (CH_1), 78.6 (CH_1), 74.9 (CH_2), 74.4 (CH_1), 74.1 (CH_1), 73.3 (CH_2), 71.6 (CH_1), 55.6 (CH_3), 35.6 (CH_2), 34.7 (CH_2), 31.9 (CH_2), 31.2 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 26.4 (CH_2), 26.3 (CH_2), 26.0 (CH_2), 25.9 (CH_3), 25.7 (CH_2), 25.4 (CH_2), 25.2 (CH_2), 22.7 (CH_2), 18.2 (C), 17.5 (CH_1), 17.4 (CH_1), 14.1 (CH_3), 12.8 (CH_3), –4.3 (CH_3), –4.7 (CH_3).

LRMS ESI+ 968 $[M+Na]^+$(100%).

HRMS ESI+ $[M+Na]^+$ found = 967.6827; calculated 967.6849.

(4*S*,7*S*,*Z*)-4-((2*S*,5*S*)-5-((*R*)-9-(Benzyloxy)-8-(*tert*-butyldimethylsilyloxy)nonyl)-tetrahydrofuran-2-yl)-2,2-diisopropyl-7-((2*S*,5*R*)-5-((*S*)-1-(methoxymethyoxy)undecyl)-tetrahydrofuran-2-yl)-4,7-dihydro-1,3,2-dioxasilepine (**2.29**)



$C_{53}H_{96}O_8Si_2$
Exact Mass: 916.6644
Mol. Wt.: 917.4955

Under an atmosphere of N_2, a stirred solution of siloxane **2.28** (0.68 g, 0.72 mmol) and Grubbs 2nd generation catalyst (12.2 mg, 0.14 mmol, 2 mol %) in dry, degassed toluene (12 mL, 0.06M) was heated at 75 °C for 40 minutes. A second batch of Grubb's 2nd generation catalyst (12.2 mg, 0.14 mmol, 2 mol %) was added and the reaction was heated again for 40 minutes. This process was repeated a further 3 times, to a total catalyst loading of 10 mol %. The reaction was concentrated *in vacuo* which gave a dark brown oil. Purification on SiO_2 (4 x 10 cm) eluting with EtOAc/hexane (1:19 $\rightarrow$ 3:17) gave alkene **2.29** (0.542 g, 0.59 mmol, 82%) as a colourless oil.

$[\alpha]^{28}_D$ –45.2 ($CHCl_3$, c 1.18).

IR ν_{max} (neat) cm^{-1} 2925 (s), 2854 (s), 1735 (w), 1463 (s), 1363 (m), 1250 (s).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.20 (5H, m, **C1, C2** and **C3**), 5.78 – 5.67 (2H, m, **C20** and **C21**), 4.73 (1H, d, *J* = 6.6 Hz, **MOMO**), 4.70 – 4.63 (2H, m, **C19** and **C22**), 4.58 (1H, d, *J* = 6.6 Hz, **MOMO**), 4.47 (2H, apparent s, **C5**), 4.00 – 3.89 (2H, m, **C18** and **C23**), 3.85 – 3.71 (3H, m, **C7, C15** and **C26**), 3.65 – 3.59 (1H, m, **C27**), 3.34 – 3.29 (5H, m, **MOMO** and **C6**), 1.90 – 1.70 (7H, m, **C16**(1H), **C17**, **C24** and **C25**), 1.49 – 1.17 (33H, m, **C8** – **C14**, **C16**(1H) and **C28** – **C36**), 1.09 – 0.99 (14H, m, ***i*–Pr$_2$Si**), 0.85 – 0.78 (12H, m, **C37** and **TBS**), 0.06 (3 H, s, **TBS**), 0.05 (3H, s, **TBS**).

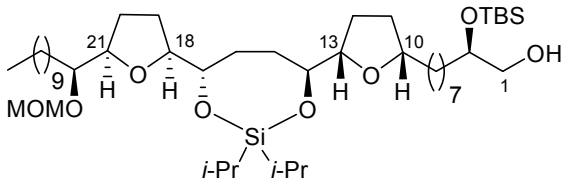
^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6 (C), 131.7 (CH_1), 131.5 (CH_1), 128.3 (CH_1), 127.6 (CH_1), 127.4 (CH_1), 96.9 (CH_2), 81.9 (CH_1), 81.5 (CH_1), 80.1 (CH_1), 78.4 (CH_1), 74.9 (CH_2), 73.3 (CH_1), 72.8 (CH_1), 71.6 (CH_1), 55.7 (CH_3), 35.8 (CH_2),

34.8 (CH_2), 32.0 (CH_2), 31.9 (CH_2), 31.3 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 26.8 (CH_2), 26.6 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 25.9 (CH_3), 25.5 (CH_2), 25.2 (CH_2), 22.7 (C), 18.2 (C), 17.6 (CH_1), 17.3 (CH_1), 17.3 (CH_1), 14.1 (CH_1), 12.3 (CH_3), 12.3 (CH_3), -4.3 (CH_3), -4.7 (CH_3).

LRMS ESI+ 940 $[M+Na]^+$(100%).

HRMS ESI+ $[M+Na]^+$ found 939.6555; calculated 939.6536.

(*R*)-2-(*tert*-Butyldimethylsilyloxy)-9-((2*S*,5*S*)-5-((4*S*,7*S*)-2,2-diisopropyl-7-((2*S*,5*R*)-5-((*S*)-1-(methoxymethyoxy)undecyl)-tetrahydrofuran-2-yl)-1,3,2-dioxasilepan-4-yl)-tetrahydrofuran-2-yl)nonan-1-ol (2.30)



$C_{46}H_{92}O_8Si_2$
Exact Mass: 828.6331
Mol. Wt.: 829.3889

Under an atmosphere of H_2, a solution of olefin **2.29** (65 mg, 0.071 mmol), palladium/charcoal (Pd 5%, on activated carbon, wet, Degussa type E101 NO/W, Aldrich, 22.6 mg, 0.011 mmol, 15 mol %), in EtOAc (4 mL) was stirred for 3 hours. The reaction was filtered through celite and washed EtOAc (20 mL). The organic phase was concentrated *in vacuo* to afford pale yellow oil. Purification on SiO_2 (1 x 9 cm) eluting with hexane/Et_2O (9:1) gave alcohol **2.30** as a colourless oil (55.8 mg, 0.067 mmol, 95%).

$[\alpha]^{27}_D$ –5.6 ($CHCl_3$, c 1.24).

IR ν_{max} (neat) cm^{-1} 3462 (br), 2926 (s), 2855 (s), 1464 (s), 1371 (m), 1254 (s), 1214 (s).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80 (1H, d, *J* = 6.7 Hz, **MOMO**), 4.65 (1H, d, *J* = 6.7 Hz, **MOMO**), 3.95 – 3.79 (6H, m, **C10**, **C13, C14**, **C17**, **C18** and **C21**), 3.73 (1H, m, **C2**), 3.68 – 3.62 (1H, m, **C22**), 3.56 (1H, ddd, *J* = 10.9, 5.5, 4.0 Hz, **C1**(1H)), 3.44 (1H, dt, *J* = 10.9, 5.5 Hz, **C1**(1H)), 3.39 (3H, s, **MOMO**), 1.94 – 1.78 (9H, m, **CX** and **OH**), 1.65 – 1.22 (36H, m, **CX**, **C3** – **C9**, **C23** – **C31**), 1.08 – 0.94 (14H, m, ***i*–Pr$_2$Si**), 0.91 (12H, s, **C32** and **TBS**), 0.09 (6H, s, **TBS**), **CX** =

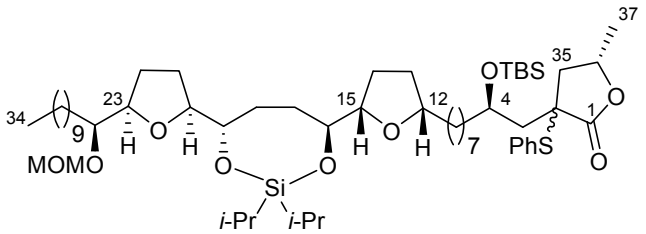
C11, **C12, C15**, **C16**, **C19**, **C20**. Represent 12H, 8H can be found in 1.94 – 1.78 and 4H can be found in 1.65 – 1.22.

^{13}C NMR (100 MHz, $CDCl_3$) δ 96.9 (CH_2), 82.9 (CH_1), 82.3 (CH_1), 81.6 (CH_1), 79.9 (CH_1), 78.5 (CH_1), 77.7 (CH_1), 76.3 (CH_1), 73.0 (CH_1), 66.3 (CH_2), 55.6 (CH_1), 35.9 (CH_2), 34.0 (CH_2), 32.9 (CH_2), 32.6 (CH_2), 32.0 (CH_2), 31.9 (CH_2), 31.4 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 27.2 (CH_2), 26.9 (CH_2), 26.5 (CH_2), 26.2 (CH_2), 25.9 (CH_3), 25.4 (CH_2), 25.3 (CH_2), 22.7 (CH_2), 18.1 (C), 17.7 (CH_3), 17.5 (CH_3), 17.4 (CH_3), 14.1 (CH_3), 12.5 (CH_1), -4.4 (CH_3), -4.6 (CH_3).

LRMS ESI+ 852 $[M+Na]^+$(100%).

HRMS ESI+ $[M+Na]^+$ found 851.6228; calculated 851.6223.

(5*S*)-3-((*R*)-2-(*tert*-Butyldimethylsilyloxy)-9-((2*S*,5*S*)-5-((4*S*,7*S*)-2,2-diisopropyl-7-((2*S*,5*R*)-5-((*S*)-1-(methoxymethyoxy)undecyl)-tetrahydrofuran-2-yl)-1,3,2-dioxasilepan-4-yl)-tetrahydrofuran-2-yl)nonyl)-5-methyl-3-phenylthio)-dihydrofuran-2(3H)-one (**2.32**)



$C_{57}H_{102}O_9SSi_2$
Exact Mass: 1018.6783
Mol. Wt.: 1019.6504

At –78 °C under an atmosphere of N_2, to a stirred solution of alcohol **2.30** (90 mg, 0.109 mmol) and 2,6-lutidine (38 µL, 0.33 mmol) in dry CH_2Cl_2 (2 mL) was slowly added Tf_2O (20 µL, 0.12 mmol). The reaction was stirred for 45 minutes then NH_4Cl (sat aq, 4 mL) and CH_2Cl_2 (10 mL) were added. The organic phase was separated then with washed $NaHCO_3$ (sat aq, 4 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification on SiO_2 (1 x 10 cm) eluting with EtOAc/hexane (1:20 $\rightarrow$ 1:9) gave triflate **2.31** as a colourless oil (94 mg, 0.098 mmol, 97%) which was used directly in the next reaction.

At –78 °C under an atmosphere of N_2, to a stirred solution of (*S*)-5-methyl-4-(phenylthio)-dihydrofuran-2(3H)-one (**1.36**) (48.6 mg, 0.23 mmol) in THF (2 mL)

was added 1M *t*-BuP_4 phosphazene base in hexanes (225 µL, 0.23 mmol). After 20 minutes a solution of triflate **2.31** (180 mg, 0.187 mmol) in THF (1 mL) was added. The reaction was stirred at –78 ºC for 5 minutes, then NH_4Cl (sat aq, 4 mL) and Et_2O (10 mL) were added. The organic layer was separated and the aqueous layer was re-extracted with Et_2O (3 x 7 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification on SiO_2 (1 x 12 cm) eluting with EtOAc/hexane (7:93) gave thiol **2.32** as a ~1:1 mixture of diastereoisomers (colourless oil, 157 mg, 0.154 mmol, 82%).

$[\alpha]^{28}_D$ –11.2 ($CHCl_3$, c 0.67).

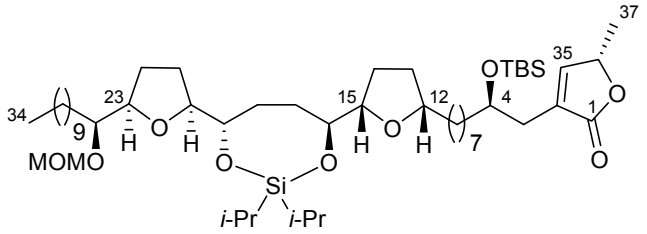
IR ν_{max} (neat) cm^{-1} 2926 (s), 2855 (s), 1759 (s), 1464 (s), 1372 (m), 1252 (s);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (2H, t, *J* = 6.8 Hz, **SPh**), 7.42 – 7.31 (3H, m, **SPh**), 4.79 (1H, d, *J* = 6.5 Hz, **MOMO**), 4.65 (1H, d, *J* = 6.5 Hz, **MOMO**), 4.63 – 4.56 + 4.56 – 4.48 (1H, m, **C36**), 4.29 – 4.23 + 3.94 – 3.91 (1H, m, **C4**), 3.89 – 3.82 (6H, m, **C12**, **C15, C16**, **C19**, **C20** and **C23**), 3.68–3.62 (1H, m, **C24**), 3.38 (3H, s, **MOMO**), 3.06 + 2.45 (1H, dd, $J_{3.06}$ = 14.4, 7.7 Hz, $J_{2.45}$ = 13.8, 10.2 Hz, **C35**(1H)), 2.33 + 2.07 (1H, dd, $J_{2.33}$ = 13.8, 5.4 Hz, $J_{2.07}$ = 14.4, 6.9 Hz, **C35**(1H)), 2.04 – 1.78 (10H, m, **C3**, **CX**), 1.65 – 1.20 (39H, m, **CX**, **C5** – **C11**, **C25** – **C33**, **C37**), 1.08 – 1.03 (14H, m, ***i*–Pr$_2$Si**), 0.93 – 0.86 (12H, m, **C34** and **TBS**), 0.17, 0.13, 0.05, 0.04 (6H, 4 x s, **TBS**), **CX** = **C13**, **C14, C17**, **C18**, **C21**, **C22**. Represent 12H, 8H can be found in 2.04 – 1.78 and 4H can be found in 1.65 – 1.20.

^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 175.5 (C), 137.5, 137.1 (CH_1), 130.9, 130.1 (C), 130.3, 130.0 (CH_1), 129.4, 129.3 (CH_1), 97.3 (CH_2), 83.3 (CH_1), 82.8 (CH_1), 82.1 (CH_1), 80.4 (CH_1), 79.0 (CH_1), 77.1 (CH_1), 76.8 (CH_1), 74.1, 73.7 (CH_1), 70.7, 70.0 (CH_1), 56.1 (CH_2), 55.9, 55.5 (C), 42.9 (CH_2), 42.2 (CH_2), 41.7 (CH_2), 40.0 (CH_2), 39.0 (CH_2), 38.5 (CH_2), 33.4 (CH_2), 33.0 (CH_2), 32.4 (CH_2), 32.3 (CH_2), 31.8 (CH_2), 30.3 (CH_2), 30.2 (CH_2), 30.2 (CH_2), 30.1 (CH_2), 30.0 (CH_2), 29.8 (CH_2), 27.6 (CH_2), 27.4 (CH_2), 26.9 (CH_2), 26.7 (CH_2), 26.5 (CH_2), 25.8 (CH_3), 24.9 (CH_2), 23.1 (CH_2), 21.8, 20.8 (CH_3), 18.5 (C), 18.2 (CH_3), 17.9 (CH_3), 17.9 (CH_3), 14.5 (CH_1), 13.0 (CH_3), –3.4 (CH_3); 19.0 (CH_3), 18.0 (C), 17.7 (CH_3), 17.5 (CH_3), 17.4 (CH_3), 14.1 (CH_1), 12.5 (CH_3), -4.4 (CH_3).

LRMS ESI+ 1041.8 $[M+Na]^+$(100%).

(*S*)-3-((*R*)-2-(*tert*-Butyldimethylsilyloxy)-9-((2*S*,5*S*)-5-((4*S*,7*S*)-2,2-diisopropyl-7-((2*S*,5*R*)-5-((*S*)-1-(methoxymethyoxy)undecyl)-tetrahydrofuran-2-yl)-1,3,2-dioxasilepan-4-yl)-tetrahydrofuran-2-yl)nonyl)-5-methylfuran-2(5H)-one (2.33)



$C_{51}H_{96}O_9Si_2$
Exact Mass: 908.6593
Mol. Wt.: 909.4735

At –10 °C under an atmosphere of N_2, to a stirred solution of thiol **2.32** (140 mg, 0.137 mmol) in CH_2Cl_2 (8.0 mL) was added *m*-CPBA (37 mg, 0.165 mmol). The reaction was stirred for 30 minutes then Me_2S (1 mL) was added and warmed to room temperature. The reaction was diluted with Et_2O (10 mL) and $NaHCO_3$ (sat aq, 10 mL), the organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil. Purification on SiO_2 (2 x 8 cm) eluting with hexane/EtOAc (9:1 $\rightarrow$ 5:1) gave ether **2.33** as a colourless oil (116 mg, 0.128 mmol, 93%).

$[\alpha]^{28}_D$ +6.1 ($CHCl_3$, c 1.35).

IR ν_{max} (neat) cm^{-1} 2926 (s), 2855 (s), 1769 (s), 1464 (s), 1383 (m), 1185 (s).

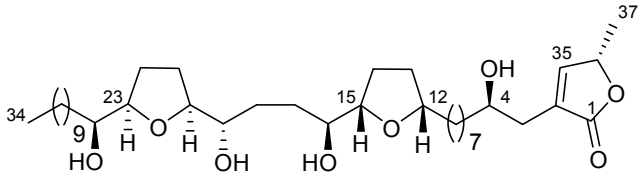
^{1}H NMR (400 MHz, $CDCl_3$) δ δ 7.12 (1H, s, **C35**), 5.00 (1H, q, *J* = 6.5 Hz, **C36**), 4.79 (1H, d, *J* = 6.5 Hz, **MOMO**), 4.65 (1H, d, *J* = 6.5 Hz, **MOMO**), 3.95 – 3.80 (7H, m, **C4**, **C12**, **C15, C16**, **C19**, **C20** and **C23**), 3.68 – 3.62 (1H, m, **C24**), 3.39 (3H, s, **MOMO**), 2.42 (2H, d, *J* = 5.5 Hz, **C3**), 1.94 – 1.78 (8H, m, **CX**), 1.63 – 1.22 (39H, m, **CX**, **C5** – **C11**, **C25** – **C33**, **C37**), 1.08 – 0.95 (14H, m, ***i*–Pr$_2$Si**), 0.91 – 0.86 (12H, m, **C34** and **TBS**), 0.06 (3H, s, **TBS**), 0.03 (3H, s, **TBS**), **CX = C13**, **C14, C17**, **C18**, **C21**, **C22**. Represent 12H, 8H can be found in 1.94 – 1.78 and 4H can be found in 1.63 – 1.22.

