Novel Synthetic Routes Towards *trans*-THFs and Application Towards the FG Fragment of Pectenotoxin-4

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by

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Declaration

This thesis and the work of which it is a record 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.

Michael John Tucker

University of Oxford, Michaelmas Term 2013

Abstract

A thesis submitted for the degree of Doctor of Philosophy.

Michael John Tucker, Magdalen College and the Chemistry Research Laboratory, MT 2013

trans-2,5-Disubstituted tetrahydrofurans (THFs) are a common structural motif in a multitude of biologically active natural products. This thesis explores new synthetic routes for their synthesis and subsequent application towards the $C_{31\text{-}40}$ fragment of pectenotoxin-4.

Chapter 1: Introduction

This chapter reviews methods for the synthesis of *trans*-2,5-disubstituted tetrahydrofurans with a special emphasis on those that have been applied towards the synthesis of natural products.

Chapter 2: Results and Discussion

The Acyloin Coupling Reaction towards trans-THFs

A brief overview of the acyloin coupling reaction is followed by description of the aim for this part of the project, using this process as a key step towards *trans*-THFs. Work directed towards the stereoselective protonation of the bis-enolate intermediate formed during the acyloin coupling is discussed. The exploitation of $A^{1,3}$ strain was the most effective strategy found to control the diastereoselectivity in the protonation of the *bis*-enolate intermediate.

Desymmetrisation Using Sharpless Asymmetric Epoxidation towards trans-THFs

Strategy developed towards the synthesis of a 2,5-disubstituted 3-hydroxy *trans*-THF is studied. The optimisation of the synthesis of *meso*-hepta-1,6-diene-3,5-diol was examined and subsequent desymmetrisation using the Sharpless asymmetric epoxidation was explored.

Approaches towards the FG Fragment of Pectenotoxin-4

The previous synthesis of the FG fragment was reviewed. Details of the retrosynthesis to be employed for the preparation of the southern hemisphere of pectenotoxin-4 are discussed. The desymmetrisation strategy previously explored was applied towards forming the F ring of pectenotoxin-4. The $C_{31\text{-}40}$ carbon skeleton was successfully formed in 12 steps using a convergent synthesis. The elucidation of an X-ray crystal structure requires further exploration to confirm the relative and absolute configuration of the THF formed.

Chapter 3: Experimental

Full experimental procedures and characterisation of compounds are reported.

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I would like to thank Professor Timothy Donohoe for allowing me the opportunity to work in his group for the last four years. His enthusiasm and ideas that he has shared have helped me throughout the course of my DPhil.

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I sincerely appreciate the help from my proof readers Chris, Anatol, Matt and Darren for making this thesis sound well good... Thank you for your patience.

It has definitely been a memorable time working in the Donohoe group. *'I don't know half of you half as well as I should like; and I like less than half of you half as well as you deserve.'-B. Baggins.* It has been a pleasure to get to know so many people and to work in an environment that essentially provides daily entertainment. From my time here I am definitely grateful to have formed such great friendships with numerous group members (honestly, too many to list) and I will miss you all.

Finally a paragraph doesn't do justice to the amount of support my family has given me throughout my time at Oxford. Without them it would have been impossible to get through the difficult times. It is safe to say that I am forever thankful for them.

Abbreviations and Acronyms

A15	Amberlyst® 15
Ac	acetyl
acac	acetylacetone
AD	asymmetric dihydroxylation
aq.	aqueous
Ar	aryl
atm	atmosphere
BMS	borane dimethyl sulfide
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br.	broad
Bt	benzothiazole
Bu	butyl
C	Celsius
conc.	concentration
cm^{-1}	wavenumbers
CSA	camphorsulfonic acid
Cp	cyclopentadienyl
Cy	cyclohexyl
dba	dibenzylideneacetone
DBB	4,4'-di-*tert*-butyl-1,1'-biphenyl
DCE	1,2-dichloroethane
DCB	3,4-dichlorobenzyl
DCC	*N*,*N'*-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHQ	dihydroquinyl
DHQD	dihydroquinidyl
DET	diethyl tartrate
DFT	density functional theory
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutyl aluminium hydride
DIPA	diisopropylamine
DIP	diisopropyl tartrate
DIPHOS-4	1,2-bis(diphenylphosphino)ethane
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio
E	electrophile
e.e.	enantiomeric excess
equiv.	equivalents
ESI^+	electrospray ionization (positive ion detection)
Et	ethyl
g	gas
G(I)	Grubbs Catalyst, 1st Generation
G(II)	Grubbs Catalyst, 2nd Generation

h	hour(s)
HG(II)	Hoveyda-Grubbs Catalyst 2nd Generation
HFIPA	hexafluoro-2-propanol
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphorictriamide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
i	*iso*
Im	imidazole
IPA	isopropyl alcohol
IR	infra-red
J	coupling constant (Hz)
L	generic ligand
LDA	lithium diisopropylamide
M	molar
mM	millimolar
m-CPBA	*meta*- chloroperoxybenzoic acid
Me	methyl
min	minute(s)
mL	millitres
mol	mole
M.P.	melting point
MOM	methoxymethyl
m.s.	molecular sieves
n	normal
NMO	*N*-methylmorpholine-*N*-oxide
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Nu	generic nucleophile
[O]	oxidant
P_n	generic protecting group (n = number)
PBB	polybrominated biphenyl
pin	2,3-dimethylbutane-2,3-diol
Ph	phenyl
pH	$-\log_{10}[H_3O^+]$
PHAL	phthalazinyl
p*K*a	$-\log_{10}K$a
PMB	*para*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
PTX	pectenotoxin
Py	pyridine
R	generic alkyl group
R*	non-racemic alkyl group
R_L	generic large substituent
R_M	generic medium substituent
ROM	ring opening metathesis

ROMP	ring opening metathesis polymerization
R_S	generic small substituent
RSM	recovered starting material
r.t.	room temperature
SAE	Sharpless asymmetric epoxidation
SEM	2-trimethylsilylethyl ether
Super-Hydride	lithium triethylborohydride
t	*tert*
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butyl ammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBODPS	*tert*-butoxy diphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
Temp.	temperature
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
$TIPSCl_2$	1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane
TLC	thin layer chromatography
TMS	trimethylsilyl
TPS	triphenylsilyl
Ts	tosyl
X	generic halogen

Chapter 1: Introduction

1.1 Synthesis and Utility of *trans*-2,5-Disubstituted Tetrahydrofurans

trans-2,5-Disubstituted tetrahydrofurans are a prevalent structural motif found in biologically active natural products, leading to various endeavours towards the synthesis of such compounds (*Figure **1***).

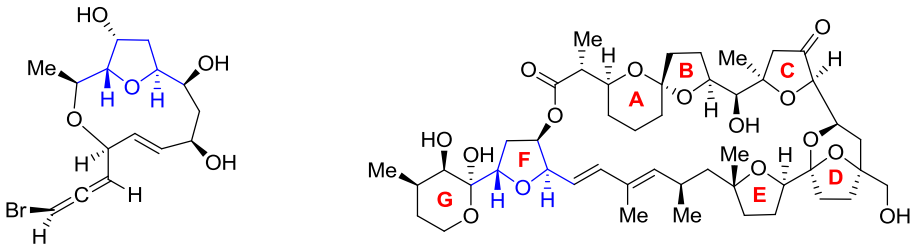


*Figure **1**: Two examples of natural products containing 2,5-disubstituted-tetrahydrofurans.*

Multiple strategies have been developed to form *trans*-THFs in high stereoselectivity, the most common of which will be discussed:

- Stereoselective C-O cyclisation (e.g. oxidative cyclisations, halocyclisation of hydroxyalkenes, cyclisation *via* opening of epoxides, Williamson etherification)
- C-C bond forming (e.g. ring closing metathesis, nucleophillic addition to THF oxonium ions)
- Rearrangement of 2,5-disubstituted THFs

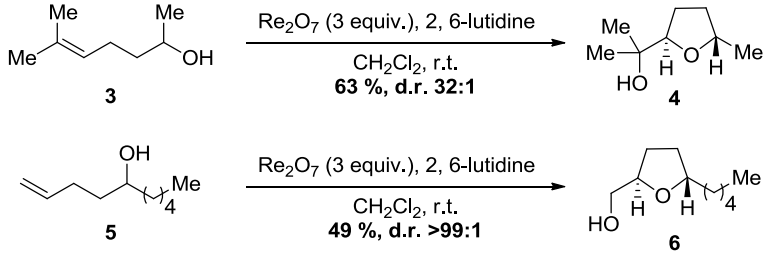
1.2 Stereoselective C-O Cyclisation

1.2.1 Oxidative Cyclisations

Oxidative cyclisation of γ-hydroxy alkenes is an attractive method to form *trans*-THFs as the stereochemistry of the hydroxy group can be transferred to the product THF.

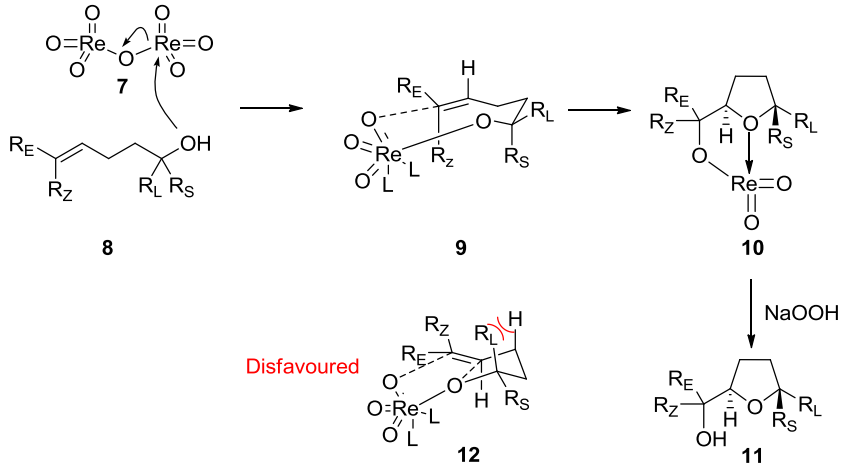
1.2.1.1 Rhenium-mediated cyclisation of γ-hydroxy alkenes

In 1992, Kennedy *et al.* reported the use of rhenium mediated cyclisations for the formation of THFs *via* an oxidative cyclisation pathway.[1] To form THFs with excellent *trans* selectivity, a stoichiometric amount of rhenium was required (*Scheme* ***1***).[2] Also a non-nucleophilic base (2,6-lutidine) was necessary to inhibit side products formed from the generation of perrhenic acid (pK_a −1.25).[3]



Scheme ***1****: Rhenium oxide mediated oxidative cyclisation.*

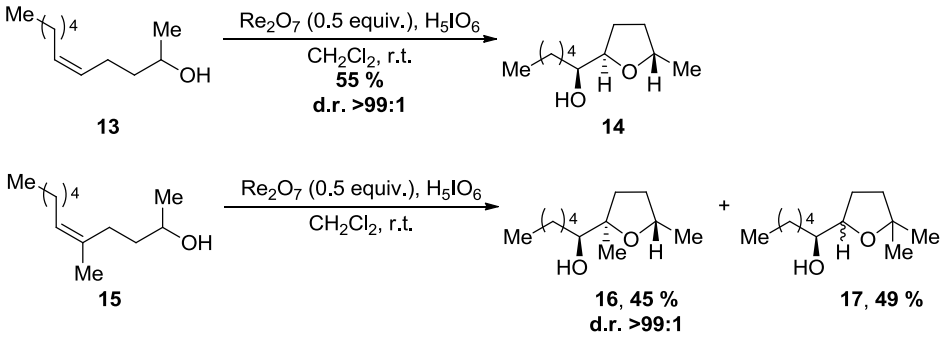
Kennedy initially proposed a [2 + 2] cycloaddition between the alkene double bond and Re=O bond to form a metalloxetane.[2] Due to spectroscopic analysis of the intermediates formed, it was later concluded that the mechanism involves a concerted [3 + 2] pericyclic reaction to form the key THF (*Scheme* ***2***).[4,5,6]



Scheme ***2****: Proposed mechanism.*

To explain the propensity for the formation of *trans*-THFs, the proposed [3 + 2] cycloaddition occurs *via* a chair-like transitition state in which the larger substituent R_L is

pseudoequatorial (**9** *vs* **12**).[6] The amount of rhenium oxide can be cut to 50 mol% when periodic acid is used as a co-oxidant with only a slight reduction in the yield.[7] The base 2,6-lutidine was no longer used due to the presence of periodic acid; thus the occurrence of side products increases, especially for trisubstituted alkenes (*Scheme **3***).



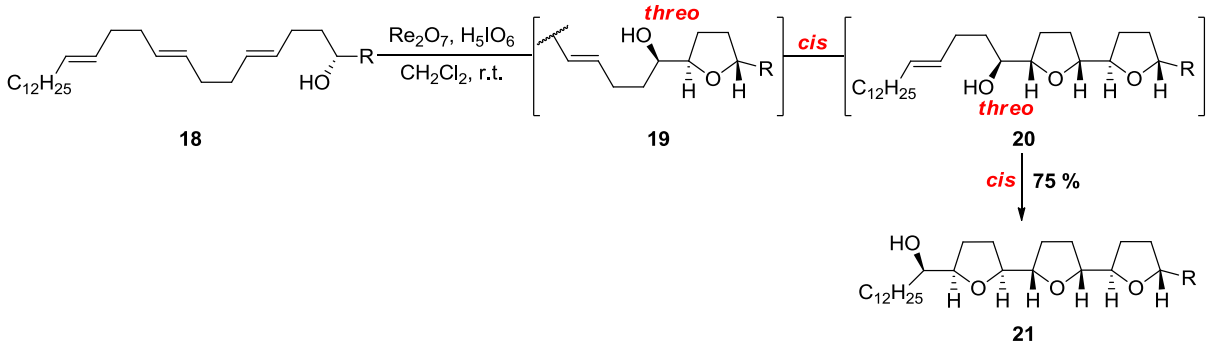
*Scheme **3**: Oxidative cyclisation of 5-hydroxyalkenes with rhenium oxide.*

Initial work carried out by Kennedy *et al.* showed through NMR spectroscopic studies that rhenium is tightly bound to the product and sodium peroxide is required to cleave the rhenium-product complex. Because of this strong binding, any turnover of rhenium is prevented and this stops the reaction being catalytic.[1]

The rhenium mediated oxidative cyclisation methodology has been applied as part of the synthesis of multiple natural products.[8-10] For example, Sinha reported the use of rhenium in the synthesis of solamin, **100**.[9] This work also explored the methodology to access natural products with multiple THF units *via* the polycyclisation of polyene alcohols. Due to the strongly coordinating effect of the rhenium to the THF product, subsequent cyclisations were slower and resulted in reduced selectivity for the formations of *trans*-THFs. After the first cyclisation, the THF alcohol product could coordinate to the rhenium in a bidentate fashion which would change the preferred conformation of the oxidative cyclisation transition state. Sinha suggested a set of rules to predict the stereochemical outcome for the *trans*/*cis* nature of the THF formed using the relative stereochemistry of the vicinal oxygen atoms:[11]

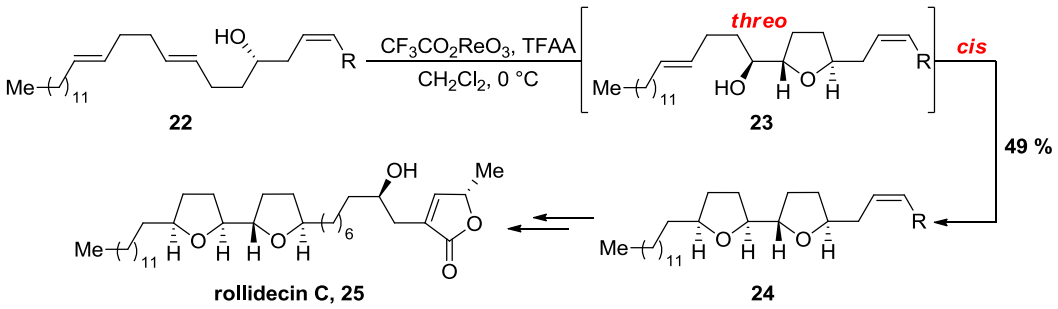
- Simple bishomoallylic alcohol, the THF formed will preferentially be *trans.*
- If the two adjacent oxygen atoms have a *threo* relationship, the next cyclisation produces a *cis*-THF ring.
- If the two adjacent oxygen atoms have an *erythro* relationship, the next cyclisation produces a *trans*-THF ring.

To test is set of rules, Sinha investigated the oxidative cyclisation of triene **18** (*Scheme **4***). Initial oxidation of *γ*-hydroxy alkene **18** gave the expected *trans*-THF **19** with the alcohol formed bearing a *threo* relationship. Thus using the rules set out by Sinha, the subsequent THF formed is *cis*. Again the alcohol formed has a *threo* relationship to the THF and the following oxidative cyclisation gave *cis* 2,5 stereochemistry.



*Scheme **4**: Applying Sinha's rules for predicting the stereochemistry of the THF formation.*

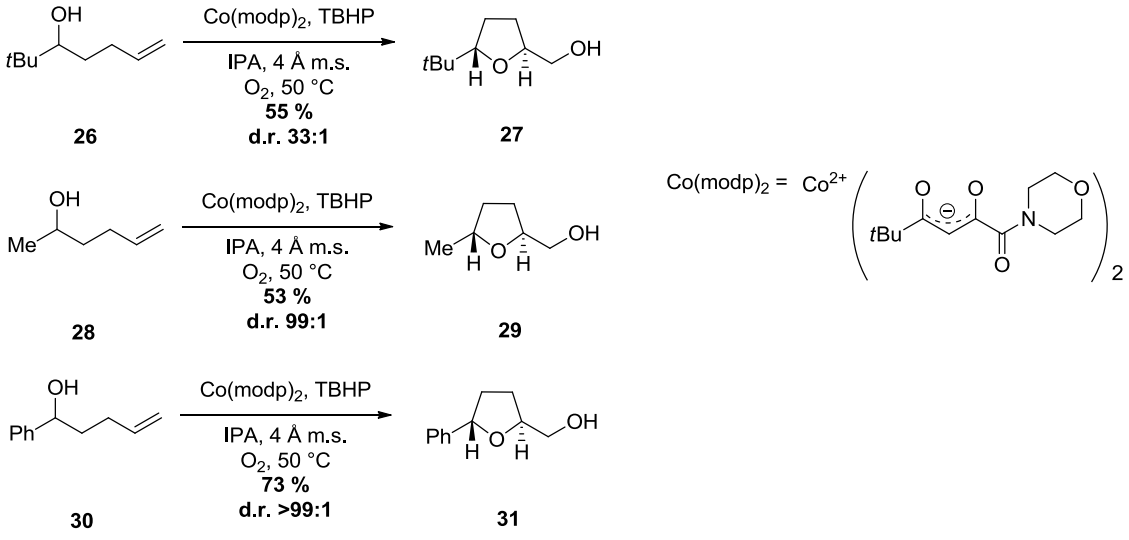
Sinha *et al.* then applied this methodology towards the synthesis of rollidecin C, **25** (*Scheme **5***).[10] The conditions were slightly modified to address the formation of undesired side products and triacyl perrhenate was chosen. It was realised that changing rhenium(VII) oxide to trifluoromethanesulfonic perrhenic anhydride disfavoured the formation of by-products formed by acidic conditions. Trifluoroacetic anhydride was also added to remove any perrhenic acid, making it unnecessary to use 2,6-lutidine.



*Scheme **5**: Application of the rhenium based cyclisation towards rollidecin C, **25**.*

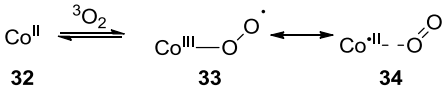
1.2.1.2 Cobalt mediated oxidative cyclisation of hydroxy olefins

Mukaiyama *et al.* reported a method to hydrate olefins using cobalt *via* an oxidation-reduction mechanism in 1990.[12] When applied to 5-hydroxyalkenes, *trans*-2,5-THFs were formed in good yields and high *trans*-selectivity. The reaction was carried out using a *β*-diketonate complex of cobalt, $Co(modp)_2$ under an oxygen atomosphere in *iso*-propanol (*Scheme **6***).



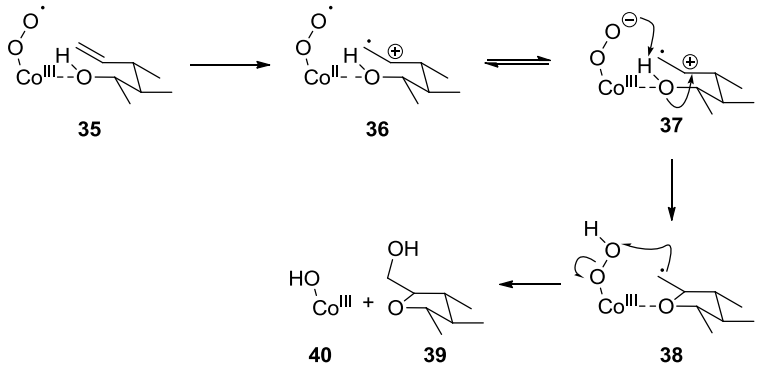
*Scheme **6**: Cobalt mediated oxidative cyclisation of 5-hydroxyalkenes.*

Hartung *et al.* proposed a mechanism for the oxidative cyclisation, *via* a radical mediated pathway.[13] It was postulated the cobalt(II) complex **34** activates bound triplet oxygen by binding as a superoxo-species (*Scheme **7***).



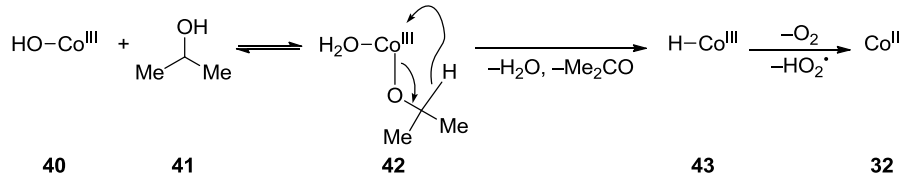
*Scheme **7**: Activation of triplet oxygen.*

The cobalt-oxygen species **34** is considered a strong Lewis acid and metal-based oxidant. Using this notion of the Lewis acidity and oxidising potential of cobalt, the complex is thought to coordinate to the hydroxy alkene which sits in a chair-like conformation in which the substituents sit in pseudo-equatorial positions to minimise diaxial strain (*Scheme **8***).



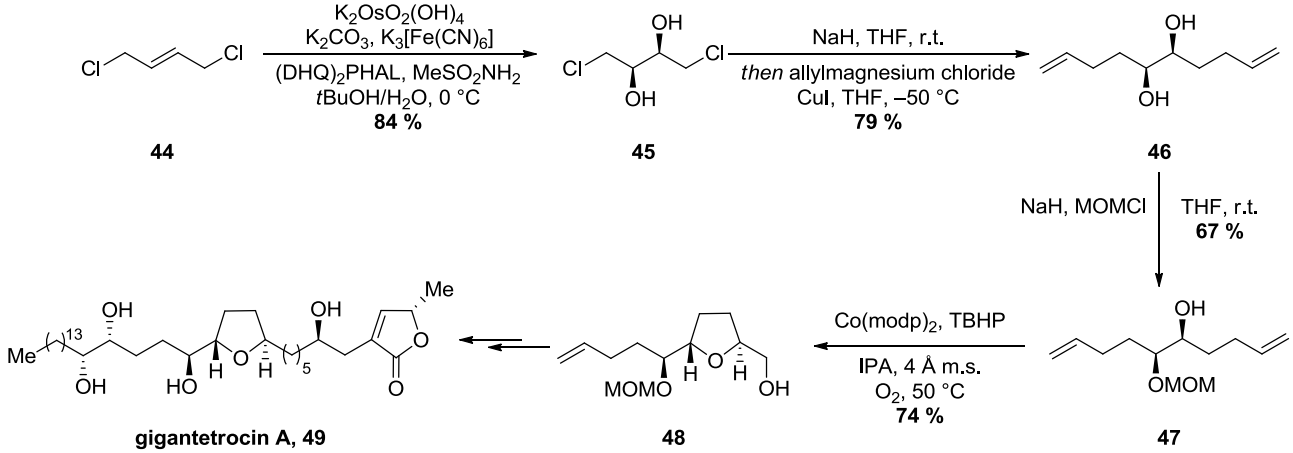
*Scheme **8**: Hartung and co-workers proposed mechanism for the cobalt mediated oxidative cyclisation.*

Cobalt(III) is a powerful oxidiser (E^{θ} = +1.84 V)[14] capable of oxidising the alkene to the corresponding radical cation **36**.[15] Stereoselective 5-*exo*-cyclisation on the cation occurs giving the *trans*-THF as well as the oxidation of Co(II) to Co(III) forming cobalt hydroperoxide **38**. The cobalt hydroperoxide bond is weak and readily cleaved, thus forming the desired hydroxyl-THF **39** and cobalt(III) hydroxide. A by-product has also been isolated whereby instead of abstracting the oxygen from the cobalt hydroperoxide species, a hydrogen from an *iso*-propanol molecule could be abstracted giving the methyl-THF product instead. Regeneration of cobalt(II) is thought to occur *via* hydride shift from a coordinated *iso*-propanol molecule giving water and acetone as by-products (*Scheme **9***).[13]



*Scheme **9**: Regeneration of cobalt(II).*

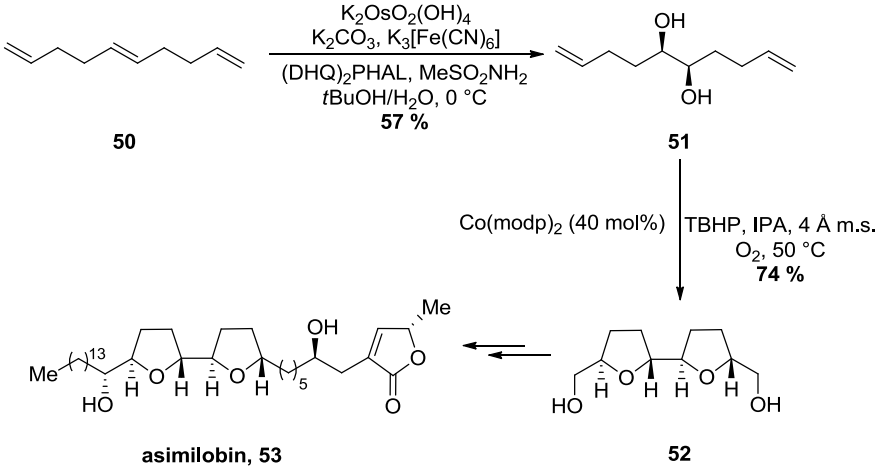
Shi *et al.* demonstrated the use of the cobalt oxidative cyclisation in the synthesis of gigantetrocin A, **49** (*Scheme **10***).[16]



*Scheme **10**: Use of cobalt oxidative cyclisation for the synthesis of gigantetrocin A, **49**.*

A Sharpless asymmetric dihydroxylation of *trans*-1,4-dichloro-2-butene **44** yielded the corresponding diol in 84% and greater than 94% e.e. The diol **45** was subsequently treated with sodium hydride, affording diepoxybutane *in situ*, followed by allylmagnesium chloride and copper(I) iodide to selectively open the epoxides at the less hindered position to give the resulting diol **46**. Desymmetrisation *via* mono-protection with MOMCl gave the precursor for the cobalt oxidative cyclisation. Thus $Co(modp)_2$ mediated oxidative cyclisation was successful in yielding the desired *trans*-THF **48** in 74%. Further manipulation of THF **48** gave gigantetrocin A, **49** in a total of 19 steps from *trans*-1, 4-dichloro-2-butene **44**.

Shi *et al.* expanded the methodology further to encompass natural products with poly *trans*-THFs such as asimilobin, **53** (*Scheme **11***).[17,18]

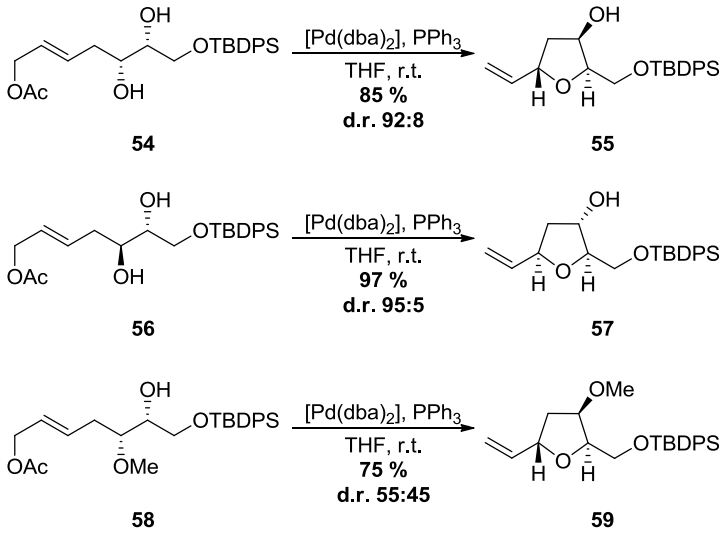


*Scheme **11**: Synthesis of asimilobin, **53**.*

Starting from triene **50**, Sharpless asymmetric dihydroxylation to the diol occurred in 57% yield and greater than 94% e.e. Exposing diol **51** to the cobalt oxidative cyclisation conditions allowed access to bis-*trans*-THF **52** in a single transformation. With this bis-THF core in hand, it was successfully functionalised to achieve the synthesis of asimilobin, **53** in 12 steps from triene **50**.

