The Development and Applications of the Lewis Acid-Mediated Osmium-Catalysed Oxidative Cyclisation

A thesis submitted to the Board of the Faculty of Physical Sciences

in partial fulfilment of the requirements for the degree of

Doctor of Philosophy

in the

University of Oxford

by

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Michaelmas Term 2011

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Declaration

This thesis and the work of which it is a record has been carried out by myself, except where I have either acknowledged help from a named person or given a reference to a published source or a thesis.

Paul Colin Michael Winship

University of Oxford, Michaelmas Term 2011

Abstract

A thesis submitted for the degree of Doctor of Philosophy

Paul Colin Michael Winship, Jesus College and the Chemistry Research Laboratory, MT 2011

The acid-mediated osmium-catalysed oxidative cyclisation of 1,2-diols bearing a pendent alkene has been shown to be a powerful method for the formation of *cis*-2,5-disubstituted tetrahydrofurans. This thesis describes the development of this methodology to broaden the scope of the general reaction, followed by applying the oxidative cyclisation to the synthesis of tetrahydrofuran containing natural products.

Introduction

This section reports a range of ractions that osmium oxo-species will facilitate, namely the formation of carbon-oxygen and carbon-nitrogen bonds in a selective manner. In addition to this a variety of similar metal-mediated oxidative cyclisations are discussed.

Results and Discussion

The process for optimising the oxidative cyclisation is documented, along with examples which directly compare newly developed methodology with existing methodology. The incorporation of a catalytic amount of a Lewis acid is shown to be more effective than using an excess of a Brønsted acid, with osmium catalyst loading being reduced to 0.2 mol%. Subsequently, this methodology is shown to facilitate the successful oxidative cyclisation of vinyl silanes to form silyl-substituted tetrahydrofurans, along with methodology to "unmask" the silane, as a potential route to lactols. Finally, the application of this methodology to synthesis is demonstrated, with the successful synthesis of neodysiherbaine A being achieved in 7 steps and the $C_{21\text{-}30}$ fragment of pectenotoxin-4 in 12 steps.

Acknowledgements

First and foremost, I would like to thank Prof Tim Donohoe for allowing me the opportunity to work in his group for the last four years. The enthusiasm he has shown and the ideas that he has shared have helped me through several problems over the course of my DPhil. I think that I have now become the longest serving member of the Donohoe group.

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Special thanks also go to the Donohoe group – past and present for their support and witty banter over the years, both inside and outside of the lab. I'm sure I will miss the "stimulating and intellectual" conversations of F7 along with the odd "cheeky pint" on a Friday night (which always seem to last several pints). I would especially like to thank the people who proof read this thesis – Chris, Louis, Mike and Raddy (in alphabetical order so there can be no argument as to who did more). I'm sure this thesis would have been more "chavvy", with misaligned Chemdraw schemes if it wasn't for them.

Finally, I would like to thank Emma for her love and support over the last 4 years, along with my parents, who have always been there for me and taken an interest in my work – even if they don't necessarily understand exactly what an "oxidative cyclisation" is, or how it will change the world.

Abbreviations and Acronyms

Ac	acetyl
ACCN	1,1'-azobis(cyclohexanecarbonitrile)
AD	asymmetric dihydroxylation
AMPA	α-hydroxy-5-methyl-4-isoxazole propionate
aq.	aqueous
BBN	borabicyclo[3.3.1]nonane
bipy	bipyridine
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br.	broad
Bu	butyl
Bt	benzothiazolyl
C	Celsius
Cbz	benzyloxycarbonyl
Chloramine-T	*N*-chlorotoluenesulfonamide sodium salt
cm^{-1}	wavenumbers
Cp*	pentamethyl-cyclopentadienyl
CSA	camphorsulfonic acid
DCE	1,2-dichloroethane
d.e.	diastereomeric excess

DHQ	dihydroquinyl
DHQD	dihydroquinidyl
DIBAL-H	diisobutyl aluminium hydride
DIPA	diisopropylamine
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
2,2-DMP	2,2-dimethoxypropane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethyl sulfoxide
dppp	1,3-bis(diphenylphosphine)propane
d.r.	diastereomeric ratio
ee	enantiomeric excess
eq	equivalents
ESI^+	electrospray ionisation (positive ion detection)
Et	ethyl
h	hour(s)
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography

HRMS	high resolution mass spectrometry
Hz	hertz
i	iso
Im.	imidazole
IND	indolinyl
IR	infra-red
J	coupling constant (Hz)
KA	kainate
L	generic ligand
LUMO	lowest unoccupied molecular orbital
M	molar or metal
min	minute(s)
mL	millilitre(s)
modp	5,5-dimethyl-1-(*N*-morpholin-1-yl)hexane-1,2,4-trione
mol	mole
MOM	methoxymethyl ether
M.P.	melting point
Ms	methanesulfonyl (mesyl)
n	normal
NIS	*N*-iodosuccinimide
NMM	*N*-methylmorpholine

NMO	*N*-methylmorpholine-*N*-oxide
nmp	5,5-dimethyl-1-(4-methylpiperazin-1-yl)hexane-1,2,4-trione
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Nu	generic nucleophile
[O]	oxidant
P	generic protecting group
Ph	phenyl
pH	$-\log_{10}[H_3O^+]$
PHAL	phthalazinyl
pK_a	$-\log_{10}K_a$
PMB	*para*-methoxybenzyl
PNO	pyridine-*N*-oxide
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
PTX	pectenotoxin
PYR	diphenylpyrimidyl
quin.	quinuclidine
R	generic alkyl group
RSM	recovered starting material

rt	room temperature
Super Hydride®	lithium triethylborohydride
t	tert
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBAPI	tetra-*n*-butylammonium periodate
TBS	*tert*-butyldimethylsilyl
TCA	*trans*-cinnamic acid
TES	triethylsilyl
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
TIPS	triisopropylsilyl
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMO	trimethylamine-*N*-oxide
TMS	trimethylsilyl
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TBODPS	*tert*-butoxydiphenylsilyl
TPAP	tetra-*n*-propylammonium perruthenate
Ts	*para*-toluenesulfonyl (tosyl)

UHP	urea-hydrogen peroxide
UV	ultraviolet
ν_{max}	infra-red absorption
X	generic halogen

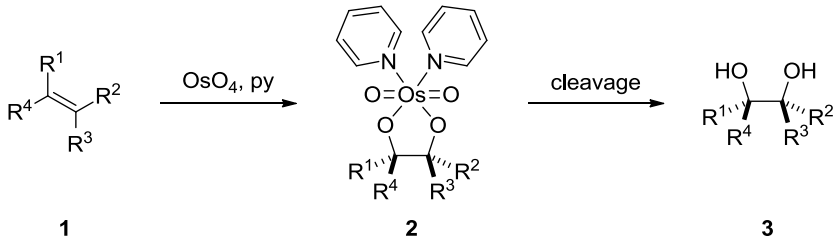
Chapter 1

Introduction

1.1 Osmium-mediated reactions in synthesis

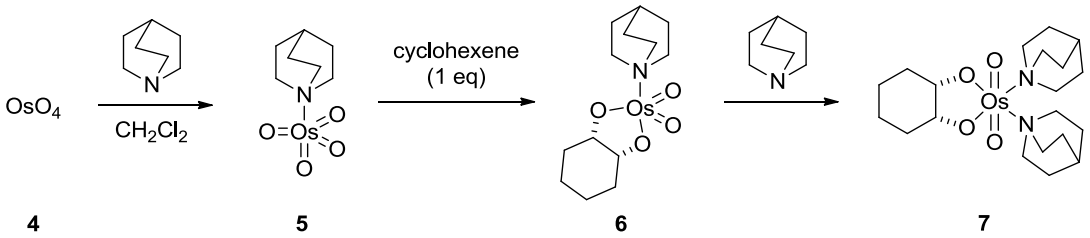
1.1.1 The osmium-mediated dihydroxylation of alkenes

Possibly the most well known use for osmium in organic synthesis is the dihydroxylation of alkenes. The reaction of osmium tetroxide with alkenes was first reported by Makowka,[1] who demonstrated that stoichiometric amounts of OsO_4 could be reacted to form stable osmate ester intermediates, which could be cleaved to liberate the corresponding diol. This process was improved by Criegee,[2] who showed that utilising an amine additive such as pyridine accelerated the reaction (Scheme **1.1**).



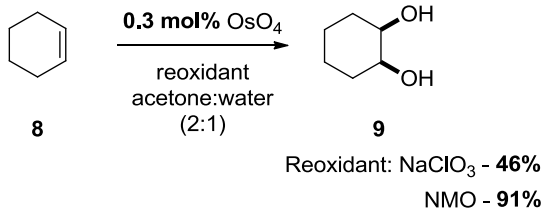
Scheme 1.1 *Stoichiometric dihydroxylation of alkenes*

It was shown that these osmate esters could be cleaved either under reductive or basic conditions to furnish the corresponding *cis*-diols. Some years later, Griffith and co-workers demonstrated that a range of adducts of the form OsO_4.L could be formed by utilising a bulky amine ligand, such as quinuclidine.[3] These adducts were shown to react with alkenes to furnish semi-stable complexes in solution (Scheme **1.2**). Further studies on this system showed that the addition of a second equivalent of amine resulted in the formation of a bis-amine complex.[4]



Scheme 1.2 *Quinuclidine stabilised osmate esters*

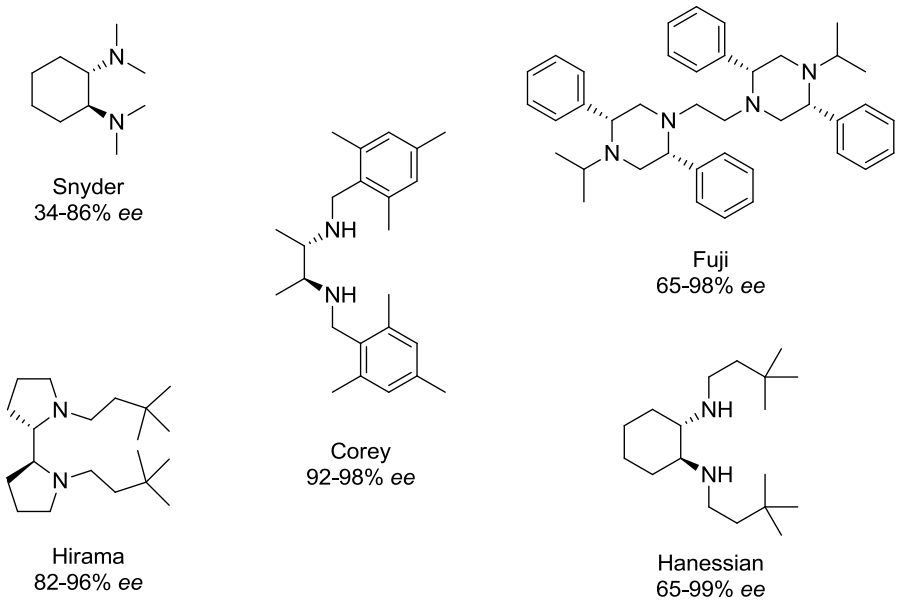
This process of dihydroxylation was first made catalytic with respect to osmium tetroxide in 1912 by Hofmann,[5] who noted that the Os(VI) formed during the reaction could be oxidised in the presence of a stoichiometric reoxidant, such as sodium or potassium chlorate. Since this discovery, several reoxidants have been shown to be capable of oxidising lower valent osmium species to Os(VIII), such as hydrogen peroxide[6] and *tert*-butylhydroperoxide[7]. However, it was not until the discovery that trimethylamine-*N*-oxide (TMO)[8] and *N*-methylmorpholine-*N*-oxide (NMO)[9] were capable of oxidising lower valent osmium species in a mild and efficient manner that this method of dihydroxylation became widely used (Scheme **1.3**).



Scheme 1.3 *Improvements to the catalytic dihydroxylation*

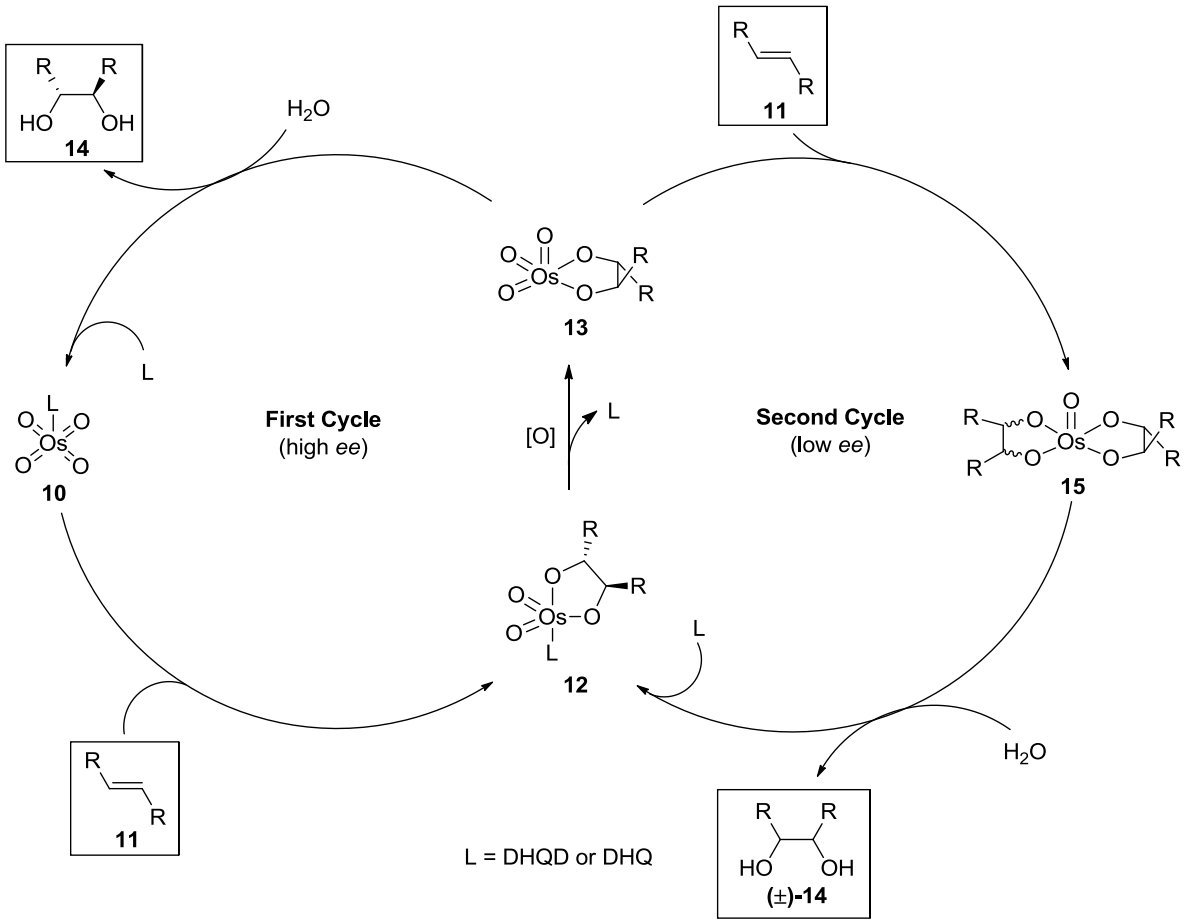
The use of NMO as a reoxidant for osmium was discovered by workers at The Upjohn Company. Using NMO with either acetone/water or *tert*-butanol/water, it was discovered that catalyst loadings of osmium tetroxide between 0.2-1.0 mol% could be used to deliver *cis*-dihydroxylated products in excellent yields.

The next step in the evolution of the osmium-mediated dihydroxylation of alkenes was making the process enantioselective. Initial attempts by Snyder,[10] Hirama,[11] Corey,[12] Fuji[13] and Hanessian[14] were made using chiral diamine ligands. However, all of these required stoichiometric amounts of osmium in order for the reaction to proceed, due to the high stability of the resulting intermediate diamine-osmate esters (Scheme **1.4**).



Scheme 1.4 *Diamines used for enantioselective stoichiometric dihydroxylation*

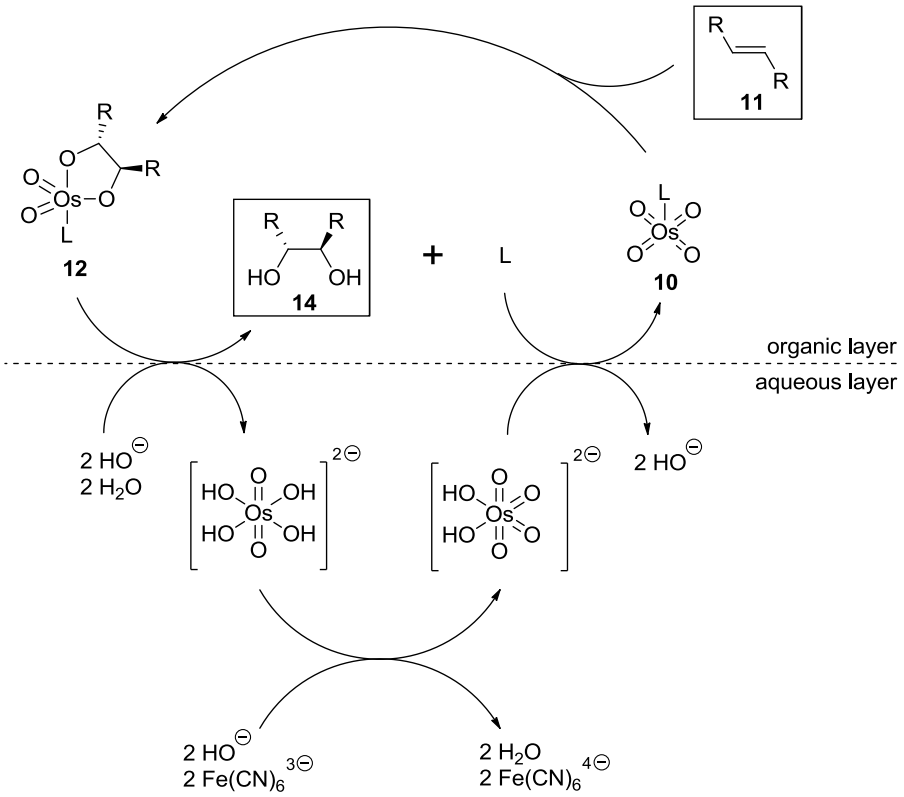
In 1988 however, Sharpless discovered that the use of the monodentate cinchona alkaloids dihydroquinidyl (DHQD) and dihydroquinyl (DHQ) in the catalytic Upjohn dihydroxylation led to asymmetric induction, with enantiomeric excesses in the range of 20-85% being reported for a range of alkenes.[15] The key property of the cinchona alkaloids was that not only did they exhibit a ligand acceleration effect (similar to that of pyridine or quinuclidine), but were subsequently hydrolysed with ease, leading to a faster overall reaction. Shortly after these findings, it was proposed that the dihydroxylation reaction could undergo one of two catalytic cycles; one providing a high enantioselectivity and the other competing pathway resulting in a much lower enantioselectivity (Scheme **1.5**).[16]



Scheme 1.5 *The two cycles undertaken during the dihydroxylation*

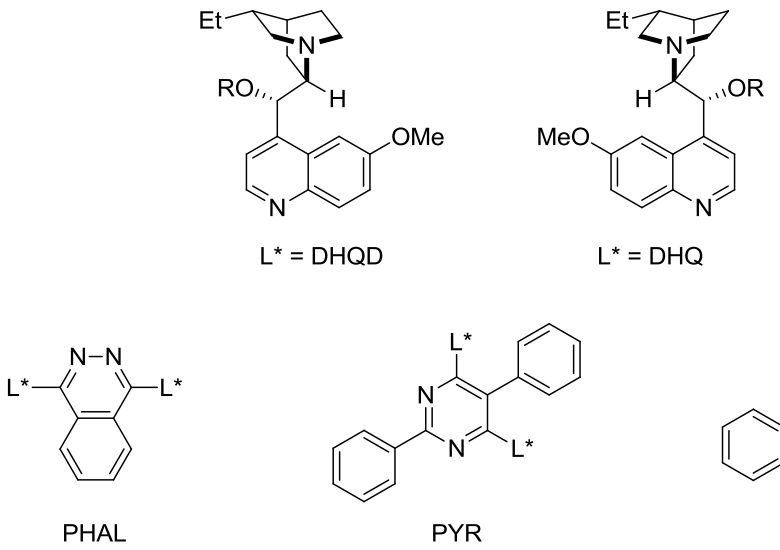
It was postulated that when hydrolysis of osmate species **13** was fast, the majority of the alkene substrate is oxidised by ligated osmium tetroxide **10**. This pathway enables the chiral ligand to dictate the stereochemistry of the resulting diol. On the contrary, when hydrolysis of **13** is slow, the catalytic cycle moves into a second cycle, whereby oxidation takes place in the absence of the cinchona ligand. The second diol formed from this operation has little enantioenrichment, leading to a substantial reduction in enantiomeric excess.

With these observations, three major improvements were made to the dihydroxylation. Firstly, the use of an inorganic reoxidant was crucial. Both Tsuji[17] and Sharpless[18] showed that choosing potassium ferricyanide ($K_3Fe(CN)_6$) as the reoxidant in a biphasic system led to dihydroxylation occurring predominantly *via* the first cycle. As intermediate **12** was soluble in organic solvent, it could be separated from the water soluble reoxidant (Scheme **1.6**).



Scheme 1.6 *Biphasic system for the asymmetric dihydroxylation*

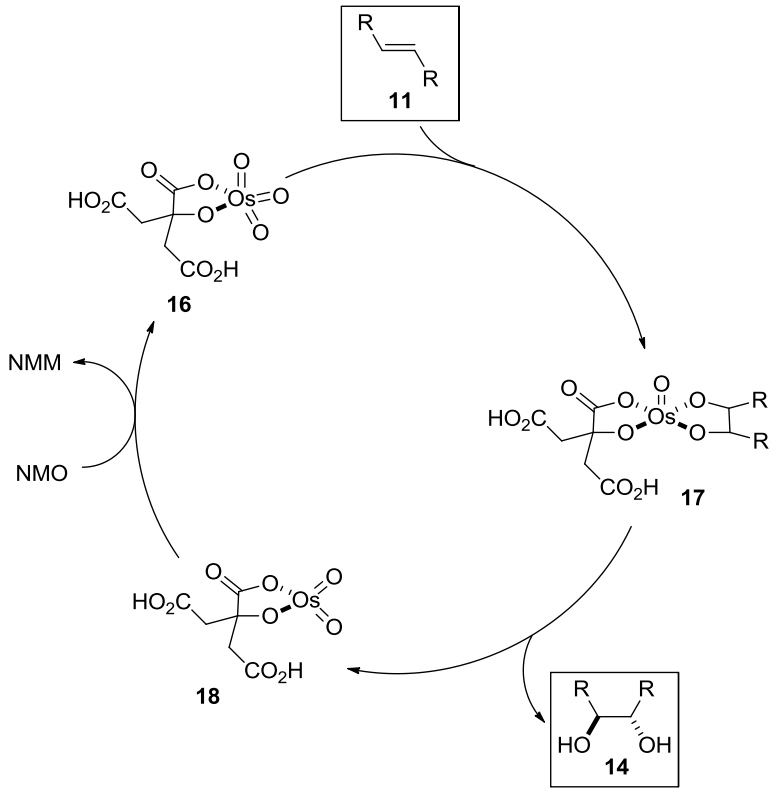
The second improvement was seen when alkyl sulfonamides were incorporated into the reaction. Sharpless showed that incorporating methanesulfonamide led to an increase in the rate of the reaction of di-, tri- and tetrasubstituted alkenes.[19] It was postulated that this was a result of the "sulfonamide effect", whereby methanesulfonamide aids the hydrolysis of osmate ester intermediate **12**, *via* nucleophilic attack at the osmium centre. The final improvement was seen by improving the effectiveness of the cinchona ligands. It was found that by linking the ligands together with an aromatic group such as PHAL[19] or PYR[20] led to a significant improvement (Scheme **1.7**). It was shown by Lohray that the effect of the second tertiary amine ligand led to the formation of a hydrophobic binding pocket for the lipophilic alkene.[21] The final problem of selectivity for the dihydroxylation of *cis*-alkenes was resolved with the development of the monomeric indoline (IND) linker.[22]



Alkene						
Ligand	PYR/PHAL	PHAL	IND	PHAL	PHAL	PYR/PHAL
ee range	30-97%	70-97%	20-80%	90-100%	90-99%	20-97%

Scheme 1.7 *Ligand compatibility with alkene class*

Moving away from the enantioselective dihydroxylation, Sharpless continued to make improvements to the general reaction of Os(VIII) with alkenes. Despite the advances made in the asymmetric dihydroxylation, certain substrate classes such as α,β-unsaturated esters and tetrasubstituted alkenes reacted poorly, resulting in low yields and long reaction times. The addition of citric acid to the Upjohn reaction led to significantly faster reaction times, with difficult substrates that would not previously undergo dihydroxylation reacting cleanly.[23] It was suggested that the addition of citric acid provided two main modes of action. Firstly, citric acid neutralises the 4-methylmorpholine produced during the reaction, maintaining the reaction at an optimum pH between 4 and 6. Secondly, it was proposed that citric acid was acting as a ligand to the osmium species, subsequently locking the dihydroxylation into a second catalytic cycle (Scheme **1.8**).



Scheme 1.8 *Citric acid dihydroxylation catalytic cycle*

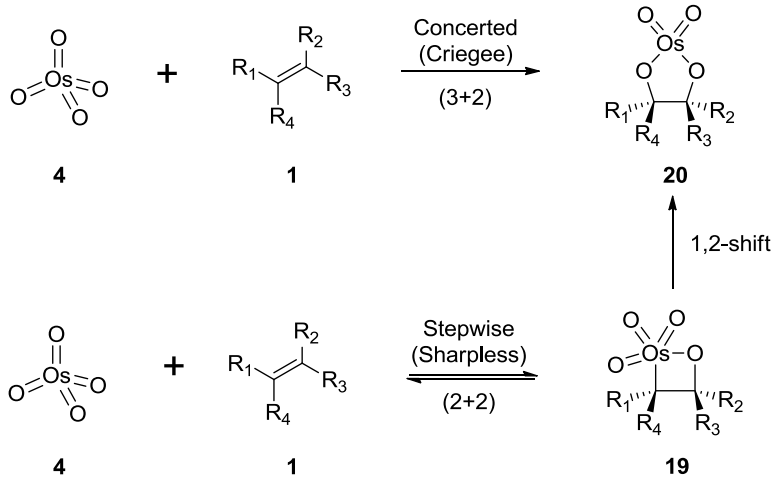
This catalytic cycle was postulated after it was observed that addition of citric acid to the asymmetric dihydroxylation conditions led to a substantial loss of enantioselectivity. The addition of 10 mol% of trisodium citrate led to a complete loss of enantioselectivity, adding weight to the argument that citric acid moves the dihydroxylation exclusively into a non-enantioselective catalytic cycle described in Scheme **1.8**.

A further effect of citric acid ligating to the osmium species is the increased rate of hydrolysis of osmate ester **17**. It is thought that this is a consequence of the pendent carboxylic acid groups forming a hydrophilic region in the vicinity of the vacant coordination site of Os(VI).

1.1.2 Inverse electron demand cycloaddition; (3+2) vs (2+2)

There have been two mechanisms suggested for the addition of osmium tetroxide across an alkene. The first was proposed by Criegee,[2] who suggested that the addition occurs *via* a concerted (3+2) cycloaddition. This mechanism was widely accepted until Sharpless proposed

a second mechanism, which consists of a (2+2) cycloaddition to give a 4-membered metallaoxetane **19**, followed by a 1,2-shift to give osmate ester **20** (Scheme **1.9**).[24]

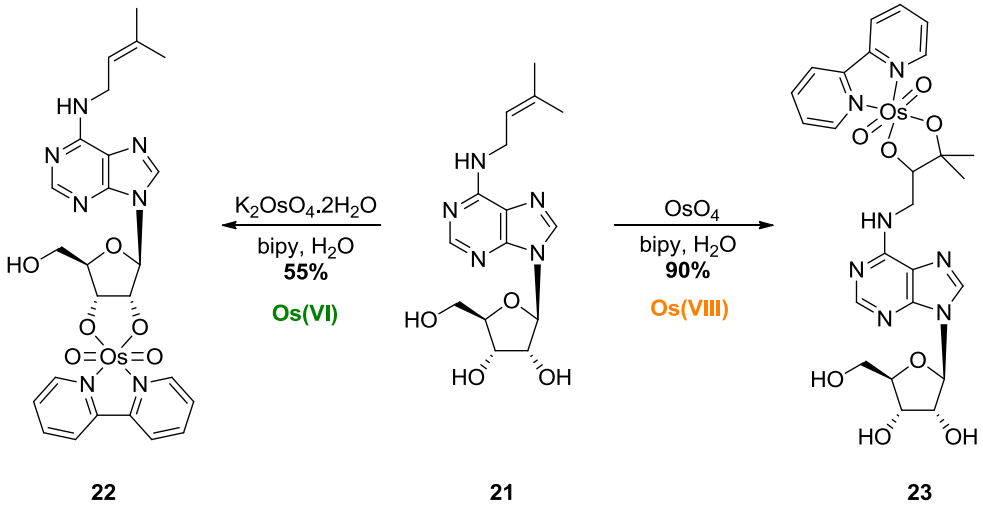


Scheme 1.9 *Plausible pathways for dihydroxylation*

In the latter case, it was postulated that the addition of the alkene across the Os=O bond was fast and reversible. The resulting metallaoxetane **19** was followed by a turnover limiting 1,2-shift. Whilst there has been support for both mechanisms,[25] Corey and co-workers provided convincing evidence for the (3+2) mechanism as a result of studying the $^{12}C/^{13}C$ kinetic isotope effects on the asymmetric dihydroxylation reaction.[26] These findings, combined with recent quantum mechanical studies that suggest the (2+2) mechanism requires a higher activation energy than the (3+2) mechanism,[27] led to the conclusion that a (3+2) mechanism is in operation.

1.1.3 The contrasting reactivity of Os(VIII) and Os(VI)

Os(VIII) and Os(VI) show fundamental differences in reactivity towards 1,2-diols and alkenes. Although highly reactive with alkenes, Os(VIII) has been shown to be virtually inert towards 1,2-diols. On the contrary, Os(VI) complexes react readily with 1,2-diols to give isolable osmate ester complexes. However, there are no literature examples where Os(VI) has undergone a reaction with an alkene. A perfect example of the relative reactivities of Os(VI) and Os(VIII) was demonstrated in 1976 on adenosine derivative **21** (Scheme **1.10**).[28]

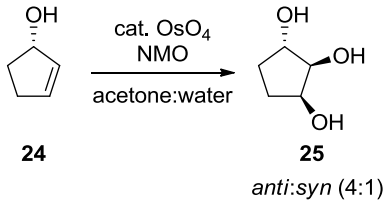


Scheme 1.10 *Contrasting reactivities of Os(VI) and Os(VIII)*

In this case, treating adenosine derivative **21** with potassium osmate(VI) dihydrate in the presence of bipyridine (bipy) and water led exclusively to the formation of semi-stable osmate ester **22** in 55% yield. However, treating **21** with osmium tetroxide in the presence of bipyridine and water led to the dihydroxylation of the trisubstituted alkene to afford **23** in 90% yield. This result clearly demonstrates the fundamentally different reactivities of Os(VI) and Os(VIII) in systems containing a 1,2-diol and an alkene.

1.1.4 The osmium-mediated oxidative cyclisation using stoichiometric osmium

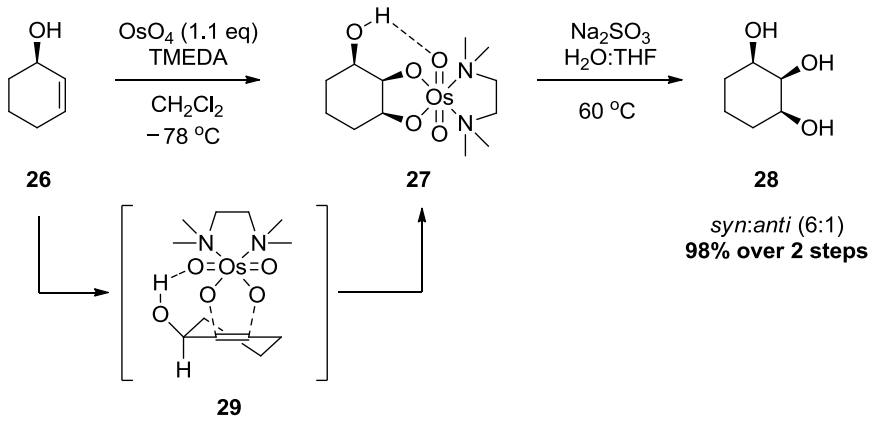
Previous studies by Kishi and co-workers have shown that cyclic alkenes bearing an allylic alcohol would react with osmium tetroxide to preferentially give *anti*-selectivity (Scheme **1.11**).[29]



Scheme 1.11 *Dihydroxylation of cyclic allylic alcohols*

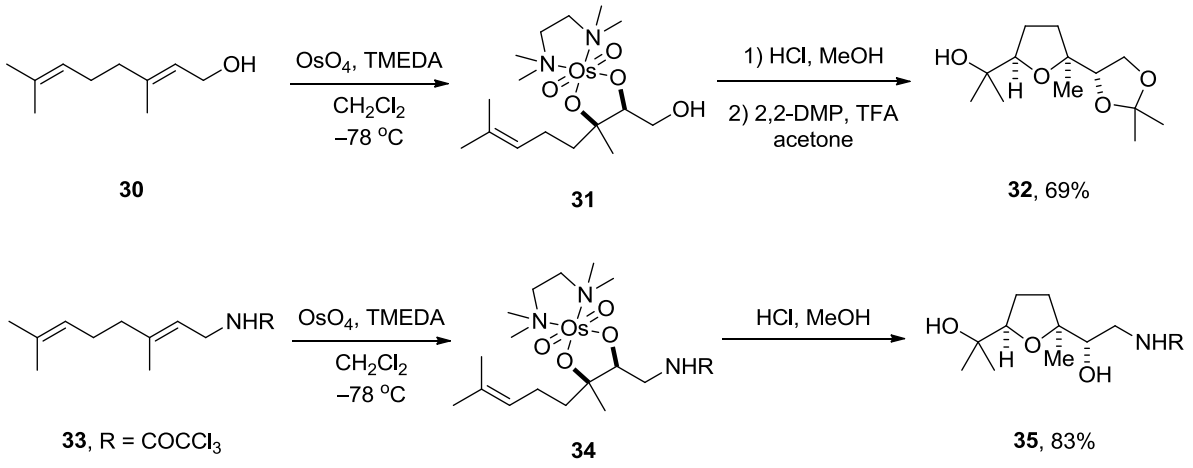
In addition to these results, Poli showed that it was possible to affect the selectivity of the reaction by changing the solvent to CH_2Cl_2 and incorporating trimethylamine-*N*-oxide as the

reoxidant.[30] These changes led to the reaction exhibiting little preference for facial selectivity, due to the aprotic solvent promoting hydrogen bonding to the allyl alcohol, but not in a sufficient level to overcome the steric bias of the substrate. A method for obtaining high facial selectivity, suitable for cyclic allylic alcohols, was developed by Donohoe and co-workers, who showed that osmium tetroxide used in combination with tetramethylethylenediamine (TMEDA) afforded osmate esters with *syn*-selectivity.[31] The resulting osmate esters could be easily hydrolysed to the corresponding triol upon treatment with sodium sulfite at elevated temperatures (Scheme **1.12**).



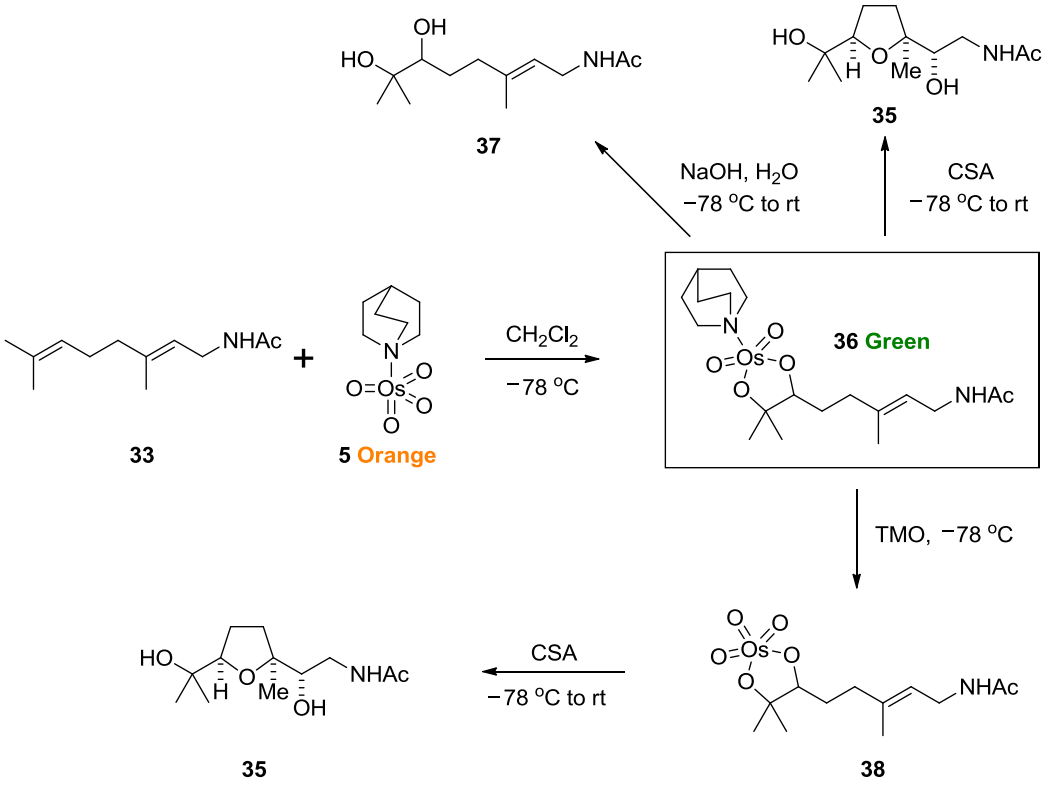
Scheme 1.12 *The Donohoe directed dihydroxylation reaction*

It has been reasoned that this observed stereoselectivity was as a result of hydrogen bonding between an osmium-oxo ligand and the acidic hydrogen of the allylic alcohol.[31] This interaction subsequently leads to a directed addition of the osmium species to the alkene in a *syn*-fashion. It was discovered that treatment of the osmate ester with methanolic hydrochloric acid led to the hydrolysis occurring at room temperature.[32] However, in 2001 Donohoe noted that selectively dihydroxylating 1,5-dienes **30** and **33**, followed by treatment with acid, led to a second oxidation occurring at the pendent alkene, presumably mediated by Os(VI) (Scheme **1.13**).[33]



Scheme 1.13 *Unexpected results using osmium*

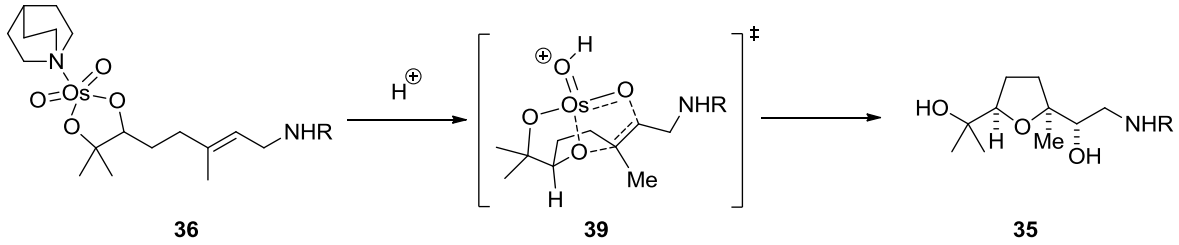
Previously, there has been no literature precedent for the oxidation of an alkene by Os(VI). In order to ascertain the nature of this cyclisation and identify the osmium species involved in the cyclisation, quinuclidine based stoichiometric experiments were performed (Scheme **1.14**).[34]



Scheme 1.14 *Stoichiometric quinuclidine experiments*

The addition of diene **33** to orange quinuclidine-osmium tetroxide complex **5** led to the dihydroxylation of the most electron-rich alkene, affording the corresponding green osmium(VI) quinuclidine complex **36**. As expected, hydrolysis of **36** under basic conditions led to the formation of diol **37**, however, treatment of **36** with camphorsulfonic acid (CSA) facilitated oxidative cyclisation to the corresponding THF **35**. This result proved that osmium(VI) is capable of undergoing an intramolecular dihydroxylation through the O-Os=O unit, although not *via* the O=Os=O unit, as in the case of Os(VIII). Oxidising Os(VI) complex **36** to the corresponding Os(VIII) complex **38** was possible using TMO. Upon treating **38** with CSA, cyclisation to the corresponding THF was also observed, demonstrating that both Os(VI) and Os(VIII) esters were capable of undergoing the oxidative cyclisation.

Due to the fact that the cyclisation was only observed under acidic conditions, Donohoe postulated that the cyclisation proceeded *via* the protonation of an osmium-oxo ligand. This in turn would allow the cycloaddition to take place *via* transition structure **39** (Scheme **1.15**).



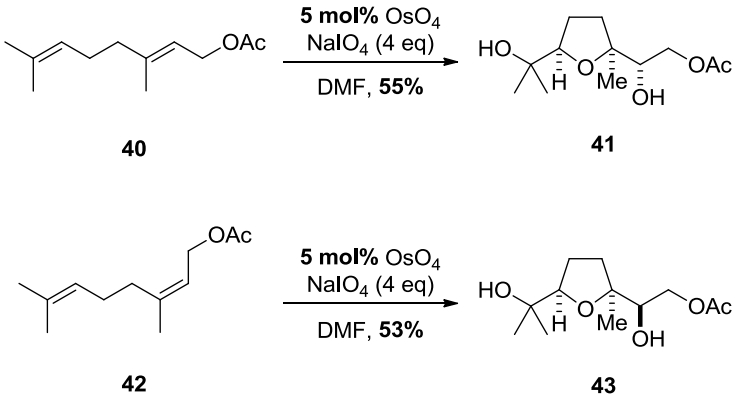
Scheme 1.15 *The proposed role of acid in the oxidative cyclisation*

It was proposed that the oxidative cyclisation proceeds *via* a (3+2) inverse electron demand cycloaddition. Therefore, the protonation of an oxo-ligand would subsequently lower the energy of O-Os=O LUMO, resulting in an increased interaction with the HOMO of the relatively electron-rich alkene.[35] This postulation is further supported by the failure of the oxidative cyclisation with electron-deficient alkenes.

1.1.5 The osmium-mediated oxidative cyclisation using catalytic osmium

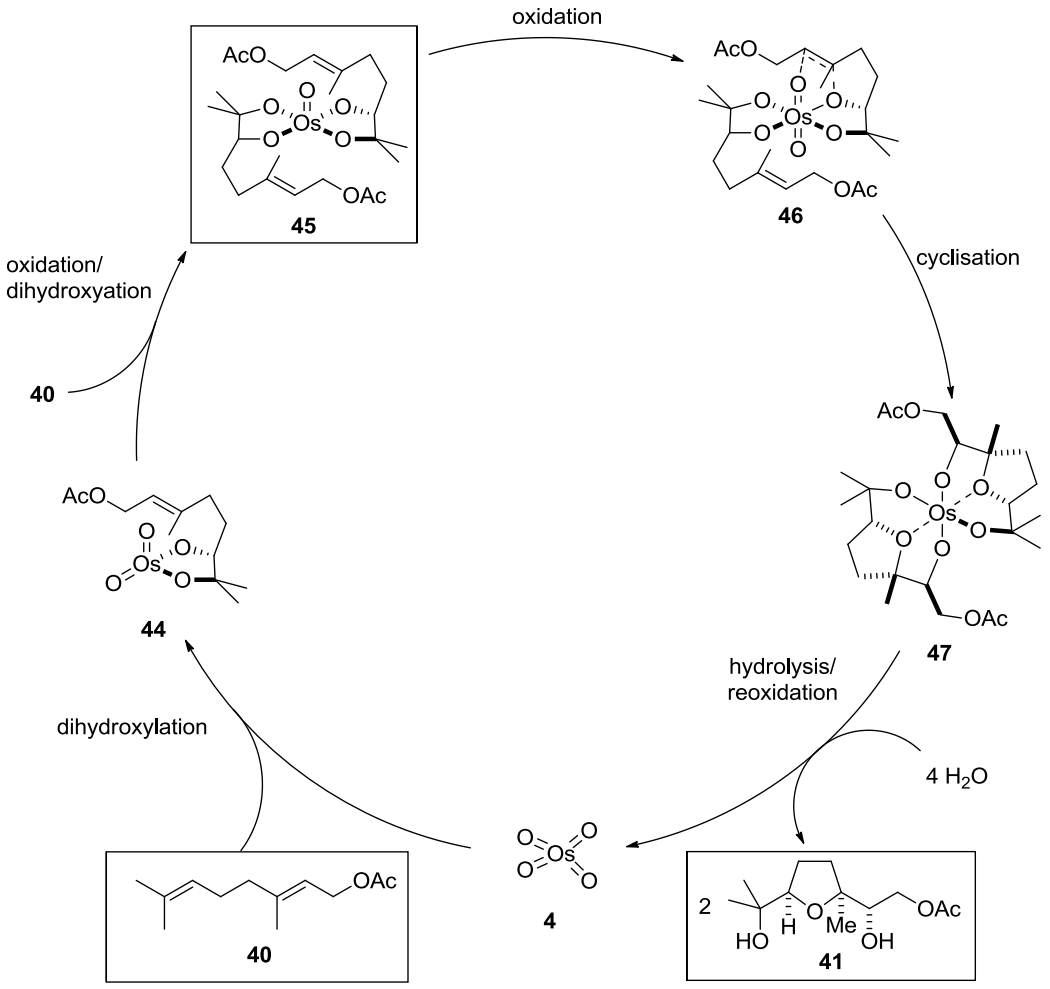
1.1.5.1 The oxidative cyclisation of 1,5-dienes

Prior to Donohoe's finding that the oxidative cyclisation of osmate(VI) esters proceeded under acidic conditions, Piccialli and co-workers reported in 1998 that the oxidative cyclisation of 1,5-dienes could be achieved under osmium(VIII) conditions, using a catalytic amount of osmium tetroxide in the presence of a stoichiometric amount of sodium periodate (Scheme **1.16**).[36]



Scheme 1.16 *Piccialli's catalytic osmium cyclisation*

Using DMF as a solvent, it was possible to form the corresponding *cis*-THFs by subjecting acetylated geraniol **40** and nerol **42** to these catalytic conditions. Piccialli discovered that a dimeric osmium(VI) intermediate **45** could be isolated from the reaction mixture, which led to the postulation that the reaction proceeded *via* the second catalytic cycle (Scheme **1.17**).[36]

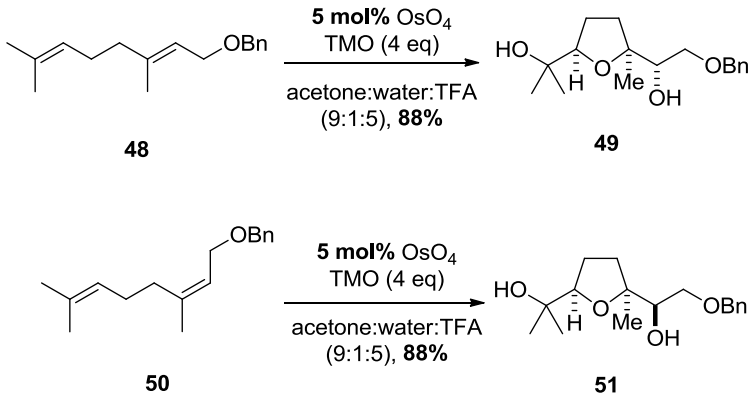


Scheme 1.17 *Catalytic cycle proposed by Piccialli*

Piccialli also discovered that re-subjecting intermediate **45** to the cyclisation conditions allowed the formation of the corresponding THF **41**, while subjecting **45** to elevated temperatures alone resulted in no reaction. This led to the assumption that Os(VI) was incapable of promoting the cyclisation and the active cyclisation catalyst was Os(VIII). However, upon examining the subsequent stoichiometric work carried out by Donohoe, it is more likely that this observation is seen as a result of sodium periodate decomposing to periodic acid *in situ*, adding weight to the idea that acid is required for the cyclisation to proceed.

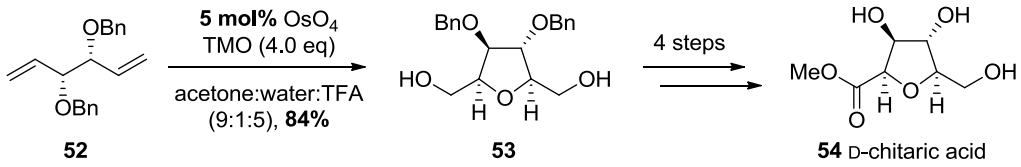
Work in the Donohoe group continued on the osmium-mediated oxidative cyclisation, which led to the subsequent discovery that stoichiometric amounts of TMO in combination with a large excess of trifluoroacetic acid (TFA) promoted the oxidative cyclisation with a

substoichiometric amount of osmium tetroxide, resulting in significantly increased yields (Scheme **1.18**).[37]



Scheme 1.18 *Donohoe's aqueous TFA oxidative cyclisation*

It was proposed that the catalytic variant of this reaction proceeded *via* a similar protonated intermediate to osmate ester **39** in the stoichiometric reaction, affording exclusively *cis*-THFs. With the development of these comparatively mild conditions, Donohoe also showed that it was possible to apply this methodology to the synthesis of D-chitaric acid (Scheme **1.19**).[37]

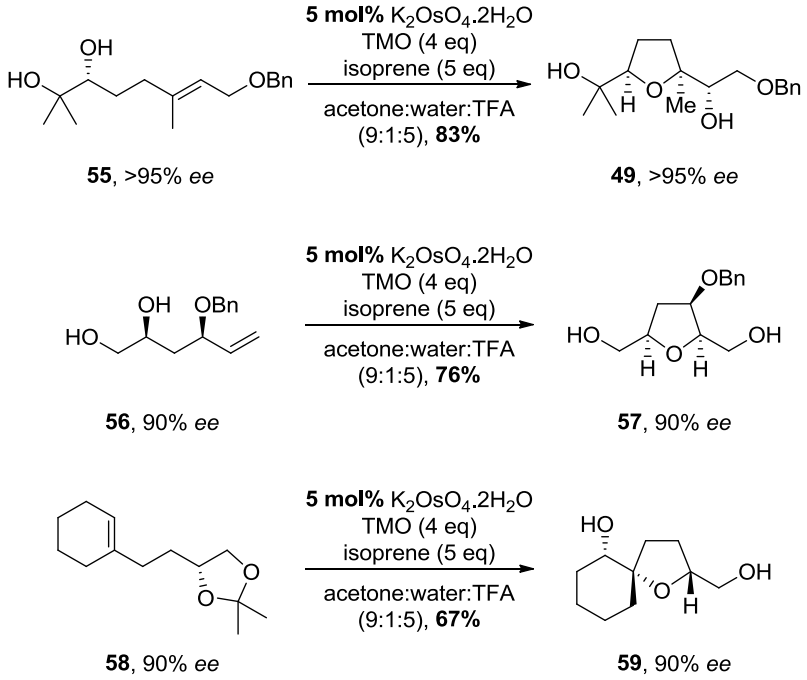


Scheme 1.19 *Application to the synthesis of D-chitaric acid*

Enantiopure diene **52** could be synthesised in 5 steps from D-mannitol. Subsquent exposure to the newly developed aqueous oxidative cyclisation conditions provided THF **53** in 84% as a single diastereomer. This can be explained as in each case the initial dihydroxylation of either alkene would occur from the top face, resulting in the same intermediate being formed due to the C_2-symmetry displayed by diene **52**. From here, a selective protection/oxidation/ deprotection strategy could be employed to form D-chitaric acid **54** in 10 steps.

1.1.5.2 The oxidative cyclisation of diols

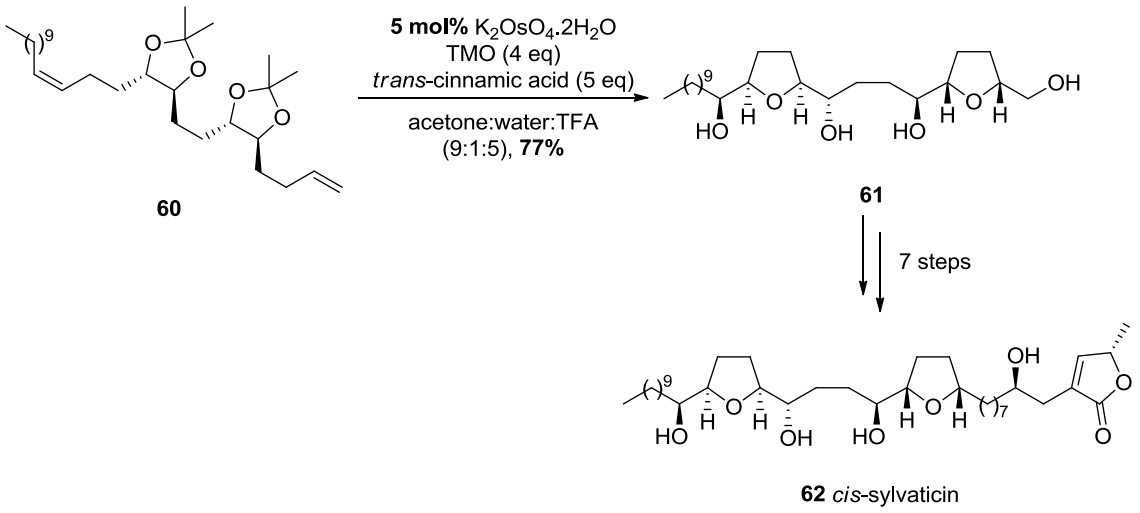
Undoubtedly, the most important discovery in the osmium-mediated oxidative cyclisation came in 2005, with the development of conditions to form enantioenriched THFs.[38] Initial attempts to incorporate the cinchona ligands into the diene cyclisation, in order to produce enantiopure THFs, were unsuccessful due to the low pH of the reaction. Donohoe and co-workers then developed a fundamentally different process whereby the osmium species could be condensed onto a pre-formed diol to give an intermediate osmate ester that could undergo the oxidative cyclisation. The enantiopurity of the starting diol could ultimately be used to induce up to two new chiral centres as a consequence of the cyclisation being diastereoselective with respect to forming *cis*-THFs and stereospecific with respect to addition across the alkene. This process also led to no erosion of enantiomeric excess (Scheme **1.20**).



Scheme 1.20 *Oxidative cyclisation to form enantioenriched THFs*

The diol cyclisation required an excess of a sacrificial alkene – either isoprene or later *trans*-cinnamic acid.[39] It was discovered that although Os(VIII) was capable of very slowly undergoing cyclisation, the preferred mode of reactivity was the dihydroxylation of the pendent

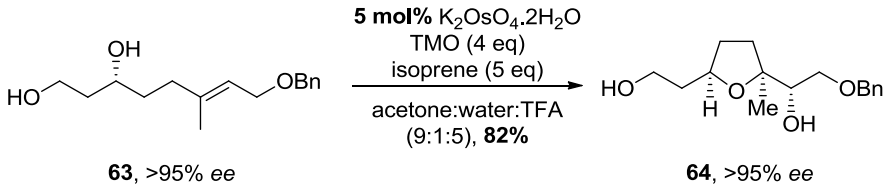
alkene (*vide supra* Chaper 1.1.3). Employing an excess of a sacrificial alkene, which could be dihydroxylated at a faster rate than the substrate alkene, was required in order to produce a source of Os(VI). The Os(VI) produced *via* the dihydroxylation of the sacrificial alkene could then in turn condense onto the 1,2-diol and subsequently cyclise under the acidic conditions. The discovery of these conditions led to an expansion in the scope of the oxidative cyclisation. With methodology in place that was capable of forming products as single enantiomers, it was possible to apply these conditions to the synthesis of substrates that would previously have been challenging to synthesise in an enantiopure manner, such as *cis*-sylvaticin (Scheme **1.21**).[40]



Scheme 1.21 *Synthesis of cis-sylvaticin*

The key step of the synthesis occurred after the formation of diacetonide **60**, whereupon treatment with the aqueous oxidative cyclisation conditions, the acetonide groups were hydrolysed, allowing the 1,2-diols to participate in a double oxidative cyclisation reaction to form bis-THF **61**, making up the core of *cis*-sylvaticin.

Donohoe also demonstrated that this methodology could be extended to 1,3-diols, which despite cyclising at a slower rate, furnished the corresponding THFs in good yields (Scheme **1.22**).[34]

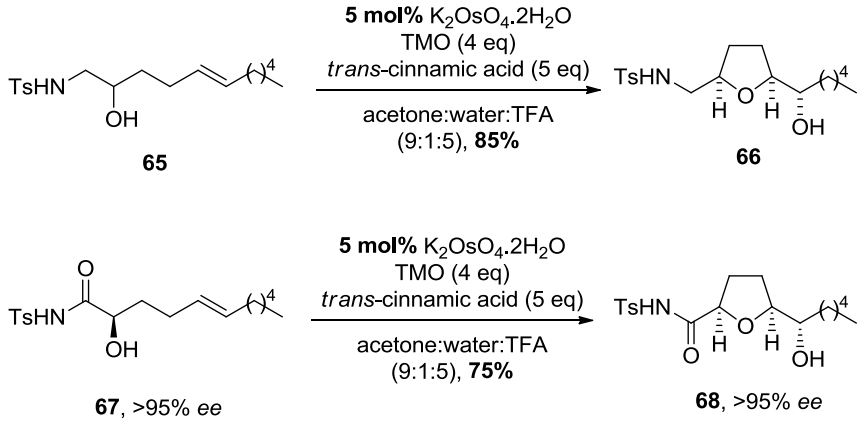


63, >95% *ee* **64**, >95% *ee*

Scheme 1.22 *Application to 1,3 diols*

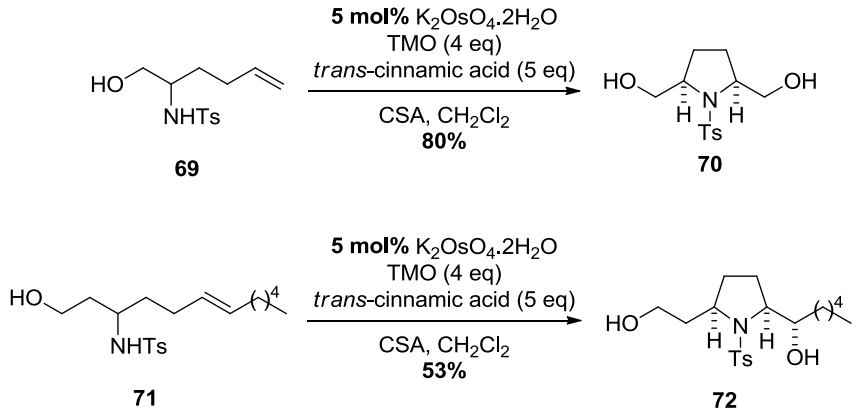
1.1.5.3 Scope of initiator groups

After it had been demonstrated that this methodology was no longer confined to cyclising the dihydroxylated derivatives of 1,5-dienes, the scope of the reaction was extended to encompass protected amino alcohols and α-hydroxy amides bearing a pendent alkene (Scheme **1.23**).[39]



Scheme 1.23 *Cyclisation to form amino-THFs*

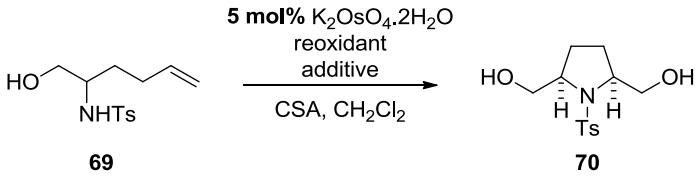
In these analogous cases, it was presumed that Os(VI) condensed to the amino alcohol unit to afford a similar osmate ester intermediate as in the diol series. It was reasoned at this point that should the relative positions of the alcohol and amine unit be reversed, that a cyclisation would result in the formation of a pyrrolidine. This theory was tested accordingly and resulted in the successful oxidative cyclisation of a range of both 1,2- and 1,3-initiators to afford the corresponding *cis*-pyrrolidines (Scheme **1.24**).[39] Furthermore, in the case of amino alcohols, it was discovered that using the milder non-aqueous conditions of camphorsulfonic acid (CSA) in CH_2Cl_2 afforded the resulting pyrrolidines in higher yields.



Scheme 1.24 *Oxidative cyclisation to form pyrrolidines*

1.1.6 Recent developments in the osmium-mediated oxidative cyclisation

Despite the successful development of conditions capable of forming enantioenriched THFs and pyrrolidines, the cyclisation remained an inefficient process due to the necessity to employ a large excess of a sacrificial alkene. After the discovery that Os(VI) was the more active cyclisation catalyst, Donohoe and co-workers focussed attention on the development of a novel reoxidant for osmium, capable of reoxidising Os(IV) to Os(VI), but not to Os(VIII). After screening a range of potential *N*-oxide-based reoxidants, it was discovered that pyridine-*N*-oxide (PNO) allowed the cyclisation of **69** to proceed in the absence of any additives to give the desired pyrrolidine **70** in higher yields than the previous cyclisation conditions (Entries 3 and 4, Table **1.1**).[41]



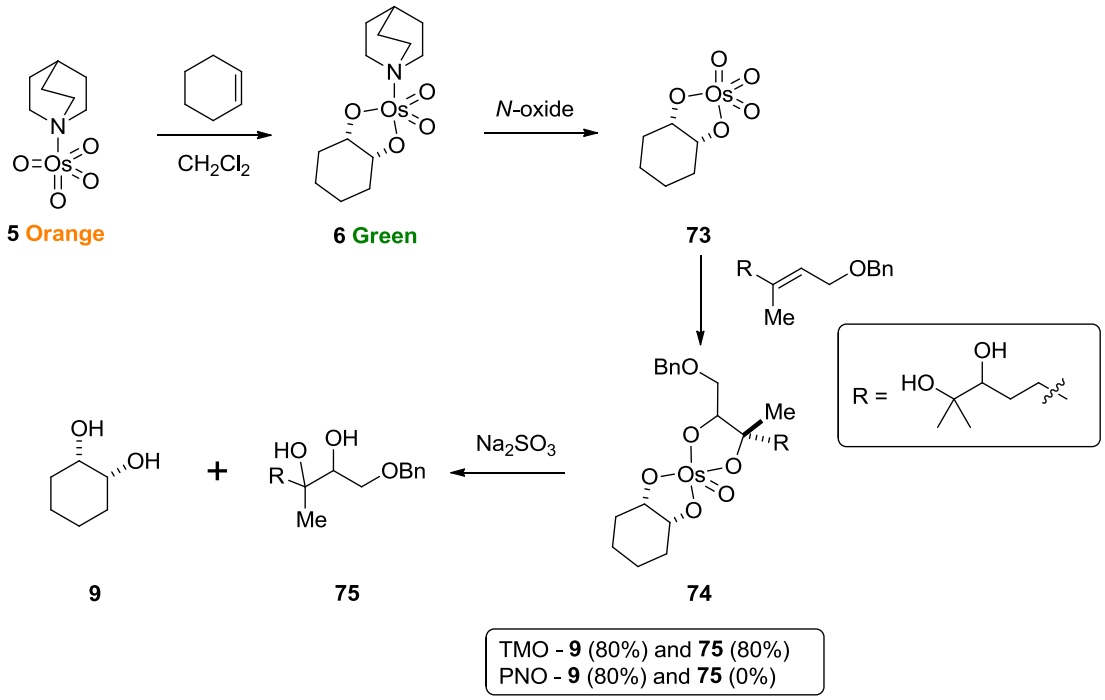
69 **70**

Entry	Reoxidant	Additive	Yield
1	TMO	-	**69%** (48 h)
2	TMO	*trans*-Cinnamic acid (6.0 eq)	**79%** (16 h)
3	PNO	-	**85%** (4 h)
4	PNO	Citric acid (0.75 eq)	**98%** (2 h)

Table 1.1 *Refinements in the oxidative cyclisation*

Furthermore, no dihydroxylated product was observed in this reaction, suggesting that no Os(VIII) was present. It was also discovered that the addition of a catalytic amount of citric acid in the cyclisation of **69** led to a significant increase in the yield of pyrrolidine **70** (Entry 4, Table **1.1**). It was reasoned that citrate had a similar effect to that observed by Sharpless and co-workers in the citric acid dihydroxylation, with the additive stabilising Os(VI) with respect to disproportionation, as well as aiding the hydrolysis of the intermediate osmate ester.[23]

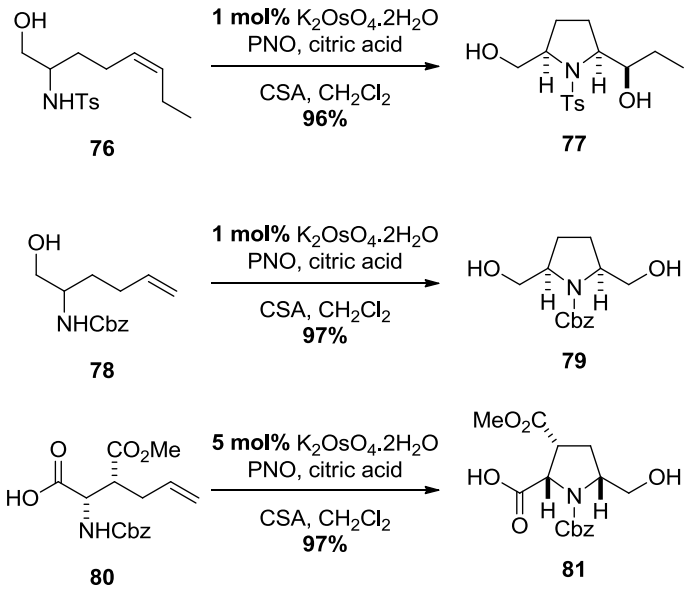
With the postulation that PNO was capable of allowing the reoxidation of Os(IV) only to Os(VI), further stoichiometric studies were conducted to confirm this theory (Scheme **1.25**).[41]



Scheme 1.25 *Stoichiometric studies on TMO vs PNO*

In a control experiment, subjecting cyclohexene to the same orange quinuclidine-osmium tetroxide complex **5** as in previous studies afforded Os(VI) complex **6** with a characteristic "bottle-green" colour. In two separate reactions, Os(VI) complex **6** was subjected to one equivalent of either TMO or PNO. Whereas treatment with TMO resulted in a colour change, with the generation of the osmate ester **73**, no colour change was observed upon the addition of PNO to Os(VI) complex **6**. Exposure of Os(VIII) ester **73** to one equivalent of a second alkene would result in a dihydroxylation to afford osmate ester **74**. It was proposed that if PNO had not oxidised Os(VI) to Os(VIII), that no second dihydroxylation would occur. After subsequently quenching both reactions with sodium sulfite, in the case where TMO had been used as a reoxidant, both diol **9** and diol **75** were isolated, confirming the oxidation of Os(VI) complex **6**. On the contrary, when PNO had been used as a reoxidant, only diol **9** was recovered, with complete recovery of starting alkene. This result confirmed the postulation that PNO was incapable of reoxidising Os(VI) to Os(VIII), yet still allowed a successful oxidative cyclisation to proceed *via* the reoxidation of Os(IV) to an active cyclisation catalyst.

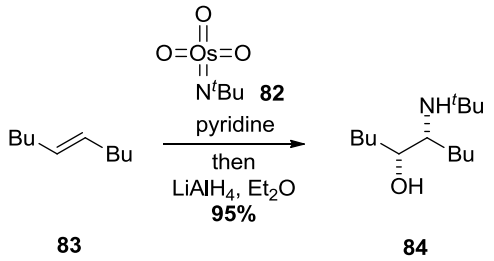
As a result of these changes, a range of amino alcohols were shown to undergo the oxidative cyclisation to the corresponding pyrrolidines, in most cases with reduced catalyst loading and faster reaction times (Scheme **1.26**).



Scheme 1.26 *Improved cyclisation of amino alcohols*

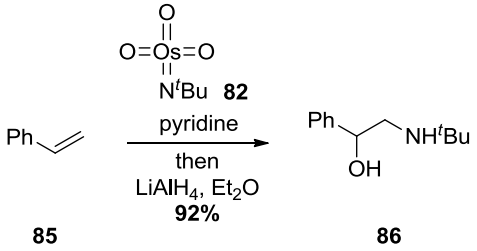
1.1.7 The osmium-mediated aminohydroxylation of alkenes

In 1975, it was discovered by Sharpless and co-workers that the treatment of a range of alkenes with a stoichiometric amount of an imido-osmium(VIII) species **82**, which was formed by the reaction of osmium tetroxide with *tert*-butylamine, resulted in the formation of amino alcohols (Scheme **1.27**).[42]



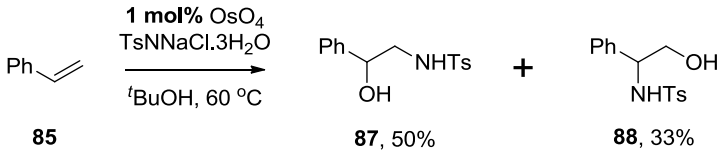
Scheme 1.27 *Initial Sharpless aminohydroxylation*

This reaction was found to be stereospecific with respect to addition across the alkene and required a reductive workup in order to liberate the amino alcohol. Also detected in the aminohydroxylation were trace amounts of the corresponding diol. This reaction demonstrated a substantial preference for the participation of the osmium-nitrogen unit undergoing a (3+2) cycloaddition over the corresponding osmium-oxygen unit. In the cases where the reaction was attempted on significantly hindered alkenes, an increase in the amount of dihydroxylated product was observed, presumable due to the large steric bulk of the *tert*-butylamino group. However, when terminal alkenes were subjected to the reaction conditions, the steric bulk of the amine group resulted in complete regiochemical control for the formation of the corresponding primary amine, such as in amino alcohol **86** (Scheme **1.28**).



Scheme 1.28 *Regiocontrol demonstrated by the aminohydroxylation reaction*

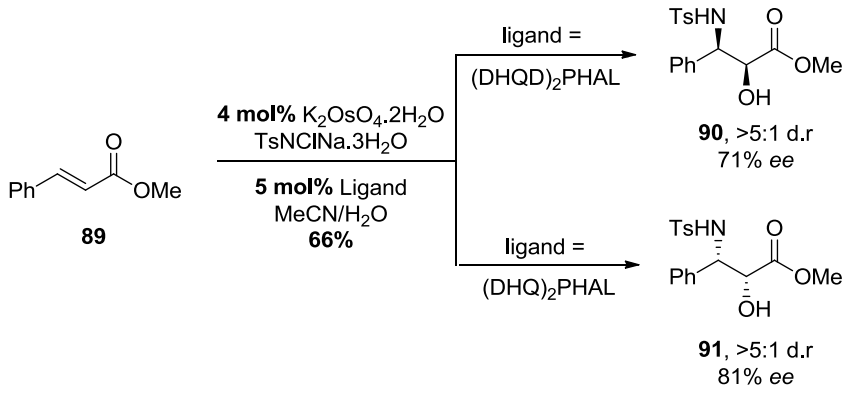
This reaction had two major drawbacks, which were consequentially addressed by Sharpless. Firstly, the use of a stoichiometric amount of osmium(VIII) was unattractive, and secondly the resulting *tert*-butyl protecting group was difficult to remove. In order to overcome both of these problems, Sharpless incorporated Chloramine-T (*N*-chlorotoluenesulfonamide sodium salt) as both the nitrogen source and reoxidant.[43] Under these conditions, it was possible to use osmium tetroxide in a catalytic manner, as well as incorporate a more labile protecting group (Scheme **1.29**).



Scheme 1.29 *Catalytic conditions for the aminohydroxylation*

As a consequence of utilising a less bulky protecting group, regioselectivity was markedly reduced. The reaction was developed into a higher yielding, more efficient process by changing the solvent to chloroform/water and incorporating benzyltriethylammonium chloride as a phase transfer catalyst.[44] Subsequently, selection of chloramines were developed by the Sharpless group, including carbamate protected chloramines, which afforded the corresponding carbamate protected amino alcohols. However, no nitrogen protecting groups were found to be as efficient as the *tert*-butyl group for delivering high levels of regioselectivity.[45]

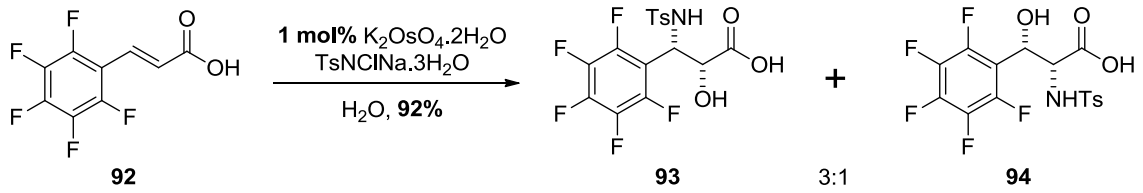
The next advance in this reaction was seen in 1996, when Sharpless and co-workers discovered that the process of aminohydroxylation could be achieved enantioselectively by incorporating cinchona alkaloid derived ligands (Scheme **1.30**).[46]



Scheme 1.30 *The catalytic asymmetric aminohydroxylation*

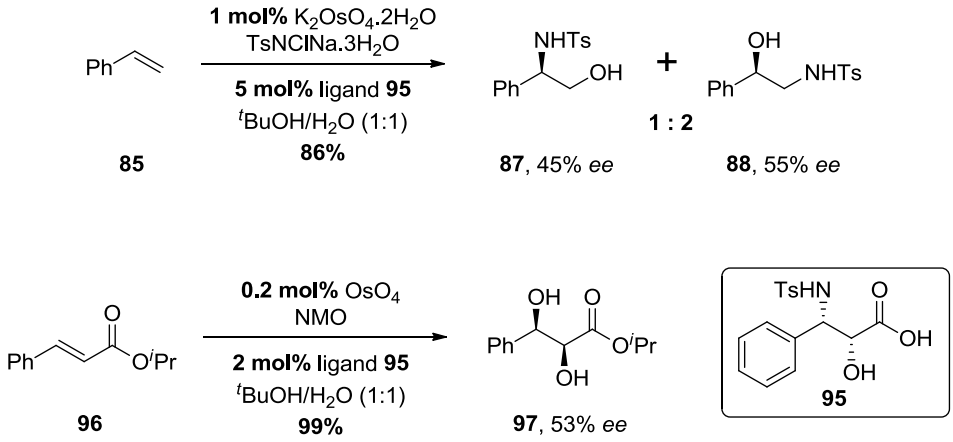
The introduction of the chiral ligands not only led to enantioenriched amino alcohols, but also improved the regioselectivity of the reaction, improving the selectivity for the formation of 3-aminosulfonyl alcohols **90** and **91** from 2:1 to >5:1 (Scheme **1.30**). A further advantage of utilising the cinchona ligands was that in some cases acceleration in the catalytic turnover was observed *via* the ligand acceleration effect. However, despite these advances, the general reaction had a poor substrate scope and still required a large excess (3.0 eq) of Chloramine-T for the reaction to proceed, which led to difficulties in isolating the desired amino alcohols.

It was subsequently discovered that the aminohydroxylation of α,β-unsaturated carboxylic acids proceeded in high yields (Scheme **1.31**).[47]



Scheme 1.31 *Aminohydroxylation of α,β-unsaturated carboxylic acids*

In the case of the α,β-unsaturated carboxylic acids, a lower catalyst loading could be used with only one equivalent of Chloramine-T required for the reaction to reach completion. This dramatically simplified the purification of the resulting amino alcohols. Furthermore, no competing dihydroxylation of the alkene was observed, which accounted in some cases for up to 40% of the increase in yield. It was proposed that this reaction succeeded due to the capability of the resulting α-hydroxycarboxylic acids to bind to osmium. In a similar fashion to citric acid in the dihydroxylation (*vide supra* **Chapter 1.1.1**), the products of this aminohydroxylation bind to osmium, resulting in the reaction being locked into a second catalytic cycle. As a result of this, no enantioselectivity was observed even with the addition of a chiral ligand. This result was exploited by Sharpless and co-workers as a starting point for developing a range of second cycle ligands for both the aminohydroxylation and dihydroxylation reactions (Scheme **1.32**).[48]

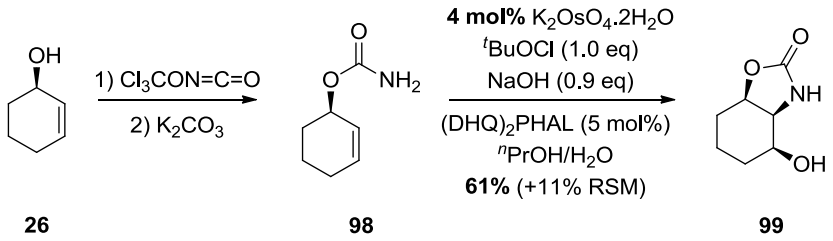


Scheme 1.32 *Second cycle ligands in the aminohydroxylation and dihydroxylation*

Ligand **95** showed promise in both the aminohydroxylation and the dihydroxylation reactions. The enantiomeric excesses of these reactions ranged from 25-70% for this class of ligands, with catalyst loadings remaining low. However, the regioselectivities of this reaction remained problematic, which has led to the development of alternative methods of influencing the regio- and stereochemistry of the aminohydroxylation reaction. Such methods include Muñiz's use of chiral auxiliaries[49] and Donohoe's use of the tethered aminohydroxylation (*vide infra* **Chapter 1.1.8**).

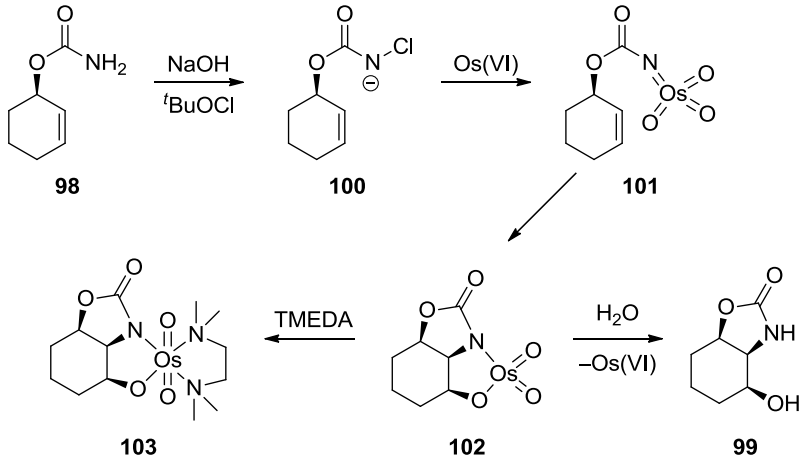
1.1.8 The osmium-mediated tethered aminohydroxylation of alkenes

Despite the advances made by Sharpless and co-workers, the limitations of the osmium catalysed aminohydroxylation are still evident, with reasonable stereoselectivity and regioselectivity limited to a small range of substrates. In order to overcome these problems, Donohoe and co-workers demonstrated that the nitrogen source could be tethered to the alkene substrate (Scheme **1.33**).[50]



Scheme 1.33 *Development of the tethered aminohydroxylation*

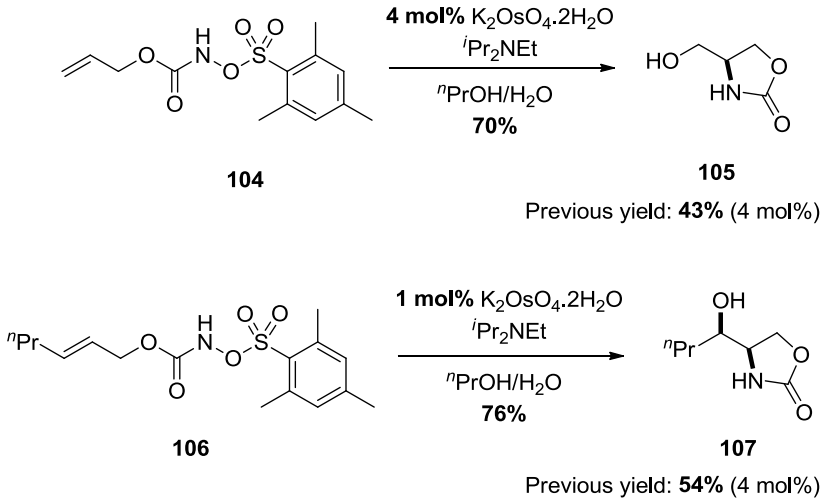
This method afforded complete regiocontrol in the aminohydroxylation process and proceeded stereospecifically, achieving *syn*-addition across the tethered alkene. In the case of cyclic substrates such as **98**, high levels of stereoselectivity were achieved. This is due to the steric constraints imposed upon intermediate imido-osmium(VIII) species **101**, which is forced to undergo a (3+2) cycloaddition from the same face as the allylic alcohol, furnishing all *syn* carbamates such as **99** (Scheme **1.34**).



Scheme 1.34 *Donohoe's proposed mechanism for the tethered aminohydroxylation*

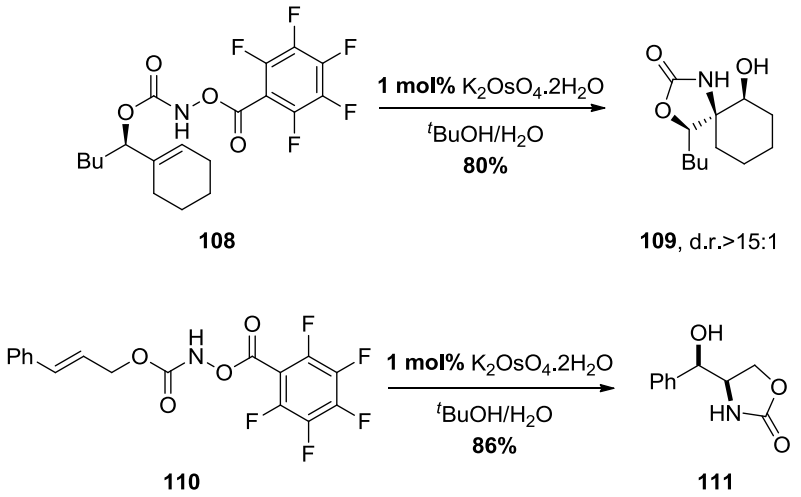
It was suggested by Donohoe that the reaction proceeded *via* the initial deprotonation/ chlorination of carbamate **98** to afford **100** as a nitrene equivalent. This species was capable of oxidising potassium osmate(VI) dihydrate to the imido-osmium(VIII) species **101**. A subsequent cycloaddition across the tethered alkene formed osmate ester **102**, which could be hydrolysed under the reaction conditions. Alternatively, osmate ester **103** could be isolated by the addition of TMEDA to **102**. The structure of TMEDA-osmate ester **103** was confirmed by X-ray crystal structure analysis to prove the configuration.

However, limitations with this methodology were evident as competing chlorination of the alkene, caused by *tert*-butyl hypochlorite, combined with incomplete conversion of the starting material led to only modest yields. In order to optimise this process, Donohoe developed a novel reoxidation process using *N*-sulfonyloxy carbamates, which resulted in the *in situ* reoxidation of Os(VI) (Scheme **1.35**).[51]



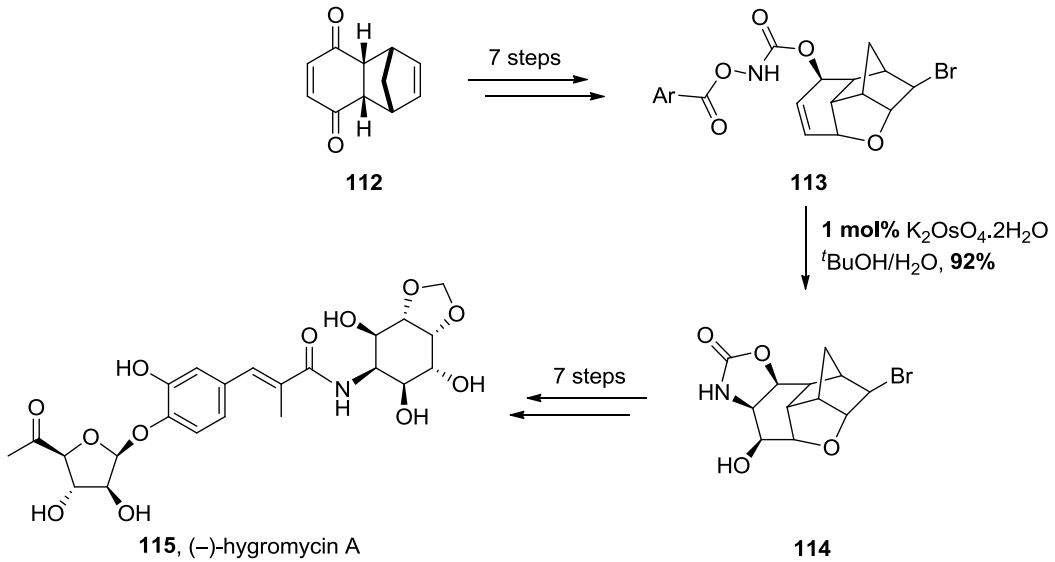
Scheme 1.35 *Improvements to the tethered aminohydroxylation*

By incorporating *N*-sulfonyloxy carbamates, no additional oxidant was required, which removed the complication of chlorinating the pendent alkene. In these cases, the catalyst loading could be reduced to 1 mol% of potassium osmate(VI) dihydrate. The tethered aminohydroxylation was further improved by the discovery of carboxylic acid-based reoxidant/leaving groups (Scheme **1.36**).[52]



Scheme 1.36 *Improvements to the tethered aminohydroxylation reaction*

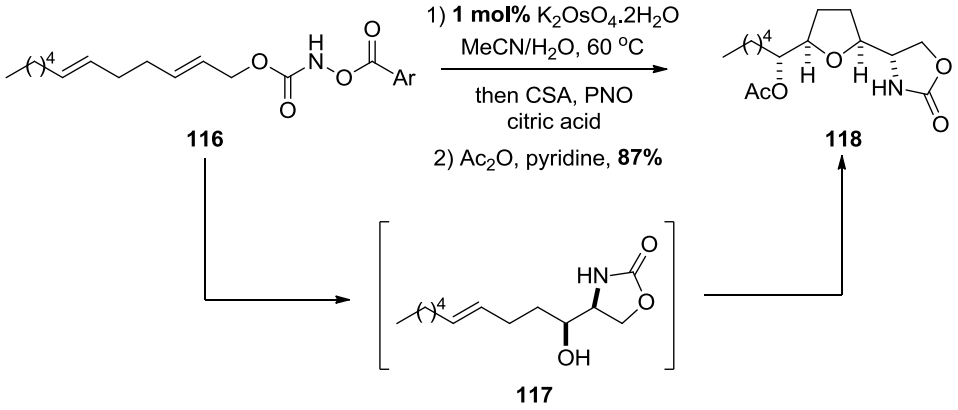
Modification of the leaving group to consist of carboxylic acids led to a more reliable reaction, with consistently high yields being achieved. This methodology was later utilised in the total synthesis of (–)-hygromycin A, which was completed by Donohoe and co-workers in 2009 (Scheme **1.37**).[53]



Scheme 1.37 *Total synthesis of (–)-hygromycin A*

The key tethered aminohydroxylation reaction proceeded to afford amino alcohol **114** in 92% yield using 1 mol% of potassium osmate catalyst. This methodology was also applied by Donohoe and co-workers to the development of a one-pot tandem tethered

aminohydroxylation/oxidative cyclisation.[54] Subsequent treatment of diene **116** with potassium osmate and pyridine-*N*-oxide/camphorsulfonic acid followed by acetylation afforded THF **118** in 87% yield over two steps (Scheme **1.38**).



