UNIVERSITY OF SOUTHAMPTON

Part 1: Permanganate Promoted Bi-Directional Oxidative Cyclisation

Part 2: Permanganate-Mediated Asymmetric Dihydroxylation

Riaz Bhunnoo

A Thesis Submitted for the Degree of Doctor of Philosophy

Department of Chemistry

March 2005

Declaration

This thesis was submitted for examination in March 2005. It does not necessarily represent the final form of the thesis as deposited in the University after examination.

The research work described in this thesis was carried out by myself, at the University of Southampton, between October 2001 and October 2004. No part of this thesis has been submitted in any previous application for a higher degree.

Riaz Bhunnoo, March 2005

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF ENGINEERING, SCIENCE AND MATHEMATICS

SCHOOL OF CHEMISTRY

Doctor of Philosophy

PART 1: PERMANGANATE PROMOTED BI-DIRECTIONAL OXIDATIVE CYCLISATION
PART 2: PERMANGANATE-MEDIATED ASYMMETRIC DIHYDROXYLATION

by Riaz Bhunnoo

The central non-adjacent *bis*-THF core of the *Annonaceous* acetogenin *cis*-sylvaticin has been established *via* the permanganate promoted asymmetric bi-directional oxidative cyclisation of a tetraene. The tetraene was obtained in five facile steps from commercially available triene **4.27** in good overall yield. Permanganate promoted asymmetric bi-directional oxidative cyclisation inserted the eight new stereogenic centres in good d.r., thus providing rapid access to this advanced intermediate. Elaboration of the *bis*-THF core is described, illustrating the possibility of both a linear and bi-directional approach to *cis*-sylvaticin. An approach to the butenolide portion of *cis*-sylvaticin is also described. The key step involved asymmetric alkynyl addition to butenolide-aldehyde **3.6** and proceeded with good levels of diastereoselectivity.

The permanganate-mediated asymmetric dihydroxylation of enones has been demonstrated in the presence of a chiral quaternary ammonium salt. Dihydroxylation of a variety of enone substrates produced the corresponding diols with good levels of enantioselectivity (50-80% *ee*). The reaction is clean and fast, producing the corresponding benzoic acid as the main by-product.

Table of Contents

Acknowledgements

Firstly, I would like to thank the analytical services including NMR, X-ray Crystallography and Mass Spectroscopy for their proficiency; in particular Julie Herniman for her constant helpfulness.

Secondly, I would like to thank the Brown group for making our lab such a unique and fun place to work. So many characters, so little space to describe them. Thanks to John for showing me the ropes when I first started, to Yulai for the interesting discussions, giving me advice and joining me in the misery when our research was going Pete Tong, to Alex for giving me help and advice over the years, to Stephen for starting so many 'insightful discussions', to Nev for sharing similar interests and finding new applications for cardice, to Carole for appreciating my house music mixes (oh, and running a lot of my NMR's), to Claire for enlightening me about northern tendencies, to Rowan for introducing me to chocolate in bread and apricot-containing cheeses and to Simon for organising so many good nights out. It's been really good working with all of you and I will miss that the most.

Thirdly, well, I would say something about Richard here but words fail me. Only joking, I can think of lots of words I'd use! Seriously though, thanks for being a good supervisor over the last three years, for all of your help and guidance and particularly for letting me dig my heels into the project and get on with it in my own way. I have thoroughly enjoyed working in your group. I am grateful to Bruno for inspiring me and always giving me useful advice. My gratitude extends to Heather Hobbs at GSK for her realistic, positive and enthusiastic attitude to synthetic chemistry and life in general.

Finally, I'd like to thank my friends and family for all their support and encouragement. My greatest thanks though, go to Clare for being there when it all became a little overwhelming, for listening to my next 'amazing' synthetic idea and nodding in the right places, for being supportive and loving and sharing all the highs and lows. I couldn't have done it without you.

Abbreviations

Ac	acetyl
AD	asymmetric dihydroxylation
AIBN	2,2'-azoisobutyronitirile
appt.	apparent
aq	aqueous
Ar	aryl
ATP	adenosine triphosphate
BINOL	binaphthol
Bn	benzyl
bp	boiling point
br	broad (NMR and IR)
Bu	butyl
Bz	benzyl
calcd.	calculated
CAN	ceric ammonium nitrate
CI	chemical ionisation
COD	cyclo-octadiene
Cp	cyclopentadiene
CPTC	chiral phase-transfer catalyst
CSA	camphorsulfonic acid
Cy	cyclohexyl
d	doublet (NMR)
DBU	1,8-diaza-bicylclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexyl-carbodiimide
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DHQ	dihydroquinine
DHQD	dihydroquinidine
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio
EAA	ethyl acetoacetate
ED_{50}	effective dose 50
ee	enantiomeric excess
EI	electron ionisation
ent	enantiomer
eq	equivalent(s)
Et	ethyl
FT	fourier transform
GC	gas chromatography
h	hour(s)
HMDS	hexamethyldisilylamide
HMPA	hexamethylphosphoric triamide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons
Hz	hertz
IMes	1,3-dimesityl-2-imidazolidine
IPA	isopropyl alcohol

IR	infrared
J	coupling constant (NMR)
LDA	lithium diisopropylamide
m	multiplet (NMR) or medium (IR)
M	molar
***m*CPBA**	*meta*-chloroperbenzoic acid
MDR	multi-drug resistant
Me	methyl
min	minute
MOM	methoxymethyl
mp	melting point
MPM	4-methoxyphenylmethyl
Ms	methanesulfonyl (mesyl)
MS	mass spectrometry
m/z	mass/charge ratio
n/a	not applicable
NADH	nicotinamide adenine dinucleotide
NMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
p	*para*
PCC	pyridinium chlorochromate
Ph	phenyl
PHAL	phthalazine
PMB	*para*-methoxybenzyl
Pr	propyl
PTC	phase-transfer catalyst
Pv	pivaloyl
py	pyridine
PYR	diphenylpyrimidine
q	quartet (NMR)
quin	quintet (NMR)
RCM	ring-closing metathesis
rt	room temperature
SAR	structure-activity relationship
s	singlet (NMR) or strong (IR)
SM	starting material
t	*tert*
t	triplet (NMR)
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
Tf	trifluoroacetate (triflate)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	toluenesulfonyl (tosyl)
UV	ultraviolet
w	weak
wt	weight

Chapter 1

The *Annonaceous* Acetogenins

This chapter gives an overview of the characteristics of the *Annonaceous* acetogenins, including their structure and biological activities. Acetogenins exhibit *in vivo* and cytotoxic antitumour activity, and provide promising leads in the combat against multi-drug resistant (MDR) tumours. These properties have stimulated wide interest in the synthesis of acetogenins and related compounds with similar structures. A few recent syntheses of non-adjacent *bis*-THF natural products are described.[34,42,50,57,62]

1.1 Introduction

The *Annonaceae* (custard-apple family) is chemically one of the least known of the tropical plant families. *Annonaceous* acetogenins, a class of natural products with a wide range of biological activities, have been under the spotlight ever since the discovery of uvaricin **1.1** in 1982 (Figure 1.1).[1] It was found that this acetogenin had *in vivo* anti-leukemic activity and this stimulated wide interest in the acetogenins.

Structurally, the acetogenins are a series of C-35/C-37 natural products derived from C-32/C-34 fatty acids that are combined with a 2-propanol unit. They are usually classified by a long aliphatic chain bearing a terminal methyl-substituted α-β-unsaturated γ-lactone ring (sometimes rearranged to a ketolactone), with one, two or three tetrahydrofuran (THF) rings located along the hydrocarbon chain and a number of oxygenated moieties (hydroxyls, acetoxyls, ketones, epoxides) and/or double bonds.[2] Some of these features are shown in the acetogenin annonisin **1.2** (Figure 1.1).

The acetogenins are readily soluble in most organic solvents. The usual method of isolation involves ethanol extraction of the dried plant followed by solvent partitioning to concentrate the compounds.[3]

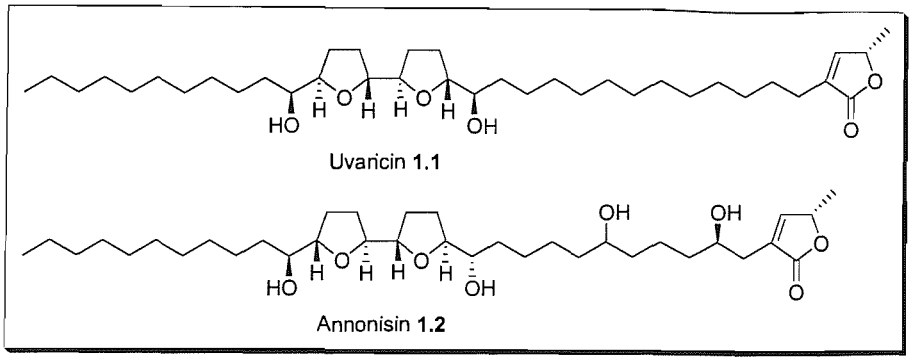


Figure 1.1 Examples of *Annonaceous* acetogenins.

1.2 Structural Classification

The *Annonaceous* acetogenins are classified into *mono*-THF **1.3**, adjacent *bis*-THF **1.4**, non-adjacent *bis*-THF **1.5**, *tris*-THF **1.6**, THP non-classical **1.7** and non-THF **1.8** acetogenins, followed by subclassification of the γ-lactone (Figure 1.2).

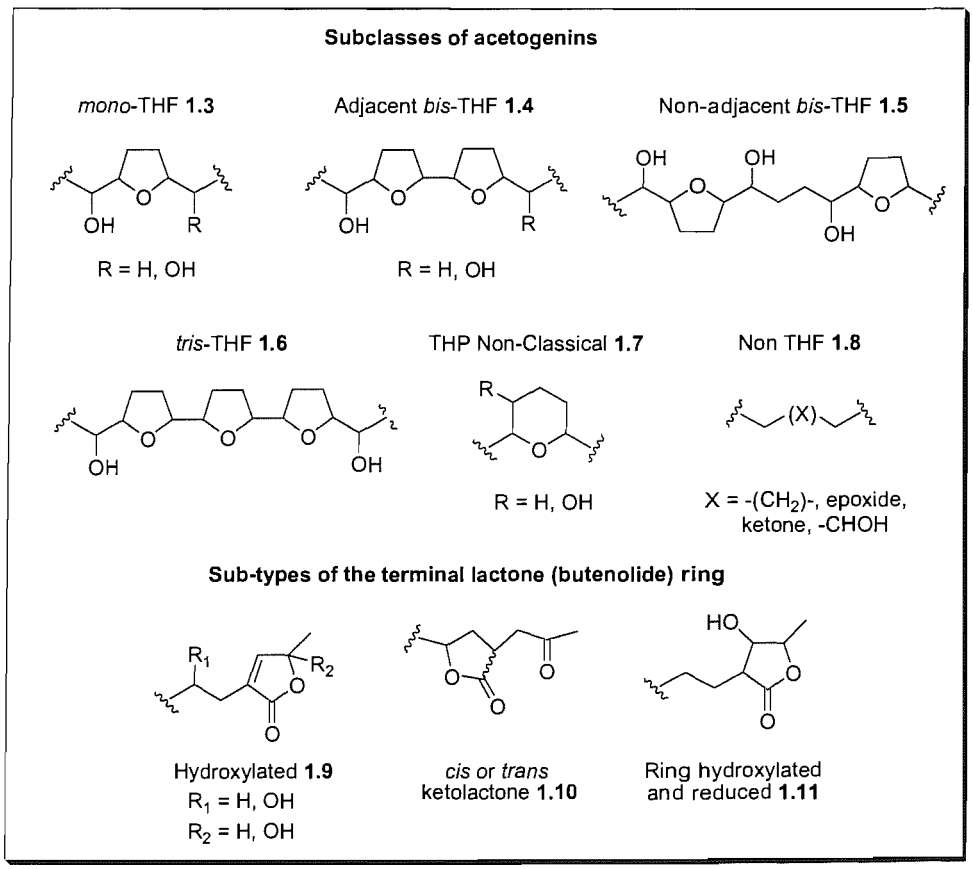


Figure 1.2 Core units for the classification of *Annonaceous* acetogenins.

1.3 Structure Activity Relationships

There are several generalisations that can be made concerning the structure-activity relationships (SAR's) of the *Annonaceous* acetogenins in relation to cytotoxicity:[4-8]

1) *bis*-Adjacent-THF acetogenins are the most potent within the family, followed by non-adjacent *bis*-THF compounds, then *mono*-THFs and finally non-THFs.
2) The terminal α-β-unsaturated γ-lactone is essential for activity.
3) The shorter C-35 acetogenins are more potent than their C-37 counterparts if the structural features are kept constant.
4) The spacer group that separates the hydroxyl-flanked THF and the γ-lactone has a crucial optimum length for maximum potency and selectivity.
5) Three hydroxyl groups (two flanking the THF ring(s) and one somewhere along the hydrocarbon chain) are responsible for the optimal positioning and polarity required for activity. Any more than four hydroxyls results in a dramatic drop in potency.

1.4 Biological Activity and Mechanism of Action

The biological effects of *Annonaceous* acetogenins have great diversity and include antimalarial,[9] antiparasitic and antimicrobial,[10] antiprotozoal,[11] and pesticidal[6,12,13] activities. They are toxic to mosquito larvae, European corn borers, spider mites, melon aphids, Mexican bean beetles, striped cucumber beetles, blowfly larvae and Colorado potato beetles.[6,14] In a study on German cockroaches,[5] high mortality was observed together with low resistance ratios. Such low pesticide resistance is likely to involve ATP-dependent factors.

The most important biological property, however, is *in vivo* and cytotoxic antitumour activity,[15-19] and acetogenins have emerged as promising new leads in the combat against MDR tumours[20,21] They are thought to be some of the most potent cytotoxic compounds known, showing inhibition of mitochondrial complex I in nanomolar concentrations.[22] The acetogenins trilobacin[23] and asiminocin[24] have exhibited ED_{50} values of $<10^{-12}$ μg/mL in several human tumour cell lines. Furthermore, acetogenins

show greater cytotoxity to cancerous cells over non-cancerous cells[14] which suggests that these agents are not general cytotoxins.

The major target site of the *Annonaceous* acetogenins is the mitochondrial NADH:ubiquinone oxidoreductase complex known as Complex I.[14,25,26] Complex I plays an important role in the maintenance of the bio-energetic function of the cells by driving approximately one third of ATP synthesis.[27]

Ubiquinone oxidoreductase, a membrane-bound enzyme, is essential in the mitochondrial electron transport system and is responsible for the transfer of electrons from NADH to O_2. It is thought that the THF core and flanking hydroxyls of acetogenins mimic the quinone head of the natural substrate ubiquinone and effectively inhibit this enzyme.[28] Inhibition of this enzyme stops the translocation of protons out of the mitochondria, and without this transmembraneous electrochemical force, the production of ATP ceases.[29] Depleted cellular ATP concentrations reduce the available cellular energy and ultimately result in cell death through apoptosis. This mechanism of action is particularly lethal to cancerous cells since they have a higher demand for ATP than regular cells.[30]

A second possible mechanism of action has also been suggested, which can occur at the plasma membrane-bound enzyme NADH oxidase as well as at Complex I.[21,31,32] The central hydrophilic core of the acetogenins could bind to the polar glycerol groups located at the end of the phospholipid membrane. Once anchored here, the hydrophobic chain and essentially the terminating butenolide can penetrate the bilayer and interact with the ubiquinone dependant site in the electron-transport system.[33] This causes ATP production to cease in the cellular membrane resulting in apoptosis, thus inhibiting the growth of cancerous cells.

1.5 Biosynthesis

Biogenetically, the *Annonaceous* acetogenins are derived from the polyketide pathway. The THF and epoxide rings are thought to arise from isolated double bonds through epoxidation and cyclisation.[3] The plants in this family choose to biosynthesise over 350 different acetogenins, with all of them being either C-32 or C-

34 fatty acid derivatives, never C-30 or C-36. The dimension of cell and mitochondrial membranes[33] (the sites of the target enzymes) may dictate this particular chain length, and it has probably evolved because it provides the optimum activity. Shorter acetogenins lose activity, and it is logical to assume that longer ones will also be less active.

1.6 Synthesis of Non-Adjacent *bis*-THF Natural Products

The synthesis of non-adjacent *bis*-THF natural products is an area where there are few examples, especially when compared with their adjacent *bis*-THF and *mono*-THF counterparts. It is an important area that requires further development especially since non-adjacent *bis*-THF compounds are some of the most potent anti-cancer agents known. The following section summarises recent literature syntheses in this area.

1.6.1 Synthesis of (+)-4-Deoxygigantecin

In 1998, Makabe *et al.* undertook the synthesis of (+)-4-deoxygigantecin (**1.12**), an acetogenin containing *trans*-THF rings (Figure 1.3).[34]

(+)-4-Deoxygigantecin (**1.12**) was isolated in 1992 by McLaughlin *et al.*[35] however its absolute configuration was never reported. Makabe assumed that the absolute stereochemistry (excluding the *C*-4 centre) was identical to that of (+)-gigantecin (**1.13**), an acetogenin whose absolute stereochemistry is known (Figure 1.3).

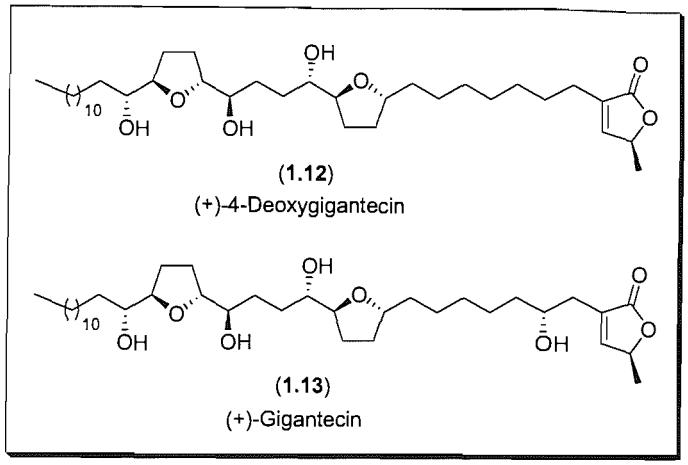
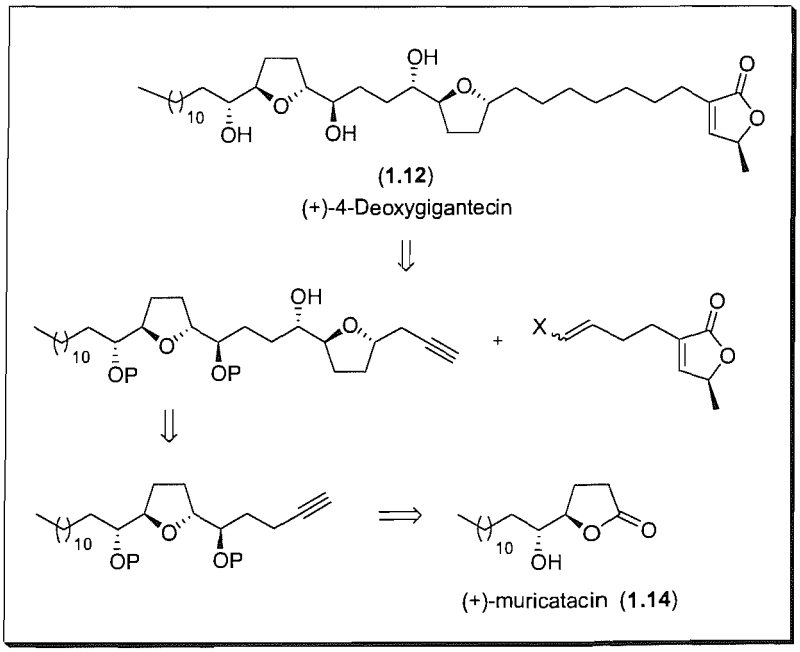


Figure 1.3 The *Annonaceous* acetogenins (+)-4-deoxygigantecin (**1.12**) and (+)-gigantecin (**1.13**).

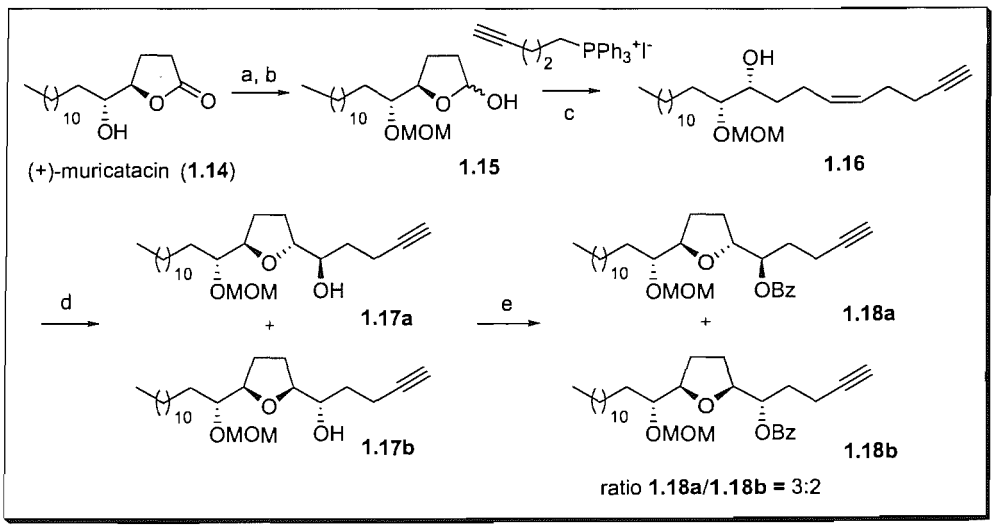
Makabe and co-workers applied methodology that they had used previously in the synthesis of the *mono*-THFs *trans*-solamin and reticulatacin.[36] In these syntheses the starting compound was (+)-muricatacin (**1.14**), a previously synthesised[37] acetogenin derivative containing two stereogenic centres which are found in both natural products (Scheme 1.1). As the same stereogenic centres are found in the acetogenin (+)-4-deoxygigantecin (**1.12**), a similar approach was adopted.



Scheme 1.1 Retrosynthetic analysis of (+)-4-deoxygigantecin.

Synthesis of Part of the Left-Hand Fragment of 4-Deoxygigantecin

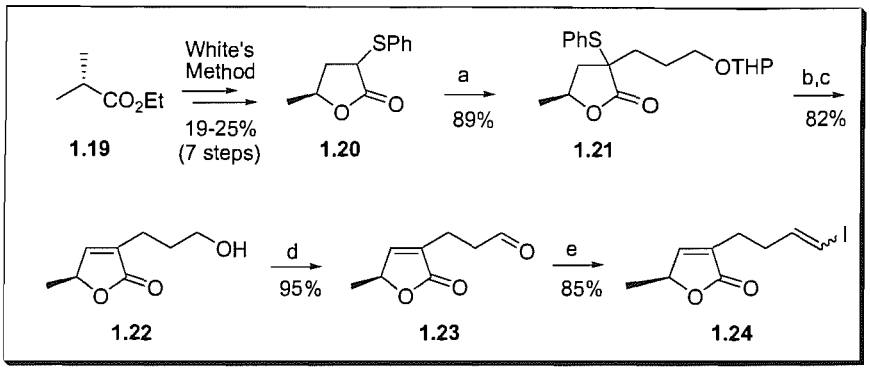
(+)-Muricatacin (**1.14**) was protected then reduced with DIBAL-H to give lactol **1.15**, which after ring-opening and olefination afforded enyne **1.16** (Scheme 1.2). Their strategy focused upon epoxidation followed by acid-catalysed epoxide opening and subsequent THF ring formation. As there was no asymmetric induction in the epoxidation, there could be no control over the stereochemistry across the THF ring. Hence when applied to enyne **1.16**, this sequence resulted in an inseparable mixture of *trans*-THF **1.17a** and *cis*-THF **1.17b** products. Separation was only possible after benzoyl protection of the alcohols, and isolation of the products revealed a 3:2 *trans*-THF **1.18a** /*cis*-THF **1.18b** ratio (Scheme 1.2).



Scheme 1.2 Synthesis of the left hand fragment of (+)-4-deoxygigantecin (**1.13**) from (−)-muricatacin (**1.14**). *Reagents and conditions:* a) MOMCl, ^{i}PrNEt, CH_2Cl_2; b) DIBAL-H, THF; c) NaOEt; d) (i) *m*CPBA; (ii) CSA; e) BzCl, pyridine.

Synthesis of the Right-Hand Fragment of 4-Deoxygigantecin

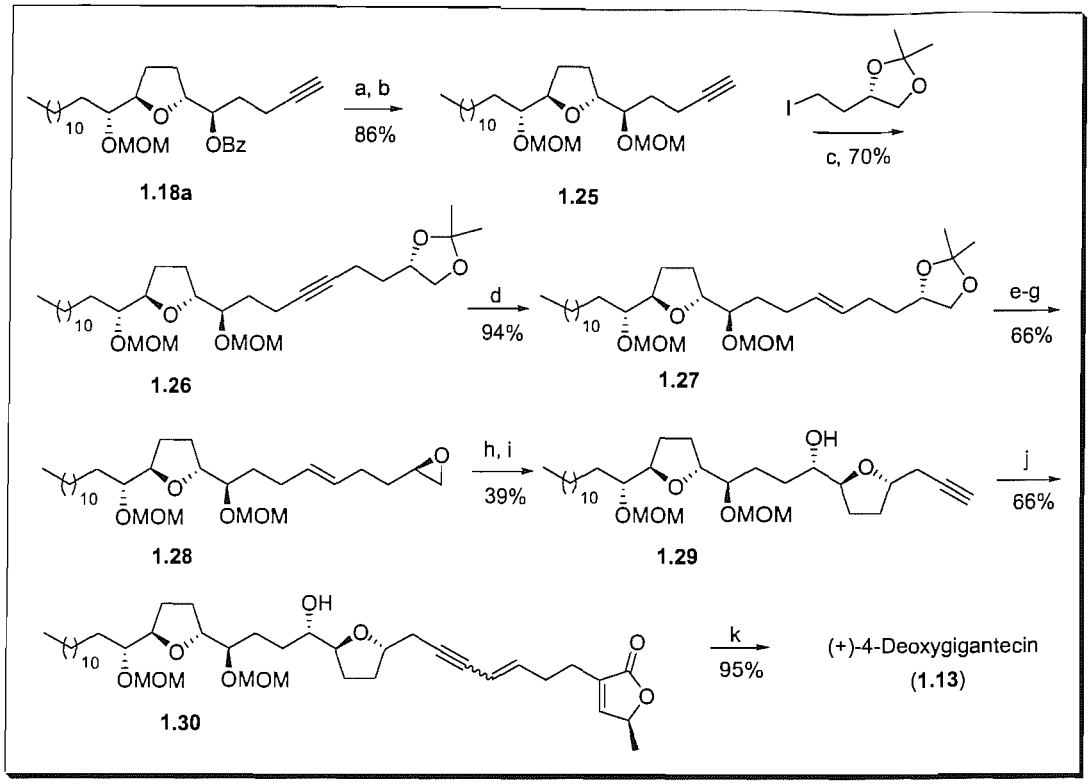
Synthesis of the right-hand fragment began with the utilisation of White's method[38] for the synthesis of γ-lactone **1.20** (Scheme 1.3). Alkylation and deprotection of lactone **1.20** followed by oxidation with *m*CPBA and thermo-elimination gave alcohol **1.22**. Oxidation of alcohol **1.22** to aldehyde **1.23** and subsequent olefination using Takai's conditions[39] gave the vinyl iodide **1.24** in excellent overall yield.



Scheme 1.3 Synthesis of butenolide portion **1.24**. *Reagents and conditions:* a) NaHMDS, $Br(CH_2)_3OTHP$, THF-HMPA; b) *p*-TsOH, MeOH; c) (i) *m*CPBA, $ClCH_2CH_2Cl$; (ii) toluene, reflux; d) Dess-Martin periodinane, CH_2Cl_2; e) $CrCl_2$, CHI_3, THF.

Completion of the Left-Hand Fragment of 4-Deoxygigantecin

Elaboration of the left-hand fragment continued in order to install a second THF ring and provide a coupling partner for vinylic iodide **1.24**. Benzoate ester **1.18a** was hydrolysed and the resulting alcohol MOM protected to give alkyne **1.25** (Scheme 1.4). Alkylation of **1.25** followed by reduction of the alkyne gave the corresponding *trans*-alkene **1.27**. Deprotection of the acetonide and selective protection of the primary alcohol enabled activation of the secondary alcohol. Subsequent silyl deprotection and epoxidisation with inversion gave epoxide **1.28** in excellent yield. The epoxide was opened with TMS-acetylene and the resulting alcohol mesylated. Sharpless dihydroxlation[40] and THF-ring formation gave *bis*-THF alkyne **1.29** in good overall yield (Scheme 1.4).

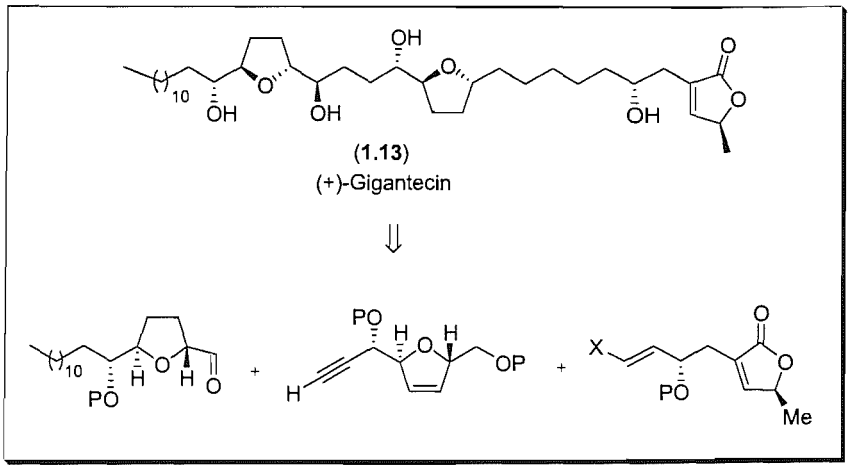


Scheme 1.4 Completion of the synthesis of (+)-4-deoxygigantecin (**1.13**). *Reagents and conditions:* a) NaOH, MeOH; b) MOMCl, $^{i}Pr_2NEt$, CH_2Cl_2; c) *n*-BuLi, THF; d) Na/NH_3, *t*-BuOH, THF; e) 60% AcOH; f) TBSCl, Et_3N, DMAP, CH_2Cl_2; g) (i) MsCl, Et_3N, CH_2Cl_2; (ii) TBAF, THF; (iii) 10% NaOH, THF; h) (i) TMS-acetylene, *n*-BuLi, $BF_3.Et_2O$, THF; (ii) TBAF, THF; i) (i) MsCl, Et_3N, CH_2Cl_2; (ii) AD mix α, *t*-BuOH-H_2O; (iii) Triton B, MeOH; j) **1.24**, $Pd(PPh_3)_4$, Et_3N, CuI, benzene; k) (i) H_2, $Rh(PPh_3)_3Cl$, benzene; (ii) $BF_3.Et_2O$, Me_2S.

Pd(0)-catalysed cross coupling[41] of alkyne **1.29** and vinyl iodide **1.24** gave enyne **1.30**, which, after catalytic hydrogenation with Wilkinson's catalyst and MOM deprotection, afforded (+)-4-deoxygigantecin (**1.13**) (Scheme 1.4). The ^1H NMR data and the optical rotation were in agreement with that recorded for the natural product, thus they had succeeded in elucidating the absolute stereochemistry of (+)-4-deoxygigantecin (**1.13**).

1.6.2 Synthesis of (+)-Gigantecin

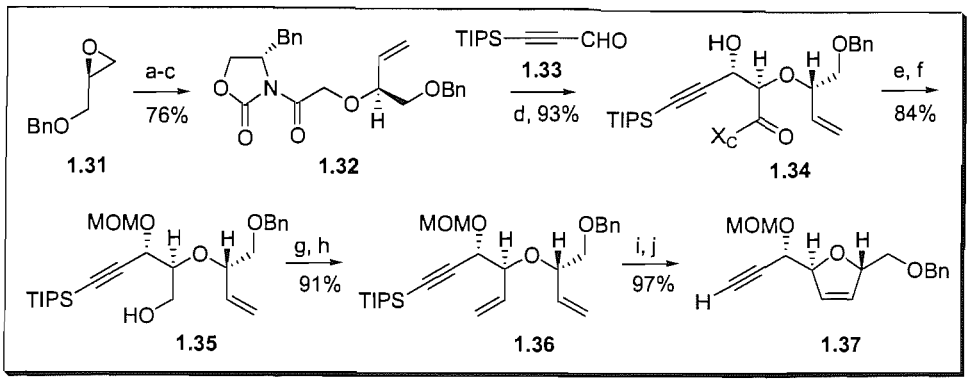
The acetogenin (+)-gigantecin (**1.13**) (Figure 1.3) is structurally identical to (+)-4-deoxygigantecin (**1.12**) except that it has an extra hydroxyl group. Crimmins *et al.*[42] used a very different approach to its synthesis however, compared to Makabe's already described synthesis of (+)-4-deoxygigantecin (**1.12**). They decided to split the natural product into three main subunits: the left hand THF fragment, the central THF fragment and the right hand butenolide fragment (Scheme 1.5). All three fragments would be accessible *via* an asymmetric glycolate aldol-ring closing metathesis sequence.



Scheme 1.5 Retrosynthetic analysis of (+)-gigantecin.

Synthesis of the Central THF Fragment of (+)-Gigantecin

The synthesis began with the formation of glycolate **1.32** in three high-yielding steps from chiral epoxide **1.31** (Scheme 1.6). The following step implemented their newly developed protocol for asymmetric aldol reactions of complex glycolyl oxazolidinone chlorotitanium enolates.[43] Under these conditions, a highly diastereoselective aldol reaction took place producing alcohol **1.34** in excellent yield and >20:1 d.r. (major: all other isomers). Protection of the secondary alcohol and reductive cleavage of the chiral auxiliary gave primary alcohol **1.35**. Oxidation to the aldehyde under Swern conditions[44] and subsequent olefination gave diene **1.36** (Scheme 1.6).

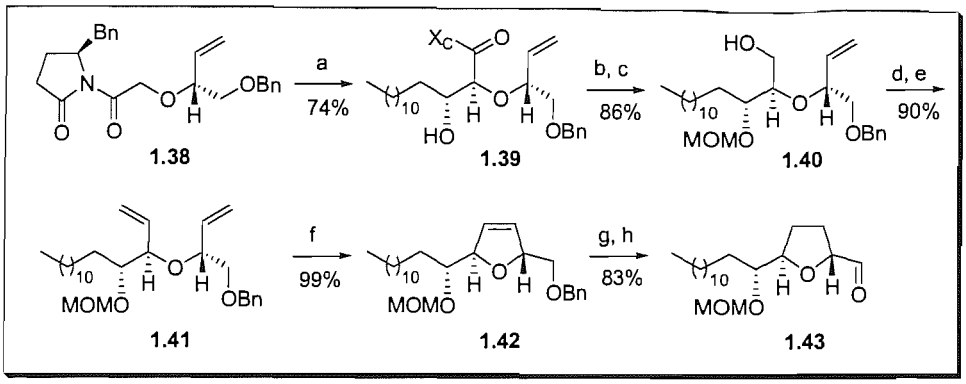


Scheme 1.6 Synthesis of the central THF fragment of (+)-gigantecin (**1.13**). *Reagents and conditions:* a) Me_3SI, *n*-BuLi, THF, −10 to 25 °C; b) NaH, $BrCH_2CO_2H$, THF; c) Me_3CCOCl, Et_3N, THF, −78 °C to 0 °C; (*R*)-lithio-4-benzyl-oxazolidin-2-one; d) $TiCl_4$, $^iPr_2NEt$, *N*-methyl-2-pyrrolidinone, CH_2Cl_2, −78 °C to −40 °C, **1.33**; e) $MeOCH_2Cl$, $^iPr_2NEt$, DMAP, CH_2Cl_2; f) $LiBH_4$, MeOH, Et_2O, 0 °C; g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; h) $Ph_3P{=}CH_2$, THF; i) $Cl_2(Cy_3P)(IMes)Ru{=}CHPh$, CH_2Cl_2, 40 °C; j) Bu_4NF, THF.

Exposure of diene **1.36** to Grubbs second-generation catalyst[45] led to selective formation of a dihydrofuran in high yield with no evidence of reaction at the acetylene (Scheme 1.6). Subsequent desilylation gave alkyne **1.37**.

Synthesis of the Left-Hand THF Fragment of (+)-Gigantecin

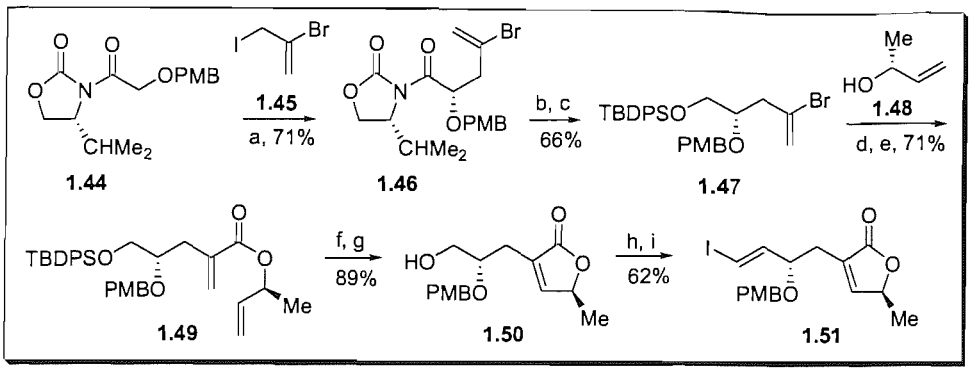
The left-hand THF fragment was constructed in similar fashion to the central THF fragment. The same aldol reaction was exploited affording alcohol **1.39** from glycolate **1.38** ((*ent*)-**1.32**) in high yield (Scheme 1.7). Protection of the secondary alcohol and reductive cleavage of the chiral auxiliary gave primary alcohol **1.40**. Oxidation of the alcohol and subsequent olefination resulted in diene **1.41**. This underwent metathesis when exposed to Grubbs second-generation catalyst affording dihydrofuran **1.42** in excellent yield. Concomitant hydrogenation of the alkene, hydrogenolysis of the benzyl protecting group and oxidation of the alcohol produced aldehyde **1.43** in good overall yield.



Scheme 1.7 Synthesis of the left-hand THF fragment. *Reagents and conditions:* a) $TiCl_4$, $^iPr_2NEt$, *N*-methyl-2-pyrrolidinone, tridecenal, CH_2Cl_2, −78 °C to −40 °C; b) $MeOCH_2Cl$, $^iPr_2NEt$, DMAP, CH_2Cl_2; c) $LiBH_4$, MeOH, Et_2O, 0 °C; d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; e) $Ph_3P{=}CH_2$, THF; f) $Cl_2(Cy_3P)(IMes)Ru{=}CHPh$, CH_2Cl_2, 40 °C; g) H_2, Pd/C, EtOH; h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2.

Synthesis of the Butenolide Fragment of (+)-Gigantecin

Alkylation of the sodium enolate of glycolate **1.44** with allylic iodide **1.45** gave **1.46** in good yield and excellent diastereoselectivity (>98:2) (Scheme 1.8). Reductive cleavage of the chiral auxiliary and protection of the resulting alcohol gave protected diol **1.47**. Lithium-halogen exchange of the vinyl bromide of **1.47** and reaction with CO_2 provided the acrylic acid derivative, which gave ester **1.49** upon inversion of alcohol **1.48** under Mitsunobu conditions.[46] Exposure of diene **1.49** to Grubbs second-generation catalyst and desilylation gave butenolide alcohol **1.50**. Oxidation of the alcohol to the aldehyde and olefination under Takai's conditions[39] afforded vinyl iodide **1.51**.

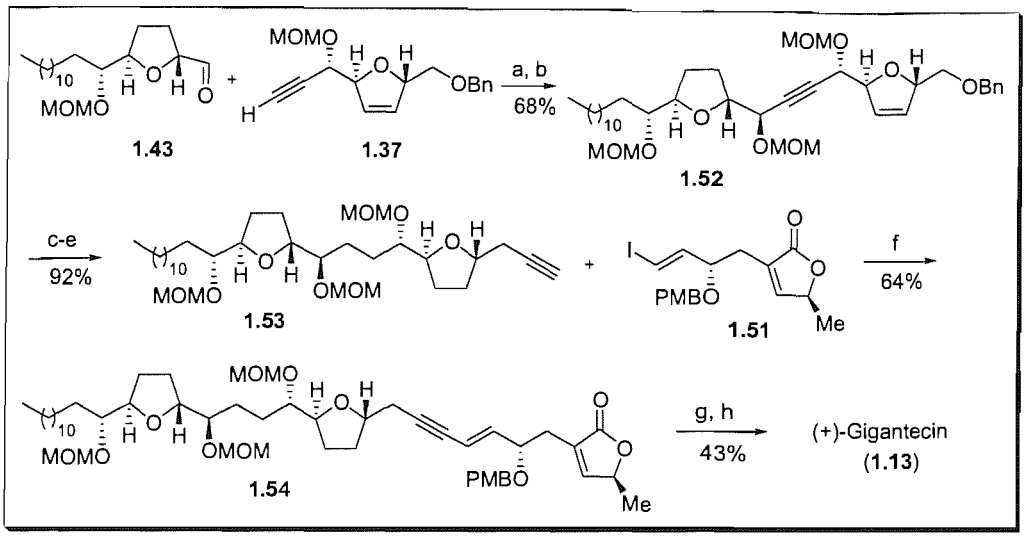


Scheme 1.8 Synthesis of the butenolide fragment. *Reagents and conditions:* a) NaHMDS, THF, −78 to 45 °C, **1.45**; b) $NaBH_4$, THF, H_2O; c) TBDPSCl, imidazole, CH_2Cl_2; d) *t*-BuLi, THF, −78 °C, CO_2; e) DEAD, Ph_3P, THF, **1.48**; f) $Cl_2(Cy_3P)(IMes)Ru{=}CHPh$, CH_2Cl_2, 40 °C; g) 3HF-Et_3N, CH_3CN; h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; i) CHI_3, $CrCl_2$, THF.

Combining the Three Fragments of (+)-Gigantecin

With the three required fragments in hand, the assembly of (+)-gigantecin (**1.13**) was undertaken (Scheme 1.9). Alkyne **1.37** was coupled to aldehyde **1.43** using the Carreira method for asymmetric acetylide addition.[47,48] The resulting propargylic alcohol was produced as a single detectable diastereomer and was subsequently protected to give enyne **1.52**.

Treatment of enyne **1.52** with hydrogen in the presence of Pd/C led to the concomitant reduction of the double and triple bonds as well as the removal of the benzyl protecting group. Formation of the triflate and ensuing displacement with lithium trimethylsilyl acetylide produced acetylene **1.53** in excellent yield. Palladium-mediated coupling[41] of acetylene **1.53** and vinyl iodide **1.51** afforded enyne **1.54**. Selective hydrogenation of the enyne followed by removal of the protecting groups afforded (+)-gigantecin (**1.13**) (Scheme 1.9).



Scheme 1.9 Combining the three fragments. *Reagents and conditions:* a) $Zn(OTf)_2$, (−)-*N*-methylephedrine, toluene, **1.37** then **1.43**; b) $MeOCH_2Cl$, $^iPr_2NEt$, DMAP, CH_2Cl_2; c) H_2, Pd/C, EtOH; d) Tf_2O, Et_3N, CH_2Cl_2, −78 °C; e) $Me_3SiC{\equiv}CH$, *n*-BuLi, THF, HMPA, −78 °C; MeOH, 25 °C; f) $Pd(PPh_3)_4$, CuI, $^iPr_2NEt$, THF; g) H_2, $Rh(PPh_3)_3Cl$, benzene, EtOH, LiI; h) $BF_3.OEt_2$, Me_2S, 0 °C.

1.6.3 Synthesis of (+)-Eurylene and (+)-14-Deacetyleurylene

The biologically active triterpene polyethers are natural products thought to be biogenetically derived from squalene. Little was known about their mechanism of action since they were formerly only available in restricted quantities from natural sources. The first total synthesis of (+)-eurylene (**1.55**) (Figure 1.4) was completed in 1996 by Ujihara *et al.*,[49] however a more attractive approach was published in 2000 by Morimoto *et al.*,[50] who utilised the same chemistry to synthesise (+)-14-deacetyleurylene (**1.56**) (Figure 1.4).

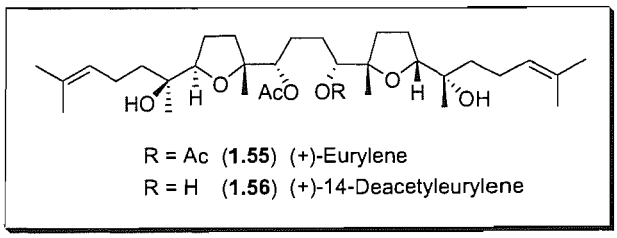
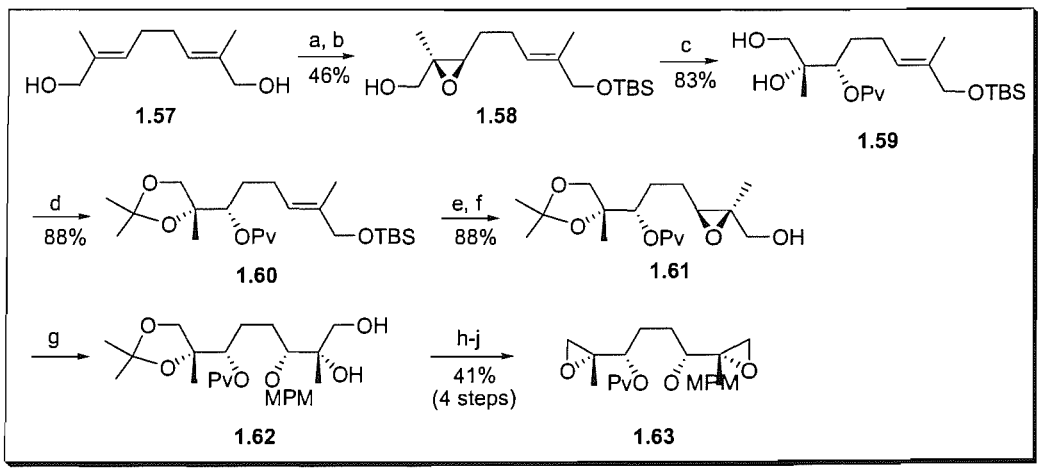


Figure 1.4 The triterpene polyethers (+)-eurylene and (+)-14-deacetyleurylene.

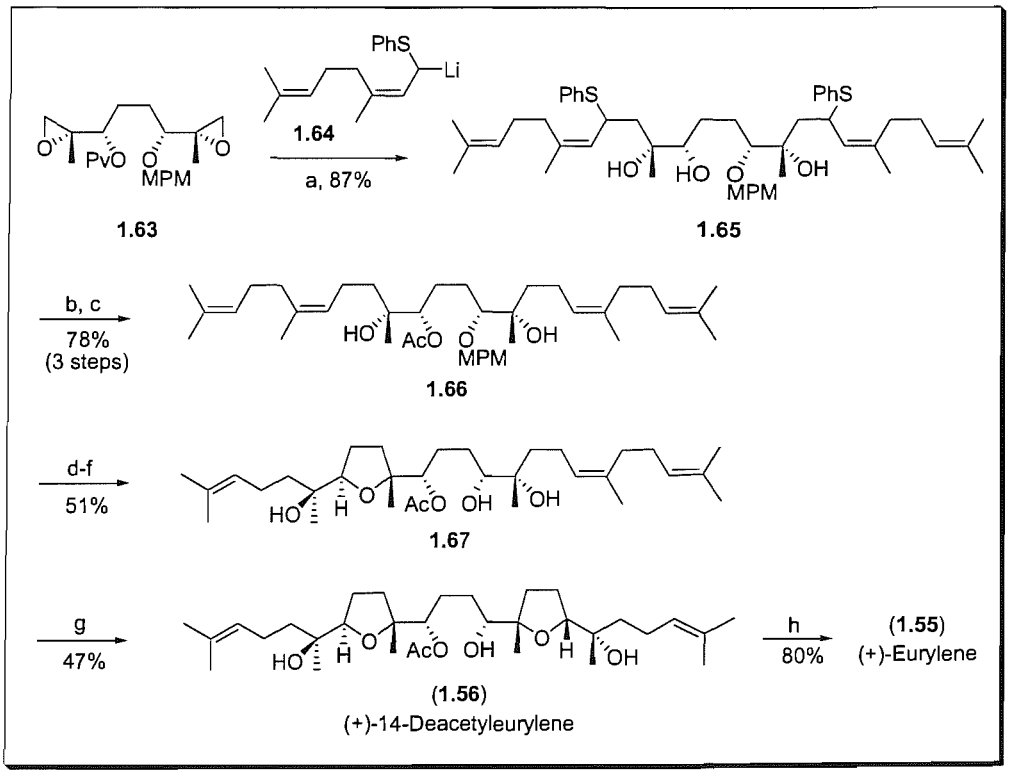
Interestingly, it has been shown that (+)-14-deacetyleurylene (**1.56**) adopts a folded conformation and exhibits prominent cytotoxic activity on KB cells, whereas (+)-eurylene (**1.55**) possessing an extended conformation does not.[51,52] The key steps in Morimoto's synthesis include the stereoselective construction of the *trans* and *cis* THF rings *via* rhenium(VII) and chromium(VI) oxidative cyclisation and differentiation of the 14-hydroxy group.

Monoprotection of known diol **1.57**[53] followed by Sharpless asymmetric epoxidation[54] of the remaining allylic alcohol gave epoxide **1.58** with excellent enantioselectivity (98% *ee*) (Scheme 1.10). The pivaloate group was introduced regioselectively by a titanium-assisted epoxide opening to give diol **1.59** which was subsequently protected as the acetal **1.60**. Desilylation of **1.60** and epoxidisation of the resulting allylic alcohol afforded epoxide **1.61**. Opening of this epoxide in the presence of $Ti(OMPM)_4$ and *p*-anisyl alcohol gave a 3:1 mixture of 1,2-diol/1,3-diol. Removal of the acetal group, activation of both primary alcohols in the resulting tetrol and treatment with base produced diepoxide **1.63** in 41% overall yield.



Scheme 1.10 Synthesis of the diepoxide unit. *Reagents and conditions:* a) TBSCl, imidazole, CH_2Cl_2, rt; b) *t*-BuOOH, $Ti(O^iPr)_4$, D-(−)-DET, CH_2Cl_2, −20 °C; c) $Ti(O^iPr)_4$, PvOH, benzene, 0 °C; d) 2,2-dimethoxypropane, CSA, CH_2Cl_2, 0 °C; e) Bu_4NF, THF, rt; f) *t*-BuOOH, $Ti(O^iPr)_4$, L-(−)-DET, CH_2Cl_2, −20 °C; g) $Ti(OMPM)_4$, MPMOH, benzene, 60 °C; h) $AcOH/H_2O$ (4:1), rt; i) MsCl, py, CH_2Cl_2, 0 °C → rt; j) K_2CO_3, MeOH, rt.

Bi-directional alkylation of diepoxide **1.63** using the lithio derivative of neryl phenyl sulfide **1.64** gave the disulfide **1.65** as a mixture of diastereomers, whilst simultaneously removing the pivalate group (Scheme 1.11). Desulfurisation under Bouvault-Blanc[55] conditions and selective acetylation of the secondary alcohol afforded diol acetate **1.66** in good overall yield. The MPM protecting group was converted into the 4-methoxybenzylidene acetal by interaction of the neighbouring hydroxyl group with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Subsequent acidic hydrolysis and oxidative cyclisation with ten equivalents of the oxorhenium(VII) complex [(CF_3CO_2) $ReO_3 \cdot 2CH_3CN$] in the presence of TFAA gave *trans*-THF product **1.67**, leaving the right-hand side of the molecule intact.

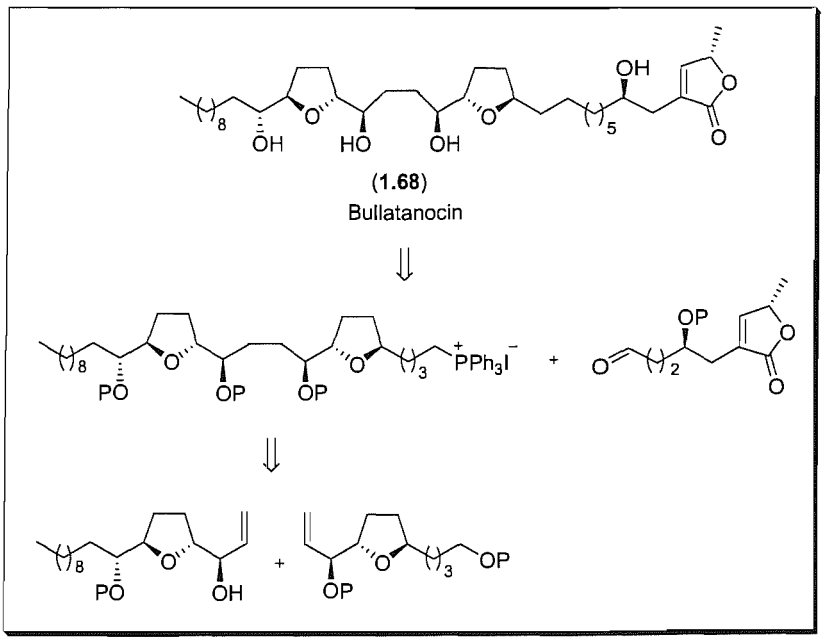


Scheme 1.11 Completion of the synthesis. *Reagents and conditions:* a) TMEDA, THF, −78 °C → 0 °C; b) Na, THF/^{i}PrOH (2:1), reflux; c) Ac_2O, py, rt; d) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), CH_2Cl_2, 0 °C; e) AcOH/H_2O (4:1), rt; f) [(CF_3CO_2) $ReO_3 \cdot 2CH_3CN$], TFAA, CH_2Cl_2/CH_3CN (9:1), −40 °C; g) PCC, CH_2Cl_2, rt; h) Ac_2O, py, rt.

Oxidative cyclisation of **1.67** with a stoichiometric amount of oxochromium(VI)-containing complex PCC, installed the second THF ring with complete *cis* diastereoselectivity affording (+)-14-deacetyleurylene (**1.56**) (Scheme 1.11). Oxidative cleavage of the vicinal diol also occurred as a side reaction. It is postulated that the oxidative cyclisation occurs regioselectively since the formation of a dialkoxychromium intermediate is favoured over a monoalkoxychromium intermediate. Selective acetylation of the 14-hydroxy group gave (+)-eurylene (**1.55**).

1.6.4 Synthesis of Bullatanocin (Squamostatin-C)

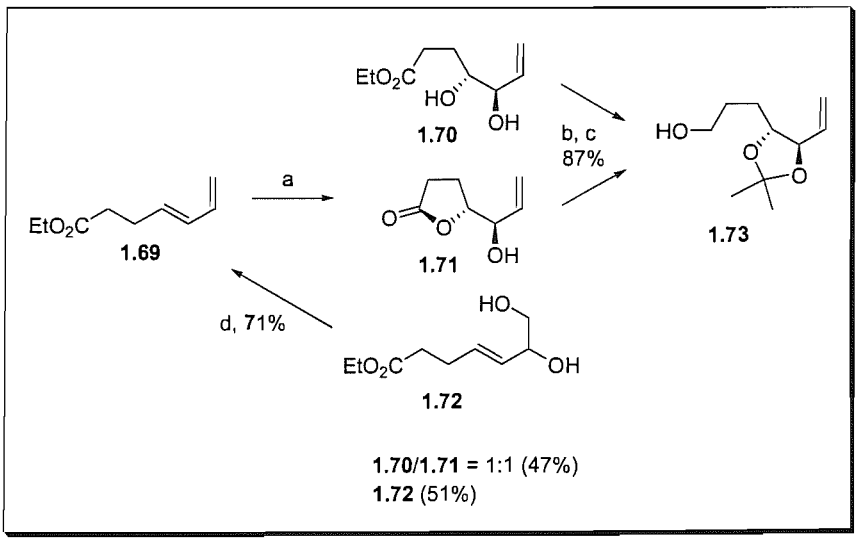
In 2003, Mootoo and Zhu described an iodoetherification and olefin metathesis approach to the synthesis of non-adjacently linked THFs.[56] They applied this methodology to the synthesis of the *Annonaceous* acetogenin bullatanocin. This approach is general, however, and could be applied to the synthesis of any non-adjacent THF acetogenin containing *trans*-THF rings. Their approach towards bullatanocin (**1.68**) focused upon an olefin cross-metathesis of two THF allylic alcohol components (Scheme 1.12), which were obtained using their previously published iodoetherification methodology.[57]



Scheme 1.12 Retrosynthetic analysis of bullatanocin.

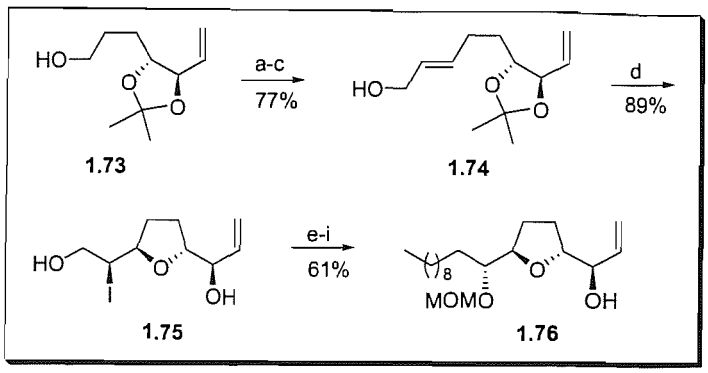
Synthesis of the THF Components of Bullatanocin

The synthesis began with Sharpless asymmetric dihydroxylation of diene **1.69**[40] (Scheme 1.13). This afforded a mixture of products due to the lack of regiocontrol; the undesired diol **1.72** was recycled back to the starting material under alcohol iodination conditions. The combined yield of the desired diol **1.70** (obtained in 92% *ee*) and the derived lactone **1.71** was 47%. Reduction of **1.70** and **1.71** and subsequent acetonation afforded alcohol **1.73**.



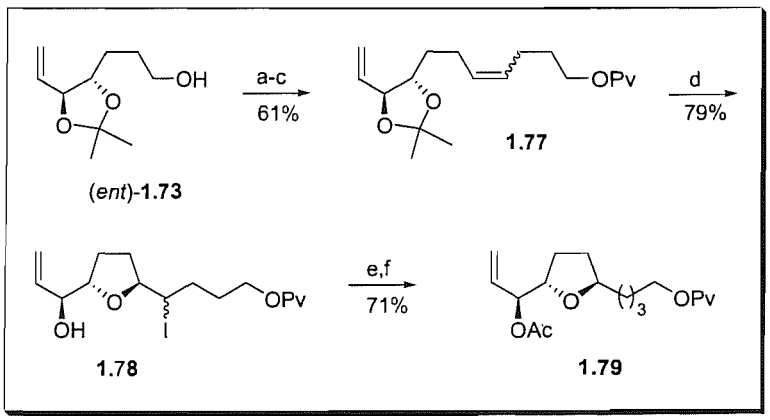
Scheme 1.13 *Reagents and conditions:* a) AD-mix-*β*; *t*-BuOH/H_2O, $MeSO_2NH_2$, 0 °C; b) DIBAL-H, THF, −78 °C → rt; c) 2,2-dimethoxypropane, CSA, CH_2Cl_2, 0 °C → rt; d) Ph_3P, I_2, imidazole, CH_2Cl_2.

Alcohol **1.73** was oxidised to the corresponding aldehyde and subsequent olefination and reduction produced allylic alcohol **1.74** as a single (*E*)-isomer in good overall yield (Scheme 1.14). Iodoetherification reaction of **1.74** using iodonium dicollidine perchlorate (IDCP) gave *trans*-THF **1.75** exclusively in 89% yield. This was converted to the epoxide under basic conditions and silylated to give the silyloxy-epoxide derivative. Opening of this epoxide with nonylmagnesiumbromide afforded allylic alcohol **1.76**.



Scheme 1.14 *Reagents and conditions:* a) PCC, CH_2Cl_2, rt; b) $Ph_3P{=}CHCO_2Me$, CH_3CN, reflux; c) DIBAL-H, CH_2Cl_2, −78 °C → rt; d) iodonium dicollidine perchlorate (IDCP), CH_3CN/H_2O, rt; e) K_2CO_3, MeOH, rt; f) TBSCl, imidazole, CH_2Cl_2, 0 °C → rt; g) $CH_3(CH_2)_8MgBr$, CuBr, THF, 0 °C; h) MOMCl, $^iPr_2NEt$, CH_2Cl_2, 0 °C → rt; i) Bu_4NF, THF, rt.

A similar protocol was used to synthesise allylic ester **1.79**. Alcohol (*ent*)-**1.73** was produced in similar yields to **1.73** using AD-mix-α in the route depicted in Scheme 1.10. Oxidation, olefination and pivalation afforded olefin **1.77** as a 3:1 *Z*:*E* mixture (Scheme 1.15).



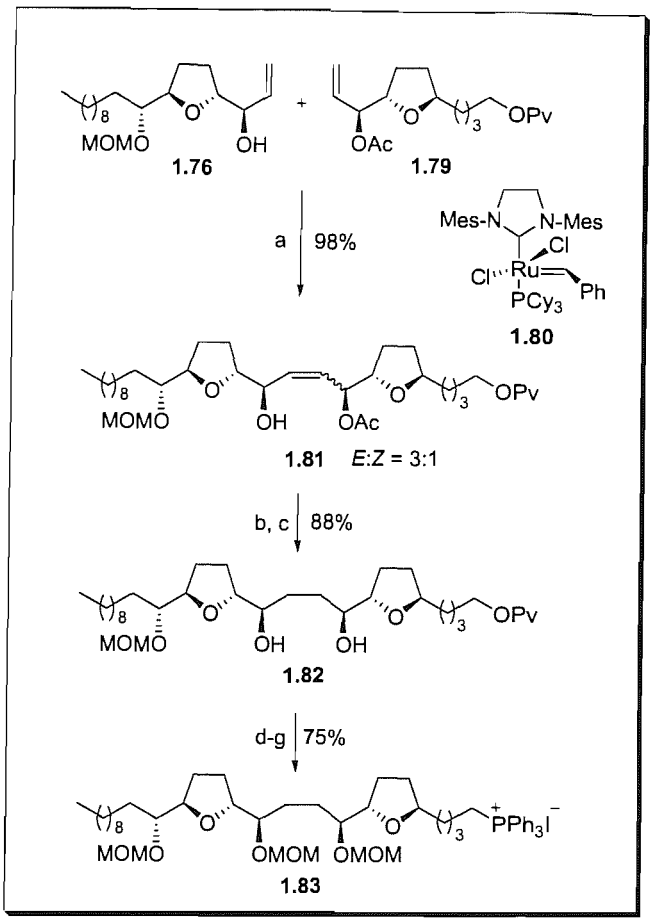
Scheme 1.15 *Reagents and conditions:* a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C → rt; b) $Ph_3P{=}CH(CH_2)_3OLi$, NaHMDS, toluene, −78 °C → rt; c) PvCl, DMAP, py, rt; d) iodonium dicollidine perchlorate (IDCP), CH_3CN/H_2O, rt; e) Bu_3SnH, AIBN, toluene, reflux; f) Ac_2O, DMAP, EtOAc, rt.

Iodoetherification led to an inseparable mixture of THF diastereomers **1.78**; the mixture of *trans*-THF/*cis*-THF was found to be 11:1 by NMR analysis. The mixture of iodides **1.78** was subjected to a radical-mediated reduction followed by acetylation. This enabled chromatographic separation of the diastereomers and thus allylic ester **1.79** was isolated as a single isomer in excellent overall yield (Scheme 1.15).

Combining the THF Fragments of Bullatanocin

Mootoo and Zhu had planned on using a segment-tethering ring-closing metathesis (RCM) protocol to connect the two THF fragments, however this approach was severely hampered by low yields in the synthesis of the tethered precursor and also in the RCM step. Instead they utilised a cross-metathesis strategy; however, as can be envisaged, this would inherently lead to the problem of homodimer formation. Another problem is that allylic esters tend to have a deactivating effect in RCM reactions.[58] They speculated that by using allylic alcohol **1.76** and a large excess of the allylic ester partner **1.79**, they would produce the heterodimer as the major product (Scheme 1.16).

After extensive experimentation, they found the optimum conditions involved using allylic alcohol **1.76** and allylic ester **1.79** in a 1:4 ratio with two equivalents of catalyst **1.80** added 18 h apart at rt. Alkene **1.81** was produced in high yield with an *E*/*Z* ratio of 3:1 (Scheme 1.16). Hydrogenation followed by selective hydrolysis of the acetate afforded diol **1.82**. MOM protection of the hydroxyl groups preceded removal of the pivalate ester. Conversion of the resulting alcohol to the iodide and treatment with triphenylphosphine in the presence of Hunig's base gave phosphonium salt **1.83** in good overall yield.

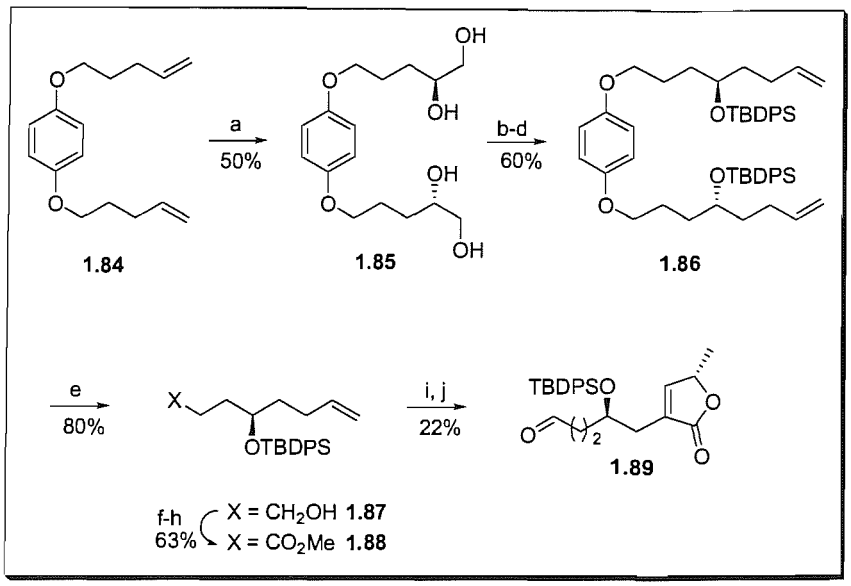


Scheme 1.16 *Reagents and conditions:* a) **1.76/1.79** (1:4), **1.80** (2 eq), CH_2Cl_2, rt; b) H_2, Pd/C, EtOAc; c) K_2CO_3, MeOH; d) MOMCl, $^iPr_2NEt$, CH_2Cl_2; e) NaOMe, MeOH; f) Ph_3P, I_2, imidazole, benzene; g) Ph_3P, $^iPr_2NEt$, CH_3CN.

Synthesis of the Butenolide Portion of Bullatanocin

The known butenolide-aldehyde **1.89** (Scheme 1.17) was synthesised using a modification of the method described by Keinan and Sinha.[59,60] Mootoo and Zhu used a route described by Hoye *et al.*[61] to synthesise methyl ester **1.88** as it was more practical than the method described by Keinan and Sinha. Thus diene **1.84** was subjected to double dihydroxylation with AD-mix-α affording tetrol **1.85**. Activation of the primary alcohols, epoxide formation, ring opening with allylmagnesium bromide and subsequent silylation produced diene **1.86** in good overall yield. Radical-mediated oxidative cleavage produced primary alcohol **1.87** which was converted to the corresponding acid *via* the aldehyde.

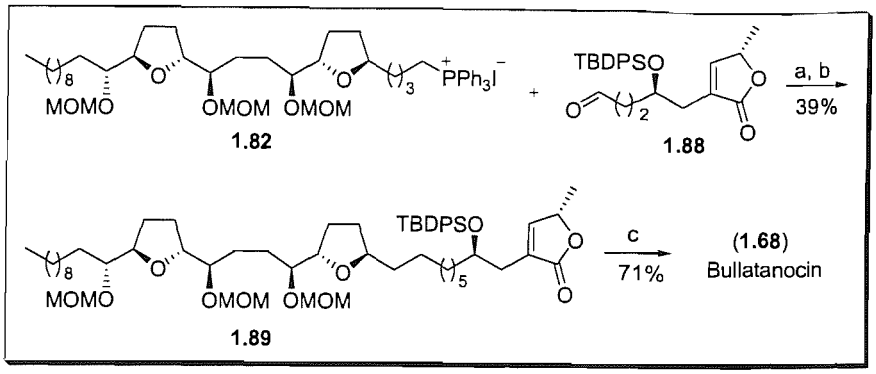
Esterification afforded methyl ester **1.88** (Scheme 1.17). Conversion to aldehyde **1.89** followed a sequence identical to that described by Keinan and Sinha.[59,60]



Scheme 1.17 *Reagents and conditions:* a) AD-mix-α, *t*-BuOH/H_2O, $MeSONH_2$, 0 °C, 12 h; b) (i) TsCl, py; (ii) K_2CO_3, MeOH; c) $HC{\equiv}CHCH_2MgBr$, CuI, THF; d) TBDPSCl, imidazole, CH_2Cl_2; e) CAN, CH_3CN/H_2O; f) PCC, CH_2Cl_2; g) $NaClO_2$, H_2O_2; h) DCC, DMAP, MeOH; i) (i) LDA, THF, −78 °C; then (*S*)-2-(tetrahydropyran-2'yloxy)propanal; (ii) 20% MeOH (aq), TsOH, rt; (j) (i) Et_3N, CH_2Cl_2, −20 → 0 °C; (ii) AD-mix-*β*, *t*-BuOH, H_2O, rt; (iii) $NaIO_4$, H_2O, CH_2Cl_2-acetone, rt.