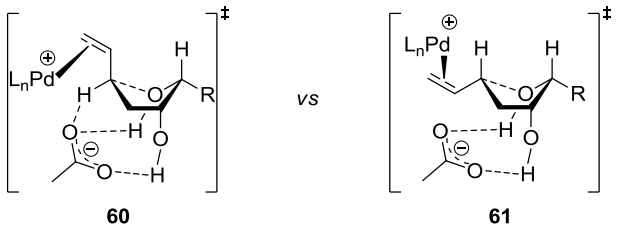
1.2.1.3 Tsuji-Trost cyclisation

Roulland *et al.* have shown the possibility of forming 2,5-disubstituted 3-hydroxy-tetrahydrofurans through the formation of a π-allyl/Pd^{II} intermediate where the acetate counterion plays a prominent directing role (*Scheme **12***).[19] *syn*-Diol **54** was successfully transformed to the corresponding *trans*-THF. Likewise the *anti*-diol **56** was converted to the *cis*-THF again giving a high diastereomeric ratio. To investigate whether the adjacent hydroxy group played a role in the high diastereoselectivity of the cyclisation, Roulland methylated the hydroxyl group. Upon treating alcohol **58** with the cyclisation conditions developed, the analogous THF **59** formed in an approximate 1:1 mixture of *trans*/*cis* isomers.



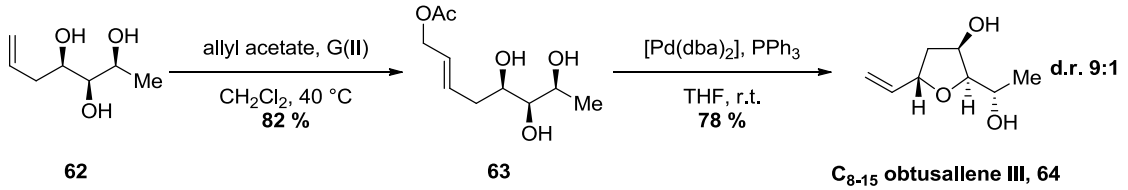
*Scheme **12**: Diastereoselective Tsuji-Trost cyclisation towards THFs.*

Using DFT calculations, Roulland proposed that the selectivity arises from noncovalent interactions involving the counterion in the transition state (*Scheme **13***).[19]



*Scheme **13**: Proposed competing transition states predicted from DFT calculations.*

Proposed transition state **60** provides an additional noncovalent bond between the counterion and the allylic hydrogen, not present in the second proposed transition state **61**. Roulland confirmed this with DFT calculations and uses this factor to explain the observed stereoselectivity. This methodology was then applied in the synthesis of the $C_{8\text{-}15}$ fragment of obtusallene III, **64** (*Scheme **14***).[19]

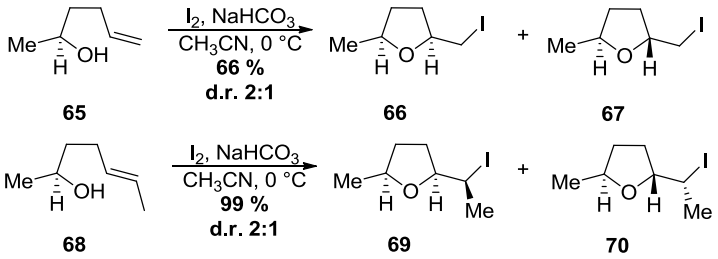


*Scheme **14**: Application of methodology towards the $C_{8\text{-}15}$ fragment of obtusallene III, **64**.*

Cross metathesis with allyl acetate yielded **63** in 82% and subsequent cyclisation to the *trans*-THF gave the $C_{8\text{-}15}$ fragment of obtusallene III, **64** in 78% yield and a diastereomeric ratio of 9:1.

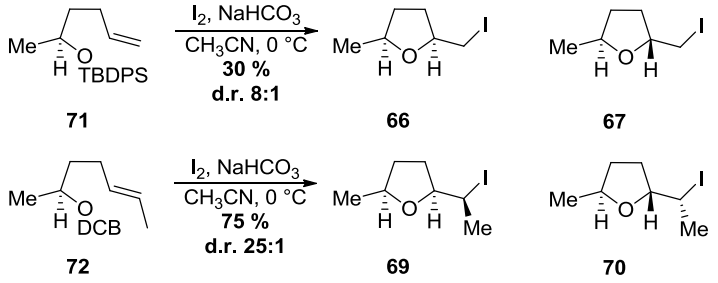
1.2.2 Halocyclisation of Hydroxyalkenes

Iodine was shown by Bartlett *et al*. to be a suitable electrophile to activate an olefin towards cyclisation of a neighboring hydroxyl group (*Scheme **15***).[20]



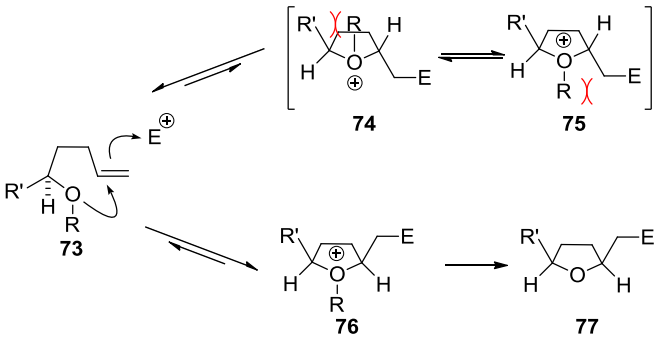
*Scheme **15**: Iodine activated cyclisation of γ-hydroxy alkenes.*

Initial cyclisation using unprotected hydroxy alkenes yielded poor stereoselectivity between the *cis* and *trans*-THF. Using a protecting group which would be hydrolysed from the oxonium ion formed upon cyclisation gave greater selectivity, albeit for the *cis*-THF (*Scheme **16***).



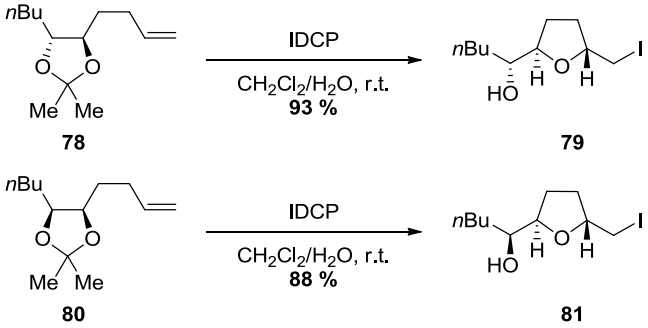
*Scheme **16**: Iodine activated cyclisation of protected γ-hydroxy alkenes.*

Bartlett proposed that the formation of the *trans*-THF is disfavoured due to the steric repulsion between the oxygen protecting group and the 2,5-substituents on the ring of **74** and **75** (*Scheme **17***).[20]



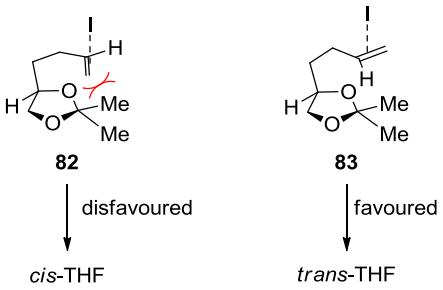
*Scheme **17**: Proposed mechanism for iodocyclisation.*

Mootoo *et al.* found that using 5,6-*O*-isopropylidines as acetal templates with iodonium dicollidine perchlorate (IDCP) allowed access to *trans*-THFs. Activation of the double bond by the iodine cation is followed by etherification by an acetal oxygen to give a THF-oxonium ion. Hydrolysis of the acetal group yields the product. Both the *erythro* and *threo* diastereoisomers give rise to *trans*-THFs (*Scheme **18***).[21]



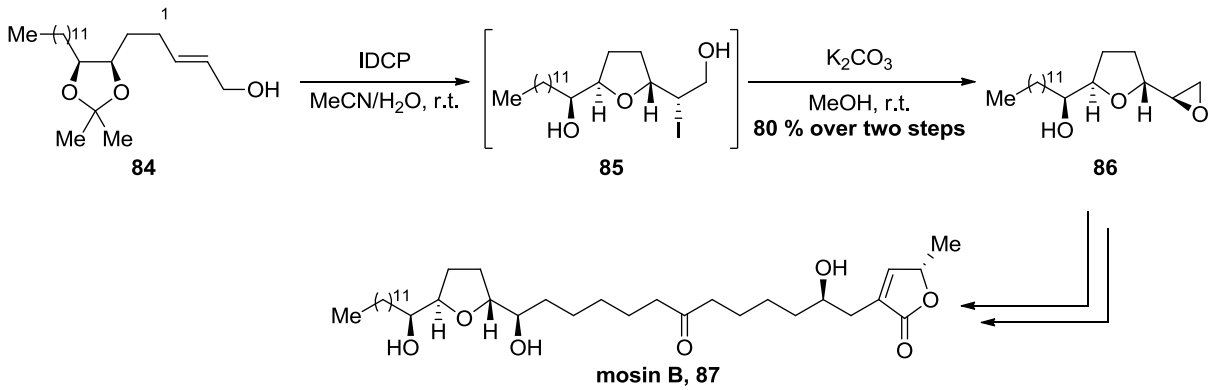
*Scheme **18**: Acetal template route to trans-THFs.*

Mootoo proposed that the stereoselectivity arises from the generation of the THF-oxonium ion. Formation of the *cis*-THF is disfavoured due to steric clashing between the methyl group of the acetonide and the alkene in **82** (*Scheme **19***).[21]



*Scheme **19**: Proposed explanation of the stereoselectivity for acetal protected iodocyclisation.*

The stereoselective cyclistion using this methodology has been applied to multiple natural products. Tanaka *et al.* reported the first synthesis of mosin B, **87** applying this method (*Scheme **20***).[22,23]



*Scheme **20**: Application of acetal template cyclisation towards mosin B, **87**.*

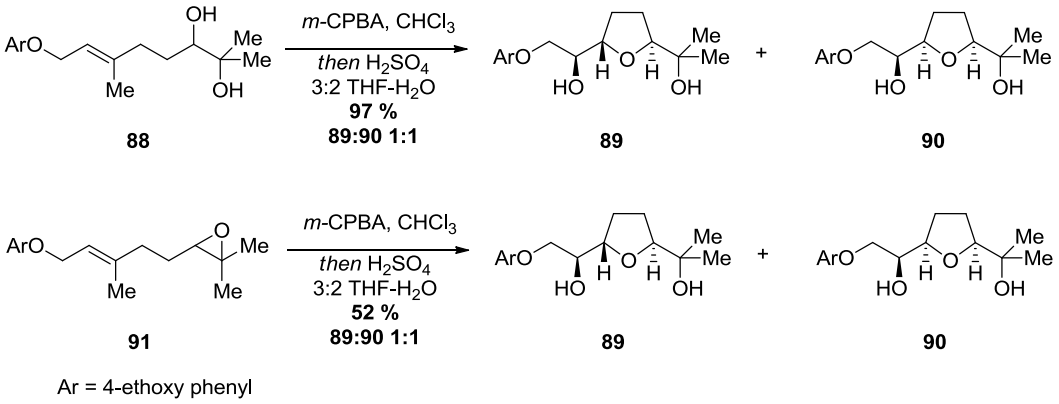
Acetal **84** was formed as a single diastereomer and was treated with IDCP to give THF **85**. Treating crude intermediate **85** with potassium carbonate, in methanol, promoted epoxidation to give **86** which was used to complete the synthesis of mosin B, **87**.

1.2.3 Cyclisation *via* Opening of Epoxides

The cyclisation of alcohols onto epoxides is an attractive method of forming THFs due to the possibility of installing epoxides stereoselectively. Thus cyclisation can be carried out in which the stereochemistry of the starting material can be transferred to the product.

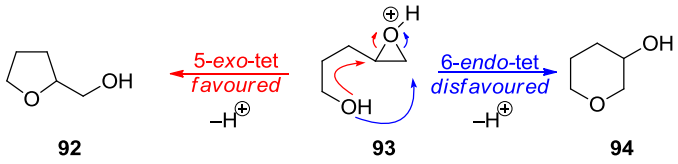
1.2.3.1 Use of *m*-CPBA

Casida *et al.* first described the intramolecular cyclisation of alcohols onto epoxides formed from *m*-CPBA.[24] Treating aryl geranyl diol **88** with *m*-CPBA gave a mixture of *cis* and *trans* isomers in approximately 1:1 ratio (*Scheme **21***).



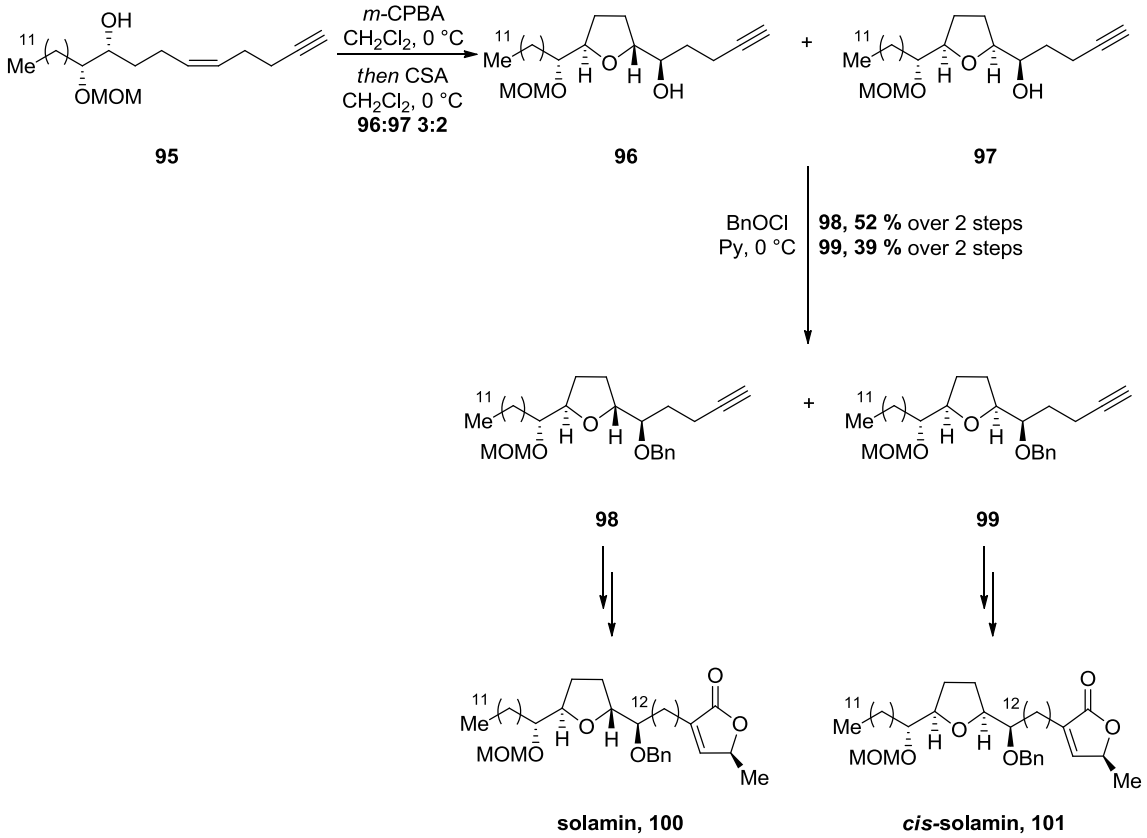
*Scheme **21**: Cyclisation of γ-hydroxy epoxides.*

The epoxide intermediate was never isolated and it was thought that it rapidly cyclised to the THF. Using Baldwin's orbital overlap explanation of ring closure, the 6-membered THP is not observed whereas the 5-membered THF is (*Scheme **22***).[25]



*Scheme **22**: Baldwin's rules for cyclisation.*

Although promising, the *m*-CPBA mediated epoxidation to form *trans*-THF is limited due to the lack of facial discrimination of the alkenes. Makebe *et al.* used the *m*-CPBA mediated epoxidation of alkene **95** to give an inseparable mixture of THFs **96** and **97** (*Scheme **23***).[26] Benzoyl protection followed by separation using preparative TLC afforded **98** and **99** which were taken further as part of the synthesis of solamin, **100** and *cis*-solamin, **101** respectively.

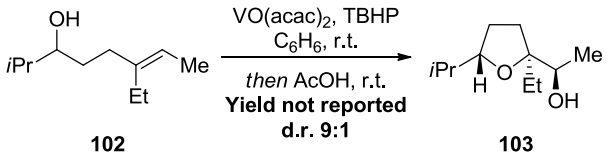


*Scheme **23**: Application towards the synthesis of solamin, **100** and cis-solamin, **101**.*

1.2.3.2 Vanadium catalysed epoxidation

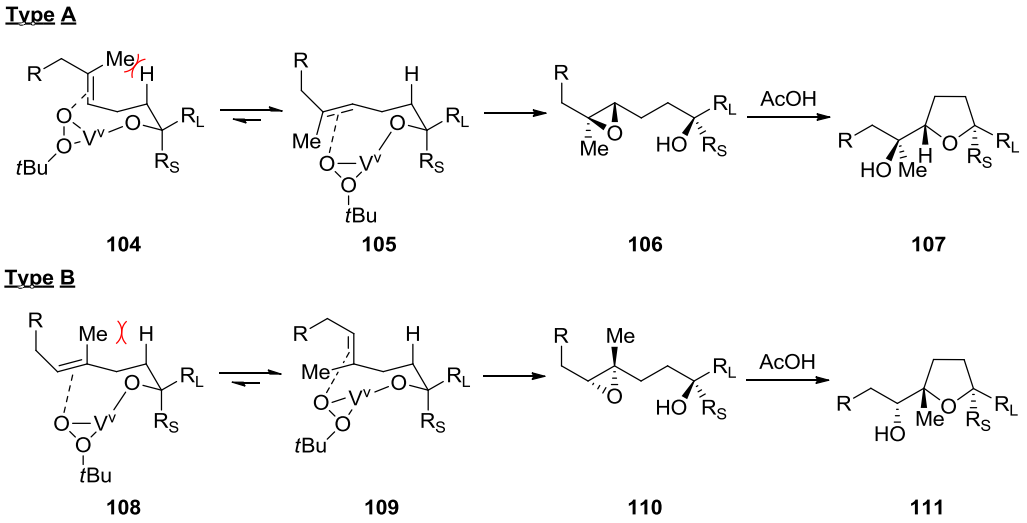
Sharpless *et al.* reported a stereo- and regioselective method to epoxidise allylic alkenes using *tert*-butyl peroxide.[27] In contrast to the non-selective epoxidation by *m*-CPBA, coordination between the alcohol and vanadium allows directed epoxidation.[28]

In 1978 Kishi and co-workers reported the synthesis of *trans*-THFs *via* the epoxidation of *δ*-hydroxy alkenes mediated by catalytic vanadium(IV) and TBHP followed by acetic acid to induce cyclisation (*Scheme **24***).[29]



*Scheme **24**: Vanadium mediated epoxidation towards THFs.*

Shirahama *et al.* extended the methodology to include further olefin substitution patterns, allowing the formation of *cis*-THFs stereoselectively (*Scheme **25***).[29]



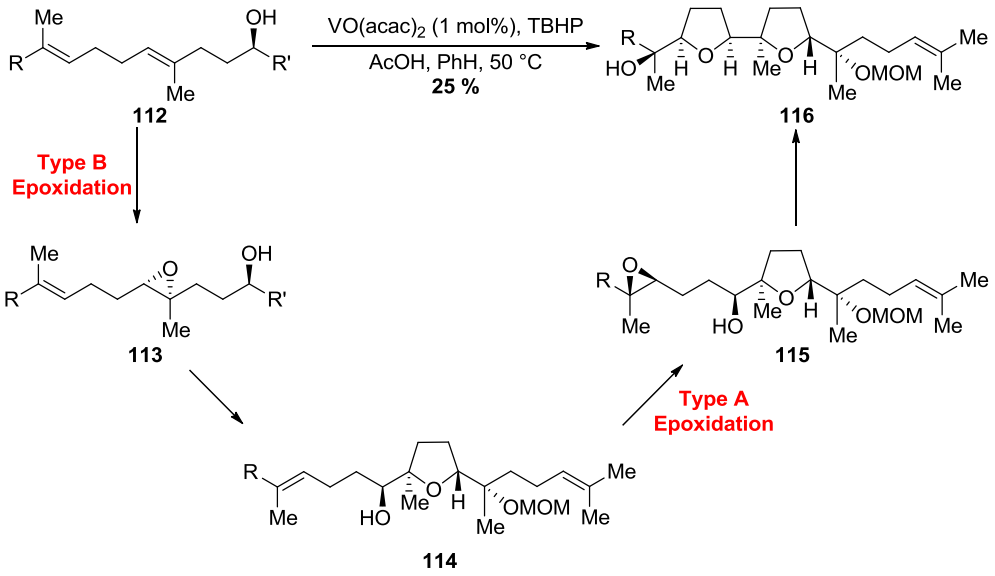
*Scheme **25**: Proposed classification of alkenes to explain the stereoselectivity of epoxidation.*

The authors found that the substitution pattern on the alkene to be oxidised predicts the favoured stereochemistry of the epoxide formed. Thus two classes were described:

Type A *syn*-Epoxides (leading to *cis*-THFs) are formed from 5-substituted 4-en-1-ols. Epoxidation *via* conformer **104** is more unfavourable due to the steric clashing of the pseudo axial proton and the vinylic methyl group in the transition state.

Type B *anti*-Epoxides (leading to *trans*-THFs) are formed from 4-substituted 4-en-1-ols. Epoxidation *via* conformer **108** is more unfavourable due to the steric clashing of the *pseudo* axial proton and the vinylic methyl group in the transition state.

Shirahama illustrated the use of this methodology in the synthesis of teutilene, a natural product containing three adjacent THF units. Two of the adjoining THF moieties conform to the predictions of stereochemistry laid out by Shirahama (*Scheme **26***).[30]

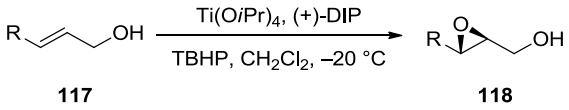


*Scheme **26**: Illustration of vanadium mediated oxidative cyclisation.*

A cascade approach in the epoxidation of **112** yielded the bis-THF **116** in 25%. Initial oxidation, using the rules set out by Shirahama, predicts that it will undergo a type B epoxidation leading to the cyclised *trans*-THF product. The second oxidation is foreseen to be a type A epoxidation leading to the *cis*-THF product.

1.2.3.3 Sharpless asymmetric epoxidation

An alternative method of selective epoxidation for the synthesis of *trans*-THFs is the Sharpless asymmetric epoxidation. In 1980, Sharpless and co-workers published conditions to epoxidise allylic alcohols in an asymmetric fashion (*Scheme **27***).[31,32]



*Scheme **27**: Sharpless asymmetric epoxidation of allylic alcohols.*

The advantage of this methodology is the ability to epoxidise either face of an alkene by using either enantiomer of tartrate. Sharpless provided a mnemonic to determine the stereochemistry of the resulting epoxide from the tartrate used (*Figure **2***).[31]

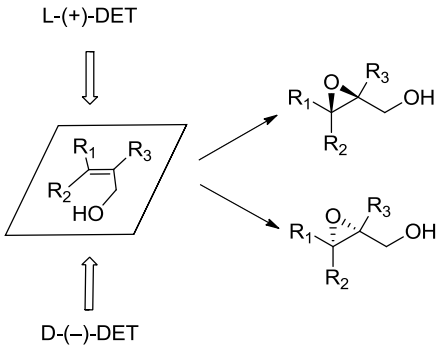


*Figure **2**: Mnemonic for the selectivity of epoxidation.*

The Sharpless epoxidation has also been applied to the kinetic resolution of racemic allylic alcohols (*Figure **3***).[33]

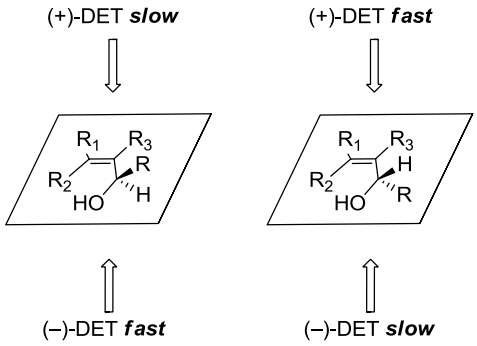
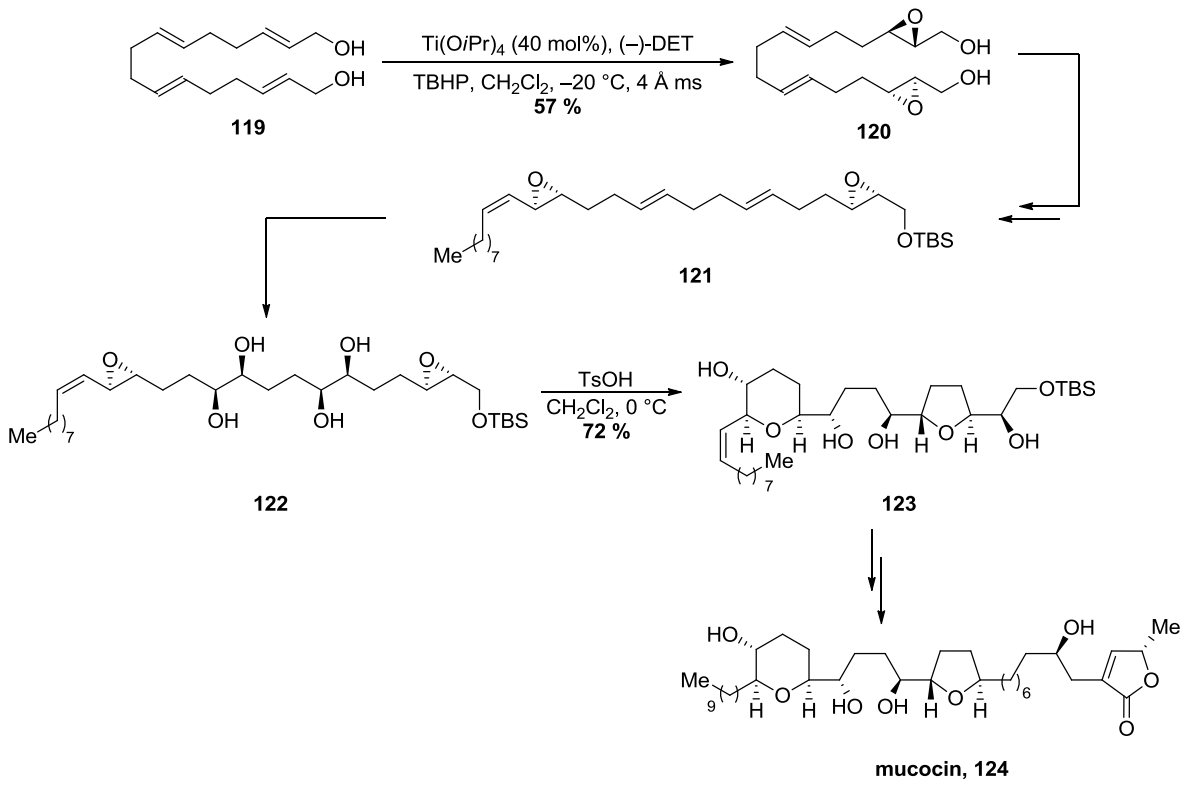


*Figure **3**: Mnemonic for the Sharpless Asymmetric Epoxidation.*

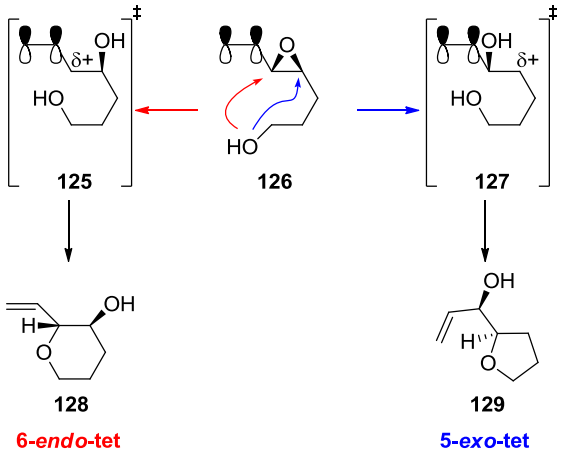
Choosing the appropriate enantiomer of tartrate allows selective access to the epoxide diastereomer that will lead to a *trans* or *cis*-THF.