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0 (C), 151.4 (CH_1), 130.9 (C), 96.9 (CH_2), 82.9 (CH_1), 82.3 (CH_1), 81.6 (CH_1), 79.9 (CH_1), 78.5 (CH_1), 77.4 (CH_1), 76.7 (CH_1),

76.3 (CH_1), 70.2 (CH_1), 55.6 (CH_1), 37.0 (CH_2), 35.9 (CH_2), 32.9 (CH_2), 32.8 (CH_2), 32.5 (CH_2), 32.0 (CH_2), 31.9 (CH_2), 31.4 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 27.1 (CH_2), 26.9 (CH_2), 26.5 (CH_2), 26.2 (CH_2), 25.9 (CH_3), 25.4 (CH_2), 25.1 (CH_2), 22.7 (CH_2), 19.0 (CH_3), 18.0 (C), 17.7 (CH_3), 17.5 (CH_3), 17.4 (CH_3), 14.1 (CH_1), 12.5 (CH_3), -4.4 (CH_3).

LRMS ESI+ 931.8 $[M+Na]^+$ (100%).

cis-Sylvaticin (**1.100**)



$C_{37}H_{66}O_8$
Exact Mass: 638.4758
Mol. Wt.: 638.9151

At room temperature under an atmosphere of N_2, to a solution of ether **2.33** (27 mg, 29.7 μmol) in CH_2Cl_2 (1 mL) was added a 5% solution of AcCl in MeOH (1 mL). The reaction was stirred at room temperature for 3 hours, then concentrated *in vacuo* to afford a pale yellow oil. Purification on SiO_2 (0.5 x 8 cm) eluting with hexane/acetone (4:1 → 7:3) gave gave *cis*-sylvaticin (**1.100**) as a waxy solid (17 mg, 26.6 μmol, 90%).
Spectroscopic characterisation agreed with published data.[66]

Melting point 63 – 65 °C.

$[\alpha]^{26}_D$ +5.0 ($CHCl_3$, c 0.86).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (1H, s, **C35**), 5.09 – 5.01 (1H, m, **C36**), 3.96 – 3.77 (5H, m, **C4**, **C12**, **C20**, **C23** and **C24**), 3.74 – 3.65 (1H, m, **C15**), 3.54 – 3.46 (1H, m, **C19**), 3.41 (1H, m, **C16**), 3.21 (1H, br s, **OH**), 2.97 (1H, br s, **OH**), 2.57 – 2.46 (2H, m, **C3**(1H) and **OH**), 2.44 – 2.35 (1H, m, **C3**(1H)), 2.04 – 1.20 (48H, m, **C5** – **C9**, **C13**, **C14, C17**, **C18**, **C21**, **C22**, **C25** – **C34**, **C37**, **OH**), 0.88 (3H, t, *J* = 6.7 Hz, **C34**).

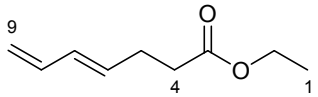
^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6 (C), 151.7 (CH_1), 131.2 (C), 83.0 (CH_1), 82.4 (CH_1), 82.1 (CH_1), 80.0 (CH_1), 77.9 (CH_1), 74.8 (CH_1), 74.1 (CH_1), 72.4 (CH_1), 69.9 (CH_1), 37.4 (CH_2), 35.9 (CH_2), 33.3 (CH_2), 33.1 (CH_2), 31.9 (CH_2), 31.3

(CH_2), 31.2 (CH_2), 30.4 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.6 (CH_2), 27.8 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 25.5 (CH_2), 24.1 (CH_2), 22.6 (CH_2), 19.1 (CH_3), 14.1 (CH_3).

LRMS ESI+ 639 $[M+H]^+$(59%), 661 $[M+Na]^+$(100%).

HRMS ESI+ $[M+Na]^+$ found 661.4647; calculated 661.4650.

(*E*)-Ethyl hepta-4,6-dienoate (**2.37**)



$C_9H_{14}O_2$
Exact Mass: 154.0994
Mol. Wt.: 154.2063

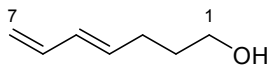
Under an atmosphere of Ar, a stirred solution of 1,4-pentadien-3-ol (**2.36**) (4.72 g, 56.1 mmol), triethyl orthoacetate (72 mL, 0.392 mol) and propionic acid (0.43 mL, 5.61 mmol) were heated at reflux for 3 hours. Excess triethyl orthoacetate was removed by distillation under reduced pressure (24°C, 12 mbar). Purification by distillation under reduced pressure (44°C, 12 mbar) gave (*E*)-ethyl hepta-4,6-dienoate (**2.37**) as a colourless oil (6.35 g, 41.2 mmol, 73%).
Spectroscopic characterisation agreed with published data.[63]

IR ν_{max} (neat) cm^{-1} 2981 (m), 1735 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.30 (1H, dt, *J* = 16.9, 10.3 Hz, **C8**), 6.09 (1H, dd, *J* = 15.0, 10.3 Hz, **C7**), 5.79 – 5.61 (1H, m, **C6**), 5.12 (1H, d, *J* = 16.9 Hz, **C9**(1H)), 4.99 (1H, d, *J* = 10.3 Hz, **C9**(1H)), 4.14 (2H, q, *J* = 7.1 Hz, **C2**), 2.51 – 2.27 (4 H, m, **C4** and **C5**), 1.26 (3H, t, *J* = 7.1 Hz, **C1**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1 (C), 137.0 (CH), 132.8 (CH), 132.1 (CH), 115.8 (CH_2), 60.5 (CH_2), 34.1 (CH_2), 28.0 (CH_2), 14.4 (CH_3).

(*E*)-Hepta-4,6-dien-1-ol (**2.38**)



$C_7H_{12}O$
Exact Mass: 112.0888
Mol. Wt.: 112.1696

Under an atmosphere of Ar, at 0 °C to a stirred solution of $LiAlH_4$ (1.25 g, 33 mmol) in Et_2O (100 mL) was added (*E*)-ethyl hepta-4,6-dienoate (**2.37**) (3.2 g, 20.9 mmol) in Et_2O (7 mL) dropwise. The reaction was stirred for 1 hour then

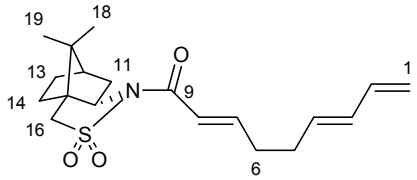
carefully quenched with water. 1M HCl (80 mL) was added and the reaction was stirred for 1 hour. The organic layer was separated and the aqueous layer was re-extracted with Et_2O (4 x 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated by distillation to remove Et_2O. Purification by distillation under reduced pressure (38°C, 0.35 mbar) gave (*E*)-hepta-4,6-dien-1-ol (**2.38**) (1.13 g, 41.2 mmol, 48%) as a colourless oil.
Spectroscopic characterisation agreed with published data.[63]

IR ν_{max} (neat) cm^{-1} 3321 (br), 2935 (s), 2874 (s), 1650 (w), 1597 (w).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.30 (1H, dt, *J* = 16.9, 10.3 Hz, **C6**), 6.08 (1H, dd, *J* = 15.1, 10.3 Hz, **C5**), 5.72 (1H, dt, *J* = 15.1, 7.1 Hz, **C4**), 5.10 (1H, d, *J* = 16.9 Hz, **C7**(1H)), 4.98 (1H, d, *J* = 10.3 Hz, **C7**(1H)), 3.66 (2H, t, *J* = 6.4 Hz, **C1**), 2.19 (2H, q, *J* = 7.1 Hz, **C3**), 1.77 – 1.60 (2H, m, **C2**), 1.45 (1H, s, **OH**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2 (CH), 134.5 (CH), 131.7 (CH), 115.3 (CH_2), 62.5 (CH_2), 32.3 (CH_2), 29.0 (CH_2).

(2*E*,6*E*)-1-((*S*)-10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-nona-2,6,8-trien-1-one (**2.35**)



$C_{19}H_{27}NO_3S$
Exact Mass: 349.1712
Mol. Wt.: 349.4876

Under an atmosphere of Ar, at –60 °C to a stirred solution of DMSO (0.7 mL, 9.8 mmol) in THF (63 mL) was added oxalyl chloride (0.85 mL, 9.8 mmol) dropwise. The reaction was stirred for 15 minutes then (*E*)-hepta-4,6-dien-1-ol (**2.38**) (1.00 g, 8.92 mmol) was added dropwise. The reaction was stirred for 15 minutes then Et_3N (3.7 mL, 26.7 mmol) was added. The reaction was stirred for 15 minutes then warmed to room temperature and stirred for 30 minutes. 1M HCl (60 mL) was added and the organic layer was separated. The aqueous layer was re-extracted with Et_2O (2 x 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated carefully *in vacuo* to afford crude 4,6-heptadienal which was used without purification in the next reaction.

Under an atmosphere of Ar, to a stirred solution of (1*R*,2*S*)-camphorsultam phosphonate (3.56 g, 9.04 mmol) in dry acetonitrile (80 mL) dried lithium chloride (170 °C/ 0.035 mbar overnight) (0.4 g, 9.0 mmol) was added. After stirring for 15 minutes DIPEA (1.3 mL, 0.75 mmol) was added. After stirring for 10 minutes, the crude 4,6-heptadienal in dry acetonitrile (2 mL) was then added. The reaction was stirred for 20 hours then a solution of brine (60 mL) was added and the organic layer was separated. The aqueous layer was re-extracted with Et_2O (3 x 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give an orange oil. Purification on SiO_2 (10 x 5 cm) eluting with hexane/EtOAc (3:1) gave triene **2.35** (1.64 g, 0.046 mmol, 52%) as a colourless oil.

$[\alpha]^{26.5}_D$ +58.3 ($CHCl_3$, *c* 1.00).

IR ν_{max} (neat) cm^{-1} 2958 (s), 1681 (s) 1638 (s).

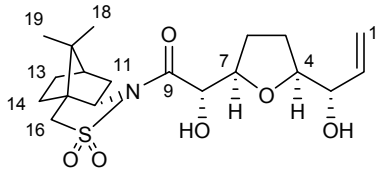
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (1H, dt, *J* = 15.2, 6.8 Hz, **C7**), 6.58 (1H, d, *J* = 15.2 Hz, **C8**), 6.29 (1H, dt, *J* = 16.8, 10.2 Hz, **C2**), 6.08 (1H, dd, *J* = 15.2, 10.2 Hz, **C3**), 5.68 (1H, dt, *J* = 15.2, 6.7 Hz, **C4**), 5.11 (1H, d, *J* = 16.8 Hz, **C1**(1H)), 4.99 (1H, d, *J* = 10.2 Hz, **C1**(1H)), 3.92 (1H, dd, *J* = 7.4, 5.3 Hz, **C10**), 3.51 (1H, d, *J* = 13.7 Hz, **C16**(1H)), 3.43 (1H, d, *J* = 13.7 Hz, **C16**(1H)), 2.42 – 2.32 (2H, m, **C6**), 2.32 – 2.22 (2H, m, **C5**), 2.20 – 2.03 (2H, m, **C11**), 2.00 – 1.82 (3H, m, **C12**, **C13**(1H) and **C14**(1H)), 1.48 – 1.30 (2H, m, **C13**(1H) and **C14**(1H)), 1.18 (3H, s, **C18**), 0.98 (3H, s, **C19**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2 (C), 149.8 (CH_1), 137.1 (CH_1), 133.2 (CH_1), 132.2 (CH_1), 121.5 (CH_1), 115.7 (CH_2), 65.3 (CH_1), 53.4 (CH_2), 48.6 (C), 48.0 (C), 44.9 (CH_1), 38.7 (CH_2), 33.1 (CH_2), 32.3 (CH_2), 31.1 (CH_2), 26.7 (CH_2), 21.0 (CH_3), 20.1 (CH_3).

LRMS ESI+ 372 $[M+Na]^+$ (100%).

HRMS ESI+ $[M+Na]^+$ calculated = 372.1609, $[M+Na]^+$ found = 372.1600.

(2*S*)-*N*-[(*S*)-2-Hydroxy-2-[(2*S*,5*R*)-5-((*S*)-1-hydroxyprop-2-enyl)tetrahydro-2-furanyl)ethanoyl]camphor-10,2-sultam (**2.34a**/**b**)



$C_{19}H_{29}NO_6S$
Exact Mass: 399.1716
Mol. Wt.: 399.5017

At –30 °C under an atmosphere of N_2, to a stirred solution of triene **2.35** (32 mg, 0.092 mmol) in acetone/acetic acid (3:2 1.65 mL) powdered $KMnO_4$ (19 mg, 0.119 mmol) was added. The reaction was stirred for 40 minutes then quenched by addition of $Na_2S_2O_3$ (sat aq, 3 mL). The organic layer was separated and the aqueous layer was re-extracted with EtOAc (10 x 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give colourless oil (16 mg). Purification on SiO_2 (1 x 18 cm) eluting with EtOAc/hexane (3:2 → 4:1) gave THF diols **2.34a**/**b** (6.5 mg, 0.016 mmol, 18%) as a colourless oil.
Spectroscopic characterisation for THF diols **2.34a**/**b**:

IR ν_{max} (neat) cm^{-1} 3465 (br), 2959 (s), 1689 (s).

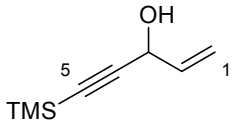
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (1H, ddd, *J* = 17.2, 10.5, 6.0 Hz, **C2**), 5.35 (1H, d, *J* = 17.2 Hz, **C1**(1H)), 5.20 (1H, d, *J* = 10.5 Hz, **C1**(1H)), 4.63 – 4.55 (2H, m, **C3** and **C8**), 4.06 – 3.91 (3H, m, **C4**, **C7** and **C10**), 3.82 (1H, d, *J* = 9.1 Hz, **OH**), 3.53 (1H, d, *J* = 13.7 Hz, **C16**(1H)), 3.45 (1H, d, *J* = 13.7 Hz, **C16**(1H)), 3.02 – 2.92 (1H, s, **OH**), 2.32 – 2.20 (1H, m, **C5** or **C6** (1H)), 2.15 – 2.02 (3H, m, **C5** or **C6** (1H) and **C11**), 2.01 – 1.82 (5H, m, **C5** or **C6** (2H), **C12**, **C13**(1H) and **C14**(1H)), 1.49 – 1.31 (2H, m, **C13**(1H) and **C14**(1H)), 1.16 (3H, s, **C18**), 0.98 (3H, s, **C19**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7 (C) 137.9 (CH), 116.8 (CH_2), 83.0 (CH), 79.1 (CH), 75.5 (CH), 73.3 (CH), 66.0 (CH), 53.2 (CH_2) 49.3 (C), 48.1 (C) 44.7 (CH), 38.4 (CH_2), 33.1 (CH_2), 28.3 (CH_2) 28.0 (CH_2), 26.5 (CH_2), 21.0 (CH_3) 20.1 (CH_3).

LRMS ESI+ 422 $[M+Na]^+$ (100%).

HRMS ESI+ $[M+Na]^+$ calculated = 422.1613, $[M+Na]^+$ found = 422.1616.

5-(Trimethylsilyl)pent-1-en-4-yn-3-ol (**2.40**)



$C_8H_{14}OSi$
Exact Mass: 154.0814
Mol. Wt.: 154.2817

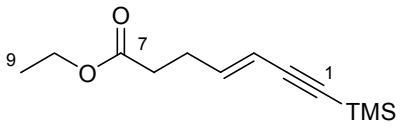
At –78 °C under an atmosphere of Ar, to a stirred solution of trimethylsilylacetylene (10 g, 0.1 mol) in dry THF (130 mL) 2.3M *n*-BuLi in hexanes (46.5 mL, 0.105 mol) was added dropwise. The reaction was stirred for 30 minutes then acrolein (7.5 mL, 0.11 mol) was added dropwise. The reaction was stirred for 30 minutes then the reaction was warmed to room temperature over 3.5 hours. The reaction was quenched with water (40 mL). A solution of brine (40 mL) was added and the organic layer was separated. The aqueous layer was re-extracted with Et_2O (3 x 100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give yellow oil. Purification by distillation under reduced pressure (32–36°C, 0.6 mbar) gave allylic alcohol **2.40** (13.3 g, 0.086 mol, 86%) as a colourless oil.
Spectroscopic characterisation agreed with published data.[148]

IR ν_{max} (neat) cm^{-1} 3726 (w), 3710 (w), 3628 (w), 2360 (s), 2341 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.97 (1H, ddd, *J* = 17.0, 10.2, 5.3 Hz, **C2**), 5.47 (1H, d, *J* = 17.0 Hz, **C1**(1H)), 5.23 (1H, d, *J* = 10.2 Hz, **C1**(1H)), 4.90 – 4.84 (1H, m, **C3**), 2.02 (1H, d, *J* = 6.5 Hz, **OH**), 0.19 (9H, s, **TMS**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 136.9 (CH_1), 116.7 (CH_2), 104.3 (C), 91.4 (C), 63.7 (CH_1), 0.0 (CH_3).

(*E*)-Ethyl 7-(trimethylsilyl)hept-4-en-6-ynoate (2.41a/b)



$C_{12}H_{20}O_2Si$
Exact Mass: 224.1233
Mol. Wt.: 224.3715

Under an atmosphere of Ar, a stirred solution of 5-(trimethylsilyl)pent-1-en-4-yn-3-ol (**2.40**) (13.3 g, 0.086 mol), triethyl orthoacetate (110 mL, 0.6 mol) and propionic acid (0.64 mL, 8.6 mmol) were heated at reflux for 3 hours. Excess triethyl orthoacetate was removed by reduced pressure distillation (42–46°C, 12 mbar). The residue was Kugelrohr distilled (60°C, 0.6 mbar) to give crude ester (16.2 g). Purification on SiO_2 (6 x 9 cm) eluting with hexane/Et_2O (19:1) gave 2

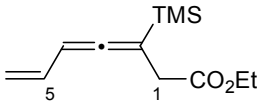
main fractions: esters **2.41a**/**b** (13.9 g, 0.062 mol, 72%) as a colourless oil, and allene **2.42** (600 mg, 2.7 mmol, 4%) as a colourless oil.
Spectroscopic characterisation for esters **2.41a**/**b** agreed with published data.[166]

IR ν_{max} (neat) cm^{-1} 2969 (m), 2901 (s), 2360 (s), 2342 (s), 2341 (s) 1736 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.32 – 6.08 (1H, m, **C4**), 5.56 (1H, d with fine splitting, *J* = 15.9 Hz, **C3**), 4.14 (2H, q, *J* = 7.1 Hz, **C8**), 2.52 – 2.29 (4H, m, **C5** and **C6**), 1.27 (3H, t, *J* = 7.1 Hz, **C9**), 0.18 (9H, s, **TMS**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7 (C), 143.6 (CH_1), 111.1 (CH_1), 103.7 (C), 93.7 (C), 60.7 (CH_2), 33.4 (CH_2), 28.4 (CH_2), 14.4 (CH_3), 0.1 (CH_3).