Completion of the Synthesis of Bullatanocin

The final sequence involved a Wittig reaction between aldehyde **1.88** and the ylide of phosphonium salt **1.82** to afford an *E/Z* mixture of alkenes (Scheme 1.18). Subsequent reduction of the *E/Z* mixture gave *bis*-THF **1.89**, which, after global deprotection, was transformed into the natural product bullatanocin (**1.68**).



Scheme 1.18 Completion of the synthesis. *Reagents and conditions:* a) *n*-BuLi, THF, −78 °C; b) H_2, $Rh(PPh_3)_3Cl$, toluene; c) AcCl, $MeOH/CH_2Cl_2$.

1.6.5 Synthesis of Squamostatin-D

A very different approach to another of the squamostatin family of non-adjacent *bis*-THF natural products was accomplished by Marshall *et al.*[62] The key steps in their synthesis of squamostatin-D (**1.90**) (Figure 1.5) included the enantioselective addition of chiral oxygenated allylic tin and indium reagents to aldehydes.

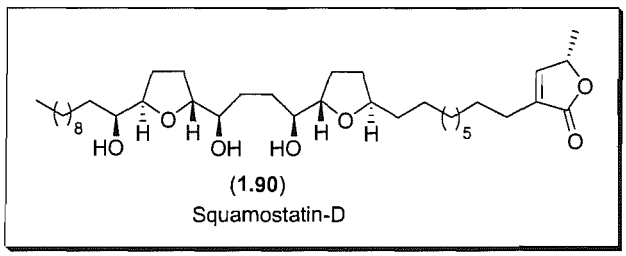
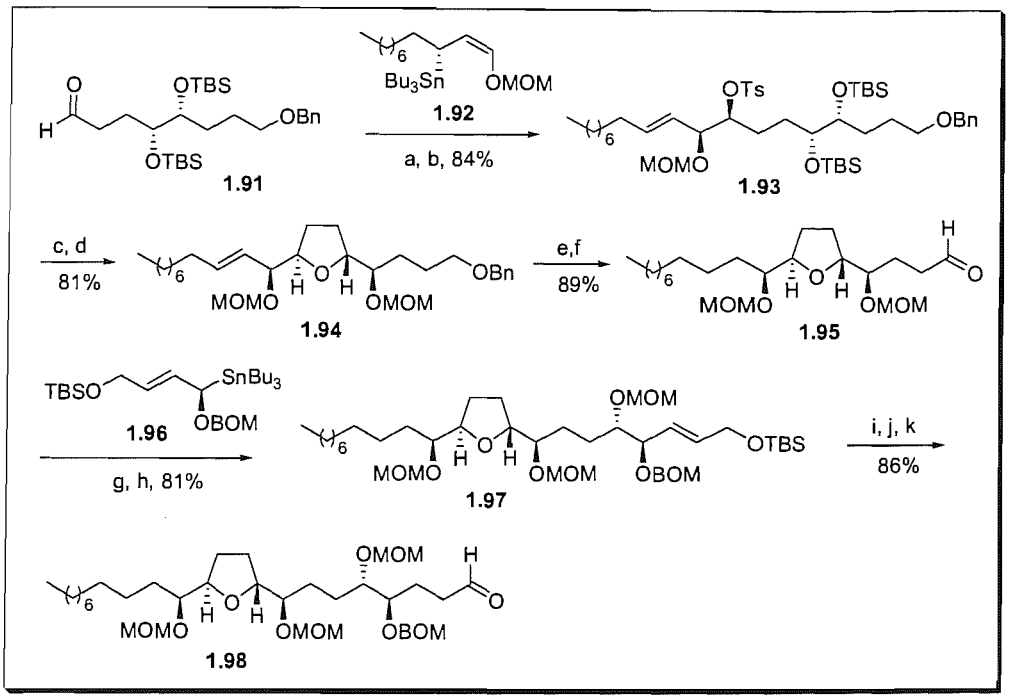


Figure 1.5 The *Annonaceous* acetogenin squamostatin-D.

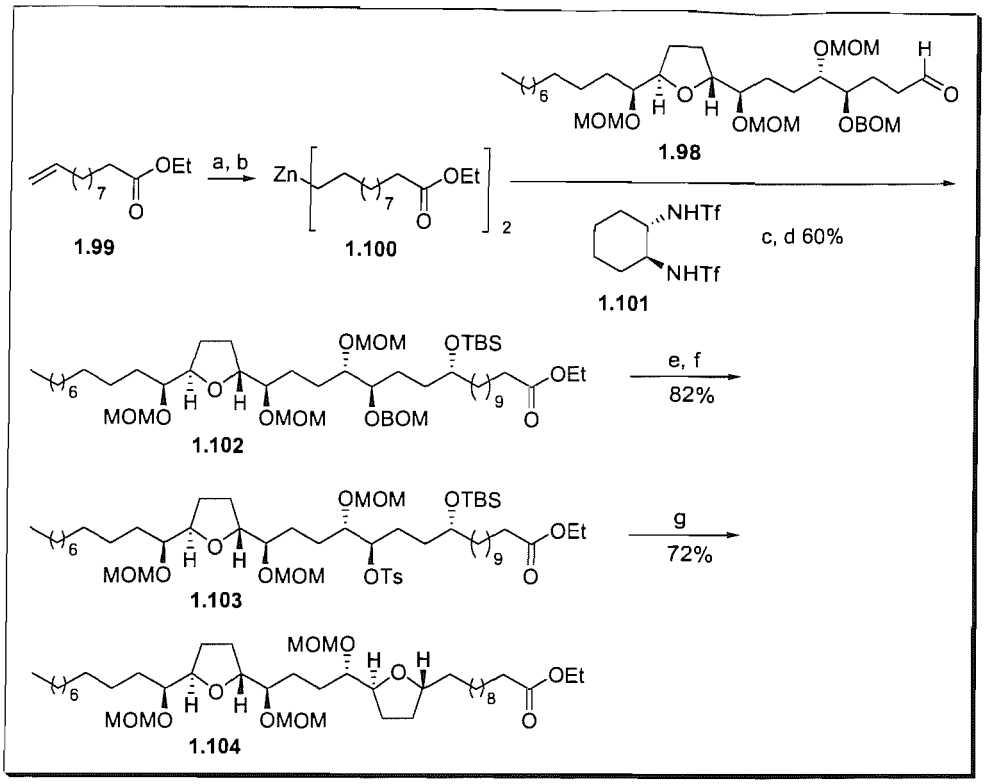
The synthesis began with the addition of (*R*)-γ-alkoxy allylic stannane **1.92**[63] to aldehyde **1.91**[64] which gave the *syn* adduct as the only product (Scheme 1.19). Activation of the resultant alcohol afforded tosylate **1.93**, which after treatment with TBAF, cyclised spontaneously to install the *trans*-THF ring in high yield. Protection of the secondary alcohol as the MOM ether afforded alkene **1.94**. Concomitant reduction of the double bond and debenzylation, followed by oxidation of the primary alcohol afforded aldehyde **1.95**. Treatment with (*S*)-α-alkoxy allylic stannane in the

presence of $InCl_3$ gave the *anti* adduct which was subsequently protected to give MOM ether **1.97**. Reduction of the double bond, desilylation and oxidation of the primary alcohol gave aldehyde **1.98** in excellent overall yield.



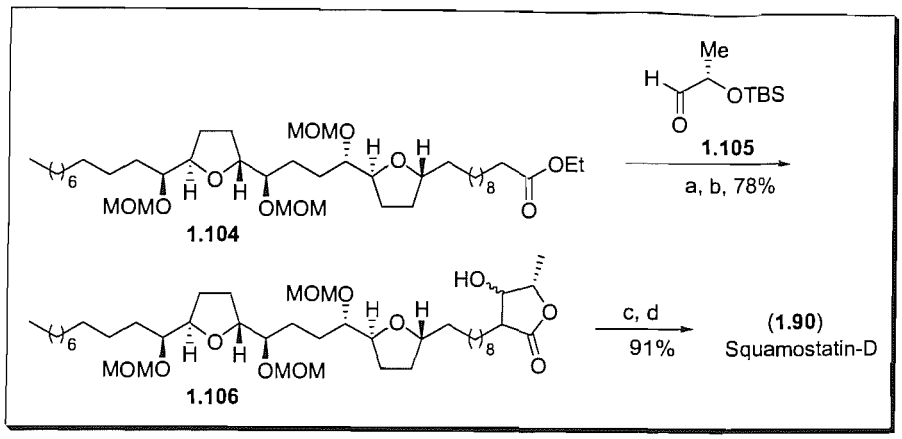
Scheme 1.19 The beginning of the synthesis of squamostatin-D (**1.90**). *Reagents and conditions:* a) **1.92**, $BF_3{\cdot}OEt_2$; b) TsCl, py; c) TBAF, THF; d) MOMCl, $^iPr_2NEt$; e) H_2/Pd-C, EtOH; f) Dess-Martin periodinane; g) **1.96**, $InCl_3$, EtOAc; h) MOMCl, $^iPr_2NEt$; i) H_2/Rh-Al_2O_3, EtOAc; j) TBAF, THF; k) Dess-Martin periodinane.

Marshall and co-workers decided to carry out an asymmetric alkynyl addition to aldehyde **1.98** in order to install the relevant stereogenic centre and introduce the side chain. Zinc reagent **1.100** was prepared from unsaturated ester **1.99** (Scheme 1.20). Addition of organozinc reagent **1.100** to aldehyde **1.98** in the presence of chiral diamine **1.101** afforded the alcohol in 90% *ee*, which was subsequently silylated to give TBS ether **1.102**. Hydrogenolysis of the BOM protecting group and activation of the resulting alcohol gave tosylate **1.103**. Cyclisation occurred spontaneously upon treatment with TBAF, thus producing *bis*-THF **1.104** in good overall yield.



Scheme 1.20 Installation of the second *trans*-THF ring. *Reagents and conditions:* a) Et_2BH; b) Et_2Zn; c) **1.98**, **1.101**, $Ti(O^iPr)_4$; d) TBSCl, imidazole, DMF; e) H_2/Pd-C, EtOAc-EtOH; f) TsCl, py; g) TBAF, THF.

The butenolide portion was introduced using a modification of the procedure described by Yao and Wu.[65] Thus TBS protected (*S*)-lactaldehyde **1.105** condensed with the lithio enolate of **1.104** to afford the aldol product (Scheme 1.21). Treatment with TBAF led to the lactone diastereomers **1.106** in high yield. Dehydration and global deprotection afforded squamostatin-D (**1.90**).



Scheme 1.21 Introduction of the butenolide segment. *Reagents and conditions:* a) **1.105**, LDA, THF; b) TBAF, THF; c) $(CF_3CO)_2O$, Et_3N; d) HCl, THF, MeOH.

1.7 Conclusions

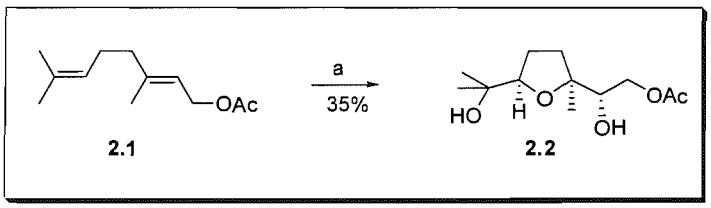
The biological activities of the *Annonaceous* acetogenins are wide-ranging. The most interesting biological property is the potent cytotoxic antitumour activity, which is largely responsible for the considerable interest in their synthesis. The synthesis of non-adjacent *bis*-THF acetogenins is challenging, reflected by the few reported approaches towards them in the literature. In the syntheses described, some of the key steps in forming the core THF rings have included asymmetric epoxidation, metathesis, oxidative cyclisation of hydroxyalkenes, iodoetherification and γ-oxygenated allymetal addition to aldehydes. Most interestingly, however, there are no syntheses that have installed the non-adjacent *bis*-THF core and adjacent stereogenic centres in one step *via* the oxidative cyclisation of a tetraene using transition metal oxo species.

Chapter 2

Oxidative Cyclisation Using Transition Metal Oxidants

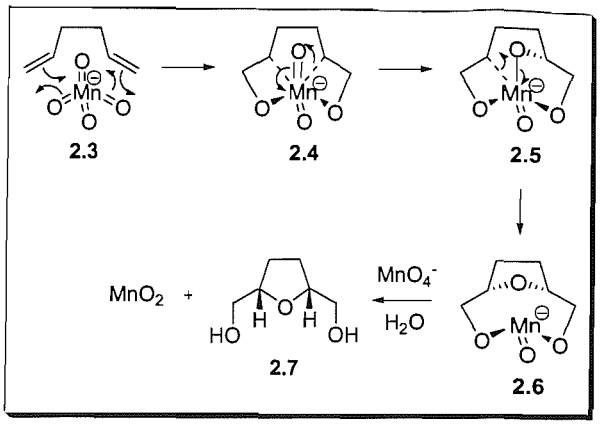
2.1 Potassium Permanganate Promoted Oxidative Cyclisation

In 1924 Kötz and Steche reported the oxidation of a 1,5-diene under neutral conditions using permanganate. They had difficulty in identifying the product however, and it was not until 1965 that Klein and Rojahn were able to elucidate the structure. Klein and Rojahn reported that the oxidation of 1,5-dienes structurally related to geraniol and nerol using potassium permanganate under slightly alkaline conditions afforded 2,5-*bis*-hydroxymethyltetrahydrofurans.[66] They obtained a crystal structure of the product from the oxidation of geranyl acetate **2.1** and found it was *cis*-THF-diol **2.2**, implying that all three oxygen atoms had been delivered from the same face (Scheme 2.1).



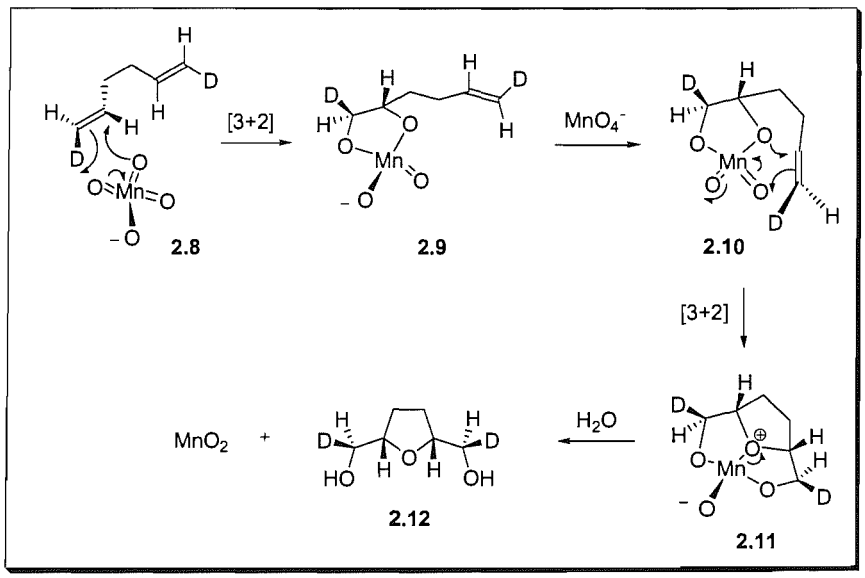
Scheme 2.1 Potassium permanganate-mediated oxidative cyclisation. *Reagents and conditions:* a) $KMnO_4$, acetone, H_2O, CO_2, ebullition.

This was of particular interest since it allowed the synthesis of *cis*-THF-diols containing four new chiral centres in one step, starting from the appropriate 1,5-diene. In 1979, the synthetic utility of this transformation was realised by Walba *et.al.*[67] Inspired by proposals from Sharpless on the mechanism of the oxidation of olefins,[68] Walba went on to propose a mechanism for the permanganate promoted oxidative cyclisation (Scheme 2.2). The mechanism focused upon two [2+2] cycloadditions of Mn=O to each double bond on one face, followed by alkyl migration with retention and then elimination of MnO_2.



Scheme 2.2 Oxidative cyclisation mechanism proposed by Walba *et al.*

At the same time work was being carried out in Baldwin's laboratory on the permanganate promoted oxidative cyclisation of deuterated 1,5-dienes.[69] He proposed a mechanism based on [3+2] cycloadditions (Scheme 2.3).



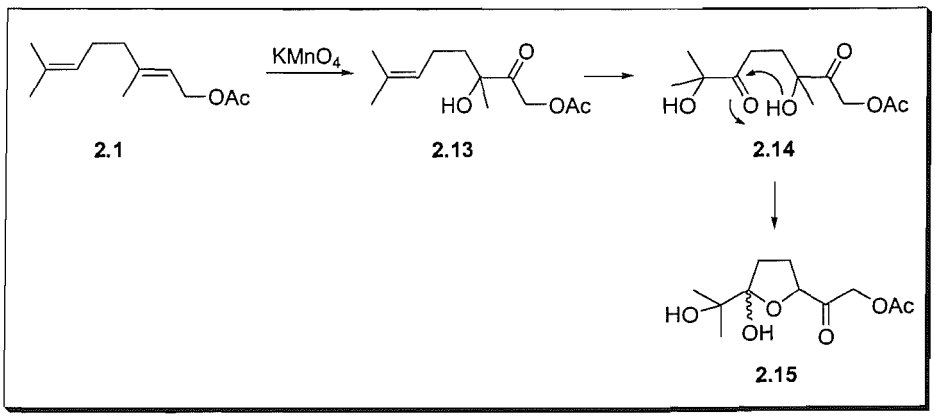
Scheme 2.3 Oxidative cyclisation mechanism proposed by Baldwin *et al.*

The first step of the proposed mechanism involves a [3+2] cycloaddition of permanganate to the more reactive double bond forming an unreactive cyclic Mn(V) ester **2.9** (Scheme 2.3). This then undergoes oxidation to a reactive Mn(VI) species **2.10**, facilitating a second [3+2] cycloaddition to the remaining double bond to form

intermediate **2.11**, all on the same face. Hydrolysis affords the *cis*-THF-diol and by-product MnO_2.

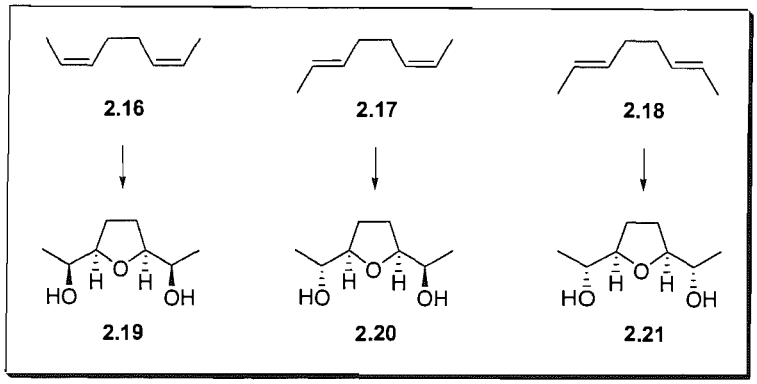
This mechanism was corroborated by Lee *et al.*[70] and Wolfe and Ingold[71] since they reported indirect evidence for the presence of a Mn(V) ester. Wolfe and Ingold proposed that the intermediate must have a co-ordination number greater than four. Strangely however, they found that when the reaction was carried out in ^{18}O labelled water, an ^{18}O atom was incorporated into the THF-diol.[71] Since neither mechanism could explain this they concluded that a decision concerning the exact nature of the Mn(V) intermediate should be deferred, and to this day the precise details of the mechanism remain unresolved.

The yield for the oxidative cyclisation reported in early work was modest. This can be explained by a number of side-reactions occurring which lowered the yield. The Mn(V) ester **2.9** could be hydrolysed prior to the second cycloaddition, which in the case of geranyl acetate **2.1** leads to the formation of an α-hydroxy ketone **2.13** (Scheme 2.4). Oxidation of the remaining double bond and subsequent hydrolysis would lead to *bis*-α-hydroxy ketone **2.14**, which could cyclise to produce lactol **2.15**.



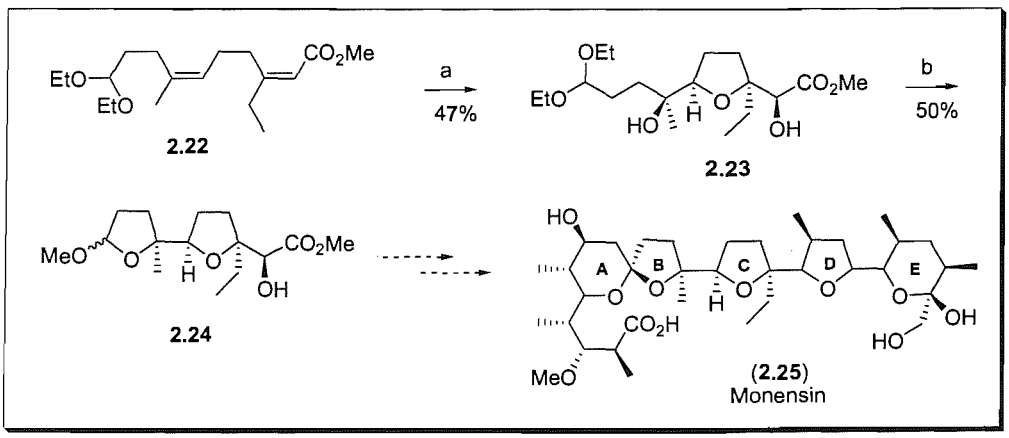
Scheme 2.4 By-products of the oxidative cyclisation.

Walba *et* al. went on to investigate the effect of the double bond geometry on the relative stereochemistry (Scheme 2.5).[67] They found that altering the geometry inherently changed the stereochemistry of the hydroxyl groups. They also looked at the selectivity of the reaction and found that the ratio of *cis*-THF/*trans*-THF was at least 97:3.



Scheme 2.5 The effect of alkene geometry on the relative stereochemistry.

With this information in hand, Walba *et al.* went on to apply this chemistry to the synthesis of natural products.[72,73] They synthesised the B/C ring fragment of monensin (**2.25**), inserting the four stereogenic centres with correct relative stereochemistry in one step (Scheme 2.6).

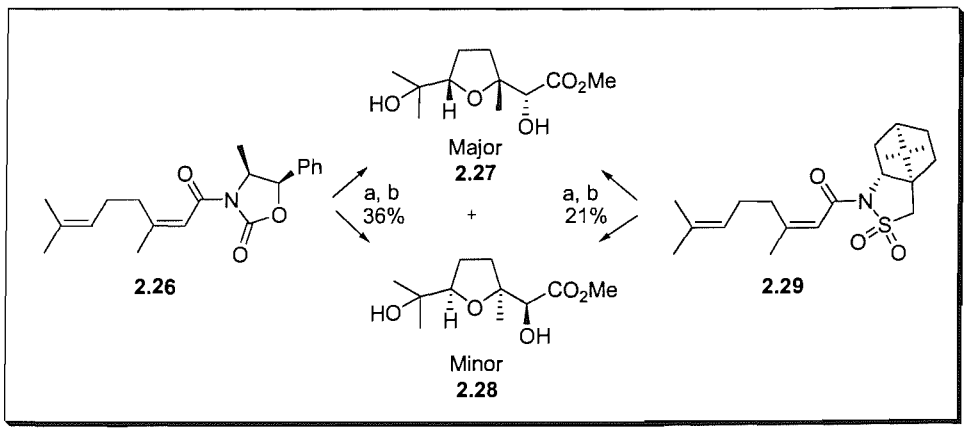


Scheme 2.6 Use of oxidative cyclisation in the synthesis towards monensin (**2.25**). *Reagents and conditions:* a) $KMnO_4$, acetone, H_2O, pH 7.5, CO_2, ebullition; b) $CH(OMe)_3$, TsOH, benzene.

Although there are two double bonds in **2.22** open to initial attack by permanganate, it is usually the electron-deficient double bond which reacts first. This can be attributed to electronic effects which have been shown to significantly affect the rate of olefin oxidation by permanganate.[74,75]

In 1990, Walba recognised that in order to realise the true potential of permanganate promoted oxidative cyclisations, the absolute stereochemistry would need to be controlled. He developed an asymmetric oxidative cyclisation[76] by making use of the fact that double bonds conjugated to a carbonyl group are more reactive to permanganate than aliphatic double bonds.[77] An amide linkage to Oppolzer's camphorsultam[78] or Evans oxazolidinone[79] thus enabled relative asymmetric induction.

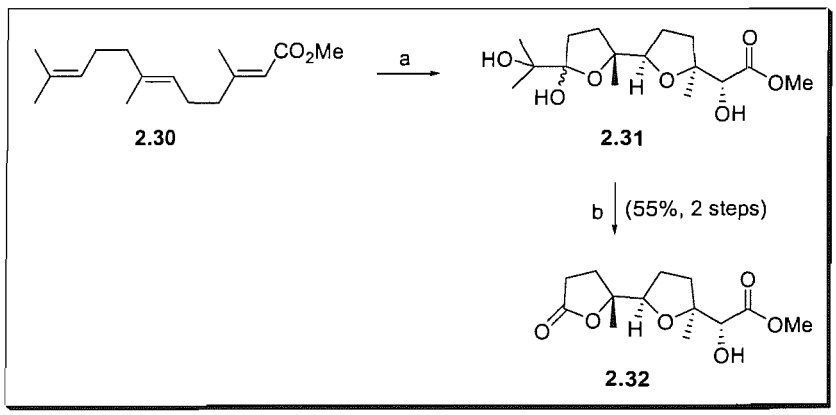
Oxidation of the oxazolidinone enoate **2.26** gave a 3:1 ratio of diastereomers, whilst oxidation with the camphorsultam enoate **2.29** gave a ratio in excess of 9:1 (Scheme 2.7). The low selectivity shown by the oxazolidinone enoate can be rationalised by the fact that it requires Lewis-acid chelation to give high selectivity. As K^+ is not a strong Lewis acid and the reaction was conducted in a polar co-ordinating solvent the selectivity was compromised.



Scheme 2.7 Asymmetric induction in the oxidative cyclisation reaction. *Reagents and conditions:* a) $KMnO_4$, acetone, H_2O, CO_2, ebullition; b) CH_3OMgBr.

Walba found that the major diastereomer **2.27** formed from oxidative cyclisation of the camphorsultam derived enoate **2.29** (Scheme 2.6) is consistent with attack from the *Re* face of the conjugated double bond. Camphorsultam enoates have been used as starting points in many acetogenin and polyether antibiotic fragment syntheses,[80-83] for example Kocienski *et al.* used this approach to synthesise the THF core of polyether ionophore salinomycin.[80]

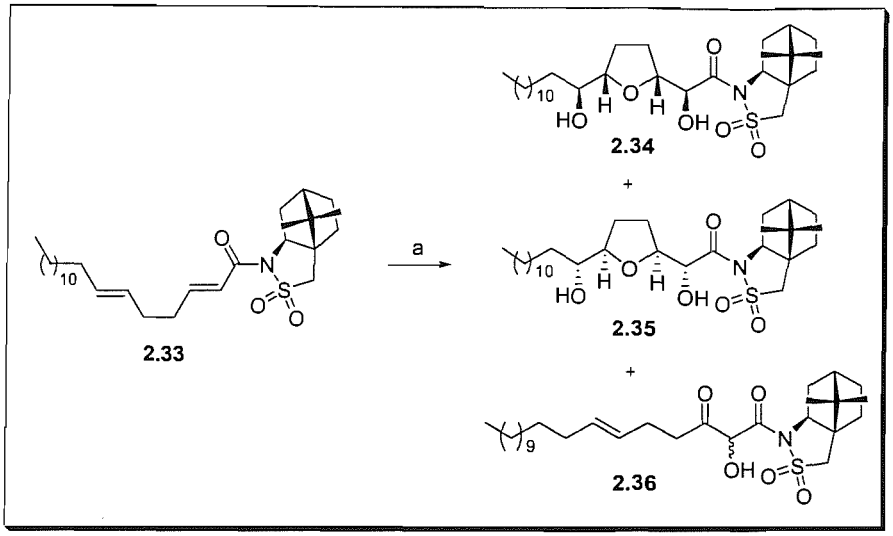
The permanganate promoted oxidative cyclisation of trisubstituted olefins is relatively high yielding and has also been used as the starting point in the synthesis of polyether antibiotic fragments.[76,84] Early work in our group focused upon the oxidation of trisubstituted 1,5,9-trienes.[85,86] After optimising the pH of the oxidative cyclisation reaction, lactone **2.32** could be accessed in good overall yield, furnishing an excellent intermediate for elaboration (Scheme 2.8).



Scheme 2.8 Oxidation of a 1,5,9-triene to a THF-lactone. *Reagents and conditions:* a) $KMnO_4$ (3 eq), AcOH (4 eq), pH 6.2 buffer, acetone-H_2O, −20 °C; b) $NaIO_4/SiO_2$, CH_2Cl_2.

Many reports however, have claimed that the permanganate promoted oxidative cyclisation of mono- and di-substituted olefins are far less encouraging than with trisubstituted olefins, with low isolated yields of the cyclisation product (5-33%).[87,88] Recent work in our group showed that when the conditions used to oxidise trisubstituted olefin **2.30** were applied to dienoyl sultam **2.33**, a low yield of 18% was obtained (ratio of **2.34/2.35** = 6.5:1); also isolated was the α-hydroxy ketone **2.36** (40%) (Scheme 2.9).

These findings were attributed to a lack of substrate solubility and hence the use of a phase-transfer reagent was investigated, as well as a number of different solvents and additives (Table 2.1).



Scheme 2.9 Oxidative cyclisation of dienoyl sultam **2.33**. *Reagents and conditions:* a) See Table 2.1.

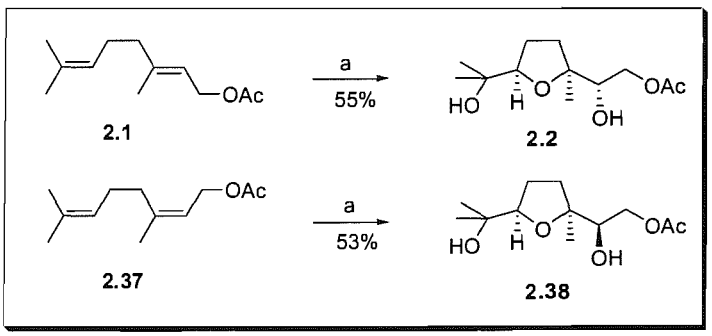
Entry	Solvent	AcOH	**2.34/2.35**[a] (d.r.)[b]
1	Acetone/H_2O/ pH 6.2 buffer	3 eq	21%, (7:1)
2[c]	CH_2Cl_2	8 eq	31%, (6.5:1)
3[c]	Toluene	8 eq	50%, n/a
4[c]	EtOAc	8 eq	55%, (6:1)
5[c]	Acetone	16 eq	62%, (6.5:1)
6[c]	Acetone	Co-solvent[d]	75%, (6.5:1)[e]

Table 2.1 The effects of varying the conditions of the oxidative cyclisation (see Scheme 2.9). [a] Combined isolated yield of THF-diols **2.34** and **2.35**; [b] Ratio of **2.34/2.35** as estimated from ^{1}H NMR; [c] Reaction carried out with the addition of 10 mol% adogen 464; [d] acetone/AcOH (3:2); [e] Reaction carried out without adogen 464 gave identical results.

The results showed that a mixed solvent system of acetone/AcOH (3:2) greatly improved the yield. Furthermore, no phase-transfer catalyst was needed since the substrate and oxidant were sufficiently soluble in this system. Interestingly, there appeared to be little change in d.r. when varying the polarity of the solvent. This implied that chelation control was not involved in determining the initial facial attack of the enoate double bond.[76]

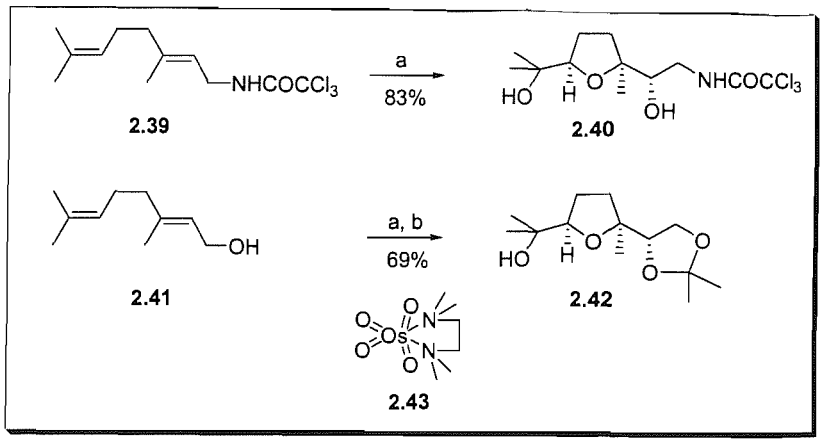
2.2 Osmium Tetroxide Catalysed Oxidative Cyclisation

Following the substantial amount of progress that had been made in the permanganate promoted oxidative cyclisation, Piccialli *et al.* investigated the use of osmium tetroxide in this reaction[89] They reported that 5 mol% of osmium tetroxide, when used in conjunction with sodium periodate as co-oxidant, induced the oxidative cyclisation of 1,5-dienes. Both geranyl acetate **2.1** and neryl acetate **2.37** were oxidised to the corresponding *cis*-THF-diols **2.2** and **2.38** in 55% and 53% yield respectively (Scheme 2.10).



Scheme 2.10 Oxidative cyclisation using osmium tetroxide. *Reagents and conditions:* a) OsO_4 (5 mol%), $NaIO_4$, DMF.

Donohoe *et al.* used an osmium tetroxide/TMEDA complex under acidic conditions to effect the oxidative cyclisation reaction.[90] They successfully oxidised 1,5-dienes to the corresponding *cis*-THF-diols in high yield using stoichiometric amounts of osmium tetroxide (Scheme 2.11). Recently, they have reported a catalytic version of this reaction using Me_3NO as the stoichiometric oxidant, with yields of the oxidative cyclisation of 1,5-dienes ranging from 60-95%.[91]



Scheme 2.11 Oxidative cyclisation using osmium tetroxide/TMEDA. *Reagents and conditions:* a) OsO_4, TMEDA, CH_2Cl_2, −78 °C; then MeOH, HCl, rt; b) $(MeO)_2CMe_2$, TFA.

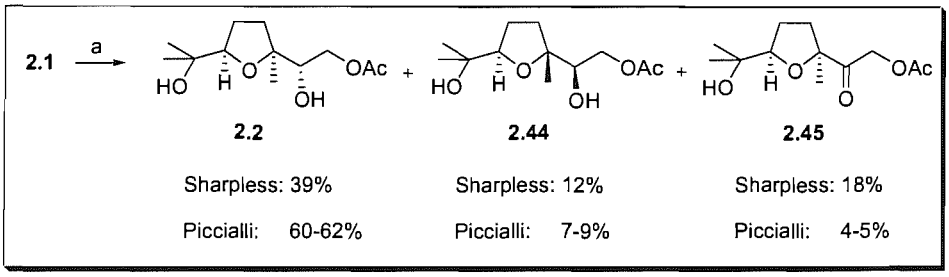
It is proposed that the osmium tetroxide/TMEDA complex acts as a willing hydrogen bond acceptor, and regioselectivity is therefore achieved using allylic amide or allylic alcohol substrates since they can direct the complex to the adjacent double bond. Mechanistically, the initial step involves the formation of an osmate ester, directly analogous to the first step of the permanganate-mediated oxidative cyclisation mechanism postulated by Baldwin[69] (Scheme 2.3).

Donohoe speculated that the role of the acid was to protonate the oxo ligands thus making the metal more electrophilic, or to promote whatever ligand exchange is necessary for the cyclisation to proceed. This is consistent with the water labelling experiments carried out by Wolfe and Ingold in permanganate-mediated oxidative cyclisations.[71] As previously mentioned, they suggested ligand exchange occurred since a labelled oxygen was incorporated into the THF-diol.

2.3 Ruthenium Tetroxide Catalysed Oxidative Cyclisation

In 1981, Sharpless *et al.* were using a catalytic ruthenium tetroxide/periodate system in order to effect the oxidative cleavage of double bonds.[92] When this system was applied to geranyl acetate **2.1**, they observed oxidative cyclisation, a process Sharpless termed as 'abnormal oxidation' (Scheme 2.12).

The yield of the oxidative cyclisation was modest and was accompanied by a *cis*-2-keto derivative by-product **2.45** (Scheme 2.12). More interestingly however, control of the geometry across the THF ring was poor, with a *cis*-THF-diol **2.2**/*trans*-THF-diol **2.44** ratio of 3:1. Sharpless postulated that the *trans*-THF-diol formed in the presence of ruthenium tetroxide and not with permanganate because of differences in bond lengths and geometries in comparable intermediates. The second row transition metal ruthenium has longer bond lengths than permanganate and hence can allow the pathway leading to *trans*-THF-diols.

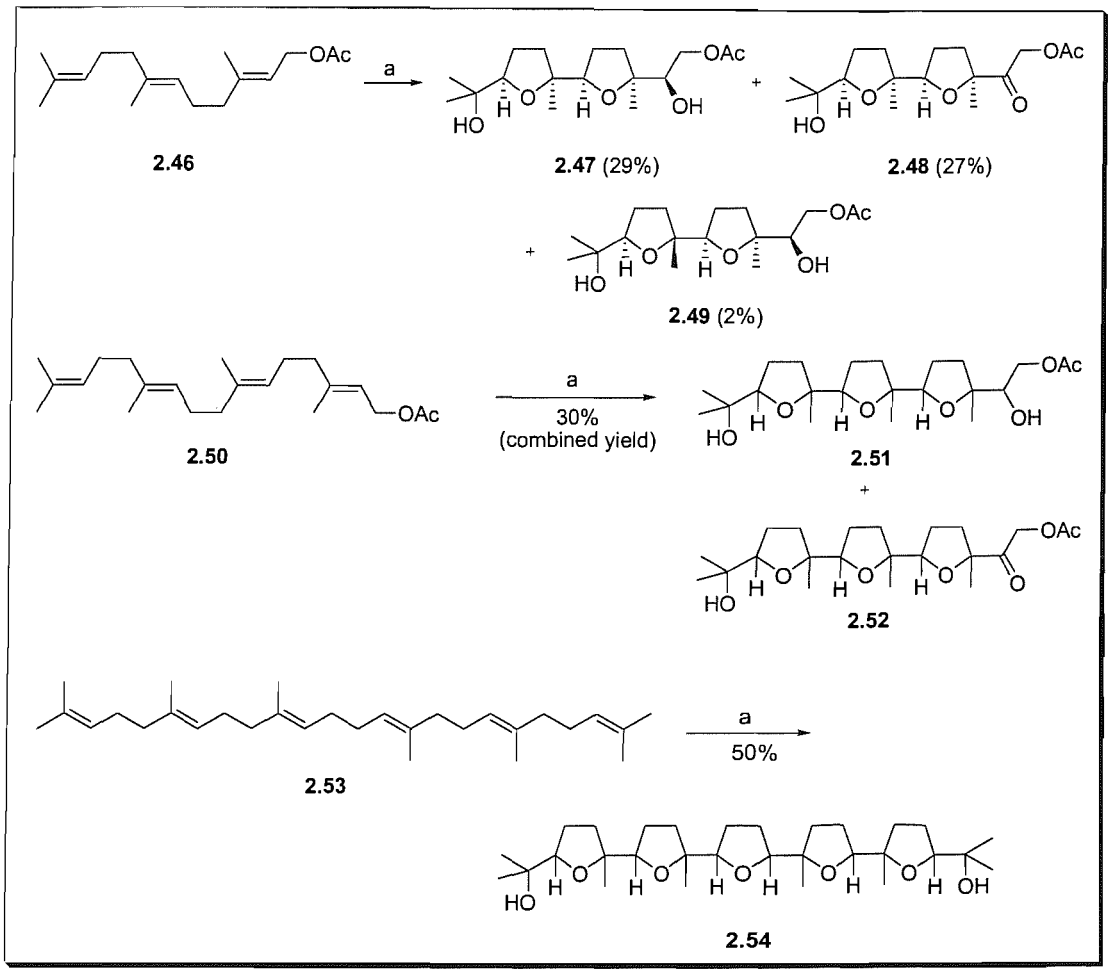


Scheme 2.12 Oxidative cyclisation using ruthenium tetroxide. *Reagents and conditions:* a) Sharpless: $RuCl_3 \cdot (H_2O)_n$ (2.2 mol%), $NaIO_4$ (4.1 eq), CCl_4, CH_3CN, H_2O; Piccialli: $RuO_2 \cdot 2H_2O$ (4 mol%), $NaIO_4$ (4 eq), EtOAc, CH_3CN, H_2O, 0 °C.

In order to address the problem of low yield, Albarella *et al.*[93] and more successfully Piccialli *et al.* investigated the oxidative cyclisation of geranyl acetate **2.1** with ruthenium tetroxide (Scheme 2.12).[94] Piccialli used this substrate because previous work in their group had shown that high yields could only be obtained when one of the double bonds was trisubstituted. The yield and efficiency of the oxidative cyclisation of geranyl acetate **2.1** was greatly improved under their new conditions, with an improved *cis*/*trans* ratio (8:1) and a reduction in yield of the by-product.

In a continuation of this work, Piccialli *et al.* looked at the ruthenium tetroxide-mediated oxidative polycyclisation process. This transformation installs up to five contiguous THF rings in a single step.[95]

Polycyclisation of farnesyl acetate **2.46** afforded *bis*-THF-diol **2.47** (29%) and the corresponding C-2 ketone **2.48** (27%) as major products, together with *trans*-THF isomer **2.49** (2%) as a minor product (Scheme 2.13). The remaining mass balance was accounted for by cleavage products. The structural relationship between **2.47** and **2.48** was confirmed by oxidation of **2.47** to **2.48**.



Scheme 2.13 Polycyclisation using ruthenium tetroxide. *Reagents and conditions:* a) $RuO_2.2H_2O$ (20 mol%), $NaIO_4$ (varying amounts: **2.46** → 4 eq, **2.49** → 5 eq, **2.52** → 8 eq), $EtOAc/CH_3CN/H_2O$ (3:3:1).

The first THF ring is formed with *cis*-stereoselectivity in accordance with the known reactivity of RuO_4.[92] The *cis*-stereoselectivity of the second THF ring can be explained by invoking recent results from the related rhenium(VII) chemistry reported by Sinha *et al.*[96] They postulated that the stereochemistry of the second cyclisation depends on the relative configuration of the two vicinal oxygen atoms installed after

the first cyclisation, and the ability of the first THF ring to chelate to the metal. A *threo* relationship between the two vicinal oxygens leads to a *cis*-THF, whilst an *erythro* relationship leads to a *trans*-THF. Piccialli and co-workers found that their results were in accordance with the former of these two rules.

The effect of varying the amounts of $RuO_2.2H_2O$ and $NaIO_4$ in the oxidation of farnesyl acetate **2.46** was investigated. It was found that when the amount of $RuO_2.2H_2O$ was kept constant, any increase in the amount of co-oxidant did not affect the yield of either product **2.47** or **2.48**. However, the amount of co-oxidant required for the reaction to go to completion does depend on the number of double bonds present in the starting material. They found that an extra equivalent of $NaIO_4$ was required for each additional double bond. When the polycyclisation reaction was carried out using 20 mol% of $RuO_2.2H_2O$, *bis*-THF-diol **2.47** was formed as the major product; when 90 mol% of $RuO_2.2H_2O$ was used, C-2 ketone **2.48** was formed as the major product. The amount of *trans*-THF isomer **2.49** remained low throughout these experiments (< 2.5%).

Attempts to decrease the amount of C-2 ketone **2.48** formed in the reaction by reducing the reaction time led to incomplete reaction and the ratio of products **2.47**/**2.48** remained unchanged.

Reduction of a ketone flanking a *cis*-THF ring had been reported with high diastereoselectivity on a very similar system to C-2 ketone **2.48**.[97] Piccialli *et al.* attempted the reduction of C-2 ketone **2.48** and obtained a 2:1 mixture of **2.47** and its C-2 epimer. Recycling the epimer *via* an oxidation/reduction sequence gave desired *bis*-THF-diol **2.47** in 79% yield over three steps. This improved the total yield of *bis*-THF-diol **2.47** from farnesyl acetate **2.46** from 29% to 51%.

Piccialli *et al.* went on to apply polycyclisation to various polyenes. Oxidation of geranylgeranyl acetate **2.50** gave a mixture of *tris*-THF diol **2.51** and the corresponding *tris*-THF ketone **2.52** in a combined 30% yield (Scheme 2.13). Oxidation of squalene **2.53** afforded *penta*-THF-diol **2.54** in 50% yield, corresponding to 87% per cyclisation.

2.4 Conclusions

There are several transition metal oxo species that have been reported to effect the oxidative cyclisation of 1,5-dienes. Permanganate oxidations are high-yielding, however they require stoichiometric amounts of oxidant; the analogous osmium tetroxide and ruthenium tetroxide oxidative cyclisations have an advantage because they are catalytic. These two transition metal oxo species have further benefits. Oxidative cyclisations with osmium tetroxide proceed in high yield, whilst ruthenium tetroxide has been shown to effect polycyclisation, a transformation which has great potential in the synthesis of natural products containing adjacent-THF rings.

However, permanganate has one major advantage over the other oxidants - it has been used effectively in asymmetric oxidative cyclisations, affording optically-enriched THF diols. The efficient synthesis of natural products ultimately requires control of the stereoselectivity; permanganate, when used in conjunction a chiral phase-transfer catalyst or in the oxidation of a substrate containing a chiral auxiliary, effectively meets this requirement.

Chapter 3

An Introduction to the Proposed Work

3.1 Synthesis Towards *cis*-Sylvaticin *via* Permanganate Promoted Bi-Directional Oxidative Cyclisation

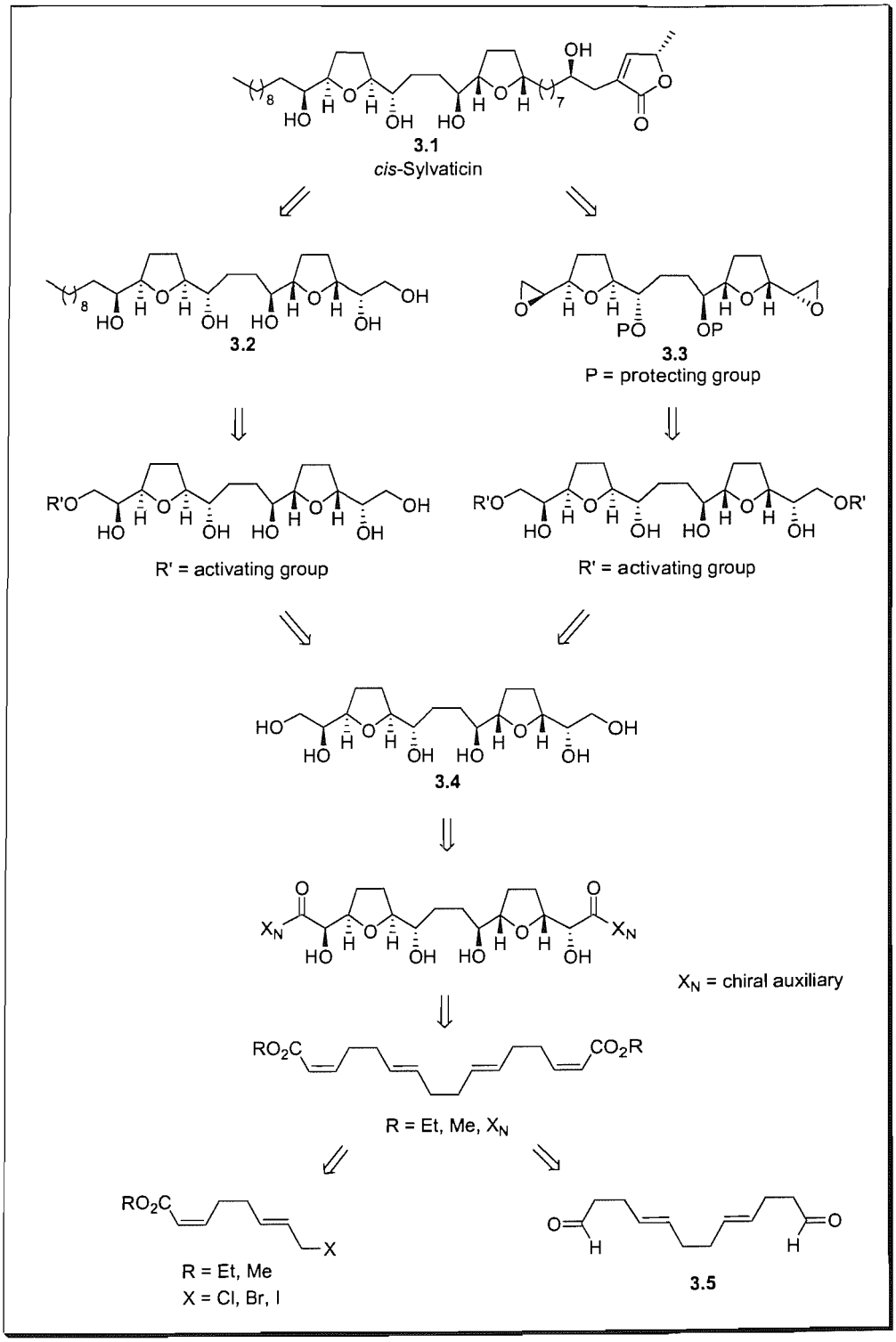
The permanganate promoted oxidation of dienes is known to afford *cis*-THF-diols in good yield inserting up to four new stereogenic centres in one step. The *mono*-THF acetogenin *cis*-solamin[81,82] and *bis*-adjacent acetogenin membranacin[83] have been successfully synthesised within our group using this reaction as a key step. Up until now, the permanganate promoted oxidation of polyenes has only been demonstrated on dienes and trienes, affording the *mono*-THF and adjacent *bis*-THF products respectively. In order to extend the synthetic utility of this reaction, we are going to investigate the bi-directional oxidative cyclisation of a C_2-symmetric tetraene. This powerful transformation will produce a non-adjacent *bis*-THF tetrol from an achiral substrate, effectively inserting eight new stereogenic centres in one step.

Asymmetric induction can be achieved *via* the use of Oppolzer's sultam.[98] Using the results from previous asymmetric oxidative cyclisations which utilised this chiral auxiliary,[76,80] we can predict which face of the tetraene will be attacked.

Initially, asymmetric oxidative cyclisations will be carried out on an easily accessible tetraene substrate in order to assess the viability of the bi-directional oxidative cyclisation. A tetraene possessing the *trans-trans-trans-trans* geometry will be investigated, and once optimal conditions have been established, these will be applied to the *cis-trans-trans-cis* tetraene substrates.

If a C_2-symmetric tetraene is used, then desymmetrisation will have to occur at some point in the synthesis. We are therefore going to investigate two approaches to *cis*-sylvaticin **3.1**, effecting desymmetrisation at different junctures (Scheme 3.1). Hexaol **3.4** can be desymmetrised by *mono*-activation, resulting in an intermediate which can then undergo further elaboration to pentaol **3.2**.

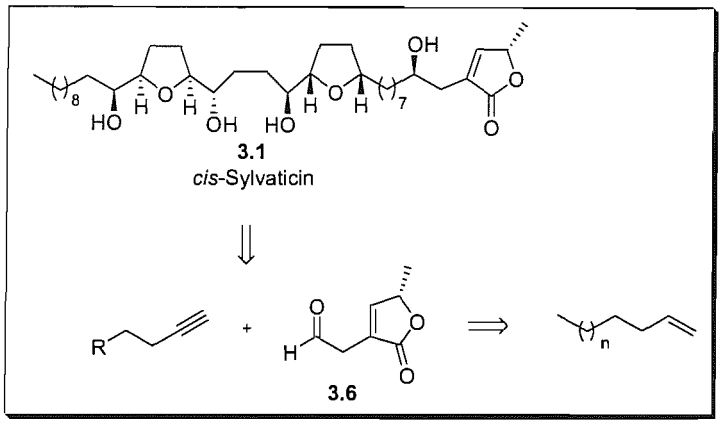
Diepoxide **3.3** can be ring-opened on the left-hand side of the molecule with nonylmagnesiumbromide leaving the other epoxide free for elaboration.



Scheme 3.1 Retrosynthetic analysis of *cis*-sylvaticin **3.1** showing both a linear and bi-directional approach.

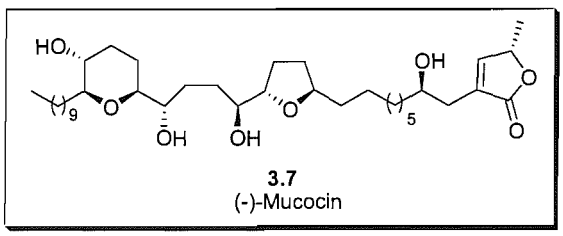
3.2 Synthesis of the Butenolide Portion

Synthesis of the right-hand side of the molecule will focus upon the use of butenolide aldehyde **3.6** (Scheme 3.2). This will be obtained from a terminal alkene using Trost's butenolide methodology.[99] The left hand side of the molecule could be converted into a terminal alkyne which would be coupled to butenolide-aldehyde **3.6** *via* an asymmetric alkynyl addition.



Scheme 3.2 Retrosynthetic analysis of the butenolide portion.

In the synthesis of (−)-mucocin **3.7** (Scheme 3.3), Evans *et al.*[100] installed the right-hand side of the molecule using an asymmetric alkynyl addition to butenolide-aldehyde **3.6** in high yield (81%) and with good selectivity (d.r. = 20:1).



Scheme 3.3 The *Annonaceous* acetogenin (−)-mucocin **3.7**.

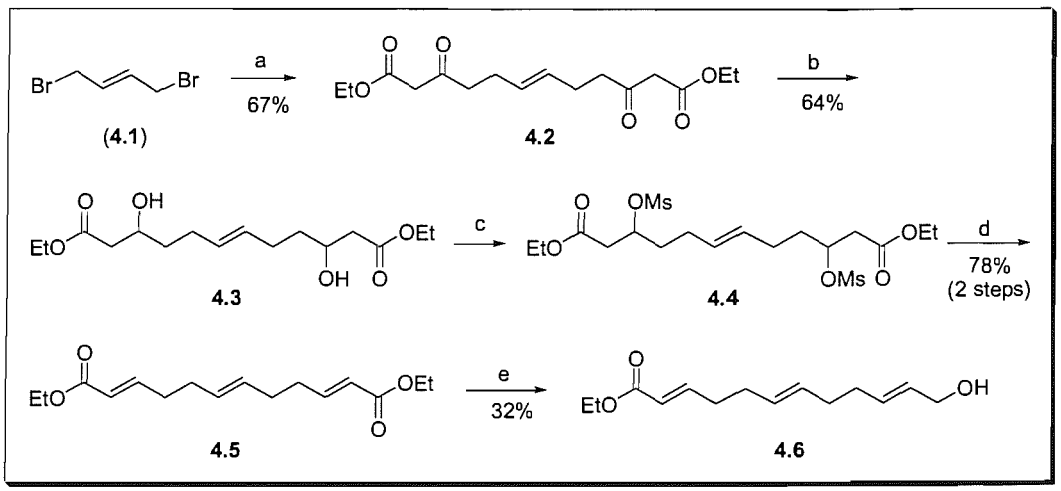
Chapter 4

Synthesis of a Non-Adjacent *bis*-THF Intermediate

The following chapter summarises our initial efforts towards the core of *cis*-sylvaticin, starting with the synthesis of the tetraene substrate for bi-directional oxidative cyclisation.

4.1 Synthesis and Extension of a Triene

Triene **4.5** was synthesised with a view to extending to a tetraene. Dialkylation of dibromide (**4.1**) produced diketone **4.2** which was subsequently reduced to give diol **4.3** in reasonable yield (Scheme 4.1). Activation of the alcohols and subsequent elimination gave triene **4.5** in good overall yield.



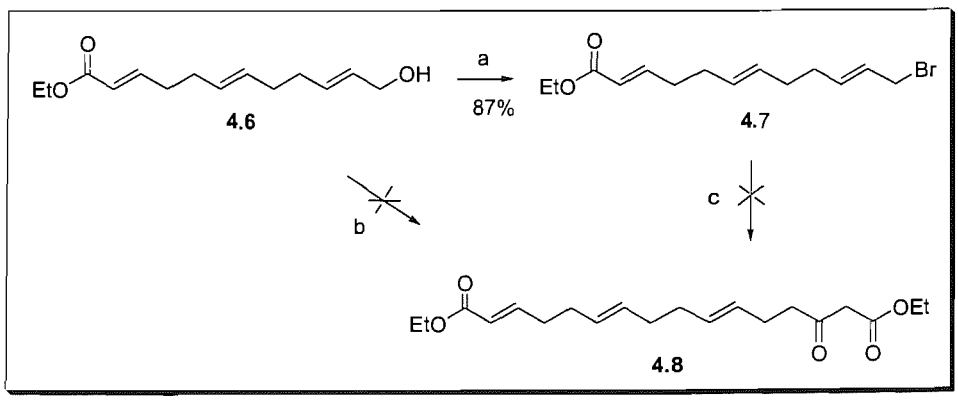
Scheme 4.1 Synthesis of a triene for extension to a tetraene. *Reagents and conditions:* a) EAA, LDA, THF, −70 °C; b) $NaBH_4$, EtOH, 0 °C; c) Et_3N, MsCl, 0 °C; d) DBU, CH_2Cl_2 , 0 °C; e) DIBAL-H, THF, −60 °C.

In order to extend the triene to a tetraene, *mono*-reduction of one of the esters had to be accomplished, to enable activation/halogenation and alkylation. It was thought that one equivalent of DIBAL-H may reduce one ester to the aldehyde and then once

formed, sodium borohydride could reduce the aldehyde selectively to the alcohol since this rarely reacts with esters.

After the addition of one equivalent of DIBAL-H there was no aldehyde present (checked by TLC stains). The diester had been reduced to the more reactive aldehyde but was immediately reduced further to give alcohol **4.6** (Scheme 4.1). Substantial amounts of diester **4.5** remained so more DIBAL-H was added. This resulted in a by-product with both esters reduced. It was found that after repeating the reduction with varying amounts of DIBAL-H, 1.8 equivalents gave the optimum result, in that the hydroxyester **4.6** was the major product, obtained in 32% yield; starting material (31%) was also recovered.

Mesylation of alcohol **4.6** and reaction of the crude mixture with the dianion of EAA should have resulted in diester **4.8** (Scheme 4.2). Unfortunately the mesylate was extremely unstable and decomposed to give a mixture of eliminated product and starting material. Conversion of alcohol **4.6** to the bromide **4.7** was therefore attempted using phosphorus tribromide. The bromide **4.7** was formed but in very low yield (< 5%), with the majority of the starting material destroyed. A subsequent attempt using triphenylphosphine and carbon tetrabromide produced the bromide **4.7** in 87% yield (Scheme 4.2). The product was sufficiently stable to silica so purification was possible.

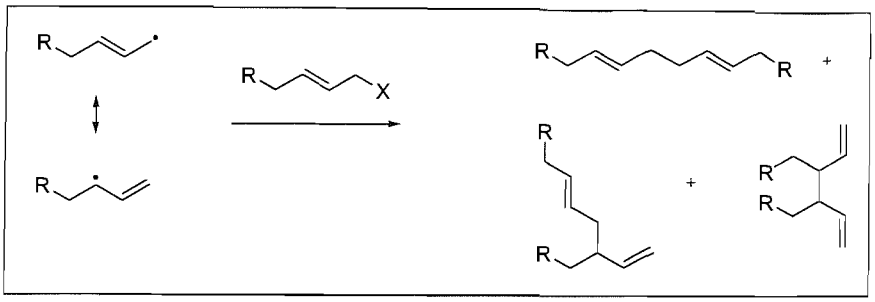


Scheme 4.2 Attempted extension to the tetraene. *Reagents and conditions:* a) CBr_4, PPh_3, CH_2Cl_2, rt; b) (i) Et_3N, MsCl, 0 °C; (ii) EAA, diisopropylamine, *n*-BuLi, THF, −70 °C; c) EAA, LDA, THF, −70 °C.

Attempted alkylation of bromide **4.7** to produce diester **4.8** was not successful (Scheme 4.2). After leaving the reaction to warm to rt, no product was evident and starting material was recovered. It is thought that deprotonation of the methylene adjacent to the enoate was the main problem, and that the bromide was relatively too stable for alkylation to compete with deprotonation.

4.2 Wurtz Coupling

A further effort towards the tetraene focused upon Wurtz coupling. It was envisaged that a diene terminating in an allylic halide could be dimerised with the use of an appropriate metal. If successful this could be extended to dimerisation of two THF fragments, each individually elaborated, thus removing the need for desymmetrisation. The results of all attempted Wurtz couplings are summarised in Table 4.1. In all cases the products could not be isolated as their non-polar nature meant they co-eluted during chromatography. It is noteworthy that only the *trans* isomers were formed as shown by ^{1}H NMR spectroscopy.



The expected Wurtz coupling product and two possible internal coupling (IC) products (see Table 4.1).

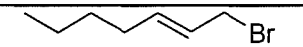
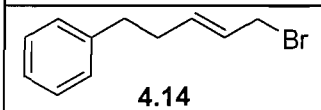
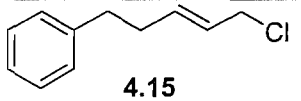
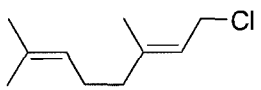
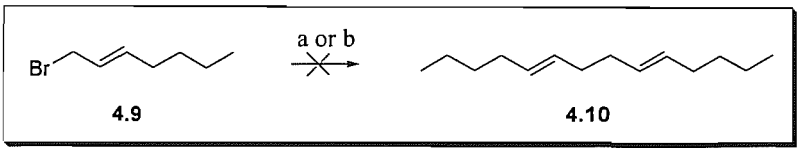
Substrate	Metal	Eq	Desired Product	Internal Coupling[a]	P/IC ratio[b]	SM/P Ratio[c]	Mass recovery
 **4.9**	Mn	1	Yes	No	n/a	1:3	10%
	Zn	1	No	No	n/a	n/a[d]	15%
 **4.14**	Ba	1	Yes	No	n/a	10:1	78%
	Ba	2	Yes	Yes	3:1	1:1	50%
 **4.15**	Ba	1.5	Yes	Yes	8:1	2:1	80%
	Ba	3	Yes	Yes	1:1:1	1:3	30%
 **4.21**	Mn	1	Yes	Yes	1:2:1	n/a[d]	18%
	Zn	1	No	No	n/a	n/a[d]	24%
	Ti	1	Yes	Yes	1:3:1	n/a[d]	35%
	Ba	1.5	Yes	Yes	8:2:1	n/a[d]	72%

Table 4.1 Wurtz coupling using different substrates, metals and conditions. [a] Includes either of the two possible internal coupling (IC) products; [b] Product (P)/Internal Coupling (IC) product ratio (if there are two internal coupling products, the last two numbers of the ratio represent these); [c] Starting Material (SM)/Desired Product (P) ratio as shown by GCMS; if retention time of the desired product was not known, the most intense peak corresponding to the product was used; [d] Not applicable (n/a) as starting material was consumed.

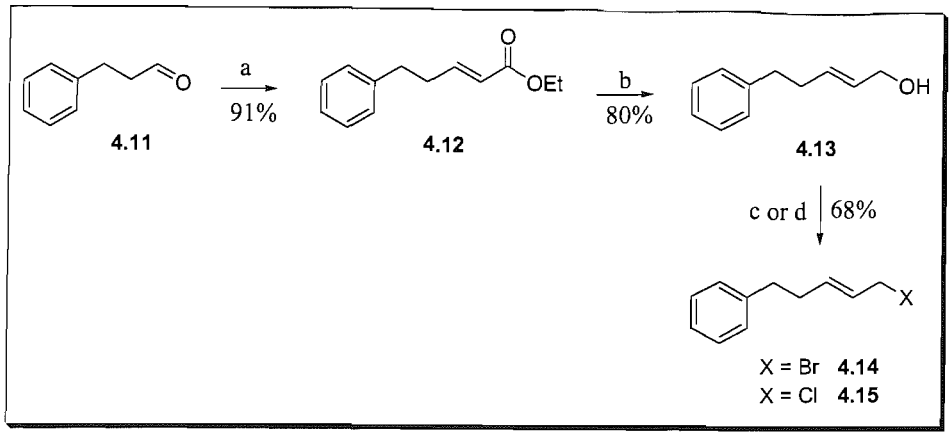
Wurtz couplings using manganese powder have been reported in the presence of carboxylic acids[101] and such a property would be useful in our synthesis. Initial couplings were attempted on the easily obtainable allylic bromide **4.9** which was coupled to form diene **4.10** in the presence of one equivalent of manganese powder (Scheme 4.3).



Scheme 4.3 Initial Wurtz coupling in the presence of manganaese and zinc. *Reagents and conditions:* a) Mn, $CuCl_2$, H_2O, rt; b) Zn, NH_4Cl, H_2O.

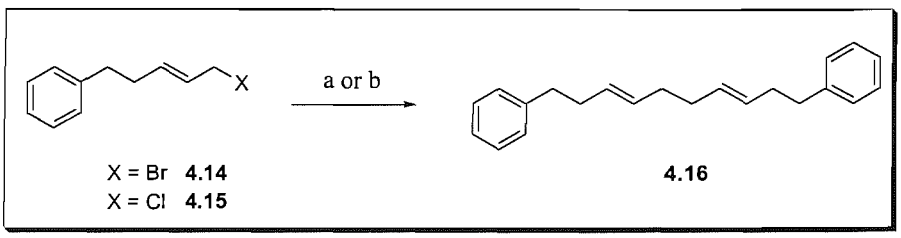
The reaction afforded several products as shown by GCMS, many with low retention times. The GCMS trace showed one of these peaks corresponded to diene **4.10** however the crude yield was very low (10%), hence manganese was not a viable reagent. The same reaction using one equivalent of zinc powder afforded many products but none of these corresponded to product as shown by GCMS. The mass recovery was also poor (15%).

It was deemed appropriate to change substrate at this juncture to facilitate product characterisation. A substrate containing a phenyl ring and with fewer methylene groups was chosen. Synthesis of allylic halides **4.14** and **4.15** began with the readily available aldehyde **4.11** (Scheme 4.4). Horner-Wadsworth-Emmons (HWE) olefination[102,103] afforded *trans*-enoate **4.12**, which was reduced to give allylic alcohol **4.13** in high yield. This was converted to allylic bromide **4.14** and allylic chloride **4.15**, both in 68% yield.



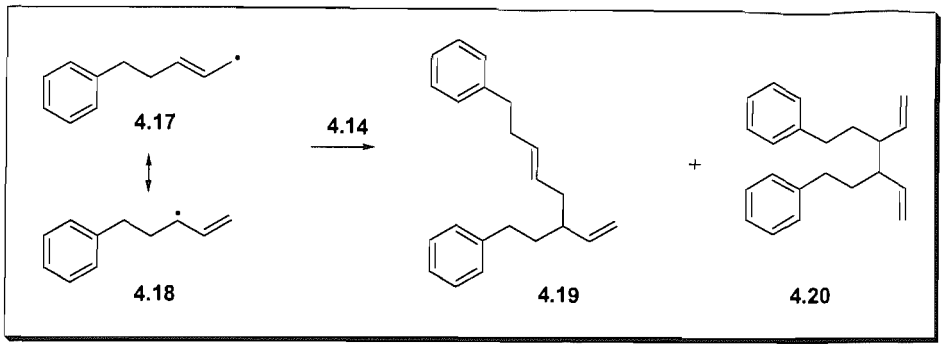
Scheme 4.4 Synthesis of allylic halides **4.14** and **4.15**. *Reagents and conditions:* a) triethylphosphonoacetate, NaH, THF, rt; b) DIBAL-H, THF, −60 °C; c) CBr_4, PPh_3, CH_2Cl_2, rt; d) Et_3N, MsCl, LiCl, DMF, 0 °C.

Wurtz coupling of allylic bromide **4.14** using one equivalent of manganese (Scheme 4.5) gave two peaks corresponding to the molecular weight of diene **4.16** and a starting material peak, as shown by GCMS.



Scheme 4.5 Couplings using allylic halides **4.14** and **4.15**. *Reagents and conditions:* a) Mn, $CuCl_2$, H_2O, rt; b) Li, biphenyl, BaI_2, THF, −78 °C.

^{1}H NMR spectroscopy showed that the desired diene **4.16** was present but also showed the presence of a terminal double bond. This could correspond to either of the internal coupling products **4.19** or **4.20** (Scheme 4.6). Protonation of intermediate **4.18** could also result in a terminal alkene; protonation of intermediate **4.17** had not occurred, however, as the methyl group was not apparent in the ^{1}H NMR spectrum. Allylic chloride **4.15** reacted identically to the bromide and the mass recovery was only 50% using either allylic halide.



Scheme 4.6 Possible internal coupling products.

Barium[104,105] was the next metal investigated. Lithium was used to form a biphenyl radical which reduced barium iodide to reactive barium metal. It was crucial to dry the barium iodide before use. This has to be carried out at the correct temperature for the correct amount of time and at the correct pressure, since changes in the lattice structure may also accompany the drying process.[105] It was found that heating barium iodide to 150 °C for two hours at 0.5 mmHg produced a pale yellow/grey powder which proved efficient in the coupling.