The development of the Sharpless asymmetric epoxidation has allowed the construction of complex polyether natural products by introducing oxygen functionality to simple carbon skeletons. One such example is the synthesis of mucocin, **124** by Sinha and co-workers (*Scheme **28***).[34]



*Scheme **28**: Synthesis of mucocin, **124** by Sinha and co-workers using the Sharpless asymmetric epoxidation.*

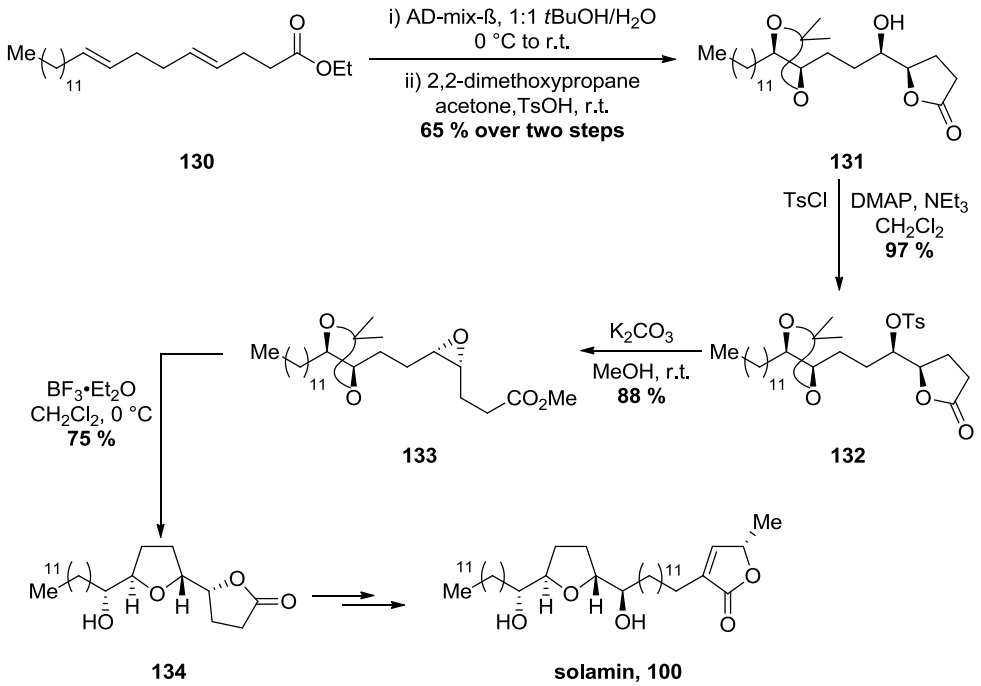
Setereoselective oxidation of **119** gave bis-epoxide **120** in 57% yield which was converted to triene **121**. Dihydroxylation under Sharpless conditions gave tetraol **122** in 94%. Addition of tosic acid induced two cyclisations, forming **123** containing a *trans*-THF and a *cis*-THP. According to Baldwin's work exploring the preference for 5-*exo*-tet cyclisation over 6-*endo*-tet,[25] the *cis*-THP should not be observed. Nicolaou and co-workers showed that allylic and benzylic epoxides preferentially cyclised in a 6-*endo*-tet fashion due to the lower energy transition state for forming the 6-membered ring (*Scheme **29***).[35]



*Scheme **29**: Proposed reason for observed THP product.*

1.2.3.4 Other epoxidation strategies

Other routes for stereoselective epoxidation have been explored, one possibility is using the Sharpless asymmetric dihydroxylation reaction followed by activation and displacement of one of the oxygens, giving the epoxide.[36] This technique was used in the synthesis of solamin, **100** by Sinha *et al.* (*Scheme **30***).[37]

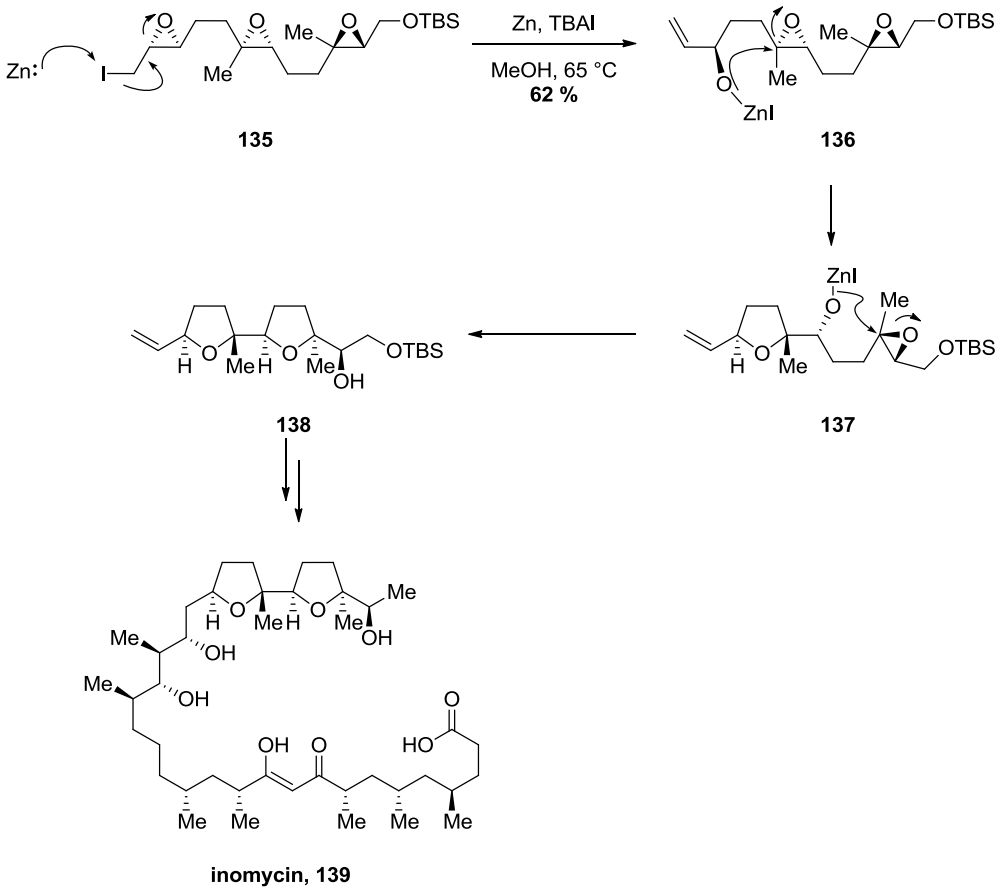


*Scheme **30**: Synthesis of solamin, **100**.*

Performing the Sharpless asymmetric dihydroxylation on diene **130** followed by acetonide protection of one pair of diols and subsequent protection of another alcohol as a lactone gave

131. Activation of the remaining hydroxyl followed by transesterification of lactone yielded epoxide **133** in 88%. Finally *in situ* acetonide deprotection and cyclisation gave *trans*-THF **134** in 75% yield which was taken on towards the synthesis of solamin, **100**.

An alternative method of intramolecular acid catalysed formation of *trans*-THFs from hydroxy epoxides was developed by Marshall *et al.* (*Scheme **31***).[38] Treating 1-iodomethyl-1,5,9-tris-epoxide **135** with zinc dust in methanol at reflux gave zinc alkoxide intermediate **136** which cyclised to form two THFs with no loss of stereochemistry. This strategy was used as part of the synthesis of inomycin, **139**.[39,40]

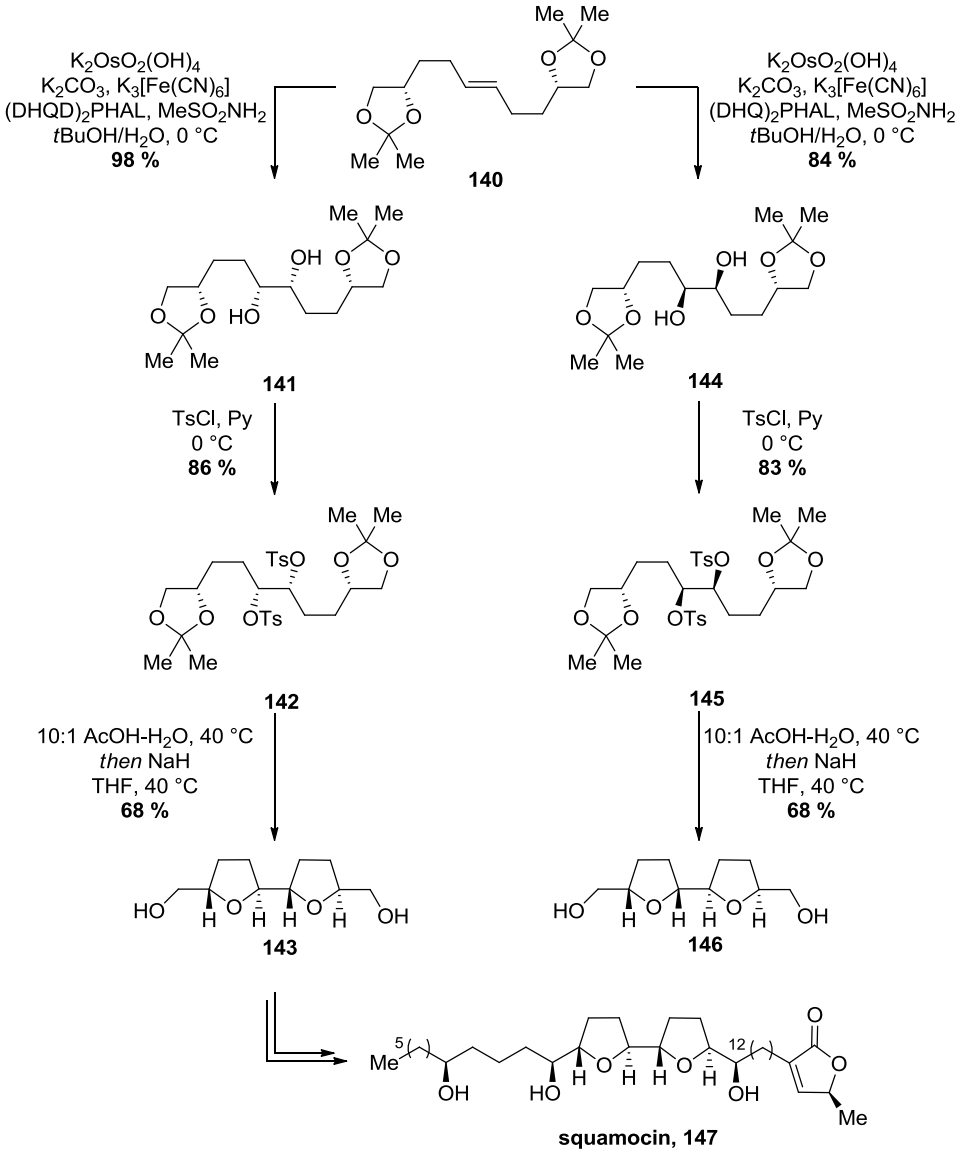


*Scheme **31**: Application towards the synthesis of inomycin, **139**.*

1.2.4 Williamson Etherification

The Williamson etherification uses the stereospecific nature of the S_N2 reaction to form the desired THF. This occurs *via* an intramolecular displacement of a leaving group, typically a

mesylate or tosylate, by an oxygen atom, usually in the form of an alkoxide, in a 5-*exo*-tet fashion. This causes the stereochemistry of the original electrophilic carbon centre to be inverted. Generally, the stereocentres at the oxygen nucleophile and the electrophilic carbon centre are installed using chemistry discussed previously, such as dihydroxylation as well as using Mitsunobu chemistry to invert stereocentres. Koert and co-workers showed an example of this type of cyclisation (*Scheme **32***).[41]

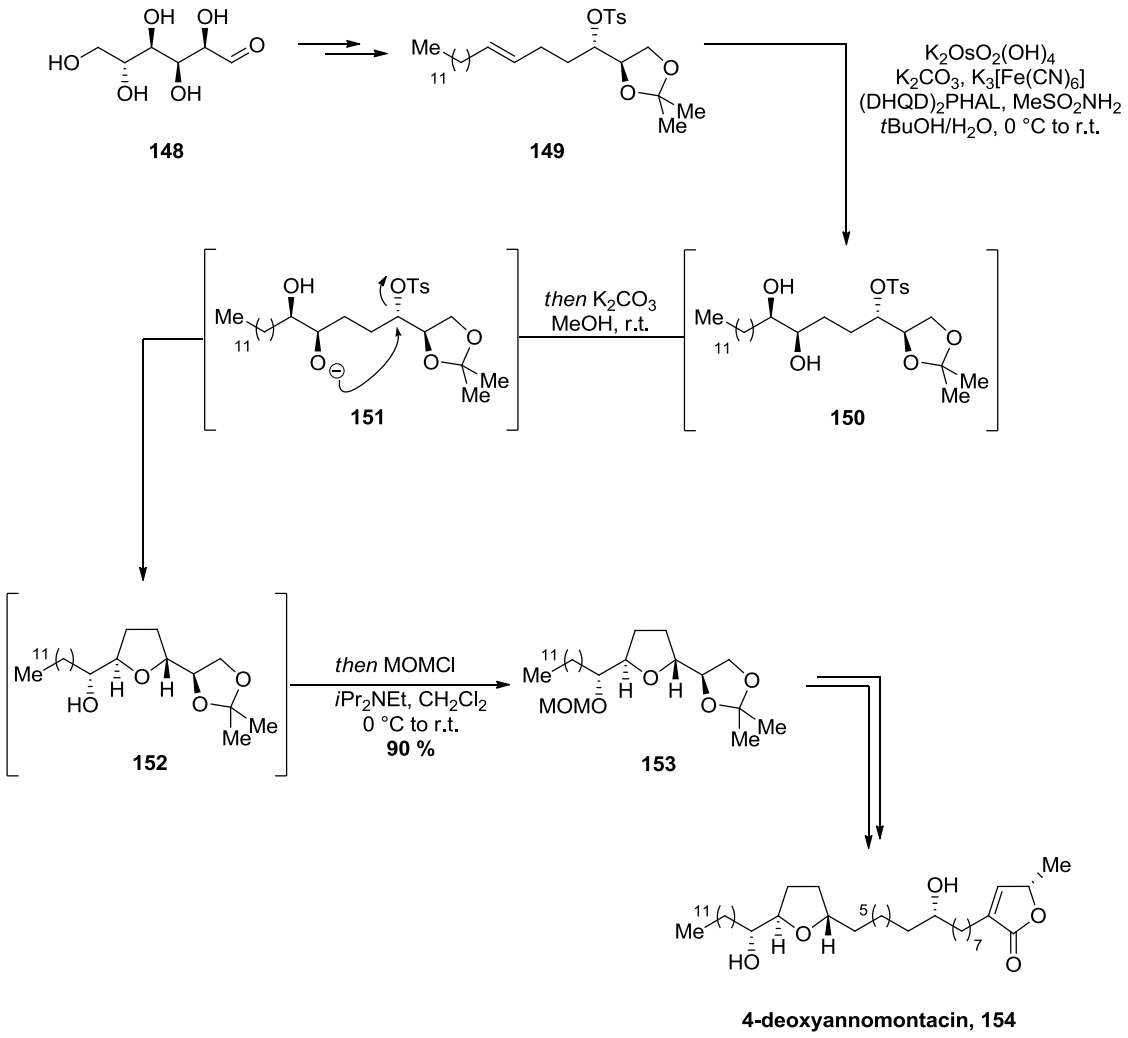


*Scheme **32**: Work towards squamocin, **147**.*

In this case, it was found that using either the α or β Sharpless AD mix led to either *trans*-THF or *cis*-THF respectively. The diol products **141** and **144** were activated by conversion to

the corresponding di-tosylate **142** and **145** respectively. Removal of the acetonide protecting group and *in situ* deprotonation of the free diol led to the cyclised **143** and **146**. Koert *et al.* took *trans* **143** and converted it into the natural product squamocin, **147**.[42]

Another example of this type of cyclisation is the first reported synthesis of 4-deoxyannomontacin, **154** by Wu *et al.* (*Scheme **33***).[43]



*Scheme **33**: Work towards the synthesis of 4-deoxyannomontacin, **154**.*

The *trans*-THF was generated by a three step process to introduce the hydroxyl groups followed by cyclisation and protection of the remaining free hydroxy group. Dihydroxylation of alkene **149** using Sharpless conditions led to the intermediate **150** which cyclised to give THF **152** using basic potassium carbonate in methanol. Subsequent protection of the

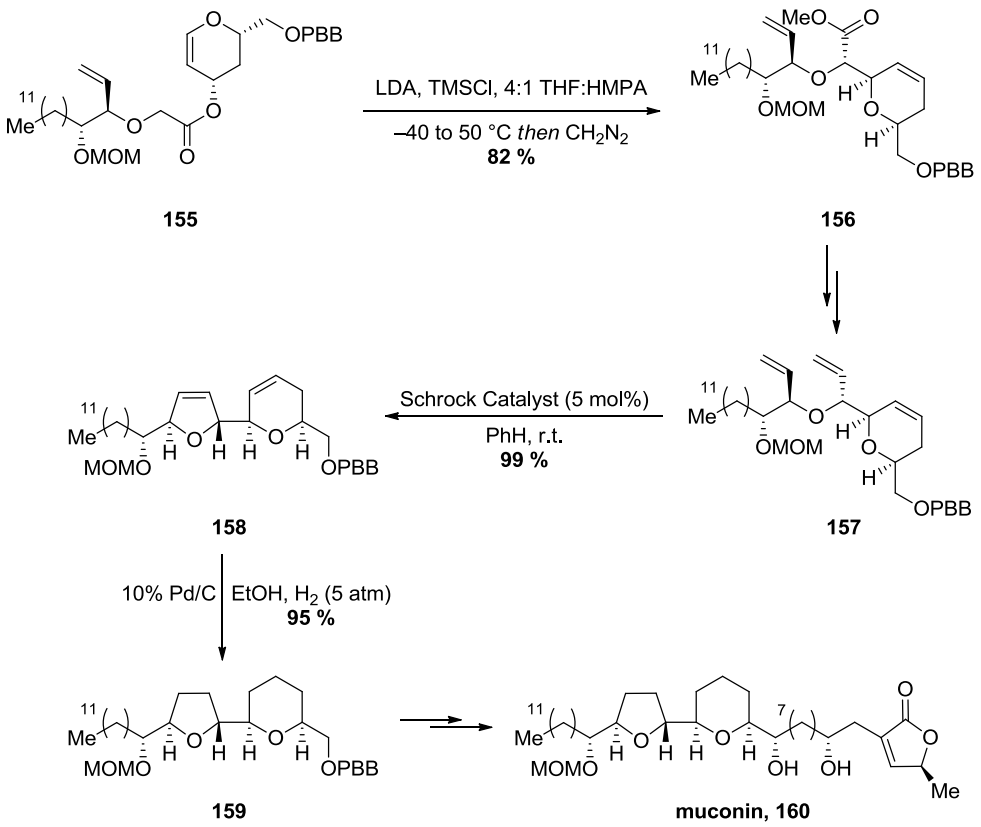
remaining alcohol using methyl chloromethyl ether gave **153**. The THF was taken further towards the synthesis of 4-deoxyannomontacin, **154**.

1.3 C-C Bond Forming Processes

1.3.1 Ring Closing Metathesis

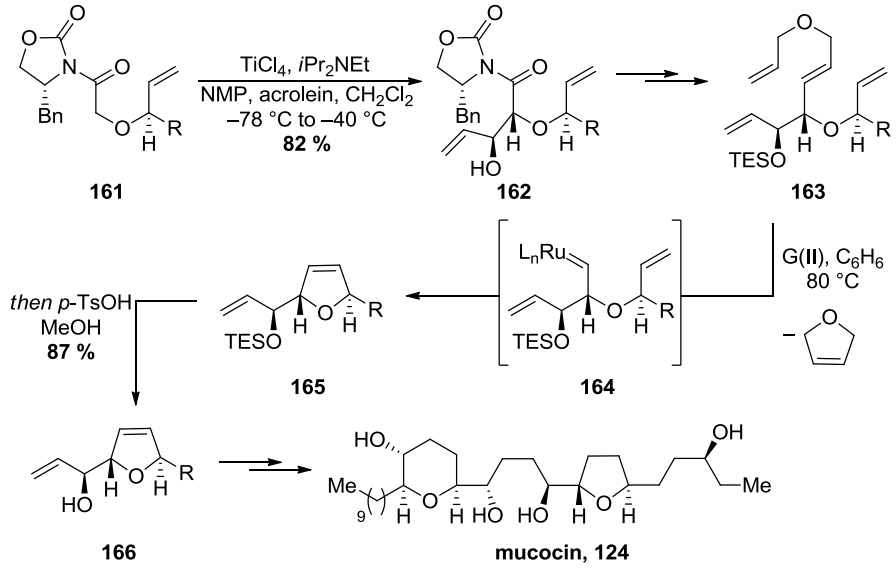
The ring closing metathesis (RCM) approach to forming THFs is different to the previous methods of THF formation as RCM depends on forming a C-C bond rather than a C-O bond. Typically the 5-membered ring is formed by subjecting a diallyl oxide under metathesis conditions to form the dihydrofuran followed by reduction of the alkene to give the desired THF. This route uses the stereochemistry at the allylic position to determine the *cis/trans* nature of the THF, not the RCM step.

In 1998, Jacobsen *et al.* reported the first total synthesis of muconin, **160** using this RCM approach (*Scheme **34***).[44] The required stereochemistry, which would eventually give the *trans*-THF, was installed *via* an Ireland-Claisen rearrangement followed by methylation by diazomethane giving **156**. After converting the ester **156** to the corresponding terminal alkene **157**, treatment of this diallyl ether with Schrock's catalyst gave the dihydrofuran **158** in excellent yield. Finally the desired THF was obtained by hydrogenation of **158** giving **159** which was taken further towards muconin, **160**.



*Scheme **34**: Synthesis of muconin, **160**.*

An alternative method to install stereochemistry α to the oxygen, leading to the *trans*-THF, is *via* a chiral auxiliary. One such example is used in the synthesis of mucocin **124** by Crimmins *et al*. (*Scheme **35***).[45]

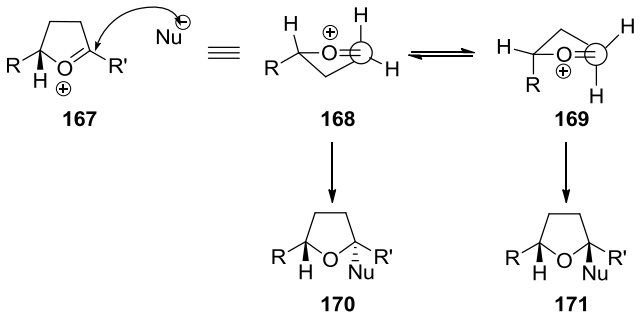


*Scheme **35**: Use of RCM in the synthesis of mucocin, **124**.*

By using an Evans chiral auxiliary, the desired stereochemistry *α* to the oxygen was installed, giving the *anti* arrangement which would eventually lead to the *trans*-THF. Crimmins used an allyloxymethyl group to ensure the metathesis catalyst would preferentially insert into its double bond *via* ring relay metathesis. Dihydrofuran **166** was used to complete the sunthesis of mucocin, **124**.

1.3.2 Nucleophillic addition to THF oxonium ions

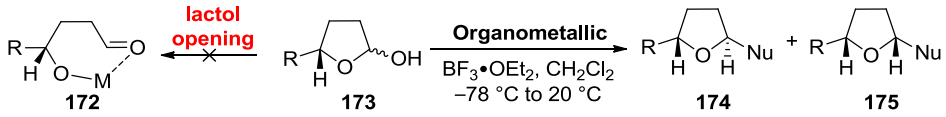
2,5-Disubstituted THF oxonium ions such as **167** can be reduced by two methods: carbon-based nucleophilic addition to a 5-substituted oxonium ion **or** a hydride nucleophile adding to a 2,5-disubstituted oxonium ion. The facial discrimination of the nucleophilic reduction to the oxonium ion is largely determined by the substituents on the backbone (i.e. the 3- and 4-carbon site) of the 5-membered ring.[46, 47] However, THFs substituted at the 2- and/or 5-position have been found to show little preference in the facial selectivity of the nucleophilic addition to **167** (*Scheme **36***).[48]



*Scheme **36**: Possible mechanism for the addition of nucleophiles on 2,5-disubstituted oxonium ions.*

Thus addition often occurs with little *cis/trans* stereoselectivity. Bulky nucleophiles can be used to improve facial discrimination. Therefore the addition of carbon nucleophiles generally gives better selectivity than hydride addition to a 2,5-disubstituted oxonium ion **167**. Carbon nucleophiles commonly give rise to the resulting *trans*-THF, due to addition occurring on the opposite face to the substituent present. Suzuki and co-workers reported the

addition of organometallic reagents to lactols to form *trans*-THFs in high selectivities (*Table **1***).



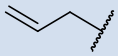
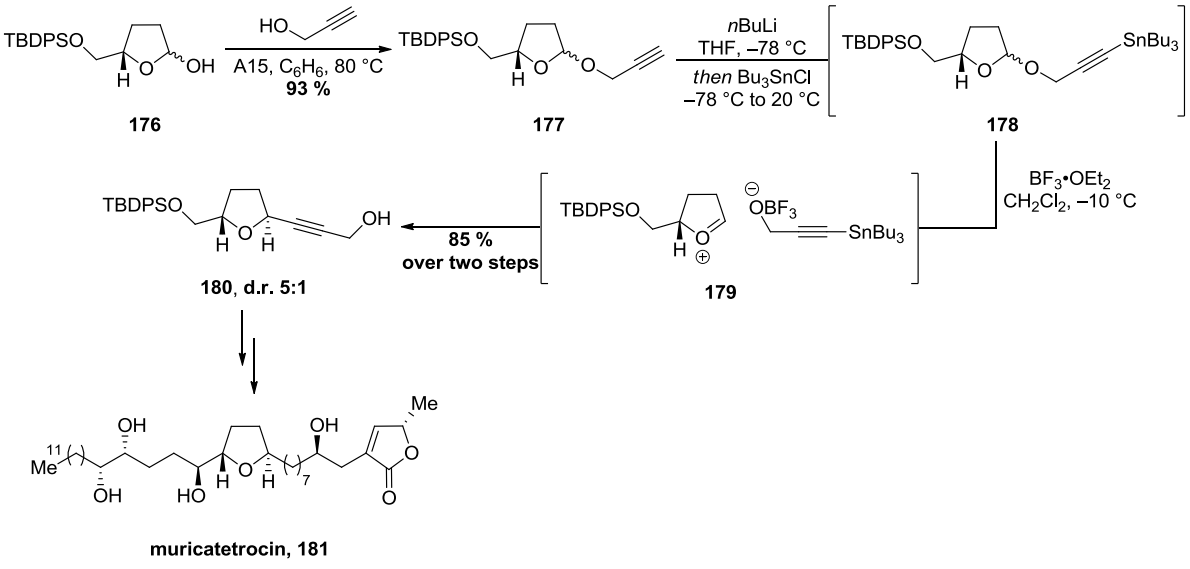
Entry	R	Organometallic	174:175	Yield
1	Me	Me_2Zn	8:1	82%
2	Me	Me_2Al	10:1	75%
3	Et	Me_2Zn	9:1	80%
4	Et	Et_3Al	13:1	61%
5		$(allyl)_2SnBr_2$	12:1	72%
6		$(vinyl)_2SnBr_2$	47:1	66%

*Table **1**: Screening of ring substituent and nucleophile on trans stereoselectivity.*

To avoid the competing lactol opening to **172**, to which further addition could occur, it was necessary to use a Lewis acid (boron trifluoride diethyl etherate) with mild organo-zinc, aluminium or tin reagents rather than highly nucleophilic organolithium or Grignard reagents.