Ethyl 3-(trimethylsilyl)hepta-3,4,6-trienoate (2.42)



$C_{12}H_{20}O_2Si$
Exact Mass: 224.1233
Mol. Wt.: 224.3715

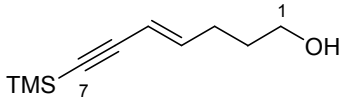
IR ν_{max} (neat) cm^{-1} 2956 (m), 1923 (m), 1735 (s), 1614 (w);

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.14 (1H, dt, *J* = 17.0, 10.2 Hz, **C5**), 5.65 (1H, d with fine splitting, *J* = 10.2 Hz, **C4**), 5.11 (1H, d with fine splitting, *J* = 17.0 Hz, **C6**(1H)), 4.86 (1H, d with fine splitting, *J* = 10.2 Hz, **C6**(1H)), 4.14 (2H, q, *J* = 7.1 Hz, **OEt**), 3.02 (1H, d, *J* = 2.4 Hz, **C1**), 1.25 (3H, t, *J* = 7.1 Hz, **OEt**), 0.12 (9H, s, **TMS**);

^{13}C NMR (75 MHz, $CDCl_3$) δ 209.8 (C), 171.6 (C), 133.1 (CH_1), 113.9 (CH_2), 90.6 (CH_1), 60.8 (CH_2), 35.9 (CH_2), 14.4 (CH_3), -1.4 (CH_3).

LRMS GCMS 224.1 $[M]^+$ (17%).

(*E*)-7-(Trimethylsilyl)hept-4-en-6-yn-1-ol (2.43a)



$C_{10}H_{18}OSi$
Exact Mass: 182.1127
Mol. Wt.: 182.3348

At –50 °C under an atmosphere of Ar, to a stirred solution of esters **2.41a**/**b** (5.5 g, 24.6 mmol) in CH_2Cl_2 (100 mL) was added 1.0M DIBAL-H in hexanes (55 mL, 55 mmol) dropwise. The reaction was gradually warmed to room temperature

over 1 hour. A solution of Rochelle's salt (sat aq, 40 mL) was added and the solution was stirred for 1 hour at room temperature. The organic layer was separated and the aqueous layer was re-extracted with Et_2O (3 x 80 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification on SiO_2 (10 x 5 cm) eluting with hexane/Et_2O (3:1) gave 3 main fractions: (*E*)-7-(trimethylsilyl)hept-4-en-6-yn-1-ol (**2.43a**) (2.4 g, 13 mmol, 53%) as a colourless oil, (*Z*)-7-(trimethylsilyl)hept-4-en-6-yn-1-ol (**2.43b**) (150 mg, 0.83 mmol, 3%) as a colourless oil, and aldehyde (875 mg, 4.7 mmol, 22%) as a colourless oil:

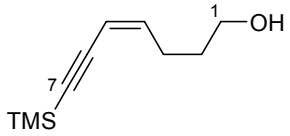
(*E*)-7-(trimethylsilyl)hept-4-en-6-yn-1-ol (**2.43a**): Spectroscopic characterisation agreed with published data.[167]

IR ν_{max} (neat) cm^{-1} 3319 (br), 2957 (m), 2360 (m), 2136 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.21 (1H, dt, *J* = 15.9, 7.0 Hz, **C4**), 5.53 (1H, d, *J* = 15.9 Hz, **C5**), 3.63 (2H, t, *J* = 6.4 Hz, **C1**), 2.31 – 2.04 (2H, m, **C3**), 1.79 – 1.50 (3H, m, **C2** and **OH**), 0.17 (9H, s, **TMS**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 145.3 (CH_1), 110.4 (CH_1), 104.0 (C), 93.1 (C), 62.2 (CH_2), 31.7 (CH_2), 29.5 (CH_2), 0.1 (CH_3).

(*Z*)-7-(Trimethylsilyl)hept-4-en-6-yn-1-ol (2.43b)



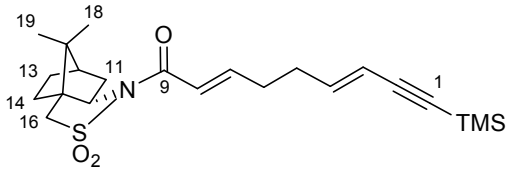
$C_{10}H_{18}OSi$
Exact Mass: 182.1127
Mol. Wt.: 182.3348

IR ν_{max} (neat) cm^{-1} 3319 (br), 2957 (m), 2136 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 (1H, dt, *J* = 10.9, 7.6 Hz, **C4**), 5.54 (1H, finely split d, *J* = 10.8 Hz, **C5**), 3.65 (2H, q, *J* = 5.9 Hz, **C1**), 2.48 – 2.39 (2H, m, **C3**), 1.76 – 1.63 (3H, m, **C2** and **OH**), 0.20 (9H, s, **TMS**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4 (CH_1), 110.3 (CH_1), 102.1 (C), 99.3 (C), 62.0 (CH_2), 31.4 (CH_2), 26.5 (CH_2), 0.1 (CH_3).

(2*E*,6*E*)-1-((*S*)-10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-9-trimethylsilanyl-nona-2,6-dien-8-yn-1-one (**2.44**)



$C_{22}H_{33}NO_3SSi$
Exact Mass: 419.195
Mol. Wt.: 419.6528

Under an atmosphere of Ar, at –60 °C to a stirred solution of DMSO (0.825 mL, 11.6 mmol) in THF (75 mL) was added oxalyl chloride (1 mL, 11.6 mmol) dropwise. The reaction was stirred for 15 minutes then (*E*)-7-(trimethylsilyl)hept-4-en-6-yn-1-ol (**2.43a**) (1.9 g, 10.4 mmol) in THF (3 mL) was added dropwise. The reaction was stirred for 15 minutes then Et_3N (4.4 mL, 31.6 mmol) was added. The reaction was stirred for 15 minutes then warmed to room temperature and stirred for 30 minutes. The white slurry was poured into ether/water (1:1 140 mL) and the organic layer was separated and washed with $NaHCO_3$ (sat aq, 70 mL), water (70 mL) and brine (70 mL). The organic phase was dried ($MgSO_4$) and concentrated carefully *in vacuo* to afford crude aldehyde (1.45 g, 8.1 mmol, 78%) as a colourless oil.

Under an atmosphere of Ar, to a stirred solution of (1*R*,2*S*)-camphorsultam phosphonate (3.7 g, 9.3 mmol) in dry acetonitrile (60 mL) dried lithium chloride (170 °C/ 0.035 mbar overnight) (0.4 g, 9.0 mmol) was added. After stirring for 15 minutes DIPEA (1.4 mL, 8.15 mmol) was added. After stirring for 10 minutes, crude aldehyde (1.45 g, 8.1 mmol, 78%) in dry acetonitrile (2 mL) was then added. The reaction was stirred for 22 hours then a solution of brine (60 mL) was added and the organic layer was separated. The aqueous layer was re-extracted with Et_2O (3 x 80 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give an orange oil. Purification on SiO_2 (14 x 5 cm) eluting with hexane/Et_2O (1:1) gave dieneyne **2.44** (2.50 g, 6.0 mmol, 58% over 2 steps) as a colourless oil.

$[\alpha]^{29.5}_D$ +57.5 ($CHCl_3$, *c* 1.53).

IR ν_{max} (neat) cm^{-1} 2959 (m), 2360 (s), 2341(s), 1682 (s), 1638 (s).

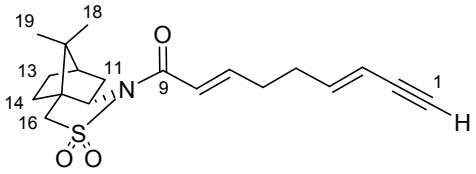
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (1H, dt, *J* = 15.1, 6.7 Hz, **C7**), 6.56 (1H, d, *J* = 15.1 Hz, **C8**), 6.16 (1H, dt, *J* = 15.9, 6.7 Hz, **C4**), 5.53 (1H, d, *J* = 15.9 Hz, **C3**), 3.91 (1H, dd, *J* = 7.4, 5.2 Hz, **C10**), 3.50 (1H, d, *J* = 13.7 Hz, **C16**(1H)), 3.42 (1 H, d, *J* = 13.7 Hz, **C16**(1H)), 2.39 – 2.21 (4H, m, **C5** and **C6**), 2.19 – 2.01 (2H, m, **C11**), 1.98 – 1.82 (3H, m, **C12**, **C13**(1H) and **C14**(1H)), 1.47 – 1.29 (2H, m, **C13**(1H) and **C14**(1H)), 1.16 (3H, s, **C18**), 0.96 (3H, s, **C19**), 0.16 (9 H, s, **TMS**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0 (C), 148.9 (CH), 143.7 (CH), 121.7 (CH), 111.1 (CH), 103.7 (C), 93.5 (C), 65.3 (CH), 53.3 (CH_2), 48.6 (C), 47.9 (C), 44.9 (CH_1), 38.6 (CH_2), 33.0 (CH_2), 31.6 (CH_2), 31.5 (CH_2), 26.6 (CH_2), 21.0 (CH_3), 20.0 (CH_3), 0.1 (CH_3).

LRMS ESI+ 442 $[M+Na]^+$ (100%).

HRMS ESI+ $[M+Na]^+$ calculated = 442.1843, $[M+Na]^+$ found = 442.1842.

(2*E*,6*E*)-1-((*S*)-10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-nona-2,6-dien-8-yn-1-one (2.45)



$C_{19}H_{25}NO_3S$
Exact Mass: 347.1555
Mol. Wt.: 347.4717

To a stirred solution of dieneyne **2.44** (140 mg, 0.33 mmol), acetic acid (40 µL, 0.67 mmol) in THF (75 mL) was added dropwise 1M TBAF in THF (670 µL, 0.67 mmol). The reaction was stirred for 4 hours and concentrated *in vacuo* to give a yellow oil. Purification on SiO_2 (6 x 3 cm) eluting with hexane/Et_2O (6:4) gave dieneyne **2.45** (85.8 mg, 0.25 mmol, 75%) as a colourless oil.

$[\alpha]^{29.5}_D$ +103.1 ($CHCl_3$, *c* 0.24).

IR ν_{max} (neat) cm^{-1} 3278 (w), 2960 (m), 2360 (s), 2342(s), 1680 (s), 1638 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (1H, dt, *J* = 15.1, 6.6 Hz, **C7**), 6.59 (1H, d, *J* = 15.1 Hz, **C8**), 6.23 (1H, dt, *J* = 15.9, 6.6 Hz, **C4**), 5.51 (1H, d, *J* = 15.9 Hz, **C3**), 3.93 (1H, dd, *J* = 7.4, 5.2 Hz, **C10**), 3.52 (1H, d, *J* = 13.8 Hz, **C16**(1H)), 3.44 (1H, d, *J* = 13.8 Hz, **C16**(1H)), 2.81 (1H, d, *J* = 2.2 Hz, **C1**), 2.44 – 2.25 (4H, m, **C5**

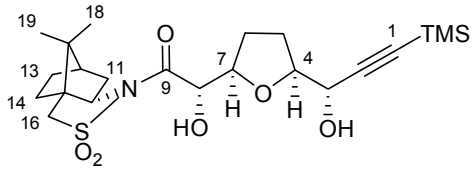
and **C6**), 2.21 – 2.05 (2H, m, **C11**), 2.00 – 1.83 (3H, m, **C12**, **C13**(1H) and **C14**(1H)), 1.49 – 1.31 (2H, m, **C13**(1H) and **C14**(1H)), 1.19 (3H, s, **C18**), 0.99 (3H, s, **C19**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1 (C), 148.9 (CH), 144.5 (CH), 121.8 (CH), 110.1 (CH), 82.3 (CH), 76.5 (C), 65.4 (CH), 53.4 (CH_2), 48.7 (C), 48.0 (C), 44.9 (CH_1), 38.7 (CH_2), 33.1 (CH_2), 31.5 (CH_2), 31.5 (CH_2), 26.7 (CH_2), 21.1 (CH_3), 20.1 (CH_3).

LRMS ESI+ 370 $[M+Na]^+$ (100%).

HRMS ESI+ $[M+Na]^+$ calculated = 370.1447, $[M+Na]^+$ found = 370.1456.

(*S*)-1-((*S*)-10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-hydroxy-2-[(2*R*,5*S*)-5-((*S*)-1-hydroxy-3-trimethylsilanyl-prop-2-ynyl)-tetrahydro-furan-2-yl]-ethanone (**2.46a**/**b**)



$C_{22}H_{35}NO_6SSi$
Exact Mass: 469.1954
Mol. Wt.: 469.6669

Method A:

At –30 °C under an atmosphere of N_2, to a stirred solution of dieneyne **2.44** (317 mg, 0.75 mmol) in acetone/acetic acid (3:2 7.4 mL) was added powdered $KMnO_4$ (156 mg, 0.1 mmol). The reaction was stirred for 30 minutes then quenched by addition of $Na_2S_2O_3$ (sat aq, 3 mL). The organic layer was separated and the aqueous layer was re-extracted with EtOAc (5 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification on SiO_2 (11 x 2.5 cm) eluting with EtOAc/hexane (1:4 → 1:1) gave gave 2 main fractions: THF diols **2.46a**/**b** (114 mg, 0.24 mmol, 32%) as a colourless oil, and hydroxy ketone **2.47** (83.4 mg, 0.19 mmol, 25%) as a pale yellow oil.

Method B:

At –50 °C under an atmosphere of N_2, to a stirred solution of $KMnO_4$ (45 mg, 0.28 mmol), adogen 464 (26 mg, 0.06 mmol), acetic acid (50μL, 0.84 mmol) and

CH_2Cl_2 (2 mL) was added dieneyne **2.44** (0.52 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) dropwise. The reaction was allowed to warm to room temperature over 1 hour then $Na_2S_2O_3$ (sat aq, 3 mL) was added and the organic layer was separated. The aqueous layer was re-extracted with EtOAc (5 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (73.4 mg). Purification on SiO_2 (9 x 2 cm) eluting with hexane/EtOAc (4:1 → 1:1) gave 2 main fractions: THF diols **2.46a**/**b** (8 mg, 0.045 mmol, 7%) as a colourless oil, and hydroxy ketone **2.47** (18 mg, 0.04 mmol, 17%) as a pale yellow oil.

Spectroscopic characterisation for THF diols **2.46a**/**b**, isolated as a 9:1 mixture of diastereoisomers:

IR ν_{max} (neat) cm^{-1} 3470 (br), 2959 (s), 2359 (w), 1686 (s).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.60 – 4.52 (2H, m, **C7** and **C8**), 4.32 (1H, dd, *J* = 6.7, 4.6 Hz, **C3**), 4.10 – 4.02 (1H, m, **C4**), 3.95 (1H, dd, *J* = 7.8, 5.1 Hz, **C10**), 3.86 (1H, d, *J* = 9.3 Hz, **OH**), 3.51 (1H, d, *J* = 13.8 Hz, **C16**(1H)), 3.44 (1H, d, *J* = 13.8 Hz, **C16**(1H)), 3.37 (1H, d, *J* = 4.6 Hz, **OH**), 2.32 – 2.22 (1H, m, **C5**(1H)), 2.13 – 1.93 (5H, m, **C5**(1H), **C6** and **C11**), 1.94 – 1.82 (3H, m, **C12**, **C13**(1H) and **C14**(1H)), 1.49 – 1.27 (2H, m, **C13**(1H) and **C14**(1H)), 1.14 (3H, s, **C18**), 0.96 (3H, s, **C19**), 0.16 (9H, s, **TMS**).

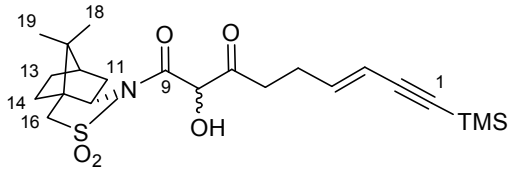
^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6 (C), 103.9 (C), 90.6 (C), 83.0 (CH), 79.5 (CH), 72.4 (CH), 65.9 (CH), 65.9 (CH), 53.1 (CH_2), 49.2 (C), 48.0 (C), 44.7 (CH_1), 38.3 (CH_2), 33.0 (CH_2), 28.1 (CH_2), 27.8 (CH_2), 26.5 (CH_2), 21.0 (CH_3), 20.0 (CH_3), 0.0 (CH_3),

Minor isomer peaks δ 171.9 (C), 102.1 (C), 91.2 (C), 82.5 (CH), 79.3 (CH), 70.2 (CH), 64.8 (CH).

LRMS ESI+ 492 $[M+Na]^+$ (100%).

HRMS ESI+ $[M+Na]^+$ calculated = 492.1847, $[M+Na]^+$ found = 492.1838.

(*E*)-1-((*S*)-10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-hydroxy-9-trimethylsilanyl-non-6-en-8-yne-1,3-dione (**2.47**)



$C_{22}H_{33}NO_5SSi$
Exact Mass: 451.1849
Mol. Wt.: 451.6516

Spectroscopic characterisation for hydroxy ketone **2.47**, isolated as a 3:2 mixture of epimers.

IR ν_{max} (neat) cm^{-1} 3465 (br), 2959 (m), 2131 (w), 1729 (s), 1686 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.15 (1H, dt, *J* = 15.9, 6.8 Hz, **C4**), 5.53 (1H, d, *J* = 15.9 Hz, **C3**), 5.16 (1H, s, **C8**), 3.99 – 3.91 (3H, m, **OH** and **C10**), 3.59 – 3.46 (2H, m, **C16**), 2.73 – 2.65 (2H, m, **C6**), 2.48 – 2.37 (2H, m, **C5**), 2.21 – 2.05 (2H, m, **C11**), 2.00 – 1.83 (3H, m, **C12**, **C13**(1H) and **C14**(1H)), 1.49 – 1.31 (2H, m, **C13**(1H) and **C14**(1H)), 1.17 (3H, s, **C18**), 0.99 (3H, s, **C19**),

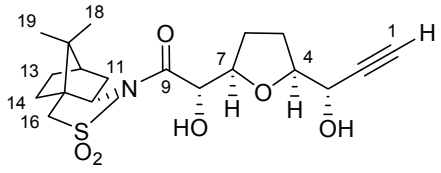
Minor isomer peaks δ 5.21 (1H, s, **C8**), 1.14 (3H, s, **C18**), 0.98 (3H, s, **C19**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 203.1 (C), 167.8 (C), 143.4 (CH), 111.5 (CH), 103.8 (C), 93.9 (C), 76.2 (CH), 65.7 (CH), 53.2 (CH_2), 49.5 (C), 48.2 (C), 44.9 (CH_1), 38.5 (CH_2), 38.1 (CH_2), 33.2 (CH_2), 33.1 (CH_2), 26.7 (CH_2), 20.7 (CH_3), 20.2 (CH_3), 0.3 (CH_3),

Minor isomer peaks δ 202.8 (C), 168.4 (C), 65.4 (CH), 20.3 (CH_3).

LRMS ESI+ 469 $[M+NH_4]^+$ (100%), 474 $[M+Na]^+$ (40%).

