UNIVERSITY OF SOUTHAMPTON

Metal-oxo and metal-carbene reagents: applications in the synthesis of natural products and related structures

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ABSTRACT

FACULTY OF ENGINEERING, SCIENCE AND MATHEMATICS

SCHOOL OF CHEMISTRY

Doctor of Philosophy

PART 1: DIASTEREOSELECTIVITY OF C-H INSERTION
PART 2: TOWARDS (–)-GALANTHAMINE
PART 3: TOTAL SYNTHESIS OF *CIS*-SYLVATICIN

By Stephen Charles Kemp

The *Annonaceous* acetogenin *cis*-sylvaticin (**3.12**) displays potent antitumour activity. Using permanganate-promoted oxidative cyclisation of 1,5-dienes we have synthesised the C3-17 and C18-34 fragments **4.32** and **4.12** and coupled them by a tethered ring-closing metathesis to provide the *cis*-sylvaticin backbone with the correct stereochemical configuration.

(–)-Galanthamine (**5.1**) is a naturally occurring alkaloid used in the treatment of Alzheimer's disease. We have attempted to synthesise galanthamine by two routes. The first strategy was based on the cyclopropanation of a diazoacetamide of type **5.56** followed by rearrangement to construct the tetracyclic core. The second strategy was based on the intramolecular nucleophilic addition/migration of azide **6.21**. Neither route was successful and reasons for this are discussed.

The key step in a recent series of syntheses of *endo*, *exo*-furofuran lignans is a highly diastereoselective C-H insertion. A study was undertaken with the aim of advancing our understanding of the process. This involved the synthesis of five analogues of the diazolactone C-H insertion precursors **7.43a-e**, followed by diazo decomposition under various conditions. This investigation has increased our knowledge of the reaction.

Contents

Declaration

The research work described in this thesis was carried out by myself, at the University of Southampton, between October 2002 and November 2005. No part of this thesis has been submitted in any previous application for a higher degree.

Stephen Kemp, September 2006

Acknowledgements

During my PhD adventure I've met loads of interesting people. John Keily took me under his wing when I was an undergraduate and taught me some lessons I couldn't have learned anywhere else. When I started my PhD it was Geoff and Alex who continued this. Alex, thanks for endless games of SoccerSlime. I hear that Santa Ball will be played at the 2012 Olympics... Now to Riaz; I'll always miss my hot lunch on Thursdays. Simon and Nev will be remembered for Battlepong and Claire for her mood swings. Rowan has been one of my best friends over the last few years; we started together but I'm lagging behind a bit! I must also mention Nigel, Jim, Rob, Paul, Yulai, Carole, Sofia, Pam, Ian, Iain, Rick, Thomas, Nadeem, Sherif and Lynda, all of whom I've had immense pleasure working with. Thanks to Neil and Joan for a top NMR service; John and Julie for mass spectrometry (thanks especially for your help towards the end, Julie); and Anne, Carl, Phil and Tony for providing stores-based services (and plenty of goings-on to gossip about). Importantly, I must thank Richard (full of information on chemistry and scooters) who has provided invaluable advice and guidance but also allowed me to learn and develop in my own way.

I spent three months with Eli Lilly and Co. at their picturesque Erl Wood Manor site. Nick Camp was my industrial supervisor who was always very enthusiastic about my work and really knew his stuff, but it was his amazing volley in the 2004 Annual Erl Wood Manor 5-A-Side Football Tournament that I'll always remember him for. The same event provides my best memory of Chris Beadle, who trod on the ball and went flying – and he was only spectating at the time! Anyway Chris, thanks for helping me find my way around the lab and the site. I must also extend my gratitude to Lilly for a CASE award and the EPSRC for a studentship.

Now to friends and family. I'm extremely grateful to all the different people I've lived with over the years for providing various distractions from chemistry and many are now friends for life. I will always be indebted to my family who have provided massive support. Mum, I hope I've made you proud. Dad, I'm sorry you aren't here today but I hope I've justified your earlier confidence in me.

Finally I have to thank Katrina who's been there every step of the way. I hope I can be as encouraging and understanding to you towards the end of your PhD as you have been for me.

Abbreviations

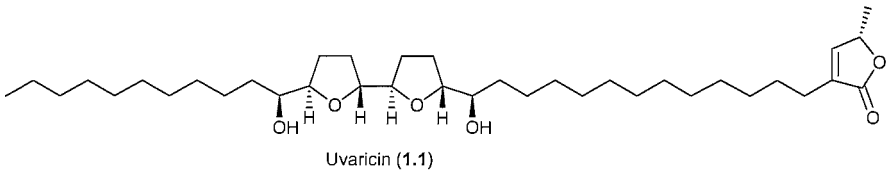
Ac	acetyl
AD	asymmetric dihydroxylation
AIBN	2,2'-azoisobutyronitirile
aq.	aqueous
Ar	aryl
bp	boiling point
br.	broad (NMR and IR)
Bu	butyl
CAN	ammonium cerium(IV) nitrate
cap	caprolactam
CI	chemical ionisation
CSA	camphorsulfonic acid
Cy	cyclohexyl
d	doublet (NMR)
de	diastereomeric excess
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
EAA	ethylacetoacetate
ee	enantiomeric excess
EI	electron ionisation
ent	enantiomer
equiv.	equivalent(s)
Et	ethyl
FT	Fourier transform
GC	gas chromatography
h	hour(s)
HMPA	hexamethylphosphoric triamide
HPLC	high performance liquid chromatography
HRMS	high resolution mass Spectrometry
Hz	hertz
i	*iso*
IR	infrared
J	coupling constant (NMR)
LDA	lithium diisopropylamide
LRMS	Low resolution mass spectrometry
m	multiplet (NMR) or medium (IR)
m	*meta*
M	mol dm^{-3}
***m*CPBA**	*meta*-chloroperbenzoic acid
MDR	multi-drug resistant
Me	methyl
min	minute
mol	mole
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	mass spectrometry
m/z	mass/charge ratio
NADH	nicotinamide adenine dinucleotide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance

p	*para*
PCC	pyridinium chlorochromate
pfb	perfluorobutyrate
Ph	phenyl
Piv	pivaloyl
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
py	pyridine
q	quartet (NMR)
RCM	ring-closing metathesis
$\mathbf{R_f}$	retention factor
rt	room temperature
s	singlet (NMR)
t	tertiary
t	triplet (NMR)
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBDPS	*t*-butyldiphenylsilyl
TBS	*t*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl, triflyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
Troc	2,2,2-trichloroethoxycarbonyl
Ts	*p*-toluenesulfonyl, tosyl
UV	ultraviolet
w	weak

Chapter 1 The *Annonaceous* acetogenins

1.1 Background

The first *Annonaceous* acetogenin to be isolated was uvaricin (**1.1**) in 1982 (Figure 1.1).[1] Uvaricin exhibited *in vivo* anti-leukemic activity and stimulated great interest in this new class of natural products.



Uvaricin (**1.1**)

Figure 1.1 The *Annonaceous* acetogenin uvaricin (**1.1**).

The acetogenins are derived from C_{32}/C_{34} fatty acids. The central portion classically consists of one, two or three THF rings, though some acetogenins have THP rings, or are acyclic (Figure 1.2).

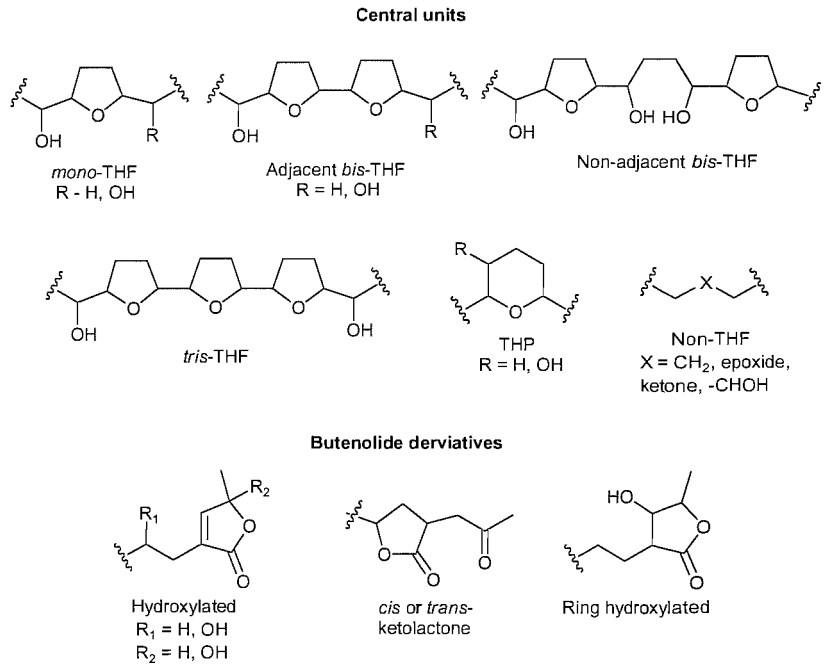


Figure 1.2 Structural elements of *Annonaceous* acetogenins.

Either side of this core is an alkyl chain which may have a number of oxygen functionalities, for example hydroxyl, acetoxy, ketone or epoxide groups. At one end there is usually a methyl-substituted α,β-unsaturated γ-lactone (butenolide), but this can be present in derivatised forms (Figure 1.2).

1.2 Biological activity

The *Annonaceous* acetogenins have a wide range of biological effects including anti-malarial,[2] antiparasitic and antimicrobial,[3] antiprotozoal[4] and pesticidal[5] properties. The most significant biological property is their potent antitumor activity. For example, trilobacin[6] and asiminocin[7] are among the most potent cytotoxic agents known, both showing ED_{50} $<10^{-12}$ μgmL^{-1} in several human tumour cell lines, and bullatacin has been found to be around 500 times more potent than taxol in mice.[8] Additionally, acetogenins show increased cytotoxicity to cancerous over non-cancerous cells,[9] and their mechanism of action means they are effective against multidrug-resistant tumours.[9,10]

The toxicity of the *Annonaceous* acetogenins is due to their interference in the production of energy within cells. They are inhibitors of NADH:ubiquinone oxidoreductase, a mitochondrial membrane-bound protein also known as complex I.[9,11,12] Two possible modes of inhibition have been suggested: firstly that the THF core mimics the natural substrate ubiquinone;[13] and secondly that the polar THF core anchors itself at the edge of the phospholipid bilayer membrane, while the butenolide, at the end of an alkyl chain, penetrates the bilayer and interacts with the enzyme, again by mimicking ubiquinone.[14] Being responsible for the transfer of electrons from NADH to O_2, complex I plays an important role the mitochondrial electron transport chain. Inhibition interrupts the translocation of H^+ from mitochondria, and without this transmembranous electrochemical force, ATP production stops.[15] Correspondingly, there is a reduction in the level of available energy, leading to cell death by apoptosis. This mechanism of action is particularly lethal to cancerous cells due to their high demand for ATP.[16]

1.3 Synthesis of non-adjacent *bis*-THF natural products

There have been many syntheses of *mono*- and adjacent *bis*-THF natural products. Non-adjacent *bis*-THF natural products have received much less attention from the synthetic community, which is surprising considering their important biological properties. There follows a discussion of the key aspects of some recent syntheses. Examples have been chosen to demonstrate a range of synthetic strategies.

1.3.1 (+)-4-Deoxygigantecin

(+)-4-Deoxygigantecin (**1.2**) was first isolated by McLaughlin in 1992,[17] but its absolute configuration had not been elucidated. When Makabe *et al* started the first synthesis of (+)-4-deoxygigantecin, published in 1998, they had to assume that it had the same stereochemistry as (+)-gigantecin (**1.3**), a closely related compound whose configuration was known (Figure 1.3).[18]

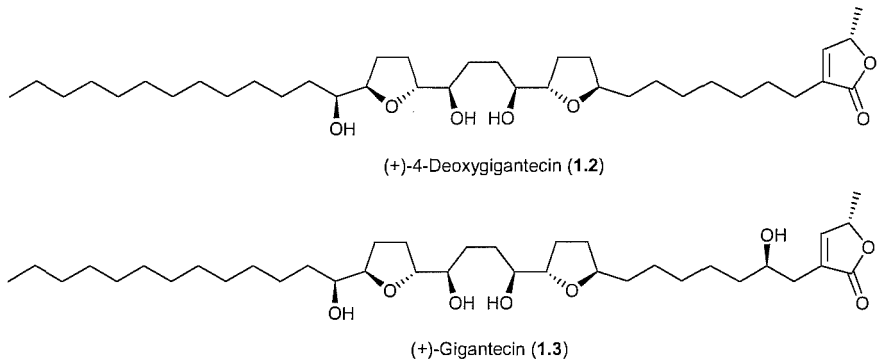
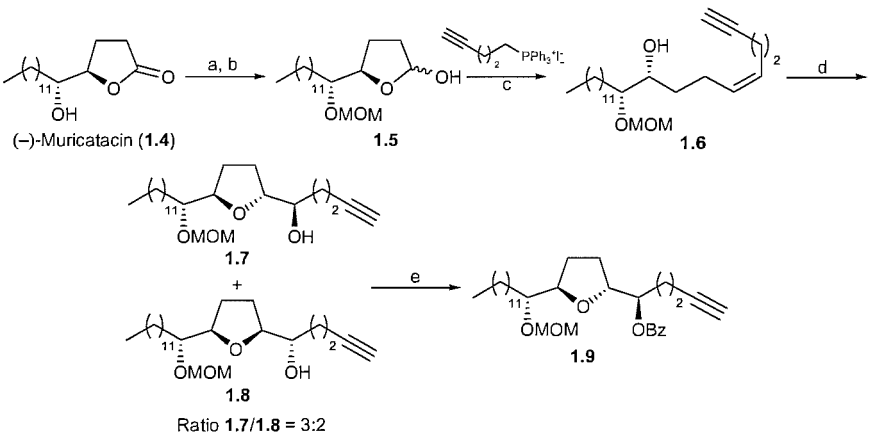


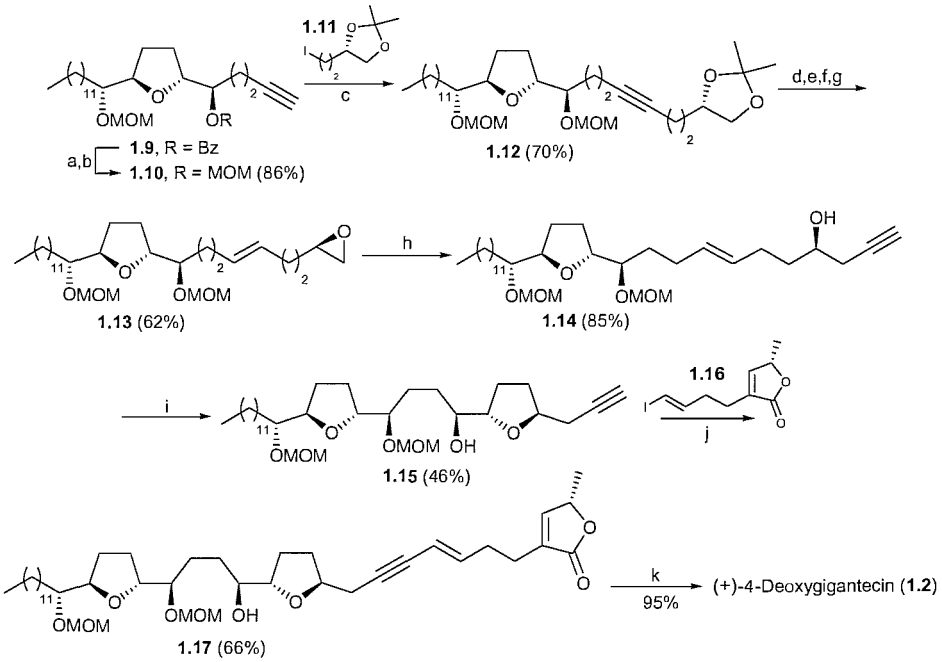
Figure 1.3 The *Annonaceous* acetogenins (+)-4-deoxygigantecin (**1.2**) and (+)-gigantecin (**1.3**).

Makabe had previously used the fragment (–)-muricatacin (**1.4**), a known acetogenin derivative,[19] in syntheses of the *mono*-THF acetogenins *trans*-solamin and reticulatacin.[20] Therefore, (–)-muricatacin was chosen as the starting material (Scheme 1.1).



Scheme 1.1 *Reagents and conditions:* a) MOMCl, $^{i}Pr_2NEt$, CH_2Cl_2, 0 °C; b) DIBAL-H, THF, –78 °C; c) NaOEt, DMF, 0 °C; d) (i) *m*CPBA, CH_2Cl_2, 0 °C; (ii) CSA, 0 °C; e) BzCl, py, 0 °C.

(–)-Muricatacin (**1.4**) was MOM protected and reduced to lactol **1.5** which underwent olefination to give **1.6** (Scheme 1.1). This was epoxidised then treated with acid, which caused cyclisation to **1.7** and **1.8** (3:2). These stereoisomers were inseparable until they had been benzoylated, then the desired compound **1.9** was isolated. Unfortunately, yields were not reported for this sequence.



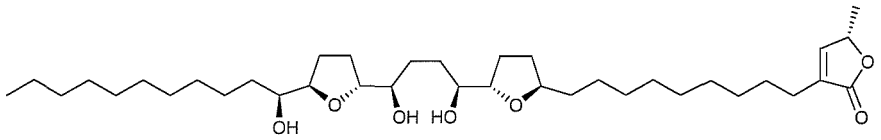
Scheme 1.2 *Reagents and conditions:* a) NaOH, MeOH; b) MOMCl, $^{i}Pr_2NEt$, CH_2Cl_2; c) $^{n}BuLi$, THF, 0 °C; d) Na/NH_3, $^{t}BuOH$, THF, –40 °C; e) 60% AcOH (aq), 60 °C; f) TBSCl, NEt_3, DMAP, CH_2Cl_2; g) (i) MsCl, NEt_3, CH_2Cl_2; (ii) TBAF, THF; (iii) 10% NaOH (aq), THF; h) (i) trimethylsilylacetylene, $^{n}BuLi$, $BF_3{\cdot}Et_2O$, THF, –78 °C; (ii) TBAF, THF; i) (i) MsCl, NEt_3, CH_2Cl_2; (ii) AD-mix-α, $^{t}BuOH$-H_2O; (iii) Triton B, MeOH; j) $Pd(PPh_3)_4$, NEt_3, CuI, C_6H_6; k) (i) H_2, $Rh(PPh_3)_3Cl$, C_6H_6; (ii) $BF_3{\cdot}Et_2O$, Me_2S.

The benzoyl group of *mono*-THF intermediate **1.9**, which facilitated the separation, was replaced by the more convenient MOM group, giving **1.10** (Scheme 1.2). This underwent a Sonogashira cross-coupling with fragment **1.11** to incorporate a protected diol unit. The alkyne was reduced to a *trans*-olefin then the protected diol was converted to an epoxide. The epoxide was opened with TMS acetylide to give **1.14** and the resulting hydroxyl was mesylated. Sharpless asymmetric epoxidation then base-mediated cyclisation gave non-adjacent *bis*-THF compound **1.15** with a diastereomeric excess of 92%. Fragment **1.16** was prepared in a sequence of

straightforward steps then cross-coupled with **1.15**. The residual alkyne and alkene in **1.17** were hydrogenated and the MOM groups hydrolysed to give (+)-4-deoxygigantecin (**1.2**). All data on the synthetic sample matched that of an authentic sample, proving the absolute configuration.

1.3.2 Squamostatin-D

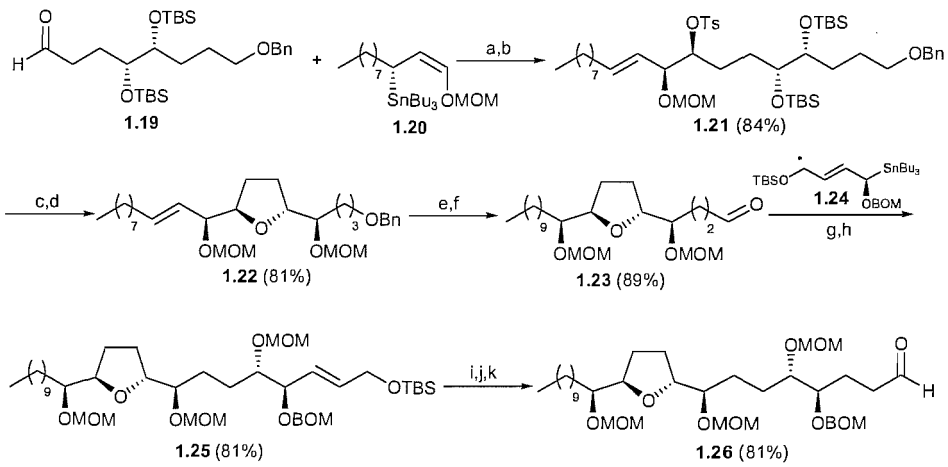
Squamostatin-D (**1.18**) was synthesised by Marshall and Jiang in 1998 using addition of allyl tin and indium reagents to aldehydes to introduce some of the key stereogenic centres (Figure 1.4).[21]



Squamostatin-D (**1.18**)

Figure 1.4 The *Annonaceous* acetogenin squamostatin-D (**1.18**)

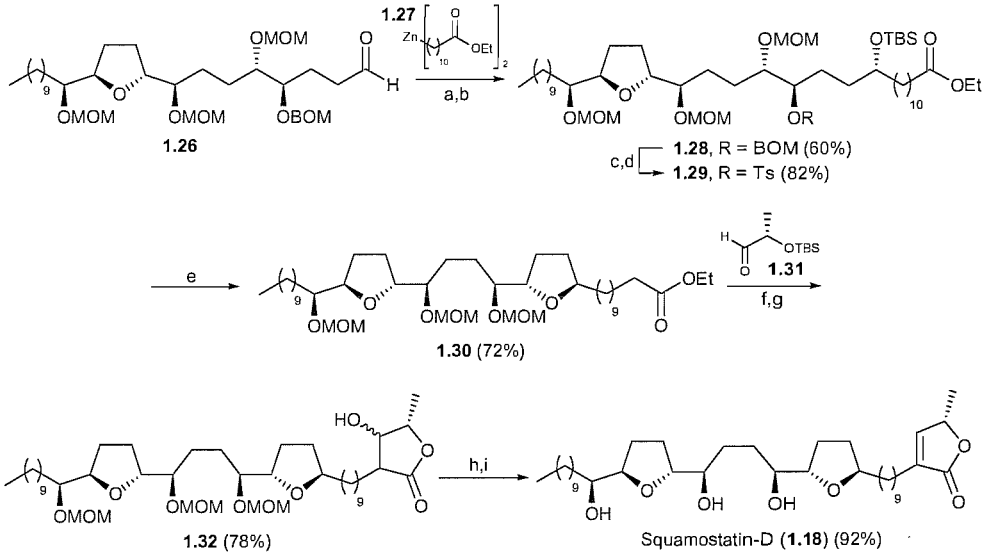
Aldehyde **1.19** and allyl tin species **1.20** are readily available from commercial starting materials. Lewis-acid promoted addition of **1.19** to **1.20** was followed by tosylation of the resulting alcohol, to give **1.21** as the sole product (Scheme 1.3). TBAF cleavage of the silyl ethers allowed an intramolecular cyclisation, then MOM protection of the free hydroxyl gave **1.22**. This was converted to aldehyde **1.23**, to which allyl stannane **1.24** was added in the presence of $InCl_3$. MOM protection of the resulting hydroxyl gave **1.25**. The alkene in **1.25** was hydrogenated before the primary alcohol was deprotected and oxidised to give aldehyde **1.26**.



Scheme 1.3 *Reagents and conditions:* a) $BF_3{\cdot}Et_2O$, CH_2Cl_2, –78 °C; b) TsCl, py; c) TBAF, THF; d) MOMCl, $^iPr_2NEt$, CH_2Cl_2; e) H_2/Pd-C, EtOH; f) Dess-Martin

periodinane, CH_2Cl_2; g) **1.24**, $InCl_3$, EtOAc, –78 °C; h) MOMCl, $^iPr_2NEt$, CH_2Cl_2; i) H_2/Rh-Al_2O_3, EtOAc; j) TBAF, THF; k) Dess-Martin periodinane, CH_2Cl_2.

The organozinc reagent **1.27**, prepared *in situ* by hydroboration and transmetallation of the corresponding alkene, was added to aldehyde **1.26** in the presence of a Lewis acid and a chiral diamine, giving the alcohol in 90% *ee*, which was then silylated to form **1.28** (Scheme 1.4). The BOM ether was cleaved and the resulting alcohol converted to tosylate **1.29**. The TBS protected alcohol was then unmasked, allowing an intramolecular nucleophilic displacement which formed the *bis*-THF compound **1.30**.

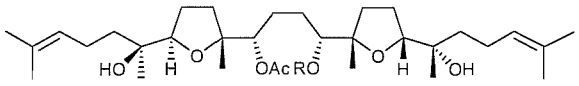


Scheme 1.4 *Reagents and conditions:* a) **1.27**, (*S*,*S*)-1,2-diaminocyclohexane triflamide, $Ti(O^iPr)_4$, $PhCH_3$, –20 °C; b) TBSCl, imidazole, DMF; c) H_2/Pd-C, EtOAc-EtOH; d) TsCl, py; e) TBAF, THF, 50 °C; f) **1.31**, LDA, THF, –78 °C; g) TBAF, THF; h) $(CF_3CO)_2O$, NEt_3, CH_2Cl_2; i) HCl, THF, MeOH.

The aldol product resulting from reaction between the enolate of **1.30** and aldehyde **1.31** was desilylated, cyclising to diastereomeric lactone **1.32**. Finally, this underwent dehydration and global deprotection to give squamostatin-D (**1.18**).

1.3.3 Triterpene polyethers (+)-eurylene and (+)-14-deacetyleurylene

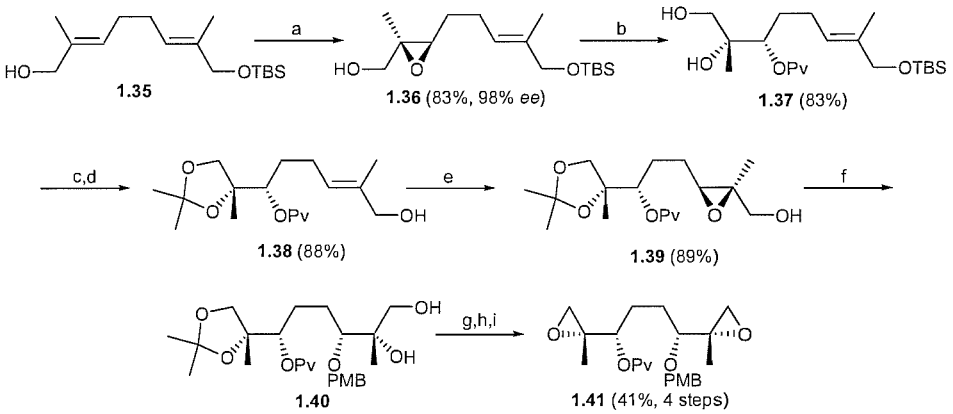
The triterpene polyethers (+)-eurylene (**1.33**) and (+)-14-deacetyleurylene (**1.34**) have in common a non-adjacent *bis*-THF core (Figure 1.5).



(+)-Eurylene (**1.33**), R = Ac
(+)-14-Deacetyleurylene (**1.34**), R =H

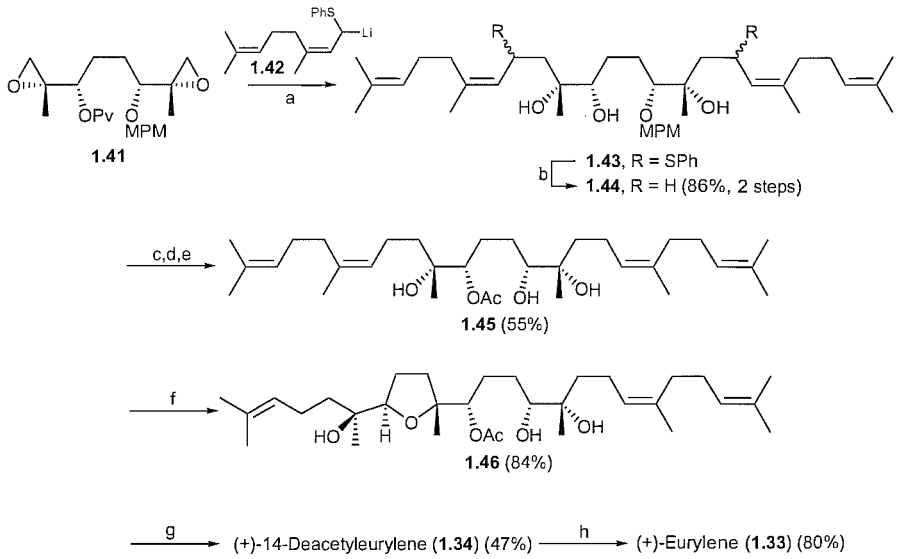
Figure 1.5 Triterpene polyethers (+)-eurylene (**1.33**) and (+)-14-deacetyleurylene (**1.34**).

In 2000, Morimoto *et al* reported an elegant synthesis of both natural products in which a functionalised core fragment was extended symmetrically.[22] The core was constructed by subjecting readily available allyl alcohol **1.35** to Sharpless asymmetric epoxidation (Scheme 1.5). The resulting epoxide **1.36** was then opened with pivalic acid.



Scheme 1.5 *Reagents and conditions:* a) ^{t}BuOOH, Ti(O^{i}Pr)$_4$, D-(–)-DET, MS 4 Å, CH_2Cl_2, –20 °C; b) Ti(O^{i}Pr)$_4$, PivOH, C_6H_6, 0 °C; c) 2,2-dimethoxypropane, CSA, CH_2Cl_2, 0 °C; d) TBAF, THF; e) ^{t}BuOOH, Ti(O^{i}Pr)$_4$, L-(–)-DET, MS 4 Å, CH_2Cl_2, – 20 °C; f) Ti(OMPM)$_4$, PMBOH, C_6H_6, 60 °C; g) AcOH-H_2O (4:1); h) MsCl, py, CH_2Cl_2, 0 °C; i) K_2CO_3, MeOH.

Diol **1.37** was protected and the silyl ether removed to give allyl alcohol **1.38**, which again underwent asymmetric epoxidation to **1.39**. The epoxide was opened with 4-methoxyphenylmethoxide. The acetonide was then hydrolysed and the resulting *bis*-1,2-diol underwent *bis*-mesylation at the primary positions. Under basic conditions the *bis*-epoxide core **1.41** was formed. The *bis*-epoxide was extended bidirectionally by *bis*-addition of **1.42** (Scheme 1.6). The sulfides in **1.43** were removed by reduction. The secondary free hydroxy was acylated then the PMB protecting group was removed in two steps to give **1.45**.



Scheme 1.6 *Reagents and conditions:* a) TMEDA, THF, –78 °C; b) Na, THF, ^{i}PrOH, reflux; c) Ac_2O, py; d) DDQ, MS 4 Å, CH_2Cl_2, 0 °C; e) AcOH-H_2O (4:1); f) [$(CF_3CO_2)ReO_3 \cdot 2CH_3CN$], TFAA, CH_2Cl_2, CH_3CN, 40 °C; g) PCC, CH_2Cl_2; h) Ac_2O, py.

Regioselective oxidative cyclisation with an oxorhenium(VII) complex gave the *trans*-THF product **1.46**. This was followed by exposure to chromium(VI), which caused a second oxidative cyclisation, this time with *cis*-diastereoselectivity, to give (+)-14-deacetyleurylene (**1.34**). This was simply acylated to produce (+)-eurylene (**1.33**).

1.3.4 Bullatanocin (squamostatin-C)

In 2003, Zhu and Mootoo constructed the non-adjacent *bis*-THF core of bullatanocin (**1.47**) (Figure 1.6) by coupling two preformed THF-containing units.[23]

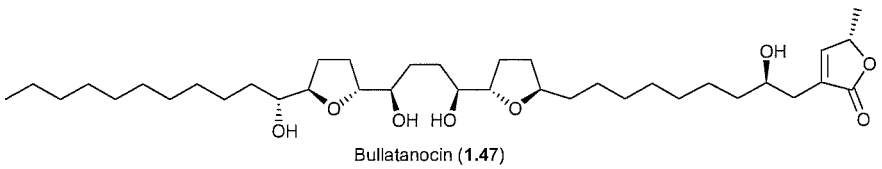
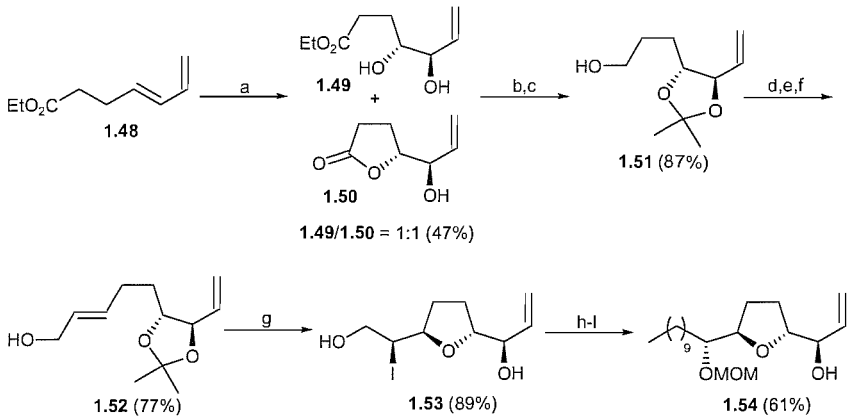


Figure 1.6 The *Annonaceous* acetogenin bullatanocin (**1.47**).

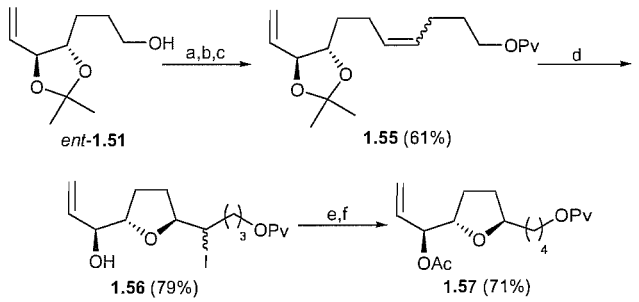
1,3-Diene **1.48** was the basis of both THF units. For the first fragment, **1.48** underwent Sharpless asymmetric dihydroxylation to give a regiomeric mixture of products. The diol **1.49** and lactone **1.50** were the desired products arising from dihydroxylation of the internal olefin (Scheme 1.7). A mixture of **1.49** and **1.50** was

reduced to give a single triol, then the 1,2-diol was protected, affording **1.51**. The enantiomer of **1.51**, to be used later, was prepared in the same way, except with the use of AD-mix-α in the dihydroxylation.



Scheme 1.7 *Reagents and conditions:* a) AD-mix-β, ^{t}BuOH, H_2O, $MeSO_2NH_2$; b) DIBAL-H, THF, –78 °C; c) 2,2-dimethoxypropane, CSA, CH_2Cl_2; d) PCC, CH_2Cl_2; e) $Ph_3P{=}CHCO_2Me$, CH_3CN, reflux; f) DIBAL-H, CH_2Cl_2, –78 °C; g) iodonium dicollidine perchlorate, CH_3CN; h) K_2CO_3, MeOH; i) TBSCl, imidazole, CH_2Cl_2; j) $CH_3(CH_2)_8MgBr$, CuBr, THF, 0 °C; k) MOMCl, $^i Pr_2NEt$, CH_2Cl_2; l) TBAF, THF.

Alcohol **1.51** was oxidised, olefinated and reduced to give (*E*)-allyl alcohol **1.52**. This underwent Zhu and Mootoo's iodoetherification reaction to give **1.53** as a single diastereomer. A long alkyl chain was then installed *via* an epoxide intermediate to give fragment **1.54**.

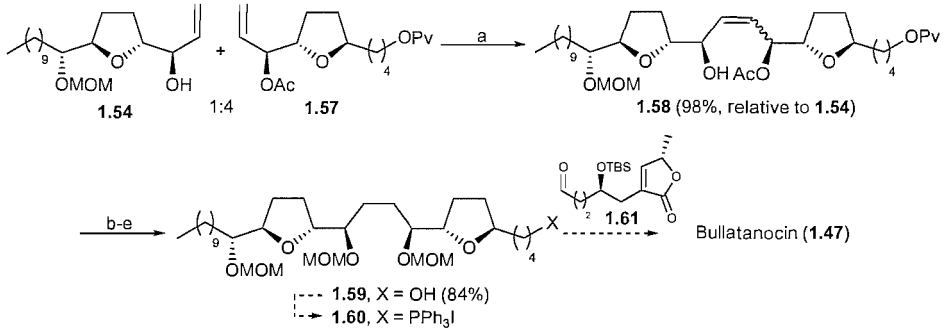


Scheme 1.8 *Reagents and conditions:* a) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, –78 °C; b) $Ph_3P{=}CH(CH_2)_3OLi$, $PhCH_3$, –78 °C; c) PivCl, py, DMAP; d) iodonium dicollidine perchlorate, CH_3CN; e) Bu_3SnH, AIBN, $PhCH_3$, reflux; f) Ac_2O, EtOAc, DMAP.

The enantiomer of **1.51** was the source of the second THF fragment. It was oxidised, olefinated and pivalylated to give **1.55** (*Z*/*E* 3:1) (Scheme 1.8). This underwent the iodoetherification reaction as before, affording cyclised product **1.56** as a mixture of

diastereomers. The desired *trans*-THF geometry was obtained in a ratio of *trans*/*cis* 11:1. The *trans*-THF product was converted to **1.57** by radical reduction of the iodide then acylation of the allylic alcohol.

It was hoped that the fragments **1.54** and **1.57** could be tethered *via* the allylic alcohols of each, then ring-closing metathesis could be used to fuse the units. However, problems with this approach meant that cross-metathesis was actually used (Scheme 1.9).

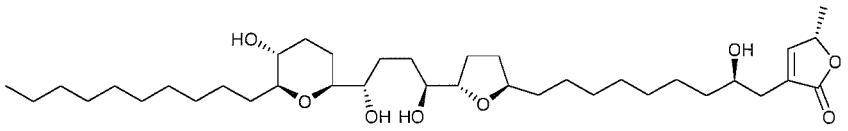


Scheme 1.9 *Reagents and conditions:* a) $Cl_2(Cy_3P)(IMes)Ru{=}CHPh$, CH_2Cl_2, reflux; b) H_2/Pd-C, EtOAc; c) K_2CO_3, MeOH; d) MOMCl, $^iPr_2NEt$, CH_2Cl_2; e) NaOMe, MeOH.

To avoid excessive *homo*-coupling, a 4-fold excess of **1.57** was needed. The desired product **1.58** was obtained in a yield of 98% (based on consumption of **1.54**) or 46% (based on consumption of **1.57**), with little of the homodimer observed. *Bis*-THF compound **1.58** was hydrogenated, deacylated, *bis*-MOM protected and depivalylated to give the bullatanocin core **1.59**. This was as far as Zhu and Mootoo took the work, but they explained that alcohol **1.60** could be converted to the corresponding phosphonium salt then undergo a Wittig reaction with the known butenolide-containing fragment **1.61**.[24] This would give an intermediate that could easily be converted to bullatanocin (**1.47**).

1.3.5 (–)-Mucocin

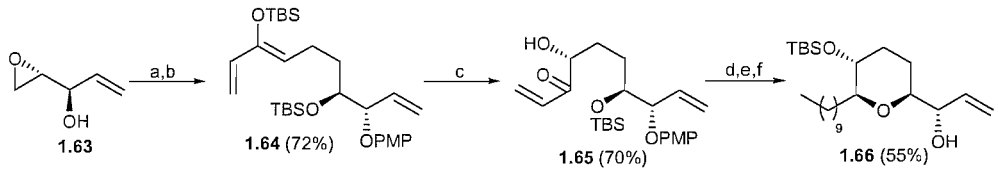
(–)-Mucocin (**1.62**) is not typical of the compounds in this discussion in that its core features non-adjacently linked THF and THP rings (Figure 1.7), but it presents a similar synthetic challenge.



(–)-Mucocin (**1.62**)

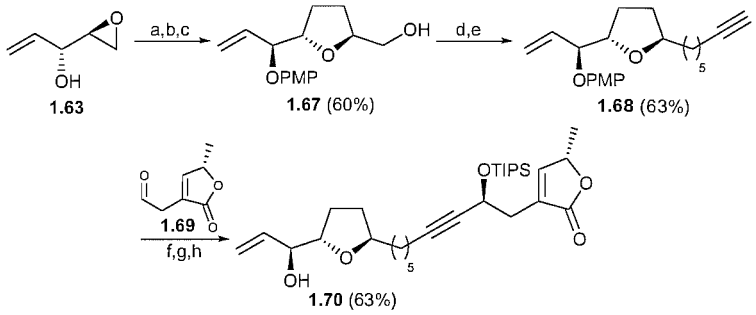
Figure 1.7 The *Annonaceous* acetogenin (–)-mucocin (**1.62**).

Evans *et al* published their synthesis of (–)-mucocin in 2003.[25] Their strategy was to link a THF fragment and a THP fragment using a tethered metathesis reaction. The starting material for both parts was known epoxide **1.63**. For the THP fragment, the allylic alcohol in **1.63** was inverted then the epoxide was opened with a homoenolate equivalent (Scheme 1.10). The resulting secondary alcohol was protected, giving **1.64**. Chemoselective Sharpless asymmetric dihydroxylation provided enone **1.65** (>99:1 dr). An alkyl chain was installed by conjugate addition, then treatment with $BiBr_3$ and *t*-butyldimethylsilane caused cyclisation to the THP by diastereoselective reductive etherification.[26] Protection of the secondary alcohol then PMP ether cleavage produced THP unit **1.66**. The reductive etherification with $BiBr_3$ is thought to proceed by *in situ* silyl-deprotection then condensation of the liberated hydroxyl onto the ketone giving a THP-derived oxonium species. This is reduced diastereoselectively by ^{t}BuMe$_2$SiH, the stereochemical outcome of which has been discussed by Woerpel *et al*.[27]



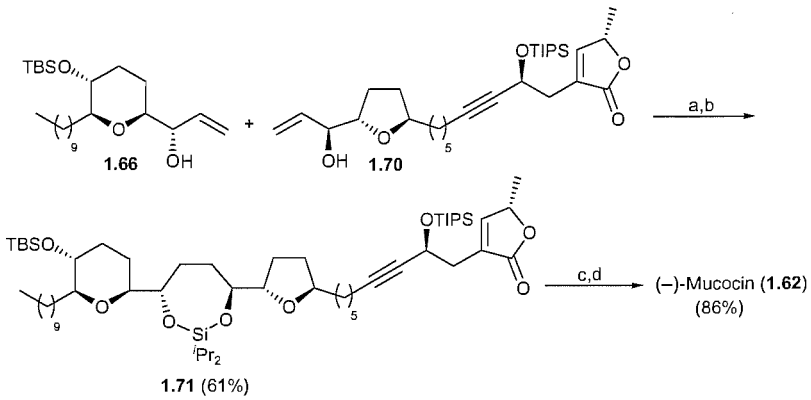
Scheme 1.10 *Reagents and conditions:* a) *p*-MeOC$_6$H$_4$OH, DIAD, PPh$_3$, THF, 0°C; b) (CH$_2$=CH)$_2$CHOTBS, *s*-BuLi, THF, –78 °C then TBSOTf, 2,6-lutidine, –78 to 0 °C; c) AD-mix-α, ^{t}BuOH, H$_2$O, MeSO$_2$NH$_2$, 0 °C; d) CH$_3$(CH$_2$)$_7$MgBr, CuCN, THF, –78 °C; e) $BiBr_3$, ^{t}BuMe$_2$SiH, MeCN, 0 °C then 2,6-lutidine, TBSOTf, 0 °C; f) (NH$_4$)$_2$Ce(NO$_3$)$_6$, MeCN, H$_2$O, –5 °C.

To make the THF portion, **1.63** was again inverted then the epoxide was opened with allylmagnesium bromide/CuCN (Scheme 1.11). This underwent a cobalt(II)-catalysed oxidative cyclisation to give the *trans*-THF **1.67** (19:1 dr). The residual primary alcohol was activated and displaced by an alkyl group featuring a silyl-protected terminal alkyne. *In situ* silyl cleavage provided **1.68**.



Scheme 1.11 *Reagents and conditions:* a) *p*-$MeOC_6H_4OH$, DIAD, PPh_3, THF, 0°C; b) CH_2=$CHCH_2MgBr$, CuCN, Et_2O, –78 °C; c) $Co(modp)_2$, O_2, ^tBuOOH, ^iPrOH, 60 °C; d) Tf_2O, NEt_3, CH_2Cl_2, –78 °C; e) $TMSC{\equiv}C(CH_2)_4MgBr$, CuI, THF, –20 °C then MeOH, TBAF, –20 °C to rt; f) $ZnEt_2$, $PhCH_3$, reflux, then (*R*)-BINOL, $Ti(O^iPr)_4$, THF, **1.69**, 0 °C; g) TIPSOTf, py, DMAP, THF, 0 °C; h) $(NH_4)_2Ce(NO_3)_6$, MeCN, H_2O, –10 °C.

Alkyne **1.68** was added enantioselectively to the butenolide-containing fragment **1.69**, which was constructed from (*S*)-propylene oxide, to give **1.70**. This completed the right-hand part of the target molecule.



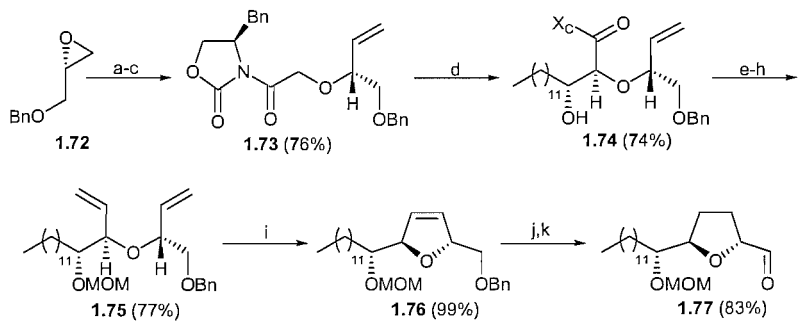
Scheme 1.12 *Reagents and conditions:* a) **1.66**, $^iPr_2SiCl_2$ (xs), CH_2Cl_2, imidazole, 0 °C to rt then **1.70**, imidazole, 0 °C to rt; b) 1.8 equiv. $Cl_2(Cy_3P)_2Ru$=CHPh, 1,2-dichloro-ethane, reflux; c) HF, MeCN, CH_2Cl_2; d) $TsNHNH_2$, NaOAc, 1,2-DME, H_2O, reflux.

In order to join the THP and THF/butenolide fragments, they were tethered by means of a diisopropylsilyl group (Scheme 1.12). The ring-closing metathesis reaction to fuse the two parts proceeded in 83% yield but required 1.8 equiv. of Grubbs' ruthenium complex. Finally, global deprotection and hydrogenation afforded (–)-mucocin (**1.62**).

1.3.6 (+)-Gigantecin

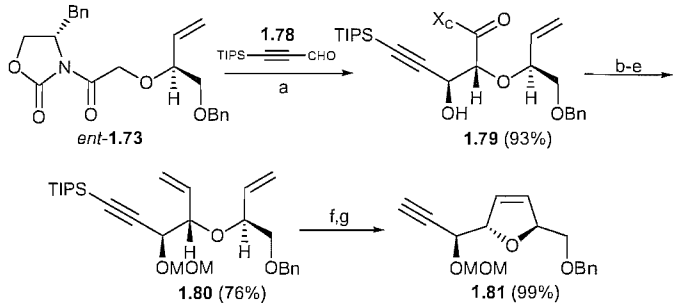
(+)-Gigantecin (**1.3**) is identical in structure to (+)-4-deoxygigantecin (**1.2**) (Figure 1.3), except for the presence of a hydroxyl near the butenolide. The approach to (+)-gigantecin published by Crimmins and She in 2004 invloved the construction and coupling of two THF-containing units, followed by introduction of a butenolide portion.[28] Each part was made by asymmetric alkylation of glycolates.

Epoxide **1.72** was homologated to an allylic alcohol which was alkylated with bromoacetate (Scheme 1.13). The resulting carboxylic acid was converted to oxazolidione glycolate **1.73**. This underwent an aldol reaction with tridecanal, giving **1.74** (>15:1 dr).



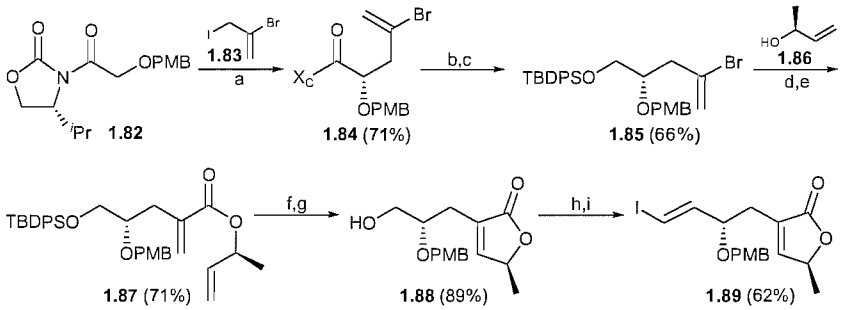
Scheme 1.13 *Reagents and conditions:* a) Me_3SI, ^nBuLi, THF, –10 °C; b) NaH, $BrCH_2CO_2H$, THF; c) Me_3CCOCl, NEt_3, THF, – 78 °C to 0 °C then (*S*)-lithio-4-benzyl-oxazolidin-2-one; d) tridecanal, $TiCl_4$, $^iPr_2NEt$, *N*-methyl-2-pyrrolidinone, CH_2Cl_2, –40 °C; e) MOMCl, $^iPr_2NEt$, DMAP, CH_2Cl_2; f) $LiBH_4$, MeOH, Et_2O, 0 °C; g) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2; h) $Ph_3P{=}CH_2$, THF; i) $Cl_2(Cy_3P)(IMes)Ru{=}CHPh$, CH_2Cl_2, reflux; j) H_2/Pd-C, EtOH; k) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2.

Epoxide **1.72** was homologated to an allylic alcohol which was alkylated with bromoacetate (Scheme 1.13). The resulting carboxylic acid was converted to oxazolidione glycolate **1.73**. This underwent an aldol reaction with tridecanal, giving **1.74** (>15:1 dr). The amide was then reduced to an alcohol, oxidised and olefinated to give diene **1.75**. Ring-closing metathesis afforded **1.76**, which was subsequently hydrogenated to give a THF ring and cleave the benzyl ether. The resulting hydroxyl was oxidised to aldehyde **1.77**, the first of the THF fragments.



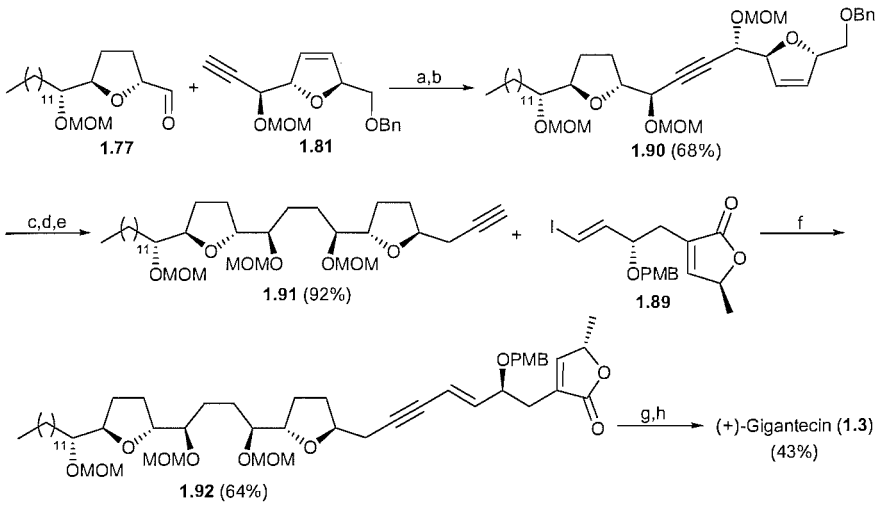
Scheme 1.14 *Reagents and conditions:* a) $TiCl_4$, $^iPr_2NEt$, *N*-methyl-2-pyrrolidinone, CH_2Cl_2, –40 °C; b) MOMCl, $^iPr_2NEt$, DMAP, CH_2Cl_2; c) $LiBH_4$, MeOH, Et_2O, 0 °C; d) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2; e) $Ph_3P{=}CH_2$, THF; f) $Cl_2(Cy_3P)(IMes)Ru{=}CHPh$, CH_2Cl_2, reflux; g) TBAF, THF.

The second fragment **1.81** was made by aldol reaction of *ent*-**1.73** with aldehyde **1.78** (>20:1 dr) (Scheme 1.14). This was converted to dienyne **1.80** as before. Ring-closing metathesis then silyl removal gave **1.81**.



Scheme 1.15 *Reagents and conditions:* a) NaHMDS, THF, –78 °C; b) $NaBH_4$, THF, H_2O; c) TBDPSCl, imidazole, CH_2Cl_2; d) ^{t}BuLi, CO_2, THF, –78 °C; e) **1.86**, DEAD, PPh_3, THF; f) $Cl_2(Cy_3P)(IMes)Ru{=}CHPh$, CH_2Cl_2, reflux; g) HF-NEt_3, CH_3CN; h) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2; i) CHI_3, $CrCl_2$, THF.

The butenolide fragment was formed by asymmetric alkyation of **1.82** with iodide **1.83** (98:2 dr) (Scheme 1.15). The product **1.84** was reduced and protected to give **1.85**. This underwent halogen-metal exchange then CO_2 was added to give an acid which reacted with chiral alcohol **1.86** under Mitsunobu conditions, affording diene **1.87**. Ring-closing metathesis formed the butenolide ring then silyl ether cleavage gave **1.88**. This was then oxidised and submitted to Takai olefination to produce vinyl iodide **1.89**.



Scheme 1.16 *Reagents and conditions:* a) $Zn(OTf)_2$, (–)-*N*-methylephedrine, $PhCH_3$; b) MOMCl, $^iPr_2NEt$, DMAP, CH_2Cl_2; c) H_2/Pd-C, EtOH; d) Tf_2O, NEt_3, CH_2Cl_2, –78 °C; e) $Me_3SiC{\equiv}CH$, ^{n}BuLi, THF, HMPA, –78 °C then MeOH, rt; f) $Pd(PPh_3)_4$, CuI, $^iPr_2NEt$, THF; g) H_2, $Rh(PPh_3)_3Cl$, LiI, C_6H_6, EtOH; h) $BF_3{\cdot}Et_2O$, Me_2S, 0 °C.

The two THF units were combined using Carreira's method for asymmetric addition of an acetylide to an aldehyde. This gave the product as a single diastereomer. After MOM protection, **1.90** was hydrogenated with concurrent benzyl ether cleavage. The resulting free alcohol was triflylated and displaced by acetylide to give **1.91**. This underwent Sonogashirà coupling with the butenolide fragment **1.89**, leading to enyne **1.92**. Hydrogenation and global deprotection produced (+)-gigantecin (**1.3**).