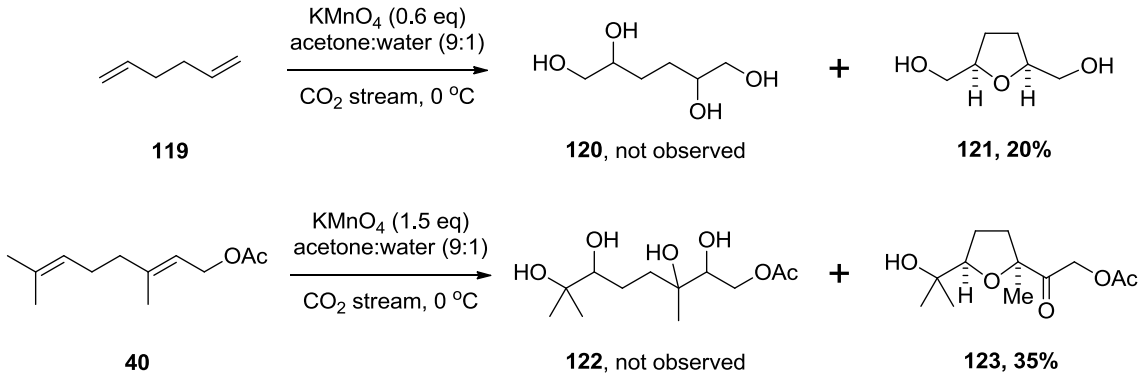
Scheme 1.38 *One-pot tethered aminohydroxylation/oxidative cyclisation*

This methodology demonstrated the ability of combined osmium chemistry to create four stereocentres with complete control of the relative stereochemistry.

1.2 Transition metal-mediated oxidative cyclisations to form THFs

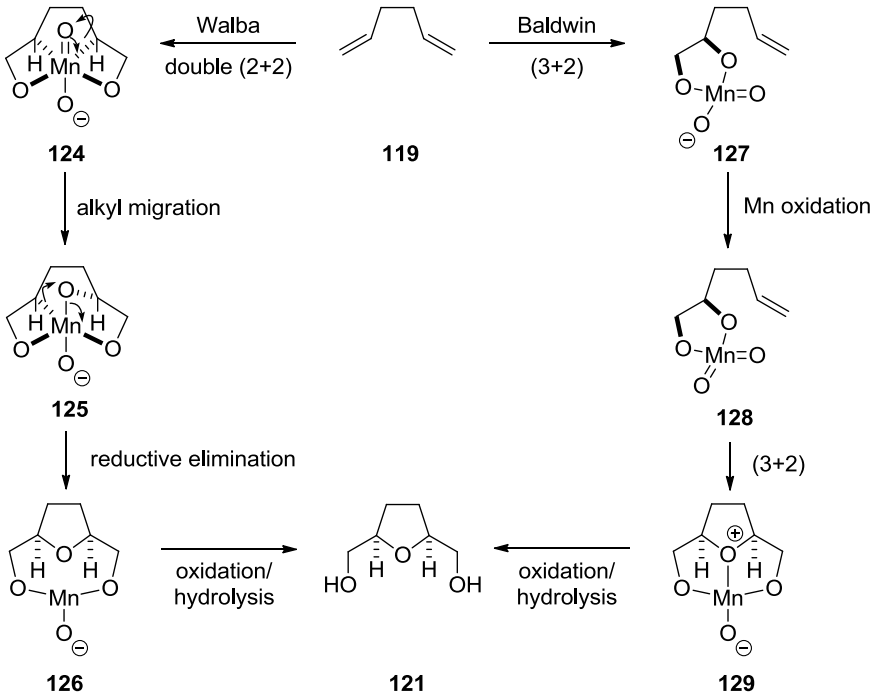
1.2.1 The permanganate-mediated oxidative cyclisation

In 1924, after the discovery that osmium tetroxide was capable of *syn*-dihydroxylating alkenes, Kötz and Steche discovered an analogous reaction using potassium permanganate.[55] During these studies it was found that the treatment of geranyl acetate **40** with permanganate did not afford the desired tetrol **122**. Klein and Rojahn repeated this work in 1965 and subsequently concluded that an oxidative cyclisation occurred to afford the corresponding 2,5-disubstituted THFs.[56] This methodology demonstrated that a range of 1,5-dienes would readily undergo an oxidative cyclisation to form THFs (Scheme **1.39**).



Scheme 1.39 *Klein and Rojahn's permanganate oxidative cyclisation of 1,5-dienes*

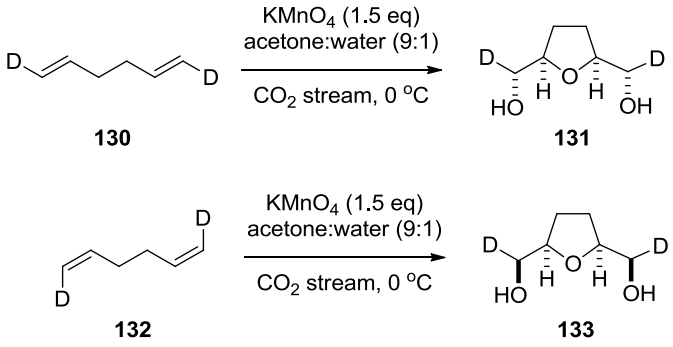
It was necessary for these reactions to be carried out under a constant stream of carbon dioxide in order to neutralise the potassium hydroxide formed during the reaction.[56] Despite the fact that these transformations were low yielding and suffered from the formation of over-oxidised products, the cyclisations were shown to be stereoselective for the formation of 2,5-*cis*-THFs. The stereospecifity of the permanganate-mediated oxidative cyclisation was proved independently in 1979 by both Walba[57] and Baldwin[58]. However, each one proposed differing mechanistic pathways by which the reaction could proceed (Scheme **1.40**).



Scheme 1.40 *Walba and Baldwin's proposed mechanisms for the cyclisation*

Walba proposed that the initial step in the reaction was a (2+2) cycloaddition across each alkene, resulting in the formation of manganese(VII) ester **124**. From this intermediate, it was proposed that an alkyl migration, followed by a reductive elimination led to the corresponding manganese(III) complex **126**. This complex was oxidised further by permanganate, before being hydrolysed to afford THF **121**. Conversely, Baldwin proposed that the initial step was a (3+2) cycloaddition to one alkene to form manganese(V) ester **127**. After subsequent oxidation of this complex, a further (3+2) cycloaddition was proposed to take place with the remaining alkene, which after hydrolysis afforded THF **121**.

Baldwin demonstrated the stereospecificity of the cyclisation using deuterium-labelled dienes. The cyclisation products of the deuterium substituted alkenes were analysed by NMR to reveal that the addition across the alkene occurred in a *syn*-fashion, as expected. Furthermore, the stereoselectivity of the cyclisation at the 2,5-ring junction was proved to be selective for the formation of *cis*-THFs (Scheme **1.41**).

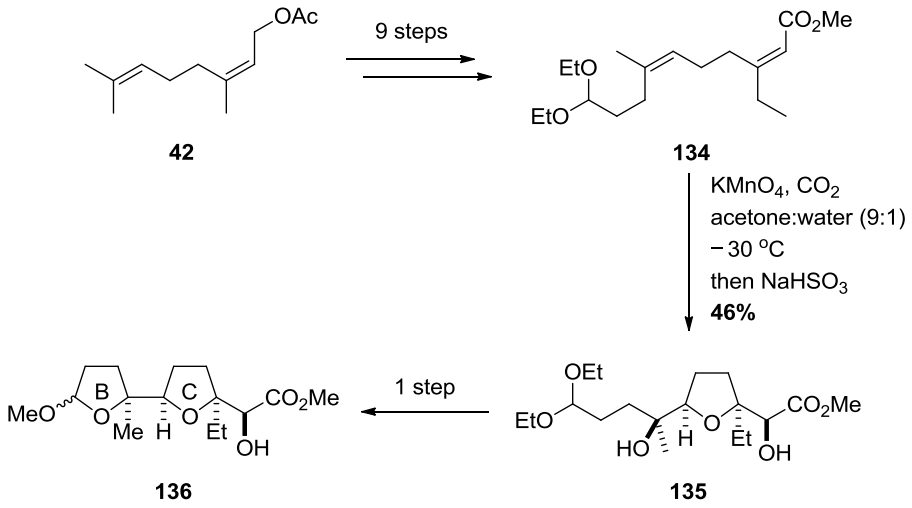


Scheme 1.41 *Deuterium studies on the permanganate cyclisation*

Walba and Baldwin's proposed mechanisms both support the observed outcome from Baldwin's deuterium-labelling studies. Both reactions result in stereospecific *syn*-addition across each alkene, with the stereoselective formation of *cis*-THFs occurring as a result of the preferred alignment of the orbitals during the second cycloaddition. Interestingly, as in the analogous reaction with osmium, calculations have shown that the initial (3+2) cycloaddition

mechanism with potassium permanganate is lower in energy than the corresponding (2+2) cycloaddition across the alkene.[59]

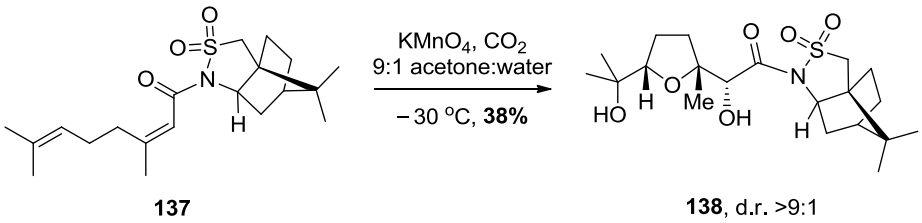
The synthetic applications of this cyclisation were demonstrated by Walba in the synthesis of the BC-ring system of (±)-monensin (Scheme **1.42**).[60]



Scheme 1.42 *Walba's synthesis of the BC-ring system of (±)-monensin*

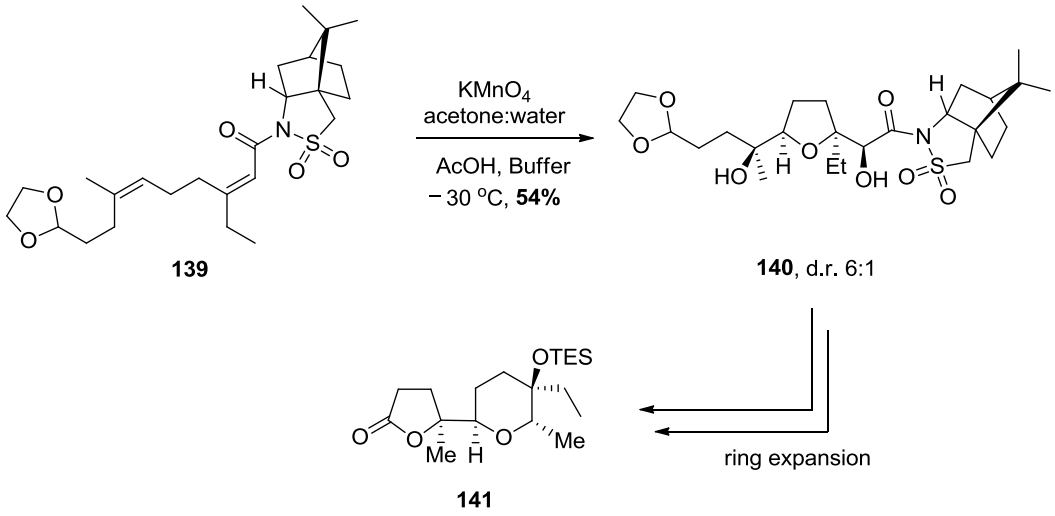
It was discovered that a reductive workup with sodium bisulfite improved the yield of the reaction significantly from 22% up to 46%. Subsequently, Weiler and Spino also demonstrated that this methodology could be used to form the terminal THF ring of (±)-ionomycin.[61]

Due to the nature of the initial cycloaddition with the alkene, this methodology was limited to the formation of racemic THFs. Walba and co-workers attempted to induce diastereoselectivity in the permanganate cyclisation using Oppolzer's sultam as a chiral auxiliary (Scheme **1.43**).[62]



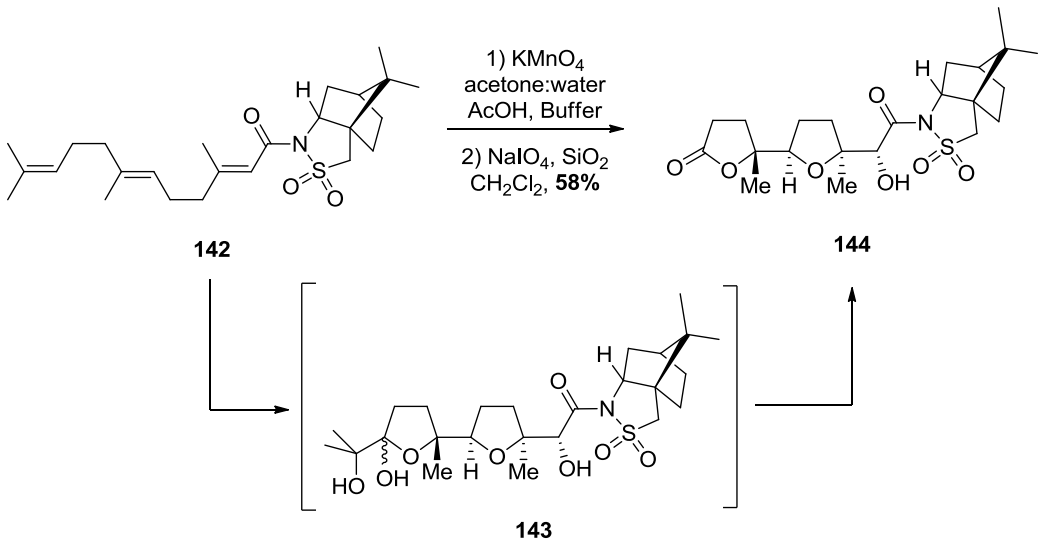
Scheme 1.43 *Walba's stereoselective permanganate cyclisation*

The initial attack of the permanganate ion took place at the electron-deficient alkene from the *Re* face. The preference for reactivity from the *Re* face was previously observed by Oppolzer in an analogous osmium-mediated dihydroxylation.[63] This reaction was modified by Kocienski and Brown, who incorporated an acetate buffer in order to increase the overall yield of the reaction. Subsequently, the transformation of diene **139** to the corresponding THF **140** was achieved in 54% yield with a diastereoselectivity of 6:1 in favour of the desired product (Scheme **1.44**).[64]



Scheme 1.44 *Buffered approach to $C_{21\text{-}30}$ fragment of salinomycin*

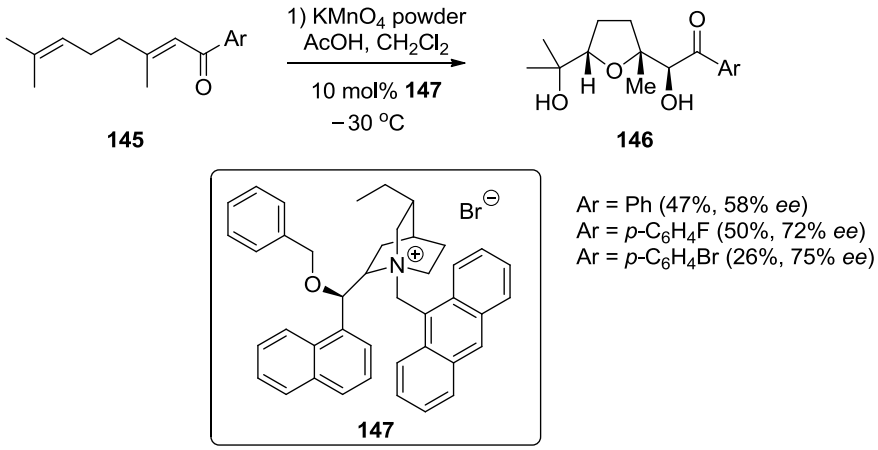
THF **140** was further manipulated *via* a ring expansion to form the $C_{21\text{-}30}$ fragment of salinomycin. This methodology was also extended to the cyclisation of 1,5,9-trienes, with similar selectivities achieved as a result of initial attack of the relatively electron rich permanganate occurring at the most electron-deficient alkene adjacent to the chiral auxiliary (Scheme **1.45**).[65]



Scheme 1.45 *1,5,9-triene cyclisation using potassium permanganate*

After the formation of the initial THF ring and hydrolysis of the manganate ester, a further oxidation of the remaining alkene occurred, affording lactol **143**. Treatment of this compound with sodium periodate resulted in the formation of lactone **144** as a single diastereomer in 58% over two steps. This strategy was later employed in the asymmetric synthesis of both *cis*-solamin[66] and membranacin[67].

Further studies into the permanganate-mediated oxidative cyclisation by Brown revealed that asymmetric induction was possible in the absence of a chiral auxiliary, by utilising a chiral phase-transfer catalyst (Scheme **1.46**).[68]

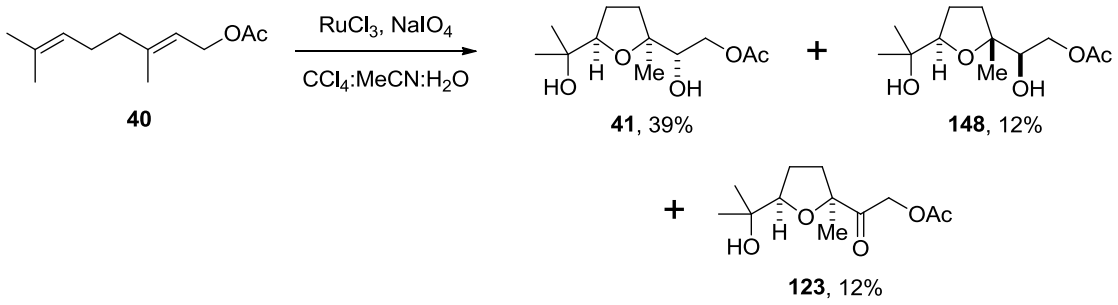


Scheme 1.46 *Permanganate-mediated cyclisation using a chiral phase-transfer catalyst*

However, this methodology was limited to the cyclisation of 1,5-dienes with a strongly electron-withdrawing group adjacent to the alkene. Treatment of geraniol derivatives under similar conditions gave THFs with low enantiomeric excesses, due to the attack of the permanganate ion occurring at both alkenes, which would result in the formation of the opposite enantiomer.

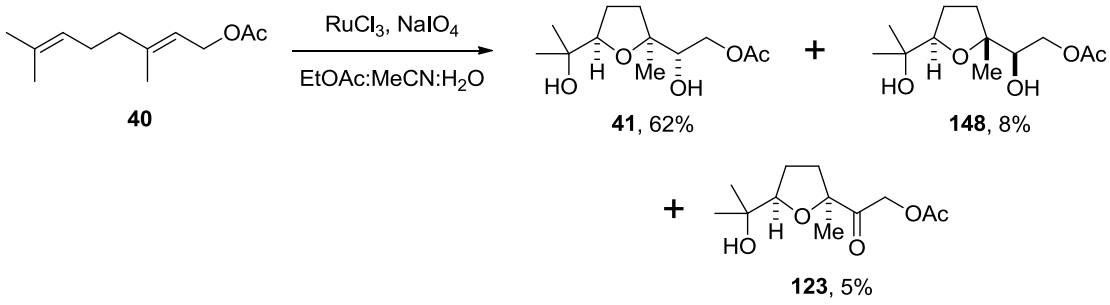
1.2.2 The ruthenium-mediated oxidative cyclisation

Ruthenium tetroxide was first shown to act as an organic oxidant in 1953, by converting sulfides to sulfoxides.[69] During studies by Sharpless and co-workers on using ruthenium tetroxide as a catalyst for the oxidative cleavage of alkenes, it was discovered that ruthenium tetroxide, generated *in situ* from ruthenium(III) chloride, could act as an oxidative cyclisation catalyst for 1,5-dienes (Scheme **1.47**).[70]



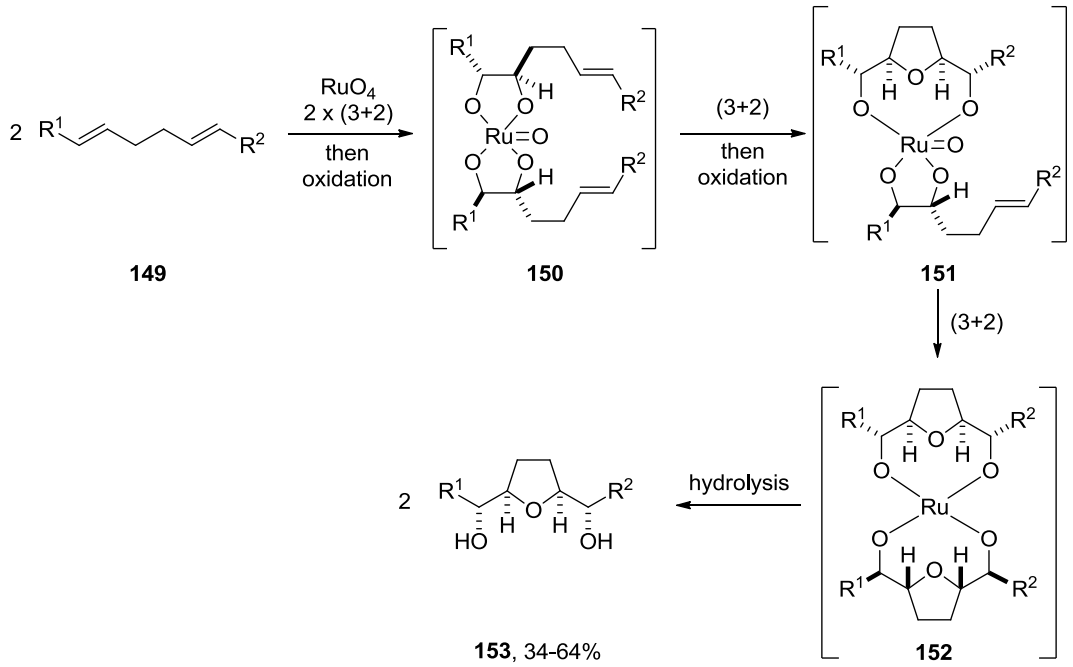
Scheme 1.47 *Ruthenium catalysed oxidative cyclisation*

Contrary to the results observed with other metal-oxo species, it was discovered that both *cis*- and *trans*-THFs were formed during the reaction. Sharpless rationalised that this was as a result of the intermediate ruthenium-oxo species having longer bond lengths, and therefore was able to also form the kinetically disfavoured *trans*-THF. Furthermore, over-oxidation of the resulting secondary alcohol was also observed. Several years later, Piccialli was able to optimise the reaction conditions to reduce the amount of the *trans*- and keto-THF side products by changing the solvent system to ethyl acetate/acetonitrile/water (Scheme **1.48**).[71]



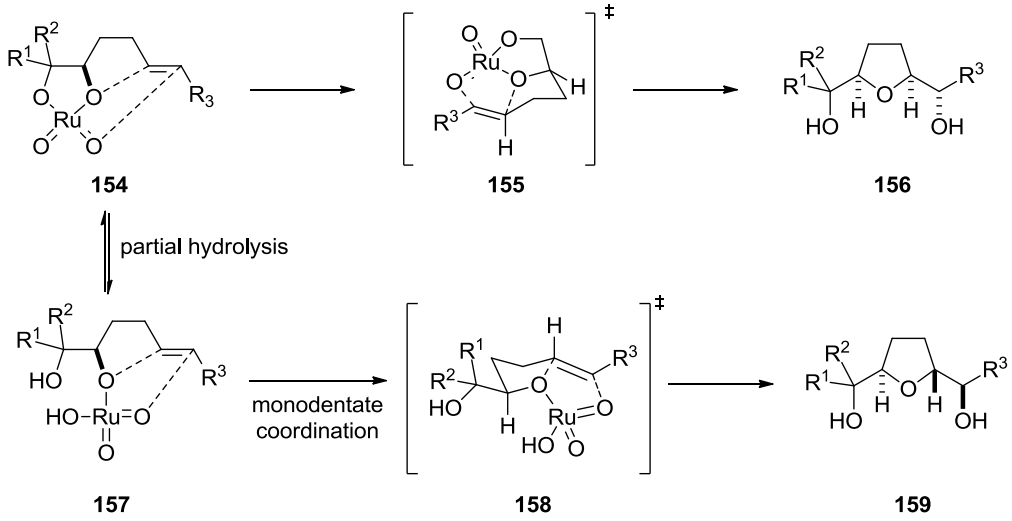
Scheme 1.48 *Piccialli's improved cyclisation conditions*

These improved conditions were shown to result in the successful cyclisation of a range of 1,5-dienes, with *cis*-THF **41** prevailing as the major product in each case. At a similar time, Sica and co-workers also published an optimised ruthenium-mediated cyclisation, proposing an analogous mechanism to that of the osmium-mediated oxidative cyclisation (Scheme **1.49**).[72]



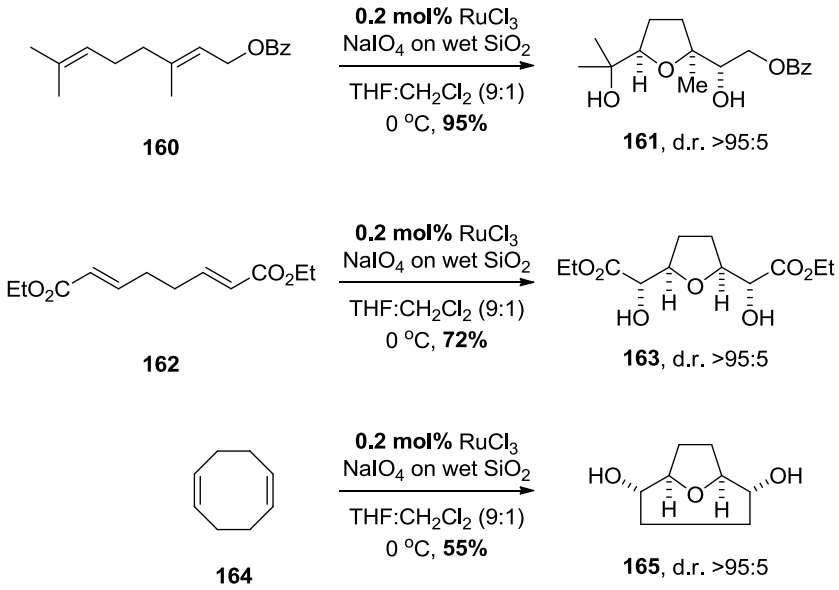
Scheme 1.49 *Sica's proposed mechanism for the ruthenium-mediated oxidative cyclisaion*

However, both Sica and Piccialli's protocols resulted in moderate yields, with a significant amount of *trans*-THF and keto-THF still being formed in the reaction. Piccialli later proposed that the *trans*-THF was formed as a result of a monodentate ruthenium cyclisation, occurring as a consequence of partial cleavage of ruthenate ester **154** (Scheme **1.50**).[73]



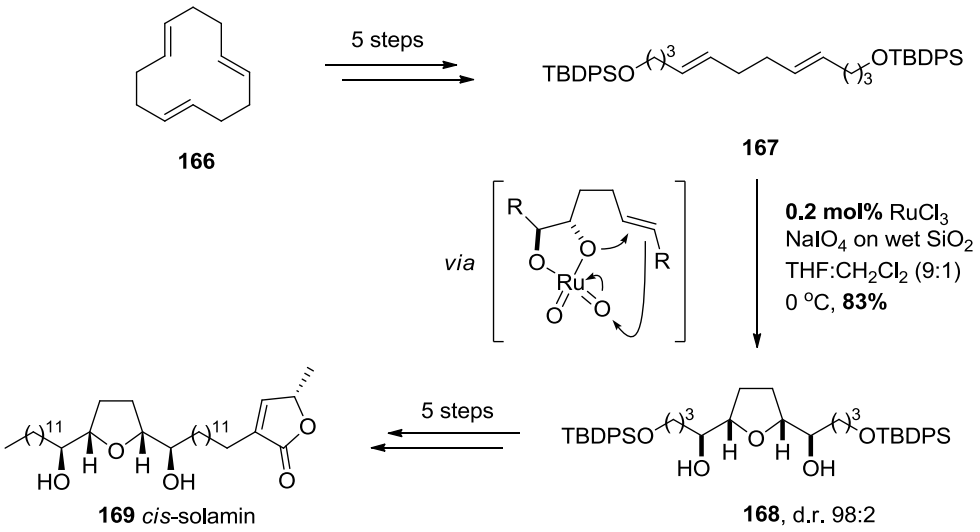
Scheme 1.50 *Competing monodentate pathway*

It was not until Stark and co-workers further modified the reaction that a reliable ruthenium-mediated cyclisation was achieved.[74] After screening a range of conditions, it was discovered that using sodium periodate on wet silica, combined with a solvent system of THF and CH_2Cl_2 at 0 ^oC, resulted in the almost exclusive formation of *cis*-THFs in high yields (Scheme **1.51**).



Scheme 1.51 *Stark's improved RuO_4 mediated oxidative cyclisation*

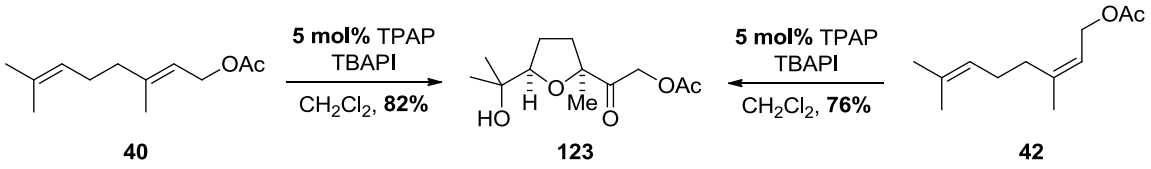
In each case, the catalyst loading of ruthenium trichloride could be reduced to 0.2 mol%, with the comparative selectivity for forming *cis*- to *trans*-THF being >95:5 in most cases. These conditions were applied to Stark's synthesis of *cis*-solamin (Scheme **1.52**).[75]



Scheme 1.52 *Stark's synthesis of cis-solamin*

Following the formation of diene **167**, the ruthenium-mediated oxidative cyclisation afforded *meso*-THF **168**, which was subsequently subjected to an enzymatic desymmetrisation before the synthesis was completed in a total of 11 steps with an overall yield of 7.5%.

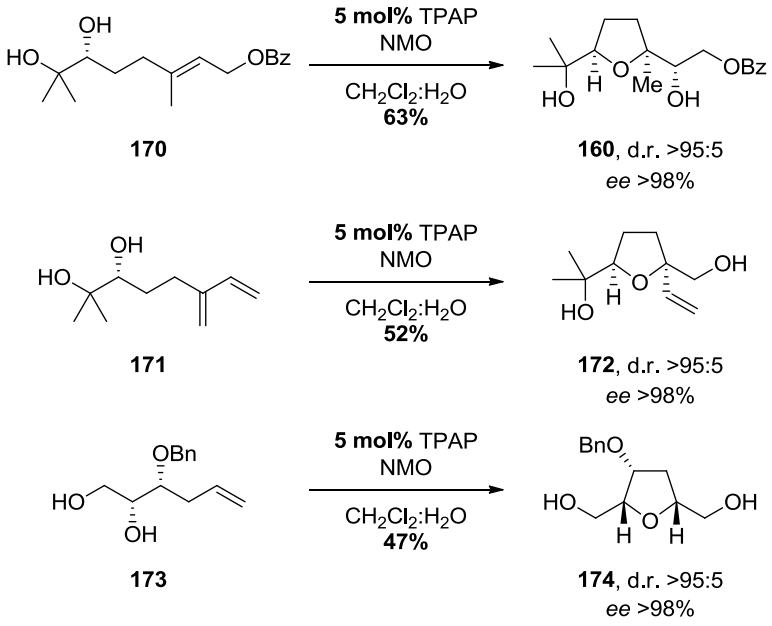
Shortly before Stark's findings, Piccialli also demonstrated that the oxidative cyclisation of 1,5-dienes could be achieved using ruthenium(VII) (Scheme **1.53**).[76]



Scheme 1.53 *TPAP-mediated oxidative cyclisation of 1,5-dienes*

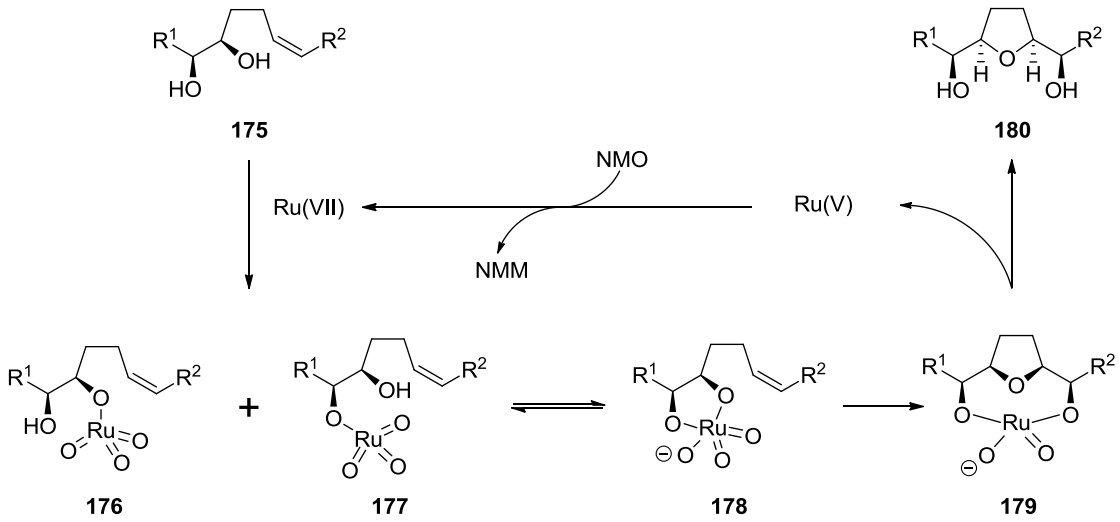
Utilising a catalytic amount of tetrapropylammonium perruthenate (TPAP) in combination with a stoichiometric amount of tetrabutylammonium periodate (TBAPI) as a reoxidant, it was possible to cyclise a wide range of substrates to the corresponding THFs. Further oxidation of the secondary alcohol occurred to afford keto-THF **123** in good yields from geraniol acetate **40**

and nerol acetate **42**. At this stage, both the RuO_4 and TPAP-mediated oxidative cyclisations were limited to the formation of racemic THFs. This was due in part to the inherent reactivity of Ru(VII) and Ru(VIII) towards alcohols and alkenes respectively. In 2010, Stark and Cheng developed a mild set of reaction conditions capable of cyclising pre-formed diols onto a pendent alkene using Ru(VII).[77] Using 5 mol% of TPAP in combination with NMO it was possible to cyclise a range of enantiopure 1,2-diols, with higher yields being achieved in the case of more substituted alcohols (Scheme **1.54**).



Scheme 1.54 *TPAP-mediated oxidative cyclisation of diols*

It was proposed that the mechanism of the reaction proceeded *via* the formation of a ruthenium(VII) monodentate ester, as in the TPAP oxidation of alcohols (Scheme **1.55**).

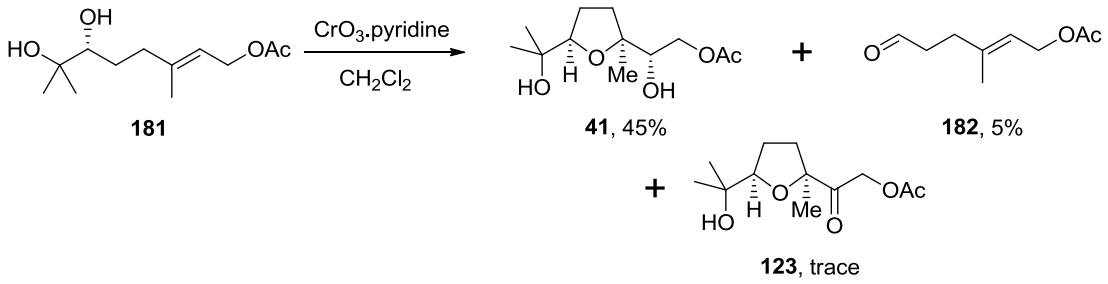


Scheme 1.55 *Catalytic cycle of TPAP cyclisation*

Monodentate esters **176** and **177** could subsequently form a bidentate chelate to the adjacent alcohol, which is driven by the Lewis acidity of the ruthenium centre. Bidentate ruthenium ester **178** could then undergo the (3+2) cycloaddition with the pendent alkene, before being hydrolysed to afford the corresponding THF. This methodology represents a powerful method for forming enantioenriched THFs, but like other ruthenium-mediated oxidative cyclisations, suffers from the occurrence of over-oxidised products.

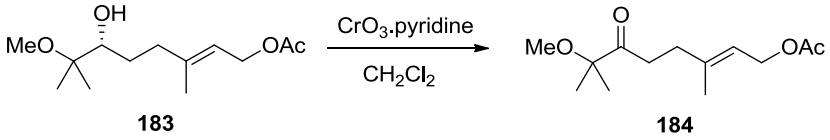
1.2.3 The chromium-mediated oxidative cyclisation

Prior to Stark's findings, the first example of a 5,6-dihydroxyalkene undergoing an oxidative cyclisation to form a THF was reported by Casida and co-workers in 1974.[78] Treatment of a 5,6-dihydroxyalkene with Collins reagent did not result in the expected oxidation, but led to the formation of a 2,5-disubstituted THF. In 1982, Walba and Stoudt demonstrated that this cyclisation afforded *cis*-THFs, with yields in the range of 45-50% (Scheme **1.56**).[79]



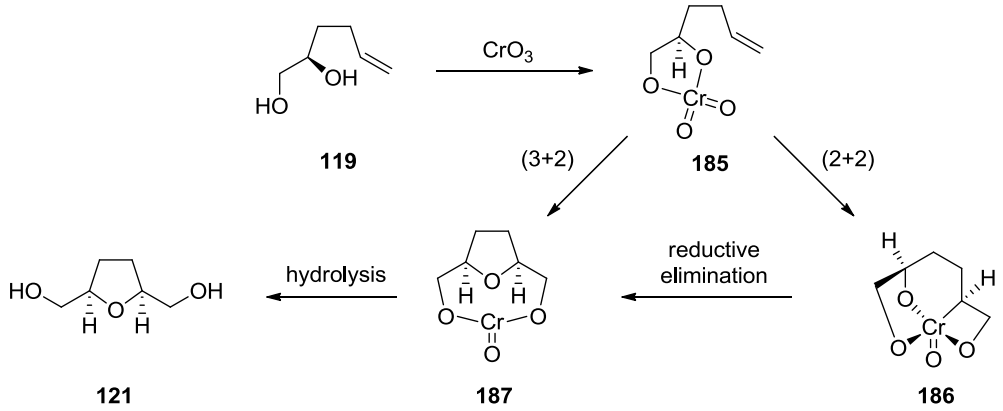
Scheme 1.56 *Walba's chromium-mediated oxidative cyclisation*

Also isolated from the reaction mixture were small quantities of the oxidatively cleaved **182** and over-oxidised keto-THF **123**. It was found that this transformation could also be achieved with pyridinium chlorochromate. Walba drew attention to a previous study by Collins in which the oxidation of the corresponding methyl ether **183** resulted in the formation of ketone **184** exclusively. However, no yield was provided for this transformation (Scheme **1.57**).[80]



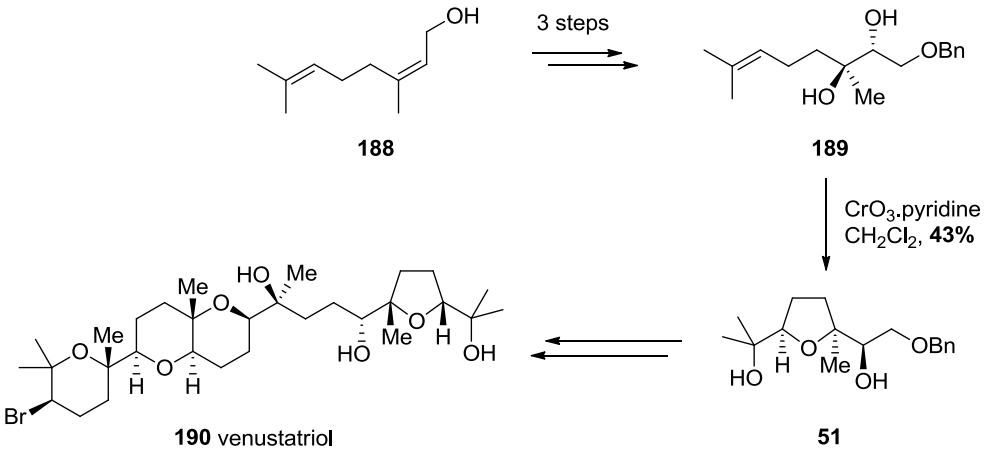
Scheme 1.57 *Jones oxidation of methyl ether **183***

This result led Walba to postulate that the mechanism of the chromium-mediated cyclisation occurred *via* a bidentate chelation to both alcohols, which would also explained the exclusive formation of *cis*-THFs (Scheme **1.58**).



Scheme 1.58 *Walba's proposed mechanism for the chromium cyclisation*

Walba postulated two possible mechanisms for the reaction. After the initial formation of a bidentate chromate ester, a (3+2) cycloaddition could take place with the pendent alkene to form Cr(IV) ester **187**. Alternatively, the same intermediate could be formed from a (2+2) cycloaddition followed by reductive elimination. Finally, hydrolysis of **187** would lead to the formation of THF **121**. The significance of this chemistry is evident, as the cyclisation of enantiopure diols, combined with the stereoselectivity and stereospecifity of the reaction, would result in the formation of enantiopure THFs. This potential was exploited by Corey and Ha as one of the key steps in the asymmetric synthesis of venustatriol (Scheme **1.59**).[81]



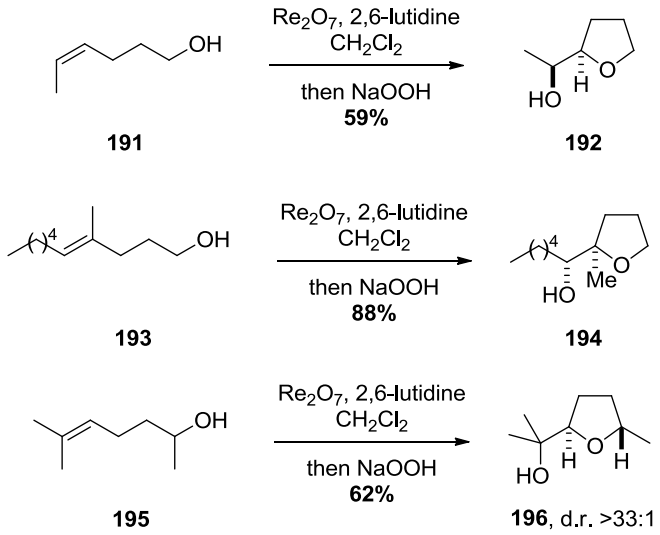
Scheme 1.59 *Corey's synthesis of venustatriol*

After the formation of enantiopure diol **189**, a successful oxidative cyclisation proceeded to afford THF **51**, which was subsequently coupled to the tricyclic-core of venustatriol. Whilst this methodology demonstrated the unique ability to form enantiopure *cis*-THFs, the toxicity of chromium(VI) coupled with a failure to render the cyclisation catalytic has led to this cyclisation being under-utilised in organic synthesis.

1.2.4 The rhenium-mediated oxidative cyclisation

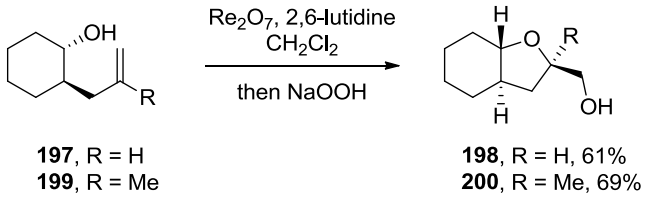
Whilst being isoelectronic with osmium tetroxide and ruthenium tetroxide, rhenium(VII) oxide (Re_2O_7) is not capable of dihydroxylating alkenes. The first example of rhenium(VII) oxide displaying reactivity towards an alkene was reported by Kennedy in 1992. It was discovered

that treating 5-hydroxyalkenes with a stoichiometric amount of Re(VII) led to the formation of *trans*-THFs with high selectivities (Scheme **1.60**).[82]



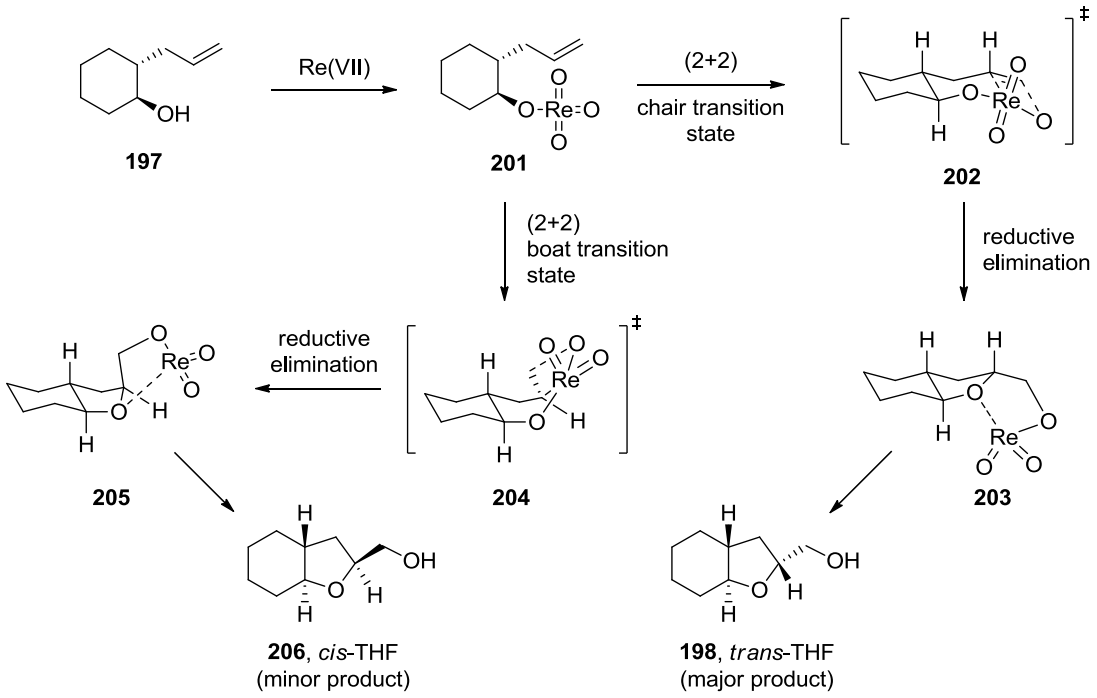
Scheme 1.60 *Rhenium(VII) oxide cyclisation*

In the case of THF **196**, it was subsequently shown that the *trans*-THF prevailed over the formation of the *cis*-THF in a ratio of >33:1. This methodology was later demonstrated to be successful in cyclising several cyclic 5-hydroxyalkenes, which also furnished the corresponding *trans*-THFs with excellent stereoselectivity (Scheme **1.61**).[83]



Scheme 1.61 *Cyclisation of cyclic substrates*

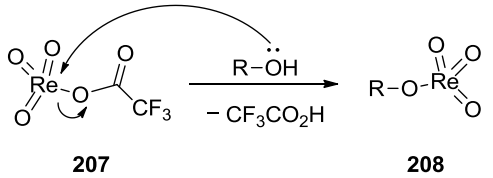
Subsequent NOE studies on THFs **198** and **200** showed that in both cases, the *trans*-THF was formed in >99:1 selectivity. It was proposed that this selectivity was observed as a consequence of a chair vs boat transition state (Scheme **1.62**).



Scheme 1.62 *Competing mechanistic pathways*

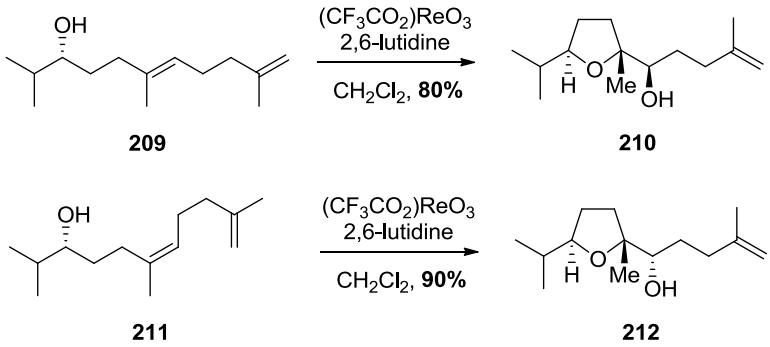
After the formation of the initial rhenium (VII) ester **201**, it was initially proposed that a (2+2) cycloaddition could take place with the pendent alkene to proceed *via* the more favoured chair-like transition state **202**, or the disfavoured boat-like transition state **204**. Subsequent reductive elimination of these complexes, followed by decomplexing the rhenium(V) species, resulted in the formation of the corresponding THFs. This methodology was also applied to the formation of spirocyclic acetals *via* a cyclisation on to cyclic enol-ethers.[84] Kennedy also demonstrated that the amount of Re_2O_7 required for the cyclisation to proceed to completion could be reduced from 3 equivalents to 0.5 equivalents when periodic acid was utilised as a reoxidant.[85]

McDonald later noted that the reaction initiated by liberating one equivalent of perrhenic acid (pK_a –1.25)[86] from Re_2O_7 which could have a detrimental effect on the reaction by facilitating the non-oxidative cyclisation of substituted alkenes.[87] It was subsequently demonstrated that changing the rhenium source to (trifluoroacetyl)perrhenate afforded milder reaction conditions, with trifluoroacetic acid (pK_a 0.53)[88] being liberated in the first step of the reaction (Scheme **1.63**).



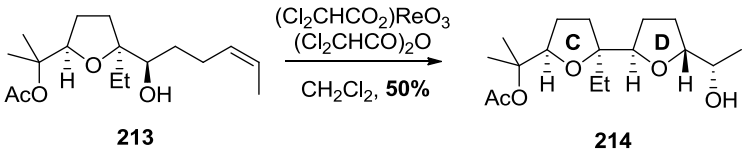
Scheme 1.63 *Trifluoroacetic acid-substituted perruthenate*

This modification led to a greatly improved procedure which afforded *trans*-THFs in excellent yields. When applying these conditions to a range of polyenes, it was noted that only the mono-cyclised THFs were isolated (Scheme **1.64**).



Scheme 1.64 *McDonald's improved rhenium-mediated cyclisation*

It was reasoned that only monocyclised THFs were isolated as a result of coordination between the Lewis acidic rhenium and the THF-oxygen. This led McDonald to speculate that removing 2,6-lutidine would result in the trifluoroacetic acid by-product, instead of being neutralised, acting to break up this interaction, allowing a subsequent cyclisation to give bicyclic *trans*,*trans*-THFs. In addition to this, it was also discovered that the addition of the corresponding halogenated-acetic anhydride increased the yield of the second cyclisation, presumably by reacting with any residual perrhenic acid.[88] These modifications, using (dichloroacetyl)perrhenate and the corresponding anhydride, were utilised in the synthesis of the CD-ring system of monensin (Scheme **1.65**).[89]

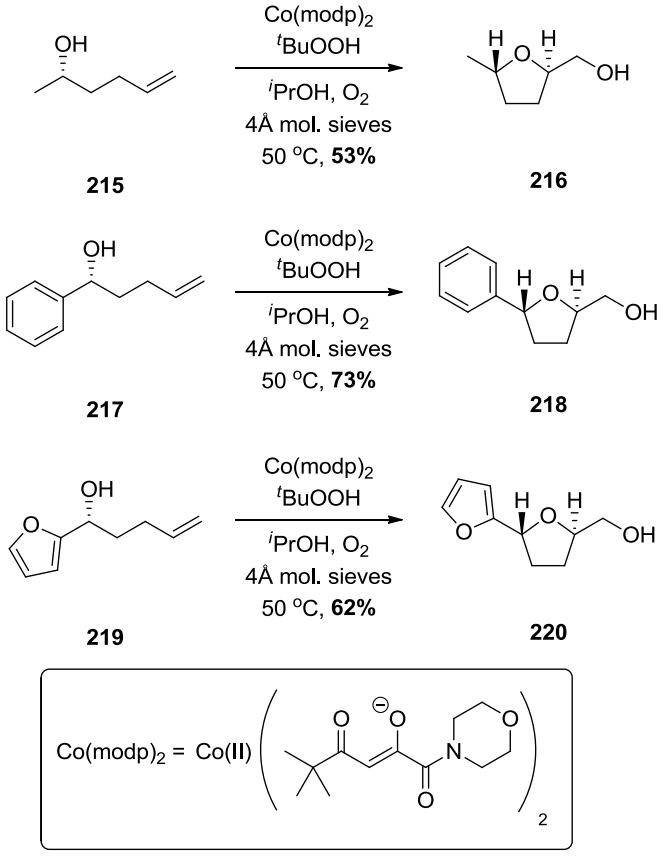


Scheme 1.65 *Synthesis of CD-ring system of monensin*

When exposed to these conditions, mono-cyclised THF **214** afforded key intermediate *cis*,*trans*-THF **214** in 50% yield. This methodology, although stoichiometric in rhenium, afforded a unique and high yielding method for the reliable formation of *trans*-THFs.

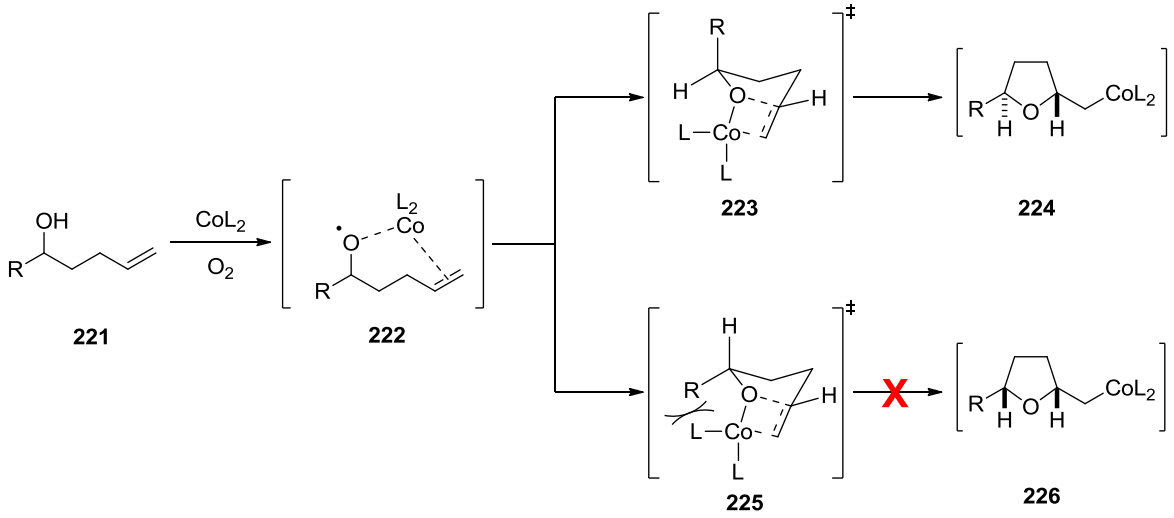
1.2.5 The cobalt-mediated oxidative cyclisation

An alternative method for forming *trans*-THFs from 5-hydroxyalkenes was reported by Mukaiyama in 1990.[90] This method consisted of utilising a cobalt(II) catalyst under an oxygen atmosphere (Scheme **1.66**).



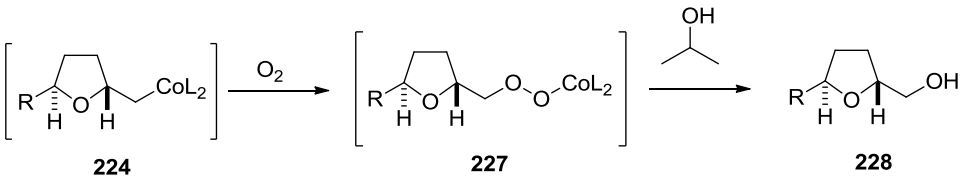
Scheme 1.66 *Cobalt-catalysed oxidative cyclisation*

After attempting to utilise $Co(TFA)_2$ as a cyclo-hydration catalyst upon alcohol **217**, a significant amount of oxidative cyclisation product **218** was isolated. Upon optimising the conditions, it was discovered that subjecting a range of 5-hydroxyalkenes to Co(II) complexes under at atmosphere of oxygen led to the clean formation of *trans*-THFs.[90] Mukaiyama postulated a radical mechanism for this transformation (Scheme **1.67**).



Scheme 1.67 *Mukaiyama's mechanism for the selectivity of the cobalt cyclisation*

After the initial alcohol **221** was converted into the corresponding radical intermediate **222** by treatment with the Co(II) catalyst and oxygen, it was proposed that this radical could then undergo a cyclisation onto the pendent alkene, which was driven by sterics to form almost exclusively the cobalt substituted *trans*-THF **224**. From this point, oxygen is able to insert into the carbon-cobalt bond to form cobalt-peroxide **227** (Scheme **1.68**).

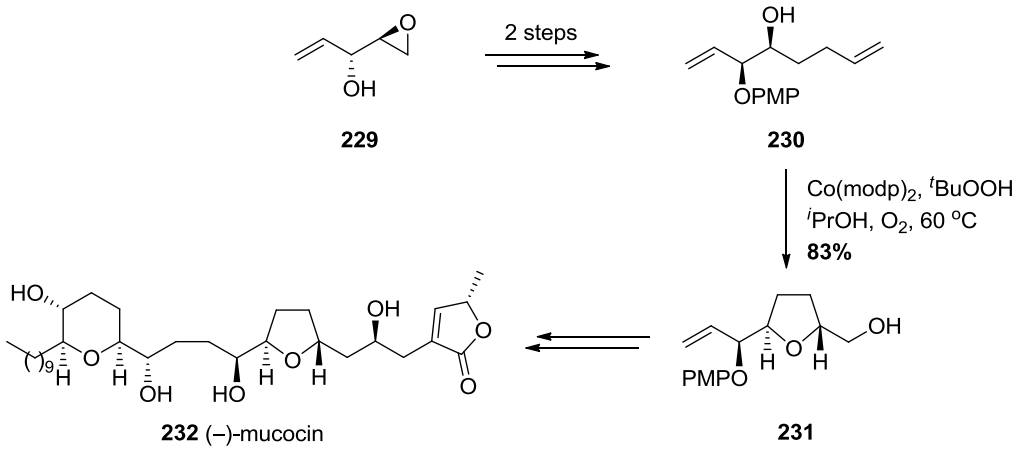


Scheme 1.68 *Mechanism for removal of cobalt*

This peroxide can then be reduced by isopropyl alcohol to afford THF **228**. Furthermore, it was discovered that the addition of hydroperoxides to the reaction led to an increase in yield. It was

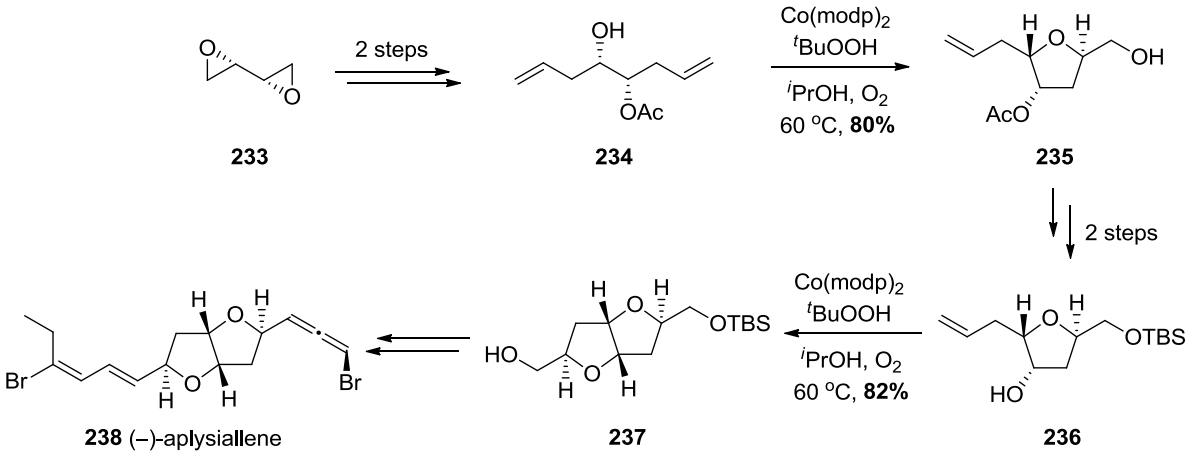
presumed that this accelerated the formation of the radical species **222**. This reaction was later examined by Hartung and co-workers, who discovered that attempting this reaction on non-terminal alkenes led to the formation of *trans*-THFs in a non-stereospecific manner, which prompted the suggestion of an alternative mechanism, whereby the reaction proceeded *via* a radical at the α-position to the newly formed THF.[91]

Despite this obstacle, Mukaiyama's methodology has been used as a key step in the synthesis of several natural products. In 2003, Evans and co-workers used the methodology to form the *trans*-THF present in (–)-mucocin (Scheme **1.69**).[92]



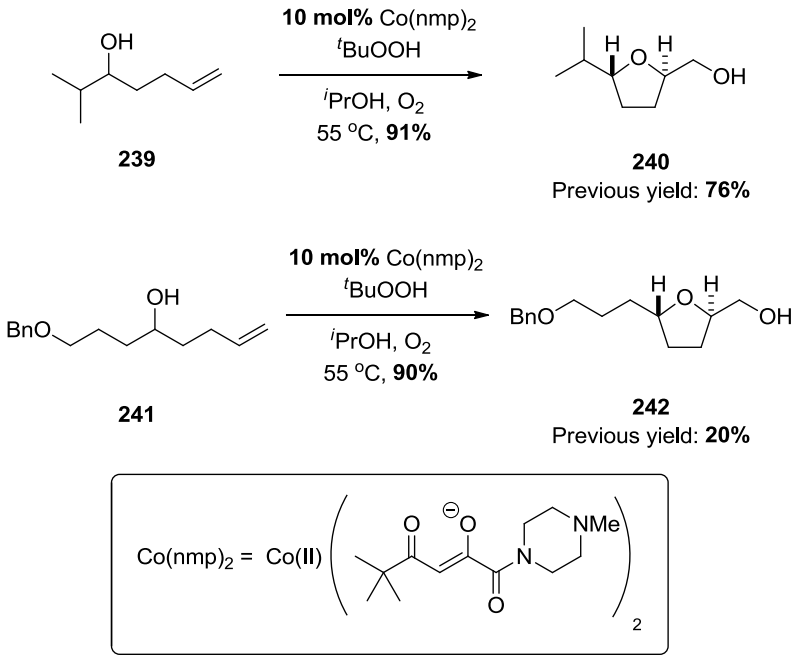
Scheme 1.69 *Evans's synthesis of (–)-mucocin*

A further example which exploits the cobalt-catalysed oxidative cyclisation was demonstrated by Pagenkopf and co-workers with the synthesis of (–)-aplysiallene.[93] This example utilised two successive cyclisations to access bis-THF **237** (Scheme **1.70**).



Scheme 1.70 *Pagenkopf's synthesis of (–)-aplysiallene*

The initial cyclisation of desymmetrised alcohol **234** to form THF **235** was followed by a second cyclisation to furnish bis-THF **237**. Despite the cyclisations proceeding in good yields, Pagenkopf noted that purification of the resulting *trans*-THFs from the cobalt catalyst was difficult. Subsequently, Pagenkopf and co-workers discovered that changing the catalyst to $Co(nmp)_2$ led to significantly higher yields when combined with an iodomethane quench (Scheme **1.71**).[94]



Scheme 1.71 *Improved cobalt cyclisation*

It was reasoned that the subtle difference in changing an oxygen atom for an *N*-methyl group resulted in a more water soluble catalyst. Furthermore, the addition of iodomethane or utilising an aqueous wash with a pH 4 buffer resulted in the complete removal of the catalyst from the organic solvent. With these improvements, the cobalt-catalysed oxidative cyclisation has become a powerful technique for forming *trans*-THFs.

1.3 Summary

Since the discovery that osmium-oxo species can act as organic oxidants in 1908, Os(VIII) has been shown to undergo a range of transformations with alkenes. This characteristic reactivity has paved the way for the development of powerful methodology, such as the Sharpless asymmetric dihydroxylation and aminohydroxylation of alkenes, along with the oxidative cyclisation of 1,5-dienes. The mechanistic aspects of the Os(VIII) dihydroxylation have been examined, with convincing experimental evidence emerging to support a (3+2) cycloaddition pathway prevailing over a (2+2) cycloaddition on the basis of kinetic isotope studies and quantum mechanical calculations. The inherent differences of reactivity between Os(VI) and Os(VIII) have been highlighted, with the latter preferentially chelating in a bidentate manner to bis-alcohols and showing no reactivity to alkene functionality in its unchelated form. This difference in reactivity has led to the development of a chiral oxidative cyclisation, which proceeds by a fundamentally different pathway to the analogous 1,5-diene cyclisation.

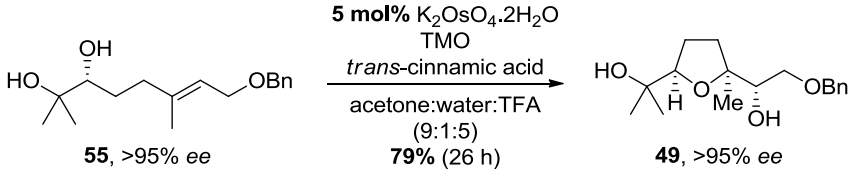
A range of other transition metals have also been shown to be capable of promoting an oxidative cyclisation to form THFs, with methods available for the selective formation of either *cis*- or *trans*-THFs depending on the choice of transition metal and the conditions used. All of these transformations have been shown to have widespread synthetic applications and have been involved in the synthesis of complex THF containing natural products. In all cases, these methods have been extensively optimised and have been applied to forming enantioenriched THFs with varied success.

Chapter 2

Optimising the Oxidative Cyclisation

2.1 Research outline

The osmium-mediated oxidative cyclisation of vicinal diols derived from 1,5-dienes has been shown to be a powerful synthetic tool (Scheme **2.1**).[38]



Scheme 2.1 *The osmium-mediated oxidative cyclisation*

This reaction gives access to enantiopure *cis*-THFs through a process that forms two defined stereocentres. This general methodology can be applied to a wide range of initiator groups, such as 1,3-diols, amino alcohols and α-hydroxy amides to give both THFs and pyrrolidines.[34] Unfortunately, the scope of this reaction is limited by the requirement to use a strong acid in order for the cyclisation to proceed.

The intention of this research is to develop a more applicable oxidative cyclisation, capable of cyclising a wider scope of substrates, whilst reducing the acidity of the reaction. If successful, this methodology could have widespread applications to the synthesis of complex molecules and, in combination with newly-developed methodology, could be applied to forming natural products such as pectenotoxin-4 (Figure **2.1**).

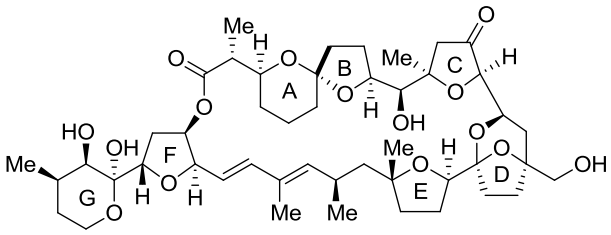
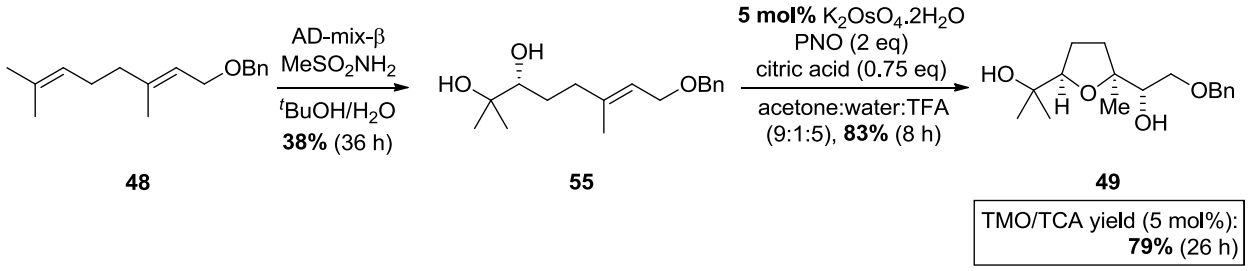


Figure 2.1 *Pectenotoxin-4*

2.2 Improving the oxidative cyclisation of diols

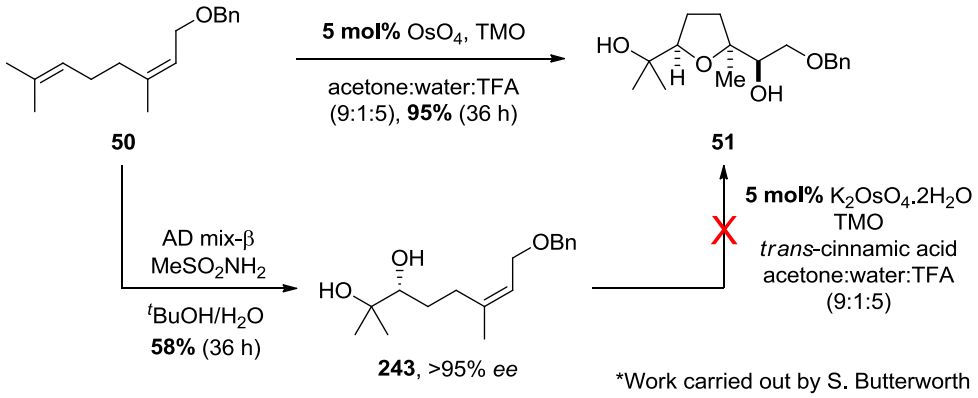
Initial studies for improving the cyclisation of 1,2-diols commenced by applying the recently developed pyridine-*N*-oxide (PNO) and citric acid conditions, from the analogous amino alcohol series,[39] to a diol system. These modified conditions were attempted on the readily available geraniol-derived benzyl diol **55**, which had been shown to undergo oxidative cyclisation under the previous trimethylamine-*N*-oxide (TMO) and *trans*-cinnamic acid (TCA) conditions (Scheme **2.2**).



Scheme 2.2 *Improved oxidative cyclisation conditions*

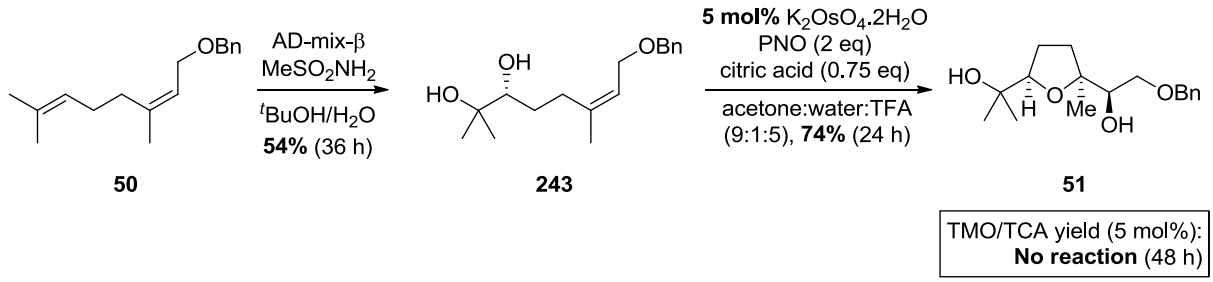
These changes to the reaction conditions resulted in an incremental increase to the yield of THF **49** from 79% to 83%. However, it was also noted that under the PNO/citric acid conditions, the reaction proceeded to completion significantly faster than in the analogous TMO/TCA cyclisation. There are several possible reasons for this observation – firstly, the addition of citric acid has previously been shown by Sharpless and co-workers to aid the hydrolytic release of the substrate from the osmate ester (*vide infra* **Chapter 2.4**).[23] Secondly, now that a source of Os(VI) can be accessed directly, the dihydroxylated *trans*-cinnamic acid by-product is no longer present to form a competing 1,2-diol osmate ester, resulting in the faster formation of the substrate-osmate ester.

With the modified conditions proving to be significantly faster, the reaction was attempted on other challenging substrates. Nerol-derived diol **243** had previously failed to cyclise under the TMO/TCA conditions, contrary to the Os(VIII)-mediated 1,5-diene cyclisation of benzyl ether **50**, which cyclised under the same conditions in 36 hours (Scheme **2.3**).[35]



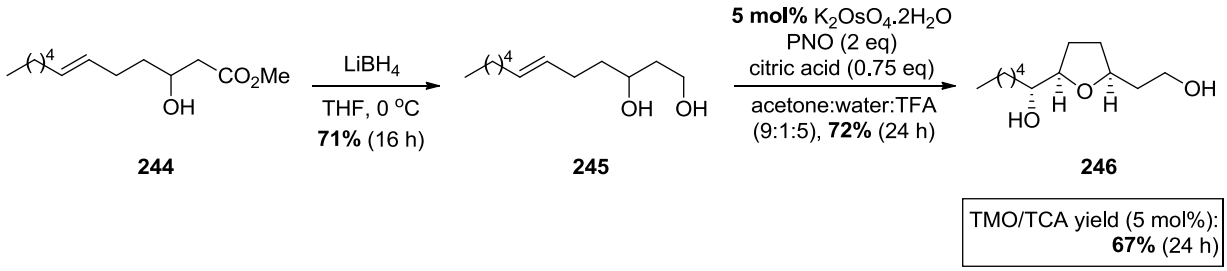
Scheme 2.3 *Attempted cyclisations of nerol derived substrates*

This result led to the hypothesis that formation of the corresponding osmate ester of **243** was slow, due to the presence of dihydroxylated *trans*-cinnamic acid forming a competing osmate ester.[35] However, another plausible explanation is that formation of the Os(VI) ester in the TMO/TCA system is likely to be highly reversible, due to dihydroxylated *trans*-cinnamic acid acting as a ligand for osmium (*vide infra* **Chaper 2.4**). This could lead to the reoxidation of Os(VI) to Os(VIII) occurring as a significantly competitive route. As the cyclisation of diol **243** is slow, an alternative cycle involving the comparatively fast reoxidation of Os(VI) to Os(VIII), followed by subsequent dihydroxylation of the sacrificial alkene could occur. This would eventually result in the exhaustion of both the sacrificial alkene and the reoxidant, resulting in no cyclisation product being observed. With this new hypothesis in mind, diol **243** was subjected to the PNO/citric acid conditions. Pleasingly, this resulted in the formation of THF **51**, which was spectroscopically identical to the corresponding THF formed from the 1,5-diene cyclisation (Scheme **2.4**).



Scheme 2.4 *Nerol-derived diol cyclisation*

Utilising these conditions in the cyclisation of 1,3-diol **245** also led to a higher yielding oxidative cyclisation. However, unlike in the case of the cyclisation of 1,2-diols, a similar rate of reaction was observed with both the TMO/TCA and the PNO/citric acid conditions (Scheme **2.5**).



Scheme 2.5 *1,3-diol cyclisation*

It has been demonstrated that the formation of a 1,3-diol osmate ester is significantly slower than with an analogous 1,2-diol.[95] As a result of this, the initial condensation of Os(VI) to afford the 1,3-osmate ester is likely to become the turnover limiting step. In both the PNO/citric acid cyclisation and the TMO/TCA cyclisation of both 1,2- and 1,3-diols, it is likely that the formation of the osmate ester occurs at a comparable rate. Consequently, with this now being the turnover limiting step, a similar reaction time is observed.

2.3 Development of less acidic conditions

2.3.1 Examining the practicalities of the PNO/citric acid cyclisation

Despite the apparent benefits of the PNO/citric acid cyclisation for 1,2-diols, there remained a number of problems with the oxidative cyclisation. Firstly, attempts to reduce the catalyst loading led to a significant deterioration in the yield of THFs **49** and **51** (Table **2.1**). This was most likely a consequence of the longer reaction times in strongly acidic conditions, which have been shown to cause Os(VI) to disproportionate to Os(IV) and Os(VIII) – the latter also capable of causing dihydroxylation side products.[23]

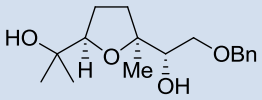
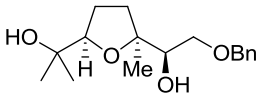
Entry	Product	5.0 mol%	2.5 mol%	1.0 mol%
1	 **49**	83%	79%	74%
2	 **51**	74%	66%	51%

Table 2.1 *Decreasing osmium loading*

Secondly, the reaction remained very strongly acidic, which in turn limited the substrate scope of the oxidative cyclisation. Attempts to reduce the amount of TFA in the cyclisation from 5.0 mL/mmol to 2.5 mL/mmol resulted in the yield of THF **49** falling to 68% (with 5.0 mol% catalyst loading).

With no obvious solution to these problems, a change in strategy was required. The exact role of acid in the cyclisation step is unknown; however, it has been suggested that the protonation of an oxo-ligand on osmium(VI) results in the osmium-centre becoming more electron-deficient, which allows an inverse electron demand (3+2) cycloaddition to take place with a comparatively electron rich-alkene. It was envisaged that in order to make the cyclisation conditions less acidic, a catalytic amount of a Lewis acid could be used in place of a Brønsted acid (Figure **2.2**).

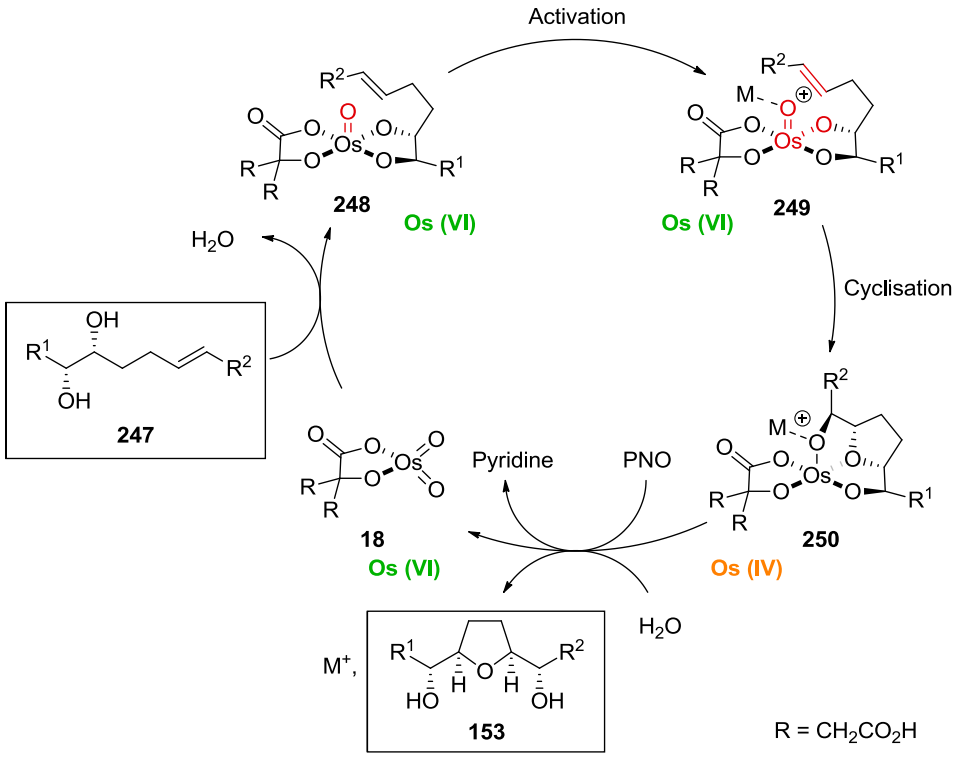
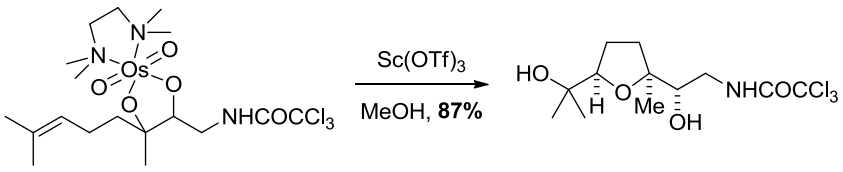


Figure 2.2 *Proposed catalytic cycle*

2.3.2 Previous attempts to incorporate Lewis acids into the cyclisation

Previous attempts by the group to utilise Lewis acids in the osmium-mediated oxidative cyclisation have been met with limited success. The first attempt utilised TMEDA-stabilised osmate ester **34**, which was subjected to an excess of scandium triflate, resulting in the clean formation of THF **35** in high yield (Scheme **2.6**).[35]

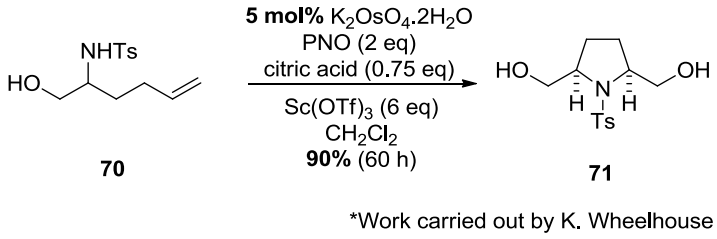


Scheme 2.6 *Stoichiometric Lewis acid cyclisation*

Despite this apparent success, problems arose whilst attempting to render this process catalytic in osmium tetraoxide. It was discovered that the Lewis acid was capable of coordinating to the TMO reoxidant, which stopped the reaction from turning over. This setback was partially

remedied by changing the reoxidant to *tert*-butylhydroperoxide. However, due to the reactive nature of the reoxidant, a large number of side products were observed, limiting the yields of the resultant THFs to around 40%.

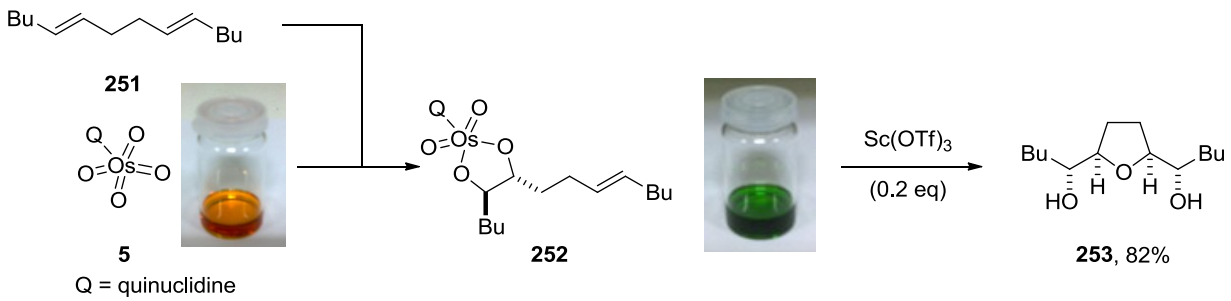
The most recent attempt by the Donohoe group to utilise a Lewis acid in the oxidative cyclisation came in the PNO/citric acid pyrrolidine cyclisation. Upon comparing the pK_a values in water of protonated TMO (4.58)[96] against PNO (0.79)[97], it was proposed that since PNO was significantly less basic than TMO, it would bind less strongly to scandium triflate. Amino alcohol **70** was treated under the milder, non-aqueous conditions, with 6 equivalents of scandium triflate replacing camphorsulfonic acid (CSA) (Scheme **2.7**).[98] After 60 hours pyrrolidine **71** was formed in 90%. This promising result demonstrated that there was scope to further develop a Lewis acid-mediated oxidative cyclisation.



Scheme 2.7 *Catalytic osmium cyclisation with Sc(OTf)$_3$*

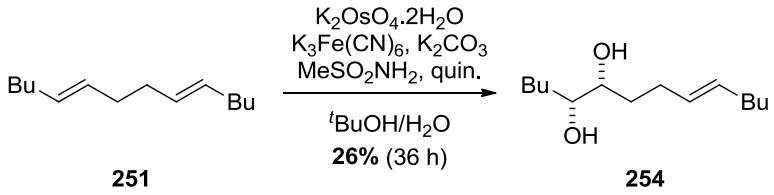
2.3.3 Initial studies using Lewis acids

In order to test the hypothesis that a Lewis acid could be utilised in a catalytic fashion to promote a cyclisation, stoichiometric studies were first conducted. As described in **Chapter 1.1.4**, when osmium tetroxide was treated with one equivalent of quinuclidine, an orange/red Os(VIII) complex was observed. The addition of a stoichiometric amount of diene **251** to this mixture resulted in the formation of Os(VI)–quinuclidine ester **252**, which displayed a characteristic "bottle green" colour. Subjecting this cyclisation intermediate to a catalytic amount of scandium triflate resulted in the complete conversion to THF **253** (Scheme **2.8**).



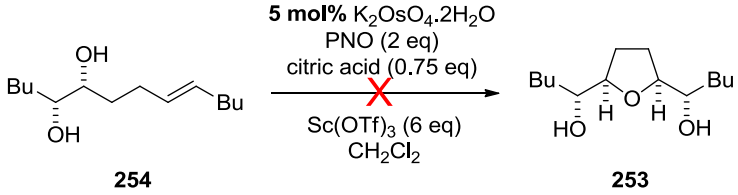
Scheme 2.8 *Stoichiometric osmate-ester cyclisation*

With the aim of building on this initial result, a suitable precursor for the diol cyclisation was synthesised. Diol **254** was formed from the dihydroxylation of diene **251** under racemic conditions (Scheme **2.9**). The formation of this mono-dihydroxylated substrate was confirmed by the appearance of a multiplet of 2H at 3.48-3.38 ppm in the ^{1}H NMR spectrum and subsequent loss of C_2-symmetry.



Scheme 2.9 *Synthesis of model substrate*

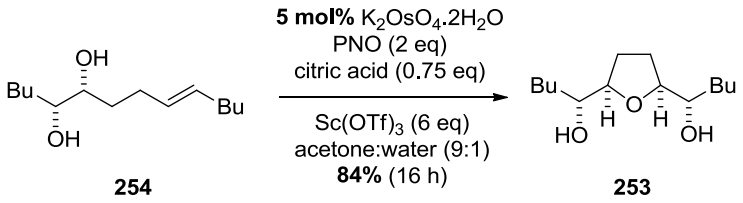
Subjecting diol **254** to both the TMO/TFA and PNO/TFA conditions afforded THF **253** in 72% (20 h) and 78% (16 h) respectively. However, upon exposure of diol **254** to the Lewis acid conditions, shown to promote the cyclisation of amino alcohol **70**, no reaction was observed (Scheme **2.10**).



Scheme 2.10 *Failed Lewis acid cyclisation*

Careful examination of the reaction mixture revealed that both citric acid and potassium osmate were poorly solubilised in dichloromethane. It was therefore reasoned that utilising an aqueous

solvent system, as in the PNO/TFA cyclisation, would overcome these solubility issues. Pleasingly, when utilising an acetone and water system, the cyclisation of **254** to the corresponding THF occurred in 84% (Scheme **2.11**).

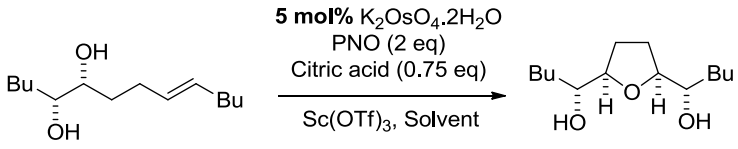


Scheme 2.11 *Aqueous Lewis acid cyclisation*

2.3.4 Optimising the Lewis acid

After this initial success, it was important to reduce the amount of scandium triflate required for the reaction to proceed. Despite being significantly less acidic than the corresponding PNO/TFA system, using an excess of scandium triflate would be undesirable for several reasons. Firstly, utilising a large excess of scandium triflate is likely to have a detrimental effect to acid sensitive functional groups. Secondly, scandium triflate is uneconomical to use in a large excess, costing £35/g with a molecular weight of 502. Furthermore, the Lewis acid cannot be recovered after the reaction, due to the presence of the citric acid and aqueous osmium complexes. In order to make this reaction economically viable and mild enough to tolerate a range of acid sensitive functional groups, it was important to utilise scandium triflate in a catalytic manner.

Unfortunately, attempts to lower the quantities of scandium triflate resulted in the formation of a side product. Although the nature of this product could not be fully identified, its ^{13}C NMR spectrum indicated unexpected peaks at both 107.8 ppm and 27.3 ppm, with the alkene functionality remaining intact. This data is consistent with the formation of an acetonide group, leading to the conclusion that acetone, when combined with a Lewis acid, was an inappropriate solvent for this reaction (Entries 1-3, Table **2.2**).