(*S*)-1-((*S*)-10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-hydroxy-2-[(2*R*,5*S*)-5-((*S*)-1-hydroxy-prop-2-ynyl)-tetrahydro-furan-2-yl]-ethanone



$C_{19}H_{27}NO_6S$
Exact Mass: 397.1559
Mol. Wt.: 397.4858

For procedure see method A THF diols **2.46a**/**b**.

[α]$^{29.5}_{D}$ +47.7 ($CHCl_3$, *c* 0.93).

IR ν_{max} (neat) cm^{-1} 3465 (br), 3300 (br), 2959 (s), 2883 (m), 2360 (m), 2342 (m), 1686 (s).

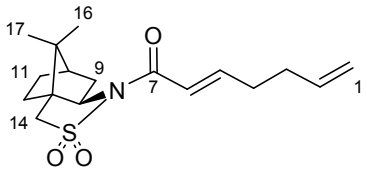
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.63 – 4.55 (2H, m, **C7** and **C8**), 4.32 (1H, dd, *J* = 5.9, 2.2 Hz, **C3**), 4.16 – 4.07 (1H, m, **C4**), 3.96 (1H, dd, *J* = 7.9, 5.0 Hz, **C10**), 3.52 (1H, d, *J* = 13.7 Hz, **C16**(1H)), 3.45 (1H, d, *J* = 13.7 Hz, **C16**(1H)), 2.45 (1H, d, *J* = 2.3 Hz, **C1**), 2.33 – 2.20 (1H, m, **C5**(1H)), 2.15 – 1.95 (5H, m, **C5**(1H), **C6** and **C11**), 1.95 – 1.83 (3H, m, **C12**, **C13**(1H) and **C14**(1H)), 1.50 – 1.30 (2H, m, **C13**(1H) and **C14**(1H)), 1.15 (3H, s, **C18**), 0.97 (3H, s, **C19**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6 (C), 82.8 (CH), 82.5 (C), 79.5 (CH), 73.8 (C), 72.7 (CH), 66.0 (CH), 65.1 (CH), 53.2 (CH_2), 49.3 (C), 48.1 (C), 44.7 (CH_1), 38.3 (CH_2), 33.1 (CH_2), 27.9 (CH_2), 26.5 (CH_2), 21.0 (CH_3), 20.1 (CH_3).

LRMS ESI+ 420 $[M+Na]^+$ (100%).

HRMS ESI+ $[M+Na]^+$ calculated = 420.1451, $[M+Na]^+$ found = 420.1450.

(*E*)-1-((*R*)-10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-hepta-2,6-dien-1-one (**2.50**)



$C_{17}H_{25}NO_3S$
Exact Mass: 323.1555
Mol. Wt.: 323.4503

Under an atmosphere of Ar, to a stirred solution of (1*S*,2*R*)-camphorsultam phosphonate (4.95 g, 12.6 mmol) in dry acetonitrile (80 mL) dried lithium chloride (170 °C/ 0.035 mbar overnight) (0.56 mg, 13.2 mmol) was added. After stirring for 15 minutes, DIPEA (2.2 mL, 12.6 mmol) was added. After stirring for 10 minutes, 4-pentenal (**2.49**) (1.2 mL, 12 mmol) in dry acetonitrile (2 mL) was added. The reaction was stirred for 20 hours. A solution of brine (50 mL) and water (30mL) were added and the organic layer was separated. The aqueous layer was re-extracted with Et_2O (3 x 80 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give an orange oil. Purification on

SiO_2 (5 x 15 cm) eluting with hexane/Et_2O (7:3) gave diene **2.50** (2.95 g, 9.1 mmol, 76%) as a colourless oil.

$[\alpha]^{27}_D$ –54.0 ($CHCl_3$, *c* 1.05).

IR ν_{max} (neat) 2959 (m), 1682 (s), 1638 (s) cm^{-1}.

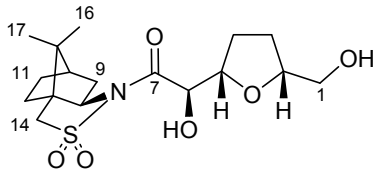
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (1H, dt, *J* = 15.1, 6.6 Hz, **C5**), 6.57 (1H, d, *J* = 15.1 Hz, **C6**), 6.22 (1H, ddt, *J* = 17.2, 10.3, 6.6 Hz, **C2**), 5.05 (1H, d, *J* = 17.2 Hz, **C1**(1H)), 5.00 (1H, d, *J* = 10.3 Hz, **C1**(1H)), 3.92 (1H, dd, *J* = 7.3, 5.1 Hz, **C8**) 3.51 (1H, d, *J* = 13.7 Hz, **C14**(1H)), 3.43 (1H, d, *J* = 13.7 Hz, **C14**(1H)), 2.40 – 2.30 (2H, m, **C3**), 2.29 – 2.19 (2H, m, **C4**), 2.15 – 2.05 (2H, m, **C9**), 1.99 – 1.84 (3H, m, **C10** and **C11**(1H) and **C12**(1H)), 1.47 – 1.34 (2H, m, **C11**(1H) and **C12**(1H)), 1.18 (3H, s, **C16**), 0.97 (3H, s, **C17**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4 (C), 150.1 (CH), 137.3 (CH), 132.2 (CH), 121.6 (CH), 115.9 (CH_2), 65.5 (CH), 53.5 (CH_2), 48.8 (C), 48.1(C), 45.0 (CH), 38.8 (CH_2), 33.2 (CH_2), 32.3 (CH_2), 32.1 (CH_2), 26.8 (CH_2), 21.2 (CH_3), 20.2 (CH_3).

LRMS ESI+ 346 $[M+Na]^+$ (100%).

HRMS ESI+ $[M+Na]^+$ calculated = 346.1453, $[M+Na]^+$ found = 346.1449.

(*R*)-1-((*R*)-10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-hydroxy-2-((2*S*,5*R*)-5-hydroxymethyl-tetrahydro-furan-2-yl)-ethanone (**2.48a**)



$C_{17}H_{27}NO_6S$
Exact Mass: 373.1559
Mol. Wt.: 373.4644

At –40 °C under an atmosphere of Ar, to a stirred solution of diene **2.50** (666 mg, 2.03 mmol) in acetone/acetic acid (4:1 65 mL) was added powdered $KMnO_4$ (417 mg, 2.6 mmol). The reaction was stirred for 1 hour, then quenched by addition of $Na_2S_2O_3$ (sat aq, 20 mL). The organic layer was separated and the aqueous layer

was re-extracted with CH_2Cl_2 (4 x 100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification on SiO_2 (3 x 11 cm) eluting with hexane/EtOAc (3:1 → 0:1) gave 3 main fractions: THF diol **2.48a** (430 mg, 1.16 mmol, 57%) as a colourless oil, THF diol **2.48b** (75 mg, 0.20 mmol, 9.9%) as a colourless oil and hydroxy ketone **2.52** (160 mg, 0.45 mmol, 22%) as a pale yellow oil.
Spectroscopic characterisation for THF diol **2.48a**.

$[\alpha]^{27}_D$ –54.0 ($CHCl_3$, *c* 1.97).

IR ν_{max} (neat) 3442 (br), 2958 (s), 1691 (s) cm^{-1}.

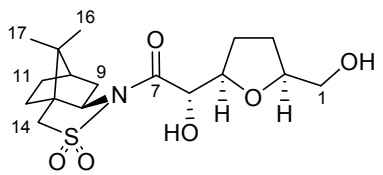
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.54 (2H, m, **C5** and **C6**), 4.16 – 4.04 (2H, m, **C2** and **C1**(1H)), 3.81 (1H, dd, *J* = 11.7, 2.9 Hz, **C1**(1H)), 3.94 (1H, dd, *J* = 7.9, 5.1 Hz **C8**), 3.57 – 3.47 (2H, m, **C14**(1H) and **OH**), 3.52 (1H, d, *J* = 13.7 Hz, **C14**(1H)), 3.43 (1H, d, *J* = 13.7 Hz, **C14**(1H)), 3.18 (1H, br s, **OH**), 2.15 – 1.99 (4H, m, **C3** and **C4**), 1.95 – 1.83 (5H, m, **C9**, **C10**, **C11**(1H) and **C12**(1H)), 1.45 – 1.35 (2H, m, **C11**(1H) and **C12**(1H)), 1.14 (3H, s, **C16**), 0.97 (3H, s, **C17**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0 (C) 80.9 (CH), 79.0 (CH), 73.5 (CH), 66.1 (CH), 64.8 (CH_2), 53.3 (CH_2), 49.3 (C) 48.2 (C), 44.9 (CH), 38.5 (CH_2), 33.2 (CH_2), 28.8 (CH_2), 27.3 (CH_2), 26.7 (CH_2), 21.1 (CH_3), 20.2 (CH_3).

LRMS ESI+ 396 $[M+Na]^+$ (100%).

HRMS ESI+ $[M+Na]^+$ calculated = 396.1451, $[M+Na]^+$ found = 396.1452.

(*S*)-1-((*R*)-10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-hydroxy-2-((2*R*,5*S*)-5-hydroxymethyl-tetrahydro-furan-2-yl)-ethanone (**2.48b**)



$C_{17}H_{27}NO_6S$
Exact Mass: 373.1559
Mol. Wt.: 373.4644

$[\alpha]^{25}_D$ –137.8 ($CHCl_3$, *c* 1.55).

IR ν_{max} (neat) 3475 (br), 2958 (s), 1698 (s) cm^{-1}.

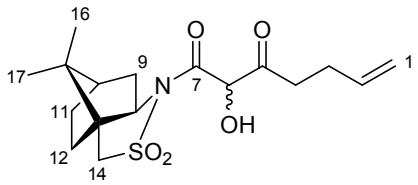
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.69 (1H, br s, **C6**), 4.52 – 4.43 (1H, m, **C5**), 4.03 (1H, m, **C2**), 3.96 (1H, dd, *J* = 7.1, 5.3 Hz, **C8**), 3.76 (1H, dd, *J* = 11.8, 3.1 Hz, **C1**(1H)), 3.64 (1H, br s, **OH**), 3.55 – 3.38 (3H, m, **C1**(1H) and **C14**), 2.23 – 1.83 (9H, m, **C3**, **C4**, **C9**, **C10**, **C11**(1H) and **C12**(1H)), 1.53 – 1.31 (2H, m, **C11**(1H) and **C12**(1H)), 1.16 (3H, s, **C16**), 0.99 (3H, s, **C17**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1 (C), 80.4 (CH), 80.3 (CH), 73.8 (CH), 65.0 (CH), 64.7 (CH_2), 53.0 (CH_2), 49.0 (C), 47.9 (C), 44.5 (CH), 37.7 (CH_2), 32.6 (CH_2), 28.1 (CH_2), 27.2 (CH_2), 26.5 (CH_2), 20.4 (CH_3), 19.9 (CH_3).

LRMS ESI+ 396 $[M+Na]^+$ (100%).

HRMS ESI+ $[M+Na]^+$ calculated = 396.1451, $[M+Na]^+$ found = 396.1450.

1-((*R*)-10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-hydroxy-hept-6-ene-1,3-dione (**2.52**)



$C_{17}H_{25}NO_5S$
Exact Mass: 355.1453
Mol. Wt.: 355.4491

IR ν_{max} (neat) 3464 (br), 2958 (s), 1728 (s), 1686 (s) cm^{-1}.

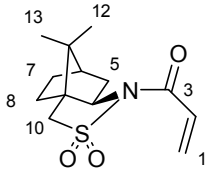
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 – 5.69 (1H, m, **C2**), 5.24 (1H, s, **C6**), 5.12 – 4.93 (2H, m, **C1**), 4.00 – 3.72 (2H, m, **C8** and **OH**), 3.57 – 3.43 (2H, m, **C14**), 3.03 – 2.78 (1H, m, **C4**(1H)), 2.76 – 2.62 (1H, m, **C4**(1H)), 2.42 – 2.30 (2H, m, **C3**), 2.21 – 2.03 (2H, m, **C9**), 2.00 – 1.84 (3H, m, **C10**, **C11**(1H) and **C12**(1H)), 1.52 – 1.30 (2H, m, **C11**(1H) and **C12**(1H)), 1.16 (3H, s, **C16**), 0.98 (3H, s, **C17**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 203.1 (C), 168.3 (C), 136.6 (CH), 115.7 (CH_2), 76.6 (CH_1), 65.3 (CH_1), 53.0 (CH_2), 49.3 (C), 48.1 (C), 44.8 (CH_1), 38.6 (CH_2), 37.9 (CH_2), 33.0 (CH_2), 27.2 (CH_2), 26.6 (CH_2), 20.6 (CH_3), 20.1 (CH_3).

LRMS ESI+ 373 $[M+NH_4]^+$ (100%).

HRMS ESI+ $[M+Na]^+$ calculated = 378.1346, $[M+Na]^+$ found = 378.1349.

1-((*R*)-10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-propenone (**2.58**)



$C_{13}H_{19}NO_3S$
Exact Mass: 269.1086
Mol. Wt.: 269.3599

At 0 °C under an atmosphere of Ar, to a stirred solution of (2*R*)-camphor sultam **2.56** (2.0 g, 9.2 mmol) in dry benzene (24 mL) and dry acetonitrile (4 mL) was added dropwise TMSCl (5.6 mL, 44.2 mmol), followed by Et_3N (1.4 mL, 10.1 mmol). The reaction was stirred for 45 minutes then warmed to room temperature and stirred for 4 hours. The reaction was concentrated *in vacuo*, the creamy solid was suspended in toluene (40 mL) and filtered. The filtrate was concentrated *in vacuo* and the white solid was used crude in the next step.

Under an atmosphere of Ar, a stirred solution of the crude white solid, acryloyl chloride (3.0 mL, 36.8 mmol), and $CuCl_2$ (123.4 mg, 0.92 mmol) in dry benzene (13 mL) were heated to reflux for 16 hours. The reaction was filtered while still warm and then washed through with EtOAc (20 mL). The filtrate was concentrated *in vacuo* to give a white solid. Purification on SiO_2 (4 x 12 cm) eluting with EtOAc/hexane (1:4) gave 1-((*R*)-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-propenone (**2.58**) (1.71 g, 6.35 mmol, 69%) as a white solid.
Spectroscopic characterisation agreed with that published.[150]

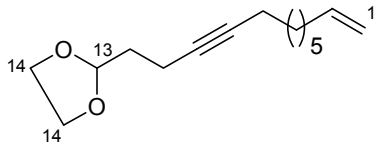
[α]$^{25}_D$ –101.5 ($CHCl_3$, *c* 0.96).

IR ν_{max} (neat) cm^{-1} 2958 (s), 2924 (s), 1674 (s), 1619 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (1H, dd, *J* = 16.6, 10.3 Hz, **C2**), 6.50 (1H, dd, *J* = 16.6, 1.6 Hz, **C1**(1H *trans* to **C2**)), 5.85 (1H, dd, *J* = 10.3, 1.6 Hz, **C1**(1H *cis* to **C2**)), 3.94 (1H, dd, *J* = 7.4, 5.3 Hz, **C4**), 3.52 (1H, d, *J* = 13.7 Hz, **C10**(1H*)*), 3.45 (1H, d, *J* = 13.7 Hz, **C10**(1H*)*), 2.24 – 2.02 (2H, m, **C5**), 2.00 – 1.81 (3H, m, **C6**, **C7**(1H) and **C8**(1H)), 1.50 – 1.30 (2 H, m, **C7**(1H) and **C8**(1H)), 1.18 (3H, s, **C12**), 0.98 (3H, s, **C13**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0 (C), 131.4 (CH_2), 128.0 (CH_1), 65.3 (CH_1), 53.3 (CH_2), 48.7 (C), 48.0 (C), 44.9 (CH_1), 38.6 (CH_2), 33.1 (CH_2), 26.7 (CH_2), 21.0 (CH_3), 20.1 (CH_3).

2-(Dodec-11-en-3-ynyl)-1,3-dioxolane (**2.61**)



$C_{15}H_{24}O_2$
Exact Mass: 236.1776
Mol. Wt.: 236.3499

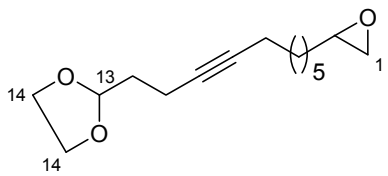
At –78 °C under an atmosphere of Ar, to a stirred solution of 2-(but-3-ynyl)-1,3-dioxolane (**2.60**) (16.3 g, 0.129 mol) in dry THF (500 mL) was added 2.45M *n*-BuLi in hexane (52.6 mL, 0.129 mol). After stirring for 40 minutes, HMPA (37 mL, 0.2 mmol) was added dropwise. After stirring for 30 minutes, bromide **2.1** (20 g, 0.104 mol) was added dropwise. The reaction was allowed to warm to room temperature and stirred for 3 hours. The reaction was slowly poured into NH_4Cl (sat aq, 250 mL) and the organic layer was separated. The aqueous layer was extracted with Et_2O (2 x 250 mL) and CH_2Cl_2 (1 x 150 mL). The combined organic phases were concentrated *in vacuo* to give a yellow oil. The yellow oil was dissolved in Et_2O (150 mL) and washed with water (3 x 150 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil. Purification on SiO_2 (15 x 8 cm) eluting with hexane/Et_2O (4:1) gave 2-(dodec-11-en-3-ynyl)-1,3-dioxolane (**2.61**) (21.3 g, 0.090 mol, 70%) as a colourless oil.

IR ν_{max} (neat) cm^{-1} 2930 (s), 2856 (s), 1640 (w).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (1H, ddt, *J* = 17.1, 10.3, 6.7 Hz, **C2**), 5.05 – 4.89 (3H, m, **C1** and **C13**), 4.01 – 3.80 (4H, m, **C14**), 2.30 (2H, tt, *J* = 7.5, 2.3 Hz, **C11**), 2.14 (2H, tt, *J* = 7.0, 2.3 Hz, **C8**), 2.10 – 2.00 (2H, m, **C3**), 1.84 (2H, td, *J* = 7.4, 4.8 Hz, **C12**), 1.54 – 1.22 (8H, m, **C4** – **C7**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1 (CH_1), 114.2 (CH_2), 103.4 (CH_1), 80.5 (C), 78.9 (C), 64.9 (CH_2), 33.7 (CH_2), 33.5 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 28.7 (CH_2), 28.6 (CH_2), 18.7 (CH_2), 13.8 (CH_2).