1.4 Conclusions

The *Annonaceous* acetogenins have attracted great interest due to their wide range of biological activities and their cytotoxicity in particular. Syntheses of non-adjacent *bis*-THF acetogenins have been achieved by a variety of interesting strategies, but there are a number of issues: long routes; extensive use of protecting groups; and the use of metathesis to fuse two THF-containing fragments, though attractive, is troublesome.

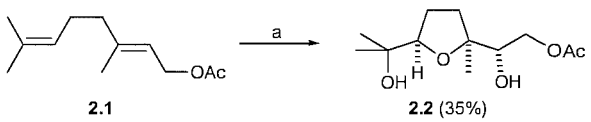
Chapter 2 Transition metal-mediated oxidative cyclisation

Tetrahydrofuran (THF) and tetrahydropyran (THP) rings are key structural and functional features of many biologically active molecules such as polyethers and marine natural products.[29,30] A number of transition metal oxidants are known to convert simple unsaturated substrates to THF and THP fragments. There follows a discussion of those metal-oxo complexes that transform dienes and hydroxyalkenes into saturated oxygen-heterocycles, focussing on development, mechanism, stereochemical outcome and synthetic applications.

2.1 Oxidative cyclisation of dienes

2.1.1 Potassium permanganate

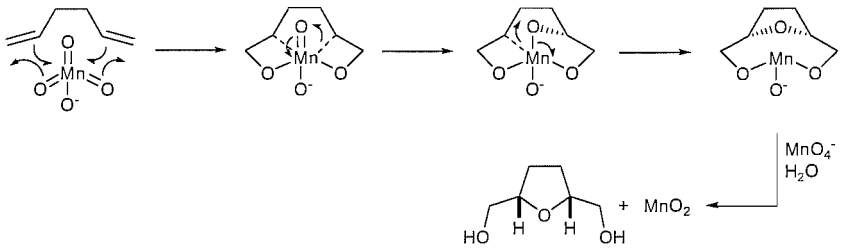
The oxidation of a 1,5-diene by permanganate was first reported in 1924 by Kötz and Steche, but they were unable to identify the product.[31] Their work was revisited in 1965 by Klein and Rojahn who identified the prouct of oxidation of geranyl acetate (**2.1**) as *cis*-THF-diol **2.2** (Scheme 2.1).[32] It appeared that all the oxygen atoms had been delivered from the same face.



2.1 **2.2** (35%)

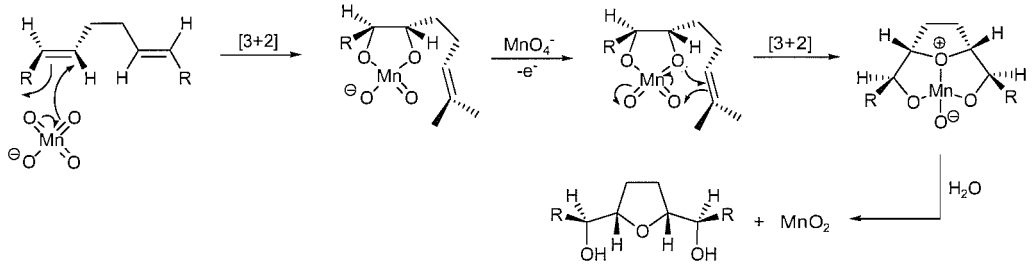
Scheme 2.1 *Reagents and conditions:* a) $KMnO_4$, acetone, H_2O, CO_2 ebullition.

Walba and Baldwin independently recognised the potential power of this reaction, in that it was possible to create four new stereogenic centres, and both published their thoughts on the mechanism in 1979. Walba's suggested mechanism involved two [2+2] cycloadditions of Mn=O to the two olefins from one face, then two alkyl migrations with retention and finally release of MnO_2 (Scheme 2.2).[33]



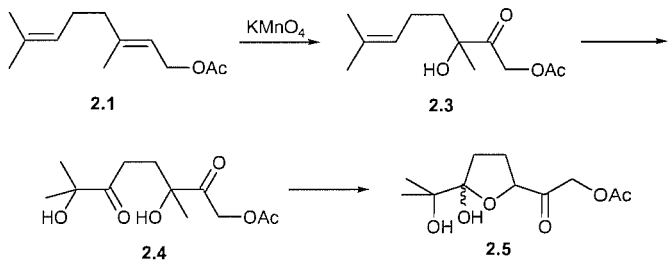
Scheme 2.2 Walba's proposed mechanism for oxidative cyclisation.

Baldwin's mechanism involves a [3+2] cycloaddition of permanganate to one olefin, giving an unreactive Mn(V) ester. This is oxidised to a Mn(VI) species which can undergo a second [3+2] cycloaddition to the second olefin from the same face. Hydrolysis releases MnO_2 and the *cis*-THF-diol (Scheme 2.3).[34]



Scheme 2.3 Baldwin's proposed mechanism for oxidative cyclisation.

Of the two, Baldwin's mechanism is more feasible because there is indirect evidence of the presence of a Mn(V) ester.[35,36] Mysteriously, Wolfe and Ingold found that the use of ^{18}O enriched water as the reaction solvent led to incorporation of ^{18}O into the product.[36] Neither of the above mechanisms can account for this, and there is still no definitive explanation.

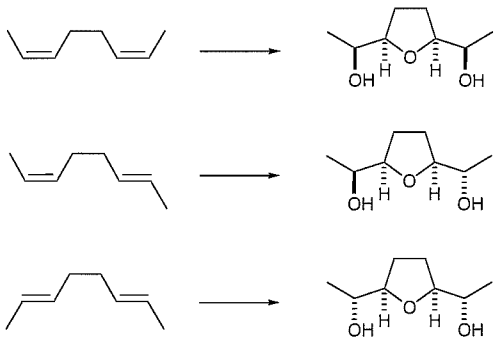


Scheme 2.4 Side reactions in the oxidative cyclisation.

A number of possible side reactions mean the yield of the oxidative cyclisation product is generally not very high. Using geranyl acetate (**2.1**) to illustrate this point, if the intermediate arising from the initial [3+2] cyclisation is hydrolysed, the result is

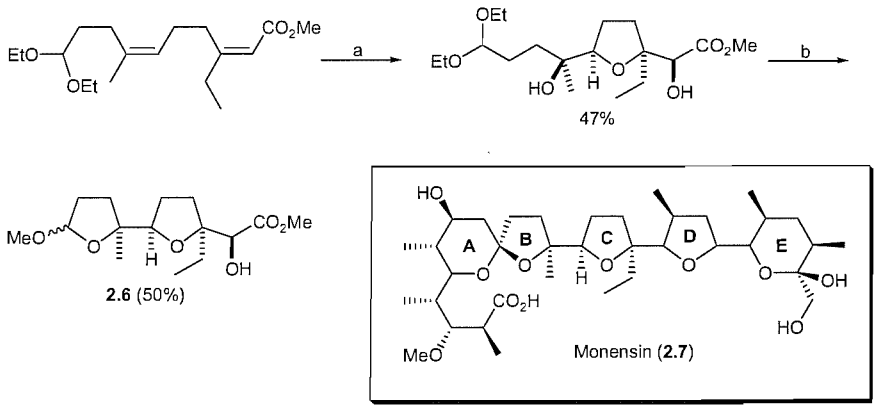
an α-hydroxyketone **2.3**. Oxidation and hydrolysis of the second olefin can give *bis*-α-hydroxyketone **2.4** which can finally cyclise to lactol **2.5** (Scheme 2.4).

Walba *et al* demonstrated that varying the alkene geometries led to all possible 2,5-*cis*-disubstituted THF relative configurations (Scheme 2.5).[33] They also found at least a 97:3 preference for the *cis*-THF arrangement over the *trans*-THF.



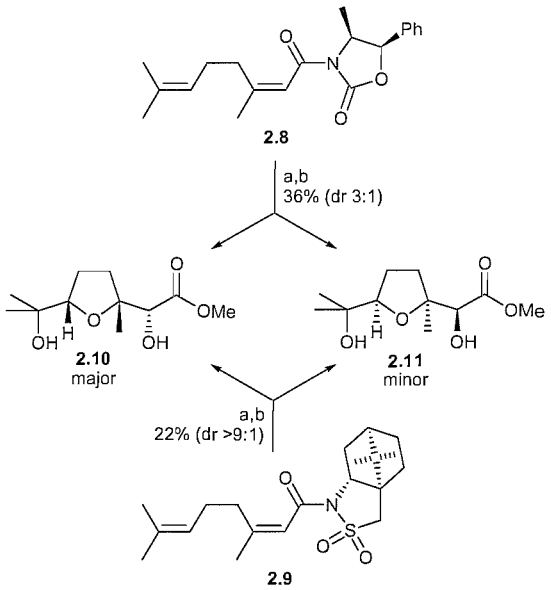
Scheme 2.5 Control of relative stereochemistry.

Walba then used this chemistry to construct the BC-ring fragment **2.6** (Scheme 2.6) of the ionophore monensin (**2.7**).[37]



Scheme 2.6 *Reagents and conditions:* a) $KMnO_4$, 10% aq. acetone, CO_2 ebullition, –30 °C; b) $HC(OMe)_3$, C_6H_6, TsOH.

Walba knew that to exploit the reaction to the full, the face of initial attack by permanganate, and thus the absolute stereochemistry of the product, would have to be controlled. Permanganate reacts preferentially at the most electron-deficient alkene due to electronic effects.[38-40] Thus neroates **2.8** and **2.9**, featuring Evans' oxazolidinone[41] and Oppolzer's camphorsultam[42] attached to the more reactive enoate alkene, were studied.[43]

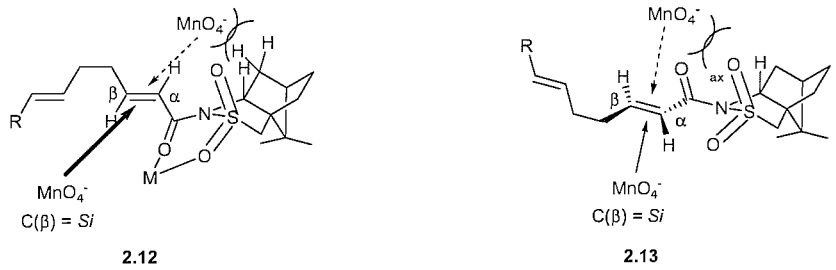


Scheme 2.7 *Reagents and conditions:* a) $KMnO_4$, acetone, H_2O, CO_2 ebbulition; b) CH_3OMgBr.

Walba found that Evans' auxiliary gave a relatively disappointing 3:1 selectivity for diasteromer **2.10**. This is due to the need for Lewis acid chelation to achieve good facial selectivity; since K^+ is a poor Lewis acid, and the reaction was carried out in a polar solvent, selectivity was low. Promisingly, Oppolzer's auxiliary promoted *Re* face attack to give a very useful diastereoselectivity of >9:1 for **2.10**. This can be rationalised by considering the following aspects of the reactive conformation of the substrate:[44]

- Conformation of CO-CC bond: of the two rotamers that allow π-conjugation, the *s-cis*-orientation is favoured for steric reasons (O < NR_2) and because (*Z*)-enolates of amides are more stable than (*E*)-enolates.
- The carbonyl group must be parallel or anti-parallel to the N-S bond in order to achieve mesomeric stabilisation with the nitrogen lone pair.
- In the most favoured conformation, the chiral auxiliary blocks one face of the alkene from attack.

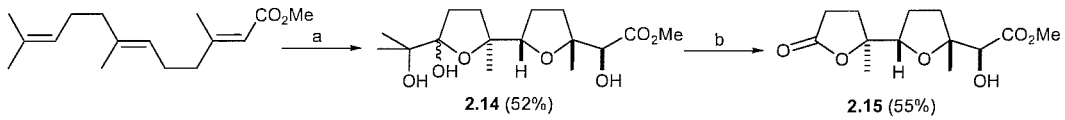
With a Lewis acid the reactive species is chelate **2.12**, where there is a *syn*-relationship between the C=O and SO_2, resulting in the back face being blocked so attack occurs at the C(β) *Si*-face (Scheme 2.8).



Scheme 2.8 Control of facial selectivity.

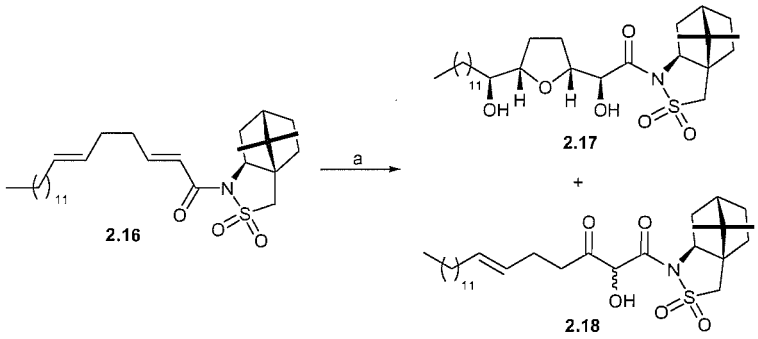
In the absence of a Lewis acid the *anti*-relationship between the C=O and SO_2 is favoured, both sterically and electronically, giving transition state **2.13**. In this case the *pseudo*-axial S=O blocks the top face and attack occurs from the C(β) *Si*-face. Note that the same face is attacked, whether or not a Lewis acid is present. An important application of this chemistry was in the total synthesis of the polyether ionophore salinomycin by Kocienski *et al.*[45]

Early work in our group investigated the permanganate-promoted oxidative cyclisation of 1,5,9-trienes,[46,47] with the result that, at the optimal pH 6.5, the yield of THF-lactol **2.14** was 52%. This arises from oxidative cyclisation as usual, then oxidation of the remaining olefin and cyclisation. THF-lactol **2.14** then underwent oxidative cleavage to the synthetically useful THF-lactone **2.15** (Scheme 2.9).



Scheme 2.9 *Reagents and conditions:* a) 3 equiv. $KMnO_4$, 4 equiv. AcOH, pH 6.2 buffer, acetone-H_2O, –20 °C; b) $NaIO_4/SiO_2$, CH_2Cl_2.

The above conditions, which worked well for trisubstituted olefins, were applied to dienoyl sultam **2.16** (featuring disubstituted alkenes) in our group's synthesis of the *mono*-THF *Annonaceous* acetogenin *cis*-solamin.[48,49] The required THF-diol **2.17** was obtained in only 21% yield (dr 6:1) (entry 1, Table 2.1), along with the α-hydroxyketone by-product **2.18** in 40% yield (Scheme 2.10). Indeed, others had reported that the oxidative cyclisation of 1,5-dienes with *mono*- and disubstituted olefins is much less efficient than with trisubstituted olefins.[34,50,51]



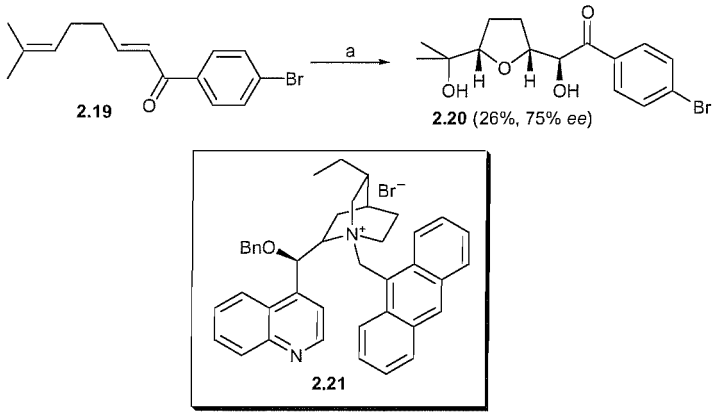
Scheme 2.10 *Reagents and conditions:* a) 1.4 equiv. $KMnO_4$, see Table 2.1 for other conditions.

Entry	Solvent	AcOH	**2.17** (dr)[a]
1	acetone/H_2O/pH 6.5 buffer	3 equiv	21% (6:1)
2[b]	CH_2Cl_2	8 equiv	31% (6:1)
3[b]	Toluene	8 equiv	50% (n/a)
4[b]	EtOAc	8 equiv	55% (6:1)
5[b]	acetone	16 equiv	62% (6:1)
6[b]	acetone	co-solvent[c]	75% (6:1)[d]

Table 2.1 Oxidative cyclisation conditions. [a] Ratio from ^1H NMR. [b] 10 mol% adogen 464 added. [c] Acetone/AcOH (3:2). [d] Reaction without adogen 464 gave similar results.

The low yield was thought to be due to substrate insolubility so a phase transfer-catalyst (adogen 464) was introduced. This, along with varying the solvent and increasing the amount of AcOH, led to vastly improved yields (Table 2.1). In fact, when AcOH was used as a co-solvent with acetone (2:3 mixture), the yield was excellent given the level of complexity introduced (entry 6, Table 2.1). Also, both the substrate and $KMnO_4$ were soluble in this solvent system so the phase-transfer catalyst was no longer required. The diastereoselectivity of 6:1 remained constant for reactions run in solvent systems of differing polarity, suggesting that chelation control is not a dominant factor in determining the face of initial attack; this supports the non-chelated transition state model **2.13** (Scheme 2.8).

A further method for controlling facial selectivity was developed in our group. Using the chiral tertiary ammonium salt **2.21** a number of phenone dienes underwent phase-transfer permanganate-mediated oxidative cyclisation.[52] For example, 1,5-diene **2.19** was converted to THF diol **2.20** with 75% *ee* (Scheme 2.11).

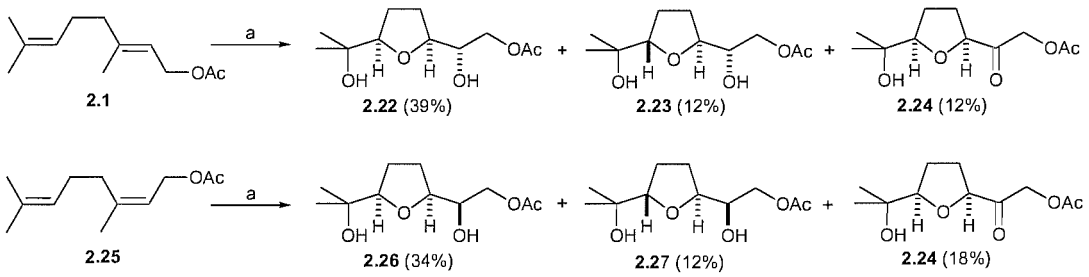


Scheme 2.11 *Reagents and conditions:* a) 1.6 equiv. $KMnO_4$, 6.5 equiv. AcOH, 10 mol% **2.21**, CH_2Cl_2, –30 °C.

More recently we have published the use of the permanganate-mediated oxidative cyclisation in the construction of *bis*-THF fragments which have been used in the synthesis of *Annonaceous* acetogenins such as membranacin[53] and 21,22-diepi-membrarollin.[54]

2.1.2 Ruthenium tetroxide

In their 1981 report on the catalytic oxidative cleavage of olefins by RuO_4, Sharpless *et al* unexpectedly observed that geranyl acetate (**2.1**) and neryl acetate (**2.25**) underwent a permanganate-type oxidative cyclisation to give THF-diols **2.22**, **2.23**, **2.26** and **2.27**, and the ketone by-product **2.24** (Scheme 2.12).[55]

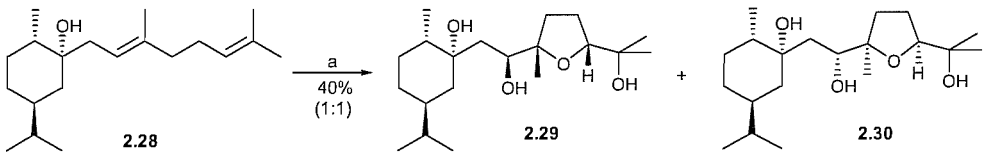


Scheme 2.12 *Reagents and conditions:* a) 2.2 mol% $RuCl_3{\cdot}(H_2O)_n$, 4.1 equiv. $NaIO_4$, CCl_4, CH_3CN, H_2O.

Interestingly, both *cis*- and *trans*-THF products were formed in significant amounts (ratio 3:1), in contrast to the permanganate variant where the *cis*-THF is very highly favoured. Sharpless suggested that ruthenium, as a second row transition metal, forms longer bonds, making accessible the geometries that lead to the *trans*-THF product. Sharpless showed that the solvent system was crucial for maintenance of the catalytic cycle. Acetonitrile was used as a co-solvent due to it being a good ligand for lower valent transition metals, and being stable under oxidising conditions (unlike commonly used ligands such as phosphines and sulfides). Acetonitrile ensures the return of ruthenium to the catalytic cycle by disrupting inactive ruthenium by-product complexes.

In 2001 improved procedures, featuring finely tuned solvent systems, were published by Sica *et al*[56] and Piccialli *et al*[57] Sica used a combination of 5 mol% $RuO_2 \cdot 2H_2O$ and 2.5 equiv. $NaIO_4$ in EtOAc/$(CH_3)_2CO$/H_2O whereas Piccialli's work offered better yields using 4 mol% $RuO_2 \cdot 2H_2O$ and 4 equiv. $NaIO_4$ in EtOAc/CH_3CN/H_2O. When geranyl acetate (**2.1**) was reacted under the latter conditions at 0 °C for 4 minutes, *cis*-THF **2.22** was provided in an improved 60-62% yield, *trans*-THF **2.23** was reduced to 7-9% and by-product **2.24** to 4-5%. The authors mentioned that, as with permanganate, yields were respectable only with substrates possessing at least one trisubstitued olefin.

The reaction has recently seen a flurry of interest. In 2005, as part of a study of marine natural product derivatives, Lindel *et al* converted the geraniol derivative **2.28** to the diastereomeric *cis*-THF diols **2.29** and **2.30** (dr 1:1) using Sica's conditions (Scheme 2.13).[58] Interestingly, no *trans*-THF products and no overoxidised ketone by-products were observed.

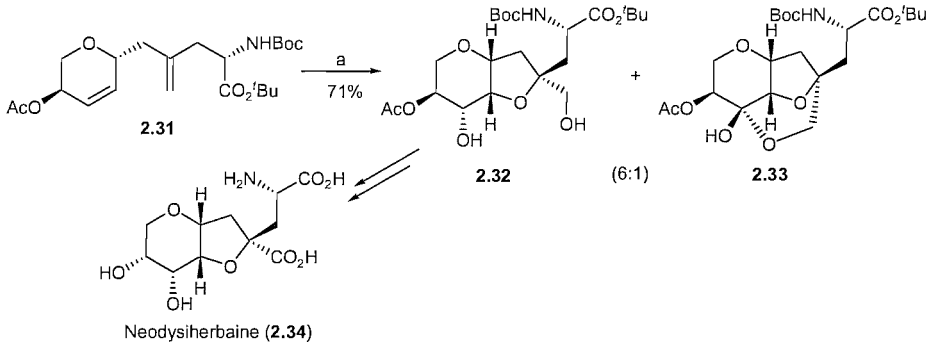


2.28 2.29 2.30

Scheme 2.13 *Reagents and conditions:* a) 5 mol% $RuO_2 \cdot 2H_2O$, 2.5 equiv. $NaIO_4$, EtOAc, acetone, H_2O.

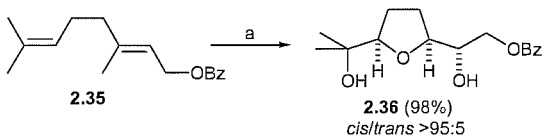
Also in 2005, Lygo *et al* demonstrated the potential of the reaction when they applied it to a very different type of 1,5-diene in their synthesis of neodysiherbaine (**2.34**).[59] The reaction of compound **2.31**, featuring a cyclic alkene, led to the fused bicyclic

product **2.32** (Scheme 2.14). A number of conditions were tried, with Sica's being the most effective.[56] The minor by-product **2.33** was also observed, arising from overoxidation. The yield is very respectable, despite both olefins being only disubstituted.



Scheme 2.14 *Reagents and conditions:* a) 5 mol% $RuO_2 \cdot 2H_2O$, 2.5 equiv. $NaIO_4$, EtOAc, acetone, H_2O.

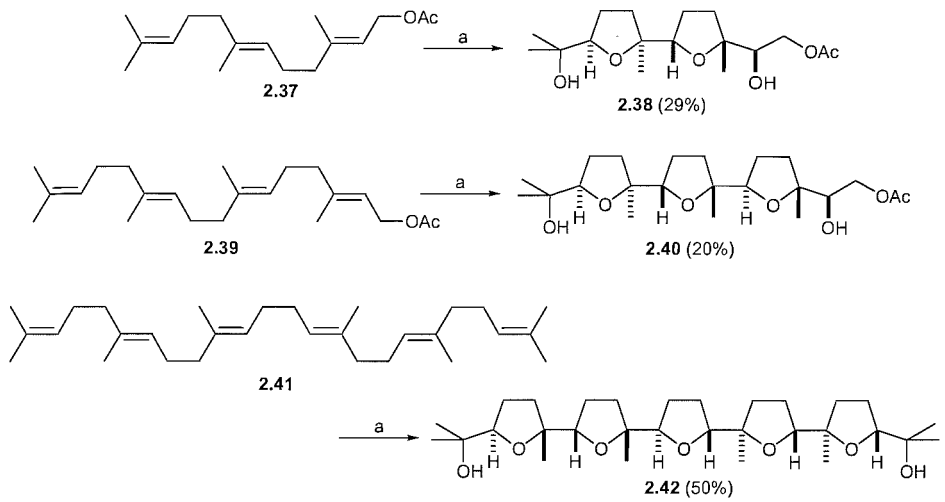
The reaction conditions were further developed by Stark *et al*, again in 2005, focusing once more on the solvent system, but also examining the use of different pre-catalysts.[60]



Scheme 2.15 *Reagents and conditions:* a) 0.2 mol% RuO_3, 3 equiv. $NaIO_4$, THF/CH_2Cl_2 (9:1), 0 °C.

It was found that the optimum solvent system was THF/CH_2Cl_2 (9:1), a previously unheard of mixture for use in this reaction. The best combination of oxidants was $RuCl_3/NaIO_4$, as originally used by Sharpless in 1981. These conditions gave massive improvements for a range of substrates and were robust on scale-up. For example geranyl benzoate (**2.35**) was converted on a gram-scale to the THF diol **2.36** in 98% yield, with a *cis*:*trans* ratio of >95:5 (Scheme 2.15). Only a trace amount of the overoxidition by-product was seen.

Piccialli *et al* have shown that RuO_4-catalysed polycyclisation can be highly efficient process.[61-63] They were able to form compounds containing 2, 3 and 5 adjacent THF rings (Scheme 2.16).

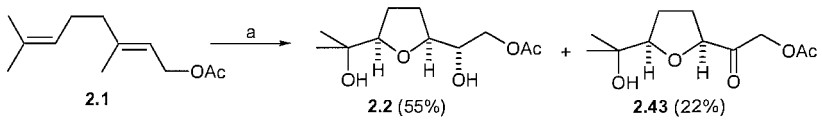


Scheme 2.16 *Reagents and conditions:* a) 20 mol% $RuO_2 \cdot 2H_2O$, $NaIO_4$ (4 equiv. for **2.37**, 5 equiv. for **2.39**, 8 equiv. for **2.41**), $EtOAc/CH_3CN/H_2O$ (3:3:1).

Initially only the configuration of the *bis*-THF product **2.38** could be elucidated,[61] with the first cyclisation giving a *cis*-THF, as would be expected, and the second also giving a *cis*-THF. Piccialli explained the result of the second cyclisation by invoking Sinha's model for the stereochemical outcome of Re(VII)-mediated tandem oxidative cyclisation of linear hydroxy polyenes (see section 2.2.3).[64] Later, however, when **2.40**[62] and **2.42**[63] had been fully characterised, Piccialli realised that Sinha's model could not explain the stereochemistry arising from branched polyene systems, and has been unable to account for the observed configurations. The 50% yield of **2.42** actually represents a highly efficient 87% for each cyclisation.

2.1.3 Perruthenate

After studying the ruthenium tetroxide-catalysed oxidative cyclisation, Piccialli went on to investigate the use of perruthenate, again with geranyl acetate (**2.1**) as a standard 1,5-diene.[65] The combination of 2 equiv. TPAP, 3 equiv. NMO and 500 equiv. AcOH in CH_2Cl_2 was found to produce reasonable yields of THF diol **2.2** (Scheme 2.17).

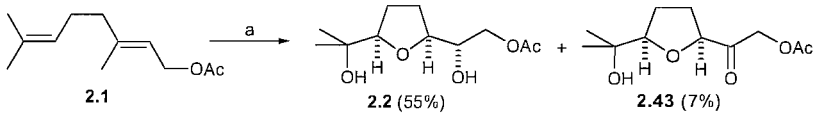


Scheme 2.17 *Reagents and conditions:* a) 2 equiv. TPAP, 3 equiv. NMO, 500 equiv. AcOH, 4 Å molecular sieves, CH_2Cl_2.

Interestingly, none of the *trans*-THF product was observed: the perruthenate method seemed to be much more selective than the RuO_4 reaction. This was true in a number of examples. AcOH was added as acidic conditions have been shown to help prevent overoxidation in OsO_4 and MnO_4^- oxidative cyclisations. Although this did work to an extent, ketone **2.43** was still formed in significant quantities. Piccialli proposed a mechanism for this reaction that followed Baldwin's reasoning for $KMnO_4$.[34]

2.1.4 Osmium tetroxide

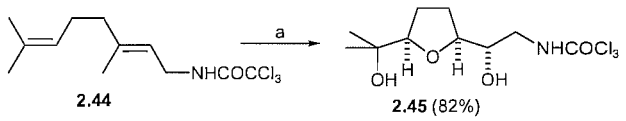
In 1998, Piccialli *et al* published the first application of OsO_4 in the oxidative cyclisation of 1,5-dienes.[66] When geranyl acetate (**2.1**) was treated with 5 mol% OsO_4 and 4 equiv. $NaIO_4$ in DMF, *cis*-THF diol **2.2** was obtained in a moderate yield, with only a small amount of the overoxidised product **2.43** formed (Scheme 2.18).



2.1 **2.2** (55%) **2.43** (7%)

Scheme 2.18 *Reagents and conditions:* a) 5 mol% OsO_4, 4 equiv. $NaIO_4$, DMF.

Around the same time, Donohoe *et al* had been investigating the use of a combination of stoichiometric OsO_4/TMEDA for hydrogen bond directed dihydroxylation. This reagent mixture effected the oxidative cyclisation of the geranyl derivative **2.44** (Scheme 2.19).[67]

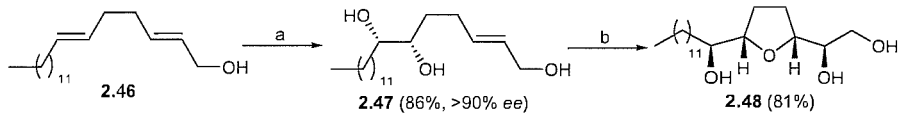


2.44 **2.45** (82%)

Scheme 2.19 *Reagents and conditions:* a) 1 equiv. OsO_4, 1 equiv. TMEDA, CH_2Cl_2, –78 °C.

The yield was very good and there was no mention of the *trans*-THF or overoxidised products. Again Baldwin's mechanism was invoked to explain the reaction.[34] Donohoe went on to develop a catalytic version of the reaction that was more general and higher yielding than Piccialli's catalytic method. On treatment with 5 mol% OsO_4 with Me_3NO as the co-oxidant under acidic conditions, geranyl benzyl ether gave solely the *cis*-THF diol in 88% yield.[68] To illustrate the generality of the reaction, a number of other 1,5-dienes were cyclised, giving the *cis*-THF diols in yields of 71-95%.

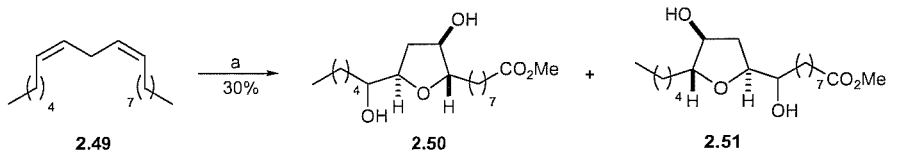
In 2005, Donohoe reported the use of his catalytic reaction in the formal asymmetric synthesis of the *Annonaceous* acetogenin *cis*-solamin.[69] Donohoe had been unable to develop an asymmetric version of the reaction, but this was overcome by first subjecting 1,5-diene **2.46** to regio- and enantioselective dihydroxylation. On exposure to the catalytic OsO_4 conditions, the chiral diol **2.47** was transformed to *cis*-THF diol **2.48**, the same product as would be obtained by direct oxidative cyclisation of **2.46** (Scheme 2.20).



Scheme 2.20 *Reagents and conditions:* a) AD-mix-α, ^{t}BuOH, H_2O, 0 °C; b) 5 mol% OsO_4, 4 equiv. Me_3NO, 6 equiv. TFA, 5 equiv. isoprene, acetone, H_2O.

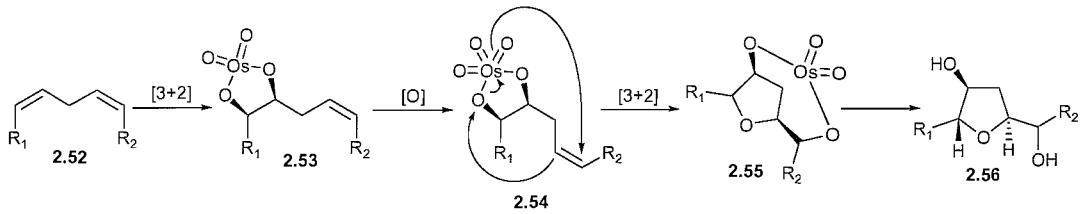
The reaction must occur by addition of the diol to an Os(VI) species to give an osmate ester. Thus the reaction was improved by inclusion of a sacrificial alkene which underwent dihydroxylation by Os(VIII), releasing the reactive Os(VI) species. This provided THF triol **2.48** in a respectable yield of 81%. This was identical to the intermediate in our group's *cis*-solamin synthesis,[48,49] and thus Donohoe's formal synthesis was complete.

Lastly, OsO_4 was employed by Borhan and Travis in an interesting oxidative cyclisation of 1,4-dienes to trisubstituted THFs.[70] Using 2.5 mol% OsO_4 with Oxone as the co-oxidant, 1,4-diene **2.49** was converted to THF products **2.50** and **2.51** (Scheme 2.21).



Scheme 2.21 *Reagents and conditions:* a) 5 mol% OsO_4, 4 equiv. Oxone, DMF.

Borhan proposed a mechanism in which the expected [3+2] cycloaddition is followed by oxidation to osmate ester **2.54** (Scheme 2.22). This then undergoes a second [3+2] cycloaddition and the final product **2.56** is released by hydrolysis. Borhan reasoned that the strained transition state in the second cycloaddition is responsible for the low yields of THF products.

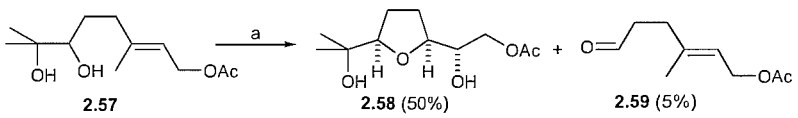


Scheme 2.22 Borhan's proposed mechanism for oxidative cyclisation of 1,4-dienes.

2.2 Oxidative cyclisation of 5-hydroxyalkenes

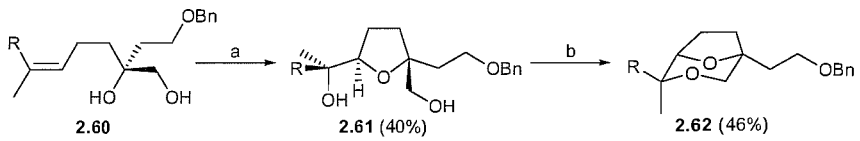
2.2.1 Chromium trioxide

Based on the earlier observation by Casida *et al* that a chromium-mediated process converted a diol derivative of a 1,5-diene to a THF-diol,[71] Walba and Stoudt investigated the action of Cr(VI) complexes on geranyl and neryl acetate diols and obtained some encouraging results.[72] For example, using CrO_3, geranyl diol derivative **2.57** was converted to *cis*-THF diol **2.58** in 50% yield and >99.5% diastereoselectivity. A small amount of the oxidative cleavage product **2.59** was also formed (Scheme 2.23). Similar results were obtained using pyridinium chlorochromate.



Scheme 2.23 *Reagents and conditions:* a) CrO_3·2py, CH_2Cl_2.

Walba realised that this reaction is in essence equivalent to the oxidative cyclisation of 1,5-dienes and proposed a mechanism involving initial addition of the diol to the Cr(VI) centre to give a Cr(VI) ester. This then proceeds to the THF product by [3+2] cycloaddition across the alkene and hydrolysis as in Baldwin's mechanism.[34]

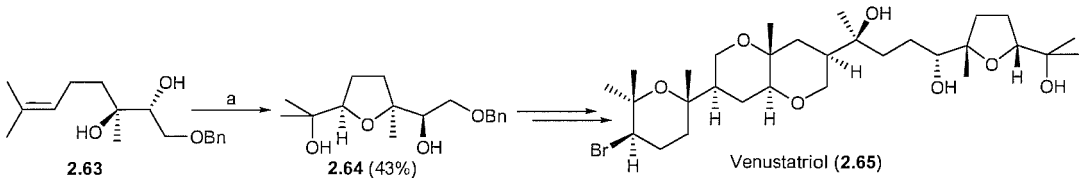


Scheme 2.24 *Reagents and conditions:* a) CrO_3·2py, CH_2Cl_2; b) (i) TsCl, py; (ii) NaH, DMF.

The reaction was later applied by Walba and Stroud in the synthesis of a biologically interesting natural product derivative.[73] The CrO_3-mediated oxidative cyclisation of

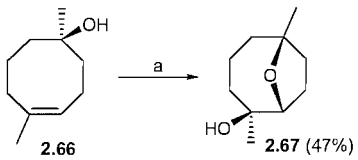
2.60 gave *cis*-THF diol **2.61** in a moderate yield (Scheme 2.24). The bicyclic compound **2.62**, an advanced intermediate in the synthesis, was formed by tosylation and cyclisation.

In 1988, Corey and Ha converted geraniol to the diol-alkene **2.63** which, on exposure to PCC, cyclised to *cis*-THF diol **2.64** in 43% yield.[74] This unit was then incorporated into their enantioselective synthesis of the antiviral agent venustatriol (**2.65**) (Scheme 2.25).



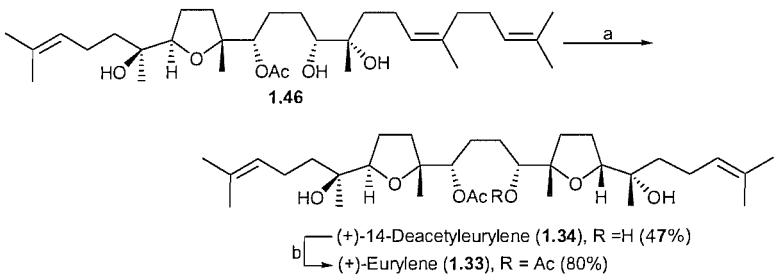
Scheme 2.25 *Reagents and conditions:* a) 1.05 equiv. PCC, CH_2Cl_2.

The transannular oxidative cyclisation of cyclooctenol substrates was investigated by Schlecht and Kim in 1989.[75] They found that on treatment with CrO_3, **2.66** was converted to the bicycle **2.67**, a structural unit found in a number of natural products (Scheme 2.26). This work also showed that diol substrates are not required for Cr(VI)-mediated oxidative cyclisation, providing the alcohol is tertiary.



Scheme 2.26 *Reagents and conditions:* a) PCC, AcOH, CH_2Cl_2.

The reaction was recently applied by Morimoto *et al* in the synthesis of (+)-eurylene (**1.33**) and (+)-14-deacetyleurylene (**1.34**) (see section 1.3.3).

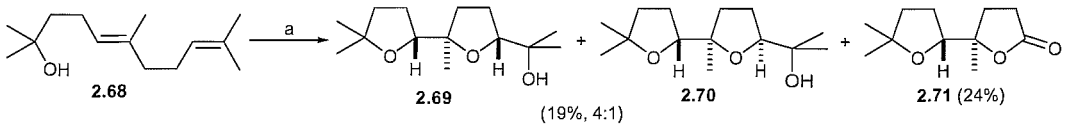


Scheme 2.27 *Reagents and conditions:* a) PCC, CH_2Cl_2; b) Ac_2O, py.

The diol-alkene portion of advanced intermediate **1.46** was transformed into the *cis*-

THF diol moiety of (+)-14 deacetyleurylene (**1.34**) (Scheme 2.27). The free secondary alcohol was then acylated to give (+)-eurylene (**1.33**).

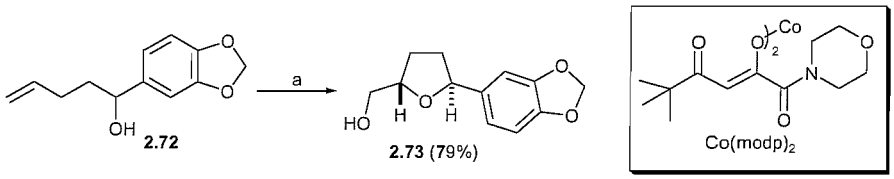
McDonald and Towne's 1994 work demonstrated the use of Cr(VI) in the tandem cyclisation of dienols.[76] Their best result occurred when substrate **2.68** was treated with PCC to provide diastereomeric *bis*-THF products **2.69** and **2.70** (Scheme 2.28). The combined yield was rather low (19%) and this was attributed to the formation of by-products such as oxidatve cleavage product **2.71**.



Scheme 2.28 *Reagents and conditions:* a) PCC, AcOH, celite, CH_2Cl_2.

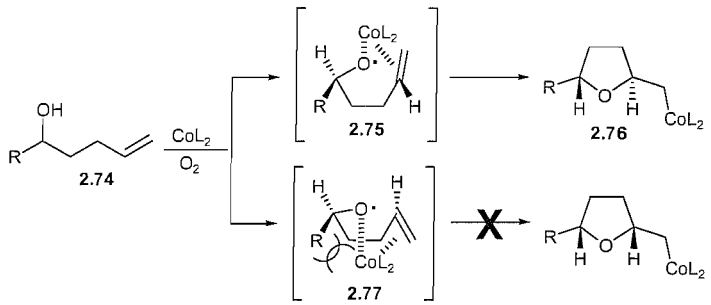
2.2.2 Cobalt complexes

In 1990, Mukaiyama and Inoki reported the oxidative cyclisation of 5-hydroxyalkenes by cobalt(II) catalysts in the presence of molecular oxygen.[77] For example, substrate **2.72** was converted to *trans*-THF **2.73** using $Co(modp)_2$ in a respectable yield of 73% with almost exclusive stereoselectivity (Scheme 2.29). It was found that the inclusion of a peroxide additive led to significant increases in the yield.



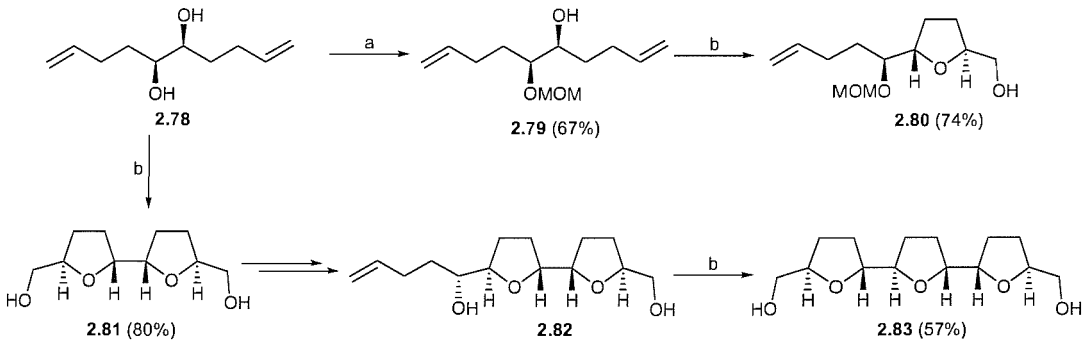
Scheme 2.29 *Reagents and conditions:* a) 20 mol% $Co(modp)_2$, 1 equiv. ^{t}BuOOH, 1 atm O_2, 4 Å molecular sieves, ^{i}PrOH, 50 °C.

The authors proposed a radical-based mechanism whereby, in the presence of a Co(II) complex and O_2, the 5-hydroxyalkene **2.74** undergoes hydrogen atom extraction and complexation to give a radical intermediate (Scheme 2.30). Of the two possible reactive conformations **2.75** and **2.77**, leading to *trans*- and *cis*-products respectively, **2.75** is the preferred geometry so the 5-*exo*-trig cyclisation affords *trans*-THF species **2.76**. Insertion of O_2 into the Co-C bond of **2.76** leads to a cobalt peroxide then the final product is released by reductive cleavage with the isopropanol solvent.



Scheme 2.30 Mechanism of Co(II)-catalysed oxidative cyclisation of 5-hydroxy-alkenes.

The reaction has proved useful in the synthesis of *Annonaceous* acetogenins possessing *trans*-THF units. Wang and Shi have shown that adjacent all-*trans mono*-, *bis*- and *tris*-THF cores can be accessed quickly using this chemistry.[78] The *mono*-THF fragment **2.80** was made simply by *mono*-*O*-protection of the *bis*-5-hydroxyalkene **2.78**, obtained by Sharpless asymmetric dihydroxylation of the correseponding triene, followed by Co(II)-catalysed oxidative cyclisation (Scheme 2.31).



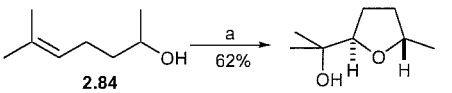
Scheme 2.31 *Reagents and conditions:* a) NaH, MOMCl, THF; b) 10 mol% $Co(modp)_2$, ^tBuOOH, O_2, ^iPrOH.

Alternatively, Co(II)-catalysed oxidative cyclisation of unprotected **2.78** gave the adjacent *bis*-THF unit **2.81**. Furthermore, this could be transformed to the adjacent *tris*-THF fragment **2.83** by the five-step conversion of **2.81** to **2.82**, which then underwent a further cyclisation by the Co(II) method. The authors later applied their methodology in asymmetric syntheses of the *mono*-THF acetogenin gigantetrocin A[79] and the adjacent *bis*-THF acetogenin asimilobin.[80]

Both Evans *et al*[25] (see section 1.3.5) and Takahashi and Nakata[81] have recently applied the Co(II)-catalysed oxidative cyclsation to form the *trans*-THF portion of the *Annonaceous* acetogenin (–)-mucocin (**1.62**).

2.2.3 Rhenium-oxo complexes

Inspired by Cr(VI) and Os(VIII)-mediated oxidative cyclisations, Kennedy and Tang studied the use of rhenium(VII) oxide (isoelectronic with OsO_4) in such reactions and disclosed their findings in a series of papers in 1992. The reaction of 5-hydroxyalkenes with Re_2O_7 provided *trans*-THF products and was therefore complementary to the use of other metals, which mainly led to *cis*-THFs. For example **2.84** was converted to *trans*-THF **2.85** in 62% yield and with dr 33:1 (Scheme 2.32).[82]

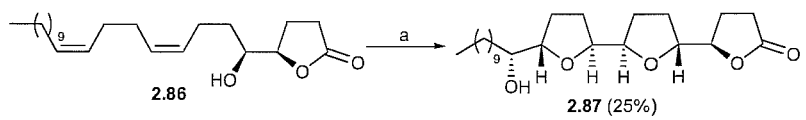


2.84 **2.85** (*trans*:*cis* 33:1)

Scheme 2.32 *Reagents and conditions:* a) 1.1 equiv. Re_2O_7, 1.1 equiv. 2,6-lutidine, CH_2Cl_2.

Pyridine or 2,6-lutidine was included in the reaction to neutralise the perrhenic acid formed through addition of the alcohol to Re_2O_7 as acidic conditions seemed to lead to by-product formation. Next Kennedy attempted to reduce the amount of Re_2O_7 required and investigated the use of co-oxidants.[83] The optimal system was found to be 50 mol% Re_2O_7 with H_5IO_6 as the co-oxidant. Kennedy explained the need for 100 mol% of Re atom by suggesting that the hydroxy-THF product forms an inactive complex with Re. This idea of chelation was later to become important in understanding the stereochemical outcome of the reaction.

The methodology was obviously applicable to the synthesis of *Annonaceous* acetogenins. Sinha and Keinan were the first to exploit it in their 1995 formal syntheses of the *trans*-THF acetogenins solamin and reticulatacin.[84] In the same paper they reported the first tandem cyclisation using Re_2O_7, producing the adjacent *bis*-THF fragment **2.87** (Scheme 2.33).

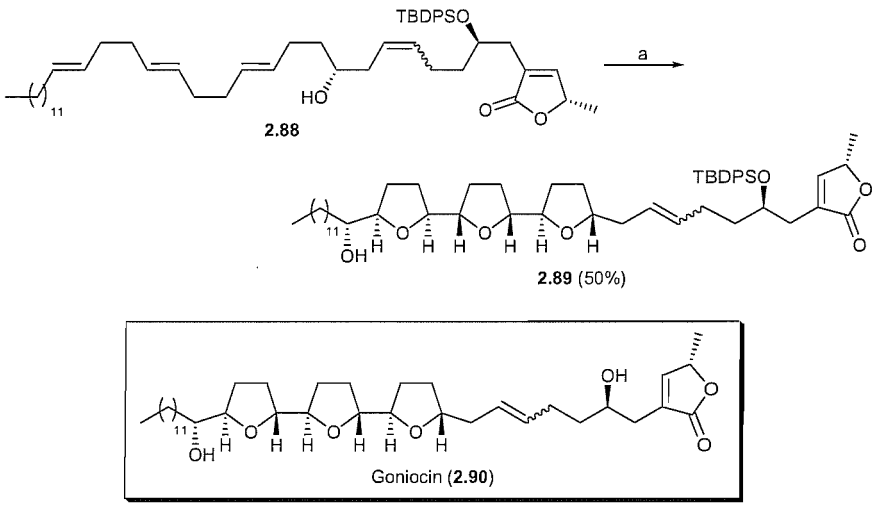


2.86 **2.87** (25%)

Scheme 2.33 *Reagents and conditions:* a) 3 equiv. Re_2O_7, 4 equiv. H_5IO_6, CH_2Cl_2.

Sinha incorporated the tandem cyclisation into a modular strategy for the construction of all 64 possible stereoisomers of the adjacent *bis*-THF diol core.[85-88]

Following Sinha's report of the tandem cyclisation, McDonald and Towne started studying the reaction but only obtained complex mixtures of products.[89] They, as Kennedy had earlier, attributed this to the production of perrhenic acid (pK_a –1.25)[90] in the initial coordination of the hydroxyl oxygen to rhenium, which in turn promotes side reactions such as non-oxidative cyclisation for substrates containing trisubstituted olefins. They set about developing a Rh(VII) reagent that incorporated a leaving group with a less acidic conjugate acid. They discovered that (trifluoroacetyl) perrhenate worked well in promoting the first cyclisation, but the second cyclisation did not occur. This was presumably because the *mono*-THF product from the first cyclisation coordinates strongly to Re, rendering it inactive. It was thought that this interaction could be disrupted in acidic conditions, but omitting the base led to complex mixtures. It was found that the addition of trifluoroacetic anhydride caused any perrhenic acid to be acylated, regenerating the active rhenium species and ensuring no perrhenic acid was present. In the absence of base, the presence of trifluoroacetic acid was sufficient to disrupt the THF-Re interaction without promoting side reactions, and thus the second cyclisation could proceed.



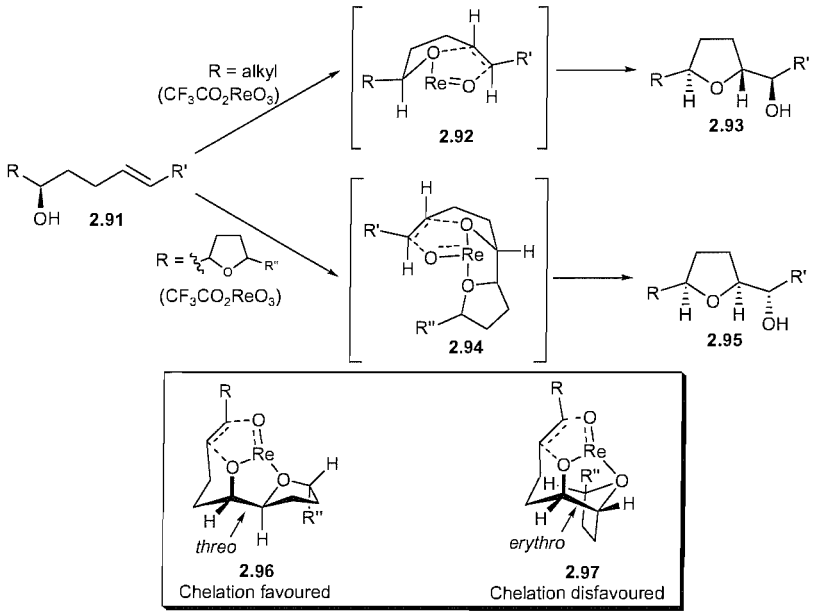
Scheme 2.34 *Reagents and conditions:* a) $CF_3CO_2ReO_3$, TFAA, CH_2Cl_2, 0 °C.

McDonald's (trifluoroacetyl)perrhenate reagent allowed further advances in the perrhenate-mediated tandem oxidative cyclisation. Sinha and co-workers used it in their triple cyclisation of a trienol **2.88**, which was expected to provide the *trans-threo-trans-threo-trans-threo tris*-THF core of the *Annonaceous* acetogenin goniocin

2.90 (Scheme 2.34).[91] A single *tris*-THF product was formed but was actually found to be the *trans-threo-cis-threo-cis-threo* species **2.89**. This reaction also demonstrated the mildness of these conditions.

Taking into account the above observation, along with previously published results,[84-86,92-95] Sinha formulated a set of rules by which to explain the stereochemical outcome of rhenium(VII)-mediated tandem oxidative cyclisation (Scheme 2.35):[64]

1. For the first cyclisation, with a simple 5-hydroxyalkene where only the hydroxy coordinates to rhenium, a *trans*-THF results. In this case transition state **2.92**, with the non-coordinating R group *pseudo*-equatorial, is favoured.
2. If the first cyclisation gives a *threo*-relationship of the newly installed oxygen atoms (this would arise from a *trans*-alkene), the next cyclisation gives a *cis*-THF. Now, with a second coordination site on Rh, conformation **2.94** is preferred.
3. If the first cyclisation gives an *erythro*-relationship of the newly installed oxygen atoms (from a *cis*-alkene), the next cyclisation gives a *trans*-THF. Here, conformation **2.94** should also be favoured, but a more detailed examination shows that the strained conformation **2.97** is required for coordination of the THF. Therefore the THF does not chelate and the cyclisation proceeds *via* the non-chelated transition state **2.92**.



Scheme 2.35 Transition states in Re(VII)-mediated oxidative cyclisation (ligands on Re omitted for clarity).