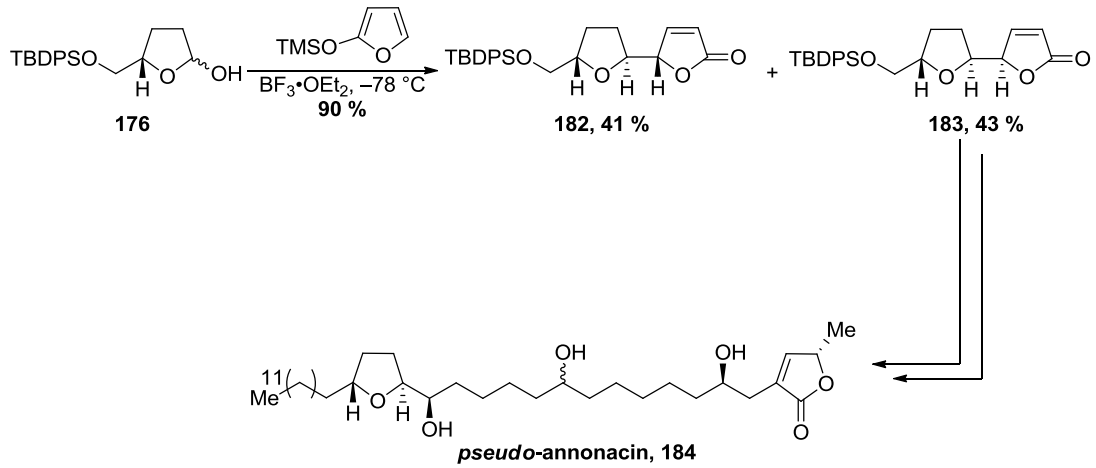
An alternative method was explored by Ley and co-workers in which they investigated the anomeric O to C rearrangement to form the desired *trans*-THF (*Scheme **37***).[49]



*Scheme **37**: Ley's work towards anomeric rearrangement and subsequent application to muricatetrocin, **181**.*

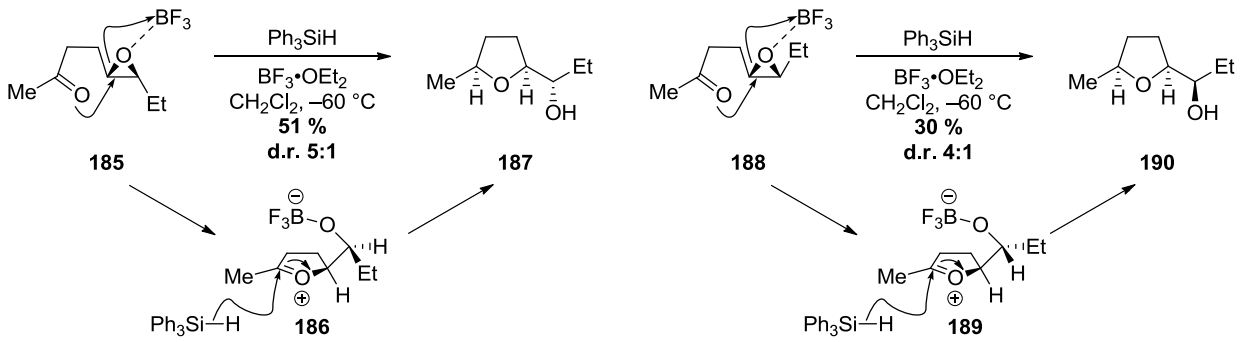
Stannane **178**, generated form deprotonating alkyne **177** followed by stanylation with tributyltin chloride, was treated with boron trifluoride diethyl etherate. This promoted an O to C rearrangement and allowed the organostannane to stereoselectivly attack the oxonium ion to form a *trans*-THF. Ley *et al.* used this methodology towards the synthesis of muricatetrocin, **181** (*Scheme **37***).[50]

Silylenol ethers have also been shown to favourably form *trans*-THFs upon addition to oxonium ions. One example was reported by Figadère and co-workers, in which they were able to diastereoselectively add an extended silyl enol ether into an oxonium ion.[47] This work was used by Hanessian and co-workers in the total synthesis of *pseudo*-annonacin A, **184** (*Scheme **38***).[51]



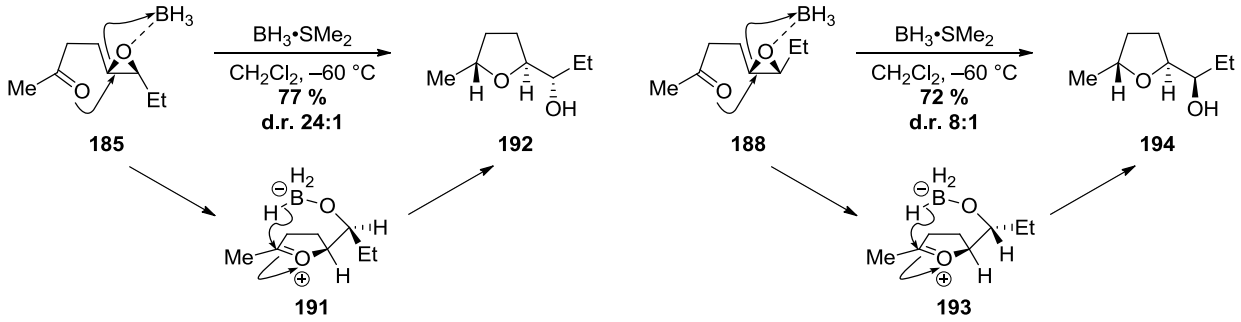
*Scheme **38**: Use of [(trimethylsilyl)oxy]furan towards pseudo-annonacin, **184**.*

The stereoselectivity of a hydride adding to an oxonium ion is significantly lower due to the nature of the size of the nucleophile. Chamberlin and co-workers explored using silanes to add into oxonium ions and found that *cis*-THFs were formed (*Scheme **39***).[52]



*Scheme **39**: Formation of cis-THFs from keto-epoxides.*

Trialkysilanes were used due to their ability to survive mild Lewis and protic acid conditions. Intermolecular attack of the hydride source on to the oxonium ion preferentially occurred with addition to the less hindered face, giving the *cis*-THF. The opposite face was hindered due to the Lewis acid. Chamberlin and co-workers then explored an intramolecular delivery of the hydride nucleophile. This reduction requires the use of a Lewis acid that becomes a hydride donor after epoxide opening (*Scheme **40***).[52]

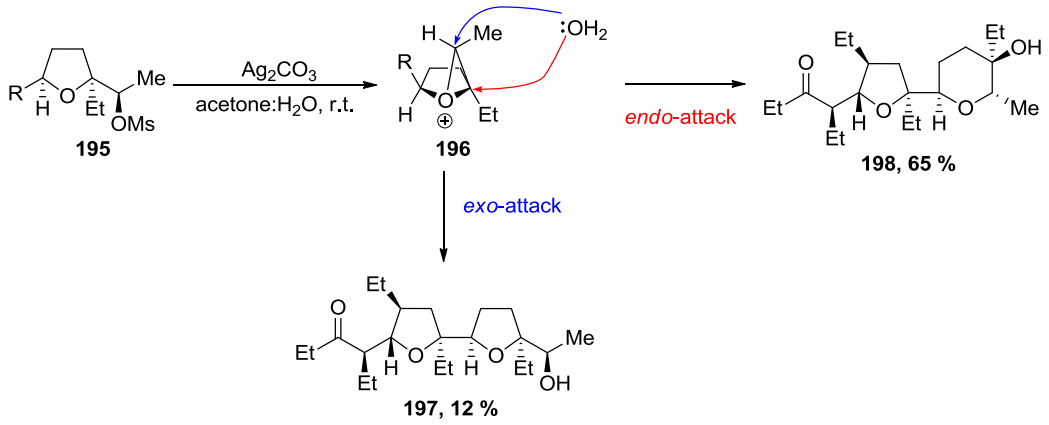


*Scheme **40**: Formation of trans-THFs from keto-epoxides.*

Borane dimethylsulfide complex allowed access to *trans*-THFs. The *trans/cis* ratio was dependent upon the concentration and in order to get a 15:1 *trans*/*cis* ratio, the concentration of the reagents in the reaction medium had to be less than 0.005 M. The dependence on concentration suggests that the intramolecular reduction was slow enough to allow intermolecular reduction to compete at higher concentrations.

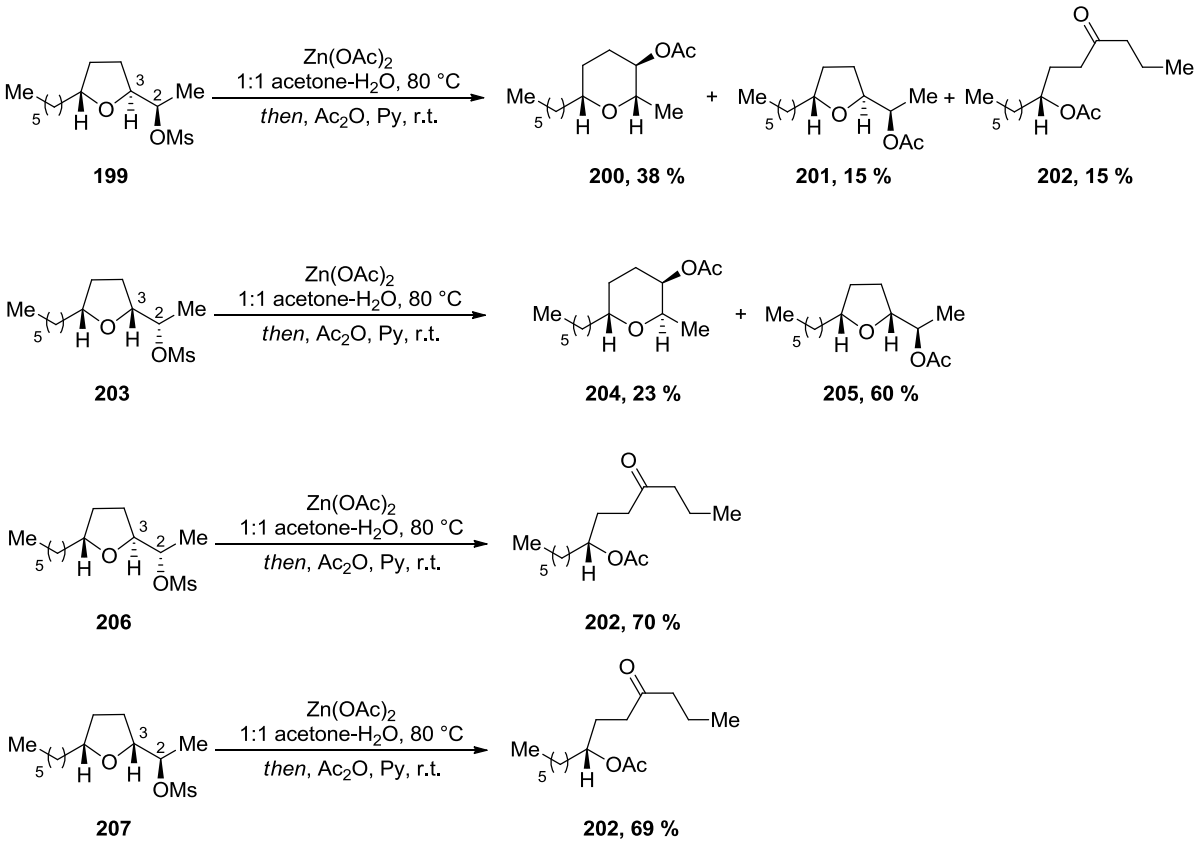
1.4 Rearrangements of 2,5-Disubstituted THFs

In 1978 Kishi and co-workers reported the rearrangement of THFs with an adjacent activated alcohol to THPs *via* ring expansion (*Scheme **41***).[53] Treating THF **195** with silver carbonate induced nucleophilic displacement of the adjacent mesylate group to give **196**. The bicyclic oxonium ion **196** was solvolysed to give either THP **198** or a THF **197** *via endo* or *exo*-attack respectively.



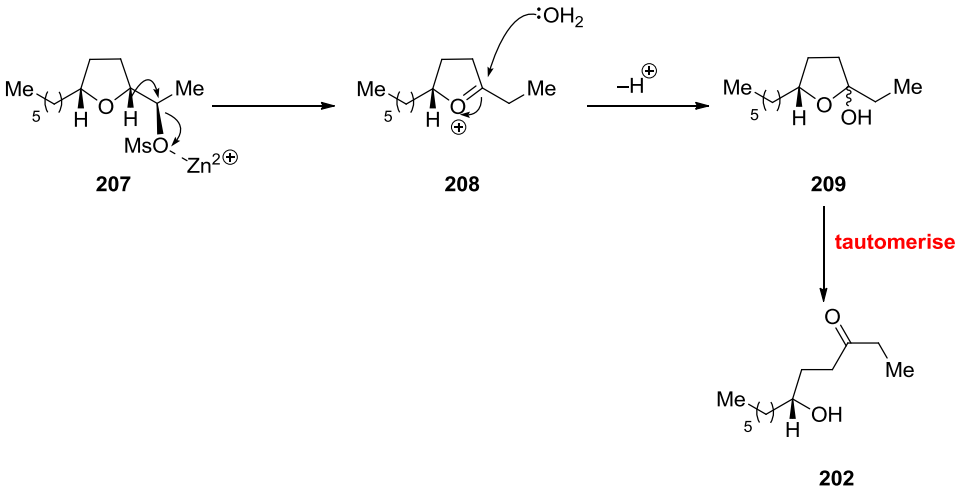
*Scheme **41**: Rearrangement of THFs with activated alcohols.*

Nakata and co-workers further investigated the rearrangement of 2,5-disubstituted THFs with adjacent mesylates with zinc acetate under refluxing acidic conditions.[53] Due to the nature of the products, they were acetylated for ease of isolation. The results indicated a dependence on the relative stereochemistry of the mesylate centre and the C-H at the ring (*Scheme **42***).



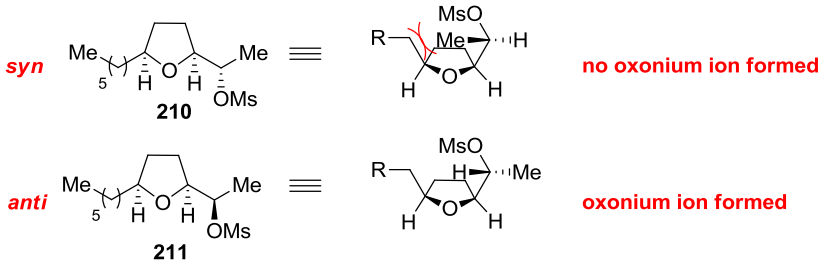
*Scheme **42**: Relationship between the stereochemistry and rearrangement of THFs.*

It was observed that THFs containing an *anti*-relationship between the ring C(2)-H and adjacent C(3)-O (**199** and **203**) underwent a reaction analogous to the reaction Kishi and co-workers reported. Conversely THFs containing a *syn*-relationship between the ring C(3)-H and adjacent C(2)-O (**206** and **207**) form ketone **202**. Brimble and co-workers had observed similar results during ring rearrangements of *syn*-*α*-iodo THF analogues.[54] It was suggested that the observed ketone **202** was formed by water adding into the intermediate oxonium ion formed by hydride shift to displace the mesylate (*Scheme **43***).



*Scheme **43**: Formation of ketone, **202**.*

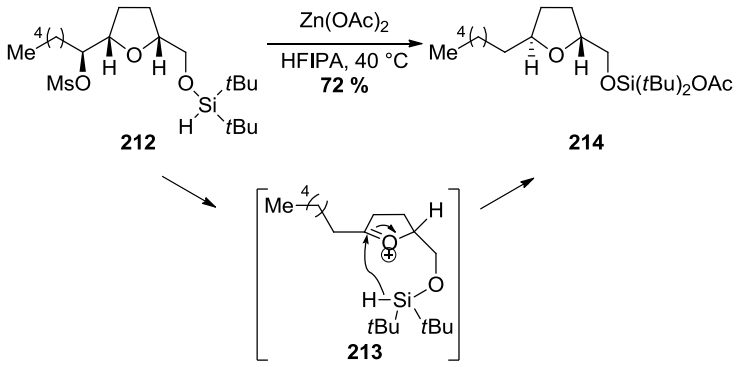
It was proposed that the relative stereochemistry of the mesylate centre and the ring junction can be explained by the difference in the hypothesised transition states (*Scheme **44***).[53]



*Scheme **44**: Conformations leading to oxonium ions.*

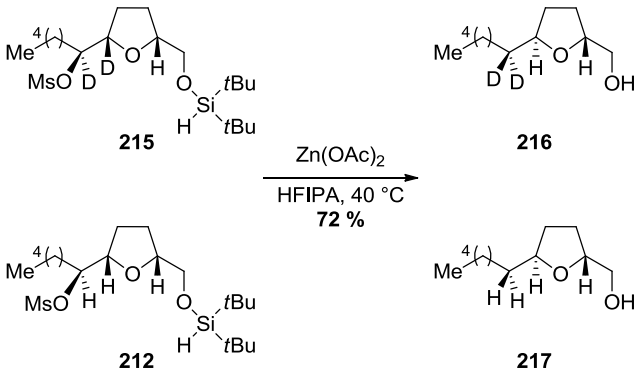
As shown in the *Scheme **44***, hydride shift requires the ring C-H and C-O bonds to have an anti-periplanar arrangement. For the *syn*-THF, the formation of an oxonium ion is disfavoured due to the *anti*-periplanar relationship invoking an increase in unfavourable steric interactions. Thus the observed products formed arise from alternative side reactions such as ring expansion and mesylate displacement. In contrast, the *anti*-THF analogue allows the *anti*-periplanar arrangement for hydride shift to occur, giving the observed ketone.

Donohoe and co-workers built on the idea of forming an oxonium ion, generated by a hydride shift to displace an activated OH group, which could then be trapped by an intramolecular source of hydride giving the desired *trans*-THF (*Scheme **45***).[55]



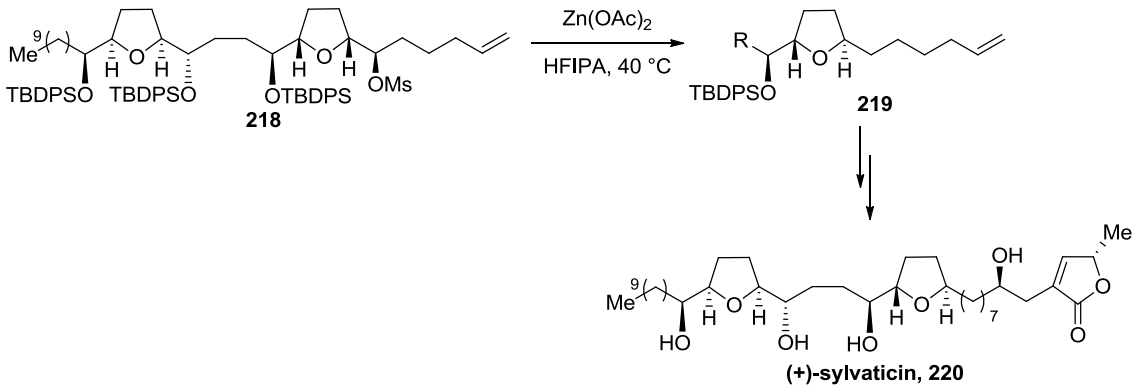
*Scheme **45**: An example of conversion of cis to trans-THF.*

To determine whether the mechanism occurs *via* an intramolecular process, doubly deuterated **215** was mixed with an excess of the protonated analogue **212** and submitted to the solvolysis conditions to give only **216** and **217** as the only products formed (*Scheme **46***). No crossover products containing one deuterium atom were detected by mass spectrometry.[55]



*Scheme **46**: Evidence for the intramolecular nature of the hydride shift.*

The methodology developed by Donohoe and co-workers was applied in the total synthesis of (+)-sylvaticin, **220** (*Scheme **47***).[56]

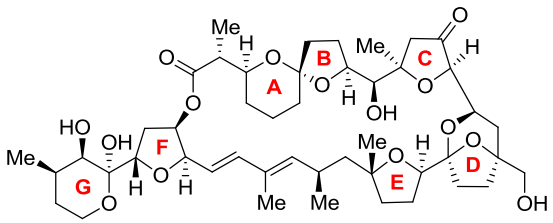


*Scheme **47**: Hydride shift methodology towards (+)-sylvaticin, **220**.*

1.5 Summary and Research Aim Overview

An overview of the numerous endeavors has shown successful methods to generate *trans*-THFs in high selectivity. A prevalent limitation is the necessity of performing multiple steps to install the THF. Ideally the *trans*-THF would be generated in a high diastereomeric ratio in fewest possible steps without the presence of reactive intermediates, such as tosylates.

The intention of this research is to develop a short, alternative and effective synthesis to create *trans*-THFs building on previous work explored in the Donohoe group. If successful, this methodology could be applied to the synthesis of complex molecules such as the F ring segment of the polyether toxin pectenotoxin-4, **2** (*Figure **4***).



2

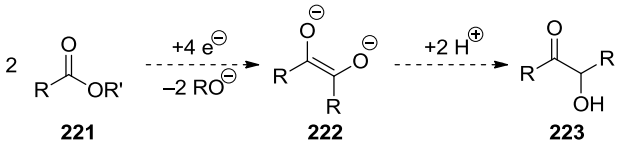
*Figure **4**: Pectenotoxin-4, **2**.*

Chapter 2: Results and Discussion

2.1 The Acyloin Coupling Reaction Towards *trans*-THFs

2.1.1 Acyloin condensation

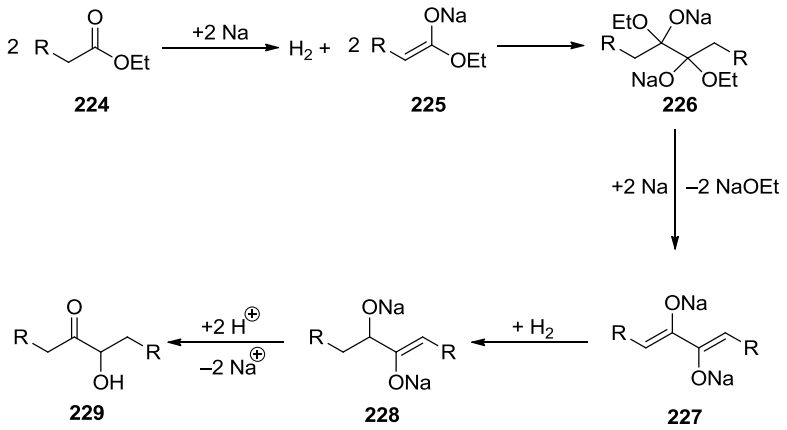
The acyloin condensation is a reductive carbon-carbon bond forming reaction between two carbonyls of esters mediated by single electron transfer. Initially discovered in 1903 by Bouveault and Blanc during a study into the sodium-mediated reduction of esters to the corresponding alcohols (*Scheme **48***).[57] The electron arises from an alkali metal, either directly or mediated *via* an electron transfer reagent. The intermediate **222** formed is an enediolate which upon protonation forms a α-hydroxy ketone **223**.



*Scheme **48**: Acyloin condensation.*

2.1.1.1 Mechanism of the acyloin condensation

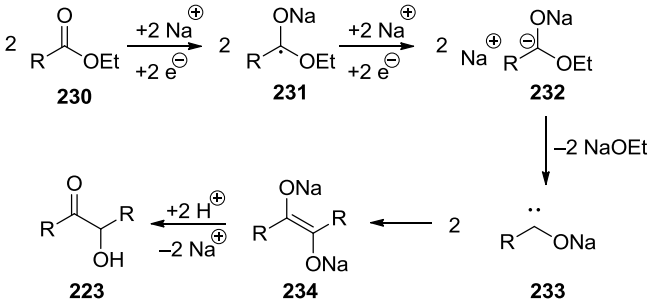
There have been multiple endeavors to elucidate the mechanism of the acyloin condensation. Scheibler *et al.* attempted to rationalize the mechanism in 1920 by suggesting initial formation of ester enolate **225** by producing hydrogen gas (*Scheme **49***).[58]



*Scheme **49**: Scheibler's proposed mechanism.*

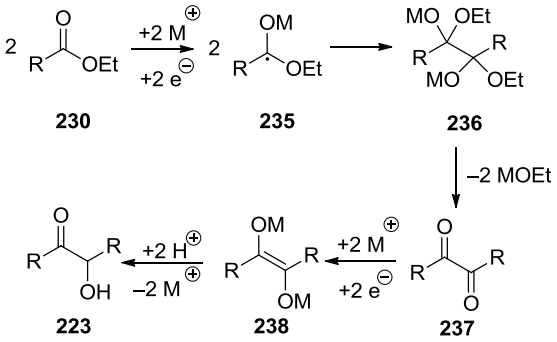
Dimerisation to form **226** was presumed to be followed by further reduction and elimination of sodium alkoxide to give **227**. Reduction of **227** to form the enolate **228**, followed by protonation would give the observed hydroxy ketone **229**.

Due to the lack of evidence for the formation of hydrogen gas, an alternative mechanism was suggested by Scheibler and co-workers using the idea of single electron transfer to form the radical anion **231** (*Scheme **50***).[59]



*Scheme **50**: Scheibler and co-workers proposed mechanism.*

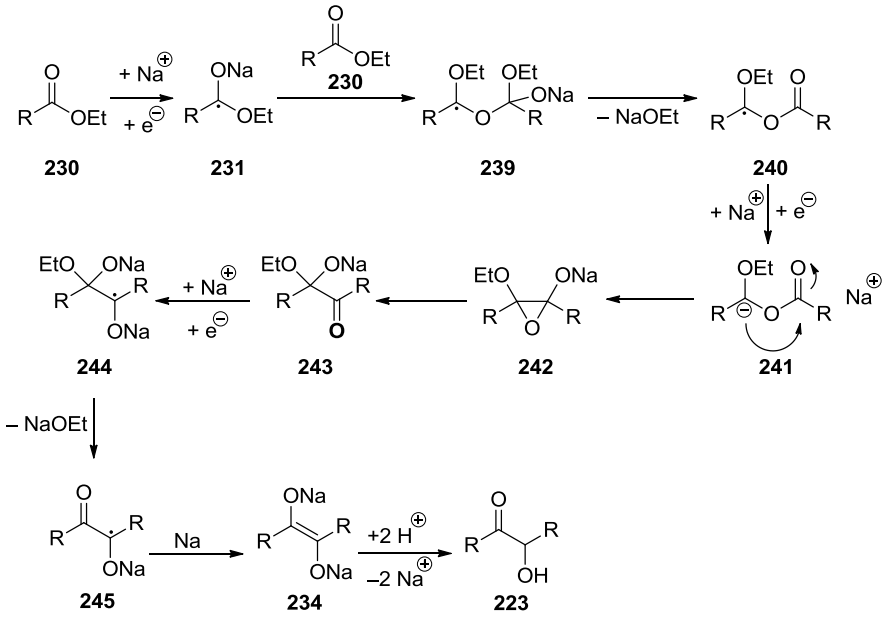
Further reduction by single electron transfer would give **232** and subsequent elimination would yield carbene **233**. Dimerisation of the carbene **233** to bis-enolate **234** and protonation would give the hydroxyl ketone **223**. McElvin subjected a series of ethyl esters to reaction with lithium in diethyl ether and observed no correlation between the nature of the ester and reaction rate.[60] Based on these findings McElvin proposed an alternative mechanism for the sodium-mediated acyloin condensation in analogy which excludes the formation of a carbene (*Scheme **51***).



*Scheme **51**: Mechanism proposed by McElvin.*

Initial reduction by single electron transfer of ester **230** forming ketyl radical **235**, which then dimerises to give **236**. Elimination of the alkoxide group would give the subsequent 1,2-diketone **237**. This would be then further reduced to the enediolate **238** and form the hydroxy ketone **223** upon protonation.

Bloomfield *et al.* suggested an alternative mechanism to avoid the formation of 1,2-diketone **237** to account for the observed side products, such as carboxylic acids, alcohols and aldehydes.[61] Bloomfield proposed initial single electron reduction of ester **230** to form radical **231** which would then attack an ester molecule **230** (*Scheme 52*).



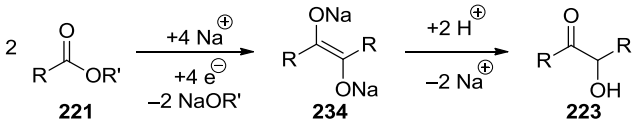
Scheme 52: Bloomfield and co-workers proposed mechanism.

Elimination of sodium ethoxide would give **240** which leads to **241** by further reduction. Intramolecular attack giving cyclic **242** followed by reduction/elimination leads to **245** which is further reduced to enediolate **234**.

2.1.1.2 Acyloin condensation conditions

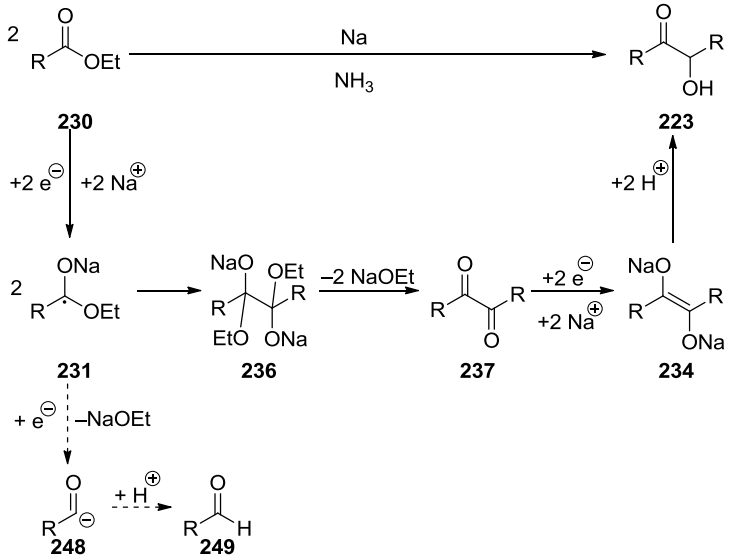
Two types of conditions arise from the coupling of esters. The reducing electron can arise from solid metal (heterogeneous) or from solvated electrons (homogeneous).

There have been several conditions reported which vary the solvent and temperature of sodium mediated acyloin condensations under heterogeneous conditions (*Scheme **53***).[62,63,64]



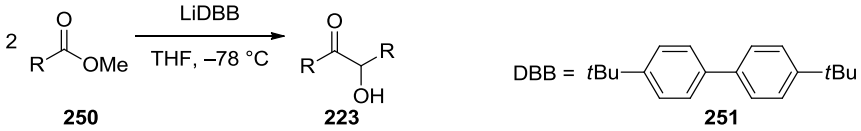
*Scheme **53**: Heterogeneous acyloin coupling.*

The first homogeneous conditions for the acyloin condensation were reported in 1940 by Mayo and co-workers.[65] A range of aliphatic and aromatic esters were submitted to sodium dissolved in liquid ammonia at −78 °C (*Scheme **54***).



*Scheme **54**: Mayo's proposed mechanism.*

Using ammonia as a solvent raised numerous disadvantages, mainly the formation of aldehyde **249** whereby ammonia can act as a proton source. In 1989, Fry and co-workers developed methodology to reductively couple alkyl esters using sodium in DBB **251** to give the corresponding hydroxyl ketones.[66] By replacing sodium with lithium, co-workers in the Donohoe group expanded this concept by subjecting a series of methyl esters under these conditions (*Table **2***).[67]



250 **223** **251**

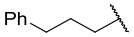
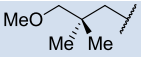
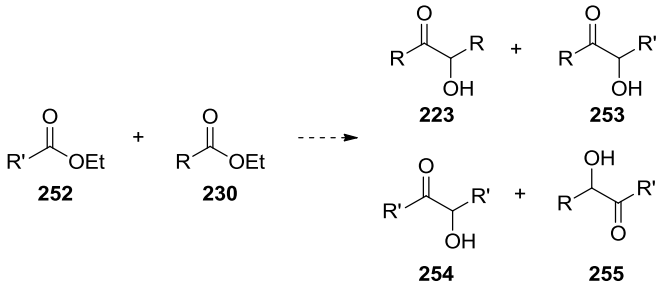
Entry	R	Yield
1	Ph	70%
2	Cy	79%
3		78%
4		71%
5		75%

*Table **2**: Summary of worked developed by Donohoe and co-workers.*

2.1.1.3 Crossed acyloin condensation

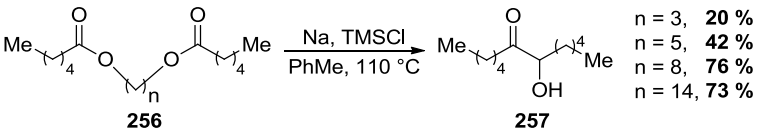
The acyloin condensation is of limited value when two dissimilar esters are submitted as a statistical mixture of products is formed resulting from the random intermolecular reaction of both esters (*Scheme **55***).