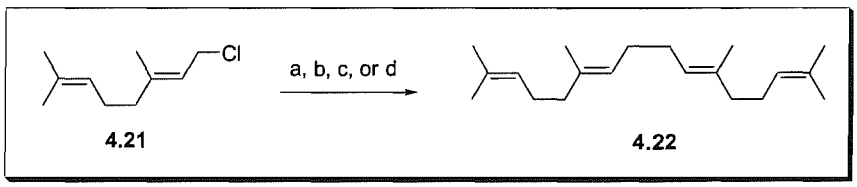
Initially, allylic chloride **4.15** was coupled using one equivalent of barium metal (Scheme 4.5). A single new peak corresponding to diene **4.16** was detected by GCMS; this was shown to be diene **4.16** by ^{1}H NMR spectroscopy. The mass recovery was good (78%) although the ratio of starting material to product was 10:1 as determined by GCMS; hence the amount of barium was increased in order to improve the conversion of starting material.

The coupling of **4.15** was attempted using 1.5 equivalents of barium metal (Scheme 4.5). The GCMS trace showed many peaks including starting material but of interest were two peaks corresponding to the molecular weight of desired diene **4.16** in a ratio of 8:1. The major product was confirmed to be diene **4.16** by ^{1}H NMR spectroscopy; the minor product was confirmed as one of the terminal double bond containing internal coupling products **4.19** or **4.20** (Scheme 4.6). The mass balance was promising (80%) although the ratio of starting material to product was still only around 2:1 as determined by GCMS.

The quantity of residual starting material remained high so two equivalents of barium metal were used in an attempt to increase the conversion. Allylic bromide **4.14** was used in the coupling (Scheme 4.5) and as expected a larger quantity of starting material had been consumed (ratio of starting material to product = 1:1 as determined by GCMS) however the mass recovery had decreased (50%). The selectivity was also compromised; the ratio of desired product **4.16** to internal coupling product **4.19** or **4.20** was reduced to 3:1 as shown by GCMS and ^{1}H NMR spectroscopy.

For completion, allylic chloride **4.15** was coupled using 3 equivalents of barium metal (Scheme 4.5). A larger amount of starting material had been consumed (ratio of starting material to product = 1:3 as determined by GCMS) however the GCMS trace was messy, showing three peaks corresponding to the molecular weight of desired diene **4.16**, as shown by GCMS (perhaps the desired product **4.16** and both internal coupling products **4.19** and **4.20**). Furthermore, the mass recovery was poor (30%). Thus it appeared that greater quantities of barium not only reduced the selectivity but also degraded the product and starting material.

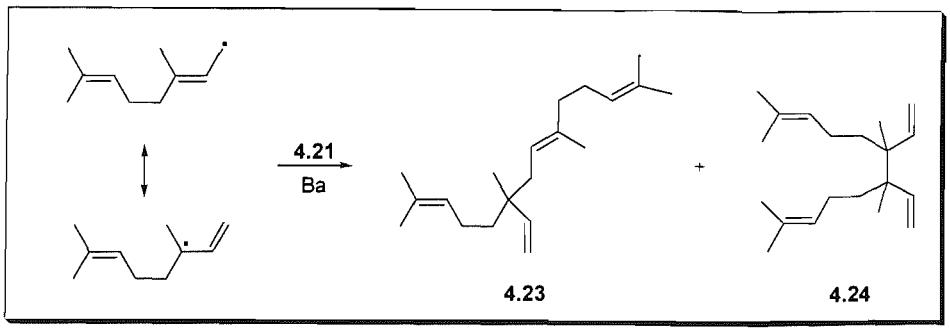
Couplings using geranyl chloride **4.21** (Scheme 4.7) were attempted since it is readily available and as a trisubstituted olefin, it can be compared and contrasted to the disubstituted olefins already investigated.



Scheme 4.7 Wurtz coupling with geranyl chloride. *Reagents and conditions:* a) Mn, $CuCl_2$, H_2O, rt; b) Zn, NH_4Cl, H_2O; c) Cp_2TiCl_2, ^{i}PrMgCl, THF, rt; d) Lithium, biphenyl, BaI_2, THF, −78 °C.

Initial coupling using one equivalent of manganese powder[101] proceeded with complete consumption of the starting material, producing three peaks corresponding to the molecular weight of desired product **4.22** as shown by GCMS (Scheme 4.7). ^{1}H NMR spectroscopy showed that these products were the desired diene **4.22** and the

internal coupling products **4.23** and **4.24** (Scheme 4.8). The mass recovery was poor (18%), in accordance with the coupling using diene **4.9** (Table 4.1).



Scheme 4.8 Possible internal coupling products.

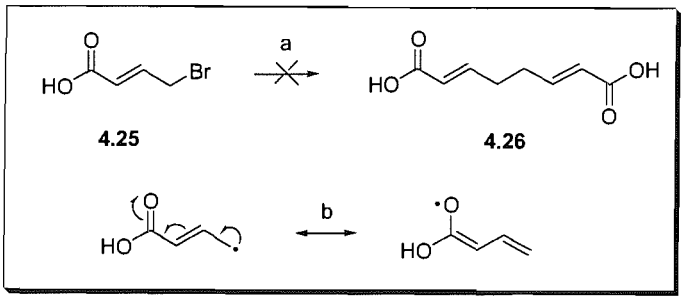
The same coupling using one equivalent of zinc (Scheme 4.7) proceeded with complete consumption of the starting material and many products as shown by GCMS, however there was no sign of the desired diene **4.22** and also a poor mass recovery (24%).

Titanium is another metal that has the capacity to induce allylic coupling of halides.[106] The active species is Cp_2TiCl which is formed *in situ* by the reduction of Cp_2TiCl_2 with ^{i}PrMgCl. Wurtz coupling with one equivalent of Cp_2TiCl (Scheme 4.7) proceeded with complete consumption of the starting material and showed three peaks corresponding to the molecular weight of desired diene **4.22**, as shown by GCMS. ^{1}H NMR spectroscopy showed that these products were the desired diene **4.22** (Scheme 4.7) and the internal coupling products **4.23** and **4.24** (Scheme 4.8). The mass recovery was not encouraging (35%).

Barium metal had proved to be fairly efficient in couplings using allylic halides **4.14** and **4.15** so the same protocol was used on geranyl chloride **4.21** (Scheme 4.7). The coupling was attempted using 1.5 equivalents of barium and this afforded diene **4.22** as the major product, together with a small amount of both internal coupling products **4.23** and **4.24** as shown by GCMS and ^{1}H NMR spectroscopy. Starting material remained (the ratio of starting material to product was 2:1) and the mass recovery was 72%. This result was similar to that obtained for disubstituted allylic chloride **4.15**

except that with the trisubstituted olefin, the selectivity was compromised as there were two internal coupling products formed instead of one.

Finally, to assess the effect of substrate polarity, a coupling using crotonoic acid **4.25** was attempted in the presence of one equivalent of manganese powder (Scheme 4.9). No reaction occurred indicating that perhaps the substrate is deactivated by the presence of the enoic acid group.



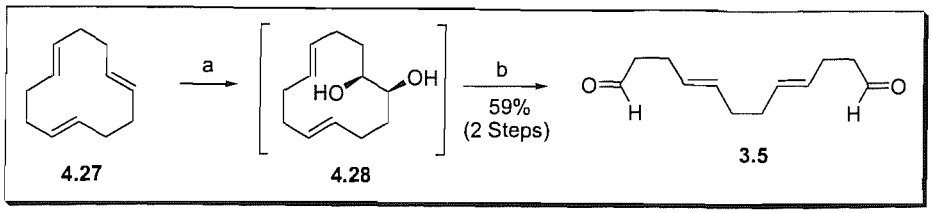
Scheme 4.9 Coupling of crotonic acid. *Reagents and conditions:* a) Mn, $CuCl_2$, H_2O, rt; b) delocalisation of the radical in crotonoic acid **4.25**.

It appears that Wurtz coupling works better for disubstituted double bonds over trisubstituted double bonds. The optimum conditions involve the use of barium metal, and as this is a highly toxic metal, its use is not attractive in synthesis. Our efforts therefore reverted back to the bi-directional approach, which required the synthesis of dialdehyde **3.5** (Scheme 3.1).

4.3 Synthesis of the Dialdehyde and Olefination

Synthesis of the dialdehyde was accomplished using an adaptation of the procedure described by Hoye *et al.*[107] Following their procedure which utilises Upjohn dihydroxylation conditions,[108] undesired polydihydroxylation occured giving dialdehyde **3.5** in a low 24% yield after oxidative cleavage (Scheme 4.10). Diol **4.28** is a white solid which appeared as the reaction progressed; after leaving the mixture to react further the solid became solubilised and polydihydroxylation occured. Hence it seemed logical to have a highly concentrated reaction mixture and to reduce the reaction time in order to promote crystallisation of the desired product. Gratifyingly,

the white solid remained and was collected by filtration. The yield of the reaction was increased and after oxidative cleavage, dialdehyde **3.5** was produced in 59% yield over two steps (Scheme 4.10).

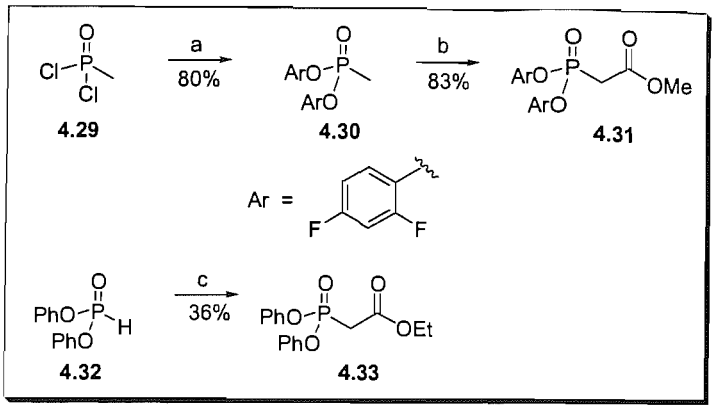


Scheme 4.10 Synthesis of dialdehyde **3.5**. *Reagents and conditions:* a) OsO_4, NMO, H_2O, CH_2Cl_2, rt; b) $NaIO_4$-SiO_2, H_2O, CH_2Cl_2, rt.

In order to obtain the correct relative stereochemistry in the oxidative cyclisation, we required the *cis*-α-*β*-unsaturated ester; this could be obtained *via* *cis*-selective olefination of dialdehyde **3.5**. A well-known *trans*-selective olefination for obtaining α-*β*-unsaturated esters is the HWE reaction.[102,103,109] The analogous *cis*-selective olefination has stimulated wide interest,[110-114] with the Still-Gennari[110] olefination or modified versions favoured in synthesis.[115-117]

These reactions use a phosphonoacetate reagent containing electron-withdrawing groups which are attached to phosphorus. It is thought that these electron-withdrawing groups make phosphorus more electropositive, thus enabling elimination of the aldehyde-phosphonoacetate adduct faster than adduct equilibration.[110] This process is assisted by a strongly dissociated base system such as KHMDS/18-crown-6.[110]

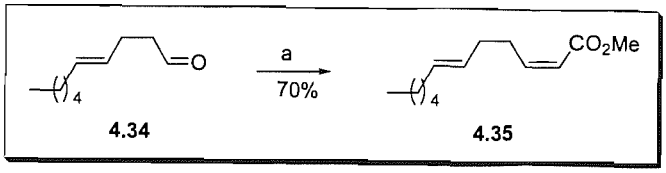
The Still-Gennari method is useful for trisubstituted α-*β*-unsaturated esters, however modifications were necessary for application of this procedure to the synthesis of disubstituted *cis*-α-*β*-unsaturated esters. These modifications have been described by Kokin *et al.*[114] and more recently Ando.[118,119] They both used different electron-withdrawing groups on phosphorus to produce disubstituted *cis*-α-*β*-unsaturated esters. Kokin and co-workers used a 2,4-difluorophenoxy group, whilst Ando used a phenoxy group (Scheme 4.11).



Scheme 4.11 Phosphonoacetate synthesis. *Reagents and conditions:* a) 2,4-difluorophenol, Et_3N, THF, 10 °C → reflux; b) LiHMDS, methyl chloroformate, THF, −78 °C → 0 °C; c) Et_3N, ethyl bromoacetate, THF, 0 °C → rt.

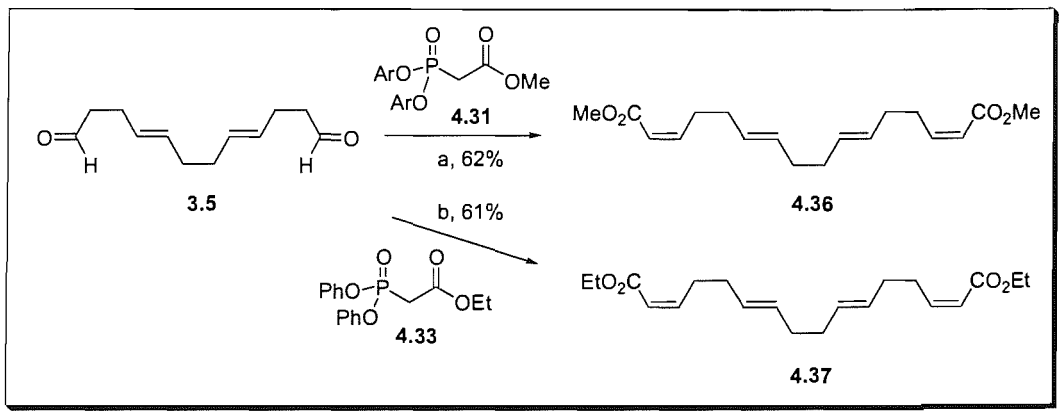
We used a modification of the procedure described by Patois and Savignac[120] in order to increase the yield of phosphonoacetate **4.31**. Addition of the anion of 2,4-difluorophenol to phosphonic dichloride **4.29** gave methylphosphonate **4.30** which was deprotonated and reacted with methyl chloroformate to afford phosphonoacetate **4.31** in two high-yielding steps (Scheme 4.11). Phosphonoacetate **4.33** was synthesised using Ando's procedure.[118] Hence deprotonation of diphenyl phosphite and reaction with ethyl bromoacetate afforded phosphonoacetate **4.33** in 36% yield. The yield was low due to impure diphenyl phosphite; it was not possible to purify this reagent so it was used crude. The synthesis of large quantities of phosphonoacetate **4.33** was still feasible however, as diphenyl phosphite is a cheap, readily available starting material.

Olefination under Still-Gennari conditions[110] using phosphonoacetate **4.31** was attempted on commercially available aldehyde **4.34** in order to elucidate the optimum reaction conditions (Scheme 4.12). There was no reaction at −78 °C so the temperature was increased until reaction occurred, monitoring carefully by TLC as any unnecessary increase in temperature could compromise the *Z*:*E* selectivity. Olefination occurred at −50 °C thus affording methyl ester **4.35** in 70% yield and a *Z*:*E* ratio of 9:1 as shown by isolated yields.



Scheme 4.12 Modified Still-Gennari olefination. *Reagents and conditions:* a) **4.31**, KHMDS, 18-crown-6, THF, −50 °C.

Applying these conditions to dialdehyde **3.5** afforded dimethyl ester **4.36** in 62% yield (Scheme 4.13). Repeated purification was necessary to separate the product as it co-eluted with two other products – the *cis-trans-trans-trans* and *trans-trans trans-trans* isomers. For this reason, it was not possible to obtain a *Z*:*E* ratio from isolated yields. Estimation of the *Z*:*E* ratio by ^{1}H NMR analysis of the crude mixture was also not possible as the isomer signals overlapped.



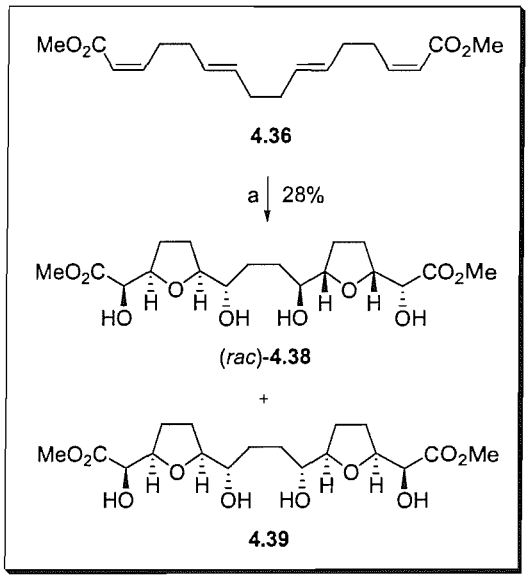
Scheme 4.13 Modified Still-Gennari olefination of dialdehyde **3.5**. *Reagents and conditions:* a) KHMDS, 18-crown-6, THF, −50 °C; b) KHMDS, 18-crown-6, THF, −10 °C; then **3.5**, −65 °C.

Olefination using phosphonoacetate **4.33** under the modified conditions led to decomposition of dialdehyde **3.5**. It was assumed that deprotonation was not occurring at −50 °C and instead the base attacked the aldehyde causing polymerisation. Again the temperature was adjusted and deprotonation was found to occur at −10 °C. Dialdehyde **3.5** was added at −78 °C and in this case olefination

occurred at −65 °C, affording diethyl ester **4.37** in 61% yield and a *Z:E* ratio of 9:1 as ascertained by isolated yields (Scheme 4.13).

4.4 Oxidative Cyclisation of a Tetraene

With two tetraenes in hand, we were now able to assess the viability of the bi-directional oxidative cyclisation reaction. We decided to use the optimum conditions for the oxidation of dienes already established within our group. As there is no control over the facial selectivity the products would be racemic, but they would still have the correct relative stereochemistry. Dimethyl ester **4.36** was stirred in a (3:2) mixture of acetone/AcOH at −30 °C and treated with 2.7 eq $KMnO_4$. The reaction afforded an inseparable mixture of *bis*-THF-tetrols (*rac*)-**4.38** and **4.39** in a combined yield of 28% (Scheme 4.14).



Scheme 4.14 Oxidative cyclisation of a tetraene. *Reagents and conditions:* a) $KMnO_4$ (2.7 eq), adogen 464, acetone/AcOH (3:2), −30 °C → 0 °C.

^1H NMR analysis of the crude mixture showed the presence of an internal double bond, implying incomplete oxidation (Figure 4.1). Hence the amount of permanganate was increased to 4 equivalents. This resulted in a messier reaction by TLC and gave a decreased yield of 24%.

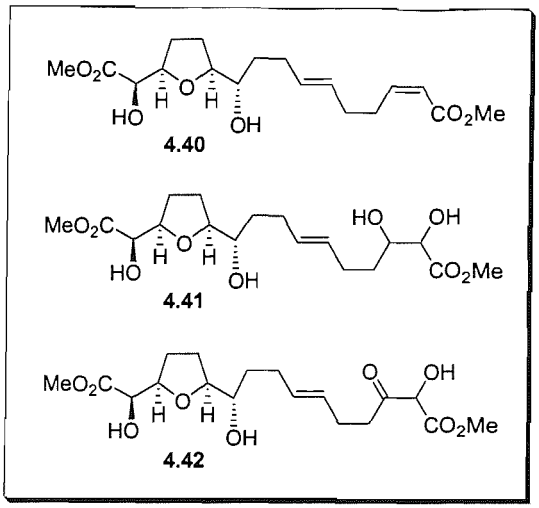
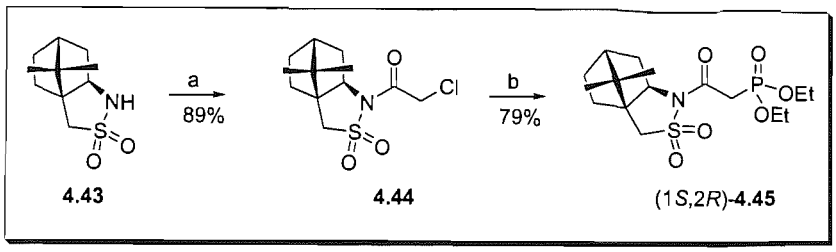


Figure 4.1 Possible incomplete oxidation by-products.

It was clear that the oxidative cyclisation reaction would require optimising. However, the concept had now been proven and we focused our attention on ascertaining the relative stereochemistry and establishing whether or not asymmetric induction was possible. The oxidation of dienoyl sultam compounds generally affords THF-diols with high crystallinity. It was hoped that the same would be true of the oxidation of tetraenoyl sultam compounds in that it would be possible to obtain a crystal structure to confirm the absolute stereochemistry.

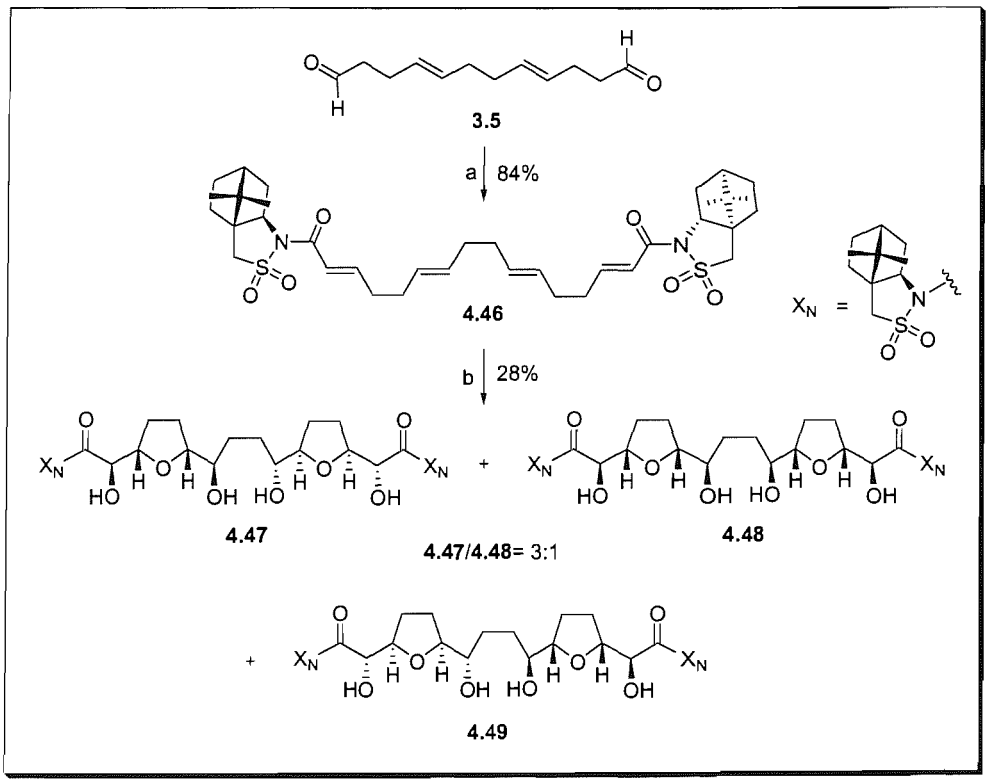
4.5 Asymmetric Oxidative Cyclisation of a Tetraene

It was decided that the most rapid access to a tetraenoyl sultam compound would be *via* olefination of dialdehyde **3.5** with the sultam-containing phosphonate (1*S*,2*R*)-**4.45** described by Oppolzer.[121,122] We were only interested in establishing asymmetric induction at this point so using a substrate with the correct double bond geometry was not essential. Reaction of (1*S*,2*R*)-camphorsultam **4.43** with chloroacetyl chloride afforded chloride **4.44** in high yield (Scheme 4.15). Arbuzov reaction with triethyl phosphite afforded phosphonate (1*S*,2*R*)-**4.45**.



Scheme 4.15 Synthesis of the sultam-bearing phosphonate (1*S*,2*R*)-**4.45**. *Reagents and conditions:* a) NaH, chloroacetyl chloride, THF, 0 °C → reflux; b) $P(OEt)_3$, xylene, reflux.

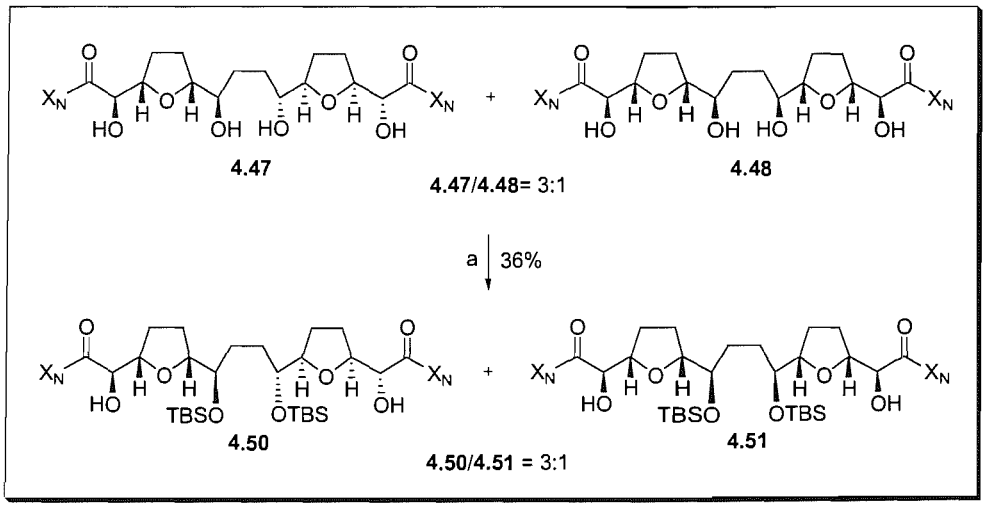
Selective *trans* HWE olefination.[102,103,109] of dialdehyde **3.5** with (1*S*,2*R*)-**4.45** afforded tetraene **4.46** in excellent yield (Scheme 4.16).



Scheme 4.16 Asymmetric oxidative cyclisation. *Reagents and conditions:* a) (1*S*,2*R*)-**4.45**, NaH, THF, 0 °C → rt; then **3.5**, 0 °C → rt; b) $KMnO_4$ (2.8 eq), acetone/AcOH (3:2), −30 °C → 0 °C.

Oxidative cyclisation with 2.8 eq of $KMnO_4$ produced an inseparable mixture of *bis*-THF-tetrols **4.47** and **4.48** in a combined yield of 28% (Scheme 4.16). Crude estimation of the ^{13}C NMR peak heights suggested a 3:1 mixture of diastereomers. The *bis*-THF-tetrol **4.49** was not isolated but is an expected minor product.

It was thought that direct reductive cleavage of the mixture of *bis*-THF-tetrols **4.47** and **4.48** would result in highly polar compounds, which would be very difficult to manipulate. Hence selective silyl protection of the central hydroxyl groups was undertaken using Corey's conditions for the silylation of hindered secondary alcohols.[123] This resulted in an inseparable mixture of *bis*-protected *bis*-THFs **4.50** and **4.51** in a combined yield of 36% (Scheme 4.17). Crude estimation of the ^{13}C NMR peak heights suggested a 3:1 mixture of diastereomers.



Scheme 4.17 Silyl protection of the central hydroxyl groups. *Reagents and conditions:* a) 2,6-lutidine, TBSOTf, CH_2Cl_2, −10 °C.

Reductive cleavage of this mixture using sodium borohydride resulted in varying degrees of desilylation thus affording a complex mixture of products. Mass spectroscopy showed that the mixture contained partially reduced and partially deprotected compounds, as well as the fully reduced and deprotected corresponding hexaol. The hexaol remained in the aqueous phase on work-up, along with other water soluble products and isolating these products proved difficult. A similar result was obtained with the more hindered TIPS *bis*-silylated tetrol.

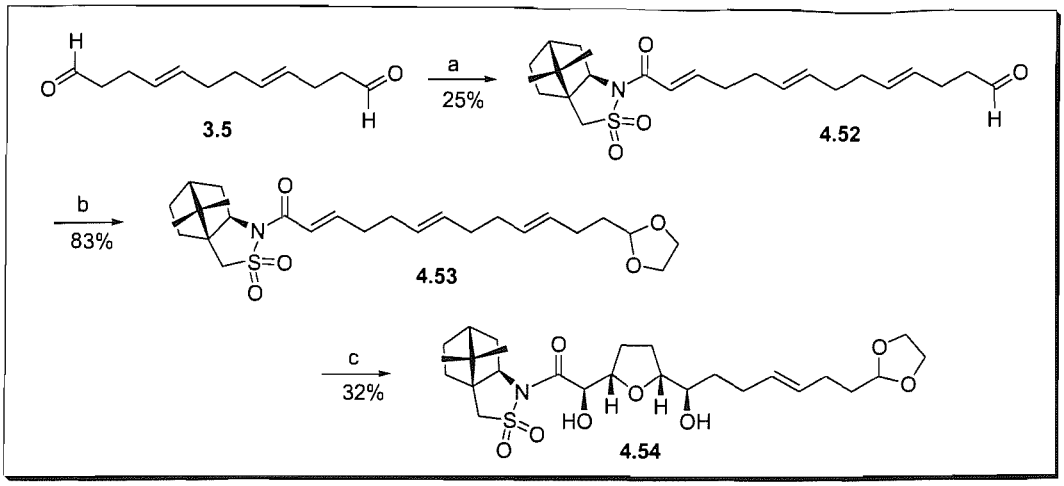
Selective protection of the central hydroxyl groups of *bis*-THF-tetrols **4.47** and **4.48** was attempted using a bridging methylene group. This was reasonably successful; however the organic solubility of the product had not increased dramatically. Protection as the more organic soluble benzylidene acetal was attempted but no reaction occurred; it is possible that the product formed but was too unstable and decomposed back to starting material.

In order to proceed, reductive cleavage of the chiral auxiliary would have to be investigated, elucidating a procedure that wouldn't require an aqueous work-up. Before undertaking this task, we investigated the possibility of desymmetrisation at the dialdehyde.

4.6 Desymmetrisation of the Dialdehyde

The oxidative cyclisation of dienes is well established within our group and so a synthesis utilising this step was envisaged, with desymmetrisation occurring at the olefination step. Sultam containing phosphonate (1*S*,2*R*)-**4.45** was added dropwise to dialdehyde **3.5** at −78 °C in order to favour *mono*-olefination (Scheme 4.18). The unoptimised yield of *mono*-olefination product **4.52** was only 25% along with a low mass recovery, implying that dialdehyde **3.5** decomposed under the basic conditions.

The remaining aldehyde was protected under Noyori's acetalisation conditions[124] affording acetal **4.53** in high yield (Scheme 4.18). Oxidative cyclisation of triene **4.53** was not as efficient as expected affording THF-diol **4.54** in 32% yield; deprotection of the aldehyde occurred under the acidic oxidation conditions and thus decomposition of the starting material resulted.



Scheme 4.18 Desymmetrisation of dialdehyde **3.5**. *Reagents and conditions:* a) (1*S*,2*R*)-**4.45**, NaH, THF, rt, 30 min; then added to **3.5**, −78 °C → −35 °C; b) 1,2-*bis*-(trimethylsilyloxy)ethane, TMSOTf, CH_2Cl_2, −78 °C; c) $KMnO_4$ (1.5 eq), acetone/AcOH (3:2), −30 °C → −15 °C.

The efficacy of this approach was hampered by low yields; hence we reverted back to the bi-directional synthesis with a view to desymmetrisation at a later juncture.

Chapter 5

Synthetic Studies Towards *cis*-Sylvaticin

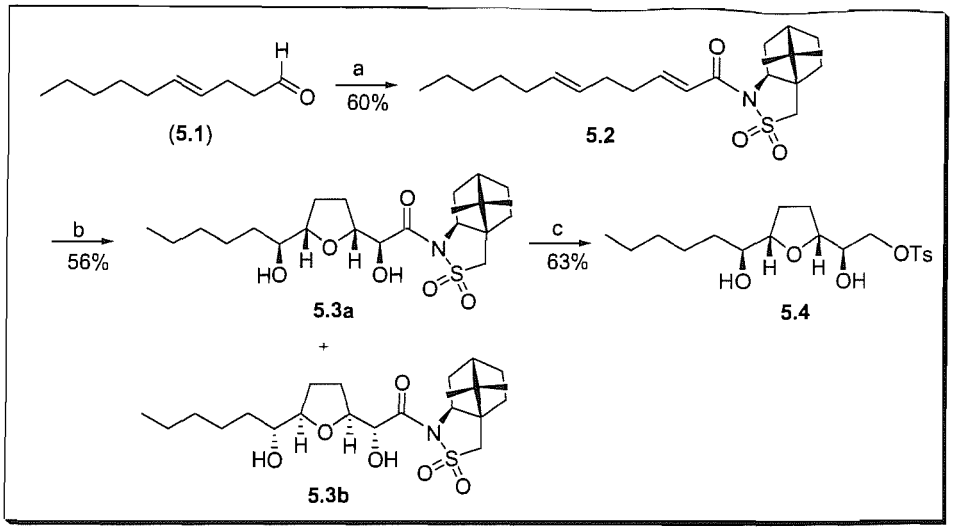
The following chapter summarises the synthesis towards *cis*-sylvaticin including an optimised route to the *bis*-THF core *via* the *cis-trans-trans-cis* tetraene, a solution to the reductive cleavage problem and our efforts in elaborating the left and right sides of the advanced *bis*-THF intermediate.

5.1 Model Reductive Cleavage Studies

Reductive cleavage of the chiral auxiliaries in **4.50** and **4.51** had produced a highly water soluble hexaol. This hexaol proved difficult to manipulate; hence we investigated the reductive cleavage using a model system in order to elucidate a procedure that would not require an aqueous work-up. Once established, this procedure could be applied in the reductive cleavage of **4.50** and **4.51**.

Model reductive cleavage studies were carried out on a simple THF-diol, which was accessible from the corresponding 1,5-diene. Olefination of *trans*-4-decenal (**5.1**) using sultam containing phosphonoacetate (1*R*,2*S*)-**4.45** gave dienoyl sultam **5.2** (Scheme 5.1). Oxidative cyclisation using 1.4 eq $KMnO_4$ produced THF-diol **5.3a** in 56% yield. ^1H NMR analysis of the crude reaction mixture showed the ratio of **5.3a/5.3b** was 7:1.

As previously mentioned, when the hexaol is exposed to water, its re-extraction into organic solvent is very difficult. After reductive cleavage of THF-diol **5.3**, the mixture was concentrated and CH_2Cl_2 was added to solubilise as much triol as possible in organic solvent prior to work-up. The organic phase was transferred to another flask and the remaining residue was worked up. The combined organic phases were concentrated and the triol was used crude in the next step. Activation of the primary alcohol afforded tosylate **5.4** in 63% yield over two steps (Scheme 5.1).

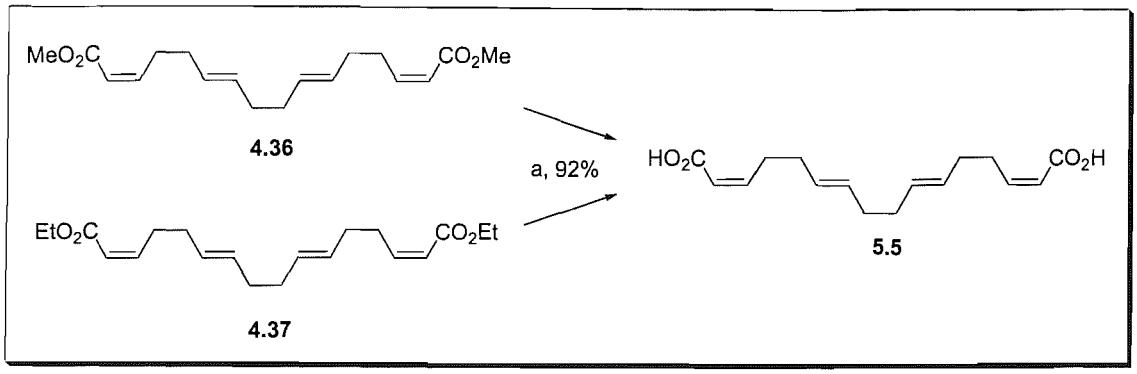


Scheme 5.1 Reduction and tosylation of THF-diol **5.3a**. *Reagents and conditions:* a) (1*R*,2*S*)-**4.45**, NaH, THF, 0 °C → rt; then (**5.1**), 0 °C → rt; b) $KMnO_4$ (1.4 eq), acetone/AcOH (3:2), −30 °C → −15 °C; c) (i) $NaBH_4$, THF/H_2O (3:1), −10 °C → 0 °C; (ii) Bu_2SnO, benzene, reflux; then TsCl, rt.

With this procedure in hand, we envisaged that this could be successfully applied to the tetraene. We decided to synthesise the correct tetraene substrate at this juncture in order to install the correct absolute stereochemistry, and then attempt the reductive cleavage.

5.2 Synthesis of the *cis-trans-trans-cis* Tetraene

Hydrolysis of esters **4.36** and **4.37** gave the corresponding diacid **5.5** in excellent yield (Scheme 5.2).

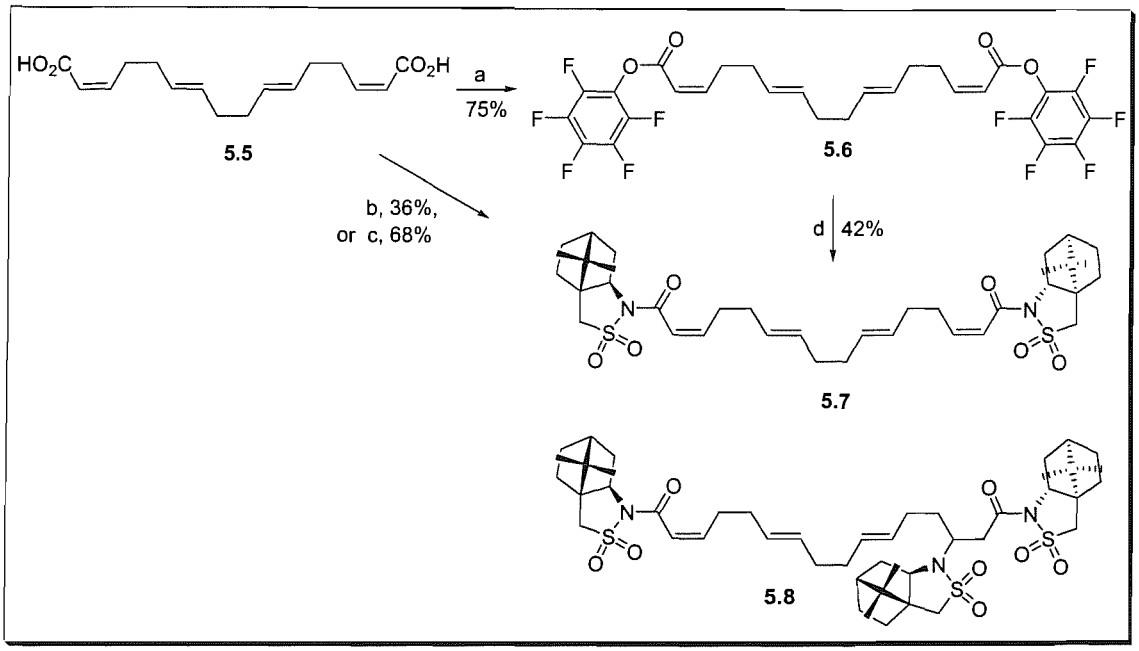


Scheme 5.2 Hydrolysis of the esters. *Reagents and conditions:* a) NaOH, $NaHCO_3$, $MeOH/H_2O$ (1:3), 95 °C; then citric acid (aq), HCl (aq).

Coupling of Oppolzer's sultam to diacid **5.5** proved to be rather challenging. Initial efforts focused upon accessing tetraene **5.7** *via* the diacid dichloride. Once formed (often denoted by a deep yellow/orange colour) the diacid dichloride was added dropwise to a solution of the deprotonated sultam. ^1H NMR analysis of the crude product indicated a mixture of products with partial isomerisation occuring at the enoate double bond. Repeated purification was necessary since the isomers co-eluted and the desired tetraene **5.7** was produced in just 36% yield (Scheme 5.3).

^1H NMR analysis of the crude diacid dichloride showed no double bond isomerisation; thus it was logical to assume this was occurring after the coupling step. In order to minimise isomerisation, the temperature of the coupling step was reduced. This reduced the isomerisation however there was now a second product as shown by TLC which was thought to be the *mono*-coupled product. Bizarrely, we found that this was actually Michael addition product **5.8** (Scheme 5.3). The yield of the desired tetraene **5.7** was 34%, the rest accounted for by Michael addition product **5.8**; thus varying the temperature was not productive.

It is likely that double bond isomerisation at the enoate occurred at higher temperature *via* Michael addition of the sultam anion followed by elimination; lowering the temperature of the reaction enabled isolation of this adduct.



Scheme 5.3 Coupling of Oppozler's sultam. *Reagents and conditions:* a) pentafluorophenol, DCC, EtOAc, rt; b) (i) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C → rt; (ii) (1*S*,2*R*)-camphorsultam **4.42**, NaH, THF, 0 °C → rt; c) (i) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C → rt; (ii) (1*S*,2*R*)-camphorsultam **4.42**, NaH, toluene, −10 °C; then rt; d) (1*S*,2*R*)-camphorsultam **4.42**, NaH, toluene, −70 °C → −10 °C.

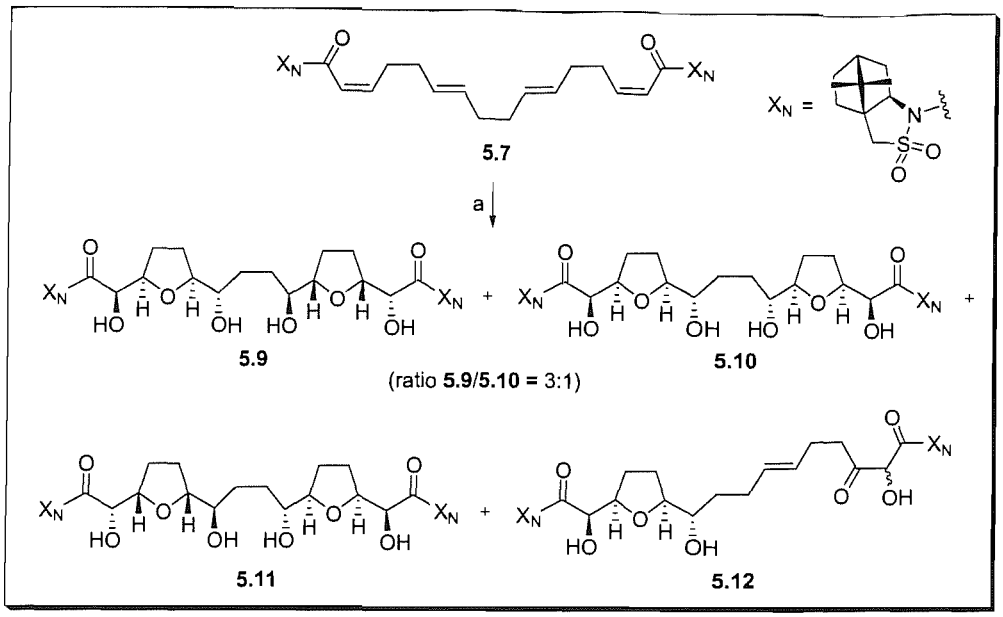
Efforts now focused upon varying the leaving group, starting with pentafluorophenol ester derivative **5.6**, which was accessed *via* a straightforward coupling to diacid **5.5** (Scheme 5.3). Unfortunately, this showed no improvement and a similar degree of isomerisation occured. Diacid **5.5** was reacted with methyl chloroformate to produce the mixed anhydride, which was then added to the deprotonated sultam at low temperature. Unfortunately, the sultam reacted at the wrong carbonyl centre resulting in starting material.

The effect of solvent on the reaction was next investigated. It is possible that a polar solvent such as THF could aid isomerisation through stabilisation of the Michael addition product previously mentioned; a less polar solvent might eliminate this

stabilistation. It had already been established that isomerisation was not occurring at the diacid dichloride formation step (as shown by analysis of the ^{1}H NMR of the crude diacid dichloride); hence we investigated the coupling of the sultam *via* the diacid dichloride in a less polar solvent system. The coupling step was carried out in toluene and gratifyingly tetraene **5.7** was afforded in 68% yield without any noticeable isomerisation of the enoate functionality (Scheme 5.3).

5.3 Optimisation of the Oxidative Cyclisation Reaction

With the *cis-trans-trans-cis* tetraene in hand, the optimal conditions for bi-directional oxidative cyclisation were investigated in order to install the non-adjacent *bis*-THF core of *cis*-sylvaticin. The results are summarised in Table 5.1. The oxidative cyclisation produced three diastereomers, two of which co-eluted and were therefore inseparable. The two co-eluting diastereomers **5.9** and **5.10** (Scheme 5.4) had identical ^{1}H and ^{13}C NMR data, and were only distinguishable after removal of the chiral auxiliaries. The third diastereomer **5.11** and the hydroxyketone by-product **5.12** were isolated after repeated purification, hence it was not possible to ascertain an exact yield for either of these.



Scheme 5.4 Oxidative cyclisation of the tetraene. *Reagents and conditions:* a) see Table 5.1.

Entry	$KMnO_4$	PTC[a]	Solvent	t/min	T/°C	Yield[b]
1	3.5 eq	Y	Acetone/AcOH (3:2)	90	−30 to −10	14%
2	3.2 eq	N	Acetone/AcOH (3:2)	30	−30 to −20	20%
3	3.2 eq	N	Acetone/AcOH (3:2)	150	−30 to −10	18%
4	2.8 eq	N	Acetone/AcOH (6:5)	25	−30 to −20	32%
5	3.8 eq	Y	Et_2O/AcOH (4:1)	150	−30 to 0	18%
6	3.5 eq	Y	EtOAc/AcOH (3:2)	60	−30 to −10	25%
7	3.2 eq	Y	EtOAc/AcOH (3:2)	90	−30 to −10	23%
8	3.2 eq	Y	EtOAc/AcOH (4:1)	90	−30 to 0	28%
9	3.5 eq	Y	EtOAc/AcOH (4:1)	90	−30 to 0	21%
10	3.0 eq	N	Acetone/H_2O[c]	30	−30 to −10	28%
	$NaMnO_4$					
11	3.0 eq	N	Acetone/H_2O[c]	30	−30 to −10	41%

Table 5.1 Oxidative cyclisation of tetraene **5.7** under different conditions (see Scheme 5.4). [a] The phase-transfer catalyst (PTC) used was 10 mol% of adogen 464 (Y = Yes, N = No); [b] Combined yield of diastereomers **5.9** and **5.10**; [c] The oxidant was added as a 0.4 M aqueous solution, which was mixed with 5.4 eq of AcOH prior to addition.

Initially, 3.5 eq of $KMnO_4$ was used to oxidise tetraene **5.7** since incomplete oxidation was observed with 2.7 eq and a decreased yield was observed with 4 eq (possibly due to oxidative cleavage). Oxidative cyclisation using the previously established solvent system of acetone/AcOH (3:2) at low temperature in the presence of a phase-transfer catalyst (PTC) gave a 14% yield (Table 5.1, Entry 1). As this solvent system is highly solubilising for polar compounds, the PTC was not necessary in subsequent experiments.

Short and long reaction times produced similar results (Table 5.1, Entries 2 & 3), in accordance with the theory that the reaction is fast at low temperature but as the amount of MnO_2 increases, further reaction is hindered as permanganate adsorbs onto its surface; the fast reaction is corroborated by the immediate colour change (purple to brown) when the oxidant is added. It was reasoned therefore, that the oxidant should be added in one portion and that the reaction should be conducted for a short amount of time at low temperature to minimise oxidative cleavage. Using 2.8 eq of $KMnO_4$ and a larger amount of AcOH in the solvent system to minimise hydroxyketone formation resulted in a 32% yield (Table 5.1, Entry 4).

Oxidative cyclisations conducted in Et_2O and EtOAc required the presence of a PTC since $KMnO_4$ has limited solubility in these solvents. The oxidation in Et_2O was very slow and required the most $KMnO_4$ to go to completion (Table 5.1, Entry 5). Even in the presence of the PTC, a larger solvent/AcOH ratio was needed to solubilise the oxidant. After warming to 0 °C the product was afforded in 18% yield. Oxidations in EtOAc produced similar yields to those in acetone; the highest yield obtained with EtOAc was 28% (Table 5.1, Entry 8).

Previous experiments within the group had shown that the use of AcOH as co-solvent increased the yield of the oxidative cyclisation of dienes by reducing the amount of the hydroxyketone by-product.[125] Prior to this finding, the group had used aqueous $KMnO_4$ in the presence of a stoichiometric amount of AcOH. Owing to the idiosyncratic nature of this reaction, these conditions were applied to tetraene **5.7**, with surprisingly promising results.

The use of 3 eq of $KMnO_4$, allowing the mixture to warm to −10 °C over 30 min gave the product in 28% yield (Table 5.1, Entry 10). ^1H NMR analysis of the crude mixture showed the by-product contained an internal double bond; this indirectly suggested the presence of hydroxyketone **5.12**.

Increasing the amount of permanganate to reduce the amount of hydroxyketone **5.12** would probably cause a drop in yield, as had been observed previously. Hence we decided to keep the amount of oxidant unchanged, instead switching the oxidant to $NaMnO_4$, since it is known to have better solubility than $KMnO_4$. Oxidative cyclisation using 3 eq of $NaMnO_4$ afforded the *bis*-THF-tetrol in 41% yield (Table 5.1, Entry 11). Unfortunately, oxidative cyclisations using $NaMnO_4$ were not as efficient on a large scale.

Predicted Ratio of Diastereomers

It was predicted, on the basis of previous experiments on the oxidative cyclisations of dienoyl sultams,[76,80] that the major product from the oxidative cyclisation of tetraene **5.7** would be **5.9** (Scheme 5.4); this gives rise to a C_2-symmetric diastereomer after cleavage of the chiral auxiliary. The oxidative cyclisations of dienoyl sultams have been shown to give an approximate 6:1 ratio of diastereomers.[82] Based on this ratio, it was predicted that the ratio of the three diastereomers from the oxidative cyclisation of tetraene **5.7** would be 3:1:0.08.

The facial selectivity can be explained by looking at the reactive conformation of the substrate prior to initial attack. In the presence of Oppolzer's sultam, facial attack of the enoate double bond is governed by the following conditions:[126]

- Reactive conformation of the CO-CC bond: of the two possible conformations which allow conjugation of the π-system, the *s-cis*-orientation is favoured both for steric reasons ($O < NR_2$) and because (*Z*)-enolates of amides are more stable than (*E*)-enolates.

- Orientation of the carbonyl group: it must lie either parallel or anti-parallel to the N-S bond. Other orientations are energetically less favoured since they lack mesomeric stabilisation with the lone pair of the amide nitrogen atom.

- In the most favoured conformation, one face of the double bond is effectively blocked by the chiral auxiliary, thus allowing selective attack upon the other face.

In the presence of a Lewis acid containing two co-ordination sites, a *syn*-relationship between the C=O and SO_2 results in the transition state as chelate **5.13** forms (Figure 5.1). The upper face of the enoate double bond is blocked by the camphor framework and hence attack is directed to the lower C(β) *Re*-face.

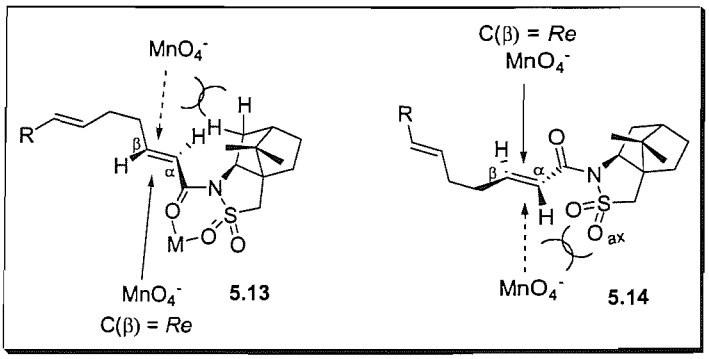


Figure 5.1 Directed facial attack of an enoyl sultam.

In the absence of a chelating Lewis acid, the *anti*-relationship between C=O and SO_2 is thought to be favoured (Figure 5.1). This is sterically favoured, but moreover electronically favoured, since this conformation minimises the dipole moment. The camphor framework in **5.14** is too distant to shield the enoate double bond, however the *pseudo*-axial S=O effectively blocks the lower face, thus directing attack to the upper C(β) *Re*-face.

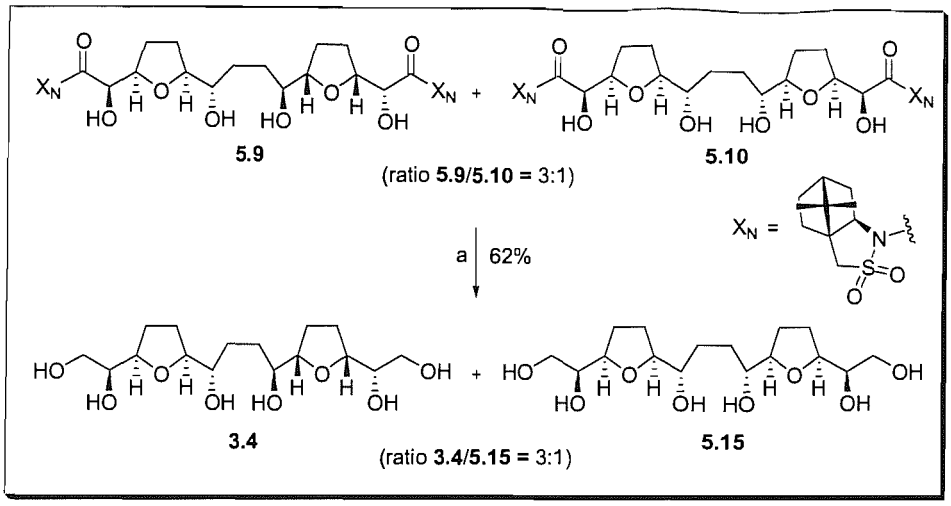
The same face is therefore attacked preferentially, regardless of whether there is a Lewis acid present or not, thus providing control over the facial selectivity.

5.4 Reductive Cleavage and Tosylation

The reductive cleavage had already been shown to work effectively on the THF-diol system, thus the same procedure was applied to the *bis*-THF tetrols. The mixture of *bis*-THF tetrols **5.9** and **5.10** was treated with $LiBH_4$ in THF at −10 °C for 30 min. The reaction appeared promising by TLC analysis so the modified work-up procedure was carried out. Hence the reaction mixture was concentrated and the residue dissolved in CH_2Cl_2. After working-up the residue, the combined organic phases showed no sign of the desired hexaol; instead it was found in the aqueous phase. We reasoned that the hexaol can easily bind boron salts thus reducing its solubility in CH_2Cl_2. It was clear that the hexaol was highly soluble in water and the use of aqueous acid in the work-up would have to be limited.

The reductive cleavage was carried out again, however on this occasion the reaction was quenched by the addition of MeOH and then a small amount of dilute HCl. The mixture was concentrated and dry loaded on to silica. We reasoned that passing the crude residue through a short plug of silica would remove the boron salts; the only concern was whether or not the hexaol would irreversibly bind silica. Gratifyingly, after eluting with up to 70% MeOH/CH_2Cl_2, hexaols **3.4** and **5.15** were produced in a combined yield of 62% (Scheme 5.5). Crude estimation of the ^{13}C NMR peak heights suggested a 3:1 mixture of diastereomers.

The yield for the reductive cleavage was rather low, which may be due to the hexaol irreversibly binding silica. Another possibility is that after reduction to the corresponding aldehydes, lactolisation occured, leading to polar products which appeared on the baseline by TLC analysis, together with the boron salts. Perhaps if the reaction had been left for longer, the lactol would eventually have been reduced.

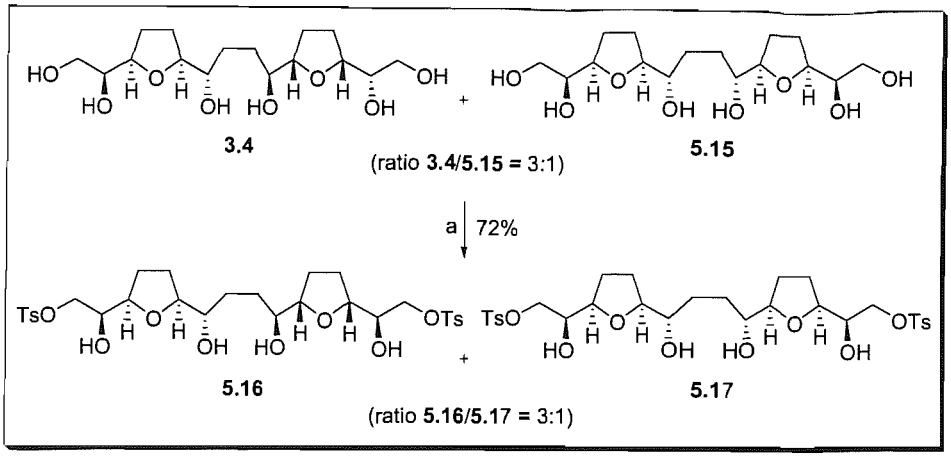


Scheme 5.5 Reductive cleavage of the chiral auxiliaries. *Reagents and conditions:* a) $LiBH_4$, THF, −10 °C.

With hexaols **3.4** and **5.15** in hand, we investigated their *bis*-tosylation. The tosylation reaction using Bu_2SnO and TsCl proceeds in two stages. Initially reaction with Bu_2SnO produces a dibutylstannoxane derivative; this then undergoes highly selective tosylation at the primary alcohol on exposure to TsCl.

Use of the previously described conditions for tosylation led to a poor conversion (47%) as the hexaol was not soluble in benzene, even when heated to reflux. Switching the solvent to MeOH increased the yield (68%) but the product was accompanied by a co-eluting UV active by-product. This complicated purification and was presumably the MeOTs adduct. We therefore switched solvent to dioxane which increased the yield of **5.16** and **5.17** to 72% and eliminated the by-products (Scheme 5.6). Crude estimation of the ^{13}C NMR peak heights suggested a 3:1 mixture of diastereomers.

The reaction in MeOH required a large excess of Et_3N to go to completion but interestingly, when we attempted the reaction initially, we used 2 eq of Et_3N which produced the *mono*-tosylate as a by-product in 10% yield. We realised that if we could optimise the yield of this by-product using the more efficient dioxane procedure, we could essentially effect desymmetrisation at this juncture.



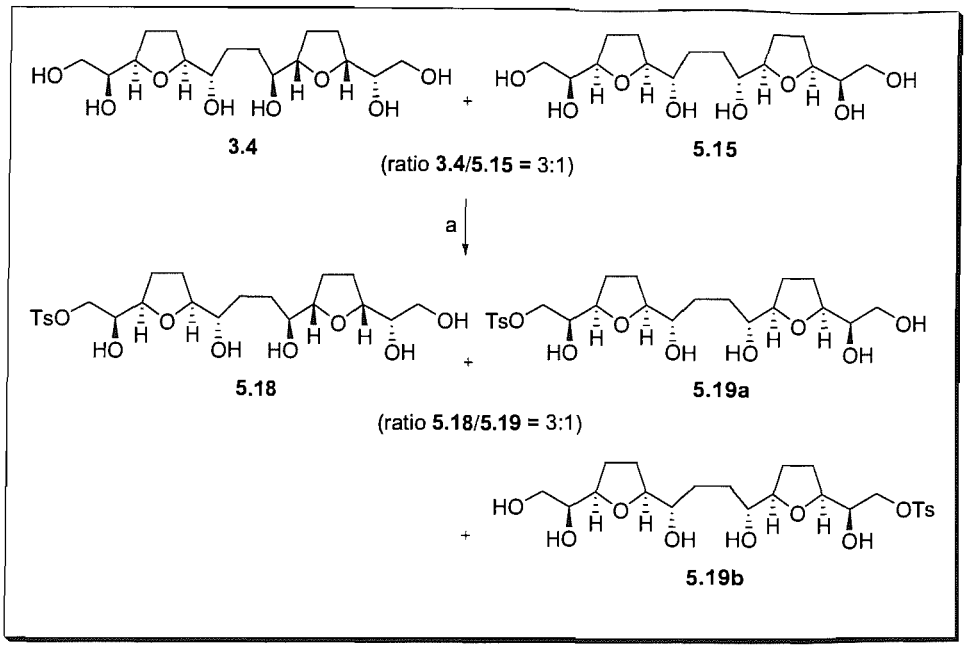
Scheme 5.6 *bis*-Tosylation of the diastereomeric hexaols. *Reagents and conditions:* a) Bu_2SnO (2.4 eq), dioxane, reflux; then TsCl (2.1 eq), rt.

5.5 Desymmetrisation *via* the *mono*-Tosylate

Initial results from the *mono*-tosylation of hexaols **3.4** and **5.15** are shown in Table 5.2. The three possible products **5.18**, **5.19a**, and **5.19b** were all inseparable and crude estimation of the ^{13}C NMR peak heights suggested a 3:1 mixture of diastereomers, presumably **5.18/5.19** (where **5.19** = **5.19a** + **5.19b**).

As the tosylation reaction proceeds in two stages, there are two points at which to vary the quantity of reagent in order to effect *mono*-addition.

Initial experiments with 1.1 eq of Bu_2SnO and TsCl gave *mono*-tosylates **5.18** and **5.19** in 29% yield with 42% recovered hexaol (Entry 1, Table 5.2). Increasing the amount of Bu_2SnO and TsCl to 1.25 eq and 1.2 eq respectively gave similar yields (Entry 2, Table 5.2). Using 1 eq of Bu_2SnO and 3 eq TsCl gave mainly starting material (54%) with 22% *mono*-tosylate (Entry 3, Table 5.2). Increasing the amount of Bu_2SnO and TsCl to 1.4 eq of each shifted the balance in favour of the *bis*-tosylate (32%) with 30% *mono*-tosylate and only 22% recovered starting material (Entry 4, Table 5.2). We decided to use 1.25 eq and 1.2 eq of Bu_2SnO and TsCl respectively (Entry 2, Table 5.2) as this gave a reasonable yield of product together with a reasonable amount of recovered starting material for recycling. Crude estimation of the ^{13}C NMR peak heights suggested a 3:1 mixture of diastereomers.



Scheme 5.7 *mono*-Tosylation and the three expected products. *Reagents and conditions:* a) Bu_2SnO, dioxane, reflux; then TsCl, rt, See Table 5.2.

Entry	Bu_2SnO	TsCl	SM	*mono*-tosylate	*bis*-tosylate
1	1.1 eq	1.1 eq	42%	29%	14%
2	1.25 eq	1.2 eq	35%	35%	21%
3	1.0 eq	3.0 eq	54%	22%	10%
4	1.4 eq	1.4 eq	22%	30%	32%

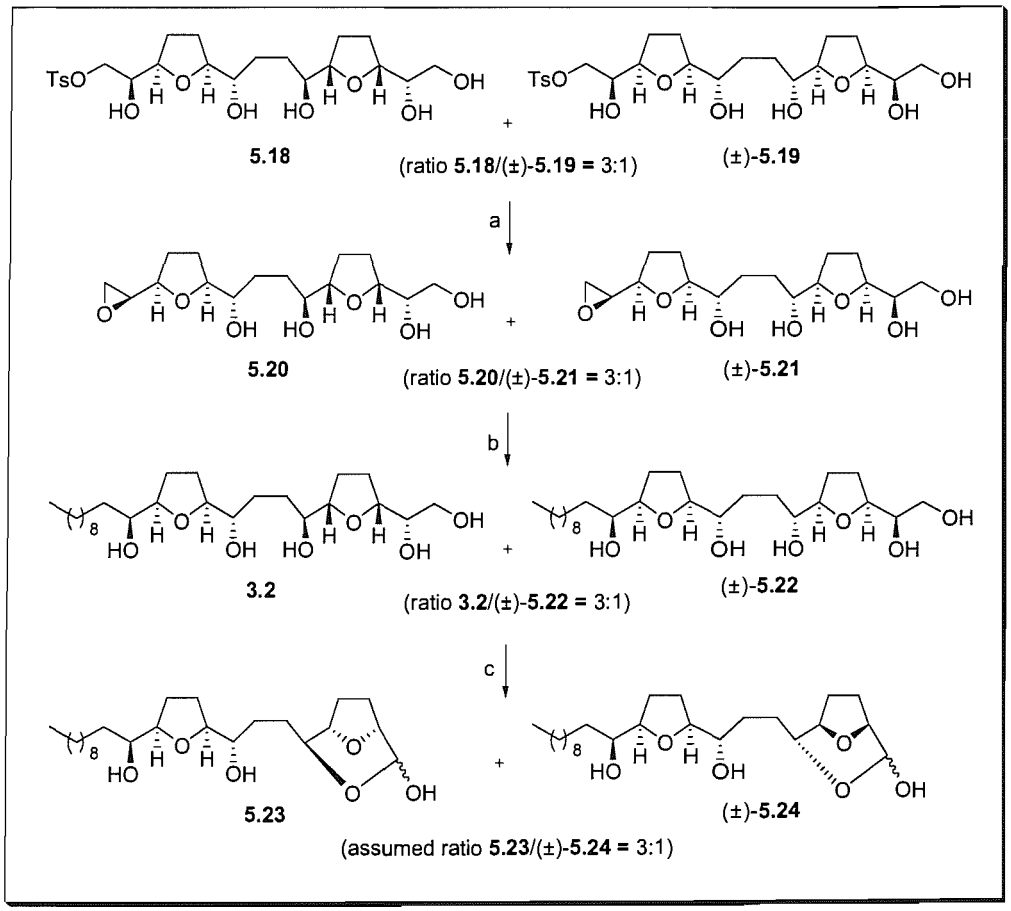
Table 5.2 Optimisation of the *mono*-tosylation reaction (see Scheme 5.7).

The *mono*-tosylates **5.18** and (±)-**5.19** were converted into the corresponding *mono*-epoxides **5.20** and (±)-**5.21** in 57% yield as a 3:1 ratio of isomers as shown by ^{13}C NMR analysis. Subsequent opening of the epoxide gave pentaols **3.2** and (±)-**5.22** in 58% yield, also as a 3:1 ratio of diastereomers as shown by crude estimation of the ^{13}C NMR peak heights.

Periodate-mediated oxidative cleavage of the 1,2-diols of pentaols **3.2** and (±)-**5.22** was attempted, as olefination of the corresponding aldehydes would effect deoxygenation at the correct position (Scheme 5.8).

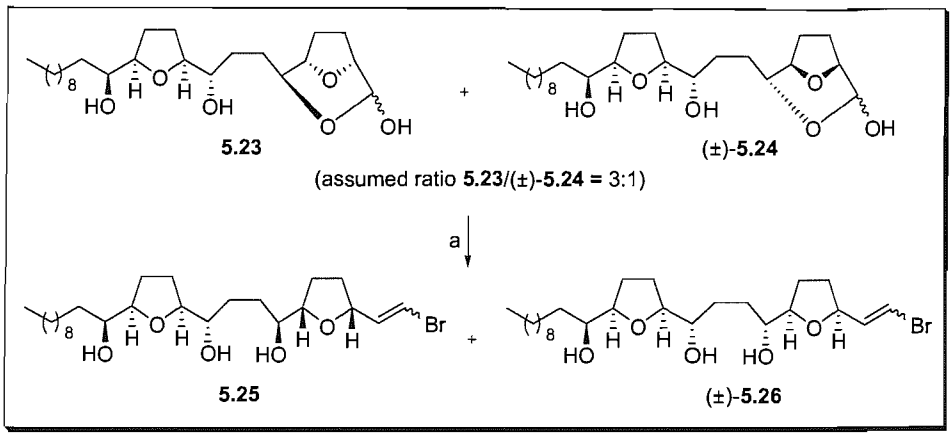
There was no sign of an aldehyde peak however, as shown by ^{1}H NMR analysis of the crude reaction mixture. The major product was isolated and the ^{1}H NMR spectrum showed a characteristic lactol peak. We rationalised that lactols **5.23** and (±)-**5.24** had formed as soon as oxidative cleavage to the aldehyde had occurred (Scheme 5.8).

Use of $Pb(OAc)_4$ in the oxidative cleavage reaction resulted in decomposition of the starting material. Due to insufficient material, the lactols could not be fully characterised, although a one-off olefination reaction was attempted on the material available.



Scheme 5.8 Elaboration of *mono*-tosylates **5.18** and (±)-**5.19**. *Reagents and conditions:* a) DBU, CH_2Cl_2, 0 °C → rt; b) nonylmagnesium bromide, CuI, THF, −70 °C → −40 °C; c) $NaIO_4$-SiO_2, H_2O, CH_2Cl_2.

Olefination was attempted using the conditions described by Sinha *et al.*[127] Thus Wittig reagent (bromomethyl)triphenylphosphonium bromide was treated with 3 eq of ^{t}BuOK at −78 °C before lactols **5.23** and (±)-**5.24** were added (Scheme 5.9).