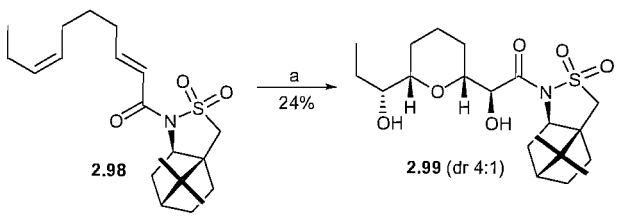
These "rules" have generally been found to be reliable, for example, with Sinha applying them in the design of a number of *Annonaceous* acetogenin syntheses[96,97] and Morimoto finding agreement in his work on polyether natural products.[98-100]

2.3 Tetrahydropyran formation

A logical extension of the above oxidative cyclisation methodologies is to apply them to 1,6-dienes and 6-hydroxyalkenes in order to form tetrahydropyran (THP) rings. The first successful report of this came from McDonald and Singhi in 1997.[101] Using their recently developed (trifluoroacetyl)perrhenate system, several simple 6-hydroxy alkenes were converted to *trans*-THPs in yields of 47-71% and with no *cis*-diastereomer observed.

Piccialli later described the RuO_4-catalysed oxidative cyclisation of two simple 1,6-dienes to give *trans*-THP diols (15-63%).[102] This was unusual as the oxidative cyclisation of 1,5-dienes normally produces *cis*-THFs. Piccialli suggested that the intermediate perruthenate ester was partially hydrolysed, giving rise to a similar intermediate as in reactions of 5- or 6-hydroxyalkenes and accordingly leading to *trans*-products.

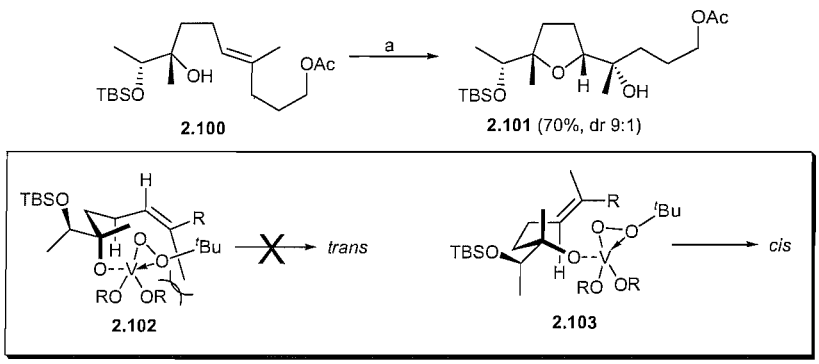
As part of on-going studies into the permanganate-promoted oxidative cyclisation our group recently published the conversion of 1,6-dienes to *cis*-THP diols, including the formation of enantiomerically enriched THP fragments.[103] For example, substrate **2.98**, containing the Oppolzer camphorsultam chiral auxiliary, was converted to *cis*-THP diol **2.99** in moderate yield and with a reasonable degree of facial control (Scheme 2.36).



Scheme 2.36 *Reagents and conditions:* a) 1.4 equiv. $KMnO_4$, AcOH/acetone (2:3), –15 °C.

2.4 Epoxidation/ring closure of 5-hydroxyalkenes

This chapter has focussed on the use of metal-oxo reagents, but the conversion of 5-hydroxyalkenes to THFs can also be achieved by the use of metal-peroxo reagents such as $VO(acac)_2$/^{t}BuOOH or ReO_3Me/H_2O_2. These reactions proceed *via* epoxidation of the alkene then epoxide opening by the hydroxy to form the THF. An important point is that with $VO(acac)_2$/^{t}BuOOH, the epoxidation is directed by the hydroxyl in the substrate, causing diastereoselective THF formation. An example is shown in Scheme 2.37 from Hanessian's total synthesis of ionomycin.[104] The product **2.101** is formed in 70% yield with dr 9:1 (*cis*:*trans*). This can be explained by considering the reactive conformations **2.102** and **2.103**. In **2.102** there is a steric clash between the vinylic methyl group and a vanadium ligand. Therefore conformation **2.103**, leading to the *cis*-THF, is favoured.



Scheme 2.37 *Reagents and conditions:* a) $VO(acac)_2$, ^{t}BuOOH, hexane, 3Å sieves.

This reaction has been investigated in great detail and will not be discussed further here as it has been the subject of a number of reviews.[105-107]

2.5 Conclusions

A variety of metal-mediated methods have been discussed which allow the rapid, stereocontrolled construction of substituted THF ring systems from simple precursors. Some of these are very well studied processes which are high-yielding and have been applied widely in synthesis, whereas others are under-developed and require further research. Together these reactions represent a complete set of tools for the construction of 2,5-disubstituted THF fragments as well as more substituted THFs and THPs.

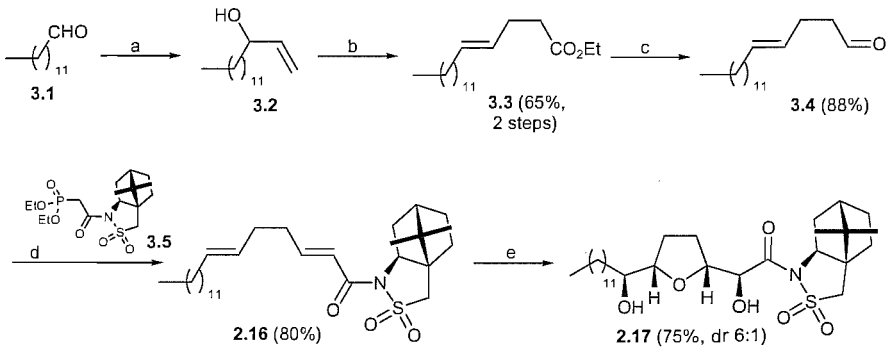
Chapter 3 Proposed synthesis of *cis*-sylvaticin

Before considering the synthesis of the non-adjacent *bis*-THF acetogenin *cis*-sylvaticin, our group's approach to the *mono*-THF acetogenin *cis*-solamin will be discussed in detail as it provides a foundation for further work.

3.1 Synthesis of *cis*-solamin

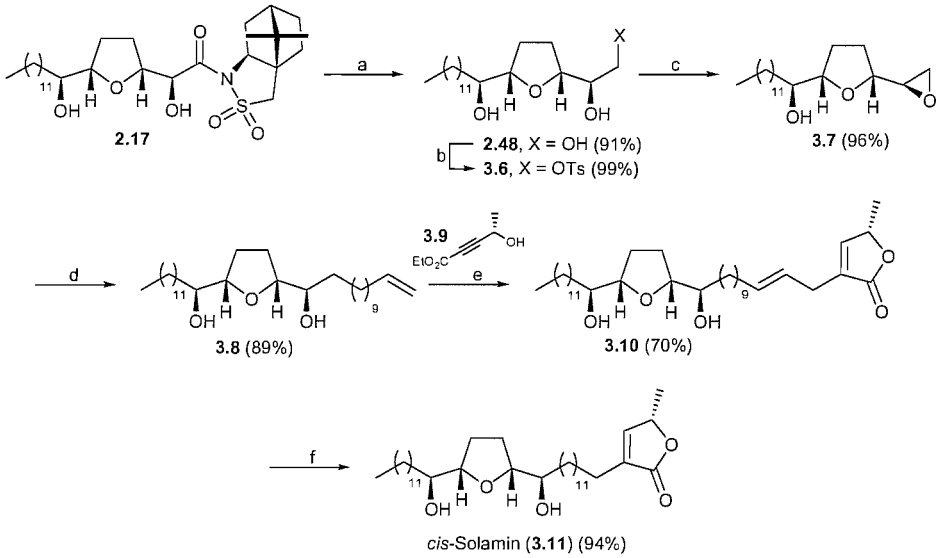
As mentioned in section 2.1.1, our group recently published the synthesis of *cis*-solamin, a *mono*-THF acetogenin with a *cis*-arrangement of substituents around the THF core, the key step being diastereoselective $KMnO_4$-mediated oxidative cyclisation to form the THF ring.[48,49]

The commercially available aldehyde **3.1** was treated with vinylmagnesium bromide, giving allyl alcohol **3.2** (Scheme 3.1). This underwent Claisen-Johnson rearrangement to ester **3.3**, which was reduced to aldehyde **3.4**. Horner-Wadsworth-Emmons olefination of **3.4** with phosphonate **3.5** (prepared in two steps from (2*S*)-10,2-camphorsultam) directly gave oxidative cyclisation substrate **2.16** (featuring Oppolzer's camphorsultam for chiral induction, as explained above) in good yield and avoided an alternative four step protocol. The optimisation of oxidative cyclisation conditions (described in section 2.1.1) led to the use of acetone/AcOH (3:2) as the solvent. This resulted in a highly satisfactory yield of 75% and dr 6:1 (*i.e.* a 64% yield of the required diastereomer **2.17**). THF diol **2.17** was separated from the minor diastereomer by chromatography on silica.



Scheme 3.1 *Reagents and conditions:* a) $CH_2CHMgBr$, THF; b) $CH_3C(OEt)_3$, 135 °C; c) DIBAL-H, $PhCH_3$, –60 °C; d) ^nBuLi, THF; e) 1.4 equiv. $KMnO_4$, AcOH/acetone (2:3), –30 °C.

With the THF core in place, attention turned to the installation of the second alkyl portion and the butenolide. Thus, THF-diol **2.17** (major diastereomer) was reduced to triol **2.48**, which was exclusively tosylated on the primary alcohol, followed by epoxide formation with DBU. This sequence of high-yielding steps resulted in epoxide **3.7**, a key intermediate for further derivatisation.



Scheme 3.2 *Reagents and conditions:* a) $NaBH_4$, THF, H_2O; b) Bu_2SnO, C_6H_6, 80 °C then TsCl, TBAB, rt; c) DBU, CH_2Cl_2; d) $CH_2{=}CH(CH_2)_9MgBr$, CuI, THF, –20 °C; e) CpRu(cod)Cl, MeOH, reflux; f) $TsNHNH_2$, NaOAc, THF, H_2O, 60 °C.

Epoxide **3.7** was alkyated by cuprate addition, with no hydroxyl protecting group required. The butenolide group was introduced using Trost's Alder-ene reaction[108] with chiral alkyne **3.9**. Hydrogenation of the residual alkene was accomplished by diimide reduction, which left the butenolide alkene intact, thus furnishing the target compound, *cis*-solamin (**3.11**).

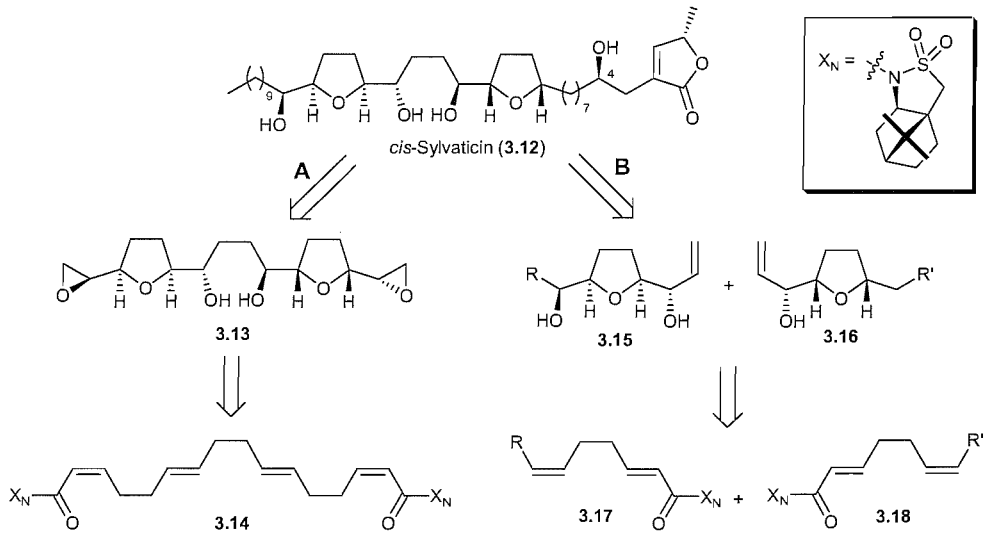
This is a short synthesis, notable for its efficiency, using no protecting groups, and is potentially very powerful in that the strategy can readily be applied to the construction of other *cis*-THF acetogenins.

3.2 Synthesis of *cis*-sylvaticin

In order to extend the use of the chemistry developed in the synthesis of *cis*-solamin, the more complex non-adjacent *bis*-THF acetogenin, *cis*-sylvaticin (**3.12**), was chosen as the next target.

3.2.1 Retrosynthesis

Two possible strategies were considered: route A, where the *bis*-THF core is constructed first, then extended in two directions; and route B, a convergent approach, whereby two *mono*-THF fragments are coupled by a tethered metathesis reaction (Scheme 3.3).



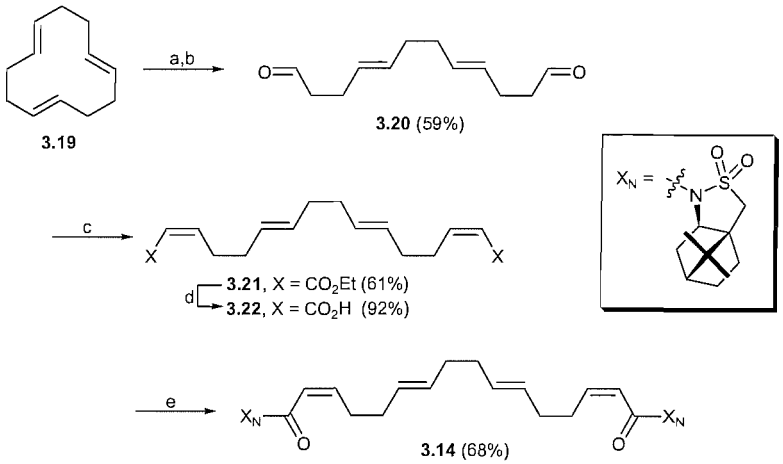
Scheme 3.3 Retrosynthetic analysis of *cis*-sylvaticin.

It was then discovered that the convergent approach of route B, using tethered metathesis of two *mono*-THF fragements, had already been tried by Mootoo[23] and Evans[25] in their syntheses of non-adjacent *bis*-THF acetogenins (see Chapter 1). Although this was still an attractive idea, with the novel *cis*-solamin chemistry almost directly applicable and plenty of scope to improve the tethered metathesis, it was decided initially to pursue route A.

3.2.2 Bi-directional approach to *cis*-sylvaticin

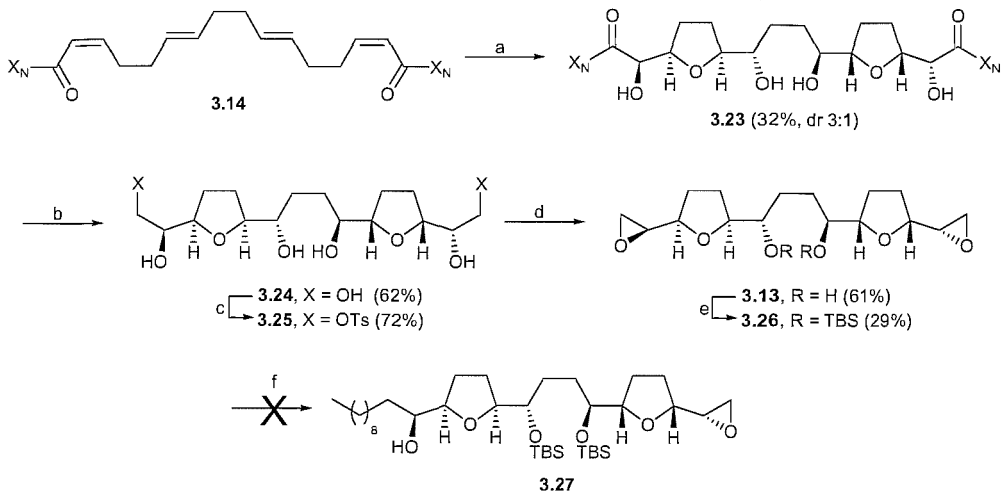
This strategy would feature an powerful key step involving double oxidative cyclisation of a tetraene, forming eight new C–O bonds, two new rings and establishing eight new stereogenic centres. Bhunnoo quickly accessed the requisite tetraene **3.14** by oxidative cleavage of *trans*, *trans*, *trans*-1,5,9-cyclododecatriene (**3.19**) to give dialdehyde **3.20** (Scheme 3.4).[109] This underwent a modified Still-Gennari olefination, yielding diethyl ester **3.21**. The diester was hydrolysed to diacid **3.22**. Following activation of **3.22** as the diacid dichloride, the anion of (1*S*, 2*R*)-

camphorsultam was then added, resulting in key tetraene **3.14**. No isomerisation of the enoate double bonds occurred if the reaction was carried out in toluene.



Scheme 3.4 *Reagents and conditions:* a) OsO_4, NMO, H_2O, CH_2Cl_2; b) $NaIO_4/SiO_2$, H_2O, CH_2Cl_2; c) $(PhO)_2POCH_2CO_2Et$, KHMDS, 18-crown-6, THF, –65 °C; d) NaOH, $NaHCO_3$, $MeOH/H_2O$ (1:3), 95 °C; e) (i) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C; (ii) X_NH, NaH, THF, –10 °C.

The double oxidative cyclisation was found to proceed in only moderate yields, even after optimisation (Scheme 3.5). The conditions developed in the *cis*-solamin synthesis, using AcOH/acetone (2:3), led to a yield of 20% of *bis*-THF tetrol **3.23** (two diastereomers). Increasing the amount of AcOH (AcOH/acetone (5:6)) led to an improved yield of 32% but no further increase in the amount of AcOH was possible as this would cause the solvent system to freeze at –30 °C (this temperature was important to reduce by-product formation). The product was an inseparable mixture of diastereomers, but the diastereoselectivity was 3:1, measured from the ^1H NMR spectrum of the mixture. Switching to $NaMnO_4$ in acetone with 5.4 eq AcOH gave the best result of 41%, but these conditions did not translate well to larger scale reactions. Through the steps of reduction, tosylation and epoxidation, the diastereomeric mixture remained inseparable, but the major diastereomer **3.26** was isolable after *bis*-TBS protection. This sequence of reactions was made very difficult by the problems of high polarity of some intermediates and complex mixtures of products. Desymmetrisation of *bis*-epoxide **3.26** was an important step, but, being short of time, Bhunnoo only had one attempt at the *mono*-alkylation. No evidence of the required product **3.27** was seen.

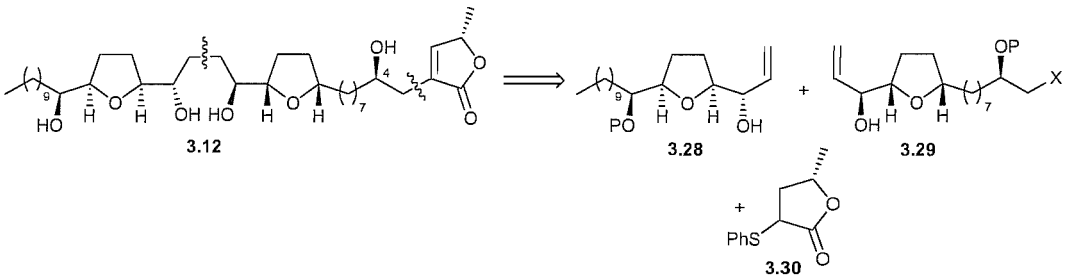


Scheme 3.5 *Reagents and conditions:* a) 3.2 equiv. $KMnO_4$, AcOH/acetone (5:6), –30 °C; b) $LiBH_4$, THF, –10 °C; c) Bu_2SnO, dioxane, reflux then TsCl, rt; d) DBU, CH_2Cl_2, 0 °C; e) TBSOTf, 2,6-lutidine, CH_2Cl_2, –10 °C; f) $CH_3(CH_2)_8MgBr$, CuI, THF, –30 °C.

This synthesis was initially attractive as it demonstrates the power of the oxidative cyclisation reaction, and the route was shown to allow very quick access to the *bis*-THF core. However, many of the intermediates were difficult to handle, the reactions produced complex mixtures and yields were generally mediocre. The other option for the synthesis of *cis*-sylvaticin was the convergent approach.

3.2.3 Planned convergent approach to *cis*-sylvaticin

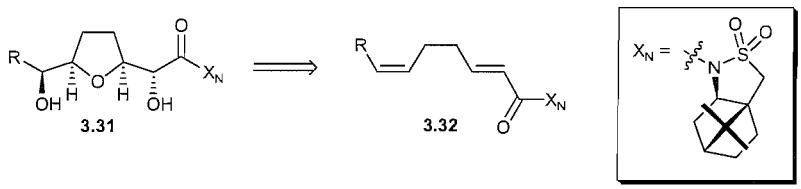
cis-Sylvaticin (**3.12**) can be disconnected into three fragments (Scheme 3.6), the two THF portions **3.28** and **3.29**, and the known lactone **3.30**.[110] We plan to couple the two THF fragments by tethering through the allylic alcohol function on each, followed by ring-closing metathesis (RCM).



Scheme 3.6 Retrosynthetic analysis of a convergent approach.

As discussed in Chapter 1, Mootoo (synthesis of bullatanocin core)[23] and Evans (synthesis of mucocin)[25] both found the tethered RCM approach to be troublesome: Mootoo instead opted for a cross metathesis requiring a four-fold excess of one fragment; and Evans found that 1.8 equiv. of Grubb's complex was required to effect the RCM. There are numerous examples in the literature of the RCM of a pair of tethered allylic alcohols to give 7-membered rings; tethers include phosphates,[111] phosphonates,[112] and dialkyl/diphenylsilyl groups.[113-116] Also the RCM conditions can be modified. Hence there is considerable scope to overcome the problems experienced by Mootoo and Evans.

To install the butenolide, the anion of lactone **3.30** undergoes facile addition to alkyl triflates.[110] The resulting sulfide is then oxidised and eliminated.



Scheme 3.7 THF diols from dienes.

The synthesis of THF fragments **3.28** and **3.29** will closely follow the methodology developed in our group's synthesis of *cis*-solamin (**3.11**).[48,49] The THF fragments **3.28** and **3.29** can be disconnected through a series of functional group interconversions to THF-diols of type **3.31**, which can be made by diastereoselective permanganate-mediated oxidative cyclisation of the corresponding 1,5-dienes **3.32** (Scheme 3.7).

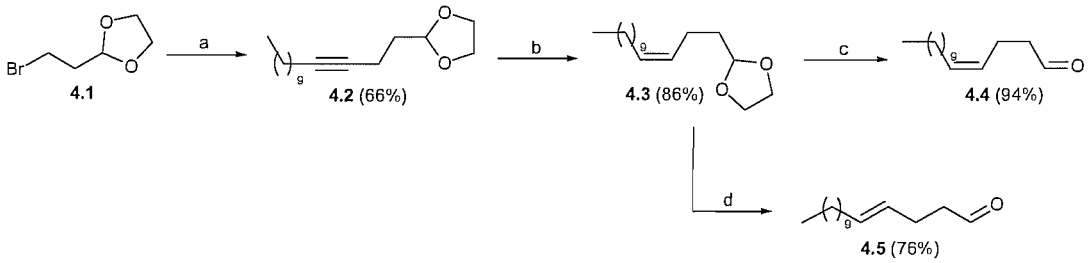
Chapter 4 Synthesis of *cis*-sylvaticin

Our retrosynthetic analysis of *cis*-sylvaticin (**3.12**) identified the THF-containing fragments **3.28** and **3.29** as key intermediates (see section 3.2.3). This chapter will discuss the synthesis of **3.28** and **3.29** and their coupling by tethered ring-closing metathesis.

4.1 Left hand fragment

Of the two THF fragments **3.28** and **3.29** identified as synthetic intermediates, the left hand section **3.28** is the simpler as it does not have a remote stereogenic oxygen-bearing centre, and so was synthesised first.

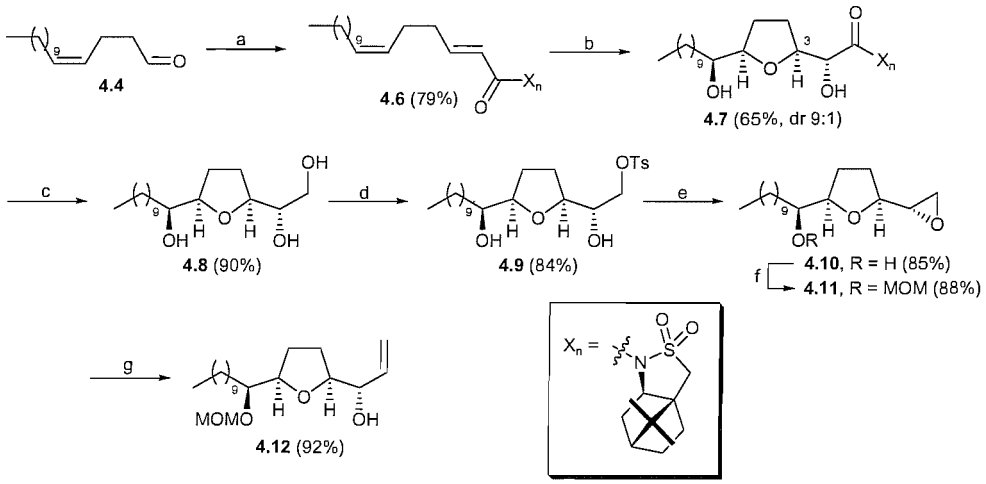
The first goal was to make aldehyde **4.4**, to which the *cis*-solamin chemistry could be applied (see section 3.1). Conveniently, aldehyde **4.4** has already been synthesised by Carballeira.[117] Following Carballeira's route, 1-dodecyne was alkylated with **4.1** to give **4.2** (Scheme 6.3). Partial hydrogenation with Lindlar catalyst and H_2 gave (*Z*)-alkene **4.3**. Carballeira then hydrolysed the acetal in **4.3** using HCl in acetone-H_2O; in our hands this method resulted in incomplete deprotection and by-product formation. After an investigation of alternative conditions it was found that heating in 80% aq. AcOH effected the deprotection cleanly.



Scheme 4.1 *Reagents and conditions:* a) 1-dodecyne, BuLi, DMPU, THF, –50 °C; b) 10 mol% Lindlar catalyst, H_2, quinoline, hexane; c) 80% aq. AcOH, 80 °C; d) CAN, MeCN, 70 °C.

The use of CAN also brought about cleavage of the dioxolane, as reported by Markó,[118] but surprisingly this was accompanied by isomerisation to (*E*)-alkene **4.5**. No *Z*-alkene was detected by ^{1}H NMR. This phenomenon has not been explored but it may constitute a new, mild method for alkene isomerisation.

With aldehyde **4.4** in hand, we could start applying the *cis*-solamin chemistry.[48,49] Initially the conditions previously used for the Horner-Wadsworth-Emmons olefination with diethyl-2-oxo-2-((2*R*)-*N*-camphor-10,2-sultam)-ethylphosphonate[119] to introduce the chiral auxiliary, employing NaH and CH_2Cl_2, were applied in the olefination of **4.4**. The reaction was found to be very unreliable, often resulting in low yields of diene **4.6** (at worst 36%). The suspected problem was deprotonation of the aldehyde, so Masamune and Roush's much milder procedure, using NEt_3 and LiCl, was applied giving the 1,5-diene **4.6** in increased yield of 79% which was highly reproducible (Scheme 6.12).[120] A variety of conditions for the oxidative cylisation have been used in our laboratories. The method developed for the *cis*-solamin synthesis, using AcOH/acetone (2:3),[48,49] was applied in the cyclisation of 1,5-diene **4.6**. The crude ^{1}H NMR spectrum indicated a remarkable 9:1 diastereoselectivity and the major diastereomer **4.7** was isolated in 65% yield. The diastereomeric ratio was determined by comparing ^{1}H NMR signals for the C-3 proton and the configurations assigned on the basis of previous observations.[49] Both the yield and diastereoselectivity are better than seen before in our group, and it may be that the *E*, *Z* geometry of 1,5-diene **4.6** is important. The established sequence of reductive cleavage to triol **4.8** then tosylation of the primary alcohol proceeded smoothly.



Scheme 4.2 *Reagents and conditions:* a) $(EtO)_2P(O)CH_2COX_n$, ^{i}Pr$_2$NEt, LiCl, MeCN; b) 1.4 equiv. $KMnO_4$, AcOH/acetone (2:3), –30 °C; c) $NaBH_4$, THF/H_2O (3:1); d) Bu_2SnO, C_6H_6, 80 °C then TsCl, TBAB, rt; e) DBU, CH_2Cl_2; f) MOMCl, ^{i}Pr$_2$NEt, CH_2Cl_2; g) Me_3SI, BuLi, THF, –10 °C.

The tosylate displacement to give epoxide **4.10** seemed to have worked well from qualitative TLC analysis of the reaction mixture. However, after purification on silica,

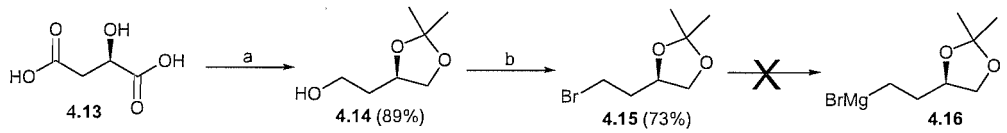
only 47% of the epoxide was recovered; the remainder was not found and it was assumed that it the epoxide was unstable to silica. From that point on chromatography was carried out with the addition of 0.5% NEt_3 to the eluent, and the problem never recurred.TBS protection of the hydroxy function in molecules similar to **4.10** has in the past proved troublesome, requiring vast excesses of reagents and prolonged reaction times.[121] This was avoided by the use of a MOM group which was introduced in high yield under standard conditions.[122] Epoxide **4.11** was then homologated to allylic alcohol **4.12** following Alcaraz's method, whereby **4.11** was treated with 3 equiv of the ylide generated by deprotonation of trimethylsulphonium iodide.[123] This gave around 75% conversion to allyl alcohol **4.12** (estimated from ^1H NMR of the crude material), but the remaining substrate **4.11** and the product **4.12** were inseparable by chromatography. It was found that using 6 equiv of the ylide gave complete conversion to the allyl alcohol **4.12**, with no trace of the epoxide. This finished the synthesis of the left hand fragment.

4.2 Right hand fragment

We envisaged this being synthesised in a broadly similar manner to the left hand fragment, with the main difference being the introduction at some point of the remote oxygen-bearing stereogenic centre (at C-4 in *cis*-sylvaticin **3.12**).

4.2.1 Chiral pool approach

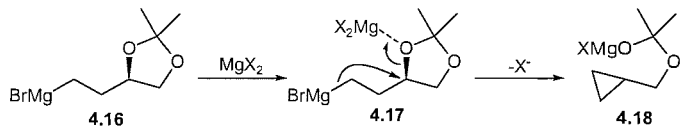
The use of (*R*)-malic acid was investigated as a source of the required stereogenic centre. Following literature procedures, it was simple to convert (*R*)-malic acid **4.13** to the useful building block **4.15** (Scheme 4.3).[124,125] This effectively contained the epoxide required in the right hand fragment **3.29**, which was present as a protected diol.



Scheme 4.3 *Reagents and conditions:* a) (i) $BH_3{\cdot}Me_2S$, $B(OMe)_3$, THF, 0 °C; (ii) 5 mol% $TsOH{\cdot}H_2O$, acetone; b) PPh_3, CBr_4, CH_2Cl_2, 0 °C.

It was hoped that the Grignard reagent **4.16** formed from **4.15** could be alkylated in order to build up the required chain length for the right hand fragment. Thus **4.15** was

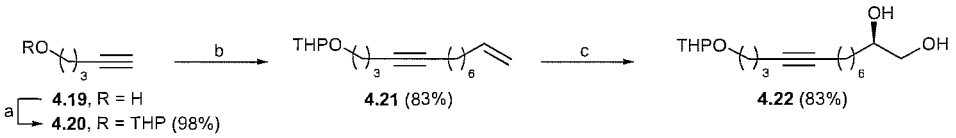
stirred in refluxing THF with Mg turnings and activated by a small amount of I_2. The Mg was consumed slowly. After treating with an electrophile the reaction was shown to contain none of the expected product. It was clear that the electrophile had not been consumed, suggesting a problem with the Grignard formation. It is possible that the Grignard reagent attacks the nearby internal electrophile under Lewis acid activation (Scheme 4.4). This rendered the Grignard useless for our purposes so it was decided to pursue another strategy.



Scheme 4.4 Possible side reaction of Grignard reagent **4.16**.

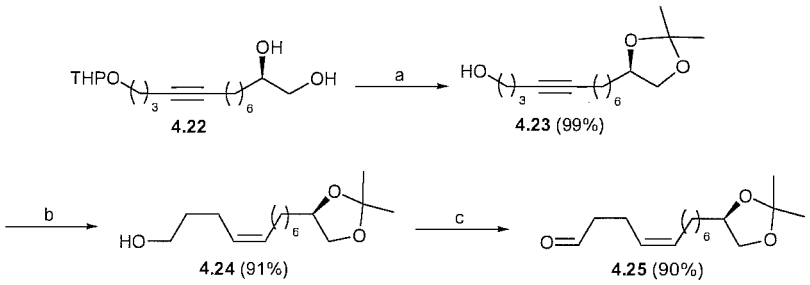
4.2.2 Sharpless asymmetric dihydroxylation approach

We reasoned that asymmetric dihydroxylation of long-chain terminal alkene **4.21** would be a simple way to access the important chiral diol **4.22**. Preparation of alkene **4.21** was initially attempted by alkylation of 4-pentyn-1-ol (**4.19**). According to the literature, the dianion of 4-pentyn-1-ol can be C-alkylated by double deprotonation,[126] but in our hands the reaction was found to be low yielding. This was overcome by protection of the hydroxy group as a THP ether, allowing the alkylation to proceed in good yield (Scheme 4.5). It was also found that HMPA was a vital co-solvent in the reaction; the use of DMPU caused a large decrease in yield.



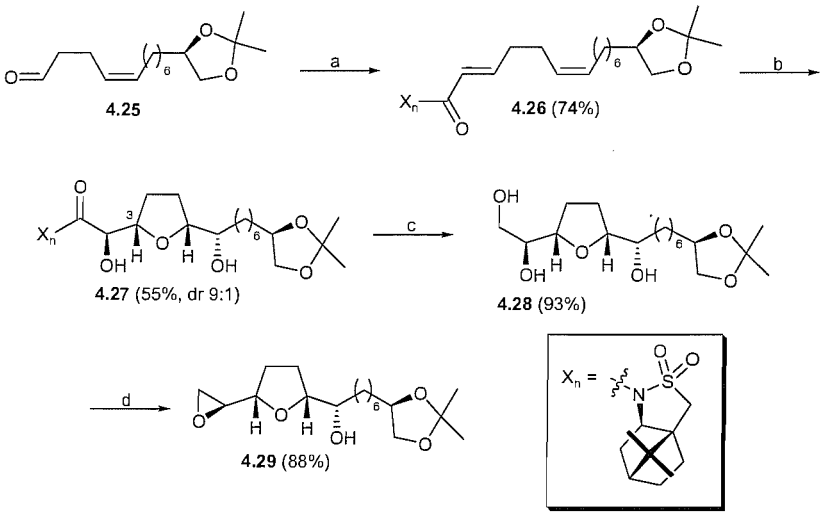
Scheme 4.5 *Reagents and conditions:* a) 10 mol% PPTS, 3,4-dihydro-2H-pyran, CH_2Cl_2; b) ^nBuLi, HMPA, THF, –78 °C then 8-bromo-1-octene; c) 0.4 mol% $K_2OsO_2(OH)_4$, 1 mol% $(DHQD)_2AQN$, $K_3Fe(CN)_6$, K_2CO_3, $H_2O/^tBuOH$ (1:1), 0 °C.

Alkene **4.21** would then be subjected to Sharpless asymmetric dihydroxylation. We chose to use the hydroquinidine (anthraquinone-1,4-diyl) diether ligand ($(DHQD)_2AQN$) as this is known to give the best *ee* for terminal olefins.[127] The dihydroxylation gave diol **4.22** in 83% and 90% *ee* (Scheme 4.5).



Scheme 4.6 *Reagents and conditions:* a) 5 mol% $TsOH{\cdot}H_2O$, MeOH then MeOH removed *in vacuo* and residue dissolved in acetone; b) 1 mol% Lindlar catalyst, H_2, quinoline, MeOH/EtOAc (2:1); c) Dess-Martin periodinane, CH_2Cl_2.

The THP protecting group of **4.22** was cleaved by stirring in MeOH with 5% TsOH then the reaction was concentrated *in vacuo*, dissolved in acetone and stirred to provide **4.23** with the 1,2-diol protected as an acetonide (Scheme 4.6). Partial hydrogenation of **4.23** gave *Z*-alkene **4.24** in good yield.[128] This was oxidised to the aldehyde **4.25** using Dess-Martin periodinane.[129]

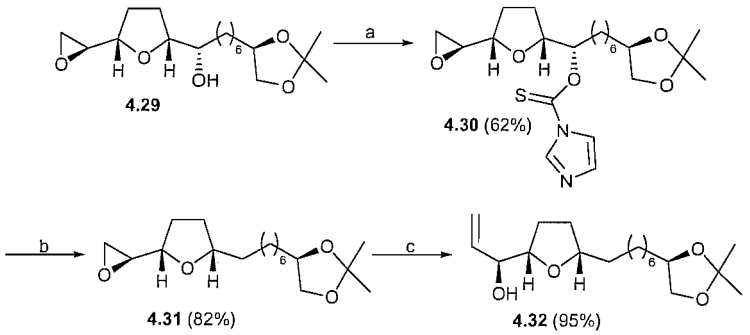


Scheme 4.7 *Reagents and conditions:* a) $(EtO)_2P(O)CH_2COX_n$, $^iPr_2NEt$, LiCl, MeCN; b) 1.4 equiv. $KMnO_4$, AcOH/acetone (2:3), –30 °C; c) $NaBH_4$, THF/H_2O (3:1); d) (i) Bu_2SnO, C_6H_6, 80 °C then TsCl, TBAB, rt; (ii) DBU, CH_2Cl_2.

Aldehyde **4.25** underwent olefination with diethyl-2-oxo-2-((2*R*)-*N*-camphor-10,2-sultam)-ethylphosphonate under the mild conditions used in the synthesis of the left hand side, leading to 1,5-diene **4.26** in good yield (Scheme 4.7). As previously, oxidative cyclisation of **4.26** with $KMnO_4$ provided the major diasteromer **4.27** in good yield (55%) and with high stereoselectivity (9:1). Again, the diastereomeric ratio

was determined by comparing ^{1}H NMR signals for the C-3 proton and the configurations assigned on the basis of previous observations.[49] Reduction of **4.27** was carried out as before, including a 2N HCl(aq) wash in the work-up but this very brief exposure to aqueous acid caused complete hydrolysis of the acetonide protecting group, revealing the remote diol. This ruined our plans for selective manipulation of the 1,2-diol adjacent to the THF and there was no way of re-protecting the remote diol exclusively. Thus the fragment **4.27** was remade from the beginning, taking care not to expose it to any aqueous acid. Tosylation then tosylate displacement gave epoxide **4.29**.

The hydroxyl group in epoxy alcohol **4.29** is not present in *cis*-sylvaticin. This would be the best time to remove it, as no other free hydroxyl groups were present at this point. We opted to use a Barton-McCombie-type deoxygenation as a radical-based method would be least likely to cause decomposition of the epoxide. The only problem we envisaged would be activation of the hindered hydroxyl as a thiocarbonyl derivative; derivatisation at this position has proved challenging in the past, notably in the TBS protection of an equivalent alcohol.[121] A range of conditions were tried and initial results were not encouraging with epoxide decomposition being a problem, but it was soon found that the thiocarbonyl imidazole derivative **4.30** was accessible in reasonable yield (Scheme 4.8), though yields were variable.



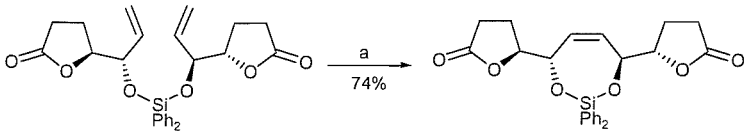
Scheme 4.8 *Reagents and conditions:* a) $(imid)_2C=S$, DMAP, CH_2Cl_2; b) $(^nBu_4N)S_2O_8$, HCO_2Na, Na_2CO_3, DMF, 65 °C; c) Me_3SI, BuLi, THF, –10 °C.

Classically, the Barton-McCombie deoxygenation uses Bu_3SnH and AIBN to effect decomposition of thiocarbonyl compounds, but we wanted to use a more modern tin-free methodology. Recently Kim *et al* reported the use of tetrabutylammonium peroxydisulfate and sodium formate to achieve deoxygenation *via* a variety of thiocarbonyl substrates.[130] This procedure was found to work quickly, causing

complete consumption of **4.30** in 45 minutes with a good yield of 82%. The deoxygenated product **4.31** was then subjected to the sulfonium ylide homologation reaction, as before, to complete the right-hand fragment **4.32**.

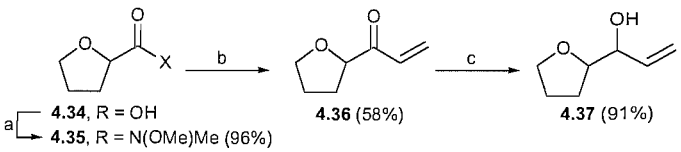
4.3 Model metathesis of tethered substrates

A number of different linkers have been used to tether a pair of allylic alcohols before RCM of the tethered species to give 7-membered rings. In the most promising example, Evans *et al* used a diphenylsilyl group to join two allyl alcohols that resemble our THF fragments (Scheme 4.9).[113]



Scheme 4.9 Evans' diphenylsilyl-tethered RCM. *Reagents and conditions:* a) 50 mol% $Cl_2(Cy_3P)_2Ru{=}CHPh$ (**4.33**), CH_2Cl_2, reflux.

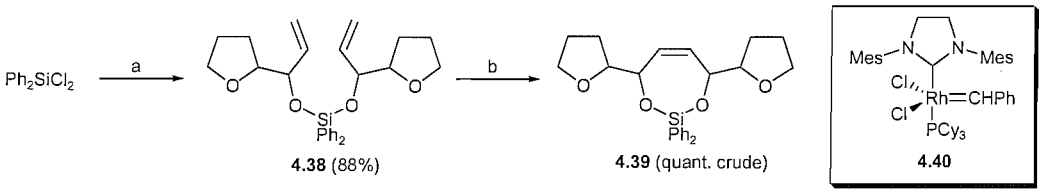
Unfortunately, the reaction requires the use of 50 mol% of the catalyst and prolonged heating in CH_2Cl_2, so the resulting 74% yield is disappointing. We decided to explore the use of different tethers and conditions using our own model substrate **4.37** (Scheme 4.10), which was synthesised from 2-tetrahydrofuroic acid (**4.34**) using literature conditions.[131]



Scheme 4.10 *Reagents and conditions:* a) carbonyldiimidazole, THF then HN(Me)OMe·HCl, NEt_3; b) $CH_2{=}CHMgBr$, THF, 0 °C; c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$ MeOH, 0 °C.

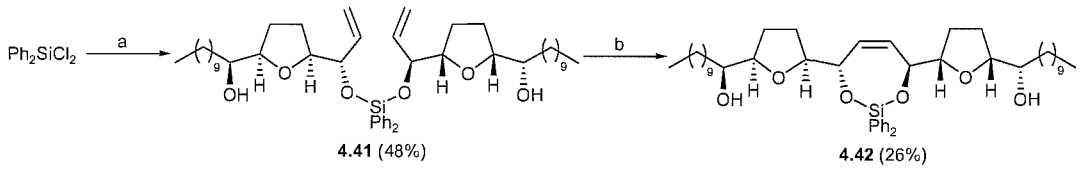
A diphenylsilyl tether was used initially as the literature shows that it tends to work well (Scheme 4.11). The tethered compound **4.38** was prepared by reacting Ph_2SiCl_2 with 2 equiv. **4.37** under basic conditions. *Bis*-alkoxysilane **4.38** in C_6D_6 was treated with 5 mol% of Grubbs' 1st generation catalyst (**4.33**) and stirred at 100 °C under microwave heating for 5 minutes. TLC showed no reaction. However, a concurrent reaction using Grubbs' 2nd generation catalyst (**4.40**) under the same conditions looked much more interesting: GCMS analysis of the crude mixture showed near-

complete consumption of the starting material within 10 minutes and generation of the expected product **4.39** (as a mixture of diastereoisomers).



Scheme 4.11 *Reagents and conditions:* a) 2 equiv. **4.37**; NEt_3, DMAP, CH_2Cl_2; b) 5 mol% **4.40**, C_6D_6, 100 °C.

This brief investigation encouraged us to go ahead with the equivalent chemistry on the real system to see how the alkyl chains would affect the RCM. We had approximately 400 mg of the left hand fragment **4.12** and approximately 50 mg of the right hand fragment **4.32**. It was decided to make the symmetrical tethered species **4.41** using only **4.12** (Scheme 4.12). This way the RCM could be explored in what was essentially the real system, without commiting any of the more precious fragment **4.32**.

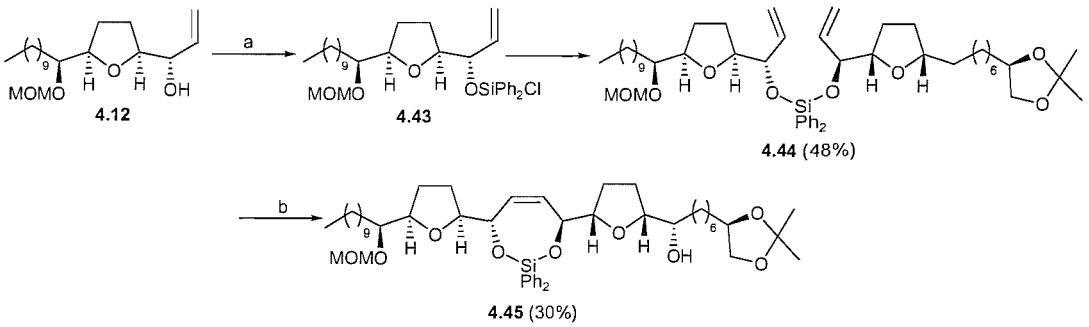


Scheme 4.12 *Reagents and conditions:* a) 2 equiv. **4.12**, NEt_3, DMAP, CH_2Cl_2; b) 10 mol% **4.40**, C_6D_6, 100 °C, 5 h.

The silyl tethering step proceeded in a much lower yield than with the simpler model substrate **4.37**, reflecting the increased steric bulk of **4.12**, but 12 mg of **4.41** was enough to try the RCM. *Bis*-alkoxysilane **4.41** was dissolved in C_6D_6 so that the RCM reaction could be directly analysed by NMR spectroscopy. Initially 10 mol% **4.40** was added and the reaction was heated in a microwave reactor as before. No change was observed after 1 hour so an extra 10 mol% of catalyst was added and heating continued. After a further 4 hours, a new spot was visible by TLC and ^1H NMR confirmed the presence of new, equivalent olefinic protons. The reaction did not go to completion but in order to determine the identity of the product the mixture was purified on silica to give the RCM product **4.42** (26%). No by-products were observed. This reaction had been a lot slower than in the model system, but with the

concept proven, and diphenylsilyl shown to be an adequate linker, our attention turned to the real system.

The diphenylsilyl-tethered compounds studied so far had been symmetrical so their preparation had been straightforward. Now, however, an unsymmetrical compound had to be prepared. With only around 50 mg of **4.32**, it was important to develop the tethering reaction quickly without conducting too many test reactions. The plan was to react **4.12** with 1 equiv. Ph_2SiCl_2 then add 1 equiv. **4.32**, and hopefully ensure a complete reaction at each stage. It was thought that reaction of the first alcohol **4.12** with Ph_2SiCl_2, in the presence of base, would be relatively facile, then upon addition of the second alcohol **4.32** further base or even DMAP would be required for reaction at the now hindered silyl centre. An initial experiment using Hünig's base and CH_2Cl_2 looked very promising, with TLC analysis of the first stage showing almost complete consumption of **4.12**, along with a small amount of the symmetrical *bis*-alkoxysilane **4.41** and another new spot thought to be the required chloroalkoxysilane **4.43** (Scheme 4.13). On addition of **4.32** and additional Hünig's base, no further reaction was observed. Thus 1 equiv. DMAP was added leading to consumption of **4.32** and the chloroalkoxysilane **4.43** and the appearance of a new spot. The reaction did not go to completion but the product was isolated and identified as the required *bis*-alkoxysilane **4.44** (48%). This material was then subjected to microwave-assisted RCM as before. Due to the need for two 10 mol% portions of catalyst **4.40** previously, this reaction was charged with 20 mol% **4.40**. After microwave heating for 5 hours TLC and ^1H NMR analysis showed some formation of the desired product **4.45**. This was isolated in 30% yield, as could be expected from the model RCM of symmetrical *bis*-alkoxysilane **4.41**.



Scheme 4.13 *Reagents and conditions:* a) 1 equiv. Ph_2SiCl_2, 1.1 equiv. $^iPr_2NEt$, CH_2Cl_2 then 1 equiv. **4.32**, 1.1 equiv. $^iPr_2NEt$, 1 equiv. DMAP; b) 20 mol% **4.40**, C_6D_6, 100 °C, 5 h.

This important result encouraged us to bring more material through the tethering step, but unfortunately the initial achievement could not be repeated. Production of the symmetrical *bis*-alkoxysilane **4.41** now seemed to be a major issue and the reaction was very unpredictable. Regrettably, due to a lack of material and time, work was discontinued before this reaction could be fully understood and exploited.

4.4 Conclusions and further work

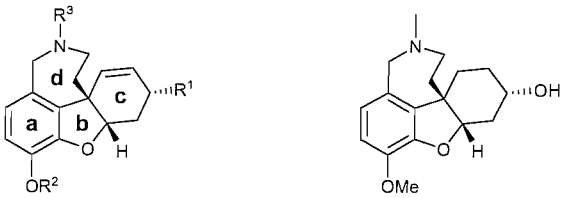
The overall strategy behind this synthesis was elegant but it was compromised early on by the lack of suitable commercially available starting materials and thus the need to construct the basic chains from what was available. Nevertheless, once the two 1,5-dienes **4.6** and **4.26** were accessed, the permanganate-mediated oxidative cyclisation was trouble-free and provided the THF diols **4.7** and **4.27** in good yields and with relatively high stereoselectivity. Both THF diols went smoothly through the sequence of functional group interconversions to the two requisite coupling partners **4.12** and **4.32**. One area of inconvenience was the two-step deoxygenation of **4.29**, which suffered from slightly disappointing yields. The key ring-closing metathesis was shown to work satisfactorily, first with a simple model, then with a model closely approximating the final system. This led to the need to develop a reaction to form the unsymmetrical *bis*-alkoxysilane **4.44**, a reaction which was found to be very capricious. Enough material was formed to attempt the RCM reaction with the real substrate and this proceeded in a highly encouraging manner. In the end, however, it was the unpredictable *bis*-alkoxysilane formation that prevented further progress.

Obstacles to be overcome in the future include the deoxygenation, which it is anticipated can be accomplished in high yield, and the *bis*-alkoxysilane formation which, with sufficient time and material, can be understood. Though the RCM did not proceed with great efficiency, it is felt that this is not a great obstacle as it was a very clean reaction with no by-products and the process can be pushed further by increasing the reaction times and/or amount of catalyst. Beyond this, no major obstruction can be seen to the total synthesis of *cis*-sylvaticin.

Chapter 5 The galanthamine alkaloids

5.1 Background

Galanthamine (**5.1**)[132] is the parent member of the galanthamine-type alkaloids (Figure 5.1) found in the *Amaryllidaceae* plant family. It has a long history of medicinal use; for hundreds of years the leaves and bulbs of plants of the *Galanthus* species have been used in Bulgarian and northern Turkish folk medicine to treat painful neurological conditions such as facial neuralgia, which arises from damage or irritation of the sensory nerve supplying most of the face.



Galanthamine (**5.1**) R^1:OH, R^2=R^3:Me
Narwedine (**5.2**) R^1:=O, R^2=R^3:Me
Norgalanthamine (**5.3**) R^1:OH, R^2:Me, R^3:H
Sanguinine (**5.4**) R^1:OH, R^2:H, R^3:Me
Leucotamine (**5.5**) R^1:$OCOCH_2CH(OH)CH_3$, R^2=R^3:Me
Lycoramine (**5.6**)

Figure 5.1 Galanthamine and related alkaloids

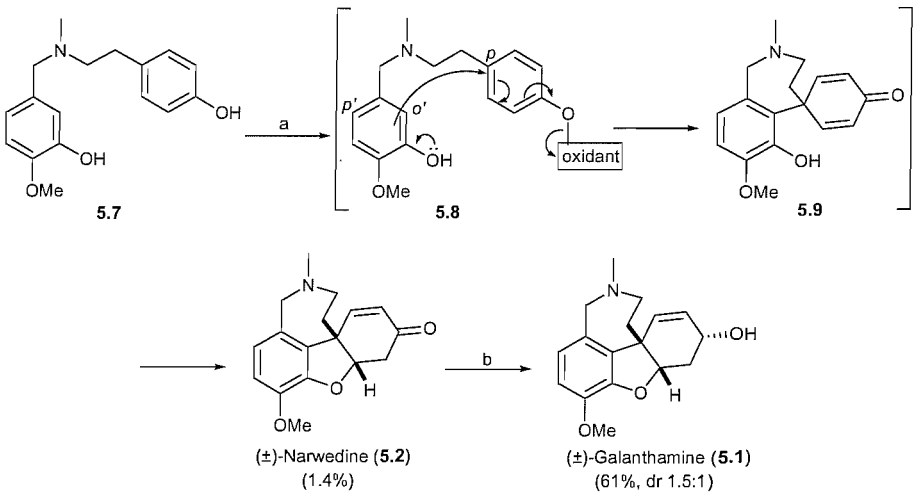
Galanthamine was first isolated in Russia in the 1940s[133,134] and in the next decade its structure was elucidated in Japan.[135] Through the 1960s, mainly in the USSR and Bulgaria, many exciting aspects of the pharmacology of galanthamine were discovered. It is recognised as an effective treatment for Alzheimer's disease,[136] and is approved for use as such in Europe and the USA. One of the main features of Alzheimer's disease is a reduction in levels of the neurotransmitter acetylcholine, leading to impaired brain function. As a potent and selective inhibitor of acetylcholinesterase,[137] galanthamine blocks the hydrolysis of acetylcholine. This leads to increased levels of the neurotransmitter, contributing to improved brain function and protecting neurons against damage from neurotoxic effects. The pharmacological profile of galanthamine has been discussed in detail in a recent review.[138]

5.2 Previous syntheses of galathamine

Galanthamine can be obtained by extraction from bulbs such as snowdrops or daffodils, but this is low yielding leading to high costs and limited supplies.[139,140] Thus a wealth of research into the synthesis of galanthamine has been published. Broadly, these synthetic efforts can be divided into two strategies: the biomimetic approach, using oxidative phenolic coupling; and non-biomimetic syntheses, which have often used an intramolecular Heck reaction. In both cases, (–)-galanthamine has been prepared in enantiomerically enriched form.