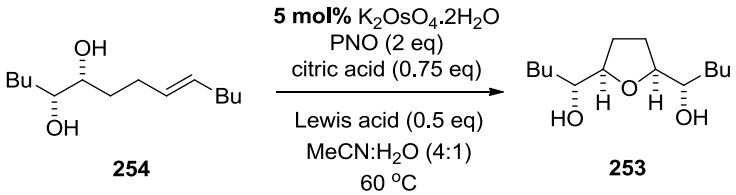
254 **253**

Entry	$Sc(OTf)_3$ (eq)	Solvent	Yield of THF 253
1	6.0	Acetone:H_2O (9:1)	84% (16 h)
2	2.0	Acetone:H_2O (9:1)	62% (40 h)
3	0.2	Acetone:H_2O (9:1)	27% (40 h)
4	0.5	^{t}BuOH:H_2O (4:1)	82% (24 h)
5	0.5	MeCN:H_2O (4:1)	84% (20 h)
6	0.1	^{t}BuOH:H_2O (4:1), 60 °C	78% (36 h)
7	0.1	MeCN:H_2O (4:1), 60 °C	82% (28 h)

Table 2.2 *Solvent and temperature variance*

In order to suppress the formation of this acetonide-based compound, a range of solvents typically used for osmium-mediated transformations were screened. It was discovered that both *tert*-butanol/water and acetonitrile/water offered a reliable alternative, with no side products being detected. Furthermore, when these systems were heated to 60 °C, the amount of scandium triflate could be lowered to 10 mol% without having a detrimental effect on the yield. From this screen it was discovered that acetonitrile/water at 60 °C was the most efficient solvent system, affording THF **253** in 82% yield after 28 hours (Entry 7, Table **2.2**).

The next variable that could be changed was the Lewis acid itself. A range of commercially available metal triflates were examined in the reaction using the new solvent system and their pH in a 0.025 M solution in water was measured (Table **2.3**).



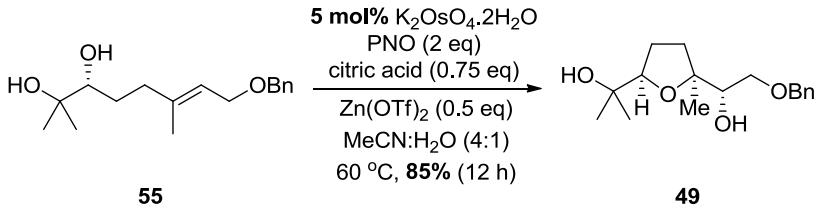
Entry	Lewis acid	pH of Lewis acid in 0.025 M solution H_2O	Yield of THF 253
1	$Ce(OTf)_3$	0	77% (8 h)
2	$Sc(OTf)_3$	1	84% (8 h)
3	$Cu(OTf)_2$	3.5	88% (10 h)
4	$Yb(OTf)_3$	4.5	82% (10 h)
5	$Y(OTf)_3$	5	80% (10 h)
6	$Zn(OTf)_2$	5.5	88% (10 h)

Table 2.3 *Variation of Lewis acid*

It was discovered that in all cases the reaction proceeded to completion, suggesting that the cyclisation was relatively insensitive towards the type of metal triflate used. The Lewis acids which afforded the highest yields in this system were copper triflate and zinc triflate. Both of these metal triflates are significantly cheaper than scandium triflate, with the added attraction that they have a lower molecular weight. At this point, it was decided that zinc triflate should be used in future reactions, on the basis that the reaction mixture had the most mildly acidic pH.

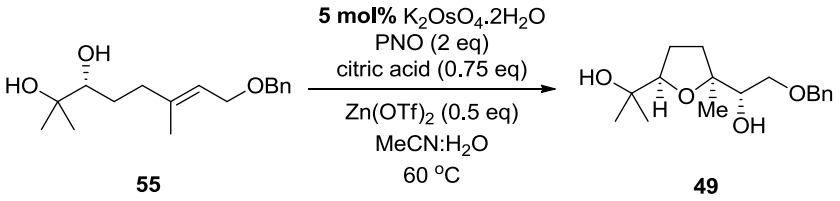
2.3.5 Variation of reagent quantities

With a set of conditions having been developed for a comparatively simple substrate, it was important to test and further optimise the reaction on a more demanding class of substrates. Therefore, geraniol derivative **55** was chosen as a substrate upon which to further probe the reaction. Subjecting diol **55** to the improved conditions, using 50 mol% of $Zn(OTf)_2$, led to the formation of THF **49** in excellent yield (Scheme **2.12**).



Scheme 2.12 *Cyclisation of a more demanding substrate*

Due to the presence of both organic and water soluble components in the reaction, it was necessary to examine the relative ratios of the solvents. A series of experiments were conducted whereby the reagent quantities and the concentration were kept constant, with only the ratios of acetonitrile and water being varied (Table **2.4**). These reactions were quenched with sodium sulfite after 3 hours and the conversion of the reaction measured by integrating the OCH_2Ph peak in the ^{1}H NMR spectrum of the crude material.



Entry	Ratio of MeCN:H_2O	Conversion after 3 h by ^{1}H NMR
1	9:1	31%
2	4:1	33%
3	2:1	86%
4	1:1	84%
5	1:2	83%

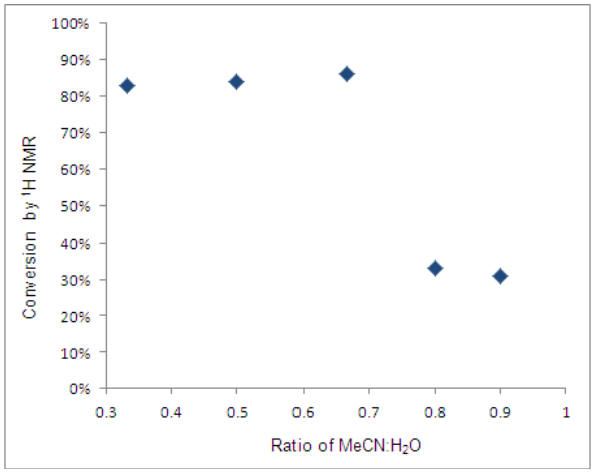
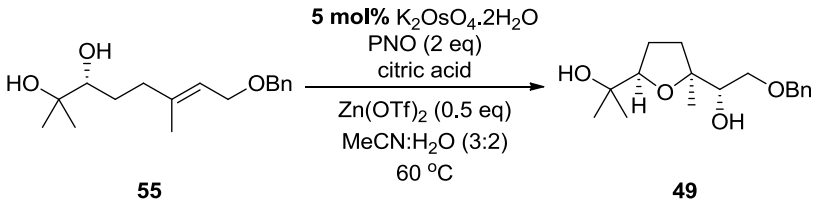


Table 2.4 *Solvent ratio variance*

It was discovered that the optimum ratio of acetonitrile to water was approximately 3:2. Unexpectedly, a significant difference in rate was observed when changing the solvent ratio from 4:1 to 2:1 acetonitrile/water (Entries 2 and 3, Table **2.4**). This can be attributed to the fact

that the reaction became significantly more efficient as the citric acid, zinc triflate and potassium osmate were fully solubilised.

Upon implementing this improved solvent system, attention turned to varying the amount of citric acid used in the cyclisation. Again, whilst keeping the other reagent quantities constant, the reactions were quenched after 3 hours and the conversion measured by integrating the ^{1}H NMR spectrum of the crude material (Table **2.5**).



55 **49**

Entry	Citric acid (eq)	Conversion after 3 h by ^{1}H NMR
1	0.00	0%
2	0.25	23%
3	0.50	57%
4	0.75	86%
5	1.0	88%
6	1.5	89%
7	2.0	91%

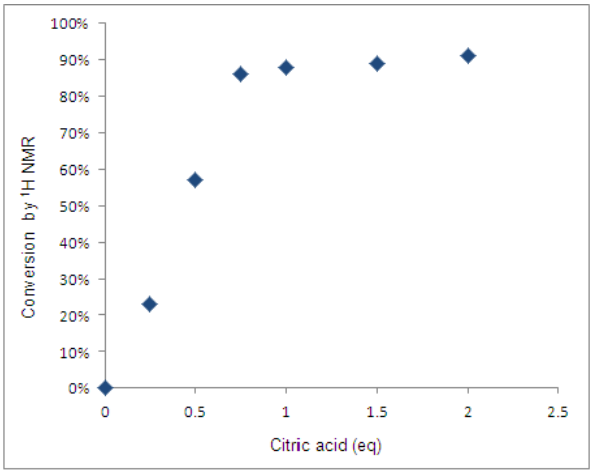
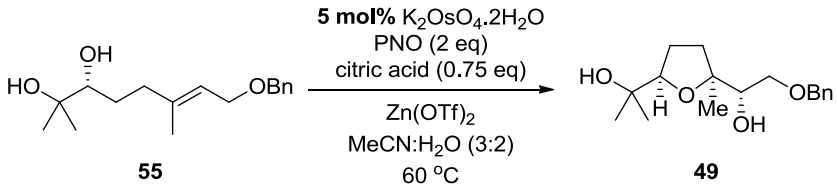


Table 2.5 *Citric acid variance*

As is evident from Table **2.5**, the rate of the cyclisation increases as more citric acid is added. However, it is clear that there is little advantage to using more than 0.75 equivalents, given that the increase in rate after this point is negligible and keeping the reaction conditions as mildly acidic as possible is of greater importance. Interestingly, under these conditions, no appreciable cyclisation was observed when citric acid was removed from the reaction, demonstrating that citric acid plays a pivotal role in the cyclisation.

Finally, the amount of zinc triflate was varied from 0 eq through to 1.5 eq (Table **2.6**). These reactions were again quenched after 3 hours and the conversion measured by integrating the ^{1}H NMR spectrum of the crude material.



55 **49**

Entry	Zinc triflate (eq)	Conversion after 3 h by ^{1}H NMR
1	0.00	52%
2	0.25	70%
3	0.50	86%
4	1.0	67%
5	1.5	65%

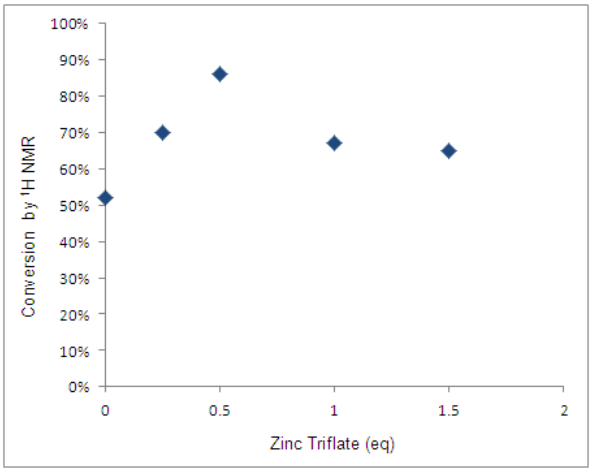
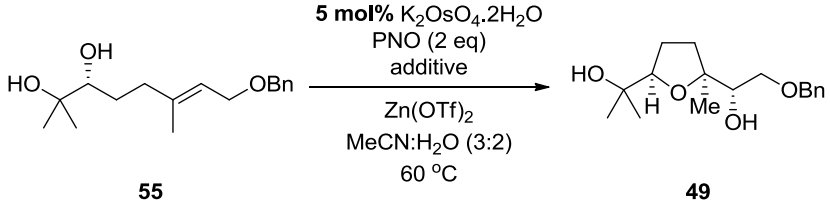


Table 2.6 *Zinc triflate variance*

The optimum amount of zinc triflate was 0.5 eq. This set of data also revealed two unexpected results. Firstly, at 60 °C in the absence of a Lewis acid, the reaction still proceeded to a significant extent (Entry 1, Table **2.6**). This confirms the result in Table **2.5** that citric acid plays a vital role in the cyclisation. The second unusual result was that using an excess of zinc triflate led to a reduction in the rate of reaction, unlike in the case of scandium triflate (Entries 4 and 5, Table **2.6**). This observation could originate from the Zn(II) cation chelating to the citric acid, which in turn inhibits the citric acid from chelating to the osmium. This effect is not replicated with scandium triflate, possibly owing to the fact that it is water stable and no Sc(III) is liberated.[99]

2.4 Investigating the role of citric acid

It was unclear exactly what role citric acid plays in the cyclisation. It is known that citrate chelates to the osmium species, fixing osmium into a second catalytic cycle,[23] but it is not clear if this chelation affects the (3 + 2) inverse electron demand cycloaddition at higher temperatures, or whether it simply acts as a Brønsted acid by protonating an oxo-ligand of the osmium species (see Figure **2.2**). It was proposed that if the rate enhancing effect of citric acid was purely a pH effect, then replacing 0.75 eq of citric acid (pK_a = 3.09, 4.75, 6.41)[100] with 2.25 eq of acetic acid (pK_a = 4.76)[101] would achieve a comparable pH, and therefore a similar rate of reaction. Similarly, if the main mode of action of citric acid was to ligate to osmium through an α-hydroxy-carboxylic acid chelate, then replacing citric acid with 0.75 eq of glycolic acid (pK_a = 3.83)[102] and 1.50 eq acetic acid would maintain a similar pH, whilst having an α-hydroxy-carboxylic acid group present to chelate to osmium. In order to test these scenarios, three cyclisation reactions were conducted on diol **55** using the different additives as described above (Table **2.7**).



55 **49**

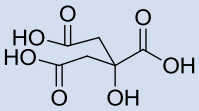
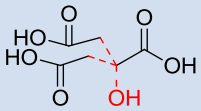
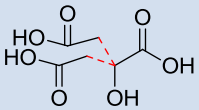
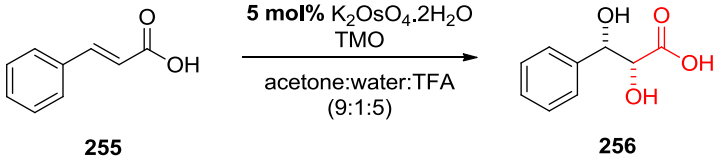
Entry	Additive	Reaction time	Entry	Additive	Reaction time
1	 0.75 eq citric acid	3.5 h	**3**	 2.25 eq AcOH	96 h
2	 0.75 eq glycolic acid + 1.50 eq AcOH	8.0 h			

Table 2.7 *Varying additive source (Reaction time = time taken for consumption of **55**)*

Interestingly, the results would suggest that the rate enhancing effect of citric acid is almost completely due to the α-hydroxy-carboxylic acid effect. In the instance that only acetic acid is present, a slow reaction is observed, suggesting that the pH has a minimal effect on the cyclisation. Conversely, glycolic acid showed a reaction rate comparable to that of citric acid, demonstrating that an α-hydroxy-carboxylic acid group is necessary for the reaction to proceed at a higher rate. This result also explains why *trans*-cinnamic acid acted as a more efficient sacrificial alkene compared with isoprene – the by-product formed from the dihydroxylation of *trans*-cinnamic acid in the TMO/TCA cyclisation bears an α-hydroxy-carboxylic acid, which is able to assist the rate of reaction (Scheme **2.12**).



Scheme 2.12 *Dihydroxylation of trans-cinnamic acid*

It is predicted that the difference in rate observed between citric acid and glycolic acid is due to the tethered carboxylic acid groups, which Sharpless and co-workers suggest are responsible for aiding the hydrolysis of the osmate ester, potentially *via* neighbouring group participation into the open coordination site of the square-pyramidal osmium complex (Figure **2.3**).[23]

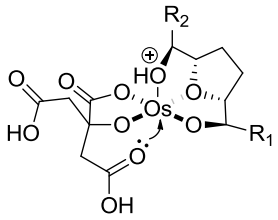
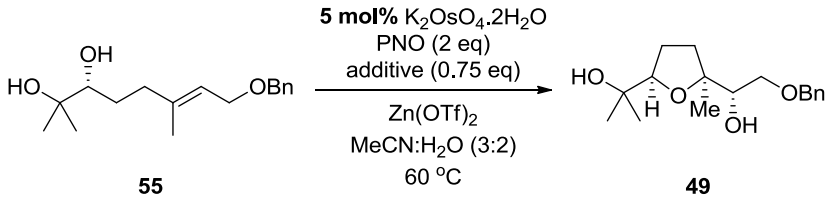


Figure 2.3 *Neighbouring group participation of carboxylic acid groups*

With this result in mind, a range of α-hydroxy-carboxylic acid derivatives were examined. Using 0.75 eq of an additive under the normal cyclisation conditions, reactions were stopped after 3.5 hours, and the conversion measured by integrating the ^{1}H NMR spectrum of the crude material (Table **2.8**).



55 **49**

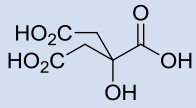
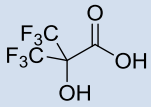
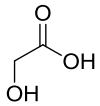
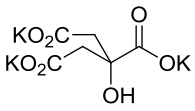
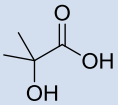
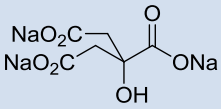
Entry	Additive	Conversion (3.5 h)	Entry	Additive	Conversion (3.5 h)
1	 **257**	100%	**4**	 **260**	75%
2	 **258**	56%	**5**	 **261**	48%
3	 **259**	63%	**6**	 **262**	31%

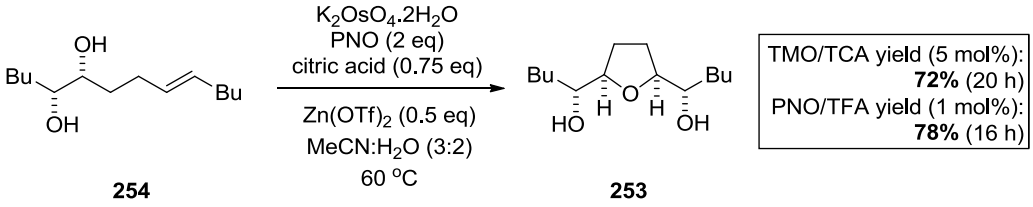
Table 2.8 *α-Hydroxy-carboxylic acids in the cyclisation*

As expected, utilising 2,2-dimethyl-2-hydroxyacetic acid **259** in the reaction instead of citric acid led to a higher rate of reaction than glycolic acid, presumably due to the Thorpe-Ingold (*gem*-dimethyl) effect.[103] A further modification was to fluorinate the methyl groups as in α-hydroxy-carboxylic acid **260**. In this case, the pK_a of the alcohol group was modified, probably making the substrate more likely to form a chelate. This change might also affect the electronics of the (3 + 2) cycloaddition favourably, by withdrawing electron density away from the osmium centre. The result of this change was a further increase in the rate of conversion, compared to both glycolic acid and 2,2-dimethyl-2-hydroxyacetic acid. However, none of these modifications were as efficient as using citric acid. Also of interest is the fact that both potassium citrate **261** and sodium citrate **262** facilitated the cyclisation to a reasonable extent. In the case of potassium citrate, the initial pH of the reaction mixture was measured to be ~pH 8. However, further studies showed that this reaction did not proceed to completion.

2.5 Comparison of the Lewis acid cyclisation to previous cyclisations

2.5.1 Examining the catalyst loading

With an optimised set of cyclisation conditions having been developed, attention turned to the possibility of reducing the catalyst loading of potassium osmate. Therefore, diol **254** was subjected to the optimised Lewis acid conditions, using a range of catalyst loadings (Table **2.9**).



Entry	1	2	3
$K_2OsO_4.2H_2O$ (mol %)	5.0	1.0	0.2
Yield of 253 (time)	89% (2 h)	92% (6 h)	90% (72 h)

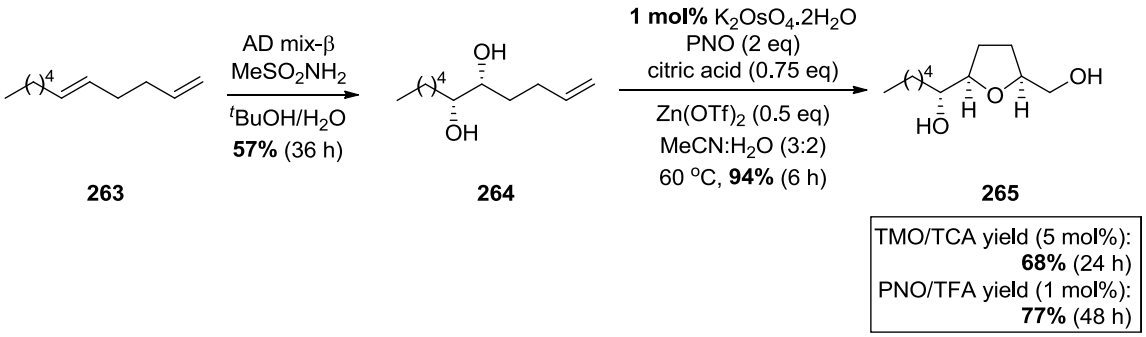
Table 2.9 *Examining catalyst loading*

Firstly, when using 5.0 mol% of the potassium osmate catalyst, it was confirmed that not only is the yield significantly higher than that observed in the analogous TFA cyclisation, but the reaction time is almost an order of magnitude shorter (Entry 1, Table **2.9**). Furthermore, upon reducing the catalyst loading to 1.0 mol%, it was evident that the yield remains high, with the reaction proceeding to completion in 6 hours. Finally, reducing the catalyst loading to 0.2 mol% led to the cyclisation reaching completion in 72 hours. It is likely that this successful reduction in catalyst loading is due to the significantly less acidic reaction conditions, which result in Os(VI) being less susceptible to disproportionation to Os(IV) and Os(VIII).

2.5.2 Substrate scope

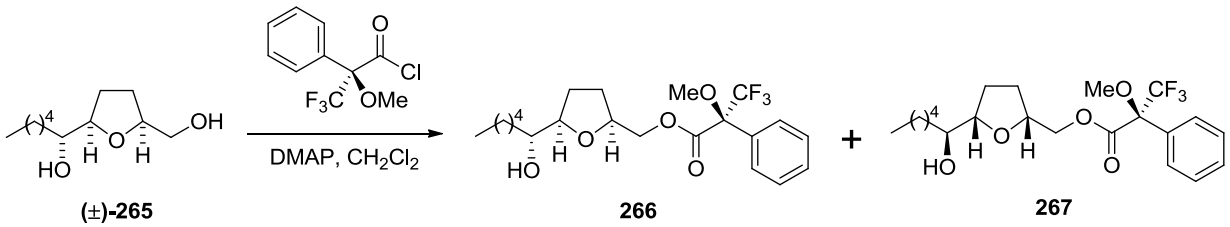
At this stage, it was important to apply these conditions to a wide range of substrates in order to demonstrate the efficiency and generality of the reaction. Diol **264** was formed from the selective Sharpless dihydroxylation of the *trans*-alkene of diene **263** in the presence of the

terminal alkene. This result was confirmed in the ^{1}H NMR spectrum analysis by the appearance of 2H at 3.49-3.39 ppm, with the distinctive ABX alkene peaks remaining intact. The cyclisation onto a terminal alkene was attempted under both the PNO/TFA conditions and Lewis acid conditions, with a catalyst loading of 1.0 mol% (Scheme **2.13**).



Scheme 2.13 *Cyclisation onto terminal alkenes*

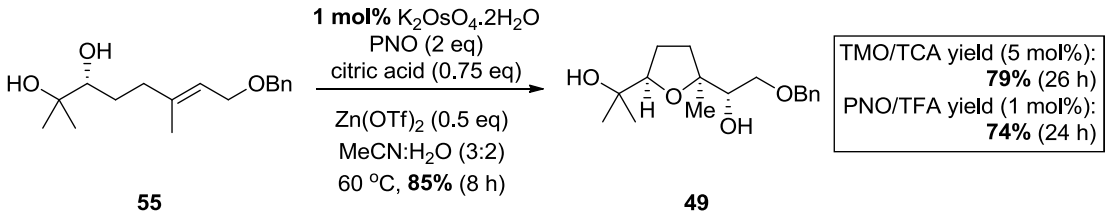
Under the previous conditions the reaction proceeded with a 77% yield in 48 hours. However, when using the Lewis acid conditions the yield was elevated to 94%, with the reaction reaching completion in 6 hours. Coupled with the high yield and fast reaction time, it was important to demonstrate that the Lewis acid cyclisation conditions led to no erosion in stereochemistry. Therefore, racemic THF **265** was prepared *via* the diene cyclisation of **263** and both THFs were derivatised to the (*S*)-Mosher's ester (Scheme **2.14**).



Scheme 2.14 *Derivatisation of THF **265***

Analysis of the ^{19}F NMR spectrum of the Mosher's ester derived from racemic **265** showed peaks of equal integration at –71.4 ppm and –71.6 ppm corresponding to both **266** and **267**. Examining the ^{19}F NMR spectrum of the Mosher's ester derived from the enantioenriched route to THF **265** revealed a dramatic reduction of the peak at –71.56 ppm, affording a calculated enantiomeric excess of 99% (See **Appendix 1**).

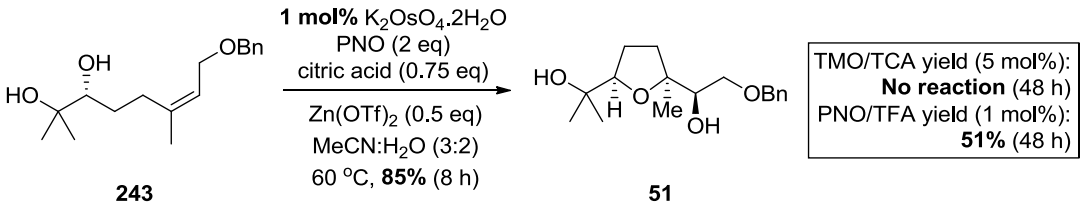
Next, geraniol derivative **55** was treated under Lewis acid conditions with a lower catalyst loading (Scheme **2.15**).



Scheme 2.15 *Cyclisation of geraniol derivative under optimised conditions*

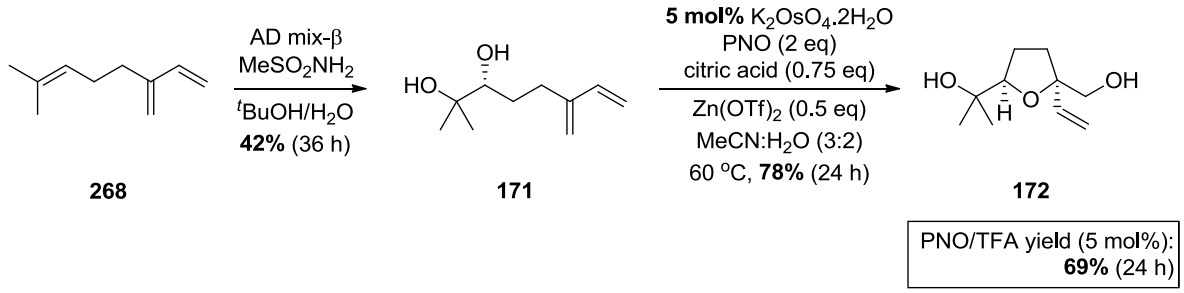
When comparing the Lewis acid cyclisation using 1.0 mol% catalyst loading, to the earlier cyclisation of **55** under PNO/TFA conditions, it is evident that the cyclisation proceeds effectively with reduced amounts of potassium osmate catalyst. Furthermore, the reaction proceeds to completion in 8 hours under these conditions, which is the same result as when using 5 times the amount of potassium osmate in the corresponding PNO/TFA cyclisation. Racemic **49** was synthesised from the corresponding diene using the TMO/TFA diene cyclisation. HPLC analysis of the UV active enantioenriched THF **49** using a Chiralpak AD column showed an enantiomeric excess of 96.5%, when compared to racemic **49**, suggesting that no erosion of stereochemistry occurred under the Lewis acid conditions (See **Appendix 1**).

This work was repeated on nerol analogue **243**, which again showed a significant level of improvement over the PNO/TFA conditions (Scheme **2.16**). Chiral HPLC analysis of **51** measured against a racemic standard revealed an enantiomeric excess of 96.7% (See **Appendix 1**).



Scheme 2.16 *Cyclisation of nerol derivative under optimised conditions*

One example which did not cyclise under the original TMO/TFA conditions was myrcene diene **268**. Pleasingly, treatment of diol **171** with both the PNO/TFA and Lewis acid conditions afforded THF **172**, using a catalyst loading of 5.0 mol% (Scheme **2.17**). Formation of the desired THF was evident by the disappearance of the C=CH_2 peak at 5.07-5.04 ppm in the ^{1}H NMR spectrum, with the appearance of two doublets at 3.59 and 3.49 ppm corresponding to the CH_2OH protons. In this case, attempts to reduce the catalyst loading were unsuccessful, as diol **171** was susceptible to polymerisation over the timescale of the reaction.



Scheme 2.17 *Cyclisation of myrcene derivative*

Despite the reaction proceeding at a similar rate under both sets of conditions, it was evident that the yield of **172** under the Lewis acid cyclisation was superior to the previous best conditions. As THF **172** had not been previously synthesised, it was necessary to prove that the *cis*-THF had been formed. Subsequent NOE studies demonstrated a positive correlation between the THF-C*H* at 3.84 ppm and the C*H*=CH_2 at 5.80 ppm, confirming the formation of the *cis*-THF (Figure **2.4**).

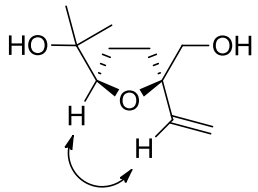
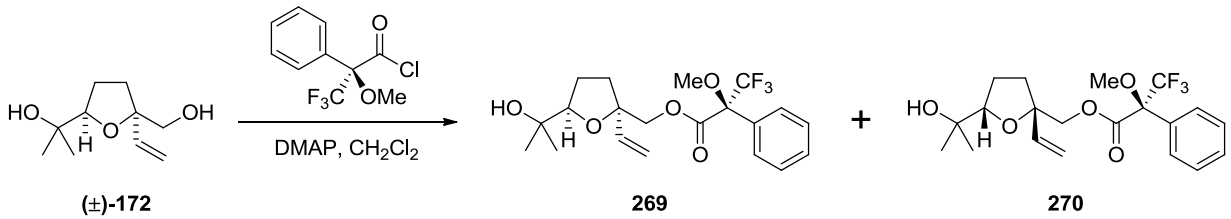


Figure 2.4 *NOE of THF **172***

Racemic **172** was synthesised by subjecting triene **268** to a Sharpless dihydroxylation, with quinuclidine replacing the chiral ligand, followed by cyclisation under the Lewis acidic

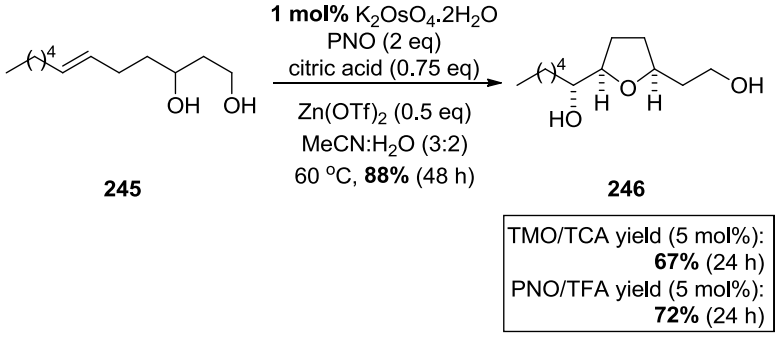
conditions. Both racemic and enantioenriched **172** were derivatised to the (*S*)-Mosher's esters (Scheme **2.18**).



Scheme 2.18 *Derivatisation of THF **172***

The ^{19}F NMR spectrum of the derivatised products showed peaks of equal integration at –71.28 ppm and –71.46 ppm corresponding to both diastereomers **269** and **270**. Upon examining the ^{19}F NMR spectrum of the derivatised THF formed from enantioenriched starting materials, it was clear that only one major peak existed at –71.28 ppm, exhibiting an enantiomeric excess of 96% (see **Appendix 1**). This was further evidence that high enantiomeric excesses were maintained throughout the Lewis acid cyclisation.

Finally, the Lewis acid conditions were extended to the cyclisation of 1,3-diol **245** (Scheme **2.19**).



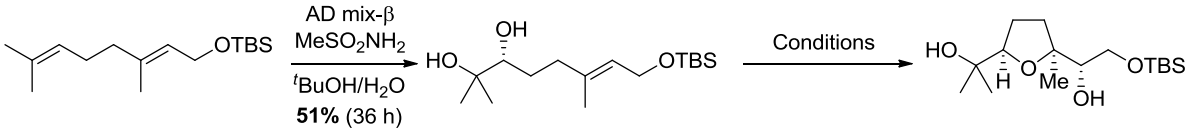
Scheme 2.19 *Cyclisation of 1,3-diol*

Previously, treatment of **245** under the PNO/TFA conditions using 5.0 mol% potassium osmate led to the cyclisation proceeding in 24 hours. Attempts to reduce the catalyst loading to 1.0 mol% resulted in the reaction failing to reach completion. Upon utilising the Lewis acid

cyclisation conditions on 1,3-diol **245**, the loading could be successfully reduced to 1.0 mol%, affording THF **246** in a high yield of 88%.

2.6 The development of buffered conditions

The ultimate aim of the Lewis acid cyclisation was to create a general reaction that would tolerate a wide range of functional groups, which would consequently make the reaction a valuable tool for the synthesis of complex molecules. As the Lewis acid conditions had been shown to be effective on acid-stable substrates, attentions were turned to making the reaction compatible with substrates that possess acid-labile protecting groups. Geraniol derivatives were chosen as substrates, due to their ease of accessibility and the presence of a hydroxyl group, which could be protected with various acid sensitive protecting groups. Firstly, the primary alcohol of geraniol was protected with a *tert*-butyldimethylsilyl group, followed by a selective dihydroxylation of the more electron-rich alkene to afford diol **272** (Table **2.10**). This substrate was then subjected to a range of conditions, using the triflates of both copper and zinc.



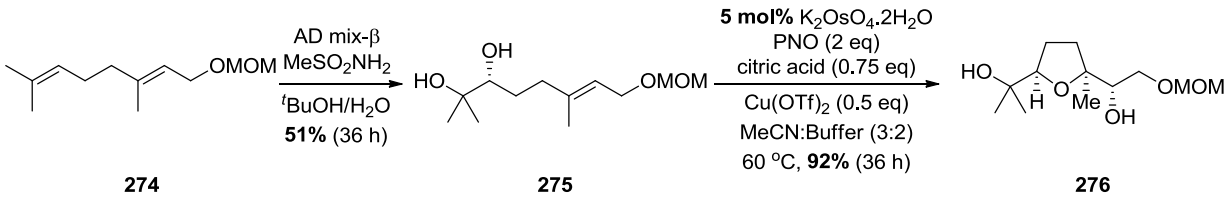
271 **272** **273**

Entry	Conditions	Yield of 275	Time
1	5 mol% $K_2OsO_4.2H_2O$, PNO, citric acid, $Zn(OTf)_2$, MeCN:H_2O (3:2), 60 °C	42%	9 h
2	5 mol% $K_2OsO_4.2H_2O$, PNO, citric acid, $Cu(OTf)_2$, MeCN:H_2O (3:2), 60 °C	51%	8 h
3	5 mol% $K_2OsO_4.2H_2O$, PNO, citric acid, $Zn(OTf)_2$, MeCN:pH 6.5 buffer (3:2), 60 °C	63%	48 h
4	5 mol% $K_2OsO_4.2H_2O$, PNO, citric acid, $Cu(OTf)_2$, MeCN:pH 6.5 buffer (3:2), 60 °C	67%	36 h

Table 2.10 *TBS protected geraniol*

It was discovered that utilising copper triflate in this reaction led to higher yields, despite the reaction having a lower pH. It was also discovered that the reactions proceeded in higher yields when a 0.67 M pH 6.5 phosphate buffer was used instead of water.[104] Unfortunately, the presence of the buffer led to a deceleration in the rate of reaction. This is presumably as a result of the pH of the reaction being higher, combined with the key reagents such as citric acid and potassium osmate being less soluble in the buffer. Furthermore, under these conditions the reaction mixture becomes biphasic. For a combination of these reasons, the catalyst loading could not be effectively reduced from 5 mol% for the buffered oxidative cyclisation.

The synthesis of MOM-protected diol **275** was completed by subjecting methoxymethyl ether **274** to the Sharpless dihydroxylation conditions (Scheme **2.20**).

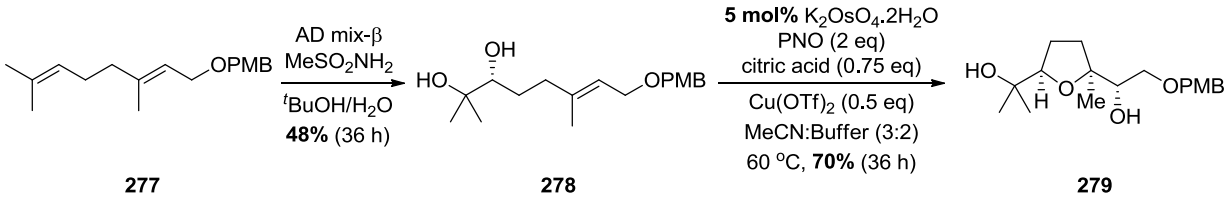


274 **275** **276**

Scheme 2.20 *MOM-protected geraniol*

Upon utilising the same buffered conditions that were applied to TBS protected **272** (see Entry 4, Table **2.10**), the oxidative cyclisation proceeded in excellent yield in 36 hours.

Finally the analogous *para*-methoxybenzyl protected diol **278**, which was synthesised in a similar fashion from geraniol, was subjected to the buffered cyclisation conditions (Scheme **2.21**).



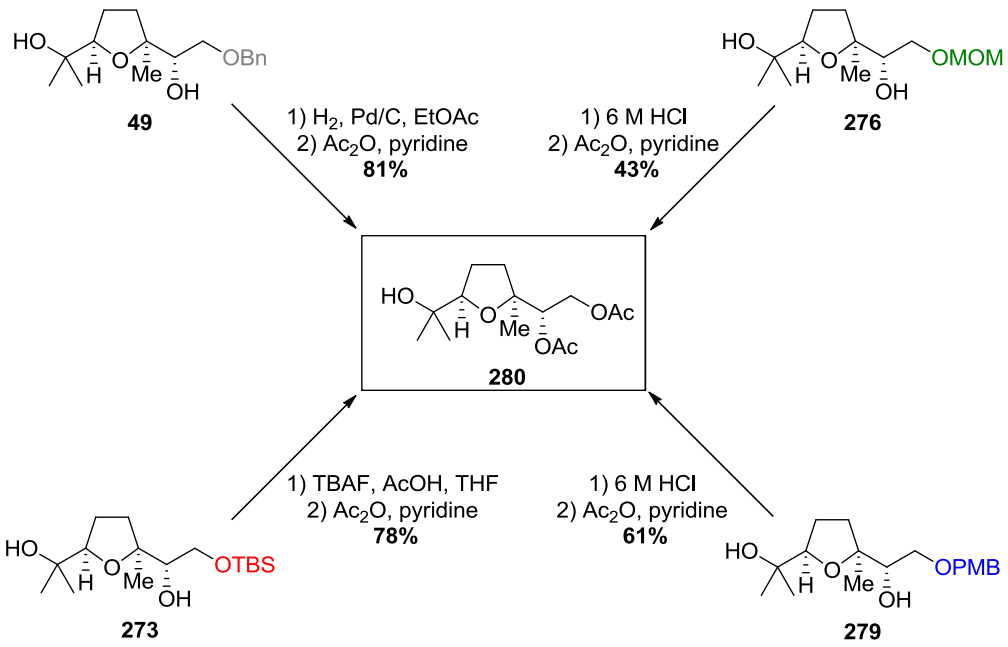
277 **278** **279**

Scheme 2.21 *PMB protected geraniol*

Pleasingly, THF **279** was formed in good yield in 36 hours. These results further demonstrate the versatility of the buffered oxidative cyclisation reaction. Conversely, subjecting diols **272**,

275 and **278** to the PNO/TFA cyclisation conditions led to complete deprotection within 1 hour in all cases.

It was important to correlate novel THFs **273**, **276** and **279** to a known THF compound. Since benzyl-THF **49** had previously been fully characterised, attempts were made to manipulate **49** and the three novel THFs towards a common intermediate. Hydrogenation of **49** with palladium on carbon, followed by acetylating the crude product led to the formation of THF **280** (Scheme **2.22**).

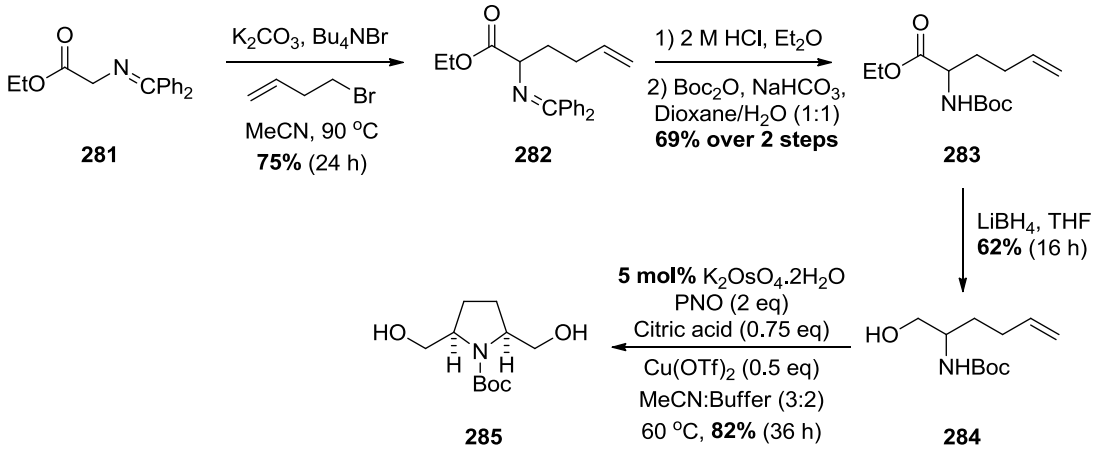


Scheme 2.22 *Correlation of products*

Subjecting **273**, **276** and **279** to appropriate deprotection conditions, followed by subsequent acetylation, all afforded THF **280**. The spectroscopic data in each of the three cases matched that of compound **280** when formed from benzyl-THF **49**, confirming that the buffered Lewis acid conditions are completely selective for *cis*-THF formation with *syn* addition across the tethered alkene.

At this point, it was intriguing to see if the buffered Lewis acid conditions could be extended to the oxidative cyclisation of Boc-protected amino alcohols. Amino alcohol **284** could be readily

accessed in 4 steps from the commercially available *N*-(diphenylmethylene)glycine ethyl ester (Scheme **2.23**).



Scheme 2.23 *Boc protected pyrrolidine cyclisation*

Initial formation of the enolate of **281** was followed by an S_N2 reaction on 4-bromobut-1-ene, which afforded α-amino ester **282** in good yield. Hydrolysis of the diphenyl-imine protecting group, followed by Boc protection of the primary amine resulted in the formation of amino ester **283**. Subsequent ester reduction was achieved using lithium borohydride, which provided cyclisation precursor **284**. Pleasingly, upon subjecting amino alcohol **284** to the buffered Lewis acid cyclisation conditions, pyrrolidine **285** was formed in 82% in 32 hours. As well as expanding the scope of the Lewis acid cyclisation to amino alcohols, this result provided confirmation that the buffered oxidative cyclisation could have a significant impact in natural product synthesis.

2.7 Conclusion

Replacing trifluoroacetic acid with a catalytic amount of a Lewis acid has provided a powerful set of conditions that maximise the potential of the osmium-mediated oxidative cyclisation. In general, reaction times are significantly shorter, yields are higher and catalyst loadings can be dramatically reduced. When these Lewis acid conditions are used in combination with a phosphate buffer, it is possible to cyclise a wide range of substrates with acid labile protecting

groups which would have been unstable to previous conditions. These groups include methoxymethyl ether (MOM), *para*-methoxybenzyl (PMB) and *tert*-butyldimethyl silyl (TBS) protected primary alcohols, and *tert*-butoxy carbonyl (Boc) protected amines.

Chapter 3

A Novel Oxidative Cyclisation on to Vinyl Silanes

3.1 Applications to vinyl silanes

3.1.1 Introduction and previous work

After the development of the Lewis acid-mediated oxidative cyclisation (*vide supra* **Chapter 2.3**), work began on applying these conditions to systems that would not have been tolerated in the previous cyclisation reaction. Attentions turned to the possibility of performing the cyclisation on substrates bearing heteroatom-substituted pendent alkenes. It was reasoned that if this type of cyclisation was successful, then the resulting THFs could be further functionalised. This could expand the scope of the oxidative cyclisation beyond the formation of THFs.

Silanes have been well documented in the literature as functional groups that can act as precursors to hydroxyl groups.[105] Upon being subjected to Fleming-Tamao type conditions, silanes can be oxidised, effectively inserting an oxygen atom into the C–Si bond. As discussed earlier (*vide supra* **Chapter 1.1.4**), one of the key components of the osmium-catalysed oxidative cyclisation is the inverse electron demand (3+2) cycloaddition between the electron-poor osmate ester and the pendent alkene. Consequently, it was predicted that vinyl silanes, despite an increase in steric bulk, would provide sufficiently electron-rich π-bonds to enable a successful oxidative cyclisation. It was hoped that, should this type of methodology be developed, it would have applications to the synthesis of lactols in complex systems. One example where this methodology could be utilised would be in the formation of the D-ring of pectenotoxin-4 (Figure **3.1**).

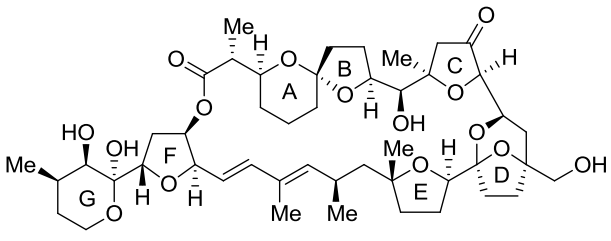
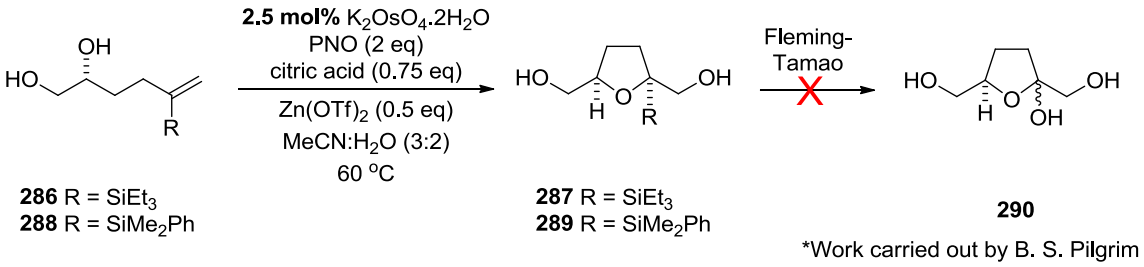


Figure 3.1 *Pectenotoxin-4*

The initial work in this area was the result of a Part II project carried out by B. S. Pilgrim (Scheme **3.1**).[106]

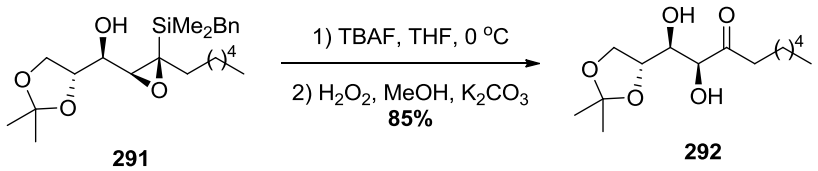


Scheme 3.1 *Previous silane cyclisations*

A range of 1,2-diols with various pendent vinyl silanes would undergo the oxidative cyclisation. Analysis of the resulting silyl-substituted THFs by NOE enhancements and single crystal X-ray diffraction demonstrated that the products formed were consistent with the mechanism of previous cyclisations, giving a *cis*-relationship between the two CH_2OH groups. Unfortunately, subsequent attempts to oxidise the resulting phenyldimethylsilyl group using Fleming-Tamao conditions were unsuccessful, leading predominantly to decomposition of the starting material. Despite this setback, the project demonstrated the ability of the Lewis acid cyclisation conditions to cyclise novel acid-sensitive substrates.

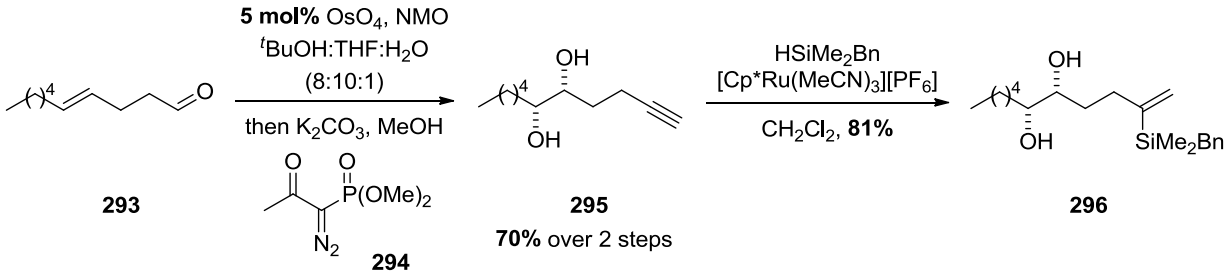
3.1.2 Incorporating the benzyldimethylsilyl group

It was decided to re-examine this work, replacing the phenyldimethylsilyl substituted alkene with a vinyl benzyldimethylsilyl group. Trost and co-workers have shown this group to be more labile than the corresponding phenyldimethylsilyl and have demonstrated that under relatively mild conditions the benzyldimethylsilyl portion can be easily oxidised in good yields (Scheme **3.2**).[107]



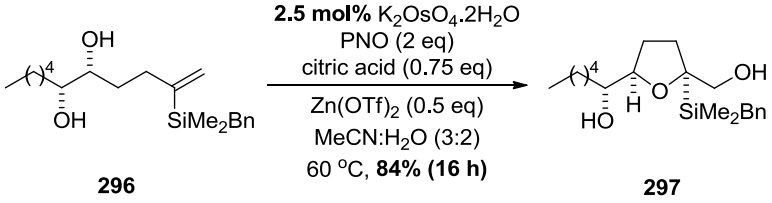
Scheme 3.2 *Trost oxidation of benzyldimethylsilyl group*

Starting from the commercially available *trans*-4-decenal, alkyne **295** was synthesised in two steps by utilising an Upjohn dihydroxylation followed by a Seyferth-Gilbert homologation (using the Bestmann-Ohira modification) (Scheme **3.3**). Subjecting alkyne **295** to hydrosilylation conditions, also developed by Trost and co-workers, led smoothly to vinyl silane **296**, with only the 1,1-disubstituted alkene detected in the ^{1}H NMR spectrum.[108]



Scheme 3.3 *Synthesis of vinyl benzyldimethylsilane **296***

After just 3 linear steps, vinyl silane **296** was ready to be subjected to the cyclisation conditions. Using 2.5 mol% of potassium osmate, THF **297** was furnished in 84% in 16 hours (Scheme **3.4**).



Scheme 3.4 *Cyclisation of vinyl benzyldimethylsilane*

In general, cyclisations onto vinyl silanes tended to be slower than the analogous cyclisations onto unsubstituted terminal alkenes. Whilst it is clear that vinyl silanes are more electron-rich, it is likely that an increase in strain is experienced during the key inverse electron demand (3+2) cycloaddition. The *cis*-relationship of the THF-C*H* and the methylsilyl protons in THF **297** was confirmed by NOE enhancements (Figure **3.2**).

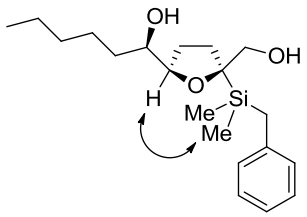
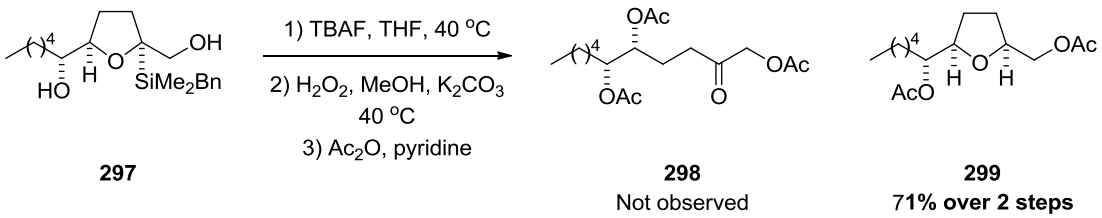


Figure 3.2 *NOE of THF **297***

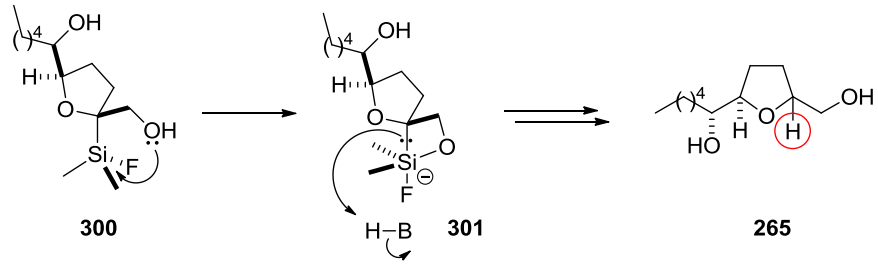
3.1.3 Oxidation of the benzyldimethylsilyl group

After the initial success of forming THF **297** in excellent yield, attention turned to oxidising the benzyldimethylsilyl group. Unfortunately, attempts to oxidise **297** with Tamao-Kumada conditions led to protodesilylation as the only observed product (Scheme **3.5**).



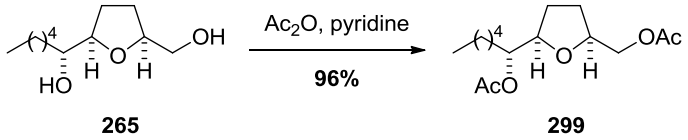
Scheme 3.5 *Unexpected protodesilylation*

Despite this outcome, the fact that the silyl group had been removed under these conditions was a promising result. Analysis of the reaction by TLC suggested that the competing protodesilylation was occurring in the first stage of the reaction, before any oxidant was added to the reaction mixture. Subsequently, it was rationalised that this protodesilylation took place *via* participation of the α-hydroxyl group with the intermediate silyl fluoride (Scheme **3.6**).



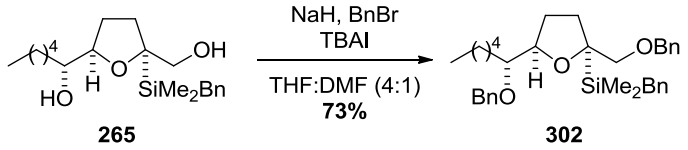
Scheme 3.6 *Hydrosilylation pathway*

In order to ascertain whether the protodesilylation proceeded with retention or inversion of configuration, THF **265** was synthesised from the corresponding alkene (*vide supra* **Chapter 2.5.2**). Although previous literature precedent shows that in most cases protodesilylation occurs with retention of stereochemistry,[105] should inversion occur under these conditions, this method could be utilised as a potential route to form *trans*-THFs. Subjecting *cis*-THF **265** to an acetylation reaction afforded **299** in excellent yield (Scheme **3.7**). The resulting diacetate exhibited identical spectroscopic properties to the protodesilylated product **299**, proving unambiguously that under these conditions, protodesilylation occurred with retention of configuration.



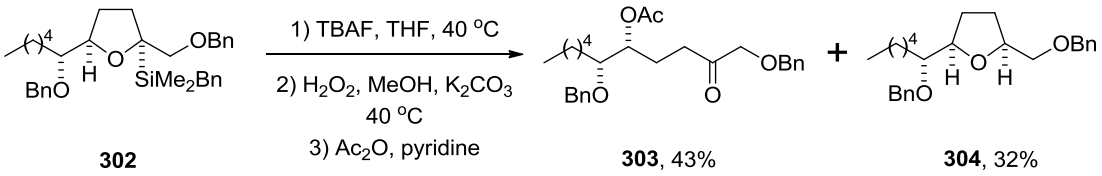
Scheme 3.7 *Acetylation of known THF **265***

Protecting the free hydroxyl groups of THF **265** should suppress protodesilylation occurring *via* this pathway. It was rationalised that utilising benzyl protecting groups in this instance would be beneficial, as this group would be stable to a range of oxidative conditions. Double benzyl protection of **265** was achieved, affording oxidation precursor **302** in good yield (Scheme **3.8**).



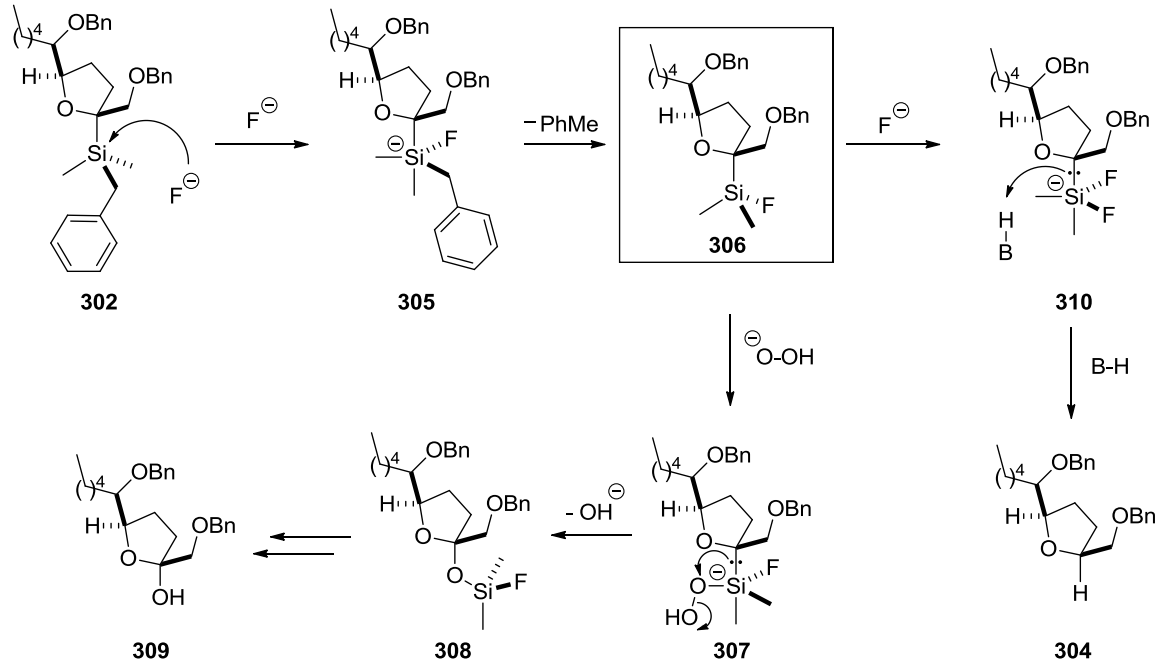
Scheme 3.8 *Benzyl protection of THF **265***

Upon subjecting **302** to the same conditions that led to the complete protodesilylation of **265**, a mixture of oxidised and protodesilylated products were observed (Scheme **3.9**).



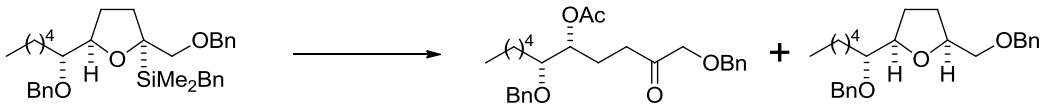
Scheme 3.9 *Attempted Fleming-Tamao oxidation*

Despite occurring at a significantly slower rate, it was clear that even when the α-hydroxyl group was protected protodesilylation was still a significantly competitive pathway. In order to understand the origin of this competing pathway, it was necessary to examine the likely mechanism of the oxidative desilylation proposed by Trost (Scheme **3.10**).[109]



Scheme 3.10 *Competing pathways*

Initial activation of the benzyldimethylsilyl group proceeds *via* the loss of toluene, forming intermediate silyl fluoride **306**.[109] In the case that a high fluoride concentration is used, a coordinatively saturated silicon difluoride **310** is formed. Since this difluoride cannot be oxidised, protodesilylation occurs. In order to suppress this pathway, a range of different oxidative conditions were carried out on **302**. In all cases the crude products were acetylated providing the open chain isomer as a single product (Table **3.1**).



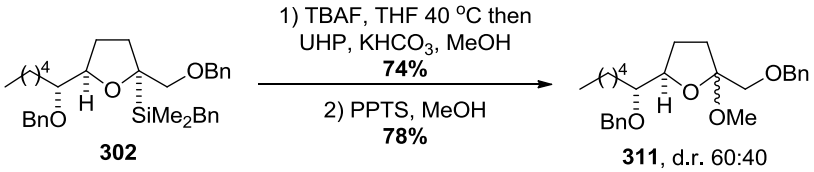
302 **303** **304**

Entry	Reagents and Conditions	Product distribution
1	1) TBAF, THF, 40 °C, 30 min, then H_2O_2, MeOH, $KHCO_3$, 40 °C, 1 hr 2) Ac_2O, pyridine	**303** – 43% **304** – 32%
2	1) TBAF, THF, 0 °C, 2 hr, then UHP, MeOH, $KHCO_3$, 0 °C, 16 hr 2) Ac_2O, pyridine	No reaction
3	1) TBAF, THF, 40 °C, 30 min, then UHP, MeOH, $KHCO_3$, 40 °C, 1 hr 2) Ac_2O, pyridine	**303** – 64% **304** – 24%
4	1) TBAF (slow add^n), THF, 40 °C, then UHP, MeOH, $KHCO_3$, 40 °C, 1 hr 2) Ac_2O, pyridine	**303** – 73% **304** – 15%

Table 3.1 *Optimisation of the oxidative desilylation*

Employing the conditions used by Trost and co-workers led to no reaction (Entry 2, Table **3.1**). Presumably, these conditions are not forcing enough to form the intermediate silicon fluoride in this system. Heating the reaction to 40 °C and using urea-hydrogen peroxide (UHP) as an anhydrous source of hydrogen peroxide resulted in an increase in the yield of **303**. Furthermore, under these conditions the amount of protodesilylated THF formed was also reduced. Optimum conditions were achieved when tetrabutylammonium fluoride was added over 30 minutes *via* syringe pump, giving a ratio of approximately 5:1 of oxidation to protodesilylation. It was possible to treat the reaction mixture (which existed as a complex mixture of diastereomeric lactol and open chain ketone in $CDCl_3$) with pyridinium *para*-toluenesulfonate (PPTS) in methanol to furnish lactol **311** as a 60:40 inseparable mixture of diastereomers (Scheme **3.11**). The diastereomeric ratio was inconsequential in this model system, as it was postulated that in

more complex systems such as the D-ring of pectenotoxin-4 (see Figure **3.1**), preference would be shown for the thermodynamically more stable diastereomer.

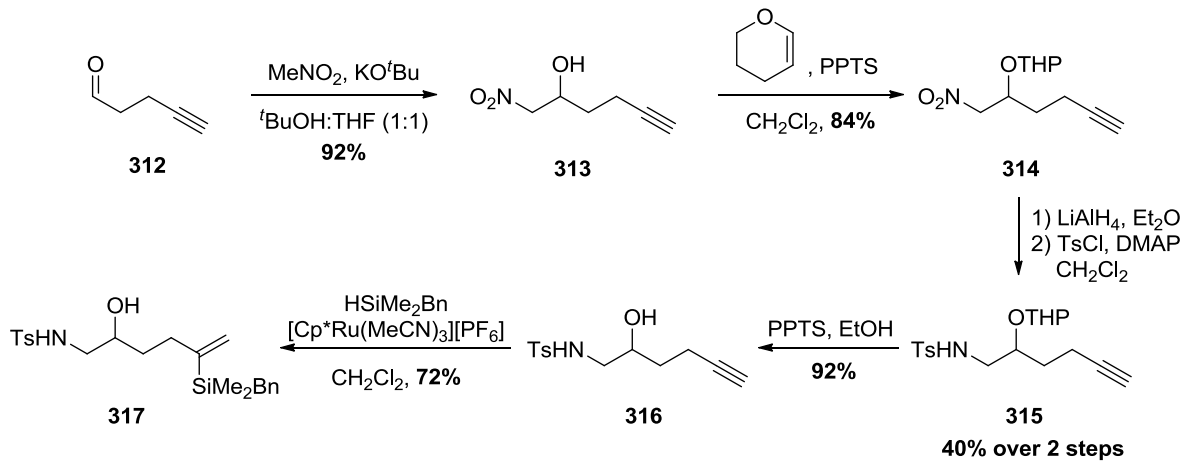


Scheme 3.11 *Formation of lactol **311***

3.1.4 Substrate scope of oxidation

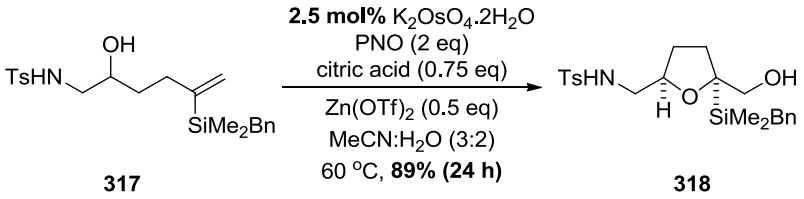
3.1.4.1 Applications to amino alcohols

Having successfully demonstrated the cyclisation/oxidation methodology on a 1,2-diol substrate, attempts were made to expand the scope of initiator groups for the cyclisation. Amino alcohols undergo the osmium-mediated oxidative cyclisation to form either pyrrolidines or THFs, depending on the relative positioning of the alcohol and amine.[39] Attempts to form silyl-substituted pyrrolidines using the Lewis acid-mediated oxidative cyclisation have previously been unsuccessful, owing to the steric clash of the amine protecting group and the vinyl silane.[106] It was reasoned that reversing the relative positioning of the amine and alcohol would allow minimum steric clash in the transition state, affording silyl-substituted THFs with an amino side chain. In order to synthesise a suitable cyclisation precursor, commercially available pentyn-4-al **312** was subjected to a Henry reaction with nitromethane, followed by protection of the free hydroxyl group as a tetrahydropyran ether. This afforded alkyne **314** in 77% over two steps (Scheme **3.12**).



Scheme 3.12 *Synthesis of amino alcohol*

Reduction of the nitro group with lithium aluminium hydride, followed by tosylation of the resulting primary amine afforded **315**. Deprotection of the THP group led to amino alcohol **316**, which upon being subjected to the hydrosilylation conditions afforded vinyl silane **317**. After synthesising the cyclisation precursor in a total of 6 steps, **317** was set up to undergo the key oxidative cyclisation reaction. Pleasingly, subjecting amino alcohol **317** to the standard Lewis acid cyclisation conditions furnished THF **318** in excellent yield (Scheme **3.13**).



Scheme 3.13 *Cyclisation of amino alcohol*

The relative stereochemistry across the ring junction of THF **318** was confirmed by NOE enhancements. It was evident that the THF-C*H* and the silyl group existed in a *cis*-2,5 relationship, which was consistent with previous examples (Figure **3.3**).

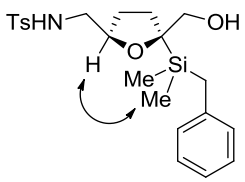
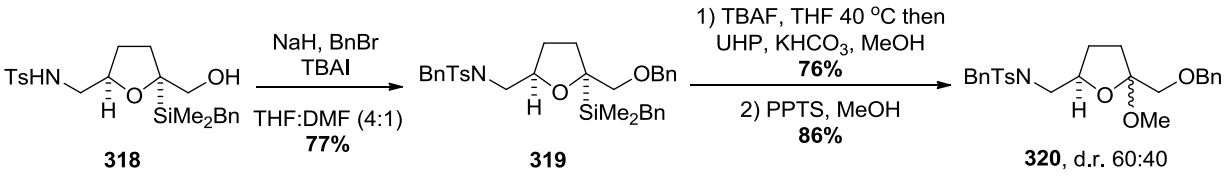


Figure 3.3 *NOE of amino THF **318***

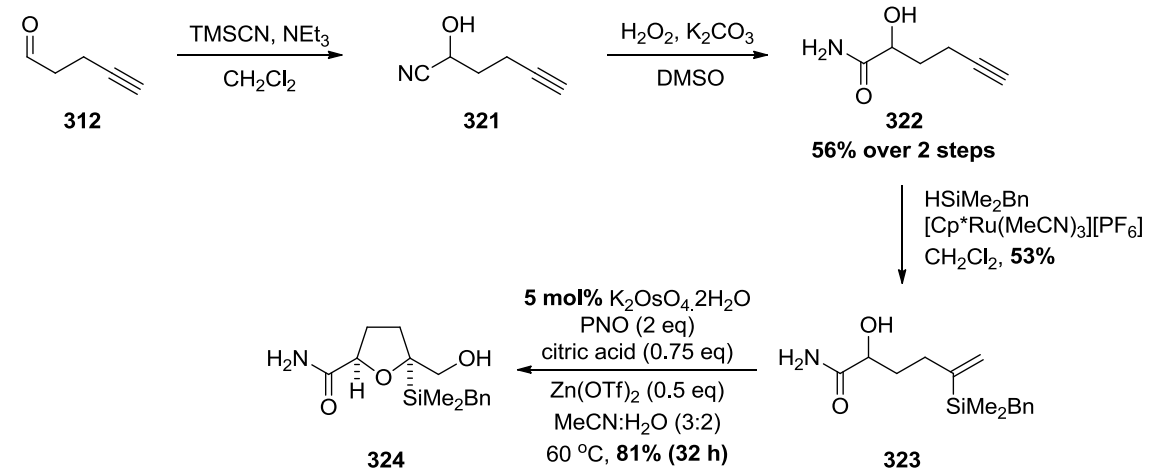
In order to demonstrate the generality of the newly developed oxidative desilylation conditions, it was important to form the corresponding lactol of THF **318**. Benzyl protection of **318** resulted in protection of both the primary alcohol and the amine (Scheme **3.14**). Exposing protected THF **319** to the oxidation conditions led to formation of the intermediate lactol in 76%. As before, the mixture was treated with pyridinium *para*-toluenesulfonate in methanol to furnish **320** as a 60:40 diastereomeric mixture.



Scheme 3.14 *Oxidation of amino alcohol*

3.1.4.2 Applications to hydroxy amides

Another substrate class shown to undergo oxidative cyclisation are α-hydroxy amides.[39] It was predicted that the silane methodology could also be extended to the cyclisation of this substrate class, in order to afford silyl substituted THFs with an amide side chain. Treatment of commercially available pentyn-4-al **312**, with trimethylsilyl cyanide afforded an intermediate nitrile, which was subsequently hydrolysed under the action of basic hydrogen peroxide to yielded α-hydroxy amide **322** (Scheme **3.15**). Hydrosilylation of the resultant alkyne led to the formation of cyclisation precursor **323**. After accessing vinyl silane **323** in just 3 linear steps, it was ready to be subjected to the key cyclisation step. Treatment of **323** under the cyclisation conditions led to the formation of THF **324** in excellent yield (Scheme **3.15**).



Scheme 3.15 *Synthesis and cyclisation of hydroxyamide*

Upon examining the NOE enhancements of THF **324**, it was evident that changing the initiator groups had no effect on the selectivity of the cyclisation. Again, a *cis*-relationship between the THF-C*H* and the silane group was observed (Figure **3.4**).

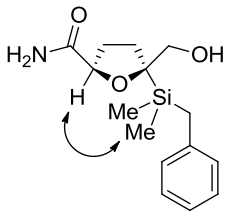
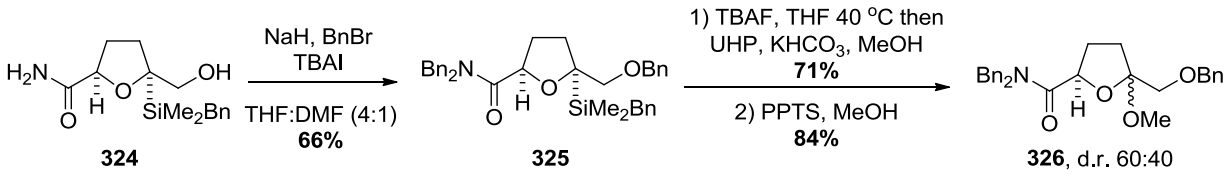


Figure 3.4 *NOE of hydroxy amide THF **324***

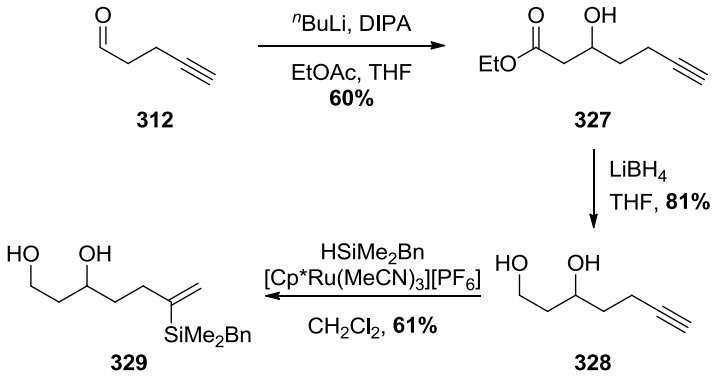
In order to show the general applications of the oxidative desilylation conditions, it was necessary to proceed through to the corresponding lactol of THF **324**. Upon benzylating THF **324**, tribenzylated **325** was isolated in good yield (Scheme **3.16**). Subjecting **325** to the oxidative desilylation conditions afforded the intermediate lactol in 71%. Subsequent treatment of this complex mixture with PPTS in methanol furnished THF **326** as a 60:40 mixture of diastereomers.



Scheme 3.16 *Oxidation of hydroxy amide*

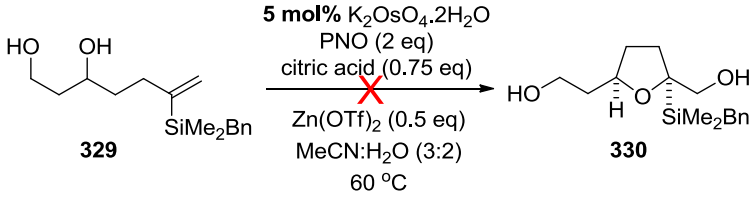
3.1.4.3 Applications to 1,3-diols

Finally, attempts were made to synthesise a 1,3-diol bearing a pendent vinyl silane. Subjecting pentyn-4-al **312** to an aldol reaction with ethyl acetate, led to the formation of β-hydroxy ester **327**. Reduction of the ester, followed by hydrosilylating the terminal alkyne afforded 1,3-diol **329** in 3 steps (Scheme **3.17**).



Scheme 3.17 *Synthesis of 1,3 diol **329***

Unlike in previous cases, attempts to cyclise **329** were unsuccessful. After 96 hours the reaction had only proceeded to 30% conversion, with the starting 1,3-diol and resulting THF proving inseparable by column chromatography (Scheme **3.18**).



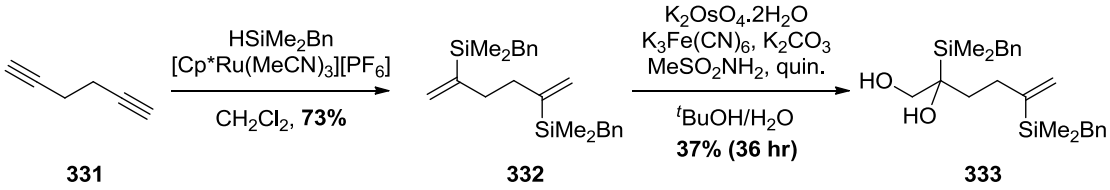
Scheme 3.18 *Unsuccessful 1,3-diol cyclisation*

The slow nature of this reaction can be attributed to the combination of a relatively slow 1,3-diol cyclisation, which has been shown to be much slower than its 1,2-analogue (*vide supra*

Chapter 2.2), coupled with a comparatively slow vinyl silane cyclisation. Attempts to increase the catalyst loading to 20 mol% were also unsuccessful, with incomplete conversion once again observed.

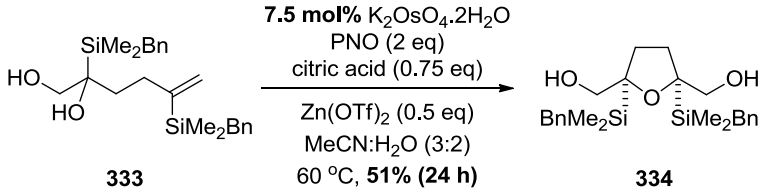
3.1.5 Alternative methods of forming silyl-substituted THFs

An alternative approach to the formation of silyl-substituted THFs was to dihydroxylate a vinyl silane precursor, followed by an oxidative cyclisation onto a pendent alkene. Diol **333** was formed by dihydrosilylating commerially available 1,5-hexadiyne, followed by mono-dihydroxylating the resulting diene (Scheme **3.19**).



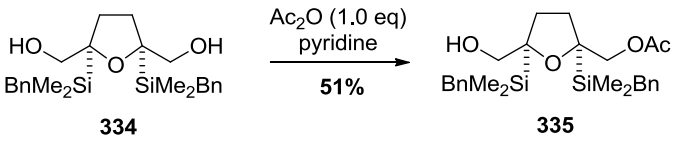
Scheme 3.19 *Synthesis of disilylated precursor*

In this case, the pendent alkene is also a vinyl silane, meaning the pseudo-*trans*-diaxial steric interaction between the two benzyldimethylsilyl groups during cyclisation might be expected to be unfavourable. Consequently, it was unclear whether this interaction would cause the cyclisation to deviate from consistently forming THFs with *cis*-selectivity or suppress the reaction altogether. After gaining access to diol **333** in a short sequence, the key oxidative cyclisation to form bis-silyl-substituted THF **334** could be attempted. Subjecting diol **333** to the cyclisation conditions, using 7.5 mol% of potassium osmate, afforded THF **334** in 51% (Scheme **3.20**).



Scheme 3.20 *Cyclisation of double silylated precursor*

In order to determine the relative stereochemistry of the benzyldimethylsilyl groups by NOE enhancements, it was necessary to desymmetrise THF **334** by mono-protecting one of the primary hydroxyl groups (Scheme **3.21**).



334 **335**

Scheme 3.21 *Mono-acetylation of double silyl THF*

It was subsequently proved by NOE enhancements that the two silyl groups were disposed in a *cis*-relationship (Figure **3.5**).

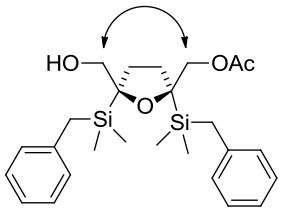
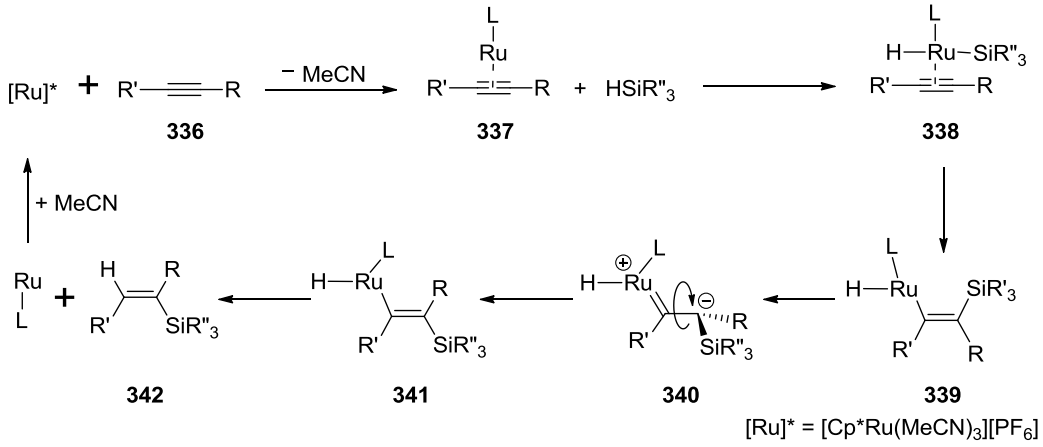


Figure 3.5 *NOE of cis-THF **335***

This result further demonstrates the remarkable stereochemical rigidity of the osmium-mediated oxidative cyclisation. With reliable methodology now in place for the sequential formation of silyl substituted THFs and subsequent desilylation, it was now important to extend this methodology to non-terminal vinyl silanes.

3.2 Attempts to extend the methodology to non-terminal silanes

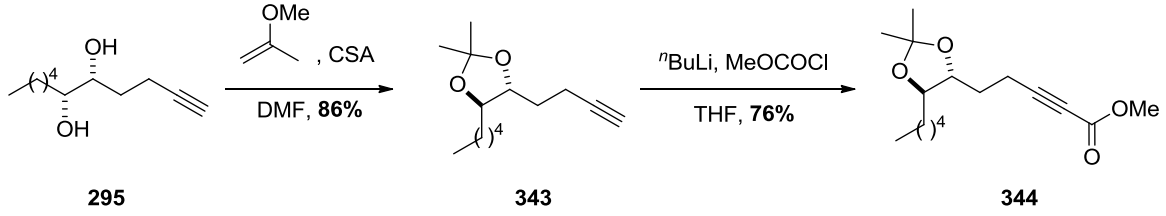
One of the advantages of cyclising onto non-terminal alkenes compared with terminal alkenes is that two stereo-centres are created as opposed to just one. It was envisaged that the synthesis of non-terminal vinyl silanes would be possible using similar hydrosilylation conditions. According to literature precedent, it is possible to achieve a selective hydrosilylation on an alkyne adjacent to a carbonyl or alcohol, with the silyl group being incorporated furthest from the oxo-species.[110] Furthermore, when using $[Cp^*Ru(MeCN)_3][PF_6]$, the alkyl groups from the starting alkyne are disposed in a *trans*-relationship in the resulting vinyl silane (Scheme **3.22**).



336 **337** **338** **339** **340** **341** **342**

Scheme 3.22 *Proposed mechanism of hydrosilylation*

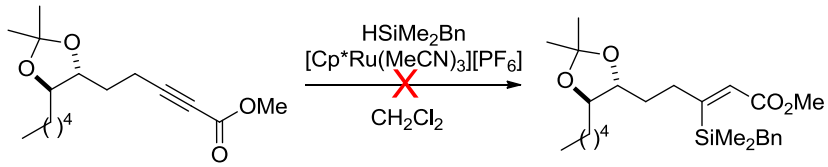
In an attempt to utilise this methodology in the regioselective formation of a non-terminal vinyl silane, diol **295** was subjected to acetonide protection (Scheme **3.23**). Deprotonation of **343**, followed by treatment with methyl chloroformate furnished ester **344**. The formation of ester **344** was confirmed by the disappearance of the alkyne proton at 1.98-1.95 ppm in the ^{1}H NMR spectrum, with the presence of a new peak at 3.78-3.75 ppm corresponding to an OCH_3.



295 **343** **344**

Scheme 3.23 *Synthesis of non-terminal alkyne*

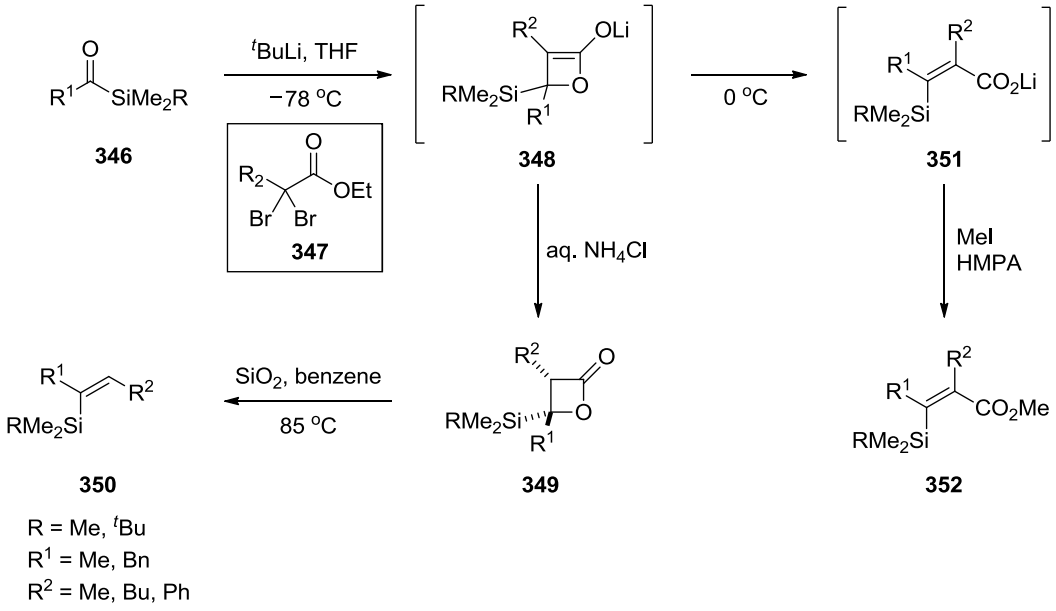
Unfortunately, subsequent treatment of **344** under hydrosilylation conditions resulted in a complex mixture of products which were inseparable by column chromatography, suggesting that a mixture of regioisomers were being produced in the reaction (Scheme **3.24**).



344 **345**

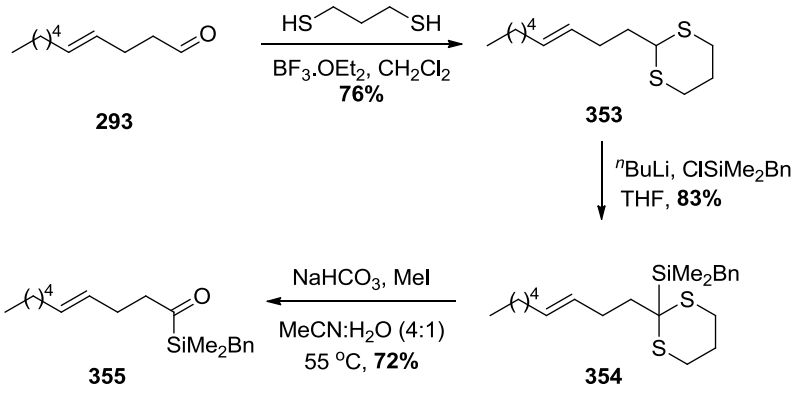
Scheme 3.24 *Attempted hydrosilylation of non-terminal alkyne*

In order to synthesise non-terminal vinyl silanes in an efficient manner, an alternative approach was required. It was recently shown by Shindo and co-workers that acyl silanes could be reacted with a range of ynolates to afford vinyl silanes (Scheme **3.25**).[111,112]



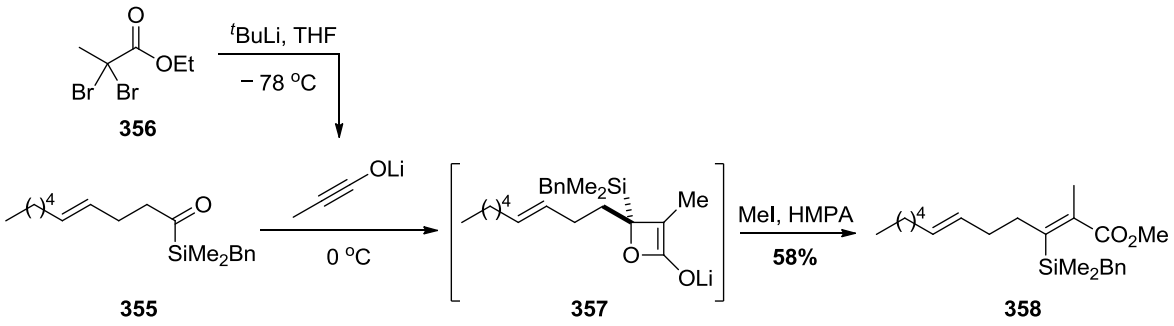
Scheme 3.25 *Shindo's vinyl silane methodology*

In order to synthesise a suitable acyl silane, *trans*-4-decenal was treated with 1,3-propane dithiol, before undergoing Umpolung type chemistry to install the benzyldimethylsilyl group (Scheme **3.26**). Subsequent dethiolation of alkene **354** was achieved with an excess of iodomethane furnishing acyl silane **355**.



Scheme 3.26 *Synthesis of acyl silane*

In accordance with the procedure reported by Shindo and co-workers, α,α-dibromo ester **356** was treated with an excess of *tert*-butyllithium (Scheme **3.27**). Upon forming the corresponding ynolate, acyl silane **355** was added, forming intermediate **357** which upon being subjected to iodomethane and hexamethyl phosphoramide, furnished tetrasubstituted vinyl silane **358** in good yield.