2-(10-(Oxiran-2-yl)dec-3-ynyl)-1,3-dioxolane (**2.62**)



$C_{15}H_{24}O_3$
Exact Mass: 252.1725
Mol. Wt.: 252.3493

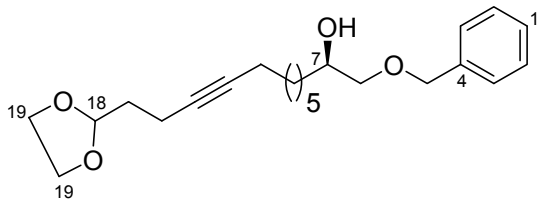
Under an atmosphere of N_2 at 0 °C, to stirred alkene **2.61** (113 mg, 0.476 mmol), was added dropwise 0.068M DDO (11 mL, 0.75 mmol), a further portion of 0.068M DDO (2.2 mL, 0.15 mmol) was added every hour, 3 times. After 4 hours the reaction was concentrated *in vacuo* to afford a yellow oil. Purification on SiO_2 (8 x 2 cm) eluting with hexane/Et_2O (3:2 → 0:1) gave 2-(10-(oxiran-2-yl)dec-3-ynyl)-1,3-dioxolane (**2.62**) (70 mg, 0.276 mmol, 58%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (1H, t, *J* = 4.8 Hz, **C13**), 3.94 – 3.73 (4H, m, **C14**), 2.87 – 2.78 (1H, m, **C2**), 2.67 (1H, dd, *J* = 5.0, 4.1 Hz, **C1**(1H)), 2.39 (1H, dd, *J* = 5.0, 2.7 Hz, **C1**(1H)), 2.22 (2H, tt, *J* = 7.4, 2.4 Hz, **C11**), 2.06 (2H, tt, *J* = 6.9, 2.4 Hz, **C8**), 1.77 (2H, td, *J* = 7.4, 4.8 Hz, **C12**), 1.54 – 1.17 (10H, m, **C3** – **C7**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 103.4 (CH_1), 80.4 (C), 79.0 (C), 64.9 (CH_2), 52.3 (CH_1), 47.1 (CH_2), 33.5 (CH_2), 32.4 (CH_2), 28.9 (CH_2), 28.9 (CH_2), 28.7 (CH_2), 25.9 (CH_2), 18.7 (CH_2), 13.7 (CH_2);

LRMS ESI+ 275 $[M+Na]^+$ (100%).

(*R*)-1-(Benzyloxy)-12-(1,3-dioxolan-2-yl)dodec-9-yn-2-ol



$C_{22}H_{32}O_4$
Exact Mass: 360.2301
Mol. Wt.: 360.4871

At 0 °C under an atmosphere of Ar, to a stirred solution of 2-(10-(oxiran-2-yl)dec-3-ynyl)-1,3-dioxolane (**2.62**) (8.83 g, 0.035 mol) and oligomeric (*S,S*)-Co(salen) (**2.13**) (75 mg, 0.088 mmol) in MeCN (2.3 mL) was added dropwise benzyl alcohol (1.64 mL, 0.0158 mol), the reaction was stirred for 24 hours. The reaction was filtered through a plug of silica with Et_2O (300 mL) and concentrated *in vacuo* to afford an orange oil. Purification on SiO_2 (15 x 4 cm) eluting with hexane/Et_2O (7:3 → 0:1) gave 2 main fractions: (*R*)-1-(benzyloxy)-12-(1,3-

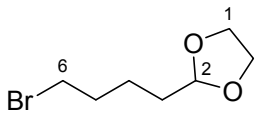
dioxolan-2-yl)dodec-9-yn-2-ol (**2.63**) (3.53 g, 0.0098 mol, 28%) as an orange oil and 2-(10-(oxiran-2-yl)dec-3-ynyl)-1,3-dioxolane (**2.62**) (5.12 g, 0.0203 mol, 58%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.22 (5H, m, **C1** – **C3**), 4.98 (1H, t, *J* = 4.8 Hz, **C18**), 4.56 (2H, apparent s, **C5**), 4.02 – 3.75 (5H, m, **C7** and **C19**), 3.51 (1H, dd, *J* = 9.4, 3.0 Hz, **C6**(1H)), 3.33 (1H, dd, *J* = 9.4, 7.9 Hz, **C6**(1H)), 2.37 (1H, br s, **OH**), 2.29 (2H, tt, *J* = 7.4, 2.3 Hz, **C16**), 2.13 (2H, tt, *J* = 6.9, 2.3 Hz, **C13**), 1.84 (2H, td, *J* = 7.4, 4.8 Hz, **C17**), 1.53 – 1.26 (10H, m, **C8** – **C12**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0 (C), 128.4 (CH_1), 127.7 (CH_1), 127.7 (CH_1), 103.4 (CH_1), 80.5 (C), 78.9 (C), 74.6 (CH_2), 73.3 (CH_2), 70.4 (CH_1), 64.9 (CH_2), 33.4 (CH_2), 33.1 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 28.7 (CH_2), 25.4 (CH_2), 18.7 (CH_2), 13.7 (CH_2).

LRMS ESI+ 383 $[M+Na]^+$ (100%).

2-(4-Bromobutyl)-1,3-dioxolane (**2.71**)



$C_7H_{13}BrO_2$
Exact Mass: 208.0099
Mol. Wt.: 209.0809

Under an atmosphere of Ar at –78 °C, a stirred solution of 5-bromopentanoate (**2.69**) (10.0 g, 0.0478 mol) in dry toluene (260 mL) was added dropwise 1.5M DIBAL-H in toluene (35.1 mL, 0.0526 mol) over 1.5 hours. The reaction was stirred for a further 1.5 hours at –78 °C at which point the reaction was quenched with MeOH (20 mL). The reaction mixture was warmed to room temperature, 5% HCl (150 mL) was added and the reaction was stirred for 40 minutes. The organic layer was separated and washed with water (150 mL). The organic phase was dried ($MgSO_4$) and carefully concentrated *in vacuo* to afford a solution of crude aldehyde **2.70** in toluene (12g).

The solution of crude aldehyde **2.70** in toluene was dissolved in dry benzene (170 mL), to this ethylene glycol (6.2 g, 0.1 mol) and TsOH (50mg, 0.3 mmol) were added. Using Dean-Stark apparatus the reaction mixture was heated to reflux for 15 hours. The reaction was diluted with $NaHCO_3$ (sat aq, 170 mL), the organic layer was separated and dried ($MgSO_4$) and concentrated by distillation.

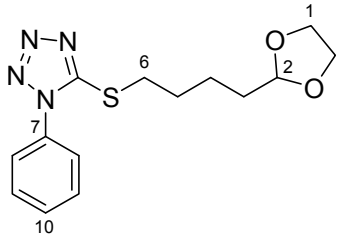
Purification on SiO_2 (8 x 7 cm) eluting with pentane/Et_2O (9:1) gave 2-(4-bromobutyl)-1,3-dioxolane (**2.71**) (8.14 g, 0.0392 mol, 82%) as a colourless liquid.
Spectroscopic characterisation agreed with that published.[157]

IR ν_{max} (neat) cm^{-1} 2977 (w), 2871 (w), 907 (s), 728(s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.86 (1H, t, *J* = 4.5 Hz, **C2**), 4.03 – 3.91 (2H, m, **C1** (1H)), 3.91 – 3.79 (2H, m, **C1**(1H)), 3.41 (2H, t, *J* = 6.8 Hz, **C6**), 1.92 (2H, tt, *J* = 7.3, 6.8 Hz, **C5**), 1.74 –1.64 (2H, m, **C3**), 1.64 – 1.50 (2H, m, **C4**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 104.2 (CH_1), 64.9 (CH_2), 33.5 (CH_2), 32.9 (CH_2), 32.6 (CH_2), 22.6 (CH_2).

5-(4-(1,3-Dioxolan-2-yl)butylthio)-1-phenyl-1*H*-tetrazole (**2.72**)



$C_{14}H_{18}N_4O_2S$
Exact Mass: 306.115
Mol. Wt.: 306.3833

At 40 °C under an atmosphere of Ar, a solution of 2-(4-bromobutyl)-1,3-dioxolane (**2.71**) (3.75 g, 18 mmol), 1-phenyl-1*H*-tetrazole-5-thiol (3.20 g, 18 mmol) and dry K_2CO_3 (61.9 mg, 0.248 mmol) in dry (dried with $MgSO_4$) acetone (90 mL) were vigorously stirred for 3 hours, then at room temperature for 3 hours. The reaction was filtered and the collected white solid was washed with acetone (90 mL). The filtrate was concentrated *in vacuo* to afford colourless oil. The colourless oil was dissolved in CH_2Cl_2/water (1:1 250 mL), the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic phases were washed with water (200 mL) then dried ($MgSO_4$) and concentrated *in vacuo* to afford a colourless oil. Purification on SiO_2 (7 x 10 cm) eluting with Et_2O/hexane (3:2 → 9:1) gave 5-(4-(1,3-dioxolan-2-yl)butylthio)-1-phenyl-1*H*-tetrazole (**2.72**) (5.06 g, 16.5 mmol, 92%) as a colourless oil.

IR ν_{max} (neat) cm^{-1} 2947 (s), 2872 (s), 1596 (m).

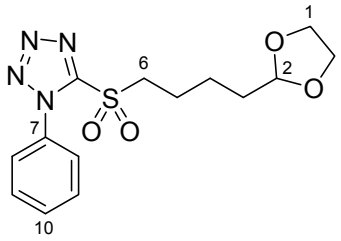
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 – 7.42 (5H, m, **C8** – **C10**), 4.85 (1H, t, *J* = 4.5 Hz, **C2**), 4.01 – 3.89 (2H, m, **C1**(1H)), 3.89 – 3.78 (2H, m, **C1**(1H)), 3.40 (2H, t, *J* = 7.3 Hz, **C6**), 1.89 (2H, quin, *J* = 7.3 Hz, **C5**), 1.75 – 1.65 (2H, m, **C3**), 1.65 – 1.51(2H, m, **C4**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3 (CH), 133.7 (CH), 130.0 (CH_1), 129.7 (CH_1), 123.8 (CH_1), 104.1 (CH_1), 64.8 (CH_2), 33.1 (CH_2), 28.9 (CH_2), 22.9 (CH_2).

LRMS ESI+ 329 $[M+Na]^+$ (63%), 635 [2M+Na] (100%).

HRMS ESI+ $[M+Na]^+$ calculated = 329.1043, $[M+Na]^+$ found = 329.1045.

5-(4-(1,3-Dioxolan-2-yl)butylsulfonyl)-1-phenyl-1*H*-tetrazole (**2.73**)



$C_{14}H_{18}N_4O_4S$
Exact Mass: 338.1049
Mol. Wt.: 338.3821

At 0 °C under an atmosphere of Ar, to a stirred solution of 5-(4-(1,3-dioxolan-2-yl)butylthio)-1-phenyl-1*H*-tetrazole (**2.72**) (2.8 g, 9.18 mmol) in ethanol (200 mL) was added $[NH_4]_6Mo_7O_{24}\bullet 4H_2O$ (6.8 g, 5.5 mmol) in 30% H_2O_2 (aq 3.5 mL). The reaction was warmed to room temperature and stirred for 63 hours. CH_2Cl_2 (100 mL) and K_2CO_3 (sat aq, 100 mL) were added, and the organic phase was separated. The aqueous layer was re-extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to afford a yellow oil. Purification on SiO_2 (8 x 8 cm) eluting with EtOAc/hexane (1:1) gave 5-(4-(1,3-dioxolan-2-yl)butylsulfonyl)-1-phenyl-1*H*-tetrazole (**2.73**) (3.09 g, 9.13 mmol, 99%) as a white solid.

IR ν_{max} (neat) cm^{-1} 2954 (s), 2881 (s), 1595 (m).

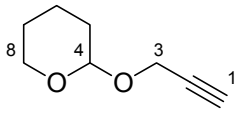
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.66 (2H, m, **C8**), 7.64 – 7.54 (3H, m, **C9** and **C10**), 4.86 (1H, t, *J* = 4.3 Hz, **C2**), 4.00 – 3.87 (2H, m, **C1**(1H)), 3.89 – 3.79 (2H, m, **C1**(1H)), 3.78 – 3.70 (2H, m, **C6**), 2.07 – 1.96 (2H, m, **C3**), 1.76 – 1.69 (2H, m, **C5**), 1.69 – 1.59 (2H, m, **C4**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6 (C), 133.2 (C), 131.6 (CH_1), 129.8 (CH_1), 125.2 (CH_1), 103.9 (CH_1), 65.1 (CH_2), 56.0 (CH_2), 33.0 (CH_2), 22.6 (CH_2), 22.1 (CH_2).

LRMS ESI+ 361 $[M+Na]^+$ (100%).

HRMS ESI+ $[M+Na]^+$ calculated = 329.0941, $[M+Na]^+$ found = 361.0936.

Tetrahydro-2-(prop-2-ynyloxy)-2*H*-pyran (**2.75**)



$C_8H_{12}O_2$
Exact Mass: 140.0837
Mol. Wt.: 140.1797

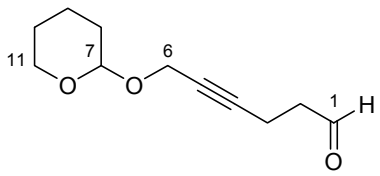
At room temperature under an atmosphere of Ar, to a stirred solution of propargylic alcohol (**2.74**) (12.56 g, 0.224 mol) and dihydropyran (17 mL, 0.187 mol) in dry CH_2Cl_2 (150 mL) was added PPTS (4.7 g, 0.0187 mol). After stirring for 16 hours the reaction was poured into $NaHCO_3$ (sat aq, 150 mL), the organic layer was separated and the aqueous layer was re-extracted with CH_2Cl_2 (2 x 150 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to afford a red oil. Purification by reduced pressure (12 mbar) distillation, collection at 68–70 °C gave tetrahydro-2-(prop-2-ynyloxy)-2*H*-pyran (**2.75**) (20.08 g, 0.143 mol, 77%) as a colourless oil.
Spectroscopic characterisation agreed with that published.[168]

IR ν_{max} (neat) cm^{-1} 3291 (s), 2942 (s), 2870 (s), 2359 (w).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.83 (1H, t, *J* = 3.1 Hz, **C4**), 4.31 (1H, dd, *J* = 15.7, 2.5 Hz, **C3**(1H)), 4.23 (1H, dd, *J* = 15.7, 2.5 Hz, **C3**(1H)), 3.94 – 3.75 (1H, m, **C8**(1H)), 3.62 – 3.47 (1H, m, **C8**(1H)), 2.42 (1H, t, *J* = 2.5 Hz, **C1**), 1.92 – 1.77 (1H, m, **C5**(1H)), 1.77 – 1.69 (1H, m, **C5**(1H)), 1.69 – 1.47 (4H, m, **C6** and **C7**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 97.0 (CH_1), 79.9 (CH_1), 74.1 (CH_1), 62.2 (CH_2), 54.2 (CH_2), 30.4 (CH_2), 25.5 (CH_2), 19.2 (CH_2).

6-(Tetrahydro-2*H*-pyran-2-yloxy)hex-4-ynal (**2.76**)



$C_{11}H_{16}O_3$
Exact Mass: 196.1099
Mol. Wt.: 196.2429

At –10 °C under an atmosphere of Ar, to a stirred solution of alkyne **2.75** (3.5 g, 24.9 mmol) in dry THF (83 mL) was added 2.26M *n*-BuLi in hexane (11 mL, 24.9 mmol). After stirring for 20 minutes, CuI•0.75DMS (6.5 g, 27.4 mmol) was added in one batch. After stirring for 45 minutes, the reaction was cooled to –78 °C and TMSI (5 g, 24.9 mmol) was added. After stirring for 5 minutes, acrolein (0.93 g, 24.9 mmol) in dry THF (5 mL) was added. The reaction was stirred at –78 °C for 2 hours, then NH_4Cl (sat aq, 100 mL) was added and the reaction was stirred at room temperature for 30 minutes. The organic layer was separated and the aqueous layer was re-extracted with Et_2O (2 x 100 mL). The combined organic phases were washed with $Na_2S_2O_3$ (sat aq, 100 mL) and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give an orange oil.

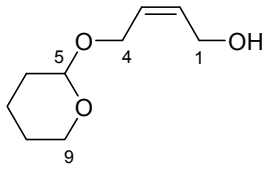
At 0 °C under an atmosphere of Ar, to a stirred solution of the orange oil in methanol (150 mL) was added K_2CO_3 (100 mg, 1 mmol). After 20 minutes NH_4Cl (sat aq, 50 mL) and Et_2O (100 mL) were added. The organic layer was separated and the aqueous layer was re-extracted with Et_2O (2 x 100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification on SiO_2 (4 x 10 cm) eluting with EtOAc/hexane (3:7) gave 6-(tetrahydro-2*H*-pyran-2-yloxy)hex-4-ynal (**2.76**) (1.71 g, 8.72 mmol, 35%) as a pale yellow oil.
Spectroscopic characterisation agreed with that published.[158]

IR ν_{max} (neat) cm^{-1} 2941 (s), 2852 (s), 1726 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (1H, t, *J* = 1.1 Hz, **C1**), 4.77 (1H, t, *J* = 3.2 Hz, **C7**), 4.31 – 4.11 (2H, m, **C6**), 3.89 – 3.76 (1H, m, **C11**(1H)), 3.57 – 3.45 (1H, m, **C11**(1H)), 2.74 – 2.60 (2H, m, **C2**), 2.60 – 2.45 (2H, m, **C3**), 1.92 – 1.77 (1H, m, **C8**(1H)), 1.77 – 1.69 (1H, m, **C8**(1H)), 1.69 – 1.47 (4H, m, **C9** and **C10**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 200.5 (CH_1), 96.9 (CH_1), 84.4 (C), 77.1 (C), 62.2 (CH_2), 54.6 (CH_2), 42.6 (CH_2), 30.4 (CH_2), 25.5 (CH_2), 19.2 (CH_2), 12.2 (CH_2).

(*Z*)-4-(Tetrahydro-2*H*-pyran-2-yloxy)but-2-en-1-ol (**2.78**)



$C_9H_{16}O_3$
Exact Mass: 172.1099
Mol. Wt.: 172.2215

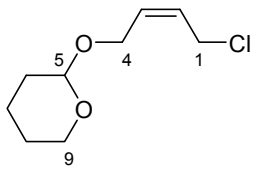
Under an atmosphere of Ar at 0 °C, to a solution of *cis*-but-2-ene-1,4-diol (17.2 g, 0.195 mol), dihydropyran (16.4 g, 0.195 mol) in CH_2Cl_2 (170 mL) and THF (430 mL) was added $TsOH•H_2O$ (2.6 g, 13.7 mmol). The reaction was stirred for 2 hours at room temperature. $NaHCO_3$ (sat aq, 250 mL) was added, the organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 200 mL). The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow liquid. Purification on SiO_2 (8 x 8 cm) eluting with Et_2O/hexane (1:1 → 4:1) gave (*Z*)-4-(tetrahydro-2*H*-pyran-2-yloxy)but-2-en-1-ol (**2.78**) (19.07 g, 0.110 mol, 57%) as a colourless oil.
Spectroscopic characterisation agreed with that published.[169]

IR ν_{max} (neat) cm^{-1} 3397 (br), 2941 (s), 2870 (s) 1620 (w).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (1H, dt with fine splitting, *J* = 11.2, 6.7 Hz, **C2**), 5.70 (1H, dt with fine splitting, *J* = 11.2, 5.9 Hz, **C3**), 4.68 (1H, t, J = 3.3 Hz, **C5**), 4.32 – 4.08 (4H, m, **C1** and **C4**), 3.92 – 3.80 (1H, m, **C9**(1H)), 3.58 – 3.47 (1H, m, **C9**(1H)), 2.31 (1H, t, J = 5.7 Hz, **OH**), 1.91 – 1.74 (1H, m, **C6**(1H)), 1.74 – 1.66 (1H, m, **C6**(1H)), 1.65 – 1.46 (4H, m, **C7** – **C8**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 132.4 (CH_1), 128.1 (CH_1), 97.5 (CH_1), 62.4 (CH_2), 62.1 (CH_2), 58.3 (CH_2), 30.4 (CH_2), 25.3 (CH_2), 19.2 (CH_2).