5.2.1 Biomimetic approach

The biomimetic strategy was pioneered by Barton *et al* in 1962, who, as part of their work on the biogenesis of galanthamine,[141] found that in the presence of an oxidant (potassium ferricyanate), 4'-*O*-methylnorbelladine (**5.7**) cyclised to give (±)-narwedine (**5.2**) in 1.4% yield (Scheme 5.1). This was finally reduced to (±)-galanthamine (**5.1**).[142]



Scheme 5.1 *Reagents and conditions:* a) $K_3[Fe(CN)_6]$, $NaHCO_3$, H_2O; b) $LiAlH_4$, Et_2O, reflux.

This method allows rapid construction of the galanthamine core from a relatively simple precursor. However, the low yield was a major drawback, thought in part to be due to the side-reaction of intramolecular attack through the *p'* position.

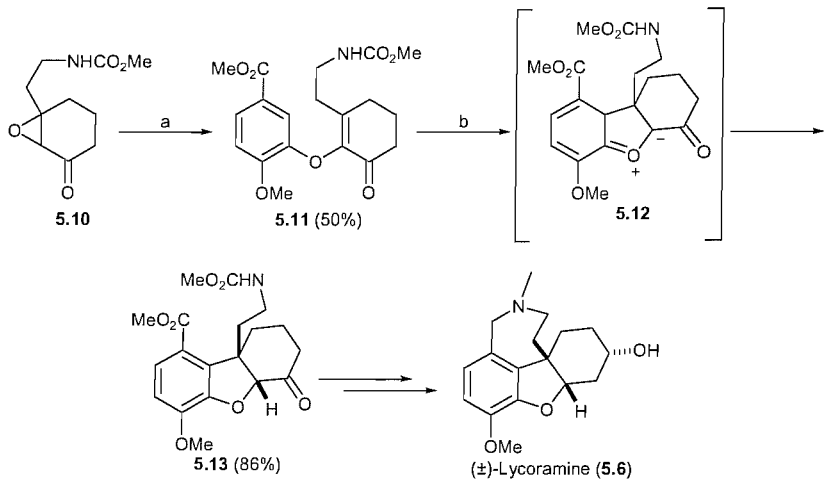
The approach has continued to attract attention and many attempts have been made to improve it. These include blocking the *p'* position with bromo,[140,143,144]

trimethylsilyl[144] or benzyloxy/methoxy[145] groups to avoid *para-para* coupling and varying the oxidant.[144-146] The best result was published by Node *et al* in 2001 who used the hypervalent iodine species phenyliodine(III) *bis*(trifluoroacetate) as the oxidant and benzyloxy as a blocking group,[145] but in general yields are only moderate.

Intermediate **5.9** can cyclise by intramolecular Michael reaction to both enantiomers of narwedine (**5.2**) meaning that the biomimetic strategy is not inherently an asymmetric process. However, ever since Barton's original work, resolution methods have been developed to deliver enantiomerically enriched material. The most advanced of these is Shieh and Carlson's total spontaneous resolution, relying on the fact that narwedine can undergo retro-Michael and reclosure reactions. The addition of 1 mol% of (+)-galanthamine (the unnatural enantiomer) to a solution of (±)-narwedine in ethanol-NEt_3 (9:1) gave (–)-narwedine in 76% yield.[139] Synthetic asymmetric methods have also been developed using remote stereogenic centres to induce asymmetry.[146,147]

5.2.2 Non-biomimetic syntheses

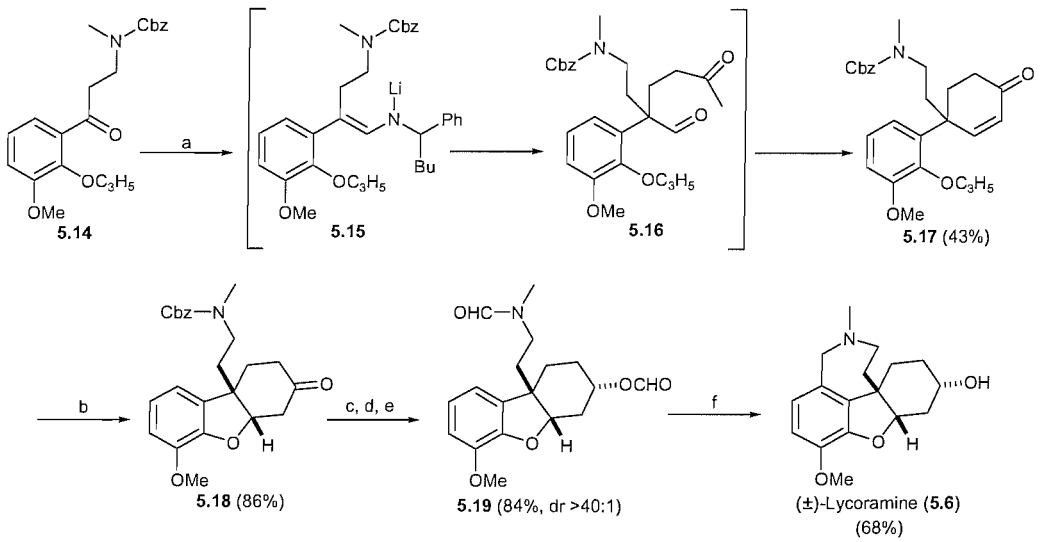
A number of non-biomimetic syntheses have actually led to lycoramine (**5.6**), but as this has the same carbon skeleton as galanthamine (**5.1**), routes to both molecules can be considered alongside each other. One of the earliest non-biomimetic syntheses was the work of Schultz *et al* in 1977 to produce lycoramine (**5.6**).[148] The epoxide **5.10**, made from 1,3-cyclohexanedione, was reacted with a suitably functionalised phenolate to give ether **5.11** (Scheme 5.2).



Scheme 5.2 *Reagents and conditions:* a) 5-carboxymethoxy-2-methoxyphenol, KH, 18-crown-6, THF, reflux; b) hν, benzene-MeOH (1:1).

Irradiation of **5.11** caused cyclisation *via* ylide **5.12**, to give tricycle **5.13**. A number of further steps were required to form the aza-ring and transpose the oxygen functionalitilty, finally producing lycoramine (**5.6**). Many of the later non-biomimetic syntheses of galanthamine-type structures would resemble this route.

Martin and Garrison published their non-biomimetic synthesis of lycoramine in 1982 (Scheme 5.3).[149] Ketone **5.14** was prepared from commercially available materials. The authors then applied their one-pot methodology for the construction of a cyclohexenone ring at a carbonyl carbon. This involved initial olefination to give a 2-azadiene, followed by addition of BuLi to give lithium enamide **5.15**. This was then alkylated with a bromoacetal to give an imino acetal and subsequent hydrolysis with HCl (aq) gave the keto aldehyde **5.16**. Finally, treatment with KOH (aq) in MeOH gave cyclohexenone **5.17**, with the important quaternary centre in place.

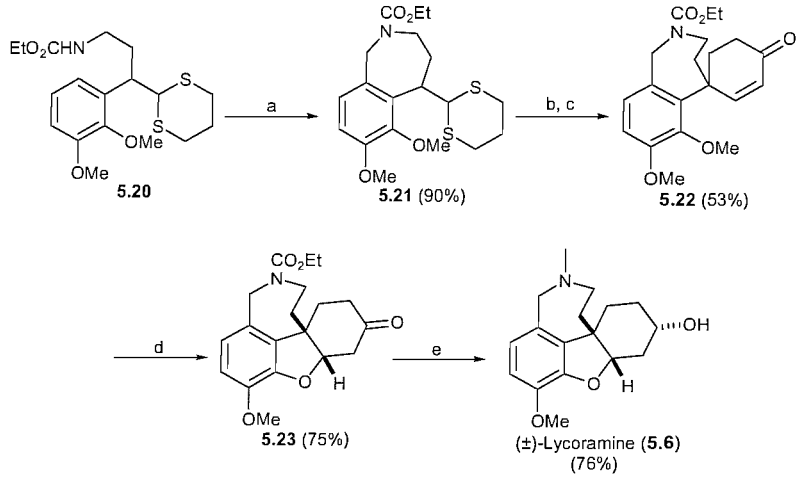


Scheme 5.3 *Reagents and conditions:* a) i) BuLi, diethyl[(benzylideneamino)methyl)] phosphonate, THF, –78 °C; ii) BuLi, –78 °C; iii) HMPA, 2-(2-bromoethyl)-2-methyl-1,3-dioxolane, –78 °C → rt; iv) HCl (aq); v) KOH (aq), MeOH; b) 7 mol% $RhCl_3.3H_2O$, EtOH, reflux; c) L-Selectride, THF, –78 °C; d) 5 mol% Pd-C, H_2 (1 atm), EtOH, conc. HCl (aq); e) AcOCHO, pyr, 80 °C; f) i) $POCl_3$, 85 °C; ii) $NaBH_4$, MeOH, –78 °C → rt.

The allyl-protected phenol was then unmasked allowing an intramolecular Michael addition to produce **5.18**. A number of functional group interconversions followed, including a highly diastereoselective reduction of the ketone (dr >40:1), leading to

diformylated **5.19**. This underwent a Bischler-Napierski reaction, then $NaBH_4$ reduction of the resulting iminium salt, with *in situ* hydrolysis of the formate ester, to give racemic lycoramine (**5.6**).

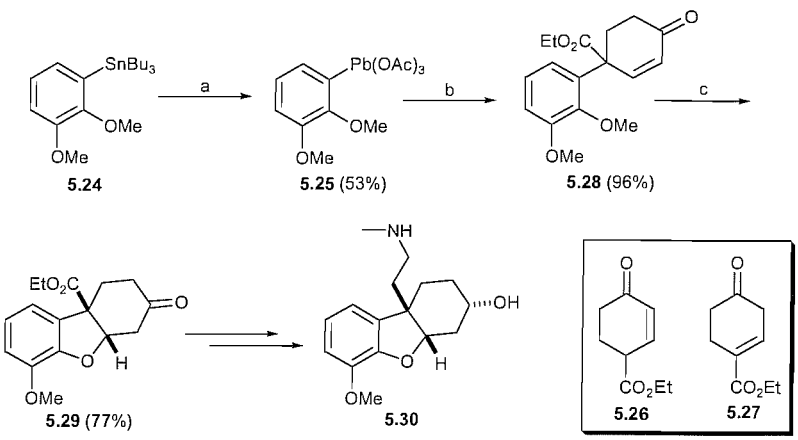
In 1984 Sanchez *et al* described their synthetic route to lycoramine (Scheme 5.4).[150] The functionalised aromatic compound **5.20** (prepared from 2,3-dimethoxy cinnamonitrile) was condensed with formaldehyde. The resulting *N*-hydroxymethyl derivative cyclised to **5.21** after heating in the presence of TsOH.



Scheme 5.4 *Reagents and conditions:* a) i) aq. formaldehyde, cat. NaOH, MeOH; ii) TsOH, C_6H_6, reflux, Dean-Stark; b) $BF_3.Et_2O$, red HgO, 15% H_2O/THF; c) i) methyl vinyl ketone, cat. DBN, THF, 0 °C; ii) NaOEt, EtOH, reflux; d) $AlCl_3$, EtSH, CH_2Cl_2; e) $LiAlH_4$, DME, –78 °C → reflux.

The dithiane protecting group was removed and the resulting aldehyde underwent base-catalysed Michael addition to methyl vinyl ketone. Further treatment with NaOEt caused an intramolecular aldol reaction then dehydration to give enone **5.22**. This was converted to the tetracycle **5.23** by Lewis acid-assisted Michael addition of the nearest methoxy oxygen, then *in situ* cleavage of the resulting oxonium species by ethyl sulfide. The product was treated with $LiAlH_4$ which reduced the ester to the required *N*-methyl substituent and, stereoselectively, the ketone to the alcohol, giving lycoramine (**5.6**).

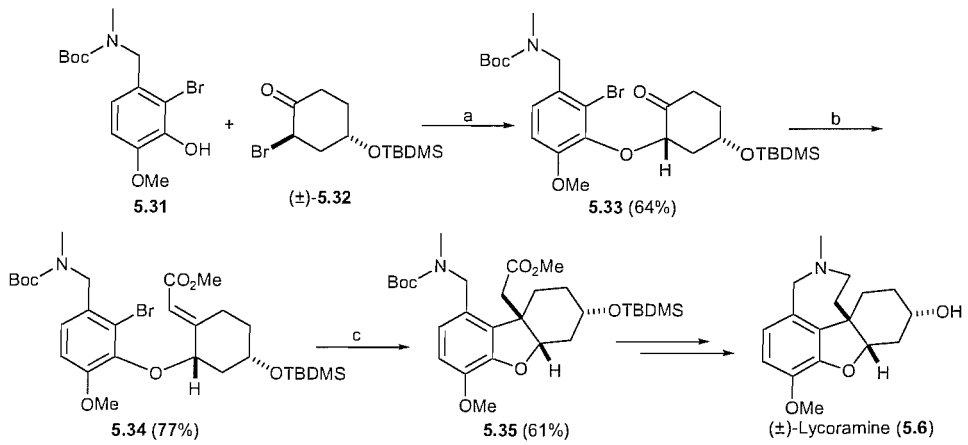
Later, in 1987, Ackland and Pinhey reported another interesting synthesis of lycoramine.[151] Applying their tin-lead exchange procedure, the readily available aryltin compound **5.24** was converted to aryllead **5.25**, an aryl cation equivalent.



Scheme 5.5 *Reagents and conditions:* a) 1 equiv. $Pb(OAc)_4$, 5 mol% $Hg(OAc)_2$, $CHCl_3$, 40 °C; b) py, $CHCl_3$, **5.26** and **5.27**, 0 → 55 °C; c) $AlCl_3$, $CHCl_3$, 0 °C.

The isomeric mixture of ketoesters **5.26** and **5.27** was arylated regioselectively with **5.25** under basic conditions, providing the key intermediate **5.28** in very good yield. Under Lewis-acidic conditions **5.28** underwent demethylation and intramolecular Michael addition to give **5.29**. Over a few straightforward steps this was converted to secondary amine **5.30**, an advanced intermediate in Martin and Garrison's synthesis, thus completing a formal synthesis of lycoramine.

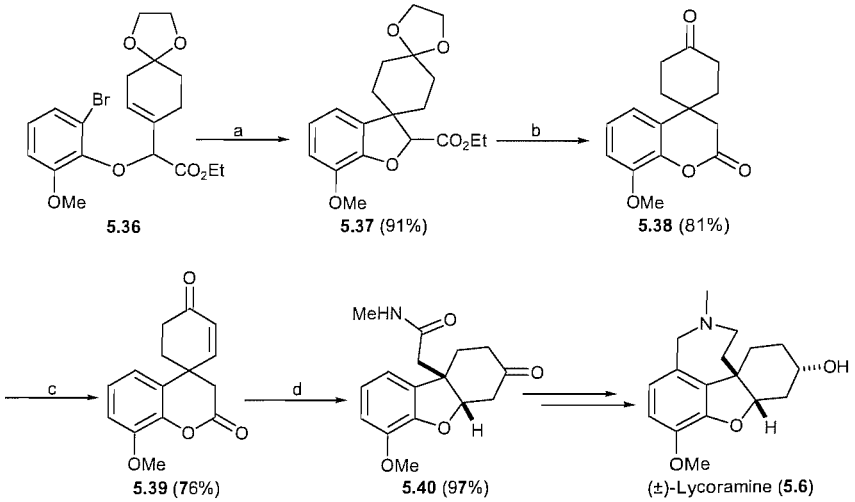
So far, through both the biomimetic and non-biomimetic approaches, a trend is apparent where the benzylic quaternary centre is constructed first, then the ether linkage is created through an intramolecular Michael addition. The only exception was Schultz's 1977 non-biomimetic synthesis. Parker and Kim's 1992 synthesis of lycoramine echoed Schultz's work and set a trend for subsequent approaches.[152]



Scheme 5.6 *Reagents and conditions:* a) TBAB, NaOH (aq), CH_2Cl_2, 0 °C → rt; b) $Ph_3P{=}CHCO_2Me$, THF, reflux; c) 10 mol% AIBN, Bu_3SnH, C_6H_6, reflux.

The fragments **5.31** and **5.32**, both readily obtained from commercially available materials, were coupled by a simple nucleophilic displacement (Scheme 5.6). The resulting bicyclic ketone **5.33** was olefinated to give α,β–unsaturated ester **5.34**. This underwent a radical cyclisation to tricycle **5.35**, which, after formation of the aza-ring and deprotection of the alcohol, gave lycoramine (**5.6**).

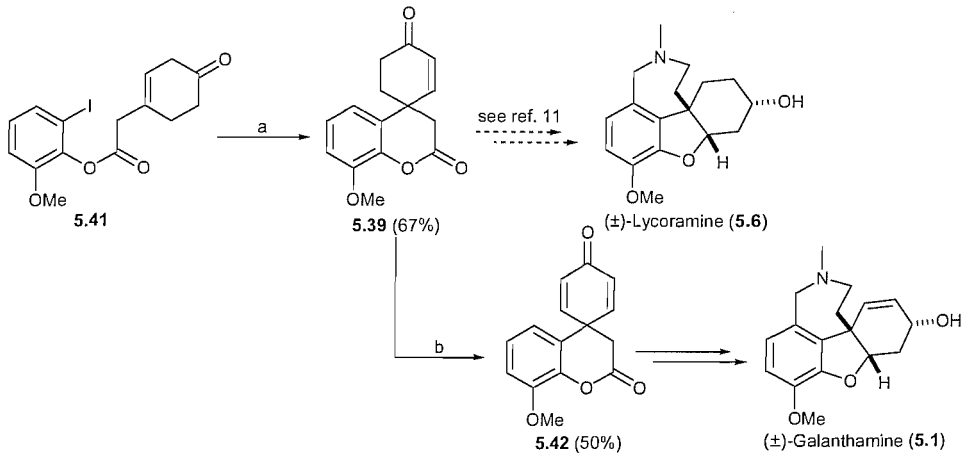
Hoshino *et al* also employed a similar strategy in their 1993 synthesis of lycoramine.[153] Under homolytic conditions, intermediate **5.36** underwent a high yielding intramolecular cyclisation, creating the quaternary centre (Scheme 5.7). SmI_2-mediated cleavage of the phenoxy ether in the α-ester position of **5.37**, followed by simultaneous lactonisation and acetal cleavage gave **5.38**, which was oxidised to enone **5.39**. Opening of the lactone in **5.39** with $MeNH_2$, then Michael addition of the resulting phenol to the enone functionality afforded **5.40**, which was converted to (±)-lycoramine (**5.6**) in two further steps.



Scheme 5.7 *Reagents and conditions:* a) 50 mol% AIBN, Bu_3SnH, $PhCH_3$, reflux; b) i) SmI_2, HMPA, MeOH, THF; ii) 3N HCl (aq); c) $(PhSeO)_2O$, $PhCH_3$, reflux; d) 40% aq. $MeNH_2$, THF.

Hoshino knew that to achieve the total synthesis of galanthamine (**5.1**), enone **5.39** would need to be oxidised to the corresponding dienone. However, attempts to oxidise **5.39** further were unsuccessful.

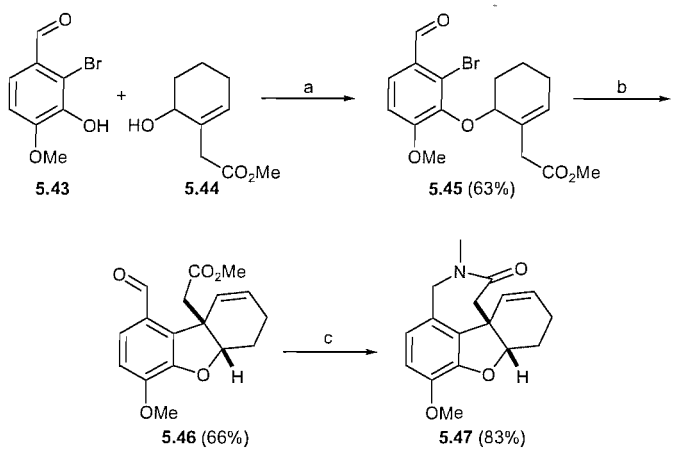
Hoshino's work was later developed by Guillou *et al* in 1999 who published a simpler alternative route to Hoshino's intermediate enone **5.39** *via* the intramolecular Heck reaction of **5.41** (Scheme 5.8), constituting a formal synthesis of lycoramine (**5.6**).[154]



Scheme 5.8 *Reagents and conditions:* a) 10 mol% $Pd_2(dba)_3$, 20 mol% dppe, TlOAc, CH_3CN, reflux; b) 4 Å molecular sieves, $(PhSeO)_2O$, CH_2Cl_2, reflux.

Guillou later completed the total synthesis of galanthamine (**5.1**).[155] This required oxidation of enone **5.39** to dienone **5.42**, a transformation that Hoshino was earlier unable to effect with the use of $(PhSeO)_2O$.[153] Guillou found that the inclusion of 4 Å molecular sieves in the reaction caused the oxidation to proceed satisfactorily (Scheme 5.8). The synthesis was then finished using Hoshino's methodology.

Recently, a number of groups have been working on an approach which is similar to that used by Parker, Hoshino and Guillou, where the radical cyclisation is replaced by an intramolecular Heck reaction. This means that after the cyclisation there is a residual alkene, which instantly makes galanthamine (**5.1**) very accessible. These reports were published in quick succession through 2000 and 2001.

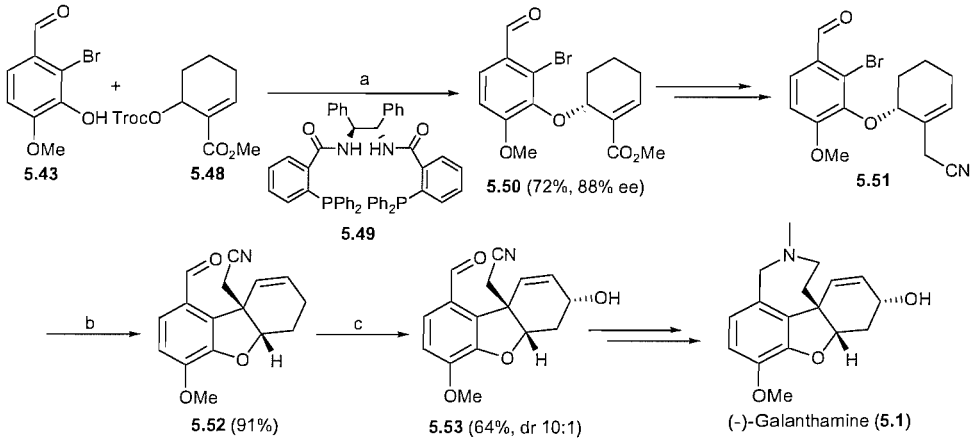


Scheme 5.9 *Reagents and conditions:* a) DEAD, PPh_3, $PhCH_3$; b) $Pd(PPh_3)_4$, K_2CO_3, $PhCH_3$, 107 °C; c) $MeNH_2$, CH_3OH, rt then $NaBH_4$, 0 °C.

The first synthesis of this type was by Fels *et al.*[156] Fragments **5.43** and **5.44** were coupled by a Mitsunobu reaction (Scheme 5.9). The resulting aryl allyl ether **5.45** underwent an intramolecular Heck reaction to give tricycle **5.46**. Reductive amination with methylamine gave a secondary amine which cyclised on work up to amide **5.47**. The authors commented that galanthamine could be accessed by reduction of the amide in **5.47** then oxidation at the allylic position, but no attempts to accomplish this were reported. Fels noted that if enantiomerically pure alcohol **5.44** was used then an asymmetric synthesis would be possible.

Parsons *et al* published a very similar synthesis and also reached the tetracyclic compound **5.47**, but they did try to advance the work by attempting allylic oxidation of **5.47**.[157] A wide range of oxidants and conditions were investigated but none effected the desired reaction.

Trost *et al* published the first non-biomimetic asymmetric synthesis of (–)-galanthamine.[158] This was accomplished not by using an enantiomerically pure alcohol of type **5.44**, as Fels had earlier suggested, but by application of Trost's palladium-catalysed asymmetric allylic alkylation of phenols.[159] 2-Bromoisovanillin (**5.43**) was alkylated by the π-allyl-palladium complex derived from **5.48** in the presence of chiral ligand **5.49**, giving aryl allyl ether **5.50** with high enantiomeric excess (Scheme 5.10).



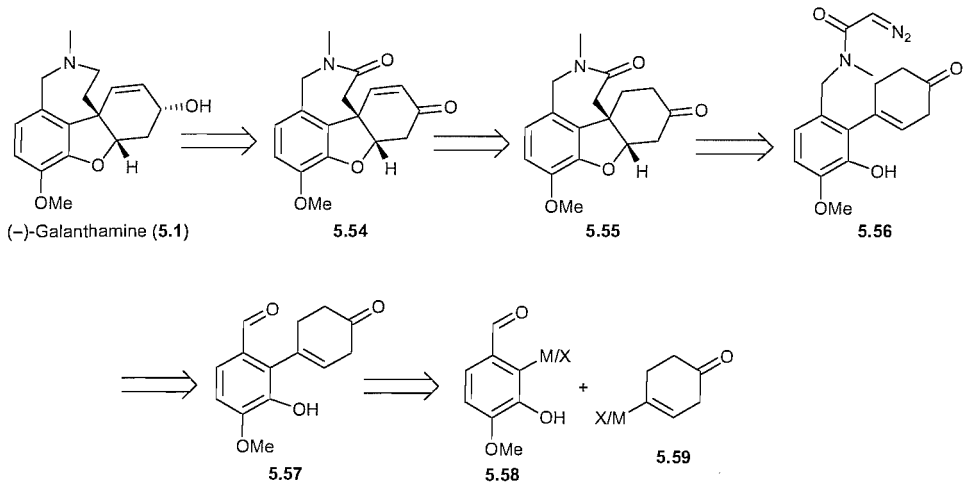
Scheme 5.10 *Reagents and conditions:* a) 3 mol% **5.49**, 1 mol% $[\eta^3\text{-}C_3H_3PdCl]_2$, NEt_3, CH_2Cl_2; b) 15 mol% $Pd(OAc)_2$, 15 mol% dppp, Ag_2CO_3, $PhCH_3$, reflux; c) SeO_2, NaH_2PO_4, dioxane, 150 °C.

Some functional group manipulation gave **5.51**, which underwent an efficient intramolecular Heck reaction resulting in **5.52**. Next, Trost discovered that the

previously troublesome allylic oxidation could be accomplished using SeO_2 which delivered **5.53** with good diastereoselectivity. Ring **d** was then constructed to complete the asymmetric synthesis of (–)-galanthamine.

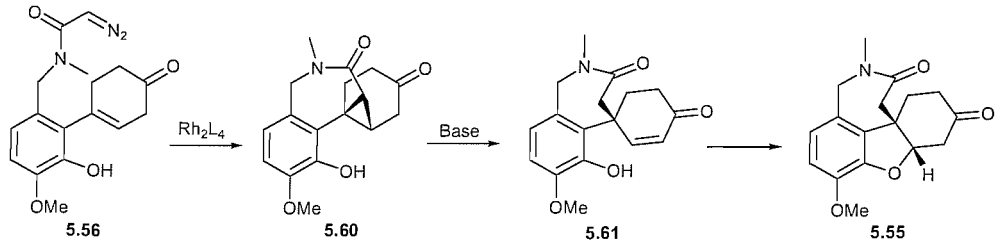
5.2.3 Proposed asymmetric route to galanthamine alkaloids

Our planned non-biomimetic synthesis is unique, being based around a rhodium-carbenoid intramolecular cyclopropanation. Retrosynthetically (–)-galanthamine (**5.1**) arises from reduction of the ketone and amide groups in **5.54** (Scheme 5.11), which in turn comes from oxidation of **5.55**.



Scheme 5.11 Retrosynthesis of (–)-galanthamine (**5.1**).

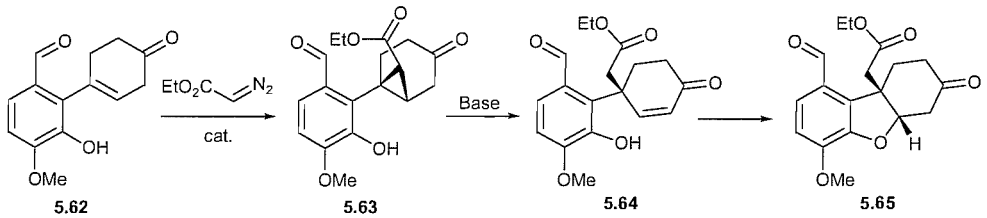
Ketone **5.55** is the result of the key cyclopropanation/rearrangement sequence (see below). Further disconnection (through a diazoacetylation and reductive amination) gives **5.57**, which can be constructed from the basic building blocks **5.58** and **5.59** by a number of coupling methods.



Scheme 5.12 Intramolecular cycloproanation-rearrangement approach to the galanthamine core.

The crucial cyclopropanation/rearrangement can be explained as follows. On treatment with a rhodium dimer complex, diazoacetamide **5.56** loses N_2 giving a rhodium carbenoid. This undergoes intramolecular cyclopropanation, resulting in the strained intermediate **5.60** (Scheme 5.12). It is hoped that this will proceed enantioselectively using a chiral rhodium dimer catalyst. Rearrangement, which may require a weak base, then provides enone **5.61** which is set up for intramolecular Michael addition to give **5.55**. (–)-Galanthamine (**5.1**) is then accessible by oxidation of **5.55** to enone **5.54** for example by treatment with IBX,[160] followed by reduction of the amide and ketone. The related alkaloid lycoramine (**5.6**) is also readily available, simply by omitting the oxidation of **5.55** to enone **5.54**.

An intramolecular cyclopropanation to form a fused 7/3-ring system has never been reported before so, if successful, the proposed strategy would represent a considerable extension of the known chemistry.



5.62 **5.63** **5.64** **5.65**

Scheme 5.13 Intermolecular cyclopropanation

If, however, the intramolecular reaction does not work, the intermolecular variant, using ethyl diazoacetate, could be a feasible alternative (Scheme 5.13).

Chapter 6 Synthesis of (–)-galanthamine

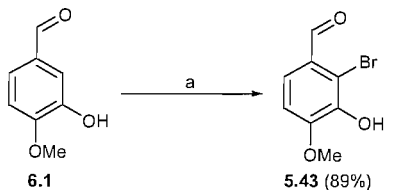
6.1 Towards the galanthamine alkaloids

From our retrosynthetic analysis of (–)-galanthamine (**5.1**) (see section 5.2.3) we identified the diazoacetamide **5.56** as a key intermediate. This chapter will discuss our attempts to synthesise **5.56** and carry out the subsequent cyclisation.

6.1.1 Synthesis of the diazoacetamide

The crucial step in our proposed synthesis of galanthamine is the $Rh_2(OAc)_4$-catalysed cyclopropanation of **5.56** (Scheme 5.12). It was important to get to this stage quickly to assess the feasibility of this reaction.

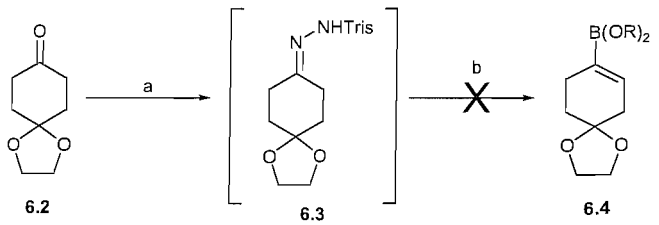
The first step would be a coupling between molecules of type **5.58** and **5.59** (Scheme 5.11). This requires the formation of either an aryl or alkenyl metallic species. Initially, isovanillin (**6.1**) was brominated regioselectively using literature conditions to give 2-bromoisovanillin (**5.43**) (Scheme 6.1).[161]



6.1 **5.43** (89%)

Scheme 6.1 *Reagents and conditions:* a) Br_2, Fe (powder), NaOAc, AcOH.

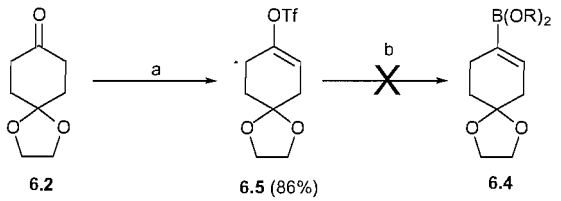
It was judged that the aryl metallic reagent would be the more difficult of the two to synthesise due to possible interference by its aldehyde and phenol functions, so work focused on making an alkenyl metallic species to couple with 2-bromoisovanillin (**5.43**), specifically alkenyl boronic acid/boronate **6.4** (Scheme 6.2).



6.2 **6.3** **6.4**

Scheme 6.2 *Reagents and conditions:* a) $TrisNHNH_2$, THF; b) i) BuLi, THF, -78 → 0 °C; ii) $B(OMe)_3$, -78 °C; iii) 2N HCl (aq).

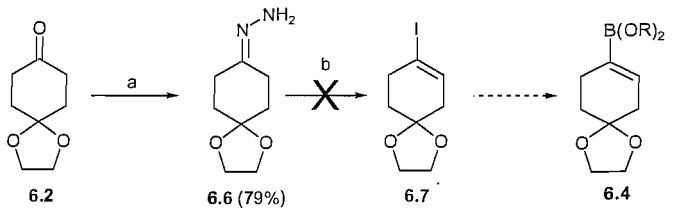
A number of strategies were investigated in the pursuit of **6.4**, all employing commercially available 1,4-cyclohexanedione *mono*-ethylene ketal (**6.2**) as the starting material. The first involved formation of **6.3**, the trisyl hydrazone of **6.2**, followed by Shapiro reaction and trapping of the intermediate alkenyl anion with $B(OMe)_3$. *In situ* hydrolysis would then furnish alkenyl boronic acid **6.4** (Scheme 6.2). This approach to alkenyl boronic acids has been shown to work previously, and has even been extended through to *in situ* Suzuki couplings.[162] Clearly, if this worked it would provide rapid access to molecules of type **6.4**. Unfortunately, it didn't work. Trisyl hydrazone **6.3** was formed easily *in situ* prior to addition of BuLi, but it was this Shapiro part of the sequence that was problematic. Thus after completing the sequence with addition of $B(OMe)_3$ followed by hydrolysis, ^1H NMR of the crude material showed no evidence of an alkene.



6.2 **6.5** (86%) **6.4**

Scheme 6.3 *Reagents and conditions:* a) Tf_2O, 2,6-di-*t*-butyl-4-methylpyridine, CH_2Cl_2, rt; b) $Pd(dppf)_2Cl_2 \cdot CH_2Cl_2$, pinacolborane, $AsPh_3$, NEt_3, dioxane, 80°C.

The second approach was based on Pd-catalysed borylation of alkenyl triflate **6.5**, readily prepared from **6.2** (Scheme 6.3).[163] This borylation can be achieved using either *bis*(pinacolato)diboron (or related diboron reagents) or pinacolborane, whose reaction with alkenyl triflates was recently reported by Masuda *et al.*[164] The former reagent is very expensive to buy and is not straightforward to make, whereas the latter is much cheaper and thus was the reagent of choice. However, Masuda's conditions failed to deliver alkenyl boronate **6.4**.

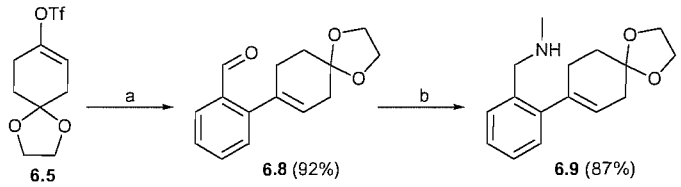


6.2 **6.6** (79%) **6.7** **6.4**

Scheme 6.4 *Reagents and conditions:* a) $N_2H_4.xH_2O$, EtOH, 50 °C; b) 1,1,3,3-tetramethylguanidine, I_2, Et_2O, rt, 2h then 90 °C, 1h.

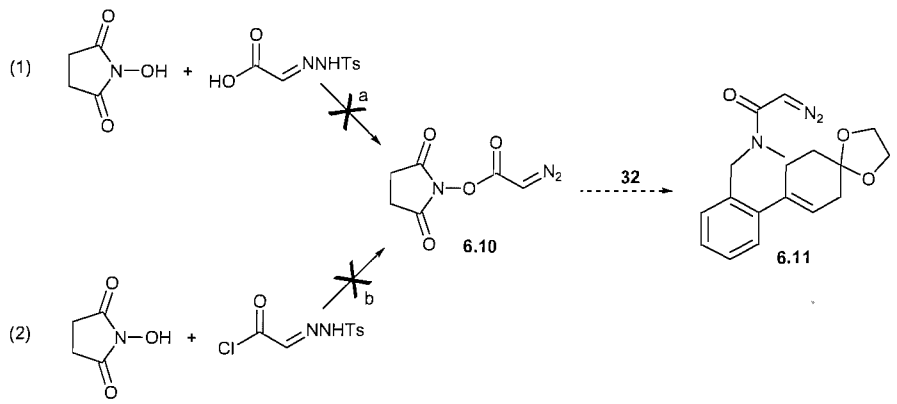
Lastly, hydrazone **6.6** was prepared in the hope that it would undergo reaction with I_2 in the presence of base to provide alkenyl iodide **6.7**,[165] which could undergohalogen-metal exchange with Li then transmetallation to boron (Scheme 6.4). However, no reaction occurred between **6.6** and I_2.

Having had no success in terms of rapid access to **6.4**, we decided to work on a model system. This would still allow us to assess the intramolecular cyclopropanation and rearrangement but would use commercially available 2-formylbenzeneboronic acid. This underwent a remarkably fast Suzuki coupling with alkenyl triflate **6.5**, the reaction being complete after 5-10 minutes at ambient temperature (Scheme 6.5).[166]



Scheme 6.5 *Reagents and conditions:* a) 2-formylbenzeneboronic acid, 5 mol% $Pd(PPh_3)_2Cl_2$, THF, Na_2CO_3, rt, 10 min; b) $MeNH_2$·HCl, NEt_3, $Ti(O^iPr)_4$, $NaBH_4$, EtOH, rt.

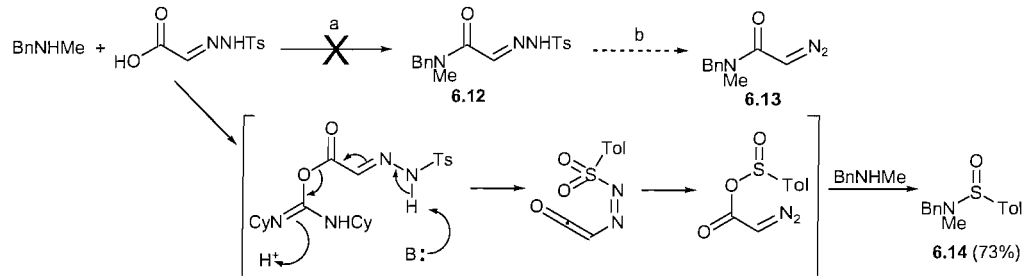
Reductive amination of **6.8** with $MeNH_2$ proved difficult, with *bis*-alkylation of $MeNH_2$ being a major problem. It was eventually found that Bhattacharyya's conditions, using $Ti(O^iPr)$,[167] provided the required amine **6.9**, with no evidence of the *bis*-alkylated product. The secondary amine **6.9** proved difficult to purify due to retention on silica, but the crude material was very clean and could be used without purification.



Scheme 6.6 *Reagents and conditions:* a) DCC, dioxane, rt; b) Na_2CO_3, CH_2Cl_2, 0 °C.

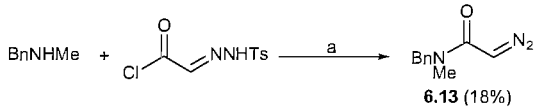
The next step was to diazoacylate **6.9** to give **6.11.** It was thought that this could be accomplished in a number of ways. Badet *et al* have shown that succinimidyl diazoacetate **6.10** is an effective reagent for the installation of the whole diazoacyl group. It is reportedly prepared by DCC coupling of N-hydroxysuccinimide and glyoxylic acid *p*-tosylhydrazone (reaction (1), Scheme 6.6).[168] However, this method failed to provide any of the required adduct **6.10**. Doyle published an alternative method which involved addition of N-hydroxysuccinimide to glyoxylic acid chloride *p*-tosylhydrazone.[169] Unfortunately, this method also proved ineffective in our hands (reaction (2), Scheme 6.6).

Some variations on this approach were tried, using benzylmethylamine as a model in order to save our limited supply of amine **6.9**. Firstly, direct coupling of benzylmethylamine to glyoxylic acid *p*-tosylhydrazone was attempted (Scheme 6.7), but did not give **6.12**, as might be expected from literature precedent.[170] Instead the reaction gave a product thought to be **6.14** (supported by mass spectrometry and ^{1}H NMR data).



Scheme 6.7 *Reagents and conditions:* a) DCC, THF, rt; b) NEt_3, MeCN, rt.

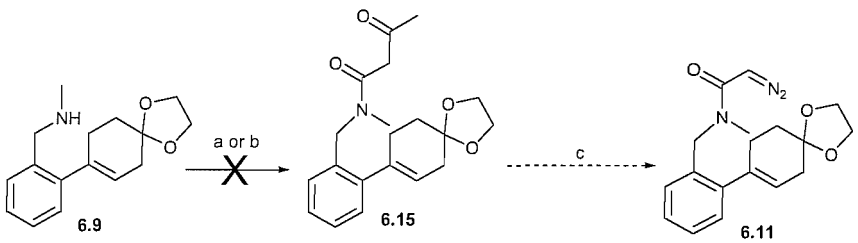
The rearrangement leading to **6.14** has not previously been reported for the DCC-mediated coupling, but is known in cases where glyoxylic acid chloride *p*-tosylhydrazone is used in conjunction with NEt_3 (Corey and Myers found in this case that the use of the weaker base DMA (N,N-dimethylaniline) in place of NEt_3 avoided the rearrangement[171]).



Scheme 6.8 *Reagents and conditions:* a) i) DMA, CH_2Cl_2, 0 °C; ii) NEt_3.

In the second variation, acylation of benzylmethylamine with glyoxylic acid chloride *p*-tosylhydrazone (employing Corey's modification, as mentioned above), followed

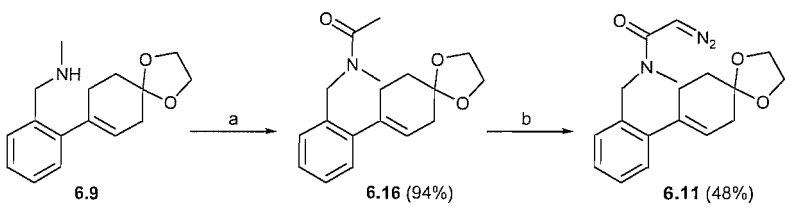
by tosylhydrazone decomposition using NEt_3 did actually provide the diazoacetamide **6.13**,[172] but the reaction was low yielding (18%) and the material was difficult to isolate due to close running impurities (Scheme 6.8). Therefore, this was deemed not to be synthetically useful. Following these unsuccessful attempts, we decided to rule out forming the diazo group by tosyl hydrazone decomposition, and instead install it by diazo transfer.



Scheme 6.9 *Reagents and conditions:* a) 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one, xylenes, 150 °C; b) diketene, CH_2Cl_2, 0 °C; c) i) diazo transfer; ii) LiOH.

We aimed to make acetoacetamide **6.15** as the substrate for diazo transfer, then deacylation using LiOH would give the required diazoacetamide **6.11**. Two acetoacylation procedures were tried (Scheme 6.9), but both were unsuccessful: firstly, heating with 2,2,6-trimethyl-1,3-dioxin-4-one yielded a complex mixture of products, probably due to decomposition of the substrate or product; secondly, reaction at rt with diketene also gave a complex mixture but due to the limited availability of diketene this reaction could not be investigated further.

Finally, diazoacetamide **6.11** was obtained by acylation of amine **6.9**,[173] followed by trifluoroacylation which activated the substrate for the subsequent diazo transfer (Scheme 6.10).[174] The trifluoroacylation-diazo transfer sequence gave diazoacetamide **6.11** in a moderate but useful 48% yield from acetamide **6.16**.

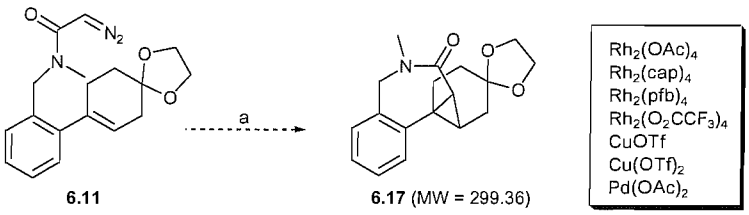


Scheme 6.10 *Reagents and conditions:* a) AcCl, $^{i}PrNEt_2$, THF, rt, 2 h; b) i) LiHMDS, THF, -78 °C then $CF_3COOCH_2CF_3$, ii) MsN_3, NEt_3, MeCN, H_2O, rt.

We were then in a position to investigate the key cyclopropanation.

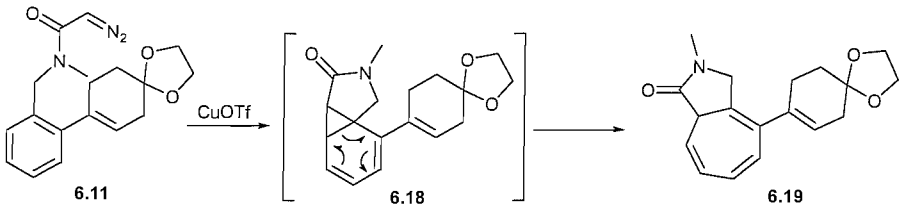
6.1.2 Cyclopropanation

A range of transition metal complexes are known to react with diazo compounds to give metal carbenoids, with rhodium dimers and Cu(I) and Cu(II) compounds being the most effective. To reflect this, a range of rhodium and copper complexes were screened for activity in our reaction (Scheme 6.3). We also included $Pd(OAc)_2$ as there have been reports of its use in this type of reaction.[175,176]



Scheme 6.11 *Reagents and conditions:* a) 5 mol% catalyst (see box), CH_2Cl_2, rt.

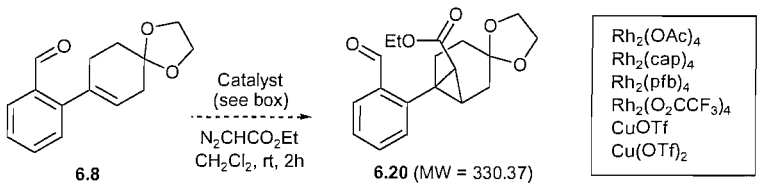
Any product formed by an intramolecular reaction of the metal carbenoid intermediate would have a mass of 299.36 so each test reaction was analysed by GCMS. Straight away we could see that $Pd(OAc)_2$ gave no such products. However, each of the other reactions produced two compounds with the expected mass. The Cu(I) and Cu(II) complexes gave these products most cleanly. The reaction was scaled up with CuOTf in order to identify the products of interest. It was clear that neither was the required cyclopropane **6.17** as the alkene C-H was still apparent in the ^{1}H NMR spectrum. One of the products was far more abundant than the other. Despite repeated attempts to isolate the major product, it could not be purified sufficiently to unambiguously identify its structure. However, it was evident from its ^{1}H NMR spectrum that the aromatic system had been disrupted. A number of examples were found in the literature of molecules of type **6.11** undergoing aromatic cyclopropanation then rearrangement to give a cycloheptatriene product (Scheme 6.12).[177] This is a facile process (competing effectively with highly favoured processes such as C-H insertion to give 5-membered rings[178-180]) and we believe that **6.11** was consumed in this way, producing cycloheptatriene **6.19**. The minor compound could not be identified.



Scheme 6.12 Formation of unwanted cycloheptatriene **6.19**.

Having tried a variety of catalysts, and given the apparent ease of the unwanted aromatic cyclopropanation pathway, we decided that no improvement in this reaction was possible.

As the intramolecular reaction did not give the desired product, our alternative plan was put into action. Thus intermolecular cyclopropanation of **6.8** with ethyl diazoacetate was investigated (Scheme 6.13).



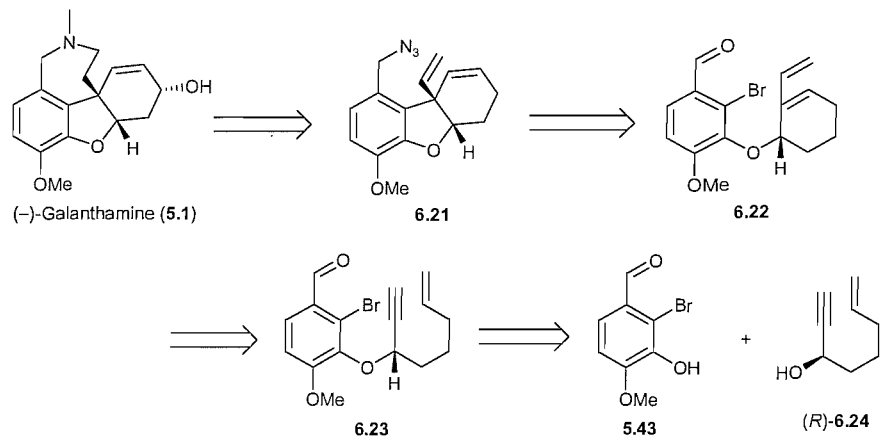
6.8 **6.20** (MW = 330.37)

Scheme 6.13

Again, a range of metal complexes were screened. This time, however, GCMS analysis of the crude mixtures showed absolutely no products with the expected mass. There is plenty of literature precedent for this reaction including examples with trisubstituted olefins so the failure was unexpected.[181-183] This initial study showed no promise so we decided not to continue work on this approach.

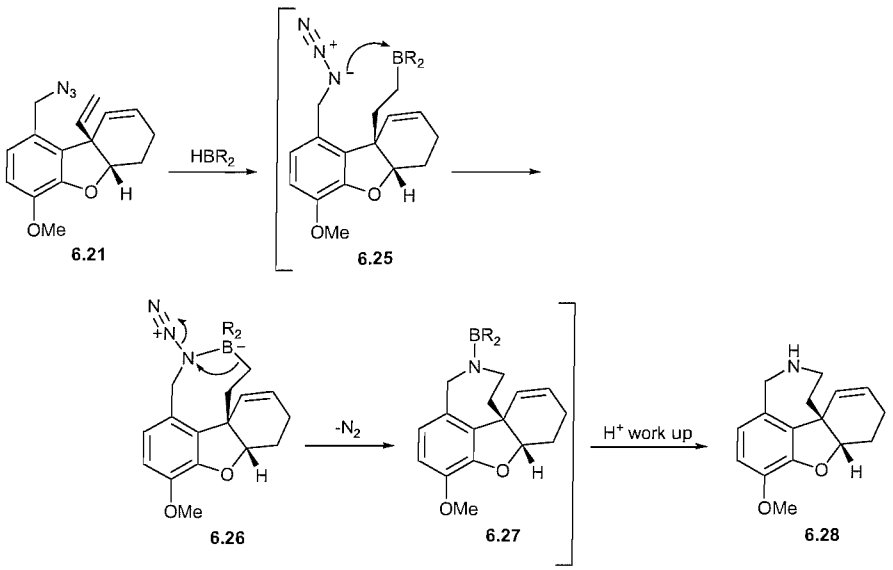
6.2 An alternative strategy

We envisaged a different approach to (–)-galanthamine (**5.1**) which, though being more conventional, would still invole some interesting chemistry (Scheme 6.14). The use of chiral alcohol (*R*)-**6.24** would provide the key stereogenic centre to facilitate a stereocontrolled synthesis.



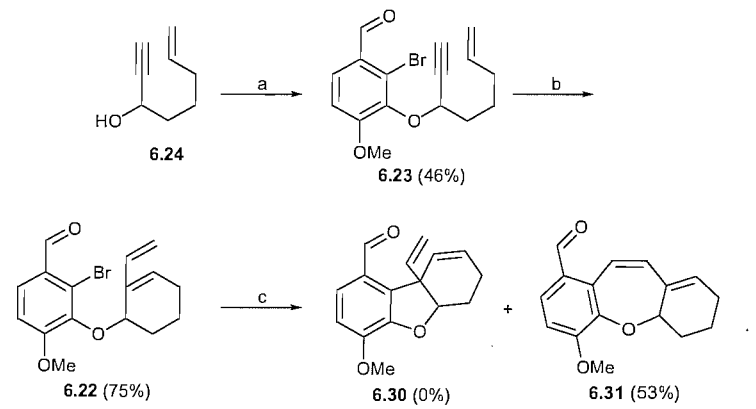
Scheme 6.14 Our new route.

We planned to convert the azide **6.21** to the galanthamine skeleton in **6.28** using a reaction developed by H. C. Brown whereby an alkyl group can be transferred from boron to nitrogen.[184] This requires hydroboration of the terminal alkene to give borane **6.25**. Nucleophilic attack of the azide onto boron then facilitates an alkyl migration, releasing N_2 (Scheme 6.15). This reaction is generally best achieved using dicyclohexylborane as the hydroborating agent. As before, the proposed work extends the existing limits of the chemistry - it has only ever been used previously to make 5- or 6-membered rings. The conversion of **6.28** to galanthamine **5.1** can be accomplished simply by *N*-methylation then allylic oxidation.[158]



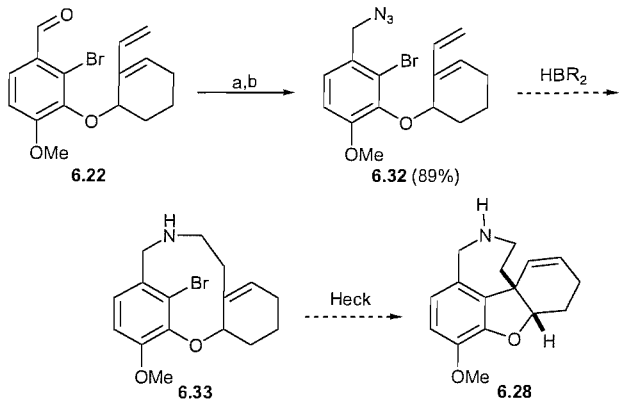
Scheme 6.15 Transfer of an alkyl group from boron to nitrogen.

Work began with the Mitsunobu reaction[185] between the known propargylic alcohol **6.24**,[186] in racemic form until the synthetic route had been proven, and 2-bromoisovanillin (**5.43**). This proceeded in a disappointing yield, possibly due to the substrates being highly hindered. A modified procedure, using sonication, has been published,[187] but this was found to offer no improvement. Enyne metathesis of **6.23** proceeded cleanly to give **6.22** in good yield (Scheme 6.16). The intramolecular Heck reaction of **6.22** was expected to occur *via* the internal olefin because this was the most electron rich and would lead to **6.30** by formation of a 5-membered ring. However, under the conditions Trost used for a similar (non-diene) substrate,[158] the reaction provided the undesired product **6.31**, with no evidence of **6.30**. Both 6-*exo*-trig and 7-*endo*-trig products were possible and the structure of **6.31** was assigned as the latter on the basis of olefinic coupling constants from ^{1}H NMR analysis.