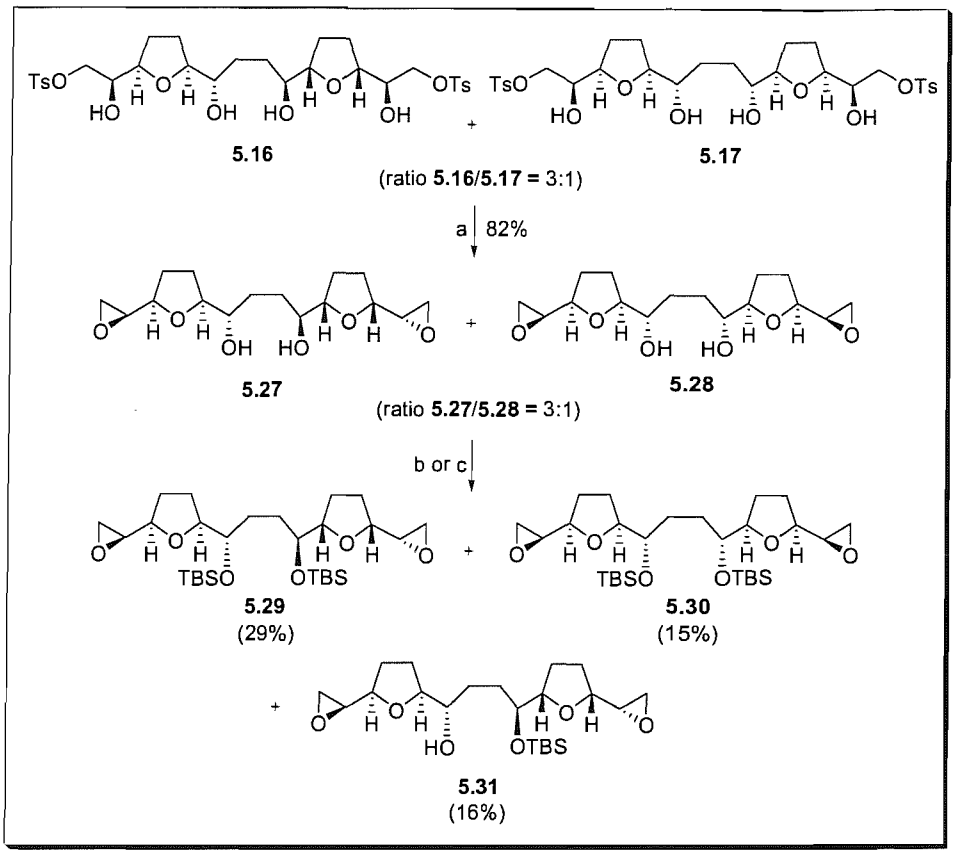
Scheme 5.9 Ring-opening of the lactols and olefination. *Reagents and conditions:* a) (bromomethyl)triphenylphosphonium bromide, ^{t}BuOK, THF, −78 °C → 0 °C, 2 h.

TLC analysis of the crude reaction mixture showed a 1:1 mixture of starting material/product and the presence of a UV active product. ^{1}H NMR analysis of the crude mixture showed a small aldehyde peak, which implied that the starting material had been a lactol and had formed the intermediate aldehyde during the reaction. Also present were weak bromo-olefin signals, which were in accordance with literature values. Mass spectrometry confirmed that the UV active product was $Ph_3P{=}O$, which also implied that the olefination had occurred, however we could not be absolutely certain that **5.25** and (±)-**5.26** were present (Scheme 5.9). As we couldn't confirm that olefination had occurred, and due to limited quantities of material we decided to concentrate on the bi-directional approach, with a view to effecting desymmetrisation at a later stage.

5.6 Bi-Directional Approach to *cis*-Sylvaticin

We had already shown that *bis*-tosylation occured in high yield. Work therefore continued on the bi-directional approach with conversion of *bis*-tosylates **5.16** and **5.17** to the corresponding *bis*-epoxides **5.27** and **5.28** in 82% yield (Scheme 5.10).

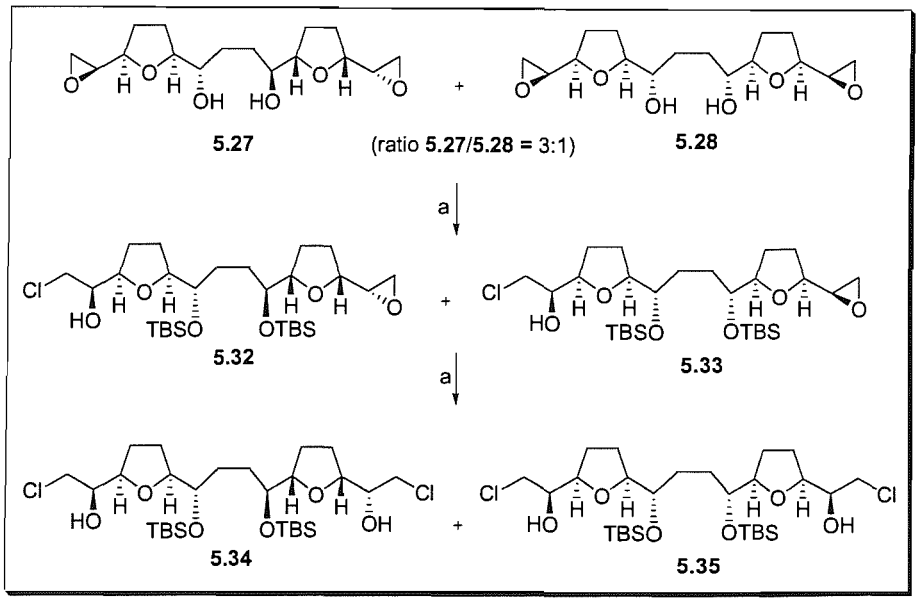
Crude estimation of the ^{13}C NMR peak heights suggested a 3:1 mixture of diastereomers. Attempts to desymmetrise here by ring-opening one epoxide were not fruitful since the starting material, *mono*-ring-opened and *bis*-ring-opened products all co-eluted, rendering purification impossible. The presence of the hydroxyl groups also made it difficult to ascertain how much cuprate was required for optimum results.



Scheme 5.10 Bi-directional extension of the *bis*-tosylate. *Reagents and conditions:* a) DBU, CH_2Cl_2, 0 °C; b) TBSCl, imidazole, DMF, rt; c) 2,6-lutidine, TBSOTf, CH_2Cl_2, −10 °C (yields shown are for this method only).

We decided to protect the alcohols as TBS ethers and initial silylation efforts utilised the mild TBSCl/imidazole method (Scheme 5.10). The reaction appeared messy by TLC analysis and afforded the desired *bis*-silylated products **5.29** and **5.30** in a low combined yield of 12%. A more polar spot by TLC analysis was thought to be the *mono*-silylated product **5.31**; this was isolated and subjected to the same silylation conditions. Mass spectrometry later showed that this polar TLC spot had actually corresponded to the inseparable *mono*-ring-opened products **5.32** and **5.33** (Scheme

5.11). Interestingly, silylation of the secondary alcohols of **5.32** and **5.33** had not taken place; instead a second ring-opening had occurred, affording the protected *bis*-chlorides **5.34** and **5.35**.



Scheme 5.11 By-products from TBS protection. *Reagents and conditions:* a) TBSCl, imidazole, DMF, rt.

Work continued on silyl protection since separation of the TBS-protected diastereomers appeared feasible. The next conditions employed were those described by Corey *et al.*,[123] in which the more reactive silylating reagent TBSOTf was used to protect the hindered secondary alcohols. It was a concern that this reagent could cause the epoxides to open, however results from the previous silylation had shown that reaction at the epoxides is a problem even under the mildest of conditions; hence this procedure was worth investigating. The reaction looked promising by TLC analysis however the mass recovery was poor. The major isomer **5.29** was isolated in 29% yield, the minor isomer **5.30** in 15% yield and the *mono*-silylated product **5.31** in 16% yield (Scheme 5.10). It is possible that TBSOTf caused epoxide opening in a similar fashion to TBSCl; since exactly two equivalents of TBSOTf were used, the central hydroxyl groups may have been silylated to a lesser degree than observed with TBSCl, and hence these water soluble products could have been lost in the aqueous phase.

Gratifyingly, we were able to obtain a crystal structure for the minor isomer **5.30**, which confirmed our assignment of its absolute stereochemistry.

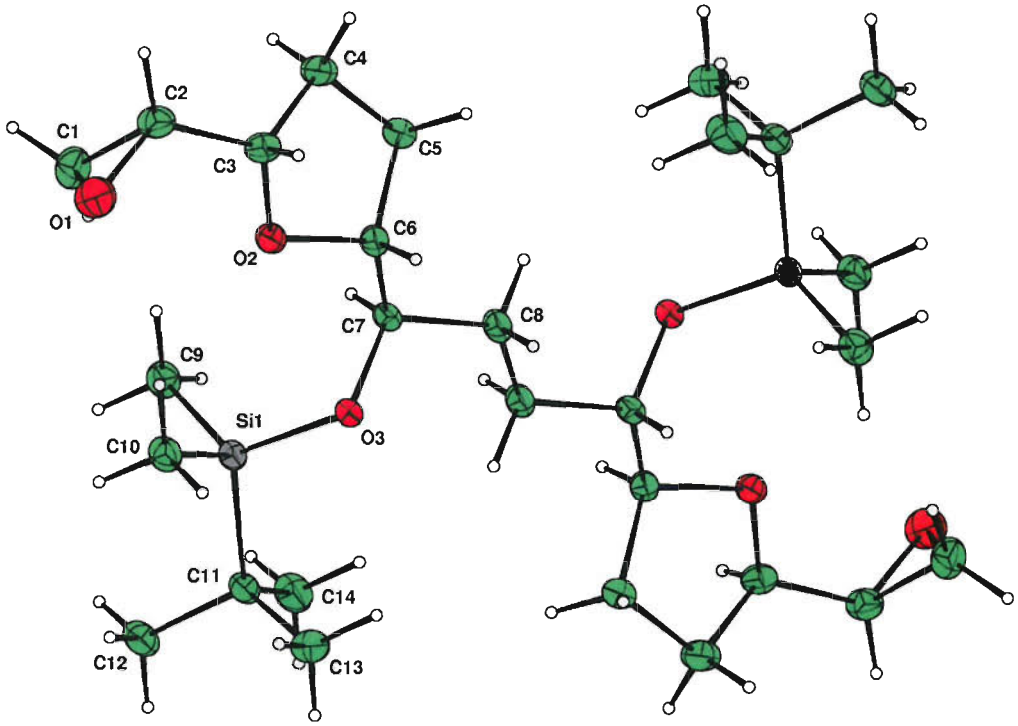
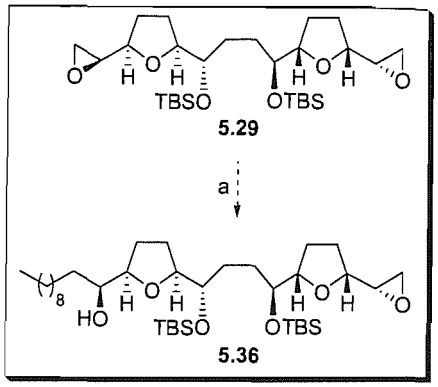


Figure 5.2 Crystal structure of the symmetrical *bis*-silylated minor isomer **5.30**, confirming the absolute stereochemistry.

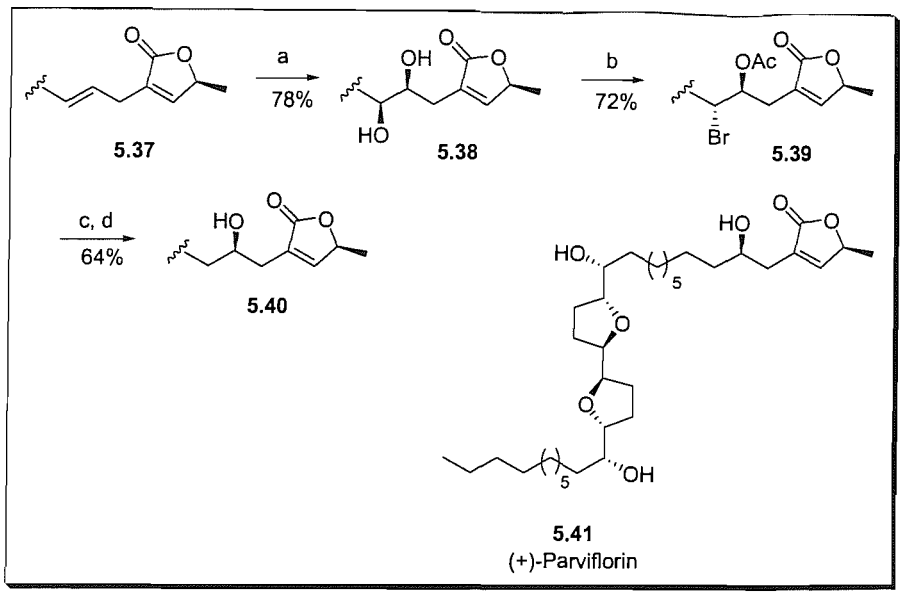
Finally, we attempted the desymmetrisation of *bis*-epoxide **5.29** (Scheme 5.12). Encouragingly, two products formed as shown by TLC analysis with good separation. The crude mass spectrum indicated the presence of the expected *mono*-ring-opened and *bis*-ring-opened products. The suspected *mono*-ring-opened product **5.36** was isolated, but showed no sign of the alkyl chain by ^{1}H NMR analysis. HRMS later showed that the ions which had corresponded to the *mono*-ring-opened and *bis*-ring-opened products were actually coincidental. The integrity of the commercially obtained Grignard reagent could not be ascertained and it is possible this reagent caused decomposition of the epoxide. Due to insufficient amounts of material and time constraints, *mono*-ring-opening was not investigated further.



Scheme 5.12 Attempted introduction of the alkyl chain. *Reagents and conditions:* a) nonylmagnesium bromide, CuI, THF, −70 °C → −30 °C.

5.7 Synthesis of the Butenolide-Aldehyde

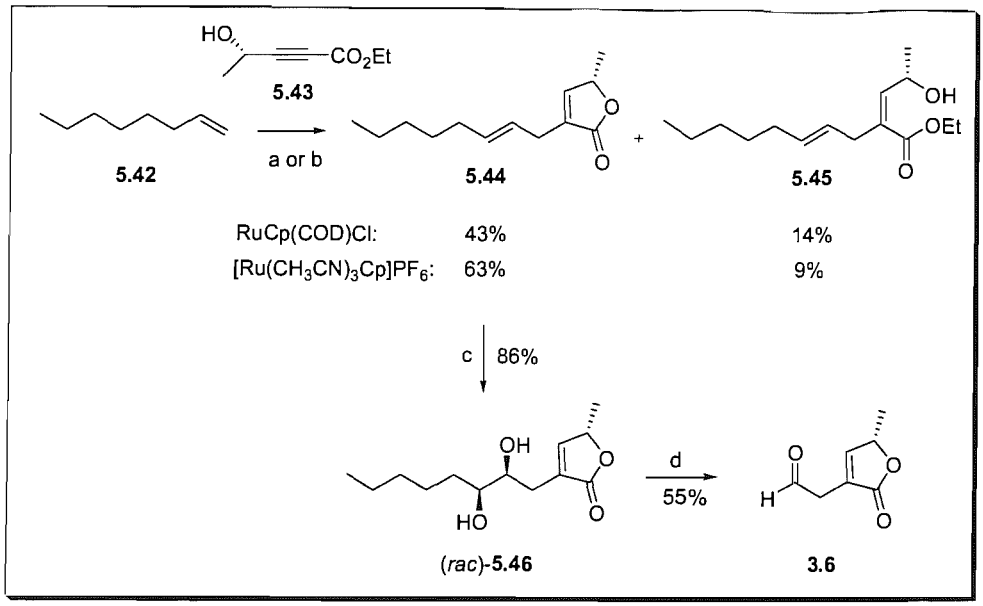
A convenient way of installing the butenolide portion into a natural product is *via* the Alder-ene reaction. This reaction converts a terminal alkene into the butenolide in conjunction with a chiral propargyl alcohol. In the synthesis of (+)-parviflorin **5.41**, Trost *et al.* used the resulting double bond from the Alder-ene reaction to install an adjacent chiral centre *via* Sharpless asymmetric dihydroxylation and bromoacetoxonium chemistry (Scheme 5.13). As *cis*-sylvaticin also has a chiral centre adjacent to the butenolide, we needed to devise a method for its installation. As previously mentioned (Section 3.2), Evans *et al.* installed the right-hand side of (−)-mucocin using an asymmetric alkynyl addition to butenolide-aldehyde **3.6** in high yield (81%) and with good selectivity (d.r. = 20:1). We decided to use Trost's Alder-ene reaction on a simple alkene to establish the butenolide core. After elaboration to the aldehyde, asymmetric alkynyl additions would be investigated.



Scheme 5.13 Part of Trost's synthesis of (+)-parviflorin using bromoacetoxonium chemistry. *Reagents and conditions:* a) $K_3Fe(CN)_6$, $(DHQ)_2PHAL$, OsO_4, $MeSO_2NH_2$, *t*-BuOH, H_2O; b) CH_3COBr, CH_2Cl_2, rt; c) Bu_3SnH, AIBN, toluene; d) MeCOCl, MeOH, rt.

Synthesis of butenolide-aldehyde **3.6** began with Alder-ene reaction of oct-1-ene **5.42** (Scheme 5.14).[99] Use of the catalyst RuCp(COD)Cl in conjunction with alkyne **5.43** gave desired butenolide **5.44** and ester **5.45** in 45% and 14% yield respectively. Use of Trost's new catalyst $[Ru(CH_3CN)_3Cp]PF_6$,[128] gave the desired product **5.44** in an improved yield of 63%, whilst reducing the yield of by-product **5.45** to 9%; furthermore the reaction proceeded at ambient temperature.

Dihydroxylation proceeded at the electron-rich alkene, producing diol **5.46** in 86% yield (Scheme 5.14). Subsequent periodate-mediated oxidative cleavage afforded butenolide-aldehyde **3.6** in 55% yield. This aldehyde proved to be very unstable so it was made freshly from the diol when required.



Scheme 5.14 Synthesis of butenolide-aldehyde **3.6**. *Reagents and conditions:* a) **5.43**, RuCp(COD)Cl, MeOH, rt → reflux; b) **5.43**, $[Ru(CH_3CN)_3Cp]PF_6$, DMF, 0 °C → rt; c) OsO_4, NMO, CH_2Cl_2, H_2O, rt; d) $NaIO_4$-SiO_2, CH_2Cl_2, H_2O, rt.

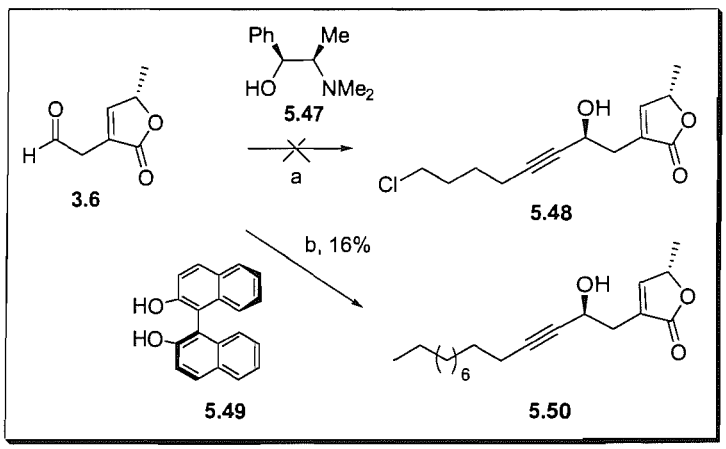
5.8 Asymmetric Alkynyl Addition

There are many methods for the asymmetric addition of an alkyne to an aldehyde; the most favoured in synthesis involve the use of organozinc reagents.[129] Highly enantioselective alkynylzinc additions to aldehydes (up to 99% *ee*) have been achieved by Carreira and co-workers.[130] They generated alkynylzinc reagents from terminal alkynes with $Zn(OTf)_2$ in the presence of an amine base and used a stoichiometric amount of a chiral amino alcohol *N*-methylephedrine to control the stereoselectivity. Pu[131] and Chan[132] were the first to use BINOL in asymmetric alkynylzinc additions. They found that BINOL in association with a dialkylzinc reagent and $Ti(^iPrO)_4$ effected highly enantioselective alkynylzinc additions to aldehydes in up to 99% *ee*.

We attempted the asymmetric addition of commercially available alkynes to butenolide aldehyde **3.6** using both methods since they both report excellent enantioselectivity.

Asymmetric addition of 6-chloro-1-hexyne to butenolide-aldehyde **3.6** in the presence of $Zn(OTf)_2$, Et_3N and *N*-methylephedrine **5.47** was unsuccessful (Scheme 5.15). ^1H NMR analysis of the crude product showed no product and no aldehyde peak. It is possible the chloride may have metallated and reacted with itself, or the aldehyde may have decomposed under the reaction conditions.

The next method attempted was that described by Pu and Chan using the more robust 1-dodecyne; this is the same method employed by Evans *et al.*[100] who achieved an 81% yield and a 20:1 d.r. Asymmetric addition of 1-dodecyne to butenolide-aldehyde **3.6** in the presence of Et_2Zn, $Ti(^iPrO)_4$ and (*R*)-BINOL **5.49** gave the propargylic alcohol **5.50** in a disappointing 16% yield and 60% *de* (Scheme 5.15). The reaction was repeated with fresh Et_2Zn which gave identical results. Possible reasons for the low yield include reaction at the wrong centre (i.e at the butenolide), or perhaps butenolide-aldehyde **3.6** did not survive the reaction conditions. This reaction was not investigated further due to insufficient material and time constraints.

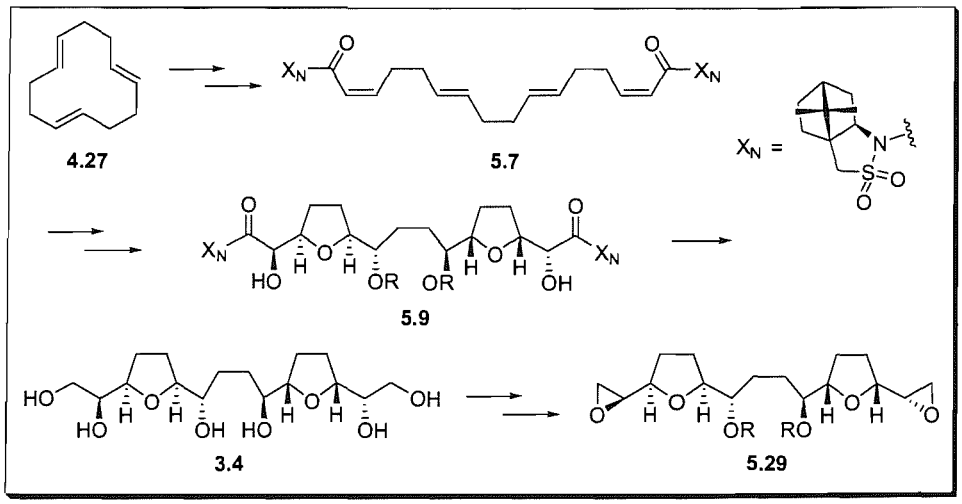


Scheme 5.15 Alkynylzinc additions to butenolide-aldehyde **3.6**. *Reagents and conditions:* a) $Zn(OTf)_2$, *N*-methylephedrine, toluene, Et_3N, rt; then 6-chloro-1-hexyne, rt; then butenolide-aldehyde **3.6**, rt; b) 1-dodecyne, Et_2Zn, toluene, reflux; then (*R*)-BINOL **5.49**, Et_2O, $Ti(^iPrO)_4$, rt; then butenolide-aldehyde **3.6**, rt.

Chapter 6

Concluding Remarks and Future Work

A quick and reasonably efficient route to the non-adjacent *bis*-THF core **5.9** of *cis*-sylvaticin has been demonstrated *via* the permanganate promoted bi-directional oxidative cyclisation of a tetraene. The tetraene substrate was available in five high yielding steps from the starting triene **4.27** (Scheme 6.1), with scope for altering the enoate double bond geometry or chiral auxiliary of tetraene **5.7**.



Scheme 6.1 Overview of the synthesis of the core of *cis*-sylvaticin (only one diastereomer is shown).

The bi-directional oxidative cyclisation of **5.7** appeared inefficient, affording **5.9** (R = H) in only 41% yield and as an estimated 3:1 mixture of diastereomers (Scheme 6.1). It should be noted, however, that this powerful transformation installs eight new stereogenic centres in one step, equating to a yield of approximately 87% per stereogenic centre taking the 3:1 ratio of diastereomers into account. Silyl protection of the central hydroxyls of **5.9** (R = H) afforded **5.9** (R = TBS/TIPS), however subsequent reductive cleavage of the chiral auxiliary proved unsuccessful. Perhaps the use of a different protecting group would enable separation of the diastereomers, either before or after reductive cleavage, thus affording an easily manipulated reduction product.

Reductive cleavage of the chiral auxiliaries gave a surprisingly low yield. We reasoned that a proportion of hexaol **3.4** had become irreversibly bound to silica after flash chromatography. Another possibility however is that incomplete reduction to the aldehyde occurred, followed by subsequent lactol formation. It would be interesting to see the effect of extended reaction time on the yield of the reaction.

The *mono*-tosylation route appeared promising but was inconclusive due to insufficient material. The optimised yield for *mono*-tosylation was 35% with 35% recovered starting material. Desymmetrisation could be improved at this juncture by anchoring one of the primary alcohols onto a solid-phase support and activating the remaining primary alcohol. This would eliminate the undesired *bis*-tosylation product and any cross-linked hexaol could be recovered after cleavage. A number of the subsequent steps could also be carried out on the solid-phase support.

The bi-directional approach appeared promising and afforded *bis*-epoxide **5.29** (R = H) in good yield (Scheme 6.1). Subsequent protection of the secondary alcohols presented an opportunity to separate the diastereomers, although this step was low yielding. Further investigation is required into the protection of secondary alcohols in the presence of epoxides, and it may be beneficial to try different protecting groups. We were able to successfully prove the absolute stereochemistry of the minor diastereomer by analysis of the x-ray crystal structure. This confirmed the predicted relative stereochemistry for the oxidative cyclisation of *cis-trans* 1,5-dienes. The absolute stereochemistry of the minor diastereomer was as we had predicted and it is therefore highly probable that our prediction for the major diastereomer is also correct.

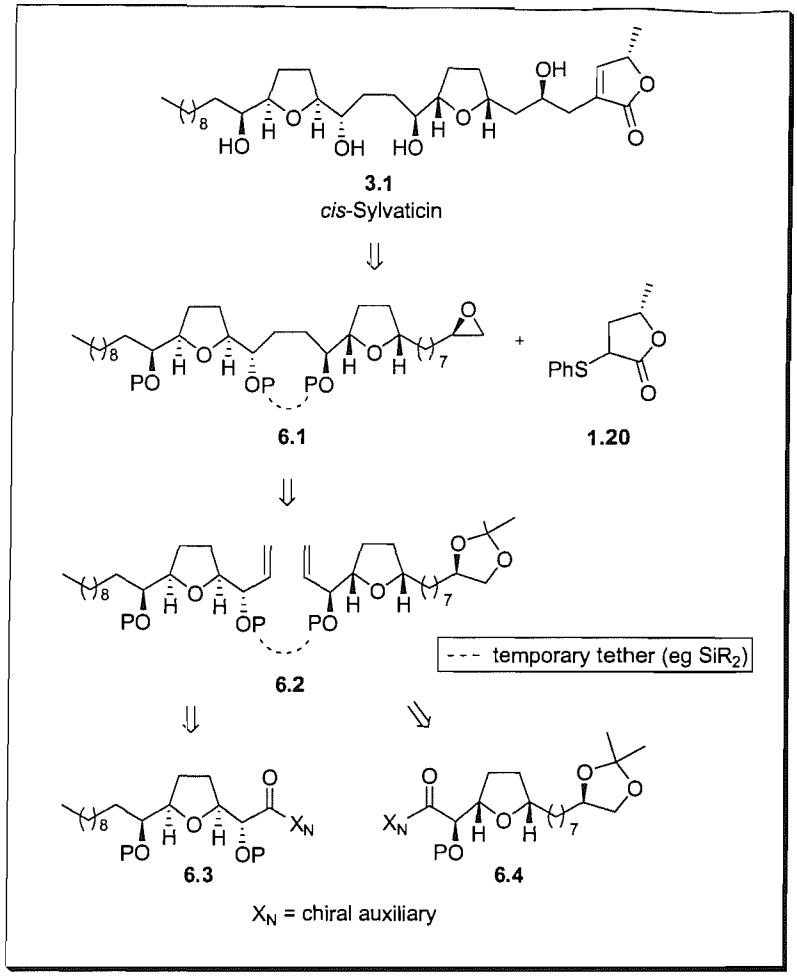
Desymmetrisation of *bis*-epoxide **5.29** (R = TBS) could not be investigated fully due to insufficient material; however opening of a *bis*-epoxide has been shown to proceed in reasonable yield[107]and it is anticipated that a similar level of efficiency would be observed in our system.

Whilst a bi-directional approach to *cis*-sylvaticin has its merits, any future approach should consider disconnecting the natural product back to the two *mono*-THF fragments **6.3** and **6.4**, with a view to connecting the fragments at a later juncture (Scheme 6.2).

The advantages of such an approach are:

- Individual elaboration of each fragment
- Oxidative cyclisation of a diene, a reaction that proceeds in high yield
- Facile separation of the two diastereomers
- Easily manipulated compounds

There are many ways in which the two fragments could be coupled, but by the far the most attractive lies in olefin metathesis since this is generally high-yielding and terminal olefins can be easily established within each fragment. As afore-mentioned (Section 1.6.4), Mootoo and Zhu used an olefin cross-metathesis reaction to synthesise the non-adjacent *bis*-THF natural product bullatanocin.[56] A more efficient metathesis approach however, would utilise a silicon-tethered cross-metathesis, eliminating dimer formation and the need for a huge excess of either coupling partner.[100] The butenolide portion and adjacent stereogenic centre could be installed by reaction of the anion of γ-lactone **1.20**[38] with epoxide **6.1** (Scheme 6.2).



Scheme 6.2 Retrosynthetic analysis of *cis*-sylvaticin with a metathesis approach towards the non-adjacent *bis*-THF core.

Chapter 7

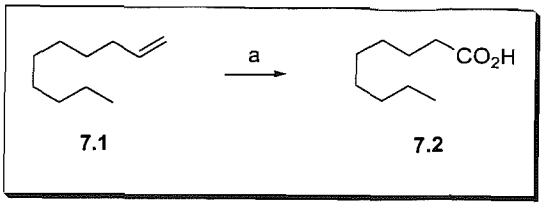
Phase-Transfer Catalysis and Dihydroxylation

The following introductory chapter summarises the use of chiral phase-transfer catalysts and chiral ligands in oxidation reactions in order to induce enantioselectivity. The use of permanganate and other oxidants in the dihydroxylation of olefins is also described.

7.1 Permanganate-Mediated Phase-Transfer Oxidation

The use of aqueous permanganate in synthesis is limited to the oxidation of organic compounds that are at least partially soluble in water. If the solubility is too low, then there is insufficient contact between the oxidant and the reductant, leading to a drastic reduction in the rate of reaction. A simple way to overcome this problem is to use polar organic solvent systems such as ethanol, acetone, pyridine, acetic acid and trifluoroacetic acid, however use of these solvents can lead to over-oxidation in some instances. An attractive alternative approach is provided by phase-transfer catalysis.

One of the first examples of the use of phase-transfer assisted permanganate oxidations involved the oxidative cleavage of 1-decene **7.1** into nonanoic acid **7.2** (Scheme 7.1).[133] Carboxylic acids are regularly observed as over-oxidation products in permanganate oxidations and this problem has been extensively investigated by Krapcho *et al.*[134] They proposed that this over-oxidation is propagated by hydroxide ions formed during the reduction of permanganate and found that the addition of acetic acid almost completely eliminated this problem.



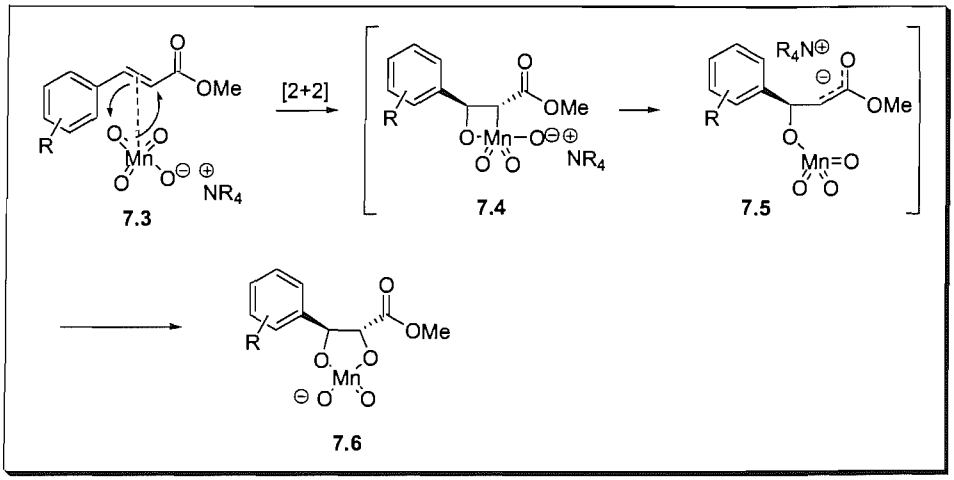
Scheme 7.1 Early phase-transfer catalysed permanganate oxidation. *Reagents and conditions:* $KMnO_4$, $Bu_4N^+Br^-$, benzene, H_2O.

Phase-transfer oxidations with permanganate can be performed in two ways: using either aqueous permanganate (liquid-liquid phase-transfer catalysis) or solid permanganate (solid-liquid phase-transfer catalysis). The factors that affect both these methods are identical; these are the ability of the phase-transfer catalyst to transport permanganate into the organic phase and the extent to which the ion pair will exist once there.[135]

Reagents such as tetrabutylammonium permanganate,[136] benzyltriethylammonium permanganate[137] and cetyltrimethylammonium permanganate[138] have been reported as efficient phase-transfer catalysts. These reagents use an organic soluble quaternary ammonium cation to transport permanganate into non-polar solvents. Additionally, crown ethers can be used as phase-transfer agents[139] through complexation of the potassium ion, thereby producing an ion pair that is soluble in organic solvents.

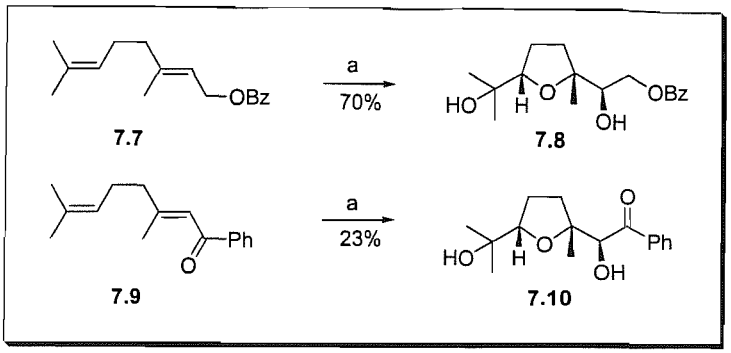
The permanganate promoted phase-transfer oxidation of alkenes was studied in depth by Lee *et al.*[74,75,140] Using methyl cinnamates as a model, they investigated the effect of phenyl ring substituents on the rate of reaction. They also looked at the effect of varying the chain lengths of the alkyl ammonium phase-transfer catalysts. The results showed that electron-withdrawing groups on the aromatic ring increased the rate of reaction and Lee therefore proposed a mechanism proceeding *via* an electron-rich transition state. Lee and co-workers also found that longer alkyl chains on the ammonium phase-transfer catalyst led to decreased rates of reaction. However, if one of the alkyl groups was replaced with a methyl group, the rate of reaction increased. Lee reasoned that the smaller methyl group allowed permanganate to get closer to the ammonium cation, thus producing a tighter ion pair; this led to the observed increase in the rate of reaction.

Lee proposed a mechanism which proceeded *via* a [2+2] cycloaddition between the olefin and permanganate eventually leading to a [3+2] product **7.6** (Scheme 7.2). After initial cycloaddition, rearrangement occurs resulting in intermediate **7.5**, which has an enolate type structure; this intermediate interacts with the ammonium cation giving it extra stabilisation. It is thought that electron-withdrawing groups on the phenyl ring increase the stability of this electron-rich intermediate. Further rearrangement results in Mn(V) ester **7.6**. Whilst this mechanism has its merits, intermediate **7.5** appears prone to racemisation. Therefore it is highly likely that the Mn(V) ester **7.6** is formed *via* a [3+2] cycloaddition, in accordance with Baldwin's mechanism (Scheme 2.3).



Scheme 7.2 Lee's proposed mechanism for permanganate-mediated phase-transfer oxidations.

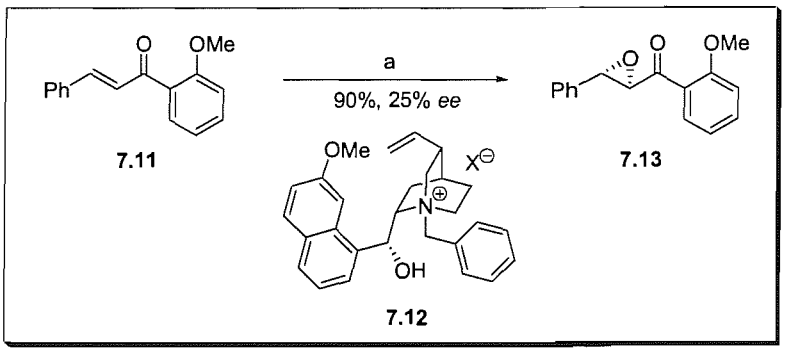
The permanganate-mediated phase-transfer oxidative cyclisations of dienes were first carried out in our group in 2001 using a liquid-liquid system.[141] Oxidative cyclisation of dienes **7.7** and **7.9** in the presence of adogen 464 gave the corresponding THF-diols **7.8** and **7.10** with varied results (Scheme 7.3). Most importantly however, it showed that this reaction could be carried out using non-polar substrates. Furthermore, asymmetric induction could be realised by simply switching to a chiral phase-transfer catalyst (CPTC).



Scheme 7.3 Permanganate-mediated phase-transfer oxidative cyclisations. *Reagents and conditions:* a) 0.4 M $KMnO_4$ (2 eq), AcOH (4 eq), adogen 464 (0.4 eq), Et_2O.

7.2 Chiral Phase-Transfer Catalysed Oxidation

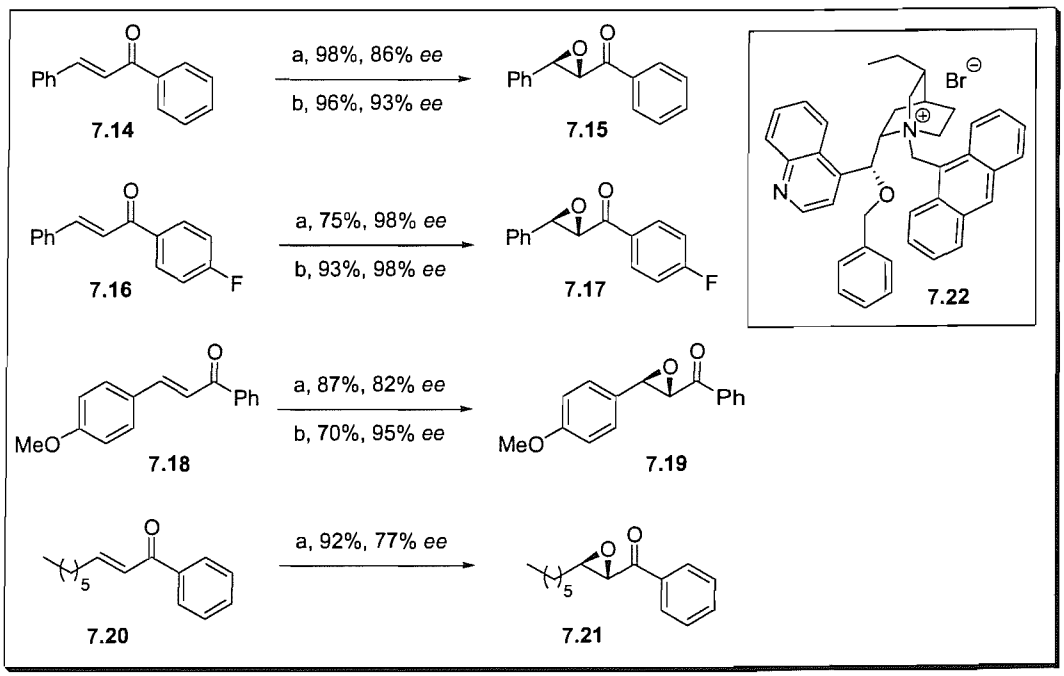
Work on chiral phase-transfer catalysts began in the 1970's with the pioneering work of Wynberg *et al.*[142] They used an alkaloid-based ammonium salt, quinine **7.12**, to catalyse the asymmetric epoxidation of chalcone derivatives (Scheme 7.4). Initially they achieved *ee*'s in the region of 25%. If the oxidant was switched from H_2O_2 to *t*-BuOOH or sodium hypochlorite, the stereochemical outcome was reversed.[143] It was later suggested that this was due to hydrogen bonding between hydrogen peroxide and the hydroxyl group.[144] Wynberg and co-workers also described the use of another alkaloid ammonium salt quibec.[143]



Scheme 7.4 Early chiral phase-transfer catalysis. *Reagents and conditions:* a) H_2O_2 (aq), **7.12** (5 mol%), toluene.

The encouraging enantioselectivity stimulated wide interest in the asymmetric epoxidation of chalcones. Several groups attempted to improve the *ee* but with limited success.[145-148]

It was not until the late 1990's that a breakthrough was made. Lygo *et al.* investigated the use of *cinchona* alkaloids in the chiral phase-transfer catalysed epoxidation of α-β-unsaturated phenones.[144,149-152] They found that benzylation of the secondary alcohol in the catalyst resulted in vastly improved *ee*'s. Thus *O*-benzyl-*N*-anthracenylmethyl cinchonidinium salts, when used in conjunction with sodium hypochlorite, gave between 70-98% *ee* (Scheme 7.5). It was also possible to prepare either enantiomer by using cinchonidine or its enantiomer cinchonine. Independently, Corey and Zhang had made the same discovery, however they had optimised the reaction conditions and were able to obtain higher *ee*'s with identical substrates (Scheme 7.5).[153]

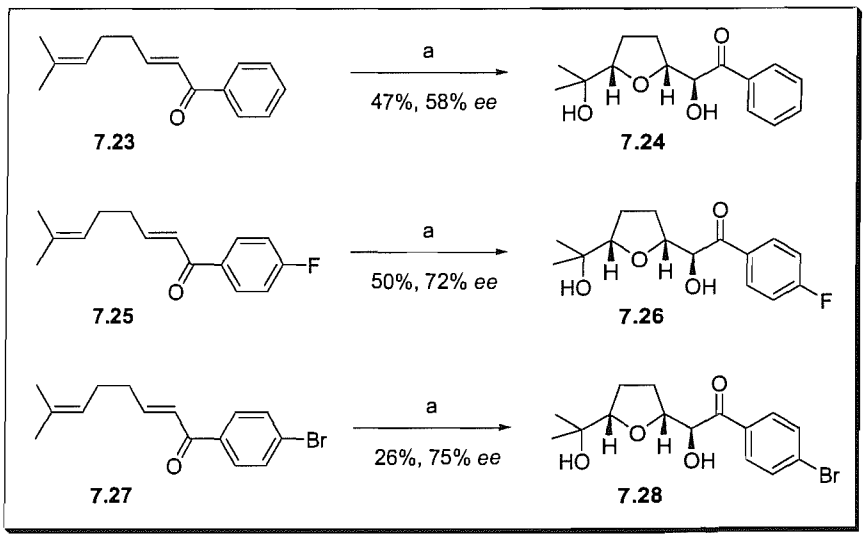


Scheme 7.5 Asymmetric epoxidation using cinchonidinium salt **7.22**. *Reagents and conditions:* a) Lygo: **7.22** (1 mol%), 15% NaOCl (aq, 2 eq), toluene, rt; b) Corey: **7.22** (10 mol%), KOCl (aq), toluene, −40 °C.

7.3 Permanganate Promoted Chiral Phase-Transfer Catalysed Oxidative Cyclisation

The results from the asymmetric epoxidation of chalcone derivatives appeared very promising. Potentially, this methodology could be applied to other reactions using similar substrates. Having already established a method for the racemic permanganate promoted phase-transfer catalysed oxidative cyclisation in our group, work began on the asymmetric version.

Oxidative cyclisation of phenone **7.23** in the presence of cinchonidinium salt **7.22** at 0 °C gave an enantiomeric excess of 39%.[154] Lowering the temperature of the reaction to −30 °C and switching from a $KMnO_4$ (aq)/CH_2Cl_2 (liquid-liquid phase-transfer) system to a $KMnO_4$ (s)/CH_2Cl_2 (solid-liquid phase-transfer) system improved the *ee* to 58% (Scheme 7.6).[141] Substitution of the phenyl ring improved the *ee* to 75% for the *para*-bromo derivative **7.27**.



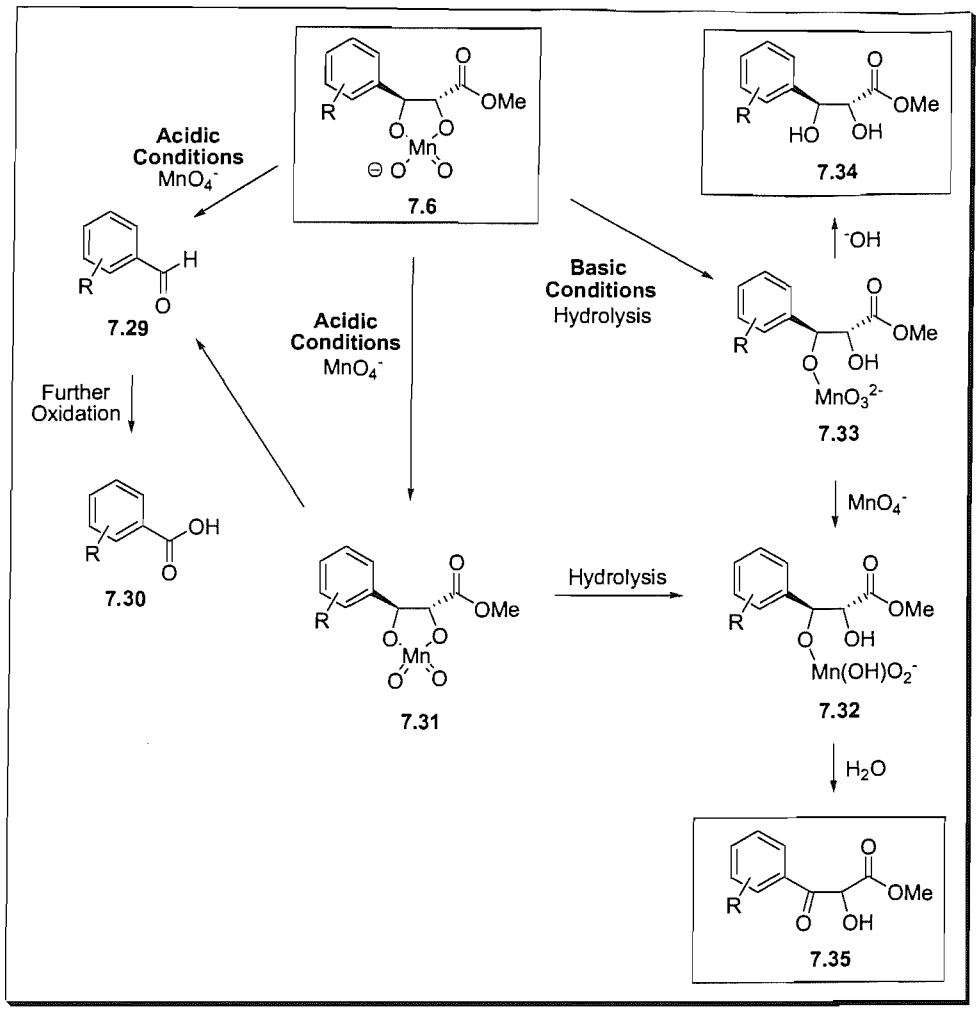
Scheme 7.6 Chiral phase-transfer catalysed oxidative cyclisation. *Reagents and conditions:* a) $KMnO_4$ (s, 1.6 eq), **7.22** (10 mol%), AcOH (6.5 eq), CH_2Cl_2, −30 °C.

These initial results were very promising and further chiral phase-transfer catalysed oxidative cyclisation reactions were carried out in our laboratory, achieving *ee*'s of up to 93%.[125] Essentially, this demonstrated the application of the chiral phase-transfer methodology to a different reaction using similar substrates.

It would be interesting to investigate whether asymmetric dihydroxylation using permanganate could also be realised.

7.4 Dihydroxylation Using Permanganate

The permanganate dihydroxylation reaction is a stereospecific process which adds two hydroxyl groups across the same face of an olefin. It has been shown that the two oxygen atoms are transferred directly from the MnO_4^- ion from experiments with ^{18}O labelled permanganate.[155] This is in accordance with the mechanism described by Lee, in which a [2+2] cycloaddition occurs between an olefin and permanganate eventually leading to [3+2] product **7.6** (Scheme 7.2). What happens next to the hypomanganate ester is highly dependent upon the reaction conditions. Under conditions of high basicity, hypomanganate ester **7.6** can undergo hydrolysis to give Mn(V) intermediate **7.33**, which is then converted into diol **7.34** or oxidised to Mn(VI) intermediate **7.32** (Scheme 7.7); both these processes are fast but dihydroxylation dominates if the hydroxide concentration is high (i.e. at high pH). Rearrangement of Mn(VI) intermediate **7.32** results in hydroxyketone **7.35**. Under acidic conditions (low hydroxide concentration), the hypomanganate ester can undergo oxidation to the cyclic manganate(VI) diester **7.31**, which undergoes cleavage to give aldehyde **7.29** at low pH, or hydrolysis *via* **7.32** to give hydroxyketone **7.35** at slightly acidic pH.[135]



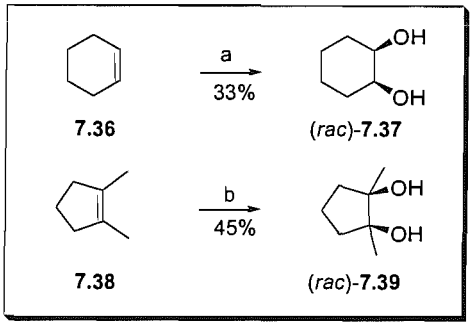
Scheme 7.7 Fate of the hypomanganate ester **7.6** under different conditions.

The pH regions in which these different reactions occur are not sharply divided and consequently a mixture of products is obtained. Competition between ring-opening by the hydroxide ion and oxidation by MnO_4^- accounts for the mixture of products at mid-range pH.

The main by-product is Mn(IV) which is apparent as colloidal MnO_2 in the reaction mixture. MnO_2 is formed in the glycol pathway through hydrolysis and disproportionation of Mn(V) to Mn(VII) and Mn(IV). Cleavage of hypomanganate ester **7.6** to aldehyde **7.29** readily occurs under strongly acidic conditions since the by-product Mn(III) is stable in acid; cleavage occurs to a lesser extent in neutral or basic solutions.[135]

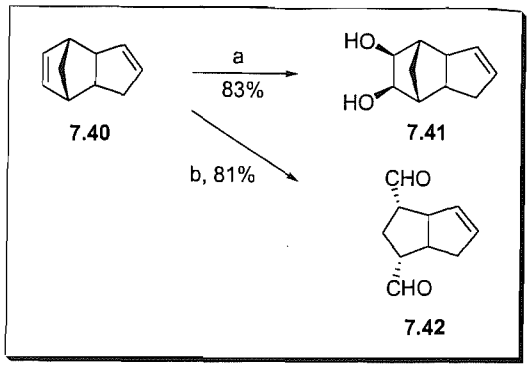
Dihydroxylation reactions using aqueous permanganate have been known for over a century. In fact this reagent was originally used for the conversion of alkenes such as malearic and fumaric acid into the corresponding diols; a process known as the Wagner dihydroxylation reaction.[156] As previously mentioned, reactions using aqueous permanganate need to be conducted in polar solvents or in conjunction with a phase-transfer catalyst to be effective.

The use of a polar solvent such as aqueous ethanol in the dihydroxylation of cyclohexene **7.36** produced the corresponding diol **7.37** in 33% yield,[157] whilst dihydroxylation of 1,2-dimethyl-cyclopentene **7.38** in aqueous acetone gave the corresponding diol **7.39** in 45% yield[158] (Scheme 7.8).



Scheme 7.8 Dihydroxylation using aqueous permanganate in polar solvents. *Reagents and conditions:* a) $KMnO_4$, H_2O/EtOH; b) $KMnO_4$, H_2O/acetone.

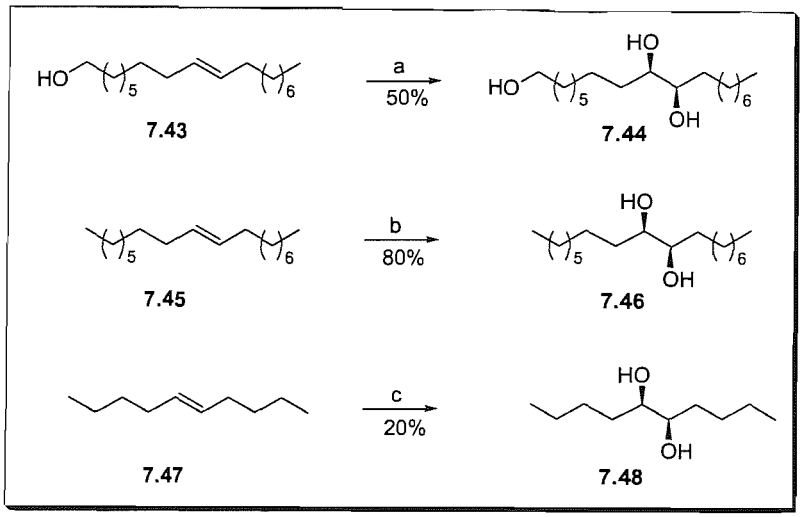
The yields obtained were low, however the use of phase-transfer catalysis greatly improved the efficacy of the reaction. In 1979, Ogino *et al.*[159] showed that benzyltriethylammonium chloride could be used as a phase-transfer reagent to effect dihydroxylation (solid-liquid phase-transfer catalysis). They oxidised alkene **7.40** to the corresponding Mn(V) diester and then quenched with aqueous solutions of varying pH (Scheme 7.9). If the aqueous solution was basic, diol **7.41** was formed; if it was acidic dialdehyde **7.42** was produced. The results were in accordance with the Lee's proposed mechanism for permanganate oxidation (Scheme 7.2) and confirmed the fate of the Mn(V) diester under basic and acidic conditions (Scheme 7.7).



Scheme 7.9 Early phase-transfer dihydroxylation using permanganate. *Reagents and conditions:* a) (i) $KMnO_4$, benzyltriethylammonium chloride, CH_2Cl_2, 0 °C; (ii) 3% NaOH; b) (i) $KMnO_4$, benzyltriethylammonium chloride, CH_2Cl_2, 0 °C; (ii) AcOH/AcONa (aq), pH 3.

The Mn(V) diester is known to be quite unstable in aqueous systems and only a transient existence had ever been detected prior to these experiments. The Mn(V) diester appeared to be long-lived in non-aqueous media, perhaps because it was complexed to the quaternary ammonium ion. Ogino postulated that the yield of the reaction was high because the Mn(V) diester was protected against oxidation by permanganate, and that in the absence of water hydrolysis could not occur. This route provided a simple method for the synthesis of a number diols and dialdehydes which would otherwise have been difficult to synthesise. It should be noted that a high yield (80%) was also obtained for the dihydroxylation of the terminal alkene 1-octene.

Diols can also be obtained from phase-transfer assisted oxidations if the reactions are carried out in contact with an aqueous solution of sodium hydroxide (liquid-liquid phase-transfer catalysis).[160] A few examples of liquid-liquid phase-transfer dihydroxylations using various phase-transfer reagents are shown (Scheme 7.10).



Scheme 7.10 Phase-transfer dihydroxylation using permanganate and various phase-transfer reagents. *Reagents and conditions:* a) $KMnO_4$, tetrabutylammonium bromide, CH_2Cl_2, 20% NaOH;[161] b) $KMnO_4$, dicyclohexano-18-crown-6, CH_2Cl_2, 40% NaOH;[162] c) $KMnO_4$, adogen 464, CH_2Cl_2, 15% NaOH.[163]

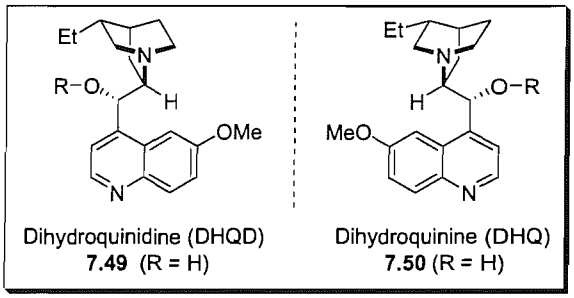
7.5 Dihydroxylation Using Osmium Tetroxide

The dihydroxylation of olefins using osmium tetroxide was first discovered in the 1930's by Criegee.[164,165] He showed that the reaction of stoichiometric amounts of OsO_4 with olefins was greatly accelerated in the presence of pyridine.

The reaction was not catalytic however and as osmium is expensive and toxic, the use of co-oxidants to re-oxidise the Os(VI) glycolate by-products needed to be investigated. Early catalytic dihydroxylations were carried out in the presence of hydrogen peroxide;[166] this led to diminished yields however due to over-oxidation. The dihydroxylation reaction was improved in 1976 by the work of Sharpless and Akashi[167] who used the cheap co-oxidant *t*-BuOOH to re-oxidise the Os(VI) glycolate by-products. Later that year, the catalytic osmylation reaction was greatly enhanced by Van Rheenen *et al.*[108] who used *N*-methylmorpholine *N*-oxide as the co-oxidant; this process became known as the Upjohn dihydroxylation reaction. Later in 1990, Minato *et al.*[168] demonstrated the efficacy of the $K_3Fe(CN)_6/K_2CO_3$ system.

It had already been shown that tertiary amines could accelerate the osmylation reaction and thus asymmetric induction was possible through the use of chiral amine ligands. This ligand acceleration effect ensures that the reaction is funnelled through a pathway involving the chiral catalyst.

Initial efforts by Sharpless to induce enantioselectivity focused upon the use of chiral pyridine derivatives. These ligands were unsuccessful however, due to their low affinity for OsO_4.[169] They focused their attention on quinuclidine derivatives, which were known to have a high affinity for OsO_4. Initial experiments using the acetate esters of *cinchona* alkaloids as chiral ligands (Figure 7.1, R = OAc) and stoichiometric amounts of OsO_4 produced the corresponding diols in moderate to good *ee*.[169] This later became catalytic when *N*-methylmorpholine *N*-oxide was employed as the co-oxidant.[170]



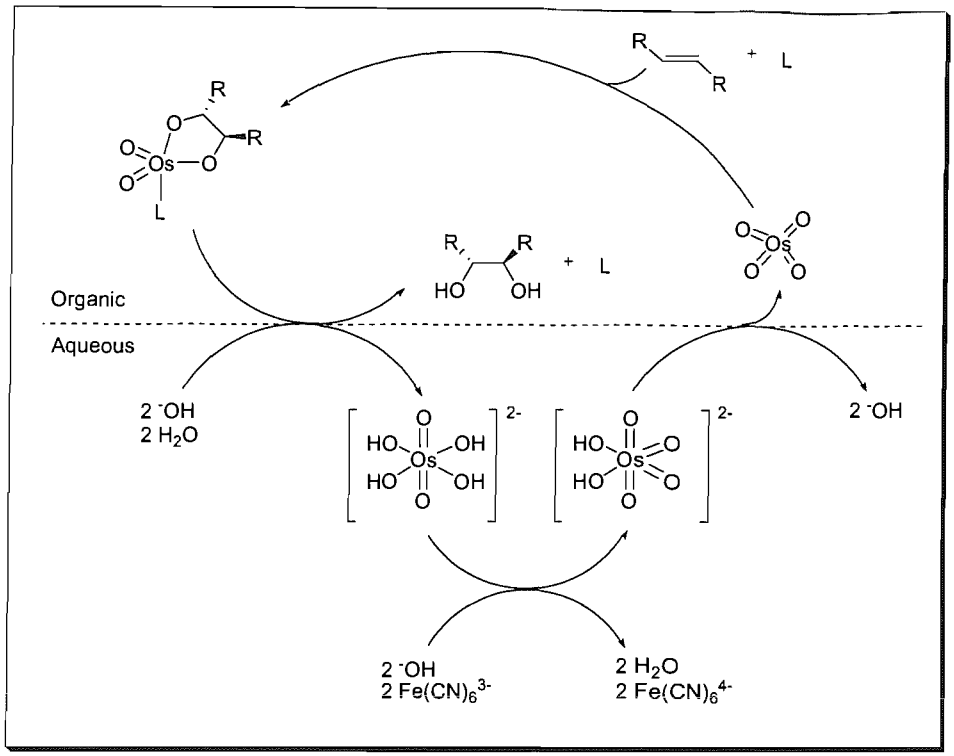
Dihydroquinidine (DHQD) **7.49** (R = H)

Dihydroquinine (DHQ) **7.50** (R = H)

Figure 7.1 *Cinchona*-based ligands for asymmetric dihydroxylation with osmium tetroxide.

The *ee*'s obtained from the catalytic reaction were moderate due to a second catalytic cycle and progress at this time was slow. There were three key discoveries in their group however which led to a dramatic increase in progress:

1. Kwong found that the second catalytic cycle could be virtually eliminated by conducting the reaction in a two-phase *t*-BuOH/H_2O system with $K_3Fe(CN)_6$ as the stoichiometric re-oxidant (Scheme 7.11).[171]



Scheme 7.11 Dihydroxylation using OsO_4 in a two-phase system.

Under these conditions, the only oxidant in the organic layer is OsO_4; this is in contrast to the Upjohn dihydroxylation system. Osmylation takes place in the organic layer. The resulting Os(VI) monoglycolate ester undergoes hydrolysis, releasing the diol and chiral ligand to the organic layer and Os(VI) to the aqueous layer, before its re-oxidation can occur; thus entry of the osmium glycolate into the second catalytic cycle is prevented. The use of $K_2OsO_2(OH)_4$ as a non-volatile osmium source, in combination with the inorganic co-oxidant $K_3Fe(CN)_6$, enabled a pre-mix to be formulated containing all the reagents including the ligand. The commercially available "AD-mix" enables the reaction to be carried out easily.

2. Amberg and Xu found that hydrolysis of the Os(VI) glycolate could be accelerated by $MeSO_2NH_2$ (the sulfonamide effect).[172] They found the reaction time could be as much as 50 times shorter in the presence of this additive. The sulfonamide effect allowed high catalytic turnovers even with sterically encumbered substrates, thus allowing *tetra*-substituted alkenes into

the scope of the reaction. Furthermore, the reaction could now be carried out at 0 °C instead of rt, which increased the selectivity.[173]

3. A new generation of ligands with two independent *cinchona* alkaloid units linked by a heterocyclic spacer were found to increase both the enantioselectivity and the scope of the reaction. These included ligands with either a phthalazine core[172] or a diphenylpyrimidine core.[174] These second generation ligands have now superceded the first generation (Figure 7.2).

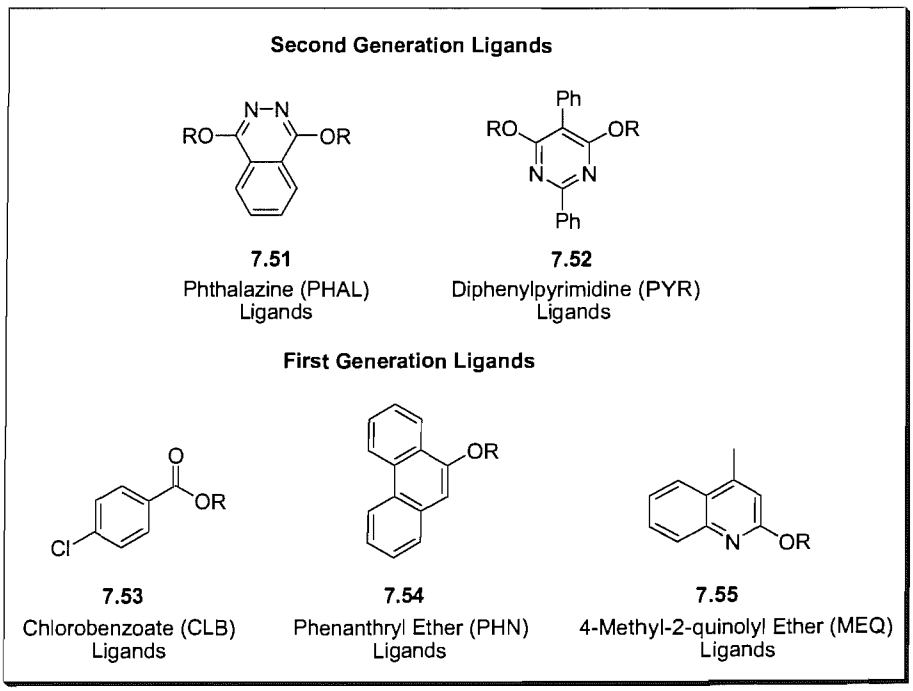


Figure 7.2 The latest generation of dimeric PHAL and PYR ligands and their predecessors (R = DHQD or DHQ).

These three key discoveries have led to a catalytic asymmetric dihydroxylation reaction which encompasses a broad range of alkenes and can induce excellent enantioselectivity (up to 99% *ee*) (Table 7.1).

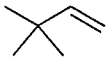
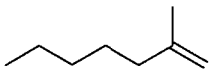
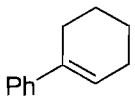
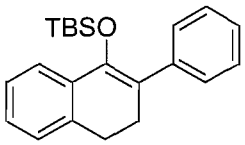
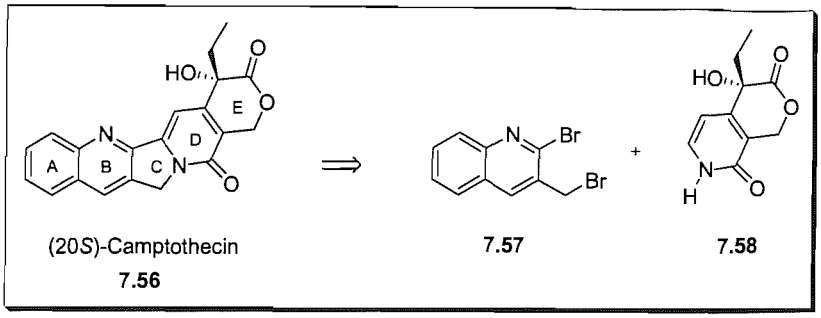
Substrate	PHAL(DHQD)	PHAL (DHQ)
	64% *ee*	66% *ee*
	78% *ee*	76% *ee*
	99% *ee*	99% *ee*
	99% *ee*	97% *ee*
	93% *ee*	95% *ee*

Table 7.1 Examples of the wide range of substrates that can undergo Sharpless asymmetric dihydroxylation.

Recent work has focused upon overcoming both the high cost of the ligands and the toxicity problem associated with OsO_4 by recycling. *Cinchona*-based alkaloids have been immobilised by attaching them to solid organic polymers or inorganic supports.[175,176] This eased the separation of the ligands but compromised the high activity and enantioselectivity. More promisingly, soluble supported ligands have also been prepared which retain the high enantioselectivity and can be precipitated and filtered out after the reaction.[177] Catalyst recovery has been accomplished by anchoring OsO_4 onto an insoluble polymer support[178] or by employing ionic liquids.[179]

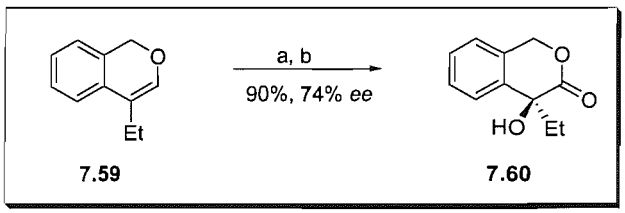
The asymmetric dihydroxylation of olefins using osmium tetroxide is now a powerful process that has found widespread application in synthesis.[180,181] One example is found in the synthesis of a fragment of the anti-cancer compound (20*S*)-camptothecin **7.56** (Scheme 7.12). This compound is an important anti-cancer lead, discovered through the screening of natural products. Comins reported a highly convergent 10-step asymmetric synthesis of this target which utilised DE fragment **7.58** as the key chiral intermediate (Scheme 7.12).[182]



Scheme 7.12 Retrosynthetic analysis of (20*S*)-camptothecin.

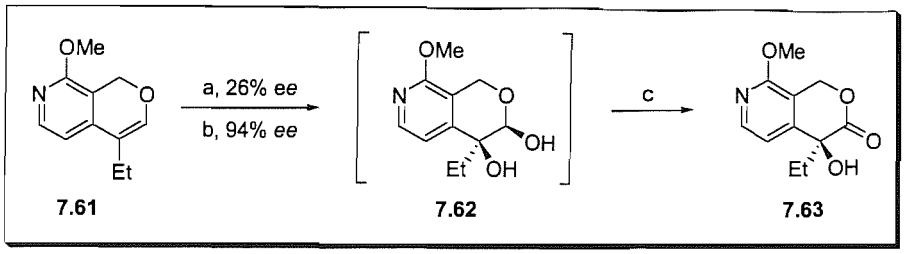
However, preparation of DE fragment **7.58** required stoichiometric amounts of the expensive chiral auxiliary (−)-8-phenylmenthol. In order to overcome this obstacle, two groups investigated the possibility of introducing chirality into fragment **7.58** using asymmetric dihydroxylation.

Curran and Ko[183] investigated the asymmetric dihydroxylation of endocyclic enol ether **7.59** (Scheme 7.13). After oxidation to the corresponding lactone, analogous fragment **7.60** was obtained in 90% yield and 74% *ee*.