252 **230** **223** **253** **254** **255**

*Scheme **55**: Statistical mixture of products formed from 1:1 mixture of esters **252** and **230**.*

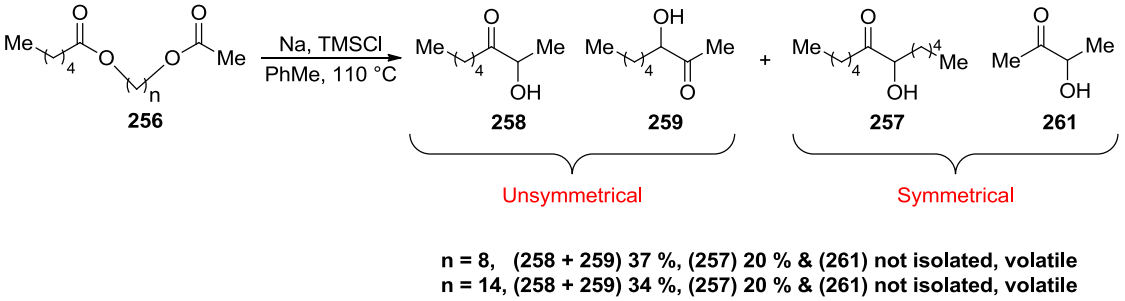
Hutchinson *et al.* reported the first tethered acyloin condensation to reliably couple two different esters together successfully.[68] They initially screened a series of different carbon tethers to determine the optimum chain length for acyloin coupling using either 1,8-octanediol or 1,14-tetradecanediol forms hydroxyl ketone **257** in a good yield (*Scheme **56***).



256 **257**

*Scheme **56**: Hutchinson's use of tethered diesters.*

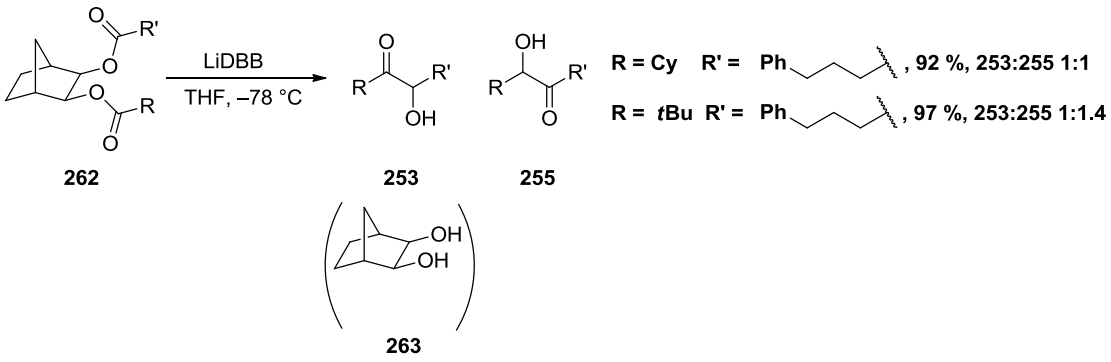
Thus, both 1,8-octanediol and 1,14-tetradecanediol were used to tether two different carboxylic acids as esters, acetic acid and hexanoic acid. Afterwards, the capability of these diesters to undergo crossed acyloin condensation using heterogeneous conditions was explored (*Scheme **57***).



*Scheme **57**: Hutchinson and co-workers approach to crossed acyloin coupling.*

Both tethers gave similar yields in forming the unsymmetrical hydroxy ketones **258** and **259** and the symmetrical acyloin **257**. The ratio of unsymmetrical to symmetrical hydroxyl ketone was approximately 2:1, meaning that a statistical product distribution was obtained. They reported that even at high dilution, under conditions designed to promote an intramolecular reaction, the products isolated still gave a 2:1 statistical distribution.

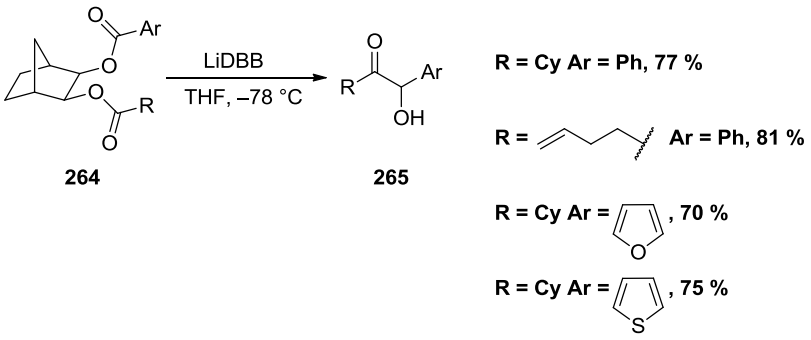
Co-workers in the Donohoe group also studied the effect of using diol **263** to act as a scaffold and tether two different carbonyls together before submitting them to LiDBB coupling conditions (*Scheme **58***).[67]



*Scheme **58**: Selection of reactions of diesters under LiDBB.*

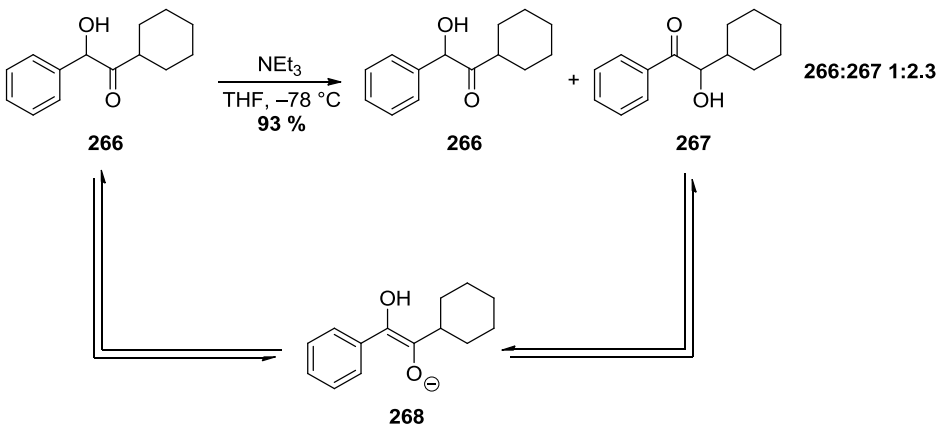
Upon submitting the diesters to LiDBB in tetrahydrofuran at low temperatures, the crossed acyloin products were produced in excellent yields. Examination of the ^{1}H NMR spectrum of the reaction mixture did not reveal any material that had derived from homo-acyloin coupling and the crossed product was formed exclusively. The products were produced as an approximate 1:1 mixture of regioisomeric hydroxy ketones.

Examining the reductive couplings of diesters bearing an aryl and an alkyl group, crossed acyloin products were again formed exclusively but also as a single regioisomer (*Scheme **59***).



*Scheme **59**: Selection of diester under LiDBB.*

In the products formed the carbonyl group was not in conjugation with the aromatic group, suggesting the product is formed under kinetic control based upon base-induced equilibration studies (*Scheme **60***).[69]

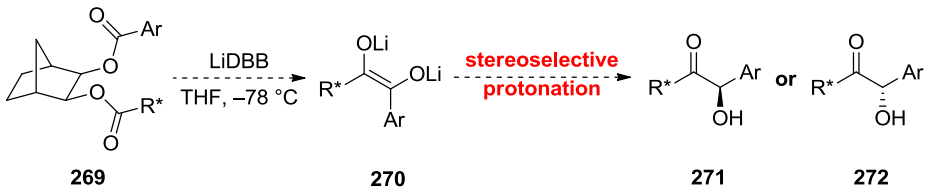


*Scheme **60**: Based induced equilibration to form thermodynamic mixture of products.*

It was shown that upon treating α-hydroxy ketone **266** under basic conditions at low temperatures formed a mixture of products. The major product formed was the opposite acyloin observed and is thought to be the thermodynamic product.

2.1.2 Research Outline

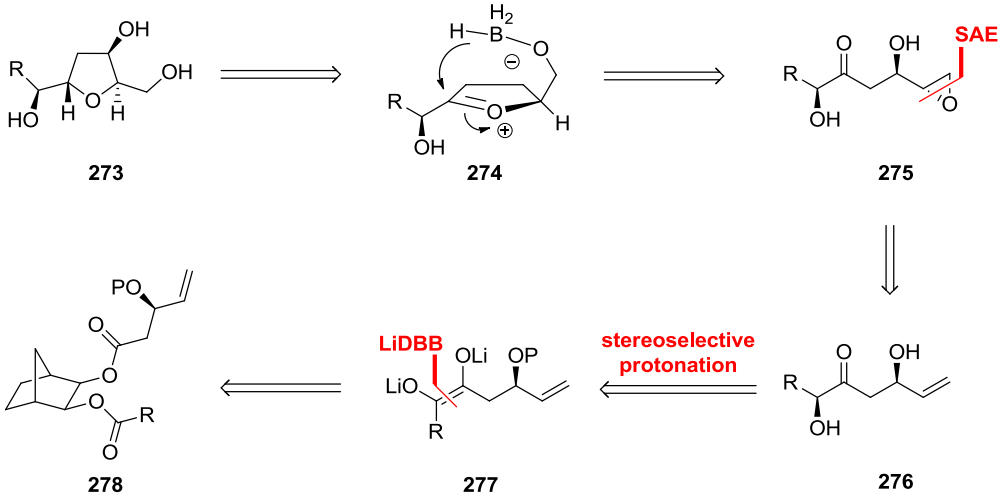
The intention of this research project was to expand upon the methodology developed by co-workers in the Donohoe group by determining if the stereochemical outcome within the formation of hydroxyl ketone **271** or **272** can be controlled. The steroselective protonation is hoped to be achieved using the stereochemical bias exhibited in the bis-enolate intermediate **270** (*Scheme **61***).



*Scheme **61**: Initial aim of research.*

Evidence for the existence of the *cis*-isomer of enediolate **270** arises from work carried out by Russell and co-workers.[70] They carried out studies of the *cis*/*trans* ratio of enediolates with regard to the counter ions employed, using esr spectroscopy. By having sodium cations as the gegenion, *trans*-enediolates were only observed. Conversely using lithium ions gave only cis enediolates which they rationalised as a result of the oxaphilic nature of lithium cations.

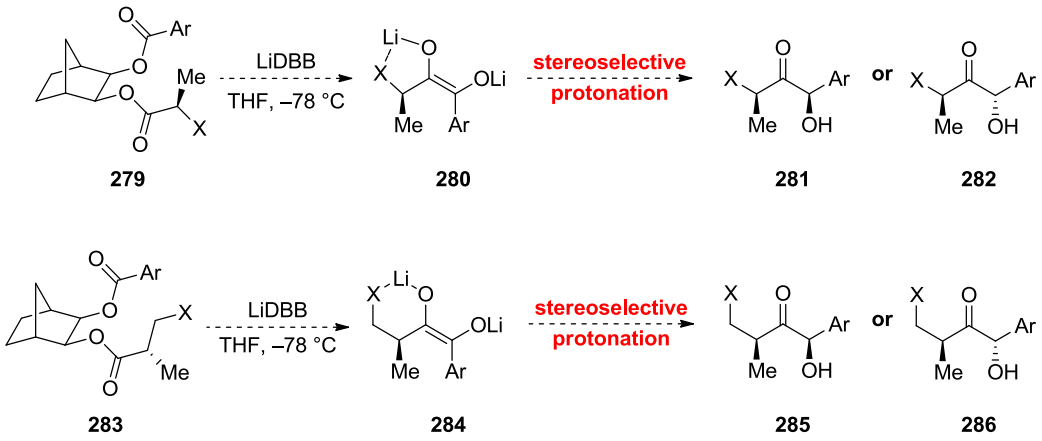
The overall aim was to be able to use this approach to perform crossed acyloin condensations to prepare compounds such as diesters **278** (*Scheme **62***). Our hypothesis was that by obtaining hydroxyl ketones such as **276**, it would enable overall access to *trans*-THFs by using methodology developed by Chamberlin to cyclise ketones onto epoxides (*See Chapter **1.3.2**).*[52]



*Scheme **62**: Overall aim of research.*

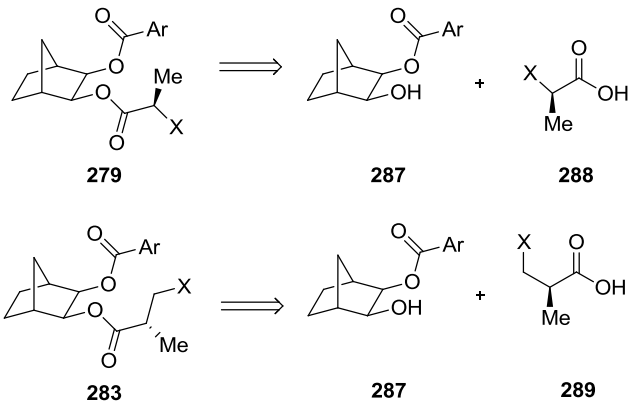
Accessing substrates similar to **276** would facilitate a short route to carry out subsequent stereoselective Sharpless asymmetric epoxidation (SAE) to reach **275**. It was postulated that treating substrates like **275** with borane dimethylsulfide complex would facilitate cyclisation as shown in *Scheme **62*** and discussed in *Chapter **1.3.2***.

Initial exploration into stereoselective protonation was pursued on simpler models. It was proposed that the use of a heteroatom, which could chelate the lithium in enediolate **280** or **284**, would induce diastereoselectivity in the final protonation of the enediolate intermediate formed in the acyloin reaction by taking advantage of the intrinsic stereocontrol of the enantiopure substrates with no need for additional chiral catalysts or auxiliaries (*Scheme **63***).



*Scheme **63**: Enolate intermediates in the chelation controlled diastereoselective protonation.*

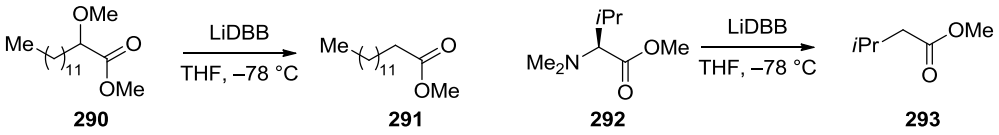
It was envisaged that compounds **279** and **283** could be produced by the coupling of hydroxy ester **287** with either carboxylic acid **288** or **289** (*Scheme **64***).



*Scheme **64**: Retrosynthetic analysis of compounds **279** and **283**.*

2.1.3 Synthesis Towards *α*-Functional Group Acyloins

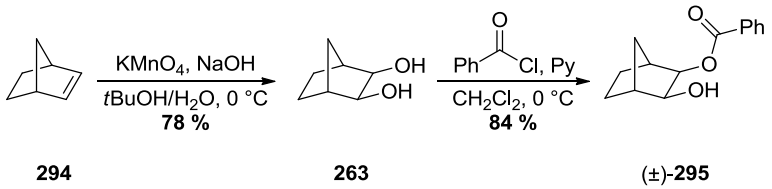
Previous work in the Donohoe group has shown that oxygen and nitrogen atoms at the *α*-position of untethered esters will eliminate under the reductive LiDBB conditions (*Scheme **65***).[71]



*Scheme **65**: Preliminary results obtained in the TJD group.*

It was hypothesised that the rate of coupling two esters could be faster than elimination of the *α*-functional group when the two acyl portions are tethered. To investigate this idea, *α*-methoxy ester (±)-**296** and *α*-dimethylamino ester (±)-**297** were synthesised from alcohol (±)-**295** (*Scheme **67***). Oxidation of commercially available norbornene **294**, followed by mono-esterification of the resulting diol **263** yielded hydroxy ester (±)-**295** in 66% yield over two steps (*Scheme **66***). Willson and co-workers determined the structure of **263** by X-ray crystallographic analysis.[72] The spectroscopic data of **263** matched the literature confirming the stereochemistry obtained. Ester (±)-**295** was obtained as a racemic mixture due to the lack

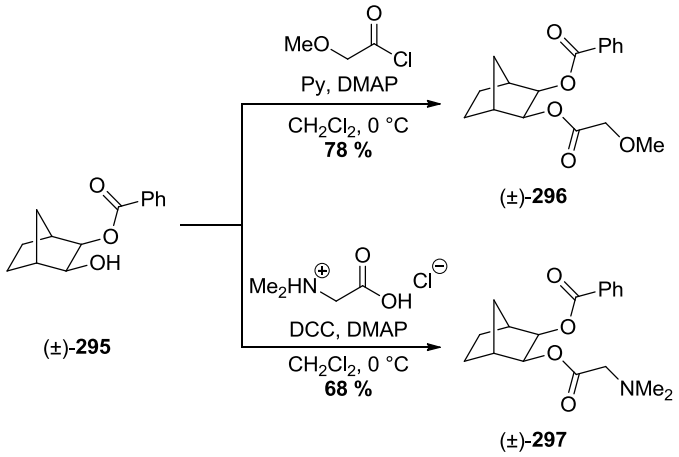
of stereochemical preference. The presence of an absorption peak at 1717 cm^{-1} in the I.R. spectrum of (±)-**295** is indicative of a carbonyl ester.



294 **263** (±)-**295**

*Scheme **66**: Synthesis of alcohol (±)-**295**.*

Treatment of alcohol (±)-**295** with 2-methoxyacetyl chloride gave *α*-methoxy ester (±)-**296**, whilst the *α*-dimethylamino analogue (±)-**297** was obtained *via* a DCC mediated coupling reaction between alcohol (±)-**295** and 2-(dimethylamino) acetic acid hydrochloride (*Scheme **67***).

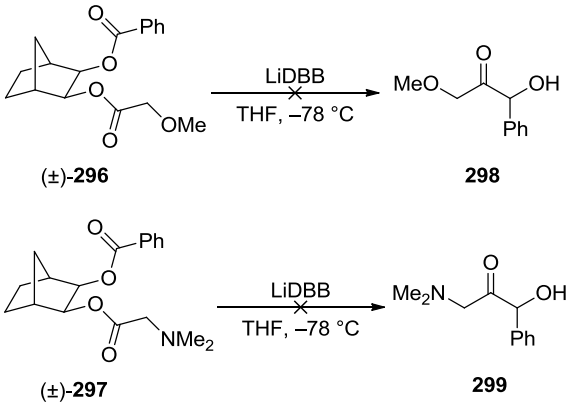


*Scheme **67**: Synthesis of α-heteroatom esters (±)-**296** and (±)-**297**.*

Due to the alcohol (±)-**295** being racemic, esterificiation led to racemic diesters. The ^1H NMR of diester (±)-**296** showed a chemical shift at δ_H 3.23 (3H, s) which is in accordance with the presence of a methoxy group present in diester (±)-**296**. Studying the ^1H NMR of (±)-**297** showed the presence of a chemical shift at δ_H 2.12 (6H, s) which is in accordance with the presence of the dimethyl amine in diester (±)-**297**.

Under the reductive conditions, both compounds (±)-**296** and (±)-**297** formed a complex mixture of products and there was no evidence of the formation of the desired acyloin

products. Moreover the characteristic chemical shifts of methoxy (δ_H ~ 3.3 ppm) or methylamino (δ_H ~ 2.0 ppm) peaks in the ^{1}H NMR spectra of the crude reaction mixtures could not be observed (*Scheme* ***68***).

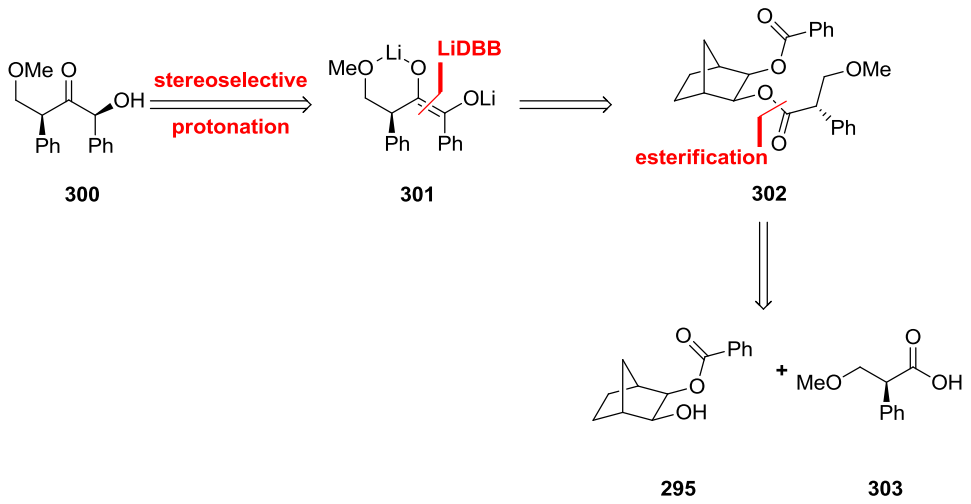


Scheme ***68****: Attempted LiDBB mediated coupling of (±)-****296*** *and (±)-****297****.*

Given the likely problems associated with *α*-fragmentation it was decided to explore the use of a heteroatom at the *β*-position instead.

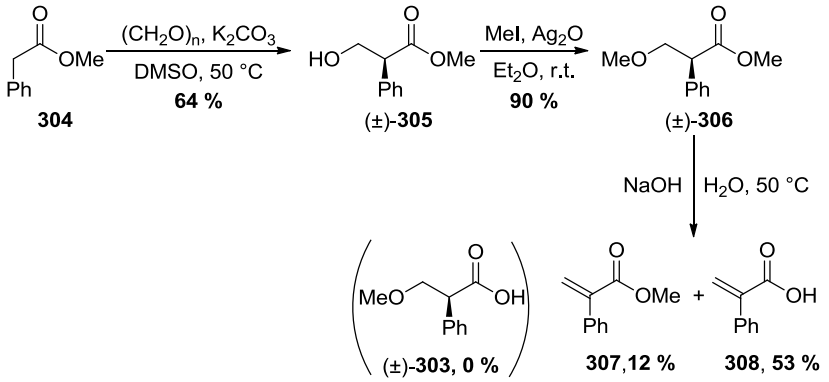
2.1.4 Synthesis Towards *β*-Heteroatom Acyloins

To investigate the stereoselectivity observed when reacting intermediate **301** with different proton sources, diester **302** would need to be synthesised from alcohol **295** and acid **303** (*Scheme* ***69***).



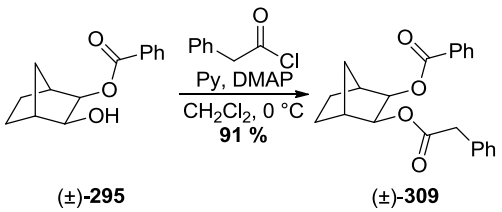
Scheme ***69****: Retrosynthetic analysis of* ***300****.*

For ease of synthesis, the racemic form of acid **303** was to be formed initially. In an attempt to access acid (±)-**303**, the analogous methyl ester (±)-**306** was prepared by firstly subjecting methyl 2-phenylacetate (±)-**304** and formaldehyde to basic reaction conditions to form *β*-hydroxy ester (±)-**305** in 64% yield. Methylation of the resulting primary alcohol yielded ester (±)-**306** in 90% yield. Under the basic conditions necessary for ester hydrolysis the additional elimination of the *β*-methoxy group was observed, giving both *α,β*-unsaturated ester **307** and acid **308** (*Scheme **70***).



*Scheme **70**: Approach towards the synthesis of β-methoxy acid (±)-**303**.*

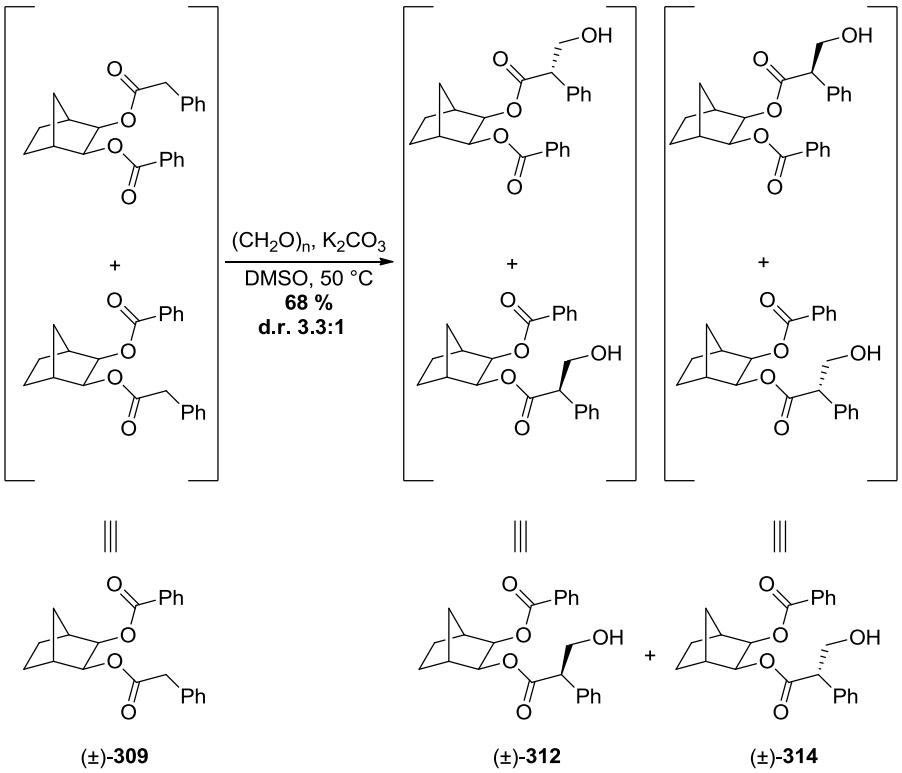
Coupling the carboxylate first followed by subsequent aldol avoids the problematic hydrolysis which led to eliminated products. Coupling the racemic alcohol (±)-**295** with phenylacetyl chloride gave the racemic diester (±)-**309**, which contained two absorption peaks in the I.R. spectrum at 1721 cm^{-1} and 1715 cm^{-1}, characteristic peaks for carbonyl functionalities (*Scheme **71**)*.



*Scheme **71**: Synthesis of diester (±)-**309**.*

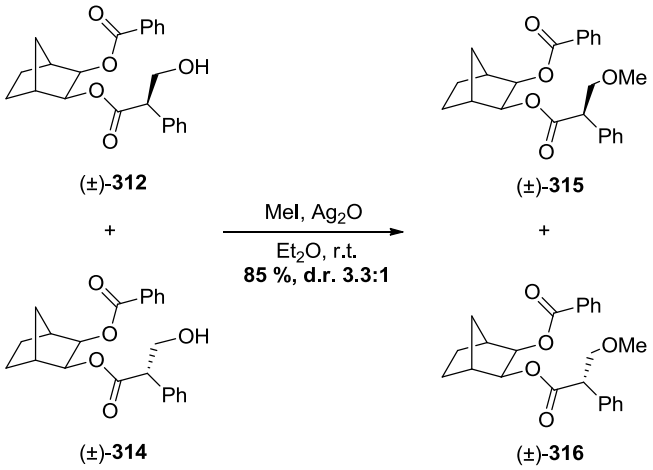
Subsequent aldol condensation with *para*-formaldehyde gave the *β*-hydroxy ester diastereoisomers (±)-**312** and (±)-**314** in a yield of 68% and in a 3.3:1 diastereomeric ratio

from (±)-**309** (*Scheme **72***). For clarity the racemic compounds are also drawn as their individual enantiomers.



*Scheme **72**: Formation of diastereoisomers (±)-**312** and (±)-**314**.*

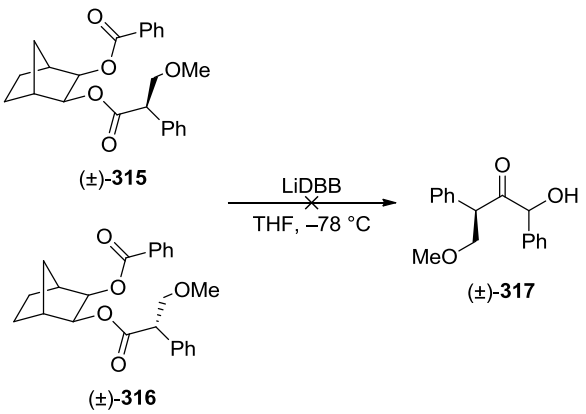
The presence of an I.R. absorption peak at 3504 cm^{-1} indicated the presence of a hydroxyl functional group. The diastereomeric ratio was calculated by measuring the integral of the chemical shift identified as the C*H*CH_2OH for each of the diastereoisomers. The diastereomeric ratio was calculated to be 3.3:1 although it was not possible to determine which of the compounds (±)-**312** or (±)-**314** was the major isomer. Subsequent methylation gave the desired *β*-methoxy diastereoisomers (±)-**315** and (±)-**316** in a combined yield of 85%, with no loss of the diastereomeric excess (*Scheme **73***).