Scheme 6.16 *Reagents and conditions:* a) DIAD, PPh_3, THF, reflux; b) 5 mol% $Cl_2(Cy_3P)_2Ru{=}CHPh$, CH_2Cl_2, reflux; c) 15 mol% $Pd(OAc)_2$, 15 mol% dppp, 3 equiv. Ag_2CO_3, $PhCH_3$, reflux.

This unexpected result was a major obstacle and the most practical way to avoid it was to re-order the synthesis as shown in Scheme 6.17 so that the hydroboration/cyclisation precedes the Heck. There is then no regioselectivity issue in the transannular Heck reaction of **6.33**.



Scheme 6.17 *Reagents and conditions:* a) $NaBH_4$, MeOH; b) $(PhO)_2P(O)N_3$, DBU, $PhCH_3$.

A foreseeable obstacle was the azide/alkylboron cyclisation which has only ever been used previously to make 5- or 6-membered rings. Now we needed to use the reaction to form a 10-membered ring.

Our existing intermediate, aldehyde **6.22**, was easily converted to azide **6.32** by $NaBH_4$ reduction to the alcohol then reaction with diphenylphosphoryl azide (89% over two steps, Scheme 6.17).[188] For the hydroboration/cyclisation, dicyclohexylborane was prepared *in situ* by reaction of $BH_3.SMe_2$ with 2 equiv. of

cyclohexene, then **6.32** was added. TLC analysis of the reaction showed a complex mixture and GCMS provided no evidence of the expected product **6.33**. Due to the multi-stage nature of the reaction, it was difficult to identify where it had failed. However, when 4-methoxystyrene was teated with "dicyclohexylborane" (prepared as above) and worked up with H_2O_2, the expected hydroxy product was not evident. This test reaction demonstrated that there was a problem with the formation of dicyclohexylborane. The quality of the $BH_3.SMe_2$ was brought into question but another batch gave no improvement. To rule out problems with the formation of the dialkylborane, the pre-formed reagents pinacolborane and 9-BBN were reacted with **6.32**. These reactions also resulted in complex mixtures with no evidence of the desired product **6.33**. Due to a lack of time this reaction was not investigated further.

6.3 Conclusions and further work

Two routes to the tetracyclic structure of the galanthamine alkaloids have been devised, both of which feature ambitious applications of known chemistry. The carbenoid cyclopropanation strategy was beset with problems in the early stages, but these were overcome by using a model system. This allowed us to investigate the key intramolecular cyclopropanation step, which was found not to work. An alternative pathway, using intermolecular cyclopropanation, was also found to be ineffective. The second strategy, featuring an intramolecular ring-closing alkyl migration, was less problematic in the early stages, but it was soon found that an important Heck reaction proceeded with the undesired regioselectivity. This prompted a redesign of the synthesis which brought forward the key ring-closing alkyl migration. The first stage of this reaction was a hydroboration and it was here that the process failed.

It is doubtful whether the cyclopropanation route can be made to work without a major redesign. It is felt that the second route could be successful if further work was carried out on the hydroboration/cyclisation step. This would be facilitated greatly if the intramolecular Heck reaction could be improved, for example by removing, or masking, the second alkene from the substrate.

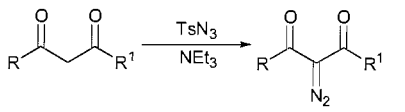
Chapter 7 α-Diazocarbonyls in synthesis

As stable, readily accessible precursors of carbenes/carbenoids, α-diazocarbonyl compounds have long been of interest to organic chemists. Under mild conditions, they undergo a great variety of reactions, and thus are valuable intermediates for organic synthesis.

7.1 Synthesis of α-diazocarbonyls

α-Diazocarbonyl compounds first became widely available in the late 1920s by the acylation of diazoalkanes,[189] the most commonly used being diazomethane (higher diazoalkanes react less efficiently[190]). Acyl chlorides,[191,192] anhydrides[193] and activated carboxylic acids (e.g. using DCC[194]) have all been used as acylating agents. A limitation is that cyclic α-diazocarbonyl compounds cannot be made in this way.

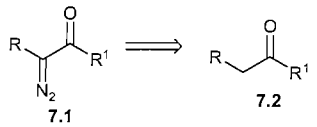
A far more useful method is the diazo transfer technique, introduced in 1967 by Regitz,[195] which is now the standard route to cyclic and acyclic α-diazocarbonyls. It involves the transfer of a diazo group from a donor (usually a sulfonyl azide) to the α-position of a carbonyl substrate, and relies on the acidity of this site. Suitably activated substrates include malonates, β-ketoesters and β-diketones, which all react under the standard Regitz conditions using TsN_3 and NEt_3 to give the corresponding diazo compounds (Scheme 7.1).[195,196]



R, R^1 = alkoxy; R, R^1 = alkyl; R = alkyl, R^1 = alkoxy

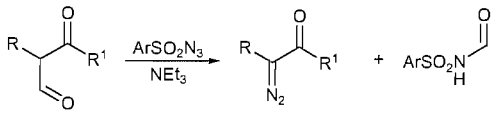
Scheme 7.1 Diazo transfer.

Where the required diazo compound is flanked by only one carbonyl group, i.e. **7.1**, the logical precursor **7.2** is only singly activated (Scheme 7.2).



Scheme 7.2 Retrosynthesis of a *mono*-carbonyl diazo compound.

This can be a problem, but is often overcome by adjusting the system of base and diazo donor. However, better results arise from prior activation of the substrate as a dicarbonyl, for example by formylating the singly activated compound.[195,196] During the diazo transfer reaction, the formyl group is removed, hence the process is known as deformylative diazo transfer, and the by-product is an *N*-formyl sulfonamide (Scheme 7.3). Acetyl[197,198] and trifluoroacetyl[199,200] groups are also commonly used.



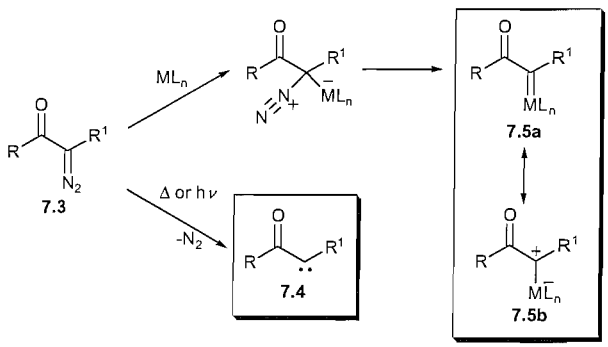
Scheme 7.3 Deformylative diazo transfer.

Many modifications to the original Regitz procedure have been developed, including the use of bases such as K_2CO_3,[201] KF,[202,203] and NaH/crown ether,[203] and diazo donors that include various arylsulfonyl azides,[204,205] MsN_3[199,206] and TfN_3.[207] Phase transfer conditions have also been used.[208] For base sensitive substrates, diazo transfer at pH 0-8 is possible using azidinium salts as diazo donors.[209]

There are other routes to α-diazocarbonyls,[210] but these are seldom employed since the advent of the diazo transfer reaction.

7.2 Carbon-carbon bond formation using α-diazocarbonyls

Diazo decomposition of α-diazocarbonyl compounds **7.3** can be effected thermally, photochemically or catalytically (with suitable transition metals) to give carbenes **7.4** or carbenoids (metal complexed carbenes) **7.5** (Scheme 7.4) which have a range of useful applications in synthetic chemistry to be discussed later.



Scheme 7.4 Diazo decomposition.

Free carbenes **7.4**, formed thermally or photochemically, are traditionally thought to show little selectivity in their reactions, whereas carbenoids **7.5** are complexed to a

metal centre so their reactivity can be tuned using the metal. Rhodium(II) acetate dimer is the most popular catalyst for diazo decomposition because it generally gives high yields and good selectivities. Importantly, the acetate ligands can be replaced with other carboxylates or amides and in this way many catalysts have been developed to alter regio- and stereoselectivity.

The carbene and carbenoid intermediates produced by diazo decomposition can undergo a range of reactions, with C-H insertion, cyclopropanation and ylide generation (followed by rearrangements) being among the most synthetically useful.

7.2.1 C-H insertion

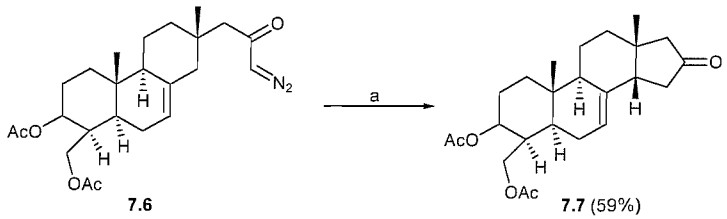
The majority of carbon-carbon bond forming reactions require the two reacting species to be suitably functionalised. Importantly, carbenes or carbenoids can insert into unactivated C-H bonds meaning that the diazo group is the only functional group required in the reactants. Accordingly, there is a potential lack of selectivity and it is true that intermolecular C-H insertions are not generally useful for this reason. Therefore most of the applications have been in intramolecular reactions.

The regio- and stereoselectivity of $Rh_2(OAc)_4$ catalysed intramolecular reactions are well understood and a number of general trends have appeared:

- Where possible, five membered ring formation is favoured.[211]
- C-H insertion normally occurs *via* the least sterically demanding course.[212]
- The level of substitution of the insertion site affects the reaction rate: reactivity is tertiary > secondary > primary when the substituents are alkyl groups. This is due to alkyl groups being inductively electron donating so more substitution means a more electronegative site, which is more vulnerable to attack by the electrophilic rhodium carbenoid.[212]
- Other nearby electron donating or withdrawing groups can respectively enhance or suppress the reactivity of a site.[213]
- Changing the ligands on the rhodium dimer can affect the regioselectivity of insertion, for example replacing the acetate ligands on $Rh_2(OAc)_4$ with acetamides (less electron withdrawing) gives a less electrophilic carbenoid which inserts at the most electron rich site.[214]

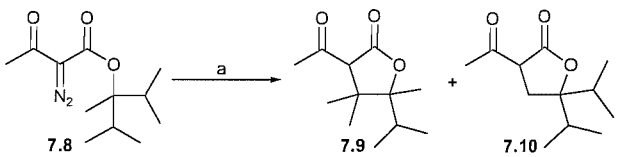
- Control of absolute stereochemistry can be achieved using chiral rhodium dimer complexes.[215]

Some examples have been chosen to illustrate the use of the C-H insertion. Wenkert *et al* converted isopimaradiene **7.6** into a steroid skeleton **7.7** *via* a regio- and stereoselective $Rh_2(OAc)_4$ catalysed C-H insertion (Scheme 7.5).[216] Taber and Ruckle found allylic methylenes to be less reactive than aliphatic methylenes,[212] but in this case the opposite is true.



Scheme 7.5 *Reagents and conditions:* a) 10 mol% $Rh_2(OAc)_4$, 1,2-dimethoxyethane.

Doyle *et al* showed that the regioselectivity of C-H insertion can be affected by the use of different rhodium dimer complexes. [214] Substrate **7.8** can cyclise by C-H insertion to two possible γ-lactone products (Scheme 6.6). Doyle found that on heating with the electron-withdrawing catalyst $Rh_2(pfb)_4$, **7.8** cyclised to give **7.9** and **7.10** in a ratio of 39:61 (entry 1, Table 7.1), almost exactly the predicted statistical mixture based on the ratio of tertiary to primary C-H bonds.



Scheme 7.6 *Reagents and conditions:* a) see Table 7.1.

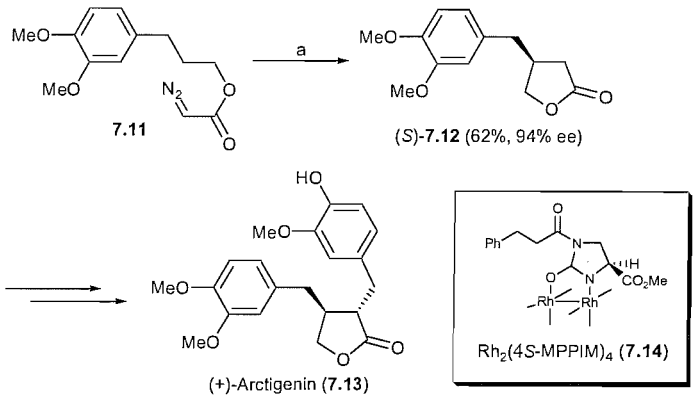
Entry	Catalyst	Conditions	Yield (**7.9** + **7.10**)	Ratio **7.9**:**7.10**
1	$Rh_2(pfb)_4$	C_6H_6, 80 °C	61%	39:61
2	$Rh_2(OAc)_4$	C_6H_6, 80 °C	97%	90:10
3	$Rh_2(cap)_4$	C_6H_6, 80 °C	89%	>99:1

Table 7.1 C-H insertion conditions

With the less electron-withdrawing complex $Rh_2(OAc)_4$, the ratio of products was 90:10 (entry 2, Table 7.1). In this case, the carbenoid is less electrophilic so reaction

at an electron-rich tertiary site is favoured. Furthermore, with the least electron-withdrawing catalyst $Rh_2(cap)_4$, reaction at the most electron rich site is highly favoured and the ratio of products is >99:1.

Doyle *et al* synthesised a number of members of the lignan lactone family of natural products using an asymmetric C-H insertion. An example is the synthesis of (+)-arctigenin (**7.13**) (Scheme 7.7).[217,218]

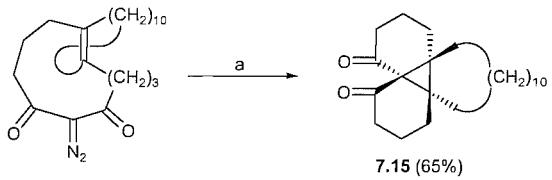


Scheme 7.7 *Reagents and conditions:* a) 1 mol% dirhodium(II) tetrakis[methyl 1-(3-phenylpropanoyl)-2-oxoimidazolidine-4(*S*)-carboxylate] (**7.14**), CH_2Cl_2, reflux.

Diazoacetate **7.11**, obtained from a cinnamic acid derivative, was treated with Rh_2(4*S*-MPPIM)$_4$ (**7.14**), an especially effective asymmetric catalyst, to give lactone **7.12** in high enantiomeric excess. Lactone **7.12** was then benzylated, followed by removal of a phenol protecting group to give (+)-arctigenin (**7.13**).

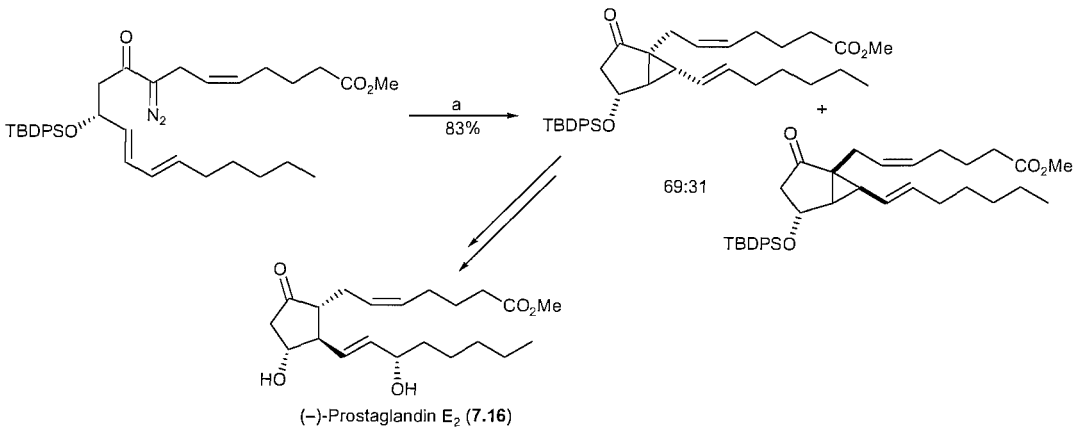
7.2.2 Cyclopropanation

Cyclopropanes are of interest because they are often found in natural products, can have important effects on biological activity and are useful as synthetic intermediates. The reaction of a carbene or carbenoid with an alkene is a convenient route to a great variety of cyclopropane containing systems. The perannulane **7.15**, an extremely hindered fused polycyclic compound, was prepared stereoselectively in this way by Marshall *et al* (Scheme 7.8).[219] The diazo decomposition was effected photochemically, with benzophenone as a photosensitizer.



Scheme 7.8 *Reagents and conditions:* a) Ph_2CO, hν, C_6H_6.

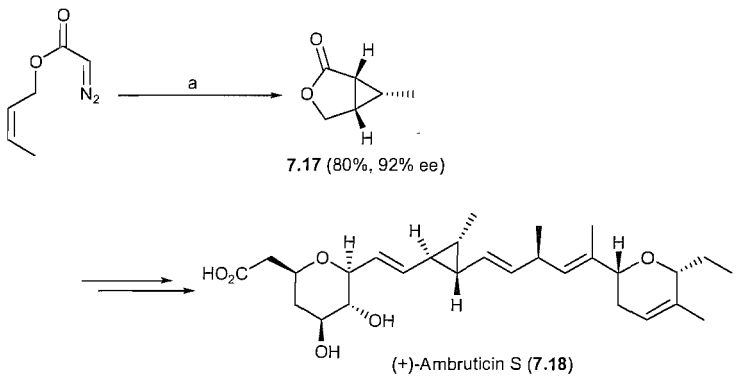
Taber and Hoerrner employed a $Rh_2(OAc)_4$-catalysed cyclopropanation in their synthesis of (–)-prostaglandin E_2 (**7.16**) (Scheme 7.9).[220]



Scheme 7.9 *Reagents and conditions:* a) 1 mol% $Rh_2(OAc)_4$, CH_2Cl_2.

This proved to be modestly diastereoselective for the required isomer (69:31), which underwent subsequent modification to yield the target compound **7.16**.

A cyclopropanation employing a rhodium(II) dimer with chiral ligands was recently used by Martin *et al* as an early step in their synthesis of the antifungal antibiotic (+)-ambruticin S (**7.18**) (Scheme 7.10).[221]

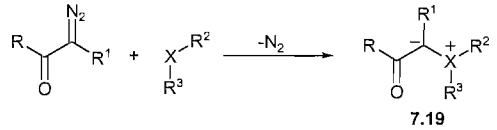


Scheme 7.10 *Reagents and conditions:* a) 5 mol% $Rh_2(5S\text{-MEPY})_4$, CH_2Cl_2.

The reaction proceeded with a high level of enantioselectivity to provide cyclopropane **7.17**.

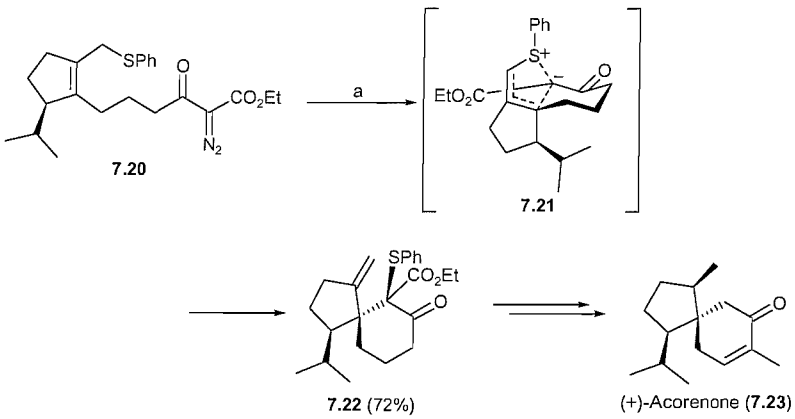
7.2.3 Ylide formation

Carbenoids are electrophilic and therefore they can react with heteroatoms to form ylides **7.19** (Scheme 7.11).



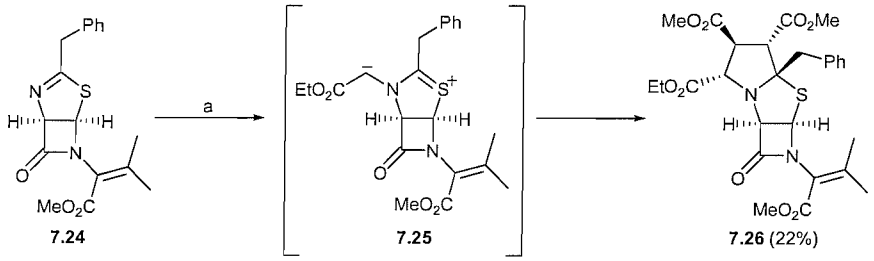
Scheme 7.11 Ylide formation.

Ylides commonly undergo dipolar additions and various rearrangements. A rearrangement was employed by Kido *et al* in the synthesis of the sesquiterpene (+)-acorenone (**7.23**) (Scheme 7.12).[222] The carbenoid generated from **7.20** was attacked by the internal sulfur nucleophile, resulting in an ylide which underwent a [2,3]sigmatropic rearrangement. The reaction proceeded through the transition state **7.21** to form spirocycle **7.22** stereoselectively.



Scheme 7.12 *Reagents and conditions:* a) 1 mol% $Rh_2(OAc)_4$, C_6H_6.

Thomas *et al* reported the intramolecular reaction of thiazoloazetidinone **7.24** with ethyl diazoacetate to give ylide **7.25** (Scheme 7.13).[223] Dipolar addition to dimethyl fumarate gave **7.26**, with no other stereoisomers detected.



Scheme 7.13 *Reagents and conditions:* a) 2 equiv. dimethyl fumarate, 3 equiv. N_2CHCO_2Et, 20 mol% $Cu(acac)_2$, CH_2Cl_2.

Although the yield is low, the reaction is notable for creating three new C-C bonds and four stereogenic centres with good selectivity.

7.3 Brown group synthesis of furofuran lignans

The carbenoid C-H insertion reaction has recently been applied by our group as the key step in the construction of a variety of *endo,exo*-furofuran lignans. Examples are Asarinin (**7.27**) and Epimagnolin A (**7.28**) (Figure 7.1).[224-227]

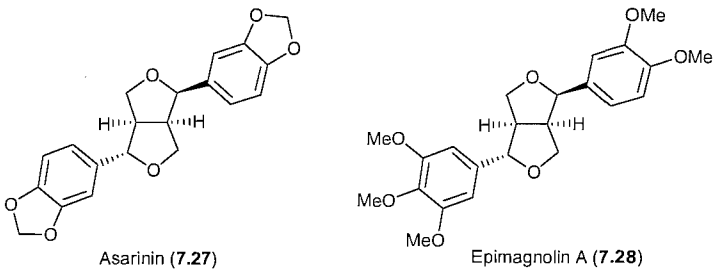
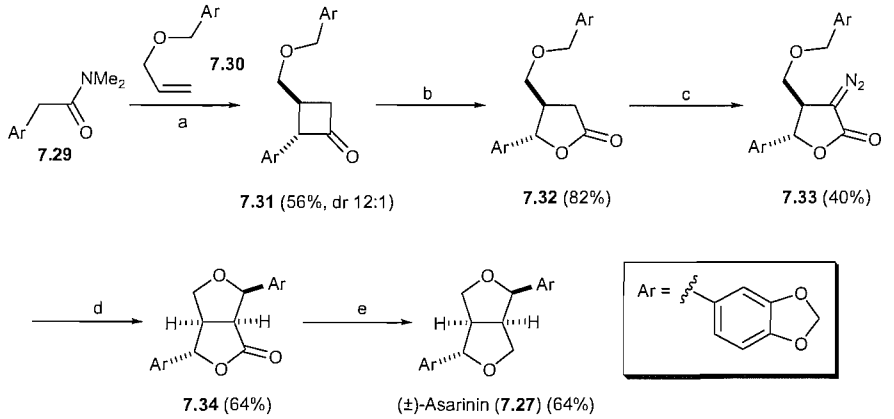


Figure 7.1 *endo,exo*-Furofuran lignans.

The furofuran class of natural products is one of the largest subgroups of the lignan family. They have been shown to have anti-HIV, anti-tumour and anti-fungal biological activities, among others.[228]

The first generation synthesis employed a [2+2] keteniminium-olefin cycloaddition to give cyclobutanone **7.31** (Scheme 7.14). This was converted to lactone **7.32** using a Baeyer-Villiger reaction. α-Diazolactone **7.33** could not be prepared by direct or deformylative diazo transfer to **7.32**, but a sequence involving formation of a triazine anion, trapping by acylation then decomposition using DMAP delivered **7.33** in 40% yield.

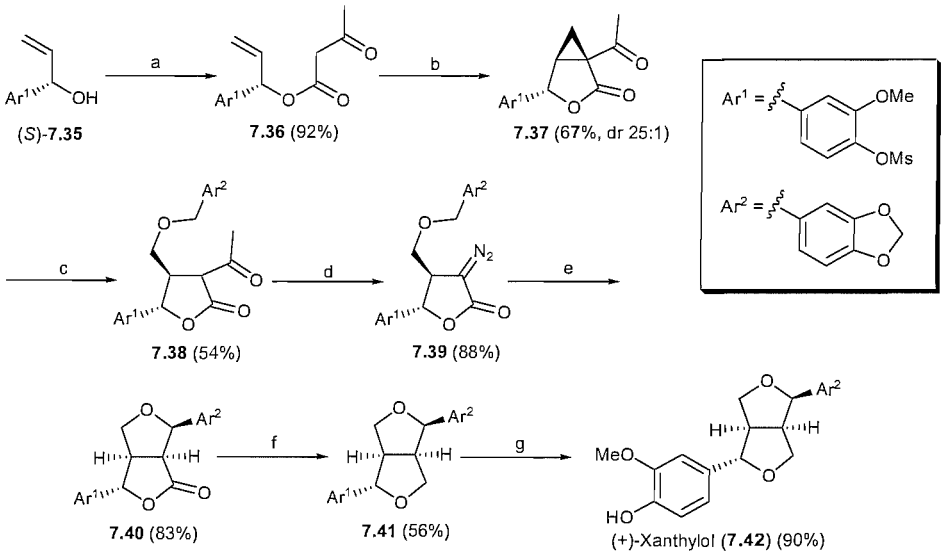


Scheme 7.14 *Reagents and conditions:* a) i) Tf_2O, CH_2Cl_2, –25 °C then K_2CO_3, 2,6-di-*t*-butylpyridine, **7.30**; ii) $NaHCO_3$ (aq); b) H_2O_2, AcOH, 70 °C; c) i) LiHMDS,

THF; ii) 4-nitrobenzenesulfonyl azide, –78 °C; iii) AcCl; iv) DMAP, THF; d) 2 mol% $Rh_2(OAc)_4$, CH_2Cl_2, rt; e) i) $LiAlH_4$, THF; ii) MsCl, pyr.

It was presumed that the key C-H insertion could be influenced to produce both the *endo/exo*- and *exo/exo*-diastereomers by using chiral rhodium(II) dimer catalysts. However, the use of achiral rhodium(II) acetate surprisingly provided the *endo/exo*-configuration exclusively. Lastly the lactone 7.**34** was reduced to the diol, then recyclised to give the natural product target **7.27**. This approach has been used to synthesise a number of *endo,exo*-furofuran lignans, but is limited by the fact that there is no control of absolute stereochemistry in the initial [2+2] cycloaddition.

The second generation route was designed to allow the asymmetric synthesis of furofurans. Allylic alcohol **7.35** was resolved enzymatically then acetoacylated to give **7.36**. This underwent oxidative cyclisation with $Mn(OAc)_3$ which selectively gave the required diastereomer of **7.37**. The electrophilic cyclopropane was opened with a benzyl alcohol under Lewis-acidic conditions (Scheme 7.15).



Scheme 7.15 *Reagents and conditions:* a) 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one, xylenes, 150 °C; b) $Mn(OAc)_3$, $Cu(OAc)_2$, KOAc, AcOH, 70 °C; c) Ar^2CH_2OH, 10 mol% $Mg(ClO_4)_2$, 2,6-di-*t*-butylpyridine; d) NaN_3, Tf_2O, $^nBu_4NBr$, 2 M NaOH/hexane/MeCN (2:1:1), 0 °C; e) 2 mol% $Rh_2(OAc)_4$, CH_2Cl_2, rt; f) i) $LiAlH_4$, THF; ii) MsCl, NEt_3, DMAP, CH_2Cl_2; g) 3M KOH (aq), MeOH, dioxane, 50 °C.

A new deacylative diazo transfer reaction was developed which meant that **7.38** could be very efficiently converted to α-diazolactone **7.39**. This type of intermediate was

encountered in the earlier work, and again the C-H insertion proceeded with excellent diastereoselectivity. Furofuranone **7.40** was reduced and reclosed as before and finally the mesylate was hydrolysed to provide (+)-xanthylol (**7.42**). This route has been used to make a number of *endo,exo*-furofurans in enantiomerically enriched form.

7.4 Aims

The diastereoselectivity of the C-H insertion used in the synthesis of *endo,exo*-furofurans was unexpected. A study has been devised that will give an insight into the origin of this phenomenon. This requires the synthesis of α-diazolactones **7.43a-e** (Figure 7.2).

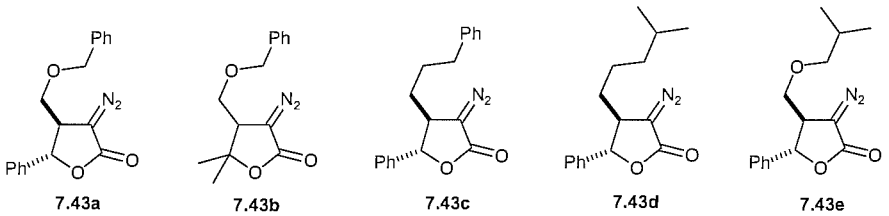
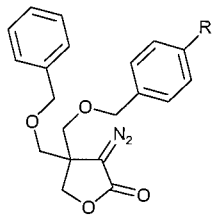


Figure 7.2 α-Diazolactones for diastereoselectivity study.

The α-diazolactones **7.43a-e** will then be decomposed by catalytic, photochemical and thermal methods in order to cause C-H insertion. It is expected that the range of steric and electronic effects, and the use of different reaction conditions, will lead to a range of diastereoselectivities. Subsequently, these reactions will be modelled and their outcomes predicted. It is hoped that the experimental and computer-generated evidence will provide some valuable insight into the reaction.



7.44

R = OMe, NO_2, etc.

Figure 7.3 Substrate for competition experiments.

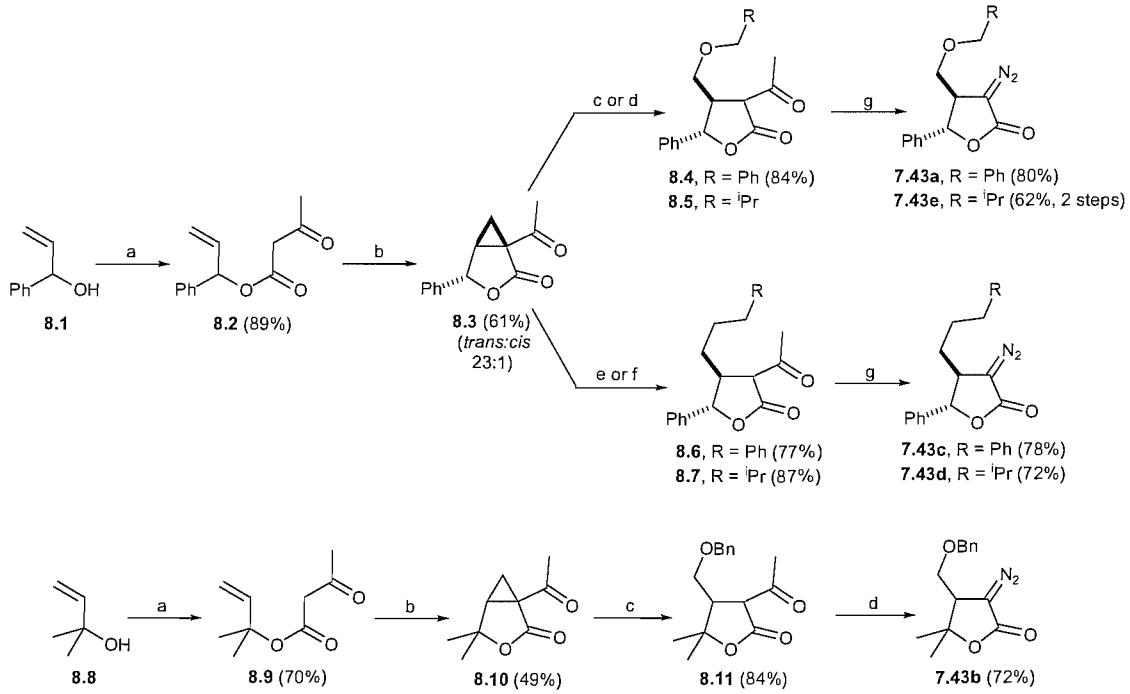
Additionally, the existing diazolactone system will be adapted to allow competition experiments in order to study how relative rates of C-H insertion vary with the electronic nature of the adjacent aryl group. Molecules of type **7.44** will be constructed and exposed to a range of diazo decomposition conditions (Figure 7.3).

Chapter 8 Diastereselectivity and relative rates of C-H insertion

In our group's synthesis of a number of furofuran lignans (section 7.3), the key step is a highly diastereoselective carbenoid C-H insertion. This chapter will discuss the synthesis of the α-diazolactones **7.43a-e** (identified in section 7.4) and the regio- and diastereoselectivity of their diazo decomposition products.

8.1 Diasteroselectivity of C-H insertion

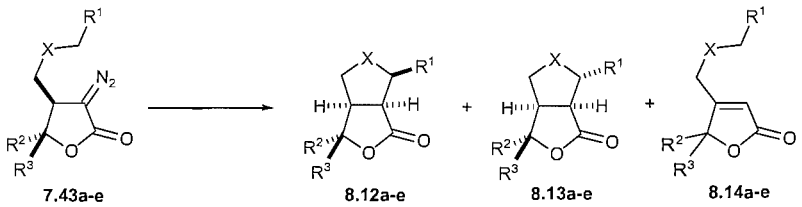
The second generation route discussed above (Scheme 7.15) is versatile and would allow the α-diazolactones **7.43a-e** to be synthesised efficiently, with four of the five available from a common intermediate.[227] Firstly, alcohol **8.1**, formed by addition of vinylmagnesium bromide to benzaldehyde, was acetoacetylated using *in situ* generated diketene (Scheme 8.1).[229] Acetoacetate ester **8.2** then underwent a highly diastereoselective Mn(III)-mediated oxidative cyclisation to give cyclopropane **8.3** as the required *trans*-isomer (*trans/cis* 23:1).[230]



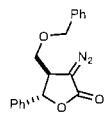
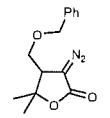
Scheme 8.1 *Reagents and conditions:* a) 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one, xylenes, 150 °C; b) $Mn(OAc)_3$, $Cu(OAc)_2$, KOAc, AcOH, 70 °C; c) BnOH, 10 mol% $Mg(ClO_4)_2$, 120 °C; d) $^{i}PrCH_2OH$, 10 mol% $Mg(ClO_4)_2$, 110 °C; e) $PhCH_2CH_2MgBr$, CuI, THF, –40 °C; f) $^{i}PrCH_2CH_2MgBr$, CuI, THF, –40 °C; g) NaN_3, Tf_2O, $^{n}Bu_4NBr$, 2 M NaOH/hexane/MeCN (2:1:1), 0 °C.

Opening of the electrophilic cyclopropane with the appropriate alcohols under $Mg(ClO_4)_2$ catalysis afforded **8.4** and **8.5**. Formation of **8.5** was accompanied by production of the corresponding enol ether (ratio 4.3:1 respectively). This has been observed previously with various alcohols, for example methanol.[227] To obtain the alkyl analogues **8.6** and **8.7**, cyclopropane **8.3** was opened with the appropriate Grignard-derived organocuprates. The four lactones then underwent deacylative diazo transfer using *in situ* generated TfN_3 under phase transfer conditions to provide α-diazolactones **7.43a,c,d** and **e**.[227] The mixture of **8.5** and its enol ether was used crude in the diazo transfer step, due to the mixture being difficult to separate, and the reaction proceeded as normal. α-Diazolactone **7.43b** was prepared in the same way as **7.43a**, starting with commercially available 2-methyl-3-buten-2-ol (**8.8**) in place of alcohol **8.1**.

Decomposition of the α-diazolactones was effected by exposure to $Rh_2(OAc)_4$ in CH_2Cl_2 at rt, heating in 1,2-dichloroethane (sealed tube) or UV radiation in CH_2Cl_2 (Scheme 8.2). The observed products were either furofuranones of type **8.12a-e** (1,5-insertion to place R^1 *endo*) and **8.13a-e** (1,5-insertion to place R^1 *exo*), or butenolides of type **8.14a-e** (1,2-hydride shift).



Scheme 8.2 Products observed from diazo decomposition. See Table 8.1.

α-Diazo lactone	Yield/%[a] (ratio of products **8.12**:**8.13**:**8.14**[b])			
	$Rh_2(OAc)_4$	80 °C	150 °C	hν
 **7.43a**	80% (>95:0:0)[c]	97% (75:0:25)[d]	95% (45:0:55)[d]	78% (0:0:100)
 **7.43b**	89% (62:38:0)	85% (0:0:100)	99% (0:0:100)[d]	99% (0:0:100)[d]

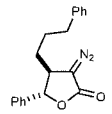
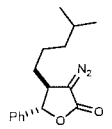
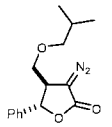
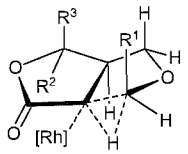
 **7.43c**	90% (53:20:27)	99% (0:0:100)[d]	86% (0:0:100)	99% (0:0:100)[c]
 **7.43d**	88% (28:5:67)	80% (0:0:100)	98% (0:0:100)[d]	83% (0:0:100)
 **7.43e**	84% (>90:0:0)	99% (61:11:28)[d]	97% (53:10:37)[d]	90% (0:0:100)

Table 8.1 [a] Combined isolated yield, unless otherwise stated. [b] Determined from crude ^{1}H NMR. [c] Contained minor impurities that could not be characterised. [d] Yield based on crude mass recovery.

Diastereoselectivity The lowest diastereoselectivity occurred for **7.43b**, which has a *gem*-dimethyl substituent in place of the phenyl group that the other α-diazolactones possess. This can be explained by considering the transition state of the C-H insertion (Scheme 8.3). When R^3 is a methyl group, there is an increased steric interaction with the nearby axial hydrogen. This has the effect that instead of the usual concave shape of a *cis*-fused bicyclic system, the transition state is flatter. Therefore there is less of a distinction between the *endo*- and *exo*- faces for the phenyl substituent on the new ring, and hence diastereoselectivity is decreased.



Scheme 8.3 Transition state model for C-H insertion.

For the other α-diazolactones, the greatest diastereoselectivity was observed for **7.43a** and **7.43e**, followed by **7.43d** then **7.43c**. It is interesting to note that this coincides with the order of electron-richness of the insertion site, which is **7.43e** > **7.43a** > **7.43d** > **7.43c**. The influence of sterics on diastereselectivity is not very clear from these experiments, because the isopropyl group roughly resembles the phenyl group sterically. It is possible that for reactions at more electron rich sites, there is a tighter transition state meaning any stereoselectivity is amplified.

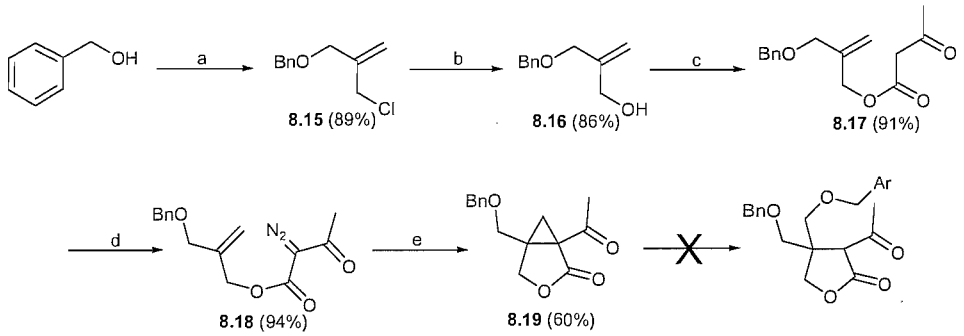
Exposure of **7.43a** to heat gave mixtures of furofuranone and butenolide in varying ratios depending on temperature, but importantly, the furofuranone always had the *endo,exo-* stereochemistry. Heating of **7.43e** also gave mixtures, but the level of stereocontrol decreased as temperature increased. This suggests that there is some interaction involving the phenyl group of **7.43a** that sets up the system very effectively for *endo,exo-* furofuranone formation.

Regioselectivity Except for **7.43a** and **7.43e**, all the α-diazolactones underwent exclusive 1,2-hydride shift when exposed to heat or UV light. Taber *et al* obtained a similar result with a different system and speculated that under their reaction conditions there was very little enthalpy of activation for both 1,2- and 1,5-insertions, and thus the regiochemical course of the reaction was instead determined by entropy of activation.[231] This explanation can be used to explain our findings, where the high-energy thermal and photochemical conditions allow entropy to dominate.

As mentioned, **7.43a** and **7.43e** avoid exclusive 1,2-hydride shift upon heating. This is possibly because they are so well activated towards 1,5-insertion, with their 1,5-insertion sites being the most electron rich. From this, it might be expected that **7.43b**, with the same side chain as **7.43a**, would have a similar regioisomeric ratio when submitted to heat or UV light. However, it is possible that the steric influence of the *pseudo-endo* methyl group in the transition state, as mentioned above, makes 1,5-insertion less favoured, giving the outcome that only 1,2-hydride shift is observed under these conditions.

8.2 Towards relative rates of C-H insertion

In order to study relative rates of C-H insertion in our α-diazolactones, we devised a synthesis based on the tried and tested route used in the above syntheses of **7.43a-e** (Scheme 8.4). To make α-diazolactones with two side chains, we decided to introduce the first at an early stage, leading to a common intermediate to which the second chain could be added divergently. The synthesis started with the *mono*-addition of benzyloxy anion to 3-chloro-2-chloromethyl-1-propene to give **8.15** in high yield.[232]



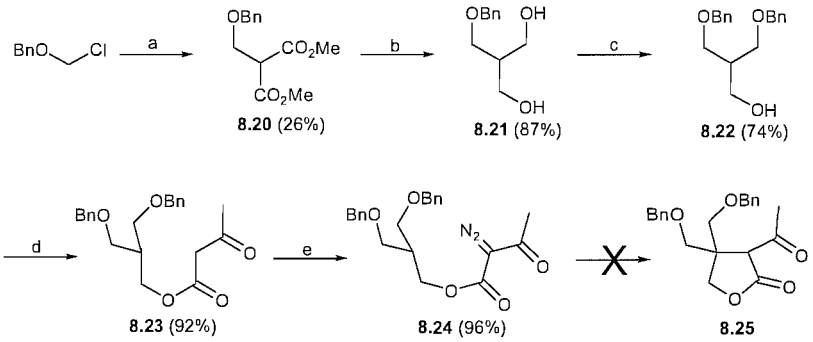
Scheme 8.4 *Reagents and conditions:* a) NaH, THF, 0 °C then 3-chloro-2-chloromethyl-1-propene, reflux; b) 1,4-dioxane, 2M NaOH, 1 mol% $^{n}Bu_4NBr$, 100 °C; c) 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one, xylenes, 150 °C; d) $4\text{-}CO_2HC_6H_4SO_2N_3$, $^{i}PrNEt_2$, MeCN; e) 3 mol% $Rh_2(OAc)_4$, CH_2Cl_2.

Allyl chloride **8.15** was hydrolysed to allyl alcohol **8.16**, which, upon exposure to diketene (formed *in situ*)[229] afforded acetoacetate ester **8.17**. The crucial Mn(III)-mediated oxidative cyclisation was found to be ineffective in converting **8.17** to cyclopropane **8.19**. This was probably because the steric bulk or electronic character of the reaction site had been altered by the presence of the side chain. Instead, **8.17** underwent diazo transfer (using 4-carboxybenzenesulfonyl azide) then treatment with $Rh_2(OAc)_4$ to give **8.19** *via* cyclopropanation.

Efforts to open cyclopropane **8.19** with benzyl alcohols and even benzyl mercaptan gave complex mixtures of products, in which there was no evidence of the required products. A survey of the literature revealed that nucleophilic openings of similarly substituted cyclopropanes are rare. This route was abandoned.

As an alternative, it was decided to try a less economical route (Scheme 8.5) with the two side chains in place from very early on. It was decided to initially try a model synthesis, where both pendant groups of the diazo lactone were the same (i.e. **8.25**). Dimethyl malonate was alkylated with benzyl chloromethyl ether to give diester **8.20**, along with the *bis*-alkylated product (ratio *mono/bis* ~1:2.5). Reduction with $LiAlH_4$ provided diol **8.21** in good yield. Treating **8.21** with NaH followed by BnBr gave alcohol **8.22**. Acetoacetylation with diketene, followed by diazo transfer generated **8.24**, which we hoped would undergo C-H insertion, as favoured by 5-membered ring formation and reaction at a tertiary C-H bond. However, on treatment with $Rh_2(OAc)_4$, the expected lactone **8.25** was not formed. Instead, the reaction gave a

mixture of products that could not be identified or isolated. The use of alternative catalysts gave no improvement in the result, so work could not continue.



Scheme 8.5 *Reagents and conditions:* a) $CH_2(CO_2Me)_2$, NaH, THF, 0 °C; b) $LiAlH_4$, THF; c) NaH, THF, 0 °C then BnBr; d) 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one, xylenes, 150 °C; e) 4-$CO_2HC_6H_4SO_2N_3$, $^iPrNEt_2$, MeCN.

8.3 Conclusions

A number of α-diazolactones with varying steric and electronic properties underwent diazo decomposition under a range of conditions. Derivative **7.43b**, with *gem*-dimethyl substituents, was found to behave very differently to its closest relation **7.43a**, with both regioselectivity and stereoselectivity compromised by the effect of a *pseudo*-axial substituent in the transition state. For the other four α-diazolactones, without a *pseudo*-axial substituent in the transition state, it was found that the more electron-rich the 1,5-insertion site, the more favoured this was over 1,2-hydride shift, though 1,2-hydride shift dominates under high temperature and photochemical conditions. When 1,5-insertion occurs, the diastereoselectivity is greater where the insertion site is most electron rich.

No study of relative rates of insertion was possible as the two attempted routes to suitable substrates were unsuccessful.

8.4 Further work

This investigation has, as intended, provided some insight into the reactions of our α-diazolactones, but it has also raised further questions and our interpretation requires further clarification. It would therefore be desirable to extend the study to look at the effects of steric bulk, examine the impact of different catalysts such as $Rh_2(pfb)_4$ and $Rh_2(Cap)_4$ and assess the role of temperature in the catalytic reactions. The computer

modelling intended to accompany our experimental work has not been carried out as a suitable expert could not be found. This tool would allow us to probe the reaction from different angles and add extra clarity to our interpretations.

Our attempts to synthesise the competition substrates failed because the cyclopropane **8.19** could not be opened using benzyl alcohols. There may be a way of overcoming this by first opening **8.19** with TMSI,[233,234] then displacing the iodide using benzyl alcohols. It is also possible that the second route, with both benzyl ether side chains installed early on, could be successful if the methyl ketone portion of diazo **8.24** were removed giving a *mono*-carbonyl diazo. These have been shown to be useful in the preparation of γ-lactones, for example by Doyle *et al.*[217,218]

Chapter 9 Experimental

General procedures

^{1}H NMR and ^{13}C NMR were recorded using a Bruker AC300 or AV300 (at 300 and 75 MHz) or a Bruker DPX400 (400 and 100 MHz) in $CDCl_3$ with chloroform (7.26 ppm ^{1}H, 77.50 ppm ^{13}C) as an internal reference or C_6D_6 with benzene (7.15 ppm ^{1}H, 128.62 ppm ^{13}C). Chemical shifts δ are given in ppm; multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br. (broad); coupling constants, *J*, are reported in Hz. Infrared spectra were recorded on a Nicolet Impact 400 FTIR spectrometer or a Nicolet 380 with a Smart Orbit adaptor. Peaks are reported in cm^{-1} with intensity s (strong), m (medium), w (weak), br (broad). Low resolution mass spectra using chemical ionisation (CI) were recorded on a Thermoquest Trace GC-MS with a 15 metre Rtx-5MS column, 0.25 mm ID, 0.25 micron. The MS source is a combined EI/CI source with a quadrupole analyser. Low resolution mass spectra using electrospray ionisation (ES) were recorded on a Fisons VG platform single quadrupole mass spectrometer.

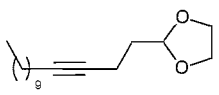
Enantiomeric excess *ee* was determined by HPLC using an HP1090 Series II instrument with a normal phase Chiral CD-Ph column, 254 nm detection and eluting with ^{i}PrOH/hexane mixtures. Optical rotation $[\alpha]_D$ was measured using a PolAAr 2001 at 589 nm with a 2 dm cell.

Thin-layer chromatography was performed on Merck silica gel plates with F_{254} indicator. Visualisation was accomplished by UV light and/or by staining in ceric ammoniun molybdate solution or potassium permanganate solution. Column chromatography was performed with 35-70 μm silica gel (Fisher Davisil).

Dichloromethane was distilled from calcium hydride and tetrahydrofuran was distilled from sodium/benzophenone before use. Where appropriate, other reagents and solvents were purified by standard techniques.[235]

All reactions were performed under a dry argon or nitrogen atmosphere in oven and/or flame dried glassware, except for reactions using water as a solvent, which were run in air.

2-Tetradec-3-ynyl-1,3-dioxolane (4.2)

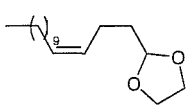


$C_{17}H_{30}O_2$

MW = 266.42

Following Carballeira's method,[117] a solution of 1-dodecyne (5.00 g, 30.1 mmol) in THF (50 mL) at –78 °C was treated with ^{n}BuLi (2.31 M in hexanes, 13.0 mL, 30.1 mmol). The reaction was allowed to warm to –50 °C over 30 min then DMPU (7.2 mL, 60.1 mmol) and 2-(2-bromoethyl)-1,3-dioxolane (3.5 mL, 30.1 mmol) were added. After stirring for 4 h, the reaction was quenched by addition of sat. aq. NH_4Cl (50 mL). The organic phase was separated and the aqueous extracted with CH_2Cl_2 (3 x 30 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo* to give a crude pale yellow oil. After purification on silica (130 x 50 mm, 1-7% EtOAc/hexane) the title compound **4.2** was obtained as a colourless oil (5.29 g, 19.9 mmol, 66%): R_f 0.63 (10% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 2954 (m), 2925 (s), 2852 (m), 1740 (s), 1454 (w), 1377 (w), 1238 (m), 1160 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 7.0 Hz, C**H**$_3$), 1.24-1.37 (14H, m, C**H**$_2$), 1.83 (2H, dt, *J* = 7.3, 4.8 Hz, C**H**$_2$CH(OR)$_2$), 2.12 (2H, tt, *J* = 7.0, 2.3 Hz, CH$_2$C**H**$_2$C≡), 2.29 (2H, tt, *J* = 7.3, 2.3 Hz, ≡CC**H**$_2$CH$_2$CH(OR)$_2$), 3.81-4.00 (4H, m, -OC**H**$_2$C**H**$_2$O-), 4.97 (1H, t, *J* = 4.8 Hz, C**H**(OR)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 103.6 (CH), 80.8 (C), 79.0 (C), 65.1 (2 x CH_2), 33.6 (CH_2), 32.0 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 22.8 (CH_2), 18.9 (CH_2), 14.2 (CH_3), 13.9 (CH_2); LRMS (EI) *m/z* (relative intensity) 266 (20%, $[M]^+$), 237 (70%, $[M–CH_3CH_2]^+$), 139 (75%), 73 (100%). Spectroscopic characteristics are consistent with those reported in the literature.[117]

2-Tetradec-(3*Z*)-enyl-1,3-dioxolane (4.3)



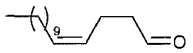
$C_{17}H_{32}O_2$

MW = 268.43

Following Carballeira's method,[117] a suspension of alkyne **4.2** (4.57 g, 17.2 mmol), Lindlar catalyst (5% Pd, 3.66 g, 1.72 mmol) and quinoline (407 μL, 3.44 mmol) in hexane was stirred in an atmosphere of H_2 at room temperature for 16 h. The catalyst was then removed by filtration. The filtrate was concentrated *in vacuo* to give a crude

pale yellow oil which was purified on silica (50 x 120 mm, 1-5% EtOAc/hexane) to provide **4.3** as a colourless oil (3.98 g, 14.8 mmol, 86%): R_f 0.70 (10% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 2958 (m), 2921 (s), 2848 (m), 1728 (m), 1458 (w), 1381 (w), 1168 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 7.0 Hz, C**H**$_3$), 1.26 (16H, br. s, C**H**$_2$), 1.71 (2H, dt, J = 7.3, 5.0 Hz, C**H**$_2$CH(OR)$_2$), 2.03 (2H, dt, J = 6.8, 6.8 Hz, C**H**$_2$CH=), 2.17 (2H, dt, J = 9.0, 8.0 Hz, =CHC**H**$_2$CH$_2$CH(OR)$_2$), 3.79-4.01 (4H, m, -OC**H**$_2$C**H**$_2$O-), 4.86 (1H, t, J = 4.8 Hz, CH(OR)$_2$), 5.32-5.43 (2H, m, C**H**=C**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.9 (CH), 128.6 (CH), 104.4 (CH), 65.0 (2 x CH_2), 34.1 (CH_2), 32.1 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 27.3 (CH_2), 22.9 (CH_2), 22.1 (CH_2), 14.2 (CH_3); LRMS (EI) *m/z* (relative intensity) 268 (20%, $[M]^+$), 239 (16%, $[M–CH_3CH_2]^+$), 225 (40%), 155 (50%), 99 (95%), 73 (100%). Spectroscopic characteristics are consistent with those reported in the literature.[117]

Pentadec-(4*Z*)-enal (4.4)



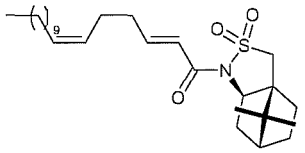
$C_{15}H_{28}O$

MW = 224.38

CAS 21944-99-0

Following Carballeira's method,[117] a solution of dioxolane **4.3** (4.50 g, 16.7 mmol) in 80% aq. AcOH was stirred at 80 °C for 5 h. The solvent was then removed *in vacuo* and the resulting crude pale yellow oil was purified on silica (50 x 130 mm, 1-5% EtOAc/hexane) giving the title compound **4.4** as a colourless oil (3.53 g, 15.7 mmol, 94%): R_f 0.39 (10% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 2958 (w), 2921 (s), 2848 (m), 1712 (w), 1462 (w), 1373 (w), 1176 (w); ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 7.0 Hz, C**H**$_3$), 1.27 (16H, br. s, C**H**$_2$), 2.04 (2H, dt, J = 7.0, 6.8 Hz, C**H**$_2$CH=), 2.37 (2H, dt, J = 7.0, 7.0 Hz, =CHC**H**$_2$CH$_2$CHO), 2.45-2.50 (2H, m, C**H**$_2$CHO), 5.28-5.47 (2H, m, C**H**=C**H**), 9.77 (1H, s, C**H**O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.3 (CH), 131.9 (CH), 127.1 (CH), 44.0 (CH_2), 32.0 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 27.4 (CH_2), 22.8 (CH_2), 20.3 (CH_2), 14.2 (CH_3); LRMS (CI, ammonia) *m/z* (relative intensity) 242 (100%, $[M+NH_4]^+$), 224 (54%, $[M]^+$). Spectroscopic characteristics are consistent with those reported in the literature.[117]

(2*R*)-*N*-[(2*E*, 6*Z*)-2,6-Heptadecadienoyl]camphor-10,2-sultam (4.6)

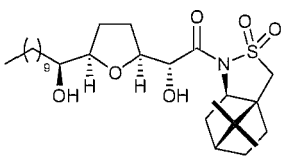


$C_{27}H_{45}NO_3S$

MW = 463.72

Following Masamune and Roush's procedure,[120] a mixture of aldehyde **4.4** (3.90 g, 17.4 mmol), diethyl-2-oxo-2-((2*R*)-*N*-camphor-10,2-sultam)-ethylphosphonate (8.21 g, 20.9 mmol) and oven-dried LiCl (886 mg, 20.9 mmol) in THF (20 mL) was treated with $^{i}Pr_2NEt$ (3.03 mL, 17.4 mmol). The reaction was stirred at room temperature for 16 h. Removal of the solvent *in vacuo* gave a crude yellow residue (9.84 g) which was purified on silica (50 x 100 mm, 0-20% EtOAc/hexane) to give the title compound **4.6** as a colourless oil (6.36 g, 13.7 mmol, 79%): R_f 0.49 (30% EtOAc/hexane); $[\alpha]^{23}_D$ – 59.9 ($CHCl_3$, *c* 0.40); IR (film) ν_{max}/cm^{-1} 2999 (w), 2954 (m), 2917 (s), 2852 (m), 1675 (m), 1634 (m), 1454 (m), 1373 (m), 1332 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 7.0 Hz, CH_2CH_3), 0.97 (3H, s, CH_3), 1.18 (3H, s, CH_3), 1.22-1.44 (18H, m, CH_2), 1.84-2.34 (11H, m), 3.43 (1H, d, *J* = 13.6 Hz, $CHHSO_2$), 3.50 (1H, d, *J* = 13.8 Hz, $CHHSO_2$), 3.92 (1H, dd, *J* = 7.5, 5.0 Hz, CHN), 5.27-5.47 (2H, m, CH=CH), 6.56 (1H, d, *J* = 15.3 Hz, =CHCON), 7.08 (1H, dt, *J* = 15.3, 7.0 Hz, CH=CHCON); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2 (C), 150.4 (CH), 131.6 (CH), 127.8 (CH), 121.3 (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), 32.8 (CH_2), 32.0 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 27.4 (CH_2), 26.6 (CH_2), 25.9 (CH_2), 22.8 (CH_2), 21.0 (CH_3), 20.0 (CH_3), 14.2 (CH_3); LRMS (ES+) *m/z* 465 (10%, $[M+H]^+$), 482 (100%, $[M+H_2O]^+$); HRMS (ES+) $[M+Na]^+$ found 486.3013, calculated 486.3012.