Scheme 7.13 Dihydroxylation of an endocyclic enol ether by Curran and Ko. *Reagents and conditions:* a) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH, H_2O, 0 °C; b) $I_2/CaCO_3$.

Independently, Fang *et al.*[184] were investigating the synthesis of the key fragment **7.58** *via* asymmetric dihydroxylation of enol ether **7.61** (Scheme 7.14). When the reaction was carried out using AD-mix-β (containing $(DHQD)_2PHAL$), lactone **7.63** was obtained in 26% *ee*. When the reaction was repeated with $(DHQD)_2PYR$ the same lactone was obtained in 94% *ee*. Furthermore, conversion of lactone **7.63** to the corresponding pyridone in dilute HCl afforded a crystalline enantiomerically pure product (> 95% *ee*) after filtration of the reaction mixture.

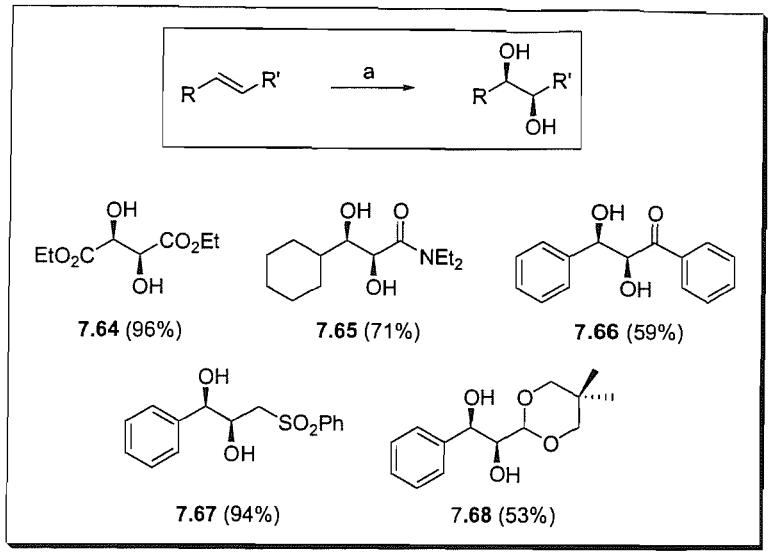


Scheme 7.14 Dihydroxylation of an endocyclic enol ether by Fang *et al. Reagents and conditions:* a) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH, H_2O, 0 °C; b) $(DHQD)_2PYR$, $K_3Fe(CN)_6$, $K_2OsO_2(OH)_4$, K_2CO_3, $MeSO_2NH_2$, *t*-BuOH, H_2O; c) $I_2/CaCO_3$.

7.6 Dihydroxylation Using Ruthenium Tetroxide

In 1994, Shing reported the use of ruthenium(VIII) tetroxide, prepared *in situ* from ruthenium(III) chloride, in the dihydroxylation of olefins.[185] Due to the high redox potential of Ru(VIII) compared to Os(VIII), over-oxidation and fission were common side reactions. Plietker and Niggeman[186-188] looked into the ruthenium tetroxide-catalysed dihydroxylation of olefins known to be unreactive to osmium tetroxide. They found that the addition of catalytic amounts of protic acids led to a significant rate acceleration and consequently reduced the catalyst loading to 0.5 mol% whilst maintaining short reaction times (Scheme 7.15). They rationalised that the presence of acid enabled rapid hydrolysis of the intermediate Ru(VI) diester.

Plietker and Niggeman also found that acid-labile functional groups such as allylic halides, esters and amides were compatible with the reaction conditions due to the short reaction time; even acetals could be dihydroxylated under adapted conditions.



Scheme 7.15 Ruthenium tetroxide-catalysed dihydroxylation. *Reagents and conditions:* a) 0.5 mol% $RuCl_3$, 20 mol% H_2SO_4, $NaIO_4$ (1.5 eq), $EtOAc/CH_3CN/H_2O$ (6:6:1), 0 °C, 5 min.

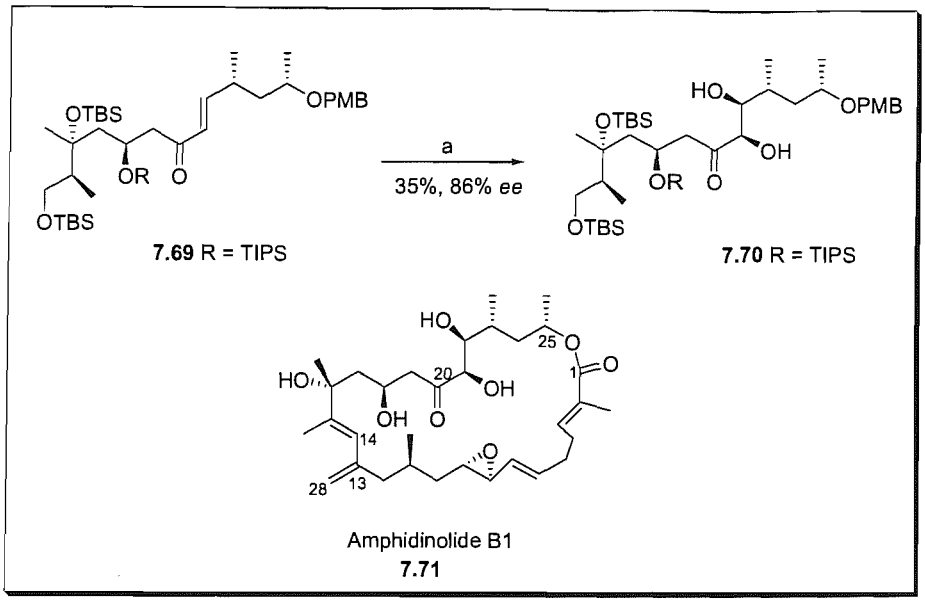
7.7 Introduction to the Proposed Work

Dihydroxylation systems using OsO_4 realise enantioinduction through the use of chiral ligands on the osmium centre[189]or chiral auxiliaries present in the substrate.[190-192] Osmium tetroxide-catalysed dihydroxylation has great synthetic utility, however as osmium is toxic, volatile and expensive, its use on an industrial scale has been discouraged.

The use of permanganate in industrial applications has become attractive owing to the recent introduction of a process for recycling manganese dioxide, the by-product from oxidations.[193] It is first oxidised to potassium manganate(VI) by oxygen in a concentrated potassium hydroxide solution and then converted to $KMnO_4$ electrochemically. Permanganate is cheap and relatively non-toxic compared with OsO_4.

Osmium tetroxide has one further pitfall in that it has a high affinity for electron-rich double bonds but is markedly less reactive towards electron-deficient double bonds. One example is in the synthesis of the C14-C25 portion of the cytotoxic natural

product amphidinolide B1 **7.71**, where asymmetric dihydroxylation of enone **7.69** produced diol **7.70** in only 35% yield after 1 ½ days (Scheme 7.16).



Scheme 7.16 The key dihydroxylation step in the synthesis of a portion of amphidinolide B1. *Reagents and conditions:* a) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH/H_2O (1:1), 0 °C, 1 ½ days.

Asymmetric induction in permanganate oxidation has been demonstrated in oxidative cyclisation reactions *via* the use of chiral auxiliaries.[76] Later on, within our group, this was extended to the use of chiral quaternary ammonium salts.[141] Good levels of enantioselectivity were obtained in the oxidation of 1,5-dienes in the presence of a chiral phase-transfer catalyst.

Inoue *et al.*[194] showed that asymmetric permanganate dihydroxylation of styrene using chiral ammonium salts such as benzylmenthyldimethyl ammonium bromide gave very low levels of enantioselectivity (< 5%). The efficiency of the asymmetric permanganate dihydroxylation reaction in the presence of a chiral phase-transfer agent is therefore yet to be proven. To our knowledge there has been no further progress in this area.

In this programme of research, dihydroxylation using permanganate will be investigated under phase-transfer conditions. Once optimised conditions have been established, asymmetric induction will be investigated through the use of a chiral phase-transfer agent.

As previously mentioned, permanganate oxidations under basic conditions favour dihydroxylation; hence these reactions will be conducted in alkaline media. Initially, dihydroxylation studies will focus upon commercially available alkenes to elucidate the optimised reaction conditions. Once established, the investigation will focus upon the asymmetric dihydroxylation of enones. These are ideal substrates as permanganate has a high affinity for electron-deficient double bonds,[74,75] and enones have been shown to undergo permanganate-mediated oxidative cyclisation to the corresponding THF-diols in good levels of enantioselectivity[125,141]

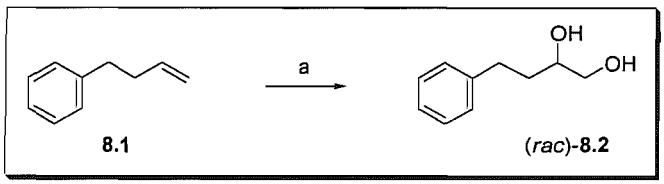
Chapter 8

Dihydroxylation Using Permanganate Under Phase-Transfer Conditions

The following chapter describes the development of a new asymmetric dihydroxylation reaction using permanganate in the presence of a chiral phase-transfer agent.

8.1 Dihydroxylation of Simple Alkenes

Initial reactions were carried out on commercially available alkene 4-phenyl-1-butene **8.1** under a variety of conditions (Scheme 8.1). Firstly, a solid-liquid phase-transfer protocol was followed as described by Ogino *et al.*[159] (Table 8.1, Entry 1). This involved the reaction of permanganate with the olefin in organic solvent in the presence of the phase-transfer catalyst adogen 464. After quenching with 3% NaOH (aq) solution, diol (*rac*)-**8.2** was afforded in 29% yield.



Scheme 8.1 Dihydroxylation of 4-phenyl-1-butene. *Reagents and conditions:* a) See Table 8.1.

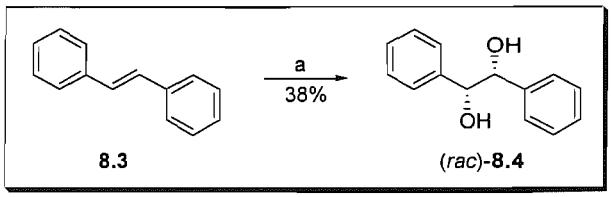
Entry	Reagents and conditions	Yield
1	$KMnO_4$ (1.5 eq), adogen 464 (1.5 eq), CH_2Cl_2, 0 °C; then 3 % NaOH (aq)	29%
2	$KMnO_4$ (1.5 eq), adogen 464 (1.5 eq), CH_2Cl_2, 3 % NaOH (aq), 0 °C	66%
3	$KMnO_4$ (1.5 eq), adogen 464 (1.5 eq), CH_2Cl_2, pH 9 buffer (aq), 0 °C	65%

Table 8.1 Dihydroxylation of 4-phenyl-1-butene (See Scheme 8.1).

The reaction was repeated using the biphasic protocol described by Weber *et.al.*[160] (Table 8.1, Entry 2). This liquid-liquid phase-transfer protocol showed a marked improvement on the solid-liquid phase-transfer protocol, producing diol (*rac*)-**8.2** in 66% yield. It is possible that strongly basic conditions would lead to decomposition of the diol, especially if this methodology is to be extended to enones; thus it was deemed advantageous to reduce the pH whilst still maintaining a high diol/hydroxyketone ratio (hydroxyketones form under mildly acidic conditions).

A pH 9 buffer was used instead of 3% NaOH (aq) in the liquid-liquid phase-transfer dihydroxylation of 4-phenyl-1-butene **8.1** (Table 8.1, Entry 3). Diol (*rac*)-**8.2** was produced in an almost identical 65% yield, thus the reduced pH had not detrimentally affected the efficiency of the reaction. The racemic mixture of products was separated by analytical chiral column chromatography and this confirmed the expected 1:1 mixture of enantiomers.

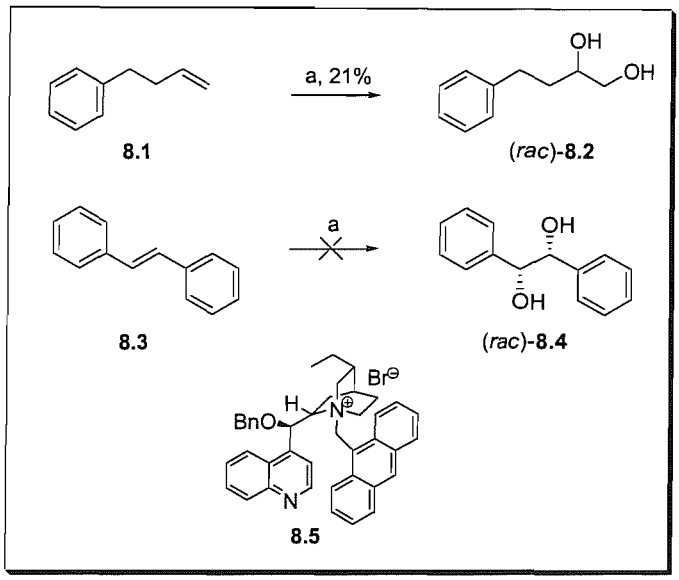
Dihydroxylation of *trans*-stilbene **8.3** was attempted using the more basic biphasic conditions (Scheme 8.2). Diol (*rac*)-**8.4** was obtained in 38% yield.



Scheme 8.2 Dihydroxylation of *trans*-stilbene. *Reagents and conditions:* a) $KMnO_4$ (1.5 eq), adogen 464 (1.5 eq), CH_2Cl_2, 3% NaOH (aq), 0 °C.

The conditions established for the dihydroxylation of 4-phenyl-1-butene **8.1** and *trans*-stilbene **8.3** appeared promising. Our efforts now focused upon introducing asymmetric induction into the dihydroxylation of these alkenes. As previously mentioned (Section 7.2 and 7.3), *cinchona*-based alkaloids are effective chiral phase-transfer agents; hence the dihydroxylation reaction was conducted in the presence of **8.5** (Scheme 8.3). Dihydroxylation of 4-phenyl-1-butene **8.1**, in the presence of **8.5** afforded diol **8.2** in 21% yield (Scheme 8.3). The yield was low since only sub-

stoichiometric amounts of the phase-transfer agent were used; furthermore, no enantiomeric excess was obtained as shown by analytical chiral chromatography.



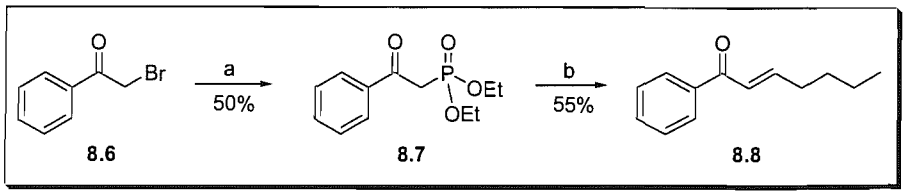
Scheme 8.3 Dihydroxylation in the presence of a chiral phase-transfer agent. *Reagents and conditions:* a) $KMnO_4$ (1.5 eq), **8.5** (20 mol%), CH_2Cl_2, pH 9 buffer (aq), 0 °C.

The dihydroxylation of *trans*-stilbene **8.3** was attempted in the presence of chiral phase-transfer agent **8.5** (Scheme 8.3). Diol **8.4** was not produced, however by-products including the hydroxyketone and benzoic acid were isolated.

The lack of asymmetric induction in the dihydroxylation of 4-phenyl-1-butene **8.1** can be rationalised by this substrate not fitting optimally within the phase-transfer catalyst; a strong interaction between the ammonium cation and the substrate is required for asymmetric induction. Given this requirement, our efforts now focused upon the application of these conditions to enones, since these substrates would fit optimally within the phase-transfer agent.

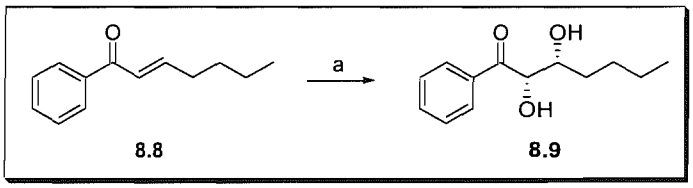
8.2 Dihydroxylation of Enones

Initially, enone substrates were synthesised using the HWE reaction.[102,103,109] Arbuzov reaction of bromide **8.6** produced phosphonate **8.7** in 50% yield (Scheme 8.4). Deprotonation and reaction with valeraldehyde afforded enone **8.8** in 55% yield. The *E*-isomer was produced exclusively, as shown by ^{1}H NMR spectroscopy.



Scheme 8.4 Enone synthesis. *Reagents and conditions:* a) $P(OEt)_3$, xylene, reflux; b) NaH, valeraldehyde, THF, rt.

Dihydroxylation of enone **8.8** using permanganate (Scheme 8.5) produced diol (*rac*)-**8.9** in 55% yield under achiral phase-transfer conditions (Table 8.2, Entry 1), whilst dihydroxylation using permanganate under chiral phase-transfer conditions produced diol **8.9** in 45% yield and an encouraging 50% *ee* (Table 8.2, Entry 2).



Scheme 8.5 Dihydroxylation of enone **8.8**. *Reagents and conditions:* a) See Table 8.2.

Entry	Reagents and conditions	Yield	*ee*
1	$KMnO_4$ (1 eq), adogen 464 (1 eq), pH 9 buffer, CH_2Cl_2, 0 °C	55%	0%
2	$KMnO_4$ (1 eq), **8.5** (100 mol%), pH 9 buffer, CH_2Cl_2, 0 °C	45%	50%

Table 8.2 Dihydroxylation of enone **8.8**.

The absolute stereochemistry of the major enantiomer was determined from the x-ray crystal structure of the 4-bromo-phenyl derivative, crystallised to enantiomeric purity from hexane.[195] The facial selectivity can be explained using Lygo's model and the mechanism proposed by Corey[153] (Figure 8.1). The α,β-unsaturated enone lies within the chiral phase-transfer agent with the aryl group wedged between the ethyl and quinoline substituents on the quinuclidine ring; simultaneously, the carbonyl oxygen is placed as close to the ammonium cation as permitted by van der Waals forces. The permanganate ion forms an ion pair with the only accessible face of the ammonium cation and it is therefore in close proximity to the lower face of the enone double bond. Subsequent attack of the double bond occurs from the lower face, thus explaining the enantioselectivity. An aryl group such as 4-fluorophenyl has a stronger edge interaction with the quinoline ring than phenyl and often leads to better enantioselectivities.

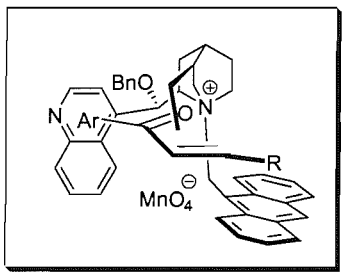
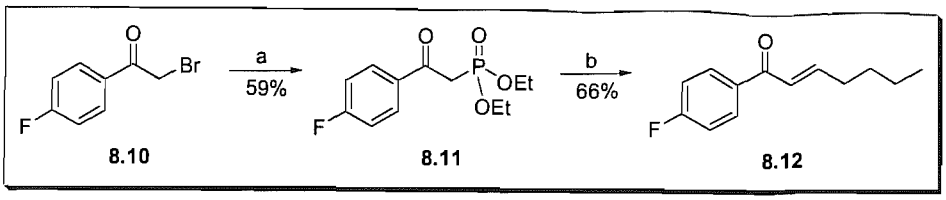


Figure 8.1 Facial selectivity in dihydroxylation reactions using cinchonidine-derived phase-transfer agent **8.5**.

Previous work within our group had shown that the chiral phase-transfer catalysed oxidative cyclisation of *para*-substituted phenone dienes gave higher *ee*'s than their unsubstituted counterparts.[141] Subsequent dihydroxylation reactions were therefore conducted on *para*-substituted phenyl enone derivatives.

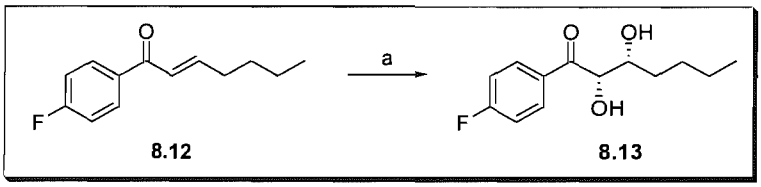
The same protocol described for the synthesis of enone **8.8** was applied to the synthesis of the 4-fluoro-phenyl enone derivative **8.12** (Scheme 8.6). Phosphonate **8.11** was afforded in 59% yield and after deprotonation and reaction with valeraldehyde, enone **8.12** was produced in 66% yield. The *E*-isomer was produced exclusively, as shown by ^{1}H NMR spectroscopy.



8.10 8.11 8.12

Scheme 8.6 Synthesis of 4-fluoro-phenyl enone. *Reagents and conditions:* a) $P(OEt)_3$, xylene, reflux; b) NaH, valeraldehyde, THF, rt.

Dihydroxylation of enone **8.12** using permanganate (Scheme 8.7) produced diol (*rac*)-**8.13** in 44% yield under achiral phase-transfer conditions (Table 8.3, Entry 1), whilst dihydroxylation using permanganate under chiral phase-transfer conditions produced diol **8.13** in 18% yield and 61% *ee* (Table 8.3, Entry 2). Lowering the temperature of the reaction to −15 °C gave a 25% yield and increased the *ee* to 67% (Table 8.3, Entry 3).



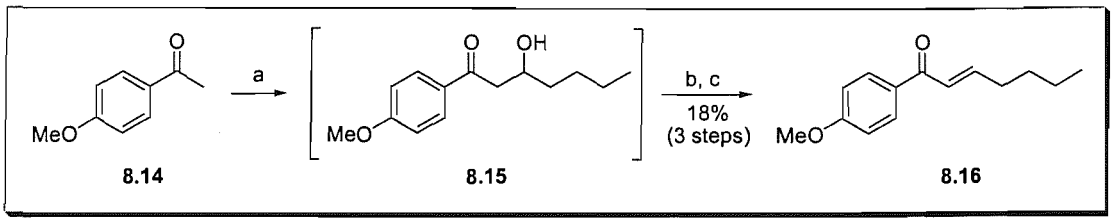
8.12 8.13

Scheme 8.7 Dihydroxylation of 4-fluoro-phenyl enone **8.12**. *Reagents and conditions:* a) See Table 8.3.

Entry	Reagents and conditions	Yield	*ee*
1	$KMnO_4$ (1 eq), adogen 464 (1 eq), pH 9 buffer, CH_2Cl_2, 0 °C	44%	0%
2	$KMnO_4$ (1 eq), **8.5** (100 mol%), pH 9 buffer, CH_2Cl_2, 0 °C	18%	61%
3	$KMnO_4$ (1 eq), **8.5** (100 mol%), pH 9 buffer, CH_2Cl_2, −15 °C	25%	67%

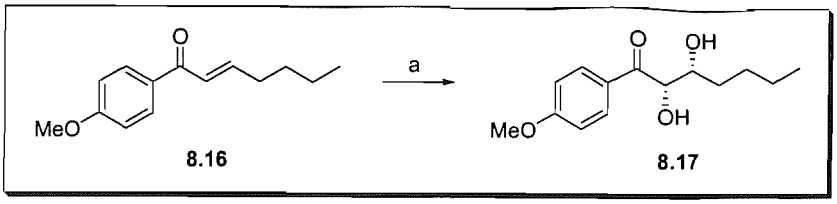
Table 8.3 Dihydroxylation of enone **8.12**.

We had now shown that substitution of the phenyl ring improved the *ee*, and that this could be further enhanced by lowering the temperature. Our investigation continued with the *para*-methoxy phenyl enone derivative **8.16** (Scheme 8.8). Synthesis of the 4-methoxy-phenyl enone derivative **8.16** *via* the established Arbuzov/HWE route was not successful however, with the formation of many by-products. The aldol reaction was therefore investigated as an alternative strategy to obtain the desired enone. Deprotonation of acetophenone **8.14** and reaction with valeraldehyde afforded hydroxyketone **8.15** (Scheme 8.8).[196] Mesylation and elimination afforded enone **8.16** in an unoptimised overall yield of 18%. The *E*-isomer was produced exclusively, as shown by ^{1}H NMR spectroscopy.



Scheme 8.8 Synthesis of the 4-methoxy-phenyl enone **8.16**. *Reagents and conditions:* a) LDA, THF, −78 °C; then valeraldehyde, −78 °C; b) MsCl, Et_3N, CH_2Cl_2; c) Et_3N, CH_2Cl_2, rt.

Dihydroxylation of enone **8.16** using permanganate (Scheme 8.9) produced the diol (*rac*)-**8.17** in 38% yield under achiral phase-transfer conditions with 14% recovered starting material (Table 8.4, Entry 1), whilst dihydroxylation using permanganate under chiral phase-transfer conditions produced diol **8.17** in 18% yield and 80% *ee* with 43% recovered starting material (Table 8.4, Entry 2). A UV active product also formed which was identified as methoxy-benzoic acid by NMR spectroscopy; hence a basic wash was introduced into the work-up procedure.



Scheme 8.9 Dihydroxylation of 4-methoxy-phenyl enone **8.16**. *Reagents and conditions:* a) See Table 8.4.

Entry	Reagents and conditions	Yield	*ee*
1	$KMnO_4$ (1 eq), adogen 464 (1 eq), pH 9 buffer, CH_2Cl_2, 0 °C	38%	0%
2	$KMnO_4$ (1 eq), **8.3** (100 mol%), pH 9 buffer, CH_2Cl_2, −60 °C	34%	80%

Table 8.4 Dihydroxylation of enone **8.16**.

8.3 Conclusions and Future Work

In conclusion, a new approach to asymmetric dihydroxylation has been developed.[197] The initial enantioselectivities are promising and although relatively large quantities of the chiral quaternary ammonium salt are required, the concept has been proven.

The substrates require the presence of a carbonyl group in order to bind optimally to the chiral phase-transfer catalyst, as confirmed by the lack of asymmetric induction in the dihydroxylation of 4-phenyl-1-butene **8.1**. The asymmetric dihydroxylation reaction is therefore currently limited to α-β-unsaturated enones that are able bind to the quaternary ammonium cation.

Future work should therefore focus upon the use of different, more oxidatively robust chiral phase-transfer agents in the dihydroxylation reaction. If a suitable chiral phase-transfer agent was found, this could have the effect of generalising the reaction to cover a wider range of substrates, reducing the amount of chiral phase-transfer agent required and improving the current enantioselectivities.

The use of different metal-oxo species should also be investigated as this opens up the possibility of a catalytic reaction.

The permanganate-mediated asymmetric dihydroxylation of enones will never contend with the osmium tetroxide-catalysed reaction. However, the racemic yields are promising and if a significant effort was put into improving the asymmetric dihydroxylation yields and enantioselectivities, the synthetic utility of this reaction would be greatly enhanced. An efficient permanganate asymmetric dihydroxylation reaction would be particularly useful in industrial applications where cost, toxicity and environmental impact are important considerations.

Chapter 9

Experimental

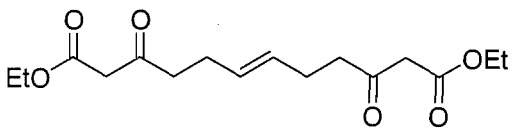
9.1 General Methods

All air and moisture sensitive reactions were carried out under an inert atmosphere using oven-dried glassware. Dichloromethane was dried by distillation over CaH_2 andTHF was distilled over Na/benzophenone prior to use. Where appropriate, all other solvents and reagents were purified according to standard methods.[198] Reactions were monitored by TLC using aluminium-backed plates coated with silica gel 60 containing a fluorescence indicator active at 254 nm; the chromatograms were visualised under UV light (254 nm) and by staining with 20% phosphomolybdic acid in ethanol, cerium sulphate/ammonium molybdate in 2M H_2SO_4 (aq) or 10% aqueous $KMnO_4$. Flash column chromatography was performed with 40-63 μm silica gel (Merck). ^1H NMR and ^{13}C NMR were recorded on either a quad. $^1H/^{13}C/^{31}P/^{19}F$ probe for computer switchable observation of ^1H, ^{13}C, ^{31}P and ^{19}F with ^2H lock (5mm) with automatic sample changer, a dual $^1H/^{13}C$ probe for computer switchable observation of ^1H and ^{13}C with ^2H lock (5mm) or a dual probehead for computer switchable observation of ^1H and ^{13}C with ^2H lock (5mm) fitted with z-gradient coils with automatic sample changer. Fourier transform infrared (FTIR) spectra were recorded on a Perkin –Elmer 1600 FT-IR instrument, a Bio-Rad FTS 135 instrument using a Golden Gate adaptor or a Nicolet Impact 400 instrument using a Thunderdome adaptor. Absorptions were recorded in wavenumbers (cm^{-1}) and are described as strong (s), medium (m), weak (w) or broad (br). Melting points were obtained in open capillary tubes and are uncorrected. Low-resolution mass spectra were obtained on a Fisons VG platform single quadrupole mass spectrometer in either chemical ionisation or electron impact ionisation mode or on a Micromass platform mass analyser with an electrospray ion source. Chiral analytical HPLC was performed on either a HP1050 or HP1090 Series II LC system using a normal phase Chiralcel OD-H, Chiralcel OB-H, Chiralpak AD-H or Chiral CD-Ph column with 210 or 254 nm detection, eluting with IPA/hexane mixtures. GC analysis was carried out using a Varian 3800 fitted with an

autosampler connected to a Hewlett-Packard 3396 Series II integrator. Where the experimental procedure is reported as using the method of an analogous procedure, the quantities of all reagents required scaling according to the molar amount used. The buffer solution used in the aqueous permanganate-promoted oxidative cyclisation was an aqueous 4:1 mixture of 1/16 M KH_2PO_4 and 1/16 M Na_2HPO_4 at pH 6.5. Potassium permanganate was freshly ground prior to use. The buffer solution used in the asymmetric dihydroxylation reactions was obtained using a pH 9 buffer tablet from Griffin.

9.2 Experimental Details

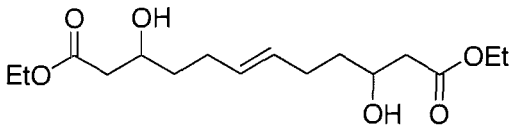
(*E*)-Diethyl 3,10-dioxododec-6-enedioate (**4.2**)



The procedure was carried out using the method described by Hoye *et al.*[199] Under an atmosphere of N_2, to a stirred solution of di*iso*propylamine (65.5 mL, 0.47 mol) in THF (400 mL) at −60 °C was added *n*BuLi (1.35 M solution in hexane, 346 mL, 0.47 mol) dropwise. The mixture was warmed to rt and stirred for 10 min before cooling to −70 °C. Ethylacetoacetate (29.8 mL, 0.23 mol) was added dropwise and the solution warmed to rt and stirred for 1 ½ h (mixture yellow → orange). The mixture was cooled to −60 °C and 1,4-dibromo-2-butene (**4.1**) (25.0 g, 0.12 mol) in THF (130 mL) was added dropwise. After 45 min the mixture was warmed to rt and H_2O (300 mL), citric acid (10% aq, 500 mL) and Et_2O (300 mL) were added. The organic layer was separated and the aqueous layer 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 (29.1 g). Purification on SiO_2 (10 x 15 cm) eluting with Et_2O/hexane (1:4 → 1:1) gave (*E*)-diethyl 3,10-dioxododec-6-enedioate **4.2** (24.5 g, 0.08 mol, 67%) as an orange solid. Spectroscopic characterisation agreed with that published.[199] IR ν_{max} (neat) 2978 (m), 2936 (m), 2903 (m), 1744 (s), 1711 (s), 1649 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.40 (2H, t, J = 3.6 Hz, 2 x $CHCH_2$), 4.16 (4H, q, J = 7.2 Hz, 2 x CH_2CH_3), 3.38 (4H, s, 2 x CH_2CO_2Et), 2.56 (4H, t, J = 7.2 Hz, 2 x

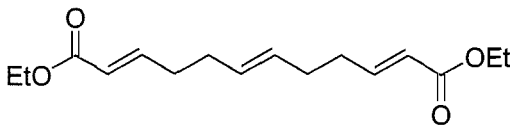
$CH_2C(O)CH_2CO_2Et$), 2.31-2.16 (4H, m, 2 x $CHCH_2$), 1.25 (6H, t, J = 7.2 Hz, 2 x CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2 (C), 167.2 (C), 129.4 (CH), 61.4 (CH_2), 49.4 (CH_2), 42.6 (CH_2), 26.3 (CH_2), 14.1 (CH_3); LRMS (ES^+) *m/z* 325 (42%, $[M+Na]^+$), 313 (65%, $[M+H]^+$), 267 (100%, $[M-OEt]^+$).

(*E*)-Diethyl 3,10-dihydroxydodec-6-enedioate (**4.3**)



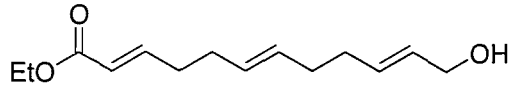
The procedure was carried out using the method described by Hoye *et al.*[199] Under an atmosphere of N_2, to a stirred solution of (*E*)-diethyl 3,10-dioxododec-6-enedioate **4.2** (13.4 g, 43.0 mmol) in EtOH (600 mL) at 0 °C was added $NaBH_4$ (3.27 g, 160 mmol) in two portions 40 min apart. After a further 1 ½ h, 2 M HCl (aq, 100 mL) was added cautiously and the mixture concentrated *in vacuo* to approximately 200 mL, whereupon CH_2Cl_2 (200 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a brown oil (10.1 g). Purification on SiO_2 (8 x 15 cm) eluting with EtOAc/hexane (1:1) gave (*E*)-diethyl 3,10-dihydroxydodec-6-enedioate **4.3** (8.63 g, 27.0 mmol, 64%) as a pale yellow oil. Spectroscopic characterisation agreed with that published.[199] IR ν_{max} (neat) 3447 (br, s), 3049 (w), 2988 (m), 2936 (m), 1720 (s), 1645 (w); ^1H NMR (300 MHz, $CDCl_3$) δ 5.43 (2H, t, J = 3.6 Hz, 2 x $CHCH_2$), 4.14 (4H, q, J = 7.1 Hz, 2 x CH_2CH_3), 4.03-3.93 (2H, m, 2 x CHOH), 3.10 (2H, s, 2 x CHOH), 2.47 (2H, dd, J = 16.4, 3.5 Hz, 2 x CHOHCHHC(O)), 2.37 (2H, dd, J = 16.4, 8.7 Hz, 2 x CHOHCHHC(O)), 2.21-1.98 (4H, m, 2 x $CHCH_2$), 1.63-1.38 (4H, m, 2 x CH_2CH_2CHOH), 1.45 (6H, t, J = 7.1 Hz, 2 x CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0 (C), 130.1 (CH), 67.4 (CH), 60.7 (CH_2), 41.3 (CH_2), 36.1 (CH_2), 28.6 (CH_2), 14.2 (CH_3); LRMS (ES^+) *m/z* 339 (100%, $[M+Na]^+$).

(2*E*,6*E*,10*E*)-Diethyl dodeca-2,6,10-trienedioate (**4.5**)



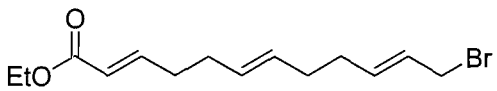
The procedure was carried out using the method described by Hoye *et al.*[199] Under an atmosphere of N_2, to a stirred solution of (*E*)-diethyl 3,10-dihydroxydodec-6-enedioate **4.3** (8.53 g, 27.0 mmol) and MsCl (4.61 mL, 59.0 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added Et_3N (8.48 mL, 60.0 mmol). After 1 ½ h H_2O (100 mL) was added, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude dimesylate **4.4** as an orange oil (12.9g, 27.0 mmol), which was used without further purification. Under an atmosphere of N_2, to a stirred solution of the crude dimesylate **4.4** (12.9g, 27.0 mmol) in CH_2Cl_2 (250 mL) at 0 °C was added DBU (9.77 mL, 65.0 mmol) dropwise. After 1 ½ h 10% citric acid (aq, 200 mL) was added, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give an orange oil (26.0 g). Purification on SiO_2 (10 x 15 cm) eluting with EtOAc/hexane (1:3 → 1:1) gave (2*E*,6*E*,10*E*)-diethyl dodeca-2,6,10-trienedioate **4.5** (5.91 g, 21.0 mmol, 78%) as a pale yellow oil. All characterisation data agreed with that published.[199] IR ν_{max} (neat) 3049 (m), 2983 (m), 2935 (w), 2898 (w), 1711 (s), 1654 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (2H, dt, *J* = 15.7, 6.6 Hz, 2 x C**H**CHC(O)), 5.82 (2H, d, *J* = 15.7 Hz, 2 x CHC**H**C(O)), 5.44 (2H, t, *J* = 3.4 Hz, 2 x C**H**CH_2CH_2), 4.19 (4H, q, *J* = 7.2 Hz, 2 x C**H**$_2CH_3$), 2.35-2.21 (4H, m, 2 x C**H**$_2$CHCHC(O)), 2.20-2.05 (4H, m, 2 x C**H**$_2CH_2$CHCHC(O)), 1.29 (6H, t, *J* = 7.2 Hz, 2 x CH_2C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7 (C), 148.4 (CH), 129.8 (CH), 121.6 (CH), 60.2 (CH_2), 32.1 (CH_2), 30.9 (CH_2), 14.3 (CH_3); LRMS (GCCI) 8.88 min, 281 (100%, $[M+H]^+$), 235 (22%, $[M-OCH_2CH_3]^+$).

(2*E*,6*E*,10*E*)-Ethyl 12-hydroxydodeca-2,6,10-trienoate (**4.6**)



Under an atmosphere of N_2, to a stirred solution of diethyl (2*E*,6*E*,10*E*)-diethyl dodeca-2,6,10-trienedioate **4.5** (1.00 g, 3.57 mmol) in THF (30 mL) at −60 °C was added DIBAL-H (1 M in hexane, 5.71 mL, 5.71 mmol) dropwise. After 1 h NH_4Cl (sat aq, 10 mL) was added followed by 2 M HCl (aq, 20 mL) and Et_2O (30 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a colourless oil (0.820 g). Purification on SiO_2 (3.5 x 15 cm) eluting with Et_2O/hexane (3:2 → 9:1) gave (2*E*,6*E*,10*E*)-ethyl 12-hydroxydodeca-2,6,10-trienoate **4.6** (0.27 g, 1.13 mmol, 32%) as a colourless oil. IR ν_{max} (neat) 3418 (br,m), 3049 (w), 2978 (m), 2926 (m), 2841 (m), 1711 (s), 1654 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.96 (1H, dt, *J* = 15.7, 6.7 Hz, C(O)CHC**H**), 5.82 (1H, dt, *J* = 15.7, 1.5 Hz, C(O)C**H**CH), 5.70-5.62 (2H, m, C**H**C**H**CH_2OH), 5.43 (2H, appt. q, *J* = 4.8 Hz, C(O)CHCHCH_2CH_2C**H**C**H**), 4.19 (2H, q, *J* = 7.1 Hz, $CH_3C\mathbf{H}_2$) 4.09 (2H, d, *J* = 4.0 Hz, $C\mathbf{H}_2OH$), 2.26 (2H, appt. q, *J* = 6.7 Hz, C(O)CHCHC$\mathbf{H}_2$), 2.21-2.02 (6H, m, C(O)CHCHCH_2C$\mathbf{H}_2$ and C$\mathbf{H}_2$CH_2CHCHCH_2OH), 1.61 (1H, br s, $CH_2O\mathbf{H}$), 1.29 (3H, t, *J* = 7.1 Hz, C$\mathbf{H}_3$CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8 (C), 148.7 (CH), 132.3 (CH), 130.8 (CH), 129.4 (CH), 129.1 (CH), 121.5 (CH), 63.7 (CH_2), 60.2 (CH_2), 32.1 (CH_2), 32.0 (2 x CH_2), 30.9 (CH_2), 14.3 (CH_3); LRMS (GCCI) 8.52 min, 239 (16%, $[M+H]^+$), 221 (59%, $[M-OH]^+$, 147 (100%, $[M-(H_2O)-(CO_2Et)]^+$); HRMS (ES^+) $C_{14}H_{22}O_3Na^+$ Calcd. 261.1461, found 261.1460.

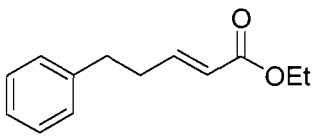
(2*E*,6*E*,10*E*)-Ethyl 12-bromododeca-2,6,10-trienoate (**4.7**)



The procedure was carried out using the method described by Zoretic *et al.*[200] Under an atmosphere of N_2, to a stirred solution of (2*E*,6*E*,10*E*)-ethyl 12-hydroxydodeca-2,6,10-trienoate **4.6** (270 mg, 1.13 mmol) and PPh_3 (440 mg, 1.70 mmol) in CH_2Cl_2 (20 mL) was added CBr_4 (560 mg, 1.70 mmol) portionwise over 10 min. After a further 20 min the mixture was concentrated *in vacuo* and hexane (20 mL) was added.

Trituration produced a white solid which was removed by filtration, washing with ice-cold hexane (20 mL). The filtrate was concentrated *in vacuo* to give a yellow oil (0.450 g). Purification on SiO_2 (3.5 x 10 cm) eluting with EtOAc/hexane (1:19) gave (2*E*,6*E*,10*E*)-ethyl 12-bromododeca-2,6,10-trienoate **4.7** (300 mg, 0.98 mmol, 87%) as a colourless oil. IR ν_{max} (neat) 3026 (w), 2978 (m), 2935 (w), 2926 (m), 2841 (m), 1716 (s), 1654 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.94 (1H, dt, *J* = 15.7, 6.7 Hz, C(O)CHC**H**), 5.82 (1H, d, *J* = 15.7 Hz, C(O)C**H**CH), 5.77-5.62 (2H, m, **CHCH**CH_2Br), 5.45-5.39 (2H, m, C(O)CHCHCH_2CH_2**CHCH**), 4.18 (2H, q, *J* = 7.1 Hz, $CH_3C\mathbf{H}_2$), 3.94 (2H, d, *J* = 6.3 Hz, $C\mathbf{H}_2$Br), 2.25 (2H, appt. q, *J* = 6.7 Hz, C(O)CHCHC$\mathbf{H}_2$), 2.21-1.98 (6H, m, C(O)CHCH$CH_2C\mathbf{H}_2$ and $C\mathbf{H}_2C\mathbf{H}_2$CHCH$CH_2$Br), 1.29 (3H, t, *J* = 7.1 Hz, $C\mathbf{H}_3CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7 (C), 148.6 (CH), 135.8 (CH), 130.3 (CH), 129.4 (CH), 126.7 (CH), 121.6 (CH), 60.2 (CH_2), 33.5 CH_2), 32.1 (CH_2), 31.9 (CH_2), 31.7 (CH_2), 30.9 (CH_2), 14.3 (CH_3); LRMS (GCCI) 8.76 min, 303 and 301 (6%, $[M+H]^+$), 223 and 221 (93%, $[M-Br]^+$), 149 (100%, $[CH_2CH_2CHCHCH_2Br]^+$); HRMS (ES^+) $C_{14}H_{21}O_2{}^{79}Br^+$ Calcd. 300.0725, found 300.0726.

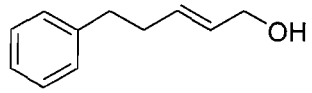
(*E*)-Ethyl 5-phenylpent-2-enoate (**4.12**)



Under an atmosphere of N_2, to a stirred solution of triethylphosphonoacetate (3.60 mL, 18.1 mmol) in THF (30 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 0.73 g, 18.1 mmol) portionwise over 10 min. 3-Phenylpropionaldehyde (**4.11**) (2.00 mL, 15.1 mmol) was added dropwise and the reaction warmed rt over 14 h. H_2O (30 mL) was added and the mixture extracted with Et_2O (2 x 50mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a pale yellow oil (3.10 g). Purification on SiO_2 (5 x 15 cm) eluting with EtOAc /hexane (1:9) gave ethyl (*E*)-ethyl 5-phenylpent-2-enoate **4.12** (2.79 g, 13.7 mmol, 91%) as a colourless oil. Spectroscopic characterisation agreed with that published.[201] IR ν_{max} (neat) 3087 (w), 3061 (w), 3023 (w), 2981 (w), 2933 (w), 2860 (w), 1716 (s), 1654 (m), 1604 (w),

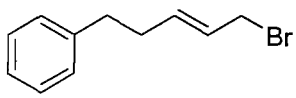
1497 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36-7.26 (2H, m, Ar-**H**), 7.25-7.17 (3H, m, Ar-**H**), 7.03 (1H, dt, *J* = 15.7, 6.8 Hz, C**H**CHCO$_2$Et), 5.87 (1H, dt, *J* = 15.7, 1.4 Hz, CHC**H**CO$_2$Et), 4.20 (2H, q, *J* = 7.1 Hz, C**H**$_2$CH$_3$), 2.79 (2H, t, *J* = 7.8 Hz, PhC**H**$_2$), 2.54 (2H, m, PhCH$_2$C**H**$_2$), 1.30 (3H, t, *J* = 7.1 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6 (C), 148.1 (CH), 140.8 (C), 128.5 (CH), 128.3 (CH), 126.1 (CH), 121.8 (CH), 60.2 (CH_2), 34.3 (CH_2), 33.9 (CH_2), 14.3 (CH_3); LRMS (ES^+) *m/z* 227 (100%, $[M+Na]^+$).

(*E*)-5-Phenylpent-2-en-1-ol (**4.13**)



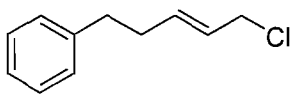
Under an atmosphere of N_2, to a stirred solution of (*E*)-ethyl 5-phenylpent-2-enoate **4.12** (5.59 g, 27.4 mmol) in THF (100 mL) was added DIBAL-H (1 M in hexane, 54.8 mL, 54.8 mmol) dropwise. After 2 h NH_4Cl (sat aq, 100 mL), 2 M HCl (aq, 20 mL) and Et_2O (100 mL) were added. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a pale yellow oil (3.82 g). Purification by vacuum distillation (105 °C, 0.5 mmHg) gave (*E*)-5-phenylpent-2-en-1-ol **4.13** (3.55 g, 22.0 mmol, 80%) as a colourless oil. Spectroscopic characterisation agreed with that published.[202] IR ν_{max} (neat) 3333 (br, m), 3027 (w), 2925 (m), 2855 (m), 1669 (w), 1603 (w), 1496 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.25 (2H, m, Ar-**H**), 7.24-7.16 (3H, m, Ar-**H**), 5.81-5.61 (2H, m, C**H**C**H**), 4.08 (2H, d, *J* = 4.3 Hz, C**H**$_2$OH), 2.73 (2H, t, *J* = 7.9 Hz, PhC**H**$_2$), 2.44-2.33 (2H, m, PhCH$_2$C**H**$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.7 (C), 132.3 (CH), 129.6 (CH), 128.5 (CH), 128.4 (CH), 125.9 (CH), 63.7 (CH_2), 35.5 (CH_2), 34.0 (CH_2); LRMS (GCCI) 7.87 min, 162 (6%, $[M]^+$), 144 (100%, $[M-H_2O]^+$).

1-((*E*)-5-Bromopent-3-enyl)benzene (**4.14**)



The title compound was prepared according to the method outlined for **4.7**, except using (*E*)-5-phenylpent-2-en-1-ol **4.13** (1.00 g, 6.17 mmol). Purification by vacuum distillation (95 °C, 0.5 mmHg) gave 1-((*E*)-5-bromopent-3-enyl)benzene **4.14** (0.950 g, 4.20 mmol, 68%) as a colourless oil. Spectroscopic characterisation agreed with that published.[203] IR ν_{max} (neat) 3027 (w), 2925 (w), 2854 (w), 1660 (w), 1603 (w), 1495 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.26 (2H, m, Ar-**H**), 7.25-7.16 (3H, m, Ar-**H**), 5.83 (1H, dt, *J* = 15.1, 6.8 Hz, C**H**CHCH$_2$Br), 5.73 (1H, dt, *J* = 15.1, 7.0 Hz, CHC**H**CH$_2$Br), 3.95 (2H, d, *J* = 7.0 Hz, C**H**$_2$Br), 2.72 (2H, t, *J* = 7.5 Hz, PhC**H**$_2$), 2.46-2.36 (2H, dt, *J* = 7.5, 6.8 Hz, PhCH$_2$C**H**$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3 (C), 135.5 (CH), 128.4 (CH), 127.0 (CH), 126.0 (CH), 35.2 (CH_2), 33.8 (CH_2), 33.3 (CH_2); LRMS (GCCI) 8.20 min, 226 and 224 (2%, $[M+H]^+$), 91 (100%, $[PhCH_2]^+$).

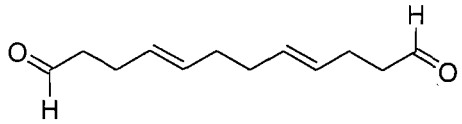
1-((*E*)-5-Chloropent-3-enyl)benzene (**4.15**)



The procedure was carried out using the method described by Zhu *et al.*[204] Under an atmosphere of N_2, to a stirred solution of (*E*)-5-phenylpent-2-en-1-ol **4.13** (1.40 g, 8.66 mmol), LiCl (1.10 g, 25.9 mmol) and Et_3N (2.41 mL, 17.3 mmol) in DMF (40 mL) at 0 °C was added MsCl (1.00 mL, 13.0 mmol). After 3 h at 0 °C the mixture was warmed to rt over 1 h and Et_2O (50 mL) was added. The organic phase was washed successively with 2 M HCl (aq, 50 mL) and brine (sat aq, 50 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give a pale yellow oil (1.23 g). Purification by vacuum distillation (105 °C, 0.5 mmHg) gave 1-((*E*)-5-chloropent-3-enyl)benzene **4.15** (1.08 g, 5.98 mmol, 69%) as a colourless oil. Spectroscopic characterisation agreed with that published.[205] IR ν_{max} (neat) 3028 (w), 2932 (w), 2857 (w), 1666 (w), 1603 (w), 1495 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26-7.36 (2H, m, Ph-**H**), 7.26-7.16 (3H, m, Ar-**H**), 5.84 (1H, dt, *J* = 15.1, 6.6 Hz, C**H**CHCH$_2$Cl), 5.67 (1H, dt, *J* = 15.1, 7.0 Hz, CHC**H**CH$_2$Cl), 4.10 (2H, d, *J* = 7.0 Hz, C**H**$_2$Cl), 2.73 (2H, t, *J* = 7.2 Hz, PhC**H**$_2$), 2.41 (2H, appt. q, *J* = 6.9 Hz, PhCH$_2$C**H**$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ

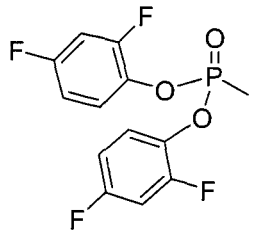
141.4 (C), 135.1 (CH), 128.4 (CH), 128.3 (CH), 126.5 (CH), 126.0 (CH), 45.4 (CH_2), 35.2 (CH_2), 33.8 (CH_2); LRMS (GCCI) 7.87 min, 182 (6%, $[M]^+$), 180 (18%, $[M]^+$), 91 (100%, $[PhCH_2]^+$).

(4*E*,8*E*)-Dodeca-4,8-dienedial (**3.5**)



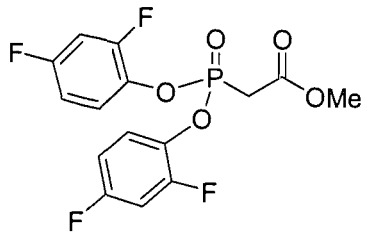
The procedure was carried out using an adaptation of the method described by Hoye *et al.*[107] To a stirred solution of *trans,trans,trans*-1,5,9-cyclododecatriene (**4.27**) (5.82 g, 35.9 mmol) and 4-methylmorpholine *N*-oxide (50% aq, 16.8 g, 71.8 mmol) in CH_2Cl_2 (10 mL) was added osmium tetraoxide (2.5% wt in 2-methyl-2-propanol, 1.83 g, 0.18 mmol) and the mixture stirred slowly at rt for 14 h (solid appeared after 2 h). The solid was collected by filtration, washing with H_2O (3 x 100 mL) giving the crude diol **4.28** as a pale brown solid (7.09 g, 36.0 mmol), which was used without further purification. To a stirred heterogeneous mixture of $NaIO_4$-SiO_2[206] (72.6 g, 60.0 mmol) in CH_2Cl_2 (100 mL) at rt was added crude diol (7.09 g, 36.0 mmol) as a heterogeneous mixture in CH_2Cl_2 (50 mL). After 15 min the mixture was filtered washing with $CHCl_3$ (3 x 50 mL) and the filtrate concentrated *in vacuo* to give a brown oil (5.60 g). Purification on SiO_2 (5 x 10 cm) eluting with EtOAc/hexane (1:19 → 1:4) gave (4*E*,8*E*)-dodeca-4,8-dienedial **3.5** (3.61 g, 18.6 mmol, 52%) as a colourless oil. Spectroscopic characterisation agreed with that published.[107,207] IR ν_{max} (neat) 2952 (w), 2931 (w), 2861 (w), 1765 (m), 1723 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.76 (2H, s, 2 x C**H**O), 5.51-5.34 (4H, m, 2 x C**H**C**H**), 2.49 (4H, t, J = 7.0 Hz, 2 x C**H**$_2$CHO), 2.39-2.28 (4H, m, 2 x C**H**$_2$CH$_2$CHO), 2.07-1.99 (4H, m, CHCHC**H**$_2$C**H**$_2$CHCH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4 (CH), 131.2 (CH), 128.4 (CH), 43.6 (CH_2), 32.4 (CH_2), 25.3 (CH_2); LRMS (ES^+) *m/z* 217 (100%, $[M+Na]^+$).

Di(2,4-difluorophenyl) methylphosphonate (**4.30**)



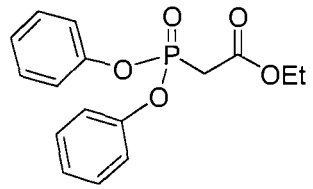
The procedure was carried out using the method described by Patois *et al.*[120] Under an atmosphere of N_2, to a stirred solution of 2,4-difluorophenol (2.88 mL, 30.1 mmol) in THF (30 mL) at 10 °C was added Et_3N (4.82 mL, 34.6 mmol) and the mixture stirred for 15 min. Methyl phosphonic dichloride (**4.29**) (2.00 g, 15.1 mmol) in THF (10 mL) was added dropwise and the reaction stirred at rt for 4 h (white ppt formed). The mixture was then heated to reflux for a further 3 h before cooling to rt. The mixture was filtered to remove $Et_3N.HCl$, washed with THF (2 x 30 mL) and concentrated *in vacuo* to give a pale yellow oil (4.90 g). Purification by vacuum distillation (124 °C, 0.5 mmHg) gave di(2,4-difluorophenyl) methylphosphonate **4.30** (3.97 g, 12.4 mmol, 83%) as a colourless oil. Spectroscopic characterisation agreed with that published.[114] IR ν_{max} (neat) 3058 (w), 1618 (w), 1507 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (1H, ddd, J = 8.8, 5.5, 1.5 Hz, COCFCHCFCHC**H**), 7.22 (1H, ddd, J = 8.8, 5.5, 1.5 Hz, COCFCHCFCHC**H**), 6.94 (2H, ddd, J = 9.9, 8.5, 2.9 Hz, 2 x CFCHCFC**H**), 6.87-6.79 (2H, m, 2 x Ar-**H**), 1.94 (3H, d, J = 18.0 Hz, C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5 (C, dd, $J_{C\text{-}F}$ = 248.0, 10.2 Hz), 153.5 (C, dd, $J_{C\text{-}F}$ = 252.0, 12.4 Hz), 133.8 (C, d $J_{C\text{-}F}$ = 12.4 Hz), 123.6 (CH, dd, $J_{C\text{-}F}$ = 9.6, 3.4 Hz), 111.6 (CH, dd, $J_{C\text{-}F}$ = 23.2, 4.0 Hz), 105.4 (CH, dd, $J_{C\text{-}F}$ = 27.1, 22.6 Hz), 11.6, (CH_3, d, $J_{C\text{-}P}$ = 144.1 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ 49.2 (1F, s, CF), 36.9 (1F, s, CF); ^{31}P NMR (121 MHz, $CDCl_3$) 34.7 (**P**(O)); LRMS (GCCI) 7.86 min, 321 (100%, $[M+H]^+$); HRMS (ES^+) $C_{13}H_{10}O_3F_4P^+$ Calcd. 321.0298, found 321.0299.

Methyl 2-di[(2,4-difluorophenyl)oxy]phosphorylethanoate (**4.31**)



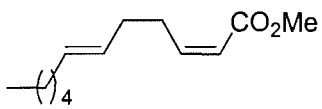
Under an atmosphere of N_2, to a stirred solution of di(2,4-difluorophenyl) methylphosphonate **4.30** (1.00 g, 3.13 mmol) in THF (30 mL) at –78 °C was added methyl chloroformate (0.25 mL, 3.28 mmol). After 10 min LiHMDS (1M in THF, 6.57 mL, 6.57 mmol) was added dropwise and the yellow mixture warmed to 0 °C over 1½ h. After this time 2 M HCl (aq, 20 mL) and CH_2Cl_2 (30 mL) were added, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (1.19 g). Purification by vacuum distillation (167 °C, 0.5 mmHg) gave methyl 2-di[(2,4-difluorophenyl)oxy]phosphorylethanoate **4.31** (1.05 g, 2.78 mmol, 89%) as a colourless oil. Spectroscopic characterisation agreed with that published.[114] IR ν_{max} (neat) 3066 (w), 1745 (m), 1619 (w), 1508 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (1H, ddd, J = 8.8, 5.5, 1.5 Hz, COCFCHCFCHC**H**), 7.22 (1H, ddd, J = 8.8, 5.5, 1.5 Hz, COCFCHCFCHC**H**), 6.86 (2H, ddd, J = 10.0, 8.3, 2.8 Hz, CFCHCFC**H**), 6.74-6.80 (2H, m, Ar-**H**), 3.73 (3H, s, OC**H**$_3$), 3.35 (2H, d, J = 22.0 Hz, C**H**$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2 (C, d, $J_{C\text{-}P}$ = 5.8 Hz), 159.9 (C, dd, $J_{C\text{-}F}$ = 248.0, 10.2 Hz), 153.7 (C, dd, $J_{C\text{-}F}$ = 252.0, 12.4 Hz), 134.0 (C, dd, $J_{C\text{-}F}$ = 12.6, 8.7 Hz), 123.7 (CH, dd, $J_{C\text{-}F}$ = 9.7, 3.4 Hz), 111.7 (CH, dd, $J_{C\text{-}F}$ = 22.8, 3.9 Hz), 105.7 (CH, dd, $J_{C\text{-}F}$ = 27.2, 22.4 Hz), 53.3 (CH_3), 34.3 (CH_2, d, $J_{C\text{-}P}$ = 140.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ 49.7 (1F, s, CF), 37.2 (1F, s, CF); ^{31}P NMR (121 MHz, $CDCl_3$) 22.8 (**P**(O)); LRMS (GCCI) 8.72 min, 379 (94%, $[M+H]^+$), 130 (100%, $[C_6H_4F_2O]^+$).

Ethyl 2-[di(phenyloxy)phosphoryl]ethanoate (**4.33**)



The procedure was carried out using the method described by Ando *et al.*[118] Under an atmosphere of N_2, to a stirred solution of ethyl bromoacetate (15.0 g, 89.8 mmol) and diphenyl phosphite (20.7 mL, 108 mmol) in CH_2Cl_2 (150 mL) at 0 °C was added Et_3N (15.0 mL, 108 mmol) dropwise (mixture orange). The mixture was warmed to rt over 14 h (mixture orange → yellow slurry) before H_2O (150 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (22.1 g). Purification on SiO_2 (12 x 15 cm) eluting with EtOAc/hexane (1:9 → 1:4) gave ethyl 2-[di(phenyloxy)phosphoryl]ethanoate **4.33** (10.2 g, 31.9 mmol, 36%) as a colourless oil. Spectroscopic characterisation agreed with that published.[118] IR ν_{max} (neat) 2986 (w), 2933 (w), 1735 (m), 1590 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.34 (4H, m, Ar-**H**), 7.32-7.20 (6H, m, Ar-**H**), 4.28 (2H, q, J = 7.3 Hz, $OC\mathbf{H}_2CH_3$), 3.31 (2H, d, J = 21.6 Hz, $C\mathbf{H}_2C(O)$), 1.32 (3H, t, J = 7.3 Hz, $OCH_2C\mathbf{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9 (C, d, $J_{C\text{-}P}$ = 6.3 Hz), 150.2 (C, d, $J_{C\text{-}P}$ = 8.8 Hz), 129.9 (CH, d, $J_{C\text{-}P}$ = 1.0 Hz), 125.6 (CH, d, $J_{C\text{-}P}$ = 1.5 Hz), 120.7 (CH, d, $J_{C\text{-}P}$ = 4.9 Hz), 62.1 (CH_2), 34.2 (CH_2, d, $J_{C\text{-}P}$ = 137.0 Hz), 14.1 (CH_3); LRMS (ES^+) *m/z* 343 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{16}H_{18}O_5P^+$ Calcd. 321.0887, found 321.0884.

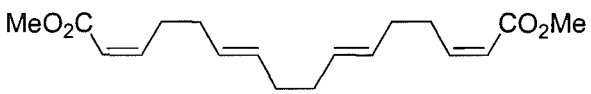
(2*Z*,6*E*)-Methyl dodeca-2,6-dienoate (**4.35**)



The procedure was carried out using the method described by Gennari *et al.*[110] Under an atmosphere of N_2, to a stirred solution of methyl 2-di[(2,4-

difluorophenyl)oxy]phosphorylethanoate **4.31** (380 mg, 0.56 mmol) and 18-crown-6 (740 mg, 2.80 mmol) in THF (10 mL) at −50 °C was added KHMDS (0.5 M in toluene, 1.12 mL, 0.56 mmol) dropwise. After 10 min *trans*-4-decenal (**4.34**) (0.10 mL, 0.53 mmol) in THF (5 mL) was added dropwise and the mixture stirred at −50 °C for 1 h. After this time 2 M HCl (aq, 20 mL) and Et_2O (30 mL) were added, the organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (0.600 g). Purification on SiO_2 (3 x 15 cm) eluting with Et_2O/hexane (1:9) gave (2*Z*,6*E*)-methyl dodeca-2,6-dienoate **4.35** (80 mg, 0.37 mmol, 70%) as a colourless oil. IR ν_{max} (neat) 2954 (m), 2926 (m), 2855 (m), 1726 (s), 1645 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.24 (1H, dt, *J* = 11.8, 7.4 Hz, C**H**CHCO$_2$Me), 5.79 (1H, dt, *J* = 11.8, 1.5 Hz, CHC**H**CO$_2$Me), 5.52-5.33 (2H, m, CH$_2$C**H**C**H**CH$_2$), 3.72 (3H, s, OC**H**$_3$), 2.73 (2H, appt. qd, *J* = 7.4, 1.5 Hz, C**H**$_2$CHCHCO$_2$Me), 2.19-2.10 (2H, m, C**H**$_2$CH$_2$CHCHCO$_2$Me), 1.98 (2H, appt. q, *J* = 6.4 Hz, CH$_3$(CH$_2$)$_3$C**H**$_2$), 1.10-1.40 (6H, m, CH$_3$C**H**$_2$C**H**$_2$C**H**$_2$), 0.90 (3H, t, *J* = 6.8 Hz, C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9 (C), 150.3 (CH), 131.6 (CH), 128.7 (CH), 119.3 (CH), 51.0 (CH_3), 32.5 (CH_2), 31.8 (CH_2), 31.4 (CH_2), 29.2 (CH_2), 28.9 (CH_2), 22.5 (CH_2), 14.1 (CH_3); LRMS (GCCI) 6.95 min, 211 (100%, $[M+H]^+$); HRMS (EI) $C_{13}H_{22}O_2^{+\cdot}$ Calcd. 210.1618, found 210.1619.

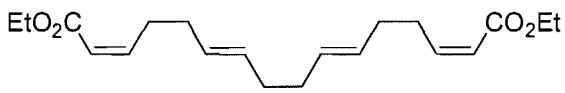
(2*Z*,6*E*,10*E*,14*Z*)-Dimethyl hexadeca-2,6,10,14-tetraenedioate (**4.36**)



The procedure was carried out using the method described by Still and Gennari[110] Under an atmosphere of N_2, to a stirred solution of methyl 2-di[(2,4-difluorophenyl)oxy]phosphorylethanoate **4.31** (5.48 g, 14.5 mmol) and 18-crown-6 (11.5 g, 43.5 mmol) in THF (100 mL) at −50 °C was added KHMDS (0.5 M in toluene, 29.0 mL, 14.5 mmol) dropwise. After 10 min (4*E*,8*E*)-dodeca-4,8-dienedial **3.5** (1.34 g, 6.90 mmol) in THF (40 mL) was added dropwise and the mixture stirred at −50 °C for 1 h. After this time NH_4Cl (sat aq, 30 mL), 2 M HCl (aq, 20 mL) and Et_2O (100 mL) were added. The organic layer was separated and the aqueous layer

was extracted with Et_2O (2 x 100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (11.0 g). Purification on SiO_2 (10 x 15 cm) eluting with Et_2O/hexane (1:9 → 1:4) gave (2*Z*,6*E*,10*E*,14*Z*)-dimethyl hexadeca-2,6,10,14-tetraenedioate **4.36** (1.46 g, 4.77 mmol, 62%) as a colourless oil. IR ν_{max} (neat) 2991 (w), 2949 (w), 2914 (w), 2845 (w), 1722 (s), 1645 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.23 (2H, dt, *J* = 11.6, 7.4 Hz, 2 x C**H**CHCO$_2$Me), 5.78 (2H, dt, *J* = 11.6, 1.8 Hz, 2 x CHC**H**CO$_2$Me), 5.50-5.37 (4H, m, 2 x CH$_2$C**H**C**H**CH$_2$), 3.71 (6H, s, 2 x OC**H**$_3$), 2.72 (4H, appt. qd, *J* = 7.4, 1.8 Hz, 2 x C**H**$_2$CHCHCO$_2$Me), 2.18-2.11 (4H, m, 2 x C**H**$_2$CH$_2$CHCHCO$_2$Me), 2.06-2.02 (4H, m, 2 x C**H**$_2$CHCHCH$_2$CH$_2$CHCHCO$_2$Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0 (C), 150.3 (CH), 131.0 (CH), 129.3 (CH), 119.6 (CH), 51.1 (CH_3), 32.7 (CH_2), 31.9 (CH_2), 29.0 (CH_2); LRMS (GCCI) 8.96 min, 307 (68%, $[M+H]^+$), 243 (100 %, $[M-2(OMe)]^+$); HRMS (EI) $C_{18}H_{27}O_4^+$ Calcd. 307.1894, found 307.1892.

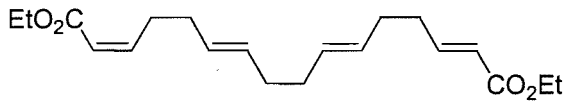
(2*Z*,6*E*,10*E*,14*Z*)-Diethyl hexadeca-2,6,10,14-tetraenedioate (**4.37**)



The procedure was carried out using the method described by Still and Gennari[110] Under an atmosphere of N_2, to a stirred solution of ethyl 2-[di(phenyloxy)phosphoryl]ethanoate **4.33** (1.98 g, 6.19 mmol) and 18-crown-6 (1.64 g, 6.19 mmol) in THF (50 mL) at −10 °C was added KHMDS (0.5 M in toluene, 12.4 mL, 6.19 mmol) dropwise (mixture yellow). After 5 min the mixture was cooled to −65 °C and (4*E*,8*E*)-dodeca-4,8-dienedial **3.5** (0.57 g, 2.95 mmol) in THF (10 mL) was added dropwise. The mixture was allowed to warm to −50 °C for 1 h before H_2O (50 mL) and Et_2O (50 mL) were added. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (2.50 g). Purification on SiO_2 (5 x 15 cm) eluting with Et_2O/hexane (3:97 → 1:19) gave (2*Z*,6*E*,10*E*,14*Z*)-diethyl hexadeca-2,6,10,14-tetraenedioate **4.37** (0.60 g, 1.80 mmol, 61%) as a colourless oil. Also isolated was (2*Z*,6*E*,10*E*,14*E*)-diethyl hexadeca-2,6,10,14-tetraenedioate **4.37a** (0.15 g, 0.45 mmol, 15%). IR ν_{max} (neat) 3038 (w), 2983 (w), 2910 (w), 2845 (w),

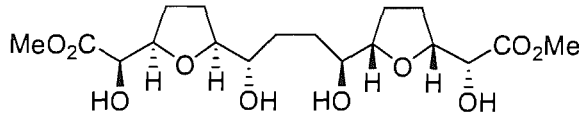
1718 (s), 1643 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.21 (2H, dt, *J* = 11.6, 7.3 Hz, 2 x C**H**CHCO$_2$Et), 5.76 (2H, dt, *J* = 11.6, 1.5 Hz, 2 x CHC**H**CO$_2$Et), 5.50-5.36 (4H, m, 2 x CH$_2$C**H**C**H**CH$_2$), 4.17 (4H, q, *J* = 7.2 Hz, 2 x C**H**$_2$CH$_3$), 2.71 (4H, appt. qd, *J* = 7.3, 1.5 Hz, 2 x C**H**$_2$CHCHCO$_2$Et), 2.14 (4H, appt. q, *J* = 7.3 Hz, 2 x C**H**$_2$CH$_2$CHCHCO$_2$Et), 2.06-2.01 (4H, m, 2 x C**H**$_2$CHCHCH$_2$CH$_2$CHCHCO$_2$Et), 1.29 (6H, t, *J* = 7.2 Hz, x CH$_2$C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6 (C), 149.8 (CH), 131.0 (CH), 129.4 (CH), 120.0 (CH), 59.9 (CH_2), 32.7 (CH_2), 32.0 (CH_2), 28.9 (CH_2), 14.4 (CH_3); LRMS (ES^+) *m/z* 357 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{20}H_{31}O_4^+$ Calcd. 335.2217, found 335.2212.