Scheme 3.27 *Formation of vinyl silane with ester*

It was rationalised by Shindo and co-workers that the stereochemistry of the resulting vinyl silane would be *cis*, based upon molecular modelling calculations which showed that the inward rotation of the silyl group was favoured by 17.5 kJ/mol over the outward rotation.[111] This was thought to be due to the interaction between the breaking C–O σ orbital and the Si vacant orbitals (3d or 4sp) (Figure **3.6**).

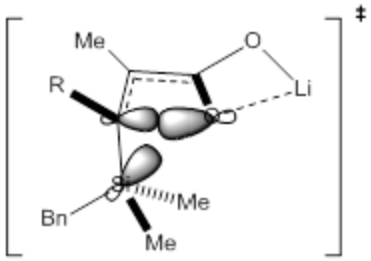


Figure 3.6 *Orbital overlap of silyl group*[111]

This model was shown to be accurate by NOE studies on the resulting tetrasubstituted vinyl silane, with the most important interaction seen between the vinyl-methyl group and the alkyl chain (Figure **3.7**).

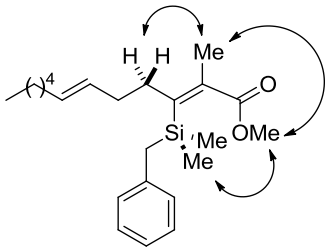
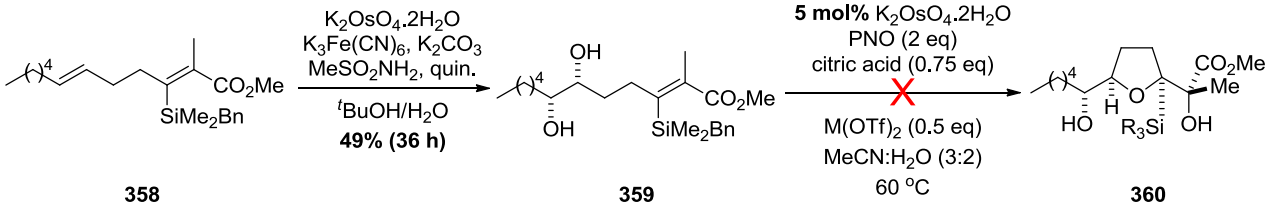


Figure 3.7 *NOE proving the alkene geometry of* ***358***

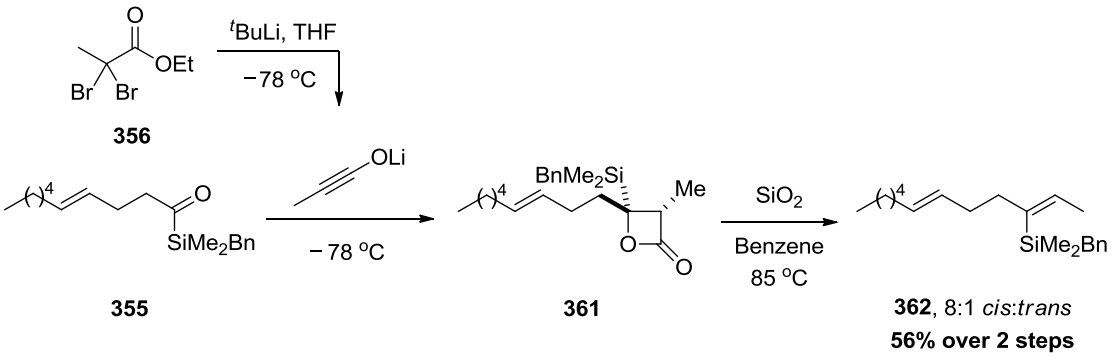
With a non-terminal vinyl silane in hand, the mono-dihydroxylation of diene **358** was achieved under a racemic modification of the Sharpless asymmetric dihydroxylation. A selective dihydroxylation was achieved at the more electron-rich *trans*-alkene to afford cyclisation precursor **359** in 5 steps (Scheme **3.28**). Vinyl silane **359** was now set up to undergo an oxidative cyclisation. Unfortunately, subsequent attempts to cyclise the resulting diol were unsuccessful, with only starting material being recovered in each case.



Scheme 3.28 *Attempted cyclisation onto tetra-substituted alkene*

Despite the additional electron density from the silane, it was likely that this cyclisation failed for a combination of reasons. Firstly, the ester functionality was likely to counteract the electron-rich silane, resulting in an overall electron-poor alkene. Additionally, there have been no reported osmium-mediated oxidative cyclisations on to tetrasubstituted alkenes. It is likely that the steric clash experienced during the cyclisation would be significant, especially with silane substitution. From this result it was evident that a less substituted, more electron-rich vinyl silane was required for the cyclisation to proceed. It was predicted that the removal of the ester functionality would achieve both of these aims. Therefore, attentions turned to the synthesis of an alternative vinyl silane. Utilising a modification reported by Shindo and co-workers whereby the initial vinyl silane reaction is quenched at –78 °C, semi stable β-lactone **361** could be isolated.[112] This intermediate was immediately decarboxylated under the action of

silica in benzene at reflux (Scheme **3.29**). This afforded vinyl silane **362** as an inseparable mixture 8:1 mixture of *cis*:*trans*. Formation of the desired vinyl silane was confirmed by the presence of an additional quartet corresponding to the C=C*H* at 6.13 ppm in the ^{1}H NMR spectrum.



Scheme 3.29 *Formation of non-terminal vinyl silane*

Again this procedure is selective for the formation of the *cis*-alkene. In this case, upon workup, protonation of the intermediate lithium-enolate occurs from the least hindered face fixing the relative stereochemistry of β-lactone **361** (Figure **3.8**).

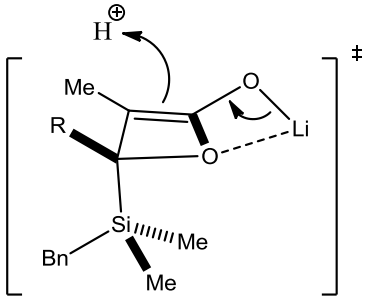


Figure 3.8 *Protonation from least hindered face*

The stereochemistry of **362** was proved by NOE correlations between the alkene proton and the adjacent alkyl chain, with a further interaction between the vinyl methyl group and the methylsilyl groups (Figure **3.9**).

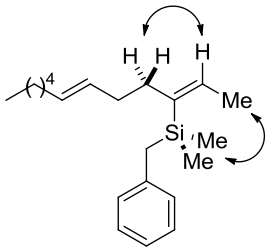
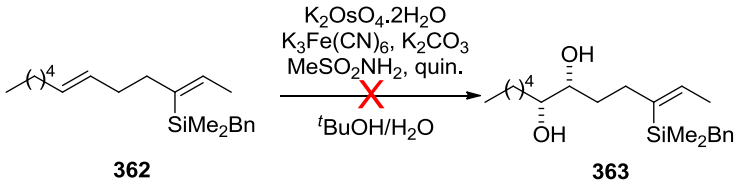


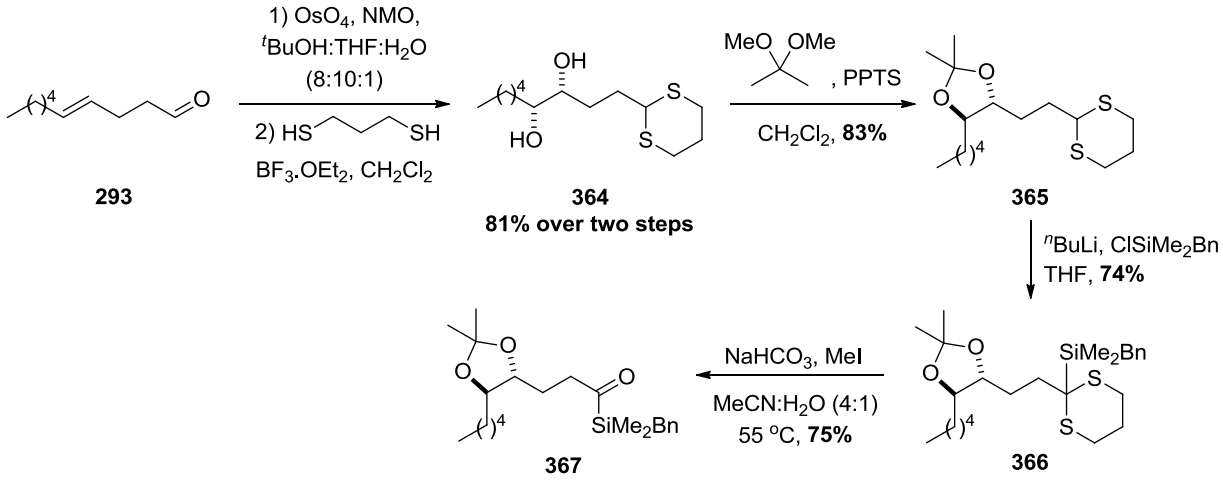
Figure 3.9 *NOE to prove alkene geometry of* ***362***

Unfortunately, attempts to selectively dihydroxylate the *trans*-alkene in the presence of the trisubstituted vinyl silane led to decomposition, presumably as a consequence of bis-dihydroxylation (Scheme **3.30**).



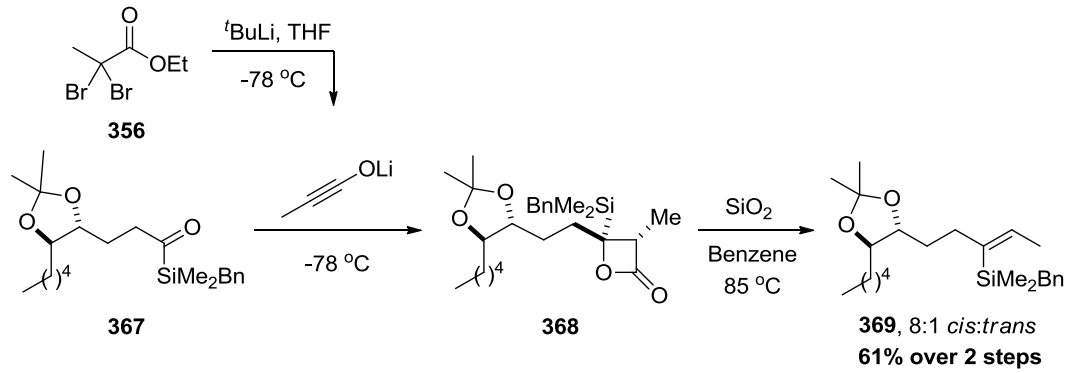
Scheme 3.30 *Failed dihydroxylation of diene* ***362***

It was clear from this result that the diol functionality should be installed at an earlier stage, prior to the formation of the vinyl silane. An alternative approach, whereby *trans*-4-decenal **293** was subjected to racemic dihydroxylation conditions, followed by treatment with 1,3-propanethiol, afforded diol **364** in excellent yield (Scheme **3.31**).



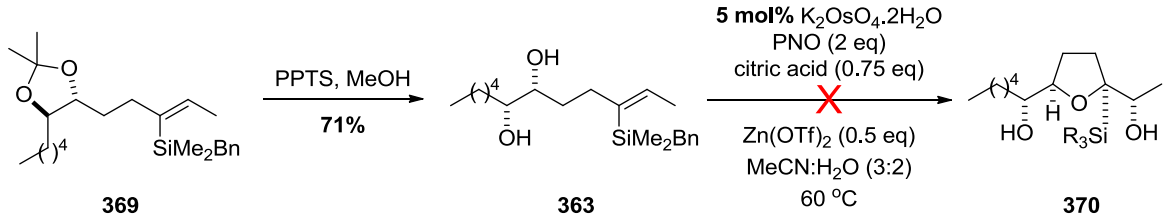
Scheme 3.31 *Synthesis of acyl silane* ***367***

Subsequent acetonide protection of **364** resulted in the formation of **365**, which could then undergo a similar synthetic sequence to the alkene analogue **355** (*vide supra* Scheme **3.26**), to afford acyl silane **367**. Subjecting acyl silane **367** to the same conditions as those used for the formation of diene **362** (Scheme **3.29**) afforded silane **369** in 61% as an inseparable 8:1 mixture of *cis*:*trans* stereoisomers (Scheme **3.32**).



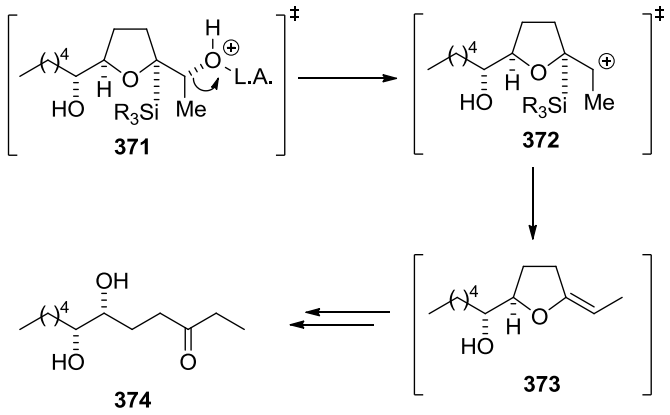
Scheme 3.32 *Formation of vinyl silane **369***

Deprotection of the acetonide under mild conditions furnished vinyl silane **363** in a total of 8 steps from *trans*-4-decenal **293** (Scheme **3.33**). Once more, NOE studies confirmed the vinyl silane to have *cis*-geometry.



Scheme 3.33 *Failed cyclisation of diol **363***

With cyclisation precursor **363** in hand, it was now possible to attempt the key oxidative cyclisation on a trisubstituted non-terminal vinyl silane. When **363** was subjected to the cyclisation conditions, despite consumption of the starting material, significant decomposition was observed, with no THF isolated. One possible decomposition pathway could proceed *via* an acid mediated Peterson elimination (Scheme **3.34**).



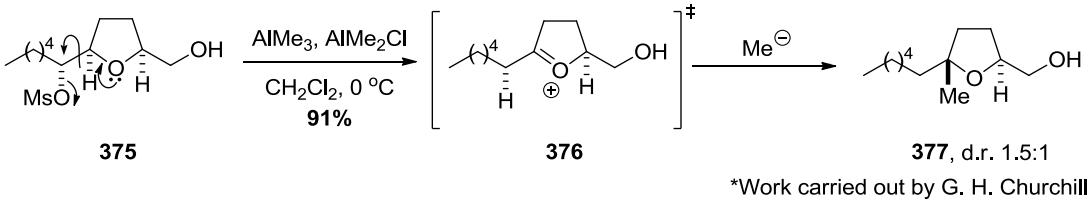
Scheme 3.34 *Potential decomposition pathway*

After the initial cyclisation, it is possible that the β-hydroxyl adjacent to the silyl group is removed under Lewis acidic conditions, resulting in a stabilised secondary carbocation. This decomposition pathway would not have been observed in the analogous terminal vinyl silane cyclisation, as the corresponding primary carbocation would be too disfavoured. Subsequent elimination of the silyl group would, after hydrolysis, lead to the formation of ketone **374**, which would presumably exist as a complex mixture of ring open and closed isomers. Subsequently, analysis of the mass spectrum of the crude material indicated a peak corresponding to an $[M+Na]^+$ peak of **374**. Despite varying the Lewis acid, no improvement was observed and it became evident that the vinyl silane methodology could not be extended to non-terminal vinyl silanes.

3.3 Attempts to use silanes for facial bias

With a possible route to synthesising the lactol functionality for the D-ring of pectenotoxin-4 now in place (*vide supra* **Chapter 3.1**), attention turned to the possibility of developing methodology for the formation of the E-ring, which bears a *trans*-THF (Figure **3.1**). Previous studies into methods of generating *trans*-THFs within the group have shown that THF **375** is a good candidate for hydride shift methodology (Scheme **3.35**).[113] Treatment of THF **375** with a strong Lewis acid led to the elimination of the mesylate group and an accompanying 1,2-hydride shift, resulting in an intermediate oxonium ion **376**. In the case that trimethyl

aluminium was incorporated as the Lewis acid, the intermediate oxonium ion was attacked by a methyl group, potentially whilst coordinating to the primary alcohol. This nucleophilic attack showed a weak preference for the formation of the *trans*-THF, with an observed diastereomeric ratio of 1.5:1.



Scheme 3.35 *Previous hydride shift methodology* [113]

If a silyl group was incorporated at the opposite ring junction to the intermediate oxonium ion in place of a hydrogen atom, it was proposed that the combined effect of the primary alcohol chelating to the nucleophilic species and the bulky silane blocking nucleophilic attack from the bottom face, would increase the diastereoselectivity of this reaction (Figure **3.10**).

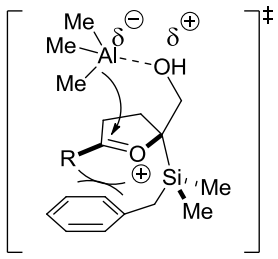
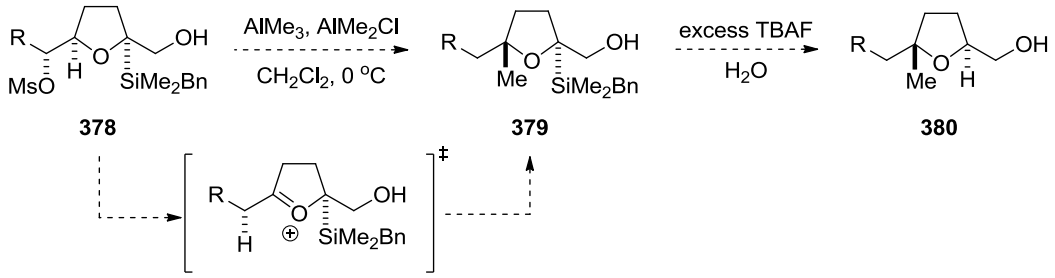


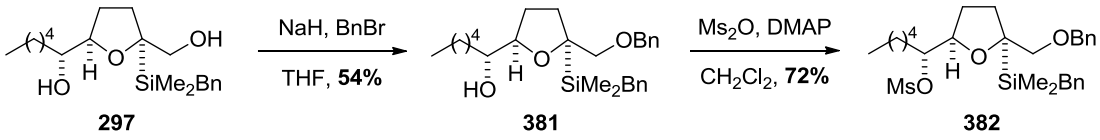
Figure 3.10 *Expected facial bias of methyl transfer*

Should the methyl group exhibit a significant bias for methyl delivery from the opposite face to the silane, the directing silyl group could be easily removed *via* protodesilylation, which has already been demonstrated to occur in good yield and with retention of stereochemistry (Scheme **3.36**).



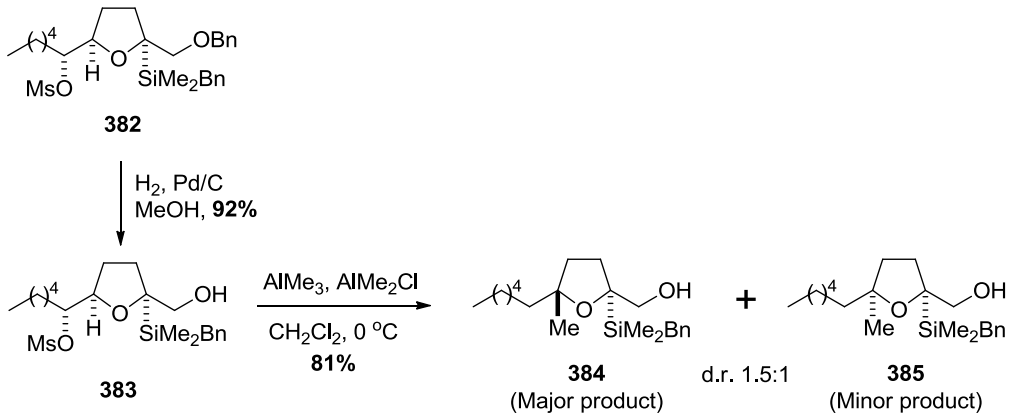
Scheme 3.36 *Proposed formation of trans-THF*

Following this rationale, THF **297** was selectively mono-benzylated at the least hindered primary alcohol before the secondary alcohol was mesylated to afford **382** (Scheme **3.37**). Formation of mesylate **382** was confirmed by the C*H*OR peak in the ^{1}H NMR spectrum shifting downfield from 3.44-3.36 ppm (R = H) to 4.58-4.51 ppm (R = Ms).



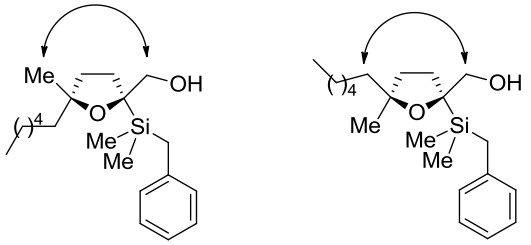
Scheme 3.37 *Formation of mesylate **382***

In order to minimise the steric bulk and maximise the potential for coordination to the aluminium species to the hydroxyl group during the hydride shift/methylation step, it was necessary to remove the benzyl protecting group. This was achieved by subjecting mesylate **382** to hydrogenation conditions, affording **383** in excellent yield (Scheme **3.38**).



Scheme 3.38 *Hydride shift using free hydroxyl group*

Upon subjecting **383** to the hydride shift conditions, the corresponding methyl-substituted THFs **384** and **385** were isolated. Disappointingly, the diastereomeric ratio observed was only 1.5:1, which when compared to the analogous reaction with no silyl-substitution at the ring junction gave similar levels of selectivity (*vide supra* Scheme **3.35**). The major isomer was shown by NOE enhancements to be the desired *trans*-THF precursor **384**. Complementary NOE studies on the minor diastereomer confirmed that the methyl group and the dimethylsilyl groups were in a *cis*-relationship to one another (Figure **3.11**).

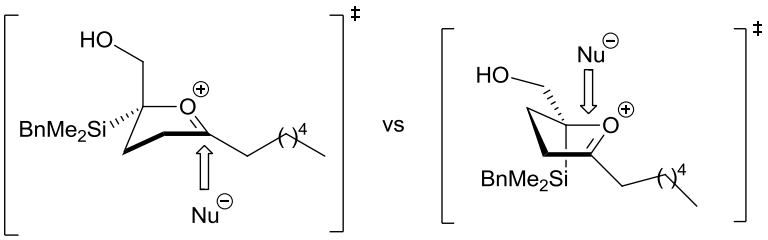


384
(major product)

385
(minor product)

Figure 3.11 *NOE enhancements for the assignment of stereochemistry*

This result was of particular surprise, as the combined effect of chelation control and steric bias would be expected to deliver high diastereoselectivity. In order to rationalise this outcome, it was necessary to examine the possible configurations of the intermediate oxocarbenium ion (Figure **3.12**).

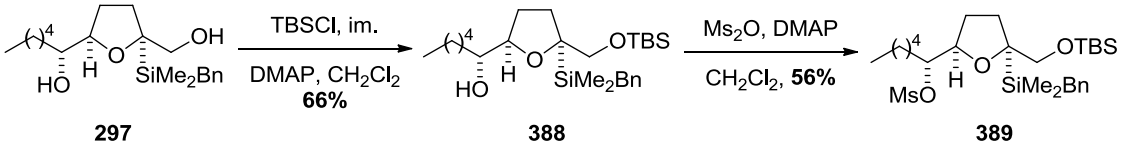


386 **387**

Figure 3.12 *Oxocarbenium intermediates*

Work conducted by Woerpel and co-workers on similar systems dictate that the intermediate oxocarbenium ion can exist in one of two envelope conformers **386** and **387**.[114] It has been demonstrated that nucleophilic addition primarily occurs *via* an "inside attack" in order to

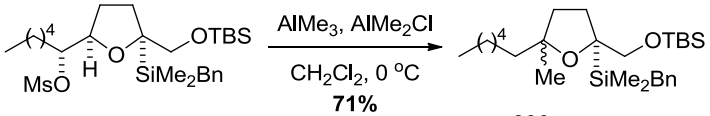
minimize eclipsing interactions in the transition state (See Figure **3.12**).[115] In the case of THF **383**, nucleophilic addition to the oxonium ion would be expected to occur *via* conformer **387** for steric reasons, thus affording the desired THF **384** as the major diastereomer. However, upon examining the two conformers, it is evident that chelation-controlled addition would only be possible *via* a disfavoured "outside attack" of conformer **386**. Consequently, chelation to the aluminium species is only likely to increase the steric bulk surrounding the hydroxyl group, which would ultimately result in poor facial discrimination. In order to probe this theory further, it was necessary to protect the primary alcohol of **383** in order to disrupt chelation to the aluminium species. It was rationalised that this would only have a minor effect on the diastereoselectivity of the reaction. The primary hydroxyl group of **297** was selectively protected using a *tert*-butyldimethylsilyl group followed by a subsequent mesylation of the remaining alcohol to afford **389** in good yield (Scheme **3.40**).



297 **388** **389**

Scheme 3.40 *Synthesis of TBS protected mesylate*

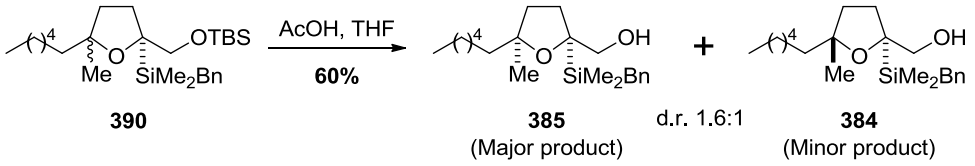
Subjecting THF **389** to the hydride shift conditions again facilitated methyl substitution at the ring junction (Scheme **3.41**).



389 **390**, d.r. 1.6:1

Scheme 3.41 *Hydride shift using TBS protected **389***

Examining the ^{1}H NMR spectrum of **390** revealed that the reaction had a diastereomeric ratio of 1.6:1. However at this point, it was not clear which diastereomer was favoured in this case. In order to distinguish which THF was the major product from the inseperable mixture of diastereomers formed, it was necessary to deprotect the primary alcohol under acidic conditions (Scheme **3.42**).



Scheme 3.42 *Correlation of products*

Acidic deprotection of **390** confirmed that the major diastereomer formed when using a bulky protecting group was THF **385**, in which the methyl group and the silyl group are *cis* to one another. The low preference for the formation of THF **385** can be rationalised upon examining the possible transition structures (Figure **3.13**).

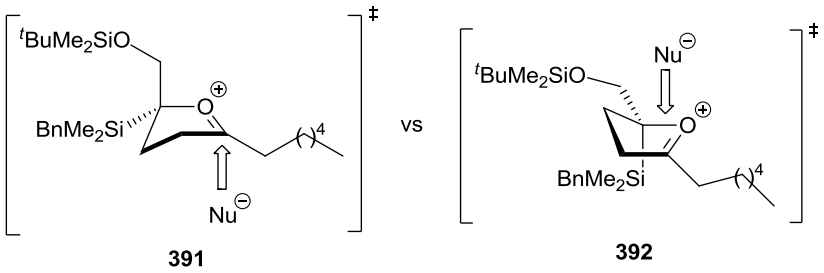


Figure 3.13 *Transition state of TBS protected THF*

It was evident that a slight preference for nucleophilic addition *via* conformer **391** existed, as this is the face opposite to the more bulky TBS group. However, due to the similar size of the benzyldimethylsilyl and *tert*-butyldimethylsilyl groups, inside attack *via* **392** also occurred in significant quantities, resulting in an observed 1.6:1 ratio of diastereomers. This result confirms that the chelation of the aluminium species did not have a positive impact upon the reaction, with only a small change in diasteroselectivity observed between a bulky *tert*-butyldimethylsilyl protected alcohol and a free alcohol. Future work in this area could concentrate on improving the facial selectivity of this reaction by incorporating a sterically bulky silane at the ring junction to allow for higher facial discrimination in the oxonium ion intermediate.

3.4 Conclusion

The cyclisation onto terminal vinyl-silanes has been demonstrated to good effect, with a range of initiator groups capable of forming the corresponding silyl substituted THFs. Subsequent oxidation of the silyl functionality has also been shown to proceed in good yields, affording the corresponding lactols, which can be isolated either in their open chain form, or as their corresponding methyl lactols. Unfortunately, this methodology could not be extended to non-terminal vinyl silanes, as the products were shown to be inherently unstable to Lewis acidic conditions. Attempts to utilise this methodology to access *trans*-THFs by encouraging facial bias were also met with limited success, due to the inability of the free hydroxyl group to coordinate nucleophilic addition to the intermediate oxonium species.

Chapter 4

Total Synthesis of Neodysiherbaine A

4.1 Introduction

Neodysiherbaine A is an excitatory amino acid isolated, along with its parent compound dysiherbaine, from the *Dysidea herbacea* Micronesian sponge by Sakai and co-workers (Figure **4.1**).[116]

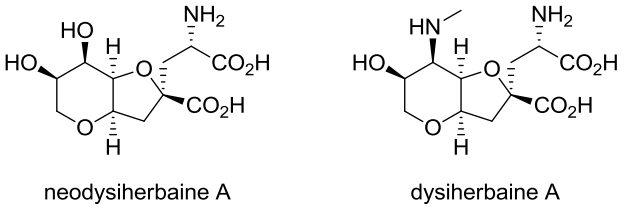
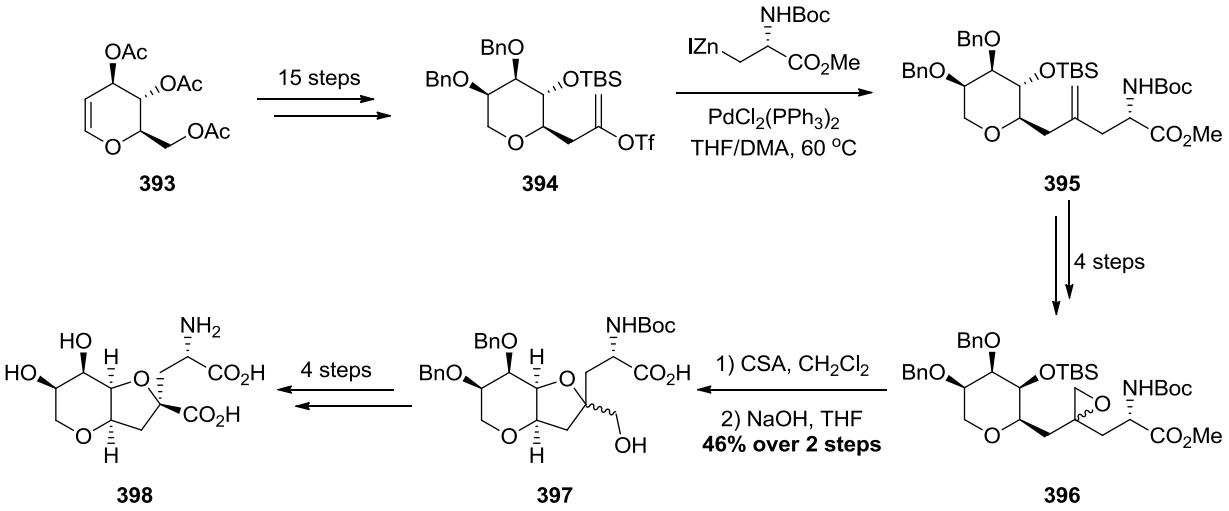


Figure 4.1 *Neodysiherbaine A and dysiherbaine*

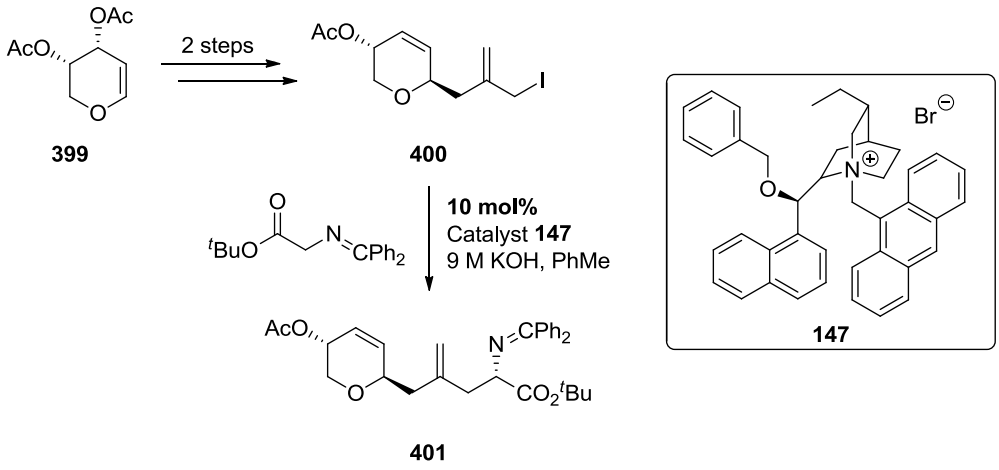
Biological studies have shown that neodysiherbaine A is a potent convulsant and is a highly selective and potent agonist at kainate (KA) and α-hydroxy-5-methyl-4-isoxazole propionate (AMPA) glutamate receptors.[117] Considering its size, it has posed a challenging synthetic target and was first synthesised in 2001 by Sakai and co-workers in 26 steps (Scheme **4.1**).[116]



Scheme 4.1 *Key steps from Sakai's synthesis of neodysiherbaine A*

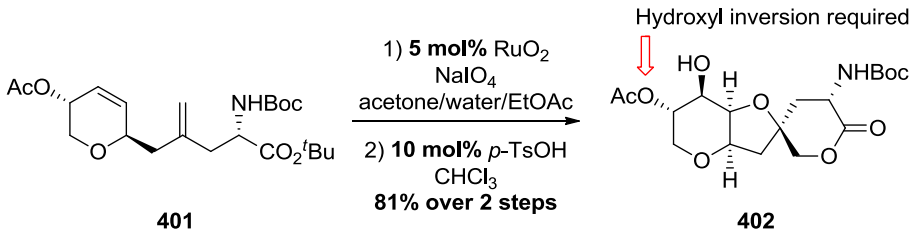
Key steps in the synthesis consisted of a Negishi coupling to install the amino acid portion of **395**, followed by an epoxidation/cyclisation approach to form THF **397**. Neodysiherbaine A has since been synthesised by Sasaki (23 steps)[118] and Hatakeyama (21 steps).[119] The shortest synthesis to date was completed by Lygo and co-workers in 15 steps with an overall yield of

23.1%. In order to install the amino acid portion, Lygo utilised an asymmetric alkylation reaction which made use of a chiral phase-transfer catalyst (Scheme **4.2**).[120]



Scheme 4.2 *Installation of amino acid portion*

In order to form the THF portion, Lygo relied on a ruthenium-mediated oxidative cyclisation which, as in the analogous case of osmium tetraoxide, initiated by dihydroxylating on the top face of the sugar portion, fixing the stereochemistry for the subsequent cyclisation (Scheme **4.3**).

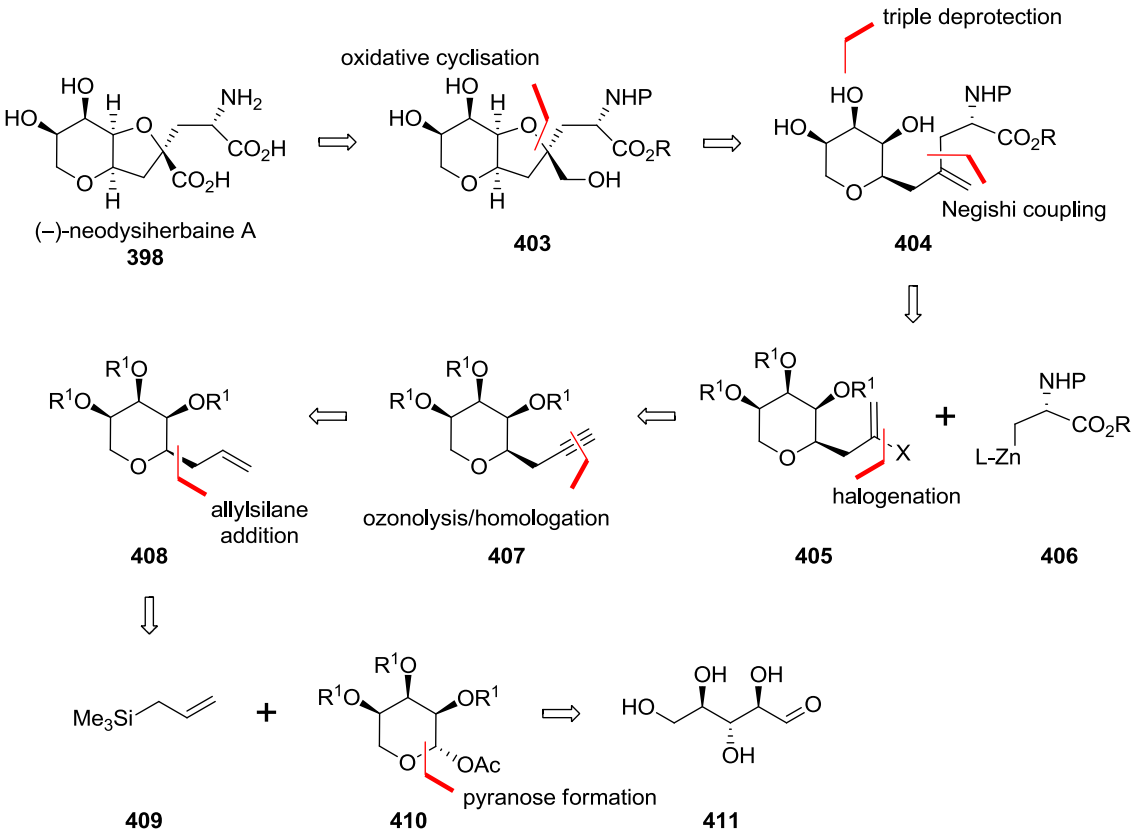


Scheme 4.3 *Ruthenium-mediated THF formation*

Despite the improvement in the yield and step count, this synthesis along with all previous syntheses involve an oxidation/reduction sequence in order to invert a hydroxyl group of the sugar moiety, in order to accommodate the formation of the THF ring.

4.2 Retrosynthetic analysis of neodysiherbaine A

Due to the presence of the THF ring, neodysiherbaine A appeared to be a good target on which to test the oxidative cyclisation methodology. The retrosynthetic analysis shown in Scheme **4.4** outlines a possible synthetic approach to the formation of neodysiherbaine A.



Scheme 4.4 *Retrosynthesis of neodysiherbaine A*

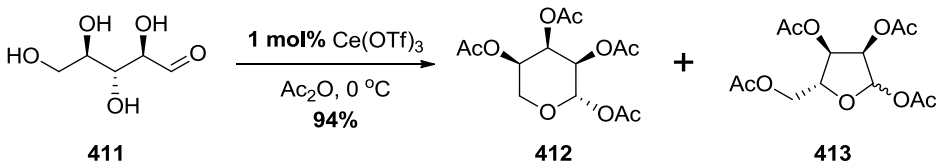
It was predicted that the carboxylic acid portion adjacent to the THF ring of neodysiherbaine A could be installed *via* a late stage oxidation of **403**, as demonstrated by Hatakeyama in the analogous synthesis of dysiherbaine.[121] As the key part of our synthesis, it was predicted that the THF ring could be installed utilising the osmium-mediated oxidative cyclisation of ribose derivative **404**. Using similar methodology to Sakai, the synthesis of **404** could be achieved *via* the Negishi coupling of vinyl silane **405** and organozinc D-serine derivative **406**. It was envisaged that the vinyl halide precursor to the Negishi coupling could be installed by a halogenation of the corresponding alkyne **407**. This in turn could be accessed by the subsequent

ozonolysis and Seyferth-Gilbert homologation of allylribose **408**. Compound **408** has previously been accessed where R^1 = Ac *via* the addition of an allyl-derived nucleophile to the anomeric centre of ribopyranose tetraacetate.[122]

4.3 Synthesis of neodysiherbaine A

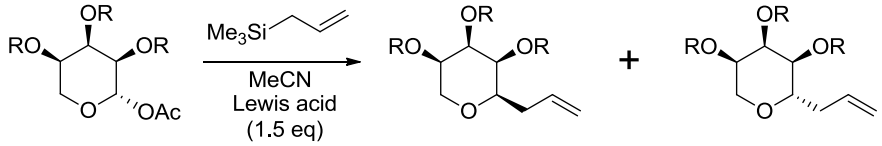
4.3.1 Synthesis of the alkenyl iodide portion

Commercially available β-D-ribose tetraacetate was prepared from D-ribose using an excess of acetic anhydride with a catalytic amount of $Ce(OTf)_3$ (Scheme **4.5**).[123]



Scheme 4.5 *The tetraacetylation of ribose*

It was reported that this procedure resulted in the exclusive formation of pyranose **412** as a 3:1 mixture of anomers. However, small amounts of the corresponding ribofuranose **413** were also observed. In order to separate the undesired furanose **413** impurity from **412**, it was necessary to recrystallise the mixture from toluene. This afforded pure β-D-ribose tetraacetate in an isolated yield of 58% from D-ribose. Previous studies on ribose-based systems have shown that treatment with a Lewis acid and allyltrimethylsilane favours formation of the desired *syn*-products **415** and **418** (Scheme **4.6**).[122, 124]



Scheme 4.6 *Previous studies on the allyltrimethylsilane addition*

Although seeming initially counterintuitive, the preference for the formation of the *syn*-product can be rationalised by a model proposed by Woerpel and co-workers.[124] The oxocarbenium ion

can exist in one of two different half-chair conformations (**420** and **421**), with subsequent nucleophilic addition of the allyl group occurring to either conformer such that the product forms *via* a twist-chair conformation in the transition state (Fürst-Plattner Rule) (Figure **4.2**).[125] Woerpel suggested that the intermediate oxocarbenium ion **421** is destabilized by the 1,3-diaxial interaction of the acetate groups, resulting in transition state **420** being lower in energy.[124] As a result of this destabilisation, **415** and **416** were shown to form in ratio of 3:1. Interestingly, when Woerpel and co-workers applied this methodology to tribenzylated ribose acetate, this ratio became 10:1 in favour of the all *syn*-product. This occurs as the steric interactions of the diaxial benzyl groups are increased and neighbouring group participation of the acetate is eradicated. However, the synthesis of the corresponding tribenzylated ribose **410** took 4 steps from D-ribose.

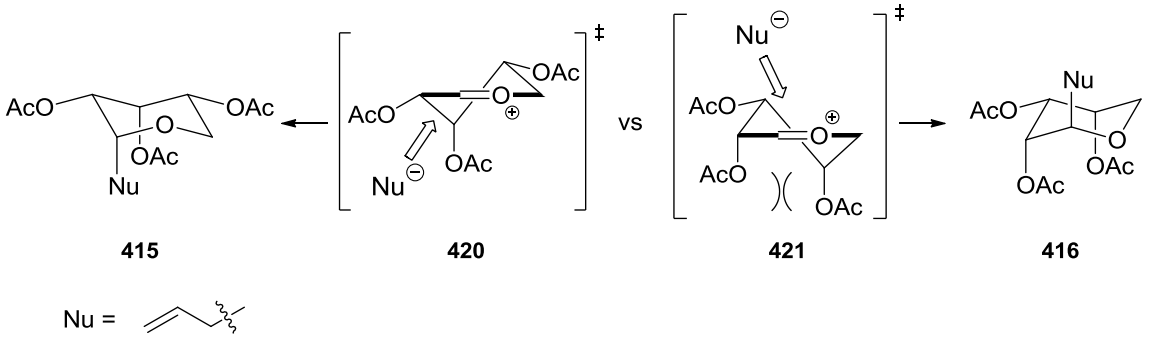
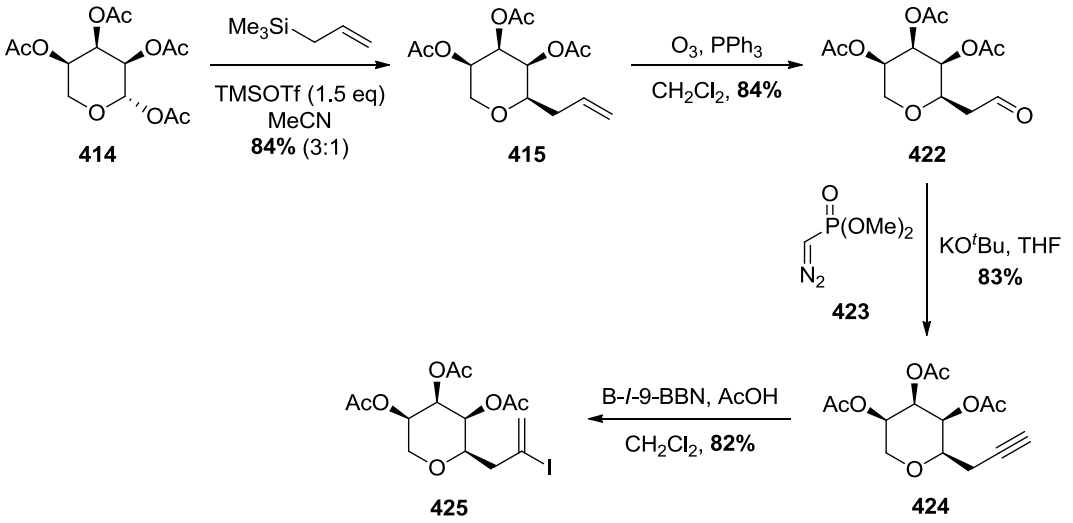


Figure 4.2 *Woerpel's proposed transition states*

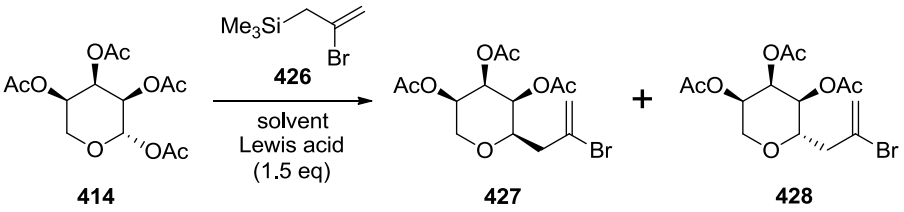
In our hands, applying these reaction conditions to β-D-ribose tetraacetate produced **415** and **416** in a ratio of 3:1, which were separable by column chromatography to afford *syn*-**415** in 61% isolated yield. Compound **415** was spectroscopically identical to that which was previously reported (Scheme **4.7**).[122]



Scheme 4.7 *Formation of alkenyl iodide **425***

Subsequent ozonolysis of the alkene afforded aldehyde **422**, which showed a characteristic singlet at 9.71 ppm in the ^{1}H NMR spectrum, corresponding to the C*H*O proton. Aldehyde **422** was then set up to undergo a Seyferth-Gilbert homologation to afford alkyne **424**. It was not possible to use the Bestmann-Ohira reagent directly in this instance, as the conditions required to deacetylate this reagent to its reactive form would also result in the removal of the acetate groups of **422**. Instead, the active catalyst dimethyl (diazomethyl)phosphonate **423** (which is significantly less stable and has to be prepared freshly) was used directly to form alkyne **424**.[126] Subsequent treatment of **424** with B-iodo-9-BBN under acidic conditions furnished Negishi precursor **425** in a total of 4 steps from commercially available starting materials. Formation of **425** was confirmed by the appearance of two singlets at 6.11 ppm and 5.82 ppm in the ^{1}H NMR spectrum, corresponding to the CH_2=C(I).

Despite this short sequence, it was predicted that an analogue of **425** could be accessed directly from ribose tetraacetate **414**. It was reasoned that similar levels of selectivity would be observed for the allylsilane addition by utilising commercially available 2-bromoallyltrimethyl silane **426** as a nucleophile. However, upon utilising the same conditions used in the synthesis of **415** to this transformation, poor conversion of tetraacetate **414** to vinyl bromide **427** was observed with no 2-bromoallyltrimethyl silane being recovered (Entry 1, Table **4.1**).



414 427 428

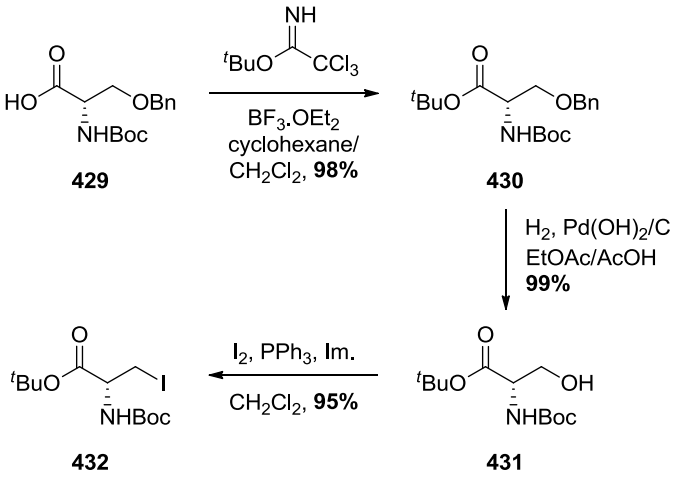
Entry	Conditions	Yield	Ratio (419:420)
1	**426** (3.0 eq), TMSOTf (1.5 eq), MeCN, rt	23%	3:1
2	**426** (1.5 eq), TMSOTf (1.5 eq), MeCN, rt	11%	3:1
3	**426** (3.0 eq), TMSOTf (0.5 eq), MeCN, rt	18%	3:1
4	**426** (3.0 eq) slow add^{n}, TMSOTf (1.5 eq), MeCN, rt	8%	3:1
5	**426** (3.0 eq), TMSOTf (1.5 eq), CH_2Cl_2, rt	0%	-
6	**426** (3.0 eq), TMSOTf (1.5 eq), MeCN, 80 ^{o}C	47%	2:1
7	**426** (3.0 eq), $BF_3.OEt_2$ (1.5 eq), MeCN, 80 ^{o}C	55%	2:1
8	**426** (3.0 eq), $SnCl_4$ (1.5 eq), MeCN, 80 ^{o}C	68%	2:1
9	**426** (3.0 eq), $SnBr_4$ (1.5 eq), MeCN, 80 ^{o}C	79%	2:1

Table 4.1 *Optimisation of allylation*

A range of conditions were attempted on this system in order to optimise this transformation. As a result, it was discovered that tin(IV) bromide was the optimum Lewis acid for this reaction (Entry 9, Table **4.1**). Despite only affording vinyl bromides **427** and **428** as a 2:1 separable mixture of diastereomers, **427** could be easily accessed in just one step from commercially available starting materials in an isolated yield of 53%.

4.3.2 Synthesis of D-serine derivative

After achieving access to both vinyl iodide **425** and vinyl bromide **427**, work began on synthesising the serine derivative **432** that would be involved in the Negishi coupling. Starting from commercially available D-Boc-Ser(OBn)-OH **429**, it was possible to form commercially available (albeit expensive) D-Boc-Ser-O^{t}Bu **431** in two steps (Scheme **4.8**).[127]

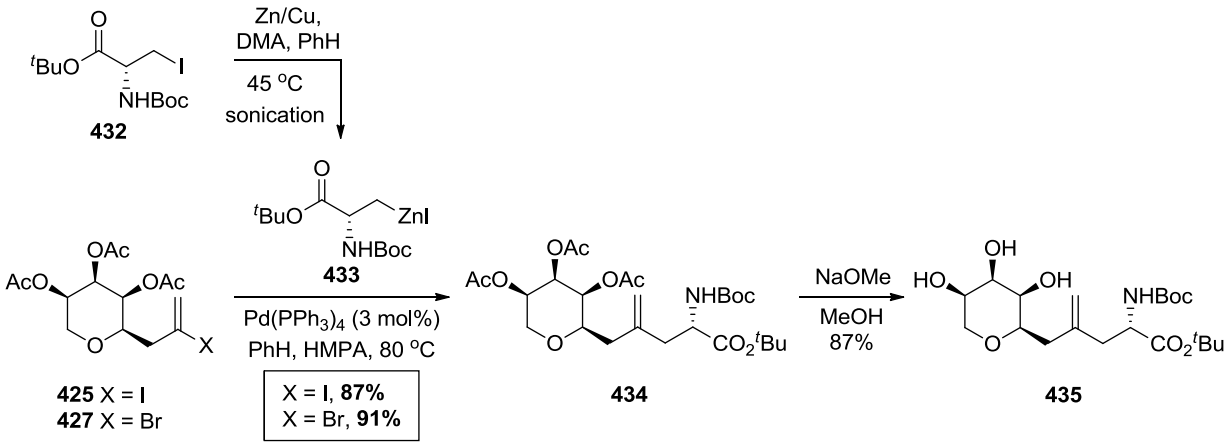


Scheme 4.8 *Synthesis of serine derivative*

Subsequent iodination of **431** *via* an Appel-type reaction furnished iodide **432** in high yield. The formation of iodide **432** was confirmed by the disappearance of the CH_2OH doublet at 3.90 ppm in the ^{1}H NMR spectrum, with a new doublet forming at 3.57 ppm. Further evidence for the formation of iodide **432** was observed with a characteristic *C*H_2I peak present at 8.9 ppm in the ^{13}C NMR spectrum.

4.3.3 Key Negishi coupling

Alkenyl iodide **425** and alkenyl bromide **427** were now ready to undergo a Negishi coupling with iodo-D-serine derivative **433** to form the 1,1-disubstituted alkene precursor to the oxidative cyclisation. Sonication of **432** with zinc/copper couple at elevated temperature led to the corresponding organozinc compound **433** (Scheme **4.9**). This was immediately added to a mixture of either **425** or **427**, in combination with a catalytic amount of tetrakis(triphenylphosphine) palladium(0), which afforded 1,1-disubstituted alkene **434** in both cases in excellent yields (87% and 91% respectively).



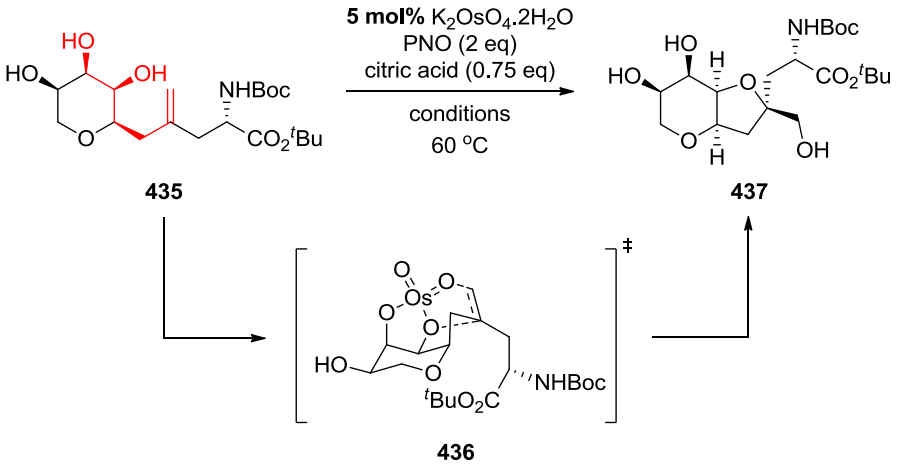
Scheme 4.9 *Negishi coupling and deacetylation*

This result was confirmed in the ^{1}H NMR spectrum by the migration of the alkenyl iodide peaks at 6.11 and 5.82 ppm (or alkenyl bromide peaks at 5.65 and 5.51 ppm) upfield to 4.90 ppm in the corresponding 1,1-disubstituted alkene. In order to access the key cyclisation precursor, it was necessary to deprotect the triol functionality of the ribose moiety. Subsequent deacetylation was achieved using a catalytic amount of sodium methoxide, to afford triol **435**.

4.3.4 Utilising the oxidative cyclisation to form the core of neodysiherbaine A

The synthesis had now reached a critical stage and was set up for a Lewis acid-mediated oxidative cyclisation. If successful, this cyclisation would have several unique features. Firstly, under previous conditions it was not possible to cyclise substrates that form THFs fused to another ring,[35] leading to the presumption that the presence of a ring on the backbone of the THF destabilised the fused 3-ring osmate ester intermediate.[128] Secondly, there have been no previous attempts to cyclise a 1,2,3-triol and at this stage it was unclear whether this would be possible: on one hand both 1,2- and 1,3-diols have been shown to cyclise to give *cis*-THFs, however there is the possibility that a triol might complex strongly to the osmium, slowing the rate of reaction or even preventing the cyclisation from proceeding. Finally, despite demonstrating the stability of the Boc group to the Lewis acid cyclisation conditions (*vide supra* **Chapter 2.6**), it was not guaranteed that this result would translate to more complex systems. In this case, the resulting THF would also be susceptible to lactonisation under acidic

conditions, with the newly formed primary alcohol attacking the ester functionality. It was decided that initially attempting the reaction under the buffered oxidative cyclisation conditions would be the best course of action. Pleasingly, THF **437** was formed in 78% yield (Entry 1, Table **4.2**).



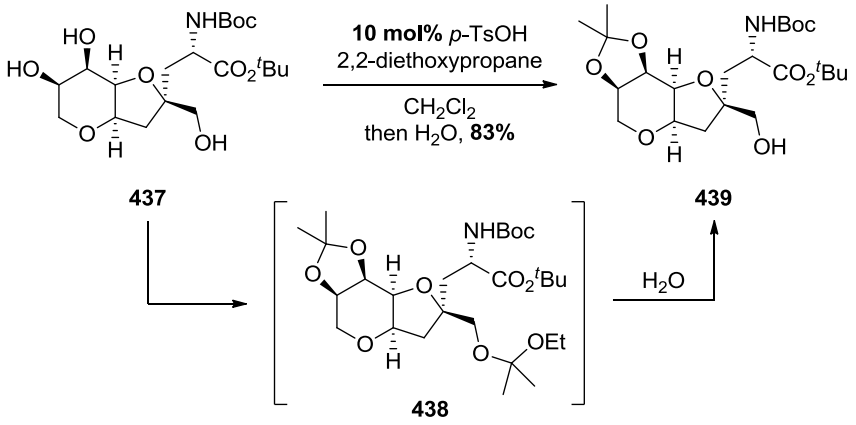
Entry	Conditions	Yield
1	$Zn(OTf)_2$, MeCN:Buffer (3:2)	78% (72 h)
2	$Cu(OTf)_2$, MeCN:Buffer (3:2)	74% (72 h)
3	**$Zn(OTf)_2$, MeCN:H_2O (3:2)**	**88% (16 h)**
4	$Cu(OTf)_2$, MeCN:H_2O (3:2)	82% (16 h)

Table 4.2 *Key oxidative cyclisation*

Varying the Lewis acid showed that zinc triflate gave the highest yields under these conditions (Entry 1, Table **4.2**). In order to see if the reaction would proceed in the absence of a buffer, the original Lewis acid conditions were attempted on triol **435** (Entries 3 and 4, Table **4.2**). Pleasingly, **435** was found to cyclise in 16 hours in excellent yield, with no deprotection of the Boc group or lactonisation observed. Utilising this methodology had led to the construction of the core of neodysiherbaine in just 4 linear steps *via* the alkenyl bromide from commercially available starting materials.

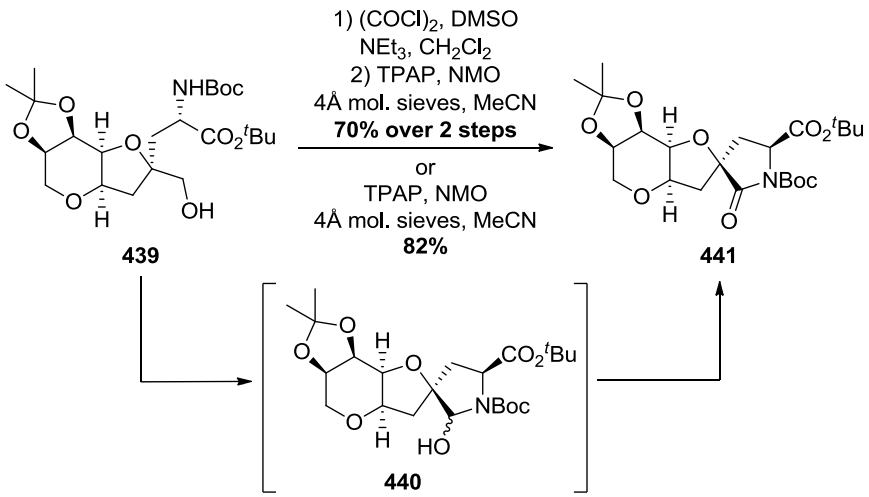
4.3.5 Completion of the synthesis

From this point, it was necessary to oxidise the primary alcohol to a carboxylic acid. It was decided that the best approach to this would be acetonide protection of the diol, followed by oxidation of the primary alcohol (Scheme **4.10**).



Scheme 4.10 *Acetonide protection of THF **437***

The optimum conditions for this transformation were found to be treatment of THF **437** with 2,2-diethoxypropane. Initially, a less polar compound was observed by TLC corresponding to acetonide protected **439** with an additional (ethoxydimethyl)methyl group evident by mass spectrometry – presumably as the primary alcohol is protected to form intermediate compound **438**. However, upon the addition of water to the reaction, this protecting group was successfully hydrolysed to furnish acetonide **439**. With the 1,2-diol successfully protected, attempts were made to form lactam **441**. Initially a two-step procedure was utilised, firstly subjecting **439** to a Swern oxidation to give the intermediate cyclic hemiaminal **440**, followed by a ruthenium mediated oxidation (Scheme **4.11**).



Scheme 4.11 *Synthesis of lactam **441***

The NMR spectrum of the crude Swern oxidation showed the key peaks of the diastereomeric *CH*OH in a 1:1 ratio at 5.47 and 5.29 ppm in the ^{1}H NMR spectrum and 110.1 and 110.0 ppm in the ^{13}C NMR spectrum. Subjecting intermediate **440** to a TPAP oxidation furnished **441** in 70% over two steps. It was subsequently discovered that this procedure could be achieved in one pot by using a TPAP catalyst loading of 30 mol%, which proceeded *via* the same hemiaminal intermediate, affording lactam **441** in 82%.

It was possible to obtain **441** in a crystalline form by recrystallisation from diethyl ether and dichloromethane. Subsequently, single X-ray analysis of this structure proved unambiguously that the relative stereochemistry of **441** was as expected (see **Appendix 2**) (Figure **4.3**).

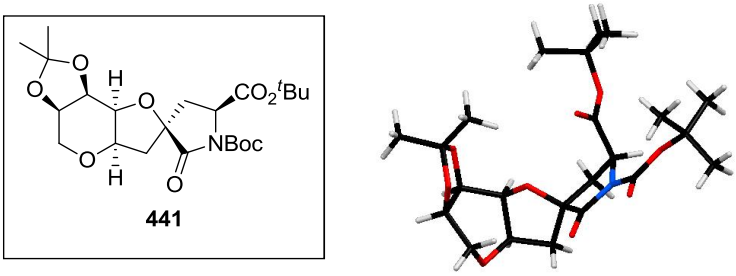
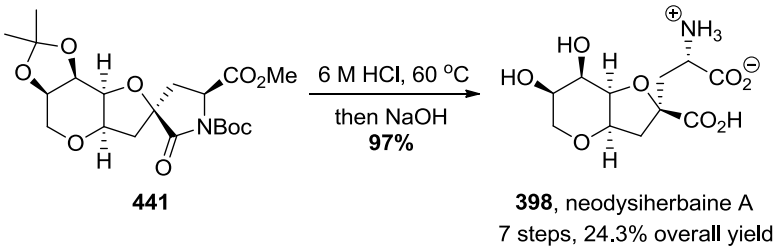


Figure 4.3 *X-ray crystal structure for **441***

Finally, lactam **441** was set to undergo a global deprotection under acidic conditions, removing the acetonide and Boc groups, and hydrolysing the *tert*-butyl ester and lactam in one

transformation. To this end, treatment of **441** with hydrochloric acid at 60 °C, followed by neutralisation with sodium hydroxide afforded neodysiherbaine A in its zwitterionic form (Scheme **4.12**).



Scheme 4.12 *Global deprotection of lactam **441***

Comparison of the ^{1}H NMR spectrum of **398** to that of natural neodysiherbaine A revealed an exceptionally good match. Furthermore comparison of the ^{13}C NMR spectrum of **398** to that of synthetic neodysiherbaine A showed each peak of our sample to be within 0.1 ppm of a sample synthesised previously by Sakai (See **Appendix 3** for comparison).[116]

4.4 Conclusion

An efficient route to neodysiherbaine A has been demonstrated, consisting of a total of 7 linear steps and 24.3% overall yield. This compares very favourably to the previous shortest synthesis of 15 linear steps. Furthermore, this route confirms the importance and utility of the Lewis acid-mediated oxidative cyclisation to the synthesis of complex molecules. The key cyclisation proceeded in the presence of a Boc group and no lactonisation of the product was observed; this was only possible as a consequence of the mild pH of the reaction and efficient cyclisation promoted by a Lewis acid. This synthesis would not have been possible using the previous Brønsted acid-based cyclisation conditions.[41]

Chapter 5

Synthesis of the $C_{21\text{-}30}$ Portion of Pectenotoxin-4

5.1 Introduction

5.1.1 Pectenotoxin family

The pectenotoxins are a large family of cyclic polyether macrolide toxins and are responsible for diarrhetic shellfish poisoning. They were first isolated from the digestive glands of scallops (*Patinopecten yessoensis*) by Yasumoto and co-workers in 1985.[129] It has since been discovered that the producers of pectenotoxins are toxic plankton (dinoflagellates).[130] To date, more than twenty pectenotoxins have been isolated, with structural variations commonly occurring at the D-ring and differing in configurations at the AB spiroketal ring (Figure **5.1**).[131]

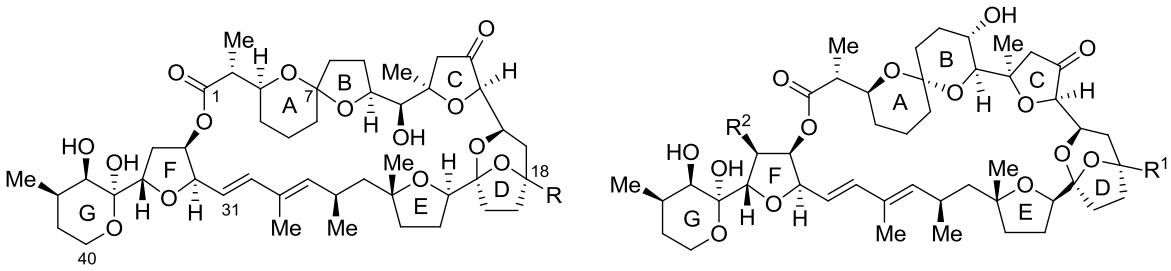


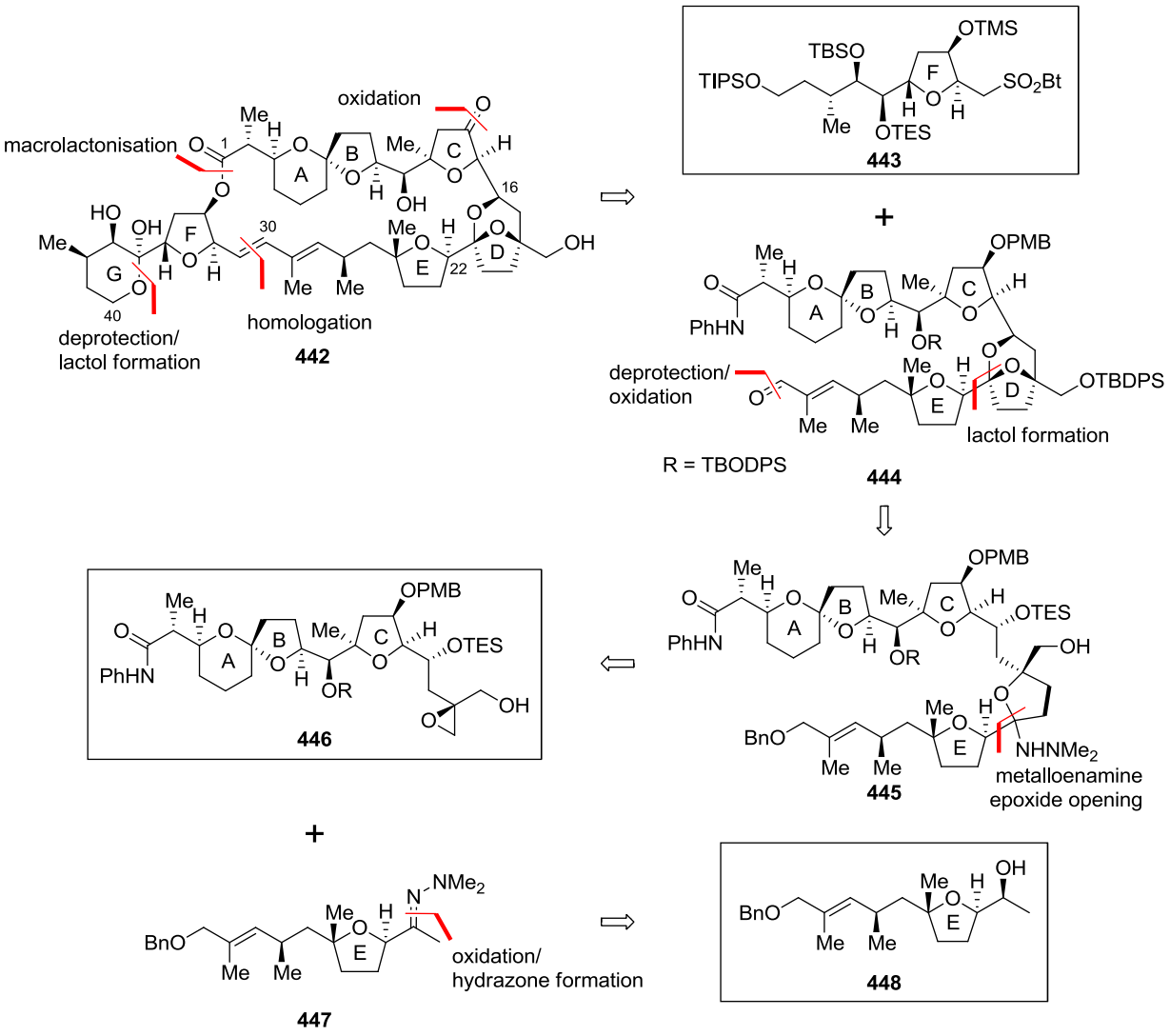
Figure 5.1 *Pectenotoxin family*

This family of natural products are of great interest due to their potent biological properties. Pectenotoxin-2 has been shown to have cytotoxic properties towards human lung (A-549), colon (HT-29) and breast (MCF-7) cancers.[132]

5.1.2 Previous synthesis

To date, there has only been one total synthesis of a pectenotoxin. Evans and co-workers completed the synthesis of pectenotoxin-4 in 36 linear steps and an overall yield of 0.3%.[133] It was also demonstrated that under acidic conditions pectenotoxin-4 could be isomerised to both pectenotoxin-1 and -8. Evans adopted a retrosynthetic approach whereby the final steps consisted of the formation of the G-ring system and subsequent global deprotection. Prior to

this, the main macrocycle of penctenotoxin was achieved *via* a homologation of **443** onto the E-ring terminus of **444**, followed by a macrolactonisation (Scheme **5.1**).



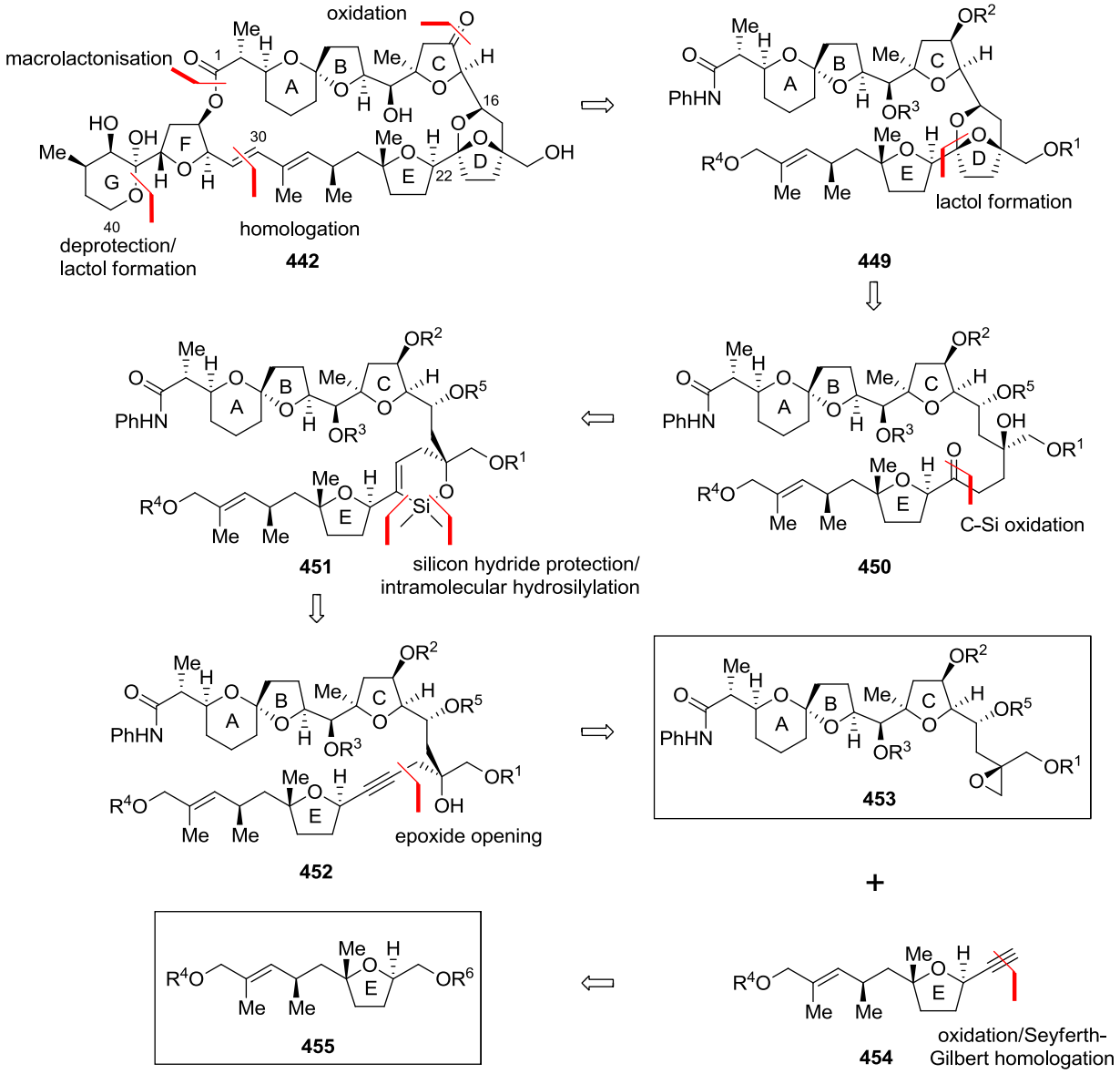
Scheme 5.1 *Evans's retrosynthesis*

The $C_{1\text{-}30}$ portion **444** could be further disconnected across the D-ring to hemiaminal **445**. This in turn was formed by a metalloenamine addition of **447** to epoxide **446**. This disconnection pathway gave rise to three main synthetic targets of pectenotoxin-4: the $C_{1\text{-}19}$ portion **446**, $C_{20\text{-}30}$ portion **448** and $C_{31\text{-}40}$ portion **443**. Using a similar disconnection strategy, work towards synthesising analogous portions of the $C_{1\text{-}19}$ and $C_{31\text{-}40}$ fragments in a more efficient manner is

underway in the Donohoe group. Therefore, an efficient synthesis of the $C_{20\text{-}30}$ portion was required, in combination with a strategy to couple this portion to the rest of the molecule.

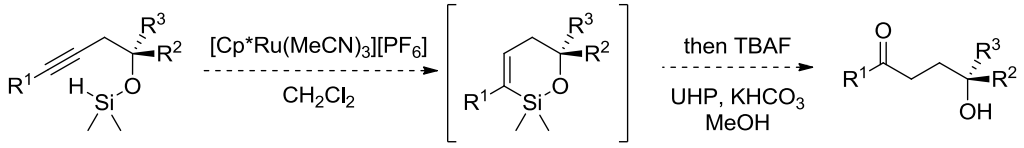
5.2 Retrosynthetic analysis of D and E-ring

The retrosynthetic analysis shown in Scheme **5.2** outlines an alternative approach to forming the D-ring of pectenotoxin-4, affording intermediate **455** as the primary target for this portion.



Scheme 5.2 *Retrosynthetic analysis for the "end-game" of pectenotoxin-4*

In a similar fashion to Evans and co-workers, it was envisaged that the FG-ring system would be installed last, due to the inherent instability of the G-ring. It was predicted that the D-ring could be synthesised by exploiting recent chemistry developed by Trost and co-workers.[110] This would allow for the formation of the corresponding ketone *via* a one-pot tethered hydrosilylation/oxidation, preferentially forming the 6-membered silyloxy-ring (Scheme **5.3**).

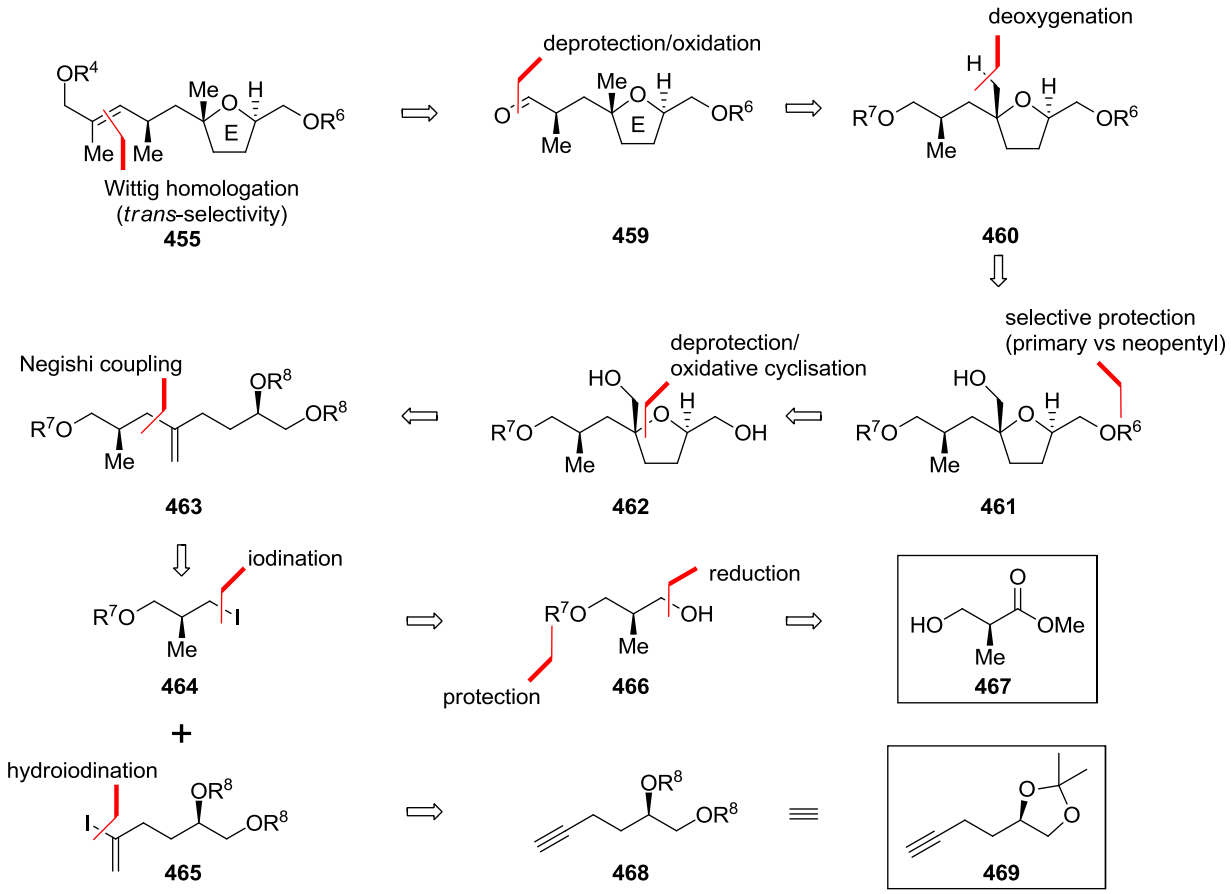


456 **457** **458**

Scheme 5.3 *One-pot hydrosilylation/oxidation*

It was proposed that the dimethylsilane group required for this transformation could be incorporated upon protecting the tertiary alcohol formed from an intermolecular alkyne addition of **454** to epoxide **453**. Fragment **453** is a known intermediate in Evans's synthesis, where R^1 = TBDPS, R^2 = PMB, R^3 = TBODPS and R^5 = TES. In this case, it would be imperative that R^1 and R^3 were not silyl ethers, due to the conditions required to oxidatively desilylate **451**. On the contrary, if R^5 remained as a silyl group, cleavage under these conditions would result in the sequence to form acetal **449** becoming one step shorter. Finally, alkyne **454** could be accessed from the sequential deprotection/oxidation of the C_{21} hydroxyl group of **455**, followed by a Seyferth-Gilbert homologation.

With this retrosynthesis in place, it was crucial to synthesise **455** in a short and efficient sequence. A possible retrosynthesis for the $C_{21\text{-}30}$ portion is shown in Scheme **5.4**.



Scheme 5.4 *Retrosynthetic analysis of the $C_{21\text{-}30}$ portion*

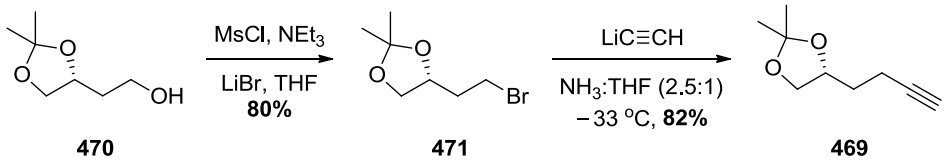
Intermediate **455** could be formed as the result of a stabilised Wittig homologation on aldehyde **459** to selectively form the *trans*-alkene, followed by further manipulation to afford the protected allyl alcohol. A deprotection and subsequent oxidation of **460** would allow access to the required aldehyde **459**. In order to synthesise the *trans*-THF portion of **460** using the osmium-mediated oxidative cyclisation, it was necessary to first synthesise *cis*-THF **461** which could subsequently undergo a deoxygenation reaction. It was evident at this stage that the selective protection of the primary alcohol within **462** in the presence of the neopentyl alcohol would be a challenging step, as definitive selectivity might be difficult to achieve under normal circumstances. Further disconnection of *cis*-THF **462** reveals that it would be the product of an oxidative cyclisation of 1,1-disubstituted alkene **463**, which could in turn result from a Negishi coupling of **465** and **464**. It was predicted that **464** could be afforded *via* an Appel type reaction of Roche ester derivative **466**. Furthermore, alkenyl iodide **465** could be formed from a

hydroiodination of alkyne **468**. Acetonide protected **469** is a known compound, which can be formed from commercially available starting materials in two steps. Evans's analogous synthesis to compound **458** (Scheme **5.2**) was completed in 14 linear steps from commercially available starting materials. Utilising the route proposed in Scheme **5.4**, would result in shortening this sequence.

5.3 Synthesis of E-ring

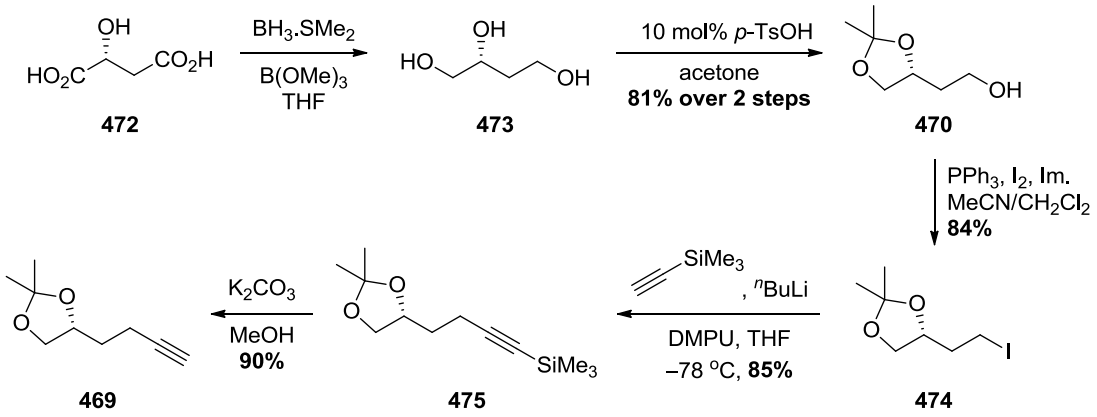
5.3.1 Synthesis of alkenyl iodide portion

Alkyne **469** has previously been synthesised from the commercially available (4*R*)-4-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolane **470** (Aldrich, £41/g) over a two-step procedure. This sequence involved a bromination at the primary alcohol followed by displacement with an alkynyllithium (Scheme **5.5**).[134]



Scheme 5.5 *Literature preparation of **469***

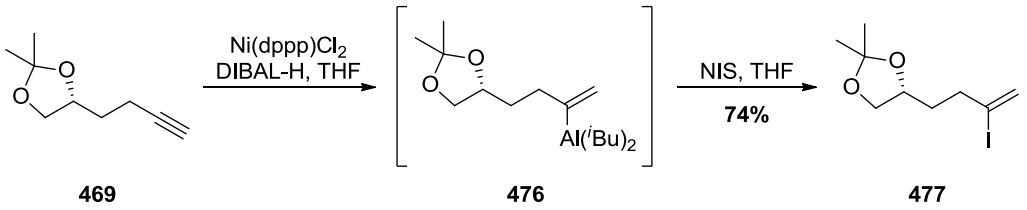
In order to access **469** in a convenient manner on a multigram scale, an alternative approach was utilised starting from D-(+)-malic acid (Aldrich, £13.90/g), which avoided the use of refluxing ammonia (Scheme **5.6**).[135]



Scheme 5.6 *Alternative route to **469***

This synthesis commenced with the reduction of D-(+)-malic acid to the corresponding 1,2,4-triol **473**. This triol could be selectively protected to afford commercially available (4*R*)-4-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolane **470** in 2 steps, with preferential formation of the five membered acetal. Subsequently, subjecting alcohol **470** to an iodination reaction, followed by an S_N2 displacement of the resulting iodide, led to the formation of silyl protected alkyne **475**. Finally, removal of the trimethylsilyl group was achieved under mild potassium carbonate/methanol conditions to afford alkyne **469** in good yield. This reliable sequence provided an efficient route to multigram quantities of **469** in 5 steps, with an overall yield of 52%.

In order to synthesise a suitable coupling partner for the key Negishi coupling from alkyne **469**, it was necessary to utilise recent methodology developed by Hoveyda and co-workers, whereby treatment of a terminal alkyne with Ni(dppp)Cl_2 and diisobutylaluminium hydride (DIBAL-H) resulted in the formation of an intermediate bearing an aluminium substituent at the internal position of the resulting alkene (Scheme **5.7**).[136] Subsequently, this intermediate could be quenched with an electrophilic halogen source in order to afford the corresponding vinyl halide.

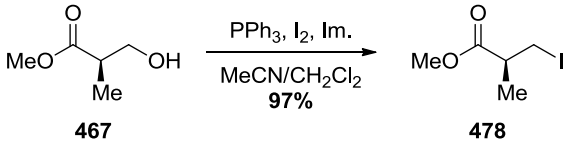


Scheme 5.7 *Formation of alkenyl iodide **477***

Applying these conditions to alkyne **469** resulted in the successful formation of alkenyl iodide **477** in 74% yield. With a reliable route now in place to synthesise Negishi precursor **477**, attention turned to the synthesis of a suitable coupling partner.

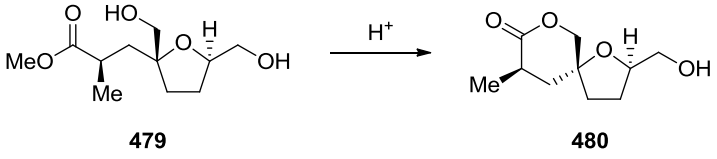
5.3.2 Formation of alkyl iodide

In order to avoid a scenario whereby a selective protection of a primary alcohol in the presence of a neopentyl alcohol is required further in the synthesis (compound **462**, Scheme **5.4**), it was necessary to utilise iodoester **478** in the key Negishi reaction. Iodoester **478** was formed in 97% yield *via* an iodination reaction of methyl (*R*)-(–)-3-hydroxy-2-methylpropionate (Scheme **5.8**).



Scheme 5.8 *Formation of iodide **478***

It was reasoned that further into the synthesis after the cyclisation step, the neopentyl alcohol could be protected intramolecularly *via* lactonisation with the ester, allowing the primary alcohol to be protected with ease (Scheme **5.9**).