(2*R*)-*N*-[(*R*)-2-Hydroxy-2-[(2*S*,5*R*)-5-((*S*)-1-hydroxyundecyl)tetrahydro-2-furanyl)ethanoyl]camphor-10,2-sultam (4.7)



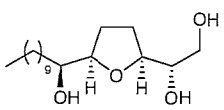
$C_{27}H_{47}NO_6S$

MW = 513.73

A solution of diene **4.6** (1.14 g, 2.45 mmol) in AcOH/acetone (2:3, 30 mL) was

cooled to –30 °C then treated with powdered $KMnO_4$ (542 mg, 3.43 mmol). After 30 min the cooling bath was removed and sat. aq. $Na_2S_2O_5$ was added portionwise to the reaction until the purple colour had disappeared. Water was added to solubilise the resulting white precipitate and the mixture was extracted with CH_2Cl_2 (4 x 50 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo* to give a crude colourless oil (dr 9:1 from ^1H NMR of crude). Chromatography on silica (50 x 130 mm, 0-25% EtOAc/hexane) provided the major diastereoisomer **4.7** as a colourless oil (823 mg, 16.0 mmol, 65%). The minor diastereisomer could not be isolated. **4.7**: R_f 0.13 (30% EtOAc/hexane); $[\alpha]^{22}_D$ –44.6 ($CHCl_3$, *c* 0.50); IR (film) ν_{max}/cm^{-1} 3260 (br. w), 2958 (m), 2925 (s), 2848 (m), 1728 (m), 1458 (w), 1332 (m), 1295 (m), 1164 (m), 1136 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 6.8 Hz), 0.96 (3H, s, C**H**$_3$), 1.15 (3H, s, C**H**$_3$), 1.22-1.50 (20H, m, C**H**$_2$, 2H sultam), 1.70-1.80 (1H, m), 1.82-1.96 (3H, m, C**H**$_2$, C**H**HCHN), 1.97-2.13 (4H, m, 2 x C**H**$_2$ THF), 2.20-2.29 (1H, m, CH**H**CHN), 3.14 (2H, br. s, O**H**), 3.44 (1H, d, *J* = 13.8 Hz, C**H**HSO$_2$), 3.51 (1H, d, *J* = 13.8 Hz, CH**H**SO$_2$), 3.89-3.97 (3H, m, CH$_2$CHOHC**H**O-, C**H**N, C**H**OHCH$_2$), 4.57 (1H, d, *J* = 2.5 Hz, C**H**OHC(O)N), 4.61 (1H, td, *J* = 5.8, 2.5 Hz, -OC**H**CHOHC(O)N); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0 (C), 83.6 (CH), 78.3 (CH), 74.3 (CH), 72.2 (CH), 65.9 (CH), 53.1 (CH_2), 49.2 (C), 48.0 (C), 44.7 (CH), 38.6 (CH_2), 33.0 (CH_2), 32.8 (CH_2), 32.0 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.0 (CH_2), 26.2 (CH_2), 24.2 (CH_2), 22.8 (CH_2), 20.9 (CH_3), 20.0 (CH_3), 14.2 (CH_3);LRMS (ES+) *m/z* 536 (100 %, $[M + Na]^+$); HRMS (ES+) $[M+Na]^+$ found 536.3020, calculated 536.3016.

(*S*)-1-[(2*S*,5*R*)-5-((*S*)-1-Hydroxyundecyl)tetrahydrofuran-2-yl]ethane-1,2-diol (4.8)



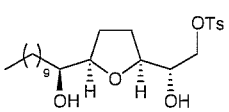
$C_{17}H_{34}O$

MW = 302.45

A solution of THF-diol **4.7** (954 mg, 1.86 mmol) in THF/H_2O (3:1, 40 mL) at 0 °C was treated with $NaBH_4$ (281 mg, 7.44 mmol). The cooling bath was removed and the reaction stirred for 2 h. Water (30 mL) was then added and the mixture extracted with CH_2Cl_2 (4 x 30 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo* giving a crude colourless oil. This was purified on silica (30 x 110 mm, 40-100% EtOAc/hexane) to give the title compound **4.8** as a colourless oil (505 mg, 1.67

mmol, 90%): R_f 0.08 (70% EtOAc/hexane); $[\alpha]^{25}_D$ +3.7 ($CHCl_3$, *c* 0.52); IR (film) ν_{max}/cm^{-1} 3432 (br. w), 2954 (m), 2921 (s), 2856 (m), 1753 (s), 1458 (w), 1413 (w), 1373 (w), 1185 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 7.0 Hz, C**H**$_3$), 1.26 (14H, br. s, C**H**$_2$), 1.44-1.50 (2H, m, C**H**$_2$), 1.75-1.80 (2H, m, C**H**$_2$CHOH), 1.95-2.04 (4H, m, 2 x C**H**$_2$ THF), 3.58 (3H, br. s, O**H**), 3.60 (1H, dt, *J* = 5.8, 3.5 Hz, C**H**OH), 3.70 (1H, td, *J* = 11.5, 3.8 Hz, C**H**OHCH$_2$CH$_2$OH), 3.71 (1H, td, *J* = 11.5, 6.0 Hz, C**H**HOH), 3.85-3.90 (1H, m, C**H**HOH), 3.90-3.95 (1H, m, C**H**O-), 4.02 (1H, td, *J* = 7.0, 3.3 Hz, C**H**O-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.3 (CH), 80.2 (CH), 74.0 (CH), 72.6 (CH), 65.4 (CH_2), 33.4 (CH_2), 32.0 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 28.7 (CH_2), 26.1 (CH_2), 24.0 (CH_2), 22.8 (CH_2), 14.2 (CH_3); LRMS (ES+) *m/z* 325 (100 %, $[M + Na]^+$); HRMS (ES+) $[M+Na]^+$ found 325.2352, calculated 325.2349.

(*S*)-2-Hydroxy-2-[(2*S*,5*R*)-5-((*S*)-1-hydroxyundecyl)tetrahydrofuran-2-yl]ethyl 4-methylbenzenesulfonate (4.9)



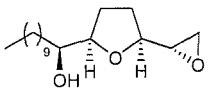
$C_{24}H_{40}O_6S$

MW = 456.64

A solution of triol **4.8** (480 mg, 1.59 mmol) in benzene (30 mL) was treated with Bu_2SnO (474 mg, 1.90 mmol) and refluxed for 3 h. The reaction was allowed to cool to rt and TsCl (333 mg, 1.75 mmol) and TBAB (256 mg, 795 μmol) were added. After 30 min the reaction was concentrated *in vacuo* to give a white residue (1.59 g) which was purified on silica (30 x 90 mm, 0-50% EtOAc/hexane) affording tosylate **4.9** as a colourless oil (608 mg, 1.33 mmol, 84%): R_f 0.50 (70% EtOAc/hexane); $[\alpha]^{23}_D$ +4.7 ($CHCl_3$, *c* 0.38); IR (film) ν_{max}/cm^{-1} 3371 (br. w), 2917 (s), 2848 (m), 1593 (w), 1458 (w), 1356 (m), 1189 (m), 1185 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 7.0 Hz, C**H**$_3$), 1.26 (14H, br. s, C**H**$_2$), 1.38-1.48 (2H, m, C**H**$_2$), 1.74-1.81 (2H, m, C**H**$_2$CHOH), 1.95-2.04 (4H, m, 2 x C**H**$_2$ THF), 2.45 (3H, s, C**H**$_3$Ar), 2.64 (2H, br. s, O**H**), 3.75 (1H, td, *J* = 6.0, 2.8 Hz C**H**OHCH$_2$CH$_2$), 3.83 (1H, td, *J* = 6.5, 2.8 Hz, C**H**OHCH$_2$OTs), 3.90 (1H, td, *J* = 6.8, 2.8 Hz, OC**H**CHOHCH$_2$CH$_2$), 4.01 (1H, td, *J* = 6.9, 2.8 Hz, OC**H**CHOHCH$_2$OTs), 4.07 (1H, dd, *J* = 10.3, 6.5 Hz, C**H**HOTs), 4.11 (1H, dd, *J* = 10.8, 5.3 Hz, CH**H**OTs), 7.34 (2H, d, *J* = 8.3 Hz,

C**H**$_{arom}$), 7.80 (2H, d, J = 8.3 Hz, C**H**$_{arom}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0 (C), 133.0 (C), 130.0 (CH), 128.1 (CH), 83.2 (CH), 78.2 (CH), 72.9 (CH), 71.9 (CH), 71.8 (CH_2), 33.4 (CH_2), 32.0 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 28.5 (CH_2), 26.0 (CH_2), 24.2 (CH_2), 22.8 (CH_2), 21.8 (CH_3), 14.2 (CH_3); LRMS (ES+) *m/z* 479 (100 %, $[M + Na]^+$; HRMS (ES+) $[M+Na]^+$ found 479.2446, calculated 479.2438.

(*S*)-1-[(2*R*,5*S*)-5-((*S*)-Oxiran-2-yl)tetrahydrofuran-2-yl]undecan-1-ol (4.10)

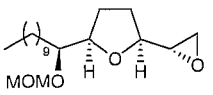


$C_{17}H_{32}O_3$

MW = 284.43

A solution of tosylate **4.9** (600 mg, 1.31 mmol) in CH_2Cl_2 (20 mL) was treated with DBU (242 μL, 1.62 mmol). After stirring for 2 h at rt, the solvent was removed giving a pale yellow oil which was purified on silica (20 x 100 mm, 0-30% EtOAc/hexane) affording epoxide **4.10** as a colourless oil (315 mg, 1.11 mmol, 48%): R_f 0.20 (40% EtOAc/hexane); $[\alpha]^{25}_D$ +4.5 ($CHCl_3$, *c* 0.40); IR (film) ν_{max}/cm^{-1} 3457 (br. w), 2917 (s), 2856 (m), 1462 (w), 1377 (w), 1291 (w), 1250 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 7.0 Hz), 1.25 (14H, br. s, CH_2), 1.42-1.54 (2H, m, CH_2), 1.74-1.84 (1H, m, C**H**HCHOH), 1.96-2.06 (4H, m, 2 x C**H**$_2$ THF), 2.07-2.14 (1H, m, CH**H**CHOH), 2.75 (1H, dd, J = 5.3, 4.3 Hz, CH(O)C**H**H), 2.84 (1H, dd, J = 5.3, 3.0 Hz, CH(O)CH**H**), 3.03 (1H, dt, J = 4.3, 2.8 Hz, C**H**(O)CH_2), 3.10 (1H, br.s, O**H**), 3.77-3.83 (1H, m, C**H**OHCH_2), 3.91 (1H, td, J = 7.0, 2.5 Hz, OC**H**CHOHCH_2), 4.08 (1H, ddd, J = 8.0, 5.5, 2.8 Hz, OC**H**CH(O)CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 84.2 (CH), 76.6 (CH), 72.9 (CH), 55.1 (CH), 44.6 (CH_2), 33.5 (CH_2), 32.4 (CH_2), 30.2 (CH_2), 30.1 (CH_2), 30.1 (CH_2), 30.1 (CH_2), 29.8 (CH_2), 26.5 (CH_2), 24.3 (CH_2), 23.2 (CH_2), 14.6 (CH_3); LRMS (ES+) *m/z* (relative intensity) 591 (100%, $[2M+Na]^+$), 348 (30%, $[M+Na+MeCN]^+$), 307 (30%, $[M+Na]^+$); HRMS (ES+) $[M+Na]^+$ found 307.2246, calculated 307.2244.

(2*R*,5*S*)-2-((*S*)-1-Methoxymethoxyundecyl)-5-((*S*)-oxiran-2-yl)tetrahydrofuran (4.11)



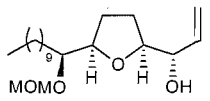
$C_{19}H_{36}O_4$

MW = 328.49

Following Sugahara and Iwabuchi's method,[122] a solution of epoxide **4.10** (120 mg,

422 μmol) and $^{i}Pr_2NEt$ (342 μL, 2.11 mmol) in CH_2Cl_2 (5 mL) at 0 °C was treated with MOMCl (96 μL, 1.27 mmol) and stirred for 16 h. The reaction was poured into water (15 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo* to give a pale yellow oil. This was purified on silica (10 x 90 mm, 0-30% EtOAc/hexane) affording epoxide **4.11** as a colourless oil (122 mg, 371 μmol, 88%): R_f 0.48 (40% EtOAc/hexane); $[\alpha]^{22}_D$ +3.2 ($CHCl_3$, *c* 0.50); IR (film) ν_{max}/cm^{-1} 2921 (s), 2856 (m), 1777 (w), 1724 (w), 1462 (w), 1381 (w), 1152 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 6.8 Hz, CH_3CH_2), 1.26 (16H, br. s, CH_2) 1.42-1.53 (2H, m, CH_2), 1.80-2.02 (4H, m, 2 x CH_2 THF), 2.62 (1H, dd, *J* = 5.0, 2.5 Hz, CH(O)CHH), 2.74 (1H, dd, *J* = 5.0, 4.0 Hz, CH(O)CHH), 2.96 (1H, m, CH(O)CH_2), 3.39 (3H, s, CH_2OCH_3), 3.63-3.74 (2H, m, CHO-, $CHCOCH_2OCH_3$), 3.91 (1H, td, *J* = 6.8, 4.3 Hz, -OCH), 4.66 (1H, d, *J* = 6.8 Hz, $CHHOCH_3$), 4.78 (1H, d, *J* = 6.8 Hz, $CHHOCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 97.1 (CH_2), 82.3 (CH), 79.5 (CH), 78.6 (CH), 55.8 (CH), 54.0 (CH_3), 44.2 (CH_2), 32.2 (CH_2), 32.0 (CH_2), 29.9 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 28.5 (CH_2), 26.3 (CH_2), 25.6 (CH_2), 22.8 (CH_2), 14.2 (CH_3); LRMS (ES+) *m/z* (relative intensity) 679 (30%, $[2M+Na]^+$), 351 (100%, $[M+Na]^+$); HRMS (ES+) $[M+Na]^+$ found 351.2510, calculated 351.2506.

(*S*)-1-[(2*R*,5*S*)-2-((*S*)-1-Methoxymethoxyundecyl)tetrahydrofuran-5-yl]prop-2-en-1-ol (4.12)



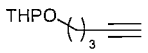
$C_{20}H_{38}O_4$

MW = 342.51

The title compound was prepared according to the method of Alcaraz *et al.*[123] A suspension of Me_3SI (372 mg, 1.83 mmol) in THF (5 mL) at −10 °C was treated with $^{n}BuLi$ (1.2 M in hexanes, 1.46 mL, 1.76 mmol) giving a milky mixture. After 30 min a solution of epoxide **4.11** (100 mg, 304 μmol) in THF (2 mL) was added. The reaction was allowed to warm to 0 °C over 30 mins then to rt and stirred for 3 h. The reaction was then quenched with water (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo* to give a colourless oil. This was purified on silica (10 x 100 mm, 0-30% EtOAc/hexane) affording allylic alcohol **4.12** as a colourless oil (96 mg, 280 μmol, 92%): R_f 0.50

(40% EtOAc/hexane); $[\alpha]^{25}_D$ +4.2 ($CHCl_3$, *c* 0.39); IR (film) ν_{max}/cm^{-1} 3454 (br), 2923 (m), 2853 (m), 1466 (w), 1377 (w); ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, *J* = 6.8 Hz, CH_2CH_3), 1.29 (16H, br. s, CH_2), 1.40-1.64 (4H, m, 2 x CH_2 THF), 1.65-1.76 (1H, m, $CHHCHOCH_2OCH_3$), 1.84-1.97 (1H, m, $CHHCHOCH_2OCH_3$), 3.22 (3H, s, OCH_3), 3.69-3.79 (3H, m, $CHOCH_2OCH_3$, CHO-, CHOH), 3.94 (1H, dt, *J* = 5.8, 5.3 Hz, -$OCHCHOHCH{=}CH_2$), 4.60 (1H, d, *J* = 6.5 Hz, -OCHHO-), 4.67 (1H, d, *J* = 6.5 Hz, -OCHHO-), 5.12 (1H, dt, *J* = 10.5, 1.8 Hz, CH=CHH), 5.44 (1H, dt, *J* = 17.3, 1.8 Hz, CH=CHH), 5.93 (1H, ddd, *J* = 17.3, 10.4, 5.5 Hz, $CH{=}CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8 (CH), 115.9 (CH_2), 98.0 (CH_2), 82.9 (CH), 82.8 (CH), 79.8 (CH), 76.2 (CH), 56.1 (CH_3), 33.2 (CH_2), 32.9 (CH_2), 30.8 (CH_2), 30.7 (CH_2), 30.6 (CH_2), 30.4 (CH_2), 28.5 (CH_2), 28.5 (CH_2), 26.6 (CH_2), 26.3 (CH_2), 23.7 (CH_2), 14.9 (CH_3); LRMS (ES+) *m/z* (relative intensity) 365 (100%, $[M+Na]^+$); HRMS (ES+) $[M+Na]^+$ found 365.2662, calculated 365.2662.

2-(Pent-4-ynyloxy)tetrahydro-2H-pyran (4.20)



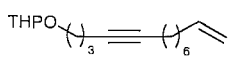
$C_{10}H_{16}O_2$

MW = 168.23

CAS 62992-46-5

A solution of 4-pentyn-1-ol (500 mg, 5.94 mmol), 3,4-dihydro-2H-pyran (750 mg, 8.91 mmol) and PPTS (149 mg, 594 μmol) in CH_2Cl_2 (10 mL) was stirred for 4 h. The reaction was then washed with water (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give **4.20** as a colourless oil (979 mg, 5.82 mmol, 98%) which was used without further purication: R_f 0.55 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3293 (w), 2942 (s), 2864 (m), 1438 (w), 1344 (w), 1197 (w); ^1H NMR (400 MHz, $CDCl_3$) δ 1.47-1.63 (4H, m, CH_2), 1.67-1.85 (4H, m, CH_2), 1.94 (1H, t, *J* = 2.8 Hz, ≡CH), 2.31 (2H, tdd, *J* = 7.0, 2.5, 1.0 Hz, $CH_2C{\equiv}$), 3.45-3.54 (2H, m, $THPOCH_2$), 3.79-3.40 (2H, m, CH_2OCHO), 4.60 (1H, dd, *J* = 4.3, 2.8 Hz, -OCHO-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 99.3 (CH), 84.5 (CH), 68.9 (CH_2), 66.3 (CH_2), 62.7 (CH_2), 31.2 (CH_2), 29.2 (CH_2), 26.0 (CH_2), 20.0 (CH_2), 15.8 (CH_2); LRMS (CI, ammonia) *m/z* (relative intensity) 85 (100%, $[O(CH_2)_3C{\equiv}CH]^+$ and $[THP]^+$). Spectroscopic characteristics are consistent with those reported in the literature.[236]

2-(Tridec-12-en-4-ynyloxy)tetrahydro-2H-pyran (4.21)

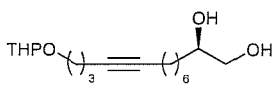


$C_{18}H_{30}O_2$

MW = 278.43

A solution of alkyne **4.20** (6.38 g, 37.9 mmol) in THF (50 mL) at –78 °C was treated with ^{n}BuLi (1.72 M in hexanes, 23.1 mL, 39.8 mmol). The reaction was allowed to warm to –50 °C over 30 min then HMPA (13.2 mL, 75.8 mmol) was added. After 10 min 8-bromo-1-octene (7.00 mL, 41.7 mmol) was added. After 3 h the reaction was quenched with sat. aq. NH_4Cl (40 mL) and extracted with EtOAc (20 mL) then CH_2Cl_2 (3 x 20 mL). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting crude pale yellow oil was purified on silica (100 x 120 mm, 0-6% EtOAc/hexane) giving the title compound **4.21** as a colourless oil (8.75 g, 61.4 mmol, 83%): R_f 0.54 (20% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 2928 (s), 2855 (m), 1137 (m), 1120 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26-1.42 (6H, m, C**H**$_2$), 1.43-1.62 (6H, m, C**H**$_2$), 1.66-1.87 (4H, m, C**H**$_2$), 2.04 (2H, br. q, *J* = 7.0 Hz, THPOCH$_2$C**H**$_2$CH$_2$), 2.13 (2H, tt, *J* = 7.0, 2.5 Hz, ≡CC**H**$_2$), 2.25 (2H, tt, *J* = 6.8, 2.5 Hz, C**H**$_2$C≡), 3.43-3.53 (2H, m, THPOC**H**$_2$), 3.81 (1H, dt, *J* = 9.8, 6.3 Hz, C**H**HOCHO), 3.87 (1H, ddd, *J* = 12.0, 7.8, 3.0 Hz, CH**H**OCHO), 4.60 (1H, t, *J* = 3.5 Hz, -OCHO-), 4.93 (1H, ddt, *J* = 10.0, 2.3, 1.3 Hz, CH=CH**H**), 4.99 (1H, ddt, *J* = 17.1, 2.0, 1.5 Hz, CH=CH**H**), 5.80 (1H, ddt, *J* = 17.1, 10.3, 6.5 Hz, C**H**=CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6 (CH), 114.7 (CH_2), 99.3 (CH), 81.0 (C), 79.9 (C), 66.6 (CH_2), 62.6 (CH_2), 34.2 (CH_2), 31.2 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 26.0 (CH_2), 20.0 (CH_2), 19.2 (CH_2), 16.2 (CH_2); LRMS (ES+) *m/z* (relative intensity) 301 (100%, $[M+Na]^+$); HRMS (ES+) $[M+Na]^+$ found 301.2141, calculated 301.2138.

(2*R*)-13-(tetrahydro-2H-pyran-2-yloxy)tridec-9-yne-1,2-diol (4.22)



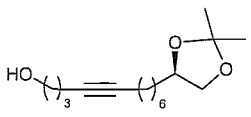
$C_{18}H_{32}O_4$

MW = 312.44

The title compound was prepared by the method described by Sharpless *et al.*[127] A mixture of hydroquinidine (anthraquinone-1,4-diyl) diether ligand ((DHQD)$_2$AQN) (277 mg, 323 μmol), $K_2OsO_2(OH)_4$ (48 mg, 129 μmol), $K_3Fe(CN)_6$ (31.9 g, 96.9

mmol) and K_2CO_3 (13.4 g, 96.9 mmol) in ^{t}BuOH (200 mL) and water (200 mL) was stirred at rt. After complete dissolution, the yellow mixture was cooled to 0 °C and enyne **4.21** (9.00 g, 32.3 mmol) added. After 16 h Na_2SO_3 (26 g) was added with vigorous stirring and the reaction was allowed to warm to rt for 1 h. The reaction was extracted with EtOAc (4 x 100 mL) and the combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting crude yellow oil was purified on silica (50 x 120 mm, 50-80% EtOAc/hexane) giving the title compound **4.22** as a very pale yellow oil (8.34 g, 26.7 mmol, 83%): R_f 0.13 (70% EtOAc/hexane); $[\alpha]^{23}_D$ –15.3 ($CHCl_3$, *c* 0.40), 90% *ee* by HPLC; IR (film) ν_{max}/cm^{-1} 3387 (br. w), 2925 (s), 2852 (m), 1438 (w), 1356 (w), 1197 (w), 1136 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23-1.62 (12H, m, C**H**$_2$), 1.66-1.87 (4H, m, C**H**$_2$), 2.05 (1H, br. t, *J* = 5.0, THPOCH$_2$C**H**HCH$_2$), 2.14 (2H, tt, *J* = 6.9, 2.2 Hz, ≡CC**H**$_2$), 2.23 (1H, br. t, *J* = 4.0, THPOCH$_2$CH**H**CH$_2$), 2.26 (2H, tt, *J* = 7.0, 2.5 Hz, C**H**$_2$C≡), 3.39-3.54 (3H, m, C**H**OH, THPOC**H**$_2$), 3.60-3.73 (2H, m, C**H**$_2$OH), 3.82 (1H, dt, *J* = 9.8, 6.3 Hz, C**H**HOCHO), 3.87 (1H, ddd, *J* = 11.3, 6.0, 3.0 Hz, CH**H**OCHO), 4.60 (1H, t, *J* = 3.0 Hz, -OCHO-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 99.2 (CH), 81.0 (C), 80.0 (C), 72.7 (CH), 67.3 (CH_2), 66.6 (CH_2), 62.5 (CH_2), 33.6 (CH_2), 31.2 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.1 (CH_2), 26.0 (CH_2), 25.9 (CH_2), 19.9 (CH_2), 19.2 (CH_2), 16.1 (CH_2); LRMS (ES+) *m/z* (relative intensity) 335 (100%, $[M+Na]^+$), 330 (90%, $[M+NH_4]^+$); HRMS (ES+) $[M+Na]^+$ found 335.2191, calculated 335.2193.

11-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]undec-4-yn-1-ol (4.23)



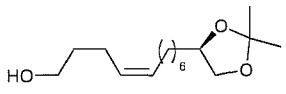
$C_{16}H_{28}O_3$

MW = 268.39

A solution of diol **4.22** (6.00 g, 19.2 mmol) and TsOH·H_2O (182 mg, 960 μmol) in MeOH (100 mL) was stirred at rt for 4 h. The solvent was then removed *in vacuo* and acetone (100 mL) was added. After stirring for 16 h the solvent was removed *in vacuo* and the resulting colourless oil purified on silica (40 x 120 mm, 20-60% EtOAc/hexane) to give the title compound **4.23** as a colourless oil (4.80 g, 17.9 mmol, 93%): R_f 0.55 (70% EtOAc/hexane); $[\alpha]^{23}_D$ –20.8 ($CHCl_3$, *c* 0.42); IR (film) ν_{max}/cm^{-1} 3432 (br), 2985 (w), 2932 (s), 2859 (m), 1434 (w), 1369 (m), 1214 (m); ^{1}H NMR (400

MHz, $CDCl_3$) δ 1.30-1.53 (14H, m, CH_2, 2 x CH_3), 1.55-1.68 (2H, m, CH_2), 1.74 (2H, tt, *J* = 6.8, 6.3 Hz, $HOCH_2CH_2CH_2C\equiv$), 2.13 (2H, tt, *J* = 6.8, 2.5 Hz, $\equiv CCH_2$), 2.27 (2H, tt, *J* = 6.8, 2.5 Hz, $HOCH_2CH_2CH_2C\equiv$), 3.50 (1H, t, *J* = 7.3 Hz, CHHO-), 3.75 (2H, t, *J* = 6.0 Hz, CH_2OH), 4.03 (1H, t, *J* = 7.3 Hz, CHHO-), 4.07 (1H, tt, *J* = 12.8, 6.5 Hz, CH_2CHO-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.1 (C), 81.5 (C), 79.9 (C), 76.6 (CH), 70.0 (CH_2), 62.6 (CH_2), 34.0 (CH_2), 32.1 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 29.1 (CH_2), 27.4 (CH_3), 26.2 (CH_3), 26.1 (CH_2), 19.2 (CH_2), 15.9 (CH_2); LRMS (ES+) *m/z* (relative intensity) 291 (100%, $[M+Na]^+$); HRMS (ES+) $[M+H]^+$ found 269.2114, calculated 269.2111.

(4*Z*)-11-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]undec-4-en-1-ol (4.24)

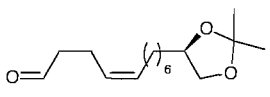


$C_{16}H_{30}O_3$

MW = 270.41

A suspension of alkyne **4.23** (3.00 g, 11.2 mmol), Lindlar catalyst (5% Pd, 238 mg, 112 μmol) and quinoline (397 μL, 3.36 mmol) in MeOH (15 mL) and EtOAc (30 mL) was stirred in an atmosphere of H_2 at room temperature for 16 h. The catalyst was then removed by filtration. The filtrate was concentrated *in vacuo* to give a crude pale yellow oil which was purified on silica (40 x 180 mm, 0-40% EtOAc/hexane) to provide *E*-alkene **4.24** as a colourless oil (2.74 g, 10.1 mmol, 91%): R_f 0.62 (70% EtOAc/hexane); $[\alpha]^{25}_D$ –17.6 ($CHCl_3$, *c* 0.44); IR (film) ν_{max}/cm^{-1} 3379 (br. w), 2925 (s), 2856 (m), 1736 (s), 1716 (s), 1458 (w), 1430 (w), 1360 (m), 1238 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 1.25-1.43 (14H, m, CH_2, 2 x CH_3), 1.43-1.52 (2H, m, CH_2CHO-), 1.61 (2H, tt, *J* = 7.0, 6.5 Hz, $HOCH_2CH_2$), 2.02 (2H, br. q, *J* = 6.5 Hz, $=CHCH_2$), 2.11 (2H, br. q, *J* = 8.3 Hz, $CH_2CH=$), 3.48 (1H, t, *J* = 7.0 Hz, CHHO-), 3.64 (2H, t, *J* = 6.2 Hz, CH_2OH), 4.03 (1H, t, *J* = 6.0 Hz, CHHO-), 4.07 (1H, tt, *J* = 12.8, 6.5 Hz, CH_2CHO-), 5.28-5.42 (2H, m, HC=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.1 (CH), 129.4 (CH), 109.1 (C), 76.6 (CH), 70.0 (CH_2), 63.0 (CH_2), 34.0 (CH_2), 33.1 (CH_2), 30.0 (CH_2), 30.0 (CH_2), 29.6 (CH_2), 27.6 (CH_2), 27.4 (CH_3), 26.2 (CH_3), 26.2 (CH_2), 24.1 (CH_2); LRMS (CI, ammonia) *m/z* (relative intensity) 271 (20%, $[M+H]^+$), 255 (80%, $[M–Me]^+$), 213 (100%); HRMS (ES+) $[M+Na]^+$ found 271.2271, calculated 271.2273.

(4*Z*)-11-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]undec-4-enal (4.25)

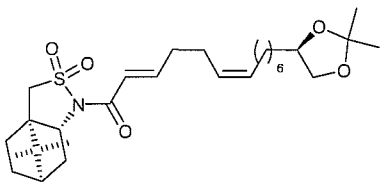


$C_{16}H_{28}O_3$

MW = 268.39

A solution of alcohol **4.24** (2.58 g, 9.54 mmol) in CH_2Cl_2 was treated with Dess-Martin periodinane (5.26 g, 12.4 mmol) for 2 h. The solvent was then removed *in vacuo* and the white residue was purified on silica (40 x 160 mm, 0-15% EtOAc/hexane) to give aldehyde **4.25** as a colourless oil (2.30 g, 8.57 mmol, 93%): R_f 0.61 (40% EtOAc/hexane); $[\alpha]^{25}_D$ –13.8 ($CHCl_3$, *c* 0.50); IR (film) ν_{max}/cm^{-1} 2985 (w), 2929 (m), 2856 (m), 2719 (w), 1725 (s), 1456 (w), 1378 (m), 1369 (m), 1214 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 1.17-1.53 (14H, m, CH_2, 2 x CH_3), 1.55-1.69 (2H, m, CH_2CHO-), 2.03 (2H, q, *J* = 6.8 Hz, =CHCH_2), 2.36 (2H, q, *J* = 7.0 Hz, $OHCCH_2CH_2CH$=), 2.48 (2H, tt, *J* = 7.0, 1.3 Hz, CH_2CHO), 3.49 (1H, t, *J* = 7.3 Hz, CHHO-), 4.02 (1H, t, *J* = 6.0 Hz, CHHO-), 4.05 (1H, tt, *J* = 12.6, 6.3 Hz, CH_2CHO-), 5.28-5.46 (2H, m, HC=CH), 9.77 (1H, s, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6 (CH), 132.1 (CH), 127.6 (CH), 109.1 (C), 76.6 (CH), 70.0 (CH_2), 44.3 (CH_2), 34.1 (CH_2), 30.0 (CH_2), 29.9 (CH_2), 29.6 (CH_2), 27.7 (CH_2), 27.5 (CH_3), 26.2 (CH_3), 26.2 (CH_2), 20.6 (CH_2); LRMS (ES+) *m/z* (relative intensity) 323 (30%, $[M+Na+MeOH]^+$), 291 (100%, $[M+Na]^+$); HRMS (ES+) $[M+Na]^+$ found 291.1931, calculated 291.1931.

(2*R*)-*N*-[(2*E*,6*Z*)-13-((4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)heptadec-2,6-dienoyl]camphor-10,2-sultam (4.26)



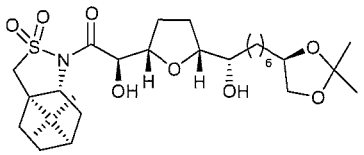
$C_{28}H_{45}NO_5S$

MW = 507.73

The title compound was prepared using Masamune and Roush's procedure.[120] A mixture of aldehyde **4.25** (2.21 g, 8.23 mmol), diethyl-2-oxo-2-((2*R*)-*N*-camphor-10,2-sultam)-ethylphosphonate (3.89 g, 9.88 mmol) and oven-dried LiCl (420 mg, 9.88 mmol) in THF (20 mL) was treated with $^iPr_2NEt$ (1.43 mL, 8.23 mmol). The reaction was stirred at room temperature for 16 h. Removal of the solvent *in vacuo* gave a crude yellow residue (7.68 g) which was purified on silica (40 x 120 mm, 0-

35% EtOAc/hexane) to give the title compound **4.26** as a colourless oil (3.09 g, 6.09 mmol, 74%): R_f 0.48 (40% EtOAc/hexane); $[\alpha]^{23}_D$ –72.2 ($CHCl_3$, *c* 0.48); IR (film) ν_{max}/cm^{-1} 2984 (w), 2931 (m), 2856 (w), 1683 (m), 1640 (m), 1459 (w), 1370 (m), 1332 (s), 1287 (m), 1266 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, s, C**H**$_3$), 1.17 (3H, s, C**H**$_3$), 1.21-1.52 (17H, m, C**H**$_2$, C**H**$_{sultam}$), 1.54-1.70 (2H, m, C**H**$_2$CHO-), 1.84-1.94 (2H, m, C**H**$_2$), 1.96-2.07 (2H, m, C**H**$_2$), 2.07-2.15 (2H, m, C**H**$_2$), 2.15-2.24 (2H, m, C**H**$_2$), 2.26-2.34 (2H, m, C**H**$_2$), 3.43 (1H, d, *J* = 13.6 Hz, C**H**HSO$_2$), 3.49 (1H, t, *J* = 7.3 Hz, C**H**HO-), 3.50 (1H, d, *J* = 13.8 Hz, CH**H**SO$_2$), 3.92 (1H, dd, *J* = 7.5, 5.0 Hz, C**H**N), 4.02 (1H, t, *J* = 6.0 Hz, CH**H**O-), 4.05 (1H, tt, *J* = 12.8, 6.2 Hz, CH$_2$C**H**O-), 5.29-5.44 (2H, m, C**H**=C**H**), 6.57 (1H, dt, *J* = 15.0, 1.4 Hz, =C**H**CON), 7.08 (1H, dt, *J* = 15.0, 7.0 Hz, C**H**=CHCON); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6 (C), 150.7 (CH), 131.7 (CH), 128.2 (CH), 121.6 (CH), 109.0 (C), 76.6 (CH), 70.0 (CH_2), 65.7 (CH), 53.7 (CH_2), 48.9 (C), 48.3 (C), 45.2 (CH), 39.0 (CH_2), 34.1 (CH_2), 33.4 (CH_2), 33.0 (CH_2), 30.0 (CH_2), 30.0 (CH_2), 29.6 (CH_2), 27.7 (CH_2), 27.5 (CH_3), 27.0 (CH_2), 26.3 (CH_3), 26.2 (CH_2), 21.3 (CH_3), 20.4 (CH_3); LRMS (ES+) *m/z* (relative intensity) 530 (100%, $[M+Na]^+$); HRMS (ES+) $[M+Na]^+$ found 530.2921, calculated 530.2910.

(2*R*)-*N*-[(*R*)-2-Hydroxy-2-[(2*S*,5*R*)-5-((*S*)-1-hydroxy-7-((4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)heptyl)tetrahydro-2-furanyl)ethanoyl]camphor-10,2-sultam (4.27)



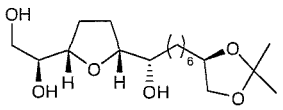
$C_{28}H_{47}NO_8S$

MW = 557.74

A solution of diene **4.26** (2.71 g, 5.34 mmol) in AcOH/acetone (2:3, 100 mL) was cooled to –30 °C then treated with powdered $KMnO_4$ (1.18 g, 7.48 mmol). After 30 min the cooling bath was removed and sat. aq. $Na_2S_2O_5$ was added portionwise to the reaction until the purple colour had disappeared. Water was added to solubilise the resulting white precipitate and the mixture was extracted with CH_2Cl_2 (4 x 50 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo* to give a crude colourless oil (dr 9:1 from ^1H NMR of crude). Chromatography on silica (50 x 220 mm, 0-40% EtOAc/hexane) provided the major diastereoisomer **4.27** as a colourless oil (1.69 g, 2.93 mmol, 55%). The minor diastereoisomer could not be isolated. **4.27**: R_f 0.12 (40% EtOAc/hexane); $[\alpha]^{25}_D$ –63.4 ($CHCl_3$, *c* 0.50); IR (film)

ν_{max}/cm^{-1} 3440 (br. w), 2929 (m), 2860 (w), 1777 (w), 1699 (m), 1462 (w), 1413 (w), 1332 (s), 1279 (m); ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (3H, s, CH_3), 1.14 (3H, s, CH_3), 1.23-1.81 (19H, m, 2 x CH_3, CH_2, CH_{sultam}), 1.82-1.97 (4H, m, CH_2), 1.96-2.15 (4H, m, 2 x CH_2 THF), 2.20-2.31 (2H, m, CH_2), 3.43 (1H, d, J = 13.9 Hz, $CHHSO_2$), 3.48 (1H, t, J = 6.8 Hz, CHHO-), 3.51 (1H, d, J = 13.9 Hz, $CHHSO_2$), 3.87-3.97 (3H, m, $CH_2CHOHCHO$-, CHN, $CHOHCH_2$), 3.98-4.15 (2H, m, CH_2CHO-, $H_2C(O)CHCHO$-), 4.57 (1H, d, J = 2.4 Hz, CHOHC(O)N), 4.61 (1H, td, J = 6.2, 2.4 Hz, -OCHCHOHC(O)N); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0 (C), 109.0 (C), 83.9 (CH), 78.6 (CH), 76.6 (CH), 74.5 (CH), 72.5 (CH), 70.0 (CH_2), 66.3 (CH), 53.5 (CH_2), 49.5 (C), 48.4 (C), 45.0 (CH), 38.7 (CH_2), 34.0 (CH_2), 33.3 (CH_2), 33.1 (CH_2), 30.0 (CH_2), 29.3 (CH_2), 27.4 (CH_2), 26.9 (CH_3), 26.4 (CH_2), 26.2 (CH_2), 26.2 (CH_3), 24.5 (CH_2), 21.2 (CH_2), 20.9 (CH_3), 20.3 (CH_3); LRMS (ES+) *m/z* (relative intensity) 540 (100%, $[M–H_2O]^+$); HRMS (ES+) $[M+Na]^+$ found 580.2195, calculated 580.2195.

(*S*)-1-[(2*S*,5*R*)-5-((*S*)-1-Hydroxy-7-((4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)heptyl)tetrahydrofuran-2-yl]ethane-1,2-diol (4.28)



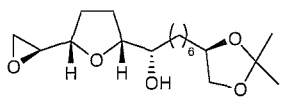
$C_{18}H_{34}O_6$

MW = 346.46

A solution of THF-diol **4.27** (1.11 g, 1.99 mmol) in THF/H_2O (3:1, 28 mL) at 0 °C was treated with $NaBH_4$ (301 mg, 8.00 mmol). The cooling bath was removed and the reaction stirred for 2 h. Water (30 mL) was then added and the mixture extracted with CH_2Cl_2 (4 x 30 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo* giving a crude colourless oil. This was purified on silica (30 x 110 mm, 50-100% EtOAc/hexane) to give the title compound **4.28** as a colourless oil (640 mg, 1.85 mmol, 93%): R_f 0.07 (70% EtOAc/hexane); $[\alpha]^{25}_D$ –12.7 ($CHCl_3$, *c* 0.50); IR (film) ν_{max}/cm^{-1} 3399 (br. s), 2929 (s), 2856 (m), 1753 (s), 1720 (s), 1458 (w), 1409 (w), 1197 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 1.25-1.69 (18H, m, CH_2), 1.78-2.01 (4H, m, 2 x CH_2 THF), 2.40 (1H, br. t, J = 4.5 Hz, OH), 2.56 (1H, br. d, J = 6.5 Hz, OH), 3.49 (1H, t, J = 7.3 Hz, CHHO-), 3.50-3.55 (1H, m, CHOH), 3.65-3.74 (2H, m, CHHOH, $CHOHCH_2CH_2OH$), 3.86 (1H, br. q, J = 6.8 Hz, CHHOH), 3.94 (1H, td, J = 6.8, 4.5 Hz, CHO-), 4.00-4.11 (3H, m, CH_2CHO-, CHHO-, CHO-); ^{13}C NMR (100

MHz, $CDCl_3$) δ 109.1 (C), 80.8 (CH), 76.6 (CH), 73.4 (CH), 70.0 (CH_2), 65.5 (CH_2), 36.3 (CH_2), 34.1 (CH_2), 31.7 (CH_2), 30.1 (CH_2), 30.0 (CH_2), 29.9 (CH_2), 28.1 (CH_2), 27.5 (CH_3), 26.7 (CH_2), 26.3 (CH_3), 26.2 (CH_2); LRMS (ES+) *m/z* (relative intensity) 329 (95%, $[M–H_2O+H]^+$), 283 (100%); HRMS (ES+) $[M+Na]^+$ found 369.2244, calculated 369.2248.

(*S*)-1-[(2*R*,5*S*)-5-((*S*)-Oxiran-2-yl)tetrahydrofuran-2-yl]-7-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]heptan-1-ol (4.29)



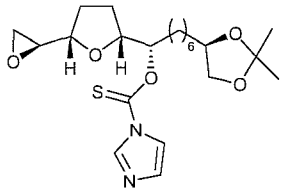
$C_{18}H_{32}O_5$

MW = 328.44

A solution of triol **4.28** (600 mg, 1.73 mmol) in benzene (40 mL) was treated with Bu_2SnO (517 mg, 2.08 mmol) and refluxed for 3 h. The reaction was allowed to cool to rt and TsCl (363 mg, 1.90 mmol) and TBAB (279 mg, 865 μmol) were added. After 30 min the reaction was concentrated *in vacuo* to give a white residue which was passed through a silica plug, washing with CH_2Cl_2. Removal of the solvent *in vacuo* gave a colourless oil. This was dissolved in CH_2Cl_2 (30 mL) and treated with DBU (516 μL, 3.46 mmol). After stirring for 2 h at rt, the reaction was concentrated *in vacuo* to give a pale yellow oil which was purified on silica (20 x 90 mm, 0-40% EtOAc/hexane) affording epoxide **4.29** as a colourless oil (420 mg, 1.29 mmol, 74%): R_f 0.18 (40% EtOAc/hexane); $[\alpha]^{25}_D$ –12.4 ($CHCl_3$, *c* 0.50); IR (film) ν_{max}/cm^{-1} 3453 (br), 2983 (w), 2931 (m), 2858 (m), 1464 (w), 1369 (m), 1252 (m), 1214 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 1.25-1.41 (14H, m, 2 x C**H**$_3$, C**H**$_2$), 1.55-1.82 (4H, m, C**H**$_2$), 1.95-2.16 (4H, m, 2 x C**H**$_2$ THF), 2.75 (1H, dd, *J* = 5.2, 4.3 Hz, CH(O)C**H**H), 2.83 (1H, dd, *J* = 5.0, 2.8 Hz, CH(O)CH**H**), 3.02 (1H, dt, *J* = 4.0, 3.0 Hz, C**H**(O)CH$_2$), 3.12 (1H, br. s, O**H**) 3.48 (1H, t, *J* = 7.3 Hz, C**H**HO-), 3.76-3.71 (1H, m, C**H**OH) 3.90 (1H, td, *J* = 7.0, 2.8 Hz -OC**H**CHOH), 4.01 (1H, t, *J* = 6.0 Hz, CH**H**O-), 4.02-4.10 (2H, m, CH$_2$C**H**O-, H$_2$C(O)CHC**H**O-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.0 (C), 84.2 (CH), 76.6 (CH), 72.8 (CH), 70.0 (CH_2), 55.1 (CH), 44.6 (CH_2), 34.1 (CH_2), 33.4 (CH_2), 30.1 (CH_2), 30.0 (CH_2), 30.0 (CH_2), 27.4 (CH_3), 26.4 (CH_2), 26.2 (CH_3), 26.2 (CH_2), 27.3 (CH_2); LRMS (ES+) *m/z* (relative intensity) 346 (100%,

$[M+H_2O]^+$), 329 (40%, $[M+H]^+$); HRMS (ES+) $[M+Na]^+$ found 351.2144, calculated 351.2142.

_O_-[(_S_)-Hydroxy-1-[(2_R_,5_S_)-5-((_S_)-oxiran-2-yl)tetrahydrofuran-2-yl]-7-[(4_R_)-2,2-dimethyl-1,3-dioxolan-4-yl]heptyl] 1H-imidazole-1-carbothioate (4.30)

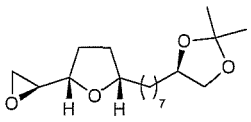


$C_{22}H_{34}N_2O_5S$

MW = 438.58

A solution of hydroxy epoxide **4.29** (100 mg, 304 μmol) and 1,1'-thiocarbonyl diimidazole (163 mg, 913 μmol) in CH_2Cl_2 was treated with DMAP (19 mg, 152 μmol). After stirring for 18 h the solvent was removed *in vacuo* and the residue was purified on silica (10 x 90 mm, 0-50% EtOAc/hexane) to give the title compound **4.30** as a colourless oil (83 mg, 1.89 μmol, 62%): R_f 0.45 (70% EtOAc/hexane); $[\alpha]^{23}_D$ – 18.6 ($CHCl_3$, *c* 0.50); IR (film) ν_{max}/cm^{-1} 2983 (m), 2932 (m), 2859 (m), 1465 (m), 1384 (s), 1327 (s), 1283 (s), 1231 (s); ^1H NMR (400 MHz, C_6D_6) δ 0.99-1.73 (22H, m, 2 x C**H**$_3$, C**H**$_2$), 2.19 (1H, dd, *J* = 5.5, 4.0 Hz, CH(O)C**H**H), 2.36 (1H, dd, *J* = 5.5, 2.5 Hz, CH(O)CH**H**), 2.48 (1H, td, *J* = 4.0, 2.5 Hz, C**H**(O)CH$_2$), 3.34 (1H, t, *J* = 7.5 Hz, C**H**HO-), 3.54 (1H, td, *J* = 6.0, 4.0 Hz, H$_2$C(O)CHC**H**O-), 3.76 (1H, dt, *J* = 7.8, 6.0 Hz, -OC**H**CHOC=S), 3.81 (1H, dd, *J* = 7.8, 6.0 Hz, CH**H**O-), 3.84-3.92 (1H, m, CH$_2$C**H**O-), 5.78 (1H, dt, *J* = 7.5, 4.8 Hz, C**H**OC=S), 6.94 (1H, s, C**H**$_{imid}$), 7.49 (1H, s, C**H**$_{imid}$), 8.38 (1H, s, C**H**$_{imid}$); ^{13}C NMR (100 MHz, C_6D_6) δ 185.5 (C), 137.4 (C), 132.2 (CH), 119.1 (CH), 109.4 (C), 85.1 (CH), 80.7 (CH), 79.0 (CH), 76.8 (CH), 70.4 (CH_2), 54.0 (CH), 43.9 (CH_2), 34.5 (CH_2), 31.4 (CH_2), 30.3 (CH_2), 30.2 (CH_2), 28.9 (CH_2), 28.0 (CH_3), 27.9 (CH_2), 26.7 (CH_2), 26.7 (CH_3), 25.7 (CH_2); LRMS (ES+) *m/z* (relative intensity) 461 (100%, $[M+Na]^+$), 439 (100%, $[M+H]^+$); HRMS (ES+) $[M+H]^+$ found 439.2264, calculated 439.2261.

(4*R*)-2,2-dimethyl-4-(7-[(2*S*,5*S*)-5-((*S*)-oxiran-2-yl)tetrahydrofuran-2-yl]heptyl)-1,3-dioxolane (4.31)

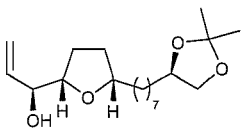


$C_{18}H_{32}O_4$

MW = 312.44

Following the procedure of Kim *et al*,[130] a solution of epoxide **4.30** (20 mg, 43 μmol), (^{n}Bu$_4$N)S_2O_8 (87 mg, 129 μmol), HCO_2Na (18 mg, 258 μmol) and Na_2CO_3 (36 mg, 344 μmol) in DMF (5 mL) was stirred at 65 °C for 45 min. After allowing to cool, the reaction was diluted with EtOAc (20 mL), washed with water (4 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified on silica (5 x 55 mm, 0-40% EtOAc/hexane) to provide the title compound **4.31** as a colourless oil (11 mg, 35 μmol, 82%): R_f 0.48 (40% EtOAc/hexane); $[\alpha]^{25}_D$ –3.8 ($CHCl_3$, *c* 0.50); IR (film) ν_{max}/cm^{-1} 2984 (m), 2930 (s), 2856 (s), 1458 (m), 1378 (m), 1369 (m), 1253 (m), 1214 (m); ^{1}H NMR (400 MHz, C_6D_6) δ 1.15-1.48 (18H, m, 2 x C**H**$_3$, C**H**$_2$), 1.48-1.68 (6H, m, C**H**$_2$CHO-, 2 x C**H**$_2$ THF), 2.30 (1H, dd, *J* = 5.5, 4.0 Hz, CH(O)C**H**H), 2.46 (1H, dd, *J* = 5.5, 2.8 Hz, CH(O)CH**H**), 2.68 (1H, dt, *J* = 4.3, 2.8 Hz, C**H**(O)CH$_2$), 3.35 (1H, t, *J* = 7.5 Hz, C**H**HO-), 3.63 (1H, td, *J* = 6.0, 4.5 Hz, H$_2$C(O)CHC**H**O-), 3.68-3.76 (1H, m, -OC**H**CH$_2$), 3.81 (1H, dd, *J* = 7.5, 6.0 Hz, CH**H**O-), 3.86-3.94 (1H, m, CH$_2$C**H**O-); ^{13}C NMR (100 MHz, C_6D_6) δ 109.3 (C), 80.9 (CH), 79.8 (CH), 76.9 (CH), 70.4 (CH_2), 54.6 (CH), 43.7 (CH_2), 36.7 (CH_2), 34.6 (CH_2), 32.1 (CH_2), 30.6 (CH_2), 30.6 (CH_2), 30.5 (CH_2), 29.4 (CH_2), 28.0 (CH_3), 27.4 (CH_2), 26.9 (CH_2), 26.7 (CH_3); LRMS (ES+) *m/z* (relative intensity) 365 (100%), 335 (70%, $[M+Na]^+$); HRMS (ES+) $[M+Na]^+$ found 335.2186, calculated 335.2192.