(2*Z*,6*E*,10*E*,14*E*)-Diethyl hexadeca-2,6,10,14-tetraenedioate (**4.37a**)



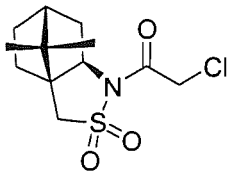
Data for isomer **4.37a**: IR ν_{max} (neat) 3033 (w), 2982 (w), 2922 (w), 2846 (w), 1718 (s), 1646 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (1H, dt, *J* = 15.8, 6.8 Hz, 2 x C**H**CHCO$_2$Et), 6.21 (1H, dt, *J* = 11.5, 7.3 Hz, 2 x EtCO$_2$CHC**H**), 5.82 (2H, dt, *J* = 15.8, 1.5 Hz, 2 x CHC**H**CO$_2$Et), 5.76 (2H, dt, *J* = 11.5, 1.5 Hz, 2 x EtCO$_2$C**H**CH), 5.50-5.36 (4H, m, 2 x CH$_2$C**H**C**H**CH$_2$), 4.17 (4H, appt. quin, *J* = 7.0 Hz, 2 x C**H**$_2$CH$_3$), 2.72 (4H, appt. qd, *J* = 7.0, 1.5 Hz, EtCO$_2$CHCHC**H**$_2$ and C**H**$_2$CHCHCO$_2$Et), 2.26 (2H, appt. q, *J* = 7.3 Hz, C**H**$_2$CH$_2$CHCHCO$_2$Et), 2.19-2.11 (2H, m, EtCO$_2$CHCHCH$_2$C**H**$_2$), 2.06-2.01 (4H, m, 2 x C**H**$_2$CHCHCH$_2$CH$_2$CHCHCO$_2$Et), 1.29 (6H, t, *J* = 7.0 Hz, x CH$_2$C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8 (C), 166.6 (C), 149.8 (CH), 148.7 (CH), 131.1 (CH), 130.8 (CH), 129.4 (CH), 128.9 (CH), 121.7 (CH), 120.0 (CH), 60.2 (CH_2), 59.9 (CH_2), 32.7 (CH_2), 32.6 (CH_2), 32.4 (CH_2), 32.0 (CH_2), 31.1 (CH_2), 29.0 (CH_2), 14.4 (2 x CH_3); LRMS (ES^+) *m/z* 357 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{20}H_{31}O_4^+$ Calcd. 335.2217, found 335.2212.

(*rac*)-methyl (2*R*)-2-[(2*R*,5*S*)-5-((1*S*,4*S*)-1,4-dihydroxy-4-(2*S*,5*R*)-5-[(1*R*)-1-hydroxy-2-(methyloxy)-2-oxoethyl]tetrahydro-2-furanylbutyl)tetrahydro-2-furanyl]-2-hydroxyethanoate (**4.38**)



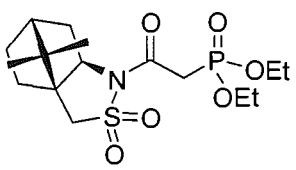
Under an atmosphere of N_2, to a stirred solution of (2*Z*,6*E*,10*E*,14*Z*)-dimethyl hexadeca-2,6,10,14-tetraenedioate **4.36** (21 mg, 0.07 mmol), AcOH (1.00 mL, 17.5 mmol), acetone (1.5 mL) and adogen 464 (10 mg) at −30 °C was added $KMnO_4$ (30 mg, 0.19 mmol) in one portion (mixture purple → brown) and the mixture warmed to 0 °C over 1 ¼ h. $Na_2S_2O_5$ (sat aq, 2 mL) was added to reduce the precipitated brown MnO_2, and the mixture stirred until clear. NaCl (sat aq, 5 mL) and EtOAc (10 mL) were added, the organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 10 mL) and CH_2Cl_2 (10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (0.030 g). Purification on SiO_2 (1 x 10 cm) eluting with MeOH/CH_2Cl_2 (1:19 → 1:9) gave (*rac*)-methyl (2*R*)-2-[(2*R*,5*S*)-5-((1*S*,4*S*)-1,4-dihydroxy-4-(2*S*,5*R*)-5-[(1*R*)-1-hydroxy-2-(methyloxy)-2-oxoethyl]tetrahydro-2-furanylbutyl)tetrahydro-2-furanyl]-2-hydroxyethanoate **4.38** (8 mg, 0.02 mmol, 28%) as a colourless oil. IR ν_{max} (neat) 3410 (br, m), 2954 (m), 2928 (m), 2883 (m), 1737 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.37 (2H, dd, *J* = 8.3, 3.8 Hz, 2 x C**H**OHCO$_2$Me), 4.27-4.19 (2H, m, 2 x C**H**CHOHCO$_2$Me), 3.88-3.81 (2H, m, 2 x CH$_2$CH$_2$CHOHC**H**), 3.73 (6H, s, 2 x OC**H**$_3$), 3.45-3.39 (2H, m, 2 x CH$_2$CH$_2$C**H**OH), 1.98-1.73 (8H, m, 2 x CHOHCHC**H**$_2$C**H**$_2$CH), 1.69-1.50 (4H, m, 2 x C**H**$_2$CHOH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9 (C), 172.8 (C), 83.3 (CH), 83.2 (CH), 80.5 (CH), 80.4 (CH), 73.9 (CH), 73.8 (CH), 72.9 (CH), 72.8 (CH), 52.7 (CH_3), 52.6 (CH_3), 31.6 (CH_2), 31.0 (CH_2), 28.4 (CH_2), 28.3 (CH_2), 25.9 (CH_2), 25.8 (CH_2); LRMS (ES^+) *m/z* 429 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{26}H_{41}O_8NSNa^+$ Calcd. 429.1731, found 429.1731.

(2*R*)-*N*-(2-Chloroethanoyl)-camphor-10,2-sultam (**4.44**)



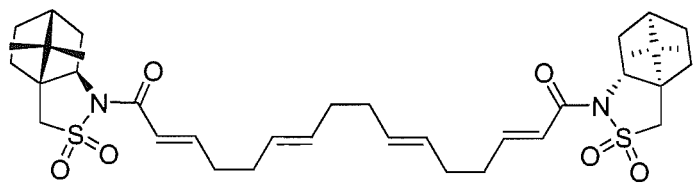
Under an atmosphere of N_2, to a stirred solution of (1*S*,2*R*)-camphorsultam **4.43** (3.00 g, 3.89 mmol) in THF (100 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 0.187 g, 4.67 mmol) portionwise and the mixture allowed to warm to rt over 30 min. The mixture was cooled to 0 °C and chloroacetyl chloride (0.37 mL, 4.67 mmol) was added dropwise. The mixture was stirred at rt for 3 h, then at reflux for a further 3 h before NH_4Cl (sat aq, 40 mL), H_2O (40 mL) and EtOAc (100 mL) were added. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow sludge (4.57 g). Purification on SiO_2 (4 x 15 cm) eluting with EtOAc/hexane (1:9 → 1:4) gave (2*R*)-*N*-(2-chloroethanoyl)-camphor-10,2-sultam **4.44** (3.60 g, 12.4 mmol, 89%) as a white solid. Spectroscopic characterisation agreed with that published.[125] Mp 110-112 °C; $[\alpha]^{25}_D$ –35.2 ($CHCl_3$, *c* 0.63); IR ν_{max} (neat) 2961 (m), 2884 (w), 1709 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.51 (2H, s, C**H**$_2$Cl), 3.93 (1H, dd, *J* = 7.7, 5.1 Hz, C**H**N), 3.54 (1H, d, *J* = 13.6 Hz, C**H**HSO$_2$), 3.47 (1H, d, *J* = 13.6 Hz, CH**H**SO$_2$), 2.25-2.07 (2H, m, C**H**$_2$CHN), 2.01-1.84 (3H, m, C**H**CH$_2$CHN and C**H**$_2$CHCH$_2$CHN), 1.50-1.31 (2H, m, C**H**$_2$CCHN), 1.16 (3H, s, C**H**$_3$C), 0.99 (3H, s, CC**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7 (C), 65.5 (CH), 52.7 (CH_2), 49.2 (C), 47.9 (C), 44.5 (CH), 42.5 (CH_2), 38.0 (CH_2), 32.8 (CH_2), 26.4 (CH_2), 20.7 (CH_3), 19.9 (CH_3); LRMS (ES^+) *m/z* 314 (100%, $[M+Na]^+$), 316 (37%, $[M+Na]^+$).

Diethyl-2-oxo-2-((2*R*)-*N*-camphor-10,2-sultam)-ethylphosphonate (**4.45**)



The procedure was carried out using the method described by Oppolzer *et al.*[121,122] Under an atmosphere of N_2, to a stirred solution of (2*R*)-*N*-(2-chloroethanoyl)-camphor-10,2-sultam **4.44** (3.60 g, 12.4 mmol) in xylene (100 mL) was added $P(OEt)_3$ (16.0 mL, 93.0 mmol) and the mixture heated at reflux for 14 h. The mixture was concentrated *in vacuo* to remove xylene and distilled under reduced pressure (100 °C, 0.5 mmHg) to remove excess $P(OEt)_3$ resulting in a yellow oil (4.10 g). Purification on SiO_2 (10 x 15 cm) eluting with EtOAc/hexane (3:2 → 4:1) gave diethyl-2-oxo-2-((2*R*)-*N*-camphor-10,2-sultam)-ethylphosphonate **4.45** (3.85 g, 9.80 mmol, 79%) as a colourless oil. Spectroscopic characterisation agreed with that published.[125] $[\alpha]^{25}_D$ – 56.2 ($CHCl_3$, *c* 0.80); IR ν_{max} (neat) 2963 (m), 2942 (m), 1692 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.19 (4H, dq, *J* = 15.5, 7.0 Hz, 2 x OCH_2CH_3), 3.89 (1H, dd, *J* = 7.7, 5.1 Hz, CHN), 3.56 (1H, dd, *J* = 20.4, 15.6 Hz, C(O)CHH), 3.53 (1H, d, *J* = 13.6 Hz, $CHHSO_2$), 3.45 (1H, d, *J* = 13.6 Hz, $CHHSO_2$), 3.22 (1H, dd, *J* = 20.4, 15.6 Hz, C(O)CHH), 2.22-2.03 (2H, m, CH_2CHN), 1.99-1.82 (3H, m, $CHCH_2CHN$ and CH_2CHCH_2CHN), 1.34 (6H, dt, *J* = 7.0, 2.2 Hz, 2 x OCH_2CH_3), 1.37-1.29 (2H, m, CH_2CCHN), 1.18 (3H, s, CH_3C), 0.97 (3H, s, CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6 (C), 65.3 (CH_2), 62.9 (CH_2, d, J_{C-P} = 6.2 Hz), 62.6 (CH_2, d, J_{C-P} = 6.2 Hz), 52.9 (CH_2), 48.3 (C), 47.8 (C), 44.6 (CH), 38.2 (CH_2), 34.9 (CH_2, d, *J* = 137.3), 32.8 (CH_2), 26.5 (CH_2), 20.7 (CH_3), 19.9 (CH_3), 16.4 (CH_3, d, *J* = 4.0 Hz), 16.3 (CH_3, d, *J* = 4.0 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) 19.9 (P(O)); LRMS (ES^+) *m/z* 416 (100%, $[M+Na]^+$).

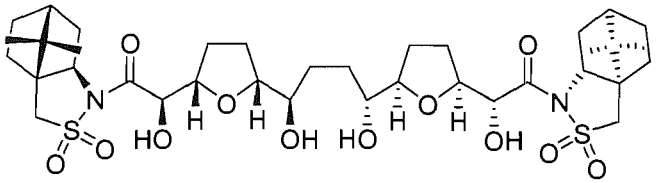
1,16-(2*R*)-*N*-[(2*E*,6*E*,10*E*,14*E*)-16-Oxo-2,6,10,14-hexadecatetraenoyl]-di-camphor-10,2-sultam (**4.46**)



Under an atmosphere of N_2, to a stirred solution of diethyl-2-oxo-2-((2*R*)-*N*-camphor-10,2-sultam)-ethylphosphonate **4.45** (405 mg, 1.04 mmol) in THF (15 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 41 mg, 1.04 mmol). The mixture was warmed to rt over 30 min before cooling to 0 °C. (4*E*,8*E*)-Dodeca-4,8-dienedial **3.5**

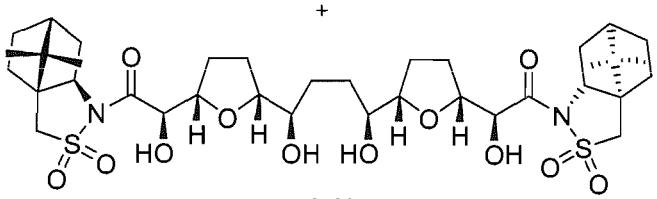
(100 mg, 0.52 mmol) in THF (5 mL) was added dropwise and the mixture warmed to rt over 14 h. H_2O (30 mL) and EtOAc (50 mL) were added, the organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (402 mg). Purification on SiO_2 (3 x 15 cm) eluting with EtOAc/hexane (1:4 → 2:3) gave 1,16-(2*R*)-*N*-[(2*E*,6*E*,10*E*,14*E*)-16-oxo-2,6,10,14-hexadecatetraenoyl]-di-camphor-10,2-sultam **4.46** as a colourless oil (292 mg, 0.44 mmol, 84%). $[\alpha]^{25}_{D}$ –78.4 ($CHCl_3$, *c* 0.56); IR ν_{max} (neat) 2959 (m), 2941 (m), 2892 (w), 2848 (w), 1680 (s), 1638 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.08 (2H, dt, *J* = 15.1, 6.8 Hz, 2 x C**H**CHC(O)), 6.56 (2H, d, *J* = 15.1 Hz, 2 x CHC**H**C(O)), 5.50-5.35 (4H, m, 2 x CH_2C**H**C**H**CH_2), 3.93 (2H, dd, *J* = 7.5, 5.3 Hz, 2 x C**H**N), 3.51 (2H, d, *J* = 13.8 Hz, 2 x C**H**HSO_2), 3.43 (2H, d, *J* = 13.8 Hz, 2 x CH**H**SO_2), 2.31 (4H, appt. q, *J* = 7.2 Hz, 2 x C**H**$_2$CHCHC(O)), 2.20-2.06 (8H, m, 2 x C**H**$_2$$CH_2$CHCHC(O) and 2 x C**H**$_2$CHN), 2.05-2.00 (4H, m, 2 x C**H**$_2$CHCHC**H**$_2$$CH_2$CHCHC(O)), 1.97-1.84 (6H, m, 2 x C**H**CH_2CHN and 2 x C**H**$_2$$CHCH_2$CHN), 1.47-1.32 (4H, m, 2 x C**H**$_2$CCHN), 1.18 (6H, s, 2 x C**H**$_3$C), 0.98 (6H, s, 2 x CC**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2 (C), 150.4 (CH), 131.2 (CH), 128.8 (CH), 121.2 (CH), 65.3 (CH), 53.3 (CH_2), 48.6 (C), 47.9 (C), 44.9 (CH), 38.7 (CH_2), 33.0 (CH_2), 32.7 (CH_2), 32.6 (CH_2), 31.0 (CH_2), 26.6 (CH_2), 21.0 (CH_3), 20.0 (CH_3); LRMS (ES^+) *m/z* 695 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{36}H_{52}O_6N_2S_2Na^+$ Calcd. 695.3159, found 695.3144.

Inseparable mixture of (2*R*)-*N*-((2*R*)-2-(2*S*,5*R*)-5-[(1*R*,4*R*)-1,4-Dihydroxy-4-((2*R*,5*S*)-5-(1*R*)-1-hydroxy-2-[(2*R*)-*N*-camphor-10,2-sultam]-2-oxoethyltetrahydro-2-furanyl)butyl]tetrahydro-2-furanyl-2-hydroxyethanoyl)-camphor-10,2-sultam (**4.47**) and (2*R*)-*N*-((2*R*)-2-(2*S*,5*R*)-5-[(1*R*,4*S*)-1,4-dihydroxy-4-((2*S*,5*R*)-5-(1*S*)-1-hydroxy-2-[(2*R*)-*N*-camphor-10,2-sultam]-2-oxoethyltetrahydro-2-furanyl)butyl]tetrahydro-2-furanyl-2-hydroxyethanoyl)-camphor-10,2-sultam (**4.48**)



4.47

+



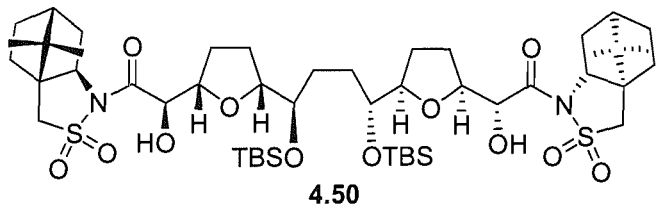
4.48

(ratio **4.47**/**4.48** = 3:1 after chromatography)

Under an atmosphere of N_2, to a stirred solution of 1,16-(2*R*)-*N*-[(2*E*,6*E*,10*E*,14*E*)-16-oxo-2,6,10,14-hexadecatetraenoyl]-di-camphor-10,2-sultam **4.46** (337 mg, 0.50 mmol), AcOH (4 mL) and acetone (6 mL) at −30 °C was added $KMnO_4$ (222 mg, 1.40 mmol) in one portion (mixture purple → brown) and the mixture warmed to −20 °C over 25 min. $Na_2S_2O_5$ (sat aq, 20 mL) was added to reduce the precipitated brown MnO_2, and the mixture stirred until clear. NaCl (sat aq, 10 mL) and EtOAc (20 mL) were added, the organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 20 mL) and CH_2Cl_2 (20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (180 mg). Purification on SiO_2 (2 x 15 cm) eluting with MeOH/CH_2Cl_2 (1:49 → 3:47) gave an inseparable mixture of (2*R*)-*N*-((2*R*)-2-(2*S*,5*R*)-5-[(1*R*,4*R*)-1,4-dihydroxy-4-((2*R*,5*S*)-5-(1*R*)-1-hydroxy-2-[(2*R*)-*N*-camphor-10,2-sultam]-2-oxoethyltetrahydro-2-furanyl)butyl]tetrahydro-2-furanyl-2-hydroxyethanoyl)-camphor-10,2-sultam **4.47** and (2*R*)-*N*-((2*R*)-2-(2*S*,5*R*)-5-[(1*R*,4*S*)-1,4-dihydroxy-4-((2*S*,5*R*)-5-(1*S*)-1-hydroxy-2-[(2*R*)-*N*-camphor-10,2-sultam]-2-oxoethyltetrahydro-2-furanyl)butyl]tetrahydro-2-furanyl-2-hydroxyethanoyl)-camphor-10,2-sultam **4.48** (108 mg, 0.14 mmol, 28%) as

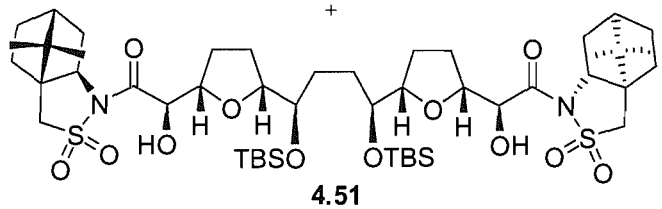
a white foam. Data for major isomer **4.47**: $[\alpha]^{25}_{D}$ –41.0 ($CHCl_3$, *c* 0.75); IR ν_{max} (neat) 3455 (w), 2961 (m), 2884 (m), 1690 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.61-4.52 (4H, m, 2 x C(O)C**H**OH and 2 x C(O)CHOHC**H**), 4.00-3.83 (2H, m, 2 x C**H**N), 3.88 (2H, td, *J* = 6.8, 4.8 Hz, 2 x CH_2C**H**CHOHCH_2), 3.55-3.41 (6H, m, 2 x C**H**HSO_2, 2 x CH**H**SO_2 and 2 x CH_2CHC**H**OHCH_2), 2.28-2.19 (2H, m, C$\mathbf{H_2}$CHN), 2.14-2.01 (6H, m, C$\mathbf{H_2}$CHN and 2 x CHOHCHC$\mathbf{H_2}$), 1.99-1.83 (10H, m, 2 x C**H**CH_2CHN, 2 x C$\mathbf{H_2}$CHCH_2CHN and 2 x CHOHCHCH_2C$\mathbf{H_2}$), 1.68 (4H, d, *J* = 3.0 Hz, 2 x CHOHC$\mathbf{H_2}$), 1.47-1.31 (4H, m, 2 x C$\mathbf{H_2}$CCHN), 1.16 (6H, s, 2 x C$\mathbf{H_3}$C), 0.97 (6H, s, 2 x CC$\mathbf{H_3}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0 (C), 83.4 (CH), 78.9 (CH), 74.0 (CH), 73.7 (CH), 66.0 (CH), 53.2 (CH_2), 49.1 (C), 48.0 (C), 44.8 (CH), 38.4 (CH_2), 33.1 (CH_2), 28.3 (CH_2), 26.5 (CH_2), 21.1 (CH_3), 20.0 (CH_3); LRMS (ES^+) *m/z* 795 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{36}H_{56}O_{12}N_2S_2Na^+$ Calcd. 795.3166, found 795.3147.

(2*R*)-*N*-((2*R*)-2-(2*S*,5*R*)-5-[(1*R*,4*R*)-1,4-Di[1-(*t*-butyl)-1,1-dimethylsilyl]oxy-4-((2*R*,5*S*)-5-(1*R*)-1-hydroxy-2-[methyl(methylsulfonyl)amino]-2-oxoethyltetrahydro-2-furanyl)butyl]tetrahydro-2-furanyl-2-hydroxyethanoyl)-camphor-10,2-sultam (**4.50**) and (2*R*)-*N*-((2*R*)-2-(2*S*,5*R*)-5-[(1*R*,4*S*)-1,4-di[1-(*t*-butyl)-1,1-dimethylsilyl]oxy-4-((2*S*,5*R*)-5-(1*S*)-1-hydroxy-2-[(2*R*)-*N*-camphor-10,2-sultam]-2-oxoethyltetrahydro-2-furanyl)butyl]tetrahydro-2-furanyl-2-hydroxyethanoyl)-camphor-10,2-sultam (**4.51**)



4.50

+



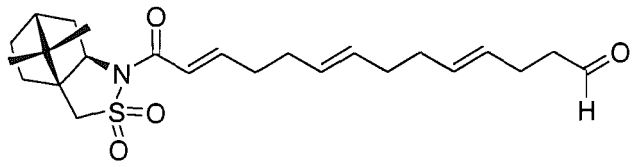
4.51

(ratio **4.50**/**4.51** = 3:1 after chromatography)

The procedure was carried out using the method described by Corey *et al.*[123] Under an atmosphere of N_2, to a stirred solution of (2*R*)-*N*-((2*R*)-2-(2*S*,5*R*)-5-[(1*R*,4*R*)-1,4-dihydroxy-4-((2*R*,5*S*)-5-(1*R*)-1-hydroxy-2-[(2*R*)-*N*-camphor-10,2-sultam]-2-

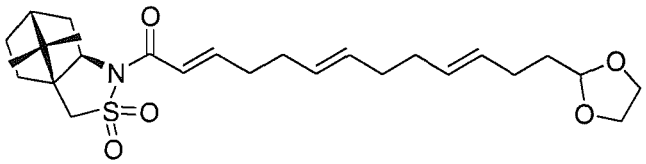
oxoethyltetrahydro-2-furanyl)butyl]tetrahydro-2-furanyl-2-hydroxyethanoyl)-camphor-10,2-sultam **4.47** and (2*R*)-*N*-((2*R*)-2-(2*S*,5*R*)-5-[(1*R*,4*S*)-1,4-dihydroxy-4-((2*S*,5*R*)-5-(1*S*)-1-hydroxy-2-[(2*R*)-*N*-camphor-10,2-sultam]-2-oxoethyltetrahydro-2-furanyl)butyl]tetrahydro-2-furanyl-2-hydroxyethanoyl)-camphor-10,2-sultam **4.48** (70 mg, 0.09 mmol) in CH_2Cl_2 (1.5 mL) at rt was added 2,6-lutidine (0.02 mL, 0.18 mmol) dropwise. The mixture was cooled to −10 °C before TBSOTf (0.04 mL, 0.18 mmol) was added dropwise. After 30 min H_2O (2 mL) and EtOAc (4 mL) were added, the organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 4 mL). The combined organic phases were washed successively with 3 M $KHSO_4$ (aq, 5 mL), H_2O (5 mL) and NaCl (sat aq, 5 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (65 mg). Purification on SiO_2 (1.5 x 15 cm) eluting with EtOAc/hexane (1:4 → 1:2) gave an inseparable mixture of (2*R*)-*N*-((2*R*)-2-(2*S*,5*R*)-5-[(1*R*,4*R*)-1,4-di[1-(*t*-butyl)-1,1-dimethylsilyl]oxy-4-((2*R*,5*S*)-5-(1*R*)-1-hydroxy-2-[methyl(methylsulfonyl)amino]-2-oxoethyltetrahydro-2-furanyl)butyl]tetrahydro-2-furanyl-2-hydroxyethanoyl)-camphor-10,2-sultam **4.50** and (2*R*)-*N*-((2*R*)-2-(2*S*,5*R*)-5-[(1*R*,4*S*)-1,4-di[1-(*t*-butyl)-1,1-dimethylsilyl]oxy-4-((2*S*,5*R*)-5-(1*S*)-1-hydroxy-2-[(2*R*)-*N*-camphor-10,2-sultam]-2-oxoethyltetrahydro-2-furanyl)butyl]tetrahydro-2-furanyl-2-hydroxyethanoyl)-camphor-10,2-sultam **4.51** (34 mg, 0.03 mmol, 36 %) as a colourless oil. Data for major isomer **4.50**: $[\alpha]^{25}_D$ –33.7 ($CHCl_3$, *c* 0.44); IR ν_{max} (neat) 3466 (w), 2959 (m), 2927 (m), 2855 (m), 1696 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.49 (2H, dd, *J* = 8.0, 3.3 Hz, 2 x C(O)C**H**OH), 4.45 (2H, td, *J* = 8.0, 3.0 Hz, 2 x C(O)CHOHC**H**), 3.99-3.90 (4H, m, 2 x C**H**N and 2 x CH_2C**H**CHOHCH_2), 3.71-3.60 (2H, m, 2 x CH_2CHC**H**OHCH_2), 3.50 (2H, d, *J* = 13.8 Hz, 2 x C**H**HSO$_2$), 3.42 (2H, d, *J* = 13.6 Hz, 2 x CH**H**SO$_2$), 2.28-2.20 (2H, m, C**H**$_2$CHN), 2.13-1.99 (6H, m, C**H**$_2$CHN and 2 x CHOHCHC**H**$_2$), 1.97-1.79 (10H, m, 2 x C**H**CH$_2$CHN, 2 x C**H**$_2$CHCH$_2$CHN and 2 x CHOHCHCH$_2$C**H**$_2$), 1.71-1.63 (4H, m, 2 x CHOHC**H**$_2$), 1.53-1.31 (4H, m, 2 x C**H**$_2$CCHN), 1.16 (6H, s, 2 x C**H**$_3$C), 0.97 (6H, s, 2 x CC**H**$_3$), 0.85 (18H, s, 2 x C(C**H**$_3$)$_3$, 0.09 (12H, s, 2 x Si(C**H**$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4 (C), 82.2 (CH), 78.2 (CH), 74.7 (CH), 73.5 (CH), 65.9 (CH), 53.2 (CH_2), 49.0 (C), 48.0 (C), 44.9 (CH), 38.5 (CH_2), 33.1 (CH_2), 29.9 (CH_2), 28.4 (CH_2), 27.1 (CH_2), 26.5 (CH_2), 26.1 (CH_3), 21.1 (CH_3), 20.0 (CH_3), 18.3 (C), −4.1 (CH_3), −4.3 (CH_3); LRMS (ES^+) *m/z* 1023 (100%, $[M+Na]^+$).

(2*R*)-*N*-[(4*E*,8*E*,12*E*)-14-Oxo-4,8,12-tetradecatrienal]-camphor-10,2-sultam (**4.52**)



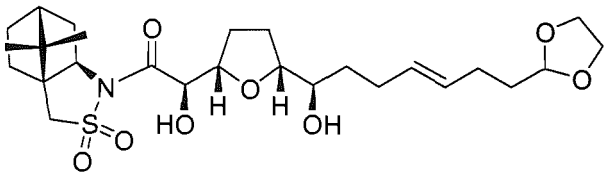
Under an atmosphere of N_2, to a stirred solution of diethyl-2-oxo-2-((2*R*)-*N*-camphor-10,2-sultam)-ethylphosphonate **4.45** (610 mg, 1.55 mmol) in THF (15 mL) at rt was added NaH (60% dispersion in mineral oil, 65 mg, 1.63 mmol) portionwise. The mixture was added to a solution of (4*E*,8*E*)-dodeca-4,8-dienedial **3.5** (300 mg, 1.55 mmol) in THF (10 mL) at –78 °C dropwise. The mixture was allowed to warm to –35 °C over 2 h before NH_4Cl (sat aq, 15 mL), H_2O (10 mL) and EtOAc (30 mL) were added. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow oil (600 mg). Purification on SiO_2 (3 x 15 cm) eluting with EtOAc/hexane (1:9 → 3:7) gave (2*R*)-*N*-[(4*E*,8*E*,12*E*)-14-Oxo-4,8,12-tetradecatrienal]-camphor-10,2-sultam **4.52** (171 mg, 0.39 mmol, 25%) as a colourless oil. $[\alpha]^{25}_D$ –56.0 ($CHCl_3$, *c* 0.38); IR ν_{max} (neat) 2955 (m), 2850 (w), 1717 (m), 1682 (s), 1638 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.75 (1H, s, C**H**O), 7.08 (1H, dt, *J* = 15.1, 6.8 Hz, C(O)CHC**H**), 6.57 (1H, dt, *J* = 15.1, 1.5 Hz, C(O)C**H**CH), 5.54-5.31 (4H, m, 2 x CH_2C**H**C**H**CH_2), 3.93 (1H, dd, *J* = 7.4, 5.2 Hz, C**H**N), 3.51 (1H, d, *J* = 13.6 Hz, C**H**HSO_2), 3.43 (1H, d, *J* = 13.6 Hz, CH**H**SO_2), 2.50 (2H, t, *J* = 7.0 Hz, CH_2C**H**$_2$CHO), 2.39-2.27 (4H, m, C(O)CHCHC**H**$_2$ and C**H**$_2$$CH_2$CHO), 2.22-2.01 (8H, m, C**H**$_2$CHN, C**H**$_2$C**H**$_2$CHCHC**H**$_2$$CH_2$CHO and C(O)CHCHC**H**$_2$C**H**$_2$), 1.97-1.85 (3H, m, C**H**CH_2CHN and C**H**$_2$CHC**H**$_2$CHN), 1.48-1.31 (2H, m, C**H**$_2$CCHN), 1.14 (3H, s, C**H**$_3$C), 0.98 (3H, s, C**H**$_3$C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6 (CH), 164.1 (C), 150.2 (CH), 131.3 (CH), 130.9 (CH), 128.8 (CH), 128.1 (CH), 121.0 (CH), 65.1 (CH), 53.2 (CH_2), 48.4 (C), 47.7 (C), 44.7 (CH), 43.5 (CH_2), 38.5 (CH_2), 32.8 (CH_2), 32.5 (CH_2), 32.4 (CH_2), 32.3 (CH_2), 30.9 (CH_2), 26.5 (CH_2), 25.2 (CH_2), 20.9 (CH_3), 19.9 (CH_3); LRMS (ES^+) *m/z* 456 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{24}H_{35}O_4NSNa^+$ Calcd. 456.2179, found 456.2180.

(2*R*)-*N*-[(2*E*,6*E*,10*E*)-13-(1,3-Dioxolan-2-yl)-2,6,10-tridecatrienoyl]-camphor-10,2-sultam (**4.53**)



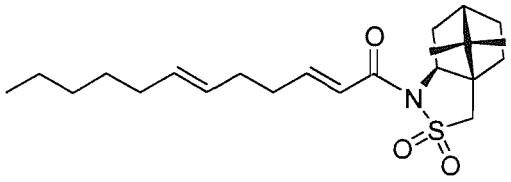
The procedure was carried out using the method described by Noyori *et al.*[124] Under an atmosphere of N_2, to a stirred solution of (2*R*)-*N*-[(4*E*,8*E*,12*E*)-14-Oxo-4,8,12-tetradecatrienal]-camphor-10,2-sultam **4.52** (167 mg, 0.39 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added 1,2-*bis*-(trimethylsilyloxy)ethane (0.47 mL, 1.93 mmol) and TMSOTf (0.09 mL, 0.51 mmol) successively. After 30 min at −78 °C the mixture was poured into $NaHCO_3$ (sat aq, 10 mL), the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (192 mg). Purification on SiO_2 (2 x 15 cm) eluting with EtOAc/hexane (1:4 → 3:7) gave (2*R*)-*N*-[(2*E*,6*E*,10*E*)-13-(1,3-dioxolan-2-yl)-2,6,10-tridecatrienoyl]-camphor-10,2-sultam **4.53** (154 mg, 0.32 mmol, 83%) as a colourless oil. $[\alpha]^{25}_D$ –53.9 ($CHCl_3$, *c* 0.44); IR ν_{max} (neat) 2985 (w), 2959 (m), 2918 (m), 2845 (w), 1681 (m), 1639 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.09 (1H, dt, *J* = 15.1, 6.9 Hz, C(O)CHC**H**), 6.56 (1H, dt, *J* = 15.1, 1.5 Hz, C(O)C**H**CH), 5.52-5.33 (4H, m, 2 x CH_2C**H**C**H**CH_2), 4.87 (1H, t, *J* = 4.8 Hz, C**H**$(O)_2$), 4.01-3.90 (3H, m, C**H**N and OC**H**HC**H**HO), 3.88-3.80 (2H, m, OCH**H**CH**H**O), 3.53 (1H, d, *J* = 13.8 Hz, C**H**HSO_2), 3.48 (1H, d, *J* = 13.8 Hz, CH**H**SO_2), 2.36-2.27 (2H, appt. q, *J* = 7.4 Hz, C(O)CHCHC**H**$_2$), 2.22-2.00 (10H, m, C**H**$_2$CHN, C**H**$_2$$CH_2CH(O)_2$, C**H**$_2$C**H**$_2$CHCHC**H**$_2$$CH_2CH(O)_2$ and C(O)CHCHC**H**$_2$C**H**$_2$), 1.99-1.85 (3H, m, C**H**CH_2CHN and C**H**$_2$C**H**CH_2CHN), 1.76-1.67 (2H, m, C**H**$_2$CH$(O)_2$), 1.48-1.31 (2H, m, C**H**$_2$CCHN), 1.18 (3H, s, C**H**$_3$C), 0.98 (3H, s, CC**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1 (C), 150.3 (CH), 131.1 (CH), 130.3 (CH), 129.4 (CH), 128.6 (CH), 121.0 (CH), 104.1 (CH), 65.1 (CH), 64.9 (2 x CH_2), 53.2 (CH_2), 48.4 (C), 47.8 (C), 44.7 (CH), 38.5 (CH_2), 33.8 (CH_2), 32.9 (2 x CH_2), 32.5 (CH_2), 32.5 (CH_2), 30.9 (CH_2), 27.1 (CH_2), 26.5 (CH_2), 20.9 (CH_3), 19.9 (CH_3); LRMS (ES^+) *m/z* 500 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{26}H_{39}O_5NSNa^+$ Calcd. 500.2441, found 500.2447.

(2*R*)-*N*-((2*R*)-2-(2*S*,5*R*)-5-[(1*R*,4*E*)-7-(1,3-Dioxolan-2-yl)-1-hydroxy-4-heptenyl]tetrahydro-2-furanyl-2-hydroxyethanoyl)-camphor-10,2-sultam (**4.54**)



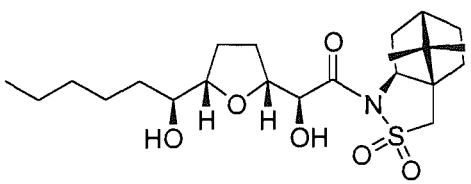
Under an atmosphere of N_2, to a stirred solution of (2*R*)-*N*-[(2*E*,6*E*,10*E*)-13-(1,3-dioxolan-2-yl)-2,6,10-tridecatrienoyl]-camphor-10,2-sultam **4.53** (143 mg, 0.30 mmol), AcOH (4 mL) and acetone (6 mL) at −30 °C was added $KMnO_4$ (71 mg, 0.45 mmol) in one portion (mixture purple → brown) and the mixture warmed to −15 °C over 1 ¼ h. $Na_2S_2O_5$ (sat aq, 5 mL) was added to reduce the precipitated brown MnO_2, and the mixture stirred until clear. NaCl (sat aq, 5 mL) and EtOAc (10 mL) were added, the organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 10 mL) and CH_2Cl_2 (10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (126 mg). Purification on SiO_2 (1.5 x 10 cm) eluting with EtOAc/hexane (2:3 → 7:3) gave (2*R*)-*N*-((2*R*)-2-(2*S*,5*R*)-5-[(1*R*,4*E*)-7-(1,3-dioxolan-2-yl)-1-hydroxy-4-heptenyl]tetrahydro-2-furanyl-2-hydroxyethanoyl)-camphor-10,2-sultam **4.54** (50 mg, 0.10 mmol, 32%). $[\alpha]^{25}_D$ − 35.2 ($CHCl_3$, *c* 0.31); IR ν_{max} (neat) 3439 (w), 2960 (m), 2887 (m), 1694 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.52-5.38 (2H, m, CH_2**C**H**C**HCH_2), 4.85 (1H, t, *J* = 4.8 Hz, C**H**$(O)_2$), 4.60-4.48 (2H, m, C(O)C**H**OH and C(O)CHOHC**H**), 4.20-4.05 (1H, m, CH_2**C**HCHOHCH_2), 3.99-3.92 (3H, m, C**H**N and OC**H**HC**H**HO), 3.91-3.81 (2H, m, OCH**H**CH**H**O), 3.56-3.40 (3H, m, C**H**HSO_2, CH**H**SO_2 and CH_2CHC**H**OHCH_2), 2.32-2.16 (2H, m, C**H**$_2$CHN), 2.15-1.99 (6H, m, CHOHCHC**H**$_2$C**H**$_2$CHCHOH and CH_2CHCHC**H**$_2$), 1.98-1.82 (5H, m, C**H**CH_2CHN, C**H**$_2$$CH_2$CHN and C**H**$_2$CHCHC$H_2$), 1.76-1.66 (2H, m, C**H**$_2$CH$(O)_2$), 1.65-1.21 (4H, m, C**H**$_2$CCHN and CHCHOHC**H**$_2$), 1.15 (3H, s, C**H**$_3$C), 0.96 (3H, s, CC**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7 (C), 130.2 (CH), 129.7 (CH), 104.1 (CH), 83.1 (CH), 78.6 (CH), 73.5 (CH), 73.3 (CH), 65.8 (CH), 64.8 (2 x CH_2), 53.0 (CH_2), 49.0 (C), 47.8 (C), 44.5 (CH), 38.2 (CH_2), 34.2 (CH_2), 33.8 (CH_2), 32.9 (CH_2), 28.7 (CH_2), 28.3 (CH_2), 28.2 (CH_2), 27.1 (CH_2), 26.4 (CH_2), 20.9 (CH_3), 19.9 (CH_3); LRMS (ES^+) *m/z* 550 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{26}H_{41}O_8NSNa^+$ Calcd. 550.2445, found 550.2444.

(2*S*)-*N*-[(2*E*,6*E*)-2,6-Dodecadienoyl]-camphor-10,2-sultam (**5.2**)



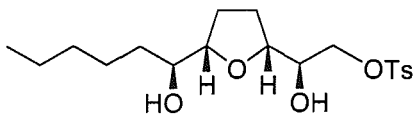
The title compound was prepared according to the method outlined for **4.46** except using (1*R*,2*S*)-**4.45** (1.40 g, 3.56 mmol) and *trans*-4-decenal (**5.1**) (0.60 mL, 3.24 mmol). Purification on SiO_2 (3.5 x 15 cm) eluting with EtOAc/hexane (1:9 → 2:3) gave (2*S*)-*N*-[(2*E*,6*E*)-2,6-dodecadienoyl]-camphor-10,2-sultam **5.2** (0.76 g, 1.94 mmol, 60%) as a colourless oil. Spectroscopic characterisation agreed with that published.[125] $[\alpha]^{25}_{D}$ + 67.3 ($CHCl_3$, *c* 0.63); IR ν_{max} (neat) 2956 (m), 2927 (m), 2855 (w), 1683 (s), 1639 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.09 (1H, dt, *J* = 15.1, 6.9 Hz, C**H**CHC(O)), 6.57 (1H, dt, *J* = 15.1, 1.5 Hz, CHC**H**C(O)), 5.51-5.34 (2H, m, CH_2C**H**C**H**CH_2), 3.93 (1H, dd, *J* = 7.5, 5.3 Hz, NC**H**), 3.51 (1H, d, *J* = 13.8 Hz, SO_2C**H**H), 3.44 (1H, d, *J* = 13.8 Hz, SO_2CH**H**), 2.32 (2H, appt. q, *J* = 7.3 Hz, C**H**$_2$CHCHC(O)), 2.20-2.06 (4H, m, C**H**$_2$$CH_2$CHCHC(O) and NCHC**H**$_2$), 1.97-1.84 (5H, m, NCH$CH_2$C**H**, NCH$CH_2$CHC**H**$_2$ and C**H**$_2$CHCH$CH_2$$CH_2$CHCHC(O)), 1.47-1.22 (8H, m, NCHCC**H**$_2$ and CH_3C**H**$_2$C**H**$_2$C**H**$_2$CHCH), 1.19 (3H, s, C**H**$_3$C), 0.98 (3H, s, CC**H**$_3$), 0.89 (3H, t, *J* = 6.9 Hz, C**H**$_3$$CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3 (C), 150.4 (CH), 132.1 (CH), 128.4 (CH), 121.2 (CH), 65.3 (CH), 53.3 (CH_2), 48.6 (C), 47.9 (C), 44.9 (CH), 38.7 (CH_2), 33.0 (CH_2), 32.7 (CH_2), 32.6 (CH_2), 31.5 (CH_2), 31.1 (CH_2), 29.3 (CH_2), 26.7 (CH_2), 22.7 (CH_2), 21.0 (CH_3), 20.1 (CH_3), 14.2 (CH_3); LRMS (ES^+) *m/z* 416 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{22}H_{35}O_3NSNa^+$ Calcd. 416.2234, found 416.2237.

(2*S*)-*N*-[(2*S*)-2-Hydroxy-2-((2*R*,5*S*)-5-((1*S*)-1-hydroxyhexyl)tetrahydro-2-furanylethanoyl)]-camphor-10,2-sultam (**5.3**)



The title compound was prepared according to the method outlined for **4.52** except using (2*S*)-*N*-((2*E*,6*E*)-2,6-dodecadienoyl)-camphor-10,2-sultam **5.2** (111 mg, 0.28 mmol) and $KMnO_4$ (62 mg, 0.39 mmol). Purification on SiO_2 (3.5 x 15 cm) eluting with EtOAc/hexane (1:9 → 2:3) gave (2*S*)-*N*-[(2*S*)-2-hydroxy-2-((2*R*,5*S*)-5-((1*S*)-1-hydroxyhexyl)tetrahydro-2-furanylethanoyl)]-camphor-10,2-sultam **5.3** (70 mg, 0.16 mmol, 56%) as a colourless oil. Spectroscopic characterisation agreed with that published.[125] $[\alpha]^{25}_D$ + 46.4 ($CHCl_3$, *c* 0.25); IR ν_{max} (neat) 3454 (w), 2954 (m), 2936 (w), 2874 (w), 1692 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.61-4.55 (2H, m, C**H**CHOHC(O) and CHC**H**OHC(O)), 3.97 (1H, dd, *J* = 5.2, 2.5 Hz, NC**H**), 3.87 (2H, td, *J* = 7.2, 4.5 Hz, $CH_2CHOHC\mathbf{H}CH_2$), 3.52 (1H, d, *J* = 13.8 Hz, $SO_2C\mathbf{H}H$), 3.49-3.44 (1H, m, $CH_2C\mathbf{H}OHCHCH_2$), 3.45 (1H, d, *J* = 13.8 Hz, $SO_2CH\mathbf{H}$), 2.29-2.22 (1H, m, NCHC**H**H), 2.15-2.03 (3H, m, NCHCH**H** and $C\mathbf{H}_2CHCHOHC(O)$), 1.98-1.84 (5H, m, $NCHCH_2C\mathbf{H}$, $NCHCH_2CHC\mathbf{H}_2$ and $C\mathbf{H}_2CH_2CHCHOHC(O)$), 1.56-1.41 (4H, m, $C\mathbf{H}_2CHOHCHCH_2$ and $NCHCC\mathbf{H}_2$), 1.40-1.25 (6H, m, $CH_3C\mathbf{H}_2C\mathbf{H}_2C\mathbf{H}_2CH_2$), 1.16 (3H, s, $C\mathbf{H}_3C$), 0.98 (3H, s, $CC\mathbf{H}_3$), 0.89 (3H, t, *J* = 6.9 Hz, $C\mathbf{H}_3CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0 (C), 83.4 (CH), 78.9 (CH), 74.0 (CH), 73.7 (CH), 66.0 (CH), 53.2 (CH_2), 49.1 (C), 48.0 (C), 44.8 (CH), 38.4 (CH_2), 33.1 (CH_2), 32.0 (CH_2), 28.5 (2 x CH_2), 28.3 (CH_2), 26.5 (CH_2), 25.6 (CH_2), 22.8 (CH_2), 21.1 (CH_3), 20.0 (CH_3), 14.2 (CH_3); LRMS (ES^+) *m/z* 466 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{22}H_{37}O_6NSNa^+$ Calcd. 466.2234, found 466.2238.

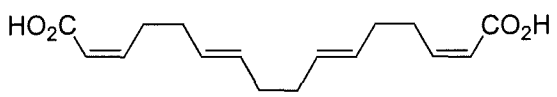
(2*R*)-2-Hydroxy-2-(2*R*,5*S*)-5-[(1*S*)-1-hydroxyhexyl]tetrahydro-2-furanylethyl 4-toluenesulfonate (**5.4**)



Under an atmosphere of N_2, to a stirred solution of (2*S*)-*N*-[(2*S*)-2-hydroxy-2-((2*R*,5*S*)-5-((1*S*)-1-hydroxyhexyl)tetrahydro-2-furanylethanoyl)]-camphor-10,2-sultam **5.3** (82 mg, 0.19 mmol) in THF (1.5 mL) and H_2O (0.5 mL) at –10 °C was added $NaBH_4$ (14 mg, 0.37 mmol) in one portion. After 30 min at –10 °C, the mixture was warmed to 0 °C over 1 h. The mixture concentrated was *in vacuo* to give a white solid (102 mg). The organic solid was dissolved in CH_2Cl_2 (5 mL) and decanted. To the

remaining inorganic solid was added 2 M HCl (aq, 5 mL), NaCl (sat aq, 5 mL) and EtOAc (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give (*R*)-1-((2*R*,5*S*)-tetrahydro-5-((*S*)-1-hydroxyhexyl)furan-2-yl)ethane-1,2-diol (68 mg) as a white solid, which was used without any further purification. Under an atmosphere of N_2, to a stirred solution of (*R*)-1-((2*R*,5*S*)-tetrahydro-5-((*S*)-1-hydroxyhexyl)furan-2-yl)ethane-1,2-diol (68 mg) in benzene (5 mL) at rt was added Bu_2SnO (0.055 g, 0.22 mmol) and the mixture heated to reflux for 3 h. The mixture was cooled to rt and TsCl (37 mg, 0.19 mmol) was added. After 14 h the mixture was concentrated *in vacuo* to give a yellow solid (110 mg). Purification on SiO_2 (3.5 x 15 cm) eluting with EtOAc/hexane (1:2 → 3:2) gave (2*R*)-2-hydroxy-2-(2*R*,5*S*)-5-[(1*S*)-1-hydroxyhexyl]tetrahydro-2-furanylethyl 4-toluenesulfonate **5.4** (45 mg, 0.12 mmol, 63%) as a colourless oil. $[\alpha]^{25}_D$ –12.5 ($CHCl_3$, *c* 0.50); IR ν_{max} (neat) 3346 (m), 2926 (m), 2856 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (2H, d, *J* = 8.3 Hz, 2 x C(S)C**H**), 7.35 (2H, d, *J* = 8.3 Hz, 2 x C(S)CHC**H**), 4.09 (2H, dd, *J* = 6.3, 1.8 Hz, CHOHC**H**$_2$OTs), 4.01 (1H, td, *J* = 6.7, 2.9 Hz, C**H**CHOHCH$_2$OTs), 3.85 (1H, td, *J* = 6.9, 4.2 Hz, CH$_2$CHOHC**H**), 3.78-3.72 (1H, m, C**H**OHCH$_2$OTs), 3.48-3.40 (1H, m, CH$_2$C**H**OHCH), 3.08 (1H, s, CHO**H**CH$_2$OTs), 2.46 (3H, s, CC**H**$_3$), 2.31 (1H, s, CHO**H**), 2.02-1.82 (4H, m, C**H**$_2$C**H**$_2$CHCHOHCH$_2$OTs), 1.50-1.41 (2H, m, C**H**$_2$CHOHCH), 1.38-1.20 (6H, m, CH$_3$C**H**$_2$C**H**$_2$C**H**$_2$CH$_2$), 0.91 (3H, t, *J* = 6.5 Hz, C**H**$_3$CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1 (C), 133.0 (C), 130.0 (CH), 128.2 (CH), 82.7 (CH), 78.6 (CH), 74.3 (CH), 71.8 (CH_2), 71.6 (CH), 34.6 (CH_2), 32.0 (CH_2), 28.2 (CH_2), 27.9 (CH_2), 25.5 (CH_2), 22.8 (CH_2), 21.8 (CH_3), 14.2 (CH_3); LRMS (ES^+) *m/z* 409 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{19}H_{30}O_6SNa^+$ Calcd. 409.1655, found 409.1657.

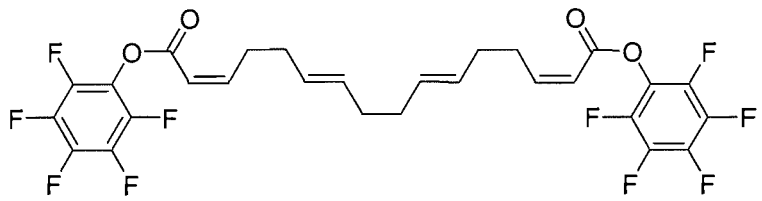
(2*Z*,6*E*,10*E*,14*Z*)-Hexadeca-2,6,10,14-tetraenedioic acid (**5.5**)



The following procedure was also followed for the hydrolysis of (2*Z*,6*E*,10*E*,14*Z*)-diethyl hexadeca-2,6,10,14-tetraenedioate **4.37**. To a stirred solution of

(2*Z*,6*E*,10*E*,14*Z*)-dimethyl hexadeca-2,6,10,14-tetraenedioate **4.36** (1.10 g, 3.60 mmol) in MeOH (11 mL) and H_2O (33 mL) were added NaOH (1.53 g, 38.2 mmol) and $NaHCO_3$ (0.30 g, 3.60 mmol) and the mixture heated at 95 °C for 3 h. The mixture was cooled to rt and washed with CH_2Cl_2 (3 x 20 mL). The aqueous phase was separated, cooled to 0 °C and acidified with 10% citric acid (aq, 30 mL) and 2 M HCl (aq, 50 mL) until pH 1. The mixture was stirred for 30 min before Et_2O (100 mL) was added. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 50 mL). The combined organic phases were washed with 10% citric acid (aq, 100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give (2*Z*,6*E*,10*E*,14*Z*)-hexadeca-2,6,10,14-tetraenedioic acid **5.5** (0.92 g, 3.31 mmol, 92%) as a pale yellow oil. No further purification was necessary. IR ν_{max} (neat) 2980 (m), 2915 (br, m), 2846 (m), 1692 (s), 1639 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.35 (2H, dt, *J* = 11.6, 7.4 Hz, 2 x **CH**CHCO$_2$H), 5.81 (2H, dt, *J* = 11.6, 1.8 Hz, 2 x CHC**H**CO$_2$H), 5.51-5.37 (4H, m, 2 x CH$_2$C**H**C**H**CH$_2$), 2.73 (4H, appt. qd, *J* = 7.4, 1.8 Hz, 2 x C**H**$_2$CHCHCO$_2$H), 2.15 (4H, appt. q, *J* = 7.4, 2 x C**H**$_2$CH$_2$CHCHCO$_2$H), 2.09-2.03 (4H, m, 2 x C**H**$_2$CHCHCH$_2$CH$_2$CHCHCO$_2$H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2 (C), 152.7 (CH), 131.0 (CH), 129.3 (CH), 119.5 (CH), 32.6 (CH_2), 31.9 (CH_2), 29.2 (CH_2); LRMS (ES^-) *m/z* 391 (100%, $[M+(CF_3CO_2)]^-$); HRMS (ES^-) $C_{16}H_{21}O_4^-$ Calcd. 277.1445, found 277.1439.

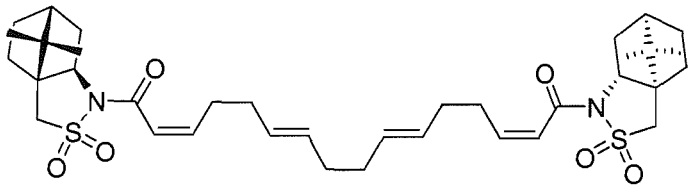
(2*Z*,6*E*,10*E*,14*Z*)-*bis*(Perfluorophenyl) hexadeca-2,6,10,14-tetraenedioate (**5.6**)



To a stirred solution of (2*Z*,6*E*,10*E*,14*Z*)-hexadeca-2,6,10,14-tetraenedioic acid **5.5** (213 mg, 0.77 mmol) and pentafluorophenol (0.16 mL, 1.53 mmol) in EtOAc (20 mL) at rt was added DCC (316 mg, 1.53 mmol) and the mixture stirred for 14 h (white ppt formed). The mixture was filtered washing with EtOAc (10 mL). The filtrate was concentrated *in vacuo* to give a white solid (840 mg). Purification on SiO_2 (3 x 15 cm) eluting with CH_2Cl_2/hexane (1:49 → 1:9) gave (2*Z*,6*E*,10*E*,14*Z*)-

bis(perfluorophenyl) hexadeca-2,6,10,14-tetraenedioate **5.6** (349 mg, 0.57 mmol, 75%) as a colourless oil. IR ν_{max} (neat) 3027 (w), 2987 (w), 2915 (w), 2846 (w), 1760 (m), 1637 (w), 1516 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.60 (2H, dt, J = 11.3, 7.4 Hz, 2 x C**H**CHC(O)), 6.08 (2H, dt, J = 11.3, 1.5 Hz, 2 x CHC**H**C(O)), 5.52-5.37 (4H, m, 2 x CH_2**CH**C**H**CH_2), 2.77 (4H, appt. qd, J = 7.4, 1.5 Hz, 2 x C**H**$_2$CHCHC(O)), 2.20 (4H, appt. q, J = 6.7 Hz, 2 x C**H**$_2$$CH_2$CHCHC(O)), 2.09-2.03 (4H, m, 2 x C**H**$_2$CHCH$CH_2$$CH_2$CHCHC(O)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6 (C), 156.3 (CH), 142.7 (C), 140.8 (C), 140.2 (C), 139.3 (C), 138.2 (C), 136.8 (C), 131.4 (CH), 128.8 (CH), 116.5 (CH), 32.6 (CH_2), 31.6 (CH_2), 29.5 (CH_2); LRMS (ES^+) *m/z* 633 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{28}H_{20}O_4F_{10}Na^+$ Calcd. 633.1094, found 633.1099.

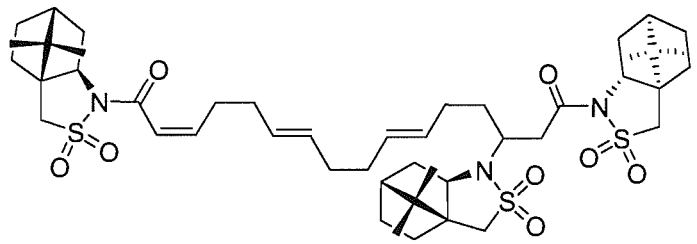
1,16-(2*R*)-*N*-[(2*Z*,6*E*,10*E*,14*Z*)-16-oxo-2,6,10,14-hexadecatetraenoyl]-di-camphor-10,2-sultam (**5.7**)



Under an atmosphere of N_2, to a stirred solution of (2*Z*,6*E*,10*E*,14*Z*)-hexadeca-2,6,10,14-tetraenedioic acid **5.5** (1.29 g, 4.64 mmol) and $(COCl)_2$ (0.81 mL, 9.28 mmol) at 0 °C in CH_2Cl_2 (15 mL) was added DMF (0.05 mL) and the mixture allowed to warm to rt over 3 h. The mixture was concentrated *in vacuo* to give the crude acid chloride (1.40 g) as an orange oil, which was used without further purification. Under an atmosphere of N_2, to a stirred solution of (1*S*,2*R*)-camphorsultam **4.42** (0.243 g, 1.13 mmol) in toluene (50 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 0.418 g, 10.4 mmol) and the mixture warmed to rt over 30 min. The mixture was cooled to −10 °C and crude acid chloride (1.40 g) in toluene (40 mL) was added dropwise. The mixture was stirred for 45 min at −10 °C then warmed to rt over 45 min. The mixture was cooled to 0 °C before H_2O (50 mL) and Et_2O (50 mL) were added. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (3.00 g). Purification on SiO_2 (5 x 15 cm) eluting with EtOAc/hexane (1:4) gave 1,16-(2*R*)-*N*-[(2*Z*,6*E*,10*E*,14*Z*)-16-oxo-

2,6,10,14-hexadecatetraenoyl]-di-camphor-10,2-sultam **5.7** (2.12 g, 3.16 mmol, 68%) as a white foam. $[\alpha]^{25}_{D}$ –72.1 ($CHCl_3$, *c* 0.75); IR ν_{max} (neat) 2959 (m), 2915 (m), 2844 (w), 1680 (s), 1630 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.45 (2H, dt, *J* = 11.5, 1.5 Hz, 2 x CHC**H**C(O)), 6.32 (2H, dt, *J* = 11.5, 7.1 Hz, 2 x C**H**CHC(O)), 5.50-5.36 (4H, m, 2 x CH_2C**H**C**H**CH_2), 3.93 (2H, dd, *J* = 7.3, 5.3 Hz, 2 x C**H**N), 3.50 (2H, d, *J* = 13.8 Hz, 2 x C**H**HSO_2), 3.43 (2H, d, *J* = 13.8 Hz, 2 x CH**H**SO_2), 2.68 (4H, appt. qd, *J* = 7.3, 1.5 Hz, 2 x C**H**$_2$CHCHC(O)), 2.20-2.06 (8H, m, 2 x C**H**$_2$CH$_2$CHCHC(O) and 2 x C**H**$_2$CHN), 2.05-2.00 (4H, m, 2 x C**H**$_2$CHCHCH$_2$CH$_2$CHCHC(O)), 1.98-1.84 (6H, m, 2 x C**H**CH$_2$CHN and 2 x C**H**$_2$CHCH$_2$CHN), 1.47-1.32 (4H, m, 2 x C**H**$_2$CCHN), 1.18 (6H, s, 2 x C**H**$_3$C), 0.98 (6H, s, 2 x CC**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3 (C), 151.8 (CH), 131.0 (CH), 129.2 (CH), 119.5 (CH), 65.2 (CH), 53.3 (CH_2), 48.5 (C), 47.9 (C), 44.9 (CH), 38.8 (CH_2), 33.0 (CH_2), 32.7 (CH_2), 31.9 (CH_2), 29.9 (CH_2), 26.7 (CH_2), 21.0 (CH_3), 20.0 (CH_3); LRMS (ES^+) *m/z* 695 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{36}H_{52}O_6N_2S_2Na^+$ Calcd. 695.3159, found 695.3144.

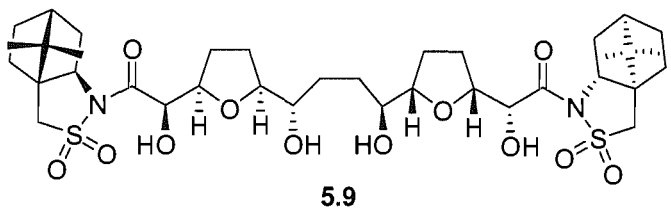
1,14-(2*R*)-*N*-((4*E*,8*E*,12*Z*)-1-[2-((2*R*)-*N*-Camphor-10,2-sultam)-2-oxoethyl]-14-oxo-4,8,12-tetradecatrienyl)-di-camphor-10,2-sultam (**5.8**)



Data for Michael addition product **5.8**: $[\alpha]^{25}_{D}$ –45.9 ($CHCl_3$, *c* 0.19); IR ν_{max} (neat) 2986 (w), 2962 (w), 2918 (w), 2892 (w), 1684 (s), 1631 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.45 (1H, dt, *J* = 11.5, 1.5 Hz, C(O)CHCH), 6.32 (1H, dt, *J* = 11.5, 7.1 Hz, C(O)CHC**H**), 5.50-5.31 (4H, m, 2 x CH_2C**H**C**H**CH_2), 4.11-4.02 (1H, m, NC**H**CH_2C(O)), 3.93 (1H, dd, *J* = 7.4, 5.2 Hz, C**H**N), 3.87 (1H, dd, *J* = 7.8, 5.0 Hz, C**H**N), 3.50 (3H, d, *J* = 13.8 Hz, 3 x C**H**HSO_2), 3.43 (3H, d, *J* = 14.1 Hz, 3 x CH**H**SO_2), 3.38 (1H, dd, *J* = 7.7, 5.2 Hz, C**H**N), 3.19 (1H, dd, *J* = 15.8, 5.3 Hz, C**H**HC(O)), 3.02 (1H, dd, *J* = 15.6, 7.9 Hz, CH**H**C(O)), 2.69 (2H, appt. qd, *J* = 7.3,

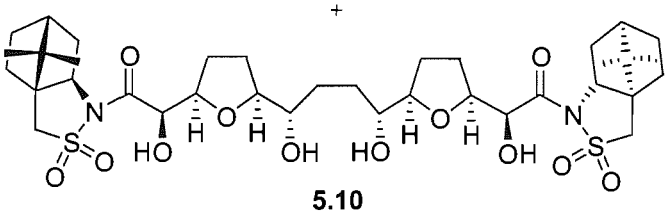
1.3 Hz, C(O)CHCHC**H**$_2$), 2.23-2.05 (10H, m, C(O)CHCHCH$_2$C**H**$_2$, C**H**$_2$C**H**$_2$CH(N)CH$_2$C(O) and 2 x C**H**$_2$CHN), 2.04-1.99 (4H, m, C(O)CHCHCH$_2$CH$_2$CHCHC**H**$_2$C**H**$_2$), 1.95-1.82 (9H, m, 3 x C**H**CH$_2$CHN and 3 x C**H**$_2$CHCH$_2$CHN), 1.80-1.67 (2H, m, C**H**$_2$CHN), 1.49-1.29 (6H, m, 3 x C**H**$_2$CCHN), 1.19 (3H, s, C**H**$_3$C), 1.17 (3H, s, C**H**$_3$C), 1.14 (3H, s, C**H**$_3$C), 0.98 (6H, s, 2 x CC**H**$_3$), 0.92 (3H, s, CC**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2 (C), 164.3 (C), 151.7 (CH), 131.0 (CH), 130.8 (CH), 129.2 (CH), 119.6 (CH), 65.4 (CH), 65.2 (CH), 64.3 (CH), 53.3 (CH_2), 53.1 (CH_2), 50.9 (CH), 49.8 (C), 49.5 (CH_2), 48.6 (C), 48.5 (C), 47.9 (C), 47.8 (C), 45.2 (CH), 44.9 (CH), 38.8 (CH_2), 38.6 (CH_2), 38.3 (CH_2), 36.5 (CH_2), 34.6 (CH_2), 33.1 (CH_2), 32.9 (CH_2), 32.8 (CH_2), 32.7 (CH_2), 31.9 (CH_2), 29.9 (CH_2), 26.7 (CH_2), 26.6 (CH_2), 21.0 (CH_3), 20.5 (CH_3), 20.3 (CH_3), 20.1 (CH_3); LRMS (ES^+) *m/z* 910 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{46}H_{69}O_8N_3S_3Na^+$ Calcd. 910.4139, found 910.4165.

Inseparable mixture of (2*R*)-*N*-((2*R*)-2-(2*R*,5*S*)-5-[(1*S*,4*S*)-1,4-Dihydroxy-4-((2*S*,5*R*)-5-(1*R*)-1-hydroxy-2-[(2*R*)-*N*-camphor-10,2-sultam]-2-oxoethyltetrahydro-2-furanyl)butyl]tetrahydro-2-furanyl-2-hydroxyethanoyl)-camphor-10,2-sultam (**5.9**) and (2*R*)-*N*-((2*R*)-2-(2*R*,5*S*)-5-[(1*S*,4*R*)-1,4-dihydroxy-4-((2*R*,5*S*)-5-(1*S*)-1-hydroxy-2-[(2*R*)-*N*-camphor-10,2-sultam]-2-oxoethyltetrahydro-2-furanyl)butyl]tetrahydro-2-furanyl-2-hydroxyethanoyl)-camphor-10,2-sultam (**5.10**)



5.9

+



5.10

(ratio **5.9**/**5.10** = 3:1) after chromatography

Method A:

Under an atmosphere of N_2, to a stirred solution of 1,16-(2*R*)-*N*-[(2*Z*,6*E*,10*E*,14*Z*)-16-oxo-2,6,10,14-hexadecatetraenoyl]-di-camphor-10,2-sultam **5.7** (922 mg, 1.37 mmol), AcOH (15 mL) and acetone (18 mL) at −30 °C was added $KMnO_4$ (607 mg, 3.84 mmol) in one portion (mixture purple → brown) and the mixture warmed to −20 °C over 25 min. $Na_2S_2O_5$ (sat aq, 20 mL) was added to reduce the precipitated brown MnO_2, and the mixture stirred until clear. NaCl (sat aq, 20 mL) and EtOAc (50 mL) were added, the organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 50 mL) and CH_2Cl_2 (50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (1.02 g). Purification on SiO_2 (3 x 15 cm) eluting with MeOH/CH_2Cl_2 (1:49 → 3:47) gave an inseparable mixture of (2*R*)-*N*-((2*R*)-2-(2*R*,5*S*)-5-[(1*S*,4*S*)-1,4-dihydroxy-4-((2*S*,5*R*)-5-(1*R*)-1-hydroxy-2-[(2*R*)-*N*-camphor-10,2-sultam]-2-oxoethyltetrahydro-2-furanyl)butyl]tetrahydro-2-furanyl-2-hydroxyethanoyl)-camphor-10,2-sultam **5.9** and (2*R*)-*N*-((2*R*)-2-(2*R*,5*S*)-5-[(1*S*,4*R*)-1,4-dihydroxy-4-((2*R*,5*S*)-5-(1*S*)-1-hydroxy-2-[(2*R*)-*N*-camphor-10,2-sultam]-2-oxoethyltetrahydro-2-furanyl)butyl]tetrahydro-2-furanyl-2-hydroxyethanoyl)-camphor-10,2-sultam **5.10** (322 mg, 0.42 mmol, 30%) as a white foam. Data for major isomer **5.9**: $[\alpha]^{25}_D$ −59.9 (MeOH, *c* 0.52); IR ν_{max} (neat) 3503 (w), 2958 (m), 2881 (m), 1692 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.71 (2H, d, *J* = 4.0 Hz, 2 x C(O)C**H**OH), 4.40-4.32 (2H, m, 2 x C(O)CHOHC**H**), 3.96-3.92 (2H, m, 2 x C**H**N), 3.87 (2H, td, *J* = 6.8, 4.8 Hz, 2 x CH_2C**H**CHOHCH_2), 3.65 (1H, br s, CHO**H**), 3.55-3.41 (6H, m, 2 x C**H**HSO$_2$, 2 x CH**H**SO$_2$ and 2 x CH_2CHC**H**OHCH_2), 2.25-2.21 (2H, m, C**H**$_2$CHN), 2.13-1.98 (6H, m, C**H**$_2$CHN and 2 x CHOHCHC**H**$_2$), 1.97-1.83 (10H, m, 2 x C**H**CH_2CHN, 2 x C**H**$_2$CHCH_2CHN and 2 x CHOHCHCH_2C**H**$_2$), 1.65 (4H, d, *J* = 2.8 Hz, 2 x CHOHC**H**$_2$), 1.49-1.31 (4H, m, 2 x C**H**$_2$CCHN), 1.16 (6H, s, 2 x C**H**$_3$C), 0.98 (6H, s, 2 x CC**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0 (C), 83.1 (CH), 79.3 (CH), 73.9 (CH), 73.0 (CH), 65.5 (CH), 53.0 (CH_2), 49.2 (C), 48.0 (C), 44.7 (CH), 38.2 (CH_2), 32.9 (CH_2), 31.0 (CH_2), 28.3 (CH_2), 26.7 (CH_2), 26.5 (CH_2), 20.9 (CH_3), 20.0 (CH_3); LRMS (ES^+) *m/z* 795 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{36}H_{56}O_{12}N_2S_2Na^+$ Calcd. 795.3167, found 795.3206.