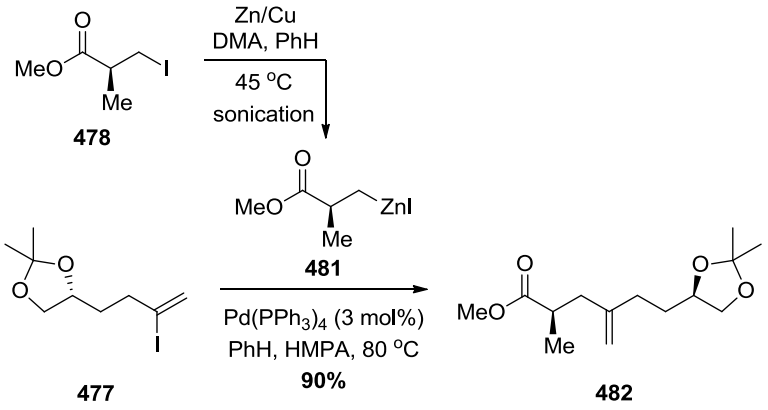


Scheme 5.9 *Lactonisation to selectively protect alcohol*

After gaining access to both coupling partners **477** and **478** in short, high yielding sequences, a position had now been reached whereby the Negishi coupling could be attempted.

5.3.3 Formation of intermediate lactone

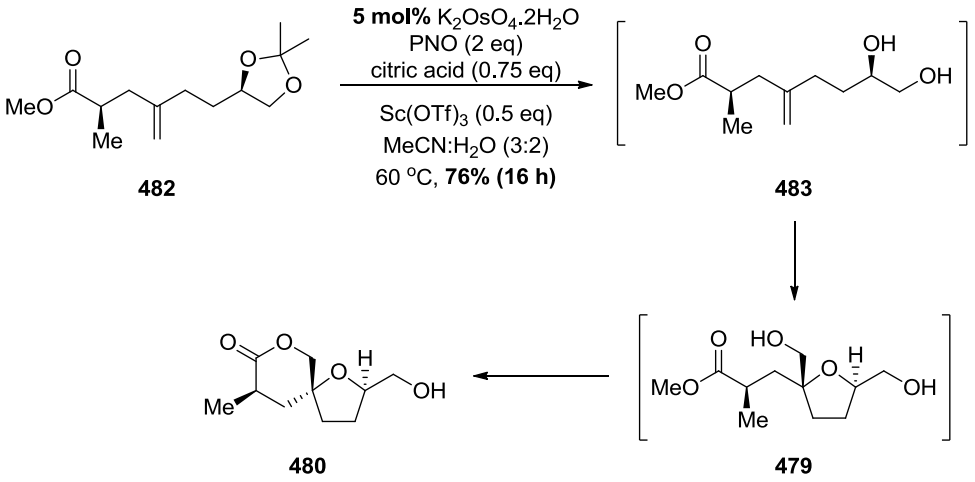
Utilising the same approach to the Negishi coupling in neodysiherbaine A (*vide supra* **Chapter 4.3.3**), iodide **478** was subjected to sonication in the presence of zinc/copper couple (Scheme **5.10**).



Scheme 5.10 *Negishi coupling to form **482***

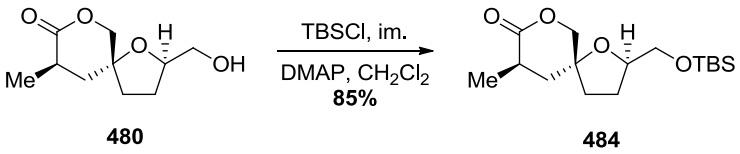
Addition of this preformed alkyl zinc reagent **481** to alkenyl iodide **477** in the presence of a palladium catalyst led to the formation of 1,1-disubstituted alkene **482** in 90% yield. It was discovered that this reaction would also proceed in the absence of HMPA as a co-solvent, however, the yield for this transformation was reduced to 76% and longer reaction times were required.

With the key 1,1-disubstituted alkene **482** in hand, it was now necessary to remove the acetonide protecting group and subject the resulting diol to the osmium-mediated oxidative cyclisation. It was predicted that utilising scandium triflate as the Lewis acid in the oxidative cyclisation would deliver conditions sufficiently acidic to remove the acetonide protecting group *in situ* and facilitate the oxidative cyclisation. Furthermore, this might also result in the subsequent lactonisation of THF **479**, effectively protecting the neopentyl alcohol. If successful, this reaction would result in three chemical transformations in a one-pot procedure. Pleasingly, subjecting **482** to the oxidative cyclisation, employing a catalytic amount of scandium triflate, resulted in the formation of lactone **480** in 76% yield (Scheme **5.11**).



Scheme 5.11 *Three steps in one-pot cyclisation*

It was also discovered that this transformation could be achieved by using copper triflate (0.5 eq) as the Lewis acid. However, in this case the yield of lactone **480** decreased to only 63%. Subsequent protection of the hydroxyl group of lactone **480** was achieved with a *tert*-butyldimethylsilyl group, resulting in the formation of intermediate **484** in high yield (Scheme **5.12**).



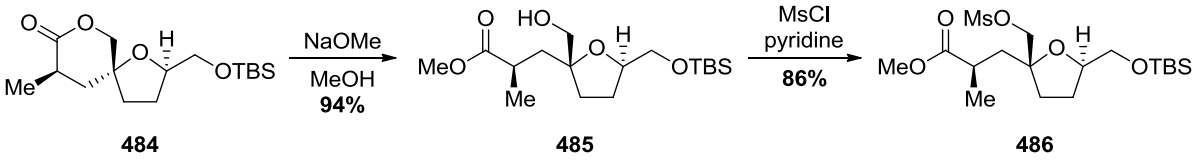
Scheme 5.12 *Protection of primary alcohol*

Now that a route to protected lactone **484** was in place, steps towards synthesising the deoxygenated THF could be made.

5.3.4 Attempted deoxygenations using sulfonyl groups

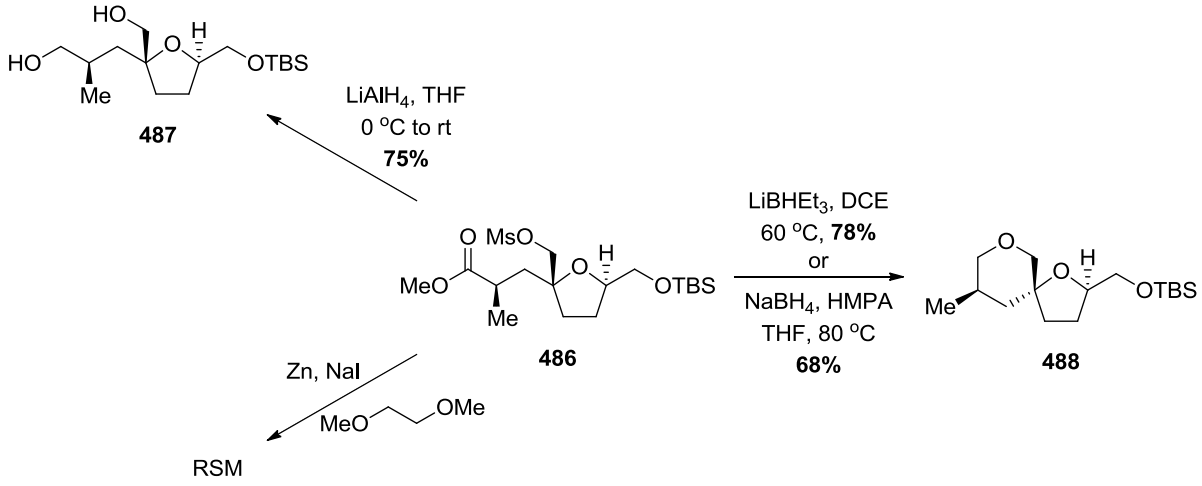
From this position, several options regarding the deoxygenation of the neopentyl alcohol and subsequent Wittig homologation were available. Initial attempts consisted of opening the lactone to the corresponding ester. Following significant literature precedent, it was reasoned that a mesylation of the resulting alcohol, followed by subsequent reduction would be possible.[137] This transformation would be an attractive prospect, as deoxygenation under these

conditions would also be accompanied by reduction of the ester, resulting in the synthesis becoming one step shorter. To this end, treatment of **484** under the action of basic methanol resulted in the formation of ester **485**. Subsequent mesylation of the resulting alcohol was achieved using mesyl chloride and pyridine to afford **486** in excellent yield (Scheme **5.13**).



Scheme 5.13 *Generation of mesylate*

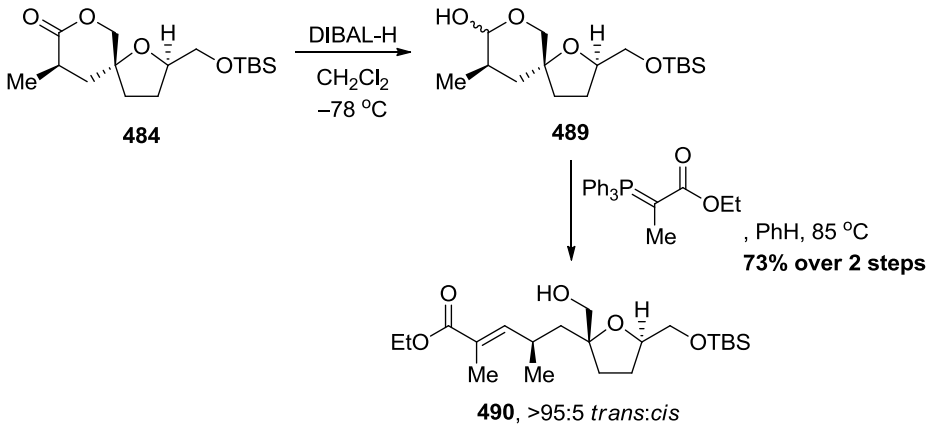
With the synthesis now at a critical point, mesylate **486** was subjected to a range of reductive deoxygenation conditions previously shown to promote the deoxygenation of neopentyl mesylates (Scheme **5.14**).[137]



Scheme 5.14 *Attempts to deoxygenate mesylate **486***

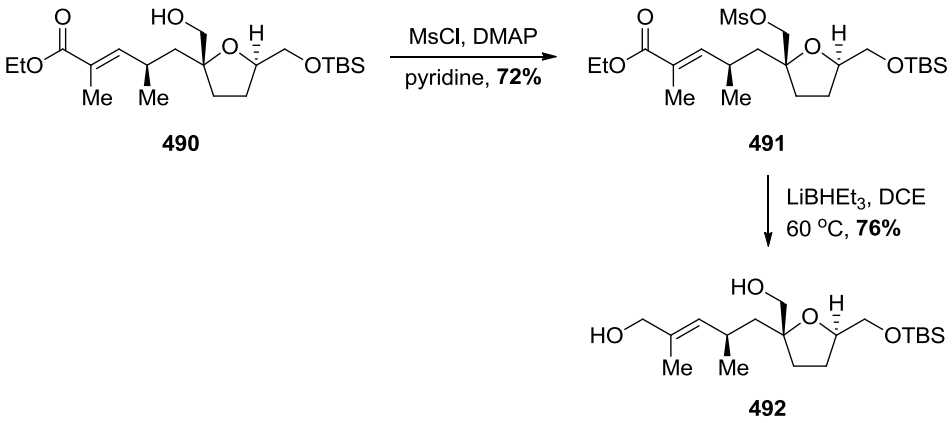
Unfortunately, these conditions did not result in the formation of the desired deoxygenated THF. When mesylate **486** was treated with an excess of lithium aluminium hydride at room temperature, cleavage of the S-O bond was observed resulting in the formation of alcohol **487** in 75% yield. Subsequent attempts with Super Hydride® (lithium triethylborohydride) or sodium borohydride at elevated temperatures led to the exclusive formation of tetrahydropyran **488**. This is presumably as a result of intramolecular attack of the newly formed alcohol

displacing the mesylate group. With the formation of tetrahydropyran **488** readily occurring at elevated temperatures, it was essential to employ an alternative system for the deoxygenation reaction, whereby displacement of the mesylate group would not occur. It was predicted that performing the Wittig-based chain extension before the deoxygenation step would prevent this from occurring. To this end, subjecting lactone **484** to a DIBAL-H reduction afforded lactol **489** and this compound was immediately subjected to a Wittig homologation to afford alcohol **490** in 73% yield over 2 steps (Scheme **5.15**).



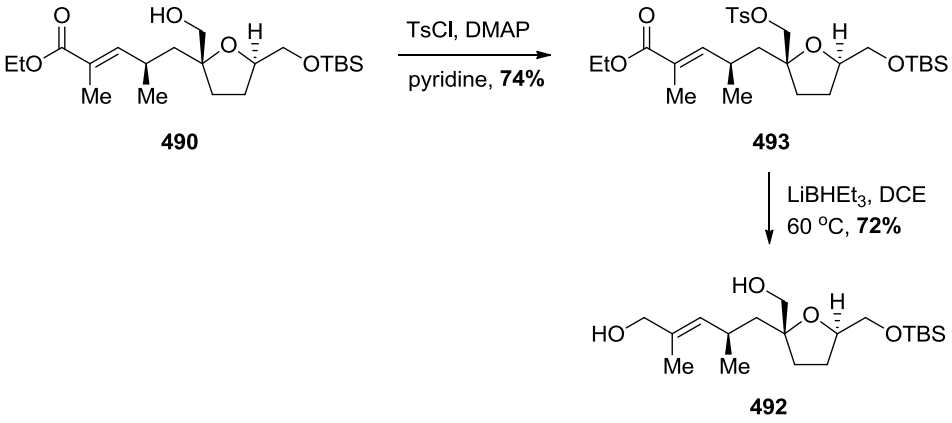
Scheme 5.15 *Wittig homologation*

From this position, the hydroxyl group of **490** could be subjected to the mesylation/reduction sequence without a competing cyclisation reaction occurring, which if successful would form the $C_{21\text{-}30}$ portion of pectenotoxin-4 in a total of 10 steps from commercially available starting materials. Whilst mesylation of alcohol **490** was achieved in 72% yield, exposure of mesylate **491** to reductive conditions with Super Hydride® again led to no C-O bond cleavage, with S-O cleavage observed instead (Scheme **5.16**).



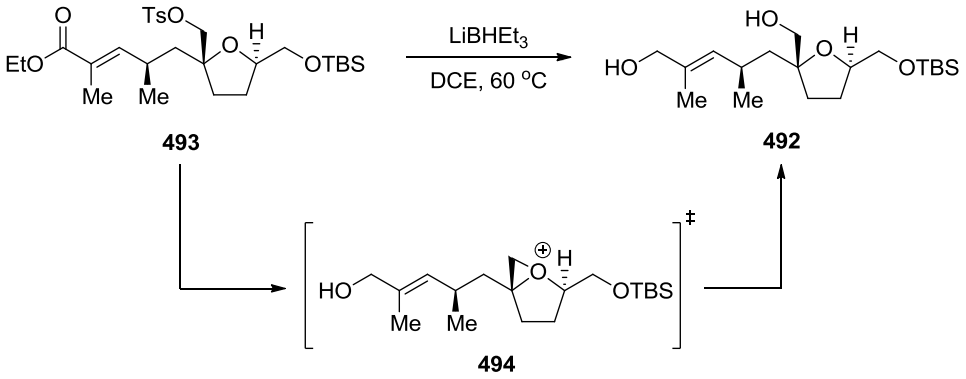
Scheme 5.16 *Unsuccessful mesylation/deoxygenation*

It was reasoned that increasing the steric hindrance of the sulfonyl group would reduce the probability of hydride attack at the sulphur atom. Tosylate protected alcohols have been shown to undergo efficient deoxygenations at similar neopentyl centres.[138] Therefore, alcohol **490** was subjected to a similar deoxygenation sequence utilising a tosylate group (Scheme **5.17**).



Scheme 5.17 *Alternative tosylation/reduction pathway*

Unfortunately, under these conditions diol **492** was again the only observed product. One possible explanation for these results was that the reaction proceeded by the lone pair of the THF-oxygen displacing the sulfonate leaving group (Scheme **5.18**).

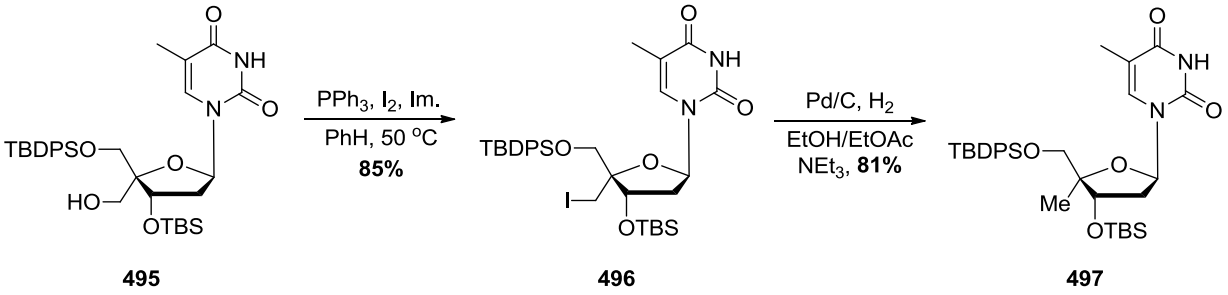


Scheme 5.18 *Proposed oxonium ion intermediate*

In this instance, the comparative size of the sulfonate group would have had little effect on the reaction. However, it is unclear why this intermediate oxonium ion was not readily attacked by a hydride source, but was presumably attacked by water upon workup. As a result of this, an alternative deoxygenation strategy was sought.

5.3.5 Alternative deoxygenation strategy and completion of the $C_{21\text{-}30}$ portion

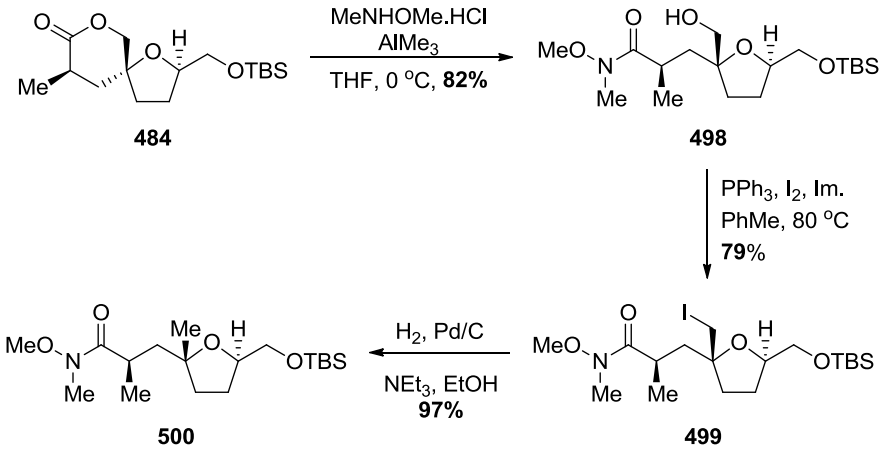
Literature precedent for the deoxygenation of similar neopentyl hydroxyl groups suggested that it would be possible to adopt an iodination/hydrogenation strategy for the formation of the E-ring (Scheme **5.19**).[139]



Scheme 5.19 *Literature iodination/hydrogenation approach to deoxygenation*

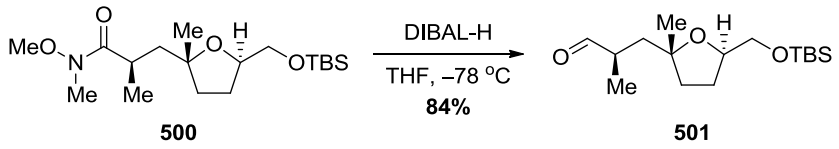
Utilising this tactic to deoxygenate alcohol **490** would be detrimental to the alkene functionality of α,β-unsaturated ester, with hydrogenation likely to occur. For this reason, it was necessary to use an alternative route. It was predicted that these conditions could be used to deoxygenate ester **485**, however, a shorter sequence from lactone **484** could be obtained by utilising Weinreb

amide methodology at an earlier stage.[140] It was reasoned that by opening lactone **484** with *N*,*O*-dimethylhydroxylamine hydrochloride, followed by subjecting the resulting alcohol to the iodination/hydrogenation conditions, would lead shorter sequence to incorporate the $C_{29\text{-}30}$ side chain. Work on this approach began by subjecting amide **498** to an Appel-type reaction, which yielded iodide **499** in 79% yield (Scheme **5.20**).



Scheme 5.20 *Weinreb amide approach to deoxygenation*

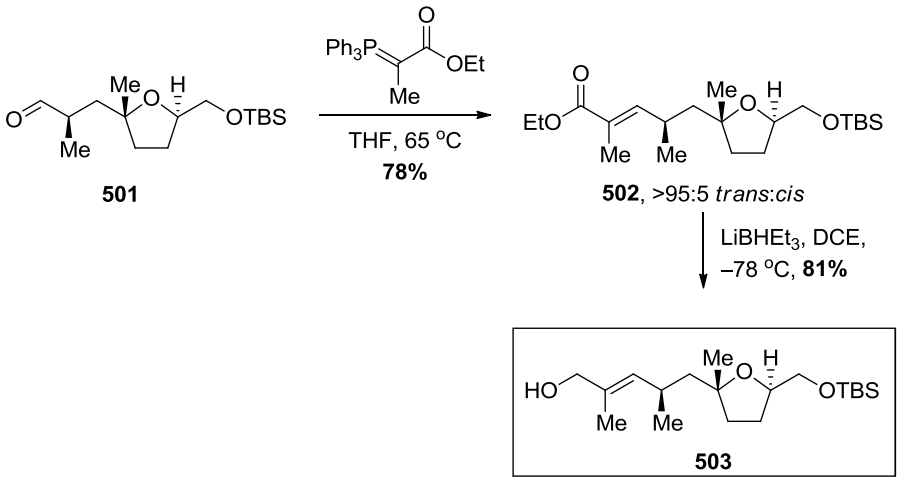
The formation of iodide **499** was confirmed by the disappearance of the C*H*$_2$OH peak at 67.2 ppm in the ^{13}C NMR spectrum, with a new peak corresponding to the C*H*$_2$I occuring at 15.9 ppm (which was confirmed to be a CH_2 in the ^{13}C DEPT spectrum). Iodide **499** could now be subjected to a hydrogenation in order to form the main core of the E-ring of pectenotoxin-4. Pleasingly, this was achieved with palladium on carbon, affording the methyl substituted *trans*-THF **500** in 97% yield. With a method now available for the formation of the E-ring of pectenotoxin-4, work could progress to install the $C_{29\text{-}30}$ side chain. As a consequence of utilising Weinreb's methodology, compound **500** was subsequently reduced to the corresponding aldehyde **501** in one step using DIBAL-H, with no over-reduced alcohol detected (Scheme **5.21**).



500 **501**

Scheme 5.21 *Formation of aldehyde **501***

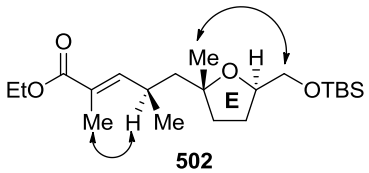
With aldehyde **501** in hand, the final steps of the synthesis could be attempted. The sequence required to complete the synthesis of the $C_{21\text{-}30}$ fragment consisted of a stabilised Wittig-homologation to give the *trans*-alkene, followed by reduction of the resulting ester. This was achieved by firstly subjecting aldehyde **501** to a slight excess of (carbethoxyethylidene) triphenylphosphine (Scheme **5.22**).



501 **503**

Scheme 5.22 *Formation of alcohol **500***

The stereochemistry of α,β-unsaturated ester **502** was confirmed as *trans* by NOE studies, which also revealed a *trans*-geometry across the E-ring THF (Figure **5.2**). Finally, reduction of ester **502** using Super Hydride® afforded the desired $C_{21\text{-}30}$ fragment of pectenotoxin-4.

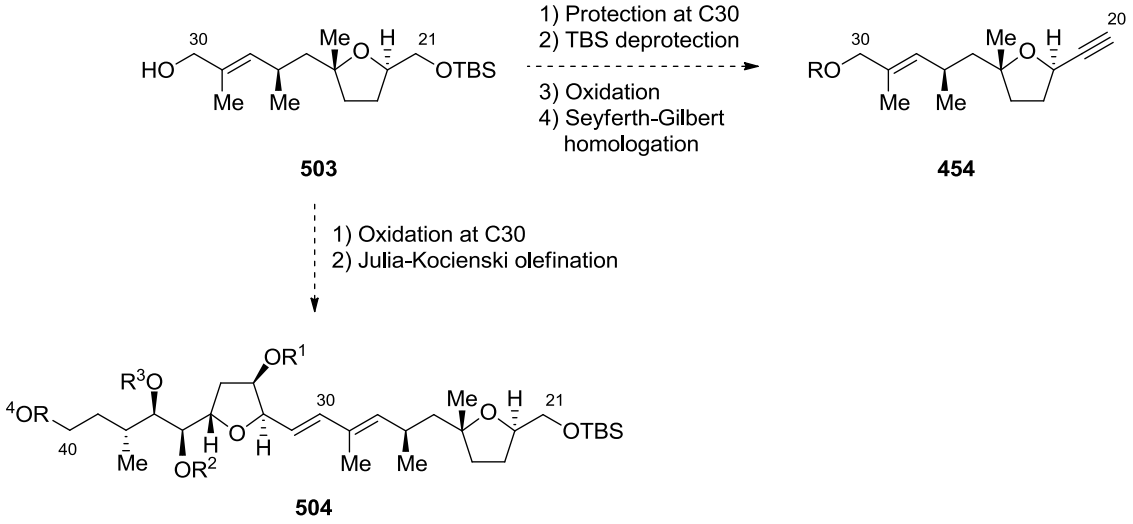


502

Figure 5.2 *NOE correlation of ester **502***

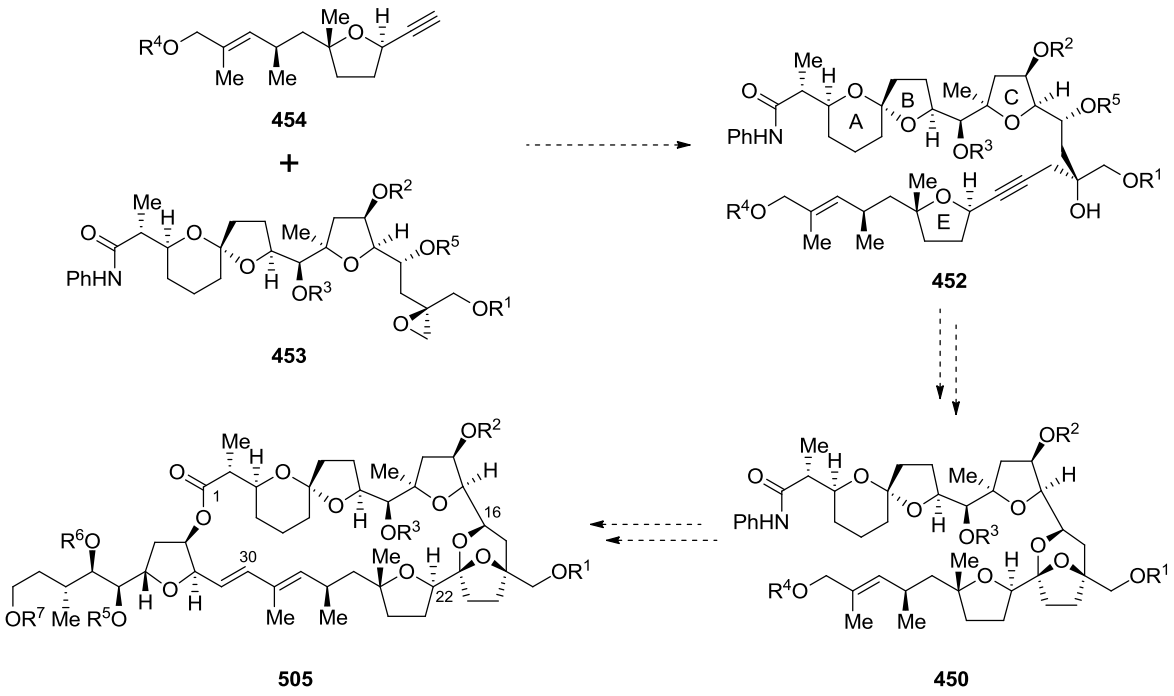
5.4 Conclusions and future work

In conclusion, a short and effective synthesis of the C_{21-30} fragment of pectenotoxin-4 has been achieved using osmium-mediated oxidative cyclisation methodology. This sequence was completed in 12 steps from commercially available starting materials and represents the shortest synthesis to date for this fragment. There are two options available from which the synthesis can progress. Firstly, **503** could undergo manipulation at the C_{30}-centre in order to couple to the FG-ring portion. This would enable the synthesis of the C_{21-40} portion, which could then undergo coupling to the ABC-ring system. Alternatively, alkyne **454** could be prepared in a further 4 steps, which could subsequently be coupled to the C_{1-19} portion (Scheme **5.23**).



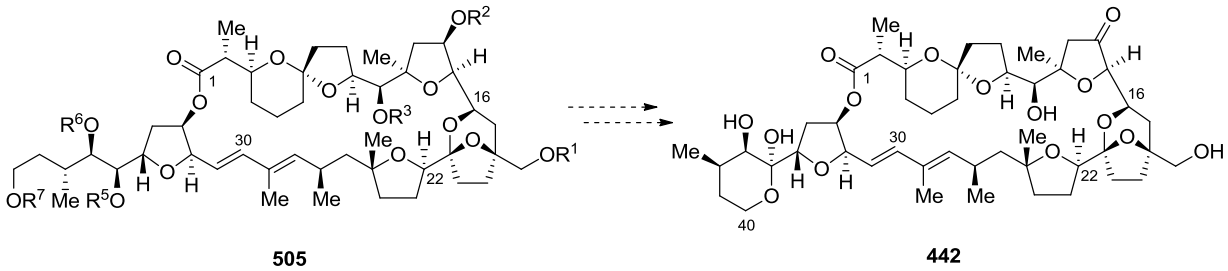
Scheme 5.23 *Extension to the C_{20-30} fragment*

Based on Evans's observations, it is likely that initial manipulation at the C_{21}-centre would prove to be a more reliable strategy. From **454**, the key coupling reaction between the alkyne at C_{20} and the epoxide of the C_{1-19} portion could take place (Scheme **5.24**).



Scheme 5.24 *Completion of the synthesis of pectenotoxin-4*

The resulting $C_{1\text{-}30}$ fragment **452** would then be set up to undergo an intramolecular hydrosilylation/oxidation sequence to form the D-ring lactol (*vide supra* **Chaper 5.2**). With the D-ring installed, **450** would be ready to undergo coupling to the $C_{31\text{-}40}$ portion. This would proceed by removal of the R^4 protecting group at C_{30}, followed by an oxidation to afford the corresponding aldehyde. As in Scheme **5.25**, this aldehyde would then undergo a Julia-Kocienski homologation to install the *trans*-alkene at $C_{30/31}$. Subsequently, employing similar conditions to Evans would allow a deprotection/lactonisation with the hydroxyl group at C_{33} to form the core macrocycle. Next, **505** could be subjected to a deprotection/oxidation at C_{14} and C_{36} (Scheme **5.25**).



Scheme 5.25 *Final steps to form pectenotoxin-4*

Finally, deprotection of the C_{40} hydroxyl group would result in the formation of the G-ring, which after a global deprotection, would deliver pectenotoxin-4.

Chapter 6

Experimental Section

6.1 Experimental techniques

^{1}H NMR spectra were recorded either on a Bruker Avance AV400 (400 MHz) or a Bruker AV500 (500 MHz) spectrometer in $CDCl_3$, D_4-MeOD, D_6-Me_2CO or D_6-DMSO and referenced to residual solvent peaks or to $SiMe_4$ as an internal standard. Chemical shifts are quoted in ppm with signal splittings recorded as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin) and multiplet (m). Coupling constants, *J*, are measured in Hz.

^{13}C NMR spectra were recorded on a Bruker AV400 or a Bruker AV500 and were referenced to $CDCl_3$, D_4-MeOD, D_6-Me_2CO or D_6-DMSO. ^{1}H and ^{13}C NMR spectra were recorded at room temperature unless otherwise stated.

Infra-red spectra were recorded on a Bruker Tensor 27 FTIR spectrometer. Spectra were analysed as thin films or pressed solids using the Infra-red Diamond ATR Module. Selected absorption peaks are given in cm^{-1}.

High Resolution Mass Spectra (HRMS) were recorded on a Brucker MicroTof spectrometer under conditions of electrospray ionisation (ESI). Values are reported as ratio of mass to charge in Daltons.

Specific optical rotations were recorded on a Perkin Elmer 241 Polarimeter at the sodium D line (589.3 nm) in ACS photo spectroscopic grade dichloromethane and are quoted in the units of 10^{-1} deg cm^2 g^{-1}. Solution concentrations are given in units of 10^{-2} g mL^{-1}.

Melting points were determined using a Leica melting point apparatus and are uncorrected.

Flash column chromatography was performed using silica gel 60 (0.033-0.070mm, BDH) using head pressure by means of a positive pressure from a nitrogen line, employing the method of Still *et al.*[141] TLC analyses were performed on Merck Kiesegel 60 F_{254} 0.25 mm precoated aluminium plates. Product spots were visualised under UV light (λ_{max} = 254 nm) and/or by staining with potassium permanganate, vanillin or phosphomolybdic acid solution.

Reagents obtained from Acros, Aldrich, Alfa Aesar, Fluorochem and Strem fine chemicals suppliers were used directly as supplied or following purification according to procedures described by Perrin and Armarego.[142]

Reactions were carried out under an inert atmosphere of argon if anhydrous conditions were required. Syringes and needles for the transfer of reagents, and flasks or other apparatus were dried in an oven before being cooled in a dessicator over self-indicating silica gel, or flame dried under vacuum.

Acetonitrile, dichloromethane, diethyl ether, methanol, tetrahydrofuran and toluene were dried by filtration though two activated alumina, purification columns.[143] Petrol refers to petroleum ether in the boiling range 30-60 ^{o}C.

6.2 General procedures

General Procedure 1: TFA mediated oxidative cyclisation[41]

To a solution of diol (1.0 mmol) in 9:1 acetone:water (20 mL) and trifluoroacetic acid (10 mL) was added pyridine *N*-oxide (2.0 mmol), citric acid (0.75 mmol) and potassium osmate dihydrate (as specified). The resultant solution was stirred until all starting material had reacted

(monitored by TLC). The reaction mixture was quenched with sodium sulfite (1.00 mmol) and stirred for 30 min before water (20 mL) and ethyl acetate (20 mL) were added. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with aqueous hydrochloric acid (1 M, 40 mL), aqueous sodium hydroxide (2 M, 3 x 40 mL), dried over sodium sulfate and concentrated *in vacuo* to give the crude product which was then purified as specified.

General Procedure 2: Dihydroxylation reaction[19]

To a stirred solution of diene (1.0 mmol) in *tert*-butanol/water (10 mL, 1:1 mixture) was added quinuclidine or $(DHQD)_2PHAL$ (0.075 mmol), potassium carbonate (2.0 mmol), methanesulfonamide (1.0 mmol) and potassium ferricyanide (2.0 mmol). The resultant mixture was stirred vigorously until all reagents had dissolved and cooled to 5 ^{o}C before potassium osmate dihydrate (0.05 mmol) was added. The mixture was left to stir at 5 ^{o}C until all starting material had reacted (monitor by TLC). The resultant mixture was then quenched with sodium sulfite (1.0 mmol) and stirred for 30 min before ethyl acetate (20 mL) was added. The two layers were separated and the organic layer washed with water (20 mL). The combined aqueous layers were then extracted with ethyl acetate (3 x 10 mL). The combined organics were dried over sodium sulfate, filtered and the solvent removed *in vacuo* to give the crude product which was then purified as specified.

General Procedure 3: Lewis acid cyclisation[144]

To a stirred solution of diol (1.0 mmol) in MeCN (12 mL) was added pyridine *N*-oxide (2.0 mmol). A solution of citric acid (0.75 mmol) in water (4 mL) and a solution of potassium osmate dihydrate (0.05 mmol) in water (4 mL) were added sequentially. The resulting green solution was then stirred for 5 min before a metal trifluoromethanesulfonate (as specified) was

added. The resultant mixture was heated to 60 ^{o}C and stirred until all starting material had reacted (monitor by TLC). The resultant mixture was then quenched with sodium sulfite (50 mg) and stirred for 30 min before ethyl acetate (20 mL) and water (10 mL) were added. The two layers were separated and the aqueous layer extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo* to give the crude product which was then purified as specified.

General Procedure 4: Buffered Lewis acid cyclisation[144]

To a stirred solution of diol (1.0 mmol) in MeCN/pH 6.5 phosphate buffer (20 mL, 3:2 mixture) was added pyridine *N*-oxide (2.0 mmol), citric acid (0.75 mmol) and copper (II) trifluoromethanesulfonate (0.5 mmol). The resultant mixture was heated to 60 ^{o}C before potassium osmate dihydrate (0.05 mmol) was added and the mixture left to stir until all starting material had reacted (monitor by TLC). The resultant mixture was then quenched with sodium sulfite (1.0 mmol) and stirred for 30 min before ethyl acetate (20 mL) and water (10 mL) were added. The two layers were separated and the aqueous layer extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo* to give the crude product which was then purified as specified.

General Procedure 5: Seyferth-Gilbert homologation[127]

To a mixture of the aldehyde (1.0 mmol), freshly purified Bestmann-Ohira reagent (1.2 mmol) and potassium carbonate (2.0 mmol) was added methanol (15 mL) and the reaction was stirred for 5 h at room temperature before the solvent was removed *in vacuo*. Diethyl ether (40 mL) was added to the resulting residue and the mixture was washed with water (50 mL), a saturated

aqueous solution of sodium bicarbonate (50 mL) and a further portion of water (50 mL). The organic layer was dried over sodium sulfate, filtered and the solvent removed *in vacuo* to give the crude product which was purified as specified.

General Procedure 6: Trost hydrosilylation[110]

A solution of alkyne (1.0 mmol) and silane (1.2 mmol) in CH_2Cl_2 (2 mL) was cooled to 0 ^oC and degassed with argon for 15 min. Pentamethylcyclopentadienyltris(acetonitrile) ruthenium (II) hexafluorophosphate (2 mol%) was added and the solution was warmed to room temperature and stirred for 16 h at this temperature. The solvent was removed *in vacuo* to give the crude product which was purified as specified.

General Procedure 7: Silicon oxidation[145]

To a solution of benzyl-protected THF (1.0 mmol) in tetrahydrofuran (10 mL) at 40 ^oC was added tetrabutylammonium fluoride (4.0 mL, 2.0 mmol, 0.5 M solution in tetrahydrofuran) *via* syringe pump addition over 30 min. The resultant mixture was stirred at 40 ^oC for a further 30 min before methanol (2.0 mL), potassium bicarbonate (3.0 mmol) and urea-hydrogen peroxide (5.0 mmol) were added. After stirring at 40 ^oC for 1 h, a saturated solution of sodium thiosulfate (15 mL) was added. The mixture was extracted with ethyl acetate (3 x 30 mL) and the combined organic layers washed with brine (30 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo* to give the crude product which was purified as specified.

General Procedure 8: Hydride shift methylation[113]

To a solution of THF (1.0 mmol) in CH_2Cl_2 (10 mL) at 0 ^oC was added trimethylaluminium (1.0 mL, 2.0 mmol, 2 M in heptane) in one portion followed by dimethylaluminium chloride (1.0 mL, 1.0 mmol, 1 M in heptane). The resultant mixture was stirred at 0 ^oC for 8 h before

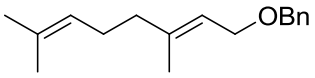
water (20 mL) and ethyl acetate (20 mL) were added and the layers separated. The aqueous layer was extracted with ethyl acetate (3 x 20 mL) and the combined organic layers washed with brine (30 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo* to give the crude product which was purified as specified.

General Procedure 9: Super hydride® reduction[146]

A solution of super hydride® (12.0 mL, 12.0 mmol, 1 M in tetrahydrofuran) was reduced *in vacuo* before a solution of sulfonate (1.0 mmol) in 1,2-dichloroethane (6 mL) was added. The resultant solution was heated to 60 ^{o}C for 16 h before ethyl acetate (20 mL) and water (20 mL) were added and the layers separated. The aqueous layer was extracted with ethyl acetate (3 x 20 mL) and the combined organic layers washed with brine (30 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo* to give the crude product which was purified as specified.

6.3 Experimental procedures

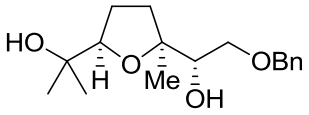
(*E*)-((3,7-Dimethylocta-2,6-dienyloxy)methyl)benzene, 48



To a stirred solution of geraniol (1.75 mL, 10.0 mmol) in tetrahydrofuran (40 mL) at 0 °C was added sodium hydride (60% dispersion in mineral oil, 0.600 g, 15.0 mmol) followed by benzyl bromide (1.78 mL, 15.0 mmol). The resultant solution was left to warm to room temperature and was stirred for 20 h before being quenched with a saturated solution of ammonium chloride (20 mL). The mixture was then extracted with diethyl ether (3 x 25 mL) and the combined organic layers were dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, petrol then Et_2O-petrol, 5:95] afforded

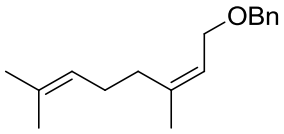
benzyl ether **48** (2.40 g, 84%) as an oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.38-7.27 (5H, m, 5 x Ar-C*H*), 5.44-5.39 (1H, m, C*H*CH_2OBn), 5.14-5.09 (1H, m, $(CH_3)_2C$=C*H*), 4.52 (2H, s, CH_2Ph), 4.07-4.02 (2H, s, CH_2OBn), 2.17-2.02 (4H, m, CH_2CH_2), 1.69 (3H, s, 1 x CH_3), 1.66 (3H, s, 1 x CH_3), 1.62 (3H, s, 1 x CH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 140.5, 128.4, 127.9, 127.5, 124.0, 120.8, 72.0, 66.6, 39.6, 26.4, 25.8, 17.7, 16.5. Data were consistent with those previously reported.[147]

2-((2*R*,5*S*)-5-((*S*)-Benzyloxy(hydroxy)methyl)-5-methyltetrahydrofuran-2-yl)propan-2-ol, 49



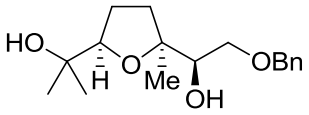
Diol **55** (50 mg, 0.18 mmol) was subjected to **General Procedure 1** (8 h) using potassium osmate dihydrate (3.3 mg, 0.0090 mmol, 5.0 mol%). Purification by flash column chromatography [SiO_2, acetone-petrol, 20:80] afforded THF **49** (44 mg, 83%) as an oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.39-7.26 (5H, m, 5 x Ar-C*H*), 4.62-4.53 (2H, m, CH_2Ph), 3.85 (1H, t, *J* = 7.1, OC*H*), 3.74 (1H, dd, *J* = 8.5, 3.3, C*H*OH), 3.69-3.63 (1H, m, CH_AH$_B$OBn), 3.61-3.54 (1H, m, CH$_A$$H_B$OBn), 3.20 (2H, br. s, 2 x O*H*), 2.28-2.17 (1H, m, THF-CH_AH$_B$), 2.06-1.85 (2H, m, THF-CH_2), 1.65-1.58 (1H, m, THF-CH$_A$$H_B$), 1.23 (3H, s, 1 x C$H_3$), 1.15 (3H, s, 1 x C$H_3$), 1.09 (3H, s, 1 x C$H_3$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 137.8, 128.5, 127.8, 85.8, 83.9, 75.4, 73.5, 71.7, 71.1, 35.1, 27.8, 26.3, 25.0, 23.3; $[\alpha]_D^{22}$ –15.0 (*c* 1.0, CH_2Cl_2). Data were consistent with those previously reported.[35]

(*Z*)-((3,7-Dimethylocta-2,6-dienyloxy)methyl)benzene, 50



To a stirred solution of nerol (1.75 mL, 10.0 mmol) in tetrahydrofuran (40 ml) at 0 °C was added sodium hydride (600 mg, 10.0 mmol) and benzyl bromide (1.78 g, 15.0 mmol) sequentially. The resultant solution was left to warm to room temperature and was stirred for 20 h before being quenched with a saturated solution of ammonium chloride (20 mL). The mixture was then extracted with diethyl ether (3 x 25 mL), and the combined organic layers dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, petrol then Et_2O-petrol, 5:95] afforded benzyl ether **50** (2.09 g, 86%) as an oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.43-7.26 (5H, m, 5 x Ar-C*H*), 5.43 (1H, td, *J* = 6.8, 1.2, C*H*CH_2OBn), 5.13-5.06 (1H, m, $(CH_3)_2$C=C*H*), 4.52 (2H, s, CH_2Ph), 4.02 (2H, dd, *J* = 6.8, 1.2, CH_2OBn), 2.10-2.05 (4H, m, CH_2CH_2), 1.78 (3H, d, *J* = 1.1, 1 x CH_3), 1.69 (3H, s, 1 x CH_3), 1.60 (3H, s, 1 x CH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 140.7, 138.6, 132.0, 128.4, 127.8, 127.5, 123.9, 121.8, 72.1, 66.4, 32.3, 26.7, 25.8, 23.6, 17.7. Data were consistent with those previously reported.[148]

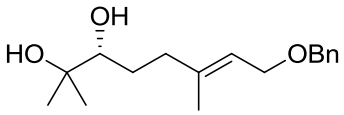
2-((2*R*,5*S*)-5-((*R*)-Benzyloxy(hydroxy)methyl)-5-methyltetrahydrofuran-2-yl)propan-2-ol, 51



Diol **243** (50 mg, 0.18 mmol) was subjected to **General Procedure 1** (24 h) using potassium osmate dihydrate (3.3 mg, 0.0090 mmol, 5.0 mol%). Purification by flash column chromatography [SiO_2, acetone-petrol, 20:80] afforded THF **51** (39 mg, 74%) as an oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.39-7.26 (5H, m, 5 x Ar-C*H*), 4.56 (2H, s, CH_2Ph), 3.88-

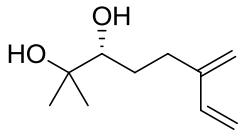
3.80 (2H, m, OC*H* + C*H*OH), 3.62 (1H, dd, *J* = 9.7, 3.2, C*H*$_A$H$_B$OBn), 3.41 (1H, dd, *J* = 9.7, 7.8, CH$_A$*H*$_B$OBn), 2.98 (2H, br. s, 2 x O*H*), 2.23-2.15 (1H, m, THF-C*H*$_A$H$_B$), 2.05-1.85 (2H, m, THF-C*H*$_2$), 1.53 (1H, ddd, *J* = 12.4, 8.3, 6.8, THF-CH$_A$*H*$_B$), 1.24 (3H, s, 1 x C*H*$_3$), 1.16 (3H, s, 1 x C*H*$_3$), 1.10 (3H, s, 1 x C*H*$_3$); **^{13}C NMR (100 MHz, CDCl$_3$)** δ_C: 138.8, 128.5, 127.8, 84.9, 84.4, 75.5, 73.4, 71.8, 71.2, 32.7, 27.7, 26.6, 25.1, 23.6; **$[\alpha]_D^{23}$** +3.1 (*c* 1.0, CH_2Cl_2). Data were consistent with those previously reported.[35]

(*R*,*E*)-8-(Benzyloxy)-2,6-dimethyloct-6-ene-2,3-diol, 55



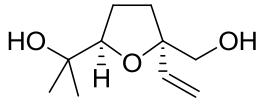
Benzyl ether **48** (1.40 g, 5.73 mmol) was subjected to **General Procedure 2** (36 h) with $(DHQD)_2PHAL$. Purification by flash column chromatography [SiO_2, acetone-petrol, 20:80] afforded diol **55** (513 mg, 38%) as an oil. **^{1}H NMR (400 MHz, CDCl$_3$)** δ_H: 7.37-7.28 (5H, m, 5 x Ar-C*H*), 5.49-5.43 (1H, m, C=C*H*), 4.52 (2H, s, C*H*$_2$Ph), 4.04 (2H, d, *J* = 6.8, C*H*$_2$OBn), 3.36 (1H, dd, *J* = 10.6, 1.8, C*H*OH), 2.32 (1H, ddd, *J* = 14.2, 9.4, 5.2, C*H*$_A$H$_B$C(CH$_3$)=CH), 2.20-2.07 (3H, m, 2 x O*H* + CH$_A$*H*$_B$C(CH$_3$)=CH), 1.69-1.57 (4H, m, C*H*$_3$C=CH + C*H*$_A$H$_B$OH), 1.50-1.39 (1H, m, CH$_A$*H*$_B$CHOH), 1.21 (3H, s, 1 x C*H*$_3$COH), 1.16 (3H, s, 1 x C*H*$_3$COH); **^{13}C NMR (100 MHz, CDCl$_3$)** δ_C: 140.3, 138.4, 128.4, 127.9, 127.6, 121.23, 78.1, 73.1, 72.2, 66.6, 36.7, 29.5, 26.5, 23.2, 16.6. **$[\alpha]_D^{22}$** +17.6 (*c* 1.0, CH_2Cl_2). Data were consistent with those previously reported.[35]

(*R*)-2-Methyl-6-methyleneoct-7-ene-2,3-diol, 171



Freshly distilled myrcene (1.00 g, 7.35 mmol) was subject to **General Procedure 2** (36 h). Purification by flash column chromatography [SiO_2, Et_2O-petrol, 80:20] afforded diol **171** (525 mg, 42%) as an oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 6.39 (1H, dd, *J* = 17.6, 10.8, C*H*=CH_2), 5.28 (1H, d, *J* = 17.6, CH=CH_AH_B), 5.09 (1H, d, *J* = 10.8, CH=CH_AH_B), 5.07-5.04 (2H, m, C=CH_2), 3.42 (1H, dd, *J* = 10.4, 1.6, C*H*OH), 2.55 (1H, ddd, *J* = 14.8, 9.6, 5.2, CH_AH_BC=CH_2), 2.34-2.20 (2H, m, 1 x O*H* + CH_AH_BC=CH_2), 1.94 (1H, br. s, 1 x O*H*), 1.74-1.64 (1H, m, CH_AH_BCHOH), 1.57-1.46 (1H, m, CH_AH_BCHOH), 1.22 (3H, s, 1 x CH_3), 1.17 (3H, s, 1 x CH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 146.1, 138.6, 116.1, 113.6, 78.2, 73.1, 30.1, 28.5, 26.5, 23.3. **$[\alpha]_D^{21}$** +17.2 (*c* 0.5, CH_2Cl_2). Data were consistent with those previously reported.[149]

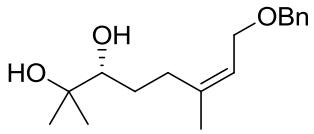
2-((2*R*,5*R*)-5-(Hydroxymethyl)-5-vinyltetrahydrofuran-2-yl)propan-2-ol, 172



Diol **171** (50 mg, 0.29 mmol) was subjected to **General Procedure 3** (24 h) using potassium osmate dihydrate (5.4 mg, 0.015 mmol, 5.0 mol%). Purification by flash column chromatography [SiO_2, acetone-petrol, 20:80] afforded *THF* **172** (39 mg, 78%) as an oil. **IR** (thin film, cm^{-1}) 3375, 2967, 1056; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 5.80 (1H, dd, *J* = 17.2, 10.8, C*H*=CH_2), 5.31 (1H, dd, *J* = 17.2, 1.6, CH=CH_AH_B), 5.13 (1H, dd, *J* = 10.8, 1.6, CH=CH_AH_B), 3.84 (1H, t, *J* = 11.2, C*H*C$(CH_3)_2$OH), 3.59 (1H, d, *J* = 11.2, CH_AH_BOH), 3.49 (1H, d, *J* = 11.2, CH_AH_BOH), 3.10 (1H, br. s, 1 x O*H*), 2.94 (1H, br. s, 1 x O*H*), 2.11 (1H, ddd, *J* = 12.0, 8.8, 6.0, THF-CH_AH_B), 1.97-1.82 (2H, m, THF-CH_2), 1.81-1.72 (1H, m,

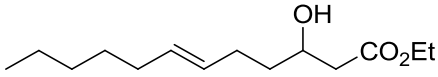
THF-CH_AH_B), 1.29 (3H, s, 1 x CH_3), 1.14 (3H, s, 1 x CH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 140.3, 114.0, 86.2, 85.7, 71.9, 67.5, 32.2, 27.6, 26.3, 25.1; **HRMS**: (ES^+, *m/z*): Calculated 209.1151 ($C_{10}H_{18}NaO_3$); Found 209.1154; **$[\alpha]_D^{22}$** +1.3 (*c* 1.0, CH_2Cl_2).

(*R*,*Z*)-8-(Benzyloxy)-2,6-dimethyloct-6-ene-2,3-diol, 243



Benzyl ether **50** (2.10 g, 8.61 mmol) was subjected to **General Procedure 2** (36 h) with $(DHQD)_2PHAL$. Purification by flash column chromatography [SiO_2, acetone-petrol, 20:80] afforded diol **243** (1.22 g, 54%) as an oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.39-7.26 (5H, m, 5 x Ar-C*H*), 5.57 (1H, t, *J* = 7.4, C*H*CH_2OBn), 4.54 (2H, s, CH_2Ph), 4.13 (1H, dd, *J* = 10.8, 7.6, C$H_A$$H_B$OBn), 3.88 (1H, dd, *J* = 10.8, 7.2, CH_AH_BOBn), 3.24 (1H, dd, *J* = 11.2, 1.6, C*H*OH), 2.49 (1H, ddd, *J* = 13.3, 10.0, 6.4, CH_AH_BC(CH_3)=CH), 2.13-2.05 (1H, m, CH_AH_BC(CH_3)=CH), 1.75 (3H, s, C(CH_3)=CH), 1.69-1.58 (1H, m, CH_AH_BCHOH), 1.50-1.39 (1H, m, CH_AH_BCHOH), 1.15 (3H, s, 1 x CH_3COH), 1.11, (3H, s, 1 x CH_3COH); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 142.7, 137.7, 128.5, 128.1, 127.9, 121.7, 76.1, 72.5, 65.6, 28.6, 28.1, 26.3, 23.3, 23.0; **$[\alpha]_D^{23}$** +15.1 (*c* 1.0, CH_2Cl_2). Data were consistent with those previously reported.[35]

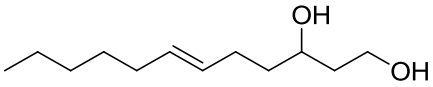
(*E*)-Ethyl 3-hydroxydodec-6-enoate, 244



To a stirred solution of diisopropylamine (1.66 mL, 11.8 mmol) in tetrahydrofuran (30 mL) at 0 °C was added *n*-butyllithium (7.40 mL, 11.8 mmol, 1.6 M in hexanes) dropwise. The reaction mixture was stirred for 20 min at 0°C before being cooled to –78 °C. Distilled ethyl acetate

(1.00 mL, 11.5 mmol) was added dropwise and the resulting mixture was stirred at –78 °C for a further 20 min. *trans*-4-Decenal (0.695 mL, 3.80 mmol) was added dropwise and the resultant mixture was stirred at –78 °C for 2 h before being quenched with a saturated solution of ammonium chloride (20 mL). The mixture was then extracted with diethyl ether (3 x 25 mL) and the combined organic layers were washed with brine (1 x 30 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, Et_2O-petrol, 30:70] afforded hydroxyl-ester **244** (0.67 g, 73%) as an oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 5.46-5.33 (2H, m, C*H*=C*H*), 4.12 (2H, q, *J* = 7.0, CH_3CH_2O), 4.00-3.95 (1H, m, C*H*OH), 3.04 (1H, d, *J* = 3.6, CHO*H*), 2.46 (1H, dd, *J* = 16.4, 3.6, $CH_AH_BCO_2Et$), 2.36 (1H, dd, *J* = 16.4, 3.6, $CH_AH_BCO_2Et$), 2.13-2.02 (2H, m, CH_2CH_2CHOH), 1.96-1.91 (2H, m, $CH_3(CH_2)_3CH_2$), 1.60-1.51 (1H, m, $CH_2CH_AH_BCHOH$), 1.50-1.41 (1H, m, $CH_2CH_AH_BCHOH$), 1.35-1.21 (6H, m, $CH_3CH_2CH_2CH_2$), 1.24 (3H, t, *J* = 7.0, CH_3CH_2O), 0.83 (3H, t, *J* = 7.2, $CH_3CH_2CH_2$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 173.0, 131.2, 128.1, 67.6, 60.6, 41.2, 36.3, 32.5, 31.3, 29.1, 28.5, 22.6, 14.1, 14.0. Data were consistent with those previously reported.[34]

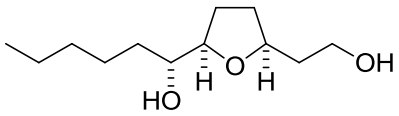
(*E*)-Dodec-6-ene-1,3-diol, 245



To a stirred solution of hydroxy-ester **244** (620 mg, 2.56 mmol) in tetrahydrofuran (35 mL) at 0 °C was added lithium borohydride (167 mg, 7.68 mmol). The resultant mixture was allowed to warm to room temperature and was stirred for 16 h before being quenched with water (20 mL).The mixture was then extracted with diethyl ether (3 x 25 mL), and the combined organic layers were washed with brine (1 x 25 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, acetone-petrol, 10:90] afforded diol **245** (362 mg, 71%) as an oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 5.52-5.37

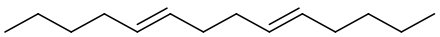
(2H, m, C*H*=C*H*), 3.94-3.80 (3H, m, CH_2OH + C*H*OH), 2.50 (2H, br. s, 2 x O*H*), 2.19-2.04 (2H, m, CH_2CH_2CHOH), 2.02-1.97 (2H, m, $(CH_2)_3$CH_2CH=CH), 1.77-1.66 (3H, m, CH_2CH_2OH + CH_AH$_B$CHOH), 1.63-1.49 (2H, m, CH$_A$$H_B$CHOH + $(CH_2)_2$CH_AH$_B$CH$_2$CH=CH), 1.38-1.21 (5H, m, CH$_3$CH_2CH_2CH$_A$$H_B$), 0.89 (3H, t, *J* = 6.8, CH_3); **^{13}C NMR (100 MHz, CDCl$_3$)** δ_C: 131.4, 129.4, 72.2, 61.9, 38.2, 37.4, 32.6, 31.4, 29.2, 28.9, 22.6, 14.1. Data were consistent with those previously reported.[34]

(±)-(*R*)-1-((2R,5S)-5-(2-Hydroxyethyl)tetrahydrofuran-2-yl)hexan-1-ol, 246



Diol **245** (50 mg, 0.25 mmol) was subjected to **General Procedure 1** (24 h) using potassium osmate dihydrate (4.6 mg, 0.013 mmol, 5 mol%). Purification by flash column chromatography [SiO_2, acetone-petrol, 15:85] afforded *THF* **246** (40 mg, 72%) as an oil. **IR** (thin film, cm^{-1}) 3386, 2954, 2931, 2860, 1464, 1067; **^{1}H NMR (400 MHz, CDCl$_3$)** δ_H: 4.07 (2H, dtd, *J* = 7.6, 7.2, 4.8, OC*H*CH$_2$CH$_2$OH), 3.81-3.76 (3H, m, OC*H*CHOH + CH$_2$OH), 3.39 (1H, q, *J* = 5.6, C*H*OH), 2.89 (1H, br. s, 1 x O*H*), 2.67 (1H, br. s, 1 x O*H*), 2.06-1.22 (14H, m, 2 x THF-CH_2, CH_2CH$_2$OH + CH$_3$(CH_2)$_4$), 0.87 (3H, t, *J* = 6.8, CH_3); **^{13}C NMR (100 MHz, CDCl$_3$)** δ_C: 82.9, 79.1, 74.1, 61.1, 37.7, 34.1, 31.9, 31.6, 27.5, 25.4, 22.6, 14.1; **HRMS**: (ES$^+$, *m/z*): Calculated 239.1618 ($C_{12}H_{24}NaO_3$); Found 239.1624.

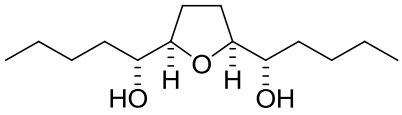
(5*E*,9*E*)-Tetradeca-5,9-diene, 251



Ammonia (200 mL) was distilled onto sodium (2.00 g, 87.0 mmol) at –78 °C. The dark blue solution was stirred for 30 min at –78 °C before being treated with a solution of 5,9-tetradecadiyne (2.85 g, 15.0 mmol) in tetrahydrofuran (10 mL). The resultant mixture was

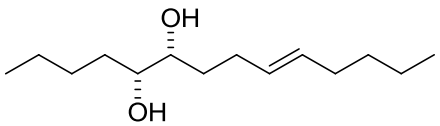
then warmed to 0 °C before being cooled back to –78 °C and quenched with a saturated solution of ammonium chloride (10 mL). The mixture was then extracted with petrol (3 x 15 mL) and the combined organic layers were dried over magnesium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, petrol] afforded diene **251** (2.1 g, 77%) as an oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 5.44-5.38 (4H, m, 2 x C*H*=C*H*), 2.06-1.93 (8H, m, 2 x CH_2CH=CHCH_2), 1.39-1.25 (8H, m, 2 x CH_3CH_2CH_2), 0.93-0.83 (6H, m, 2 x CH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 130.7, 129.7, 32.8, 32.3, 31.8, 22.2, 14.0. Data were consistent with those previously reported.[150]

(1*R*,1'*S*)-1,1'-((2*R*,5*S*)-Tetrahydrofuran-2,5-diyl)dipentan-1-ol, 253



Diol **254** (50 mg, 0.22 mmol) was subjected to **General Procedure 3** (6 h) using potassium osmate dihydrate (0.81 mg, 0.0022 mmol, 1.0 mol%). Purification by flash column chromatography [SiO_2, acetone-petrol, 20:80] afforded THF **253** (49 mg, 92%) as an oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 3.86-3.79 (2H, m, 2 x OC*H*), 3.43-3.39 (2H, m, 2 x C*H*OH), 3.00 (2H, br. s, 2 x CHO*H*), 1.97-1.88 (2H, m, THF-CH_2), 1.77-1.69 (2H, m, THF-CH_2), 1.48-1.28 (12H, m, 2 x CH_2CH_2CH_2CH_3), 0.90 (6H, t, *J* = 10.8, 2 x CH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 82.9, 74.3, 33.7, 28.1, 27.8, 22.7, 14.1. Data were consistent with those previously reported.[35]

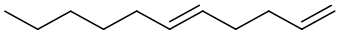
(±)-(*E*)-Tetradec-9-ene-5,6-diol, 254



Diene **251** (1.00 g, 5.15 mmol) was subjected to **General Procedure 2** (36 h) with quinuclidine. Purification by flash column chromatography [SiO_2, Et_2O-petrol, 50:50] afforded

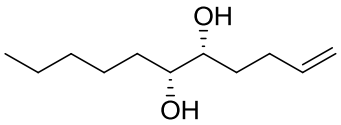
diol **254** (300 mg, 26%) as an oil. **IR** (thin film, cm^{-1}) 3374 (br), 2957, 2929, 2859, 1457, 1057; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 5.48 (1H, dt, *J* = 15.4, 6.0, C*H*=CH$(CH_2)_3CH_3$) 5.42 (1H, dt, *J* = 15.4, 5.8, CH=C*H*$(CH_2)_3CH_3$), 3.48-3.38 (2H, m, 2 x C*H*OH), 2.25-1.92 (6H, m, CH_2CH=CHCH_2 + CH(OH)C$H_2$$CH_2$CH=CH), 1.64-1.25 (12H, m, CH_3(CH_2)$_3$CHOH + CH_3(CH_2)$_2$$CH_2$CH=CH + 2 x O*H*), 0.97-0.84 (6H, m, 2 x CH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 131.4, 129.5, 74.5, 74.1, 33.4, 33.3, 32.3, 31.7, 28.8, 27.8, 22.8, 22.2, 14.1, 14.0; **HRMS**: (ES^+, *m/z*): Calculated 251.1982 ($C_{14}H_{28}NaO_2$); Found 251.1982.

(*E*)-Undeca-1,5-diene, 263



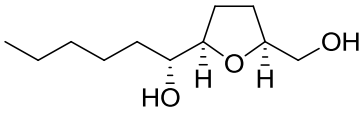
Methyltriphenylphosphonium bromide (6.43 g, 18.0 mmol) was dried by heating *in vacuo* at 90 °C for 2 h. It was then cooled to 0 °C. Tetrahydrofuran (60 mL) was added, followed by *n*-butyllithium (13.1 mL, 21.0 mmol, 1.6 M solution in hexanes). The resultant orange solution was stirred at 0 °C under argon for 30 min then cooled to –78 °C before *trans*-4-decenal (2.73 mL, 15.0 mmol) was added dropwise. The resultant mixture was warmed to room temperature over 4 h and quenched with saturated ammonium chloride solution (50 mL). The aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic layers were washed with water (100 mL), dried over magnesium sulfate, filtered and the solvent was removed *in vacuo*. Purification by flash column chromatography [SiO_2, Et_2O-petrol, 1:99] to afford diene **263** as an oil (2.30 g, 84%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 5.89-5.77 (1H, m, C*H*=CH_2), 5.49-5.36 (2H, m, C*H*=C*H*), 5.02 (1H, dd, *J* = 17.2, 1.8 CH=C$H_A$$H_B$), 4.96 (1H, dd, *J* = 10.0, 1.8, CH=$CH_A$$H_B$), 2.17-1.95 (4H, m, CH=CHCH_2CH_2), 1.40-1.21 (8H, m, CH_3(CH_2)$_4$), 0.93-0.83 (3H, m, CH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 138.6, 131.0, 129.4, 114.4, 33.9, 32.6, 32.0, 31.4, 29.3, 22.6, 14.1. Data were consistent with those previously reported.[113]

Undec-1-ene-5,6-diol, 264



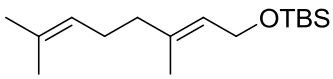
Diene **263** (1.00 g, 6.57 mmol) was subjected to **General Procedure 2** (36 h) with $(DHQD)_2PHAL$. Purification by flash column chromatography [SiO_2, Et_2O-petrol, 80:20] afforded *diol* **264** (697 mg, 57%) as an oil. **IR** (thin film, cm^{-1}) 3374, 2955, 2932, 2860, 1453, 1416, 1379, 1069, 911; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 5.85 (1H, ddt, *J* = 17.0, 10.2, 6.6, C*H*=CH_2), 5.07 (1H, dd, *J* = 17.0, 1.6, CH=C$H_A$$CH_B$), 5.00 (1H, d, *J* = 10.2, CH=CH_ACH_B), 3.49-3.39 (2H, m, 2 x C*H*OH), 2.33-2.12 (2H, m, CH_2CH=CH), 1.67-1.23 (10H, m, $(CH_2)_4$ + C$H_2$$CH_2$CH=$CH_2$), 0.90 (3H, t, *J* = 6.8, C$H_3$$CH_2$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 138.4, 115.1, 74.5, 74.0, 33.6, 32.7, 31.9, 30.0, 25.3, 22.6, 14.1; **HRMS**: (ES^+, *m/z*): Calculated 209.1512 ($C_{11}H_{22}NaO_2$); Found 209.1512; **$[\alpha]_D^{20}$** +29.8 (*c* 1.0, CH_2Cl_2).

(*R*)-1-((2*R*,5*S*)-5-(Hydroxymethyl)tetrahydrofuran-2-yl)hexan-1-ol, 265



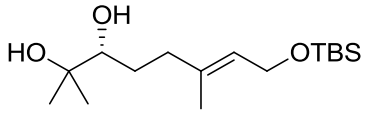
Diol **264** (50 mg, 0.27 mmol) was subjected to **General Procedure 3** (16 h) using potassium osmate dihydrate (0.99 mg, 0.0027 mmol, 1.0 mol%). Purification by flash column chromatography [SiO_2, acetone-petrol, 20:80] afforded *THF* **265** (51 mg, 94%) as an oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 4.14-4.06 (1H, m, C*H*OH), 3.83 (1H, dd, *J* = 6.6, 12.6, CH(OH)C*H*OCH), 3.75 (1H, dd, *J* = 11.6, 2.8, CH_2C*H*OCH), 3.51 (1H, dd, *J* = 11.6, 5.2, C$H_A$$H_B$OH), 3.46-3.40 (1H, m, $CH_A$$H_B$OH), 3.07 (2H, br. s, 2 x O*H*), 1.99-1.88 (2H, m, THF-CH_2), 1.84-1.67 (2H, m, THF-CH_2), 1.57-1.17 (8H, m, $CH_3(CH_2)_4$), 0.89 (3H, t, *J* = 6.8, CH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 83.1, 80.0, 74.4, 65.1, 34.0, 31.9, 26.2, 27.2, 25.4, 22.64, 14.1; **$[\alpha]_D^{21}$** +9.5 (*c* 0.5, CH_2Cl_2). Data were consistent with those previously reported.[113]

(*E*)-*tert*-Butyl(3,7-dimethylocta-2,6-dienyloxy)dimethylsilane, 271



To a stirred solution of geraniol (500 mg, 3.24 mmol) in CH_2Cl_2 (20 mL) at 0 °C were added imidazole (11 mg, 1.6 mmol), chloro *tert*-butyldimethylsilane (650 mg, 4.34 mmol) and triethylamine (0.600 mL, 4.34 mmol) sequentially. The resultant solution was left to warm to room temperature and was stirred for 16 h before being quenched with a saturated solution of ammonium chloride (10 mL). The mixture was then extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers washed with brine (20 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, petrol then Et_2O-petrol, 5:95] afforded silyl ether **271** (830 mg, 95%) as an oil.**^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 5.32 (1H, td, *J* = 6.4, 1.2, C*H*CH_2OSi), 5.11 (1H, tt, *J* = 6.8, 1.2 C*H*=$C(CH_3)_2$), 4.21 (2H, dd, *J* = 6.4, 0.6, CH_2OSi), 2.14-1.98 (4H, m, CH_2CH_2), 1.69 (3H, s, 1 x CH_3), 1.63 (3H, s, 1 x CH_3), 1.61 (3H, s, 1 x CH_3), 0.93-0.90 (9H, m, SiC(CH_3)$_3$), 0.10-0.07 (6H, m, Si(CH_3)$_2$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 136.8, 131.5, 124.4, 124.1, 60.4, 39.6, 26.4, 26.0, 25.7, 18.5, 17.7, 16.3, –5.0. Data were consistent with those previously reported.[151]

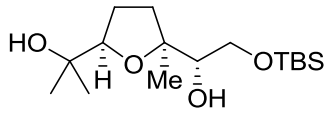
(*E*)-8-(*tert*-Butyldimethylsilyloxy)-2,6-dimethyloct-6-ene-2,3-diol, 272



Silyl ether **271** (1.40 g, 5.22 mmol) was subjected to **General Procedure 2** (36 h) using $(DHQD)_2PHAL$. Purification by flash column chromatography [SiO_2, Et_2O-petrol, 80:20] afforded *diol* **272** (285 mg, 51%) as an oil. **IR** (thin film, cm^{-1}) 3407, 2960, 2932, 2858, 1704, 1647, 1381, 1257, 1155, 1083; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 5.36 (1H, td, *J* = 6.4, 1.2, C*H*=C) 4.18 (2H, d, *J* = 6.4, CH_2OSi), 3.34 (1H, br. d, *J* = 10.4, C*H*OH), 2.52 (1H, br. d, *J* = 4.0, CHO*H*), 2.34-2.24 (2H, m, CH_AH$_B$C(CH_3)=CH + CO*H*), 2.07 (1H, ddd, *J* = 15.2, 8.4,

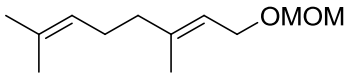
6.8, $CH_AH_BC(CH_3)$=CH), 1.64 (3H, s, C(CH_3)=CH), 1.66-1.54 (1H, m, CH_AH_BCHOH), 1.46-1.33 (1H, m, CH_AH_BCHOH), 1.19 (3H, s, 1 x (CH_3)COH), 1.15 (3H, s, 1 x (CH_3)COH), 0.90 (9H, m, SiC(CH_3)$_3$), 0.06 (6H, m, Si(CH_3)$_2$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 137.0, 124.8, 78.1, 73.1, 60.2, 36.6, 29.5, 26.5, 26.0, 23.2, 18.5, 16.4, –5.1; **HRMS**: (ES^+, *m/z*): Calculated 325.2170 ($C_{16}H_{34}NaO_3Si$); Found 325.2169; **$[\alpha]_D^{20}$** +8.3 (*c* 1.0, CH_2Cl_2).

2-((2*R*,5*S*)-5-((*S*)-2-(*tert*-Butyldimethylsilyloxy)-1-hydroxyethyl)-5-methyltetrahydrofuran-2-yl)propan-2-ol, 273



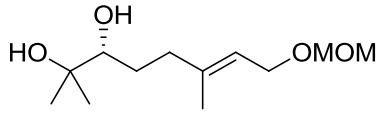
Diol **272** (50 mg, 0.17 mmol) was subjected to **General Procedure 4** (36 h) using potassium osmate dihydrate (3.0 mg, 0.0083 mmol, 5.0 mol%). Purification by flash column chromatography [SiO_2, Et_2O-petrol, 20:80] afforded *THF* **273** (35 mg, 67%) as an oil. **IR** (thin film, cm^{-1}) 3396 (br), 2958, 2930, 2857, 1471, 1257, 1115, 1069; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 3.87 (1H, dd, *J* = 7.2, 6.2, THF-C*H*), 3.79 (1H, dd, *J* = 9.2, 3.8, CH_AH_BOTBS), 3.69 (1H, t, *J* = 9.2, CH_AH_BOTBS), 3.60 (1H, dd, *J* = 9.2, 3.8, C*H*OH), 3.45 (1H, br. s, O*H*), 3.02 (1H, br. s, O*H*), 2.31 (1H, ddd, *J* = 12.4, 9.0, 7.2, CH_AH_BCHOC), 2.09-2.00 (1H, m, CH_AH_BCOCH), 1.97-1.87 (1H, m, CH_AH_BCOCH), 2.31 (1H, ddd, *J* = 12.0, 8.4, 6.2, CH_AH_BCHOC), 1.25 (3H, s, 1 x CH_3), 1.16 (3H, s, 1 x CH_3), 1.10 (3H, s, 1 x CH_3), 0.92-0.90 (9H, m, C(CH_3)$_3$), 0.10-0.08 (6H, m, Si(CH_3)$_2$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 85.9, 83.5, 76.4, 71.8, 63.6, 35.1, 27.9, 26.0, 25.9, 25.0, 23.4, 18.3, –5.4, –5.3; **HRMS**: (ES^+, *m/z*): Calculated 341.2119 ($C_{16}H_{34}NaO_3Si$); Found 341.2118; **$[\alpha]_D^{20}$** –7.4 (*c* 1.0, CH_2Cl_2).

(*E*)-1-(Methoxymethoxy)-3,7-dimethylocta-2,6-diene, 274



To a stirred solution of geraniol (500 mg, 3.24 mmol) in CH_2Cl_2 (20 mL) at 0 °C were added diisopropylethyl amine (1.70 mL, 9.72 mmol) and methyl chloromethyl ether (490 μL, 6.48 mmol) sequentially. The resultant solution was left to warm to room temperature and was stirred for 20 h before being quenched with water (10 mL). The mixture was extracted with diethyl ether (3 x 20 mL) and the combined organic layers washed washed with brine (20 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, petrol, Et_2O-petrol, 5:95] afforded MOM ether **274** (602 mg, 93%) as an oil.**^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 5.34 (1H, tq, *J* = 6.8, 1.2, C*H*CH_2OMOM) 5.08 (1H, tt, *J* = 7.0, 1.2, C*H*=$C(CH_3)_2$), 4.62 (2H, s, CH_2OMe) 4.07 (2H, d, *J* = 6.8, CH_2OMOM), 3.37 (3H, s, OCH_3), 2.14-2.01 (4H, m, CH_2CH_2), 1.69-1.65 (6H, m, C(CH_3)$_2$=CH), 1.59 (3H, s, CH_2(CH_3)C=CH); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 140.9, 131.6, 123.9, 120.1, 95.4, 63.6, 55.1, 39.6, 26.4, 25.7, 17.6, 16.3. Data were consistent with those previously reported.[152]

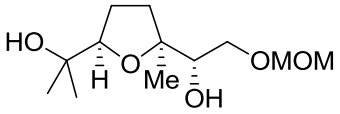
(*R*,*E*)-8-(Methoxymethoxy)-2,6-dimethyloct-6-ene-2,3-diol, 275



Methoxymethyl-ether **274** (500 mg, 2.52 mmol) was subjected to **General Procedure 2** (36 h) with $(DHQD)_2PHAL$. Purification by flash column chromatography [SiO_2, acetone-petrol, 20:80] afforded *diol* **275** (302 mg, 51%) as an oil. **IR** (thin film, cm^{-1}) 3443 br., 2932, 2884, 1448, 1383, 1149, 1041; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 5.39 (1H, td, *J* = 7.0, 1.2, C*H*CH_2OMOM), 4.61 (2H, s, CH_2OMe), 4.06 (2H, d, *J* = 7.0, CH_2OMOM), 3.36 (3H, s, OMe), 3.31 (1H, ddd, *J* = 10.6, 4.4, 1.8, C*H*OH), 2.69 (1H, d, *J* = 4.4, CHO*H*), 2.42 (1H, s,

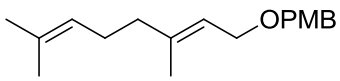
CO*H*), 2.30 (1H, ddd, *J* = 14.6, 9.4, 5.2, C*H*$_A$H$_B$C(CH$_3$)=CH), 2.09 (1H, ddd, *J* = 14.6, 9.4, 6.6, CH$_A$*H*$_B$C(CH$_3$)=CH), 1.68 (3H, s, (C*H*$_3$)=CH), 1.64-1.54 (1H, m, C*H*$_A$H$_B$CHOH), 1.47-1.37 (1H, m, CH$_A$*H*$_B$CHOH), 1.18 (3H, s, 1 x C*H*$_3$COH), 1.13 (3H, s, 1 x C*H*$_3$COH); **^{13}C NMR (100 MHz, CDCl$_3$)** δ_C: 140.8, 120.6, 95.6, 78.0, 73.1, 63.7, 55.2, 36.7, 29.5, 26.4, 23.2, 16.4; **HRMS**: (ES$^+$, *m/z*): Calculated 255.1567 ($C_{12}H_{24}NaO_4$); Found 255.1568; **$[\alpha]_D^{20}$** +22.3 (*c* 1.0, CH_2Cl_2).

2-((2*R*,5*S*)-5-((*S*)-1-Hydroxy-2-(methoxymethoxy)ethyl)-5-methyltetrahydrofuran-2-yl)propan-2-ol, 276



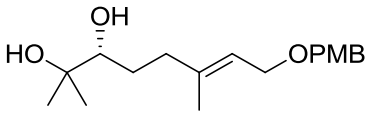
Diol **275** (50 mg, 0.22 mmol) was subjected to **General Procedure 4** (36 h) using potassium osmate dihydrate (4.0 mg, 0.0011 mmol, 5.0 mol%). Purification by flash column chromatography [SiO_2, acetone-petrol, 20:80] afforded *THF* **276** (49 mg, 92%) as an oil. **IR** (thin film, cm^{-1}) 3418 (br), 2972, 2934, 2884, 1464, 1378, 1151, 1035; **^{1}H NMR (400 MHz, CDCl$_3$)** δ_H: 4.66 (2H, s, C*H*$_2$OMe), 3.84 (1H, t, *J* = 7.2, C*H*OC), 3.77 (1H, dd, *J* = 10.2, 2.8, C*H*$_A$H$_B$OMOM), 3.70-3.66 (1H, m, C*H*OH), 3.55 (1H, dd, *J* = 10.2, 8.6, CH$_A$*H*$_B$OMOM), 3.38 (3H, s, OMe), 3.29 (1H, s, CHO*H*), 3.22 (1H, s, CO*H*), 2.20 (1H, ddd, *J* = 12.4, 9.2, 6.0, C*H*$_A$H$_B$C(CH$_3$)O), 2.04-1.85 (2H, m, C*H*$_2$CHO), 1.62 (1H, ddd, *J* = 12.4, 8.6, 7.2, CH$_A$*H*$_B$C(CH3)O), 1.23 (3H, s, 1 x C*H*$_3$), 1.17 (3H, s, 1 x C*H*$_3$), 1.09 (3H, s, 1 x C*H*$_3$); **^{13}C NMR (100 MHz, CDCl$_3$)** δ_C: 96.9, 85.7, 83.9, 75.7, 71.7, 69.5, 55.4, 35.2, 27.7, 26.3, 25.0, 23.2; **HRMS**: (ES$^+$, *m/z*): Calculated 271.1516 ($C_{12}H_{24}NaO_5$); Found 271.1514; **$[\alpha]_D^{20}$** –5.2 (*c* 1.0, CH_2Cl_2).

(*E*)-1-((3,7-Dimethylocta-2,6-dienyloxy)methyl)-4-methoxybenzene, 277



To a stirred solution of geraniol (1.75 mL, 10.0 mmol) in tetrahydrofuran (40 mL) at 0 °C was added sodium hydride (60% dispersion on mineral oil, 0.600 g, 15.0 mmol) followed by 4 methoxybenzyl bromide (2.20 mL, 15.0 mmol). The resultant solution was left to warm to room temperature and was stirred for 20 h before being quenched with a saturated solution of ammonium chloride (20 mL). The mixture was then extracted with diethyl ether (3 x 25 mL) and the combined organic layers dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, petrol, Et_2O-petrol, 5:95] afforded PMB-ether **277** (2.52 g, 92%) as an oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.31-7.26 (2H, m, 2 x Ar-C*H*), 6.92-6.87 (2H, m, 2 x Ar-C*H*), 5.40 (1H, td, *J* = 6.8, 1.2, C=C*H*CH_2OPMB), 5.14-5.09 (1H, m, $(CH_3)_2$C=C*H*), 4.45 (2H, s, CH_2Ar), 4.01 (2H, d, *J* = 6.8, CH_2OPMB), 3.82 (3H, s, OCH_3), 2.16-2.08 (2H, m, CH_2C(CH_3)=CH), 2.07-2.02 (2H, m, C$H_2$$CH_2$C($CH_3$)=CH), 1.69 (3H, s, 1 x CH_3), 1.65 (3H, s, 1 x CH_3), 1.62 (3H, s, 1 x CH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 159.1, 140.3, 131.7 130.7, 129.4, 124.0, 120.9, 113.7, 71.6, 66.3, 55.3, 39.6, 26.4, 25.7, 17.7, 16.5. Data were consistent with those previously reported.[153]

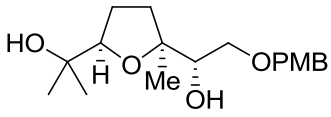
(*R*,*E*)-8-(4-Methoxybenzyloxy)-2,6-dimethyloct-6-ene-2,3-diol, 278



PMB-ether **277** (500 mg, 1.82 mmol) was subjected to **General Procedure 2** (36 h) with $(DHQD)_2$PHAL. Purification by flash column chromatography [SiO_2, acetone-petrol, 20:80] afforded *diol* **278** (270 mg, 48%) as an oil. **IR** (thin film, cm^{-1}) 3418, 2971, 1609, 1513, 1250, 1034; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.30-7.25 (2H, m, 2 x Ar-C*H*), 6.90-6.86 (2H, m, 2 x Ar-C*H*), 5.44 (1H, td, *J* = 6.8, 1.2, C=C*H*), 4.44 (2H, s, CH_2Ar), 3.99 (2H, d, *J* = 6.8,

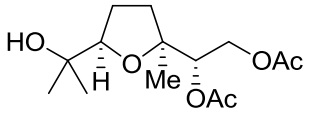
C*H*$_2$OPMB), 3.80 (3H, s, OC*H*$_3$), 3.34 (1H, dd, *J* = 10.4, 1.8, C*H*OH), 2.36 (2H, br. s, 2 x O*H*), 2.31 (1H, ddd, *J* = 14.4, 9.6, 5.2, C*H*$_A$H$_B$C(CH$_3$)=CH), 2.15-2.06 (1H, m, CH$_A$*H*$_B$C(CH$_3$)=CH), 1.66 (3H, s, C(C*H*$_3$)=CH), 1.64-1.56 (1H, m, C*H*$_A$H$_B$CHOH), 1.49-1.40 (1H, m, CH$_A$*H*$_B$CHOH), 1.20 (3H, s, 1 x C*H*$_3$COH), 1.15 (3H, s, 1 x C*H*$_3$COH); **^{13}C NMR (100 MHz, CDCl$_3$)** δ_C: 159.2, 140.1, 130.5, 129.4, 121.3, 113.8, 78.1, 73.1, 71.9, 66.3, 55.3, 36.6, 29.5, 26.5, 23.2, 16.5; **HRMS**: (ES$^+$, *m/z*): Calculated 331.1880 ($C_{18}H_{28}NaO_4$); Found 331.1886; **$[\alpha]_D^{20}$** +5.6 (*c* 0.5, CH_2Cl_2).

2-((2*R*,5*S*)-5-((*S*)-1-Hydroxy-2-(4-methoxybenzyloxy) ethyl)-5-methyltetrahydrofuran-2-yl)propan-2-ol, 279



Diol **278** (100 mg, 0.325 mmol) was subjected to **General Procedure 4** (36 h) using potassium osmate dihydrate (6.0 mg, 0.016 mmol, 5.0 mol%). Purification by flash column chromatography [SiO_2, acetone-petrol, 20:80] afforded *THF* **279** (74 mg, 70%) as an oil. **IR** (thin film, cm^{-1}) 2971, 2872, 1712, 1612, 1514, 1249; **^{1}H NMR (400 MHz, CDCl$_3$)** δ_H: 7.29-7.24 (2H, m, 2 x Ar-C*H*), 6.91-6.86 (2H, m, 2 x Ar-C*H*), 4.50 (2H, m, C*H*$_2$Ar), 3.85 (1H, t, *J* = 7.2, OC*H*), 3.81 (3H, s, OC*H*$_3$), 3.72 (1H, dd, *J* = 8.4, 3.2, C*H*OH), 3.64 (1H, dd, *J* = 9.6, 3.2, C*H*$_A$H$_B$OPMB), 3.55 (1H, dd, *J* = 9.6, 8.4, CH$_A$*H*$_B$OPMB), 3.20 (1H, br. s, 1 x O*H*), 3.03 (1H, br. s, 1 x O*H*), 2.24 (1H, ddd, *J* = 12.4, 9.0, 6.4, THF-C*H*$_A$H$_B$), 2.06-1.96 (1H, m, THF-CH$_A$*H*$_B$), 1.94-1.85 (1H, m, THF-C*H*$_A$H$_B$), 1.60 (1H, ddd, *J* = 12.4, 8.4, 7.2, THF-CH$_A$*H*$_B$), 1.23 (3H, s, 1 x C*H*$_3$), 1.15 (3H, s, 1 x C*H*$_3$), 1.09 (3H, s, 1 x C*H*$_3$); **^{13}C NMR (100 MHz, CDCl$_3$)** δ_C: 159.3, 129.9, 129.5, 113.9, 85.8, 83.9, 75.4, 73.1, 71.7, 70.7, 55.3, 35.1, 27.8, 26.3, 25.0, 23.3; **HRMS**: (ES$^+$, *m/z*): Calculated 347.1829 ($C_{18}H_{28}O_5Na$); Found 347.1819; **$[\alpha]_D^{20}$** –9.8 (*c* 1.0, CH_2Cl_2).