2-((*Z*)-4-Chlorobut-2-enyloxy)-tetrahydro-2*H*-pyran (**2.79**)



$C_9H_{15}ClO_2$
Exact Mass: 190.0761
Mol. Wt.: 190.6672

At 0 °C under an atmosphere of Ar, to a solution of 4-(tetrahydro-2*H*-pyran-2-yloxy)but-2-en-1-ol (**2.78**) (17.33 g, 0.1 mol), DIPEA (19.2 mL, 0.11 mol) in CH_2Cl_2 (100 mL) was added dropwise MsCl (8.1 mL, 0.105 mol). The reaction

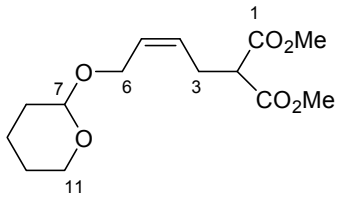
was stirred for 15 minutes at 0 °C, then at room temperature for 2 hours. $NaHCO_3$ (sat aq, 250 mL) was added, the organic layer was separated and the aqueous layer was re-extracted with Et_2O (2 x 100 mL). The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford an orange oil. Purification on SiO_2 (10 x 10 cm) eluting with Et_2O/hexane (0:1 → 1:4) gave 2-((*Z*)-4-chlorobut-2-enyloxy)-tetrahydro-2*H*-pyran (**2.79**) (13.4 g, 0.070 mol, 70%) as a colourless oil.
Spectroscopic characterisation agreed with that published.[170]

IR ν_{max} (neat) cm^{-1} 2942 (s), 2870 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 – 5.72 (2H, m, **C2** and **C3**), 4.63 (1H, t, *J* = 3.4 Hz, **C5**), 4.36 – 4.27 (1H, m, **C4**(1H)), 4.18 – 4.10 (3H, m, **C1** and **C4**(1H)), 3.92 – 3.80 (1H, m, **C9**(1H)), 3.58 – 3.47 (1H, m, **C9**(1H)), 1.92 – 1.74 (1H, m, **C6**(1H)), 1.74 – 1.66 (1H, m, **C6**(1H)), 1.65 – 1.46 (4H, m, **C7** – **C8**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 130.5 (CH_1), 128.3 (CH_1), 97.9 (CH_1), 62.2 (CH_2), 62.0 (CH_2), 39.2 (CH_2), 30.5 (CH_2), 25.4 (CH_2), 19.4 (CH_2).

Dimethyl 2-((*Z*)-4-(tetrahydro-2*H*-pyran-2-yloxy)but-2-enyl)malonate (**2.80**)



$C_{14}H_{22}O_6$
Exact Mass: 286.1416
Mol. Wt.: 286.3209

At room temperature under an atmosphere of Ar, to a solution of dimethyl malonate (10.2 g, 0.077 mol) in DMF (700 mL) was added portion-wise NaH dispensed in 60% mineral oil (4.2 g, 0.105 mol). The reaction was stirred for 1.5 hours until no further gas evolved. 2-((*Z*)-4-Chlorobut-2-enyloxy)-tetrahydro-2*H*-pyran (**2.79**) (13.4 g, 0.070 mol) was added and the reaction was stirred overnight (16 hours). Water (250 mL) was added followed by extraction with Et_2O (4 x 300 mL). The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford a heterogeneous yellow liquid. The heterogeneous yellow liquid was re-dissolved in Et_2O (250 mL) and washed with water (5 x 100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow

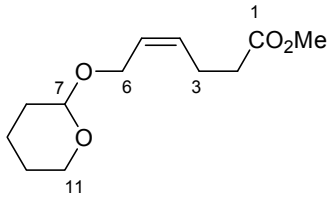
liquid. Purification on SiO_2 (10 x 10 cm) eluting with Et_2O/hexane (0:1 → 1:0) gave dimethyl 2-((*Z*)-4-(tetrahydro-2*H*-pyran-2-yloxy)but-2-enyl)malonate (**2.80**) (3.58 g, 12.5 mmol, 18%) as a colourless oil.
Spectroscopic characterisation agreed with that published.[170]

IR ν_{max} (neat) cm^{-1} 2950 (m), 2850 (m), 1733 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73 – 5.63 (1H, m, **C4**), 5.56 – 5.45 (1H, m, **C5**), 4.65 – 4.60 (1H, m, **C7**), 4.32 – 4.23 (1H, m, **C6**(1H)), 4.14 – 4.05 (1H, m, **C6**(1H)), 3.92 – 3.80 (1H, m, **C11**(1H)), 3.73 (6H, s, **OMe**), 3.56 – 3.47 (1H, m, **C11**(1H)), 3.43 (1H, t, *J* = 7.5 Hz, **C2**), 2.69 (2H, t, *J* = 7.5 Hz, **C3**), 1.88 – 1.73 (1H, m, **C8**(1H)), 1.73 – 1.64 (1H, m, **C8**(1H)), 1.63 – 1.46 (4H, m, **C9** – **C10**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2 (C), 129.4 (CH_1), 127.8 (CH_1), 98.0 (CH_1), 62.6 (CH_2), 62.2 (CH_2), 52.5 (CH_3), 51.5 (CH_1), 30.6 (CH_2), 27.0 (CH_2), 25.4 (CH_2), 19.4 (CH_2).

(*Z*)-Methyl 6-(tetrahydro-2*H*-pyran-2-yloxy)hex-4-enoate (2.81)



$C_{12}H_{20}O_4$
Exact Mass: 228.1362
Mol. Wt.: 228.2848

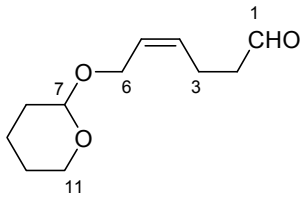
Under an atmosphere of Ar, a solution of dimethyl 2-((*Z*)-4-(tetrahydro-2*H*-pyran-2-yloxy)but-2-enyl)malonate (**2.80**) (3.5 g, 12.2 mmol), potassium acetate (2.4 g, 24.2 mmol) in DMSO (33 mL) and water (0.44 mL) were heated to reflux for 5 hours. The reaction was poured into water (30 mL) and extracted with Et_2O (3 x 50 mL). The combined organic phases were washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford an orange oil. Purification on SiO_2 (5 x 10 cm) eluting with Et_2O/hexane (3:7) gave (*Z*)-methyl 6-(tetrahydro-2*H*-pyran-2-yloxy)hex-4-enoate (**2.81**) (2.08 g, 9.11 mmol, 75%) as a colourless oil.
Spectroscopic characterisation agreed with that published.[170]

IR ν_{max} (neat) cm^{-1} 2944 (s), 2871 (m), 1736 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.67 – 5.49 (2H, m, **C4** and **C5**), 4.65 – 4.60 (1H, m, **C7**), 4.27 (1H, dd, *J* = 11.9, 4.9 Hz, **C6**(1H)), 4.08 (1H, dd, *J* = 11.9, 6.1 Hz, **C6**(1H)), 3.92 – 3.80 (1H, m, **C11**(1H)), 3.67 (3H, s, **OMe**), 3.56 – 3.47 (1H, m, **C11**(1H)), 2.47 – 2.33 (4H, m, **C2** – **C3**), 1.91 – 1.73 (1H, m, **C8**(1H)), 1.73 – 1.66 (1H, m, **C8**(1H)), 1.66 – 1.45 (4H, m, **C9** – **C10**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5 (C), 131.2 (CH_1), 127.7 (CH_1), 98.1 (CH_1), 62.8 (CH_2), 62.4 (CH_2), 51.7 (CH_3), 34.1 (CH_2), 30.8 (CH_2), 25.6 (CH_2), 23.2 (CH_2), 19.7 (CH_2).

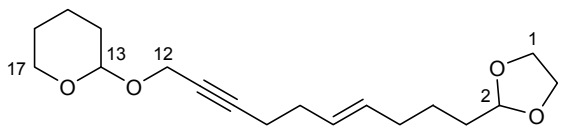
(*Z*)-6-(Tetrahydro-2*H*-pyran-2-yloxy)hex-4-enal (**2.82**)



$C_{11}H_{18}O_3$
Exact Mass: 198.1256
Mol. Wt.: 198.2588

At –78 °C under an atmosphere of Ar, a stirred solution of (*Z*)-methyl 6-(tetrahydro-2*H*-pyran-2-yloxy)hex-4-enoate (**2.81**) (1.0 g, 4.38 mmol) in dry toluene (20 mL) was added dropwise 1M DIBAL-H in hexane (4.6 mL, 4.6 mmol). The reaction was stirred for a further 1.5 hour at –78 °C at which point the reaction was quenched with EtOAc (3 mL). Rochelles salt (sat aq, 50 mL) was added and the reaction was stirred at room temperature for 1 hour. The organic layer was separated and the aqueous layer was re-extracted with Et_2O (2 x 50 mL). The combined organic phases were washed with water, dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil. Purification on SiO_2 (3 x 13 cm) eluting with Et_2O/hexane (0:1 → 3:7) gave (*Z*)-6-(tetrahydro-2*H*-pyran-2-yloxy)hex-4-enal (**2.82**) (720 mg, 3.63 mmol, 83%) as a colourless oil which was used directly in the next step.

2-((*E*)-10-(1,3-Dioxolan-2-yl)dec-6-en-2-ynyloxy)-tetrahydro-2*H*-pyran (**2.83**)



$C_{18}H_{28}O_4$
Exact Mass: 308.1988
Mol. Wt.: 308.4125

At –55 °C under an atmosphere of Ar, to a stirred solution of sulfone **2.73** (1.35 g, 4 mmol) in dry DME (25 mL) was added 0.5M KHMDS in toluene (8 mL, 4 mmol). After stirring for 1 hour, aldehyde **2.76** (790 mg, 4 mmol) in dry DME (5 mL) was added dropwise. After stirring for 1 hour, the reaction was gradually warmed to room temperature. The reaction was diluted with water/Et_2O (1:1 50 mL), the organic layer was separated and the aqueous layer was re-extracted with Et_2O (3 x 50 mL). The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification on SiO_2 (15 x 4 cm) eluting with hexane/EtOAc (48:1 → 23:2) gave 2-((*E*)-10-(1,3-dioxolan-2-yl)dec-6-en-2-ynyloxy)-tetrahydro-2*H*-pyran (**2.83**) (622 mg, 2.02 mmol, 51%) as a colourless oil which was a mixture of stereoisomers (*E*:*Z* = 6:1)

IR ν_{max} (neat) cm^{-1} 2940 (s), 2869 (s), 1736 (w).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52 – 5.39 (2H, m, **C6** and **C7**), 4.85 (1H, t, *J* = 4.8 Hz, **C2**), 4.81 (1H, t, *J* = 3 3 Hz, **C13**), 4.25 (2H, m, **C12**), 4.01 – 3.91 (2H, m, **C1**(2H)), 3.90 – 3.80 (3H, m, **C1**(2H) and **C17**(1H)), 3.57 – 3.49 (1H, m, **C17**(1H)), 2.30 – 2.15 (4H, m, **C8** and **C9**), 2.13 – 2.00 (2H, m, **C5**), 1.91 – 1.79 (1H, m, **C14**(1H)), 1.79 – 1.43 (9H, m, **C3**, **C4**, **C14**(1H), **C15** and **C16**).

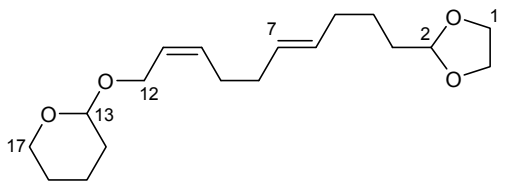
^{13}C NMR (101 MHz, $CDCl_3$) δ 131.4 (CH_1), 129.0 (CH_1), 104.7 (CH_1), 96.8 (CH_1), 86.3 (C), 76.3 (C), 65.0 (CH_2), 62.2 (CH_2), 54.8 (CH_2), 33.5 (CH_2), 32.5 (CH_2), 31.9 (CH_2), 30.5 (CH_2), 25.6 (CH_2), 24.0 (CH_2), 19.5 (CH_2), 19.3 (CH_2),

Z isomer peaks δ 130.9 (CH_1), 128.4 (CH_1), 33.6 (CH_2), 27.3 (CH_2), 26.7 (CH_2), 24.2 (CH_2), 19.4 (CH_2).

LRMS ESI+ 331 $[M+Na]^+$ (100%).

HRMS ESI+ $[M+Na]^+$ calculated = 331.1880, $[M+Na]^+$ found = 331.1880.

2-((2*Z*,6*E*)-10-[1,3]Dioxolan-2-yl-deca-2,6-dienyloxy)-tetrahydro-pyran (**2.84**)



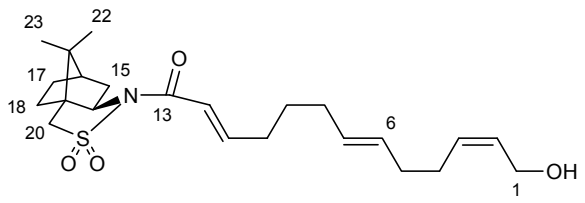
$C_{18}H_{30}O_4$
Exact Mass: 310.2144
Mol. Wt.: 310.4284

Under an atmosphere of H_2, a solution of alkyne **2.83** (200 mg, 0.65 mmol), quinoline (15 µL, 0.13 mmol) and Lindlar catalyst (Pd 5%, calcium carbonate poisoned with Pb) (43 mg, 0.02 mmol) in hexane (10 mL) was stirred for 2 hours. The reaction was filtered through celite and washed through with EtOAc (30 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to afford a pale yellow oil. Purification on SiO_2 (12 x 2 cm) eluting with hexane/EtOAc (23:2) gave 2-((2*Z*,6*E*)-10-[1,3]dioxolan-2-yl-deca-2,6-dienyloxy)-tetrahydropyran (**2.84**) (141 mg, 0.454 mmol, 70%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 – 5.52 (2H, m, **C10** and **C11**), 5.44 – 5.35 (2H, m, **C6** and **C7**), 4.85 (1H, t, *J* = 4.8 Hz, **C2**), 4.63 (1H, br t, *J* = 3.5 Hz, **C13**), 4.29 – 4.22 (1H, m, **C12**(1H)), 4.12 – 4.03 (1H, m, **C12**(1H)), 3.99 – 3.93 (2H, m, **C1**(2H)), 3.93 – 3.80 (3H, m, **C1**(2H) and **C17**(1H)), 3.56 – 3.46 (1H, m, **C17**(1H)), 2.18 – 2.09 (2H, m, **C9**), 2.09 – 1.98 (4H, m, **C5** and **C8**), 1.90 – 1.78 (1H, m, **C14**(1H)), 1.76 – 1.42 (9H, m, **C3**, **C4**, **C14**(1H), **C15** and **C16**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 133.1 (CH_1), 130.6 (CH_1), 130.0 (CH_1), 126.3 (CH_1), 104.7 (CH_1), 98.1 (CH_1), 65.0 (CH_2), 63.0 (CH_2), 62.4 (CH_2), 33.5 (CH_2), 32.7 (CH_2), 32.5 (CH_2), 30.9 (CH_2), 27.8 (CH_2), 25.7 (CH_2), 24.1 (CH_2), 19.7 (CH_2).

(2*E*,7*E*,11*Z*)-1-((*R*)-10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-13-hydroxy-trideca-2,7,11-trien-1-one (**2.85**)



$C_{23}H_{35}NO_4S$
Exact Mass: 421.2287
Mol. Wt.: 421.5933

At 0 °C under an atmosphere of Ar, to a stirred solution of acetal **2.84** (100 mg, 0.324 mmol) in methanol (3.7 mL) was added $TsOH•H_2O$ (12.3 mg, 0.0648 mmol). The reaction was stirred for 3 hours, then $NaHCO_3$ (sat aq, 4 mL) was added and extracted with Et_2O (3 x 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil.

The yellow oil was dissolved in 1,4-dioxane: water: conc. H_2SO_4 (49.5: 49.5: 1) (4 mL) and heated to refluxed for 4.5 hours. The reaction was diluted with Et_2O (20 mL) and washed with water (10 mL), $NaHCO_3$ (sat aq, 2 x 5 mL) and brine (5 mL). The organic layer were dried (Na_2SO_4) and concentrated *in vacuo* to afford a pale yellow oil which was used crude in the next step.

Under an atmosphere of N_2, to a stirred solution of (1*S*,2*R*)-camphorsultam phosphonate (104 mg, 0.27 mmol) in dry acetonitrile (4 mL) was added dried lithium chloride (170 °C/ 0.035 mbar overnight) (11.4 mg, 0.27 mmol). After stirring for 15 minutes, dry DIPEA (47 µL, 0.27 mmol) was added. After stirring for 10 minutes, the pale yellow oil in dry acetonitrile (0.25 mL) was added. The reaction was stirred for 20 hours. The reaction was diluted with water (5 mL), brine (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification on SiO_2 (1 x 14 cm) eluting with Et_2O/hexane (1:1) gave triene **2.85** (50 mg, 0.119 mmol, 37%) as a colourless oil.

$[\alpha]^{25.5}_{D}$ –44.5 ($CHCl_3$, c 1.0).

IR ν_{max} (neat) cm^{-1} 3460 (br), 2958 (s), 1681 (s), 1637 (s).