Method B:

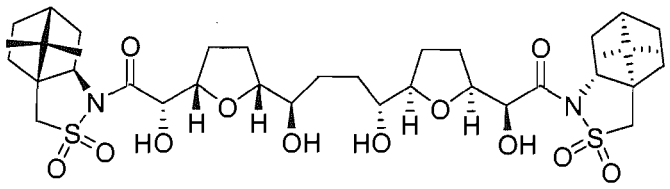
Under an atmosphere of N_2, to a stirred solution of 1,16-(2*R*)-*N*-[(2*Z*,6*E*,10*E*,14*Z*)-16-oxo-2,6,10,14-hexadecatetraenoyl]-di-camphor-10,2-sultam **5.7** (514 mg, 0.77 mmol), phosphate buffer (1.20 mL) and acetone (20 mL) at −30 °C was added a mixture of $KMnO_4$ (0.4 M aq, 5.80 mL, 2.30 mmol) and AcOH (0.24 mL, 4.13 mmol) dropwise over 10 min. The mixture was allowed to warm to −10 °C over 30 min. $Na_2S_2O_5$ (sat aq, 20 mL) was added to reduce the precipitated brown MnO_2, and the mixture stirred until clear. NaCl (sat aq, 20 mL) and EtOAc (50 mL) were added, the organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 50 mL) and CH_2Cl_2 (50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a pale yellow foam (490 mg). Purification on SiO_2 (1.5 x 15 cm) eluting with MeOH/CH_2Cl_2 (1:49 → 3:47) gave an inseparable mixture of (2*R*)-*N*-((2*R*)-2-(2*R*,5*S*)-5-[(1*S*,4*S*)-1,4-dihydroxy-4-((2*S*,5*R*)-5-(1*R*)-1-hydroxy-2-[(2*R*)-*N*-camphor-10,2-sultam]-2-oxoethyltetrahydro-2-furanyl)butyl]tetrahydro-2-furanyl-2-hydroxyethanoyl)-camphor-10,2-sultam **5.9** and (2*R*)-*N*-((2*R*)-2-(2*R*,5*S*)-5-[(1*S*,4*R*)-1,4-dihydroxy-4-((2*R*,5*S*)-5-(1*S*)-1-hydroxy-2-[(2*R*)-*N*-camphor-10,2-sultam]-2-oxoethyltetrahydro-2-furanyl)butyl]tetrahydro-2-furanyl-2-hydroxyethanoyl)-camphor-10,2-sultam **5.10** (166 mg, 0.22 mmol, 28%) as a white foam. Spectroscopic data were identical to that reported above.

Method C:

Under an atmosphere of N_2, to a stirred solution of 1,16-(2*R*)-*N*-[(2*Z*,6*E*,10*E*,14*Z*)-16-oxo-2,6,10,14-hexadecatetraenoyl]-di-camphor-10,2-sultam **5.7** (109 mg, 0.16 mmol), phosphate buffer (0.25 mL) and acetone 4.20 mL) at −30 °C was added a mixture of $NaMnO_4$ (0.4 M aq, 1.22 mL, 0.49 mmol) and AcOH (0.05 mL, 0.88 mmol) dropwise over 10 min. The mixture was allowed to warm to −10 °C over 30 min. $Na_2S_2O_5$ (sat aq, 20 mL) was added to reduce the precipitated brown MnO_2, and the mixture stirred until clear. NaCl (sat aq, 20 mL) and EtOAc (50 mL) were added, the organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 50 mL) and CH_2Cl_2 (50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a pale yellow foam (102 mg). Purification on SiO_2 (1.5 x 15 cm)

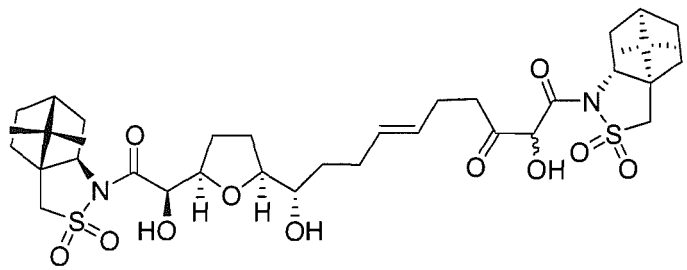
eluting with MeOH/CH_2Cl_2 (1:49 → 3:47) gave an inseparable mixture of (2*R*)-*N*-((2*R*)-2-(2*R*,5*S*)-5-[(1*S*,4*S*)-1,4-dihydroxy-4-((2*S*,5*R*)-5-(1*R*)-1-hydroxy-2-[(2*R*)-*N*-camphor-10,2-sultam]-2-oxoethyltetrahydro-2-furanyl)butyl]tetrahydro-2-furanyl-2-hydroxyethanoyl)-camphor-10,2-sultam **5.9** and (2*R*)-*N*-((2*R*)-2-(2*R*,5*S*)-5-[(1*S*,4*R*)-1,4-dihydroxy-4-((2*R*,5*S*)-5-(1*S*)-1-hydroxy-2-[(2*R*)-*N*-camphor-10,2-sultam]-2-oxoethyltetrahydro-2-furanyl)butyl]tetrahydro-2-furanyl-2-hydroxyethanoyl)-camphor-10,2-sultam **5.10** (51 mg, 0.07 mmol, 41%) as a white foam. Spectroscopic data were identical to that reported above.

(2*R*)-*N*-((2*S*)-2-(2*S*,5*R*)-5-[(1*R*,4*R*)-1,4-dihydroxy-4-((2*R*,5*S*)-5-(1*S*)-1-hydroxy-2-[(2*R*)-*N*-camphor-10,2-sultam]-2-oxoethyltetrahydro-2-furanyl)butyl]tetrahydro-2-furanyl-2-hydroxyethanoyl)-camphor-10,2-sultam (**5.11**)



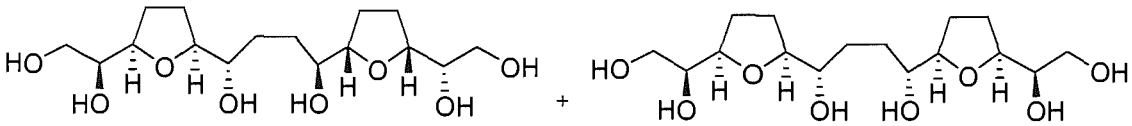
Data for minor isomer **5.11**: $[\alpha]^{25}_D$ –54.9 (MeOH, *c* 0.38); IR ν_{max} (neat) 3475 (w), 2961 (m), 2918 (m), 2887 (m), 1691 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.75-4.68 (2H, m, 2 x C(O)C**H**OH), 4.41-4.32 (2H, m, 2 x C(O)CHOHC**H**), 3.94 (2H, dd, *J* = 7.9, 5.0 Hz, 2 x C**H**N), 3.90-3.84 (2H, m, 2 x $CH_2C\mathbf{H}CHOHCH_2$), 3.59-3.40 (6H, m, 2 x C**H**HSO_2, 2 x CH**H**SO_2 and 2 x $CH_2CHC\mathbf{H}OHCH_2$), 2.27-2.17 (2H, m, $C\mathbf{H}_2CHN$), 2.15-2.00 (6H, m, $C\mathbf{H}_2CHN$ and 2 x $CHOHCHC\mathbf{H}_2$), 1.99-1.83 (10H, m, 2 x $C\mathbf{H}CH_2CHN$, 2 x $C\mathbf{H}_2CHCH_2CHN$ and 2 x $CHOHCHCH_2C\mathbf{H}_2$), 1.68-1.64 (4H, m, 2 x $CHOHC\mathbf{H}_2$), 1.50-1.25 (4H, m, 2 x $C\mathbf{H}_2CCHN$), 1.16 (6H, s, 2 x $C\mathbf{H}_3C$), 0.98 (6H, s, 2 x $CC\mathbf{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0 (C), 83.2 (CH), 79.3 (CH), 74.0 (CH), 73.1 (CH), 65.5 (CH), 53.0 (CH_2), 49.2 (C), 48.0 (C), 44.7 (CH), 38.2 (CH_2), 32.9 (CH_2), 31.0 (CH_2), 28.3 (CH_2), 26.7 (CH_2), 26.6 (CH_2), 20.9 (CH_3), 20.0 (CH_3); LRMS (ES^+) *m/z* 795 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{36}H_{56}O_{12}N_2S_2Na^+$ Calcd. 795.3167, found 795.3206.

Inseparable mixture of (2*R*)-*N*-[(2*R*,6*Z*,10*S*)-2,10-dihydroxy-10-((2*S*,5*R*)-5-(1*R*)-1-hydroxy-2-[(2*R*)-*N*-camphor-10,2-sultam]-2-oxoethyltetrahydro-2-furanyl)-3-oxo-6-decenoyl]-camphor-10,2-sultam and (2*R*)-*N*-[(2*S*,6*Z*,10*S*)-2,10-dihydroxy-10-((2*S*,5*R*)-5-(1*R*)-1-hydroxy-2-[(2*R*)-*N*-camphor-10,2-sultam]-2-oxoethyltetrahydro-2-furanyl)-3-oxo-6-decenoyl]-camphor-10,2-sultam (**5.12**)



Data for hydroxyketone **5.12** (selected data - 5:1 mixture of inseparable isomers): $[\alpha]^{25}_{D}$ –58.9 (MeOH, *c* 0.31); IR ν_{max} (neat) 3467 (w), 2960 (m), 2922 (m), 2884 (w), 1762 (m), 1688 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51-5.36 (2H, m, $CH_2CHCHCH_2$), 5.13 (1H, s, C(O)C**H**C(O)), 4.68 (2H, d, *J* = 5.5 Hz, C(O)C**H**OH), 4.40-4.33 (2H, m, C(O)CHOHC**H**), 4.13 (1H, s, C(O)CHO**H**C(O)), 3.97 (1H, dd, *J* = 7.7, 5.0 Hz, C**H**N), 3.93 (1H, dd, *J* = 7.5, 5.0 Hz, C**H**N), 3.87 (1H, td, *J* = 6.8, 5.0 Hz, $CH_2CHCHOHCH_2$), 3.65 (1H, br s, CHO**H**), 3.58 (1H, d, *J* = 13.8 Hz, C**H**HSO_2), 3.54 (1H, d, *J* = 13.5 Hz, C**H**HSO_2), 3.50 (1H, d, *J* = 13.5 Hz, CH**H**SO_2), 3.46 (1H, d, *J* = 14.1 Hz, CH**H**SO_2), 3.44-3.37 (1H, m, $CH_2CHCHOHCH_2$), 2.65 (2H, t, *J* = 7.3 Hz, C**H**$_2$C(O)), 2.36-2.26 (2H, m, C**H**$_2$$CH_2$C(O)), 2.25-2.13 (2H, m, C**H**$_2$CHN), 2.12-1.99 (4H, m, C**H**$_2$CHN and CHOHCHC**H**$_2$), 1.98-1.81 (10H, m, 2 x C**H**CH_2CHN, 2 x C**H**$_2$$CHCH_2$CHN, CHOHCHCH$_2$C**H**$_2$ and CHOHCH$_2$C**H**$_2$), 1.60-1.51 (2H, m, CHOHC**H**$_2$), 1.49-1.31 (4H, m, 2 x C**H**$_2$CCHN), 1.16 (6H, s, 2 x C**H**$_3$C), 0.98 (6H, s, 2 x CC**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9 (C), 171.0 (C), 167.7 (C), 131.6 (CH), 128.3 (CH), 83.1 (CH), 79.1 (CH), 76.1 (CH), 73.2 (CH), 72.9 (CH), 65.5 (CH), 53.0 (CH_2), 49.2 (C), 48.0 (C), 44.8 (CH), 44.6 (CH), 39.3 (CH_2), 38.1 (CH_2), 33.9 (CH_2), 33.0 (CH_2), 32.9 (CH_2), 28.8 (CH_2), 28.2 (CH_2), 26.8 (CH_2), 26.6 (CH_2), 26.5 (CH_2), 26.3 (CH_2), 21.1 (CH_3), 20.9 (CH_3), 20.0 (CH_3); LRMS (ES^+) *m/z* 777 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{36}H_{54}O_{11}N_2S_2Na^+$ Calcd. 777.3061, found 777.3047.

Inseparable mixture of (1*S*,4*S*)-1,4-*bis*((2*S*,5*R*)-tetrahydro-5-((*S*)-1,2-dihydroxyethyl)furan-2-yl)butane-1,4-diol (**3.4**) and (1*R*,4*S*)-1-((2*R*,5*S*)-tetrahydro-5-((*R*)-1,2-dihydroxyethyl)furan-2-yl)-4-((2*S*,5*R*)-tetrahydro-5-((*S*)-1,2-dihydroxyethyl)furan-2-yl)butane-1,4-diol (**5.15**)



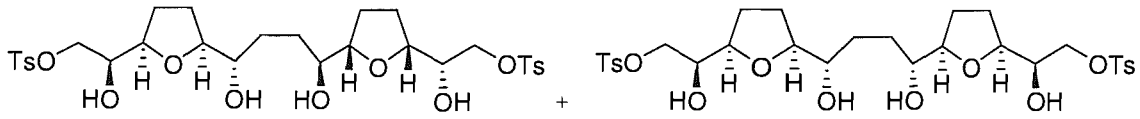
3.4 + **5.15**

(ratio **3.4**/**5.15** = 3:1)

Under an atmosphere of N_2, to a stirred solution of (2*R*)-*N*-((2*R*)-2-(2*R*,5*S*)-5-[(1*S*,4*S*)-1,4-dihydroxy-4-((2*S*,5*R*)-5-(1*R*)-1-hydroxy-2-[(2*R*)-*N*-camphor-10,2-sultam]-2-oxoethyltetrahydro-2-furanyl)butyl]tetrahydro-2-furanyl-2-hydroxyethanoyl)-camphor-10,2-sultam **5.9** and (2*R*)-*N*-((2*R*)-2-(2*R*,5*S*)-5-[(1*S*,4*R*)-1,4-dihydroxy-4-((2*R*,5*S*)-5-(1*S*)-1-hydroxy-2-[(2*R*)-*N*-camphor-10,2-sultam]-2-oxoethyltetrahydro-2-furanyl)butyl]tetrahydro-2-furanyl-2-hydroxyethanoyl)-camphor-10,2-sultam **5.10** (323 mg, 0.42 mmol) in THF (5 mL) at –10 °C was added $LiBH_4$ (2 M in THF, 0.84 mL, 1.67 mmol) dropwise. After 30 min at –10 °C, MeOH (3 mL) and 2 M HCl (0.5 mL) were added and the mixture concentrated *in vacuo* to give a white solid (355 mg). Purification on SiO_2 (2 x 10 cm) eluting with MeOH/CH_2Cl_2 (1:9 → 7:3) gave an inseparable mixture of (1*S*,4*S*)-1,4-*bis*((2*S*,5*R*)-tetrahydro-5-((*S*)-1,2-dihydroxyethyl)furan-2-yl)butane-1,4-diol **3.4** and (1*R*,4*S*)-1-((2*R*,5*S*)-tetrahydro-5-((*R*)-1,2-dihydroxyethyl)furan-2-yl)-4-((2*S*,5*R*)-tetrahydro-5-((*S*)-1,2-dihydroxyethyl)furan-2-yl)butane-1,4-diol **5.15** (90 mg, 0.26 mmol, 62%) as a pale yellow oil. Data for major isomer **3.4**: $[\alpha]^{25}_D$ + 3.6 (MeOH, *c* 0.13); IR ν_{max} (neat) 3339 (s), 2941 (m), 2924 (m), 2883 (m) cm^{-1}; ^1H NMR (400 MHz, MeOD) δ 3.75 (2H, td, *J* = 6.8, 5.3 Hz, 2 x C**H**CHOHCH$_2$OH), 3.66 (2H, td, *J* = 6.5, 5.0 Hz, 2 x CH$_2$CHOHC**H**), 3.53 (2H, td, *J* = 5.3, 5.1 Hz, 2 x C**H**OHCH$_2$OH), 3.46 (2H, dd, *J* = 11.0, 4.5 Hz, 2 x CHOHC**H**HOH), 3.37 (2H, dd, *J* = 11.0, 6.3 Hz, 2 x CHOHCH**H**OH), 3.33-3.27 (2H, m, 2 x CH$_2$C**H**OHCH), 1.83-1.72 (4H, m, 2 x C**H**$_2$CHCHOHCH$_2$OH), 1.67-1.58 (4H, m, C**H**$_2$CH$_2$CHCHOHCH$_2$OH), 1.52-1.44 (4H, m, 2 x C**H**$_2$CHOHCH); ^{13}C NMR (100 MHz, MeOD) δ 83.9 (CH), 81.5 (CH), 74.8 (CH), 74.5 (CH), 65.0 (CH$_2$), 31.0 (CH$_2$), 28.6 (CH$_2$), 27.3 (CH$_2$); LRMS (ES^+)

m/z 373 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{16}H_{30}O_8Na^+$ Calcd. 373.1833, found 373.1840.

Inseparable mixture of (2*S*)-2-((2*R*,5*S*)-5-(1*S*,4*S*)-1,4-Dihydroxy-4-[(2*S*,5*R*)-5-((1*R*)-1-hydroxy-2-[4-toluenesulfonyl]oxyethyl)tetrahydro-2-furanyl]butyltetrahydro-2-furanyl)-2-hydroxyethyl 4-toluenesulfonate (**5.16**) and (2*S*)-2-((2*R*,5*S*)-5-(1*S*,4*R*)-1,4-dihydroxy-4-[(2*R*,5*S*)-5-((1*R*)-1-hydroxy-2-[4-toluenesulfonyl]oxyethyl)tetrahydro-2-furanyl]butyltetrahydro-2-furanyl)-2-hydroxyethyl 4-toluenesulfonate (**5.17**)



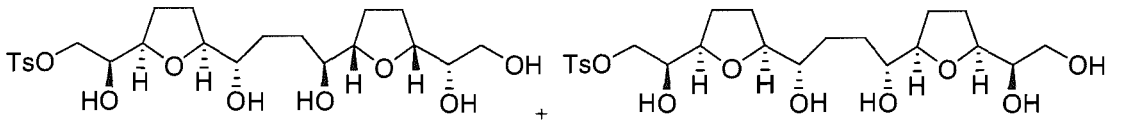
5.16 **5.17**

(ratio **5.16/5.17** = 3:1)

The title compound was prepared according to the method outlined for **5.4**, except using a mixture of (1*S*,4*S*)-1,4-*bis*((2*S*,5*R*)-tetrahydro-5-((*S*)-1,2-dihydroxyethyl)furan-2-yl)butane-1,4-diol **3.4** and (1*R*,4*S*)-1-((2*R*,5*S*)-tetrahydro-5-((*R*)-1,2-dihydroxyethyl)furan-2-yl)-4-((2*S*,5*R*)-tetrahydro-5-((*S*)-1,2-dihydroxyethyl)furan-2-yl)butane-1,4-diol **5.15** (31 mg, 0.09 mmol), 2.4 eq Bu_2SnO and 2.1 eq TsCl. Purification on SiO_2 (1.5 x 15 cm) eluting with MeOH/CH_2Cl_2 (1:49 → 1:24) gave an inseparable mixture of (2*S*)-2-((2*R*,5*S*)-5-(1*S*,4*S*)-1,4-dihydroxy-4-[(2*S*,5*R*)-5-((1*R*)-1-hydroxy-2-[4-toluenesulfonyl]oxyethyl)tetrahydro-2-furanyl]butyltetrahydro-2-furanyl)-2-hydroxyethyl 4-toluenesulfonate **5.16** and (2*S*)-2-((2*R*,5*S*)-5-(1*S*,4*R*)-1,4-dihydroxy-4-[(2*R*,5*S*)-5-((1*R*)-1-hydroxy-2-[4-toluenesulfonyl]oxyethyl)tetrahydro-2-furanyl]butyltetrahydro-2-furanyl)-2-hydroxyethyl 4-toluenesulfonate **5.17** (41 mg, 0.06 mmol, 72%) as a colourless oil. Data for major isomer **5.16**: $[\alpha]^{25}_D$ –5.5 ($CHCl_3$, *c* 0.50); IR ν_{max} (neat) 3347 (m), 2949 (m), 2920 (m), 2884 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (4H, d, *J* = 8.3 Hz, 4 x C(S)C**H**), 7.35 (4H, d, *J* = 8.3 Hz, 4 x C(S)CHC**H**), 4.09 (2H, td, *J* = 6.6, 6.0 Hz, 2 x $TsOCH_2CHOH$), 4.02-3.89 (6H, m, 2 x $TsOCH_2CHOHCH$), 3.84-3.74 (2H, m, 2 x $CH_2CHCHOHCH_2CH_2$), 3.61 (1H, br s, O**H**), 3.48-3.38 (2H, m, 2 x $CH_2CHCHOHCH_2CH_2$), 2.45 (6H, s, 2 x CCH_3), 1.99-1.88 (4H, m, 2 x $TsOCH_2CHOHCHCH_2$), 1.87-1.75 (4H, m, 2 x $TsOCH_2CHOHCHCH_2CH_2$), 1.68-

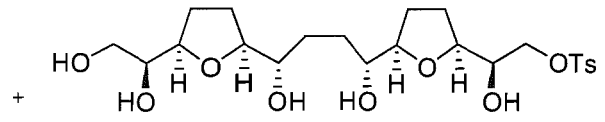
1.55 (4H, m, $CHOHCH_2CH_2CHOH$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2 (C), 132.8 (C), 130.1 (CH), 128.1 (CH), 82.8 (CH), 79.5 (CH), 74.6 (CH), 71.4 (CH_2), 71.1 (CH), 31.2 (CH_2), 28.2 (CH_2), 26.0 (CH_2), 21.8 (CH_3); LRMS (ES^+) *m/z* 681 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{30}H_{42}O_{12}S_2Na^+$ Calcd. 681.2010, found 681.2003. Compound **5.17** (selected data - IR, ^1H NMR, LRMS & HRMS identical to **5.16**): ^{13}C NMR (100 MHz, $CHCl_3$) δ 145.2 (C), 132.8 (C), 130.1 (CH), 128.1 (CH), 82.7 (CH), 79.4 (CH), 74.3 (CH), 71.4 (CH_2), 71.1 (CH), 31.2 (CH_2), 28.1 (CH_2), 26.0 (CH_2), 21.8 (CH_3).

Inseparable mixture of (2*S*)-2-[(2*R*,5*S*)-5-((1*S*,4*S*)-4-(2*S*,5*R*)-5-[(1*S*)-1,2-Dihydroxyethyl]tetrahydro-2-furanyl-1,4-dihydroxybutyl)tetrahydro-2-furanyl]-2-hydroxyethyl 4-toluenesulfonate (**5.18**), (2*S*)-2-[(2*R*,5*S*)-5-((1*S*,4*R*)-4-(2*R*,5*S*)-5-[(1*R*)-1,2-dihydroxyethyl]tetrahydro-2-furanyl-1,4-dihydroxybutyl)tetrahydro-2-furanyl]-2-hydroxyethyl 4-toluenesulfonate (**5.19a**) and (2*R*)-2-[(2*S*,5*R*)-5-((1*R*,4*S*)-4-(2*S*,5*R*)-5-[(1*S*)-1,2-dihydroxyethyl]tetrahydro-2-furanyl-1,4-dihydroxybutyl)tetrahydro-2-furanyl]-2-hydroxyethyl 4-toluenesulfonate (**5.19b**)



5.18 + **5.19a**

(ratio **5.18/5.19** = 3:1)

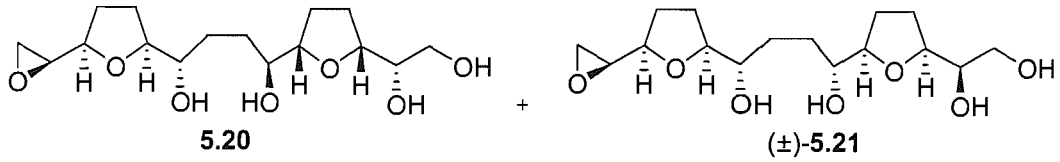


5.19b

Under an atmosphere of N_2, to a stirred solution of (1*S*,4*S*)-1,4-*bis*((2*S*,5*R*)-tetrahydro-5-((*S*)-1,2-dihydroxyethyl)furan-2-yl)butane-1,4-diol **3.4** and (1*R*,4*S*)-1-((2*R*,5*S*)-tetrahydro-5-((*R*)-1,2-dihydroxyethyl)furan-2-yl)-4-((2*S*,5*R*)-tetrahydro-5-((*S*)-1,2-dihydroxyethyl)furan-2-yl)butane-1,4-diol **5.15** (20 mg, 0.06 mmol) in dioxane (1 mL) at rt was added Bu_2SnO (18 mg, 0.07 mmol) and the mixture heated to reflux for 2½ h. The mixture was cooled to rt before TsCl (13 mg, 0.07 mmol) was added. After 14 h the mixture was concentrated *in vacuo* to give a yellow solid (45 mg). Purification on SiO_2 (3.5 x 15 cm) eluting with $MeOH/CH_2Cl_2$ (3:47 → 1:9) gave an inseparable

mixture of (2*S*)-2-[(2*R*,5*S*)-5-((1*S*,4*S*)-4-(2*S*,5*R*)-5-[(1*S*)-1,2-dihydroxyethyl]tetrahydro-2-furanyl-1,4-dihydroxybutyl)tetrahydro-2-furanyl]-2-hydroxyethyl 4-toluenesulfonate **5.18**, (2*S*)-2-[(2*R*,5*S*)-5-((1*S*,4*R*)-4-(2*R*,5*S*)-5-[(1*R*)-1,2-dihydroxyethyl]tetrahydro-2-furanyl-1,4-dihydroxybutyl)tetrahydro-2-furanyl]-2-hydroxyethyl 4-toluenesulfonate **5.19a** and (2*R*)-2-[(2*S*,5*R*)-5-((1*R*,4*S*)-4-(2*S*,5*R*)-5-[(1*S*)-1,2-dihydroxyethyl]tetrahydro-2-furanyl-1,4-dihydroxybutyl)tetrahydro-2-furanyl]-2-hydroxyethyl 4-toluenesulfonate **5.19b** (10 mg, 0.02 mmol, 35%) as a colourless oil. Data for major isomer **5.18**: $[\alpha]^{25}_{D}$ –11.8 ($CHCl_3$, *c* 0.50); IR ν_{max} (neat) 3374 (m), 2949 (w), 2909 (w), 2879 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (2H, d, *J* = 8.3 Hz, 2 x C(S)C**H**), 7.35 (2H, d, *J* = 8.3 Hz, 2 x C(S)CHC**H**), 4.08-4.01 (2H, m, $TsOCH_2CHOHC\mathbf{H}$ and $C\mathbf{H}CHOHCH_2OH$), 4.02-3.89 (3H, m, $TsOC\mathbf{H}_2CHOH$ and $CH_2C\mathbf{H}CHOHCH_2CH_2$), 3.89-3.78 (2H, m, $CH_2CH_2CHOHC\mathbf{H}$), 3.70-3.62 (1H, m, $TsOCH_2C\mathbf{H}OH$), 3.60-3.52 (1H, m, $C\mathbf{H}OHCH_2OH$), 3.51-3.41 (2H, m, $C\mathbf{H}OHCH_2CH_2C\mathbf{H}OH$), 2.45 (3H, s, $CC\mathbf{H}_3$), 2.00-1.74 (8H, m, $TsOCH_2CHOHCHC\mathbf{H}_2C\mathbf{H}_2$ and $C\mathbf{H}_2C\mathbf{H}_2CHCHOHCH_2OH$), 1.69-1.61 (4H, m, $CHOHC\mathbf{H}_2C\mathbf{H}_2CHOH$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3 (C), 132.9 (C), 130.2 (CH), 128.3 (CH), 82.9 (CH), 82.7 (CH), 80.9 (CH), 79.8 (CH), 74.6 (CH), 73.5 (CH), 71.4 (CH_2), 70.8 (CH), 64.0 (CH_2), 31.4 (CH_2), 28.5 (CH_2), 25.6 (CH_2), 21.9 (CH_3); LRMS (ES^+) *m/z* 527 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{23}H_{36}O_{10}SNa^+$ Calcd. 527.1921, found 527.1924. Compounds **5.19a** and **5.19b** (selected data - IR, ^1H NMR, LRMS & HRMS identical to **5.18**): ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2 (C), 132.8 (C), 130.1 (CH), 128.1 (CH), 82.7 (CH), 79.4 (CH), 74.3 (CH), 71.4 (CH_2), 71.1 (CH), 31.2 (CH_2), 28.1 (CH_2), 26.0 (CH_2), 21.8 (CH_3).

Inseparable mixture of (1*S*,4*S*)-1-((2*S*,5*R*)-tetrahydro-5-((*S*)-1,2-dihydroxyethyl)furan-2-yl)-4-((2*S*,5*R*)-tetrahydro-5-((*S*)-oxiran-2-yl)furan-2-yl)butane-1,4-diol (**5.20**) and (±)-(1*R*,4*S*)-1-((2*R*,5*S*)-tetrahydro-5-((*R*)-1,2-dihydroxyethyl)furan-2-yl)-4-((2*S*,5*R*)-tetrahydro-5-((*S*)-oxiran-2-yl)furan-2-yl)butane-1,4-diol (**5.21**)



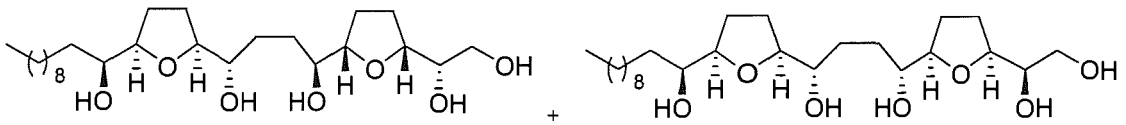
5.20 + (±)-**5.21**

(ratio **5.20**/(±)-**5.21** = 3:1)

Under an atmosphere of N_2, to a stirred solution of (2*S*)-2-[(2*R*,5*S*)-5-((1*S*,4*S*)-4-(2*S*,5*R*)-5-[(1*S*)-1,2-dihydroxyethyl]tetrahydro-2-furanyl-1,4-dihydroxybutyl)tetrahydro-2-furanyl]-2-hydroxyethyl 4-toluenesulfonate **5.18**, (2*S*)-2-[(2*R*,5*S*)-5-((1*S*,4*R*)-4-(2*R*,5*S*)-5-[(1*R*)-1,2-dihydroxyethyl]tetrahydro-2-furanyl-1,4-dihydroxybutyl)tetrahydro-2-furanyl]-2-hydroxyethyl 4-toluenesulfonate **5.19a** and (2*R*)-2-[(2*S*,5*R*)-5-((1*R*,4*S*)-4-(2*S*,5*R*)-5-[(1*S*)-1,2-dihydroxyethyl]tetrahydro-2-furanyl-1,4-dihydroxybutyl)tetrahydro-2-furanyl]-2-hydroxyethyl 4-toluenesulfonate **5.19b** (106 mg, 0.21 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added DBU (0.05 mL, 0.32 mmol). The mixture was allowed to warm to rt over 1 ½ h then concentrated *in vacuo* to give a pale yellow oil (148 mg). Purification on SiO_2 (1.5 x 15 cm) eluting with MeOH/CH_2Cl_2 (3:47 → 1:9) gave an inseparable mixture of (1*S*,4*S*)-1-((2*S*,5*R*)-tetrahydro-5-((*S*)-1,2-dihydroxyethyl)furan-2-yl)-4-((2*S*,5*R*)-tetrahydro-5-((*S*)-oxiran-2-yl)furan-2-yl)butane-1,4-diol **5.20** and (±)-(1*R*,4*S*)-1-((2*R*,5*S*)-tetrahydro-5-((*R*)-1,2-dihydroxyethyl)furan-2-yl)-4-((2*S*,5*R*)-tetrahydro-5-((*S*)-oxiran-2-yl)furan-2-yl)butane-1,4-diol **5.21** (40 mg, 0.12 mmol, 57%) as a colourless oil. Data for major isomer: $[\alpha]^{25}_D$ + 6.9 (MeOH, *c* 0.44); IR ν_{max} (neat) 3361 (m), 2952 (w), 2921 (w), 2880 (w) cm^{-1}; ^1H NMR (400 MHz, MeOH) δ 3.76 (1H, td, *J* = 6.5, 5.3 Hz, C**H**CHOHCH$_2$OH), 3.73-3.69 (1H, m, CH$_2$(O)CHC**H**), 3.68-3.63 (2H, m, CH$_2$C**H**CHOHCH$_2$CH$_2$ and CH$_2$CHOHC**H**), 3.53 (1H, td, *J* = 5.7, 5.4 Hz, C**H**OHCH$_2$OH), 3.48 (1H, dd, *J* = 11.0, 4.5 Hz, CHOHC**H**HOH), 3.38 (1H, dd, *J* = 11.3, 6.3 Hz, CHOHCH**H**OH), 3.34-3.26 (2H, m, C**H**OHCH$_2$CH$_2$C**H**OH), 2.90 (1H, td, *J* = 4.3, 2.8 Hz, CH$_2$(O)C**H**CH), 2.63 (2H, dd, *J* = 5.0, 4.3 Hz, C**H**H(O)CH), 2.50 (2H, dd, *J* = 5.0, 2.8 Hz, 2 x CH**H**(O)CH), 1.86-1.72 (4H, m, CH$_2$(O)CHCHC**H**H,

$CH_2(O)CHCHCH_2CHH$ and $CH_2CHCHOHCH_2OH$), 1.70-1.55 (4H, m, $CH_2(O)CHCHCHH$, $CH_2(O)CHCHCH_2CHH$ and $CH_2CH_2CHCHOHCH_2OH$), 1.53-1.43 (4H, m, $CHOHCH_2CH_2CHOH$); ^{13}C NMR (100 MHz, MeOD) δ 84.7 (CH), 83.9 (CH), 81.5 (CH), 80.3 (CH), 74.7 (CH), 74.6 (CH), 74.5 (CH), 65.0 (CH_2), 54.2 (CH), 46.2 (CH_2), 30.9 (CH_2), 30.5 (CH_2), 28.6 (CH_2), 28.5 (CH_2), 28.3 (CH_2), 27.3 (CH_2); LRMS (ES^+) *m/z* 355 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{16}H_{28}O_7Na^+$ Calcd. 355.1727, found 355.1719. Compounds (±)-**5.21** (selected data - IR, ^1H NMR, LRMS & HRMS identical to **5.20**): ^{13}C NMR (100 MHz, MeOD) δ 84.6 (CH), 83.9 (CH), 75.3 (CH), 75.2 (CH), 74.8 (CH), 28.5 (CH_2).

Inseparable mixture of (1*S*,4*S*)-1-((2*S*,5*R*)-tetrahydro-5-((*S*)-1,2-dihydroxyethyl)furan-2-yl)-4-((2*S*,5*R*)-tetrahydro-5-((*S*)-1-hydroxyundecyl)furan-2-yl)butane-1,4-diol (**3.2**) and (±)-(1*R*,4*S*)-1-((2*R*,5*S*)-tetrahydro-5-((*R*)-1,2-dihydroxyethyl)furan-2-yl)-4-((2*S*,5*R*)-tetrahydro-5-((*S*)-1-hydroxyundecyl)furan-2-yl)butane-1,4-diol (**5.22**)



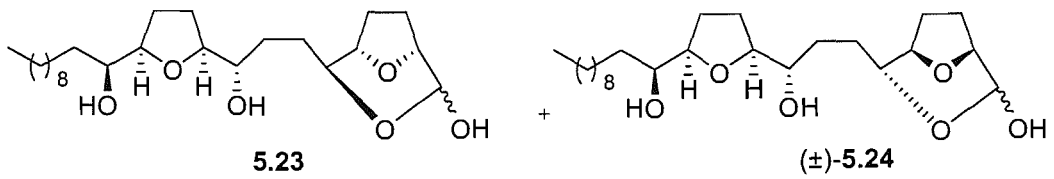
3.2 + **(±)-5.22**

(ratio **3.2**/(±)-**5.22** = 3:1)

Under an atmosphere of N_2, to a stirred solution of CuI (86 mg, 0.45 mmol) in THF (3 mL) at −70 °C was added nonylmagnesium bromide (1M in Et_2O, 0.90 mL, 0.90 mmol) dropwise. The mixture was warmed to −20 °C over 20 min (mixture white → grey) then cooled to −70 °C. A solution of (1*S*,4*S*)-1-((2*S*,5*R*)-tetrahydro-5-((*S*)-1,2-dihydroxyethyl)furan-2-yl)-4-((2*S*,5*R*)-tetrahydro-5-((*S*)-oxiran-2-yl)furan-2-yl)butane-1,4-diol **5.20** and (±)-(1*R*,4*S*)-1-((2*R*,5*S*)-tetrahydro-5-((*R*)-1,2-dihydroxyethyl)furan-2-yl)-4-((2*S*,5*R*)-tetrahydro-5-((*S*)-oxiran-2-yl)furan-2-yl)butane-1,4-diol **5.21** (25 mg, 0.08 mmol) in THF (3 mL) was added dropwise and the mixture warmed to −40 °C over 1 h. NH_4Cl / NH_4OH (4:1, aq, 10 mL) and EtOAc (10 mL) were added, the organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic phases were washed with NaCl (sat aq, 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow foam (25 mg). Purification on SiO_2 (1 x 15 cm) eluting with MeOH/CH_2Cl_2 (3:47 → 1:9)

gave an inseparable mixture of (1*S*,4*S*)-1-((2*S*,5*R*)-tetrahydro-5-((*S*)-1,2-dihydroxyethyl)furan-2-yl)-4-((2*S*,5*R*)-tetrahydro-5-((*S*)-1-hydroxyundecyl)furan-2-yl)butane-1,4-diol **3.2** and (±)-(1*R*,4*S*)-1-((2*R*,5*S*)-tetrahydro-5-((*R*)-1,2-dihydroxyethyl)furan-2-yl)-4-((2*S*,5*R*)-tetrahydro-5-((*S*)-1-hydroxyundecyl)furan-2-yl)butane-1,4-diol **5.22** (20 mg, 0.04 mmol, 58%) as a colourless oil. Data for major isomer **3.2**: $[\alpha]^{25}_{D}$ + 4.2 (MeOH, *c* 0.56); IR ν_{max} (neat) 3351 (m), 2924 (w), 2854 (w) cm^{-1}; ^{1}H NMR (400 MHz, MeOD) δ 3.76 (1H, td, *J* = 6.5, 5.3 Hz, C**H**CHOHCH$_2$OH), 3.70-3.63 (3H, m, CH$_3$(CH$_2$)$_8$CHOHC**H**, CH$_2$C**H**CHOHCH$_2$CH$_2$ and CHOHCH$_2$CH$_2$CHOHC**H**), 3.56-3.50 (2H, m, CH$_3$(CH$_2$)$_8$C**H**OHCH and C**H**OHCH$_2$OH), 3.48 (1H, dd, *J* = 11.3, 4.6 Hz, CHOHC**H**HOH), 3.38 (1H, dd, *J* = 11.3, 6.3 Hz, CHOHCH**H**OH), 3.33-3.26 (2H, m, C**H**OHCH$_2$CH$_2$C**H**OH), 1.83-1.72 (4H, m, CH$_3$(CH$_2$)$_8$CH$_2$CHOHCHC**H**$_2$ and C**H**$_2$CHCHOHCH$_2$OH), 1.71-1.57 (4H, m, CH$_3$(CH$_2$)$_8$CH$_2$CHOHCHCH$_2$C**H**$_2$ and C**H**$_2$CH$_2$CHCHOHCH$_2$OH), 1.52-1.44 (4H, m, CHOHC**H**$_2$C**H**$_2$CHOH), 1.41-1.28 (2H, m, CH$_3$(CH$_2$)$_8$C**H**$_2$CHOH), 1.24-1.12 (16H, m, CH$_3$(C**H**$_2$)$_8$), 0.76 (3H, t, *J* = 6.8 Hz, C**H**$_3$); ^{13}C NMR (100 MHz, MeOD) δ 84.5 (CH), 84.3 (CH), 84.1 (CH), 81.9 (CH), 75.1 (CH), 74.9 (CH), 74.0 (CH), 65.4 (CH$_2$), 34.9 (CH$_2$), 33.4 (CH$_2$), 31.2 (CH$_2$), 31.1 (CH$_2$), 30.8 (CH$_2$), 29.2 (CH$_2$), 29.0 (CH$_2$), 27.7 (CH$_2$), 27.4 (CH$_2$), 26.4 (CH$_2$), 24.1 (CH$_2$), 14.8 (CH$_3$); LRMS (ES$^+$) *m/z* 483 (100%, [M+Na]$^+$); HRMS (ES$^+$) $C_{25}H_{48}O_7Na^+$ Calcd. 483.3292, found 483.3284. Compounds (±)-**5.22** (selected data - IR, ^{1}H NMR, LRMS & HRMS identical to **3.2**): ^{13}C NMR (100 MHz, MeOD) δ 84.5 (CH), 84.2 (CH), 84.0 (CH), 75.2 (CH), 74.8 (CH), 65.5 (CH$_2$), 33.5 (CH$_2$), 31.5 (CH$_2$), 30.9 (CH$_2$).

Inseparable mixture of (1*R*,4*S*,5*S*)-4-{(*S*)-3-Hydroxy-3-[(2*S*,5*R*)-5-((*S*)-1-hydroxy-undecyl)-tetrahydro-furan-2-yl]-propyl}-3,8-dioxa-bicyclo[3.2.1]octan-2-ol (**5.23**) and (±)-(1*S*,4*R*,5*R*)-4-{(*S*)-3-hydroxy-3-[(2*S*,5*R*)-5-((*S*)-1-hydroxy-undecyl)-tetrahydro-furan-2-yl]-propyl}-3,8-dioxa-bicyclo[3.2.1]octan-2-ol (**5.24**)

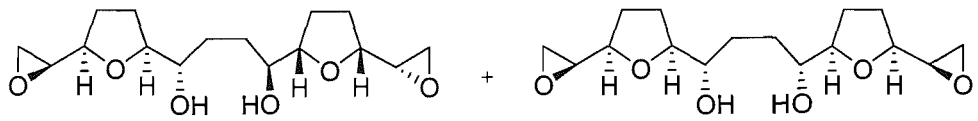


5.23 + (±)-**5.24**

(ratio **5.23**/(±)-**5.24** = 3:1)

To a stirred heterogeneous mixture of $NaIO_4$-SiO_2[206] (26 mg, 13 μmol) in CH_2Cl_2 (1 mL) at rt was added a solution of (1*S*,4*S*)-1-((2*S*,5*R*)-tetrahydro-5-((*S*)-1,2-dihydroxyethyl)furan-2-yl)-4-((2*S*,5*R*)-tetrahydro-5-((*S*)-1-hydroxyundecyl)furan-2-yl)butane-1,4-diol **3.2** and (±)-(1*R*,4*S*)-1-((2*R*,5*S*)-tetrahydro-5-((*R*)-1,2-dihydroxyethyl)furan-2-yl)-4-((2*S*,5*R*)-tetrahydro-5-((*S*)-1-hydroxyundecyl)furan-2-yl)butane-1,4-diol **5.22** (2.3 mg, 5 μmol) in CH_2Cl_2 (1 mL) (mixture → pink). After 45 min the mixture was filtered washing with $CHCl_3$ (2 x 2 mL) and the filtrate concentrated *in vacuo* to give a pale pink oil (3.0 mg). Purification on SiO_2 (1 x 10 cm) eluting with MeOH/CH_2Cl_2 (1:49 → 3:47) gave an inseparable mixture of (1*R*,4*S*,5*S*)-4-{(*S*)-3-hydroxy-3-[(2*S*,5*R*)-5-((*S*)-1-hydroxy-undecyl)-tetrahydro-furan-2-yl]-propyl}-3,8-dioxa-bicyclo[3.2.1]octan-2-ol **5.23** and (±)-(1*S*,4*R*,5*R*)-4-{(*S*)-3-hydroxy-3-[(2*S*,5*R*)-5-((*S*)-1-hydroxy-undecyl)-tetrahydro-furan-2-yl]-propyl}-3,8-dioxa-bicyclo[3.2.1]octan-2-ol **5.24** (2.1 mg, 4.5 μmol, 90%) as a colourless oil. ^{1}H NMR (400 MHz, MeOD) δ 4.32 (1H, dd, *J* = 17.8, 4.5 Hz, $CH_2COC\mathbf{H}OH$), 3.79-3.68 (4H, m, $CH_3(CH_2)_8CH_2CHOHC\mathbf{H}$, $C\mathbf{H}CHOHCH_2CH_2$, $CH_2C(O)C\mathbf{H}$ and $CH_2C(O)CHCH_2CH_2C\mathbf{H}$), 3.61-3.55 (1H, m, $CHOHCH_2CH_2C\mathbf{H}(O)$), 3.39-3.29 (2H, m, $CH_3(CH_2)_8CH_2C\mathbf{H}OH$ and $CH_2CHC\mathbf{H}OHCH_2$), 1.85-1.71 (8H, m, $CH_3(CH_2)_8CH_2CHOHCHC\mathbf{H}_2C\mathbf{H}_2$ and $C\mathbf{H}_2C\mathbf{H}_2CHCH(O)OH$), 1.56-1.47 (4H, m, $CHOHC\mathbf{H}_2C\mathbf{H}_2C(O)$), 1.44-1.33 (2H, m, $CH_3(CH_2)_8C\mathbf{H}_2CHOH$), 1.27-1.15 (16H, m, $CH_3(C\mathbf{H}_2)_8$), 0.80 (3H, t, *J* = 6.8 Hz, $C\mathbf{H}_3$); LRMS (ES^+) *m/z* 451 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{26}H_{484}O_6Na^+$ Calcd. 451.3030, found 451.3032.

Inseparable mixture of (1*S*,4*S*)-1,4-*bis*((2*S*,5*R*)-tetrahydro-5-((*S*)-oxiran-2-yl)furan-2-yl)butane-1,4-diol (**5.27**) and (1*R*,4*S*)-1-((2*R*,5*S*)-tetrahydro-5-((*R*)-oxiran-2-yl)furan-2-yl)-4-((2*S*,5*R*)-tetrahydro-5-((*S*)-oxiran-2-yl)furan-2-yl)butane-1,4-diol (**5.28**)



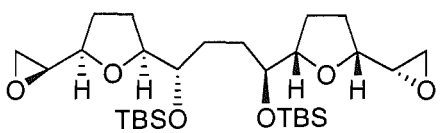
5.27 **5.28**

(ratio **5.27**/**5.28** = 3:1)

Under an atmosphere of N_2, to a stirred solution of (2*S*)-2-((2*R*,5*S*)-5-(1*S*,4*S*)-1,4-dihydroxy-4-[(2*S*,5*R*)-5-((1*R*)-1-hydroxy-2-[4-toluenesulfonyl]oxyethyl)tetrahydro-2-

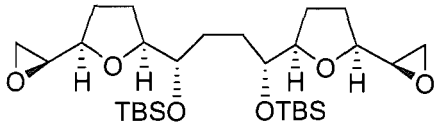
furanyl]butyltetrahydro-2-furanyl)-2-hydroxyethyl 4-toluenesulfonate **5.16** and (2*S*)-2-((2*R*,5*S*)-5-(1*S*,4*R*)-1,4-dihydroxy-4-[(2*R*,5*S*)-5-((1*R*)-1-hydroxy-2-[4-toluenesulfonyl]oxyethyl)tetrahydro-2-furanyl]butyltetrahydro-2-furanyl)-2-hydroxyethyl 4-toluenesulfonate **5.17** (102 mg, 0.16 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added DBU (0.07 mL, 0.47 mmol) and the mixture stirred for 3 h. The mixture was concentrated *in vacuo* to give a pale yellow oil (108 mg). Purification on SiO_2 (1.5 x 15 cm) eluting with MeOH/CH_2Cl_2 (1:49 → 1:24) gave an inseparable mixture of (1*R*,4*R*)-1,4-*bis*((2*R*,5*S*)-tetrahydro-5-((*R*)-oxiran-2-yl)furan-2-yl)butane-1,4-(1*S*,4*S*)-1,4-*bis*((2*S*,5*R*)-tetrahydro-5-((*S*)-oxiran-2-yl)furan-2-yl)butane-1,4-diol **5.27** and (1*R*,4*S*)-1-((2*R*,5*S*)-tetrahydro-5-((*R*)-oxiran-2-yl)furan-2-yl)-4-((2*S*,5*R*)-tetrahydro-5-((*S*)-oxiran-2-yl)furan-2-yl)butane-1,4-diol **5.28** (40 mg, 0.13 mmol, 82%) as a colourless oil. Data for major isomer **5.27**: $[\alpha]^{25}_D$ + 5.6 ($CHCl_3$, *c* 0.69); IR ν_{max} (neat) 3440 (m), 2947 (m), 2919 (m), 2875 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.92-3.85 (2H, m, 2 x $CH_2(O)CHCH$), 3.84-3.77 (2H, m, 2 x $CH_2CHCHOH$), 3.54-3.43 (2H, m, 2 x $CH_2CHCHOH$), 3.06-3.00 (2H, m, 2 x $CH_2(O)CHCH$), 2.81 (2H, appt. t, *J* = 5.0 Hz, 2 x $CHH(O)CH$), 2.62 (2H, dd, *J* = 5.0, 2.6 Hz, 2 x $CHH(O)CH$), 2.01-1.89 (4H, m, 2 x $CH_2(O)CHCHCHH$ and 2 x $CH_2(O)CHCHCH_2CHH$), 1.88-1.72 (4H, m, 2 x $CH_2(O)CHCHCHH$ and 2 x $CH_2(O)CHCHCH_2CHH$), 1.71-1.58 (4H, m, $CHOHCH_2CH_2CHOH$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.3 (CH), 79.5 (CH), 74.2 (CH), 53.2 (CH), 45.9 (CH_2), 29.7 (CH_2), 27.7 (CH_2), 27.6 (CH_2); LRMS (ES^+) *m/z* 337 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{16}H_{26}O_6Na^+$ Calcd. 337.1621, found 337.1621. Compound **5.28** (selected data - IR, ^1H NMR, LRMS & HRMS identical to **5.27**): ^{13}C NMR (100 MHz, $CHCl_3$) δ 83.4 (CH), 79.4 (CH), 74.8 (CH), 53.5 (CH), 45.8 (CH_2), 30.2 (CH_2), 27.8 (CH_2), 27.7 (CH_2).

(*t*-Butyl)[((1*S*,4*S*)-4-[1-(*t*-butyl)-1,1-dimethylsilyl]oxy-1-(2*R*,5*S*)-5-[(2*S*)oxiran-2-yl]tetrahydro-2-furanyl-4-(2*S*,5*R*)-5-[(2*S*)oxiran-2-yl]tetrahydro-2-furanylbutyl)oxy]dimethylsilane (**5.29**)



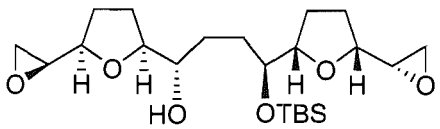
The title compound was prepared according to the method outlined for **4.48** except using a mixture of (1*R*,4*R*)-1,4-*bis*((2*R*,5*S*)-tetrahydro-5-((*R*)-oxiran-2-yl)furan-2-yl)butane-1,4-(1*S*,4*S*)-1,4-*bis*((2*S*,5*R*)-tetrahydro-5-((*S*)-oxiran-2-yl)furan-2-yl)butane-1,4-diol **5.27** and (1*R*,4*S*)-1-((2*R*,5*S*)-tetrahydro-5-((*R*)-oxiran-2-yl)furan-2-yl)-4-((2*S*,5*R*)-tetrahydro-5-((*S*)-oxiran-2-yl)furan-2-yl)butane-1,4-diol **5.28** (28 mg, 0.09 mmol). Purification on SiO_2 (3.5 x 15 cm) eluting with EtOAc/hexane (2:23) gave (*t*-Butyl)[((1*S*,4*S*)-4-[1-(*t*-butyl)-1,1-dimethylsilyl]oxy-1-(2*R*,5*S*)-5-[(2*S*)oxiran-2-yl]tetrahydro-2-furanyl-4-(2*S*,5*R*)-5-[(2*S*)oxiran-2-yl]tetrahydro-2-furanylbutyl)oxy]dimethylsilane **5.29** (14.1 mg, 30 μmol, 29%) as a colourless oil. Also recovered was (*t*-butyl)[((1*S*,4*R*)-4-[1-(*t*-butyl)-1,1-dimethylsilyl]oxy-4-(2*R*,5*S*)-5-[(2*R*)oxiran-2-yl]tetrahydro-2-furanyl-1-(2*R*,5*S*)-5-[(2*S*)oxiran-2-yl]tetrahydro-2-furanylbutyl)oxy]dimethylsilane **5.30** (7.0 mg, 13 μmol, 15%) as a crystalline solid and (1*S*,4*S*)-4-[1-(*t*-butyl)-1,1-dimethylsilyl]oxy-1-(2*R*,5*S*)-5-[(2*S*)oxiran-2-yl]tetrahydro-2-furanyl-4-(2*S*,5*R*)-5-[(2*S*)oxiran-2-yl]tetrahydro-2-furanylbutan-1-ol **5.31** (0.006 g, 0.014 mmol, 16%) as a colourless oil. Mp 51-52 °C; $[\alpha]^{25}_{D}$ –6.3 ($CHCl_3$, *c* 0.44); IR ν_{max} (neat) 2954 (m), 2930 (m), 2883 (m), 2856 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.85 (2H, td, *J* = 6.9, 6.0 Hz, 2 x $CH_2CHCHOTBS$), 3.73 (2H, dt, *J* = 6.5, 5.8 Hz, 2 x $CH_2(O)CHCH$), 3.66-3.59 (2H, m, 2 x $CH_2CHCHOTBS$), 2.99-2.94 (2H, m, 2 x $CH_2(O)CHCH$), 2.79 (2H, appt. t, *J* = 5.0 Hz, 2 x $CHH(O)CH$), 2.64 (2H, dd, *J* = 5.0, 2.5 Hz, 2 x $CHH(O)CH$), 2.02-1.93 (2H, m, 2 x $CH_2(O)CHCHCHH$), 1.90-1.75 (4H, m, 2 x $CH_2(O)CHCHCHH$ and 2 x $CH_2(O)CHCHCH_2CHH$), 1.74-1.67 (2H, m, 2 x $CH_2(O)CHCHCH_2CHH$), 1.55-1.50 (4H, m, $CHOHCH_2CH_2CHOH$), 0.90 (18H, s, 6 x CCH_3), 0.08 (6H, s, 2 x $SiCH_3$), 0.07 (6H, s, 2 x $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.7 (CH), 79.5 (CH), 75.1 (CH), 53.4 (CH), 45.9 (CH_2), 29.2 (CH_2), 28.5 (CH_2), 26.8 (CH_2), 26.1 (CH_3), 18.4 (C), −4.0 (CH_3), −4.5 (CH_3); LRMS (ES^+) *m/z* 565 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{28}H_{54}O_6Si_2Na^+$ Calcd. 565.3351, found 565.3357.

(*t*-Butyl)[((1*S*,4*R*)-4-[1-(*t*-butyl)-1,1-dimethylsilyl]oxy-4-(2*R*,5*S*)-5-[(2*R*)oxiran-2-yl]tetrahydro-2-furanyl-1-(2*R*,5*S*)-5-[(2*S*)oxiran-2-yl]tetrahydro-2-furanylbutyl)oxy]dimethylsilane (**5.30**)



Data for isomer **5.30** (IR, LRMS & HRMS identical to **5.29**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (2H, td, *J* = 6.9, 6.0 Hz, 2 x CH_2C**H**CHOTBS), 3.73 (2H, dt, *J* = 6.5, 5.8 Hz, 2 x CH_2(O)CHC**H**), 3.64-3.58 (2H, m, 2 x CH_2CHC**H**OTBS), 2.98-2.94 (2H, m, 2 x CH_2(O)C**H**CH), 2.79 (2H, appt. t, *J* = 5.0 Hz, 2 x C**H**H(O)CH), 2.63 (2H, dd, *J* = 5.0, 2.5 Hz, 2 x CH**H**(O)CH), 2.02-1.93 (2H, m, 2 x CH_2(O)CHCHC**H**H), 1.90-1.76 (4H, m, 2 x CH_2(O)CHCHCH**H** and 2 x CH_2(O)CHCHCH_2C**H**H), 1.75-1.67 (4H, m, 2 x CH_2(O)CHCHCH_2CH**H** and CHOHC**H**$_2$$CH_2$CHOH), 1.55-1.50 (2H, m, CHOHCH_2C**H**$_2$CHOH), 0.90 (18H, s, 6 x CC**H**$_3$), 0.08 (6H, s, 2 x SiC**H**$_3$), 0.07 (6H, s, 2 x SiC**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.9 (CH), 79.5 (CH), 75.3 (CH), 53.4 (CH), 45.9 (CH_2), 29.4 (CH_2), 28.5 (CH_2), 26.9 (CH_2), 26.1 (CH_3), 18.4 (C), −4.1 (CH_3), −4.4 (CH_3).

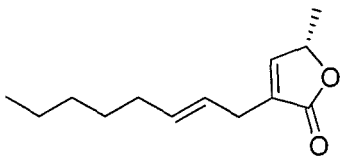
(1*S*,4*S*)-4-[1-(*t*-Butyl)-1,1-dimethylsilyl]oxy-1-(2*R*,5*S*)-5-[(2*S*)oxiran-2-yl]tetrahydro-2-furanyl-4-(2*S*,5*R*)-5-[(2*S*)oxiran-2-yl]tetrahydro-2-furanylbutan-1-ol (**5.31**)



Data for monosilylated product **5.31**: $[\alpha]^{25}_{D}$ –5.9 ($CHCl_3$, *c* 0.31); IR ν_{max} (neat) 3453 (w), 2951 (m), 2928 (m), 2881 (m), 2857 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92-3.84 (2H, m, CH_2C**H**CHOH and CH_2CHCH(OTBS)C**H**), 3.83-3.73 (2H, m, CH_2(O)CHC**H** and C**H**CHCH_2(O)), 3.67 (1H, td, *J* = 5.7, 5.5 Hz, CH_2C**H**OTBSCH), 3.44 (1H, td, *J* = 10.8, 5.9 Hz, CH_2CHC**H**OH), 3.05-2.97 (2H, m, CH_2(O)C**H**CH and CHC**H**CH_2(O)), 2.82 (1H, dd, *J* = 5.0, 4.0 Hz, C**H**H(O)CH), 2.79 (1H, dd, *J* = 5.0, 4.0 Hz, CHCH**H**(O)), 2.65 (1H, dd, *J* = 5.0, 2.7 Hz, CH**H**(O)CH), 2.61 (1H, dd, *J* = 5.0,

2.7 Hz, CHC**H**H(O)), 2.05-1.60 (12H, m, 2 x CH_2(O)CHCHC$\mathbf{H_2}$C$\mathbf{H_2}$, CHOHC$\mathbf{H_2}$C$\mathbf{H_2}$CH(OTBS) and C$\mathbf{H_2}$C$\mathbf{H_2}$CHCHCH_2(O)), 0.90 (9H, s, 3 x CC$\mathbf{H_3}$), 0.09 (3H, s, SiC$\mathbf{H_3}$), 0.08 (3H, s, SiC$\mathbf{H_3}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.2 (CH), 82.5 (CH), 79.3 (CH), 79.2 (CH), 74.5 (CH), 53.3 (CH), 53.0 (CH), 45.7 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 28.3 (CH_2), 27.8 (CH_2), 27.7 (CH_2), 26.9 (CH_2), 26.1 (CH_3), 18.2 (C), −4.1 (CH_3), −4.4 (CH_3); LRMS (ES^+) *m/z* 451 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{22}H_{40}O_6SiNa^+$ Calcd. 451.2486, found 451.2487.

(*S*)-5-Methyl-3-((*E*)-oct-2-enyl)furan-2(5*H*)-one (**5.44**)



Method A:

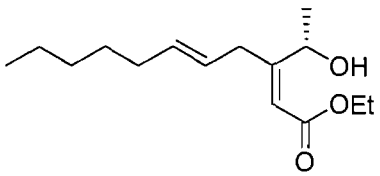
The procedure was carried out using the method described by Trost *et al.*[99] Under an atmosphere of N_2, to a stirred solution of oct-1-ene **5.42** (50 mg, 0.45 mmol) and (*S*)-ethyl 4-hydroxypent-2-ynoate **5.43** (76 mg, 0.53 mmol) in degassed MeOH (1.5 mL) at rt was added RuCp(COD)Cl (2.0 mg, 6 μmol) and the mixture heated at reflux for 2 h. The mixture was concentrated *in vacuo* to give a yellow oil (62 mg), which was dissolved in Et_2O (0.5 mL) and passed through SiO_2 (1 x 8 cm) eluting with EtOAc/hexane (1:2). The organic phase was concentrated *in vacuo* to give a pale yellow oil (60 mg). Purification on SiO_2 (1 x 15 cm) eluting with acetone/hexane (1:19 → 1:9) gave (*S*)-5-methyl-3-((*E*)-oct-2-enyl)furan-2(5*H*)-one **5.44** (40 mg, 0.19 mmol, 43%) as a colourless oil. Also isolated was (2*Z*,4*E*)-ethyl 2-((*S*)-2-hydroxypropylidene)dec-4-enoate **5.45** (16 mg, 0.06 mmol, 14%) as a colourless oil. Spectroscopic characterisation agreed with that published.[99] Data for compound **5.44**: IR ν_{max} (neat) 2957 (w), 2926 (m), 2857 (w), 1750 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (1H, d, *J* = 1.5 Hz, C**H**CHCH$_3$), 5.58 (1H, dt, *J* = 15.3, 5.7 Hz, CH_2CHC**H**CH_2), 5.47 (1H, dt, *J* = 15.3, 5.5 Hz, CH_2C**H**CHCH_2), 5.04-4.97 (1H, m, C**H**CH_3), 2.96 (2H, d, *J* = 5.7 Hz, CHCHC$\mathbf{H_2}$), 2.03 (2H, appt. q, *J* = 6.9 Hz, C$\mathbf{H_2}$CHCH), 1.41 (3H, d, *J* = 6.8 Hz, CHC$\mathbf{H_3}$), 1.39-1.24 (6H, m, CH_3C$\mathbf{H_2}$C$\mathbf{H_2}$C$\mathbf{H_2}$),

0.89 (3H, t, J = 6.9 Hz, C**H**$_3$CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1 (C), 149.0 (CH), 133.8 (CH), 133.2 (C), 123.9 (CH), 77.7 (CH), 32.0 (CH_2), 31.0 (CH_2), 28.6 (CH_2), 28.0 (CH_2), 22.1 (CH_2), 18.7 (CH_3), 13.6 (CH_3); LRMS (ES^+) *m/z* 231 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{13}H_{20}O_2Na^+$ Calcd. 231.1355, found 231.1354.

Method B:

Under an atmosphere of N_2, to a stirred solution of oct-1-ene **5.42** (0.450 g, 4.02 mmol) and (*S*)-ethyl 4-hydroxypent-2-ynoate **5.43** (570 mg, 4.02 mmol) in DMF (10 mL) at 0 °C was added $[Ru(CH_3CN)_3Cp]PF_6$ (8.7 mg, 0.21 mmol) and the mixture warmed to rt over 2 h. H_2O (20 mL) and EtOAc (20 mL) were added, the organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a pale yellow oil (262 mg). Purification on SiO_2 (2.5 x 15 cm) eluting with acetone/hexane (1:24) gave (*S*)-5-methyl-3-((*E*)-oct-2-enyl)furan-2(5*H*)-one **5.44** (529 mg, 2.54 mmol, 63%) as a colourless oil. Also isolated was (2*Z*,4*E*)-ethyl 2-((*S*)-2-hydroxypropylidene)dec-4-enoate **5.45** (88 mg, 0.35 mmol, 9%) as a colourless oil. Spectroscopic data were identical to that reported above.

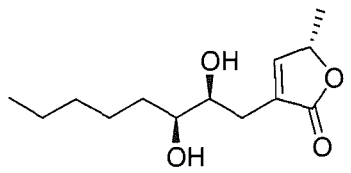
(2*Z*,4*E*)-Ethyl 2-((*S*)-2-hydroxypropylidene)dec-4-enoate (**5.45**)



Spectroscopic characterisation agreed with that published.[99] Data for hydroxyester **5.45**: IR ν_{max} (neat) 3432 (w), 2957 (w), 2926 (m), 2856 (w), 1714 (s), 1647 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99 (1H, s, C**H**CCHOHCH$_3$), 5.53 (1H, dt, J = 15.4, 6.6 Hz, CH$_2$CHC**H**CH$_2$), 5.43 (1H, dt, J = 15.4, 5.5 Hz, CH$_2$C**H**CHCH$_2$), 4.34 (1H, dq, J = 10.3, 6.3 Hz, C**H**OHCH$_3$), 4.17 (2H, q, J = 7.2 Hz, C**H**$_2$CH$_3$), 3.54 (1H, dd, J = 13.6, 5.8 Hz, CHCHC**H**H), 3.08 (1H, dd, J = 13.6, 6.8 Hz, CHCHCH**H**), 1.98 (2H, appt. q, J = 6.8 Hz, C**H**$_2$CHCH), 1.72 (1H, d, J = 4.0 Hz, CHO**H**), 1.39-1.24 (6H, m, CH$_3$C**H**$_2$C**H**$_2$C**H**$_2$), 1.33 (3H, d, J = 6.3 Hz, CHC**H**$_3$), 1.29 (3H, t, J = 7.2 Hz,

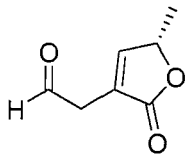
CH_2CH_3), 0.88 (3H, t, J = 6.9 Hz, CH_3CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8 (C), 163.4 (C), 133.1 (CH), 126.7 (CH), 114.3 (CH), 70.9 (CH), 60.0 (CH_2), 32.8 (CH_2), 32.6 (CH_2), 31.5 (CH_2), 29.2 (CH_2), 22.6 (CH_2), 22.4 (CH_3), 14.4 (CH_3), 14.2 (CH_3); LRMS (ES^+) *m/z* 277 (100%, $[M+Na]^+$).

(*rac*)-(*S*)-3-(2,3-Dihydroxyoctyl)-5-methylfuran-2(5*H*)-one (**5.46**)



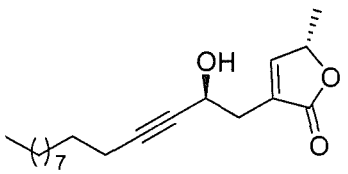
To a stirred solution of (*S*)-5-methyl-3-((*E*)-oct-2-enyl)furan-2(5*H*)-one **5.44** (27 mg, 0.13 mmol) and 4-methylmorpholine *N*-oxide (50% aq, 61 mg, 0.26 mmol) in CH_2Cl_2 (1 mL) at rt was added osmium tetraoxide (2.5% wt in 2-methyl-2-propanol, 66 mg, 6.5 μmol). After 1 ½ h HSO_3 (aq, 2 mL), NaCl (sat aq, 2 mL) and CH_2Cl_2 (4 mL) were added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (40 mg). Purification on SiO_2 (1 x 15 cm) eluting with EtOAc/hexane (2:3 → 3:2) gave (*rac*)-(*S*)-3-(2,3-dihydroxyoctyl)-5-methylfuran-2(5*H*)-one **5.46** (27 mg, 0.11 mmol, 86%) as a colourless oil. Spectroscopic characterisation agreed with that published.[208] IR ν_{max} (neat) 3440 (m), 2953 (w), 2931 (m), 2859 (w), 1735 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (1H, s, C**H**CHCH$_3$), 5.11-5.02 (1H, m, C**H**CH$_3$), 3.70-3.62 (1H, m, C**H**OHCH$_2$), 3.47-3.39 (1H, m, CH$_2$C**H**OH), 3.08 (1H, dd, J = 10.3, 5.8 Hz, CHOHC**H**H), 2.60-2.47 (3H, m, CHOHCH**H** and C**H**$_2$CHOH), 1.56-1.46 (2H, m, CH$_3$C**H**$_2$), 1.43 (3H, dd, J = 6.8, 1.0 Hz, CHC**H**$_3$), 1.37-1.24 (4H, m, CH$_3$CH$_2$C**H**$_2$C**H**$_2$), 0.89 (3H, t, J = 6.8 Hz, C**H**$_3$CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0 (C), 152.4 (CH), 131.0 (C), 78.4 (CH), 73.9 (CH), 72.6 (CH), 33.7 (CH_2), 31.9 (CH_2), 30.3 (CH_2), 25.5 (CH_2), 22.7 (CH_2), 19.1 (CH_3), 14.1 (CH_3); LRMS (ES^+) *m/z* 265 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{13}H_{22}O_4Na^+$ Calcd. 265.1410, found 265.1408.