(*S*)-1-((2*S*,5*R*)-5-(2-Hydroxypropan-2-yl)-2-methyltetrahydrofuran-2-yl)ethane-1,2-diyl diacetate, 280



From THF 49 (Bn)**:**

To a stirred solution of *THF* **49** (200 mg, 0.680 mmol) in ethyl acetate (5 mL) was added palladium on carbon (218 mg, 0.400 mmol). The flask was evacuated and purged five times with H_2. The reaction was stirred for 6 h at room temperature and then diluted with ethyl acetate (15 mL). The organic phase was filtered and the filtrate was concentrated *in vacuo*. The resultant crude mixture was dissolved in pyridine (2 mL), and acetic anhydride (2 mL) was added. The reaction was stirred for 16 h at room temperature before the solvent was removed *in vacuo*. Purification by flash column chromatography [SiO_2, acetone-petrol, 20:80] to afford *THF* **280** as an oil (159 mg, 81%). **IR** (thin film, cm^{-1}) 3507, 2976, 1744, 1372, 1054; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 5.12 (1H, dd, *J* = 8.8, 2.6, C*H*$_A$H$_B$OAc), 4.37 (1H, dd, *J* = 12.0, 2.6, CH$_A$*H*$_B$OAc), 4.05 (1H, dd, *J* = 12.0, 8.8, C*H*OAc), 3.83-3.76 (1H, m, C*H*C(CH$_3$)$_2$OH), 2.61 (1H, br. s, O*H*), 2.11 (3H, s, 1 x C*H*$_3$CO$_2$R), 2.02 (3H, s, 1 x C*H*$_3$CO$_2$R), 2.03-1.94 (2H, m, THF-C*H*$_2$), 1.90-1.82 (1H, m, THF-C*H*$_A$H$_B$), 1.75-1.64 (1H, m, THF-CH$_A$*H*$_B$, C(CH$_3$)$_A$(C*H*$_3$)$_B$), 1.23 (3H, s, 1 x C*H*$_3$), 1.20 (3H, s, 1 c C*H*$_3$), 1.08 (3H, s, 1 x C*H*$_3$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 171.1, 170.8, 85.9, 82.9, 76.2, 70.6, 63.4, 35.6, 27.8, 26.1, 24.8, 23.1, 21.8, 20.8; **HRMS**: (ES$^+$, *m/z*): Calculated 311.1465 ($C_{14}H_{24}NaO_6$); Found 311.1468; **$[\alpha]_D^{22}$** –21.2 (*c* 1.0, CH_2Cl_2).

From THF 273 (TBS)**:**

To a stirred solution of *THF* **273** (300 mg, 0.943 mmol) in tetrahydrofuran (10 mL) at room temperature under argon was added acetic acid (0.165 mL, 2.83 mmol) and

tetrabutylammonium fluoride (2.83 mL, 2.83 mmol, 1 M solution in tetrahydrofuran) sequentially. The resultant mixture was stirred at room temperature for 3 h before the solvent was removed *in vacuo*. The resultant crude mixture was dissolved in pyridine (3 mL), and acetic anhydride (3 mL) was added. The reaction was stirred for 16 h at room temperature before the solvent was removed *in vacuo*. Purification by flash column chromatography [SiO_2, acetone-petrol, 20:80] to afford *THF* **280** as an oil (212 mg, 78%). Data were consistent with those reported above for *THF* **280**.

From THF 276 (MOM)**:**

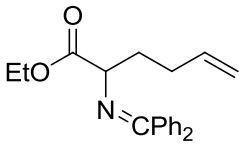
To a stirred solution of *THF* **276** (200 mg, 0.806 mmol) in methanol (5 mL) was added aqueous hydrochloric acid (6 M, 5 mL). The reaction was stirred for 1 h before being brought to pH 7 with a saturated aqueous solution of $NaHCO_3$. The resulting mixture was extracted with ethyl acetate (4 x 20 mL) and the combined organic phases were washed with brine (20 mL), dried with sodium sulfate, filtered and concentrated *in vacuo*. The resultant crude mixture was dissolved in pyridine (2 mL), and acetic anhydride (2 mL) was added. The reaction was stirred for 16 h at room temperature before the solvent was removed *in vacuo*. Purification by flash column chromatography [SiO_2, acetone-petrol, 20:80] to afford *THF* **280** as an oil (100 mg, 43%). Data were consistent with those reported above for *THF* **280**.

From THF 279 (PMB)**:**

To a stirred solution of *THF* **279** (150 mg, 0.463 mmol) in methanol (5 mL) was added aqueous hydrochloric acid (6 M, 5 mL). The resulting mixture was stirred at room temperature for 1 h before the reaction was brought to pH 7 with a saturated aqueous solution of $NaHCO_3$. The mixture was extracted with ethyl acetate (4 x 20 mL) and the combined organic phases were washed with brine (20 mL), dried with sodium sulfate, filtered and concentrated *in vacuo*. The

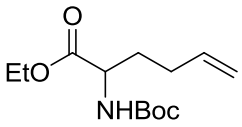
resultant crude mixture was dissolved in pyridine (2 mL), and acetic anhydride (2 mL) was added. The reaction was stirred for 16 h at room temperature before the solvent was removed *in vacuo*. Purification by flash column chromatography [SiO_2, acetone-petrol, 20:80] to afford *THF* **280** as an oil (81 mg, 61%). Data were consistent with those reported above for *THF* **280**.

Ethyl 2-(diphenylmethyleneamino)hex-5-enoate, 282



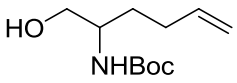
To a heterogeneous mixture of N-(diphenylmethene)glycine ethyl ester (3.00 g, 11.2 mmol), finely grounded potassium carbonate (4.64 g, 33.6 mmol) and tetrabutylammonium bromide (0.360 g, 1.12 mmol) in MeCN (10 mL) was added 4-bromo-1-butene (1.70 mL, 16.8 mmol) and the resulting mixture was heated at 90 °C for 24 h before the reaction mixture was cooled to room temperature and filtered. The solvent was removed *in vacuo* and the resultant residue partitioned in ethyl acetate (10 mL) and water (10 mL). The organic layer was dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, Et_2O-petrol, 10:90] afforded ester **282** (2.7 g, 75%) as an oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.67-7.18 (10H, m, CPh_2), 5.73 (1H, ddt, *J* = 17.0, 10.4, 6.4, C*H*=CH_2), 4.97 (1H, dd, *J* = 17.0, 1.6, CH=CH_AH$_B$), 4.90 (1H, dd, *J* = 10.4, 1.6, CH=CH$_A$$H_B$), 4.25-4.11 (2H, m, OC$H_2$), 4.07 (1H, t, *J* = 6.0, NC*H*), 2.15-1.93 (4H, m, CH_2CH_2), 1.27 (3H, t, *J* = 7.2, OCH$_2$CH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 172.3, 170.6, 139.6, 137.8, 136.5, 130.3, 128.8, 128.6, 128.5, 128.1, 127.9, 115.0, 64.9, 60.9, 33.0, 30.2, 14.3. Data were consistent with those previously reported.[154]

Ethyl 2-(*tert*-butoxycarbonylamino)hex-5-enoate, 283



To a stirred solution of **282** (2.00 g, 6.23 mmol) in diethyl ether (12 mL) at 0 °C was added aqueous hydrochloric acid (2 M, 11.2 mL, 5.60 mmol) dropwise. After 30 min the reaction was warmed to room temperature and stirring continued for 5 h. The resulting two layers were separated and the aqueous layer neutralised to pH 8 with sodium bicarbonate before being extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over sodium sulfate, filtered and the solvent removed *in vacuo*. The crude product was then dissolved in a 1:1 mixture of dioxane/water (18 mL) before di-*tert*-butyl dicarbonate (2.03 g, 9.34 mmol) and sodium bicarbonate (1.57 g, 18.69 mmol) were added the resultant mixture was stirred for 18 h before ethyl acetate (40 mL) and water (25 mL) were added. The layers were separated and the organic layer washed with brine (30 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, petrol, Et_2O-petrol, 5:95] afforded amino-ester **283** (1.10 g, 69%) as an oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 5.80 (1H, ddt, *J* = 17.2, 10.4, 6.4, C*H*=CH_2), 5.10-4.98 (3H, m, CH=CH_2 + N*H*Boc), 4.34-4.26 (1H, m, C*H*NHBoc), 4.20 (2H, qd, *J* = 7.2, 2.0, OCH_2), 2.19-2.06 (2H, m, CH_2CH=CH_2), 1.97-1.85 (1H, m, CH_AH$_B$CHNHBoc), 1.77-1.65 (1H, m, CH$_A$$H_B$CHNHBoc), 1.45 (9H, s, C(CH_3)$_3$), 1.29 (3H, t, *J* = 7.2, OCH$_2$CH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 172.8, 155.3, 137.1, 115.6, 79.8, 61.3, 53.1, 32.1, 29.5, 28.3, 14.2. Data were consistent with those previously reported.[154]

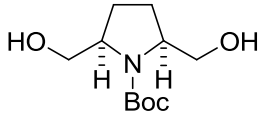
***tert*-Butyl 1-hydroxyhex-5-en-2-ylcarbamate, 284**



To a stirred solution of amino-ester **283** (200 mg, 0.78 mmol) in tetrahydrofuran (5 mL) at 0 °C was added lithium borohydride (2.0 M solution in tetrahydrofuran, 0.58 mL, 1.16 mmol). The

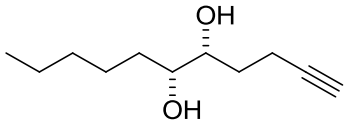
resultant mixture was allowed to warm to room temperature and was stirred for 16 h before being quenched with water (10 mL). The mixture was then extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were washed with brine (15 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, Et_2O-petrol,70:30] afforded amino alcohol **284** (104 mg, 62%) as an oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 5.82 (1H, ddt, *J* = 17.0, 10.4, 6.4, C*H*=CH_2), 5.05 (3H, m, CH=CH_2 + N*H*Boc), 4.34-4.26 (1H, m, C*H*NHBoc), 4.20 (2H, qd, *J* = 7.2, 2.0, OCH_2), 2.19-2.06 (2H, m, CH_2CH=CH_2), 1.97-1.85 (1H, m, CH_AH$_B$CHNHBoc), 1.77-1.65 (1H, m, CH$_A$$H_B$CHNHBoc), 1.45 (9H, s, C(CH_3)$_3$), 1.29 (3H, t, *J* = 7.2, OCH$_2$CH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 156.2, 139.4, 115.5, 78.2, 64.3, 52.5, 31.0, 30.7, 29.1. Data were consistent with those previously reported.[155]

(2*R*,5*S*)-*tert*-Butyl 2,5-bis(hydroxymethyl)pyrrolidine-1-carboxylate, 285



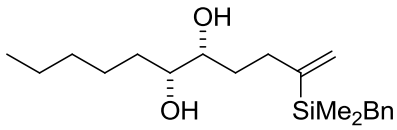
Amino alcohol **284** (50 mg, 0.23 mmol) was subjected to **General Procedure 4** (36 h) using potassium osmate dihydrate (3.0 mg, 0.0083 mmol, 5.0 mol%). Purification by flash column chromatography [SiO_2, Et_2O-petrol,20:80] afforded pyrrolidine **285** (44 mg, 82%) as an oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 4.54 (1H, br. s, 1 x O*H*), 4.04-3.72 (4H, m, 2 x CH_2OH), 3.51 (2H, dd, *J* = 11.2, 4.8, 2 x N-C*H*), 3.23 (1H, br. s, 1 x O*H*) 2.24-1.72 (4H, m, 2 x THF-CH_2), 1.47 (9H, s, C(CH_3)$_3$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 156.5, 80.7, 66.2, 64.4, 60.7, 60.5, 28.5, 26.9. Data were consistent with those previously reported.[156]

(±)-(5*R*,6*R*)-Undec-1-yne-5,6-diol, 295



To a stirred solution of (*E*)-dec-4-enal (771 mg, 5.00 mmol) and 4-methylmorpholine *N*-oxide (1.14 g, 10.0 mmol) in water/tetrahydrofuran/*tert*-butanol (1:10:8, 50 mL) was added osmium tetroxide (64 mg, 5.0 mol%) and the resulting solution was stirred for 16 h at room temperature. Na_2SO_3 (200 mg) was added and the mixture was stirred for 30 min after which water (40 mL) was added and the mixture extracted with ethyl acetate (3 × 40 mL). The combined organics were dried over sodium sulfate, filtered and the solvent removed *in vacuo* afforded the crude product which was then subjected to **General Procedure 5**. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 10:90 then 20:80] afforded *diol* **295** as an oil (640 mg, 70% over two steps). **IR** (thin film)/cm^{-1} 3311 br., 2960, 2859, 2118, 1435, 1379, 1262, 1132, 1066, 941, 633; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 3.56 (1H, ddd, *J* = 9.0, 5.0, 4.1, 1 x C*H*OH), 3.42 (1H, ddd, *J* = 9.0, 5.0, 3.8, 1 x C*H*OH), 2.63 (2H, br. s, 2 x O*H*), 2.38-2.33 (2H, m, CH_2C≡CH), 1.98 (1H, t, *J* = 2.7, C≡C*H*), 1.76-1.61 (2H, m, CH_2CH_2C≡CH), 1.53-1.23 (8H, m, CH_3(CH_2)$_4$), 0.89 (3H, t, *J* = 6.8, CH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 84.1, 74.4, 73.1, 68.9, 33.5, 32.3, 31.9, 25.3, 22.6, 14.9, 14.1; **HRMS** (ES^+, *m/z*): Calculated 207.1356 ($C_{11}H_{20}NaO_2$); Found 207.1359.

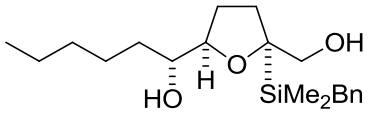
(±)-(5*S*,6*S*)-2-(Dimethyl(benzyl)silyl)undec-1-ene-5,6-diol, 296



Diol **295** (200 mg, 1.09 mmol) was subjected to **General Procedure 6** with benzyldimethylsilane. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 5:95 then 10:90 then 20:80] afforded *vinyl silane* **296** as an oil (294 mg, 81%). **IR** (thin film)/cm^{-1}

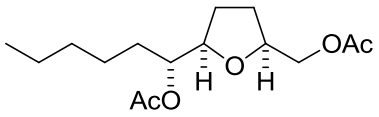
3384 br., 3024, 2931, 1493, 1452, 1248, 1057, 831; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.28-7.18 (2H, m, 2 x Ar-C*H*), 7.11-6.98 (3H, m, 3 x Ar-C*H*), 5.67-5.64 (1H, m, C=CH_AH_B), 5.39-5.35 (1H, m, C=CH_AH_B), 3.44-3.37 (2H, m, 2 x C*H*OH), 2.30 (1H, ddd, *J* = 14.8, 10.0, 5.4, CH_AH_BC(SiR_3)=CH_2), 2.18 (2H, s, CH_2Ph), 2.17-2.10 (1H, m, CH_AH_BC(SiR_3)=CH_2), 1.90 (2H, br. s, 2 x CHO*H*), 1.65-1.25 (10H, m, 2 x CH_2CHOH + CH_3(CH_2)$_3$), 0.95-0.87 (3H, m, CH_3(CH_2)$_4$), 0.08 (6H, s, Si(CH_3)$_2$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 150.2, 139.9, 128.3, 128.1, 125.3, 124.0, 74.5, 74.2, 33.6, 32.7, 31.9, 31.9, 25.5, 25.4, 22.6, 14.1, −3.4; **HRMS** (ES^+, *m/z*): Calculated 357.2220 ($C_{20}H_{34}NaO_2Si$); Found 357.2220.

(±)-(*R*)-1-((2*R*,5*R*)-5-(dimethyl(benzyl)silyl)-5-(hydroxymethyl)tetrahydrofuran-2-yl)hexan-1-ol, 297



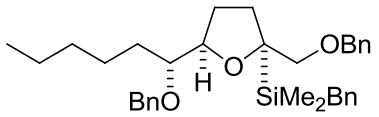
Vinyl silane **296** (200 mg, 0.571 mmol) was subjected to **General Procedure 3** using potassium osmate dihydrate (5.3 mg, 0.014 mmol, 2.5 mol%) at 60 ^oC for 16 h. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 10:90 then 25:75] afforded *THF* **297** as an oil (176 mg, 84%). **IR** (thin film)/cm^{-1} 3357 br., 2930, 1493, 1452, 1247, 1206, 1056, 818; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.26-7.18 (2H, m, 2 x Ar-C*H*), 7.13-7.00 (3H, m, 3 x Ar-C*H*), 3.79-3.71 (2H, m, CH_AH_BOH + C*H*OC), 3.52-3.42 (2H, m, CH_AH_BOH + C*H*OH), 3.17 (2H, br. s, 2 x O*H*), 2.24-2.14 (2H, m, CH_2Ph), 1.96-1.82 (4H, m, THF-CH_2), 1.59-1.26 (8H, m, CH_3(CH_2)$_4$), 0.91 (3H, t, *J* = 6.6, 0.02 (3H, s, CH_3(CH_2)$_4$), 0.01 (6H, s, Si(CH_3)$_2$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 139.6, 128.3, 128.2, 124.1, 83.8, 80.2, 74.3, 68.1, 34.5, 31.9, 30.4, 29.4, 25.5, 23.3, 22.7, 14.1, −5.4, −5.4; **HRMS** (ES^+, *m/z*): Calculated 373.2169 ($C_{20}H_{34}NaO_3Si$); Found 373.2162.

(±)-((2*S*,5*R*)-5-((*R*)-1-Acetoxyhexyl)tetrahydrofuran-2-yl)methyl acetate, 299



To a solution of *THF* **265** (50 mg, 0.22 mmol) in acetic anhydride (1.0 mL) was added pyridine (1.0 mL). The resulting solution was stirred at room temperature for 16 h before the solvent was removed *in vacuo*. Purification by flash column chromatography [SiO_2, Et_2O-petrol, 10:90] afforded *diacetate* **299** as an oil (66 mg, 96%). **IR** (thin film)/cm^{-1} 2956, 2862, 1741, 1371, 1241, 1043; **^{1}H NMR (400 MHz, CD_3Cl)** δ_H: 4.91-4.83 (1H, m, C*H*OAc), 4.17-4.08 (2H, m, C*H*C*H*$_A$H$_B$OAc), 4.04-3.95 (2H, m, C*H*CHOAc + CH$_A$*H*$_B$OAc), 2.07 (3H, s, 1 x COC*H*$_3$), 2.06 (3H, s, 1 x COC*H*$_3$), 2.00-1.86 (2H, m, THF-C*H*$_2$), 1.71-1.63 (2H, m, THF-C*H*$_2$), 1.61-1.52 (2H, m, C*H*$_2$CHOAc), 1.34-1.20 (6H, m, CH$_3$(C*H*$_2$)$_3$), 0.90-0.80 (3H, m, C*H*$_3$CH$_2$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 171.0, 170.8, 80.3, 77.0, 75.3, 66.4, 31.7, 30.9, 28.1, 27.4, 25.0, 22.5, 21.1, 20.9, 14.0; **HRMS** (ES^+, *m/z*): Calculated 309.1672 ($C_{15}H_{26}NaO_5$); Found 309.1670.

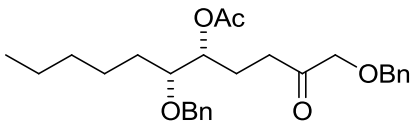
(±)-Benzyl((2*R*,5*R*)-5-((*R*)-1-(benzyloxy)hexyl)-2-(benzyloxymethyl)tetrahydrofuran-2-yl)dimethylsilane, 302



To a solution of *THF* **297** (450 mg, 1.29 mmol) in tetrahydrofuran (5.6 mL) and DMF (1.3 mL) at 0 ^oC was added sodium hydride (60% dispersion on mineral oil, 215 mg, 5.25 mmol). The resulting mixture was stirred for 30 min before benzyl bromide (0.630 mL, 31.0 mmol) and tetrabutylammonium iodide (52.0 mg, 0.130 mmol) were added. The mixture was warmed to room temperature and stirred for 16 h before brine (100 mL) was added. The mixture was extracted with ethyl acetate (3 x 100 mL) and the combined organics washed with brine (3 x 100 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-hexanes, 10:90] afforded *benzylated THF* **302** as

an oil (501 mg, 73%). **IR** (thin film)/cm^{-1} 2954, 2930, 2859, 1494, 1453, 1071, 1027, 818, 735; **^{1}H NMR (400 MHz, CDCl$_3$)** δ_H: 7.30-7.01 (10H, m, 2 x OCH$_2$C$_6$*H*$_6$), 7.22 (2H, t, *J* = 7.4, 2 x SiCH$_2$Ar-C*H*), 7.09 (1H, t, *J* = 7.2, 1 x SiCH$_2$Ar-C*H*), 7.04 (2H, d, *J* = 7.6, 2 x SiCH$_2$Ar-C*H*), 4.88 (1H, d, *J* = 11.6, CHOC*H*$_A$H$_B$Ph), 4.66 (1H, d, *J* = 11.6, CHOCH$_A$*H*$_B$Ph), 4.48 (2H, s, CH$_2$OC*H*$_2$Ph), 3.94-3.86 (1H, m, C*H*OC), 3.47 (1H, d, *J* = 9.2, C*H*$_A$H$_B$OBn), 3.45 (1H, d, *J* = 9.2, CH$_A$*H*$_B$OBn), 3.39-3.32 (1H, m, C*H*OBn), 2.25 (2H, d, *J* = 1.6, SiC*H*$_2$Ph), 2.05-1.95 (1H, m, THF-C*H*$_A$H$_B$), 1.90-1.80 (2H, m, THF-C*H*$_2$), 1.76-1.65 (1H, m, THF-CH$_A$*H*$_B$), 1.60-1.21 (8H, m, CH$_3$(C*H*$_2$)$_4$), 0.91 (3H, t, *J* = 7.2, C*H*$_3$(CH$_2$)$_4$), 0.05 (3H, s, 1 x SiC*H*$_3$), 0.04 (3H, s, 1 x SiC*H*$_3$); **^{13}C NMR (100 MHz, CDCl$_3$)** δ_C: 140.3, 139.6, 138.7, 128.4, 128.3, 128.2, 128.1, 127.6, 127.5, 127.4, 84.6, 82.6, 78.2, 76.1, 73.5, 73.1, 32.0, 31.8, 30.8, 28.7, 25.4, 23.4, 22.7, 14.2, −5.4, −5.5; **HRMS** (ES$^+$, *m/z*): Calculated 553.3108 (C$_{34}$H$_{46}$NaO$_3$Si); Found 553.3108.

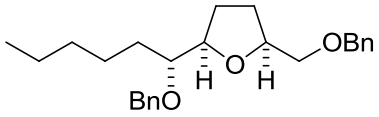
(±)-(5*R*,6*R*)-1,6-Bis(benzyloxy)-2-oxoundecan-5-yl acetate, 303



Benzylated THF **302** (150 mg, 0.283 mmol) was subjected to **General Procedure 7**. The resulting crude product was dissolved in pyridine (2 mL) and acetic anhydride (2 mL) and stirred at room temperature for 16 h before the solvent was removed *in vacuo*. Purification by flash column chromatography [SiO$_2$, Et$_2$O-petrol, 20:80] afforded *ketone* **303** as an oil (91 mg, 73%). **IR** (thin film)/cm^{-1} 2926, 1736, 1453, 1374, 1239, 1070; **^{1}H NMR (400 MHz, CDCl$_3$)** δ_H: 7.39-7.25 (10H, m, 10 x Ar-C*H*), 5.03 (1H, dt, *J* = 9.2, 4.2, C*H*OAc), 4.60 (2H, s, 1 x C*H*$_2$Ph), 4.58 (2H, s, 1 x C*H*$_2$Ph), 4.03 (2H, s, C*H*$_2$OBn), 3.42 (1H, dt, *J* = 8.0, 4.2, C*H*OBn), 2.46 (2H, t, *J* = 7.2, C*H*$_2$C(=O)CH$_2$OBn), 2.04 (3H, s, C*H*$_3$C(=O)), 2.03-1.95 (1H, m, C*H*$_A$H$_B$CHOAc), 1.91-1.80 (1H, m, CH$_A$*H*$_B$CHOAc), 1.59-1.20 (8H, m, CH$_3$(C*H*$_2$)$_4$), 0.88 (3H,

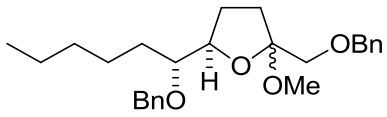
s, C*H*$_3$(CH$_2$)$_4$); **^{13}C NMR (100 MHz, CDCl$_3$)** δ_C: 207.8, 170.9, 138.4, 137.2, 128.5, 128.4, 128.0, 128.0, 127.9, 127.7, 79.2, 74.9, 73.4, 73.4, 72.4, 35.1, 31.9, 29.8, 25.3, 23.3, 22.6, 21.1, 14.1; **HRMS** (ES$^+$, *m/z*): Calculated 463.2455 ($C_{27}H_{36}NaO_5$); Found 463.2456.

(2*R*,5*S*)-2-((*R*)-1-(Benzyloxy)hexyl)-5-((benzyloxy)methyl)tetrahydrofuran, 304



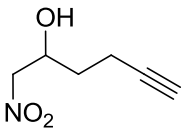
To a solution of *THF* **265** (100 mg, 0.495 mmol) in tetrahydrofuran (2.5 mL) and DMF (0.5 mL) at 0 ^{o}C was added sodium hydride (60% dispersion on mineral oil, 59.0 mg, 1.49 mmol). The resulting mixture was stirred for 30 min before benzyl bromide (176 µl, 1.49 mmol) and tetrabutylammonium iodide (19 mg, 0.060 mmol) were added. The mixture was warmed to room temperature and stirred for 16 h before brine (20 mL) was added. The mixture was extracted with ethyl acetate (3 x 20 mL) and the combined organics washed with brine (3 x 20 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO$_2$, EtOAc-hexanes, 5:95] afforded *benzylated THF* **304** as an oil (157 mg, 83%). **IR** (thin film)/cm^{-1} 3030, 2929, 1494, 1097, 734; **^{1}H NMR (400 MHz, CD$_3$Cl)** δ_H: 7.37-7.23 (10H, m, 10 x Ar-C*H*), 4.75 (1H, d, *J* = 11.6, CH$_2$OC*H*$_A$H$_B$Ph), 4.62-4.56 (3H, m, CHOC*H*$_2$Ph + CH$_2$OCH$_A$*H*$_B$Ph), 4.17-4.10 (1H, m, C*H*CH$_2$OBn), 4.05-3.98 (1H, m, C*H*CHOBn), 3.51 (2H, qd, *J* = 9.8, 5.2, C*H*$_2$OBn), 3.39-3.33 (1H, m, C*H*OBn), 1.96-1.82 (2H, m, THF-C*H*$_2$), 1.76-1.62 (2H, m, THF-C*H*$_2$), 1.51-1.15 (8H, m, CH$_3$(C*H*$_2$)$_4$), 0.87 (3H, t, *J* = 7.0, C*H*$_3$CH$_2$); **^{13}C NMR (100 MHz, CDCl$_3$)** δ_C: 139.3, 138.5, 128.3, 128.2, 128.0, 127.6, 127.5, 127.4, 82.4, 81.5, 78.4, 73.4, 73.0, 72.8, 32.0, 30.9, 28.2, 27.4, 25.4, 22.7, 14.1; **HRMS** (ES$^+$, *m/z*): Calculated 405.2400 ($C_{25}H_{34}NaO_3$); Found 405.2399.

(±)-(5*R*)-5-((*R*)-1-(Benzyloxy)hexyl)-2-(benzyloxymethyl)-2-methoxytetrahydrofuran, 311



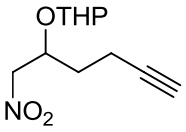
Benzylated THF **302** (76 mg, 0.14 mmol) was subjected to **General Procedure 7**. The resulting crude product was purified by flash column chromatography [SiO_2, petrol/EtOAc, 4:1] to afford the intermediate lactol as an oil (42 mg, 74%), as a complex mixture of isomers. The intermediate lactol (37 mg, 88 μmol) was dissolved in methanol (1 mL) and CH_2Cl_2 (1 mL) under argon before pyridinium *para*-toluenesulfonate (4.0 mg, 0.018 mmol) was added. The resultant mixture was stirred at room temperature for 5 h before the solvent was removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 15:85] afforded *lactol methyl ether* **311** as an oil and a (60:40) mixture of diastereomers (30 mg, 78%). **IR** (thin film)/cm^{-1} 2930, 2860, 1722, 1496, 1545, 1097, 1028, 736; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: (diastereomeric 60:40) 7.33-7.15 (10H, m, 10 x Ar-C*H*), 4.75 (0.4H, d, *J* = 11.6, 0.4 $CH_2OCH_AH_BPh$), 4.65 (0.6H, d, *J* = 11.6, 0.6 $CH_2OCH_AH_BPh$), 4.75-4.47 (3H, m, $CHOCH_2Ph$ + $CH_2OCH_AH_BPh$), 4.16-4.09 (0.6H, m, 0.6 OC*H*), 4.07-3.99 (0.4H, m, 0.4 OC*H*), 3.66-3.58 (1H, m, CH_AH_BOBn), 3.33-3.23 (2H, m, CH_AH_BOBn + C*H*OBn), 3.19 (3H, s, OCH_3), 2.04-1.51 (4H, m, 2 x THF-CH_2), 1.44-1.10 (8H, m, $CH_3(CH_2)_4$), 0.84-0.76 (3H, m, CH_3CH_2); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: (diastereomeric 60:40) 139.3, 139.2, 138.3(2), 128.4(2), 128.3(2), 127.9, 127.9, 127.9, 127.8, 127.7, 127.7, 127.4, 127.4, 108.2, 108.0, 84.6, 82.5, 81.8, 81.2, 73.5, 73.5, 72.9, 72.8, 70.7, 70.3, 49.0, 49.0, 34.7, 34.1, 32.1, 32.0, 31.1, 30.7, 27.5, 27.0, 25.4, 25.1, 22.7(2), 14.1(2); **HRMS** (ES^+, *m/z*): Calculated 435.2506 ($C_{26}H_{36}NaO_4$); Found 435.2490.

1-Nitrohex-5-yn-2-ol, 313



To a solution of 4-pentynal (2.00 g, 24.4 mmol) in *tert*-butanol (24 mL) and tetrahydrofuran (24 mL) at 0 ^{o}C was added nitromethane (3.96 mL, 73.0 mmol) and potassium *tert*-butoxide (0.547 g, 4.88 mmol). The resulting solution was warmed to room temperature for 1.5 h before water (20 mL) was added. The resultant mixture was extracted with ethyl acetate (3 × 40 mL), and the combined organics washed with brine (60 mL), dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-hexanes, 10:90 then 20:80] afforded *alkyne* **313** as an oil (3.2 g, 92%). **IR** (thin film)/cm^{-1} 3531 br., 3418 br., 3293, 2928, 1555, 1385, 1100, 894; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 4.56-4.40 (3H, m, C*H*$_2$NO$_2$ + C*H*OH), 3.05 (1H, d, *J* = 5.2, CHO*H*), 2.44-2.38 (2H, m, C*H*$_2$C≡CH), 2.05 (1H, t, *J* = 2.6, C≡C*H*), 1.76-1.69 (2H, m, C*H*$_2$CHOH); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 82.9, 80.4, 69.9, 67.4, 32.0, 14.5; **HRMS** (ES^{+}, *m/z*): Calculated 144.0655 ($C_6H_{10}NO_3$); Found 144.0670.

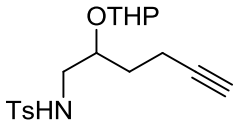
2-(1-Nitrohex-5-yn-2-yloxy)tetrahydro-2H-pyran, 314



To a solution of *alkyne* **313** (1.80 g, 12.6 mmol) in CH_2Cl_2 (90 mL) under argon was added 2,3-dihydropyran (1.59 g, 18.9 mmol) and pyridinium *para*-toluenesulfonate (0.316 g, 1.26 mmol). The resulting mixture was stirred at room temperature for 16 h before the solvent was removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-hexanes, 10:90] afforded *alkyne* **314** as an oil and as a (1:1) mixture of diastereoisomers (2.40 g, 84%). **IR** (thin film)/cm^{-1} 3295, 2945, 1557, 1384, 1130, 1076, 1034, 989; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: (diastereomeric 1:1) 4.73-4.65 (1.5H, m, OC*H*O + 0.5 C*H*$_A$H$_B$NO$_2$), 4.57-4.43

(2.5H, m, 0.5 C*H*$_A$H$_B$NO$_2$ + CH$_A$*H*$_B$NO$_2$ + C*H*OTHP), 3.92-3.78 (1H, m, CH$_2$C*H*$_A$H$_B$O), 3.55-3.45 (1H, m, CH$_2$CH$_A$*H*$_B$O), 2.44-2.30 (2H, m, C*H*$_2$C≡C*H*), 2.03-1.45 (9H, m, (C*H*$_2$)$_3$CH$_2$O + C*H*$_2$CHOTHP); **^{13}C NMR (100 MHz, CDCl$_3$)** δ_C: (diastereomeric 1:1) 99.8, 99.6, 83.2, 82.7, 79.4, 78.4, 73.6, 73.5, 69.7, 69.4, 63.3, 63.0, 32.0, 30.9, 30.8, 30.7, 25.2, 25.2, 19.8, 19.7, 14.5, 14.3; **HRMS** (ES$^+$, *m/z*): Calculated 250.1050 ($C_{11}H_{17}NNaO_4$); Found 250.1049.

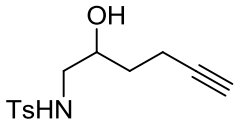
4-Methyl-*N*-(2-(tetrahydro-2H-pyran-2-yloxy)hex-5-ynyl)benzenesulfonamide, 315



A 3-neck flask fitted with a dropping funnel and reflux condenser containing a solution of *alkyne* **314** (800 mg, 3.52 mmol) in diethyl ether (10 mL) was heated at reflux. A solution of lithium aluminium hydride (8.80 mL, 8.80 mmol, 1.0 M solution in Et$_2$O), was added slowly over 1 h. The reaction was cooled to room temperature and stirred for 16 h before a saturated solution of sodium sulfate (3 mL) was added dropwise. The resulting mixture was filtered through a pad of Celite®, and washed with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and the solvent removed *in vacuo*. The resultant oil was dissolved in CH$_2$Cl$_2$ (35 mL) before *N*,*N*-dimethylaminopyridine (860 mg, 7.04 mmol) and *para*-toluenesulfonyl chloride (738 mg, 3.87 mmol) were added. The resultant mixture was stirred at room temperature for 16 h before water (20 mL) was added. The reaction mixture was extracted with diethyl ether (4 × 50 mL) and the combined organics washed with brine (50 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO$_2$, EtOAc-hexanes, 10:90 then 30:70] afforded *amine* **315** as an oil and a 1:1 mixture of diastereomers (500 mg, 40% over 2 steps). **IR** (thin film)/cm^{-1} 3284 br., 2942, 1441, 1329, 1160, 1025; **^{1}H NMR (400 MHz, CDCl$_3$)** δ_H: (diastereomeric 1:1) 7.76-7.71 (2H, m, 2 x Ar-C*H*), 7.33-7.27 (2H, m, 2 x Ar-C*H*), 6.15 (0.5H, dd, *J* = 8.0, 2.2, 0.5

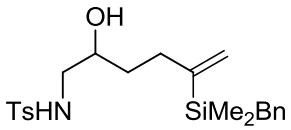
CH_2NHTs), 4.72 (0.5H, t, J = 6.0, 0.5 CH_2NHTs), 4.51-4.48 (0.5H, m, 0.5 OC*H*O), 4.38 (0.5H, dd, J = 7.6, 2.4, 0.5 OC*H*O), 4.00-3.94 (0.5H, m, 0.5 CH_AH_BO), 3.89-3.81 (1H, m, 0.5 CH_AH_BO + 0.5 CH_AH_BO), 3.74-3.67 (0.5H, m, 0.5 CH_AH_BO), 3.52-3.42 (1H, m, C*H*OTHP), 3.18-3.08 (1H, m, CH_AH_BNHTs), 2.96-2.89 (0.5H, m, 0.5 CH_AH_BNHTs), 2.84-2.77 (0.5H, m, 0.5 CH_AH_BNHTs), 2.43 (1.5H, s, 0.5 $ArCH_3$), 2.42 (1.5H, s, 0.5 $ArCH_3$), 2.28-2.18 (2H, m, $CH_2C{\equiv}CH$), 1.93-1.90 (1H, m, C≡C*H*), 1.87-1.37 (8H, m, $CH_2CHOTHP$ + $(CH_2)_3CH_2O$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: (diastereomeric 1:1) 143.5, 143.1, 137.2, 136.8, 129.8, 129.6, 127.2, 127.1, 102.0, 97.8, 83.6, 83.1, 77.9, 73.6, 69.2, 68.8, 65.3, 63.4, 47.6, 45.2, 31.9, 31.6, 31.3, 30.9, 25.2, 25.0, 21.5, 21.4, 14.7, 14.5; **HRMS** (ES^+, *m/z*): Calculated 374.1397 ($C_{18}H_{25}NNaO_4S$); Found 374.1395.

***N*-(2-Hydroxyhex-5-ynyl)-4-methylbenzenesulfonamide, 316**



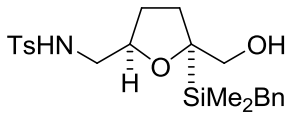
To a solution of *amine* **315** (500 mg, 1.42 mmol) in ethanol (9 mL) at 55 ^oC was added pyridinium para-toluenesulfonate (36 mg, 0.14 mmol). The resulting mixture was stirred for 7 h before the solvent was removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-hexanes, 30:70] afforded *hydroxy amine* **316** as an oil (351 mg, 92%). **IR** (thin film)/cm^{-1} 3501 br., 3289 br., 2925, 1598, 1433, 1323, 1158, 1090; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.68 (2H, d, J = 8.2, 2 x Ar-C*H*), 7.24 (2H, d, J = 8.2, 2 x Ar-C*H*), 5.27 (1H, br. s, CH_2NHTs), 3.84-3.77 (1H, m, C*H*OH), 3.04-2.96 (1H, m, CH_AH_BNHTs), 2.83-2.73 (1H, m, CH_AH_BNHTs), 2.61 (1H. br. s, CHO*H*), 2.36 (3H, s, $ArCH_3$), 2.22 (2H, td, J = 7.0, 2.8, $CH_2C{\equiv}CH$), 1.89 (1H, t, J = 2.8, C≡C*H*), 1.55 (2H, q, J = 7.0, CH_2CHOH); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 143.6, 136.6, 129.8, 127.1, 83.5, 69.3, 69.3, 48.6, 32.8, 21.5, 14.7; **HRMS** (ES^+, *m/z*): Calculated 290.0821 ($C_{13}H_{17}NNaO_3S$); Found 290.0821.

_N_-(5-(Benzyldimethylsilyl)-2-hydroxyhex-5-enyl)-4-methylbenzenesulfonamide, 317



Hydroxy amine **316** (305 mg, 1.14 mmol) was subjected to **General Procedure 6**. Purification by flash column chromatography [SiO_2, EtOAc-hexanes, 90:10] afforded *vinyl silane* **317** as an oil (341 mg, 72%). **IR** (thin film)/cm^{-1} 3491 br., 3284 br., 2954, 1599, 1493, 1353, 1159, 831; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.71 (2H, d, *J* = 8.0, 2 x Ts-C*H*), 7.26 (2H, d, *J* = 8.0, 2 x Ts-C*H*), 7.16-7.11 (2H, m, 2 x Bn-C*H*), 7.04-6.97 (1H, m, 1 x Bn-C*H*), 6.94-6.91 (2H, m, 2 x Bn-*CH*), 5.54-5.51 (1H, m, C=CH_AH_B), 5.29-5.26 (1H, m, C=CH_AH_B), 5.05-4.99 (1H, br. m, CH_2NHTs), 3.64-3.52 (1H, m, C*H*OH), 2.99 (1H, ddd, *J* = 13.2, 7.2, 3.2, CH_AH_BNHTs), 2.72 (1H, ddd, *J* = 12.8, 8.0, 4.8, CH_AH_BNHTs), 2.38 (3H, s, Ar-CH_3), 2.16-1.94 (5H, m, CH_2Bn + CH_2C(SiR_3)=CH_2 + CHO*H*), 1.45-1.37 (2H, m, CH_2CHOH), 0.00 (6H, s, 2 x SiCH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 149.6, 143.6, 139.9, 136.7, 129.8, 128.3, 128.2, 125.6, 124.1, 70.2, 70.2, 48.7, 33.6, 31.5, 25.6, 21.6, −3.5; **HRMS** (ES^+, *m/z*): Calculated 440.1686 ($C_{22}H_{31}NNaO_3SSi$); Found 440.1684.

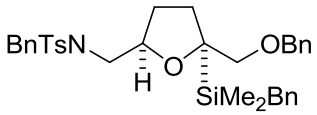
(±)-_N_-(((2_R_,5_R_)-5-(Benzyldimethylsilyl)-5-(hydroxymethyl)tetrahydrofuran-2-yl)methyl)-4-methylbenzenesulfonamide, 318



Vinyl silane **317** (165 mg, 0.396 mmol) was subject to **General Procedure 3** (24 h) using potassium osmate dihydrate (3.6 mg, 0.0099 mmol, 2.5 mol%) at 60 ^oC for 24 h. Purification by flash column chromatography [SiO_2, EtOAc-hexanes, 20:80] afforded *THF* **318** as an oil (152 mg, 89%). **IR** (thin film)/cm^{-1} 3484 br., 3286 br., 2956, 1599, 1451, 1324, 1159, 1058, 815; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.78 (2H, d, *J* = 8.0, 2 x Ts-C*H*), 7.33 (2H, d, *J* = 8.0, 2

x Ts-C*H*), 7.27-7.20 (2H, m, 2 x Bn-C*H*), 7.14-7.07 (1H, m, 1 x Bn-C*H*), 7.03-6.98 (2H, m, 2 x Bn-C*H*), 3.97-3.90 (1H, m, OC*H*), 3.69 (1H, d, J = 11.2, CH_AH$_B$OH), 3.40 (1H, d, J = 11.2, CH$_A$$H_B$OH), 3.25 (1H, dd, J = 12.8, 3.6, CH_AH$_B$NHTs), 3.00 (1H, dd, J = 12.8, 5.6, CH$_A$$H_B$NHTs), 2.44 (3H, s, Ar-CH$_3$), 2.15 (2H, d, J = 2.8, CH_2Bn), 1.95-1.76 (4H, m, 2 x THF-CH_2), 0.01 (3H, s, 1 x SiCH_3), 0.00 (3H, m, 1 x SiCH_3); **^{13}C NMR (100 MHz, CDCl$_3$)** δ_C: 143.3, 139.4, 137.1, 129.7, 128.3, 128.3, 127.1, 124.3, 80.8, 78.7, 67.7, 47.1, 30.1, 29.5, 23.2, 21.5, −5.4; **HRMS** (ES$^+$, *m/z*): Calculated 456.1635 ($C_{22}H_{31}NNaO_4SSi$); Found 456.1632.

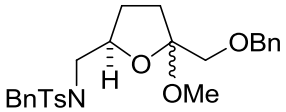
(±)-*N*-Benzyl-*N*-(((2*R*,5*R*)-5-(benzyldimethylsilyl)-5-(benzyloxymethyl)tetrahydrofuran-2-yl)methyl)-4-methylbenzenesulfonamide, 319



To a solution of *THF* **318** (45 mg, 0.15 mmol) in tetrahydrofuran (1.2 mL) and DMF (0.3 mL) at 0 ^oC was added sodium hydride (60% dispersion on mineral oil, 25 mg, 0.61 mmol). The resulting mixture was stirred for 30 min before benzyl bromide (73 μL, 0.61 mmol) and tetrabutylammonium iodide (6 mg, 0.02 mmol) were added. The mixture was warmed to room temperature and stirred for 16 h before brine (20 mL) was added. The mixture was extracted with ethyl acetate (3 x 30 mL) and the combined organics washed with brine (3 x 30 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-hexanes, 10:90] afforded *benzylated THF* **319** as an oil (67 mg, 77%). **IR** (thin film)/cm^{-1} 2957, 2869, 1599, 1453, 1342, 1158, 1023, 937; **^{1}H NMR (400 MHz, CDCl$_3$)** δ_H: 7.85 (2H, d, J = 8.2, 2 x Ts-C*H*), 7.47-7.35 (12H, m, 2 x Ts-C*H* + 10 x OBn-C*H*), 7.33-7.27 (2H, m, 2 x SiBn-C*H*), 7.20-7.15 (1H, m, 1 x SiBn-C*H*), 7.07-7.02 (2H, m, 2 x SiBn-C*H*), 4.61 (2H, d, J = 4.0, OCH_2Ph), 4.51 (2H, s, NCH_2Ph), 3.93-3.84 (1H, m, OC*H*), 3.64 (1H, dd, J = 14.8, 4.0, CH_AH$_B$OBn), 3.40 (2H, q, J = 9.2, CH_2NBnTs), 3.15 (1H, dd, J = 14.8, 7.6, CH$_A$$H_B$OBn), 2.50 (3H, s, Ar-C$H_3$), 2.16 (2H, d, J = 4.4, SiCH_2Ph), 1.98-

1.92 (1H, m, THF-C*H*$_A$H$_B$), 1.89-1.75 (2H, m, THF-C*H*$_2$), 1.68-1.60 (1H, m, THF-CH$_A$*H*$_B$), 0.00 (3H, s, 1 x SiC*H*$_3$), −0.02 (3H, s, 1 x SiC*H*$_3$); **^{13}C NMR (100 MHz, CDCl$_3$)** δ_C: 143.1, 139.9, 138.4, 137.9, 136.7, 129.6, 128.6, 128.4, 128.3, 128.3, 128.1, 127.6, 127.5, 127.5, 127.2, 124.0, 79.4, 79.3, 76.0, 73.5, 52.1, 51.9, 30.5, 30.4, 23.2, 21.5, −5.6, −5.6; **HRMS** (ES$^+$, *m/z*): Calculated 636.2574 ($C_{36}H_{43}NNaO_4SSi$); Found 636.2572.

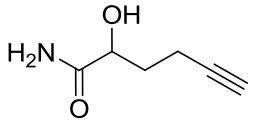
(±)-(*R*)-*N*-Benzyl-*N*-((5-(benzyloxymethyl)-5-methoxytetrahydrofuran-2-yl)methyl)-4-methylbenzenesulfonamide, 320



Benzylated THF **319** (47 mg, 77 μmol) was subjected to **General Procedure 7**. The resulting crude product was purified by flash column chromatography [SiO_2, petrol/EtOAc, 4:1] to afford the intermediate lactol as an oil (28 mg, 76%), as a complex mixture of isomers. The intermediate lactol (18 mg, 37 μmol) was dissolved in methanol (1 mL) and CH_2Cl_2 (1 mL) under argon before pyridinium *para*-toluenesulfonate (2 mg, 8 μmol) was added. The resultant mixture was stirred at room temperature for 2 h before the solvent was removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 15:85] afforded *lactol methyl ether* **320** as an oil, and a (60:40) mixture of diastereomers (16 mg, 86%). **IR** (thin film)/cm^{-1} 3385 br., 2924, 1599, 1454, 1339, 1159, 1090; **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ_H: (diastereomeric 60:40) 7.75 (0.8H, d, *J* = 8.5, 0.4 2 x Ts-C*H*), 7.72 (1.2H, d, *J* = 10.5, 0.4 2 x Ts-C*H*), 7.43-7.37 (2H, m, 2 x Ts-C*H*), 7.36-7.21 (10H, m, 10 x Bn-C*H*), 4.47 (1.2H, d, *J* = 4.0, 0.6 OC*H*$_2$Ph), 4.44 (0.8H, d, *J* = 4.0, 0.4 OC*H*$_2$Ph), 4.38-4.35 (2H, m, NC*H*$_2$Ph), 3.96-3.88 (1H, m, OC*H*), 3.49-3.43 (1H, m, C*H*$_A$H$_B$OBn), 3.28-3.19 (2H, m, CH$_A$*H*$_B$OBn + C*H*$_A$H$_B$NBnTs), 3.11 (0.4H, dd, *J* = 14.5, 7.0, 0.4 CH$_A$*H*$_B$NBnTs), 3.03-2.96 (1.8H, m, 0.6 CH$_A$*H*$_B$NBnTs + 0.4 OC*H*$_3$), 2.90 (1.8H, s, 0.6 OC*H*$_3$), 2.41-2.37 (3H, m, Ar-C*H*$_3$), 1.90-1.82 (1H, m, THF-C*H*$_A$H$_B$), 1.82-1.65 (2H, m, THF-C*H*$_2$), 1.56-1.39 (1H, m, THF-CH$_A$*H*$_B$);

^{13}C NMR (125 MHz, DMSO-d_6) δ_C: (diastereomeric 60:40) 138.3, 138.3, 137.0, 137.0, 136.6, 136.4, 129.8, 129.8, 128.3, 128.2, 128.0, 127.9, 127.5, 127.4, 127.4, 127.4, 127.0, 127.0, 108.2, 108.2, 78.3, 77.0, 72.4, 72.4, 70.4, 70.1, 52.8, 52.0, 52.0, 51.7, 48.3, 48.2, 33.1, 32.5, 28.3, 27.6, 21.0; **HRMS** (ES^+, *m/z*): Calculated 518.1972 ($C_{28}H_{33}NNaO_5S$); Found 518.1973.

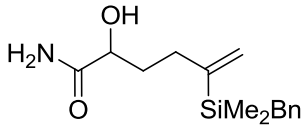
2-Hydroxyhex-5-ynamide, 322



To a solution of 4-pentynal (1.00 g, 12.2 mmol) in CH_2Cl_2 (60 mL) was added triethylamine (2.04 mL, 14.6 mmol). The resulting solution was cooled to 0 ^oC before trimethylsilyl cyanide (1.52 mL, 12.2 mmol) was added dropwise over a period of 5 min. The resulting mixture was warmed to room temperature and stirred for 4 h before water (30 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organics were carefully washed with aqueous hydrochlorid acid (2 M, 50 mL), brine (50 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. The crude product was dissolved in DMSO (1.5 mL) and cooled to 0 ^oC before potassium carbonate (0.328 g, 2.38 mmol) and hydrogen peroxide (1.62 g, 16.7 mmol, 33% in water) were added. The resulting mixture was warmed to room temperature (where a large exotherm ensued) and stirred for 30 min. The resulting suspension was diluted with water (3 mL) and filtered. The solid was washed with ethyl acetate (20 mL), before the aqueous layer was extracted with ethyl acetate (5 × 30 mL) and the combined organics washed with a saturated solution of sodium thiosulfate (30 mL), brine (30 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. The resulting crude solid was washed with diethyl ether (2 mL) to remove less polar impurities and dried *in vacuo* to afford *hydroxy amide* **322** as prisms (850 mg, 56%). **IR** (KBr disc)/cm^{-1} 3284, 2544, 2379, 1671, 1608, 1400, 1290, 1095, 1062, 934, 762; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.05 (1H, br. s, 1 x N*H*), 6.55 (1H, br. s, 1 x N*H*), 4.76 (1H, br. s,

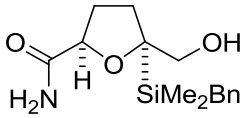
CHO*H*), 4.09 (1H, dd, *J* = 8.4, 3.2, C*H*OH), 2.36-2.30 (2H, m, CH_2C≡CH), 2.07-1.96 (2H, m, C≡CH + CH_AH$_B$CHOH), 1.79-1.70 (1H, m, CH$_A$$H_B$CHOH); **^{13}C NMR (100 MHz, CDCl$_3$)** δ_C: 176.3, 83.9, 70.4, 69.6, 34.3, 14.5; **HRMS** (ES$^+$, *m/z*): Calculated 150.0525 ($C_6H_9NNaO_2$); Found 150.0523; **M.P.** 102-104 ^oC.

5-(Benzyldimethylsilyl)-2-hydroxyhex-5-enamide, 323



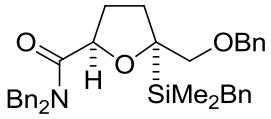
Hydroxy amide **322** (650 mg, 5.12 mmol) was subject to **General Procedure 4**. Purification by flash column chromatography [SiO_2, acetone-petrol, 30:70] afforded *vinyl silane* **323** as an oil (756 mg, 53%). **IR** (thin film)/cm^{-1} 3027, 2934, 1687, 1335, 1295, 1145, 936, 837; **^{1}H NMR (400 MHz, CDCl$_3$)** δ_H: 7.21 (2H, t, *J* = 7.4, 2 x Ar-C*H*), 7.11-7.05 (1H, m, Ar-C*H*), 7.00 (2H, d, *J* = 7.4, 2 x Ar-C*H*), 6.43 (1H, br. s, NH_AH$_B$), 5.87 (1H, br. s, NH$_A$$H_B$), 5.67-5.65 (1H, m, C=C$H_AH_B$), 5.40-5.37 (1H, m, C=CH$_A$$H_B$), 4.14-4.08 (1H, m, C*H*OH), 2.95 (1H, d, *J* = 5.2, CHO*H*), 2.27-2.21 (2H, m, CH_2CHOH), 2.18 (2H, s, CH_2Ph), 2.00-1.90 (1H, m, CH_AH$_B$C(SiR$_3$)=CH$_2$), 1.79-1.67 (1H, m, CH$_A$$H_B$C(SiR$_3$)=CH$_2$), 0.08 (6H, s, Si(C$H_3$)$_2$); **^{13}C NMR (100 MHz, CDCl$_3$)** δ_C: 176.7, 149.6, 139.9, 128.3, 128.1, 125.8, 124.1, 71.7, 33.8, 31.0, 25.5, −3.4, −3.5; **HRMS** (ES$^+$, *m/z*): Calculated 300.1390 ($C_{15}H_{23}NNaO_2Si$); Found 300.1390.

(±)-(2*R*,5*R*)-5-(Benzyldimethylsilyl)-5-(hydroxymethyl)tetrahydrofuran-2-carboxamide, 324



Vinyl silane **323** (120 mg, 0.433 mmol) was subjected to **General Procedure 3** using potassium osmate dihydrate (8.0 mg, 0.022 mmol, 5.0 mol%) at 60 ^{o}C for 32 h. Purification by flash column chromatography [SiO_2, acetone-petrol, 50:50] afforded *THF* **324** as an oil (103 mg, 81%). **IR** (KBr disc)/cm^{-1} 3267, 2501, 2358, 1648, 1450, 1246, 1203, 1155, 1067, 808; **^{1}H NMR (400 MHz, MeOD-*d*$_4$)** δ_H: 7.19-7.13 (2H, m, 2 x Ar-C*H*), 7.05-6.97 (3H, m, 3 x Ar-C*H*), 4.23-4.17 (1H, m, OC*H*), 3.67 (1H, d, *J* = 11.8, CH_AH$_B$OH), 3.52 (1H, d, *J* = 11.8, CH$_A$$H_B$OH), 2.29-2.15 (1H, m, THF-CH_AH$_B$), 2.20 (2H, d, *J* = 4.4, CH_2Bn), 2.04-1.90 (3H, m, THF-CH$_A$$H_B$ + THF-CH_2), 0.00 (6H, d, *J* = 4.4, 2 x SiCH_3); **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ_C: 175.7, 139.6, 128.1, 128.1, 123.9, 82.1, 79.4, 65.7, 31.1, 29.2, 22.7, −5.3, −5.4; **HRMS** (ES$^+$, *m/z*): Calculated 316.1339 ($C_{15}H_{23}NNaO_3Si$); Found 316.1339; **M.P.** 133-135 ^{o}C.

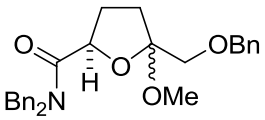
(±)-(2*R*,5*R*)-*N*,*N*-Dibenzyl-5-(benzyldimethylsilyl)-5-(benzyloxymethyl)tetrahydro- furan-2-carboxamide, 325



To a solution of *THF* **324** (45 mg, 0.15 mmol) in tetrahydrofuran (1.2 mL) and DMF (0.3 mL) at 0 ^{o}C was added sodium hydride (60% dispersion on mineral oil, 25 mg, 0.61 mmol). The resulting mixture was stirred for 30 min before benzyl bromide (73 μL, 0.61 mmol) and tetrabutylammonium iodide (6 mg, 0.02 mmol) were added. The mixture was warmed to room temperature and stirred for 16 h before brine (20 mL) was added. The mixture was extracted with ethyl acetate (3 x 30 mL) and the combined organics washed with brine (3 x 30 mL), dried

over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 15:85] afforded *benzylated-THF* **325** as an oil (57 mg, 66%). **IR** (thin film)/cm^{-1} 2956, 1651, 1451, 1245, 1096, 820; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.46-7.27 (15H, m, 15 x OBn-C*H*), 7.24-7.18 (2H, m, 2 x SiBn-C*H*), 7.12-7.06 (1H, m, 1 x SiBn-C*H*), 7.00-6.96 (2H, m, 2 x SiBn-C*H*), 4.78-4.53 (7H, m, 3 x OCH_2Ph + OC*H*), 3.62 (1H, d, *J* = 9.2, CH_AH$_B$OBn), 3.57 (1H, d, *J* = 9.2, CH_AH$_B$OBn), 2.71-2.60 (1H, m, THF-CH_AH$_B$), 2.21 (2H, s, SiCH_2Ph), 2.19-2.14 (1H, m, THF-CH$_A$$H_B$), 2.13-2.04 (1H, m, THF-CH_AH$_B$), 1.96 (1H, ddd, *J* = 12.0, 10.0, 7.8, THF-CH$_A$$H_B$), 0.01 (3H, s, 1 x SiC$H_3$), 0.00 (3H, s, 1 x SiC$H_3$); **^{13}C NMR (100 MHz, acetone-d_6)** δ_C: 171.6, 140.0, 138.5, 137.2, 137.0, 128.7, 128.6, 128.3, 128.3, 128.3, 128.1, 127.8, 127.5, 127.5, 127.3, 127.2, 123.9, 80.4, 77.9, 75.7, 73.6, 49.7, 47.9, 31.2, 28.5, 23.4, −5.3, −5.3; **HRMS** (ES^+, *m/z*): Calculated 586.2748 ($C_{36}H_{41}NNaO_3Si$); Found 586.2747.

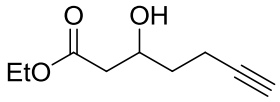
(±)-(*R*)-*N*,*N*-dibenzyl-5-(benzyloxymethyl)-5-methoxytetrahydrofuran-2-carboxamide, 326



Benzylated-THF **325** (50 mg, 89 μmol) was subjected to **General Procedure 7**. The resulting crude product was purified by flash column chromatography [SiO_2, EtOAc-petrol, 4:1] to afford the intermediate lactol as an oil (27 mg, 71%), as a complex mixture of isomers. The intermediate lactol (15 mg, 35 μmol) was dissolved in methanol (1 mL) and CH_2Cl_2 (1 mL) under argon before pyridinium *para*-toluenesulfonate (2 mg, 8 μmol) was added. The resultant mixture was stirred at room temperature for 2 h before the solvent was removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 15:85] afforded *lactol methyl ether* **326** as an oil, and a (60:40) mixture of diastereomers (13 mg, 84%). **IR** (thin film)/cm^{-1} 2922, 1656, 1452, 1157, 1075; **^{1}H NMR (500 MHz, DMSO-d_6)** δ_H: (diastereomeric

60:40) 7.39-7.14 (15H, m, 15 x Ar-C*H*), 4.91-4.87 (0.6H, m, 0.6 OC*H*), 4.80-4.71 (0.8H, m, 0.4 OC*H* + 0.2 x CH_2Ph), 4.65-4.37 (5.2H, m, 2.6 x CH_2Ph), 4.31-4.26 (0.4H, m, 0.2 x CH_2Ph), 3.64 (0.6H, d, J = 10.5, 0.6 CH_AH$_B$OBn), 3.56 (0.4H, d, J = 10.5, 0.4 CH_AH$_B$OBn), 3.44 (0.6H, d, J = 10.5, 0.6 CH$_A$$H_B$OBn), 3.40 (0.4H, d, J = 10.5, 0.4 CH$_A$$H_B$OBn), 3.17 (1.2H, s, 0.4 OCH_3), 3.08 (1.8H, s, 0.6 OCH_3), 2.36-2.28 (0.4H, m, 0.2 THF-CH_2), 2.20-1.96 (3H, m, 1.5 THF-CH_2), 1.93-1.86 (0.6H, m, 0.3 THF-CH_2); **^{13}C NMR (125 MHz, DMSO-d_6)** δ_C: (diastereomeric 60:40) 170.2, 170.2, 138.3, 138.2, 137.3, 137.2, 137.1, 137.0, 128.7, 128.6, 128.4, 128.2, 128.2, 127.5, 127.5, 127.4, 127.3, 127.3, 127.1, 126.9, 126.8, 109.1, 108.8, 76.7, 75.6, 72.5, 72.4, 70.7, 70.0, 49.5, 49.3, 48.7, 48.7, 47.8, 47.8, 33.4, 33.0, 27.4, 27.3; **HRMS** (ES$^+$, *m/z*): Calculated 468.2145 ($C_{28}H_{31}NNaO_4$); Found 468.2143.

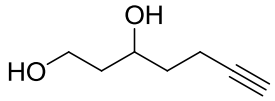
Ethyl 3-hydroxyhept-6-ynoate, 327



To a stirred solution of diisopropylamine (1.60 mL, 11.47 mmol) in tetrahydrofuran (30 mL) at 0 °C was added *n*-Butyllithium (7.17 mL, 1.6 M solution in hexanes) dropwise. The resulting mixture was stirred for 20 min at 0 ^{o}C before being cooled to –78 ^{o}C. Distilled ethyl acetate (1.00 mL, 11.1 mmol) was added dropwise and the resulting mixture was stirred at –78 °C for a further 20 min. Pentyn-4-al (300 mg, 3.66 mmol) was added dropwise and the resultant mixture was stirred at –78 °C for 2 h before being quenched with a saturated solution of ammonium chloride (20 mL). The mixture was then extracted with diethyl ether (3 x 25 mL), and the combined organic layers were washed with brine (1 x 30 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, Et_2O-petrol, 40:60] afforded hydroxyl-ester **327** (370 mg, 60%) as an oil. **IR** (thin film)/cm^{-1} 3451 br., 3295, 2935, 1730, 1302, 1157, 1092; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 4.21-4.11 (3H, m, C*H*OH + CH_2O), 3.13 (1H, d, J = 3.8, CHO*H*), 2.52 (1H, dd, J = 16.8, 3.6, CH_AH$_B$CO$_2$Et),

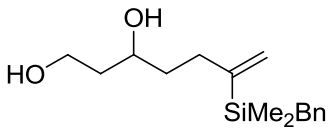
2.44 (1H, dd, J = 16.8, 8.8, $CH_AH_BCO_2Et$), 2.36 (2H, dt, J = 7.2, 2.4, CH_2CH_2CHOH), 1.96 (1H, t, J = 2.4, C≡C*H*), 1.77-1.61 (2H, m, CH_2C), 1.27 (3H, t, J = 7.2, CH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 172.8, 83.8, 68.8, 66.6, 60.8, 41.1, 34.9, 14.7, 14.1; **HRMS** (ES^+, *m/z*): Calculated 193.0835 ($C_9H_{14}NaO_3$); Found 193.0841.

Hept-6-yne-1,3-diol, 328



To a stirred solution of *ester* **327** (319 mg, 1.89 mmol) in tetrahydrofuran (25 mL) at 0 ^oC was added lithium borohydride (123 mg, 5.66 mmol) in one portion. The resulting mixture was stirred at room temperature for 15 h before water (40 mL) was added and the mixture extracted with ethyl acetate (3 × 40 mL). The combined organics were washed with brine (50 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 60:40] afforded *diol* **328** as an oil (195 mg, 81%). **IR** (thin film)/cm^{-1} 3295 br., 2947, 1435, 1057; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 4.05-3.96 (1H, m, C*H*OH), 3.92-3.77 (2H, m, CH_2OH), 3.31, (1H, d, J = 4.0, CHO*H*), 3.03 (1H, t, J = 4.8, CH_2OH), 2.33 (2H, td, J = 7.0, 2.4, CH_2CH_2OH), 1.98 (1H, t, J = 2.4, C≡C*H*), 1.75-1.62 (4H, m, $CH_2CH_2CH(OH)$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 84.0, 70.6, 68.9, 61.4, 38.1, 35.9, 14.8; **HRMS** (ES^+, *m/z*): Calculated 151.0730 ($C_7H_{12}NaO_2$); Found 151.0731.

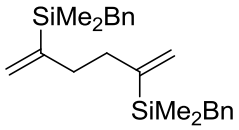
6-(Benzyldimethylsilyl)hept-6-ene-1,3-diol, 329



Diol **328** (165 mg, 1.30 mmol) was subjected to **General Procedure 6**. Purification by flash column chromatography [SiO_2, Et_2O-petrol, 10:90] afforded *vinyl silane* **329** as an oil (217 mg,

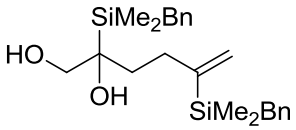
61%). **IR** (thin film)/cm^{-1} 3356 br., 2940, 1600, 1451, 1057, 831; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.21 (2H, t, *J* = 7.6, 2 x Ar-C*H*), 7.07 (1H, t, *J* = 7.6, Ar-C*H*), 7.00 (2H, d, *J* = 7.6, 2 x Ar-C*H*), 5.66-5.64 (1H, m, C=CH_AH_B), 5.37-5.34 (1H, m, C=CH_AH_B), 3.95 (3H, m, C*H*OH + CH_2OH), 2.60 (2H, br. s, CHO*H* + CH_2O*H*), 2.28-2.06 (4H, m, CH_2CH_2OH + CH_2OBn), 1.73-1.53 (4H, m, CH_2CH_2C(SiR_3)=CH_2), 0.08 (6H, s, Si(CH_3)$_2$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 150.1, 139.9, 128.3, 128.1, 125.3, 124.0, 72.1, 61.8, 36.8, 31.8, 29.3, 25.5, -3.5; **HRMS** (ES^+, *m/z*): Calculated 301.1551 ($C_{16}H_{26}NaO_2Si$); Found 301.1551.

Hexa-1,5-diene-2,5-diylbis(benzyldimethylsilane), 332



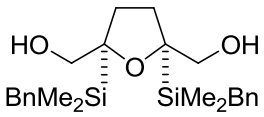
1,5-Hexadiyne (200 mg, 2.56 mmol) was subjected to **General Procedure 6**. Purification by flash column chromatography [SiO_2, Et_2O-petrol, 1:99] afforded *vinyl silane* **332** as an oil (704 mg, 73%). **IR** (thin film)/cm^{-1} 3024, 2956, 1600, 1493, 1249, 1206, 1154, 1056, 832; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.27-7.21 (4H, m, 4 x Ar-C*H*), 7.14-7.07 (2H, m, 2 x Ar-C*H*), 7.05-7.01 (4H, m, 4 x Ar-C*H*), 5.67-5.65 (2H, m, 2 x C=CH_AH_B), 5.39-5.36 (2H, m, 2 x C=CH_AH_B), 2.25-2.15 (8H, m, 2 x CH_2Ph + CH_2CH_2), 0.10 (12H, s, 4 x SiCH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 150.3, 139.9, 128.3, 128.2, 125.1, 124.1, 35.4, 25.6, –3.5; **HRMS** (ES^+, *m/z*): Calculated 401.2091 ($C_{24}H_{34}NaSi_2$); Found 401.2090.

2,5-Bis(benzyldimethylsilyl)hex-5-ene-1,2-diol, 333



Vinyl Silane **332** (250 mg, 0.661 mmol) was subjected to **General Procedure 2** (36 h) with quinuclidine. Purification by flash column chromatography [SiO_2, Et_2O-petrol, 40:60] afforded *diol* **333** as an oil (101 mg, 37%). **IR** (thin film)/cm^{-1} 3418 br., 2956, 1600, 1493, 1249, 1057, 833; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.27-7.18 (4H, m, 4 x Ar-C*H*), 7.14-7.00 (6H, m, 6 x Ar-C*H*), 5.66-5.63 (1H, m, C=CH_AH_B), 5.39-5.35 (1H, m, C=CH_AH_B), 3.72 (1H, d, *J* = 11.0, CH_AH_BOH), 3.60 (1H, d, *J* = 11.0, CH_AH_BOH), 2.24 (2H, s, 1 x CH_2Ph), 2.18 (2H, s, 1 x CH_2Ph), 2.15-2.07 (2H, m, CH_2C(SiR_3)=CH_2), 1.74-1.59 (4H, m, CH_2CH_2C(SiR_3)=CH_2 + 2 x O*H*), 0.10 (6H, s, 2 x SiCH_3), 0.05 (3H, s, 1 x SiCH_3), 0.04 (3H, s, 1 x SiCH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 150.4, 139.9, 139.6, 128.4, 128.3, 128.3, 128.3, 125.4, 124.3, 124.1, 70.0, 67.6, 35.4, 29.9, 25.8, 23.5, −3.4, −4.8, −4.9; **HRMS** (ES^+, *m/z*): Calculated 435.2146 ($C_{24}H_{36}NaO_2Si_2$); Found 435.2146.

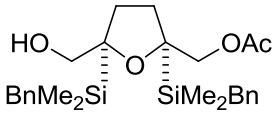
(±)-((2*R*,5*S*)-2,5-Bis(benzyldimethylsilyl)tetrahydrofuran-2,5-diyl)dimethanol, 334



Diol **333** (72 mg, 0.17 mmol) was subject to **General Procedure 3** (36 h) using potassium osmate dihydrate (4.82 mg, 0.013 mmol, 7.5 mol%) at 60 ^oC for 24 h. Purification by flash column chromatography [SiO_2, EtOAc-hexanes, 80:20] afforded *THF* **334** as an oil (38 mg, 51%). **IR** (thin film)/cm^{-1} 3375 br., 3023, 2956, 1600, 1493, 1247, 1044, 818; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.26-7.20 (4H, m, 4 x Ar-C*H*), 7.13-7.03 (6H, m, 6 x Ar-C*H*), 3.73 (2H, d, *J* = 11.4, 2 x CH_AH_BOH), 3.59 (2H, d, *J* = 11.4, 2 x CH_AH_BOH), 2.94 (2H, br. s, 2 x CH_2O*H*), 2.29 (4H, s, 2 x CH_2Ph), 1.89-1.80 (4H, m, 2 x THF-CH_2), 0.07 (6H, s, 2 x SiCH_3), 0.04 (6H, s,

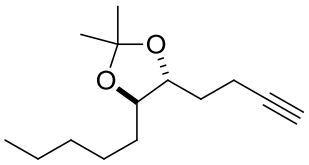
2 x SiCH_3); **^{13}C NMR (100 MHz, CDCl$_3$)** δ_C: 139.7, 128.4, 128.2, 124.2, 81.1, 68.9, 31.3, 23.8, −4.6, −4.7; **HRMS** (ES$^+$, *m/z*): Calculated 451.2095 ($C_{24}H_{36}NaO_3Si_2$); Found 451.2096.

(±)-((2*R*,5*S*)-2,5-Bis(benzyldimethylsilyl)-5-(hydroxymethyl)tetrahydrofuran-2-yl)methyl acetate, 335



A solution of *THF* **334** (70 mg, 0.16 mmol) in pyridine (2 mL) and acetic anhydride (0.15 µL, 0.16 mmol) and stirred at room temperature for 16 h before the solvent was removed *in vacuo*. Purification by flash column chromatography [SiO_2, Et_2O-petrol, 20:80] afforded *mono-acetate* **335** as an oil (39 mg, 51%). **IR** (thin film)/cm^{-1} 3502 br., 3024, 2956, 1740, 1600, 1493, 1246, 1053, 819; **^{1}H NMR (400 MHz, CDCl$_3$)** δ_H: 7.28-7.18 (4H, m, 3 x Ar-C*H*), 7.14-7.01 (6H, m, 6 x Ar-C*H*), 4.46 (1H, d, *J* = 12.0, CH_AH$_B$OAc), 4.00 (1H, d, *J* = 12.0, CH$_A$$H_B$OAc), 3.16 (2H, s, CH_2OH), 2.30-2.22 (4H, m, 2 x CH_2Ph), 2.15 (3H, s, C$H_3CO_2CH_2$), 1.94-1.67 (4H, m, 2 x THF-CH_2), 0.08-0.01 (12H, m, 4 x SiCH_3); **^{13}C NMR (100 MHz, CDCl$_3$)** δ_C: 171.3, 139.9, 139.4, 128.4, 128.3, 128.3, 128.2, 124.3, 124.1, 81.5, 79.0, 70.9, 68.4, 31.4, 31.7, 23.9, 23.6, 21.2, −4.6, −4.6, −4.7, −5.0; **HRMS** (ES$^+$, *m/z*): Calculated 493.2201 ($C_{26}H_{38}NaO_4Si_2$); Found 493.2205.

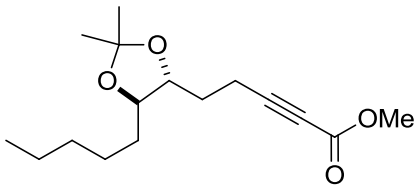
(±)-(4*R*,5*R*)-4-(But-3-ynyl)-2,2-dimethyl-5-pentyl-1,3-dioxolane, 343



To a solution of *diol* **295** (300 mg, 1.62 mmol) and 2-methoxy propene (0.270 mL, 2.84 mmol) in dimethylformamide (5 mL) was added camphorsulfonic acid (39 mg, 0.16 mmol). The

resulting solution was stirred at room temperature for 16 h after which water (30 mL) was added and the mixture extracted with ethyl acetate (3 × 30 mL). The combined organics were washed with water (4 x 30 mL), brine (30 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 5:95] afforded *acetonide* **343** as an oil (319 mg, 86%). **IR** (thin film)/cm^{-1} 3313, 2986, 2933, 1457, 1379, 1242, 1068, 874; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 3.71 (1H, td, *J* = 7.6, 3.2, 1 x C*H*OR), 3.67-3.60 (1H, m, 1 x C*H*OR), 2.44-2.26 (2H, m, CH_2C≡CH), 1.98-1.95 (1H, m, C≡C*H*), 1.82-1.67 (2H, m, CH_2CH$_2$C≡CH), 1.56-1.49 (2H, m, (CH$_2$)$_3$CH_2OR), 1.38 (3H, s, 1 x CCH_3), 1.38 (3H, s, 1 x CCH_3), 1.36-1.28 (6H, m, CH$_3$(CH_2)$_3$), 0.89 (3H, t, *J* = 6.8, CH$_2$CH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 108.1, 83.8, 80.6, 79.4, 68.6, 32.8, 32.0, 31.9, 27.3, 27.2, 25.7, 22.5, 15.3, 14.0; **HRMS** (ES^+, *m/z*): Calculated 247.1669 ($C_{14}H_{24}NaO_2$); Found 247.1669.

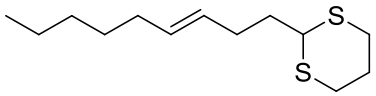
(±)-Methyl 5-((4*R*,5*R*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)pent-2-ynoate, 344



To a solution of *acetonide* **343** (100 mg, 0.446 mmol) in tetrahydrofuran (2 mL) at –78 ^{o}C was added *n*-butyllithium (0.307 mL, 0.491 mmol, 1.6 M in hexanes) dropwise. The resulting solution was stirred at –78 ^{o}C for 1 h before methyl chloroformate (41 μL, 0.54 mmol) was added dropwise. The resulting solution was stirred at –78 ^{o}C for 1 h before being warmed to 0 ^{o}C and stirred for a further 1.5 h. Ammonium chloride (10 mL) was added and the mixture was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 5:95 to 10:90] afforded *ester* **344** as an oil (96 mg, 76%). **IR** (thin film)/cm^{-1} 2934, 2862, 2240, 1719, 1435, 1379, 1256, 1073; **^{1}H NMR**

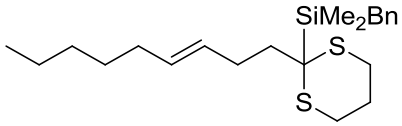
(400 MHz, $CDCl_3$) δ_H: 3.78-3.75 (3H, m, OC*H*$_3$), 3.70-3.60 (2H, m, 2 x C*H*OR), 2.61-2.40 (2H, m, C*H*$_2$C≡CH), 1.89-1.70 (2H, m, C*H*$_2$CH$_2$C≡CH), 1.57-1.49 (2H, m, $(CH_2)_3CH_2OR$), 1.38 (3H, s, 1 x CC*H*$_3$), 1.37 (3H, s, 1 x CC*H*$_3$), 1.35-1.25 (6H, m, $CH_3(CH_2)_3$), 0.90 (3H, t, *J* = 6.4, CH_2CH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 154.1, 108.3, 88.9, 80.6, 79.3, 73.1, 52.6, 32.8, 31.9, 31.1, 27.3, 27.2, 25.7, 22.5, 15.6, 14.0; **HRMS** (ES^+, *m/z*): Calculated 305.1723 ($C_{16}H_{26}NaO_4$); Found 305.1724.

(*E*)-2-(Non-3-enyl)-1,3-dithiane, 353



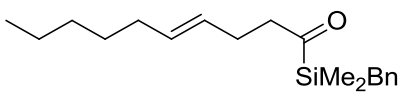
To a solution of *trans*-4-decenal (1.50 g, 9.74 mmol) and 1,3 propanedithiol (1.17 mL, 11.6 mmol) in CH_2Cl_2 (40 mL) at 0 ^oC was added boron trifluoride dietherate (4.66 mL, 36.9 mmol). The resulting solution was warmed to room temperature and stirred for 16 h before water (30 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (50 mL) before being dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 0:100 then 3:97] afforded *thiol* **353** as an oil (1.80 g, 76%). **IR** (thin film)/cm^{-1} 2926, 2854, 1422, 1275, 1179, 969; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 5.52-5.31 (2H, m, C*H*=C*H*), 4.02 (1H, t, *J* = 7.0, SC*H*S), 2.91-2.78 (4H, m, 2 x C*H*$_2$S), 2.27-1.85 (8H, m, C*H*$_2$CH$_2$S + 2 x C*H*$_2$CH=CH + C*H*$_2$CHS), 1.39-1.21 (6H, m, $CH_3(CH_2)_3$), 0.88 (3H, t, *J* = 7.0); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 132.0, 128.2, 46.8, 35.2, 32.5, 31.4, 30.4, 29.4, 29.2, 26.1, 22.5, 14.1; **HRMS** (ES^+, *m/z*): Calculated 244.1319 ($C_{13}H_{24}S$); Found 244.1327.

(*E*)-Benzyldimethyl(2-(non-3-enyl)-1,3-dithian-2-yl)silane, 354



To a solution of *thiol* **353** (500 mg, 2.05 mmol) in tetrahydrofuran (10 mL) at –40 ^{o}C was added *n*-butyllithium (1.41 mL, 2.26 mmol, 1.6 M in hexanes) dropwise. The resulting solution waqs warmed to –20 ^{o}C for 3 h before chlorobenzyldimethyl silane (0.370 mL, 2.05 mmol) in tetrahydrofuran (1.0 mL) was added. The resulting solution was warmed to room temperature and stirred for 16 h before ethyl acetate (20 mL) and water (20 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (20 mL) before being dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 0:100 then 1:99] afforded *silane* **354** as a yellow oil (667 mg, 83%). **IR** (thin film)/cm^{-1} 2925, 1600, 1493, 1452, 1249, 1158, 1057, 825; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.23 (2H, t, *J* = 7.6, 2 x Ar-C*H*), 7.13-7.03 (3H, m, 3 x Ar-C*H*), 5.55-5.40 (2H, m, C*H*=C*H*), 3.14-3.03 (2H, m, CH_2CSi), 2.49 (2H, dt, *J* = 14.0, 3.6, 1 x CH_2S), 2.40 (2H, s, CH_2Ph), 2.33-2.26 (2H, m, 1 x CH_2S), 2.25-2.17 (2H, m, CH_2CH$_2$CSi), 2.13-1.87 (4H, m, CH$_2$CH$_2$S + (CH$_2$)$_3$CH_2CH=CH), 1.43-1.26 (6H, m, CH$_3$(CH_2)$_3$), 0.91 (3H, t, *J* = 6.8), 0.12 (6H, s, Si(CH_3)$_2$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 139.3, 131.2, 129.3, 128.6, 128.2, 124.3, 38.6, 37.7, 32.6, 31.4, 31.1, 29.4, 25.0, 23.5, 23.5, 23.0, 22.6, 14.1, –4.7; **HRMS** (ES$^+$, *m/z*): Calculated 415.1920 ($C_{22}H_{36}NaS_2Si$); Found 415.1917.

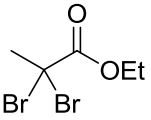
(*E*)-1-(Benzyldimethylsilyl)dec-4-en-1-one, 355



To a solution of *silane* **354** (600 mg, 1.53 mmol) and sodium bicarbonate (1.29 g, 15.3 mmol) in MeCN:water (15 mL, 4:1) was added iodomethane (1.91 mL, 30.6 mmol). The resultant

mixture was stirred at 55 °C for 8 h before water (30 mL) and ethyl acetate (50 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (50 mL) before being dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 0:100 then 1:99] afforded *acyl silane* **355** as a yellow oil (314 mg, 72%). **IR** (thin film)/cm^{-1} 3025, 2957, 1642, 1493, 1250, 1206, 1156, 838; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.22 (2H, t, *J* = 7.2, 2 x Ar-C*H*), 7.11 (1H, t, *J* = 7.2, 1 x Ar-C*H*), 6.99 (2H, d, *J* = 7.2, 2 x Ar-C*H*), 5.45-5.25 (2H, m, C*H*=C*H*), 2.57-2.50 (2H, m, $CH_2COSiMe_2Bn$), 2.27 (2H, s, CH_2Ph), 2.16 (2H, q, *J* = 6.8, $CH_2CH_2COSiMe_2Bn$), 1.95 (2H, q, *J* = 6.8, $(CH_2)_3CH_2CH{=}CH$), 1.37-1.21 (6H, m, $CH_3(CH_2)_3$), 0.89 (3H, t, *J* = 6.8, $CH_3(CH_2)_4$), 0.18 (6H, s, $Si(CH_3)_2$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 138.3, 131.3, 128.5, 128.4, 128.2, 124.5, 49.1, 32.5, 31.4, 29.2, 25.0, 23.3, 22.5, 19.9, 14.1, –5.0; **HRMS** (ES^+, *m/z*): Calculated 325.1958 ($C_{19}H_{30}NaOSi$); Found 325.1959.

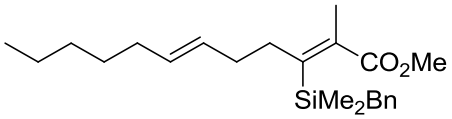
Ethyl 2,2-dibromopropanoate, 356



A solution of diisopropylamine (2.45 mL, 17.4 mmol) and *n*-butyllithium (10.9 mL, 17.4 mmol, 1.6 M in hexanes) in tetrahydrofuran (40 mL) was stirred at –78 °C for 15 min before ethyl-2-bromopropionate (3.00 g, 16.6 mmol) in tetrahydrofuran (4 mL) was added dropwise. The resulting solution was stirred for 30 min before 1,2 dibromo tetrachloroethane (8.10 g, 24.9 mmol) was added in one portion. The resulting solution was stirred at –78 °C for 30 min before a saturate solution of sodium bicarbonate (10 mL) was added. The mixture was extracted with hexane (3 x 50 mL), and the combined organic layers washed with water (100 mL), brine (100 mL) dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by distillation [49 °C, 2.2 mm/Hg] afforded dibromide **356** as an oil (2.7 g, 63%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.34 (2H, q, J = 7.2, CH_2O), 2.65 (3H, s, CH_3CBr$_2$), 1.36 (3H, t, J = 7.2, CH_3CH$_2$O); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 166.8, 63.7, 52.3, 37.3, 13.7. Data were consistent with those previously reported.[111]

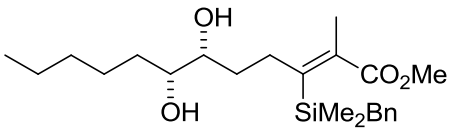
(±)-(2*Z*,6*E*)-Methyl 3-(benzyldimethylsilyl)-2-methyldodeca-2,6-dienoate, 358



To a solution of dibromide **356** (228 mg, 0.887 mmol) in tetrahydrofuran at –78 ^{o}C was added *tert*-butyllithium (2.05 mL, 3.50 mmol, 1.7 M in hexanes). The resultant solution was stirred at –78 ^{o}C for 3 h before being warmed to 0 ^{o}C for 10 min before being warmed to room temperature. A solution of *acyl silane* **355** (200 mg, 0.662 mmol) in tetrahydrofuran (1 mL) was added and the resultant solution stirred at room temperature for 1.5 h before iodomethane (0.524 mL, 8.40 mmol) and hexamethylphosphoramide (1.42 mL, 8.40 mmol) were added. The mixture stirred for 16 h before a saturated solution of ammonium chloride (20 mL) was added. The mixture was extracted with ethyl acetate (3 x 20 mL) and the combined organic layers washed with brine (20 mL), dried over sodium sulfate, filtered and the solvent removed in vacuo. The crude reside was dissolved in benzene (5 mL) before silica (107 mg) was added. The resultant suspension was stirred at 80 ^{o}C for 22 h before being filtered, and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 3:97] afforded *ester* **358** as an oil (154 mg, 58%). **IR** (thin film)/cm^{-1} 2927, 1715, 1600, 1274, 1151, 1070, 825; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.25-7.16 (2H, m, 2 x Ar-C*H*), 7.09-6.98 (3H, m, 3 x Ar-C*H*), 5.39-5.32 (2H, m, C*H*=C*H*), 3.79 (3H, s, CH_3O), 2.33 (2H, s, CH_2Ph), 2.25-2.17 (2H, m, CH_2C(SiMe$_2$Bn)=CH), 2.00-1.93 (5H, m, C=CCH_3 + CH_2CH$_2$C(SiMe$_2$Bn)=CH), 1.84 (2H, m, (CH$_2$)$_3$CH_2CH=CH), 1.39-1.21 (6H, m, CH$_3$(CH_2)$_3$), 0.90 (3H, t, J = 6.8, CH_3(CH$_2$)$_4$), 0.11 (3H, s, SiCH_3), 0.10 (3H, s, SiCH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 170.0, 152.6,

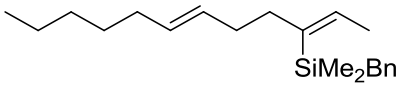
140.6, 138.0, 131.1, 128.5, 128.2, 128.0, 123.9, 51.6, 33.5, 32.5, 31.5, 31.4, 29.2, 26.0, 22.5, 15.8, 14.1, –1.5; **HRMS** (ES^+, *m/z*): Calculated 395.2377 ($C_{23}H_{36}NaO_2Si$); Found 395.2379.

(±)-(6*R*,7*R*,*Z*)-Methyl-3-(benzyldimethylsilyl)-6,7-dihydroxy-2-methyldodec-2-enoate, 359



Ester **358** (130 mg, 0.349 mmol) was subject to **General Procedure 2** (36 h), using quinuclidine as a ligand. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 30:70] afforded *diol* **359** (69 mg, 49%) as an oil. **IR** (thin film)/cm^{-1} 3407 br., 3024, 2953, 1714, 1600, 1435, 1274, 1199, 1058, 825; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.18 (2H, t, 2 x Ar-C*H*), 7.06-6.96 (3H, m, 3 x Ar-C*H*), 3.79 (3H, s, CH_3O), 3.30-3.24 (2H, m, 2 x C*H*OH), 2.42-2.32 (3H, s, CH_2Ph + CH_AH$_B$C(SiMe$_2$Bn)=C), 2.20-2.03 (3H, m, CH$_A$$H_B$C(SiMe$_2$Bn)=C + 2 x O*H*), 1.98 (3H, s, C=CCH$_3$), 1.49-1.20 (10H, m, CH$_3$(CH_2)$_3$ + 2 x CH_2CHOH), 0.91 (3H, t, *J* = 6.8, CH_3(CH$_2$)$_4$), 0.12 (3H, s, SiCH_3), 0.11 (3H, s, SiCH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 169.9, 152.3, 140.7, 138.3, 128.5, 128.0, 123.5, 74.4, 74.3, 51.7, 33.5, 32.1, 31.8, 29.4, 26.0, 25.3, 22.6, 15.7, 14.0, –1.3; **HRMS** (ES^+, *m/z*): Calculated 429.2432 ($C_{23}H_{38}NaO_4Si$); Found 429.2428.