*Scheme **73**: Methylation of the diastereoisomers (±)-**312** and (±)-**314**.*

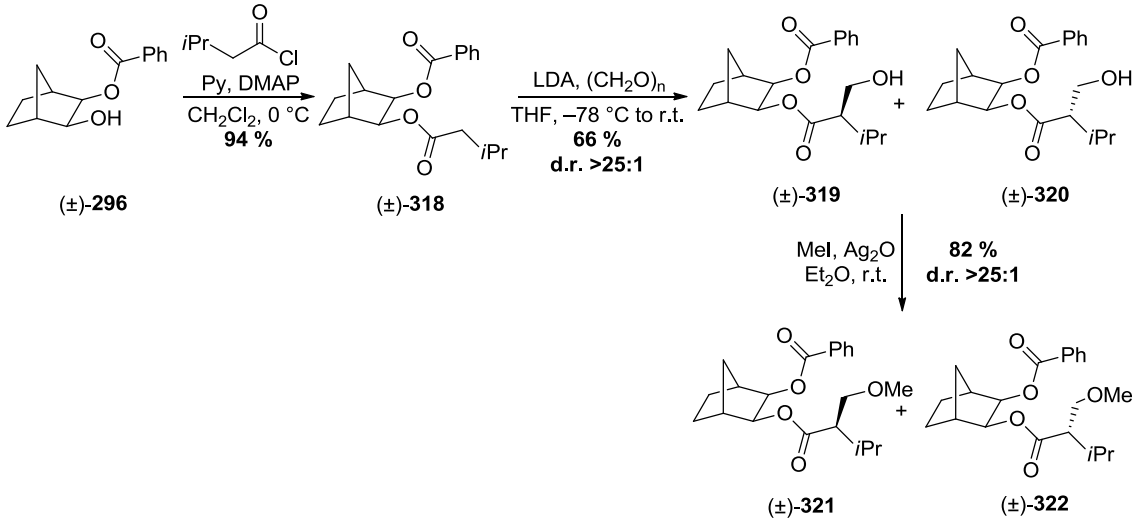
The loss of the O-H absorption peak in the I.R spectrum and the presence of peaks at δ_H 3.22 ppm and δ_H 3.09 ppm in the ^{1}H NMR spectra of the isolated products are indicative of O*CH*$_3$ protons suggesting successful methylation of the hydroxyl group.

Multiple products were formed when a mixture of compounds (±)-**315** and (±)-**316** was submitted to the LiDBB conditions. The ^{1}H NMR spectra of the crude reaction mixtures showed distinctive peaks corresponding to terminal protons, suggesting that the LiDBB conditions had promoted elimination of the *β*-methoxy group. It was suspected that the stabilisation of the conjugate base by the *α*-phenyl group resulted in an increased acidity of the *α*-proton, finally leading to elimination. Thus, it was assumed that this side reaction could be prevented by using an aliphatic group, such as *iso*-propyl instead of the aromatic moiety (*Scheme **74***).



*Scheme **74**: Attempt at LiDBB mediated acyloin condensation.*

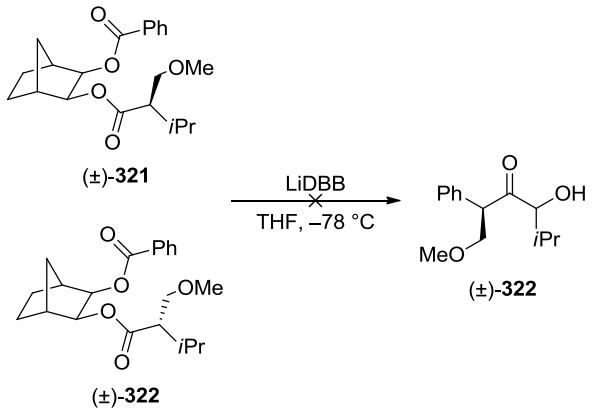
Thus diester (±)-**318** was synthesised starting from alcohol (±)-**319** and *iso*-valeryl chloride in 94% yield (*Scheme **75***). *β*-Hydroxy esters (±)-**319** and (±)-**320** were formed in a combined yield of 66%, with a diastereomeric ratio >25:1. Interestingly this is a higher diastereomeric ratio to that obtained forming (±)-**312** and (±)-**314**. This was attributed to the change in the base used for the aldol condensation. Potassium carbonate was not basic enough to carry out the reaction, reflecting the greater acidity of benzylic protons, and thus lithium diisopropylamide was required increasing the ratio of diastereoisomers. Again the ratio was determined by comparing the integrals of the chemical shift peaks corresponding to the C*H*CH_2OH in the ^1H NMR spectrum.



*Scheme **75**: Synthesis of diesters (±)-**321** and (±)-**322**.*

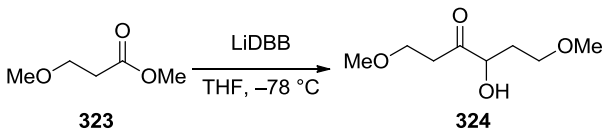
Finally methylation of the resulting hydroxy esters gave (±)-**321** and (±)-**322** in a combined yield of 82%, with no erosion of the diastereomeric ratio. Formation of the product was evident from the OCH_3 chemical shift peak at δ_H 3.17 ppm.

However, under the same LiDBB conditions, multiple products formed and the ^{1}H NMR spectrum of the crude reaction mixture still showed terminal protons, indicating that elimination of the methoxy group was taking place (*Scheme **76***).



*Scheme **76**: Attempt at LiDBB mediated acyloin condensation.*

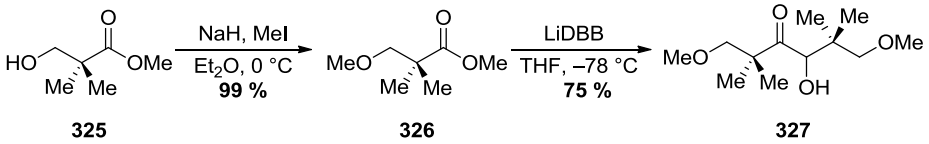
To investigate if the elimination could be prevented, different conditions and work-up procedures were employed using the intermolecular acyloin coupling of commercially available methyl 3-methoxypropanoate **323** as a model substrate (*Table **3***).



Entry	Type of Addition of Ester 323	Quench	Result
1	Fast addition	Methanol	7% Mass recovery No methoxy ^{1}H NMR peak
2	Slow addition	Methanol	6% Mass recovery No methoxy ^{1}H NMR peak
3	Fast addition	NH_4Cl(aq)	8% Mass recovery No methoxy ^{1}H NMR peak
4	Slow addition	NH_4Cl(aq)	12% Mass recovery No methoxy ^{1}H NMR peak
5	Reverse addition	NH_4Cl(aq)	2% Mass recovery No methoxy ^{1}H NMR peak

*Table **3**: Conditions and work-up procedures investigated for acyloin condensation of ester **323**.*

Both fast and slow addition (over two hours) of a solution of methyl ester **323** in tetrahydrofuran still gave poor mass recovery. Switching from the methanol quench to a more acidic saturated aqueous solution of ammonium chloride again gave similarly poor mass recovery (Entry 3-4). Adding the LiDBB solution to the substrate also proved unsuccessful (Entry 5). In all cases the ^{1}H NMR spectrum of the crude material gave no indication of the product or the characteristic methoxy peaks; the low mass recovery was attributed to the volatility of the elimination products. To examine whether elimination of the *β*-methoxy group was causing the poor mass recovery, *gem*-dimethyl methyl ester **326** was synthesised in quantitative yield from the commercially available alcohol **325** (*Scheme 77*).



325 **326** **327**

*Scheme 77: Methylation of **325** and acyloin condensation of methyl ester **326**.*

Under the LiDBB conditions acyloin **327** was formed in 75% yield, suggesting elimination had occurred in the previous cases (*Scheme 77*). Under these reductive conditions, *β*-elimination of the methoxy group proceeds efficiently and would prevent any chance of effectively controlling diastereoselectivity of the final protonation step. An alternative method to induce stereoselective protonation was explored.

2.1.5 Diastereoselective Protonation Using Allylic 1,3 Strain

The influence of allylic 1,3 ($A^{1,3}$) strain in chemical reactions is a well recognised method for controlling the outcome of diastereoselective reactions.[73] It was decided to use this approach to probe the stereoselectively protonating the *bis*-enolate shown in *Figure 5*. This uses work conducted by Russell and co-workers[70] and the hypothesis that the bis-enolate exists as the *cis* isomer exclusively.

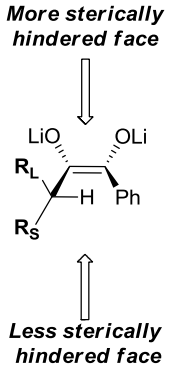
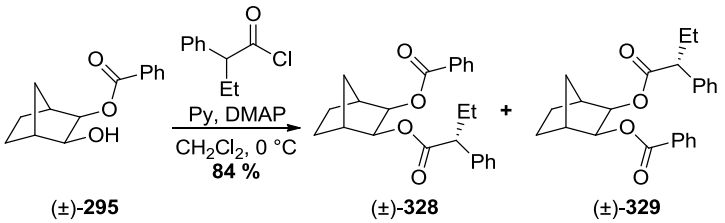


*Figure **5**: Proposed model for stereoselective protonation.*

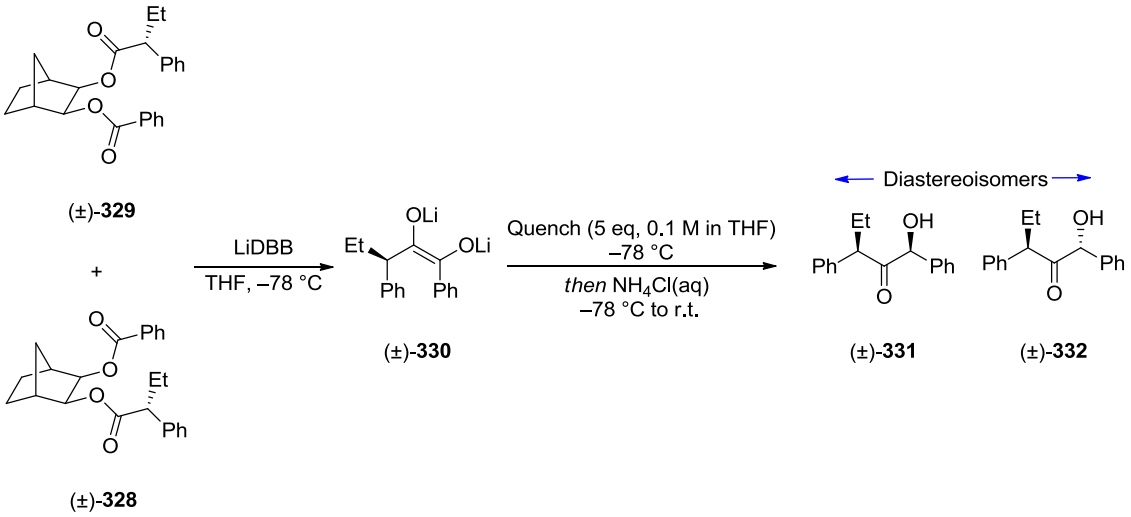
Diesters (±)-**328** and (±)-**329** were synthesised from alcohol (±)-**295** and commercially available 2-phenylbutanoyl chloride in a combined yield of 84%, with a 1:1 diastereomeric ratio (*Scheme **78***).



*Scheme **78**: Synthesis of acyloin precursors (±)-**328** and (±)-**329**.*

The diastereomeric ratio was determined by measuring the integrals of the peaks in the ^{1}H NMR spectrum at δ_H 3.28 ppm and δ_H 3.17 ppm corresponding to the protons at C*H*CO_2 for each diastereomer.

With diesters (±)-**328** and (±)-**329** in hand, the level of diastereoselectivity afforded to the acyloin products was explored by systematically investigating different quenching methods and proton sources (*Table **4***).



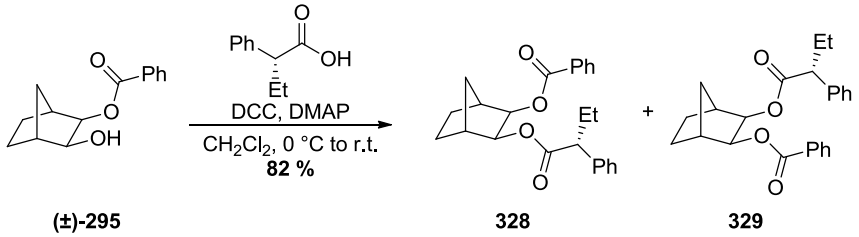
Entry	Quench	Diastereoselectivity[a]	Yield[b]
1	NH_4Cl(aq)	1.2:1	18%
2	MeOH[c]	2.0:1	23%
3	MeOH	1.3:1	34%
4	*t*BuOH	1.5:1	25%
5	PhOH	1.9:1	32%
6	2,6-Di-*tert*-butyl-4-methylphenol	3.9:1	56%
7	2,6-Di-*tert*-butyl-4-methylphenol[d]	3.8:1	57%
8	2,6-Di-*tert*-butyl-4-methylphenol[e]	3.6:1	52%
9	Pyridine hydrogen chloride	2.6:1	47%
10	2,6-Di-*tert*-butyl-4-methylpyridine hydrogen chloride	4.6:1	58%
11	2,6-Dichloropyridine hydrogen chloride	3.2:1	49%
12	Benzoic acid	1.8:1	23%

*(a) Diastereoisomeric ratio (±)-**331**:(±)-**332**; (b) Yield of isolated diastereomer (±)-**331**; (c) Without NH_4Cl(aq); (d) 1.5 hours, then NH_4Cl(aq); (e) DBE added before quench.*
*Table **4**: Table of results for different quenching methods and sources.*

To observe the ratio of product isomers, the DBB had to be removed by rapidly flushing the crude mixture through a pad of silica. The diastereomeric ratios were determined from the ^{1}H NMR spectra of the crude reaction mixtures. Later experiments demonstrated that (±)-**331** was the major diastereomer (see below). The results showed that diastereoisomers (±)-**331** and (±)-**332** were preferentially formed (Entries 1-12), which was in line with other cross acyloin reactions on aliphatic and aryl esters (*See Chapter **2.1.1.3***). *tert*-Butanol gave a

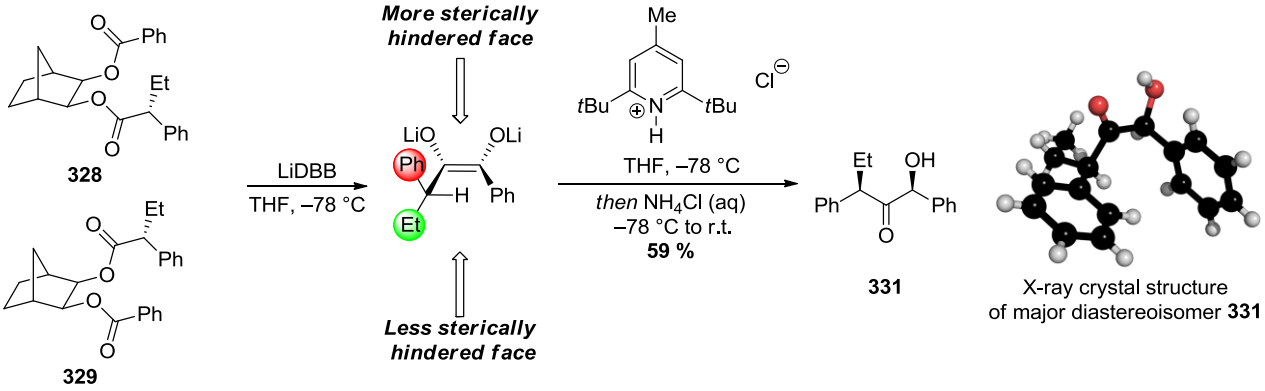
similar diastereomeric ratio of 1.5:1 (Entry 4) compared to methanol (1.3:1, Entry 3). Using phenol the diastereoselectivity (1.9:1, Entry 5) was enhanced. It was anticipated that using hindered analogues of phenol the ratio of diastereoisomers formed would improve. The diastereoselectivity was further augmented by using 2,6-di-*tert*-butyl-4-methylphenol, a hindered equivalent to phenol, thus increasing the diastereoselectivity to 3.9:1 (Entry 6). 2,6-Di-*tert*-butyl-4-methylpyridine hydrochloride gave the best diastereoselectivity of 4.6:1 (Entry 10), which was attributed to the acidic proton being further shielded by the *tert*-butyl groups.

Diastereoisomer **331** was required in scalemic form to check if racemisation had occurred. Coupling of (*R*)-2-phenylbutanoic acid and alcohol (±)-**295** using DCC gave a 1:1 mixture of diesters **328** and **329** in 82% yield (*Scheme **79***).



*Scheme **79**: Formation of **328** and **329**.*

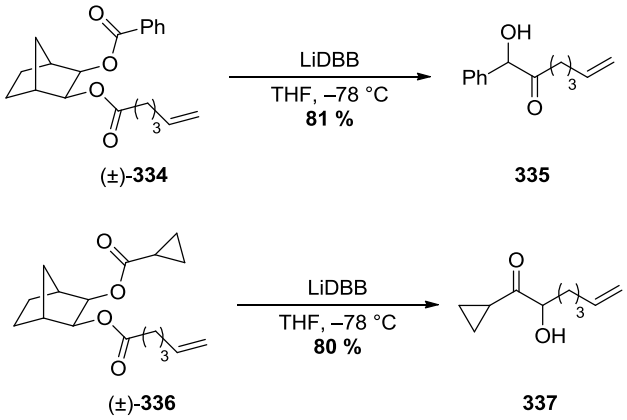
This mixture was then submitted to the LiDBB conditions and quenched with 2,6-di-*tert*-butyl-4-methylpyridine hydrochloride, giving **331** in 59% yield and an X-ray crystal structure of this compound was obtained. The relative configuration of this isomer was in line with that predicted by the allylic 1,3 strain effect, assuming the enediolate existed as the *cis* isomer (in accordance with work by Russell and co-workers)[70] (*Scheme **80***).



*Scheme **80**: **329** and submitted to LiDBB conditions and proposed allylic 1,3 strain model.*

The model proposed in *Scheme **80*** assumes the enediolate exists as a *cis* isomer. This hypothesis leads to the observed stereochemical outcome in which the hydroxyl group is syn to the ethyl group. Mosher's esters of racemic and scalemic acyloin **331** provided evidence that racemisation had not occurred under the LiDBB conditions (*See Appendix **1.1***).

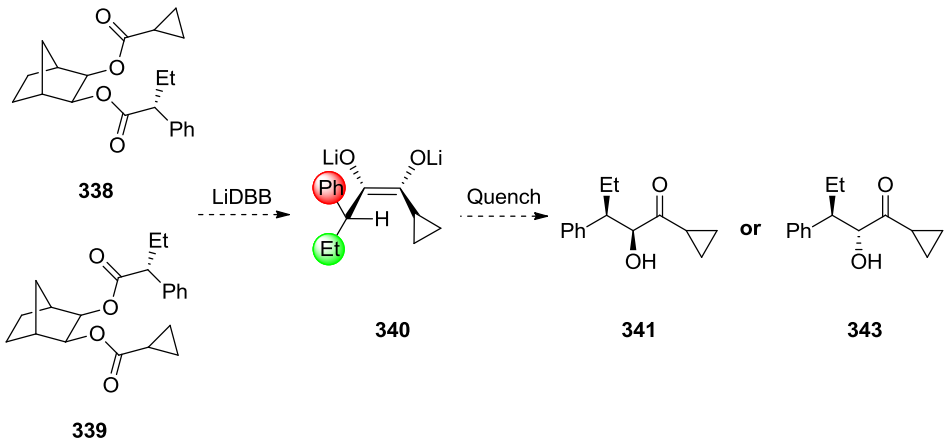
As previously discussed in *Chapter **2.1.1.3***, the crossed acyloin condensation developed in the Donohoe group is selective for the formation of hydroxy ketones whereby the hydroxy group is selectively formed adjacent to the aryl group (*Scheme **59***). Work carried out by co-workers in the Donohoe group has also revealed the reverse selectivity for the other regioisomer whereby the carbonyl is adjacent to the cyclic substituent when using cyclopropanecarboxylate as one of the substitutents (*Scheme **81***).[74]



*Scheme **81**: Reported acyloin condensation of (±)-**334** and (±)-**336**.[74]*

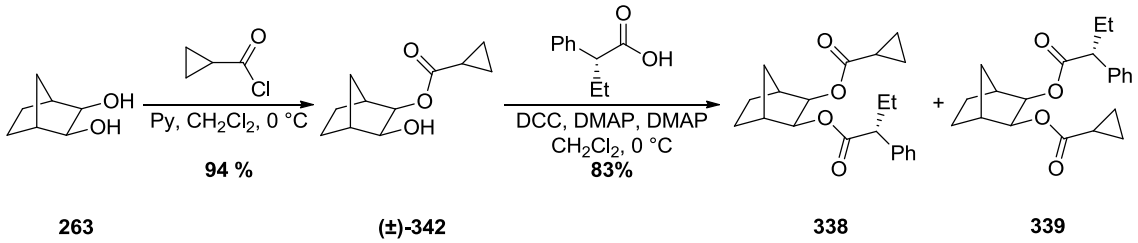
This reflects the observation that the hydroxy ketone formed is the kinetic product (*See Chapter **2.1.1.3***); when the aromatic substituent is replaced with a cyclopropyl group, the hydroxyl formed is adjacent to the aliphatic substituent. This reflects the strong π-donor characteristic cyclopropanes possess in stabilising *α*-cations.[75]

Using this result, it was envisaged that the hydroxyl group from the acyloin formed would be adjacent to the stereocenter, thus leading to increased stereoselectivity (*Scheme **82***).



*Scheme **82**: Proposed stereoselective protonation.*

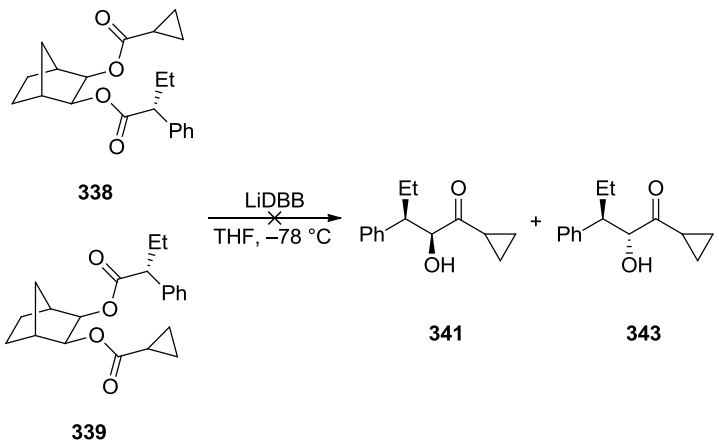
To investigate this approach the synthesis of diesters **338** and **339** was attempted using acylation chemistry discussed previously (*Scheme **83***).



*Scheme **83**: Synthesis of the inseparable mixture of diastereomers **338** and **339**.*

Acylation using cyclopropanecarbonyl chloride yielded the hydroxyl ester (±)-**342** in 94%. Subsequent esterifcation using (*R*)-(−)-2-phenylbutyric acid gave diastereoisomers **338** and **339** as a 1:1 inseparable mixture in 83% yield.

Submitting this mixture to the established LiDBB conditions, no hydroxyl ketone product could be isolated from the reaction mixture (*Scheme **84***).



*Scheme **84**: Approach towards a crossed acyloin condensation of a mixture of **338** and **339**.*

Examining the ^{1}H NMR spectrum of the crude reaction mixture showed a lack of a chemical shift with a peak typical for hydroxy ketones (δ_H 5.00-5.50 ppm). Also TLC of the crude reaction mixture showed multiple product spots formed. The propensity for ring opening of cyclopropanes is well known[76] and it was decided due to the difficulties associated with radical ring opening not to explore this area further.

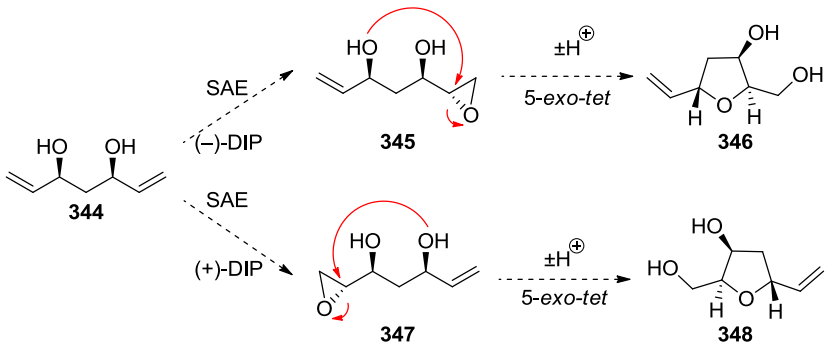
2.1.6 Conclusion

The crossed acyloin condensation using the homogeneous LiDBB conditions developed by the Donohoe group is a shows the possibility to couple two different esters together. This methodology was further explored to stereoselectively protonate the product formed and was successful in the case of using the diester of (*R*)-(−)-2-phenylbutyric acid and benzoic acid. Due to the nature of the LiDBB conditions, it was unsuccessful in coupling esters featuring further heteroatoms and we decided to discontinue research into this reaction.

2.2 Desymmetrisation using Sharpless Asymmetric Epoxidation Towards *trans*-THFs

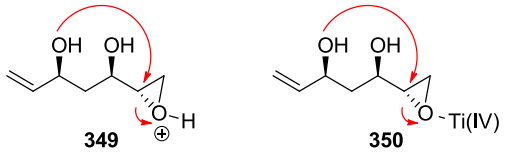
2.2.1 Aim and Previous Work

As discussed in the introduction (*See Chapter **1.2.3.3***), the Sharpless asymmetric epoxidation (SAE) is a powerful method to oxidise allylic alcohols stereoselectively. Moreover, we thought that it could be employed towards the synthesis of *trans*-THFs. We envisaged utilising the SAE to desymmeterise the *meso*-diol **344**, using different tartrate-derived enantiomers to selectively differentiate not only the two enantiotopic allylic alkenes but also their diastereotopic faces, and thereby generating an epoxide which could perform a cyclisation to give the desired THF (*Scheme* **85**).



*Scheme **85**: Proposed desymmetrisation of meso-diol **344**.*

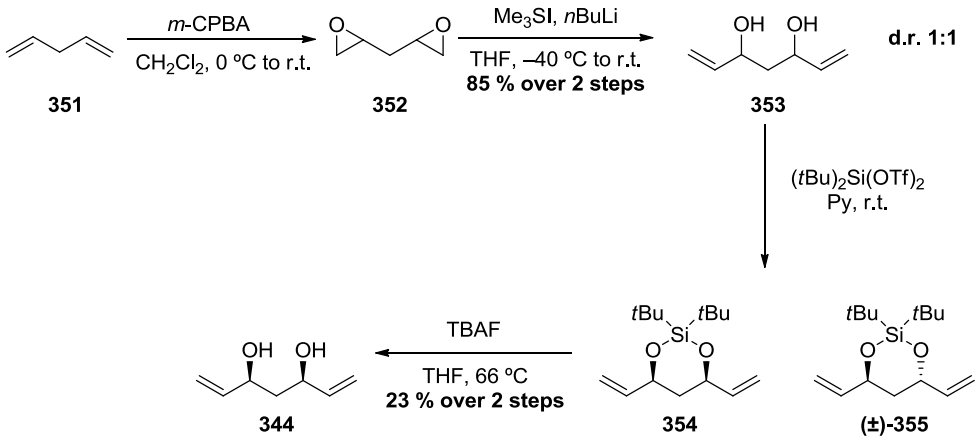
Utilising the appropriate tartrate-derived enantiomer, for example (−)-DIP, epoxidation would occur on one allylic alcohol to give epoxide **345**. The presence of a hydroxyl group should induce cyclisation whereby the alcohol acts as a nucleophile onto the electrophilic epoxide, *via* 5-*exo*-tet cyclisation to give the desired *trans*-THF **346**. It was presumed that the cyclisation could be induced by either a protonation of the epoxide afterwards or *in situ* by the titanium (IV) species acting as an oxaphilic Lewis acid (*Scheme* **86**).



*Scheme **86**: Proposed mechanism of 5-exo-tet cyclisation.*

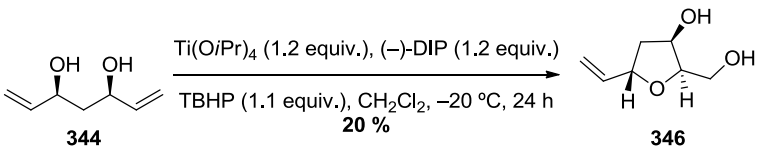
This investigation was initially carried out by co-worker Ali Jahanshahi in the Donohoe group exploring the utility of a one-pot SAE and cyclisation of *meso*-diol **344**.[74]

The *meso*-diol **344** was formed from penta-1,4-diene **351** in 4 steps in 20% overall yield with a challenging bis-epoxide opening reaction (*Scheme **87***).



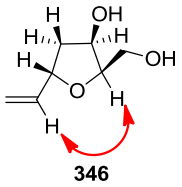
*Scheme **87**: Previous synthesis of **344**.*

Oxidation to the bis-epoxide **352** was found to be challenging as the epoxide formed was difficult to handle and the reaction was unreliable. Moreover, **353** was isolated as a mixture of isomers. After silyl protection the isomers were separated using flash column chromatography yielding diol analogues **354** and (±)-**355**. Finally deprotection of **354** gave the diol **344**. SAE epoxidation was carried out using (−)-DIP tartrate to give THF **346** (*Scheme **88***).



*Scheme **88**: Reported THF formation by Ali Jahanshahi.*

Conditions developed by Ali Jahanshahi were reported to give THF **346** in 20% yield and > 90% e.e. (confirmed through the preparation of Mosher ester derivatives). The structure was confirmed through NOE based NMR studies giving through space interactions between the appropriate protons (*Scheme **89***).