(*S*)-1-[(2*S*,5*S*)-5-(7-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]heptyl)tetrahydrofuran-2-yl]prop-2-en-1-ol (4.32)



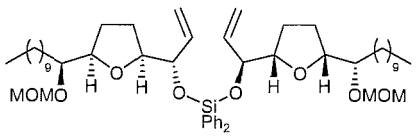
$C_{19}H_{34}O_4$

MW = 326.47

The title compound was prepared according to the method of Alcaraz *et al.*[123] A suspension of Me_3SI (188 mg, 922 μmol) in THF (5 mL) at –10 °C was treated with ^{n}BuLi (1.45 M in hexanes, 627 μL, 909 μmol) giving a milky mixture. After 30 min a

solution of epoxide **4.31** (48 mg, 154 μmol) in THF (2 mL) was added. The reaction was allowed to warm to 0 °C over 30 mins then to rt and stirred for 3 h. The reaction was then quenched with water (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo* to give a pale yellow oil. This was purified on silica (10 x 60 mm, 0-25% EtOAc/hexane) affording allylic alcohol **4.32** as a colourless oil (48 mg, 146 μmol, 95%): R_f 0.50 (40% EtOAc/hexane); $[\alpha]^{23}_D$ –12.4 ($CHCl_3$, *c* 0.52); IR (film) ν_{max}/cm^{-1} 3473 (br), 2983 (m), 2930 (s), 2857 (s) 1457 (w), 1369 (m), 1216 (m); ^1H NMR (400 MHz, C_6D_6) δ 1.21-1.52 (18H, m, 2 x C**H**$_3$, C**H**$_2$), 1.45-1.54 (6H, m, C**H**$_2$CHO-, 2 x C**H**$_2$ THF), 2.52 (1H, d, *J* = 3.8 Hz, O**H**), 3.35 (1H, t, *J* = 7.5 Hz, C**H**HO-), 3.63-3.73 (2H, m, -OC**H**CH$_2$, HOCHC**H**O-), 3.81 (1H, dd, *J* = 7.5, 6.0 Hz, CH**H**O), 3.87-3.97 (2H, m, CH$_2$C**H**O-, C**H**OH), 5.10 (1H, dt, *J* = 10.5, 1.8 Hz, CH=CH**H**), 5.41 (1H, dt, *J* = 17.3, 1.8 Hz, CH=CH**H**), 5.93 (1H, ddd, *J* = 17.3, 10.4, 5.5 Hz, C**H**=CH$_2$); ^{13}C NMR (100 MHz, C_6D_6) δ 138.8 (CH), 116.5 (CH_2), 109.3 (C), 82.8 (CH), 80.7 (CH), 76.9 (CH), 76.4 (CH), 70.4 (CH_2), 36.9 (CH_2), 34.6 (CH_2), 32.2 (CH_2), 30.6 (CH_2), 30.5 (CH_2), 30.5 (CH_2), 28.1 (CH_2), 28.0 (CH_3), 27.3 (CH_2), 26.9 (CH_2), 26.7 (CH_3); LRMS (ES+) *m/z* (relative intensity) 349 (100%, $[M+Na]^+$); HRMS (ES+) $[M+Na]^+$ found 349.2341, calculated 349.2349.

Di[((*S*)-1-[(2*R*,5*S*)-2-((*S*)-1-methoxymethoxyundecyl)tetrahydrofuran-5-yl]-2-propenyl)oxy](diphenyl)silane (4.41)



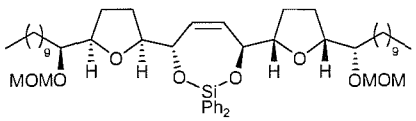
$C_{52}H_{84}O_8Si$

MW = 865.33

A solution of allylic alcohol **4.12** (20 mg, 58.2 μmol) and Ph_2SiCl_2 (6 μL, 29.1 μmol) in CH_2Cl_2 (500 μL) was treated with NEt_3 (10 μL, 64.0 mmol) and DMAP (7 mg, 58.2 μmol). After stirring at rt for 16 h the solvent was removed *in vacuo* and the resulting white residue was purified on silica (5 x 60 mm, 0-10% EtOAc/hexane) giving the title compound **4.41** as a colourless oil (12 mg, 13.9 μmol, 48%): R_f 0.59 (20% EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (6H, t, *J* = 6.8 Hz, 2 x CH_2CH_3), 1.26 (32H, br. s, C**H**$_2$), 1.38-1.54 (4H, m, 2 x C**H**$_2$CHOCH$_2$OCH$_3$), 1.66-1.87 (8H, m, 4 x C**H**$_2$ THF), 3.34 (6H, s, 2 x OC**H**$_3$), 3.53-3.61 (2H, m, 2 x

C**H**OCH$_2$OCH$_3$), 3.75-3.84 (2H, m, 2 x -OC**H**CHOSi), 3.87-3.95 (2H, m, 2 x C**H**O-), 4.43 (2H, t, *J* = 5.5 Hz, 2 x C**H**OSi), 4.55 (2H, d, *J* = 6.8 Hz, 2 x -OC**H**HO-), 4.68 (2H, d, *J* = 6.8 Hz, 2 x -OC**H**HO-), 5.11 (2H, dt, *J* = 10.4, 1.3 Hz, 2 x CH=C**H**H), 5.24 (2H, dt, *J* = 17.0, 1.5 Hz, 2 x CH=CH**H**), 5.86 (2H, ddd, *J* = 17.1, 10.6, 5.8 Hz, 2 x C**H**=CH$_2$), 7.27-7.43 (6H, m, **H**$_{arom}$), 7.59-7.67 (4H, m, **H**$_{arom}$).

(4*S*,7*S*)-4,7-Di[(2*S*,5*R*)-5-((1*S*)-1-[(methyloxymethoxyundecyl)tetrahydrofuran-2-yl]-2,2-diphenyl-4,7-dihydro-1,3,2-dioxasilepine (4.42)

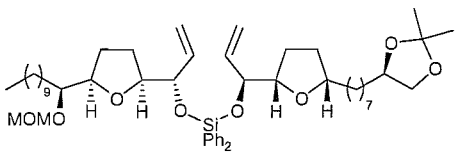


$C_{50}H_{80}O_8Si$

MW = 837.28

A solution of diene **4.41** (12 mg, 13.9 μmol) and benzylidene[1,3-*bis*(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium (1.2 mg, 1.4 μmol) in degassed C_6D_6 (1 mL) was heated in a microwave reactor at 100 °C for 5 h. The solvent was removed *in vacuo* and the brown residue purified on silica (5 x 50 mm, 0-20% EtOAc) to give recovered **4.41** (5.1 mg) and the target compound **4.42** as a colourless oil (3.0 mg, 3.58 μmol, 26%): R_f 0.48 (20% EtOAc/hexane); ^{1}H NMR (300 MHz, C_6D_6) δ 0.98-1.00 (6H, m, 2 x CH_2CH_3), 1.07-1.78 (36H, m, CH_2), 1.80-2.08 (8H, m, 4 x CH_2 THF), 3.27 (6H, s, 2 x OCH_3), 3.79-3.92 (4H, m, 2 x -OC**H**CHOSi, 2 x C**H**OCH$_2$OCH$_3$), 3.94-4.05 (2H, m, 2 x C**H**O-), 4.64 (2H, d, *J* = 6.6 Hz, 2 x -OC**H**HO-), 4.87 (2H, d, *J* = 6.6 Hz, 2 x -OC**H**HO-), 4.90-4.94 (2H, m, 2 x C**H**OSi), 5.96 (2H, s, C**H**=C**H**), 7.06-7.31 (6H, m, **H**$_{arom}$), 7.92-7.99 (4H, m, **H**$_{arom}$).

[(*S*)-1-[(2*S*,5*S*)-5-(7-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]heptyl)tetrahydrofuran-2-yl]-2-propenyl]oxy[(*S*)-1-[(2*R*,5*S*)-2-((*S*)-1-methoxymethoxyundecyl)tetrahydrofuran-5-yl]-2-propenyloxy]diphenylsilane (4.44)



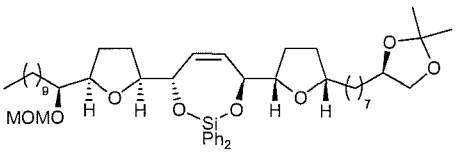
$C_{51}H_{80}O_8Si$

MW = 849.29

A solution of allylic alcohol **4.12** (10 mg, 29.1 μmol) and Ph_2SiCl_2 (7 μL, 29.1 μmol) in CH_2Cl_2 (500 μL) was treated with ^{i}Pr$_2$NEt (6 μL, 32 μmol). After 2 h, the second

alcohol **4.32** (10 mg, 29.1 μmol) in CH_2Cl_2 (500 μL) and $^iPr_2NEt$ (6 μL, 32 μmol) were added. No further reaction was seen so DMAP (4 mg, 29.1 μmol) was added and the reaction was stirred for 14 h. The solvent was then removed *in vacuo* and the resulting residue was purified on silica (5 x 60 mm, 0-20% EtOAc/hexane) giving the title compound **4.44** as a colourless oil (12 mg, 14.1 μmol, 48%): R_f 0.48 (20% EtOAc/hexane); ^{1}H NMR (300 MHz, C_6D_6) δ 0.91 (3H, t, J = 6.8 Hz, CH_3), 1.14-1.89 (46H, m, CH_2, 2 x CH_3), 3.26 (3H, s, OCH_3), 3.62-3.98 (6H, m, CH_2 dioxolane, -OC**H**CH_2, C**H**OCH_2OCH_3, 2 x -OC**H**CHOSi), 3.99-4.18 (2H, m, CH(OMOM)C**H**O-, C**H** dioxolane), 4.62 (1H, d, J = 6.6 Hz, -OC**H**HO-), 4.67-4.77 (2H, m, 2 x C**H**OSi), 4.81 (1H, d, J = 6.6 Hz, -OCH**H**O-), 5.07-5.14 (2H, m, 2 x CH=C**H**H), 5.35-5.46 (2H, m, 2 x CH=CH**H**), 6.03 (2H, ddd, J = 17.1, 10.7, 5.6 Hz, 2 x C**H**=CH_2), 7.04-7.30 (6H, m, $\mathbf{H}_{arom}$), 7.78-8.06 (4H, m, $\mathbf{H}_{arom}$).

(4*S*,7*S*)-4-[(2*S*,5*S*)-5-(7-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]heptyl)tetrahydrofuran-2-yl]-7-[(2*R*,5*S*)-2-((*S*)-1-methoxymethoxyundecyl)tetrahydrofuran-5-yl]-2,2-diphenyl-4,7-dihydro-1,3,2-dioxasilepine (4.45)



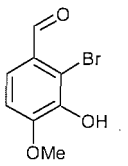
$C_{49}H_{76}O_8Si$

MW = 821.21

A solution of diene **4.44** (12 mg, 14.1 μmol) and benzylidene[1,3-*bis*(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium (6 mg, 7 μmol) in degassed C_6D_6 (1 mL) was heated in a microwave reactor at 100 °C for 5 h. The solvent was removed *in vacuo* and the brown residue purified on silica (5 x 50 mm, 0-20% EtOAc) to give recovered **4.44** (7.9 mg) and the target compound **4.45** as a colourless oil (3.4 mg, 4.23 μmol, 30%): R_f 0.35 (20% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 2978 (w), 2926 (s), 2854 (m), 1465 (w), 1430 (w), 1368 (w), 1214 (w), 1126 (m); ^{1}H NMR (400 MHz, C_6D_6) δ 0.83-0.95 (3H, m, CH_3), 1.09-2.03 (46H, m, CH_2, 2 x CH_3), 3.25 (3H, s, OCH_3), 3.71-3.94 (6H, m, CH_2 dioxolane, -OC**H**CH_2, C**H**OCH_2OCH_3, 2 x -OC**H**CHOSi), 3.94-4.11 (2H, m, CH(OMOM)C**H**O-, C**H** dioxolane), 4.62 (1H, d, J = 6.8 Hz, -OC**H**HO-), 4.85 (1H, d, J = 6.8 Hz, -OCH**H**O-), 4.91-5.02 (2H, m, 2 x C**H**OSi), 5.98 (2H, br. d, J = 3.3 Hz, C**H**=C**H**), 7.06-7.25

(6H, m, $\mathbf{H}_{arom}$), 7.91-7.98 (4H, m, $\mathbf{H}_{arom}$); LRMS (ES+) *m/z* (relative intensity) 844 (100%, $[M+Na]^+$).

2-Bromo-3-hydroxy-4-methoxybenzaldehyde (5.43)



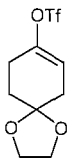
$C_8H_7BrO_3$

MW = 231.04

CAS 2973-58-2

The title compound was prepared as described by Fuchs *et al.*[161] A suspension of isovanillin (**24**) (2.90 g, 19.1 mmol), NaOAc (3.13 g, 38.2 mmol) and Fe powder (107 mg, 1.91 mmol) in AcOH (100 mL) was treated dropwise with a solution of Br_2 (1.08 mL, 21.0 mmol) in AcOH (20 mL). After stirring for 1 h, the reaction was poured onto ice-cold water (200 mL). The resulting white solid was collected by filtration, washed (ice-cold water) and dried at reduced pressure over P_2O_5 to give title compound **5.43** as a powdery white solid (3.93 g, 17.0 mmol, 89%). This was used without further purification. **5.43**: mp 205-208 °C; R_f 0.49 (70% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3016 (w), 2945 (w), 2884 (w), 2841 (w), 1668 (s), 1593 (m), 1564 (m), 1498 (m), 1295 (s), 1238 (w), 1205 (m), 1167 (w), 1134 (w); ^1H NMR (300 MHz, $CDCl_3$) δ 4.01 (3H, s, OC**H**$_3$), 6.10 (1H, s, ArO**H**), 6.92 (1H, d, J = 8.5 Hz, $\mathbf{H}_{arom}$), 7.58 (1H, d, J = 8.5 Hz, $\mathbf{H}_{arom}$), 10.26 (1H, s, C**H**O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0 (CH), 151.8 (C), 143.3 (C), 127.4 (C), 122.9 (CH), 113.0 (C), 109.4 (CH), 56.7 (CH_3); LRMS (ES+) *m/z* (relative intensity) 463 (2%, $[2M+H]^+$), 413 (100%), 285 (5%, $[M+Na+MeOH-H]^+$), 211 (10%), 151 (32%, $[M-Br]^+$), 135 (50%), 77 (13%, Ph^+). Spectroscopic characteristics are consistent with those reported in the literature.[161]

1,4-Dioxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate (6.5)



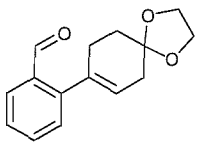
$C_9H_{11}F_3O_5S$

MW = 288.24

The title compound was prepared by the method of Jigajinni and Wightman.[163] A

solution of cyclohexane-1,4-dione *mono*-ethylene ketal **6.2** (100 mg, 640 μmol) and 2,6-di-*t*-butylpyridine (216 μL, 960 μmol) in CH_2Cl_2 (5 mL) was treated with Tf_2O (151 μL, 896 μmol). The reaction was allowed to stir for 16 h before removal of the solvent *in vacuo*. The resulting brown residue was purified on silica (20 x 90 mm, 5-15% EtOAc/hexane) to provide **6.5** as a colourless oil (144 mg, 500 μmol, 78%): R_f 0.44 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 2964 (w), 2936 (w), 2888 (w), 1692 (w), 1418 (s), 1375 (m), 1247 (s), 1205 (s), 1143 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 1.90 (2H, t, J = 6.5 Hz, =CC**H**$_2$CH$_2$), 2.39-2.42 (2H, m, =CHC**H**$_2$), 2.54 (2H, ttd, J = 6.5, 2.5, 1.5 Hz, =CCH$_2$C**H**$_2$), 3.98 (2H, td, J = 3.0, 2.0 Hz, OC**H**$_2$CH$_2$O), 4.00 (2H, td, J = 3.0, 2.0 Hz, OCH$_2$C**H**$_2$O), 5.66 (1H, tt, J = 4.0, 1.4 Hz, CH$_2$=C**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3 (C), 120.2 (C), 117.0 (C), 116.0 (CH), 106.2 (C), 64.8 (CH_2), 34.3 (CH_2), 31.1 (CH_2), 26.5 (CH_2); LRMS (ES+) *m/z* (relative intensity) 413 (100%), 343 (2%, $[M+Na+MeOH]^+$), 311 (28%, $[M+Na]^+$).

2-(1,4-Dioxaspiro[4.5]dec-7-en-8-yl)benzaldehyde (6.8)



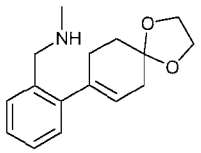
$C_{15}H_{16}O_3$

MW = 244.29

The title compound was prepared using the procedure described by Occhiato.[166] A suspension of triflate **6.5** (400 mg, 1.39 mmol), 2-formylbenzeneboronic acid (313 mg, 2.09 mmol) and $Pd(PPh_3)_2Cl_2$ in THF (10 mL) was treated with 2 M aqueous Na_2CO_3 (5 mL). After stirring for 10 min at rt the reaction had become dark brown with a white precipitate. The reaction was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo* resulted in a dark brown oil (467 mg). Purification on silica (30 x 100 mm, 5-20% EtOAc/hexane) gave **6.8** as a colourless oil (312 mg, 1.28 mmol, 92%): R_f 0.35 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3058 (w), 3021 (w), 2950 (m), 2922 (m), 2879 (m), 2846 (w), 2747 (w), 1692 (s), 1649 (w), 1593 (m), 1370 (m), 1243 (m), 1195 (m), 1120 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 1.94 (2H, t, J = 6.3 Hz, =CC**H**$_2$CH$_2$), 2.45-2.49 (2H, m, =CHC**H**$_2$), 2.60 (2H, ttd, J = 6.5, 4.0, 2.0 Hz, =CCH$_2$C**H**$_2$), 4.03 (4H, s, OC**H**$_2$C**H**$_2$O), 5.53 (1H, tt, J = 3.8, 1.8 Hz, CH$_2$=C**H**), 7.33 (1H, br. d, J = 7.5 Hz, **H**$_{arom}$), 7.37 (1H, br. t, J = 7.5 Hz, **H**$_{arom}$), 7.53 (1H, td, J = 7.5,

1.5 Hz, $\mathbf{H}_{arom}$), 7.90 (1H, dd, J = 7.8, 1.5 Hz, $\mathbf{H}_{arom}$), 10.16 (1H, s, **CHO**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7 (CH), 147.6 (C), 134.9 (C), 134.0 (C), 133.6 (CH), 128.9 (CH), 127.9 (CH), 127.8 (CH), 127.4 (CH), 107.5 (C), 64.7 (CH_2), 36.3 (CH_2), 31.5 (CH_2), 30.7 (CH_2); LRMS (ES+) *m/z* (relative intensity) 299 (5%, $[M+Na+MeOH]^+$), 267 (100%, $[M+Na]^+$); HRMS (ES+) $[M+Na]^+$ found 267.0994, calculated 267.0991.

N-[2-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)benzyl]-N-methylamine (6.9)

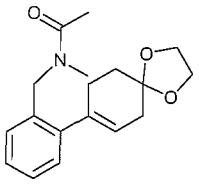


$C_{16}H_{21}NO_2$

MW = 259.34

The title compound was prepared using the procedure described by Bhattacharyya.[167] A solution of NEt_3 (799 μL, 5.73 mmol) in EtOH (20 mL) was treated with $MeNH_2$·HCl (387 mg, 5.73 mmol), $Ti(O^iPr)_4$ (1.69 mL, 5.73 mmol) and aldehyde **6.8** (700 mg, 2.87 mmol). After stirring at rt for 7 h, $NaBH_4$ (163 mg, 4.31 mmol) was added portionwise and the reaction allowed to stir for a further 9 h. The reaction was then poured onto aq. NH_3 (2M, 100 mL) and the resulting white precipitate removed by filtration. The filtrate was extracted with CH_2Cl_2 (3 x 20 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo* to give crude **32** as a very pale brown oil (650 mg, 2.51 mmol, 87%). The material seemed to be retained on silica, so purification was difficult, but the crude material was already very clean and thus was used without further purification. **32**: R_f 0.41 (70% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3418 (br, m), 2945 (m), 2926 (m), 2879 (m), 1644 (w), 1474 (m), 1441 (m), 1370 (m), 1257 (m), 1115 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90 (2H, t, J = 6.4 Hz, =CC$\mathbf{H}_2$CH$_2$), 2.41 (3H, s, NC$\mathbf{H}_3$), 2.42-2.50 (2H, m, =CHC$\mathbf{H}_2$), 3.74 (2H, s, C$\mathbf{H}_2$N), 4.03 (4H, br. s, OC$\mathbf{H}_2$C$\mathbf{H}_2$O), 5.49 (1H, tt, J = 3.8, 1.7 Hz, CH$_2$=C**H**), 7.11-7.15 (1H, m, $\mathbf{H}_{arom}$), 7.22 (2H, m, $\mathbf{H}_{arom}$), 7.33-7.36 (1H, m, $\mathbf{H}_{arom}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3 (C), 138.0 (C), 136.7 (C), 129.1 (CH), 128.6 (CH), 127.0 (CH), 123.3 (CH), 107.8 (C), 64.6 (2 x CH_2), 53.2 (CH_2), 35.9 (CH_2), 35.7 (CH_3), 31.5 (CH_2), 30.3 (CH_2); LRMS (CI, ammonia) *m/z* (relative intensity) 260 (86%, $[M+H]^+$), 244 (35%, $[M-CH_3]^+$), 228 (22%, $[M-H-NHCH_3]^+$), 214 (42%, $[M-CH_2NHCH-H]^+$), 158 (100%), 142 (78%), 128 (61%), 115 (47%), 99 (68%), 86 (49%); HRMS (ES+) $[M+H]^+$ found 260.1643, calculated 260.1645.

N-[2-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)benzyl]-N-methylacetamide (6.16)

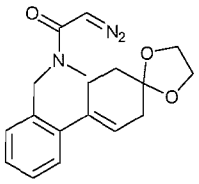


$C_{18}H_{23}NO_3$

MW = 301.38

The title compound was prepared using the procedure described by Henry.[173] A solution of amine **6.9** (300 mg, 1.16 mmol) in THF (10 mL) was treated with Hünig's base (393 μL, 2.31 mmol) then AcCl (123 μL, 1.74 mmol). The reaction was stirred at rt for 2 h then quenched with saturated aqueous $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo* to give a crude yellow oil (362 mg). Purification on silica (20 x 110 mm, 20-100% EtOAc/hexane) gave **6.16** as a colourless oil (330 mg, 1.09 mmol, 94%): R_f 0.10 (70% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 2950 (m), 2926 (m), 2889 (m), 1640 (s), 1479 (m), 1432 (m), 1403 (m), 1366 (m), 1247 (m), 1115 (m); ^1H NMR (300 MHz, $CDCl_3$) δ 1.88 (2H, t, J = 6.2 Hz, =CC**H**$_2$CH$_2$ (rotomer)), 1.90 (2H, t, J = 6.2 Hz, =CC**H**$_2$CH$_2$ (rotomer)), 2.10 (3H, s, COC**H**$_3$ (rotomer)), 2.17 (3H, s, COC**H**$_3$ (rotomer)), 2.41-2.44 (4H, m, =CHC**H**$_2$C**H**$_2$), 2.83 (3H, s, NC**H**$_3$ (rotomer)), 2.90 (3H, s, NC**H**$_3$ (rotomer)), 4.01 (4H, br. s, OC**H**$_2$C**H**$_2$O (rotomer)), 4.03 (4H, br. s, OC**H**$_2$C**H**$_2$O (rotomer)), 4.50 (2H, s, C**H**$_2$N (rotomer)), 4.64 (2H, s, C**H**$_2$N (rotomer)), 5.45 (1H, br. s, =C**H**), 7.08-7.27 (4H, m, **H**$_{arom}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5 (C (rotomer)), 171.1 (C (rotomer)), 143.4 (C (rotomer)), 142.9 (C (rotomer)), 137.4 (C (rotomer)), 137.1 (C (rotomer)), 134.2 (C (rotomer)), 133.6 (C (rotomer)), 129.1 (CH (rotomer)), 128.7 (CH (rotomer)), 127.4 (CH (rotomer)), 127.3 (CH (rotomer)), 127.0 (CH (rotomer)), 125.8 (CH (rotomer)), 124.1 (CH (rotomer)), 123.9 (CH (rotomer)), 107.7 (CH (rotomer)), 107.6 (CH (rotomer)), 64.6 (2 x CH_2 (rotomer)), 63.9 (2 x CH_2 (rotomer)), 51.9 (CH_2), 47.8 (CH_2), 36.0 (CH_2 (rotomer)), 36.0 (CH_2 (rotomer)), 35.6 (CH_3 (rotomer)), 33.9 (CH_3 (rotomer)), 31.5 (CH_2 (rotomer)), 31.5 (CH_2 (rotomer)), 30.3 (CH_2 (rotomer)), 30.2 (CH_2 (rotomer)), 21.9 (CH_3 (rotomer)), 21.5 (CH_3 (rotomer)); LRMS (CI, ammonia) *m/z* (relative intensity) 302 (36%, $[M+H]^+$), 141 (12%), 115 (16%), 86 (46), 74 (50%), 56 (10%), 43 (100%, Ac^+); HRMS (ES+) $[M+Na]^+$ found 324.1573, calculated 324.1570.

2-Diazo-N-[2-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)benzyl]-N-methylacetamide (6.11)

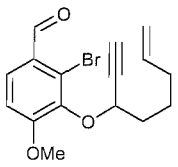


$C_{18}H_{21}N_3O_3$

MW = 327.38

The title compound was prepared according to the procedure described by Oka and Numata.[174] A solution of LiHMDS (1 M in THF, 1.2 mL, 1.21 mmol) in THF (8 mL) at –78 °C was treated dropwise with acetamide **6.16** (261 mg, 866 μmol) in THF (2 mL). After stirring for 30 min, $CF_3COOCH_2CF_3$ (174 μL, 1.30 mmol) was added. The reaction was stirred for a further 30 min at –78 °C then saturated aqueous NH_4Cl (10 mL) was added, followed by extraction with CH_2Cl_2 (3 x 10 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo* to give a pale yellow oil (365 mg). This was dissolved in a mixture of MeCN (8 mL), NEt_3 (160 μL, 1.15 mmol) and water (16 μL, 886 μmol). To this was added a solution of MsN_3 (140 mg, 1.15 mmol) in MeCN (2 mL) and the reaction was stirred for 16 h. Aqueous NaOH (2 M, 10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow oil (388 mg). This was purified on silica (20 x 110 mm, 10-70% EtOAc/hexane) affording diazoacetamide **6.11** as a yellow oil (136 mg, 415 μmol, 48%): R_f 0.29 (70% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3064 (w), 3011 (w), 2945 (m), 2931 (m), 2889 (m), 2103 (s), 1730 (w), 1616 (s), 1479 (s), 1403 (s), 1115 (s); ^1H NMR (300 MHz, $CDCl_3$) δ 1.89 (2H, t, J = 6.4 Hz, =CC**H**$_2$CH$_2$), 2.35-2.46 (2H, m, =CHC**H**$_2$), 2.70-2.99 (5H, m, =CCH$_2$C**H**$_2$, NC**H**$_3$), 4.02 (4H, br. s, OC**H**$_2$C**H**$_2$O), 4.28-4.73 (2H, m, C**H**$_2$N), 4.95 (1H, br. s, C**H**N$_2$), 5.46 (1H, br. t, J = 1.8 Hz, CH$_2$=C**H**), 7.13-7.19 (2H, m, **H**$_{arom}$), 7.20-7.25 (2H, m, **H**$_{arom}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4 (C), 137.2 (C), 128.9 (CH), 127.5 (2 x CH), 127.3 (CH), 124.2 (CH), 107.6 (CH), 64.6 (2 x CH_2), 36.1 (CH_2), 34.5 (CH_3), 31.5 (CH_2), 30.3 (CH_2).

2-Bromo-3-[(1-ethynylhex-5-enyl)oxy]-4-methoxybenzaldehyde (6.23)

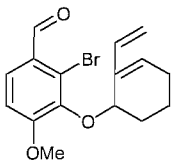


$C_{16}H_{17}BrO_3$

MW = 337.22

To a solution of propargyl alcohol **6.24** (4.00 g, 32.2 mmol), 2-bromoisovanillin (**5.43**) (12.5 g, 54.0 mmol), and PPh_3 (16.8 g, 64.4 mmol) in THF (10 mL) was added dropwise DIAD (12.7 mL, 64.4 mmol). The reaction was stirred at reflux for 7 h then the solvent was removed *in vacuo* and the resulting residue purified on silica (30 x 150 mm, 0-15% EtOAc/hexane). This gave the target compound **6.23** as a very pale yellow oil (4.95 g, 14.7 mmol, 46%): R_f 0.51 (20% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3289 (w), 2938 (w), 2860 (w), 1679 (s), 1577 (s), 1479 (m), 1279 (s), 1246 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 1.67-1.81 (2H, m, =CHCH$_2$C**H**$_2$), 2.02 (1H, td, *J* = 6.8, 3.5 Hz, -OCHC**H**H), 2.04 (1H, td, *J* = 6.8, 3.5 Hz, -OCHCH**H**), 2.18 (2H, q, *J* = 6.8 Hz, =CHC**H**$_2$), 2.37 (1H, d, *J* = 2.0 Hz, ≡CH), 3.94 (3H, s, -OCH$_3$), 5.00 (1H, br. d, *J* = 10.3 Hz, =C**H**H), 5.06 (1H, br. d, *J* = 17.3 Hz, =CH**H**), 5.17 (1H, td, *J* = 6.3, 2.0 Hz, -OC**H**C≡CH), 5.86 (1H, ddt, *J* = 17.0, 6.8, 6.5 Hz, C**H**=CH$_2$), 6.95 (1H, d, *J* = 8.5 Hz, **H**$_{arom}$), 7.75 (1H, d, *J* = 8.5 Hz, **H**$_{arom}$), 10.28 (1H, s, C**H**O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4 (CH), 158.7 (C), 143.8 (C), 138.5 (CH), 127.7 (C), 126.6 (CH), 124.3 (C), 115.1 (CH_2), 111.0 (CH), 81.4 (C), 75.5 (CH), 71.7 (CH), 56.4 (CH_3), 35.3 (CH_2), 33.5 (CH_2), 24.4 (CH_2); LRMS (ES+) *m/z* (relative intensity) 393 (100%, $[M+Na+MeOH]^+$), 391 (100%, $[M+Na+MeOH]^+$), 361 (80%, $[M+Na]^+$), 359 (80%, $[M+Na]^+$); HRMS (ES+) $[M+Na]^+$ found 359.0254, calculated 359.0253.

2-Bromo-4-methoxy-3-[(2-vinylcyclohex-2-en-1-yl)oxy]benzaldehyde (6.22)



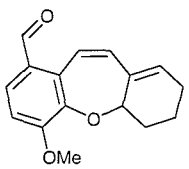
$C_{16}H_{17}BrO_3$

MW = 337.22

A solution of enyne **6.23** (181 mg, 537 μmol) and *bis*(tricyclohexylphosphine) benzylideneruthenium(IV) dichloride (22 mg, 27 μmol) in CH_2Cl_2 (20 mL) was heated at reflux for 2 h. The solvent was removed *in vacuo* and the brown residue purified on silica (10 x 90 mm, 0-15% EtOAc) to the target compound **6.22** as a

colourless oil (135 mg, 400 μmol, 75%): R_f 0.48 (20% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 2942 (w), 2864 (w), 1724 (w), 1683 (s), 1573 (s), 1479 (m), 1438 (w), 1377 (w), 1274 (s), 1250 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 1.48-1.65 (2H, m, -OCHC**H**H and $CH_2C\mathbf{H}HCH_2$), 1.99-2.05 (1H, m, -OCHCH**H**), 2.08-2.22 (2H, m, $CH_2CH\mathbf{H}CH_2$ and C=CHC**H**H), 2.29-2.39 (1H, m, C=CHCH**H**), 3.95 (3H, s, $-OCH_3$), 4.89 (1H, d, *J* = 11.0 Hz, =C**H**H), 5.33 (1H, d, *J* = 17.8 Hz, =CH**H**), 5.38 (1H, t, *J* = 3.3 Hz, -OC**H**C-), 6.08 (1H, dd, *J* = 5.3, 3.0 Hz, C=C**H**CH_2), 6.34 (1H, dd, *J* = 17.6, 11.1 Hz, C**H**=CH_2), 6.93 (1H, d, *J* = 8.6 Hz, $\mathbf{H}_{arom}$), 7.68 (1H, d, *J* = 8.8 Hz, $\mathbf{H}_{arom}$), 10.27 (1H, s, C**H**O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7 (CH), 158.5 (C), 144.5 (C), 138.2 (CH), 135.6 (C), 133.3 (CH), 127.9 (C), 125.6 (CH), 124.0 (C), 111.9 (CH_2), 110.9 (CH), 73.3 (CH), 56.2 (CH_3), 28.2 (CH_2), 26.0 (CH_2), 17.5 (CH_2); LRMS (ES+) *m/z* (relative intensity) 393 (90%, $[M+Na+MeOH]^+$), 391 (85%, $[M+Na+MeOH]^+$), 361 (100%, $[M+Na]^+$), 359 (95%, $[M+Na]^+$); HRMS (ES+) $[M+Na]^+$ found 359.0259, calculated 359.0253.

4-Methoxy-5a,6,7,9a-tetrahydrodibenzo[b,f]oxepine-1-carbaldehyde (6.31)



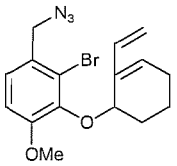
$C_{16}H_{16}O_3$

MW = 256.30

Following Trost's method,[158] a solution of diene **6.22** (130 mg, 386 μmol), $Pd(OAc)_2$ (13 mg, 58 μmol), 1,3-*bis*(diphenylphosphino)propane (24 mg, 58 μmol) and $AgCO_3$ (319 mg, 1.16 mmol) in toluene was heated at reflux for 1 h. The solvent was removed *in vacuo* leaving a black residue which was purified on silica (10 x 90 mm, 0-30% EtOAc/hexane) to give **6.31** as a colourless oil (52 mg, 203 μmol, 53%): R_f 0.45 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 2942 (w), 2868 (w), 2835 (w), 1765 (w), 1728 (w), 1683 (m), 1556 (m), 1438 (m), 1274 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 1.58-1.69 (1H, m, $CH_2C\mathbf{H}HCH_2$), 1.82-1.90 (1H, m, $CH_2CH\mathbf{H}CH_2$), 2.01 (1H, tdd, *J* = 12.3, 9.3, 3.3 Hz, -OCHCH**H**), 2.11-2.20 (1H, m, =CHC**H**H), 2.24-2.35 (2H, m, =CHCH**H** and -OCHCH**H**), 3.93 (3H, s, $OC\mathbf{H}_3$), 4.41 (1H, t, *J* = 6.8 Hz, $OC\mathbf{H}CH_2$), 5.96 (1H, t, *J* = 3.8 Hz, =C**H**CH_2), 6.51 (1H, d, *J* = 12.3 Hz, -CH=C**H**C=), 6.88 (1H, d, *J* = 8.3 Hz, $\mathbf{H}_{arom}$), 7.23 (1H, d, *J* = 12.0 Hz, -C**H**=CHC=), 7.50 (1H, d, *J* = 8.3 Hz,

$\mathbf{H}_{arom}$), 10.16 (1H, s, C**H**O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8 (CH), 155.7 (C), 149.1 (C), 139.3 (C), 135.8 (CH), 131.9 (CH), 131.4 (CH), 131.3 (C), 127.4 (C), 119.9 (CH), 109.6 (CH), 81.3 (CH), 56.4 (CH_3), 30.0 (CH_2), 26.0 (CH_2), 20.9 (CH_2); LRMS (CI) *m/z* (relative intensity) 257 (100%, $[M+H]^+$); HRMS (ES+) $[M+Na]^+$ found 279.0997, calculated 279.0991.

2-Bromo-1-(azidomethyl)-4-methoxy-3-[(2-vinylcyclohex-2-en-1-yl)oxy]benzene (6.32)



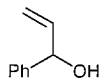
$C_{16}H_{18}BrN_3O_2$

MW = 364.24

A solution of diene **6.22** (83 mg, 246 μmol) in MeOH (5 mL) at 0 °C was treated portionwise with $NaBH_4$ (10 mg, 246 μmol). The cooling bath was removed and the reaction was stirred for 1 h. Water (10 mL) was then added and the mixture extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo* giving a crude colourless oil. This was dissolved in toluene (5 mL) and treated with diphenyl phosphorazidate (80 μL, 369 μmol) and DBU (55 μL, 369 μmol) giving a cloudy mixture which later separated into two phases. After stirring for 16 h the reaction was washed with water (10 mL) then 2M HCl (10 mL). The organic phase was concentrated *in vacuo* and purified on silica (10 x 90 mm, 0-15% EtOAc/hexane) to give the title compound **6.32** as a colourless oil (80 mg, 219 mmol, 89%): R_f 0.48 (20% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3003 (w), 2933 (w), 2868 (w), 2827 (w), 2100 (s), 1589 (w), 1483 (s), 1438 (m), 1295 (m), 1270 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43-1.62 (2H, m, -OCHC**H**H and CH_2C**H**HCH_2), 1.94-2.04 (1H, ddt, *J* = 14.6, 4.8, 3.5 Hz, -OCHCH**H**), 2.05-2.20 (2H, m, CH_2CH**H**CH_2 and C=CHC**H**H), 2.26-2.36 (1H, m, C=CHCH**H**), 3.89 (3H, s, -OCH_3), 4.43 (2H, s, C**H**$_2N_3$) 4.91 (1H, d, *J* = 11.0 Hz, =C**H**H), 5.40 (1H, d, *J* = 17.6 Hz, =CH**H**), 5.40 (1H, t, *J* = 3.3 Hz, -OC**H**C-), 6.06 (1H, dd, *J* = 5.0, 2.8 Hz, C=C**H**CH_2), 6.36 (1H, dd, *J* = 17.6, 11.0 Hz, C**H**=CH_2), 6.86 (1H, d, *J* = 8.5 Hz, $\mathbf{H}_{arom}$), 7.05 (1H, d, *J* = 8.5 Hz, $\mathbf{H}_{arom}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9 (C), 145.3 (C), 138.9 (CH), 136.2 (C), 133.3 (CH), 128.4 (C), 124.8 (CH), 121.1 (C), 112.4 (CH_2), 111.4 (CH), 73.4 (CH), 56.3 (CH_3), 55.4 (CH), 28.5 (CH_2), 26.4 (CH_2), 18.0 (CH_2); LRMS (ES+) *m/z*

(relative intensity) 386 (25%, $[M+Na]^+$), 381 (100%, $[M+NH_4]^+$); HRMS (ES+) $[M+Na]^+$ found 386.0471, calculated 386.0475.

1-Phenylprop-2-en-1-ol (8.1)



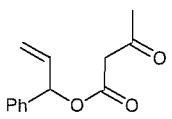
$C_9H_{10}O$

MW = 134.18

CAS 4393-06-0

A solution of benzaldehyde (4.8 mL, 47.1 mmol) in THF (30 mL) was added dropwise over 30 minutes to vinyl magnesium bromide (1 M in THF, 42.8 mL, 42.8 mmol), stirred under N_2 at –20 °C. After a further 30 minutes at –20 °C, the reaction was quenched with ice cold saturated aqueous NH_4Cl solution (50 mL), followed by extraction with Et_2O (3 x 50 mL). The organics were combined, dried (Na_2SO_4) and concentrated *in vacuo* giving a pale yellow oil (7.07 g) which was purified on silica (50 x 130 mm, 10-40% EtOAc/hexane) to provide **8.1** as a very pale yellow oil (5.67 g, 42.3 mmol, 99 %): R_f 0.42 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3363 (br. s), 3084 (m), 3062 (m), 3028 (m), 1641 (w), 1601 (w); ^1H NMR (300 MHz, $CDCl_3$) δ 2.08 (1H, br. s, O**H**), 5.19-5.24 (2H, m, =C**H**$_2$), 5.37 (dt, *J* = 16.9, 1.1 Hz, C**H**=CH$_2$), 6.07 (1H, ddd, *J* = 16.9, 10.7, 5.5 Hz, PhC**H**), 7.26-7.39 (5H, m, **H**$_{arom}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0 (C), 140.6 (CH), 129.0 (CH), 128.2 (CH), 126.8 (CH), 115.6 (CH), 75.8 (CH_2); LRMS (CI, ammonia) *m/z* (relative intensity) 135 (6%, $[M+H]^+$), 134 (51%, M^+), 133 (64%, $[M–H]^+$), 117 (100%, $[M–OH]^+$), 105 (47%), 77 (28%, Ph^+), 55 (16%). Spectroscopic characteristics are consistent with those reported in the literature.[237]

1-Phenylprop-2-enyl 3-oxobutanoate (8.2)



$C_{13}H_{14}O_3$

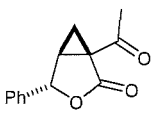
MW = 218.25

CAS 112163-00-5

The title compound was prepared using the procedure described by Clemens *et al.*[229] A solution of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (5.1 mL, 39.1 mmol) and alcohol

8.1 (5.00 g, 37.3 mmol) in xylenes (25 mL) was prepared in a conical flask. This was placed in a preheated oil bath and stirred at 150 °C for 30 minutes, then allowed to cool to room temperature. Purification on silica (50 x 80 mm, 10-40% EtOAc-hexane) gave **8.2** as a pale orange oil (7.22 g, 33.1 mmol, 89%): R_f 0.43 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3088 (w), 3065 (w), 3033 (w), 2931 (w), 1743 (s), 1717 (s), 1643 (m), 1409 (m), 1360 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (3H, s, $COCH_3$), 3.50 (2H, s, -CH_2-), 5.29 (1H, dt, J = 10.5, 1.3 Hz, CHH=), 5.33 (1H, dt, J = 17.1, 1.3 Hz, CHH=), 6.00 (1H, ddd, J = 16.3, 10.5, 6.0 Hz, CH_2=CH), 6.32 (1H, dt, J = 6.0, 1.3 Hz, PhCH), 7.30-7.37 (5H, m, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.8 (C), 166.5 (C), 138.7 (C), 136.0 (CH), 129.1 (CH), 128.9 (CH), 127.6 (CH), 127.4 (CH), 118.1 (CH_2), 77.7 (C), 50.7 (CH_2), 30.6 (CH_3); LRMS (CI, ammonia) *m/z* (relative intensity) 134 (15%), 133 (26%, $[M–CH_2COCH_3]^+$), 118 (43%), 117 (100%, $[M–OCH_2COCH_3]^+$), 105 (26%), 91 (21%), 78 (15%), 77 (13%, Ph^+). Spectroscopic characteristics are consistent with those previously recorded in the group.[238]

(1R*,4S*,5S*)-1-Acetyl-4-phenyl-3-oxabicyclo[3.1.0]hexan-2-one (8.3)



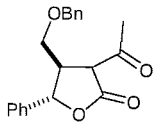
$C_{13}H_{12}O_3$

MW = 216.24

The title compound was prepared using the method of Bertrand *et al.*[230] To a solution of $Mn(OAc)_3{\cdot}2H_2O$ (18.43 g, 68.7 mmol), $Cu(OAc)_2{\cdot}H_2O$ (6.24 g, 34.4 mmol) and KOAc (3.37 g, 57.3 mmol) in AcOH (250 mL), stirred at 75 °C, was added a solution of acetoacetate **8.2** (5.00 g, 22.9 mmol) in AcOH (50 mL). After 20 minutes the colour had changed from brown to a deep turquoise. After allowing to cool the reaction was quenched with saturated aq. $Na_2S_2O_3$ solution (500 mL) and extracted with CH_2Cl_2 (2 x 500 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo* to afford a brown oil which was purified on silica (50 x 130 mm, 10-40% EtOAc/hexane) to give **8.3** as an off-white crystalline solid (3.00 g, 13.9 mmol, 61%) (23:1 mixture of diastereoisomers): mp 74-77 °C; R_f 0.35 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3064 (w), 3035 (w), 3007 (w), 2922 (w), 1782 (s), 1701 (s), 1384 (m), 1360 (m), 1318 (m); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (1H, dd, J = 5.5, 4.1 Hz, CHH), 2.18 (1H, dd, J = 7.7, 4.0 Hz, CHH), 2.63 (3H, s, CH_3), 2.83 (1H, dd, J 8.1, 5.5 Hz, $CHCH_2$), 5.33 (1H, s, PhCH), 7.28-7.44 (5H, m, H_{arom}); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 200.7 (C), 172.9 (C), 139.0 (C), 129.7 (CH), 129.6 (CH), 125.8 (CH), 125.8 (CH), 79.9 (CH), 37.4 (C), 37.2 (CH), 29.9 (CH_3), 24.8 (CH_2); LRMS (CI, ammonia) *m/z* (relative intensity) 234 (8%, $[M+NH_4]^+$), 217 (100%, $[M+H]^+$), 199 (49%), 173 (30%, $[M-COCH_3]^+$), 157 (12%), 145 (34%), 129 (68%), 115 (25%), 91 (24%), 77 (40%), 51 (12%). Spectroscopic characteristics are consistent with those previously recorded in the group.[238]

(4R*,5S*)-3-acetyl-4-[(benzyloxy)methyl]-5-phenyldihydrofuran-2(3H)-one (8.4)

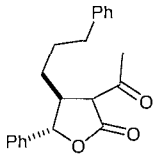


$C_{20}H_{20}O_4$

MW = 324.38

$Mg(ClO_4)_2$ (94 mg, 420 μmol) was added to a solution of cyclopropane **8.3** (900 mg, 4.16 mmol) in BnOH (2.2 mL, 20.8 mmol). The reaction mixture was placed in a preheated oil bath and stirred at 100 °C for 4 hours. The reaction was then allowed to cool to room temperature then partitioned between CH_2Cl_2 (40 mL) and water (40 mL). The organic phase was collected and the aqueous was extracted with CH_2Cl_2 (2 x 40 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo*. Residual BnOH was removed by Kügelrohr distillation and the residue was purified on silica (50 x 100 mm, 5-40% EtOAc/hexane) to give **8.4** as an orange oil (1.14 g, 3.51 mmol, 84%): R_f 0.42 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3064 (w), 3030 (w), 2860 (w), 1777 (s), 1716 (s), 1451 (m), 1356 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 2.48 (3H, s, $COCH_3$), 3.07-3.15 (1H, m, C**H**CH_2), 3.49 (2H, dd, *J* = 3.5, 2.0 Hz, CH**C**H_2), 4.01 (1H, d, *J* = 10.8 Hz, C**H**$COCH_3$), 4.47 (1H, d, J = 11.8 Hz, OC**H**HPh), 4.55 (1H, d, J = 12.1 Hz, OCH**H**Ph), 5.29 (1H, d, *J* = 9.5 Hz, PhC**H**), 7.21-7.41 (10H, m, $\mathbf{H}_{arom}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9 (C), 171.8 (C), 137.9 (C), 137.7 (C), 129.5 (CH), 129.2 (CH), 129.1 (CH), 129.0 (CH), 128.9 (CH), 128.6 (CH), 128.4 (CH), 128.1 (CH), 126.8 (CH), 81.4 (CH), 73.7 (CH_2), 65.5 (CH_2), 56.0 (CH), 46.7 (CH), 30.7 (CH_3); LRMS (CI, ammonia) *m/z* (relative intensity) 342 (6%, $[M+NH_4]^+$), 325 (18%, $[M+H]^+$), 281 (7%, $[M-COCH_3]^+$), 217 (21%), 175 (50%), 117 (32%), 106 (72%), 91 (100%, $PhCH_2^+$), 78 (31%). Spectroscopic characteristics are consistent with those previously recorded in the group.[238]

(4S*,5S*)-3-acetyl-5-phenyl-4-(3-phenylpropyl)dihydrofuran-2(3H)-one (8.6)



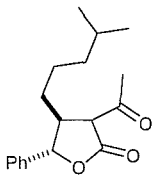
$C_{21}H_{22}O_3$

MW = 322.41

Mg turnings (1.22 g, 50.0 mmol) were heated to ca. 400 °C for 5 mins under N_2. After cooling to room temperature, THF (130 mL) was added, along with a single small crystal of I_2. The resulting yellow mixture was treated with (2-bromoethyl)benzene (1.0 mL, 7.30 mmol). After heating at reflux for a few minutes, the mixture became colourless so the remaining bromide (4.7 mL, 34.3 mmol) was added. Heating at reflux for a further 90 minutes gave a yellow-grey mixture, concentration 0.275 M (standardised by the $I_2/Na_2S_2O_3$ method). The Grignard reagent (55.6 mL, 15.26 mmol) was added dropwise to a slurry of CuI (1.586 g, 7.63 mmol) in THF (40 mL) at –60 °C. This was allowed to warm to –40 °C over 30 minutes, resulting in a dark grey slurry. After cooling back to –60 °C, cyclopropane **8.3** (1.500 g, 6.94 mmol) in THF (15 mL) was added dropwise. The reaction was allowed to warm to –40 °C while stirring for 90 minutes. It was then allowed to warm to room temperature, followed by quenching by addition of saturated aqueous NH_4Cl solution (100 mL). After stirring vigorously for 15 minutes, the organic phase was collected and the aqueous was extracted with Et_2O (3 x 100 mL). The combined organics were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a brown oil (3.20 g) which was purified on silica (40 x 110 mm, 0-15% EtOAc/hexane) to provide **8.6** as a pale yellow oil (1.715 g, 5.32 mmol, 77%): R_f 0.42 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3027 (w), 2929 (w), 2859 (w), 1765 (s), 1719 (s), 1496 (w), 1454 (m), 1358 (m), 1227 (m), 1168 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 1.40-1.79 (4H, m, $CHCH_2CH_2$), 2.43-2.72 (2H, m, CH_2Ph), 2.49 (3H, s, $COCH_3$), 3.09-3.17 (1H, m, $CHCH_2$), 3.55 (1H, d, J = 10.6 Hz, $CHCOCH_3$), 4.93 (1H, d, J = 9.3 Hz, PhCH), 7.02-7.43 (10H, m, H_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8 (C), 171.9 (C), 141.8 (C), 137.9 (C), 129.7 (CH), 129.3 (CH), 129.0 (CH), 128.9 (CH), 128.8 (CH), 127.3 (CH), 126.6 (CH), 126.4 (CH), 125.5 (CH), 85.9 (CH), 60.6 (CH), 45.4 (CH), 35.8 (CH_2), 31.4 (CH_2), 30.8 (CH_3), 29.4 (CH_2); LRMS (CI, ammonia) *m/z* (relative intensity) 340 (10%, $[M+NH_4]^+$), 323 (25%, $[M+H]^+$), 279 (20%, $[M–COCH_3]^+$), 220

(100%), 203 (4%, $[M–PhCH_2CH_2CH_2]^+$), 117 (18%, $PhCHCHCH_2^+$), 91 (72%, $PhCH_2^+$); HRMS (EI) $[M–H_2O]^+$ found 304.1457, calculated 304.1463.

(4S*,5S*)-3-acetyl-4-(4-methylpentyl)-5-phenyldihydrofuran-2(3H)-one (8.7)



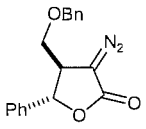
$C_{18}H_{24}O_3$

MW = 288.39

The title compound was prepared by the same method as **8.6**, whereby Mg turnings (1.22 g, 50.0 mmol) were heated to ca. 400 °C for 5 mins under N_2. After cooling to room temperature, THF (130 mL) was added, along with a single small crystal of I_2. The resulting yellow mixture was treated with 1-bromo-3-methylbutane (1.0 mL, 8.32 mmol). After heating at reflux for a few minutes, the mixture became colourless so the remaining bromide (4.0 mL, 33.3 mmol) was added. Heating at reflux for a further 90 minutes gave a yellow-grey mixture, concentration 0.271 M (standardised by the $I_2/Na_2S_2O_3$ method). The Grignard reagent (56.3 mL, 15.26 mmol) was added dropwise to a slurry of CuI (1.586 g, 7.63 mmol) in THF (40 mL) at –60 °C. This was allowed to warm to –40 °C over 30 minutes, resulting in a dark grey slurry. After cooling back to –60 °C, cyclopropane **8.3** (1.503 g, 6.94 mmol) in THF (15 mL) was added dropwise. The reaction was allowed to warm to –40 °C while stirring for 90 minutes. It was then allowed to warm to room temperature, followed by quenching by addition of saturated aqueous NH_4Cl solution (100 mL). After stirring vigorously for 15 minutes, the organic phase was collected and the aqueous was extracted with Et_2O (3 x 100 mL). The combined organics were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a brown oil (2.074 g) which was purified on silica (40 x 100 mm, 10% EtOAc/hexane) to provide **8.7** as a pale yellow oil (1.749 g, 6.06 mmol, 87%): R_f 0.52 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 2953 (w), 2929 (w), 2868 (w), 1765 (s), 1720 (s), 1458 (w), 1360 (m), 1228 (m), 1164 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 0.77 (3H, d, J = 4.5 Hz, CH_3CHCH_3), 0.79 (3H, d, J = 4.8 Hz, CH_3CHCH_3), 1.03-1.17 (4H, m, CH_2CH_2), 1.38-1.47 (2H, m, $CHCH_2$), 1.52-1.59 (1H, m, $CH(CH_3)_2$), 2.50 (3H, s, $COCH_3$), 3.04-3.12 (1H, m, $CHCH_2$), 3.58 (1H, d, J = 10.3 Hz, $CHCOCH_3$), 4.96 (1H, d, J = 9.0 Hz, PhCH), 7.34-7.41 (5H, m,

$\mathbf{H}_{arom}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9 (C), 172.1 (C), 138.0 (C), 129.6 (CH), 129.3 (CH), 128.8 (CH), 127.3 (CH), 125.5 (CH), 86.2 (CH), 60.7 (CH), 45.9 (CH), 39.2 (CH_2), 32.5 (CH_2), 30.9 (CH_3), 28.2 (CH), 25.6 (CH_2), 22.4 (CH_3), 22.3 (CH_3); LRMS (CI, ammonia) *m/z* (relative intensity) 306 (32%, $[M+NH_4]^+$), 289 (100%, $[M+H]^+$), 245 (20%, $[M-COCH_3]^+$), 186 (20%), 117 (16%, $PhCHCHCH_2^+$), 91 (22%, $PhCH_2^+$); HRMS (ES+) $[M+Na]^+$ found 311.1619, calculated 311.1617.