2-((*S*)-2,5-Dihydro-5-methyl-2-oxofuran-3-yl)acetaldehyde (**3.6**)



To a stirred heterogeneous mixture of $NaIO_4$-SiO_2[206] (207 mg, 0.17 mmol) in CH_2Cl_2 (100 mL) at rt was added (*rac*)-(*S*)-3-(2,3-dihydroxyoctyl)-5-methylfuran-2(5*H*)-one **5.46** (25 mg, 0.10 mmol) as a heterogeneous mixture in CH_2Cl_2 (3 mL). After 45 min the mixture was filtered, washing with $CHCl_3$ (3 x 5 mL) and the filtrate concentrated *in vacuo* to give a pale brown oil (23 mg). Purification on SiO_2 (1 x 15 cm) eluting with EtOAc/hexane (1:1) gave 2-((*S*)-2,5-dihydro-5-methyl-2-oxofuran-3-yl)acetaldehyde **3.6** (8.0 mg, 0.06 mmol, 55%) as a colourless oil. Spectroscopic characterisation agreed with that published.[100] IR ν_{max} (neat) 2986 (w), 2934 (w), 2909 (m), 2851 (w), 1749 (s), 1726 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.80 (1H, s, C**H**O), 7.42 (1H, d, J = 1.4 Hz, C**H**CHCH$_3$), 5.12 (1H, qd, J = 6.9, 1.4 Hz, C**H**CH$_3$), 3.49 (2H, d, J = 1.0 Hz, CHOC**H**$_2$), 1.47 (3H, d, J = 6.9 Hz, CHC**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2 (C), 173.2 (C), 153.6 (CH), 125.3 (C), 78.5 (CH), 39.3 (CH_2), 19.1 (CH_3); LRMS (ES^+) *m/z* 163 (100%, $[M+Na]^+$).

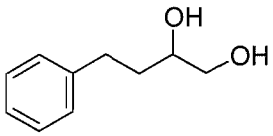
(*S*)-3-((*S*)-2-Hydroxytetradec-3-ynyl)-5-methylfuran-2(5*H*)-one (**5.50**)



Under an atmosphere of N_2, to a stirred solution of dodec-1-yne (238 mg, 1.43 mmol) in toluene (1 mL) was added diethylzinc (0.15 mL, 1.43 mmol) and the mixture heated to reflux for 1 h. The mixture was cooled to rt before (*R*)-BINOL (41 mg, 0.14 mmol), Et_2O (6 mL) and Ti(^{i}PrO)$_4$ (0.11 mL, 0.36 mmol) were added sequentially (mixture → yellow slurry). After 1 h 2-((*S*)-2,5-dihydro-5-methyl-2-oxofuran-3-yl)acetaldehyde **3.6** (50 mg, 0.36 mmol) in Et_2O (2 mL) was added dropwise and the mixture stirred for 2 h. After this time 2 M HCl (aq, 10 mL) and Et_2O (20 mL) were

added, the organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (227 mg). Purification on SiO_2 (2 x 15 cm) eluting with EtOAc/hexane (1:4 → 1:3) gave (*S*)-3-((*S*)-2-hydroxytetradec-3-ynyl)-5-methylfuran-2(5*H*)-one **5.50** (16 mg, 0.05 mmol, 16 %) as a colourless oil. $[\alpha]^{25}_D$ + 9.3 ($CHCl_3$, *c* 0.48); IR ν_{max} (neat) 3418 (w), 2925 (m), 2854 (m), 1746 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (1H, d, *J* = 1.3 Hz, C**H**CHCH$_3$), 5.06 (1H, qd, *J* = 6.9, 1.3 Hz, C**H**CH$_3$), 4.68-4.60 (1H, m, C**H**OH), 2.71 (2H, d, *J* = 5.8 Hz, CHOHC**H**$_2$), 2.18 (2H, td, *J* = 7.2, 1.8 Hz, C**H**$_2$CCCHOH), 1.52-1.46 (2H, m, C**H**$_2$CH$_2$CCCHOH), 1.45 (3H, dd, *J* = 6.9, 1.9 Hz, CHC**H**$_3$), 1.38-1.24 (14H, m, CH$_3$(C**H**$_2$)$_7$), 0.89 (3H, t, *J* = 6.7 Hz, C**H**$_3$CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0 (C), 152.5 (CH), 130.1 (CH), 86.7 (C), 80.1(C), 78.5 (CH), 60.9 (CH), 34.3 (CH_2), 32.0 (CH_2), 29.7 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 28.7 (CH_2), 22.8 (CH_2), 19.2 (CH_2), 18.7 (CH_3), 14.2 (CH_3); LRMS (ES^+) *m/z* 329 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{19}H_{30}O_3Na^+$ Calcd. 329.2087, found 329.2082.

(*rac*)-4-Phenylbutane-1,2-diol (**8.2**)



Method A:

The procedure was carried out using the method described by Ogino *et al.*[159] Under an atmosphere of N_2, to a stirred solution of 4-phenyl-1-butene (**8.1**) (0.68 ml, 4.54 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added a mixture of $KMnO_4$ (1.08 g, 6.81 mmol), adogen 464 (3.16 g, 6.81 mmol) and CH_2Cl_2 (80 mL) dropwise (mixture purple → brown). The addition was at such a rate to maintain the temperature between 0-3 °C. The addition was complete after 40 min and the mixture stirred for a further 40 min. After this time 3% NaOH (aq, 60 mL) was added and the mixture was allowed to warm to rt over 14 h. $Na_2S_2O_5$ (sat aq, 20 mL) was added to reduce the precipitated brown MnO_2, and the mixture stirred until clear. The organic layer was

separated, and after the addition of NaCl (sat aq, 30 mL) the aqueous layer was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (2.60 g). Purification on SiO_2 (3.5 x 15 cm) eluting with EtOAc/hexane (1:1) gave (*rac*)-4-phenylbutane-1,2-diol **8.2** (0.20 g, 1.20 mmol, 29%) as a colourless oil. Spectroscopic characterisation agreed with that published.[209] IR ν_{max} (neat) 3380 (m), 2936 (w), 2931 (w), 1607 (w), 1498 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.25 (2H, m, Ar-**H**), 7.24-7.15 (3H, m, Ar-**H**), 3.78-3.68 (1H, m, C**H**OH), 3.64 (1H, dd, *J* = 11.4, 7.7 Hz, C**H**HOH), 3.46 (1H, dd, *J* = 11.4, 7.7 Hz, CH**H**OH), 3.15 (2H, br d, CHO**H**CH_2O**H**), 2.88-2.75 (1H, m, PhCH**H**CH_2), 2.74-2.72 (1H, m, PhC**H**HCH_2), 1.84-1.70 (2H, m, PhCH_2C**H**$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.9 (C), 128.6 (CH), 128.5 (2 x CH), 126.1 (2 x CH), 71.7 (CH), 66.9 (CH_2), 34.8 (CH_2), 31.9 (CH_2); LRMS (ES^+) *m/z* 189 (100%, $[M+Na]^+$); 0% ee (ChiralPak OD-H, 20% IPA/hex, 9.36, 7.57 min).

Method B:

Under an atmosphere of N_2, to a stirred solution of 4-phenyl-1-butene **8.1** (0.68 mL, 4.54 mmol) in CH_2Cl_2 (120 mL) at 0 °C was added adogen 464 (3.16 g, 6.81 mmol) and 3% NaOH (aq, 60 mL). $KMnO_4$ (1.08 g, 6.81 mmol) was added portionwise over 45 min (mixture purple → brown) and the mixture stirred for a further 2 h at 0 °C. $Na_2S_2O_5$ (sat aq, 30 mL) was added to reduce the precipitated brown MnO_2, and the mixture stirred until clear. The organic layer was separated, and after the addition of NaCl (sat aq, 30 mL) the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (2.40 g). Purification on SiO_2 (3.5 x 15 cm) eluting with EtOAc/hexane (1:1) gave (*rac*)-4-phenylbutane-1,2-diol **8.2** (0.50 g, 3.00 mmol, 66%) as a colourless oil. Spectroscopic characterisation agreed with that published.[209] Spectroscopic data were identical to that reported above.

Method C:

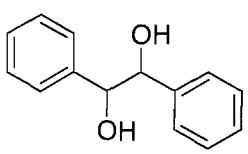
Under an atmosphere of N_2, to a stirred solution of 4-phenyl-1-butene **8.1** (0.68 mL, 4.54 mmol) in CH_2Cl_2 (120 mL) at 0 °C was added adogen 464 (3.16 g, 6.81 mmol)

and pH 9 buffer (aq, 60 mL). $KMnO_4$ (1.08 g, 6.81 mmol) was added portionwise over 45 min (mixture purple → brown) and the mixture stirred for a further 2 h at 0 °C. $Na_2S_2O_5$ (sat aq, 30 mL) was added to reduce the precipitated brown MnO_2, and the mixture stirred until clear. The organic layer was separated, and after the addition of NaCl (sat aq, 30 mL) the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (2.40 g). Purification on SiO_2 (3.5 x 15 cm) eluting with EtOAc/hexane (1:1) gave (*rac*)-4-phenylbutane-1,2-diol **8.2** (0.49 g, 2.97 mmol, 65%) as a colourless oil. Spectroscopic characterisation agreed with that published.[209] Spectroscopic data were identical to that reported above.

Method D:

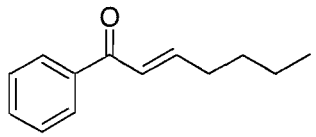
Under an atmosphere of N_2, to a stirred solution of 4-phenyl-1-butene **8.1** (0.10 mL, 0.45 mmol) in CH_2Cl_2 (12 mL) at 0 °C was added 20 mol% chiral phase transfer catalyst **8.5** (60 mg, 0.09 mmol) and pH 9 buffer (aq, 6 mL). $KMnO_4$ (110 mg, 0.68 mmol) was added portionwise over 45 min (mixture purple → brown) and the mixture stirred for a further 2 h at 0 °C. $Na_2S_2O_5$ (sat aq, 10 mL) was added to reduce the precipitated brown MnO_2, and the mixture stirred until clear. The organic layer was separated, and after the addition of NaCl (sat aq, 10 mL) the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (102 mg). Purification on SiO_2 (1.5 x 15 cm) eluting with EtOAc/hexane (1:1) gave 4-phenylbutane-1,2-diol **8.2** (16 mg, 0.10 mmol, 21%, 0% *ee*) as a colourless oil. Spectroscopic characterisation agreed with that published.[209] Spectroscopic data were identical to that reported above.

(*rac*)-1,2-Diphenylethane-1,2-diol (**8.4**)



The procedure was carried out using the method described by Weber *et.al.*[160] Under an atmosphere of N_2, to a stirred solution of *trans*-stilbene **8.3** (0.50 g, 2.77 mmol) in CH_2Cl_2 (120 mL) at 0 °C was added adogen 464 (1.93 g, 4.16 mmol) and 3% NaOH (aq, 60 mL). $KMnO_4$ (0.66 g, 4.16 mmol) was added portionwise over 45 min (mixture purple → brown) and the mixture stirred for a further 30 min at 0 °C. $Na_2S_2O_5$ (sat aq, 30 mL) was added to reduce the precipitated brown MnO_2, and the mixture stirred until clear. The organic layer was separated, and after the addition of NaCl (sat aq, 30 mL) the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (2.50 g). Purification on SiO_2 (3.5 x 15 cm) eluting with EtOAc/hexane (2:3) gave (*rac*)-1,2-diphenylethane-1,2-diol **8.4** (0.23 g, 1.06 mmol, 38%) as a white solid. Spectroscopic characterisation agreed with that published.[210] Mp 136-137 °C (lit. 135-136 °C)[211]; IR ν_{max} (neat) 3495 (s), 3384 (s), 2893 (m), 1601 (w), 1491 (w); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.20 (4H, m, Ar-**H**), 7.18-7.10 (6H, m, Ar-**H**), 4.71 (2H, br s, C**H**OHC**H**OH), 3.00 (2H, br s, CHO**H**CHO**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9 (C), 128.3 (CH), 128.1 (2 x CH), 127.1 (2 x CH), 76.7 (CH); LRMS (GCCI) 8.67 min, *m/z* 184 (2%, $[M+NH_4]^+$), 214 (7%, $[M]^+$), 197 (24%, $[M-OH]^+$), 180 (24%, $[M-2(OH)]^+$), 105 (100%, $[PhC(O)]^+$).

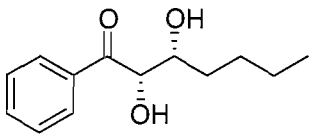
(*E*)-1-Phenylhept-2-en-1-one (**8.8**)



Under an atmosphere of N_2, to a stirred solution of diethyl 2-oxo-2-phenylethylphosphonate **8.7** (2.10 g, 6.85 mmol) in THF (50 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 0.33 g, 8.22 mmol) and the mixture stirred for 15 min. Valeraldehyde (0.73 mL, 6.85 mmol) was added dropwise and the mixture warmed to rt over 14 h. H_2O (50 mL) was added and the mixture was extracted with Et_2O (2 x 50mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a pale yellow oil (1.40 g). Purification by vacuum distillation (115 °C, 0.5 mmHg) gave (*E*)-1-phenylhept-2-en-1-one **8.8** as a colourless

oil (0.83 g, 3.79 mmol, 55%). Spectroscopic characterisation agreed with that published.[212] IR ν_{max} (neat) 2957 (m), 2929 (m), 2871 (w), 1672 (m), 1619 (m), 1598 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.97-7.91 (2H, m, Ar-**H**), 7.60-7.44 (3H, m, Ar-**H**), 7.08 (1H, dt, *J* = 15.4, 6.9 Hz, C(O)CHC**H**), 6.89 (1H, dt, *J* = 15.4, 1.3 Hz, C(O)C**H**CH), 2.34 (2H, qd, *J* = 6.9, 1.3 Hz, CHC$\mathbf{H}_2$), 1.59-1.30 (4H, m, CHCH$_2$C$\mathbf{H}_2$C$\mathbf{H}_2$), 0.95 (3H, t, *J* = 7.2 Hz, CH$_2$C$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.2 (C), 150.3 (CH), 138.2 (C), 132.7 (CH), 128.7 (CH), 126.0 (CH), 32.7 (CH_2), 30.4 (CH_2), 22.5 (CH_2), 14.0 (CH_3); LRMS (GCCI) 7.76 min, *m/z* 189 (100%, $[M+H]^+$), 105 (35%, $[PhC(O)]^+$).

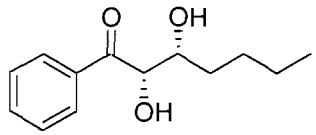
(*rac*)-(2*S*,3*R*)-2,3-Dihydroxy-1-phenylheptan-1-one (**8.9**)



Under an atmosphere of N_2, to a stirred solution of (*E*)-1-phenylhept-2-en-1-one **8.8** (250 mg, 1.33 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added adogen 464 (620 mg, 1.33 mmol) and pH 9 buffer (10 mL). $KMnO_4$ (210 mg, 1.33 mmol) was added portionwise over 15 min (mixture purple → brown) and the mixture allowed to stir for a further 45 min. $Na_2S_2O_5$ (sat aq, 20 mL) was added to reduce the precipitated brown MnO_2, and the mixture stirred until clear. The organic layer was separated, and after the addition of NaCl (sat aq, 10 mL) the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (862 mg). Purification on SiO_2 (3.5 x 15 cm) eluting with EtOAc/hexane (1:4) gave (*rac*)-(2*S*,3*R*)-2,3-dihydroxy-1-phenylheptan-1-one **8.9** (160 mg, 0.72 mmol, 54%) as a colourless oil. IR ν_{max} (neat) 3432 (s, br), 3058 (m), 2950 (s), 2931 (s), 2860 (m), 1682 (s), 1593 (s), 1578 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00-7.80 (2H, m, Ar-**H**), 7.68-7.40 (3H, m, Ar-**H**), 5.02 (1H, d, *J* = 1.3 Hz, C(O)C**H**OH), 3.94 (1H, td, *J* = 6.9, 1.3 Hz, C(O)CHOHC**H**OH), 1.80-1.10 (6H, m, CHOHC$\mathbf{H}_2$C$\mathbf{H}_2$C$\mathbf{H}_2$), 0.93 (3H, t, *J* = 7.1 Hz, CH$_2$C$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.5 (C), 134.2 (C), 133.9 (CH), 130.3 (CH), 129.1 (CH), 128.7 (CH), 75.6 (CH),

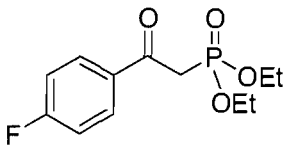
73.1 (CH), 34.6 (CH_2), 28.2 (CH_2), 22.8 (CH_2), 14.2 (CH_3); LRMS (ES^+) *m/z* 245 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{13}H_{18}O_3Na^+$ Calcd. 245.1148, found 245.1149.

(2*S*,3*R*)-2,3-Dihydroxy-1-phenylheptan-1-one (**8.9**)



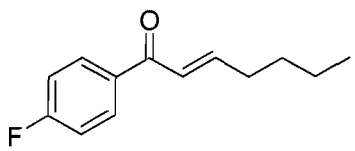
Under an atmosphere of N_2, to a stirred solution of (*E*)-1-phenylhept-2-en-1-one **8.8** (75 mg, 0.40 mmol) in CH_2Cl_2 (7 mL) at 0 °C was added phase-transfer catalyst **8.5** (63 mg, 0.40 mmol) and pH 9 buffer (3 mL). $KMnO_4$ (63 mg, 0.40 mmol) was added portionwise over 15 min (mixture purple → brown) and the mixture allowed to stir for a further 45 min. $Na_2S_2O_5$ (sat aq, 10 mL) was added to reduce the precipitated brown MnO_2, and the mixture stirred until clear. The organic layer was separated, and after the addition of NaCl (sat aq, 5 mL) the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (343 mg). Purification on SiO_2 (2.5 x 15 cm) eluting with EtOAc/hexane (1:4) gave (2*S*,3*R*)-2,3-dihydroxy-1-phenylheptan-1-one **8.9** (41 mg, 0.19 mmol, 45%, 50% *ee*) as a colourless oil. $[\alpha]^{25}_D$ –78.1 ($CHCl_3$, *c* 0.66); IR ν_{max} (neat) 3446 (m, br), 3058 (m), 2955 (m), 2932 (m), 2861 (m), 1681 (s), 1598 (m), 1579 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00-7.80 (2H, m, Ar-**H**), 7.68-7.40 (3H, m, Ar-**H**), 5.02 (1H, d, *J* = 1.3 Hz, C(O)C**H**OH), 3.94 (1H, td, *J* = 6.9, 1.3 Hz, C(O)CHOHC**H**OH), 1.80-1.10 (6H, m, CHOHC**H**$_2$C**H**$_2$C**H**$_2$), 0.93 (3H, t, *J* = 7.1 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.5 (C), 134.2 (C), 133.9 (CH), 130.3 (CH), 129.1 (CH), 128.7 (CH), 75.6 (CH), 73.1 (CH), 34.6 (CH_2), 28.2 (CH_2), 22.8 (CH_2), 14.2 (CH_3); LRMS (ES^+) *m/z* 245 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{13}H_{18}O_3Na^+$ Calcd. 245.1148, found 245.1149; 50% *ee* (ChiralPak OD-H, 20% IPA/hex, 6.18, 5.24 min).

Diethyl 2-(4-fluorophenyl)-2-oxoethylphosphonate (**8.11**)



The procedure was carried out using the method described by Oppolzer *et al.*[122] Under an atmosphere of N_2, to a stirred solution of 2-bromo-4-fluoroacetophenone (7.90 g, 36.4 mmol) (**8.10**) in xylene (50 mL) was added $P(OEt)_3$ (8.80 mL, 51.0 mmol) and the mixture heated at reflux for 3 h. The solution was concentrated *in vacuo* and the residue dissolved in Et_2O (50 mL). The organic layer was extracted with 1M NaOH (aq, 2 x 50 mL). The aqueous layer was acidified (pH 4) with 2M HCl (aq, 50 mL) and then extracted with Et_2O (2 x 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a pale yellow oil (6.38 g). Purification by vacuum distillation (140 °C, 0.5 mmHg) gave diethyl 2-(4-fluorophenyl)-2-oxoethylphosphonate **8.11** (5.90 g, 21.5 mmol, 59%) as a colourless oil. Spectroscopic characterisation agreed with that published.[212] IR ν_{max} (neat) 2988 (w), 1706 (m), 1597 (w), 1261 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.09-8.01 (2H, m, Ar-**H**), 7.18-7.00 (2H, m, Ar-**H**), 4.13 (4H, app. quin, J = 7.2 Hz, 2 x $C\mathbf{H}_2CH_3$), 3.59 (2H, d, J = 22.8 Hz, C(O)$C\mathbf{H}_2$), 1.37-1.17 (6H, t, J = 7.2 Hz, 2 x $CH_2C\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.5 (C, d, $J_{C\text{-}P}$ = 27 Hz), 166.2 (C, d, $J_{C\text{-}F}$ = 1019 Hz), 133.1 (C), 132.0 (CH, d, $J_{C\text{-}F}$ = 38 Hz), 115.9 (CH, d, $J_{C\text{-}F}$ = 87 Hz), 62.9 (CH_2, d, $J_{C\text{-}P}$ = 26 Hz), 38.7 (CH_2, d, $J_{C\text{-}P}$ = 514 Hz), 16.4 (CH_3, d, $J_{C\text{-}P}$ = 24 Hz); LRMS (GCCI) 8.29 min, *m/z* 275 (100%, $[M+H]^+$), 123 (41%, $[C_6H_4FC(O)]^+$).

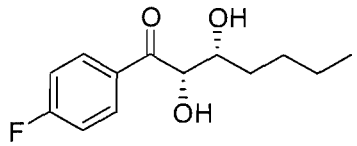
(*E*)-1-(4-Fluorophenyl)hept-2-en-1-one (**8.12**)



Under an atmosphere of N_2, to a stirred solution of diethyl 2-(4-fluorophenyl)-2-oxoethylphosphonate **8.11** (5.16 g, 18.8 mmol) in THF (100 mL) at 0 °C was added

NaH (60% dispersion in mineral oil, 0.75 g, 18.8 mmol) and the mixture stirred for 15 min. Valeraldehyde (1.66 mL, 15.7 mmol) was added dropwise and the reaction warmed to rt over 14 h. H_2O (100 mL) was added and the mixture extracted with Et_2O (2 x 100mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a pale yellow oil (4.20 g). Purification on SiO_2 (6 x 15 cm) eluting with EtOAc/hexane (1:9) gave (*E*)-1-(4-fluorophenyl)hept-2-en-1-one **8.12** (2.14 g, 10.4 mmol, 66%) as a colourless oil. IR ν_{max} (neat) 2959 (w), 2930 (w), 2872 (w), 1670 (m), 1620 (s), 1597 (s), 1506 (m), 1224 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10-7.92 (2H, m, Ar-**H**), 7.22-7.01 (3H, m, Ar-**H** and C(O)CHC**H**), 6.86 (1H, dt, J = 15.4, 1.3 Hz, C(O)C**H**CH), 2.33 (2H, qd, J = 7.0, 1.3 Hz, CHC$\mathbf{H}_2$), 1.60-1.31 (4H, m, $CHCH_2C\mathbf{H}_2C\mathbf{H}_2$), 0.95 (3H, t, J = 7.2 Hz, $CH_2C\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.4 (C), 165.6 (C, d, J_{C-F} = 1008 Hz), 150.5 (CH), 134.4 (C), 131.2 (CH, d, J_{C-F} = 36 Hz), 125.5 (CH), 115.8 (CH, d, J_{C-F} = 87 Hz), 32.7 (CH_2), 30.4 (CH_2), 22.5 (CH_2), 14.0 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ 52.6 (1F, s, CF); LRMS (GCCI) 7.65 min, *m/z* 207 (100%, $[M+H]^+$), 123 (32%, $[C_6H_4FC(O)]^+$); HRMS (EI) $C_{13}H_{15}OF^{+\cdot}$ Calcd. 206.1107, found 206.1103.

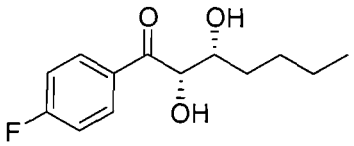
(*rac*)-(2*S*,3*R*)-1-(4-Fluorophenyl)-2,3-dihydroxyheptan-1-one (**8.13**)



Under an atmosphere of N_2, to a stirred solution of (*E*)-1-(4-fluorophenyl)hept-2-en-1-one **8.12** (100 mg, 0.49 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added adogen 464 (230 mg, 0.49 mmol) and pH 9 buffer (10 mL). $KMnO_4$ (80 mg, 0.49 mmol) was added portionwise over 15 min (mixture purple → brown) and the mixture allowed to stir for a further 45 min. $Na_2S_2O_5$ (sat aq, 20 mL) was added to reduce the precipitated brown MnO_2, and the mixture stirred until clear. The organic layer was separated, and after the addition of NaCl (sat aq, 10 mL) the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (420 mg). Purification on SiO_2 (1.5 x 15 cm) eluting with EtOAc/hexane (1:4) gave (*rac*)-(2*S*,3*R*)-1-(4-fluorophenyl)-2,3-dihydroxyheptan-1-

one **8.13** (52 mg, 0.22 mmol, 44%) as a white solid. Mp 56-57 °C; IR ν_{max} (neat) 3570 (m), 3470 (m), 2959 (m), 2926 (m), 2874 (w), 1682 (s), 1602 (s), 1507 (m), 1243 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.98-7.89 (2H, m, Ar-**H**), 7.40-7.00 (2H, m, Ar-**H**), 4.97 (1H, s, C(O)C**H**OH), 3.91 (1H, t, J = 6.2 Hz, C(O)CHOHC**H**OH), 1.80-1.30 (6H, m, CHOHC$\mathbf{H_2}$C$\mathbf{H_2}$C$\mathbf{H_2}$), 0.95 (3H, t, J = 7.0 Hz, $CH_2C\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9 (C), 166.6 (C, d, J_{C-F} = 765 Hz), 133.0 (C), 131.7 (CH, d, J_{C-F} = 28 Hz), 116.6 (CH, d, J_{C-F} = 65 Hz), 75.5 (CH), 73.2 (CH), 34.5 (CH_2), 28.2 (CH_2), 22.8 (CH_2), 14.2 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ 58.9 (1F, s, CF); LRMS (ES^+) *m/z* 263 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{13}H_{17}O_3FNa^+$ Calcd. 263.1054, found 263.1055; Elemental calcd. for $C_{13}H_{17}O_3F$: C, 64.99; H, 7.13. Found: C, 64.74; H, 6.82.

(2*S*,3*R*)-1-(4-Fluorophenyl)-2,3-dihydroxyheptan-1-one (**8.13**)



Method A:

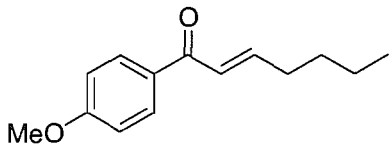
Under an atmosphere of N_2, to a stirred solution of (*E*)-1-(4-fluorophenyl)hept-2-en-1-one **8.12** (70 mg, 0.34 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added phase-transfer catalyst **8.5** (220 mg, 0.34 mmol) and pH 9 buffer (10 mL). $KMnO_4$ (54 mg, 0.34 mmol) was added portionwise over 15 min (mixture purple → brown) and the mixture allowed to stir for a further 45 min. $Na_2S_2O_5$ (sat aq, 20 mL) was added to reduce the precipitated brown MnO_2, and the mixture stirred until clear. The organic layer was separated, and after the addition of NaCl (sat aq, 10 mL) the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (270 mg). Purification on SiO_2 (2.5 x 15 cm) eluting with EtOAc/hexane (1:4) gave (2*S*,3*R*)-1-(4-fluorophenyl)-2,3-dihydroxyheptan-1-one **8.13** (15 mg, 0.06 mmol, 18%, 61% *ee*) as a white solid. $[\alpha]^{25}_D$ –4.2 ($CHCl_3$, *c* 0.31); Mp 56-57 °C; IR ν_{max} (neat) 3570 (m), 3470 (m), 2959 (m), 2926 (m), 2874 (w), 1682 (s), 1602 (s), 1507 (m), 1243 (s) cm^{-1}; ^1H NMR (300

MHz, $CDCl_3$) δ 7.98-7.89 (2H, m, Ar-**H**), 7.40-7.00 (2H, m, Ar-**H**), 4.97 (1H, s, C(O)C**H**OH), 3.91 (1H, t, J = 6.2 Hz, C(O)CHOHC**H**OH), 1.80-1.30 (6H, m, CHOHC**H**$_2$C**H**$_2$C**H**$_2$), 0.95 (3H, t, J = 7.0 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9 (C), 166.6 (C, d, J_{C-F} = 765 Hz), 133.0 (C), 131.7 (CH, d, J_{C-F} = 28 Hz), 116.6 (CH, d, J_{C-F} = 65 Hz), 75.5 (CH), 73.2 (CH), 34.5 (CH_2), 28.2 (CH_2), 22.8 (CH_2), 14.2 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ 58.9 (1F, s, CF); LRMS (ES^+) *m/z* 263 (100%, $[M+Na]^+$); HRMS (ES^+) $C_{13}H_{17}O_3FNa^+$ Calcd. 263.1054, found 263.1055; Elemental calcd. for $C_{13}H_{17}O_3F$: C, 64.99; H, 7.13. Found: C, 64.74; H, 6.82; 61% *ee* (ChiralPak OD-H, 5% IPA/hex, 13.9, 12.7 min).

Method B:

As for method A using (*E*)-1-(4-fluorophenyl)hept-2-en-1-one **8.12** (70 mg, 0.34 mmol), except that the reaction was conducted at −15 °C and stirred for 3 h. Purification on SiO_2 (2.5 x 15 cm) eluting with EtOAc/hexane (1:4) gave (2*S*,3*R*)-1-(4-fluorophenyl)-2,3-dihydroxyheptan-1-one **8.13** (20 mg, 0.08 mmol, 25%, 67% *ee*) as a white solid. Spectroscopic data were identical to that reported above except: $[\alpha]^{25}_D$ −5 ($CHCl_3$, *c* 0.33); 67% *ee* (ChiralPak OD-H, 5% IPA/hex, 13.9, 12.7 min).

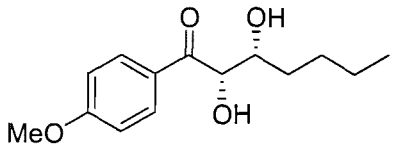
(*E*)-1-(4-Methoxyphenyl)hept-2-en-1-one (**8.16**)



The procedure was carried out using the method described by Oare *et al.*[196] Under an atmosphere of N_2, to a stirred solution of di*iso*propylamine (2.14 mL, 15.2 mmol) in THF (30 mL) at −20 °C was added *n*BuLi (1.85 M in hexane, 8.20 mL, 15.2 mmol) dropwise. The mixture was cooled to −70 °C and 4-methoxyacetophenone (**8.14**) (2.20 g, 14.6 mmol) in THF (20 mL) was added dropwise. After 30 min at −70 °C, valeraldehyde (1.70 mL, 16.0 mmol) was added and the mixture stirred for a further 45 min. $NaHCO_3$ (sat aq, 30 mL) was added, the layers were separated and the aqueous phase was extracted with Et_2O (2 x 50 mL). The combined organic phases

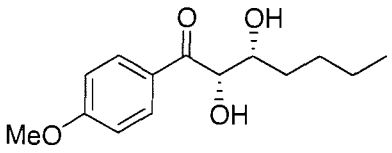
were washed successively with cold 1% HCl (aq, 100 mL), $NaHCO_3$ (sat aq, 100 mL) and NaCl (sat aq, 100 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude aldol product **8.15** (1.88 g, 7.97 mmol, 55%) as a yellow oil, which was used without further purification. Under an atmosphere of N_2, to a stirred solution of crude aldol product **8.15** (1.88 g, 7.97 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added Et_3N (1.33 mL, 9.56 mmol). After 15 min MsCl (1.10 mL, 9.56 mmol) was added dropwise and the mixture stirred for a further 3 h. H_2O (50 mL) was added, the layers were separated and the aqueous extracted with Et_2O (2 x 50 mL). The combined organic phases were washed successively with cold 1% HCl (aq, 100 mL), $NaHCO_3$ (sat aq, 100 mL) and NaCl (sat aq, 100 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude mesylate as a pale yellow oil (1.20 g, 3.82 mmol). This was used without any further purification. Under an atmosphere of N_2, to a stirred solution of crude mesylate (1.20 g, 3.82 mmol) in CH_2Cl_2 (30 mL) at rt was added Et_3N (0.64 mL, 4.58 mmol). After 14 h, H_2O (50 mL) was added, the layers were separated and the aqueous extracted with Et_2O (2 x 50 mL). The combined organic phases were washed successively with cold 1% HCl (aq, 100 mL), $NaHCO_3$ (sat aq, 100 mL) and H_2O (100 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give a pale yellow oil (0.85 g). Purification on SiO_2 (3.5 x 15 cm) eluting with EtOAc/hexane (1:9) gave (*E*)-1-(4-methoxyphenyl)hept-2-en-1-one **8.16** (0.56 g, 2.59 mmol, 18%) as a colourless oil. Spectroscopic characterisation agreed with that published.[196] IR ν_{max} (neat) 2957 (w), 2931 (w), 2872 (w), 1665 (m), 1618 (s), 1598 (s), 1510 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00-7.92 (2H, m, 2 x $CH_3OCCHCH$**H**), 7.06 (1H, dt, J = 15.4, 7.1 Hz, C(O)CHC**H**), 6.99-6.85 (3H, m, 2 x CH_3OCC**H**CH and C(O)C**H**), 3.88 (3H, s, O**C**H_3), 2.32 (2H, q, J = 7.1 Hz, CH**C**H_2), 1.57-1.32 (4H, m, $CHCH_2C$**H**$_2$**C**H_2), 0.94 (3H, t, J = 7.2 Hz, CH_2C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.3 (C), 163.4 (C), 149.2 (CH), 131.0 (CH), 125.6 (CH), 113.9 (CH), 55.6 (CH_3), 32.7 (CH_2), 30.5 (CH_2), 22.5 (CH_2), 14.0 (CH_3); LRMS (GCCI) 8.60 min, 219 (61%, $[M+H]^+$), 135 (100%, $[C_6H_4(OCH_3)CO]^+$).

(*rac*)-(2*S*,3*R*)-2,3-Dihydroxy-1-(4-methoxyphenyl)heptan-1-one (**8.17**)



Under an atmosphere of N_2, to a stirred solution of (*E*)-1-(4-methoxyphenyl)hept-2-en-1-one **8.16** (70 mg, 0.32 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added adogen 464 (150 mg, 0.32 mmol) and pH 9 buffer (10 mL). $KMnO_4$ (51 mg, 0.32 mmol) was added portionwise over 15 min (mixture purple → brown) and the mixture allowed to stir for a further 45 min. $Na_2S_2O_5$ (sat aq, 20 mL) was added to reduce the precipitated brown MnO_2, and the mixture stirred until clear. The organic layer was separated, and after the addition of NaCl (sat aq, 10 mL) the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (240 mg). The crude was dissolved in Et_2O (20 mL) and washed with $NaHCO_3$ (sat aq, 25 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give a pale yellow oil (210 mg). Purification on SiO_2 (2.5 x 15 cm) eluting with EtOAc/hexane (1:2) gave (*rac*)-(2*S*,3*R*)-2,3-dihydroxy-1-(4-methoxyphenyl)heptan-1-one **8.17** (29 mg, 0.12 mmol, 38%) as a white solid. Mp 91-92 °C; IR ν_{max} (neat) 3451 (w), 3390 (m), 2936 (m), 2865 (w), 2841 (w), 1673 (m), 1602 (s), 1569 (w), 1512 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.93-7.86 (2H, m, 2 x $(CH_3O)CCHCH$), 7.02-6.95 (2H, m, 2 x $(CH_3O)CCHCH$), 4.95 (1H, s, $C(O)CHOH$), 3.91 (1H, t, J = 6.8 Hz, $CHOHCH_2$), 3.89 (3H, s, OCH_3), 1.90-1.60 (2H, m, $CHOHCH_2$), 1.60-1.10 (4H, m, $CH_2CH_2CH_3$), 0.82 (3H, t, J = 7.2 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.6 (C), 164.4 (C), 131.1 (C), 126.6 (CH), 114.3 (CH), 75.1 (CH), 73.4 (CH), 55.7 (CH_3), 34.7 (CH_2), 28.8 (CH_2), 22.8 (CH_2), 14.2 (CH_3); LRMS (ES^+) *m/z* 527 (65%, $[2M+Na]^+$), 253 (21%, $[M+H]^+$), 153 (100%, $[C_6H_5(MeO)C(O)]^+$); Elemental calcd. for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.43; H, 7.73.

(2*S*,3*R*)-2,3-Dihydroxy-1-(4-methoxyphenyl)heptan-1-one (**8.17**)



Method A:

Under an atmosphere of N_2, to a stirred solution of (*E*)-1-(4-methoxyphenyl)hept-2-en-1-one **8.16** (70 mg, 0.32 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added phase-transfer catalyst **8.5** (210 mg, 0.32 mmol) and pH 9 buffer (10 mL). $KMnO_4$ (51 mg, 0.32 mmol) was added portionwise over 15 min (mixture purple → brown) and the mixture allowed to stir for a further 45 min. $Na_2S_2O_5$ (sat aq, 20 mL) was added to reduce the precipitated brown MnO_2, and the mixture stirred until clear. The organic layer was separated, and after the addition of NaCl (sat aq, 10 mL) the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic phases were washed with $NaHCO_3$ (sat aq, 25 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow solid (250 mg). Purification on SiO_2 (2.5 x 15 cm) eluting with EtOAc/hexane (1:2) gave (2*S*,3*R*)-2,3-dihydroxy-1-(4-methoxyphenyl)heptan-1-one **8.17** (34 mg, 0.13 mmol, 42%, 60% *ee*) as a white solid. $[\alpha]^{25}_D$ –14.1 ($CHCl_3$, *c* 0.54); mp 91-92 °C; IR ν_{max} (neat) 3451 (w), 3390 (m), 2936 (m), 2865 (w), 2841 (w), 1673 (m), 1602 (s), 1569 (w), 1512 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.93-7.86 (2H, m, 2 x $(CH_3O)CCHCH$), 7.02-6.95 (2H, m, 2 x $(CH_3O)CCHCH$), 4.95 (1H, s, C(O)C**H**OH), 3.91 (1H, t, *J* = 6.8 Hz, C**H**OHCH_2), 3.89 (1H, s, OCH_3), 1.90-1.60 (2H, m, CHOHCH_2), 1.60-1.10 (4H, m, CH_2C$H_2$$CH_3$), 0.82 (3H, t, *J* = 7.2 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.6 (C), 164.4 (C), 131.1 (C), 126.6 (CH), 114.3 (CH), 75.1 (CH), 73.4 (CH), 55.7 (CH_3), 34.7 (CH_2), 28.8 (CH_2), 22.8 (CH_2), 14.2 (CH_3); LRMS (ES^+) *m/z* 527 (65%, $[2M+Na]^+$), 253 (21%, $[M+H]^+$), 153 (100%, $[C_6H_5(MeO)C(O)]^+$); Elemental calcd. for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.43; H, 7.73; 60% *ee* (ChiralPak OB-H, 10% IPA/hex, 21.6, 17.3 min).

Method B:

Under an atmosphere of N_2, to a stirred solution of phase-transfer catalyst **8.5** (210 mg, 0.32 mmol) in CH_2Cl_2 (20 mL) at −60 °C was added $KMnO_4$ (51 mg, 0.32 mmol) in one portion. After 5 min (*E*)-1-(4-methoxyphenyl)hept-2-en-1-one **8.16** (70 mg, 0.32 mmol) in CH_2Cl_2 (5 mL) was added dropwise and the mixture stirred for 90 min. A mixture of pH 9 buffer (10 mL) and $Na_2S_2O_5$ (sat aq, 10 mL) was added to reduce the precipitated brown MnO_2, and the mixture stirred until clear. The organic layer was separated, and after the addition of NaCl (sat aq, 10 mL) the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic phases were washed with $NaHCO_3$ (sat aq, 25 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow solid (240 mg). Purification on SiO_2 (2.5 x 15 cm) eluting with EtOAc/hexane (1:2) gave (2*S*,3*R*)-2,3-dihydroxy-1-(4-methoxyphenyl)heptan-1-one **8.17** (27 mg, 0.11 mmol, 34%, 80% *ee*) as a white solid. Spectroscopic data were identical to that reported above except $[\alpha]^{25}_D$ –31 ($CHCl_3$, *c* 0.44); 80% *ee* (ChiralPak OB-H, 10% IPA/hex, 21.6, 17.3 min).

Chapter 10

References

1. Jolad, S. D.; Hoffmann, J. J.; Schram, K. H.; Cole, J. R.; Tempesta, M. S.; Kriek, G. R.; Bates, R. B. *J. Org. Chem.* **1982**, *47*, 3151-3153.
2. Alali, F. Q.; Liu, X. X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504-540.
3. Gu, Z. M.; Zhao, G. X.; Oberlies, N. H.; Zeng, L.; McLaughlin, J. L. *Recent Ad. Phytochem.* **1995**, *29*, 249-310.
4. Oberlies, N. H.; Chang, C. J.; McLaughlin, J. L. *J. Med. Chem.* **1997**, *40*, 2102-2106.
5. Alali, F. Q.; Kaakeh, W.; Bennett, G. W.; McLaughlin, J. L. *J. Econ. Entomol.* **1998**, *91*, 641-649.
6. He, K.; Zeng, L.; Ye, Q.; Shi, G. E.; Oberlies, N. H.; Zhao, G. X.; Njoku, J.; McLaughlin, J. L. *Pestic. Sci.* **1997**, *49*, 372-378.
7. Landolt, J. L.; Ahammadsahib, K. I.; Hollingworth, R. M.; Barr, R.; Crane, F. L.; Buerck, N. L.; McCabe, G. P.; McLaughlin, J. L. *Chem.-Biol. Interact.* **1995**, *98*, 1-13.
8. Miyoshi, H.; Ohshima, M.; Shimada, H.; Akagi, T.; Iwamura, H.; McLaughlin, J. L. *Biochim. Biophys. Acta-Bioenerg.* **1998**, *1365*, 443-452.
9. Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G. E.; Gu, Z. M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, *13*, 275-306.
10. Wang, X.-W.; Xie, H. *Drug future* **1999**, *24*, 159-165.
11. Fang, X. P.; Rieser, M. J.; Gu, Z. M.; Zhao, G. X.; McLaughlin, J. L. *Phytochem. Anal.* **1993**, *4*, 27-67.
12. He, K.; Zhao, G. X.; Shi, G. E.; Zeng, L.; Chao, J. F.; McLaughlin, J. L. *Bioorg. Med. Chem.* **1997**, *5*, 501-506.
13. Johnson, H. A.; Oberlies, N. H.; Alali, F. Q.; McLaughlin, J. L. *Biologically Active Natural Products* **2000**, 173-183.
14. Ahammadsahib, K. I.; Hollingworth, R. M.; McGovren, J. P.; Hui, Y. H.; McLaughlin, J. L. *Life Sci.* **1993**, *53*, 1113-1120.
15. Hopp, D. C.; Zeng, L.; Gu, Z. M.; McLaughlin, J. L. *J. Nat. Prod.* **1996**, *59*, 97-99.

16. Hopp, D. C.; Zeng, L.; Gu, Z. M.; Kozlowski, J. F.; McLaughlin, J. L. *J. Nat. Prod.* **1997**, *60*, 581-586.

17. Gu, Z. M.; Fang, X. P.; Zeng, L.; Wood, K. V.; McLaughlin, J. L. *Heterocycles* **1993**, *36*, 2221-2228.

18. Zhao, G. X.; Miesbauer, L. R.; Smith, D. L.; McLaughlin, J. L. *J. Med. Chem.* **1994**, *37*, 1971-1976.

19. Zhao, G. X.; Ng, J. H.; Kozlowski, J. F.; Smith, D. L.; McLaughlin, J. L. *Heterocycles* **1994**, *38*, 1897-1908.

20. Oberlies, N. H.; Croy, V. L.; Harrison, M. L.; McLaughlin, J. L. *Cancer Lett.* **1997**, *115*, 73-79.

21. Morre, D. J.; Decabo, R.; Farley, C.; Oberlies, N. H.; McLaughlin, J. L. *Life Sci.* **1994**, *56*, 343-348.

22. Gallardo, T.; Saez, J.; Granados, H.; Tormo, J. R.; Velez, I. D.; Brun, N.; Torres, B.; Cortes, D. *J. Nat. Prod.* **1998**, *61*, 1001-1005.

23. Zhao, G. X.; Chao, J. F.; Zeng, L.; Rieser, M. J.; McLaughlin, J. L. *Bioorg. Med. Chem.* **1994**, *37*, 1971-1976.

24. Zhao, G. X.; Hui, Y. H.; Rupprecht, J. K.; McLaughlin, J. L.; Wood, K. V. *J. Nat. Prod.* **1992**, *55*, 347-356.

25. Londershausen, M.; Leicht, W.; Lieb, F.; Moeschler, H.; Weiss, H. *Pestic. Sci.* **1991**, *33*, 427-438.

26. Lewis, M. A.; Arnason, J. T.; Philogene, B. J.; Rupprecht, J. K.; McLaughlin, J. L. *Pestic. Biochem. Physiol.* **1993**, *45*, 15-23.

27. Gallardo, T.; Carmen Zafra-Polo, M.; Tormo, J. R.; Carmen González, M.; Franck, X.; Estornell, E.; Cortes, D. *J. Med. Chem.* **2000**, *43*, 4793-4800.

28. Tormo, J. R.; Estornell, E.; Gallardo, T.; Carmen González, M.; Cavé, A.; Granell, S.; Cortes, D.; Carmen Zafra-Polo, M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 681-684.

29. Weiss, H.; Friedrich, T.; Hofhaus, G.; Preis, D. *Eur. J. Biochem.* **1991**, *197*, 563-576.

30. Chavez, D.; Iglesias-Prieto, R.; Lotina-Hennsen, B. *Physiol. Plant.* **2001**, *111*, 262-268.

31. Esposti, M. D.; Ghelli, A.; Ratta, M.; Cortes, D.; Estornell, E. *Biochem. J.* **1994**, *301*, 161-167.

32. Lopez-Lazaro, M.; Martin-Cordero, C.; Bermejo, A.; Cortes, D.; Ayuso, M. J. *Anticancer. Res.* **2001**, *21*, 3493-3497.
33. Shimada, H.; Grutzner, J. B.; Kozlowski, J. F.; McLaughlin, J. L. *Biochemistry* **1998**, *37*, 854-866.
34. Makabe, H.; Tanaka, A.; Oritani, T. *Tetrahedron* **1998**, *54*, 6329-6340.
35. Fang, X. P.; Anderson, J. E.; Smith, D. L.; Wood, K. V.; McLaughlin, J. L. *Heterocycles* **1992**, *34*, 1075-1083.
36. Makabe, H.; Tanaka, A.; Oritani, T. *J. Chem. Soc.-Perkin Trans. 1* **1994**, 1975-1981.
37. Makabe, H.; Tanaka, A.; Oritani, T. *Biosci. Biotech. Biochem.* **1993**, *57*, 1028.
38. White, J. D.; Somers, T. C.; Reddy, G. N. *J. Org. Chem.* **1992**, *57*, 4991-4998.
39. Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408-7410.
40. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483-2547.
41. Sonogashira, R. K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *12*, 4467-4470.
42. Crimmins, M. T.; She, J. *J. Am. Chem. Soc.* **2004**, *126*, 12790-12791.
43. Crimmins, M. T.; She, J. *Synlett* **2004**, 1371-1374.
44. Swern, D.; Mancuso, A. J.; Huang, S.-L. *J. Org. Chem.* **1978**, *43*, 2480-2482.
45. Morgan, J. P.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953-956.
46. Mitsunobu, O. *Synthesis* **1981**, 1-28.
47. Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605-2606.
48. Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806-1807.
49. Ujihara, K.; Shirahama, H. *Tetrahedron Lett.* **1996**, *37*, 2039-2042.
50. Morimoto, Y.; Muragaki, K.; Iwai, T.; Morishita, Y.; Kinoshita, T. *Angew. Chem. Int. Ed.* **2000**, *39*, 4082-4084.
51. Itokawa, H.; Kishi, E.; Morita, H.; Takeya, Y.; Iitaka, Y. *Tetrahedron Lett.* **1991**, *32*, 1803-1804.
52. Morita, H.; Kishi, E.; Takeya, Y.; Itokawa, H.; Iitaka, Y. *Phytochem.* **1993**, *34*, 765-771.
53. Lindel, T.; Franck, B. *Tetrahedron Lett.* **1995**, *36*, 9465-9468.
54. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765-5780.

55. Hashimoto, M.; Harigaya, H.; Yanagiya, M.; Shirahama, H. *J. Org. Chem.* **1991**, *56*, 2299-2311.
56. Zhu, L.; Mootoo, D. R. *Org. Lett.* **2003**, *5*, 3475-3478.
57. Dabideen, D.; Ruan, Z.; Mootoo, D. R. *Tetrahedron* **2002**, *58*, 2077-2084.
58. Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58-71.
59. Sinha, S. C.; Sinha, A.; Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1997**, *119*, 12014-12015.
60. Avedissian, H.; Sinha, S. C.; Yazbak, A.; Sinha, A.; Neogi, P.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **2000**, *65*, 6035-6051.
61. Hoye, T. R.; Mayer, M. J.; Vos, T. J.; Ye, Z. *J. Org. Chem.* **1998**, *63*, 8554-8557.
62. Marshall, J. A.; Jiang, H. *J. Org. Chem.* **1998**, *63*, 7066-7071.
63. Marshall, J. A.; Jiang, H. *Tetrahedron Lett.* **1998**, *39*, 1493-1496.
64. Marshall, J. A.; Hinkle, K. W. *Tetrahedron Lett.* **1998**, *39*, 1303-1306.
65. Yao, Z.-J.; Wu, Y.-L. *Tetrahedron Lett.* **1994**, *35*, 157-160.
66. Klein, E.; Rojahn, W. *Tetrahedron* **1965**, *21*, 2353-2358.
67. Walba, D. M.; Wand, M. D.; Wilkes, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 4396-4397.
68. Sharpless, K. B.; Teranishi, A. Y.; Backvall, J. E. *J. Am. Chem. Soc.* **1977**, *99*, 3120-3128.
69. Baldwin, J. E.; Crossley, M. J.; Lehtonen, E. M. *J. Chem. Soc.-Chem. Commun.* **1979**, 918-919.
70. Lee, D. G.; Brownridge, J. R. *J. Am. Chem. Soc.* **1973**, *95*, 3033-3034.
71. Wolfe, S.; Ingold, C. F. *J. Am. Chem. Soc.* **1981**, *103*, 940-941.
72. Walba, D. M.; Stoudt, G. S. *J. Org. Chem.* **1983**, *48*, 5404-5406.
73. Walba, D. M.; Edwards, P. D. *Tetrahedron Lett.* **1980**, *21*, 3531-3534.
74. Lee, D. G.; Brown, K. C.; Karaman, H. *Can. J. Chem.-Rev. Can. Chim* **1986**, *64*, 1054-1059.
75. Lee, D. G.; Brown, K. C. *J. Am. Chem. Soc.* **1982**, *104*, 5076-5081.
76. Walba, D. M.; Przybyla, C. A.; Walker, C. B. *J. Am. Chem. Soc.* **1990**, *112*, 5624-5625.
77. Henbest, H. B.; Jackson, W. R.; Robb, B. C. G. *J. Chem. Soc.* **1966**, 803-807.

78. Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Helv. Chim. Acta.* **1984**, *67*, 1397-1401.

79. Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1984**, *106*, 4261-4263.

80. Kocienski, P. J.; Brown, R. C. D.; Pommier, A.; Procter, M.; Schmidt, B. *J. Chem. Soc.-Perkin Trans. 1* **1998**, 9-39.

81. Cecil, A. R. L.; Brown, R. C. D. *Org. Lett.* **2002**, *4*, 3715-3718.

82. Cecil, A. R. L.; Hu, Y. L.; Vicent, M. J.; Duncan, R.; Brown, R. C. D. *J. Org. Chem.* **2004**, *69*, 3368-3374.

83. Head, G. D.; Whittingham, W. G.; Brown, R. C. D. *Synlett* **2004**, 1437-1439.

84. Spino, C.; Weiler, L. *Tetrahedron Lett.* **1987**, *28*, 731-734.

85. Brown, R. C. D.; Hughes, R. M.; Keily, J.; Kenney, A. *Chem. Commun.* **2000**, 1735-1736.

86. Brown, R. C. D.; Bataille, C. J.; Hughes, R. M.; Kenney, A.; Luker, T. J. *J. Org. Chem.* **2002**, *67*, 8079-8085.

87. Bertrand, P.; Gesson, J. P. *Tetrahedron Lett.* **1992**, *33*, 5177-5180.

88. Gale, J. B.; Yu, J.-G.; Hu, X. E.; Khare, A.; Ho, D. K.; Cassady, J. M. *Tetrahedron Lett.* **1993**, *34*, 5847-5850.

89. de Champdore, M.; Lasalvia, M.; Piccialli, V. *Tetrahedron Lett.* **1998**, *39*, 9781-9784.

90. Donohoe, T. J.; Winter, J. J. G.; Helliwell, M.; Stemp, G. *Tetrahedron Lett.* **2001**, *42*, 971-974.

91. Donohoe, T. J.; Butterworth, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 948-951.

92. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3937-3938.

93. Alabarella, L.; Musumeci, D.; Sica, D. *Eur. J. Org. Chem.* **2001**, 997-1003.

94. Piccialli, V.; Cavallo, N. *Tetrahedron Lett.* **2001**, *42*, 4695-4699.

95. Bifulco, G.; Caserta, T.; Gomez-Paloma, L.; Piccialli, V. *Tetrahedron Lett.* **2002**, *43*, 9265-9269.

96. Sinha, S. C.; Keinan, E.; Sinha, S. C. *J. Am. Chem. Soc.* **1998**, *120*, 9076-9077.

97. McDonald, F. E.; Schultz, C. C. *Tetrahedron* **1997**, *53*, 16435-16448.

98. Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969-2004.

99. Trost, B. M.; Muller, J. J.; Martinez, J. *J. Am. Chem. Soc.* **1995**, *117*, 1888-1899.

100. Evans, P. A.; Cui, J.; Gharpure, S. J.; Polosukhin, A.; Zhang, H.-R. *J. Am. Chem. Soc.* **2003**, *125*, 14702-14703.
101. Ma, J. H.; Chan, T. H. *Tetrahedron Lett.* **1998**, *39*, 2499-2502.
102. Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863-927.
103. Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87-99.
104. Yanagisawa, A.; Habaue, S.; Yasue, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 6130-6141.
105. Yanagisawa, A.; Hibino, H.; Habaue, S.; Hisada, Y.; Yamamoto, H. *J. Org. Chem.* **1992**, *57*, 6386-6387.
106. Yanlong, Q.; Guisheng, L.; Huang, Y. Z. *J. Organomet. Chem.* **1990**, *381*, 29-34.
107. Hoye, T. R.; Ye, Z. X. *J. Am. Chem. Soc.* **1996**, *118*, 1801-1802.
108. VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973-1976.
109. Wadsworth, W. S. *Org. React.* **1977**, *25*, 73-77.
110. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405-4408.
111. Breuer, E.; Bannet, D. M. *Tetrahedron Lett.* **1977**, 1141-1144.
112. Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873-3888.
113. Patois, C.; Savignac, P. *Tetrahedron Lett.* **1991**, *32*, 1317-1320.
114. Kokin, K.; Motoyoshiya, J.; Hayashi, S.; Aoyama, H. *Synth. Commun.* **1997**, *27*, 2387-2392.
115. Wang, Y.; Janjic, J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2002**, *124*, 13670-13671.
116. Mulzer, J.; Öhler, E.; Enev, V. S.; Hanbauer, M. *Adv. Synth. Catal.* **2002**, *344*, 573-584.
117. Ralph, J.; Zhang, Y. *Tetrahedron* **1998**, *54*, 1349-1354.
118. Ando, K. *J. Org. Chem.* **1999**, *64*, 8406-8408.
119. Ando, K. *J. Org. Chem.* **2000**, *65*, 4745-4749.
120. Patois, C.; Savignac, P. *Synth. Commun.* **1991**, *21*, 2391-2396.
121. Oppolzer, W.; Dupuis, D. *Tetrahedron Lett.* **1985**, *26*, 5437-5441.
122. Oppolzer, W.; Dupuis, D.; Poli, G.; Raynham, T. M.; Bernardinelli, G. *Tetrahedron Lett.* **1988**, *29*, 5885-5888.
123. Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455-3458.
124. Noyori, R.; Suzuki, M.; Tsunoda, T. *Tetrahedron Lett.* **1980**, *21*, 1357-1358.

125. Cecil, A. R. L. Thesis for Doctor of Philosophy, University of Southampton, 2004.
126. Reiser, O. O. S. In *Organic Synthesis, Highlights IV*; Schmalz, H.-G., Ed.; Wiley-VCH (Weinheim): 2000, p 11-16.
127. Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1993**, *115*, 4891-4892.
128. Trost, B. M.; Toste, F. D. *Tetrahedron Lett.* **1999**, *40*, 7739-7743.
129. Pu, L. *Tetrahedron* **2003**, *59*, 9873-9886.
130. Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806-1807.
131. Gao, G.; Moore, D.; Xie, R.-G.; Pu, L. *Org. Lett.* **2002**, *4*, 4143-4146.
132. Li, X.-S.; Lu, G.; Kwok, W. H.; Chan, A. S. C. *J. Am. Chem. Soc.* **2002**, *124*, 12636-12637.
133. Starks, C. M. *J. Am. Chem. Soc.* **1971**, *93*, 195.
134. Krapcho, A. P.; Larson, J. R.; Eldridge, J. M. *J. Org. Chem.* **1977**, *42*, 3749.
135. Lee, D. G. Phase Transfer Assisted Permanganate Oxidations. In *Oxidation in Organic Chemistry*; Trahanovsky, W. S., Ed.; Academic: New York: 1982; Vol. Part D, p 147-205.
136. Sala, T.; Sargent, M. V. *J. Chem. Soc. Chem. Comm.* **1978**, 253-257.
137. Schmidt, H. J.; Schafer, H. J. *Angew. Chem. Int. Ed.* **1979**, *18*, 68-69.
138. Bhushan, V.; Rathore, R.; Chandrasekaran, S. *Synthesis* **1984**, 431-433.
139. Sam, D. J.; Simmons, H. E. *J. Am. Chem. Soc.* **1972**, *94*, 4024.
140. Lee, D. G.; Lee, E. J.; Brown, K. C. *Acs Symposium Series* **1987**, *326*, 82-95.
141. Brown, R. C. D.; Keily, J. F. *Angew. Chem. Int. Ed.* **2001**, *40*, 4496-4498.
142. Helder, R.; Hummelen, J. C.; Laane, R. W. P. M.; Wiering, J. S.; Wynberg, H. *Tetrahedron Lett.* **1976**, 1831-1834.
143. Hummelen, J. C.; Wynberg, H. *Tetrahedron Lett.* **1978**, 1089-1092.
144. Lygo, B.; Wainwright, G. *Tetrahedron Lett.* **1998**, *39*, 1599-1602.
145. Mazaleyrat, J. P. *Tetrahedron Lett.* **1983**, *24*, 1243-1246.
146. Banfi, S.; Colonna, S. *Synth. Commun.* **1983**, *13*, 1049-1052.
147. Dehmlow, E. V.; Knufinkle, V. *Liebigs Ann. Chem.* **1991**, 283-285.
148. Dehmlow, E. V.; Schrader, S. *Polish J. Chem.* **1994**, *68*, 2199-2208.
149. Lygo, B.; Crosby, J.; Wainwright, G. *Tetrahedron Lett.* **1997**, *38*, 2343-2345.
150. Lygo, B.; Wainwright, G. *Tetrahedron Lett.* **1997**, *38*, 8595-8597.
151. Lygo, B.; Wainwright, G. *Tetrahedron* **1999**, *55*, 6289-6300.

152. Lygo, B.; Daniel, C. M. *Tetrahedron Lett.* **2001**, *42*, 1343-1346.
153. Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **1999**, *1*, 1287-1290.
154. Keily, J. F. Thesis for Doctor of Philosophy, University of Southampton, 2002.
155. Wiberg, K. B.; Saegebarth, K. A. *J. Am. Chem. Soc.* **1957**, *79*, 2822-2823.
156. Wagner, G. *J. Russ. Phys. Chem. Soc.* **1895**, *27*, 219.
157. Clarke, M. F.; Owen, L. N. *J. Chem. Soc.* **1949**, 315-317.
158. Bartlett, P. D.; Bavley, A. *J. Am. Chem. Soc.* **1938**, *60*, 2416-2417.
159. Ogino, T.; Mochizuki, K. *Chem. Lett.* **1979**, 443-446.
160. Weber, W. P.; Shepherd, J. P. *Tetrahedron Lett.* **1972**, 4907-4909.
161. Okimoto, T.; Swern, D. *J. Am. Oil Chem. Soc.* **1977**, *54*, 867A.
162. Foglia, T. A.; Barr, P. A.; Malloy, A. J. *J. Am. Oil Chem. Soc.* **1977**, *54*, 858A.
163. Lee, D. G.; Chang, V. S. *J. Org. Chem.* **1978**, *43*, 1532-1534.
164. Criegee, R. *Angew. Chem.* **1937**, *50*, 153-154.
165. Criegee, R. *Angew. Chem.* **1938**, *51*, 519-520.
166. Milas, N. A.; Trepagnier, J. H.; Nolan, J. T.; Iliopulos, M. I. *J. Am. Chem. Soc.* **1959**, *81*, 4730-4731.
167. Sharpless, K. B.; Akashi, K. *J. Am. Chem. Soc.* **1976**, *98*, 1986-1987.
168. Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 766-768.
169. Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263-4265.
170. Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968-1970.
171. Kwong, H.-L.; Sorato, C.; Ogino, Y.; Chen, H.; Sharpless, K. B. *Tetrahedron Lett.* **1990**, *31*, 2999-3001.
172. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M.; Xu, D. Q.; Zhang, X. L. *J. Org. Chem.* **1992**, *57*, 2768-2771.
173. Gobel, T.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1993**, *32*, 1329-1331.
174. Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785-3787.
175. Salvadori, P.; Pini, D.; Petri, A. *Synlett* **1999**, *8*, 1181-1190.
176. Bolm, C.; Gerlach, A. *Eur. J. Org. Chem.* **1998**, 21-27.
177. Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 7632-7633.
178. Yang, J. W.; Han, H.; Roh, E. J.; Lee, S. G.; Song, C. E. *Org. Lett.* **2002**, *4*, 4685-4688.

179. Song, C. E.; Jung, D.; Roh, E. J.; Lee, S.; Chi, D. Y. *Chem. Commun.* **2002**, 3038-3039.

180. Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis 2nd ed*; Ojima, I., Ed.; Wiley-VCH: New York: 2000, p 357-398.

181. Bolm, C.; Hildebrand, J. P.; Muñiz, K. In *Catalytic Asymmetric Synthesis 2nd ed*; Ojima, I., Ed.; Wiley-VCH: New York: 2000, p 399-428.

182. Comins, D. L.; Baevsky, M. F.; Hong, H. *J. Am. Chem. Soc.* **1992**, *114*, 10971-10972.

183. Curran, D. P.; Ko, S.-B. *J. Org. Chem.* **1994**, *59*, 6139-6142.

184. Fang, F. G.; Xie, S.; Lowery, M. W. *J. Org. Chem.* **1994**, *59*, 6142-6143.

185. Shing, T. K. M.; Tai, V.-W. F.; Tam, E. K. W. *Angew. Chem.* **1994**, *106*, 2408-2410.

186. Plietker, B.; Niggeman, M. *Org. Lett.* **2003**, *68*, 3353-3355.

187. Plietker, B.; Niggeman, M. *Org. Biomol. Chem.* **2004**, *2*, 1116-1120.

188. Plietker, B.; Niggeman, M. *Org. Biomol. Chem.* **2004**, *2*, 2403-2407.

189. Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem.* **1995**, *107*, 1159-1171.

190. Colombo, L.; Gennari, C.; Poli, G.; Scolastico, C.; Demunari, S. *Tetrahedron Lett.* **1985**, *26*, 5459-5462.

191. Hatakeyama, S.; Matsui, Y.; Suzuki, M.; Sakurai, K.; Takano, S. *Tetrahedron Lett.* **1985**, *26*, 6485-6488.

192. Oppolzer, W.; Barras, J.-P. *Helv. Chim. Acta.* **1987**, *70*, 1666-1675.

193. Singh, N.; Lee, D. G. *Org. Process Res. Dev.* **2001**, *5*, 599-603.

194. Inoue, K.; Hiromichi, N.; Masanobu, H.; Yasuzo, U. *Yukagaku* **1980**, *29*, 397-401.

195. Hu, Y.; Hursthouse, M. B. *Personal Communication*.

196. Oare, D. A.; Henderson, M. A.; Sanner, M. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 132-157.

197. Bhunnoo, R. A.; Hu, Y.; Lainé, D. I.; Brown, R. C. D. *Angew. Chem. Int. Ed.* **2002**, *41*, 3479-3480.

198. Perrin, D. D.; Armarego, W. L. F. *Purification of laboratory chemicals*; 3 ed.; Butterworth-Heinemann Ltd: Oxford, 1994.

199. Hoye, T. R.; Suhadolnik, J. C. *Tetrahedron* **1986**, *42*, 2855-2862.

200. Zoretic, P. A.; Wang, M.; Zhang, Y. Z.; Shen, Z. Q.; Ribeiro, A. A. *J. Org. Chem.* **1996**, *61*, 1806-1813.
201. Shimizu, M.; Ando, R.; Kuwajima, I. *J. Org. Chem.* **1984**, *49*, 1230-1238.
202. Nunez, M. T.; Martin, V. S. *J. Org. Chem.* **1990**, *55*, 1928-1932.
203. Hon, Y.-S.; Chang, Y.-C.; Gong, M.-L. *Heterocycles* **1990**, *31*, 191-195.
204. Zhu, Q.; Qiao, L.; Wu, Y. *J. Org. Chem.* **2001**, *66*, 2692-2699.
205. Khorana, N.; Purohit, A.; Herrick-Davis, K.; Teitler, M.; Glennon, R. A. *Bioorg. Med. Chem.* **2003**, *11*, 717-722.
206. Zhong, Y. L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622-2624.
207. Neogi, P.; Doundoulakis, T.; Yazbak, A.; Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1998**, *120*, 11279-11284.
208. Trost, B. M.; Calkins, T. L. *Tetrahedron Lett.* **1995**, *36*, 6021-6024.
209. Park, J.; Pedersen, S. F. *Tetrahedron* **1992**, *48*, 2069-2080.
210. Dobler, C.; Mehltretter, G. M.; Sundermeier, U.; Beller, M. *J. Am. Chem. Soc.* **2000**, *122*, 10289-10297.
211. Huang, Y. Z.; Shen, Y. C.; Chen, C. *Tetrahedron Lett.* **1985**, *26*, 5171-5172.
212. Bradshaw, J. S.; Knudsen, R. D.; Parish, W. W. *J. Org. Chem.* **1975**, *40*, 529.

Chapter 11

Appendix

X-ray data for **5.30**

Table 1. Crystal data and structure refinement details.

Identification code	04sot0866 (RB4095/55rptTS)
Empirical formula	$C_{28}H_{54}O_6Si_2$
Formula weight	542.89
Temperature	120(2) K
Wavelength	0.71069 Å
Crystal system	Triclinic
Space group	*P*–1
Unit cell dimensions	a = 7.417(5) Å α = 68.383(5)°
	b = 10.385(5) Å β = 83.788(5)°
	c = 10.651(5) Å γ = 82.900(5)°
Volume	755.1(7) Å^3
Z	1 (centrosymmetric molecule)
Density (calculated)	1.194 Mg / m^3
Absorption coefficient	0.155 mm^{-1}
F(000)	298
Crystal	Block; Colourless
Crystal size	0.14 × 0.07 × 0.05 mm^3
θ range for data collection	3.33 – 27.63°
Index ranges	$-9 \le h \le 9, -13 \le k \le 13, -13 \le l \le 13$
Reflections collected	12517
Independent reflections	3491 [R_{int} = 0.0547]
Completeness to θ = 25.00°	99.8 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9923 and 0.9786
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3491 / 0 / 168
Goodness-of-fit on F^2	1.018
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0455, *wR2* = 0.0981
R indices (all data)	*R1* = 0.0665, *wR2* = 0.1072
Largest diff. peak and hole	0.335 and –0.283 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993). **Special details**: All hydrogen atoms were placed in idealised positions and refined using a riding model.

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
Si1	3046(1)	7921(1)	2355(1)	16(1)	1
O1	8750(2)	5503(2)	1236(2)	34(1)	1
O2	5243(2)	4935(1)	2778(1)	20(1)	1
O3	2539(2)	6566(1)	3717(1)	17(1)	1
C1	7453(3)	5502(2)	328(2)	31(1)	1
C2	7846(2)	4270(2)	1511(2)	24(1)	1
C3	6593(2)	3831(2)	2759(2)	21(1)	1
C4	5482(2)	2640(2)	2873(2)	23(1)	1
C5	3736(2)	2889(2)	3710(2)	22(1)	1
C6	3946(2)	4277(2)	3863(2)	19(1)	1
C7	2189(2)	5222(2)	3767(2)	17(1)	1
C8	907(2)	4572(2)	4995(2)	21(1)	1
C9	2417(2)	7710(2)	804(2)	24(1)	1
C10	5503(2)	8176(2)	2219(2)	23(1)	1
C11	1691(2)	9487(2)	2609(2)	20(1)	1
C12	2187(3)	10826(2)	1461(2)	26(1)	1
C13	2105(3)	9555(2)	3962(2)	29(1)	1
C14	–358(2)	9377(2)	2626(2)	29(1)	1