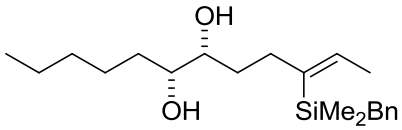
Benzyl((2*Z*,6*E*)-dodeca-2,6-dien-3-yl)dimethylsilane, 362



To a solution of dibromide **356** (228 mg, 0.887 mmol) in tetrahydrofuran (9 mL) at –78 °C was added *tert*-butyllithium (2.05 mL, 3.50 mmol, 1.7 M in hexanes). The resultant solution was stirred at –78 °C for 3 h before being warmed to 0 °C for 10 min and being cooled back to –78 °C. A solution of *acyl silane* **355** (200 mg, 0.662 mmol) in tetrahydrofuran (1 mL) was

added and the resultant solution stirred at –78 °C for 2.5 h before a saturated solution of ammonium chloride (10 mL) was added. The mixture was extracted with ethyl acetate (3 x 20 mL) and the combined organic layers washed with brine (20 mL), dried over sodium sulfate, filtered and the solvent removed in vacuo. The crude reside was dissolved in benzene (5 mL) before silica (107 mg) was added. The resultant suspension was stirred at 80 °C for 22 h before being filtered, and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 0:100 then 2:98] afforded *diene* **362** as an oil (110 mg, 56%, 8:1 *cis*:*trans*). **IR** (thin film)/cm^{-1} 2925, 2855, 1601, 1493, 1452, 1249, 1206, 1154, 834; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.23 (2H, t, *J* = 7.6, 2 x Ar-C*H*), 7.09 (1H, t, *J* = 7.6, 1 x Ar-C*H*), 6.99 (2H, d, *J* = 7.6, 2 x Ar-C*H*), 6.13 (1H, q, *J* = 6.8, C=C*H*CH_3), 5.42-5.35 (2H, m, C*H*=C*H*), 2.26 (2H, s, CH_2Ph), 2.09-1.91 (6H, m, CH_2C=CH + 2 x CH_2CH=CH), 1.73 (3H, d, *J* = 6.8, CH_3CH=C), 1.43-1.25 (6H, m, CH_3(CH_2)$_3$), 0.93 (3H, t, *J* = 6.8, CH_3(CH_2)$_4$), 0.15 (6H, s, Si(CH_3)$_2$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 140.2, 138.0, 137.9, 130.6, 129.9, 128.3, 128.1, 124.0, 38.5, 34.0, 32.6, 31.4, 29.3, 26.4, 22.6, 17.9, 14.2, –1.9; **HRMS** (ES^+, *m/z*): Calculated 337.2322 ($C_{21}H_{34}NaSi$); Found 337.2324.

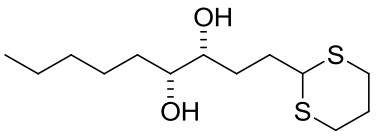
(±)-(6*R*,7*R*,*Z*)-3-(Benzyldimethylsilyl)dodec-2-ene-6,7-diol, 363



To a solution of *vinyl silane* **369** (150 mg, 0.387 mmol) in wet methanol (12 mL) was added pyridine *para*-toluenesulfonate (120 mg, 0.479 mmol). The resultant solution was stirred at 60 °C for 2 h before being cooled to room temperature, and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 40:60] afforded *diol* **363** as an oil (95 mg, 71%). **IR** (thin film)/cm^{-1} 3386 br., 2931, 2858, 1600, 1452, 1250, 1057, 834; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.20 (2H, t, *J* = 7.2, 2 x Ar-C*H*), 7.07 (1H, t, *J* = 7.2, 1 x

Ar-C*H*), 7.01 (2H, d, *J* = 7.2, 2 x Ar-C*H*), 6.16 (1H, q, *J* = 6.8, C=C*H*CH_3), 3.34-3.27 (2H, m, 2 x C*H*OR), 2.24 (2H, s, CH_2Ph), 2.23-2.14 (1H, m, C$H_A$$H_B$C(SiMe$_2$Bn)=CH), 2.07-1.97 (3H, m, $CH_A$$H_B$C(SiMe$_2$Bn)=CH + 2 x O*H*), 1.76 (3H, d, *J* = 6.8, CH_3CH=C), 1.52-1.16 (10H, m, CH_2CH$_2$C(SiMe$_2$Bn)=CH + (CH_2)$_4$CHOR), 0.91 (3H, t, *J* = 6.8), 0.15 (3H, s, SiCH_3), 0.15 (3H, s, SiCH_3); **^{13}C NMR (100 MHz, CDCl$_3$)** δ_C: 140.2, 138.3, 138.1, 128.3, 128.1, 124.0, 74.4, 74.2, 34.5, 34.5, 33.5, 31.9, 26.4, 25.4, 22.7, 18.0, 14.1, –1.9, –1.9; **HRMS** (ES$^+$, *m/z*): Calculated 371.2377 ($C_{21}H_{36}NaO_2Si$); Found 371.2376.

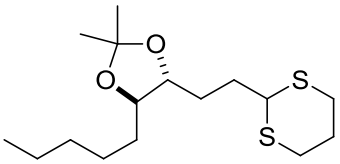
(±)-(3*R*,4*R*)-1-(1,3-dithian-2-yl)nonane-3,4-diol, 364



To a solution of *trans*-4-decenal (5.00 g, 32.5 mmol) and 4-methyl morpholine *N*-oxide (7.50 g, 65.0 mmol) in water/tetrahydrofuran/*tert*-butanol (1:10:8, 325 mL) was added osmium tetroxide (412 mg, 5.0 mol%). The resulting solution was stirred for 16 h at room temperature. Na_2SO_3 (1.0 g) was added and the mixture was stirred for 30 min after which water (100 mL) was added and the mixture extracted with ethyl acetate (3 × 200 mL). The combined organics were dried over sodium sulfate, filtered and the solvent removed *in vacuo*. The crude residue was dissolved in CH_2Cl_2 (150 mL) and 1,3 propanedithiol (4.41 mL, 44.6 mmol) was added. The solution was then colled to 0 ^oC before borontrifluoride dietherate (17.4 mL, 141 mmol) was added. The resultant solution was warmed to room temperature for 16 h before aqueous sodium hydroxide (1 M, 50 mL) was added. The mixture was extracted with ethyl acetate (3 x 100 mL) and the combined organic layers washed with brine (200 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. The crude mixture was heated to 70 ^oC *in vacuo* in order to remove excess 1,3 propanedithiol. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 20:80 to 40:60] afforded *diol* **364** as an oil (8.40 g,

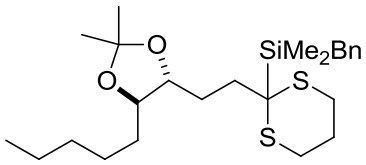
81%). **IR** (thin film)/cm^{-1} 3406, 2930, 1454; **^{1}H NMR (400 MHz, CDCl$_3$)** δ_H: 4.06 (1H, t, *J* = 6.8, SC*H*S), 3.43-3.35 (2H, m, 2 x C*H*OH), 2.91-2.78 (4H, m, 2 x CH_2S), 2.57 (2H, br. s, 2 x CHO*H*), 2.15-2.06 (1H, m, CH_AH$_B$CH$_2$S), 2.04-1.92 (1H, m, CH$_A$$H_BCH_2$S), 1.91-1.78 (2H, C$H_2$CHS), 1.76-1.68 (1H, m, CH_AH$_B$CH$_2$CHS), 1.66-1.55 (1H, m, CH$_A$$H_BCH_2$CHS), 1.54-1.20 (8H, m, CH$_3$(CH_2)$_4$), 0.87 (3H, t, *J* = 6.8); **^{13}C NMR (100 MHz, CDCl$_3$)** δ_C: 74.5, 74.0, 47.5, 33.4, 31.8, 31.7, 30.5, 30.3, 25.9, 25.3, 22.6, 14.1; **HRMS** (ES$^+$, *m/z*): Calculated 301.1266 ($C_{13}H_{26}NaO_2S_2$); Found 301.1267.

(±)-(4*R*,5*R*)-4-(2-(1,3-Dithian-2-yl)ethyl)-2,2-dimethyl-5-pentyl-1,3-dioxolane, 365



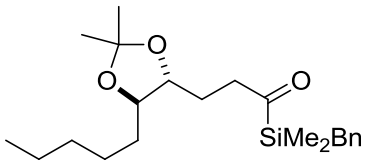
To a solution of *diol* **364** (4.20 g, 15.1 mmol) in CH_2Cl_2 (30 mL) was added 2,2-dimethoxypropane (45.3 mL, 3 mL/mmol) and pyridine *para*-toluenesulfonate (144 mg, 0.57 mmol) sequentially. The resulting solution was stirred at room temperature for 3 h before the solvent was removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 0:100 to 5:95] afforded *acetonide* **365** as an oil (4.01 g, 83%). **IR** (thin film)/cm^{-1} 2931, 1377, 1242, 1081; **^{1}H NMR (400 MHz, CDCl$_3$)** δ_H: 4.06 (1H, t, *J* = 6.8, SC*H*S), 3.64-3.54 (2H, m, 2 x C*H*OR), 2.92-2.80 (4H, m, 2 x CH_2S), 2.16-2.08 (1H, m, CH_AH$_B$CH$_2$S), 2.06-1.95 (1H, m, CH$_A$$H_BCH_2$S), 1.93-1.75 (3H, C$H_2$CHS + C$H_AH_BCH_2$CHS), 1.71-1.61 (1H, m, CH$_A$$H_BCH_2$CHS), 1.55-1.40 (3H, m, (CH$_2$)$_2$CH_AH$_B$CH_2CHOR), 1.37 (6H, s, C(CH_3)$_2$), 1.38-1.25 (5H, m, CH$_3$(CH_2)$_2$CH$_A$$H_B$), 0.89 (3H, t, *J* = 7.2, CH_3(CH$_2$)$_4$); **^{13}C NMR (100 MHz, CDCl$_3$)** δ_C: 108.0, 80.9, 80.9, 47.5, 32.9, 31.9, 31.8, 30.3, 30.2, 30.0, 27.4, 27.3, 26.0, 25.8, 22.5, 14.0; **HRMS** (ES$^+$, *m/z*): Calculated 341.1579 ($C_{16}H_{30}NaO_2S_2$); Found 341.1577.

(±)-Benzyl(2-(2-((4*R*,5*R*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)ethyl)-1,3-dithian-2-yl)dimethylsilane, 366



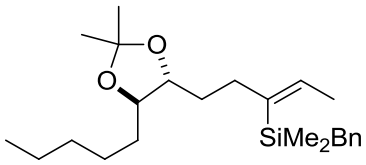
To a solution of *acetonide* **365** (4.00 g, 12. 5 mmol) in tetrahydrofuran (50 mL) at –40 ^{o}C was added *n*-butyllithium (8.60 mL, 13.8 mmol, 1.6 M in hexanes) dropwise. The resulting solution was warmed to –20 ^{o}C for 3 h before chlorobenzyldimethyl silane (2.77 mL, 12. 5 mmol) in tetrahydrofuran (10 mL) was added. The resulting solution was warmed to room temperature and stirred for 16 h before ethyl acetate (100 mL) and water (100 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine (200 mL) before being dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc–petrol, 0:100 to 3:97] afforded *silane* **366** as a yellow oil (4.34 g, 74%). **IR** (thin film)/cm^{-1} 2932, 2859, 1600, 1493, 1377, 1249, 1083, 825; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.22 (2H, t, *J* = 7.6, 2 x Ar-C*H*), 7.12-7.04 (3H, m, 3 x Ar-C*H*), 3.69-3.58 (2H, m, 2 x C*H*OR), 3.14-3.04 (2H, m, CH_2CSi), 2.56-2.45 (3H, m, CH_2S + CH_AH$_B$S), 2.39 (2H, s, CH_2Ph), 2.37-2.27 (1H, m, CH$_A$$H_B$S), 2.13-2.04 (1H, m, C$H_AH_BCH_2$S), 2.00-1.87 (1H, m, CH$_A$$H_BCH_2$S), 1.83-1.63 (2H, m, C$H_2CH_2$CSi), 1.57-1.46 (3H, m, (CH$_2$)$_2$CH_AH$_B$CH_2CHOR), 1.41 (3H, s, 1 x CCH_3), 1.41 (3H, s, 1 x CCH_3), 1.39-1.30 (5H, m, CH$_3$(CH_2)$_2$CH$_A$$H_B$), 0.91 (3H, t, *J* = 6.8, CH_3(CH$_2$)$_4$), 0.11 (6H, s, Si(CH_3)$_2$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 139.2, 128.6, 128.2, 124.3, 108.0, 81.1, 80.9, 38.7, 33.3, 33.1, 31.9, 31.3, 27.4, 27.3, 25.9, 25.0, 23.4, 23.0, 22.6, 14.1, –4.6, –4.6; **HRMS** (ES$^+$, *m/z*): Calculated 489.2288 ($C_{25}H_{42}NaO_2S_2Si$); Found 489.2289.

(±)-1-(Benzyldimethylsilyl)-3-((4*R*,5*R*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)propan-1-one, 367



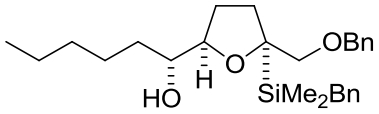
To a solution of *silane* **366** (2.00 g, 4.26 mmol) and sodium bicarbonate (3.58 g, 42.6 mmol) in MeCN:water (50 mL, 4:1) was added iodomethane (5.30 mL, 85.2 mmol). The resultant mixture was stirred at 55 ^{o}C for 8 h before water (100 mL) and ethyl acetate (150 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine (200 mL) before being dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 0:100 then 3:97] afforded *acyl silane* **367** as a yellow oil (1.21 g, 75%). **IR** (thin film)/cm^{-1} 2932, 1643, 1493, 1377, 1249, 1057, 840; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.22 (2H, t, *J* = 7.2, 2 x Ar-C*H*), 7.09 (1H, t, *J* = 7.2, 1 x Ar-C*H*), 6.99 (2H, d, *J* = 7.2, 2 x Ar-C*H*), 3.58-3.45 (2H, m, 2 x C*H*OR), 2.74 (1H, dd, *J* = 8.8, 5.6, CH_AH$_B$COSiMe$_2$Bn), 2.63 (1H, dd, *J* = 8.4, 6.4, CH$_A$$H_B$COSiMe$_2$Bn), 2.27 (2H, s, C$H_2$Ph), 1.86-1.76 (1H, m, C$H_AH_BCH_2$COSiMe$_2$Bn), 1.62-1.43 (4H, m, CH$_A$$H_BCH_2$COSiMe$_2$Bn + (CH$_2$)$_2CH_AH_BCH_2$CHOR), 1.36 (3H, s, 1 x CCH_3), 1.36 (3H, s, 1 x CCH_3), 1.35-1.29 (5H, m, CH$_3$(CH_2)$_2$CH$_A$$H_B$), 0.91 (3H, t, *J* = 6.4, CH_3(CH$_2$)$_4$), 0.20 (6H, s, Si(CH_3)$_2$) ; **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 138.2, 128.5, 128.1, 124.6, 107.9, 81.0, 80.2, 45.7, 32.8, 32.8, 32.0, 27.3, 27.3, 25.8, 24.9, 23.3, 22.6, 14.1, –4.9, –5.0; **HRMS** (ES$^+$, *m/z*): Calculated 399.2326 ($C_{22}H_{36}NaO_3Si$); Found 399.2322.

(±)-Benzyl((*Z*)-5-((4*R*,5*R*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)pent-2-en-3-yl)dimethylsilane, 369



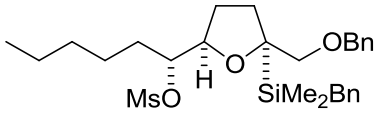
To a solution of dibromide **356** (356 mg, 1.38 mmol) in tetrahydrofuran (9 mL) at –78 °C was added *tert*-butyllithium (3.23 mL, 5.51 mmol, 1.7 M in hexanes). The resultant solution was stirred at –78 °C for 3 h before being warmed to 0 °C for 10 min and was subsequently cooled back to –78 °C. A solution of *acyl silane* **367** (400 mg, 1.10 mmol) in tetrahydrofuran (2 mL) was added and the resultant solution stirred at –78 °C for 2.5 h before a saturated solution of ammonium chloride (20 mL) was added. The mixture was extracted with ethyl acetate (3 x 40 mL) and the combined organic layers washed with brine (40 mL), dried over sodium sulfate, filtered and the solvent removed in vacuo. The crude reside was dissolved in benzene (10 mL) before silica (200 mg) was added. The resultant suspension was stirred at 80 °C for 22 h before being filtered, and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 2:98 then 4:96] afforded *vinyl silane* **369** as an oil (253 mg, 61%, 8:1 *cis*:*trans*). **IR** (thin film)/cm^{-1} 2932, 1493, 1453, 1377, 1249, 1102, 835; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.20 (2H, t, *J* = 7.6, 2 x Ar-C*H*), 7.07 (1H, t, *J* = 7.6, 1 x Ar-C*H*), 7.00 (2H, d, *J* = 7.6, 2 x Ar-C*H*), 6.15 (1H, q, *J* = 6.8, C=C*H*CH_3), 3.55-3.47 (2H, m, 2 x C*H*OR), 2.24 (2H, s, CH_2Ph), 2.23-2.13 (1H, m, C$H_A$$H_B$C($SiMe_2$Bn)=CH), 2.03-1.93 (1H, m, $CH_A$$H_B$C($SiMe_2$Bn)=CH), 1.74 (3H, d, *J* = 6.8, CH_3CH=C), 1.54-1.25 (16H, m, C$H_2$$CH_2$C($SiMe_2$Bn)=CH + (C$H_2$)$_4$CHOR + C(C$H_3$)$_2$), 0.91 (3H, t, *J* = 6.8, CH_3(CH_2)$_4$), 0.15 (3H, s, SiCH_3), 0.13 (3H, s, SiCH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 140.1, 138.1, 137.9, 128.3, 128.1, 124.0, 107.8, 80.9, 80.7, 34.7, 34.4, 33.0, 32.0, 27.3, 27.3, 26.4, 25.9, 22.6, 17.9, 14.1, –1.9, –2.0; **HRMS** (ES^+, *m/z*): Calculated 411.2609 ($C_{24}H_{40}NaO_2Si$); Found 411.2686.

(±)-(*R*)-1-((2*R*,5*R*)-5-(Benzyldimethylsilyl)-5-(benzyloxymethyl)tetrahydrofuran-2-yl)hexan-1-ol, 381



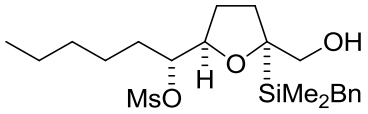
To a solution of *THF* **297** (1.00 g, 2.86 mmol) in tetrahydrofuran (15 mL) at 0 ^{o}C was added sodium hydride (60% dispersion on mineral oil, 460 mg, 11.4 mmol). The resulting solution was stirred for 5 min before benzyl bromide (0.342 mL, 2.86 mmol) was added dropwise. The resulting solution as warmed to room temperature and stirred for 16 h before ethyl acetate (50 mL) and water (50 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (100 mL) before being dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 10:90 then 20:80] afforded *monobenzyl* **381** as an oil (684 mg, 54%). **IR** (thin film)/cm^{-1} 3453 br., 2955, 2958, 1727, 1494, 1453, 1153, 1058; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.42-7.28 (5H, m, $OCH_2C_6H_6$), 7.21 (2H, t, *J* = 7.4, 2 x $SiCH_2Ar$-C*H*), 7.08 (1H, t, *J* = 7.4, 1 x $SiCH_2Ar$-C*H*), 7.00 (2H, d, *J* = 7.4, 2 x $SiCH_2Ar$-C*H*), 4.55 (1H, d, *J* = 12.0, $CH_2OCH_AH_BPh$), 4.48 (1H, d, *J* = 12.0, $CH_2OCH_AH_BPh$), 3.71 (1H, q, *J* = 6.4, C*H*OC), 3.49 (1H, d, *J* = 9.6, CH_AH_BOBn), 3.44-3.36 (2H, m, CH_AH_BOBn + C*H*OH), 2.55 (1H, br. s, CHO*H*), 2.18 (2H, d, *J* = 4.8, $SiCH_2Ph$), 2.07-1.99 (1H, m, THF-CH_AH_B), 1.94-1.80 (3H, m, THF-CH_2 + THF-CH_AH_B), 1.57-1.26 (8H, m, $CH_3(CH_2)_4$), 0.92 (3H, t, *J* = 6.8, $CH_3(CH_2)_4$), 0.01 (3H, s, 1 x $SiCH_3$), 0.00 (3H, s, 1 x $SiCH_3$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 139.9, 138.2, 128.3, 128.3, 128.1, 127.7, 127.7, 127.6, 124.0, 83.9, 78.6, 75.7, 74.4, 73.5, 34.4, 32.0, 31.0, 28.7, 25.4, 23.3, 22.7, 14.1, –5.5; **HRMS** (ES^+, *m/z*): Calculated 463.2639 ($C_{27}H_{40}NaO_3Si$); Found 463.2635.

(±)-(*R*)-1-((2*R*,5*R*)-5-(Benzyldimethylsilyl)-5-(benzyloxymethyl)tetrahydrofuran-2-yl)hexyl methanesulfonate, 382



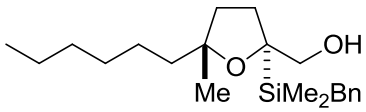
To a solution of *monobenzyl* **381** (140 mg, 0.318 mmol) in CH_2Cl_2 (5 mL) at 0 ^oC was added methanesulfonic anhydride (165 mg, 0.952 mmol) and *N*,*N*-dimethylaminopyridine (155 mg, 1.27 mmol). The resulting solution was warmed to room temperature and stirred for 16 h. Diethyl ether (20 mL) and water (20 mL) were added and the layers separated. The aqueous layer was washed with diethyl ether (3 x 20 mL), and the combined organic layers washed with brine (40 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 10:90 then 20:80] afforded *mesylate* **382** as an oil (120 mg, 72%). **IR** (thin film)/cm^{-1} 2956, 2869, 1352, 1172, 922; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.40-7.27 (5H, m, $OCH_2C_6H_6$), 7.21 (2H, t, *J* = 7.4, 2 x $SiCH_2Ar$-C*H*), 7.08 (1H, t, *J* = 7.4, 1 x $SiCH_2Ar$-C*H*), 6.97 (2H, d, *J* = 7.4, 2 x $SiCH_2Ar$-C*H*), 4.58-4.51 (1H, m, C*H*OMs), 4.49 (2H, s, CH_2OCH_2Ph), 3.94-3.86 (1H, m, C*H*OC), 3.43 (2H, s, CH_2OBn), 3.09 (3H, s, $CHOSO_2CH_3$), 2.15 (2H, s, $SiCH_2Ph$), 2.01-1.83 (3H, m, THF-CH_AH_B + THF-CH_2), 1.77-1.64 (1H, m, THF-CH_AH_B), 1.62-1.20 (8H, m, $CH_3(CH_2)_4$), 0.90 (3H, t, *J* = 6.8, $CH_3(CH_2)_4$),–0.01 (3H, s, 1 x $SiCH_3$), –0.03 (3H, s, 1 x $SiCH_3$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 139.5, 138.2, 128.4, 128.3, 128.2, 127.8, 127.7, 124.2, 88.7, 82.2, 79.4, 76.0, 73.6, 38.8, 32.1, 31.6, 31.1, 29.4, 24.4, 23.4, 22.4, 14.0, –5.2, –5.5; **HRMS** (ES^+, *m/z*): Calculated 541.2414 ($C_{28}H_{42}NaO_5SSi$); Found 541.2417.

(±)-(*R*)-1-((2*R*,5*R*)-5-(Benzyldimethylsilyl)-5-(hydroxymethyl)tetrahydrofuran-2-yl)hexyl methanesulfonate, 383



A solution of *mesylate* **382** (250 mg, 0.483 mmol) in methanol (10 mL) was purged with argon five times. To this solution was added palladium on carbon (50 mg, 10% wt), and the mixture was purged with H_2 gas five times. The resulting solution was stirred under at atmosphere of H_2 gas for 24 h before being filtered through Celite® and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 15:85 to 20:80] afforded *alcohol* **383** as an oil (191 mg, 92%). **IR** (thin film)/cm^{-1} 3531 br., 2956, 2870, 1347, 1171, 1055, 921; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.22 (2H, t, *J* = 7.4, 2 x $SiCH_2Ar$-C*H*), 7.08 (1H, t, *J* = 7.4, 1 x $SiCH_2Ar$-C*H*), 7.01 (2H, d, *J* = 7.4, 2 x $SiCH_2Ar$-C*H*), 4.60 (1H, td, *J* = 8.4, 3.2, C*H*OMs), 3.98-3.91 (1H, m, C*H*OC), 3.64 (1H, d, *J* = 12.0, CH_AH_BOBn), 3.46 (1H, d, *J* = 12.0, CH_AH_BOBn), 3.16 (3H, s, $CHOSO_2CH_3$), 2.19 (2H, d, *J* = 1.6, $SiCH_2Ph$), 1.99-1.86 (3H, m, THF-CH_AH_B + THF-CH_2), 1.78-1.69 (1H, m, THF-CH_AH_B), 1.64-1.22 (8H, m, $CH_3(CH_2)_4$), 0.91 (3H, t, *J* = 6.8, $CH_3(CH_2)_4$), 0.04 (3H, s, 1 x $SiCH_3$), 0.02 (3H, s, 1 x $SiCH_3$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 139.3, 128.3, 128.3, 124.3, 87.8, 82.1, 81.3, 67.5, 38.9, 31.7, 31.4, 30.5, 29.7, 24.7, 23.4, 22.4, 13.9, –5.1, –5.3; **HRMS** (ES^+, *m/z*): Calculated 451.1945 ($C_{21}H_{36}NaO_5SSi$); Found 451.1945.

(±)-((2*R*,5*R*)-2-(Benzyldimethylsilyl)-5-hexyl-5-methyltetrahydrofuran-2-yl)methanol, 384



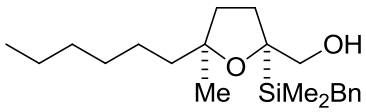
From mesylate 383:

Mesylate **383** (50 mg, 0.12 mmol) was subjected to **General Procedure 8**. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 0:100 then 5:95] afforded *THF* **384** as an oil (20 mg, 49%). **IR** (thin film)/cm^{-1} 3442 br., 2931, 1493, 1453, 1246, 1055, 818; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.22 (2H, t, *J* = 7.6, 2 x Ar-C*H*), 7.08 (1H, t, *J* = 7.6, 1 x Ar-C*H*), 7.02 (2H, d, *J* = 7.6, 2 x Ar-C*H*), 3.60 (1H, d, *J* = 10.8, CH_AH$_B$OH), 3.52 (1H, d, *J* = 11.2, CH$_A$$H_B$OH), 2.22 (2H, s, C$H_2$Ph), 2.13 (1H, br. s, O*H*), 1.99-1.89 (1H, m, THF-CH_AH$_B$), 1.82-1.68 (3H, m, THF-CH$_A$$H_B$ + THF-CH$_2$), 1.51-1.38 (3H, m, CH$_3$(CH$_2$)$_3$CH_AH$_B$CH_2), 1.37-1.28 (7H, m, CH$_3$(CH_2)$_3$CH$_A$$H_B$), 1.27 (3H, m, CC$H_3$), 0.90 (3H, t, *J* = 6.8, CH_3(CH$_2$)$_5$), 0.01 (3H, s, SiCH_3), –0.01 (3H, s, SiCH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 140.0, 128.3, 128.1, 124.0, 84.4, 79.7, 68.2, 42.4, 37.7, 31.9, 30.4, 29.9, 27.5, 24.9, 23.6, 22.7, 14.1, –5.0, –5.1; **HRMS** (ES^+, *m/z*): Calculated 371.2377 ($C_{21}H_{36}NaO_2Si$); Found 371.2375.

From THF 390:

To a stirred solution of *THF* **390** (20 mg, 0.037 mmol) in tetrahydrofuran (1 mL) was added acetic acid (120 μL, 2.11 mmol). The resultant mixture was stirred at room temperature for 3 h before the solvent was removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 15:85 to 20:80] afforded *THF* **384** as an oil (3.4 mg, 23%). Data were consistent with those reported above.

(±)-((2*R*,5*S*)-2-(Benzyldimethylsilyl)-5-hexyl-5-methyltetrahydrofuran-2-yl)methanol, 385



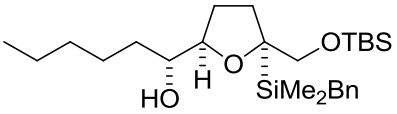
From mesylate 383:

Mesylate **383** (50 mg, 0.12 mmol) was subjected to **General Procedure 8**. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 0:100 then 5:95] afforded *THF* **385** as an oil (13 mg, 32%). **IR** (thin film)/cm^{-1} 3442 br., 2930, 1493, 1453, 1246, 1018, 818; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.21 (2H, t, *J* = 7.2, 2 x Ar-C*H*), 7.07 (1H, t, *J* = 7.2, 1 x Ar-C*H*), 7.03 (2H, d, *J* = 7.2, 2 x Ar-C*H*), 3.57-3.43 (2H, m, CH_2OH), 2.22 (2H, s, CH_2Ph), 2.11 (1H, br. s, O*H*), 2.01-1.96 (1H, m, THF-CH_AH$_B$), 1.87-1.80 (1H, m, THF-CH$_A$$H_B$), 1.69-1.64 (2H, m, THF-CH_2), 1.40-1.22 (10H, m, CH$_3$(CH_2)$_5$), 1.15 (3H, m, CCH_3), 0.91-0.86 (3H, m, CH_3(CH$_2$)$_5$), 0.02 (3H, s, SiCH_3), 0.00 (3H, s, SiCH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 140.0, 128.3, 128.1, 124.0, 84.8, 79.3, 67.8, 43.6, 37.1, 31.8, 30.4, 29.9, 26.5, 24.7, 23.6, 22.6, 14.1, –5.1, –5.2; ; **HRMS** (ES^+, *m/z*): Calculated 371.2377 ($C_{21}H_{36}NaO_2Si$); Found 371.2377.

From THF 390:

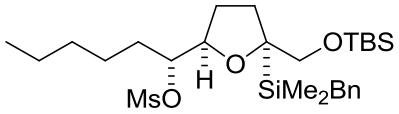
To a stirred solution of *THF* **390** (20 mg, 0.037 mmol) in tetrahydrofuran (1 mL) was added acetic acid (120 μL, 2.11 mmol). The resultant mixture was stirred at room temperature for 3 h before the solvent was removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 15:85 to 20:80] afforded *THF* **385** as an oil (5.6 mg, 37%). Data were consistent with those reported above.

(±)-(*R*)-1-((2*R*,5*R*)-5-(Benzyldimethylsilyl)-5-((*tert*-butyldimethylsilyloxy)methyl) tetrahydrofuran-2-yl)hexan-1-ol, 388



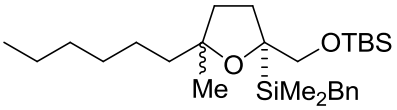
To a solution of *THF* **297** (100 mg, 0.285) in CH_2Cl_2 (6 mL) was added *N*,*N*-dimethylaminopyridine (8.7 mg, 0.071 mmol) and imidazole (79 mg, 1.2 mmol). The resulting solution was stirred at room temperature for 10 min before chloro *tert*-butyldimethylsilane (48 mg, 0.32 mmol) was added. The resulting solution was stirred at room temperature for 1 h before ethyl acetate (20 mL) and water (20 mL) were added and the layers separated. The aqueous layer was washed with ethyl acetate (3 x 20 mL), and the combined organic layers washed with brine (40 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 10:90 then 20:80] afforded *THF* **388** as an oil (87 mg, 66%). **IR** (thin film)/cm^{-1} 3424 br., 2955, 2857, 1462, 1250, 1078, 836; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.21 (2H, t, *J* = 7.6, 2 x Ar-C*H*), 7.07 (1H, t, *J* = 7.6, 2 x Ar-C*H*), 7.02 (2H, d, *J* = 7.6, 1 x Ar-C*H*), 3.67 (1H, dt, *J* = 8.0, 6.0, OC*H*), 3.55 (1H, d, *J* = 10.0, CH_AH$_B$OTBS), 3.48 (1H, d, *J* = 10.0, CH$_A$$H_B$OTBS), 3.38 (1H, dq, *J* = 8.0, 4.8, C*H*OH), 2.19 (2H, d, *J* = 4.0, CH_2Ph), 2.06-1.94 (1H, m, THF-CH_AH$_B$), 1.91-1.75 (3H, m, THF-CH$_A$$H_B$ + THF-CH_2), 1.66 (1H, br. s, CHO*H*), 1.54-1.25 (8H, m, CH$_3$(CH_2)$_4$), 0.93-0.87 (12H, m, CH_3CH$_2$ + SiC(CH_3)$_3$), 0.07-0.05 (6H, m, 2 x OSiCH_3), 0.00 (3H, s, 1 x CSiCH_3), –0.01 (3H, s, 1 x CSiCH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 140.0, 128.3, 128.1, 124.0, 83.8, 79.4, 75.6, 68.0, 34.3, 32.0, 30.4, 28.5, 26.0, 25.4, 23.3, 22.6, 14.1, –5.4, –5.5, –5.5; **HRMS** (ES^+, *m/z*): Calculated 487.3034 ($C_{26}H_{48}NaO_3Si_2$); Found 487.3032.

(±)-(*R*)-1-((2*R*,5*R*)-5-(Benzyldimethylsilyl)-5-((*tert*-butyldimethylsilyloxy)methyl) tetrahydrofuran-2-yl)hexyl methanesulfonate, 389



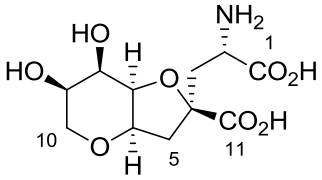
To a solution of *THF* **388** (73 mg, 0.16 mmol) in CH_2Cl_2 (5 mL) at 0 ^oC was added methanesulfonic anhydride (82 mg, 0.47 mmol) and *N*,*N*-dimethylaminopyridine (78 mg, 0.64 mmol). The resulting solution was warmed to room temperature and stirred for 16 h. Diethyl ether (10 mL) and water (10 mL) were added and the layers separated. The aqueous layer was washed with diethyl ether (3 x 10 mL), and the combined organic layers washed with brine (20 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 0:100 then 10:90] afforded *mesylate* **389** as an oil (49 mg, 56%). **IR** (thin film)/cm^{-1} 2955, 1494, 1354, 1251, 1174, 1080, 836; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.22 (2H, t, *J* = 7.6, 2 x Ar-C*H*), 7.09 (1H, t, *J* = 7.6, 1 x Ar-C*H*), 7.00 (2H, d, *J* = 7.6, 2 x Ar-C*H*), 4.52 (1H, td, *J* = 8.0, 3.6, OC*H*), 3.87 (1H, ddd, *J* = 11.2, 8.0, 5.6, C*H*OMs), 3.51-3.48 (2H, m, CH_2OTBS), 3.11 (3H, s, SO_2CH_3), 2.17 (2H, s, CH_2Ph), 2.02-1.80 (3H, m, THF-CH_2 + THF-CH_AH_B), 1.74-1.64 (1H, m, THF-CH_AH_B), 1.60-1.22 (8H, m, $CH_3(CH_2)_4$), 0.94-0.86 (12H, m, $C(CH_3)_3$ + CH_3CH_2), 0.08 (6H, s, 2 x OSiCH_3), 0.00 (3H, s, 1 x CSiCH_3), –0.01 (3H, s, 1 x CSiCH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 139.6, 128.3, 128.2, 124.2, 88.4, 82.1, 80.2, 68.1, 38.8, 32.2, 31.6, 30.6, 29.0, 26.0, 24.4, 23.4, 22.4, 14.0, –5.3, –5.5, –5.5; **HRMS** (ES^+, *m/z*): Calculated 565.2810 ($C_{27}H_{50}NaO_5SSi_2$); Found 565.2806.

(±)-(*R*)-Benzyl(2-((*tert*-butyldimethylsilyloxy)methyl)-5-hexyl-5-methyltetrahydrofuran-2-yl)dimethylsilane, 390



Mesylate **389** (45 mg, 0.083 mmol) was subjected to **General Procedure 8**. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 0:100 then 10:90] afforded a 1.6:1 diastereomeric mixture of *THF* **390** as an oil (27 mg, 71%). **IR** (thin film)/cm^{-1} 2957, 2858, 1463, 1257, 1091, 836; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.20 (2H, t, *J* = 7.6, 2 x Ar-C*H*), 7.09-7.00 (3H, m, 3 x Ar-C*H*), 3.62-3.46 (2H, m, CH_2OTBS), 2.24-2.21 (2H, m, CH_2Ph), 1.99-1.68 (3H, m, THF-CH_2 + THF-CH_AH$_B$), 1.62-1.54 (3H, m, THF-CH$_A$$H_B$ + $CH_3(CH_2)_4CH_2$), 1.51-1.22 (11H, CCH_3 + $CH_3(CH_2)_4$), 0.94-0.86 (12H, m, SiC(CH_3)$_3$ + $CH_3(CH_2)_4$), 0.08 (3H, s, CSiCH_3), 0.08 (3H, s, CSiCH_3), –0.01 (3H, s, 1 x Si(CH_3)$_2$), –0.02 (3H, s, 1 x Si(CH_3)$_2$); **^{13}C NMR (125 MHz, $CDCl_3$)** δ_C: 140.6, 140.5, 128.4, 128.3, 128.0, 128.0, 123.7, 123.7, 84.3, 84.2, 79.5, 79.1, 68.3, 68.0, 43.5, 42.3, 36.8, 35.9, 31.9, 31.9, 30.4, 30.2, 30.0, 29.9, 27.3, 26.6, 26.0, 26.0, 25.5, 25.0, 23.6, 23.6, 22.6, 22.6, 14.1, 14.1, –5.2, –5.2, –5.2, –5.3, –5.4, –5.4, –5.5, –5.5; **HRMS** (ES^+, *m/z*): Calculated 485.3242 ($C_{27}H_{50}NaO_2Si_2$); Found 485.3237.

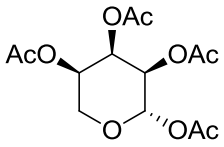
Neodysiherbaine A, 398



A solution of *lactam* **441** (21.0 mg, 44.8 μmol) in aqueous hydrochloric acid (6 M, 2.0 mL) was stirred at 60 ^oC for 20 h before the solvent was removed *in vacuo*. The resulting solid was dissolved in water (0.5 mL) and aqueous sodium hydroxide (0.5 M) was added until the solution became basic. Amberlite IR-120 (H^+) ion exchange resin was added to neutralise the solution before the solution was concentrated *in vacuo*. Purification by ion-exchange

chromatography [Dowex 50WX4-200, H_2O-5% NH_4OH] and lyophilised to afford neodysiherbaine-A **398** as a solid (12.7 mg, 97%). **^{1}H NMR (500 MHz, D_2O)** δ_H: 4.07 (1H, br. s, ^{7}C*H*), 3.99 (1H, br. s, ^{6}C*H*), 3.75 (1H, t, *J* = 3.5, ^{2}C*H*), 3.69 (1H, dd, *J* = 12.5, 2.0, ^{10}CH_AH$_B$), 3.55 (1H, br. s, ^{9}C*H*), 3.41 (2H, br. d, *J* = 12.5, ^{2}C*H* + ^{10}CH$_A$$H_B$), 2.50 (1H, d, *J* = 14.5, ^{3}CH_AH$_B$), 2.42 (1H, d, *J* = 14.0, ^{5}CH_AH$_B$), 2.01 (1H, dd, *J* = 14.0, 3.5, ^{5}CH$_A$$H_B$), 1.81 (1H, dd, *J* = 15.0, 12.0, ^{3}CH$_A$$H_B$); **^{13}C NMR (125 MHz, $CDCl_3$)** δ_C: 180.9, 174.6, 88.2, 81.2, 77.4, 70.3, 68.6, 67.9, 54.4, 45.3, 39.9. Data were consistent with those previously reported.[117]

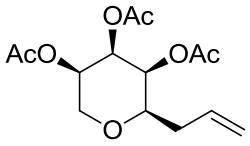
(2*S*,3*R*,4*R*,5*R*)-Tetrahydro-2H-pyran-2,3,4,5-tetrayl tetraacetate, 414



To a solution of *D*-ribose **411** (5.00 g, 33.3 mmol) in acetic anhydride (100 mL) at 0 ^{o}C was added cerium trifluoromethanesulfonate (1 mol%, 196 mg, 0.333 mmol). The resulting solution was warmed to room temperature and stirred for 16 h, before ethyl acetate (300 mL) and water (200 mL) were added. The layers were separated, and the organic layer washed with brine (200 mL) before being dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 50:50] afforded tetraacetates **414** and **413** as a mixture of anomers (9.93 g, 94%). Recrystallisation from toluene afforded the desired α-anomer **414** (6.07 g, 58%) as prisms. **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 6.03 (1H, d, *J* = 4.8, OC*H*OAc), 5.48 (1H, t, *J* = 3.4, CHC*H*(OAc)CH), 5.15 (1H, dt, *J* = 6.0, 3.4, CH$_2$C*H*OAc), 5.04 (1H, t, *J* = 4.0, OCH(OAc)C*H*(OAc)), 4.02 (1H, dd, *J* = 12.0, 3.4, CH_AH$_B$CHOAc), 3.90 (1H, dd, *J* = 12.0, 6.0, CH$_A$$H_B$CHOAc), 2.13 (3H, s, 1 x OAc), 2.10 (3H, s, 1 x OAc), 2.09 (3H, s, 1 x OAc), 2.09 (3H, s, 1 x OAc); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 169.9, 169.8, 169.5, 168.8, 90.9, 67.3, 66.1, 62.7, 20.8, 20.8, 20.7, 20.6; $[\alpha]_D^{22}$ -55.1 (*c* 1.0,

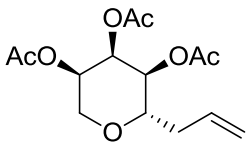
CH_2Cl_2); $[\alpha]_D^{22}$ –55.1 (*c* 1.0, CH_2Cl_2); **M.P.** 102-104 °C. Data were consistent with those previously reported.[124]

(2*S*,3*S*,4*R*,5*R*)-2-Allyltetrahydro-2H-pyran-3,4,5-triyl triacetate, 415



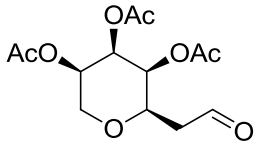
To a solution of tetraacetate **414** (7.00 g, 22.2 mmol) and allyltrimethylsilane (10.5 mL, 66.5 mmol) in dry MeCN (70 mL) at 0 °C was added trimethylsilyl trifluoromethanesulfonate (4.80 mL, 26.6 mmol). The resulting solution was warmed to room temperature and stirred for 16 h, before ethyl acetate (100 mL) and water (100 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (200 mL) before being dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 25:75 then 30:70] afforded allyl-ribose **415** as prisms (4.01 g, 61%). Also isolated was allyl-ribose **416** as an oil (1.34 g, 20%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 5.82-5.70 (1H, m, C*H*=CH_2), 5.24-5.21 (1H, m, 1 x C*H*OAc), 5.18-5.15 (1H, m, 1 x C*H*OAc), 5.13-5.09 (1H, m, 1 x C*H*OAc), 5.07-5.05 (2H, m, CH=CH_2), 4.13 (1H, dd, *J* = 13.6, 1.6, CH_AH$_B$CHOAc), 3.70 (1H, dd, *J* = 13.6, 1.6, CH$_A$$H_B$CHOAc), 3.55 (1H, t, *J* = 6.8, C*H*CH_2CH=CH_2), 2.49-2.40 (1H, m, CH_AH$_B$CH=CH_2), 2.27-2.18 (1H, m, CH$_A$$H_B$CH=$CH_2$), 2.16 (3H, s, 1 x C$H_3$$CO_2$CH), 2.15 (3H, s, 1 x C$H_3$$CO_2$CH), 2.00 (3H, s, 1 x C$H_3$$CO_2$CH); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 170.4, 170.3, 169.8, 132.9, 118.3, 77.5, 69.0, 68.3, 67.8, 66.7, 35.4, 21.0, 20.7, 20.6; $[\alpha]_D^{22}$ –21.2 (*c* 1.0, CH_2Cl_2); **M.P.** 44-48 °C. Data were consistent with those previously reported.[123]

(2*S*,3*S*,4*R*,5*R*)-2-Allyltetrahydro-2H-pyran-3,4,5-triyl triacetate, 416



Allyl-ribose **416** was isolated as a minor product in the synthesis of allyl-ribose **415**. **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 5.83 (1H, ddt, *J* = 16.8, 10.4, 6.8, C*H*=CH_2), 5.63 (1H, br. s, CHC*H*(OAc)CH), 5.16-5.06 (2H, m, CH=CH_2), 4.98 (1H, ddd, *J* = 10.8, 5.4, 2.8, 1 x CH_2C*H*OAc), 4.73 (1H, dd, *J* = 10.4, 3.2, OCHC*H*OAc), 3.86 (1H, dd, *J* = 10.6, 5.4, C$H_A$$H_B$CHOAc), 3.73 (1H, ddd, *J* = 10.4, 7.6, 3.2, C*H*CH_2CH=CH_2), 3.63 (1H, t, *J* = 10.8, $CH_A$$H_B$CHOAc), 2.39-2.32 (1H, m, C$H_A$$H_B$CH=$CH_2$), 2.21-2.16 (4H, m, $CH_A$$H_B$CH=$CH_2$ + 1 x C$H_3$$CO_2$CH), 2.01 (3H, s, 1 x C$H_3$$CO_2$CH), 2.01 (3H, s, 1 x C$H_3$$CO_2$CH); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 170.1, 169.4, 169.3, 133.4, 117.6, 73.0, 69.8, 68.1, 66.7, 63.5, 35.8, 20.8, 20.7, 20.6; $[\alpha]_D^{22}$ –10.6 (*c* 1.0, CH_2Cl_2). Data were consistent with those previously reported.[123]

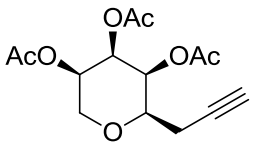
(2*R*,3*S*,4*R*,5*R*)-2-(2-Oxoethyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate, 422



A solution of allyl-ribose **415** (4.20 g, 14.0 mmol) in CH_2Cl_2 was cooled to -78 ^oC. Ozone gas was bubbled though this mixture until a blue colour persisted. Nitrogen gas was then bubbled though this mixture until the blue colour has disappeared, and a negative starch test was observed. Triphenylphosphine (11.0 g, 42.0 mmol) was then added and the solution was warmed to room temperature. The resulting solution was stirred for 16 h before the solvent was removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 60:40 then 70:30] afforded *aldehyde* **422** as prisms (3.55 g, 84%). **IR** (thin film)/cm^{-1} 1738, 1376,

1260, 1227, 1100, 1028, ; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 9.72-9.70 (1H, m, C*H*O), 5.20-5.17 (1H, m, 1 x C*H*OAc), 5.16-5.13 (1H, m, 1 x C*H*OAc), 5.10 (1H, t, *J* = 3.6 1 x C*H*OAc), 4.13 (1H, ddd, *J* = 8.0, 4.4, 1.2, C*H*CH_2CHO), 4.05 (1H, dd, *J* = 13.6, 2.0, C$H_A$$H_B$CHOAc), 3.74 (1H, dd, *J* = 13.6, 1.6, C$H_A$$H_B$CHOAc), 2.76 (1H, ddd, *J* = 17.2, 8.0, 2.0, C$H_A$$H_B$CHO), 2.49 (1H, ddd, *J* = 17.2, 4.4, 0.8, C$H_A$$H_B$CHO), 2.11 (3H, s, 1 x C$H_3$$CO_2$CH), 2.10 (3H, s, 1 x C$H_3$$CO_2$CH), 1.95 (3H, s, 1 x C$H_3$$CO_2$CH); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 198.7, 170.3, 170.2, 169.6, 72.4, 68.8, 68.2, 67.8, 66.3, 44.7, 20.9, 20.6, 20.5; **HRMS** (ES^+, *m/z*): Calculated 325.0894 ($C_{13}H_{18}NaO_8$); Found 325.0894; **$[\alpha]_D^{22}$** –16.6 (*c* 1.0, CH_2Cl_2); **M.P.** 126-130 °C.

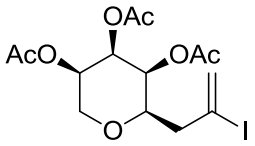
(2*R*,3*S*,4*R*,5*R*)-2-(Prop-2-yn-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate, 424



To a solution of potassium *tert*-butoxide (1.57 g, 13.3 mmol) in tetrahydrofuran (70 mL) at –78 °C was added dimethyl (diazomethyl)phosphonate (2.00 g, 13.3 mmol) dropwise. The resulting solution was stirred for 15 min before *aldehyde* **423** (2.00 g, 6.67 mmol) in tetrahydrofuran (13 mL) was added dropwise. The resulting solution was stirred for 30 min before being warmed to room temperature, when ethyl acetate (150 mL) and a saturated solution of ammonium chloride (20 mL) were added. The layers were separated and the organic layer washed with brine (70 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 30:70] afforded *alkyne* **424** as prisms (1.65g, 83%). **IR** (thin film)/cm^{-1}1741, 1368, 1226, 1120, 1091; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 5.42-5.39 (1H, m, 1 x C*H*OAc), 5.17-5.14 (1H, m, 1 x C*H*OAc), 5.11 (1H, t, *J* = 4.0 1 x C*H*OAc), 4.13 (1H, dd, *J* = 13.6, 2.0, C$H_A$$H_B$CHOAc), 3.76-3.69 (2H, m, C$H_A$$H_B$CHOAc + C*H*$CH_2$C≡CH), 2.57 (1H, ddd, *J* = 16.8, 6.4, 2.4, C$H_A$$H_B$C≡CH), 2.49 (1H, ddd, *J* = 16.8, 8.0, 2.4, C$H_A$$H_B$C≡CH), 2.16 (3H, s, 1 x C$H_3$$CO_2$CH), 2.14 (3H, s, 1 x

C*H*$_3$CO$_2$CH), 2.02 (1H, t, *J* = 2.4, C≡C*H*), 2.00 (3H, s, 1 x C*H*$_3$CO$_2$CH); **^{13}C NMR (100 MHz, CDCl$_3$)** δ_C: 170.3, 170.1, 169.7, 78.4, 76.0, 71.0, 69.0, 68.1, 66.9, 66.5, 21.0, 20.9, 20.7, 20.6; **HRMS** (ES$^+$, *m/z*): Calculated 321.0945 ($C_{14}H_{18}NaO_7$); Found 321.0938; **$[\alpha]_D^{21}$** –46.0 (*c* 1.0, CH_2Cl_2); **M.P.** 64-66 ^oC.

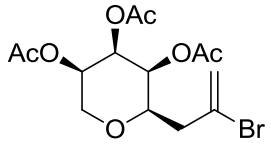
(2*R*,3*S*,4*R*,5*R*)-2-(2-Iodoallyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate, 425



To a stirred solution of 9-Iodo-9-borabicyclo[3.3.1]nonane (1.29 mL, 1.29 mmol, 1.0 M in hexanes) in CH_2Cl_2 (8 mL) was added *alkyne* **424** (350 mg, 1.17 mmol) in CH_2Cl_2 (5 mL) dropwise over 10 min. The resulting solution was stirred at 0 ^oC for 2 h before acetic acid (201 μL) was added. This mixture was then stirred for 30 min at 0 ^oC before being poured in to water (10 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with aqueous sodium hydroxide (2 M, 30 mL), brine (20 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 20:80 to 30:70] afforded *vinyl iodide* **425** as an oil (412 mg, 82%). **IR** (thin film)/cm^{-1} 1739, 1367, 1260, 1225, 1090; **^{1}H NMR (400 MHz, CDCl$_3$)** δ_H: 6.11 (1H, d, *J* = 1.3, C*H*$_A$H$_B$=C), 5.82 (1H, d, *J* = 1.3, CH$_A$*H*$_B$=C), 5.24-5.21 (1H, m, 1 x C*H*OAc), 5.20-5.17 (1H, m, 1 x C*H*OAc), 5.14 (1H, t, *J* = 4.0 1 x C*H*OAc), 4.14 (1H, dd, *J* = 13.6, 2.0, C*H*$_A$H$_B$CHOAc), 3.83 (1H, dd, *J* = 13.6, 1.2, CH$_A$*H*$_B$CHOAc), 3.75 (1H, ddd, *J* = 8.0, 4.8, 1.2, C*H*CH$_2$C(I)=CH$_2$), 2.72 (1H, dd, *J* = 14.8, 8.0, C*H*$_A$H$_B$C(I)=CH$_2$), 2.52 (1H, dd, *J* = 14.8, 4.8, CH$_A$*H*$_B$C(I)=CH), 2.17 (3H, s, 1 x C*H*$_3$CO$_2$CH), 2.15 (3H, s, 1 x C*H*$_3$CO$_2$CH), 2.01 (3H, s, 1 x C*H*$_3$CO$_2$CH); **^{13}C NMR (100 MHz, CDCl$_3$)** δ_C: 170.3, 170.2, 169.7, 129.2, 104.7, 76.3, 69.1, 68.2, 67.6, 66.5, 46.3,

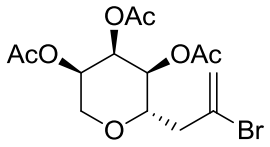
21.0, 20.7, 20.6; **HRMS** (ES^+, *m/z*): Calculated 449.0068 ($C_{14}H_{19}INaO7$); Found 449.0057; $[\alpha]_D^{21}$ –1.3 (*c* 1.0, CH_2Cl_2).

(3*S*,4*R*,5*R*)-2-(2-Bromoallyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate, 427



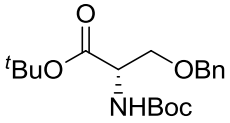
To a flame dried flask was added tetraacetate **414** (5.00 g, 15.7 mmol) and 2-bromoallyl silane **426** (8.40 g, 44.0 mmol) in anhydrous MeCN (80 mL). The resultant solution was cooled to 0 ^oC before tin (VI) bromide (10.3 g, 23.6 mmol) was added portionwise. The resultant mixture was then heated to 85 ^oC for 5 h before ethyl acetate (200 mL) and water (150 mL) were added. The layers were separated and the aqueous layer extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with a saturated solution of sodium bicarbonate (100 mL), brine (100 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 20:80 to 30:70] afforded *vinyl bromide* **427** as prisms (3.13 g, 53%). Also isolated was diastereomer **428** as an oil (1.54g, 26%). **IR** (thin film)/cm^{-1} 1742, 1369, 1275, 1261, 1224, 1091; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 5.65 (1H, br. s, CH_AH$_B$=C), 5.51 (1H, d, *J* = 1.8, CH$_A$$H_B$=C), 5.24-5.22 (1H, m, 1 x C*H*OAc), 5.20-5.17 (1H, m, 1 x C*H*OAc), 5.13 (1H, t, *J* = 4.0, 1 x C*H*OAc), 4.13 (1H, dd, *J* = 13.6, 2.0, CH_AH$_B$CHOAc), 3.90 (1H, ddd, *J* = 8.0, 5.2, 1.2, C*H*CH$_2$C(Br)=CH$_2$), 3.75 (1H, dd, *J* = 13.6, 1.2, CH$_A$$H_B$CHOAc), 2.79 (1H, dd, *J* = 14.8, 8.0, CH_AH$_B$C(Br)=CH$_2$), 2.54 (1H, dd, *J* = 14.8, 5.2, CH$_A$$H_B$C(Br)=CH), 2.16 (3H, s, 1 x CH_3CO$_2$CH), 2.15 (3H, s, 1 x CH_3CO$_2$CH), 2.00 (3H, s, 1 x CH_3CO$_2$CH); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 170.3, 170.2, 169.7, 128.2, 120.3, 75.3, 69.1, 68.2, 67.7, 66.5, 42.9, 21.0, 20.7, 20.6; **HRMS** (ES^+, *m/z*): Calculated 401.0206 ($C_{14}H_{19}{}^{79}BrNaO_7$); Found 401.0193; $[\alpha]_D^{21}$ +4.2 (*c* 1.0, CH_2Cl_2); **M.P.** 51-54 ^oC.

(2*S*,3*S*,4*R*,5*R*)-2-(2-Bromoallyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate, 428



Vinyl bromide **428** was isolated as a minor product in the synthesis of vinyl bromide **427**. **IR** (thin film)/cm^{-1} 1748, 1370, 1246, 1216, 1108; **^{1}H NMR (400 MHz, CDCl$_3$)** δ_H: 5.68 (1H, br. s, C=C*H*$_A$H$_B$), 5.64 (1H, t, *J* = 2.8, 1 x C*H*OAc), 5.52 (1H, d, *J* = 1.4, C=CH$_A$*H*$_B$), 4.98 (1H, ddd, *J* = 10.8, 5.6, 2.8, 1 x C*H*OAc), 4.74 (1H, dd, *J* = 10.0, 2.8, 1 x C*H*OAc), 3.98 (1H, td, *J* = 9.2, 3.2, C*H*CH$_2$C(Br)=CH$_2$), 3.87 (1H, dd, *J* = 10.8, 5.6, C*H*$_A$H$_B$CHOAc), 3.65 (1H, t, *J* = 10.8, CH$_A$*H*$_B$CHOAc), 2.60 (1H, dd, *J* = 14.8, 3.2, C*H*$_A$H$_B$C(Br)=CH$_2$), 2.52 (1H, dd, *J* = 14.8, 9.2, CH$_A$*H*$_B$C(Br)=CH$_2$), 2.19 (3H, s, 1 x C*H*$_3$CO$_2$CH), 2.02 (3H, s, 1 x C*H*$_3$CO$_2$CH), 2.01 (3H, s, 1 x C*H*$_3$CO$_2$CH); **^{13}C NMR (100 MHz, CDCl$_3$)** δ_C: 170.1, 169.4, 169.4, 128.8, 119.7, 71.2, 69.8, 68.0, 66.6, 63.5, 43.6, 20.8, 20.7, 20.6; **HRMS** (ES$^+$, *m/z*): Calculated 401.0206 ($C_{14}H_{19}{}^{79}BrNaO_7$); Found 401.0197; **$[\alpha]_D^{21}$** –2.3 (*c* 1.0, CH_2Cl_2).

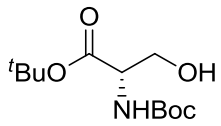
(*S*)-*tert*-Butyl 3-(benzyloxy)-2-(*tert*-butoxycarbonylamino)propanoate, 430



To a solution of Boc-Ser(Bzl)-OH **429** (15.0 g, 50.9 mmol) in CH_2Cl_2 (60 mL) was added *tert*-butyl 2,2,2-trichloroacetimidate (18.2 mL, 102 mmol) in cyclohexane (110 mL). Boron trifluoride diethyl etherate (1.03 mL, 1.12 mmol) was added and the resultant mixture was stirred at room temperature for 20 h before ethyl acetate (200 mL) and a saturated solution of sodium bicarbonate (100 mL) were added. The layers were separated and the aqueous layer extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 20:80 to 30:70] afforded

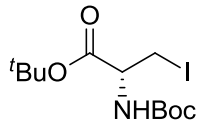
ester **430** as prisms (17.5 g, 98%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.38-7.26 (5H, m, 5 x Ar-C*H*), 5.37 (1H, d, *J* = 8.4, CHN*H*Boc), 4.57 (1H, d, *J* = 12.4, CH_AH$_B$Ph), 4.48 (1H, d, *J* = 12.4, CH$_A$$H_B$Ph), 4.33 (1H, dt, *J* = 8.4, 2.8, C*H*NHBoc), 3.86 (1H, dd, *J* = 9.2, 2.8, CH_AH$_B$OBn), 3.66 (1H, dd, *J* = 9.2, 2.8, CH$_A$$H_B$OBn), 1.45 (18H, s, 2 x OC(CH_3)$_3$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 169.7, 155.4, 137.6, 128.4, 128.3, 127.7, 127.6, 82.0, 79.7, 73.3, 70.5, 54.5, 28.3, 28.0; **$[\alpha]_D^{21}$** +8.1 (*c* 1.0, CH_2Cl_2); **M.P.** 39-41 ^{o}C. Data were consistent with those previously reported.[127]

(*S*)-*tert*-Butyl 2-(*tert*-butoxycarbonylamino)-3-hydroxypropanoate, 431



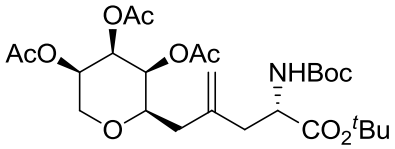
A solution of ester **430** (17.5g, 49.9 mmol) in ethyl acetate:acetic acid (5:1, 140 mL) was purged with argon five times. To this solution was added palladium (II) hydroxide on carbon (1.8 g, 10% wt), and the mixture was purged with H_2 gas five times. The resulting solution was stirred under at atmosphere of H_2 gas for 24 h before being filtered through Celite® and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 10:90 to 20:80] afforded alcohol **431** as prisms (12.9 g, 99%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 5.47 (1H, br. s, CHN*H*Boc), 4.30-4.22 (1H, m, C*H*NHBoc), 3.90 (2H, d, *J* = 4.0, CH_2OH), 1.49 (9H, s, 1 x OC(CH_3)$_3$), 1.45 (9H, s, 1 x OC(CH_3)$_3$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 176.4, 155.9, 82.7, 80.1, 64.1, 56.3, 28.3, 28.0; **$[\alpha]_D^{21}$** –23.4 (*c* 1.0, EtOH); **M.P.** 72-75 ^{o}C. Data were consistent with those previously reported.[127]

(*R*)-*tert*-Butyl 2-((*tert*-butoxycarbonyl)amino)-3-iodopropanoate, 432



To a solution of triphenylphosphine (6.30 g, 23.9 mmol) and imidazole (1.70 g, 24.9 mmol) in CH_2Cl_2 (200 mL) at 0 ^oC was added iodine (6.30 g, 24.9 mmol) in 3 portions over 30 min. To this was added a solution of alcohol **431** (5.00 g, 19.2 mmol) in CH_2Cl_2 (20 mL) dropwise. The resultant solution was stirred at 0 ^oC for 1 h before being warmed to room temperature for 1 h. Methanol (10 mL) was added and the solvent was removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 4:96] afforded *iodide* **432** as prisms (6.75 g, 95%). **IR** (thin film)/cm^{-1} 3379 , 2979, 1715, 1496, 1368, 1346, 1259, 1154; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 5.35 (1H, d, *J* = 7.2, CHN*H*Boc), 4.35 (1H, dt, *J* = 7.2, 3.6, C*H*NHBoc), 3.57 (2H, d, *J* = 3.6, CH_2I), 1.51 (9H, s, 1 x OC(CH_3)$_3$), 1.49 (9H, s, 1 x OC(CH_3)$_3$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 168.5, 154.9, 83.3, 80.2, 53.7, 28.3, 28.0, 8.9; **HRMS** (ES^+, *m/z*): Calculated 394.0486 ($C_{12}H_{22}INNaO_4$); Found 394.0472; $[\alpha]_D^{22}$ +19.7 (*c* 1.0, CH_2Cl_2); **M.P.** 67 71 ^oC.

(2*R*,3*S*,4*R*,5*R*)-2-((*S*)-5-(*tert*-Butoxy)-4-((*tert*-butoxycarbonyl)amino)-2-methylene-5-oxopentyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate, 434



From vinyl iodide 425:

To a solution of *iodide* **432** (1.04 g, 2.82 mmol) and zinc/copper couple (1.00 g) in benzene (8.0 mL) was added dimethylacetamide (0.80 mL). The resulting suspension was sonicated at 45 ^oC for 1 h before being added dropwise to a degassed solution of *vinyl iodide* **425** (400 mg,

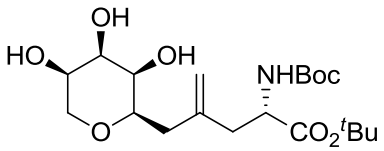
0.939 mmol), tetrakis(triphenylphosphine)palladium(0) (32.5 mg, 0.0282 mmol) and hexamethylphosphoramide (0.80 mL) in benzene (8.0 mL). The resultant mixture was heated to 80 ^{o}C for 2 h before being diluted with ethyl acetate (200 mL) and filtered through Celite®. The filtrate was then washed with a saturated solution of sodium bicarbonate (20 mL), brine (20 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Double purification by flash column chromatography [SiO_2, EtOAc-petrol, 20:80 to 35:65] then [SiO_2, EtOAc-petrol, 28:72 to 35:65] afforded *alkene* **434** as a yellow oil (445 mg, 87%). **IR** (thin film)/cm^{-1} 3374, 2977, 1741, 1509, 1367, 1227, 1154; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 5.19-5.17 (1H, m, 1 x C*H*OAc), 5.16-5.12 (1H, m, 1 x C*H*OAc), 5.07 (1H, t, *J* = 3.6, 1 x C*H*OAc), 4.97 (1H, d, *J* = 7.6, N*H*Boc), 4.90 (2H, br. s, C=CH_2), 4.27-4.19 (1H, m, C*H*NH), 4.12-4.05 (1H, m, CH_AH$_B$CHOAc), 3.73-3.66 (2H, m, OC*H*CHOAc + CH$_A$$H_B$CHOAc), 2.50 (1H, dd, *J* = 14.4, 6.0, CH_AH$_B$CHNH), 2.43 (1H, dd, *J* = 14.4, 7.6, CH_AH$_B$CHOCH$_2$), 2.34 (1H, dd, *J* = 14.4, 6.8, CH$_A$$H_B$CHNH), 2.18 (1H, dd, *J* = 14.4, 4.0, CH$_A$$H_B$CHOCH$_2$), 2.15 (3H, s, 1 x C$H_3CO_2$CH), 2.13 (3H, s, 1 x C$H_3CO_2$CH), 1.98 (3H, s, 1 x C$H_3CO_2$CH), 1.43 (9H, s, 1 x C(CH_3)$_3$), 1.41 (9H, s, 1 x C(CH_3)$_3$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 171.4, 170.4, 170.4, 169.7, 155.1, 140.3, 116.5, 82.0, 79.6, 76.4, 68.8, 68.3, 68.2, 66.6, 52.6, 39.2, 37.0, 28.3, 28.0, 21.0, 20.7, 20.6; **HRMS** (ES$^+$, *m/z*): Calculated 566.2572 ($C_{26}H_{41}NNaO_{11}$); Found 566.2565; $[\alpha]_D^{22}$ +5.9 (*c* 1.0, CH_2Cl_2).

From vinyl bromide 427:

To a solution of *iodide* **432** (7.32 g, 19.8 mmol) and zinc/copper couple (7.30 g) in benzene (50 mL) was added dimethylacetamide (5.0 mL). The resulting suspension was sonicated at 45 ^{o}C for 1 h before being added dropwise to a degassed solution of *vinyl bromide* **427** (2.50 g, 6.60 mmol), tetrakis(triphenylphosphine)palladium(0) (229 mg, 0.220 mmol) and hexamethylphosphoramide (2.5 mL) in benzene (50 mL). The resultant mixture was heated to 80 ^{o}C for 2 h before being diluted with ethyl acetate (200 mL) and filtered through Celite®. The

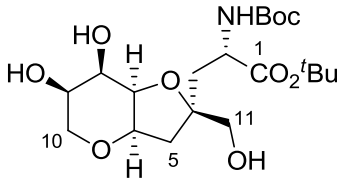
filtrate was then washed with a saturated solution of sodium bicarbonate (100 mL), brine (100 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Double purification by flash column chromatography [SiO_2, EtOAc-petrol, 20:80 to 35:65] then [SiO_2, EtOAc-petrol, 28:72 to 35:65] afforded *alkene* **434** as a yellow oil (3.26 g, 91%).

(*S*)-*tert*-Butyl 2-((*tert*-butoxycarbonyl)amino)-4-(((2*R*,3*R*,4*R*,5*R*)-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)methyl)pent-4-enoate, 435



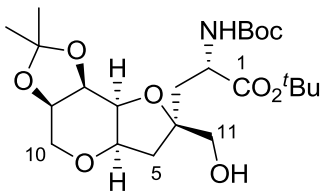
To a solution of *alkene* **434** (2.40 g, 4.40 mmol) in methanol (18 mL) was added sodium methoxide (0.5 M in methanol, 0.44 mL, 0.22 mmol). The resulting solution was stirred for 2 h before being neutralised with Amberlite IR-120(H) ion exchange resin. The resulting mixture was filtered, and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 70:30 to 100:00] afforded *triol* **435** as an oil (1.60 g, 87%). **IR** (thin film)/cm^{-1} 3372 br, 2976, 1714, 1507, 1367, 1246, 1154; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 5.18 (1H, d, *J* = 8.6, N*H*Boc), 4.90 (1H, s, C=CH_AH_B), 4.85 (1H, s, C=CH_AH_B), 4.30 (1H, td, *J* = 8.6, 5.2, C*H*NH), 4.22 (1H, d, *J* = 7.2, 1 x O*H*), 4.08 (1H, d, *J* = 12.8, CH_AH_BCHOH), 3.84-3.76 (3H, m, 1 x C*H*OH + 2 x O*H*), 3.65 (1H, d, *J* = 9.2, 1 x C*H*OH), 3.56-3.44 (3H, m, CH_AH_BCHOH + OC*H*CHOH + 1 x C*H*OH) 2.54-2.44 (3H, m, CH_2CHNH + CH_AH_BCHOCH_2), 2.28 (1H, dd, *J* = 13.8, 9.2, CH_AH_BCHOCH_2), 1.44 (9H, s, 1 x C(CH_3)$_3$), 1.41 (9H, s, 1 x C(CH_3)$_3$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 171.5, 155.7, 140.8, 114.9, 82.2, 80.1, 77.5, 71.3, 70.6, 70.0, 69.3, 52.3, 41.3, 35.9, 28.3, 28.0; **HRMS** (ES^+, *m/z*): Calculated 440.2255 ($C_{20}H_{35}NNaO_8$); Found 440.2246; $[\alpha]_D^{22}$ –18.8 (*c* 1.0, CH_2Cl_2).

(2*S*)-*tert*-Butyl 2-((*tert*-butoxycarbonyl)amino)-3-((2*R*,6*R*,7*R*)-6,7-dihydroxy-2-(hydroxymethyl)hexahydro-2H-furo[3,2-b]pyran-2-yl)propanoate, 437



Triol **435** (900 mg, 2.16 mmol) was subjected to **General Procedure 3** (24 h) using $K_2OsO_4.2H_2O$ (5 mol%) and zinc triflate afforded *THF* **437** (818 mg, 88%) as an oil. No further purification was required. **IR** (thin film)/cm^{-1} 3380 br, 2978, 1710, 1367, 1249, 1154; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 5.53 (1H, d, *J* = 7.8, N*H*Boc), 4.39 (1H, br. s, 1 x O*H*), 4.26-4.17 (1H, m, ^{7}C*H*), 4.14 (1H, br. s, 1 x O*H*), 4.11-4.07 (1H, m, ^{2}C*H*), 4.06-4.02 (1H, m, ^{6}C*H*), 3.98 (1H, d, *J* = 12.4, $^{10}CH_AH_B$), 3.87 (1H, br. s, 1 x C*H*OH), 3.83 (1H, br. s, 1 x C*H*OH), 3.77 (1H, d, *J* = 11.2, $^{11}CH_AH_B$), 3.61 (1H, d, *J* = 11.2, $^{11}CH_AH_B$), 3.44 (1H, d, *J* = 12.4, $^{10}CH_AH_B$), 2.17-1.91 (4H, m, $^5CH_2$ + $^3CH_2$), 1.44 (9H, s, 1 x C(CH_3)$_3$), 1.42 (9H, s, 1 x C(CH_3)$_3$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 172.0, 155.7, 85.2, 82.2, 80.0, 79.0, 77.6, 69.5, 67.6, 67.1, 66.5, 51.4, 41.3, 38.9, 28.3, 27.9; **HRMS** (ES^+, *m/z*): Calculated 456.2204 ($C_{20}H_{35}NNaO_9$); Found 456.2191; $[\alpha]_D^{22}$ –8.4 (*c* 1.0, CH_2Cl_2); **M.P.** 69-71 °C.

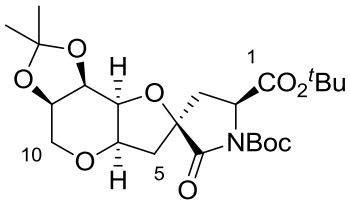
(2*S*)-*tert*-Butyl 2-((*tert*-butoxycarbonyl)amino)-3-((3a*R*,7*R*,8b*R*)-7-(hydroxymethyl)-2,2-dimethylhexahydro-3aH-[1,3]dioxolo[4,5-d]furo[3,2-b]pyran-7-yl)propanoate, 439



To a stirred solution of *THF* **437** (300 mg, 0.693 mmol) in CH_2Cl_2 (4 mL) was added 2,2-diethylpropane (4 mL) and *para*-toluenesulfonic acid (13 mg, 0.069 mmol) sequentially. The resultant solution was stirred for 30 min at room temperature before water (4 mL) was

added. This solution was stirred for 30 minutes before a saturated solution of sodium bicarbonate (4 mL) was added, and the mixture extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 50:50 to 70:30] afforded *acetonide* **439** as an oil (270 mg, 83%). **IR** (thin film)/cm^{-1} 3395 br, 2980, 1714, 1499, 1367, 1247, 1154, 1046; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 5.48 (1H, br. d, *J* = 6.4, CHN*H*), 4.51 (1H, dd, *J* = 6.6, 5.2, ^{8}C*H*), 4.29 (1H, q, *J* = 5.6, ^{6}C*H*), 4.17 (1H, dd, *J* = 6.6, 1.6, ^{9}C*H*), 4.14-4.06 (2H, m, ^{2}C*H* + ^{7}C*H*), 3.97 (1H, d, *J* = 13.4, ^{10}CH_AH_B), 3.78 (1H, br. d, *J* = 11.4, ^{11}CH_AH_B), 3.50 (1H, dd, *J* = 11.4, 9.2, ^{11}CH_AH_B), 3.42 (1H, dd, *J* = 13.4, 1.6, ^{10}CH_AH_B), 3.36 (1H, dd, *J* = 9.2, 1.6, CH_2OH), 2.51 (1H, dd, *J* = 13.4, 5.2, ^{5}CH_AH_B), 2.09 (1H, dd, *J* = 13.4, 7.2, ^{5}CH_AH_B), 1.96 (1H, dd, *J* = 14.4, 3.6, ^{3}CH_AH_B), 1.83 (1H, dd, *J* = 14.4, 8.8, ^{3}CH_AH_B), 1.56 (3H, s, 1 x C(CH_3), 1.45 (9H, s, 1 x C(CH_3)$_3$), 1.44 (9H, s, 1 x C(CH_3)$_3$), 1.36 (3H, s, 1 x C(CH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 171.6, 154.1, 110.2, 85.1, 81.7, 79.7, 77.2, 74.1, 71.8, 71.7, 67.3, 66.3, 51.9, 39.4, 39.0, 28.3, 27.9, 26.0, 25.7; **HRMS** (ES^+, *m/z*): Calculated 496.2517 ($C_{23}H_{39}NNaO_9$); Found 496.2509 ; **$[\alpha]_D^{22}$** –19.6 (*c* 1.0, CH_2Cl_2).

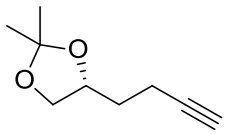
(3a*R*,3'*R*,5'*S*,8b*R*)-Di-*tert*-butyl 2,2-dimethyl-2'-oxohexahydrospiro[[1,3]dioxolo[4,5-d]furo[3,2-b]pyran-7,3'-pyrrolidine]-1',5'-dicarboxylate, 441



To a solution of *acetonide* **439** (110 mg, 0.233 mmol) and powdered 4Å molecular sieves in MeCN (2.5 mL) was added 4-methylmorpholine-*N*-oxide (136 mg, 1.16 mmol). The resultant solution was stirred for 10 minutes before tetrapropylammonium perruthenate (12 mg, 0.035 mmol) was added. The dark solution was stirred at room temperature for 3 h before a

further portion of tetrapropylammonium perruthenate (12 mg, 0.035 mmol) was added. The resulting mixture was stirred for a further 3 h at room temperature before ethyl acetate (10 mL) was added, and the mixture filtered through a pad of Celite® and washed with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 70:30 to 80:20] afforded *lactam* **441** as prisms (89 mg, 82%). **IR** (thin film)/cm^{-1} 2978, 1788, 1745, 1369, 1322, 1249, 1170, 1068; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 4.46-4.36 (3H, m, ^2CH + ^6CH + ^8CH), 4.28 (1H, dt, J = 7.2, 4.4, ^9CH), 4.06 (1H, dd, J = 6.0, 4.4, ^7CH), 3.99 (1H, dd, J = 12.4, 4.4, $^{10}CH_AH_B$), 3. 62 (1H, d, J = 12.4, 4.4, $^{10}CH_AH_B$), 2.63 (1H, dd, J = 13.2, 5.6, $^3CH_AH_B$), 2.25 (1H, dd, J = 13.6, 4.4, $^5CH_AH_B$), 2.23-2.15 (2H, m, $^3CH_AH_B$ + $^5CH_AH_B$), 1.52 (9H, s, 1 x $C(CH_3)_3$), 1.51 (3H, s, 1 x $C(CH_3)$), 1.47 (9H, s, 1 x $C(CH_3)_3$), 1.34 (3H, s, 1 x $C(CH_3)$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 170.1, 168.9, 149.6, 110.5, 83.6, 83.0, 82.3, 75.8, 75.4, 72.0, 71.3, 65.9, 56.0, 41.7, 36.2, 27.9, 26.4, 25.5; **HRMS** (ES^+, *m/z*): Calculated 492.2204 ($C_{23}H_{35}NNaO_9$); Found 492.2192; $[\alpha]_D^{22}$ –15.1 (*c* 1.0, CH_2Cl_2); **M.P.** 185-189 °C.[166]

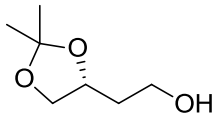
(*R*)-4-(But-3-yn-1-yl)-2,2-dimethyl-1,3-dioxolane, 469



To a stirred solution of silyl-alkyne **475** (11.6 g, 51.9 mmol) in methanol (60 mL) was added potassium carbonate (7.86 g, 56.4 mmol). The resulting mixture was stirred for 4 h at room temperature before being filtered and the solvent removed *in vacuo* onto silica. Purification by flash column chromatography [SiO_2, Et_2O-petrol, 5:95 to 10:90] afforded alkyne **469** as an oil (7.20 g, 90%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 4.25-4.17 (1H, m, CHOR), 4.08 (1H, dd, J = 8.0, 6.0, CH_AH_BOR), 3.58 (1H, t, J = 7.2, CH_AH_BOR), 2.35-2.28 (2H, m, CH_2C≡C), 1.96 (1H, t, J = 2.8, C≡CH), 1.88-1.68 (2H, m, CH_2CH_2C≡C), 1.41 (3H, s, 1 x CH_3), 1.36 (3H, s, 1

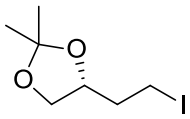
x C*H*$_3$); **^{13}C NMR (125 MHz, CDCl$_3$)** δ_C: 108.9, 83.5, 74.7, 69.1, 68.7, 32.6, 26.9, 25.6, 15.0; **$[\alpha]_D^{22}$** +4.4 (*c* 1.0, CH_2Cl_2). Data were consistent with those previously reported.[134]

(*R*)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethanol, 470



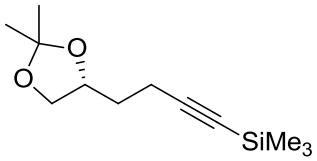
To a solution of borane dimethyl sulphide **472** (31.9 mL, 336 mmol) in tetrahydrofuran (150 mL) at 0 ^oC was added trimethoxyborane (36.2 mL, 325 mmol). The resulting solution was stirred at 0 ^oC for 5 minutes before (*R*)-malic acid (15.0 g, 112 mmol) in tetrahydrofuran (75 mL) was added. The resulting solution was stirred at room temperature for 16 h before methanol (30 mL) was added cautiously. The solvent was removed *in vacuo* and the resulting residue purified by filtration through a plug of silica [SiO_2, MeOH-EtOAc, 20:80]. The resulting triol was immediately dissolved in acetone (450 mL) before *para*-toluenesulfonic acid (638 mg, 3.36 mmol) was added. The resulting mixture was stirred for 16 h before the solvent was removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 60:40 to 80:20] afforded acetonide **470** as an oil (13.2 g, 81%).**^{1}H NMR (400 MHz, CDCl$_3$)** δ_H: 4.21-4.08 (1H, m, C*H*OR), 4.01 (1H, dd, *J* = 6.0, 8.4, CH_AH$_B$OR), 3.68 (2H, t, *J* = 5.2, CH_2OH), 3.54-3.47 (1H, m, CH$_A$$H_B$OR), 2.90 (1H, br. s, O*H*), 1.81-1.65 (2H, m, CH_2CH$_2$OH), 1.32 (3H, s, 1 x C(CH_3)), 1.28 (3H, s, 1 x C(CH_3)); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 108.7, 74.5, 69.2, 59.9, 35.9, 26.8, 25.6; **$[\alpha]_D^{22}$** +2.8 (*c* 1.0, CH_2Cl_2). Data were consistent with those previously reported.[134]

(*R*)-4-(2-Iodoethyl)-2,2-dimethyl-1,3-dioxolane, 474



To a solution of triphenylphosphine (29.8 g, 114 mmol) and imidazole (11.1 g, 163 mmol) in diethyl ether (250 mL) and acetonitrile (80 mL) at 0 ^{o}C was added iodine (28.8 g, 114 mmol) portionwise over 30 minutes. After complete addition of iodine, acetonide **470** (11.8 g, 81.4 mmol) was added dropwise. The resulting solution was stirred at 0 ^{o}C for 1 h before being warmed to room temperature for 1 h. The reaction was quenched by the addition of methanol (40 mL) and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, Et_2O-petrol, 10:90 to 20:80] afforded iodide **474** as an oil (17.5 g, 84%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 4.21-4.14 (1H, m, C*H*OR), 4.08 (1H, dd, *J* = 8.0, 6.4, CH_AH$_B$OR), 3.57 (1H, t, *J* = 7.2, CH$_A$$H_B$OR), 3.31-3.18 (2H, m, C$H_2$I), 2.14-1.98 (2H, m, C$H_2CH_2$I), 1.40 (3H, s, 1 x C$H_3$), 1.35 (3H, s, 1 x C$H_3$); **^{13}C NMR (125 MHz, $CDCl_3$)** δ_C: 109.2, 75.7, 68.6, 37.9, 27.0, 25.5, 1.2; $[\alpha]_D^{23}$ +21.8 (*c* 1.0, CH_2Cl_2). Data were consistent with those previously reported.[135]

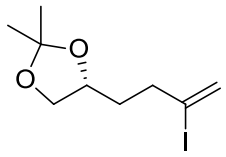
(*R*)-(4-(2,2-Dimethyl-1,3-dioxolan-4-yl)but-1-yn-1-yl)trimethylsilane, 475



To a stirred solution of ethynyltrimethylsilane (13.7 mL, 99.2 mmol) in tetrahydrofuran (160 mL) at –78 ^{o}C was added 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (36.2 mL, 298 mmol) followed by *n*-butyllithium (1.6 M in hexanes, 66.1 mL, 105.7 mmol). The resulting solution was stirred for 5 minutes before iodide **474** (16.8 g, 66.1 mmol) in tetrahydrofuran (40 mL) was added. The resultant solution was stirred at –78 ^{o}C for 15 minutes before being

warmed to room temperature and stirred for a further 1 h. The reaction was quenched with a saturated solution of ammonium chloride (80 mL) and the resulting mixture extracted with diethyl ether (3 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, Et_2O-petrol, 5:95 to 15:85] afforded silyl-alkyne **475** as an oil (12.6 g, 85%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 4.18 (1H, quin, J = 6.4, C*H*OR), 4.11-4.06 (1H, m, CH_AH$_B$OR), 3.62-3.56 (1H, m, CH$_A$$H_B$OR), 2.42-2.26 (2H, m, C$H_2$C≡C), 1.88-1.79 (1H, m, CH_AH$_B$CH$_2$C≡C), 1.77-1.68 (1H, m, CH$_A$$H_BCH_2$C≡C), 1.40 (3H, s, 1 x C$H_3$), 1.36 (3H, s, 1 x C$H_3$), 0.16-0.13 (9H, m, Si(CH_3)$_3$); **^{13}C NMR (125 MHz, $CDCl_3$)** δ_C: 108.7, 106.2, 85.0, 75.0, 69.2, 32.7, 26.9, 25.6, 16.4, 0.1; **$[\alpha]_D^{22}$** +7.2 (*c* 1.0, CH_2Cl_2). Data were consistent with those previously reported.[135]

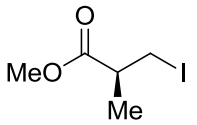
(*R*)-4-(3-Iodobut-3-en-1-yl)-2,2-dimethyl-1,3-dioxolane, 477



[1,3-Bis(diphenylphosphino)propane]dichloronickel(II) (706 mg, 1.30 mmol) was added to a flame dried schlenk tube and purged with argon for 10 minutes before tetrahydrofuran (45 mL) and diisobutylaluminium hydride (1.0 M in cyclohexane, 56.4 mL, 56.4 mmol) were added sequentially. The resultant black mixture was cooled to 0 ^oC before alkyne **469** (6.60 g, 43.4 mmol) in tetrahydrofuran (15 mL) was added dropwise. The resulting mixture was warmed to room temperature and stirred for 2 h before being cooled to 0 ^oC. To this was added a solution of *N*-iodosuccinimide (19.4 g, 86.8 mmol) in tetrahydrofuran (120 mL) dropwise. The resulting mixture was warmed to room temperature and stirred for a further 1 h before Rochelles solution (150 mL) was added. This mixture was extracted with diethyl ether (3 x 200 mL). The combined organic layers were washed with brine (300 mL), dried over sodium

sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, Et_2O-petrol, 5:95 to 15:85] afforded *alkenyl iodide* **477** as an oil (9.05 g, 74%). **IR** (thin film)/cm^{-1} 2985, 2937, 1618, 1369, 1259, 1214, 1157, 1064; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 6.07 (1H, d, J = 1.2, C=CH_AH$_B$), 5.71 (1H, d, J = 1.2, C=CH$_A$$H_B$), 4.13-4.02 (2H, m, C$H$OR + C$H_AH_B$OR), 3.58-3.52 (1H, m, CH$_A$$H_B$OR), 2.61-2.41 (2H, m, C$H_2$C(I)=CH$_2$), 1.81-1.74 (2H, m, C$H_2CH_2$C(I)=CH$_2$), 1.41 (3H, s, 1 x C$H_3$), 1.34 (3H, s, 1 x C$H_3$); **^{13}C NMR (125 MHz, $CDCl_3$)** δ_C: 126.0, 111.0, 108.9, 74.5, 69.2, 41.7, 33.3, 27.0, 25.7; **HRMS** (ES^+, *m/z*): Calculated 305.0008 ($C_9H_{15}INaO_2$); Found 305.0011; **$[\alpha]_D^{22}$** –1.2 (*c* 1.0, CH_2Cl_2).

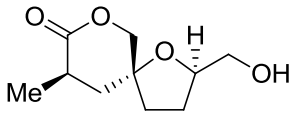
(*S*)-Methyl 3-iodo-2-methylpropanoate, 478



To a solution of triphenylphosphine (27.8 g, 106 mmol) and imidazole (7.49 g, 110 mmol) in diethyl ether (240 mL) and acetonitrile (80 mL) at 0 ^oC was added iodine (27.9 g, 110 mmol) portionwise over 30 minutes. After complete addition of iodine, (*R*)-(-)-3-hydroxy-2-methylpropionic acid methyl ester **467** (10.0 g, 84.7 mmol) was added dropwise. The resulting solution was stirred at 0 ^oC for 1 h before being warmed to room temperature for 1 h. The reaction was quenched by the addition of methanol (40 mL) and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, Et_2O-petrol, 5:95] afforded *iodide* **478** as an oil (18.6 g, 97%). **IR** (thin film)/cm^{-1} 2985, 2937, 2871, 1741, 1617, 1454, 1370, 1213, 1064; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 3.73 (3H, d, J = 0.8, OCH_3), 3.38 (1H, ddd, J = 9.6, 6.4, 0.8, CH_AH$_B$I), 3.26 (1H, ddd, J = 9.6, 6.4, 0.8, CH$_A$$H_B$I), 2.81 (1H, q, J = 6.8, CHCH$_3$), 1.28 (3H, d, J = 7.2, CHCH_3); **^{13}C NMR (125 MHz, $CDCl_3$)** δ_C: 173.8, 52.1, 42.2, 18.2, 6.9;

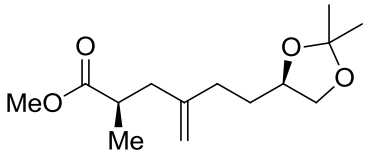
HRMS (ES^+, *m/z*): Calculated 250.9539 ($C_5H_9INaO_4$); Found 250.9542; $[\alpha]_D^{22}$ –24.3 (*c* 1.0, CH_2Cl_2).