(4R*,5S*)-4-[(Benzyloxy)methyl]-3-diazo-5-phenyldihydrofuran-2(3H)-one (7.43a)



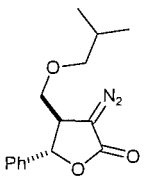
$C_{18}H_{16}N_2O_3$

MW = 308.34

CAS 214468-69-6

Tf_2O (3.5 mL, 12.3 mmol) was added to a stirred solution of NaN_3 (1.60 g, 24.6 mmol) and $^nBu_4NBr$ (10 mg, 30.8 μmol) in NaOH (2N, 50 mL) and hexane (30 mL) at 0 °C. After stirring for 10 minutes, lactone **8.4** (1.00 g, 3.08 mmol) in MeCN (30 mL) was added and reaction was stirred for a further 10 minutes. The reaction was allowed to warm to room temperature then partitioned between EtOAc (100 mL) and water (100 mL). The aqueous phase was reextracted with EtOAc (2 x 100 mL) then the organics were combined, washed with brine (100 mL), dried (Na_2SO_4) and the solvent removed *in vacuo* to give a yellow crude oil. Purification on silica (50 x 80 mm, 5-40% EtOAc/hexane) gave **7.43a** as a bright yellow oil (756 mg, 2.45 mmol, 80%): R_f 0.42 (40 % EtOAc - hexane); IR (film) ν_{max}/cm^{-1} 3064 (w), 3026 (w), 2860 (w), 2099 (s), 1739 (s), 1451 (m), 1370 (m); ^1H NMR (300 MHz, $CDCl_3$) δ 3.71-3.82 (3H, m, **CHCH$_2$**), 4.59 (2H, s, OC**H$_2$**Ph), 5.16 (1H, d, *J* = 4.1 Hz, PhC**H**), 7.29-7.40 (10H, m, $\mathbf{H}_{arom}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7 (C), 139.3 (C), 137.6 (C), 129.4 (CH), 129.4 (CH), 129.2 (CH), 129.1 (CH), 128.9 (CH), 128.6 (CH), 128.2 (CH), 128.1 (CH), 125.8 (CH), 80.8 (CH), 74.1 (CH_2), 71.1 (CH_2), 45.8 (CH) (no $C=N_2$ observed). Spectroscopic characteristics are consistent with those previously recorded in the group.[238]

(4R*,5S*)-3-diazo-4-(isobutoxymethyl)-5-phenyldihydrofuran-2(3H)-one (7.43e)



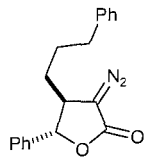
$C_{15}H_{18}N_2O_3$

MW = 274.32

$Mg(ClO_4)_2$ (52 mg, 231 μmol) was added to a solution of cyclopropane **8.3** (500 mg, 2.31 mmol) in 2-methyl-1-propanol (1.1 mL, 11.6 mmol). The reaction mixture was stirred at reflux for 30 min. The reaction was then allowed to cool to room temperature after which it was partitioned between CH_2Cl_2 (25 mL) and water (25 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL) then the combined extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give a crude orange oil (722 mg) (containing lactone **8.5** and the corresponding enol ether (4.3:1)).

Tf_2O (1.7 mL, 9.80 mmol) was added to a stirred solution of NaN_3 (1.27 g, 19.6 mmol) and $^nBu_4NBr$ (8 mg, 24.5 μmol) in NaOH (2N, 25 mL) and hexane (20 mL) at 0 °C. After stirring for 10 minutes, the crude oil from above (710 mg) in MeCN (20 mL) was added and reaction was stirred for a further 15 minutes. After allowing the reaction to warm to room temperature it was partitioned between EtOAc (50 mL) and water (50 mL). The aqueous phase was reextracted with EtOAc (3 x 50 mL) then the combined organics were dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow solid (1.07 g). Purification on silica (40 x 80 mm, 10% EtOAc/hexane) gave **7.43e** as a bright yellow oil (393 mg, 1.43 mmol, 62% from cyclopropane **8.3**): R_f 0.49 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 2955 (w), 2926 (w), 2870 (w), 2099 (s), 1744 (s), 1375 (m), 1266 (m), 1115 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (6H, d, J = 6.3 Hz, $CH(CH_3)_2$), 1.85 (1H, septet, J = 6.3 Hz, $CH(CH_3)_2$), 3.27 (2H, dd, J = 6.3, 1.0 Hz, $OCH_2CH(CH_3)_2$), 3.68-3.78 (3H, m, $PhCHCHCH_2O$), 5.15 (1H, d, J = 4.3, PhCH), 7.33-7.42 (5H, m, H_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8 (C), 139.5 (C), 129.4 (CH), 129.3 (CH), 125.8 (CH), 80.9 (CH), 79.1 (CH_2), 72.5 (CH_2), 46.0 (CH), 28.9 (CH_3), 19.7 (CH_3) (no $C=N_2$ observed).

(4S*,5S*)-3-diazo-5-phenyl-4-(3-phenylpropyl)dihydrofuran-2(3H)-one (7.43c)

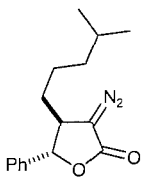


$C_{19}H_{18}N_2O_2$

MW = 306.37

Tf_2O (2.3 mL, 13.9 mmol) was added to a stirred solution of NaN_3 (1.81 g, 27.8 mmol) and $^nBu_4NBr$ (11 mg, 34.8 μmol) in NaOH (2N, 50 mL) and hexane (40 mL) at 0 °C. After stirring for 10 min, lactone **8.6** (1.12 g, 3.48 mmol) in MeCN (40 mL) was added and reaction was stirred for a further 10 min. The yellow reaction was allowed to warm to room temperature then partitioned between EtOAc (100 mL) and water (100 mL). The aqueous phase was reextracted with EtOAc (2 x 100 mL) then the organics were combined, washed with brine (100 mL), dried (Na_2SO_4) and the solvent removed *in vacuo* to give the crude product as a yellow solid (1.71 g). Purification on silica (40 x 90 mm, 10% EtOAc/hexane) gave **7.43c** as a bright yellow oil (834 mg, 2.72 mmol, 78%): R_f 0.48 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3059 (w), 3026 (w), 2931 (w), 2855 (w), 2089 (s), 1734 (s), 1493 (w), 1455 (w) 1375 (m), 1257 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 1.70-1.79 (2H, m, $CHCH_2$), 1.81-1.89 (2H, m, $CHCH_2CH_2$), 2.65 (t, J = 7.6 Hz, CH_2Ph), 3.48 (1H, q, J = 5.0 Hz, $CHCH_2$), 5.05 (1H, d, J = 5.0 Hz), 7.11-7.13 (2H, m, H_{arom}), 7.18-7.22 (1H, m, H_{arom}), 7.24-7.34 (4H, m, H_{arom}), 7.34-7.41 (3H, m, H_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8 (C), 141.5 (C), 139.4 (C), 129.4 (CH), 129.4 (CH), 129.0 (CH), 128.8 (CH), 126.7 (CH), 126.1 (CH), 84.5 (CH), 45.3 (CH), 36.0 (CH_2), 33.5 (CH_2), 28.5 (CH_2) (no $C=N_2$ observed).

(4S*,5S*)-3-diazo-4-(4-methylpentyl)-5-phenyldihydrofuran-2(3H)-one (7.43d)



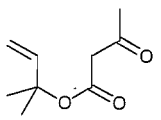
$C_{16}H_{20}N_2O_2$

MW = 272.35

Tf_2O (3.2 mL, 18.9 mmol) was added to a stirred solution of NaN_3 (2.46 g, 37.8 mmol) and $^nBu_4NBr$ (15 mg, 47.2 μmol) in NaOH (2N, 50 mL) and hexane (40 mL) at 0 °C. After stirring for 10 min, lactone **8.7** (1.36 g, 4.72 mmol) in MeCN (40 mL) was added and reaction was stirred for a further 15 min. The yellow reaction was

allowed to warm to room temperature then partitioned between EtOAc (100 mL) and water (100 mL). The aqueous phase was reextracted with EtOAc (2 x 100 mL) then the organics were combined, washed with brine (100 mL), dried (Na_2SO_4) and the solvent removed *in vacuo* to give a yellow crude oil (1.98 g). Purification on silica (40 x 90 mm, 10% EtOAc/hexane) gave **7.43d** as a bright yellow oil (924 mg, 3.39 mmol, 72%): R_f 0.54 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 2955 (w), 2926 (w), 2865 (w), 2089 (s), 1734 (s), 1455 (w), 1375 (m), 1256 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (3H, d, J = 6.8 Hz, C**H**$_3$), 0.86 (3H, d, J = 6.8 Hz, C**H**$_3$), 1.17-1.24 (2H, m, C**H**$_2$), 1.37-1.45 (2H, m, C**H**$_2$), 1.53 (1H, septet, J = 6.5 Hz, C**H**$(CH_3)_2$), 1.82 (2H, dt, J = 8.8, 7.0 Hz, C**H**$_2$), 3.49 (1H, td, J = 6.5, 5.3 Hz,), 5.09 (1H, d, J = 5.3 Hz), 7.32-7.43 (5H, m, **H**$_{arom}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0 (C), 139.6 (C), 129.4 (C), 129.4 (CH), 126.1 (CH), 84.7 (CH), 45.5 (CH), 39.0 (CH_2), 34.5 (CH_2), 28.2 (CH), 24.6 (CH_2), 22.9 (CH_3), 22.8 (CH_3) (no $C{=}N_2$ observed).

1,1-Dimethylprop-2-enyl 3-oxobutanoate (8.9)



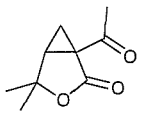
$C_9H_{14}O_3$

MW = 170.21

CAS 15973-38-3

The title compound was prepared using the procedure described for **8.2** whereby 2-methyl-3-buten-2-ol (**8.8**) (12.1 mL, 116 mmol) was reacted with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (8.3 mL, 58.1 mmol). Purification on silica (50 x 100 mm, 10-40% EtOAc/hexane) gave **8.9** as a yellow oil (6.90 g, 40.5 mmol, 70 %): R_f 0.51 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3091 (w), 2983 (w), 2936 (m), 1716 (s), 1645 (s), 1413 (s), 1380 (s), 1364 (s); ^1H NMR (300 MHz, $CDCl_3$) δ 1.52 (6H, s, $(CH_3)_2C$), 2.24 (3H, s, C**H**$_3$C=O), 3.36 (2H, s, -C**H**$_2$-), 5.09 (1H, d, J = 11.0 Hz, C**H**H=CH), 5.18 (1H, d, J = 17.7 Hz, CH**H**=CH), 6.07 (1H, dd, J = 17.7, 11.0 Hz, CH_2=C**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5 (C), 166.4 (C), 142.3 (CH), 113.8 (CH_2), 82.7 (C), 51.7 (CH_2), 30.6 (CH_3), 26.8 (CH_3); LRMS (CI, ammonia) *m/z* (relative intensity) 171 (1%, $[M+H]^+$), 127 (48%, $[M–COCH_3]^+$), 108 (52%), 85 (18%, $[M–COCH_2COCH_3]^+$ or $[COCH_2COCH_3]^+$), 69 (61%, $[M–OCOCH_2COCH_3]^+$), 68 (59%). Spectroscopic characteristics are consistent with those reported in the literature.[239]

(1R*,5S*)-1-Acetyl-4,4-dimethyl-3-oxabicyclo[3.1.0]hexan-2-one (8.10)



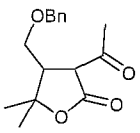
$C_9H_{12}O_3$

MW = 168.19

CAS 16148-96-2

The title compound was prepared by reacting acetoacetate ester **8.9** (1.00 g, 5.88 mmol) under the conditions described for **8.3**. Purification on silica (30 x 100 mm, 10-40% EtOAc/hexane) gave **8.10** as a pale yellow oil which crystallised on standing (0.48 g, 2.9 mmol, 49 %): mp 32-35 °C; R_f 0.29 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3092 (w), 2978 (w), 2931 (w), 1763 (s), 1697 (s), 1380 (m), 1314 (m); ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (3H, s, CH_3), 1.48 (1H, dd, J = 5.5, 4.4 Hz, $CHCH_2$), 1.50 (3H, s, CH_3), 1.97 (1H, dd, J = 7.7, 4.4 Hz, CHH), 2.59 (3H, s, CH_3C=O), 2.61 (1H, dd, J = 8.1, 5.9 Hz, CHH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3 (C), 172.5 (C), 81.8 (C), 40.4 (CH), 39.3 (C), 29.9 (CH_3), 29.8 (CH_3), 24.3 (CH_3), 23.6 (CH_2); LRMS (CI, ammonia) *m/z* (relative intensity) 186 (54%, $[M+NH_4]^+$), 169 (100%, $[M+H]^+$), 153 (61%, $[M-CH_3]^+$), 135 (12%), 111 (19%), 81 (18%), 53 (10%). Spectroscopic characteristics are consistent with those previously recorded in the group.[238]

3-Acetyl-4-[(benzyloxy)methyl]-5,5-dimethyldihydrofuran-2(3H)-one (8.11)



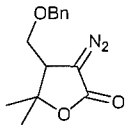
$C_{16}H_{20}O_4$

MW = 276.34

$Mg(ClO_4)_2$ (40 mg, 178 μmol) was added to a solution of cyclopropane **8.10** (300 mg, 1.78 mmol) in BnOH (0.9 mL, 8.92 mmol). The reaction mixture was placed in a preheated oil bath and stirred at 100 °C for 4 hours. The reaction was then allowed to cool to room temperature. The BnOH was removed by Kugelrohr distillation and the residue purified on silica (50 x 110 mm, 10-40% EtOAc/hexane) to afford the title compound **8.11** as a thick yellow oil (414 mg, 1.50 mmol, 84%): R_f 0.37 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 2978 (w), 2868 (w), 1762 (s), 1719 (s), 1362 (m); ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (3H, s, CH_3), 1.52 (3H, s, CH_3), 2.43 (3H, s, CH_3C=O), 3.09 (1H, ddd, J = 11.0, 7.0, 5.5 Hz, $CHCH_2$), 3.47 (1H, dd, J = 9.9, 7.4

Hz, CHC**H**H), 3.52 (1H, dd, J = 9.9, 5.9 Hz, CHCH**H**), 3.63 (1H, d, J = 11.0 Hz, C**H**COCH$_3$), 4.45 (1H, d, J = 11.8 Hz, C**H**HPh), 4.51 (1H, d, J = 11.8 Hz, CH**H**Ph), 7.25-7.38 (5H, m, **H**$_{arom}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9 (C), 171.2 (C), 138.0 (C), 129.0 (CH), 128.4 (CH), 128.1 (CH), 85.6 (C), 73.8 (CH_2), 68.1 (CH_2), 56.9 (CH), 46.5 (CH), 30.6 (CH_3), 29.1 (CH_3), 23.4 (CH_3); LRMS (CI, ammonia) *m/z* (relative intensity) 294 (8%, $[M+NH_4]^+$), 277 (61%, $[M+H]^+$), 169 (24%, $[M–OBn]^+$), 127 (16%), 91 (100%, $PhCH_2^+$). Spectroscopic characteristics are consistent with those previously recorded in the group.[238]

4-[(Benzyloxy)methyl]-3-diazo-5,5-dimethyldihydrofuran-2(3H)-one (7.43b)



$C_{14}H_{16}N_2O_3$

MW = 260.30

Tf_2O (0.9 mL, 5.08 mmol) was added to a stirred solution of NaN_3 (660 mg, 10.2 mmol) and ^{n}Bu$_4$NBr (4 mg, 12 μmol) in NaOH (2N, 20 mL) and hexane (10 mL) at 0 °C. After stirring for 10 minutes, lactone **8.11** (350 mg, 1.27 mmol) in MeCN (10 mL) was added and reaction was stirred for a further 10 minutes. After allowing the reaction to warm to room temperature it was partitioned between EtOAc (50 mL) and water (50 mL). The aqueous phase was reextracted with EtOAc (2 x 50 mL) then the organics were combined, washed with brine (50 mL), dried (Na_2SO_4) and the solvent removed *in vacuo* to give a yellow crude oil. Purification on silica (30 x 100 mm, 5-40% EtOAc/hexane) gave **7.43b** as a bright yellow oil (238 mg, 914 μmol, 72%): R_f 0.34 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 2979 (w), 2865 (w), 2095 (s), 1733 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (3H, s, C**H**$_3$), 1.49 (3H, s, C**H**$_3$), 3.54 (1H, dd, J = 8.8, 5.1 Hz, C**H**CH$_2$), 3.63 (1H, t, J = 8.5 Hz, CHC**H**H), 3.76 (1H, dd, J = 8.5, 5.1 Hz, CHCH**H**), 4.53 (1H, d, J = 11.8 Hz, C**H**HPh), 4.58 (1H, d, J = 11.8 Hz, CH**H**Ph), 7.30-7.41 (5H, m, **H**$_{arom}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5 (C), 137.7 (C), 129.1 (CH), 128.5 (CH), 128.1 (CH), 128.1 (CH), 83.6 (C), 74.2 (CH_2), 69.8 (CH_2), 46.7 (CH), 29.9 (CH_3), 23.2 (CH_3) (no C=N$_2$ observed). Spectroscopic characteristics are consistent with those previously recorded in the group.[238]

Typical catalytic diazo decomposition

$Rh_2(OAc)_4$ (4.2 mg, 9.54 μmol) was added to a stirred solution of α-diazolactone **7.43a** (98 mg, 318 μmol) in CH_2Cl_2 (2 mL) at room temperature, resulting in the evolution of N_2 gas. After 2 h the green reaction was partitioned between CH_2Cl_2 (10 mL) and water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) then the combined organics were dried (Na_2SO_4) and concentrated *in vacuo* to give a colourless oil (95 mg). This was purified on silica (20 x 100 mm, 10-30% EtOAc/hexane) to give furofuranone **8.12a** as a colourless crystalline solid (71 mg, 253 μmol, 80%).

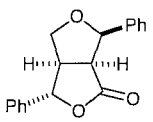
Typical thermal diazo decomposition

A solution of α-diazolactone **7.43a** (53 mg, 172 μmol) in $Cl(CH_2)_2Cl$ (3 mL) was heated to 150 °C in a sealed tube. Evolution of N_2 gas was observed. The reaction was monitored by IR and on disappearance of the diazo absorption at ca. 2090 cm^{-1} (1 h) it was allowed to cool to room temperature. The solvent was removed *in vacuo*, giving a pale yellow oil (46 mg) that was examined by ^1H NMR.

Typical photochemical diazo decomposition

A solution of α-diazolactone **7.43a** (51 mg, 165 μmol) in $Cl(CH_2)_2Cl$ (3 mL) was irradiated with UV light. The reaction was monitored by IR and on disappearance of the diazo absorption at ca. 2090 cm^{-1} (5 h) the solvent was removed *in vacuo*, giving a pale yellow oil (49 mg) that was examined by ^1H NMR.

(1S*,2R*,5R*,6S*)-6-Phenyl-2-phenyl-3,7-dioxabicyclo[3.3.0]octan-8-one (8.12a)



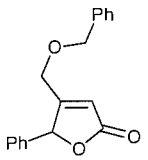
$C_{18}H_{16}O_3$

MW = 280.33

Colourless crystalline solid: mp 118-121 °C; R_f 0.42 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 2959 (w), 2865 (w), 2363 (m), 2335 (m), 1772 (s), 1451 (w), 1167 (m), 1058 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 3.26 (1H, ddd, J = 8.8, 6.3, 4.8 Hz,

OCH_2CH), 3.60 (1H, t, J = 8.8 Hz, O_2CCH), 3.96 (1H, dd, J = 9.8, 4.8 Hz, OCH**H**), 4.34 (1H, d, J = 9.8 Hz, OC**H**H), 5.11 (1H, d, J = 8.5 Hz, PhC**H**O), 5.32 (1H, d, J 6.2 = Hz, PhC**H**CO_2), 7.31-7.40 (10H, m, $\mathbf{H}_{arom}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8 (C), 140.1 (C), 136.5 (C), 129.5 (CH), 129.2 (CH), 129.0 (CH), 126.7 (CH), 125.9 (CH), 85.9 (CH), 84.4 (CH), 72.5 (CH_2), 52.0 (CH), 51.7 (CH); LRMS (EI) *m/z* (relative intensity) 280 (8%, M^+), 117 (100%, $PhCHCHCH_2^+$), 91 (52%, $PhCH_2^+$), 77 (60%, Ph^+). Spectroscopic characteristics are consistent with those reported in the literature.[225]

4-[(benzyloxy)methyl]-5-phenylfuran-2(5H)-one (8.14a)

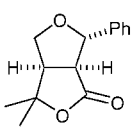


$C_{18}H_{16}O_3$

MW = 280.33

Colourless oil: R_f 0.38 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3064 (w), 3030 (w), 2903 (w), 2851 (w), 1791 (m), 1753 (s), 1649 (w), 1451 (m), 1247 (m), 1143 (m), 1096 (m); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15 (1H, d, J = 1.5 Hz, =CC$\mathbf{H}_2$O), 4.50 (1H, d, J = 11.8 Hz, OC**H**HPh), 4.59 (1H, d, J = 12.1 Hz, OCH**H**Ph), 5.93 (1H, d, J = 1.5 Hz, PhC**H**), 6.22 (1H, q, J = 1.5 Hz, C=C**H**), 7.25-7.34 (4H, m, $\mathbf{H}_{arom}$), 7.35-7.47 (6H, m, $\mathbf{H}_{arom}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1 (C), 169.2 (C), 137.3 (C), 134.7 (C), 130.0 (CH), 129.6 (CH), 129.6 (CH), 129.1 (CH), 128.6 (CH), 128.2 (CH), 128.2 (CH), 127.1 (CH), 116.5 (CH), 84.4 (CH), 73.8 (CH_2), 65.6 (CH_2); LRMS (CI, ammonia) *m/z* (relative intensity) 281 (7%, $[M+H]^+$), 207 (17%), 154 (34%), 105 (100%), 91 (97%, $PhCH_2^+$), 77 (62%, Ph^+); HRMS (EI) $[M]^+$ found 280.1093, calculated 280.1099.

(1S*,2S*,5R*)-6,6-Dimethyl-2-phenyl-3,7-dioxabicyclo[3.3.0]octan-8-one (8.13b)



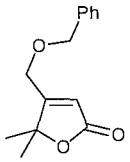
$C_{14}H_{16}O_3$

MW = 232.28

Colourless oil; R_f 0.38 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3059 (w), 3026 (w), 2978 (m), 2865 (w), 1758 (s), 1375 (m), 1271 (s), 1129 (s); ^{1}H NMR (300 MHz,

$CDCl_3$) δ 1.46 (3H, s, C**H**$_3$), 1.47 (3H, s, C**H**$_3$), 2.96 (1H, ddd, *J* = 8.4, 7.7, 7.7 Hz, C**H**CH$_2$), 3.45 (1H, dd, *J* = 8.8, 3.3 Hz, C**H**CO$_2$), 3.91 (1H, dd, *J* = 9.5, 7.7 Hz, CH**H**), 4.19 (1H, dd, *J* = 9.5, 7.4 Hz, CH**H**), 5.30 (1H, d, *J* = 3.3 Hz, OC**H**Ph), 7.26-7.42 (5H, m, **H**$_{arom}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2 (C), 141.4 (C), 129.1 (CH), 128.3 (CH), 125.8 (CH), 125.8 (CH), 84.3 (C), 83.7 (CH), 69.4 (CH_2), 56.0 (CH), 50.9 (CH), 30.6 (CH_3), 23.9 (CH_3); LRMS (EI) *m/z* (relative intensity) 232 (49%, M^+), 187 (23%), 164 (100%), 146 (69%), 127 (35%), 105 (90%), 91 (55%, CH_2Ph^+). Spectroscopic characteristics are consistent with those previously recorded in the group.[240]

4-[(benzyloxy)methyl]-5,5-dimethylfuran-2(5H)-one (8.14b)

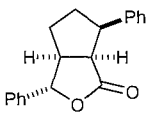


$C_{14}H_{16}O_3$

MW = 232.28

Pale yellow oil: R_f 0.30 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 2978 (w), 2926 (w), 2860 (w), 1753 (s), 1247 (m), 1105 (m); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (6H, s, (C**H**$_3$)$_2$), 4.28 (2H, d, *J* = 1.8 Hz, =CC**H**$_2$O), 4.61 (2H, s, OC**H**$_2$Ph), 5.99 (1H, t, *J* = 1.8 Hz, PhC**H**O), 7.33-7.42 (5H, m, **H**$_{arom}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4 (C), 137.4 (C), 129.1 (CH), 128.7 (CH), 128.2 (CH), 115.8 (CH), 86.4 (C), 73.8 (CH_2), 65.2 (CH_2), 25.8 (CH_3); LRMS (EI) *m/z* (relative intensity) 233 (18%, $[M+H]^+$), 141 (16%, $[M-CH_2Ph]^+$), 126 (61%), 111 (33%), 91 (100%, $PhCH_2^+$), 77 (35%, Ph^+); HRMS (EI) $[M]^+$ found 232.1101, calculated 232.1099.

(3S*,3S*,6R*,6R*)-3,6-diphenylhexahydro-1H-cyclopenta[c]furan-1-one (8.12c)



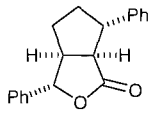
$C_{19}H_{18}O_2$

MW = 278.35

Colourless crystalline solid: mp 136-139 °C; R_f 0.41 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3059 (w), 3026 (w), 2955 (w), 2870 (w), 1768 (s), 1498 (w), 1451 (w), 1162 (m); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.02-2.24 (4H, m, C**H**$_2$C**H**$_2$), 3.60 (1H, m, CH$_2$C**H**CHPh), 3.41 (1H, dd, *J* = 9.9, 8.5 Hz, CO$_2$C**H**CHPh), 3.49-3.58 (1H, m,

$CO_2CHCHPh$), 5.15 (1H, d, J = 5.5 Hz, PhC**H**O), 7.25-7.43 (10H, m, $\mathbf{H}_{arom}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9 (C), 141.3 (C), 138.9 (C), 129.3 (CH), 128.8 (CH), 128.6 (CH), 127.6 (CH), 125.6 (CH), 86.6 (CH), 50.1 (CH), 49.7 (CH), 32.4 (CH_2), 30.9 (CH_2); LRMS (EI) *m/z* (relative intensity) 278 (32%, M^+), 232 (40%), 193 (24%), 144 (100%), 129 (80%), 115 (68%), 91 (52%, $PhCH_2^+$), 77 (60%, Ph^+); HRMS (EI) $[M]^+$ found 278.1308, calculated 278.1307.

(3S*,3S*,6S*,6R*)-3,6-diphenylhexahydro-1H-cyclopenta[c]furan-1-one (8.13c)

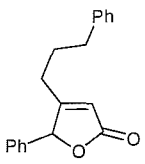


$C_{19}H_{18}O_2$

MW = 278.35

Colourless oil: R_f 0.49 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3059 (w), 3026 (w), 2950 (w), 2865 (w), 1763 (s), 1493 (w), 1446 (w), 1327 (w), 1176 (m), 1157 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 1.83-1.99 (2H, m, CHC**H**$_2$), 2.24-2.41 (2H, m, C**H**$_2$CHPh), 3.05-3.12 (1H, m, CH_2C**H**CHPh), 3.27 (1H, dd, J = 9.3, 4.5 Hz, CO_2C**H**CHPh), 3.66 (1H, br. td, J = 6.8, 4.8 Hz, $CO_2CHCHPh$), 5.34 (1H, d, J = 2.8 Hz, PhC**H**O), 7.22-7.43 (10H, m, $\mathbf{H}_{arom}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9 (C), 144.0 (C), 141.1 (C), 129.4 (CH), 129.1 (CH), 128.7 (CH), 127.4 (CH), 127.1 (CH), 125.4 (CH), 86.1 (CH), 52.1 (CH), 49.8 (CH), 49.4 (CH), 35.0 (CH_2), 33.1 (CH_2); LRMS (EI) *m/z* (relative intensity) 278 (36%, M^+), 233 (23%), 187 (37%), 144 (63%), 143 (64%), 129 (55%), 117 (100%), 91 (52%), 77 (24%); HRMS (EI) $[M]^+$ found 278.1307, calculated 278.1307.

5-phenyl-4-(3-phenylpropyl)furan-2(5H)-one (8.14c)



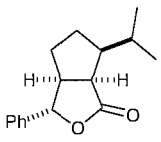
$C_{19}H_{18}O_2$

MW = 278.35

Pale yellow oil: R_f 0.44 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3026 (w), 2926 (w), 2855 (w), 1753 (s), 1451 (m), 1167 (m); ^1H NMR (300 MHz, $CDCl_3$) δ 1.84 (2H, m, CH_2C**H**$_2CH_2$), 2.17 (2H, t, J = 7.4 Hz, =CC**H**$_2CH_2$), 2.59 (2H, dt, J = 12.5, 7.4 Hz, C**H**$_2$Ph), 5.72 (1H, d, J = 1.5 Hz, PhC**H**O), 5.94 (1H, q, J = 1.5 Hz, C=C**H**), 7.07-7.10

(2H, m, $\mathbf{H}_{arom}$), 7.17-7.22 (3H, m, $\mathbf{H}_{arom}$), 7.25-7.30 (2H, m, $\mathbf{H}_{arom}$), 7.38-7.40 (3H, d, J = 6.2 Hz, $\mathbf{H}_{arom}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1 (C), 141.3 (C), 134.8 (C), 129.9 (CH), 129.5 (CH), 129.0 (CH), 128.8 (CH), 127.3 (CH), 126.7 (CH), 115.6 (CH), 86.3 (CH), 35.5 (CH_2), 29.0 (CH_2), 28.0 (CH_2); LRMS (EI) *m/z* (relative intensity) 278 (12%, M^+), 173 (100%, $[M–CH_2CH_2Ph]^+$), 105 (63%, $PhCH_2CH_2^+$), 91 (71%, $PhCH_2^+$), 77 (31%, Ph^+); HRMS (EI) $[M]^+$ found 278.1311, calculated 278.1307.

(3S*,3S*,6S*,6R*)-6-isopropyl-3-phenylhexahydro-1H-cyclopenta[c]furan-1-one (8.12d)

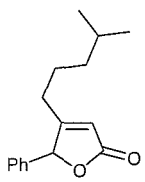


$C_{16}H_{20}O_2$

MW = 244.34

Very pale yellow oil: R_f 0.58 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3064 (w), 3035 (w), 2950 (m), 2865 (w), 1768 (s), 1635 (w), 1455 (w), 1167 (m), 1124 (m), 1030 (m); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (3H, d, J = 6.6 Hz, $\mathbf{CH}_3$), 1.15 (3H, d, J = 6.2 Hz, $\mathbf{CH}_3$), 1.25-1.41 (1H, m, C**H**H), 1.79-1.88 (2H, m, CH**H**), 1.88-2.06 (4H, m, 2 x $\mathbf{CH}_2$), 2.87-2.95 (1H, m, $\mathbf{CH}(CH_3)_2$), 3.19 (1H, t, J = 8.8 Hz, $\mathbf{CHCO}_2$), 5.06 (1H, d, J = 4.0 Hz, PhC**H**), 7.27-7.41 (5H, m, $\mathbf{H}_{arom}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0 (C), 141.7 (C), 129.2 (CH), 128.6 (CH), 125.4 (CH), 87.0 (CH), 53.8 (CH), 48.8 (CH), 46.4 (CH), 33.1 (CH_2), 29.9 (CH_2), 28.8 (CH), 23.4 (CH_3), 22.8 (CH_3); LRMS (CI) *m/z* (relative intensity) 262 (8%, $[M+NH_4]^+$), 245 (100%, $[M+H]^+$), 117 (35%), 91 (50%, CH_2Ph^+); HRMS (EI) $[M]^+$ found 244.1457, calculated 244.1463.

4-(4-methylpentyl)-5-phenylfuran-2(5H)-one (8.14d)



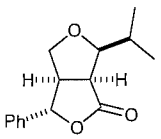
$C_{16}H_{20}O_2$

MW = 244.34

Pale yellow oil: R_f 0.51 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3059 (w), 3030 (w), 2950 (m), 2865 (m), 1791 (m), 1753 (s), 1635 (m), 1455 (m), 1257 (m), 1167

(m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (3H, d, J = 0.8 Hz, C**H**$_3$), 0.84 (3H, d, J = 0.8 Hz, C**H**$_3$), 1.14 (2H, q, J = 7.5, C**H**$_2$), 1.40-1.58 (3H, m, C**H**$(CH_3)_2$ and C**H**$_2$), 2.08-2.13 (2H, m, C**H**$_2$), 5.72 (1H, d, J = 1.2 Hz, PhC**H**), 5.91 (1H, q, J = 1.5 Hz, C=C**H**), 7.18-7.24 (2H, m, **H**$_{arom}$), 7.34-7.41 (3H, m, **H**$_{arom}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9 (C), 173.6 (C), 135.0 (C), 129.9 (CH), 129.5 (CH), 127.3 (CH), 115.5 (CH), 86.4 (CH), 38.7 (CH_2), 28.9 (CH_2), 28.1 (CH), 25.2 (CH_2), 22.9 (CH_3), 22.8 (CH_3); LRMS (EI) *m/z* (relative intensity) 245 (32%, $[M+H]^+$), 244 (30%, M^+), 215 (42%), 184 (51%), 173 (84%, $[M–CH_2CH_2CH(CH_3)_2]^+$), 159 (41%, $[M–CH_2CH_2CH_2CH(CH_3)_2]^+$), 139 (37%), 128 (42%), 105 (100%), 91 (57%, CH_2Ph^+), 77 (64%, Ph^+); HRMS (EI) $[M]^+$ found 244.1460, calculated 244.1463.

(1S*,2R*,5R*,6S*)-6-Phenyl-2-isopropyl-3,7-dioxabicyclo[3.3.0]octan-8-one (8.12e)

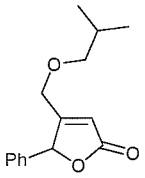


$C_{15}H_{18}O_3$

MW = 246.31

Colourless oil: R_f 0.51 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3064 (w), 3030 (w), 2964 (m), 2865 (m), 1768 (s), 1328 (m), 1252 (m), 1172 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (3H, d, J = 6.6 Hz, C**H**$_3$), 1.15 (3H, d, J = 6.5 Hz, C**H**$_3$), 2.11 (1H, dseptet, J = 9.0, 6.5 Hz, C**H**$(CH_3)_2$), 3.13 (1H, dddd, J = 9.0, 5.5, 5.5, 1.0 Hz, CH_2C**H**), 3.34 (1H, dd, J = 9.0, 7.3 Hz, C**H**CO_2), 3.46 (1H, dd, J = 9.0, 7.2 Hz, OC**H**^{i}Pr), 3.76 (1H, dd, J = 9.5, 5.5 Hz, OC**H**H), 4.15 (1H, d, J = 9.5 Hz, OCH**H**), 5.18 (1H, d, J = 5.0 Hz, PhC**H**O), 7.28-7.41 (5H, m, **H**$_{arom}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9 (C), 140.5 (C), 129.4 (CH), 129.1 (CH), 125.7 (CH), 89.0 (CH), 86.1 (CH), 72.9 (CH_2), 51.0 (CH), 48.1 (CH), 29.8 (CH), 20.4 (CH_3), 20.3 (CH_3); LRMS (EI) *m/z* (relative intensity) 246 (12%, M^+), 228 (6%, $[M–H_2O]^+$), 203 (16%, $[M–{}^iPr]^+$), 175 (70%), 158 (50%), 129 (32%), 117 (52%), 91 (100%, CH_2Ph^+), 77 (46%, Ph^+); HRMS (EI) $[M]^+$ found 246.1251, calculated 246.1256.

4-[(2-methyl)propyloxymethyl]-5-phenylfuran-2(5H)-one (8.14e)

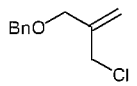


$C_{15}H_{18}O_3$

MW = 246.31

Very pale yellow oil: R_f 0.45 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3068 (w), 3040 (w), 2959 (w), 2870 (w), 1786 (m), 1753 (s), 1645 (m), 1455 (w), 1247 (w), 1139 (m), 1101 (m); ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (6H, d, J = 7.0 Hz, 2 x $\mathbf{CH_3}$), 1.84 (1H, septet, J = 6.6 Hz, $\mathbf{CH}(CH_3)_2$), 3.15 (1H, dd, J = 8.8, 16.9 Hz, $OCHHCH(CH_3)_2$), 3.17 (1H, dd, J = 8.8, 16.9 Hz, $OCH\mathbf{H}CH(CH_3)_2$), 4.04 (2H, s, $=CC\mathbf{H_2}O$), 5.87 (1H, d, J = 1.5 Hz, PhC**H**), 6.12 (1H, q, J = 1.5 Hz, =**CH**), 7.22-7.26 (2H, m, $\mathbf{H}_{arom}$), 7.37-7.42 (3H, m, $\mathbf{H}_{arom}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2 (C), 169.8 (C), 134.8 (C), 129.9 (CH), 129.6 (CH), 129.5 (CH), 127.1 (CH), 126.5 (CH), 116.2 (CH), 84.4 (CH), 78.8 (CH_2), 66.6 (CH_2), 28.9 (CH), 19.7 (CH_3); LRMS (CI) *m/z* (relative intensity) 264 (6%, $[M+NH_4]^+$), 247 (50%, $[M+H]^+$), 175 (64%), 105 (82%), 91 (18%, CH_2Ph^+), 77 (42%, Ph^+), 43 (100%, $^iPr^+$); HRMS (EI) $[M]^+$ found 246.1265, calculated 246.1256.

({[2-(chloromethyl)prop-2-enyl]oxy}methyl)benzene (8.15)



$C_{11}H_{13}ClO$

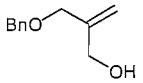
MW = 196.68

CAS 113964-32-2

The title compound was prepared according to the method of Klumpp *et al.*[232] BnOH (661 μL, 6.39 mmol) was added in one portion to a suspension of hexane-washed NaH (60% dispersion in mineral oil, 383 mg, 9.58 mmol) in THF (20 mL) at 0 °C. After stirring for 30 min, the reaction was allowed to warm to rt and 3-chloro-2-chloromethyl-1-propene (1.597 g, 12.8 mmol) was added, giving an orange colour. The reaction was heated at reflux for 2 h then allowed to cool to rt before quenching with saturated aqueous $NaHCO_3$ (100 mL), followed by extraction with Et_2O (4 x 100 mL). The combined organics were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow oil (1.705 g) which was purified on silica (40 x

100 mm, 5% EtOAc/hexane) to provide **8.15** as a colourless oil (1.12g, 5.69 mmol, 89%): R_f 0.60 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3082 (w), 3059 (w), 3030 (w), 2936 (w), 2855 (m), 1493 (w), 1451 (m), 1361 (w), 1261 (m), 1096 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (2H, s, CH_2=CC**H**$_2$), 4.14 (2H, s, CH_2=CC**H**$_2$), 4.53 (2H, s, PhC**H**$_2$), 5.27 (1H, d, J = 1.2 Hz, C**H**H=C), 5.27 (1H, s, CH**H**=C), 7.27-7.38 (5H, m, **H**$_{arom}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5 (C), 138.5 (C), 128.9 (CH), 128.2 (CH), 117.3 (CH_2), 72.9 (CH_2), 70.8 (CH_2), 45.7 (CH_2); LRMS (CI, ammonia) *m/z* (relative intensity) 199 (21%, $[M+H]^+$), 197 (55%), 107 (5%, $PhCH_2O^+$), 91 (100%, CH_2Ph^+), 77 (35%, Ph^+). Spectroscopic characteristics are consistent with those reported in the literature.[232]

2-[(benzyloxy)methyl]prop-2-en-1-ol (8.16)



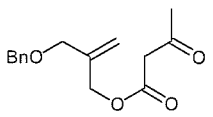
$C_{11}H_{14}O_2$

MW = 178.23

CAS 109240-66-6

The title compound was prepared by treating a solution of allyl chloride **8.15** (49 mg, 249 μmol) in 1,4-dioxane (1.5 mL) with 2N NaOH (1.5 mL) and ^{n}Bu$_4$NBr (800 μg, 2.4 μmol) and stirring the reaction at 100 °C for 9 h. After allowing it to cool to rt, the reaction was partitioned between CH_2Cl_2 (20 mL) and water (20 mL). The aqueous phase was then extracted with CH_2Cl_2 (3 x 20 mL) and the combined organics were dried (Na_2SO_4) and concentrated *in vacuo*, to give a colourless oil (45 mg) which was purified on silica (12 x 70 mm, 20% EtOAc/hexane) affording **8.16** as a colourless oil (38 mg, 2.13 μmol, 86%): R_f 0.29 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3385 (br. m), 3082 (w), 3059 (w), 3026 (w), 2917 (w), 2860 (m), 1493 (w), 1451 (m), 1361 (w), 1068 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.93 (1H, s, O**H**), 4.10 (2H, s, CH_2=CC**H**$_2$), 4.20 (2H, s, CH_2=CC**H**$_2$), 4.53 (2H, s, PhC**H**$_2$), 5.17 (1H, s, C**H**H=C), 5.21 (1H, s, CH**H**=C), 7.28-7.36 (5H, m, **H**$_{arom}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.4 (C), 138.4 (C), 128.9 (CH), 128.2 (CH), 114.1 (CH_2), 72.8 (CH_2), 72.3 (CH_2), 65.1 (CH_2); LRMS (CI, ammonia) *m/z* (relative intensity) 179 (20%, $[M+H]^+$), 145 (37%), 143 (32%), 107 (10%, $PhCH_2O^+$), 105 (22%), 91 (100%, CH_2Ph^+), 77 (47%, Ph^+).

2-[(benzyloxy)methyl]prop-2-enyl 3-oxobutanoate (8.17)

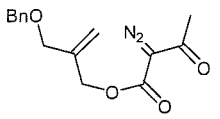


$C_{15}H_{18}O_4$

MW = 262.31

The title compound was prepared according to the method described for **8.2** whereby alcohol **8.16** (1.98 g, 11.1 mmol) was reacted with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (1.5 mL, 11.7 mmol). Purification on silica (50 x 90 mm, eluting with hexane (200 mL), then 20% EtOAc/hexane) gave **8.17** as a colourless oil (2.64 g, 10.1 mmol, 91%): R_f 0.44 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3082 (w), 3054 (w), 3030 (w), 2926 (w), 2855 (w), 1744 (s), 1716 (s), 1649 (w), 1493 (w), 1455 (m), 1356 (m), 1314 (m), 1266 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (3H, s, $COCH_3$), 3.46 (2H, s, $COCH_2CO$), 4.04 (2H, s, CH_2OCH_2Ph), 4.51 (2H, s, $PhCH_2$), 4.71 (2H, s, CO_2CH_2), 5.26 (1H, s, CHH=C), 5.29 (1H, s, CHH=C), 7.27-7.37 (5H, m, H_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7 (C), 167.2 (C), 140.6 (C), 138.5 (C), 128.9 (CH), 128.2 (CH), 128.2 (CH), 116.6 (CH_2), 72.7 (CH_2), 71.2 (CH_2), 66.0 (CH_2), 50.4 (CH_2), 30.7 (CH_3); LRMS (ES+) *m/z* (relative intensity) 547 (8%, $[2M+Na]^+$), 542 (7%, $[2M+NH_4]^+$), 301 (13%, $[M+K]^+$), 285 (25%, $[M+Na]^+$), 280 (100%, $[M+NH_4]^+$), 263 (13%, $[M+H]^+$); HRMS (ES+) $[M+Na]^+$ found 285.1095, calculated 285.1097.

2-[(benzyloxy)methyl]prop-2-enyl 2-diazo-3-oxobutanoate (8.18)



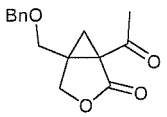
$C_{15}H_{16}N_2O_4$

MW = 288.30

The title compound was prepared by treating a solution of **8.17** (1.83 g, 6.98 mmol) in MeCN (40 mL), stirred at rt, with diisopropylethylamine (2.8 mL, 16.1 mmol). After 5 min, 4-carboxybenzenesulfonyl azide (2.06 g, 9.07 mmol) was added. After 2 h, the white precipitate was removed by filtration and washed with Et_2O. The filtrate was diluted with Et_2O (200 mL) and washed with water (200 mL). The aqueous phase was extracted with Et_2O (2 x 200 mL) then the combined organics were washed with saturated aqueous $NaHCO_3$ (200 mL) and brine (200 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a pale yellow oil (2.03 g). This was purified on silica (50 x 80 mm, 10% EtOAc/hexane) to provide **8.18** as a colourless oil (1.89 g, 6.56 mmol, 94%): R_f 0.48 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3087 (w), 3059 (w),

3026 (w), 2931 (w), 2851 (w), 2141 (s), 1720 (s), 1659 (s), 1455 (m), 1366 (s), 1314 (s), 1247 (m), 1153 (m), 1077 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (3H, s, C**H**$_3$), 4.04 (2H, s, C**H**$_2$OCH$_2$Ph), 4.51 (2H, s, PhC**H**$_2$), 4.80 (2H, s, CO$_2$C**H**$_2$), 5.26 (1H, s, C**H**H=C), 5.31 (1H, s, CH**H**=C), 7.28-7.37 (5H, m, **H**$_{arom}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5 (C), 161.5 (C), 140.4 (C), 138.2 (C), 128.9 (CH), 128.3 (CH), 128.2 (CH), 117.0 (CH_2), 72.7 (CH_2), 71.0 (CH_2), 65.9 (CH_2), 28.7 (CH_3) (no C=N$_2$ observed).

1-acetyl-5-[(benzyloxy)methyl]-3-oxabicyclo[3.1.0]hexan-2-one (8.19)

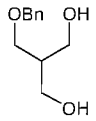


$C_{15}H_{16}O_4$

MW = 260.29

A solution of diazo acetoacetate **8.18** (100 mg, 347 μmol) in CH_2Cl_2 (2 mL) was added dropwise over 10 min to a stirred suspension of $Rh_2(OAc)_4$ (5 mg, 10.4 μmol) in CH_2Cl_2 (1 mL). Evolution of N_2 was observed from the green mixture. After 30 min the reaction was concentrated *in vacuo* and loaded onto silica (20 x 90 mm) and purified (eluting with 10-15% EtOAc/hexane) to give **8.19** as a pale yellow oil (54 mg, 207 μmol, 60%): R_f 0.37 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3087 (w), 3064 (w), 3030 (w), 2997 (w), 2969 (w), 2903 (w), 2860 (w), 1768 (s), 1697 (s), 1451 (m), 1493 (w), 1361 (s), 1276 (m), 1209 (m), 1091 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (1H, d, *J* = 4.8 Hz, CC**H**HC), 2.26 (1H, d, *J* = 4.8 Hz, CCH**H**C), 2.53 (3H, s, C**H**$_3$), 3.40 (1H, d, *J* = 11.0 Hz, PhCH$_2$OC**H**H), 3.80 (1H, d, *J* = 11.0 Hz, PhCH$_2$OC**H**H), 4.21 (1H, d, *J* = 9.2 Hz, C**H**HO$_2$C), 4.39 (1H, d, *J* = 11.8 Hz, PhC**H**H), 4.43 (1H, d, *J* = 11.8 Hz, PhCH**H**), 4.49 (1H, d, *J* = 8.8 Hz, CH**H**O$_2$C), 7.22-7.38 (5H, m, **H**$_{arom}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.5 (C), 173.9 (C), 137.8 (C), 129.0 (CH), 128.5 (CH), 128.2 (CH), 73.8 (CH_2), 69.4 (CH_2), 66.1 (CH_2), 43.4 (C), 39.7 (C), 30.3 (CH_3), 24.8 (CH_2); LRMS (CI) *m/z* (relative intensity) 261 (4%, $[M+H]^+$), 91 (74%, CH_2Ph^+), 77 (24%, Ph^+), 43 (100%); HRMS (ES+) $[M+Na]^+$ found 283.0939, calculated 283.0941.

2-[(Benzyloxy)methyl]propane-1,3-diol (8.21)



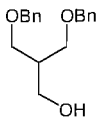
$C_{11}H_{16}O_3$

MW = 196.25

CAS 117087-18-0

The title compound was prepared by the method described by Guanti *et al*,[241] whereby a solution of diester **8.20** (1.358 g, 5.38 mmol) in THF (10 mL) was added to an ice-cooled suspension of $LiAlH_4$ (817 mg, 21.5 mmol) in THF (60 mL). After 10 min the reaction was allowed to warm to rt. After 4.5 h the reaction was cooled to 0 °C and EtOAc (20 mL) was added carefully, followed by MeOH (5 mL) and aqueous HCl (2N, 50 mL). The aqueous phase was extracted with EtOAc (2 x 100 mL) then the combined organics were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a pale yellow oil (984 mg). This was purified on silica (40 x 80 mm, 15-100% EtOAc/hexane) to give diol **8.21** as a colourless oil (917 mg, 4.67 mmol, 87%): R_f 0.17 (70% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3380 (br. s), 3082 (w), 3059 (w), 3026 (w), 2931 (m), 2879 (m), 1730 (w), 1455 (m), 1361 (m), 1205 (m), 1086 (m); ^1H NMR (300 MHz, $CDCl_3$) δ 2.04 (1H, septet, J = 5.5 Hz, C**H**), 2.37 (2H, s, 2 x O**H**), 3.63 (2H, d, J = 5.5 Hz, BnOC**H**$_2$), 3.81 (4H, d, J = 5.5 Hz, 2 x C**H**$_2$OH), 4.52 (2H, s, PhC**H**$_2$O), 7.27-7.39 (5H, m, **H**$_{arom}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3 (C), 129.0 (CH), 128.3 (CH), 128.1 (CH), 74.0 (CH_2), 71.0 (CH_2), 63.8 (CH_2), 43.2 (CH); LRMS (ES+) *m/z* (relative intensity) 219 (100%, $[M+Na]^+$). Spectroscopic characteristics are consistent with those reported in the literature.[242]

3-(benzyloxy)-2-[(benzyloxy)methyl]propan-1-ol (8.22)



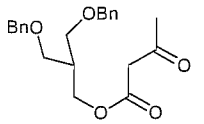
$C_{18}H_{22}O_3$

MW = 286.37

A solution of diol **8.21** (1.17 g, 5.96 mmol) in THF (4 mL) was added to an ice-cooled suspension of hexane-washed NaH (60% dispersion in mineral oil, 238 mg, 5.96 mmol) in THF (8 mL). After stirring at 0 °C for 30 min, BnBr (709 μL, 5.96 mmol) was added then stirring was continued at 0 °C for 1h. The reaction was quenched at 0 °C by careful addition of saturated aqueous NH_4Cl (50 mL) then extracted with Et_2O

(3 x 50 mL). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give a pale yellow oil (1.798 g). This was purified on silica (40 x 90 mm, 5-30% EtOAc/hexane) to give **8.22** as a colourless oil (1.263 g, 4.41 mmol, 74%): R_f 0.23 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3432 (br. m), 3082 (w), 3064 (w), 3026 (w), 2907 (m), 2865 (s), 1498 (m), 1455 (s), 1366 (m), 1209 (w), 1096 (s); ^1H NMR (300 MHz, $CDCl_3$) δ 2.19 (1H, septet, J = 5.5 Hz, C**H**), 3.59 (1H, d, J = 9.2 Hz, BnOC**H**H), 3.61 (1H, d, J = 9.2 Hz, BnOC**H**H), 3.63 (1H, d, J = 9.2 Hz, BnOCH**H**), 3.65 (1H, d, J = 9.6 Hz, BnOCH**H**), 3.80 (2H, d, J = 4.8 Hz, C**H**$_2$OH), 4.51 (4H, s, 2 x PhC**H**$_2$O), 7.27-7.38 (10H, m, **H**$_{arom}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5 (C), 128.9 (CH), 128.2 (CH), 128.1 (CH), 73.9 (CH_2), 70.7 (CH_2), 64.8 (CH_2), 41.9 (CH); LRMS (ES+) *m/z* (relative intensity) 596 (79%, $[2M+Na]^+$), 591 (4%, $[2M+NH_4]^+$), 325 (17%, $[M+K]^+$), 309 (100%, $[M+Na]^+$), 304 (6%, $[M+NH_4]^+$); HRMS (ES+) $[M+Na]^+$ found 309.1462, calculated 309.1461.

3-(Benzyloxy)-2-[(benzyloxy)methyl]propyl 3-Oxo-butyrate (8.23)



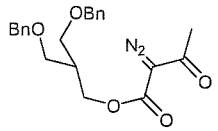
$C_{22}H_{26}O_5$

MW = 370.45

The title compound was prepared according to the method described for **8.2** whereby alcohol **8.22** (715 mg, 2.50 mmol) was reacted with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (359 μL, 2.75 mmol). Purification on silica (40 x 90 mm, eluting with hexane (200 mL), then 10-25% EtOAc/hexane) gave **8.23** as a colourless oil (857 mg, 2.31 mmol, 92%): R_f 0.38 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3082 (w), 3059 (w), 2912 (m), 2855 (m), 1744 (s), 1716 (s), 1649 (m), 1455 (m), 1361 (m), 1314 (m), 1148 (m), 1096 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 2.22 (3H, s, C**H**$_3$), 2.34 (1H, septet, J = 5.8 Hz, C**H**), 3.39 (2H, s, COC**H**$_2$CO), 3.51 (1H, d, J = 9.3 Hz, BnOC**H**H), 3.53 (1H, d, J = 9.3 Hz, BnOC**H**H), 3.55 (1H, d, J = 9.3 Hz, BnOCH**H**), 3.57 (1H, d, J = 9.3 Hz, BnOCH**H**), 4.29 (2H, d, J = 6.0 Hz, C**H**$_2$O$_2$C), 4.49 (4H, s, 2 x PhC**H**$_2$O), 7.27-7.36 (10H, m, **H**$_{arom}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9 (C), 167.5 (C), 138.7 (C), 128.8 (CH), 128.1 (CH), 128.0 (CH), 73.7 (CH_2), 68.6 (CH_2), 64.4 (CH_2), 50.5 (CH_2), 39.9 (CH), 30.6 (CH_3); LRMS (ES+) *m/z* (relative intensity) 763 (47%,

$[2M+Na]^+$), 409 (32%, $[M+K]^+$), 393 (100%, $[M+Na]^+$), 388 (36%, $[M+NH_4]^+$); HRMS (ES+) $[M+Na]^+$ found 393.1672, calculated 393.1672.

3-(Benzyloxy)-2-[(benzyloxy)methyl]propyl 2-diazo-3-oxo-butyrate (8.24)



$C_{22}H_{24}N_2O_5$

MW = 396.45

A solution of **8.23** (731 mg, 2.11 mmol) in MeCN (15 mL), stirred at rt, was treated with diisopropylethylamine (845 μL, 4.85 mmol). After 5 min, 4-carboxybenzenesulfonyl azide (623 mg, 2.74 mmol) was added. After 2 h, the white precipitate was removed by filtration and washed with Et_2O. The filtrate was diluted with Et_2O (50 mL) and washed with water (50 mL). The aqueous phase was extracted with Et_2O (2 x 50 mL) then the combined organics were washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a pale yellow oil. Purification of the crude material on silica (30 x 100 mm, 5-10% EtOAc/hexane) gave **8.24** as a colourless oil (801 mg, 2.02 mmol, 96%): R_f 0.47 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1} 3082 (w), 3059 (w), 3030 (w), 2907 (m), 2860 (m), 2141 (s), 1716 (s), 1654(s), 1451 (m), 1366 (s), 1314 (s), 1247 (m), 1153 (m), 1077 (s); ^1H NMR (300 MHz, $CDCl_3$) δ 2.35 (1H, septet, J = 5.9 Hz, C**H**), 2.42 (3H, s, C**H**$_3$), 3.49 (1H, d, J = 9.6 Hz, BnOC**H**H), 3.51 (1H, d, J = 9.6 Hz, BnOC**H**H), 3.54 (1H, d, J = 9.6 Hz, BnOCH**H**), 3.56 (1H, d, J = 9.2 Hz, BnOCH**H**), 4.37 (2H, d, J = 5.9 Hz, C**H**$_2$O$_2$C), 4.49 (4H, s, 2 x PhC**H**$_2$O), 7.28-7.37 (10H, m, **H**$_{arom}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.5 (C), 161.7 (C), 138.5 (C), 128.8 (CH), 128.2 (CH), 128.1 (CH), 73.7 (CH_2), 68.3 (CH_2), 64.3 (CH_2), 39.9 (CH), 28.7 (CH_3) (no C=N_2 observed).

Chapter 10 References

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