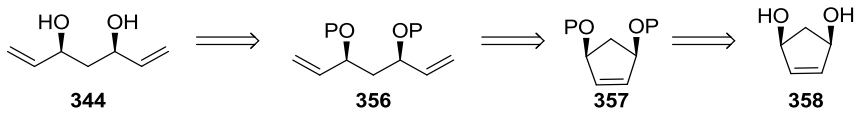


*Scheme **89**: NOE interactions as reported by Ali Jahanshahi.*

While this route utilises the SAE to give access to *trans*-THF **346**, the current limitations are the lack of an efficient route to the precursor **344** and the moderate yield of the SAE itself. Furthermore a confirmation of the e.e. value by HPLC needed to be performed. Thus the objectives of this work are to overcome these limitations in turn to develop a reliable route to THF **346**.

2.2.2 Synthesis of *meso*-Diol 344

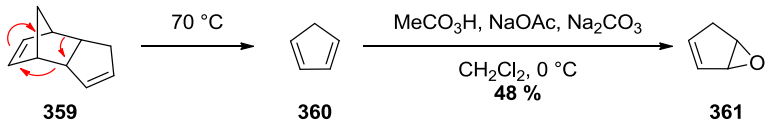
The first objective was the development of an efficient route towards the *meso*-diol **344** from commercially available sources. It was thought that the bis-alkene **356** could be formed from the cyclopentene precursor **357** by exploiting ring opening metathesis (ROM) chemistry (*Scheme **90***).



*Scheme **90**: Proposed retrosynthesis of diol **344**.*

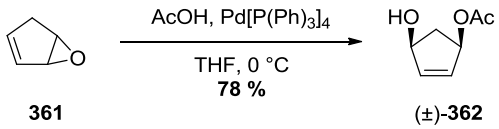
By inducing strain on cyclopentene diol **358**, such as by steric clashing or invoking ring strain by bridging the two hydroxy groups *via* a tether, it was envisaged that ROM with ethylene gas might be encouraged.

Although diol **358** is commercially available, it was easily accessed in three steps from dicyclopentadiene **359**. Synthesis of diol cyclopentene **358** started with the epoxidation of cyclopentadiene **360**, cracked from commercially available dicyclopentadiene **359** *via* a retero Diels-Alder reaction (*Scheme* **91**).



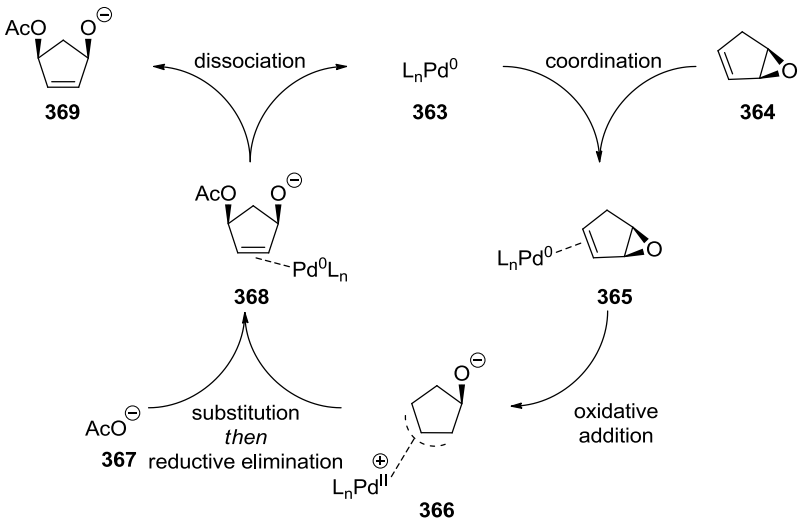
*Scheme **91**: Formation of epoxide **361**.*

Cracking dicyclopentene **359** at 70 °C, followed by epoxidation using peracectic acid at 0 °C yielded the epoxide **361** in 48%, proven by the chemical shifts at δ_H 3.83-3.76 ppm and δ_H 3.73-3.68 ppm in the proton NMR spectrum, typical proton shifts of allylic epoxides. The spectroscopic data matched the literature reported data for **361**.[77] Treatment of epoxide **361** with acetic acid and tetrakis(triphenylphosphine)palladium(0) under Tsuji-Trost type conditions, gave allylic alcohol (±)-**362** in 73% yield (*Scheme **92***).



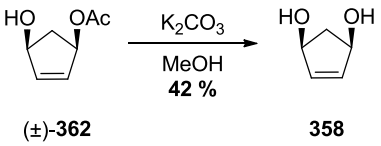
*Scheme **92**: Formation of cyclopentene (±)-**362**.*

The reaction occurs with initial coordination of palladium across the double bond to form an η^2 palladium complex **365** (*Scheme **93***).



*Scheme **93**: Mechanism for the formation of **369**.*

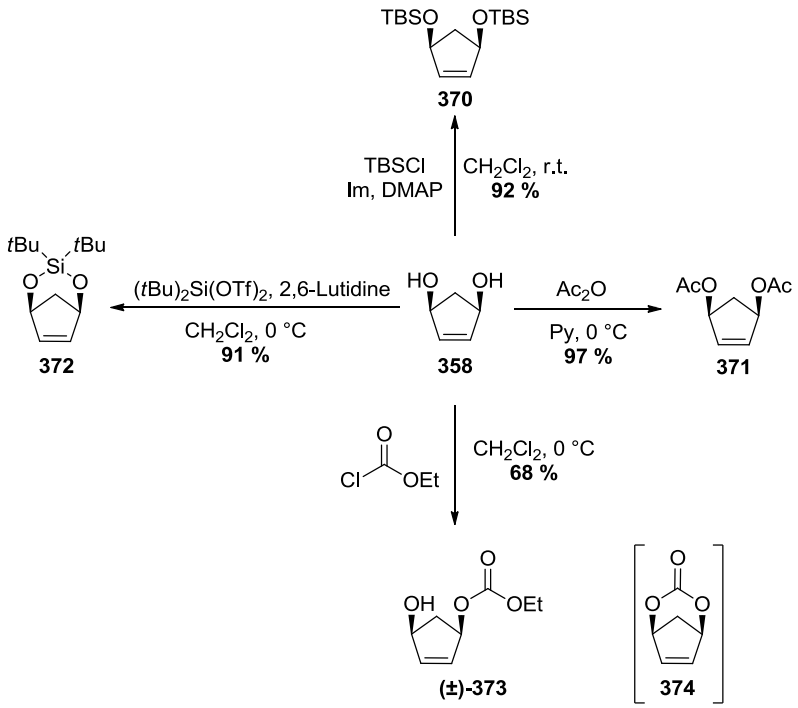
The palladium then oxidatively adds to the less hindered face of the cyclopentene epoxide. This gives the η^3 π-allyl complex **366** which is subsequently attacked by an acetate anion **367** to the opposite face to the palladium complex to form **368**. The nucleophile attacks the less hindered carbon of the η^3 complex to reduce steric collision. These two steps, oxidative addition and nucleophilic attack, determine the cis-stereochemistry of the product. As before the spectroscopic data matched the reported data for (±)-**362**.[77] Methanolysis of the acetate **362** yielded the diol **358** in 42% (*Scheme **94***).



*Scheme **94**: Formation of diol **358**.*

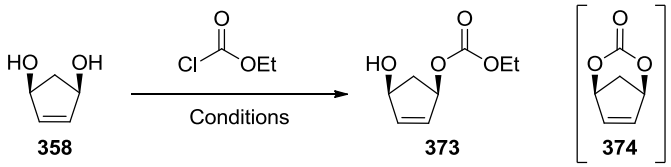
The low yield of **358** was attributed to the polar nature of the diol causing it to be difficult to be isolated and purified. The spectroscopic data of **358** was identical to the reported literature data.[78]

Therefore starting with cyclopentene diol **358**, a range of protected cyclopentene derivatives were synthesised (*Scheme* **95**).



*Scheme **95**: Reactions of cyclopentene diol **358**.*

Reaction of TBSCl with cyclopentene diol **358** gave the desired bis-silicon protected product **370** in an excellent 92% yield, confirmed by the integrals of methyl protons from the TBS protecting group in the ^{1}H NMR spectrum of the isolated product. Acylating diol **358** with acetic anhydride and pyridine yielded the diacetate product **371** in 97% yield, indicated by a peak with the chemical shift of δ_C 170.7 ppm in the ^{13}C NMR spectrum of the isolated product. The tethered silicon protection of diol **358** using di-*tert*-butylsilyl bis(trifluoromethanesulfonate) gave the silicon protected product in 91% yield. This was supported by the presence of the *tert*-butyl moieties of the silyl group at δ_H 0.97 ppm and 0.89 ppm. Finally, the reaction of ethyl chloroformate with diol **358** did not provide the carbonate **374**, instead a side product **373** was identified. Alternative conditions were explored to form carbonate **374** (*Table* **5**).

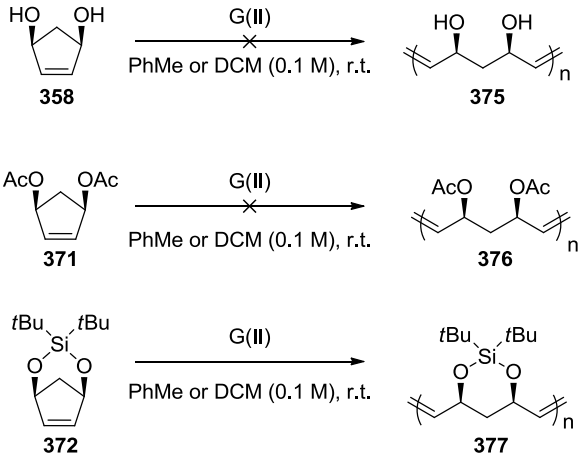


Entry	Conditions	Yield of 373	Yield of 374
1	CH_2Cl_2, r.t.	49%	n/o
2	CH_2Cl_2, reflux	33%	n/o
3	NaH, THF, 0 °C	25%	n/o
4	NaH, THF, reflux	12%	n/o

*Table **5**: Conditions screened to form carbonate **374**.*

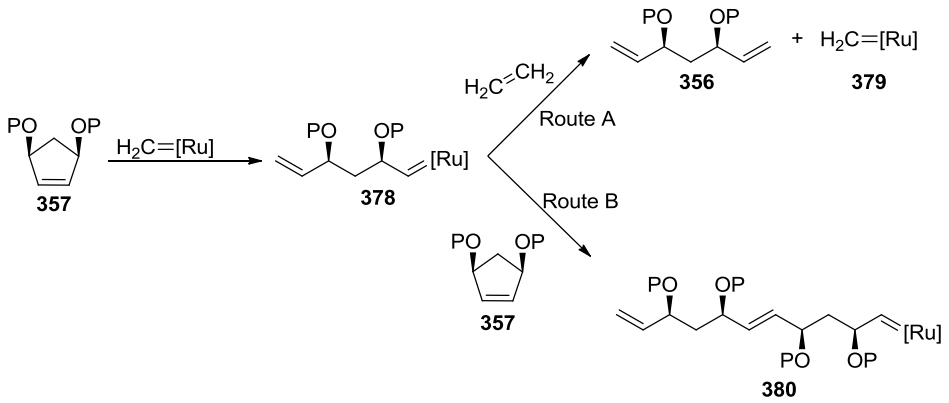
It was found that the formation of carbonate **374** was unfavourable. Although entropically advantageous, the generation of the cyclic carbonate would be energetically unfavoured due to the strain induced on the ring created. However, with compounds **370**, **371** and **372** in hand, suitable substrates for the following ROM were provided.

In 2002, Grubbs *et al.* reported ROMP on the silicon protected cyclopentene diol **372**, which had failed on the free diol **358** and the diacetate analogue **371** (*Scheme **96***).



*Scheme **96**: ROMP on cyclopentene derivatives reported by Grubbs.*[79]

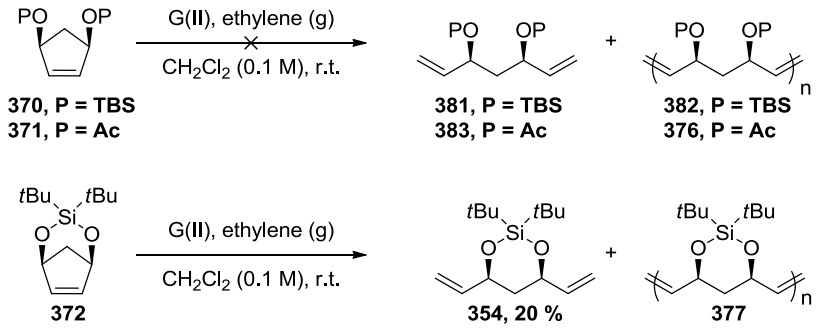
The driving force of ROMP is the relief of ring strain induced by the bridging silicon group. It was thought by using ethylene gas as a reagent selective ROM could be performed, while ROMP could be prevented (*Scheme **97***).



*Scheme **97**: Proposed mechanism for ROM of compound **357**.*

Initial ROM of cyclopentene **357** would give compound **378**. This ruthenium complex would have the opportunity to either react with a molecule of ethylene gas or starting cyclopentene **357**. Route B would give the unwanted dimer **380**, whereas Route A would give the desired monomer **356**. This would be useful in forming the bis-alkene **344** in an efficient short synthesis. Moreover, due to the nature of the conditions the stereocentres should be unaffected.

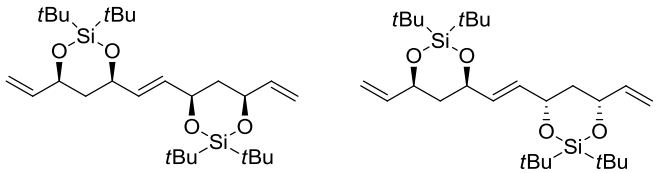
Thus each cyclopentene derivative was submitted to the ROM conditions developed by Grubbs,[79] with ethylene gas from a balloon attached to a needle bubbled through the reaction mixture at room temperature. All reactions were performed on a 100 mg scale (*Scheme **98***).



*Scheme **98**: Initial attempts employing ROM.*

Submitting the two substrates **370** and **371** to these conditions gave only recovered starting material. It was anticipated that the close proximity of the TBS groups on **370** and the acetate groups on **371** would favour a ring opening reaction due to the relief of strain. The lack of

reactivity under these conditions is in agreement to what Grubbs reported for **372**.[79] Nevertheless, it was anticipated that the presence of ethylene gas may favour the reaction by initiating the catalyst to perform the desired ROM.[80] Finally, it was found that performing the ROM on **372** yielded the 1,6-heptadiene **354** in 20%. Confirmation of the identity of the isolated product was obtained by analysing the ^{1}H NMR spectrum which indicated the presence of three different vinylic protons with chemical shifts of δ_H 5.90 ppm, 5.29 ppm and 5.13 ppm, typical for a terminal alkene and identical to the data reported by Ali Jahanshashi.[74] The rest of the material was obtained as a mixture of polymers, the major being cross metathesis products of two monomeric units (*Scheme **99***).

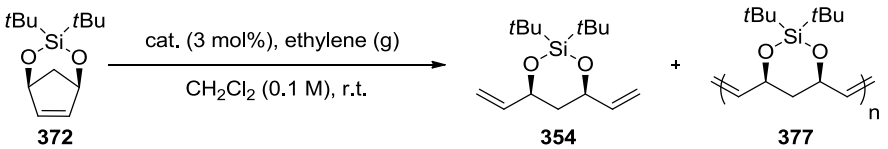


(±)-**384** **385**

*Scheme **99**: Major products isolated.*

This dimer was identified using mass spectrometry, revealing a peak at 531 $[M + Na]^+$. The spectroscopic data for this compound matched the data Grubbs and coworkers had reported on the dimers (±)-**384** and **385** from the ROMP of **372.**[79]

In order to suppress polymerisation of the bridged silicon tethered **372**, initial screening of different metathesis catalysts was carried out on **372** (*Table **6***).



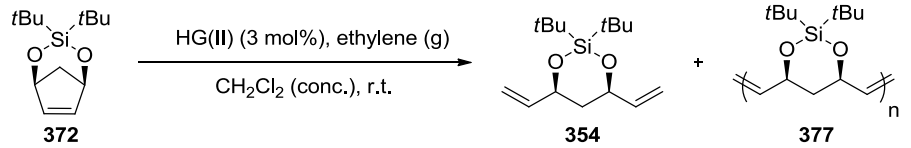
372 **354** **377**

Entry	Catalyst	Yield of 354
1	G(II)	20%
2	G(I)	22%
3	HG(II)	30%

*Table **6**: Catalysts screened.*

The catalysts screened were Grubbs catalyst, first generation (G(I)) and Hoveyda-Grubbs second generation catalyst (HG(II)). Using G(I) gave a comparable yield to G(II), which can be interpreted as the two catalysts having similar reactivity towards the ROM process (Entry 2). HG(II) gave a higher yield than the previous two catalysts, which suggests the catalyst is more selective at performing a cross metathesis with ethylene gas than G(I) or G(II). With this result in hand, attention turned to the concentration of the reaction mixture.

The reaction concentration was thought to be important in reducing polymerisation; lowering the concentration of cyclopentene **372** would favour formation of the monomeric product. Thus a series of concentrations were explored to minimise polymerisation (*Table 7*).



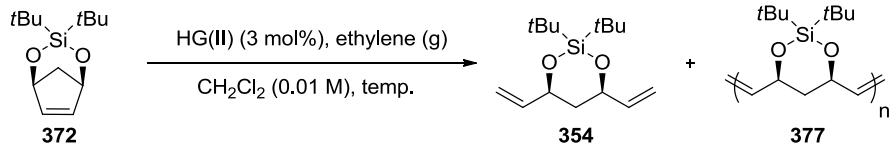
372 **354** **377**

Entry	Concentration	Yield of 354
1	0.10 M	30%
2	0.05 M	62%
3	0.01 M	68%
4	0.01 M	78%[(a)]

(a) *Slow addition of **372** via a syringe pump.*
Table 7: Conditions screened for concentration.

Clearly decreasing the concentration of the reaction mixture disfavoured polymerization (Entries 1-3). Performing the reaction at high dilution reduces the propensity for a monomer ruthenium carbenoid to react with a molecule of **372**. The reaction in entry 4 examined the use of a syringe pump. A solution of cyclopentene **372** was dissolved in dichloromethane (0.02 M) and added dropwise (30 mL/h) to an ethylene gas bubbled solution of HG(II) in dichloromethane (0.02 M) resulting in a total concentration of 0.01 M relative to **372**. This procedure improved the yield reflecting the concentration dependence of the reaction and was used hereafter.

At lower temperatures, gases are generally more soluble and so the reaction was performed at 0 °C and at −78 °C to see if the yield was improved (*Table **8***).



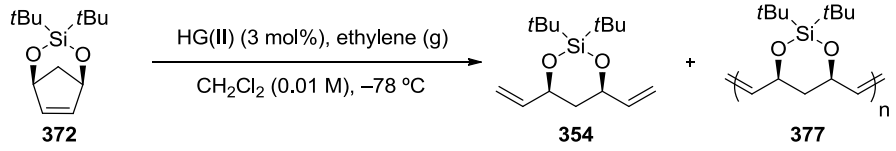
372 **354** **377**

Entry	Temperature	Yield
1	r.t.	78%
2	0 °C	73%
3	−78 °C	89%

*Table **8**: ROM performed at variable temperatures.*

Decreasing the temperature proved to be an efficient tool to increase the yield of the isolated monomeric product **354** (Entry 1-3). Performing the reaction at −78 °C did give the highest yield and it was decided to carry out further reactions at this temperature.

The screening experiments were all carried out on a 100 mg scale based on **372**. With optimised conditions in hand, the reaction was carried out on a larger 400 mg scale (*Table **9***); the yield decreased substantially, giving a mixture of polymerised side-products as the major product (Entry 1).



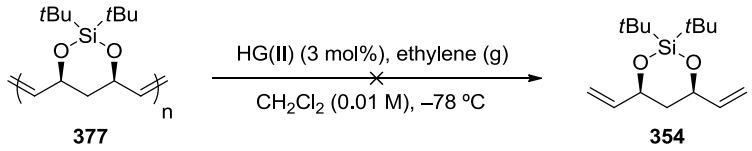
372 **354** **377**

Entry	Scale of reaction (mass of 372)	Yield of 354
1	400 mg	17%[(a)]
2	100 mg	89%[(b)]
3	200 mg	52%[(b)]
4	300 mg	40%[(b)]
5	400 mg	34%[(b)]

(a) *Ethylene gas was delivered by a needle attached to a balloon. (b) Ethylene gas was delivered by a sintered frit attached to a balloon.*

*Table **9**: ROM performed on different scale of **372**.*

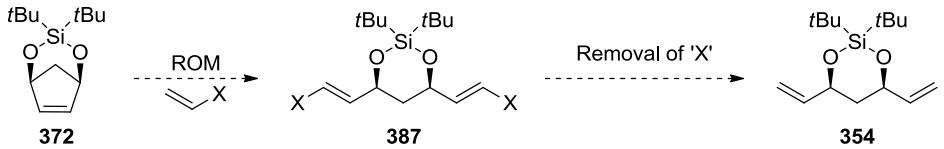
As the scale increased it was envisioned that the delivery of ethylene gas to the reaction mixture needed to change from being bubbled through with a needle attached to a balloon. Using a glass rod which has a sintered frit at the bottom would allow the gas to disperse through the solution much more efficiently than through the end of a needle. Using this method of delivery, a range of reactions using different amounts of starting material was explored. Generally the yield of **354** decreases upon performing the reaction on a larger scale (Entry 2-5). Using the glass frit does improve the yield on 400 mg of **354** reaction, but it is not effective enough to generate sufficient amounts of material. It was envisaged that resubmitting the mixture of polymerised side-product **377** to the reaction conditions could provide a method to reuse unwanted **377** (*Scheme **100***).



*Scheme **100**: Attempted cross-metathesis of **377** with ethylene gas.*

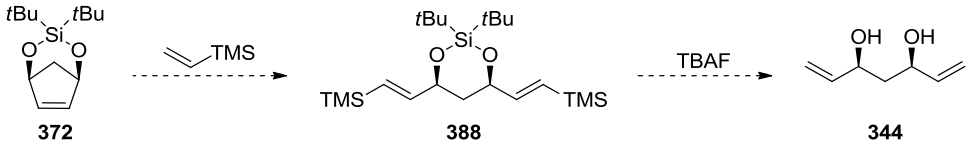
However, using the optimised reaction conditions only starting material was recovered. The crude reaction mixture showed no evidence of **354**. Thus the limitation of performing this reaction successfully on a large scale (>100 mg of cyclopentene **372**) required the exploration of an alternative route.

One problematic factor of the ROM reaction was found to be the delivery of the ethylene gas to the reaction mixture. To circumvent this obstacle we envisaged using a higher boiling alkene to ethylene, whereby it exists as a liquid and not a gas, to perform the ROM (*Scheme **101***).



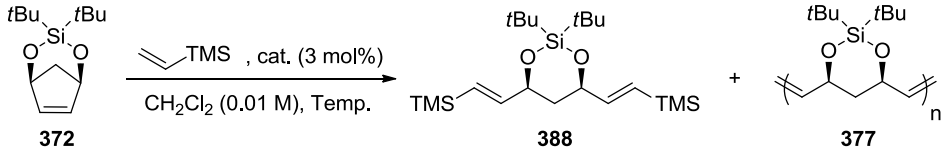
*Scheme **101**: ROM with ethylene gas surrogate.*

After successfully performing a ROM reaction, the substituent X attached to the alkene moieties would then be removed giving the desired terminal bis-alkene compound **354**. One example of a terminal alkene which fits this criterion is vinyltrimethylsilane (b.p. 55 °C) (*Scheme **102***).



*Scheme **102**: Proposed route to diol **344**.*

The use of TBAF to remove silicon protecting groups is well documented and treating **388** would give diol **344**.[81] Based on the protocol developed for the employment of ethylene gas different reaction conditions were investigated, using an excess of vinyl TMS (4.40 equiv.) in place of ethylene (*Table **10***).



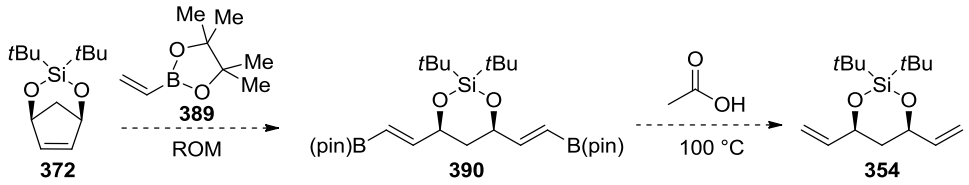
Entry	cat.	Temp.	Yield of 388
1	HG(II)	−78 °C	n/o
2	HG(II)	0 °C	n/o
3	HG(II)	r.t.	n/o
4	HG(II)	40 °C	n/o
5	G(I)	40 °C	n/o
6	G(II)	40 °C	n/o

*Table **10**: Screening of conditions to favour formation of **372**.*

Performing the reaction at −78 °C did not yield any desired **388** (Entry 1). The mass of the material isolated, characterized as the side product **377**, indicated the staring material had been converted fully to an undesired polymer. This indicated the vinyl TMS was not reacting under these low temperature conditions. Even increasing the temperature gave the polymer **377** exclusively (Entry 2-4). In general HG(II) possesses different reactivity towards terminal

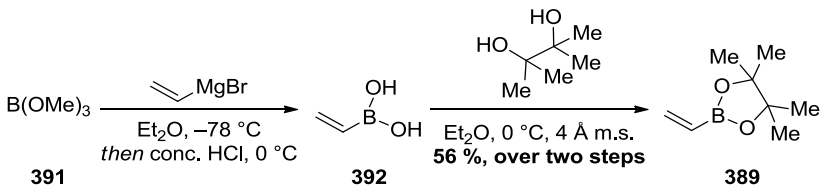
alkenes in comparison to G(I) or G(II),[82] but it still gave the same result (Entry 5-6). We suggested that the TMS group provides enough steric repulsion to prevent the catalysts from reacting with the olefin. An alternative olefin was then investigated.

Another approach is to use a pinacol borane functional group attached to a terminal alkene. With this in mind it was anticipated that performing a ring opening metathesis on **372** in the presence of vinyl pinacol borane **389** would give **390** (*Scheme **103***).[83]



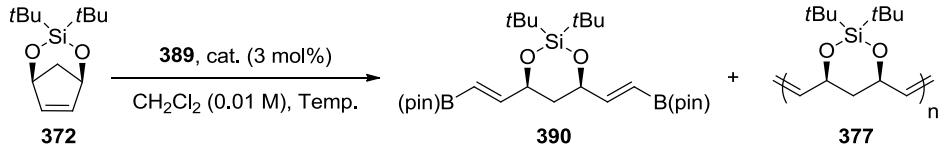
*Scheme **103**: Proposed ROM route.*

Using the idea of protodeboronation, removal of the pinacol boronate would yield **354**. The desired precursor vinyl pinacol borane was easily accessed from trimethyl borate in 2 steps (*Scheme **104***).[84]



*Scheme **104**: Formation of pinacol vinyl borane **389**.*

With the vinyl pinacol borane **389** in hand, different conditions were investigated to successfully conduct a ROM on cyclopentene **372** (*Table **11***).

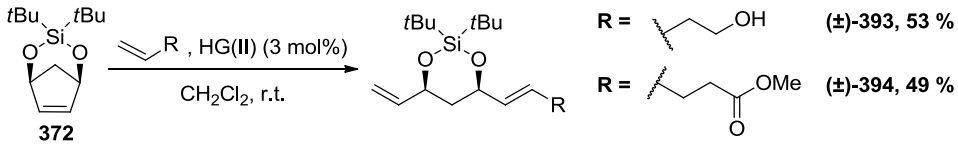


Entry	cat.	Temp.	Yield of 390
1	HG(II)	0 °C	n/o
2	HG(II)	40 °C	n/o
3	G(I)	40 °C	n/o
4	G(II)	40 °C	n/o

*Table **11**: Conditions screened for ROM of **372** with **389**.*

No desired product **390** was observed from ROM approaches with pinacol borane at either 0 or 40 °C for HG(II); only the polymer **377** was observed (Entry1-2). Even replacing the catalyst by G(I) or G(II) gave the same outcome (Entry 3-4), and in all cases, no starting material was recovered. Similar to vinyl TMS, it was proposed that vinyl boronate **389** was not reactive enough to prevent the competing ROMP.

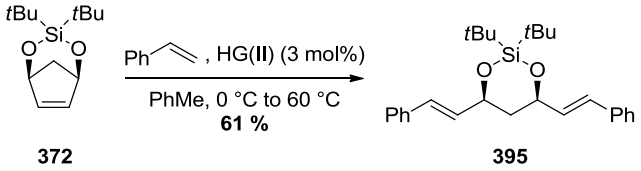
To test if any olefin would selectively perform a ROM with **372**, it was decided to carry out a ring opening metathesis using alkenes that do not provide such steric bulk close to the double bond (*Scheme **105***).