(2*R*,5*R*,9*R*)-2-(Hydroxymethyl)-9-methyl-1,7-dioxaspiro[4.5]decan-8-one, 480



Alkene **482** (4.36 g, 17.0 mmol) was subjected to **General Procedure 3** (16 h) using $K_2OsO_4.2H_2O$ (2.5 mol%, 157 mg, 0.426 mmol) and scandium trifluoromethanesulfonate which afforded *lactone* **480** (2.57 g, 76%) as an oil. No further purification was required. **IR** (thin film)/cm^{-1} 3436 br., 2938, 2877, 1727, 1460, 1379, 1260, 1151, 1031; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 4.15-4.05 (3H, m, OC*H* + CCH_2O), 3.66 (1H, dd, *J* = 11.6, 3.2, CH_AH$_B$OH), 3.43 (1H, dd, *J* = 11.6, 5.6, CH$_A$$H_B$OH), 2.81 (1H, dq, *J* = 13.2, 6.8, C*H*CH_3), 2.10 (1H, dd, *J* = 14.0, 6.8, CH_AH$_B$CHCH$_3$), 2.00-1.70 (5H, m, 2 x THF-CH_2 + O*H*), 1.59 (1H, dd, *J* = 14.0, 13.2, CH$_A$$H_B$CHCH$_3$), 1.18 (3H, d, *J* = 6.8, CHCH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 174.7, 79.8, 79.4, 75.3, 64.7, 39.8, 35.4, 32.3, 26.5, 16.2; **HRMS** (ES^+, *m/z*): Calculated 223.0941 ($C_{10}H_{16}NaO_4$); Found 223.0941; $[\alpha]_D^{22}$ –6.6 (*c* 1.0, CH_2Cl_2).

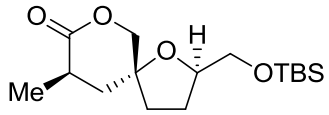
(*R*)-Methyl 6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methyl-4-methylenehexanoate, 482



To a solution of *iodide* **478** (11.4 g, 50.0 mmol) in benzene (200 mL) was added zinc/copper couple (11.0 g) and *N*,*N*-dimethylacetamide (20.0 mL). The resulting suspension was degassed with argon before being sonicated at 45 ^oC for 2 h. In a separate two-neck flask containing a solution of alkenyl-iodide **477** (7.00 g, 25.0 mmol) in benzene (200 mL) was added

tetrakis(triphenylphosphine)palladium(0) (867 mg, 0.750 mmol). The resulting yellow solution was degassed with argon before hexamethylphosphoramide (20.0 mL) was added. The solution of the organozinc was added to the solution of alkenyl-iodide **477** *via* a cannular. The combined mixture was heated at 80 ^{o}C for 2 h before being diluted with ethyl acetate (400 mL) and filtered through Celite®. The filtrate was then washed with a saturated solution of sodium bicarbonate (200 mL), brine (200 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 10:90 to 15:85] afforded *alkene* **482** as a yellow oil (5.70 g, 90%). **IR** (thin film)/cm^{-1} 2985, 2938, 1738, 1557, 1370, 1213, 1162, 1068; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 4.80 (1H, s, C=CH_AH$_B$), 4.76 (1H, s, C=CH$_A$$H_B$), 4.10-4.02 (2H, m, C$H$OR + C$H_AH_B$OR), 3.66 (3H, s, OC$H_3$) 3.53 (1H, t, J = 7.2, CH$_A$$H_B$OR), 2.70-2.61 (1H, m, C$HCH_3$), 2.44 (1H, dd, J = 14.4, 7.2, CH_AH$_B$CHCH$_3$), 2.17-1.96 (3H, m, CH$_A$$H_B$CHCH$_3$ + CH$_2$CH_2C=CH$_2$), 1.83-1.73 (1H, m, CH_AH$_B$COR), 1.67-1.59 (1H, m, CH$_A$$H_B$COR), 1.41 (3H, s, 1 x C$H_3$), 1.35 (3H, s, 1 x C$H_3$), 1.14 (3H, d, J = 7.2, CHCH_3); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 176.8, 145.9, 111.3, 108.7, 75.6, 69.3, 55.6, 40.2, 37.8, 31.6, 26.9, 25.7, 16.9; **HRMS** (ES$^+$, *m/z*): Calculated 279.1567 ($C_{14}H_{24}NaO_4$); Found 279.1562; $[\alpha]_D^{22}$ –15.7 (*c* 1.0, CH_2Cl_2).

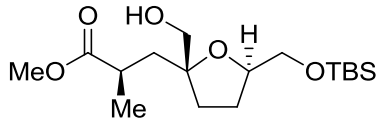
(2*R*,5*R*,9*R*)-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-9-methyl-1,7-dioxaspiro [4.5]decan-8-one, 484



To a solution of *lactone* **480** (2.50 g, 12.5 mmol) in CH_2Cl_2 (130 mL) was added *N*,*N*-dimethylaminopyridine (153 mg, 1.25 mmol) and imidazole (1.70 g, 25.0 mmol). The resultant solution was stirred until all of the reagents had dissolved. *tert*-Butyldimethylsilyl chloride (2.08 g, 13.8 mmol) was added in one portion, and the resulting mixture stirred for 2 h

before ethyl acetate (300 mL) and water (100 mL) were added. The resultant mixture was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 10:90 to 20:80] afforded *TBS-lactone* **484** as an oil (3.32 g, 85%). **IR** (thin film)/cm^{-1} 2930, 2857, 1737, 1462, 1378, 1255, 1134, 1079; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 4.18-4.08 (3H, m, OC*H* + CCH_2O), 3.63 (1H, dd, *J* = 10.8, 4.0, CH_AH$_B$OTBS), 3.57 (1H, dd, *J* = 10.8, 4.0, CH$_A$$H_B$OTBS), 2.85 (1H, m, C*H*CH$_3$), 2.12 (1H, dd, *J* = 13.6, 6.4, CH_AH$_B$CHCH$_3$), 2.04-1.85 (3H, m, THF-CH_2 + THF-CH_AH$_B$), 1.77-1.70 (1H, m, THF-CH$_A$$H_B$), 1.63 (1H, t, *J* = 13.6, CH$_A$$H_B$CHCH$_3$), 1.22 (3H, d, *J* = 6.8, CHCH_3), 0.88 (9H, s, SiC(CH_3)$_3$), 0.05 (6H, s, Si(CH_3)$_2$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 175.0, 80.0, 79.3, 75.2, 65.2, 40.1, 35.6, 32.3, 26.8, 25.9, 18.3, 16.0, –5.3, –5.5; **HRMS** (ES^+, *m/z*): Calculated 337.1806 ($C_{16}H_{30}NaO_4Si$); Found 337.1806; **$[\alpha]_D^{22}$** +2.2 (*c* 1.0, CH_2Cl_2).

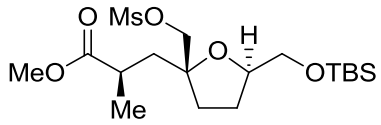
(*R*)-Methyl 3-((2*R*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-(hydroxymethyl) tetrahydrofuran-2-yl)-2-methylpropanoate, 485



To a solution of *TBS-lactone* **484** (200 mg, 0.63 mmol) in methanol (3 mL) was added sodium methoxide (0.5M in methanol, 0.12 mL, 0.06 mmol). The resulting solution was stirred for 3 h before being carefully neutralised with Amberlite IR-120(H) ion exchange resin. The resulting mixture was filtered, and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 20:80 to 30:70] afforded *ester* **485** as an oil (207 mg, 94%). **IR** (thin film)/cm^{-1} 3466 br., 2953, 2930, 2858, 1737, 1462, 1377, 1257, 1157, 1089; **^{1}H NMR (400 MHz, D_6-DMSO)** δ_H: 4.52 (1H, t, *J* = 5.6, O*H*), 3.87-3.79 (1H, m, OC*H*), 3.55-

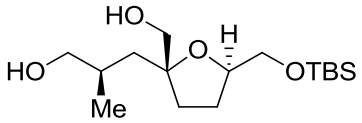
3.53 (4H, m, OCH_3 + CH_AH$_B$OTBS), 3.47 (1H, d, J = 4.8, CH$_A$$H_B$OTBS), 3.18 (1H, dd, J = 10.8, 5.6, CH_AH$_B$OH), 3.08 (1H, dd, J = 10.8, 5.6, CH$_A$$H_B$OH), 2.55-2.51 (1H, m, C$HCH_3$), 1.95-1.79 (3H, m, 2 x THF-CH_AH$_B$ + CH_AH$_B$CHCH$_3$), 1.70-1.59 (2H, m, 2 x THF-CH$_A$$H_B$), 1.50 (1H, dd, J = 14.0, 3.6, CH$_A$$H_B$CHCH$_3$), 1.08 (3H, d, J = 6.8, CHCH_3), 0.86 (9H, s, SiC(CH_3)$_3$), 0.02 (6H, s, Si(CH_3)$_2$); **^{13}C NMR (100 MHz, D$_6$-DMSO)** δ_C: 177.6, 85.6, 80.7, 67.6, 66.4, 52.0, 41.5, 35.5, 32.2, 28.2, 26.7, 19.8, 18.9, –4.5; **HRMS** (ES$^+$, *m/z*): Calculated 369.2068 ($C_{17}H_{34}NaO_5Si$); Found 369.2066; **$[\alpha]_D^{22}$** +1.2 (*c* 1.0, CH_2Cl_2).

(*R*)-Methyl 3-((2*R*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-(((methylsulfonyl)oxy)methyl)tetrahydrofuran-2-yl)-2-methylpropanoate, 486



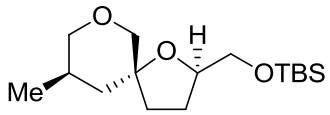
To a solution of *ester* **485** (160 mg, 0.46 mmol) in pyridine (1.00 mL) was added methanesulfonyl chloride (142μL, 1.85 mmol). The resultant solution was stirred for 16 h before the solvent was removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 20:80 to 30:70] afforded *mesylate* **486** as an oil (168 mg, 86%). **IR** (thin film)/cm^{-1} 2953, 2931, 2858, 1735, 1462, 1357, 1253, 1175, 1093; **^{1}H NMR (400 MHz, CDCl$_3$)** δ_H: 4.08-3.98 (3H, m, OCH + CH$_2$OMs), 3.66 (3H, s, OCH_3), 3.64-3.52 (2H, m, CH_2OTBS), 3.05 (3H, s, SO$_2$CH_3), 2.59 (1H, dqd, J = 10.4, 6.8, 3.2, CH(CH$_3$)CO$_2$Me), 2.22 (1H, dd, J = 14.4, 10.4, CH_AH$_B$CHCH$_3$), 2.02-1.77 (4H, m, 2 x THF-CH_2), 1.60 (1H, dd, J = 14.4, 3.2, CH$_A$$H_B$CHCH$_3$), 1.20 (3H, d, J = 6.8, CH(CH_3)CO$_2$Me), 0.89 (9H, s, SiC(CH_3)$_3$), 0.05 (6H, s, Si(CH_3)$_2$); **^{13}C NMR (100 MHz, CDCl$_3$)** δ_C: 177.6, 83.3, 81.7, 73.8, 65.8, 52.1, 41.0, 38.0, 35.7, 32.9, 27.9, 26.4, 19.6, 18.8, –4.93; **HRMS** (ES$^+$, *m/z*): Calculated 447.1843 ($C_{18}H_{36}NaO_7SSi$); Found 447.1846; **$[\alpha]_D^{22}$** +3.7 (*c* 1.0, CH_2Cl_2).

(*R*)-3-((2*R*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-(hydroxymethyl) tetrahydrofuran-2-yl)-2-methylpropan-1-ol, 487



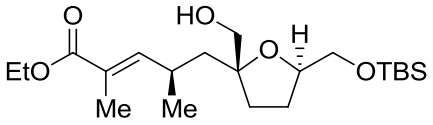
To a solution of lithium aluminium hydride (21 mg, 0.56 mmol) in tetrahydrofuran (2.00 mL) at –78 ^{o}C was added *mesylate* **486** (30 mg, 0.07 mmol) in tetrahydrofuran (1.00 mL). The resulting mixture was warmed to room temperature over 16 h before ethyl acetate (3 mL) was added. Water (5 mL) was added, and the resulting mixture extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 40:60 to 60:40] afforded *diol* **487** as an oil (17 mg, 75%). **IR** (thin film)/cm^{-1} 3394 br., 2954, 2929, 2859, 1463, 1255, 1044; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 4.23-4.16 (1H, m, OC*H*), 3.91 (1H, dd, *J* = 11.2, 2.8, CH_AH$_B$OTBS), 3.58 (1H, dd, *J* = 11.2, 2.0, CH$_A$$H_B$OTBS), 3.56-3.49 (2H, m, CCH_AH$_B$OH + CHCH_AH$_B$OH), 3.40 (1H, d, *J* = 11.2, CCH$_A$$H_B$OH), 3.34 (1H, dd, *J* = 10.0, 7.6, CHCH$_A$$H_B$OH), 3.28 (1H, br. s, 1 x O*H*), 2.38-2.18 (1H, m, C*H*CH$_3$), 2.10-2.02 (1H, m, THF-CH_AH$_B$), 1.96-1.80 (3H, m, THF-CH_2 + THF-CH$_A$$H_B$), 1.73 (1H, dd, *J* = 14.8, 6.8, CCH_AH$_B$CHCH$_3$), 1.64 (1H, br. s, 1 x O*H*), 1.38 (1H, dd, *J* = 14.8, 3.6, CCH$_A$$H_B$CHCH$_3$), 0.96 (3H, d, *J* = 6.8, CHCH_3), 0.92 (9H, s, SiC(CH_3)$_3$), 0.10 (6H, s, Si(CH_3)$_2$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 87.1, 81.0, 70.6, 69.5, 65.0, 41.6, 33.5, 31.6, 30.1, 27.9, 26.4, 20.0, 19.0, –5.1, –5.1; **HRMS** (ES$^+$, *m/z*): Calculated 341.2119 ($C_{16}H_{34}NaO_4Si$); Found 341.2110; $[\alpha]_D^{22}$ +8.3 (*c* 0.5, CH_2Cl_2).

tert-Butyldimethyl(((2*R*,5*R*,9*R*)-9-methyl-1,7-dioxaspiro[4.5]decan-2-yl)methoxy)silane, 488



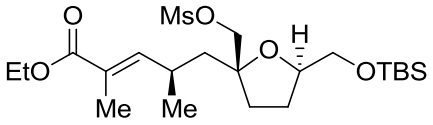
To a stirred solution of *mesylate* **486** (40 mg, 0.09 mmol) in 1,2-dichloroethane (1 mL) at 60 ^{o}C was added super-hydride® (1.0M in tetrahydrofuran, 0.75 mL, 0.75 mmol). The resulting solution was stirred at 60 ^{o}C for 3 h before a saturated solution of ammonium chloride (2 mL) was added. The resultant mixture was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers washed with brine (10 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 5:95 to 10:90] afforded *tetrahydropyran* **488** as an oil (22 mg, 78%). **IR** (thin film)/cm^{-1} 2954, 2929, 2858, 1461, 1359, 1254, 1213, 1101; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 4.13-4.06 (1H, m, OC*H*), 3.87 (1H, dd, *J* = 11.2, 4.0, OCH_AH$_B$CHCH$_3$), 3.72 (1H, dd, *J* = 10.6, 4.0, CH_AH$_B$OTBS), 3.64 (1H, dd, *J* = 11.2, 2.0, OCH_AH$_B$CO), 3.53 (1H, dd, *J* = 10.6, 6.4, CH$_A$$H_B$OTBS), 3.27 (1H, d, *J* = 11.2, OCH$_A$$H_B$CO), 2.91 (1H, t, *J* = 11.2, OCH$_A$$H_B$CHCH$_3$), 2.15-1.98 (2H, m, C*H*CH$_3$ + THF-CH_AH$_B$), 1.92-1.76 (2H, m, CCH_AH$_B$CHCH$_3$ + THF-CH$_A$$H_B$), 1.70-1.62 (1H, m, THF-CH_AH$_B$), 1.59-1.50 (1H, m, THF-CH$_A$$H_B$), 1.08 (1H, t, *J* = 12.8, CCH$_A$$H_B$CHCH$_3$), 0.89 (9H, s, SiC(C$H_3$)$_3$), 0.80 (3H, d, *J* = 6.8, CHCH_3), 0.06 (6H, s, Si(CH$_3$)$_2$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 80.3, 79.5, 75.0, 74.0, 66.0, 42.7, 34.0, 27.7, 27.7, 25.9, 18.3, 17.1, –5.3, –5.4; **HRMS** (ES$^+$, *m/z*): Calculated 323.2013 ($C_{16}H_{32}NaO_3Si$); Found 341.2021; **$[\alpha]_D^{22}$** +23.4 (*c* 1.0, CH_2Cl_2).

(*R*,*E*)-Ethyl 5-((2*R*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-(hydroxymethyl) tetrahydrofuran-2-yl)-2,4-dimethylpent-2-enoate, 490



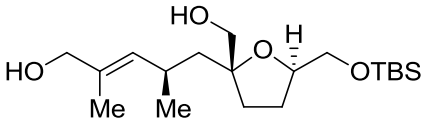
To a solution of *TBS-lactone* **484** (108 mg, 0.34 mmol) in CH_2Cl_2 (1 mL) at –78 ^oC was added diisobutylaluminium hydride (1.0M in hexanes, 0.38 mL, 0.38 mmol). The resultant mixture was stirred for 1 h at –78 ^oC before ethyl acetate (3 mL) was added, and the mixture warmed to room temperature. Rochelles solution (10 mL) was added and the mixture was stirred vigorously for 30 minutes before being extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. The crude residue was dissolved in benzene (5 mL) before (carbethoxyethylidene)triphenylphosphorane (132 mg, 0.37 mmol) was added. The resultant solution was stirred at 85 ^oC for 5 days before the solvent was removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 5:95 to 20:80] afforded *ester* **490** as an oil (102 mg, 73%). **IR** (thin film)/cm^{-1} 3468 br., 2955, 2929, 1709, 1463, 1364, 1254, 1093; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 6.65 (1H, d, J = 10.4, C=C*H*), 4.18 (2H, q, J = 7.2, CH_3CH_2O), 4.01-3.94 (1H, m, OC*H*), 3.83 (1H, dd, J = 10.6, 3.2, CH_AH_BOTBS), 3.57-3.52 (2H, m, CH_AH_BOTBS + CH_AH_BOH), 3.35 (1H, d, J = 11.2, CH_AH_BOH), 3.01 (1H, br. s, O*H*), 2.72-2.61 (1H, m, $CHCH_3$), 2.16-1.95 (2H, m, 2 x THF-CH_AH_B), 1.85 (3H, s, CH_3C=CH), 1.83-1.70 (2H, m, 2 x THF-CH_AH_B), 1.67-1.65 (2H, m, CH_2CHCH_3), 1.28 (3H, t, J = 7.2, CH_3CH_2O), 1.01 (3H, d, J = 6.8), 0.90 (9H, s, $SiC(CH_3)_3$), 0.07 (6H, s, $Si(CH_3)_2$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 168.4, 148.3, 124.9, 86.0, 79.4, 69.3, 64.7, 60.4, 44.7, 33.2, 29.5, 27.8, 25.9, 21.5, 18.5, 14.3, 12.2, –5.5, –5.6; **HRMS** (ES^+, *m/z*): Calculated 423.2537 ($C_{21}H_{40}NaO_5Si$); Found 423.2522; $[\alpha]_D^{22}$ –23.7 (*c* 1.0, CH_2Cl_2).

(*R*,*E*)-Ethyl 5-((2*R*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-(((methylsulfonyl)oxy)methyl)tetrahydrofuran-2-yl)-2,4-dimethylpent-2-enoate, 491



To a stirred solution of *ester* **490** (50 mg, 0.125 mmol) in pyridine (1 mL) was added methanesulfonyl chloride (39 µL, 0.500 mmol) and *N*,*N*-dimethylaminopyridine (1.5 mg, 0.013 mmol). The resultant solution was stirred for 4 h at room temperature before ethyl acetate (5 mL) and water (3 mL) were added. The layers were separated and the aqueous layer extracted with ethyl acetate (3 x 3 mL) before the combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 10:90 to 15:85] afforded *mesylate* **491** as a colourless oil (43 mg, 72%). **IR** (thin film)/cm^{-1} 2957, 2930, 2858, 1708, 1462, 1360, 1257, 1176, 1094; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 6.65 (1H, dd, *J* = 10.0, 1.5, C=C*H*), 4.18 (2H, q, *J* = 7.0, CH_3CH_2O), 4.03 (1H, d, *J* = 10.0, CH_AH_BOMs), 4.01-3.98 (1H, m, OC*H*), 3.96 (1H, d, *J* = 10.0, CH_AH_BOMs), 3.61 (1H, dd, *J* = 10.0, 4.5, CH_AH_BOTBS), 3.56 (1H, dd, *J* = 10.0, 4.0, CH_AH_BOTBS), 3.03 (3H, s, SO_2CH_3), 2.79-2.70 (1H, m, $CHCH_3$), 1.95-1.81 (6H, m, THF-CH_2 + $CH_AH_BCHCH_3$ + CH_3C=CH), 1.77-1.70 (2H, m, THF-CH_2), 1.32-1.23 (4H, m, $CH_AH_BCHCH_3$ + CH_3CH_2O), 1.04 (3H, d, *J* = 7.0, $CHCH_3$), 0.90 (9H, s, $SiC(CH_3)_3$), 0.06 (6H, s, $Si(CH_3)_2$); **^{13}C NMR (125 MHz, $CDCl_3$)** δ_C: 168.3, 147.9, 124.5, 83.2, 80.3, 72.5, 65.3, 60.5, 43.4, 37.3, 33.3, 29.4, 27.3, 25.9, 21.4, 18.3, 14.3, 12.3, –5.4; **HRMS** (ES^+, *m/z*): Calculated 501.2313 ($C_{22}H_{42}NaO_7SSi$); Found 501.2312; **$[\alpha]_D^{23}$** –13.8 (*c* 1.0, CH_2Cl_2).

(*R*,*E*)-5-((2*R*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-(hydroxymethyl)tetrahydrofuran-2-yl)-2,4-dimethylpent-2-en-1-ol, 492



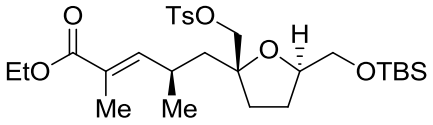
From mesylate 491:

Mesylate **491** (30 mg, 0.0628 mmol) was subjected to **General Procedure 9**. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 20:90 to 40:60] afforded *diol* **492** as a colourless oil (17 mg, 76%). **IR** (thin film)/cm^{-1} 3409 br., 2955, 2928, 2859, 1463, 1275, 1260, 1059; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 5.28 (1H, dd, *J* = 9.6, 0.8, C=C*H*), 4.06-4.00 (1H, m, OC*H*), 3.98 (2H, d, *J* = 4.4, CH=C(CH_3)CH_2OH), 3.86 (1H, dd, *J* = 10.8, 2.8, CH_AH$_B$OTBS), 3.59-3.53 (2H, m, CH$_A$$H_B$OTBS + CH_2C(CH_2R)CH_AH$_B$OH), 3.37 (1H, t, *J* = 10.4, CH_2C(CH_2R)CH$_A$$H_B$OH), 3.08 (1H, dd, *J* = 9.6, 2.8, CH=C(CH_3)CH_2O*H*), 2.62-2.51 (1H, m, C*H*(CH_3)), 2.13-1.96 (2H, m, THF-CH_2), 1.89-1.73 (2H, m, THF-CH_2), 1.69 (3H, s, CH=C(CH_3)CH_2OH), 1.63-1.55 (2H, m, CH(CH_3)CH_2), 1.41 (1H, t, *J* = 5.6, CH_2C(CH_2R)CH_2O*H*), 0.97 (3H, d, *J* = 6.8, CH(CH_3)), 0.92 (9H, s, SiC(CH_3)$_3$), 0.09 (6H, s, Si(CH_3)$_2$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 133.3, 131.9, 86.3, 79.3, 69.2, 69.0, 65.0, 45.3, 33.4, 28.3, 25.9, 22.8, 18.5, 13.7, –5.5; **HRMS** (ES^+, *m/z*): Calculated 381.2432 ($C_{19}H_{38}NaO_4Si$); Found 381.2430; **$[\alpha]_D^{22}$** –2.6 (*c* 1.0, CH_2Cl_2).

From tosylate 493:

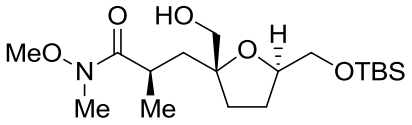
Tosylate **493** (30 mg, 0.0542 mmol) was subjected to **General Procedure 9**. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 20:90 to 40:60] afforded *diol* **492** as a colourless oil (14 mg, 72%). Data were consisten with those reported above.

(*R*,*E*)-Ethyl 5-((2*R*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-((tosyloxy)methyl)tetrahydrofuran-2-yl)-2,4-dimethylpent-2-enoate, 493



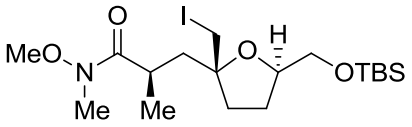
To a stirred solution of *ester* **490** (50 mg, 0.125 mmol) in pyridine (1 mL) was added *para*-toluenesulfonyl chloride (95 mg, 0.500 mmol) and *N*,*N*-dimethylaminopyridine (1.5 mg, 0.013 mmol). The resultant solution was stirred for 7 h at room temperature before ethyl acetate (5 mL) and water (3 mL) were added. The layers were separated and the aqueous layer extracted with ethyl acetate (3 x 3 mL) before the combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 10:90 to 15:85] afforded *tosylate* **493** as a colourless oil (51 mg, 74%). **IR** (thin film)/cm^{-1} 2956, 2929, 2858, 1708, 1462, 1366, 1256, 1178, 1097; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 7.76 (2H, d, *J* = 8.0, 2 x Ts-C*H*), 7.33 (2H, d, *J* = 8.0, 2 x Ts-C*H*), 6.65 (1H, dd, *J* = 10.0, 1.5, C=C*H*), 4.18 (2H, qd, *J* = 7.0, 1.5, CH_3CH_2O), 3.92-3.86 (1H, m, OC*H*), 3.79 (1H, d, *J* = 9.5, CH_AH_BOTs), 3.72 (1H, d, *J* = 9.5, CH_AH_BOTs), 3.49 (2H, d, *J* = 4.5, CH_2OTBS), 2.70-2.60 (1H, m, $CHCH_3$), 2.45 (3H, s, $ArCH_3$), 1.91-1.80 (2H, m, THF-CH_2), 1.79 (3H, d, *J* = 1.5, CH_3C=CH), 1.75-1.63 (3H, m, THF-CH_2 + $CH_AH_BCHCH_3$), 1.29 (3H, t, *J* = 7.0, CH_3CH_2O), 1.25-1.25 (1H, m, $CH_AH_BCHCH_3$), 0.99 (3H, d, *J* = 7.0), 0.86 (9H, s, $SiC(CH_3)_3$), 0.01 (3H, s, 1 x $SiCH_3$), 0.00 (3H, s, 1 x $SiCH_3$); **^{13}C NMR (125 MHz, $CDCl_3$)** δ_C: 168.3, 148.0, 144.7, 132.8, 129.8, 127.9, 125.1, 83.1, 80.2, 72.7, 65.1, 60.4, 43.4, 32.9, 29.3, 27.3, 25.9, 21.6, 21.3, 18.3, 14.3, 12.2, –5.4, –5.5; **HRMS** (ES^+, *m/z*): Calculated 577.2626 ($C_{28}H_{46}NaO_7SSi$); Found 577.2623; $[\alpha]_D^{23}$ –16.8 (*c* 1.0, CH_2Cl_2).

(*R*)-3-((2*R*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-(hydroxymethyl)tetrahydrofuran-2-yl)-*N*-methoxy-*N*,2-dimethylpropanamide, 498



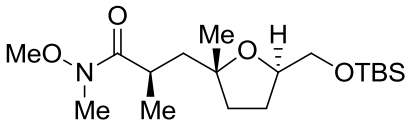
To a stirred solution of *N*,*O*-dimethylhydroxylamine hydrochloride (936 mg, 9.55 mmol) in tetrahydrofuran (10 mL) at 0 °C was added trimethylaluminium (4.78 mL, 9.55 mmol, 2.0 M in heptane). The resulting solution was stirred at 0 °C for 10 min before a solution of *lactone* **484** (600 mg, 1.91 mmol) in tetrahydrofuran (10 mL) was added dropwise. The resultant solution was stirred at 0 °C for 5 h before ethyl acetate (30 mL) and a saturated aqueous solution of potassium sodium tartrate (30 mL) were added. The layers were separated and the aqueous layer extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with a saturated aqueous solution of potassium sodium tartrate (30 mL), brine (30 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 40:60] afforded *amide* **498** as a colourless oil (590 mg, 82%). **IR** (thin film)/cm^{-1} 3458 br., 2930, 2858, 1638, 1463, 1389, 1255, 1090; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 4.09-4.02 (1H, m, OC*H*), 3.72 (3H, s, OCH_3), 3.71 (1H, dd, *J* = 10.8, 3.6, CH_AH$_B$OTBS), 3.55 (1H, dd, *J* = 10.8, 2.8, CH$_A$$H_B$OTBS), 3.39-3.31 (1H, m, CH_AH$_B$OH), 3.30-3.22 (2H, m, CH$_A$$H_B$OH + CH$_2$O*H*), 3.20 (3H, s, NC$H_3$), 3.18-3.07 (1H, m, C*H*CH$_3$), 2.25 (1H, dd, *J* = 14.4, 10.0, CH(CH$_3$)CH_AH$_B$), 2.07 (1H, ddd, *J* = 12.4, 8.4, 4.0, THF-CH_AH$_B$CH), 1.94-1.84 (2H, m, THF-CH_2C), 1.67 (1H, ddd, *J* = 12.4, 9.2, 8.4, THF-CH$_A$$H_B$CH), 1.41 (1H, dd, *J* = 14.4, 2.8, CH(CH$_3$)CH$_A$$H_B$), 1.14 (3H, d, *J* = 7.2, CHCH_3), 0.91-0.87 (9H, m, SiC(CH_3)$_3$), 0.06 (3H, s, 1 x Si(CH_3)), 0.05 (3H, s, 1 x Si(CH_3)); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 178.7, 85.4, 79.6, 67.2, 65.3, 61.4, 40.4, 34.5, 32.5, 31.0, 27.5, 25.9, 19.8, 18.4, –5.4, –5.5; **HRMS** (ES^+, *m/z*): Calculated 398.2333 ($C_{18}H_{37}NaO_5Si$); Found 398.2333; $[\alpha]_D^{23}$ –40.1 (*c* 1.0, CH_2Cl_2).

(*R*)-3-((2*R*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-(iodomethyl)tetrahydrofuran-2-yl)-*N*-methoxy-*N*,2-dimethylpropanamide, 499



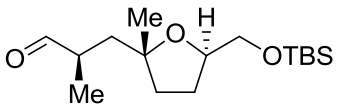
To a stirred solution of *amide* **498** (582 mg, 1.55 mmol) in toluene (16 mL) was added triphenylphosphine (813 mg, 3.10 mmol), imidazole (211 mg, 3.10 mmol) and iodine (667 mg, 2.64 mmol) sequentially. The resulting solution was heated to 80 ^{o}C for 3 h before being cooled to room temperature. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with an aqueous solution of sodium thiosulfate (0.1 M, 50 mL), brine (100 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 20:80 to 30:70] afforded *iodide* **499** as a colourless oil (600 mg, 79%). **IR** (thin film)/cm^{-1} 2956, 2930, 2857, 1665, 1463, 1386, 1255, 1085; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 4.12-4.04 (1H, m, OC*H*), 3.72 (3H, s, OCH_3), 3.60 (2H, d, *J* = 4.4, CH_2OTBS), 3.32 (1H, d, *J* = 10.0, CH_AH$_B$I), 3.22 (1H, d, *J* = 10.0, CH$_A$$H_B$I), 3.18 (3H, s, NC$H_3$), 3.13-2.99 (1H, m, C*H*CH$_3$), 2.27 (1H, dd, *J* = 14.4, 8.8, CH(CH$_3$)CH_AH$_B$), 2.06-1.78 (5H, m, 2 x THF-CH_2 + CH(CH$_3$)CH$_A$$H_B$), 1.19 (3H, d, *J* = 6.8, CHCH_3), 0.89 (9H, s, SiC(CH_3)$_3$), 0.06 (6H, s, Si(CH_3)$_2$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 178.2, 83.4, 80.6, 65.6, 61.6, 41.7, 35.5, 32.6, 30.8, 27.8, 25.9, 19.5, 18.3, 15.9, –5.3, –5.4; **HRMS** (ES$^+$, *m/z*): Calculated 508.1350 ($C_{18}H_{36}INNaO_4Si$); Found 508.1352; $[\alpha]_D^{23}$ –10.4 (*c* 1.0, CH_2Cl_2).

(*R*)-3-((2*R*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-methyltetrahydrofuran-2-yl)-*N*-methoxy-*N*,2-dimethylpropanamide, 500



To a stirred solution of *iodide* **499** (50 mg, 0.10 mmol) in ethanol (2 mL) was added palladium on carbon (10.8 mg, 10 mol%, 10% wt) and triethylamine (14 μL, 0.010 mmol). The resulting mixture was purged argon three times and with H_2 gas five times, before being stirred under at atmosphere of H_2 for 2 h. The resulting mixture was filtered through Celite® and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 5:95 to 10:90] afforded *amide* **500** as an oil (36 mg, 97%). **IR** (thin film)/cm^{-1} 2931, 2858, 1667, 1463, 1386, 1254, 1102; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 3.98 (1H, m, OC*H*), 3.72 (3H, s, OCH_3), 3.62 (1H, dd, *J* = 10.4, 4.8, CH_AH$_B$OTBS), 3.52 (1H, dd, *J* = 10.4, 5.6, CH$_A$$H_B$OTBS), 3.18 (3H, s, NC$H_3$), 3.16-3.07 (1H, m, C*H*CH$_3$), 2.09 (1H, dd, *J* = 14.0, 8.8, CH(CH$_3$)CH_AH$_B$), 2.01-1.90 (1H, m, THF-CH_AH$_B$), 1.83-1.59 (3H, m, THF-CH$_A$$H_B$ + THF-CH_2) 1.51 (1H, dd, *J* = 14.0, 3.6, CH(CH$_3$)CH$_A$$H_B$), 1.18-1.12 (6H, m, CH(CH_3) + CCH_3), 0.89 (9H, s, SiC(CH_3)$_3$), 0.05 (6H, s, Si(CH_3)$_2$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 178.9, 82.8, 79.2, 66.3, 61.4, 44.0, 37.6, 31.2, 28.2, 26.4, 25.9, 19.7, 18.4, –5.3, –5.3; **HRMS** (ES^+, *m/z*): Calculated 382.2384 ($C_{18}H_{37}NNaO_4Si$); Found 382.2384; $[\alpha]_D^{23}$ –12.2 (*c* 1.0, CH_2Cl_2).

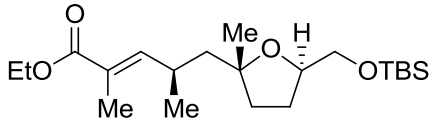
(*R*)-3-((2*R*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-methyltetrahydrofuran-2-yl)-2-methylpropanal, 501



To a stirred solution of *amide* **500** (40 mg, 0.11 mmol) in tetrahydrofuran (2.0 mL) at –78 °C was added diisobutylaluminium hydride (0.220 mL, 0.220 mmol, 1.0M in hexanes). The

resulting solution was stirred at –78 °C for 3 h before being quenched with ethyl acetate (5 mL). The resulting mixture was warmed to room temperature before a saturated aqueous solution of potassium sodium tartrate (5 mL) was added. The layers were separated and the aqueous layer extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with brine (15 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 5:95 to 10:90] afforded *aldehyde* **501** as a colourless oil (28 mg, 84%). **IR** (thin film)/cm^{-1} 2958, 2930, 2858, 1724, 1462, 1375, 1252, 1097; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 9.41 (1H, d, *J* = 4.0, C*H*=O), 3.83-3.75 (1H, m, OC*H*), 3.56-3.53 (2H, m, CH_2OTBS), 2.50-2.40 (1H, m, C*H*(CH_3)), 2.08 (1H, dd, *J* = 14.4, 9.6, C$H_A$$H_BCHCH_3$), 1.91-1.64 (4H, m, 2 x THF-CH_2), 1.55 (1H, dd, *J* = 14.4, 3.6, C$H_A$$H_BCHCH_3$), 1.20 (3H, s, CC$H_3$), 1.09 (3H, d, *J* = 7.2, CH(CH_3)), 0.89 (9H, s, SiC(CH_3)$_3$), 0.05 (6H, s, Si(CH_3)$_2$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 203.9, 82.6, 79.5, 65.6, 43.1, 42.6, 36.1, 28.3, 28.0, 25.9, 18.3, 15.3, –5.3, –5.4; **HRMS** (ES^+, *m/z*): Calculated 323.2013 ($C_{16}H_{32}NaO_3Si$); Found 323.2013; $[\alpha]_D^{23}$ +11.2 (*c* 1.0, CH_2Cl_2).

(*R*,*E*)-Ethyl 5-((2*R*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-methyltetrahydrofuran-2-yl)-2,4-dimethylpent-2-enoate, 502

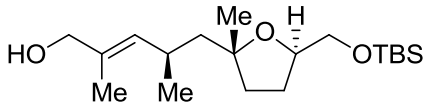


To a stirred solution of aldehyde **501** (20 mg, 0.067 mmol) in benzene (2.0 mL) was added (carbethoxyethylidene)triphenylphoshphine (36 mg, 0.10 mmol). The resulting mixture was heated to 80 °C for 36 h before being cooled to room temperature and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 3:97 to 6:94] afforded *ester* **502** as a colourless oil (20 mg, 78%). **IR** (thin film)/cm^{-1} 2958, 2930, 2858, 1711, 1463, 1366, 1252, 1099; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 6.64 (1H, dd, *J* = 10.0, 1.2,

C=C*H*), 4.19 (2H, q, *J* = 7.2, CH_3CH_2O), 3.96-3.87 (1H, m, OC*H*), 3.62 (1H, dd, *J* = 10.4, 4.0, CH_AH_BOTBS), 3.62 (1H, dd, *J* = 10.4, 5.6, CH_AH_BOTBS), 2.77-2.65 (1H, m, $CHCH_3$), 1.96-1.76 (5H, m, THF-CH_2, C=C(CH_3)CO_2Et), 1.73-1.55 (4H, m, THF-CH_2, $CH(CH_3)CH_2$), 1.30 (3H, t, *J* = 7.2, CH_3CH_2O), 1.16 (3H, s, $CH_2(CH_2R)CCH_3$), 1.03 (3H, d, *J* = 7.2, $CH(CH_3)$), 0.89 (9H, s, $SiC(CH_3)_3$), 0.05 (6H, s, $Si(CH_3)_2$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 168.5, 149.0, 124.9, 83.1, 79.1, 66.1, 60.4, 48.0, 37.5, 30.1, 28.3, 26.9, 25.9, 21.5, 18.4, 14.3, 12.3, –5.3, –5.4; **HRMS** (ES^+, *m/z*): Calculated 407.2588 ($C_{21}H_{40}NaO_4Si$); Found 407.2576;

$[\alpha]_D^{23}$ –9.2 (*c* 1.0, CH_2Cl_2).

(*R*,*E*)-5-((2*R*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-methyltetrahydrofuran-2-yl)-2,4-dimethylpent-2-en-1-ol, 503



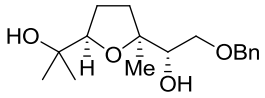
To a stirred solution of *ester* **502** (15 mg, 0.0391 mmol) in dichloroethane (1.0 mL) at –78 °C was added super hydride® (0.156 mL, 0.156 mmol, 1 M in tetrahydrofuran) dropwise. The resulting solution was stirred at –78 °C for 2 h before water (2 mL) and ethyl acetate (3 mL) were added. The resulting mixture was warmed to room temperature before the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 3 mL) and the combined organic layers washed with brine (5 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [SiO_2, EtOAc-petrol, 20:80] afforded *alcohol* **503** as a colourless oil (10.8 mg, 81%). **IR** (thin film)/cm^{-1} 3392 br., 2956, 2928, 2858, 1462, 1254, 1100, 1008, 837; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 5.27 (1H, dd, *J* = 9.6, 1.2, C=C*H*), 4.00-3.96 (2H, m, CH_2OH), 3.95-3.89 (1H, m, OC*H*), 3.61 (1H, dd, *J* = 10.4, 5.2, CH_AH_BOTBS), 3.54 (1H, dd, *J* = 10.4, 5.6, CH_AH_BOTBS), 2.63-2.52 (1H, m, $CHCH_3$), 1.97-1.87 (1H, m, THF-CH_AH_B), 1.82-1.72 (2H, m, THF-CH_AH_B + THF-CH_AH_B),

1.69 (3H, s, C=C(C*H*$_3$)CH$_2$OH), 1.66-1.48 (4H, m, THF-CH$_A$*H*$_B$ + CH(CH$_3$)C*H*$_2$ + CH$_2$O*H*), 1.18 (3H, s, CH$_2$(CH$_2$R)CC*H*$_3$), 0.97 (3H, d, *J* = 6.8, CH(C*H*$_3$)), 0.90 (9H, s, SiC(C*H*$_3$)$_3$), 0.06 (6H, s, Si(C*H*$_3$)$_2$); **^{13}C NMR (100 MHz, CDCl$_3$)** δ_C: 134.1, 131.5, 83.4, 79.0, 69.1, 66.5, 48.4, 37.2, 28.9, 28.4, 27.2, 25.9, 22.6, 18.4, 13.7, –5.3; **HRMS** (ES$^+$, *m/z*): Calculated 365.2482 ($C_{19}H_{38}NaO_3Si$); $[\alpha]_D^{23}$ –1.2 (*c* 0.5, CH_2Cl_2).

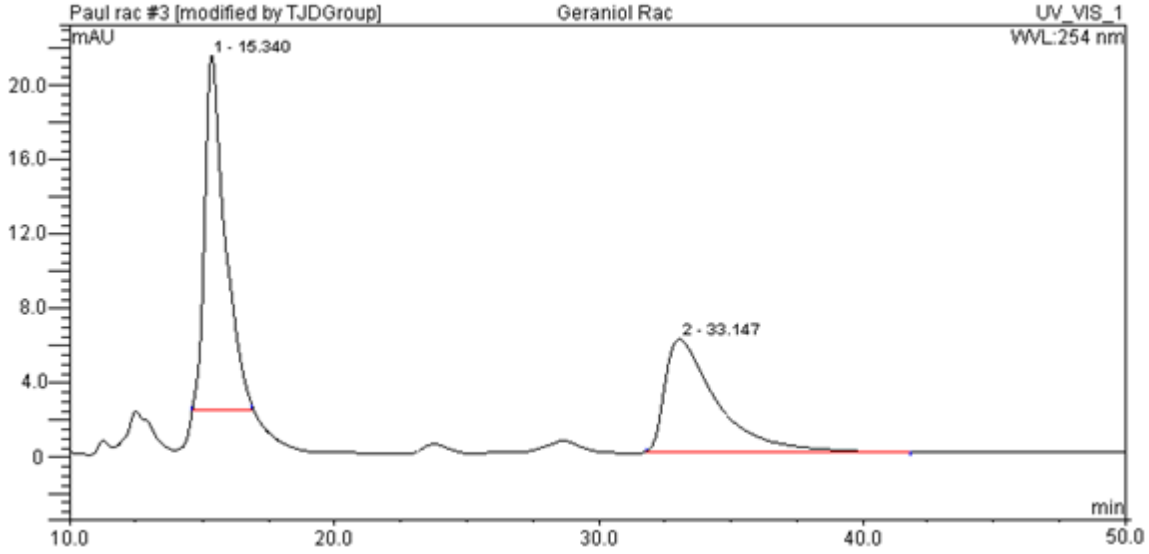
Appendix 1

HPLC and Mosher's Esters

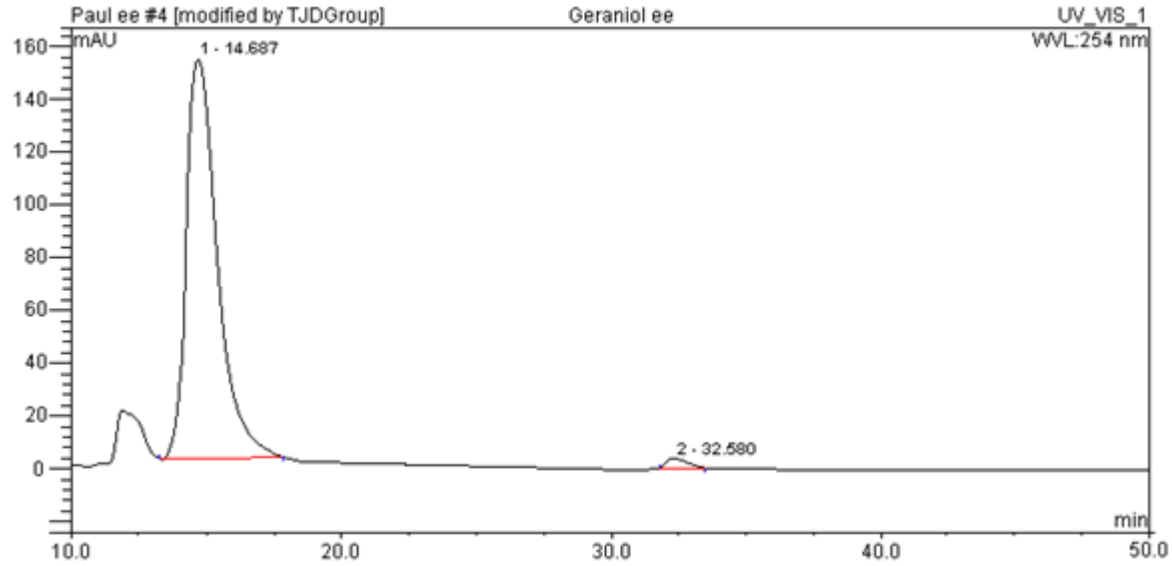
2-((2*R*,5*S*)-5-((*S*)-Benzyloxy(hydroxy)methyl)-5-methyltetrahydrofuran-2-yl)propan-2-ol, 49



Racemic:

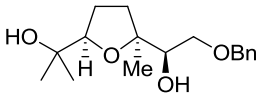


Enantioenriched:

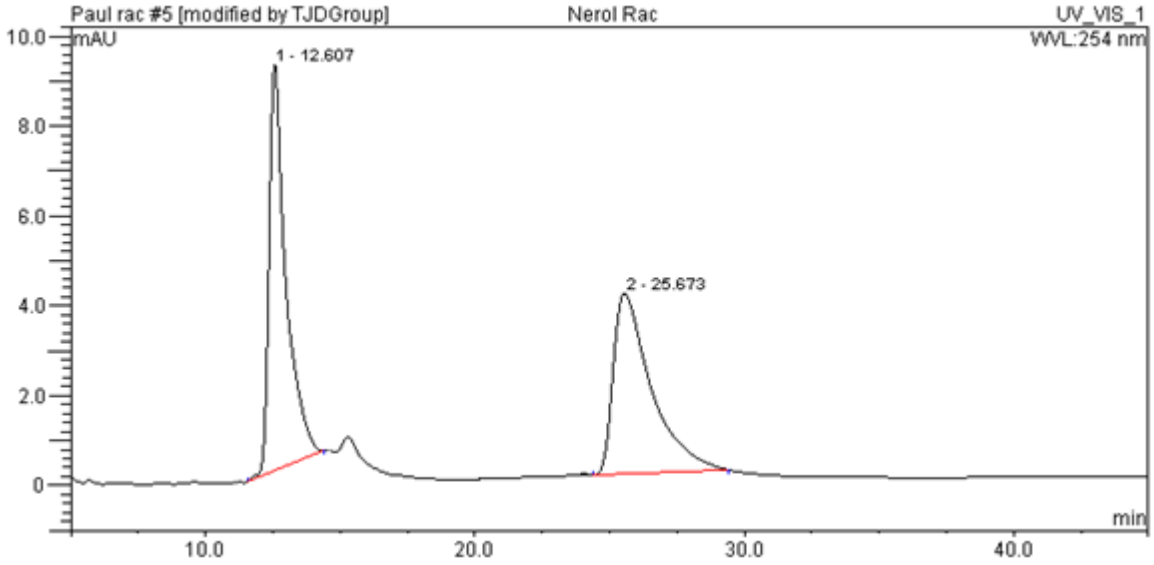


No.	Ret.Time min	Area mAU*min	Rel.Area %	Type
1	14.69	190.584	98.27	BMB*
2	32.58	3.357	1.73	BMB*
Total:		193.941	100.00	**96.5% ee**

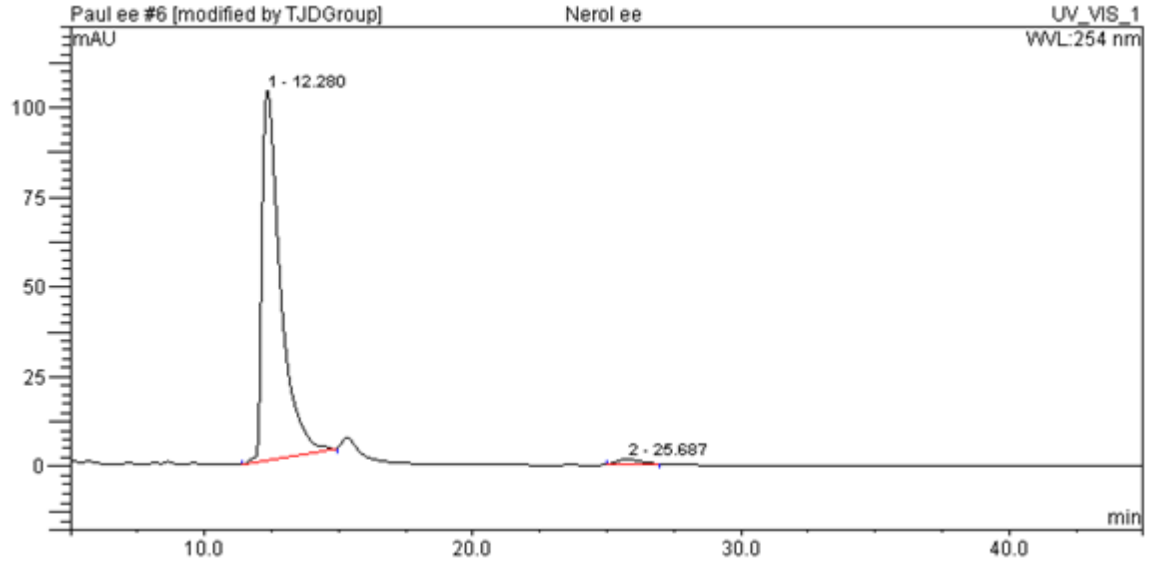
2-((2*R*,5*S*)-5-((*R*)-Benzyloxy(hydroxy)methyl)-5-methyltetrahydrofuran-2-yl)propan-2-ol, 51



Racemic:

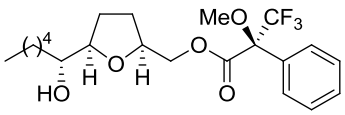


Enantioenriched:

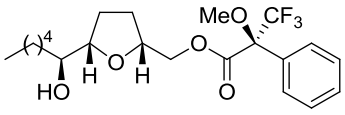


No.	Ret.Time min	Area mAU*min	Rel.Area %	Type
1	12.28	81.877	98.33	BMB*
2	25.69	1.390	1.67	BMB*
Total:		83.268	100.00	**96.7% ee**

(*S*)-((2*S*,5*R*)-5-((*R*)-1-Hydroxyhexyl)tetrahydrofuran-2-yl)methyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate, 266

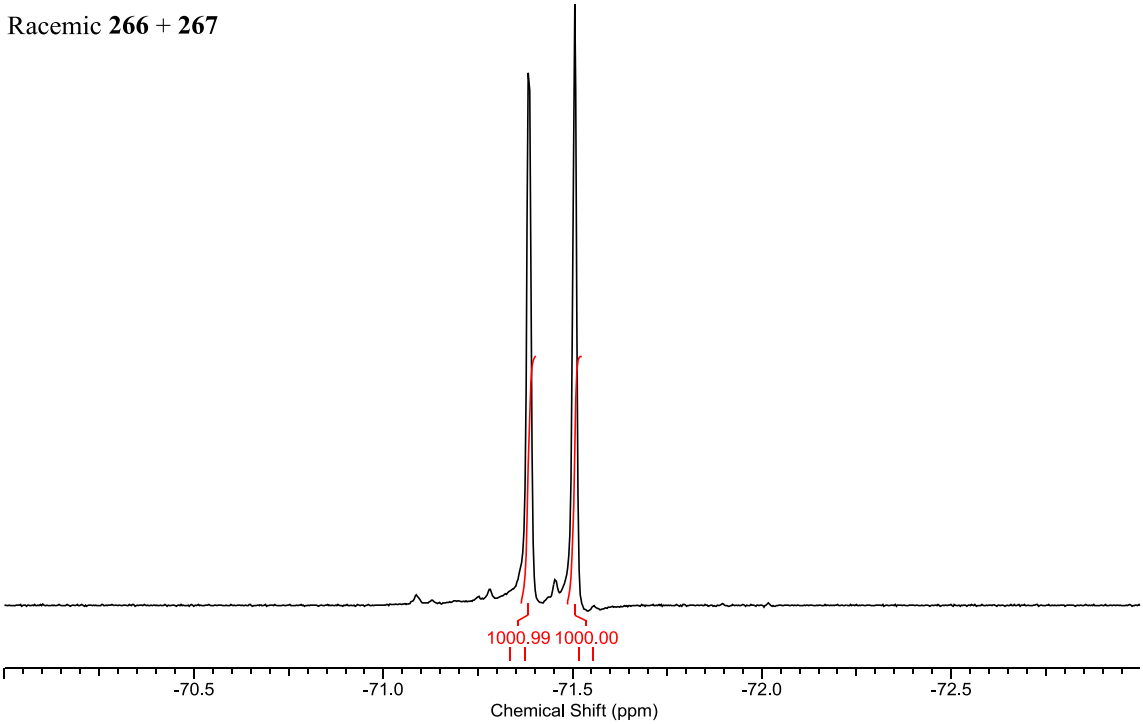


266

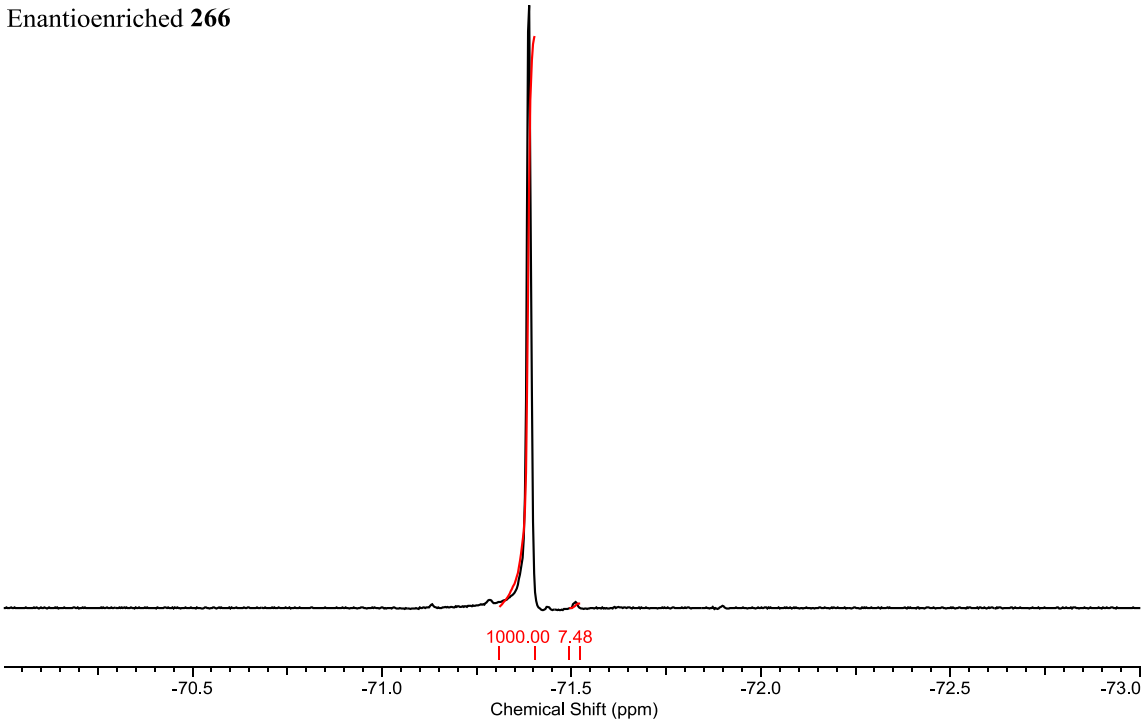


267

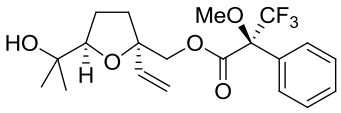
Racemic **266** + **267**



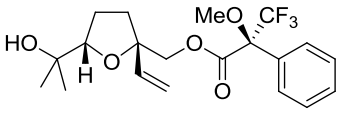
Enantioenriched **266**



(*S*)-((2*R*,5*R*)-5-(2-Hydroxypropan-2-yl)-2-vinyltetrahydrofuran-2-yl)methyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate, 269

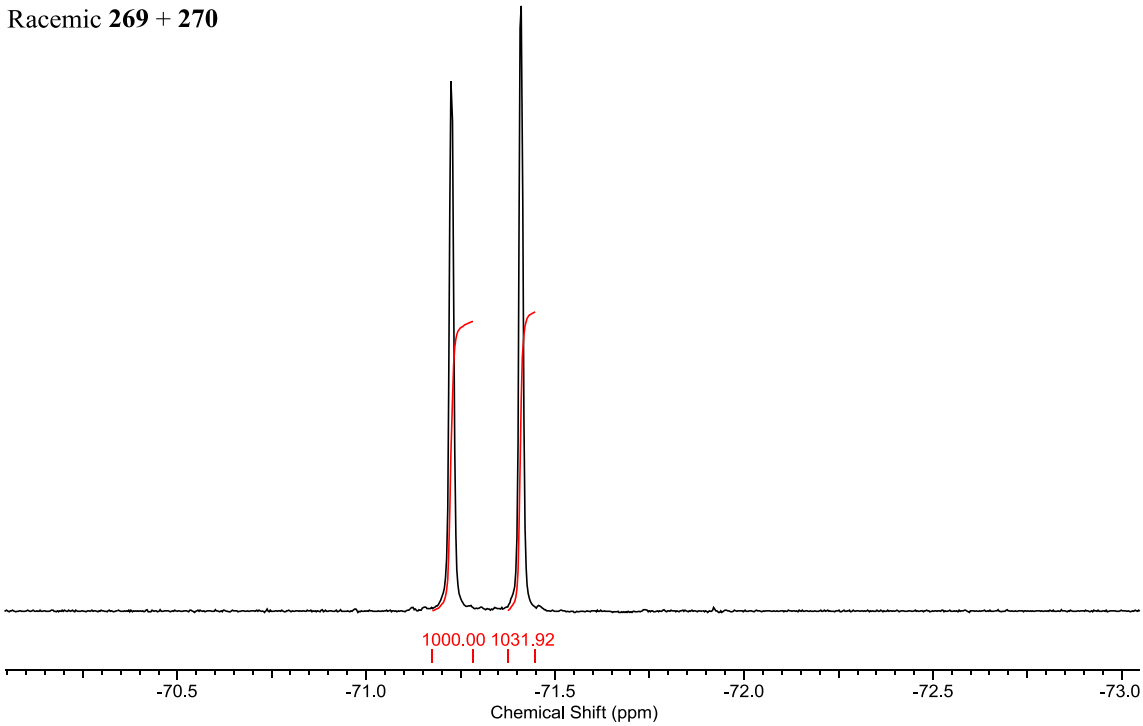


269

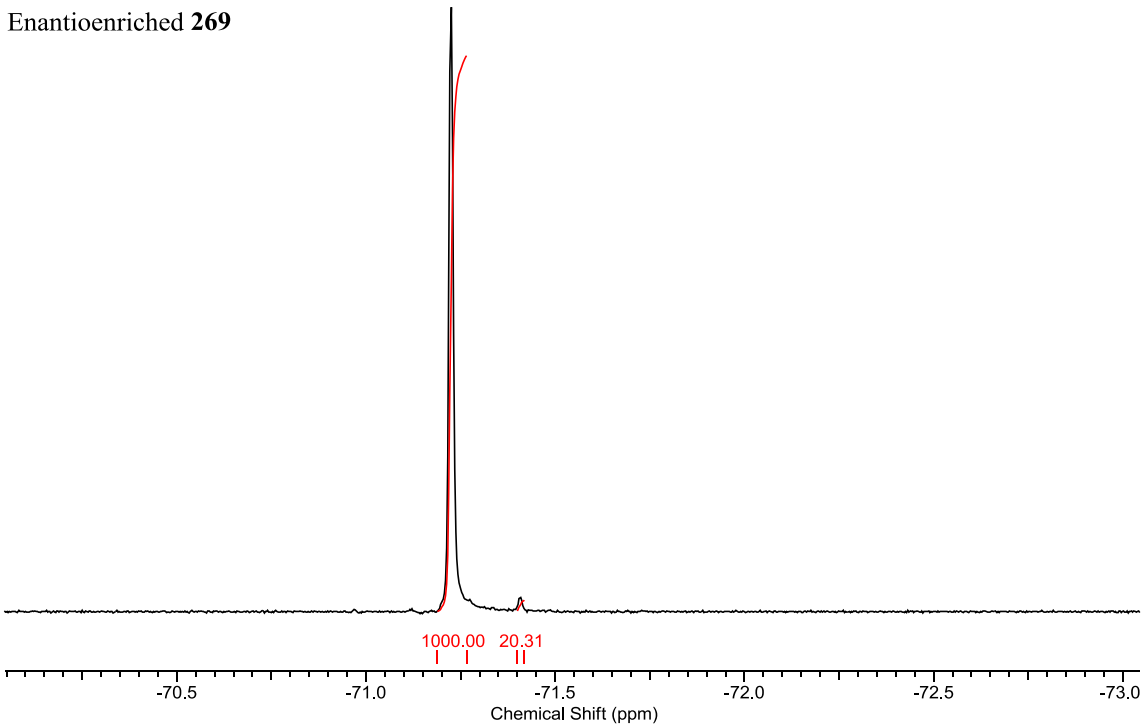


270

Racemic **269** + **270**



Enantioenriched **269**



Appendix 2

Single Crystal X-ray Diffraction

Single-crystal X-ray diffraction report for compound 441

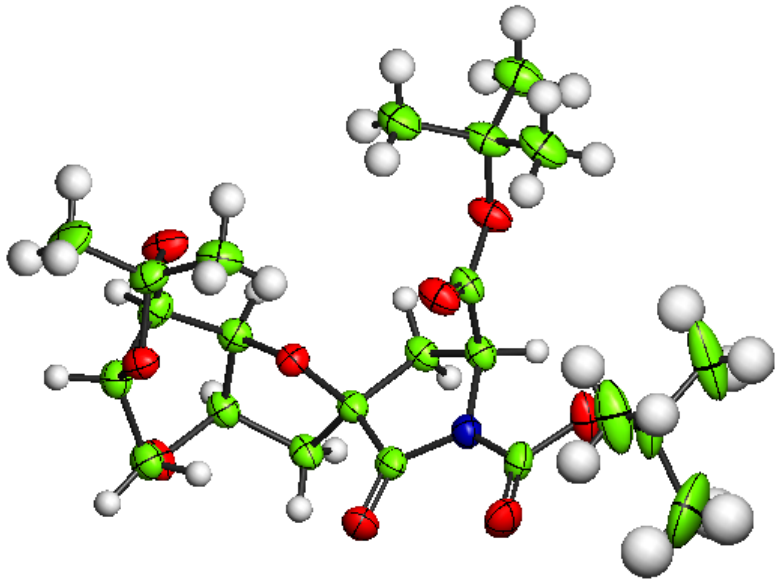


Figure A2.1 *Crystal structure of **441***

Crystals of **441** were grown from CH_2Cl_2 and Et_2O. A single crystal having dimensions approximately ***0.02*** × ***0.02*** × ***0.05 mm*** was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N_2 using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius Kappa CCD diffractometer (graphite-monochromated Mo K_α radiation, λ = 0.71073 Å). Intensity data were processed using the DENZO-SMN package.

Examination of the systematic absences of the intensity data showed the space group to be ***P 1 21 1***. The structure was solved in this space group using the direct-methods program SIR92, which located all non-hydrogen atoms. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F^2 using the CRYSTALS program suite. Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogens were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give ***R = 0.0775, wR***

=0.1436. Attached is a thermal ellipsoid plot (CAMERON) at 50 % probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

Crystal identification	005tjd11
Chemical formula	$C_{23}H_{35}N_1O_9$
Formula weight	469.53
Temperature (K)	150
Wavelength (Å)	0.6889
Crystal system	Monoclinic
Space group	P 1 21 1
a (Å)	6.003(5)
b (Å)	11.227(8)
C (Å)	18.583(15)
α (°)	90
β (°)	90.351(7)
γ (°)	90
Cell volume ($Å^3$)	1252.5(17)
Z	2
Calculated density (Mg/m^3)	1.245
Absorption coefficient (mm^{-1})	0.096
F_{000}	504
Crystal size (mm)	0.02 × 0.02 × 0.05
Description of crystal	Clear Pale Colourless Block
Absorption correction	Multi-scan
Transmission coefficients (min, max)	0.73, 1.00
θ range for data collection (°)	$1.062 \leq \theta \leq 30.844$
Index ranges	$-8 \leq h \leq 8, -14 \leq k \leq 9, -27 \leq l \leq 27$
Reflections measured	15039
Unique reflections	4038
R_{int}	0.0775
Observed reflections (I > -3σ(I))	15039
Refinement method	Full-matrix least-squares on Fsqd
Parameters refined	298
Weighting scheme	Prince 1982
Goodness of fit	0.9440

Table A2.1 *Crystal structure and refinement details*

Atom	x	y	z	U_{equiv}
O(1)	0.3893(3)	0.6939(2)	0.08293(12)	0.0376
C(2)	0.3256(5)	0.5853(4)	0.04804(17)	0.0417
O(3)	0.0858(4)	0.5862(3)	0.04614(13)	0.0485
C(4)	0.0059(5)	0.6988(4)	0.06915(16)	0.0405
C(5)	0.2129(5)	0.7782(3)	0.07256(17)	0.0377
C(6)	0.2032(5)	0.8654(3)	0.13480(18)	0.0391
O(7)	–0.0207(4)	0.9071(2)	0.14269(13)	0.0421
C(8)	–0.1714(5)	0.8174(3)	0.16788(17)	0.0363
C(9)	–0.1111(4)	0.6928(3)	0.14110(16)	0.0354
O(10)	0.0315(3)	0.6432(2)	0.19564(11)	0.0319
C(11)	–0.0665(5)	0.6777(3)	0.26295(16)	0.0322
C(12)	–0.1649(5)	0.8021(3)	0.25004(17)	0.0374
C(13)	0.1258(5)	0.6765(3)	0.31856(15)	0.0334
O(14)	0.2697(4)	0.7510(2)	0.32427(13)	0.0428
N(15)	0.0986(4)	0.5751(3)	0.36002(13)	0.0342
C(16)	–0.0810(5)	0.4989(3)	0.33338(17)	0.0347
C(17)	–0.2280(5)	0.5841(3)	0.29007(17)	0.0358
C(18)	0.0186(5)	0.3957(3)	0.29063(18)	0.0369
O(19)	0.2134(3)	0.3890(2)	0.27486(14)	0.0444
O(20)	–0.1407(4)	0.3173(2)	0.27446(15)	0.0452
C(21)	–0.0881(5)	0.2054(3)	0.2361(2)	0.0462
C(22)	0.0684(6)	0.1314(4)	0.2814(3)	0.0570
C(23)	0.0059(7)	0.2335(4)	0.1617(2)	0.0561
C(24)	–0.3155(6)	0.1465(4)	0.2302(3)	0.0575
C(25)	0.2504(5)	0.5355(3)	0.41279(16)	0.0385
O(26)	0.1698(4)	0.4366(3)	0.44195(14)	0.0513
C(27)	0.3005(6)	0.3658(5)	0.4946(2)	0.0626
C(28)	0.1554(7)	0.2576(6)	0.5064(4)	0.1026
C(29)	0.5202(7)	0.3300(6)	0.4624(3)	0.0863
C(30)	0.3325(14)	0.4367(8)	0.5632(3)	0.1226
O(31)	0.4203(4)	0.5858(3)	0.42835(13)	0.0520
C(32)	0.4037(7)	0.4810(4)	0.0922(2)	0.0552
C(33)	0.4115(7)	0.5847(5)	–0.0289(2)	0.0604

Table A2.2 *Atomic coordinates and equivalent isotropic thermal parameters ($Å^2$) of non-hydrogen atoms*

Atom	x	y	z	U_{iso}
H(41)	–0.0963	0.7308	0.0322	0.0513
H(51)	0.2334	0.8221	0.0269	0.0479
H(61)	0.2997	0.9338	0.1253	0.0497
H(62)	0.2515	0.8268	0.1792	0.0494
H(81)	–0.3238	0.8397	0.1522	0.0471
H(91)	–0.2491	0.6466	0.1368	0.0445
H(121)	–0.3115	0.8095	0.2711	0.0492
H(122)	–0.0649	0.8617	0.272	0.049
H(161)	–0.1619	0.4666	0.3743	0.0447
H(172)	–0.3044	0.5423	0.2511	0.0457
H(171)	–0.339	0.6188	0.3222	0.0459
H(222)	0.0948	0.056	0.2585	0.0858
H(221)	0.0007	0.1174	0.3276	0.0857
H(223)	0.2067	0.1723	0.2896	0.0859
H(232)	0.0116	0.1604	0.1338	0.0879
H(233)	–0.086	0.2923	0.1373	0.0879
H(231)	0.1549	0.2656	0.1666	0.0876
H(241)	–0.3046	0.0724	0.2037	0.0866
H(243)	–0.4163	0.199	0.2055	0.0866
H(242)	–0.3693	0.1307	0.2781	0.0864
H(282)	0.2289	0.2031	0.5387	0.1569
H(281)	0.1248	0.2184	0.4616	0.1571
H(283)	0.0169	0.2822	0.5275	0.1569
H(292)	0.5921	0.2733	0.4938	0.1351
H(293)	0.4944	0.2946	0.4156	0.1351
H(291)	0.6136	0.3997	0.4573	0.1349
H(303)	0.424	0.3932	0.5968	0.19
H(301)	0.1887	0.4517	0.5843	0.1899
H(302)	0.4032	0.5115	0.552	0.1899
H(321)	0.3504	0.4084	0.0699	0.0872
H(323)	0.564	0.4786	0.0932	0.0867
H(322)	0.3473	0.4854	0.1412	0.0871
H(332)	0.3485	0.5164	–0.0537	0.094
H(331)	0.3655	0.6564	–0.0535	0.0937
H(333)	0.5723	0.5785	–0.0279	0.0936

Table A2.3 *Atomic coordinates and isotropic thermal parameters ($Å^2$) of hydrogen atoms*

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	0.0304(9)	0.0427(13)	0.0396(11)	–0.0058(10)	0.0012(8)	–0.0012(9)
C(2)	0.0368(14)	0.049(2)	0.0389(15)	–0.0118(15)	0.0024(11)	–0.0014(14)
O(3)	0.0351(11)	0.0610(16)	0.0494(13)	–0.0205(13)	0.0002(9)	–0.0027(11)
C(4)	0.0324(13)	0.057(2)	0.0323(14)	–0.0016(14)	–0.0045(10)	0.0010(14)
C(5)	0.0339(13)	0.0423(19)	0.0368(15)	0.0054(13)	0.0023(11)	0.0022(13)
C(6)	0.0323(13)	0.0420(18)	0.0430(16)	0.0029(14)	0.0063(11)	–0.0022(13)
O(7)	0.0362(11)	0.0368(13)	0.0534(13)	0.0087(11)	0.0084(9)	0.0047(9)
C(8)	0.0283(12)	0.0367(17)	0.0441(15)	0.0051(13)	0.0034(11)	–0.0001(12)
C(9)	0.0256(11)	0.0418(17)	0.0389(14)	0.0001(14)	–0.0002(10)	–0.0009(12)
O(10)	0 0.0288(9)	0.0339(11)	0.0331(9)	–0.0018(8)	0.0019(7)	0.0039(8)
C(11)	1 0.0320(12)	0.0300(15)	0.0347(13)	–0.0017(12)	0.0073(10)	0.0004(11)
C(12)	0.0380(15)	0.0311(17)	0.0430(16)	0.0005(13)	0.0091(12)	0.0027(12)
C(13)	0.0328(12)	0.0351(17)	0.0323(13)	–0.0016(12)	0.0079(10)	–0.0001(12)
O(14)	0.0404(11)	0.0438(13)	0.0441(12)	–0.0003(11)	–0.0006(9)	–0.0114(10)
N(15)	0.0350(11)	0.0358(14)	0.0320(11)	0.0026(10)	0.0050(9)	–0.0008(11)
C(16)	0.0291(13)	0.0355(16)	0.0396(15)	0.0035(12)	0.0063(11)	–0.0001(11)
C(17)	0.0279(12)	0.0343(16)	0.0454(15)	0.0013(14)	0.0059(11)	–0.0006(12)
C(18)	0.0312(13)	0.0315(16)	0.0483(17)	0.0069(13)	0.0064(12)	–0.0010(12)
O(19)	0.0302(10)	0.0378(13)	0.0653(15)	–0.0036(11)	0.0099(10)	–0.0021(9)
O(20)	0.0308(10)	0.0359(13)	0.0691(15)	–0.0054(12)	0.0052(10)	–0.0045(9)
C(21)	0.0341(15)	0.0330(18)	0.072(2)	–0.0083(16)	0.0062(14)	–0.0026(13)
C(22)	0.0445(18)	0.035(2)	0.091(3)	0.003(2)	0.0036(19)	0.0006(16)
C(23)	0.058(2)	0.041(2)	0.070(3)	–0.0047(19)	0.0104(19)	–0.0060(17)
C(24)	0.0412(17)	0.049(2)	0.082(3)	-0.008(2)	0.0046(17)	–0.0060(16)
C(25)	0.0373(15)	0.050(2)	0.0282(13)	0.0049(13)	0.0079(11)	–0.0003(14)
O(26)	0.0379(11)	0.0644(18)	0.0518(14)	0.0276(13)	0.0065(10)	–0.0011(11)
C(27)	0.0421(17)	0.091(3)	0.054(2)	0.042(2)	0.0104(15)	0.004(2)
C(28)	0.041(2)	0.125(5)	0.141(5)	0.098(5)	0.003(3)	–0.002(3)
C(29)	0.045(2)	0.103(4)	0.111(4)	0.062(4)	0.025(2)	0.017(2)
C(30)	0.154(6)	0.170(8)	0.044(3)	0.034(4)	–0.002(3)	0.026(6)
O(31)	0.0505(13)	0.0667(17)	0.0386(12)	0.0015(13)	–0.0080(10)	–0.0097(13)
C(32)	0.052(2)	0.048(2)	0.066(2)	–0.0100(19)	–0.0032(18)	–0.0041(17)
C(33)	0.055(2)	0.084(3)	0.0421(18)	–0.021(2)	0.0145(15)	–0.003(2)

Table A2.4 *Anisotropic thermal parameters ($Å^2$)*

Bond	Angle	Bond	Angle
C(2) – O(1) – C(5)	107.9(2)	**C(11) – C(13) – O(14)**	125.7(3)
O(1) – C(2) – O(3)	105.6(3)	**C(11) – C(13) – N(15)**	106.8(3)
O(1) – C(2) – C(32)	109.5(3)	**O(14) – C(13) – N(15)**	127.4(3)
O(3) – C(2) – C(32)	109.1(3)	**C(13) – N(15) – C(16)**	112.5(2)
O(1) – C(2) – C(33)	109.7(3)	**C(13) – N(15) – C(25)**	124.7(3)
O(3) – C(2) – C(33)	108.7(3)	**C(16) – N(15) – C(25)**	121.7(3)
C(32) – C(2) – C(33)	113.8(4)	**N(15) – C(16) – C(17)**	103.6(3)
C(2) – O(3) – C(4)	109.8(3)	**N(15) – C(16) – C(18)**	109.2(2)
O(3) – C(4) – C(5)	104.8(2)	**C(17) – C(16) – C(18)**	115.3(3)
O(3) – C(4) – C(9)	112.7(3)	**C(16) – C(17) – C(11)**	103.9(2)
C(5) – C(4) – C(9)	111.7(3)	**C(16) – C(18) – O(19)**	123.7(3)
C(4) – C(5) – O(1)	102.7(3)	**C(16) – C(18) – O(20)**	109.6(2)
C(4) – C(5) – C(6)	111.9(3)	**O(19) – C(18) – O(20)**	126.7(3)
O(1) – C(5) – C(6)	110.8(3)	**C(18) – O(20) – C(21)**	121.0(2)
C(5) – C(6) – O(7)	109.2(3)	**O(20) – C(21) – C(22)**	109.4(3)
C(6) – O(7) – C(8)	113.5(2)	**O(20) – C(21) – C(23)**	110.0(3)
O(7) – C(8) – C(9)	112.6(2)	**C(22) – C(21) – C(23)**	112.8(3)
O(7) – C(8) – C(12)	113.0(3)	**O(20) – C(21) – C(24)**	102.1(3)
C(9) – C(8) – C(12)	102.5(3)	**C(22) – C(21) – C(24)**	110.9(3)
C(8) – C(9) – C(4)	111.0(3)	**C(23) – C(21) – C(24)**	111.1(4)
C(8) – C(9) – O(10)	105.5(2)	**N(15) – C(25) – O(26)**	108.2(3)
C(4) – C(9) – O(10)	111.3(2)	**N(15) – C(25) – O(31)**	124.4(3)
C(9) – O(10) – C(11)	105.3(2)	**O(26) – C(25) – O(31)**	127.4(3)
O(10) – C(11) – C(12)	105.6(2)	**C(25) – O(26) – C(27)**	121.7(3)
O(10) – C(11) – C(13)	105.7(2)	**O(26) – C(27) – C(28)**	102.9(3)
C(12) – C(11) – C(13)	113.5(3)	**O(26) – C(27) – C(29)**	110.0(3)
O(10) – C(11) – C(17)	111.5(3)	**C(28) – C(27) – C(29)**	110.5(5)
C(12) – C(11) – C(17)	115.9(2)	**O(26) – C(27) – C(30)**	109.7(5)
C(13) – C(11) – C(17)	104.4(2)	**C(28) – C(27) – C(30)**	111.8(5)
C(8) – C(12) – C(11)	105.3(3)	**C(29) – C(27) – C(30)**	111.6(5)

Table A2.5 *Bond angles (°) (Excluding H atoms)*

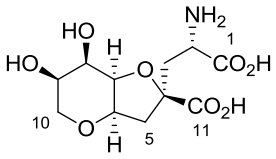
Bond	Length	Bond	Length
O(1) – C(2)	1.432(4)	**C(13) – O(14)**	1.206(4)
O(1) – C(5)	1.432(4)	**C(13) – N(15)**	1.385(4)
C(2) – O(3)	1.440(4)	**N(15) – C(16)**	1.460(4)
C(2) – C(32)	1.503(6)	**N(15) – C(25)**	1.407(4)
C(2) – C(33)	1.523(5)	**C(16) – C(17)**	1.527(4)
O(3) – C(4)	1.418(5)	**C(16) – C(18)**	1.529(5)
C(4) – C(5)	1.530(5)	**C(18) – O(19)**	1.210(4)
C(4) – C(9)	1.516(4)	**C(18) – O(20)**	1.333(4)
C(5) – C(6)	1.517(5)	**O(20) – C(21)**	1.480(5)
C(6) – O(7)	1.432(4)	**C(21) – C(22)**	1.507(6)
O(7) – C(8)	1.434(4)	**C(21) – C(23)**	1.529(6)
C(8) – C(9)	1.529(5)	**C(21) – C(24)**	1.521(5)
C(8) – C(12)	1.537(5)	**C(25)– O(26)**	1.328(4)
C(9) – O(10)	1.435(4)	**C(25) – O(31)**	1.200(4)
O(10) – C(11)	1.439(4)	**O(26) – C(27)**	1.482(5)
C(11) – C(12)	1.534(5)	**C(27) – C(28)**	1.512(7)
C(11) – C(13)	1.545(4)	**C(27) – C(29)**	1.506(6)
C(11) – C(17)	1.518(4)	**C(27) – C(30)**	1.514(9)

Table A2.6 *Bond lengths (Å) (Excluding C-H bonds)*

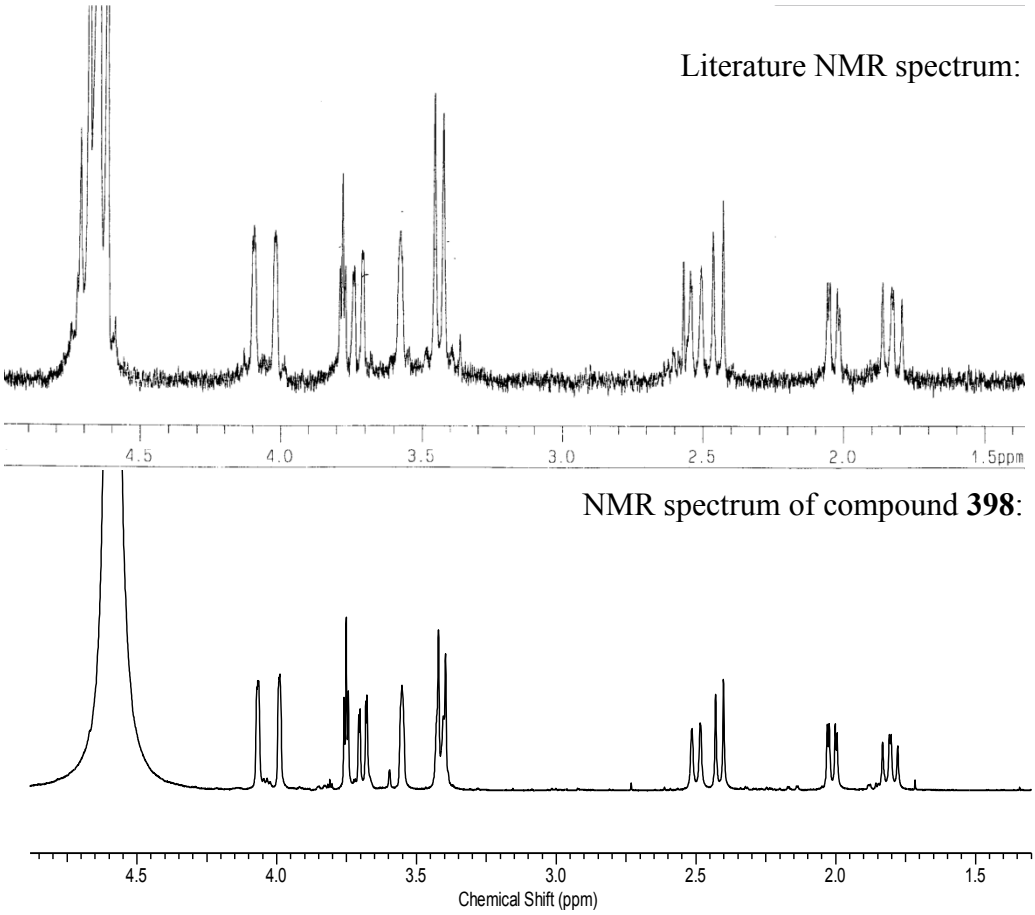
Appendix 3

Neodysiherbaine A Data

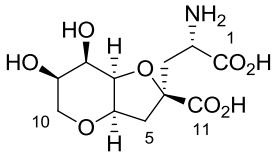
Natural neodysiherbaine A vs synthetic neodysiherbaine A

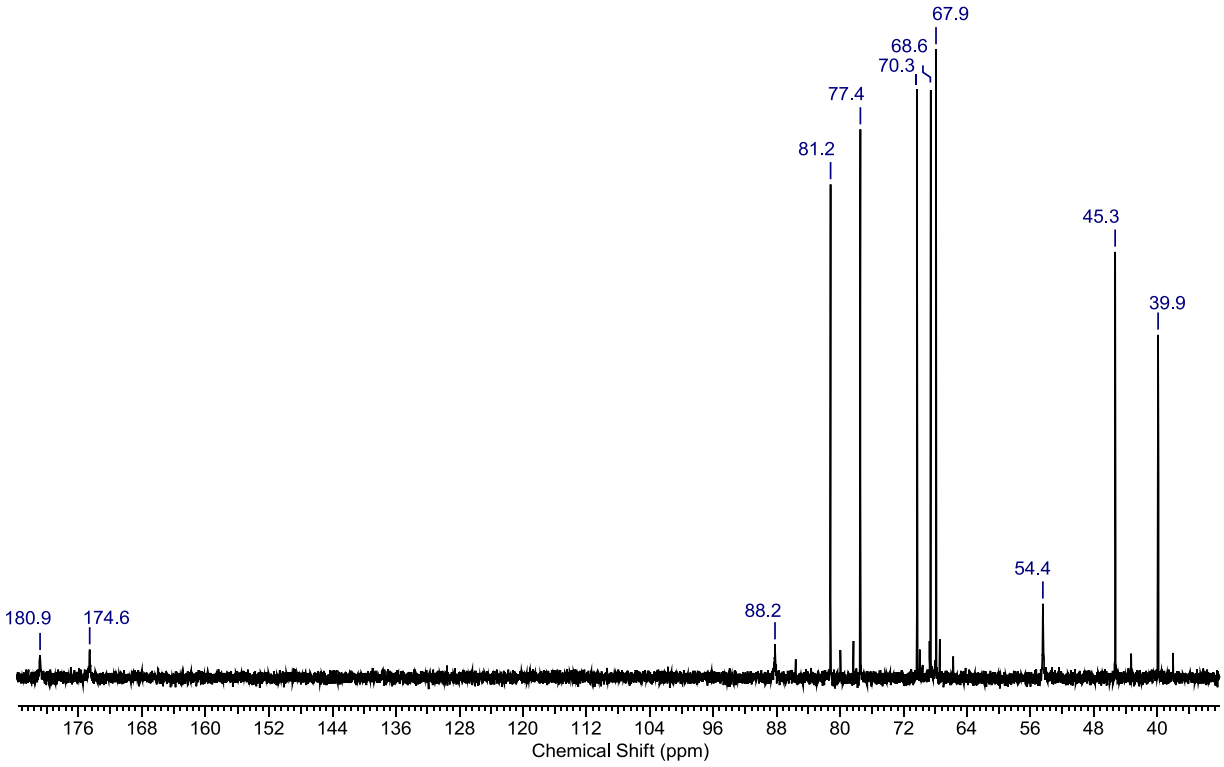


^{1}H NMR spectrum (500 MHz, D_2O)



^{13}C NMR spectrum (125 MHz, D_2O) of compound 398





Carbon number	11	1	4	7	6	8	10	9	2	5	3
Sakai (500 MHz, D_2O)	180.9	174.5	88.2	81.1	77.4	70.3	68.5	67.9	54.4	45.3	39.9
Compound 398 (500 MHz, D_2O)	180.9	174.6	88.1	81.2	77.4	70.3	68.6	67.9	54.4	45.3	39.9
Difference (Δ ppm)	0	0.1	0	0.1	0	0	0.1	0	0	0	0

Appendix 4

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