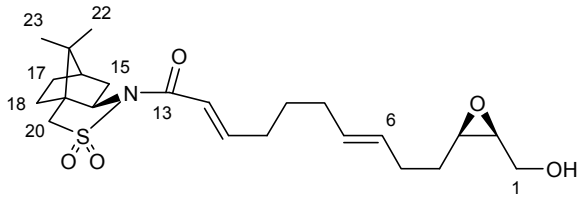
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (1H, dt, *J* = 15.1, 7.0 Hz, **C11**), 6.55 (1H, d, *J* = 15.1 Hz, **C12**), 5.70 – 5.47 (2H, m, **C2** and **C3**), 5.46 – 5.34 (2H, m, **C6** and **C7**), 4.19 (2H, d, *J* = 5.9 Hz, **C1**), 3.93 (1H, dd, *J* = 7.4, 5.4 Hz, **C14**), 3.52 (1H, d, *J* = 13.7 Hz, **C20**(1H)), 3.44 (1H, d, *J* = 13.7 Hz, **C20**(1H)), 2.30 – 2.20 (2H, m, **C10**), 2.20 – 1.97 (8H, m, **C8**, **C4**, **C5** and **C15**), 1.97 – 1.83 (3H, m, **C16**, **C17**(1H) and **C18**(1H)), 1.63 (1H, br s, **OH**), 1.60 – 1.48 (2H, m, **C9**), 1.48 – 1.30 (2H, m, **C17**(1H) and **C18**(1H)), 1.18 (3H, s, **C22**), 0.98 (3H, s, **C23**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3 (C), 150.9 (CH_1), 132.4 (CH_1), 130.4 (CH_1), 130.4 (CH_1), 129.0 (CH_1), 121.2 (CH_1), 65.4 (CH_1), 58.8 (CH_2), 53.4 (CH_2), 48.6 (C), 48.0 (C), 44.9 (CH_1), 38.7 (CH_2), 33.1 (CH_2), 32.6 (CH_2), 32.0 (CH_2), 32.0 (CH_2), 27.8 (CH_2), 27.6 (CH_2), 26.7 (CH_2), 21.0 (CH_3), 20.1 (CH_3).

LRMS ESI+ 444 $[M+Na]^+$ (100%).

HRMS ESI+ $[M+Na]^+$ calculated = 444.2179, $[M+Na]^+$ found = 444.2173.

(2*E*,7*E*)-1-((*R*)-10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-10-((2*R*,3*S*)-3-hydroxymethyl-oxiranyl)-deca-2,7-dien-1-one (**2.66**)



$C_{23}H_{35}NO_5S$
Exact Mass: 437.2236
Mol. Wt.: 437.5927

At –25 °C under an atmosphere of Ar, to a stirred solution of DET-(+) (106 µL, 0.624 mmol) and powdered 4Å molecular sieves (100 mg) in dry CH_2Cl_2 (1.9 mL) was added Ti(O*i*-Pr)$_4$ (152 µL, 0.52 mmol). The reaction was stirred for 10 minutes then allylic alcohol **2.85** (55 mg, 0.13 mmol) was added. The reaction was stirred for 5 minutes then ~5.5M *t*-BuCOOH (260 µL, 1.4 mmol) in nonane was added, the reaction was stirred at –25 °C for 67 hours. 10% Tartaric acid (aq 2 mL) was added, the reaction was stirred at –25 °C for 30 minutes then at room temperature for 1 hour. The organic layer was collected, washed with water then dried (Na_2SO_4) and concentrated *in vacuo* to give a colourless oil. At 0 °C under an atmosphere of Ar, the colourless oil was dissolved in Et_2O (2 mL) and 1M NaOH (1 mL) was added. The reaction was stirred for 30 minutes then washed with brine (1 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to give a colourless oil. Purification on SiO_2 (10 x 1.5 cm) eluting with hexane/Et_2O (1:1 → 0:1) gave epoxide **2.66** (25.6 mg, 0.059 mmol, 45%) as a colourless oil.

$[\alpha]^{25.5}_D$ –60.6 ($CHCl_3$, c 1.25).

IR ν_{max} (neat) cm^{-1} 3451 (br), 2935 (s), 1681 (s), 1637 (s).

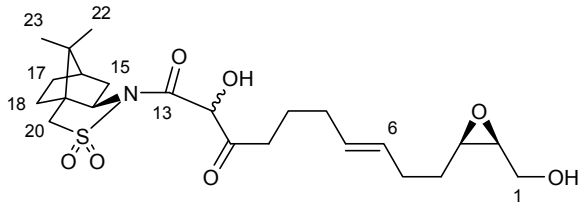
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (1H, dt, *J* = 15.1, 7.0 Hz, **C11**), 6.55 (1H, d, *J* = 15.1 Hz, **C12**), 5.47 – 5.41 (2H, m, **C6** and **C7**), 3.93 (1H, dd, *J* = 7.4, 5.4 Hz, **C14**), 3.89 – 3.77 (1H, m, **C1**(1H)), 3.72 – 3.63 (1H, m, **C1**(1H)), 3.52 (1H, d, *J* = 13.7 Hz, **C20**(1H)), 3.44 (1H, d, *J* = 13.78 Hz, **C20**(1H)), 3.19 – 3.12 (1H, m, **C2**), 3.07 – 3.00 (1H, m, **C3**), 2.32 – 1.99 (8H, m, **C5**, **C8**, **C10** and **C15**), 1.99 – 1.83 (3H, m, **C16**, **C17**(1H) and **C18**(1H)), 1.80 – 1.49 (5H, m, **C4**, **C9** and **OH**), 1.48 – 1.31 (2H, m, **C17**(1H) and **C18**(1H)), 1.17 (3H, s, **C22**), 0.98 (3H, s, **C23**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3 (C), 150.7 (CH_1), 130.7 (CH_1), 129.9 (CH_1), 121.2 (CH_1), 65.3 (CH_1), 61.1 (CH_2), 57.0 (CH_1), 53.3 (CH_2), 48.6 (C), 47.9 (C), 44.9 (CH_1), 38.7 (CH_2), 33.0 (CH_2), 31.9 (CH_2), 31.9 (CH_2), 29.7 (CH_2), 28.1 (CH_2), 27.7 (CH_2), 26.7 (CH_2), 21.0 (CH_3), 20.1 (CH_3).

LRMS ESI+ 460 $[M+Na]^+$ (100%).

HRMS ESI+ $[M+Na]^+$ calculated = 460.2128, $[M+Na]^+$ found = 460.2128.

(*E*)-1-((*R*)-10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-hydroxy-10-((2*R*,3*S*)-3-hydroxymethyl-oxiranyl)-dec-7-ene-1,3-dione (**2.86**)



$C_{23}H_{35}NO_7S$
Exact Mass: 469.2134
Mol. Wt.: 469.5915

At –40 °C under an atmosphere of Ar, to a stirred solution of diene **2.66** (23 mg, 0.0515 mmol) in acetone/acetic acid (3:1 1.3 mL) was added powdered $KMnO_4$ (8.6 mg, 0.067 mmol). The reaction was stirred for 1 hour, then quenched by addition of $Na_2S_2O_3$ (sat aq, 1 mL). The organic layer was separated and the aqueous layer was re-extracted with EtOAc (5 x 1 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification on SiO_2 (1 x 7 cm) eluting with EtOAc/hexane (1:1) gave hydroxy ketone **2.86** (7.2 mg, 0.015 mmol, 30%) as a colourless oil.

IR ν_{max} (neat) cm^{-1} 3431 (br), 2940 (s), 1726 (s), 1689 (s).

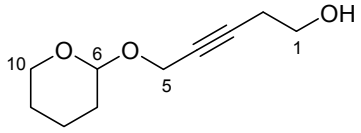
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50 – 5.37 (2H, m, **C6** and **C7**), 5.22 (1H, br d, *J* = 6.7 Hz, **C12**), 3.95 (1H, dd, *J* = 7.7, 4.9 Hz, **C14**), 3.85 (1H, dd, *J* = 12.1, 4.3 Hz, **C1**(1H)), 3.69 (1H, dd, *J* = 12.1, 6.8 Hz, **C1**(1H)), 3.53 (1H, d, *J* = 13.8 Hz, **C20**(1H)), 3.47 (1H, d, *J* = 13.8 Hz, **C20**(1H)), 3.19 – 3.14 (1H, m, **C2**), 3.07 – 3.01 (1H, m, **C3**), 2.76 (1H, dt, *J* = 18.1, 7.4 Hz, **C10**(1H)), 2.62 – 2.53 (1H, m, **C10**(1H)), 2.27 – 1.98 (6H, m, **C8**, **C5** and **C15**), 1.98 – 1.85 (3H, m, **C16**, **C17**(1H) and **C18**(1H)), 1.81 – 1.54 (5H, m, **C4**, **C9** and **OH**), 1.50 – 1.31 (2H, m, **C17**(1H) and **C18**(1H)), 1.17 (3H, s, **C22**), 0.99 (3H, s, **C23**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0 (C), 168.5 (C), 130.5 (CH_1), 130.2 (CH_1), 76.6 (CH_1), 65.2 (CH_1), 61.1 (CH_2), 57.1 (CH_1), 56.9 (CH_1), 53.0 (CH_2), 49.3 (C), 48.1 (C), 44.7 (CH_1), 38.6 (CH_2), 38.0 (CH_2), 33.0 (CH_2), 31.7 (CH_2), 29.8 (CH_2), 28.1 (CH_2), 26.6 (CH_2), 22.8 (CH_2), 20.6 (CH_3), 20.1 (CH_3).

LRMS ESI+ 492 $[M+Na]^+$ (100%).

HRMS ESI+ $[M+Na]^+$ calculated = 492.2026, $[M+Na]^+$ found = 492.2031.

5-(Tetrahydro-2*H*-pyran-2-yloxy)pent-3-yn-1-ol (**2.93**)



$C_{10}H_{16}O_3$
Exact Mass: 184.1099
Mol. Wt.: 184.2322

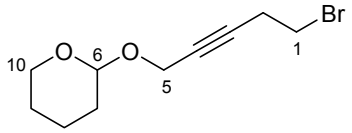
At –40 °C under an atmosphere of Ar, to a stirred solution of alkyne **2.75** (10.0 g, 0.071 mol) in dry THF/Et_2O (1:2 30mL) was added 2.41M *n*-BuLi in hexane (32 mL, 0.078 mol). After stirring for 30 minutes, dry HMPA (10 mL) was added producing a clear orange solution. The reaction was warmed to room temperature, ethylene oxide (~15 mL, 0.4 mol) added *via* a cannula. A cold finger reflux condenser (solid CO_2/acetone) was attached. The reaction was stirred overnight (16 hours). Et_2O (200 mL) was added, then reaction mixture was washed with brine/water (4:1 3 x 100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give an orange oil. Purification on SiO_2 (10 x 10 cm) eluting with hexane/Et_2O (1:1) gave 5-(tetrahydro-2*H*-pyran-2-yloxy)pent-3-yn-1-ol (**2.93**) (8.30 g, 0.045 mol, 63%).
Spectroscopic characterisation agreed with that published.[171]

IR ν_{max} (neat) cm^{-1} 3408 (br), 2941 (s), 2870 (s), 1345 (w).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.80 (1H, t, *J* = 3.1 Hz, **C6**), 4.36 – 4.16 (2H, m, **C5**), 3.92 – 3.78 (1H, m, **C10**(1H)), 3.73 (2H, t, *J* = 6.3 Hz, **C1**), 3.59 – 3.49 (1H, m, **C10**(1H), 2.50 (2H, tt, *J* = 6.3, 2.1 Hz, **C2**), 2.03 (1H, br s, **OH**), 1.92 – 1.45 (6H, m, **C7** – **C9**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 96.7 (CH_1), 83.2 (C), 77.3 (C), 61.8 (CH_2), 60.6 (CH_2), 54.5 (CH_2), 30.0 (CH_2), 25.1 (CH_2), 29.9 (CH_2), 19.1 (CH_2).

2-(5-Bromopent-2-ynyloxy)-tetrahydro-2*H*-pyran (**2.94**)



$C_{10}H_{15}BrO_2$
Exact Mass: 246.0255
Mol. Wt.: 247.1289

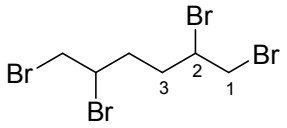
At 0 °C under an atmosphere of Ar, to a stirred solution of alcohol **2.93** (2 g, 10.86 mmol), tetrabromomethane (4.15 g, 12.49 mmol) and pyridine (200 µL) in CH_2Cl_2 (30 mL) was added PPh_3 (3.7 g, 14.12 mmol) in CH_2Cl_2 (5 mL). The reaction was stirred for 2 hours, then warmed to room temperature and stirred for a further 2 hours. The reaction was concentrated *in vacuo*, the residue was suspended in CH_2Cl_2/hexane (1:5 30 mL) then filtered, the filtrate was concentrated *in vacuo* to gave a yellow oil. Purification on SiO_2 (3 x 10 cm) eluting with hexane/Et_2O (9:1) gave 2-(5-bromopent-2-ynyloxy)-tetrahydro-2*H*-pyran (**2.94**) (2.19 g, 8.86 mmol, 82%) as a colourless oil.
Spectroscopic characterisation agreed with that published.[171]

IR ν_{max} (neat) cm^{-1} 2240 (w).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.82 (1H, t, *J* = 3.2 Hz, **C6**), 4.37 – 4.15 (2H, m, **C5**), 3.91 – 3.76 (1H, m, **C10**(1H)), 3.59 – 3.49 (1H, m, **C10**(1H)), 3.44 (2H, t, *J* = 7.3 Hz, **C1**), 2.80 (2H, tt, *J* = 7.3, 2.1 Hz, **C2**), 1.88 – 1.48 (6H, m, **C7** – **C9**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 96.7 (CH_1), 83.0 (C), 78.1 (C), 62.0 (CH_2), 54.3 (CH_2), 30.2 (CH_2), 29.4 (CH_2), 25.3 (CH_2), 23.3 (CH_2), 19.1 (CH_2).

1,2,5,6-Tetrabromohexane (**2.98**)



$C_6H_{10}Br_4$
Exact Mass: 397.7516
Mol. Wt.: 401.7596

Under an atmosphere of Ar at –70 °C, to a solution of hexa-1,5-diene (24 g, 0.292 mol) in CH_2Cl_2 (400 mL) was added bromine (93.3 g, 0.584 mol) in CH_2Cl_2 (100 mL) via a dropping funnel. The reaction was gradually warmed to room temperature and stirred for 16 hours. The reaction was concentrated *in vacuo* to afford a brown solid. Purification by recrystallisation with methanol gave bromide **2.98** as a white solid (97.12 g, 0.244 mol, 83%).

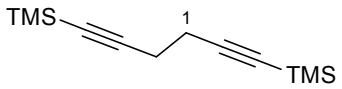
Melting point 57–65 °C.

IR ν_{max} (neat) cm^{-1} 2945 (w), 2915 (w), 1436 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 – 4.11 (2H, m, **C2**), 3.89 (2H, 2 x dd, *J* = 10.2, 4.3 Hz, **C1**(2H)), 3.65 (2H, 2 x t, *J* = 10.2 Hz, **C1**(2H)), 2.61 – 2.46 (1H, m, **C3**), 2.44 – 2.28 (1H, m, **C3**), 2.20 – 2.01 (1H, m, **C3**), 2.01 – 1.84 (1H, m, **C3**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 51.7 (CH_1), 51.2 (CH_1), 36.0 (CH_2), 35.9 (CH_2), 33.8 (CH_2), 33.7 (CH_2).

1,6-*Bis*(trimethylsilyl)hexa-1,5-diyne



$C_{12}H_{22}Si_2$
Exact Mass: 222.126
Mol. Wt.: 222.4741

At –78 °C under an atmosphere of Ar, to a stirred solution of dry DIPA (70 mL, 0.5 mol) in dry THF (300 mL) was added 2.5M *n*-BuLi in hexane (200 mL, 0.5 mol). The reaction was warmed to room temperature for 5 minutes then re-cooled to –78 °C then bromide **2.98** (32.7 mL, 0.082 mol) in THF (50 mL) was added slowly. The reaction was warmed to room temperature and stirred for 1 hour then re-cooled to –78 °C. TMSCl (21.9 mL, 0.172 mol) was then added slowly and the reaction was warmed to room temperature and stirred for 1 hour. The reaction was carefully quenched with water and diluted with Et_2O (300 mL), the organic layer was collected then washed with 2M HCl (250 mL x 2), dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil. Purification on SiO_2 (8

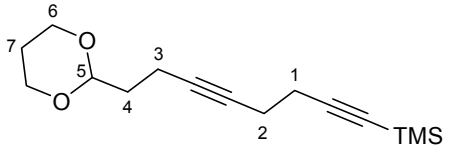
x 4 cm) eluting with hexane gave 1,6-bis(trimethylsilyl)hexa-1,5-diyne (**2.99**) (5.88 g, 0.0265 mol, 32%) as a white solid.
Spectroscopic characterisation agreed with that published.[172]

Melting point 58 – 62 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (4H, s, **C1**), 0.16 (18H, s, **TMS**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 105.3 (C), 85.7 (C), 20.2 (CH_2), 0.3 (CH_3).

(8-(1,3-Dioxan-2-yl)octa-1,5-diynyl)trimethylsilane (**2.100**)



$C_{15}H_{24}O_2Si$
Exact Mass: 264.1546
Mol. Wt.: 264.4354

At –78 °C under an atmosphere of Ar, to a stirred solution of TMS alkyne **2.99** (4.12 g, 18.6 mmol) in dry THF (30 mL) was added 1.5M methyl lithium-lithium bromide complex in Et_2O (18.5 mL, 27.8 mmol). The reaction was warmed to room temperature and stirred for 3 hours, dark cloudy orange solution was produced. The reaction was re-cooled to –78 °C then dry HMPA (15 mL) was added, after 15 minutes 2-(2-bromoethyl)-1,3-dioxane (5 mL, 37.1 mmol) was added. The reaction was gradually warmed to room temperature and stirred for 16 hours. The reaction was slowly poured into NH_4Cl (sat aq, 50 mL), the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were concentrated *in vacuo* to give an orange oil. The orange oil was dissolved in Et_2O (150 mL) and washed with water (3 x 150 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to afford an orange oil. Purification on SiO_2 (13 x 4 cm) eluting with hexane/EtOAc (9:1 → 1:1) gave (8-(1,3-dioxan-2-yl)octa-1,5-diynyl)trimethylsilane (**2.100**) (900 mg, 3.40 mmol, 18%) as a colourless oil.

IR ν_{max} (neat) cm^{-1} 2959 (s), 2850 (s), 2176 (s);

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.63 (1H, t, *J* = 5.3 Hz, **C5**), 4.10 (2H, m, **C6**(1H)), 3.77 (2H, m, **C6**(1H)), 2.46 – 2.31 (4H, m, **C1** and **C2**), 2.25 (2H, t with fine

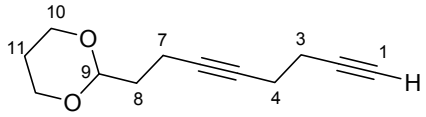
splitting, *J* = 7.2 Hz, **C3**), 2.18 – 1.98 (1H, m, **C7**(1H)), 1.76 (2H, dt, *J* = 7.2, 5.3 Hz, **C4**), 1.34 (1H, d with fine splitting, *J* = 13.5 Hz, **C7**(1H)), 0.15 (9H, s, **TMS**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 105.9 (C), 101.1 (CH_1), 85.5 (C), 80.5 (C), 78.7 (C), 67.1 (CH_2), 34.5 (CH_2), 26.0 (CH_2), 20.7 (CH_2), 19.2 (CH_2), 13.8 (CH_2), 0.3 (CH_3).

LRMS ESI+ 287 $[M+Na]^+$ (100%).

HRMS ESI+ $[M+Na]^+$ calculated = 287.1438, $[M+Na]^+$ found = 287.1436.

2-(Octa-3,7-diynyl)-1,3-dioxane (**2.101**)



$C_{12}H_{16}O_2$
Exact Mass: 192.115
Mol. Wt.: 192.2542

At room temperature under an atmosphere of Ar, to a stirred solution of acetal **2.100** (900 mg, 3.41 mmol) in dry methanol (13 mL) was added dry K_2CO_3 (471 mg, 3.41 mmol). The reaction was stirred for 4 hours then concentrated *in vacuo* to afford a white solid. The white solid was dissolved in water (20 mL) and extracted with EtOAc (3 x 30 mL). The organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford a colourless oil. Purification on SiO_2 (12 x 3.5 cm) eluting with hexane/EtOAc (9:1) gave 2-(octa-3,7-diynyl)-1,3-dioxane (**2.101**) (617 mg, 3.21 mmol, 94%) as a colourless oil.

IR ν_{max} (neat) cm^{-1} 3287 (s), 2964 (s), 2851 (s).

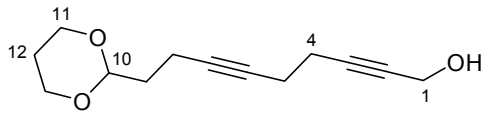
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.65 (1H, t, *J* = 5.3 Hz, **C9**), 4.09 (2H, m, **C10**(1H)), 3.77 (2H, m, **C10**(1H)), 2.42 – 2.32 (4H, m, **C3** and **C4**), 2.25 (2H, t, *J* = 7.2 Hz, **C7**), 2.16 – 1.97 (1H, m, **C11**(1H)), 2.01 (1H, s, **C1**), 1.76 (2H, dt, *J* = 7.2, 5.3 Hz, **C8**), 1.34 (1H, d with fine splitting, *J* = 13.4 Hz, **C11**(1H)).

^{13}C NMR (75 MHz, $CDCl_3$) δ 101.1 (CH_1), 83.2 (CH_2), 80.7 (CH_2), 78.5 (CH_2), 69.2 (CH_1), 67.0 (CH_2), 34.5 (CH_2), 26.0 (CH_2), 19.3 (CH_2), 19.1 (CH_2), 13.8 (CH_2).

LRMS ESI+ 215 $[M+Na]^+$ (100%).

HRMS ESI+ [M+H] calculated = 193.1223, [M+H] found = 193.1224.

9-(1,3-Dioxan-2-yl)nona-2,6-diyn-1-ol (**2.92**)



$C_{13}H_{18}O_3$
Exact Mass: 222.1256
Mol. Wt.: 222.2802

At –78 °C under an atmosphere of Ar, to a stirred solution of alkyne **2.101** (600 mg, 3.12 mmol) in dry THF (10 mL) was added 2.5M *n*-BuLi in hexane (1.45 mL, 3.6 mmol). The reaction was stirred for 45 minutes then paraformaldehyde (560 mg, 18.7 mmol) was added. The reaction was gradually warmed to room temperature and stirred for 3 hours. The reaction was slowly poured into NH_4Cl (sat aq, 20 mL), the organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic phases were concentrated *in vacuo* to give a yellow oil. Purification on SiO_2 (12 x 4 cm) eluting with hexane/EtOAc (7:3 → 1:1) gave 9-(1,3-dioxan-2-yl)nona-2,6-diyn-1-ol (**2.92**) (683 mg, 3.07 mmol, 98%) as a colourless oil.

IR ν_{max} (neat) cm^{-1} 3416 (br), 2963 (s), 2927 (s), 2852 (s).

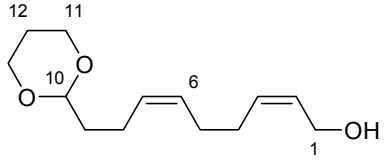
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.65 (1H, t, *J* = 5.2 Hz, **C10**), 4.29 – 4.20 (2H, m, **C1**), 4.10 (2H, m, **C11**(1H)), 3.77 (2H, m, **C11**(1H)), 2.47 – 2.30 (4H, m, **C4** and **C5**), 2.25 (2H, t with fine splitting, *J* = 7.3 Hz, **C8**), 2.07 (1H, dtt, *J* = 13.5, 12.4, 4.9 Hz, **C12**(1H)), 1.86 (1H, t, *J* = 6.1 Hz, **OH**), 1.77 (2H, dt, *J* = 7.3, 5.2 Hz, **C9**), 1.34 (1H, d with fine splitting, *J* = 13.5 Hz, **C12**(1H)).

^{13}C NMR (75 MHz, $CDCl_3$) δ 101.1 (CH_1), 85.0 (C), 80.7 (C), 79.4 (C), 78.8 (C), 67.1 (CH_2), 51.4 (CH_2), 34.5 (CH_2), 26.0 (CH_2), 19.6 (CH_2), 19.1 (CH_2), 13.8 (CH_2).

LRMS ESI+ 245 $[M+Na]^+$ (100%).

HRMS ESI+ $[M+Na]^+$ calculated = 245.1148, $[M+Na]^+$ found = 245.1150.

(2*Z*,6*Z*)-9-(1,3-Dioxan-2-yl)nona-2,6-dien-1-ol (**2.102**)



$C_{13}H_{22}O_3$
Exact Mass: 226.1569
Mol. Wt.: 226.312

Under an atmosphere of H_2, a solution of alkyne **2.92** (60 mg, 0.27 mmol), Lindlar catalyst (Pd 5%, calcium carbonate poisoned with Pb) (30 mg, 0.014 mmol) in EtOAc (4 mL) was stirred for 30 minutes. The reaction was filtered through celite and washed through with EtOAc (50 mL). The filtrate was dried ($MgSO_4$) and concentrated *in vacuo* to afford a pale yellow oil. Purification on SiO_2 (12 x 1.5 cm) eluting with hexane/EtOAc (1:1) gave (2*Z*,6*Z*)-9-(1,3-dioxan-2-yl)nona-2,6-dien-1-ol (**2.102**) (50 mg, 0.22 mmol, 82%) as a colourless oil.

IR ν_{max} (neat) cm^{-1} 3406 (br), 3009 (s), 2956 (s), 2926 (s), 2851 (s), 1653 (w).

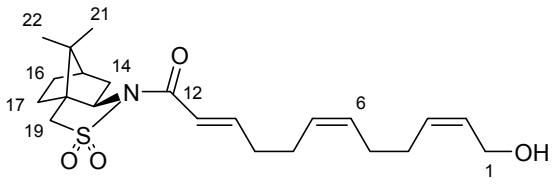
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76 – 5.47 (2H, m, **C2** and **C3**), 5.47 – 5.29 (2H, m, **C6** and **C7**), 4.51 (1H, t, *J* = 5.2 Hz, **C10**), 4.17 (2H, d, *J* = 6.3 Hz, **C1**), 4.10 (2H, dd with fine splitting, *J* = 12.0, 4.9 Hz, **C11^{eq}**), 3.75 (2H, td, *J* = 12.0, 2.5 Hz, **C11^{ax}**), 2.18 – 1.98 (8H, m, **C4, C5, C8 and C12^{ax}**), 1.70 – 1.56 (2H, m, **C9**), 1.52 (1H, br s, **OH**), 1.33 (1H, d with fine splitting, *J* = 13.5 Hz, **C12^{eq}**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 132.4 (CH_1), 129.9 (CH_1), 129.5 (CH_1), 129.1 (CH_1), 101.9 (CH_1), 67.1 (CH_2), 58.6 (CH_2), 35.2 (CH_2), 27.6 (CH_2), 27.2 (CH_2), 26.0 (CH_2), 22.0 (CH_2).

LRMS ESI+ 249 $[M+Na]^+$ (100%).

HRMS ESI+ $[M+Na]^+$ calculated = 249. 1461, $[M+Na]^+$ found = 249.1462.

(2*E*,6*Z*,10*Z*)-1-((*R*)-10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-12-hydroxy-dodeca-2,6,10-trien-1-one (**2.103**)



$C_{22}H_{33}NO_4S$
Exact Mass: 407.213
Mol. Wt.: 407.5667

To a solution of acetal **2.102** (47 mg, 0.21 mmol) in 1,4-dioxane: water: conc. H_2SO_4 (49.5 : 49.5: 1) (1 mL) was refluxed for 5 hours. The reaction was diluted with Et_2O (10 mL) and washed with water (5 mL), $NaHCO_3$ (sat aq, 2 x 5 mL) and

brine (5 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to afford a pale yellow oil which was used in the next step.

Under an atmosphere of Ar, to a stirred solution of (1*S*,2*R*)-camphorsultam phosphonate (90 mg, 0.23 mmol) in dry acetonitrile (1 mL) was added dried lithium chloride (170 °C/ 0.035 mbar overnight) (10 mg, 0.23 mmol). After stirring for 15 minutes, dry DIPEA (40 µL, 0.23 mmol) was added. After stirring for 10 minutes, the crude aldehyde in dry acetonitrile (0.1 mL) was then added. The reaction was stirred for 20 hours. The reaction was diluted with water (5 mL) and brine (5 mL) then extracted with Et_2O (3 x 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification on SiO_2 (14 x 1.5 cm) eluting with EtOAc/hexane (1:1) gave triene **2.103** (25.3 mg, 0.062 mmol, 30%) as a colourless oil.

$[\alpha]^{28}_D$ –69.6 ($CHCl_3$, c 1.25).

IR ν_{max} (neat) cm^{-1} 3416 (br), 2939 (s), 1681 (s), 1637 (s).

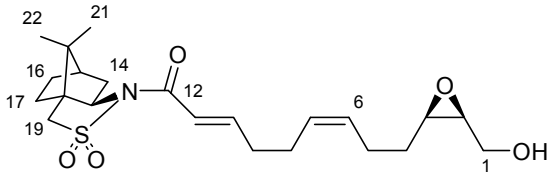
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (1H, dt, *J* = 15.1, 6.7 Hz, **C10**), 6.56 (1H, d, *J* = 15.1 Hz, **C11**), 5.64 (1H, dt, *J* = 11.0, 6.5 Hz, **C2**), 5.58 – 5.47 (1H, m, **C3**), 5.47 – 5.32 (2H, m, **C6** and **C7**), 4.18 (2H, d, *J* = 6.5 Hz, **C1**), 3.93 (1H, dd, *J* = 7.2, 5.4 Hz, **C13**), 3.52 (1H, d, *J* = 13.8 Hz, **C19**(1H)), 3.44 (1H, d, *J* = 13.8 Hz, **C19**(1H)), 2.37 – 2.26 (2H, m, **C9**), 2.26 – 2.17 (2H, m, **C8**), 2.18 – 2.02 (6H, m, **C4**, **C5** and **C14**), 2.00 – 1.81 (3H, m, **C15**, **C16**(1H) and **C17**(1H)), 1.68 (1H, br s, **OH**), 1.49 – 1.29 (2H, m, **C16**(1H) and **C17**(1H)), 1.17 (3H, s, **C21**), 0.98 (3H, s, **C22**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2 (C), 150.3 (CH_1), 132.2 (CH_1), 130.3 (CH_1), 129.3 (CH_1), 128.8 (CH_1), 121.3 (CH_1), 65.3 (CH_1), 58.6 (CH_2), 53.3 (CH_2), 48.6 (C), 48.0 (C), 44.9 (CH_1), 38.7 (CH_2), 33.0 (CH_2), 32.6 (CH_2), 27.5 (CH_2), 27.4 (CH_2), 26.7 (CH_2), 26.0 (CH_2), 21.0 (CH_3), 20.1 (CH_3).

LRMS ESI+ 430 $[M+Na]^+$ (100%).

HRMS ESI+ $[M+Na]^+$ calculated = 430.2023, $[M+Na]^+$ found = 430.2023.

(2*E*,6*Z*)-1-((*R*)-10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-9-((2*R*,3*S*)-3-hydroxymethyl-oxiranyl)-nona-2,6-dien-1-one (**2.89**)



$C_{22}H_{33}NO_5S$
Exact Mass: 423.2079
Mol. Wt.: 423.5661

At –25 °C under an atmosphere of Ar, to a stirred solution of DET-(+) (16.6 mg, 0.081 mmol) and powdered 4Å molecular sieves (30 mg) in dry CH_2Cl_2 (1 mL) was added Ti(O*i*-Pr)$_4$ (20 μL, 0.067 mmol). The reaction was stirred for 10 minutes then allylic alcohol **2.103** (25 mg, 0.061 mmol) was added. The reaction was stirred for 5 minutes then ~5.5M *t*-BuCO_3H (25 μL, 0.123 mmol) in nonane was added, the reaction was stirred at –25 °C for 24 hours. 10% Tartaric acid (aq 1 mL) was added, the reaction was stirred at –25 °C for 30 minutes then room temperature for 1 hour. The organic layer was collected, washed with water then dried (Na_2SO_4) and concentrated *in vacuo* to give a colourless oil. At 0 °C under an atmosphere of Ar, the colourless oil was dissolved in Et_2O (2 mL) and 1M NaOH (1 mL) was added. The reaction was stirred for 30 minutes then washed with brine (1 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give a colourless oil. Purification on SiO_2 (7 x 1 cm) eluting with hexane/EtOAc (1:1) gave epoxide **2.89** (17.6 mg, 0.042 mmol, 68%) as a colourless oil.

[α]$^{27}_D$ –63.9 ($CHCl_3$, c 0.88).

IR ν_{max} (neat) cm^{-1} 3460 (br), 2958 (s), 1681 (s), 1637 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (1H, dt, *J* = 15.1, 6.6 Hz, **C10**), 6.57 (1H, d, *J* = 15.1 Hz, **C11**), 5.52 – 5.35 (2H, m, **C6** and **C7**), 3.93 (1H, dd, *J* = 7.2, 5.4 Hz, **C13**), 3.88 – 3.76 (1H, m, **C1** (1H)), 3.76 – 3.64 (1H, m, **C1** (1H)), 3.52 (1H, d, *J* = 13.8 Hz, **C19**(1H)), 3.44 (1H, d, *J* = 13.8 Hz, **C19**(1H)), 3.19 – 3.11 (1H, m, **C2**), 3.03 (1H, td, *J* = 6.4, 4.4 Hz, **C3**), 2.38 – 2.16 (6H, m, **C5**, **C8** and **C9**), 2.16 – 2.02 (2H, m, **C14**), 2.02 – 1.82 (3H, m, **C15**, **C16**(1H) and **C17**(1H)), 1.78 –

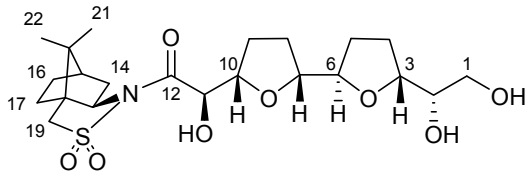
1.49 (3H, m, **C4** and **OH**), 1.49 – 1.30 (2H, m, **C16**(1H) and **C17**(1H)), 1.18 (3H, s, **C21**), 0.98 (3H, s, **C22**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2 (C), 150.1 (CH_1), 129.7 (CH_1), 129.3 (CH_1), 121.4 (CH_1), 65.4 (CH_1), 60.9 (CH_2), 56.8 (CH_1), 53.4 (CH_2), 48.6 (C), 48.0 (C), 44.9 (CH_1), 38.7 (CH_2), 33.0 (CH_2), 32.5 (CH_2), 28.1 (CH_2), 26.7 (CH_2), 25.9 (CH_2), 24.5 (CH_2), 21.0 (CH_3), 20.1 (CH_3).

LRMS ESI+ 446 $[M+Na]^+$ (100%).

HRMS ESI+ $[M+Na]^+$ calculated = 446.1972, $[M+Na]^+$ found = 446.1965.

(*R*)-2-[(2*R*,5*S*,2'*R*,5'*R*)-5'-((*S*)-1,2-Dihydroxy-ethyl)-octahydro-[2,2']bifuranyl-5-yl]-1-((*R*)-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-hydroxy-ethanone (**2.90a**/**b**)



$C_{22}H_{35}NO_8S$
Exact Mass: 473.2083
Mol. Wt.: 473.5802

At –40 °C under an atmosphere of Ar, to a stirred solution of diene **2.89** (17 mg, 0.04 mmol) in acetone/acetic acid (3:1 1 mL) was added powdered $KMnO_4$ (8.26 mg, 0.053 mmol). The reaction was stirred for 1 hour, then quenched by addition of $Na_2S_2O_3$ (sat aq, 1 mL). The organic layer was separated and the aqueous layer was re-extracted with EtOAc (5 x 1 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification on SiO_2 (1 x 7 cm) eluting with EtOAc/methanol (1:0 → 20:1) gave triols **2.90a**/**b** (8.6 mg, 0.24 mmol, 45%) as a colourless oil.

IR ν_{max} (neat) cm^{-1} 3408 (br), 2957 (s), 1695 (s).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76 (1H, br s, **OH**), 4.74 – 4.67 (1H, m, **C10**), 4.49 – 4.40 (1H, m, **C11**), 4.31 – 4.24 (1H, m, **C7**) 4.14 – 4.03 (2H, m, **C3**, **C6**), 4.02 – 3.96 (1H, m, **C15**), 3.73 – 3.65 (1H, m, **C1**(1H)), 3.65 – 3.58 (1H, m, **C1**(1H)), 3.58 – 3.48 (2H, m, **C2** and **C19**(1H)), 3.48 – 3.40 (1H, m, **C19**(1H)), 2.25 – 2.15 (1H, m, **C14**(1H)), 2.15 – 1.98 (5H, m, **C8**, **C9** and **C14**(1H)), 1.98 – 1.83 (7H, m,

C4, **C5**, **C15**, **C16**(1H) and **C17**(1H)), 1.50 – 1.30 (2H, m, **C16**(1H) and **C17**(1H)), 1.19 (3H, s, **C21**), 0.98 (3H, s, **C22**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0 (C), 82.4 (CH_1), 81.3 (CH_1), 81.1 (CH_1), 79.6 (CH_1), 75.3 (CH_1), 73.8 (CH_1), 66.5 (CH_1), 64.0 (CH_2), 53.6 (CH_2), 48.9 (C), 48.0 (C), 45.1 (CH_1), 38.7 (CH_2), 33.4 (CH_2), 28.9 (CH_2) 2 overlaying peaks, 28.2 (CH_2), 26.5 (CH_2), 25.3 (CH_2), 21.3 (CH_3), 20.1 (CH_3).

LRMS ESI+ 496 $[M+Na]^+$ (100%).

HRMS ESI+ $[M+Na]^+$ calculated = 496.1976, $[M+Na]^+$ found = 496.1967.

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