*Scheme **105**: ROM on **372**.*

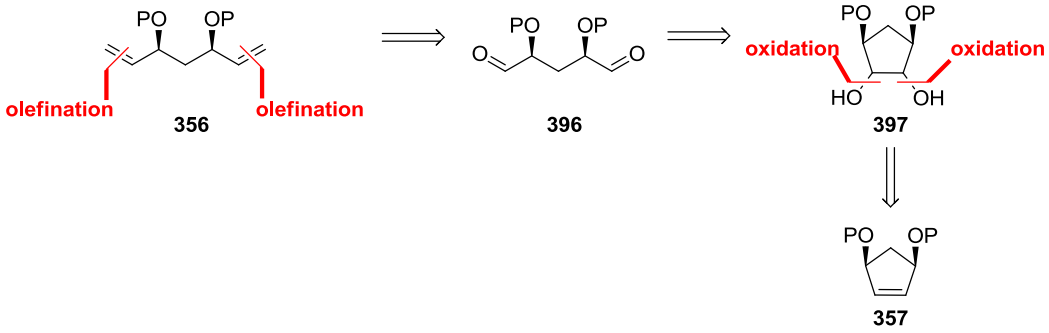
Both olefins gave the ROM products (±)-**393** and (±)-**394**, albeit in a modest yield. Carrying out the ROM with the olefin but-3-en-1-ol gave (±)-**393**, confirmed from the ^{1}H NMR spectrum of the isolated product showing both terminal alkene protons at δ_H 5.12-4.87 ppm and non-terminal olefin protons at δ_H 5.55 ppm and δ_H 5.42-5.22 ppm. From the ^{1}H NMR spectrum of the crude reaction material, the *trans*:*cis* diastereomeric ratio was found to be 10:1. Similarly the olefin methyl pent-4-enoate gave the ROM metathesis product (±)-**394**.

The ROM using a terminal alkene was explored further by James Neuhaus in the Donohoe group.[85] One interesting example explored was the ROM using styrene (*Scheme **106***).



*Scheme **106**: An example of ROM carried out by James Neuhaus forming **395**.*[85]

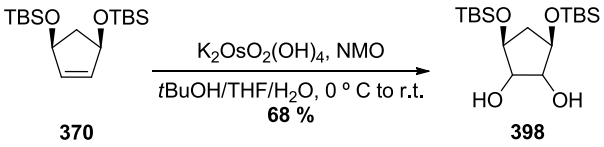
Due to the difficulties associated with the ROM of **372**, a different approach was explored which enabled the formation of **344** but avoided the ROM/ROMP competing step. This approach led to an alternative retrosynthesis of **356** (*Scheme **107***).



*Scheme **107**: Alternative retrosynthesis of **356**.*

It was assumed that bis-alkene **356** would arise from double olefination of dialdehyde **396**. The dialdehyde **396** could be accessed from oxidative cleavage of diol, which in turn arises from dihydroxylation of cyclopentene **357**.

Based on this strategy the oxidation of bis-TBS cyclopentene **370** was attempted (*Scheme **108***).

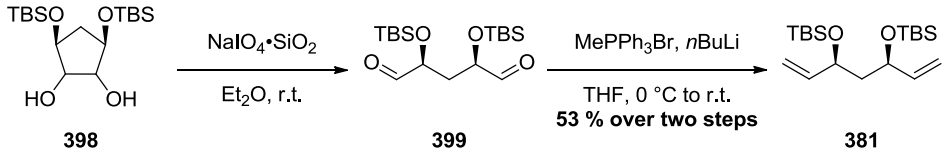


*Scheme **108**: Dihydroxylation of **370**.*

The ^{1}H NMR spectrum of the product showed the lack of any peak with a chemical shift corresponding to alkene protons present in the starting material **370** at δ_H 5.72 ppm and the

presence of a new peak with a chemical shift of δ_H 3.97-3.87 ppm suggesting that the alkene had been successfully oxidised to the diol as a single diastereoisomer. The stereochemistry of the diol installed was not determined due to the fact that this information was destroyed in the following oxidative cleavage of **398**.

With diol **398** in hand, the focus now turned to the oxidative cleavage of **398** to dialdehyde **399**. Due to the nature of aldehydes with stereocentres *α* to the carbonyl and the propensity to epimerise, it was deemed necessary to use mild conditions which would minimise the amount of time handling the aldehyde intermediate. Shing had developed conditions to help with purifying oxidative cleavage reactions of diols by using silica supported sodium periodate.[86] Thus diol **398** was treated with immobilised sodium periodate in diethyl ether at room temperature (*Scheme **109***).

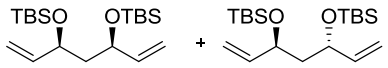


398 **399** **381**

*Scheme **109**: Conversion of diol **398** to bis-alkene **381**.*

A solution of diol **398** and silica supported sodium periodate in diethyl ether was stirred for 4 hours, filtered and concentrated *in vacuo*. Examination of the ^{1}H NMR spectrum of the crude reaction material showed a peak with a chemical shift at δ_H 9.55 ppm, which is indicative of an aldehyde proton. Also the protons assigned in the ^{1}H NMR spectrum of the starting diol **398** corresponding to the C*H*OH moieties at δ_H 3.97-3.87 ppm were not present. Also the ^{13}C NMR spectrum showed a chemical shift at δ_H 203.6 ppm which is typical for a carbonyl carbon. Upon closer examination of the crude reaction material the ^{1}H NMR spectrum showed an impurity which could correspond to the epimerised material. It was decided to carry the material through to see if the minor diastereoisomer could be separated from the desired *meso* compound **381**.

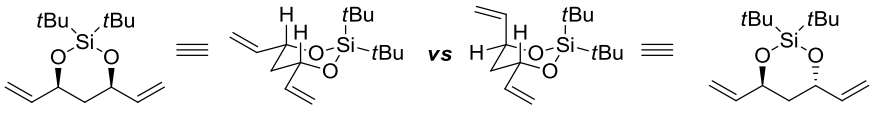
A double Wittig olefination was required to convert the dialdehyde **399** to bis-alkene **381**. The reagent methyltriphenylphosphonium bromide was deprotonated with *n*-butyl lithium at 0 °C to give a characteristic red colour indicating the formation of the desired ylide. A solution of dialdehyde in tetrahydrofuran was added to this solution of ylide and the resulting reaction mixture changed the colour from red to yellow. After subsequent quenching and purification of the reaction material, the resulting bis-alkene **381** was isolated. Spectroscopic data confirmed the lack of the aldehyde peak at δ_H 9.55 ppm and the presence of alkene protons at δ_H 5.79 ppm, δ_H 5.12 ppm and δ_H 5.01 ppm. Further evidence for **381** arose from examining the ^{13}C NMR with the chemical shifts at δ_C 141.5 ppm and δ_C 114.1 ppm, characteristic for terminal alkenes. From the ^{1}H NMR spectrum of the isolated bis-alkene, it was unclear as to whether the material had epimerised to give a mixture of diastereoisomers (*Scheme **110***). Also the presence of two TBS groups caused the compound to become extremely non-polar and it was difficult to see if any diastereiomers had formed by TLC due to the large Rf value **381** possesses (Rf = 0.7, neat 40-60 petroleum ether).



381 **(±)-400**

*Scheme **110**: Possible mixture of diastereoisomers.*

To identify if epimerisation occurred, the TBS groups were replaced with the bidentate silicon protecting group to give **372**. By preparing a cyclic derivative, any diastereoisomers formed should be visible in the ^{1}H NMR spectrum due to the nature of the compounds (*Scheme **111***).

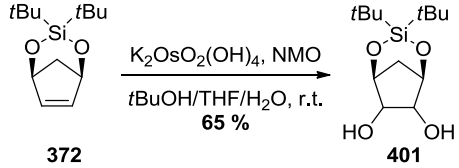


354 **401**

*Scheme **111**: Structures of diastereoisomers.*

It was expected that the C*H*$_3$ protons of the *tert*-butyl group of each diastereoisomer **354** and **401** would be chemically inequivalent. This would enable the two isomers to be distinguishable in the ^{1}H NMR spectrum.

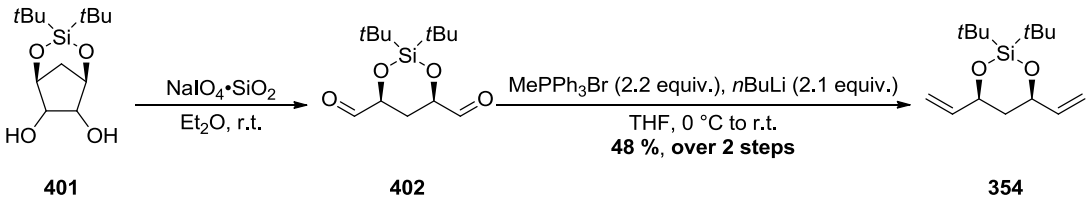
Based on this concept, work began converting cyclopentene **372** to form the desired bis-alkene **344**. Starting from cyclopentene **372** and submitting it to dihydroxylation conditions gave the expected diol **401** (*Scheme **112***).



*Scheme **112**: Dihydroxylation of cyclopentene **372**.*

The generation of diol **401** was confirmed by the absorption frequency of an O-H stretch at 3286 cm^{-1} in the I.R. spectrum. The lack of the chemical shift in the ^{1}H NMR corresponding to the alkene protons of the starting material at δ_H 6.39 ppm provides further evidence that **371** was oxidised.

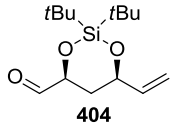
The oxidative cleavage conditions used previously were thought to be suitable to oxidise **401**. Thus treating a solution of diol **401** in diethyl ether with silica supported sodium periodate yielded the predicted dialdehyde **402** (*Scheme **113***).



*Scheme **113**: Two step process to convert diol **401** to diene **354**.*

As before, studying the ^{1}H NMR of the crude reaction material of **402** showed the proton chemical shift corresponding to the presence of an aldehyde at δ_H 9.64 ppm. This dialdehyde was used in the next step without any further purification due to the possibility of

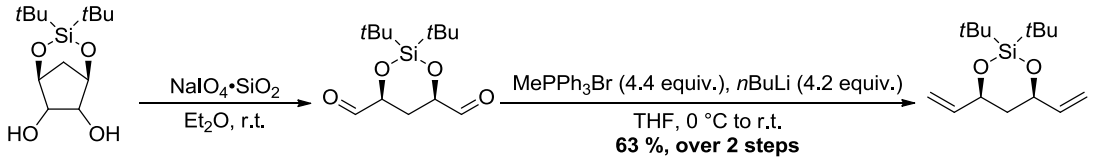
epimerisation associated with aldehydes containing an α-stereocentre. Thus treating the dialdehyde **402** to the same Wittig olefination conditions used on **398** gave the expected bis-alkene **354** in a modest 48% yield. A side product was also identified, which had the appropriate chemical shifts indicating the presence of an aldehyde (δ_H 9.59 ppm) and a terminal alkene (δ_H 5.77 ppm, δ_H 5.33-5.22 ppm and δ_H 5.05 ppm). Based on this information the side product was established as the mono-olefinated product **404** (*Scheme **114***).



404

*Scheme **114**: Identified intermediate **404**.*

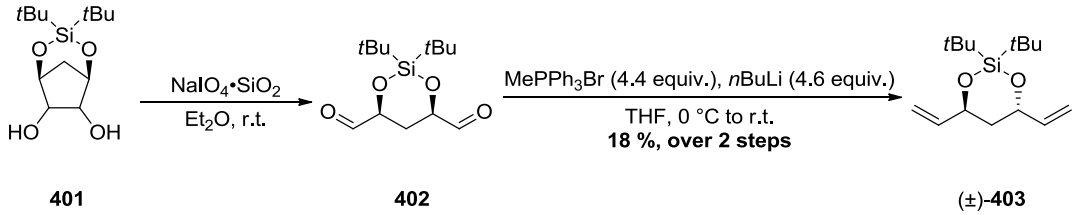
Therefore, the number of equivalents of the methyltriphenylphosphonium bromide salt and *n*butyl lithium was increased to ensure complete conversion (*Scheme **115***).



401 **402** **354**

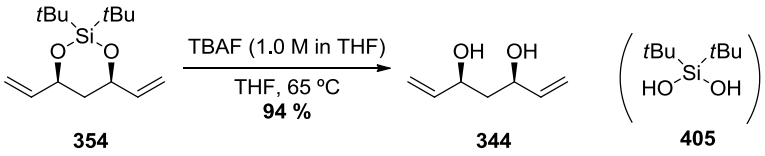
*Scheme **115**: Modified two step process to convert diol **401** to diene **354**.*

The yield was improved to 63% and the product was confirmed as the bis-alkene **354** from close inspection of the spectroscopic data. Peaks were present in the ^{1}H NMR spectrum with chemical shift at δ_H 5.87 ppm, δ_H 5.48-5.25 ppm and δ_H 5.10 ppm and no peaks with a chemical shift indicating an aldehyde. Interestingly due to the *meso* nature of the bis-alkene **354** the symmetrical nature of the compound indicated a single diastereoisomer. To confirm the Wittig olefination occurred without epimerization the dialdehyde **402** was treated to Wittig conditions using an excess of base to purposely form the other diastereoisomer before the olefination occurred (*Scheme **116***).



*Scheme **116**: Formation of diastereoisomer (±)-**403***

Using an excess of *n*butyl lithium to promote epimerisation, diastereomer (±)-**403** was obtained in a very low yield of 18%. This low yield arose from the side reactions associated with treating aldehydes under basic conditions, such as polymerisation. The key information about structure (±)-**403** was obtained from the ^{1}H NMR spectrum of the isolated material. The chemical shifts of the C*H*$_3$ protons of the *t*Bu group of the diastereomer (±)-**403** were located at δ_H 0.92 ppm and δ_H 0.89 ppm. The two analogous peaks for *meso* **344** were present at δ_H 1.08 ppm and 1.04 ppm. This strongly suggested that the *meso* **354** is formed as a single diastereomer as there are no additional peaks present in the ^{1}H NMR spectrum. Finally all that was required to obtain the necessary *meso*-diol, was to remove the bidentate silicon group. Deprotection using tetra-*n*-butylammonium fluoride to remove the silyl protecting group was successful (*Scheme **117***).



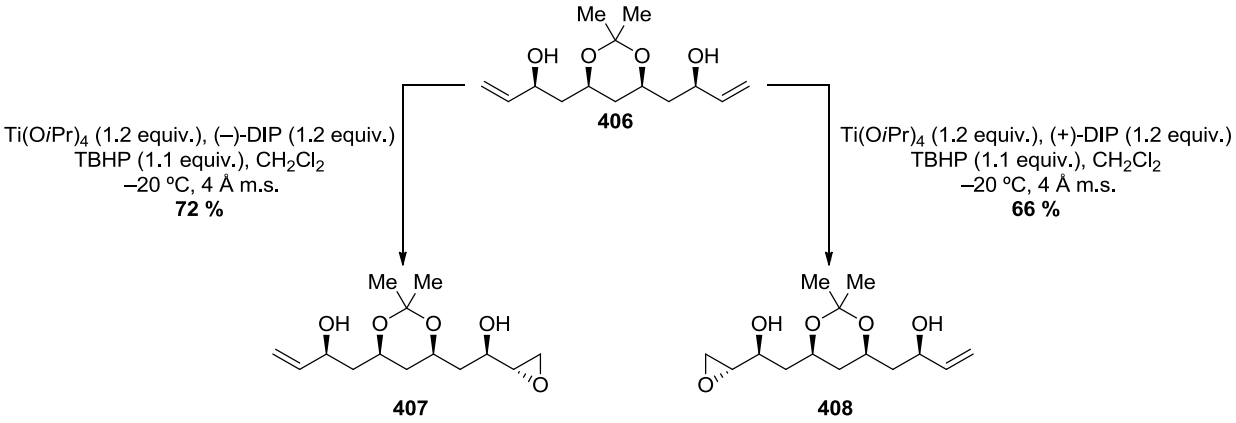
*Scheme **117**: Deprotection of **354**.*

Analysis of the ^{1}H NMR spectrum showed the lack of C*H*$_3$ protons correlating to the *tert*-butyl silicon group present in the starting material. A by-product of the deprotection was found to be the silicon diol **344** (*Scheme **117***). The by-product was confirmed from the ^{1}H NMR spectrum showing the peak of the C*H*$_3$ protons at δ_H 1.07 ppm and the presence of an O-H absorption peak at 3326 cm^{-1} in the I.R. spectrum. This compound almost co-elutes with diol **405** and it is vital to be removed from diol **344**, as the next step uses oxaphilic titanium for the SAE. In contrast to the ROM pathway this new route was scalable, and it was possible

to carry through material on a gram scale. With a successful route now in place to form diol **344**, attention turned to studying the desymmetrisation of *meso*-diol **344**.

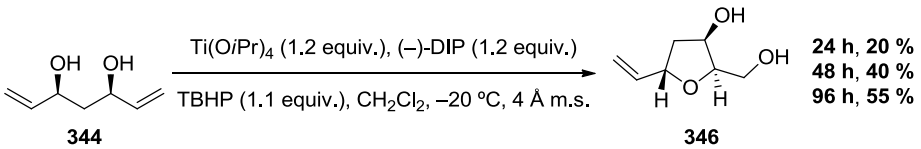
2.2.3 Optimisation of SAE on *meso*-Diol 344

Desymmetrisation of *meso*-diol **344** was initially investigated by Ali Jahanshahi in the Donohoe group[74] using conditions derived from Schreiber and co-workers for enantiotopic desymmetrisation of *meso*-diol **406** (*Scheme **118***).[87]



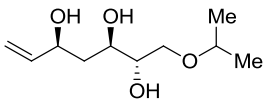
*Scheme **118**: Schreiber's applications of enantiotopic SAE.*

Schreiber reported that when using either enantiomer of DIP the epoxidation of **406** took up to 12 days to complete, but the author did not comment on the additional hydroxyl group present in the molecule or on any other factor that might cause this slow rate of epoxidation. The slow rate of epoxidation was also observed for the SAE of *meso*-diol **344** reported by Ali Jahanshahi (*Scheme **119***).



*Scheme **119**: Reported yields and reaction times from Ali Jahanshahi in the Donohoe group.[74]*

In addition, the crude mixtures contained a combination of recovered starting material and a side product which was isolated and characterised as the triol **409** (*Scheme **120***).

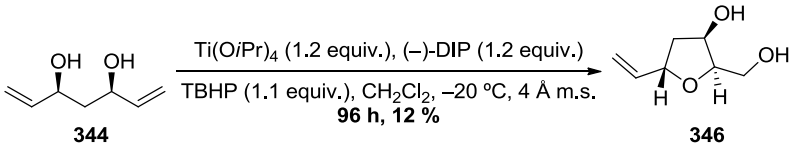


409

*Scheme **121**: Reported isolated triol.*[74]

This undesired side product seemed to arise from the reaction of the intermediate epoxide with a molecule of *iso*-propyl alcohol, one of the ligands of the titanium complex. With preliminary work carried out, my focus turned to optimising the formation of **346**.

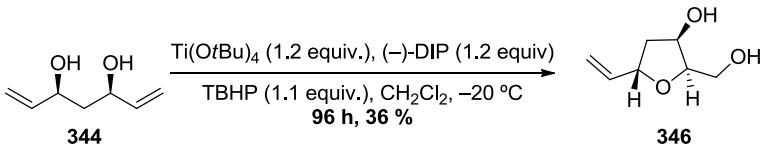
Using the exact conditions developed earlier a first attempt to form THF **346** was carried out (*Scheme **122***).



344 **346**

*Scheme **122**: Preliminary attempt at SAE.*

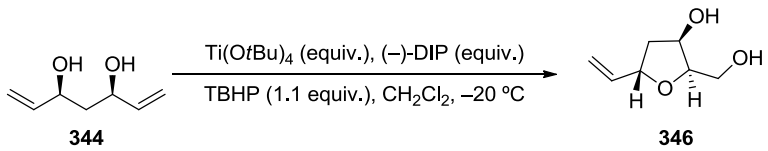
In general it was difficult to reproduce the outcome obtained previously especially with regard to the yield. It was found that the reaction was highly sensitive to moisture, thus it was essential to keep the reaction anhydrous. Recovering only 53% of the starting material from the crude reaction mixture, it was assumed that the rest of the starting material had been transformed to the triol **409** isolated previously by Ali Jahanshahi in the Donohoe group.[74] It has been reported that epoxy alcohols with terminal epoxides are sensitive to nucleophillic ring opening, especially in the presence of a Lewis acid such as titanium(IV).[88,32] To test this theory, the SAE was carried out using titanium(IV) *tert*-butoxide (*Scheme **123***), which has been shown to prevent this side reaction in similar cases due to the lower nucleophilicity of *tert*-butanol.[89,90,91]



344 **346**

*Scheme **123**: SAE using Ti(OtBu)4.*

The yield drastically increased, strongly suggesting the unwanted pathway had been inhibited. It was decided to screen a range of different conditions to optimise the yield of **346** (*Table **12***).



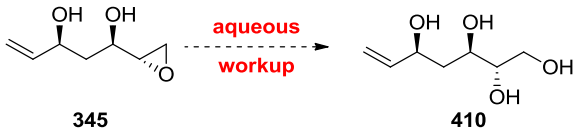
344 **346**

Entry	equiv. of Ti(O*t*Bu)$_4$	equiv. of (-)-DIP	Time	Yield of 346
1	1.20	1.20	96 h	36%
2	0.10	0.10	96 h	23%
3	0.50	0.50	96 h	30%
4	1.20	0.10	96 h	9%
5	0.10	1.20	96 h	44%
6	0.10	1.20	120 h	49%

*Table **12**: Screening of different conditions of SAE on diol **344**.*

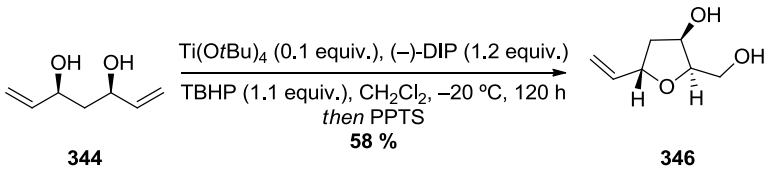
Lowering the number of equivalents of both the catalyst and tartrate to sub-stoichiometric amounts led to decreased yield (Entries 2-3). It was decided to vary the number of equivalents of Ti(O*t*Bu)$_4$ relative to the amount of tartrate used. The yield was drastically reduced when using an excess of the metal catalyst (Entry 4). The amount of recovered starting material was also low, although TLC of the crude reaction mixture showed full consumption of the starting material. Due to the oxaphilic nature of titanium(IV) it was believed that the starting material formed a tightly bound chelate and was lost upon aqueous workup when an excess of titanium species was used. Reversing the ratio by using an excess of tartrate and a catalytic amount of Ti(O*t*Bu)$_4$ gave a good yield of THF **346** (Entry 5). It was suggested that the titanium would favour chelating to the excess of tartrate relative to the *meso*-diol **344**. Allowing the reaction to proceed for a further 24 h did not improve the yield substantially (Entry 6). Moreover, the amount of product and starting material isolated also indicated the formation of a side product. Analysis of the TLC of the crude reaction mixture

showed the presence of an intermediate which upon quenching the reaction was no longer detectable by TLC. It was hypothesised that this intermediate was the epoxide formed in the SAE which reacted with water under the conditions of the aqueous work-up giving **410** (*Scheme **124***).



*Scheme **124**: Formation of tetrol.*

Thus it was deemed necessary to ensure the complete cylisation of any remaining epoxy alcohol **345** under non-aqueous conditions. A catalytic amount of pyridinium p-toluenesulfonate (PPTS), typically 5 mol%, has been previously used to cyclise alcohols onto epoxides.[92] Thus treating the reaction mixture with PPTS after epoxidation was complete improved the yield to 58% (*Scheme **125***).



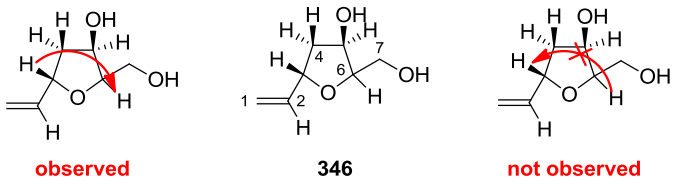
*Scheme **125**: Optimised synthesis of **346**.*

To confirm the identity of THF **346**, the ^{1}H NMR spectrum of the isolated material was examined. The peaks with chemical shifts at δ_H 5.77 ppm, 5.24 ppm and δ_H 5.10 ppm are typical of a terminal alkene. The ^{13}C NMR spectrum of the THF **346** revealed four peaks with the chemical shifts consistent for carbon atoms attached to oxygen atoms at δ_C 87.0 ppm, 79.6 ppm, 73.6 ppm and 63.3 ppm where only one of these peaks represented is a methylene carbon (determined through analysis of the DEPT spectrum). The I.R. spectrum also showed the presence of an O-H absorption peak at 3381 cm^{-1}. The mass spectrum displayed a peak corresponding to the THF **346** (167 ([M + Na]$^{+}$, 100%). The ^{1}H NMR spectrum of the isolated material also showed the presence of an impurity (~12% of the isolated product

mass) which could not be removed by column chromatography. The impurity is thought to arise from the SAE itself meaning that it could be a diastereomer of the THF, but it could not be isolated to be fully characterised. Although inseparable at this point, derivatisation of the THF made it possible for the minor product to be removed at a later stage (*See Chapter **2.3.5.1***). The data obtained for **346** was in agreement with that reported by Ali Jahanshahi in the Donohoe group.[74]

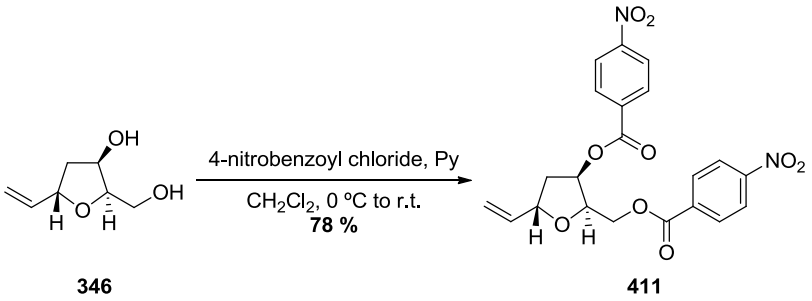
2.2.4 Analysis of Relative Stereochemistry

Examining the NOE based NMR study obtained by Ali Jahanshahi, it was realised that the data might have been misinterpreted. The corrected NOE interactions are shown below (*Scheme **126***).



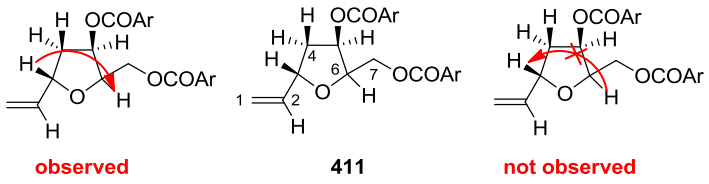
*Scheme **126**: Revised NOE interactions.*

The revised data showed the presence of a through space interaction from C(3)-H to C(6)-H. Interestingly this interaction was not reciprocated when C(6)-H was irradiated. Also the protons located at C(4) did not show any through space coupling with C(6)-H or C(7)-H_2. This made the NOE study difficult to interprete, and we decided that the NOE studies were not conclusive. It was also thought that the presence of the minor diastereomer in the sample could be affecting the NMR spectrum and thus the THF was derivatised in a bid to remove the impurity. THF **346** was converted to the diester **411** in 78% yield using 4-nitrobenzoyl chloride (*Scheme **127***).



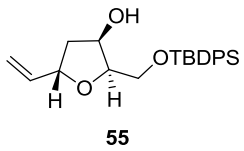
*Scheme **127**: Esterification of THF **346**.*

The ^{1}H NMR spectrum of the isolated product showed a drastic change in the chemical shift downfield for the protons assigned as C*H*OH, δ_H 3.86- 3.78 ppm to 5.55 ppm. Also the lack of an O-H absorption peak in the I.R. spectrum indicated the protection of both hydroxyl groups in **411** which was further supported by the presence of carbonyl absorption peaks at 1723 cm^{-1} and 1728 cm^{-1}. However, a small amount of impurity was still present (calculated to be 11% from the ^{1}H NMR spectrum). Interestingly the NOE study on **411** revealed similar correlations and a lack of clarity as to those observed for the previous compound **346** (*Scheme **128***).



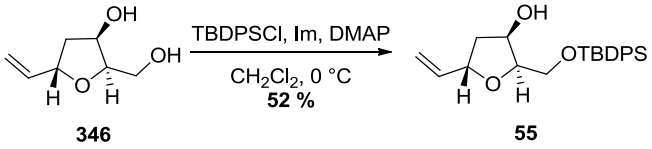
*Scheme **128**: NOE based NMR interactions of **411**.*

Again there was a through space interaction from C(3)-H to C(6)-H, but it was not reciprocated from C(6)-H to C(3)-H, and again the NOE study was not conclusive. The difficulty in determining the structure from NOE studies resulted in an attempt to use an alternative method required to confirm the structure. In 2012, Roulland and co-workers reported the synthesis of a similar *trans*-THF **55** (*See Chapter **1.2.1.3**, Scheme **129***).[19]



*Scheme **129**: Reported compound **55**.*

It was envisaged that THF **346** could be converted to **55**, and then we could use the data reported for this compound by Roullund to unambiguously prove the relative stereochemistry of **55**. Thus THF **346**, with approximately 12% impurity, was treated with TBDPSCl resulting in **55** being isolated as the major product (*Scheme **130***).



346 **55**

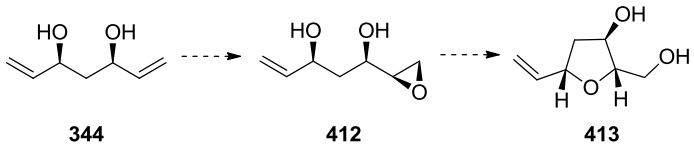
*Scheme **130**: TBDPS protection of THF **55**.*

With the spectroscopic data in hand a comparison of the ^{13}C NMR data was made (*Table **13***).

Lit. 55[19]	Compound 55	Δ ppm	Assignment
138.6	138.5	−0.1	*C*H=CH$_2$
135.7	135.6	−0.1	Ar*C*
135.6	135.5	−0.1	Ar*C*
130.1	130.0	−0.1	Ar*C*
128.0	127.8	−0.2	Ar*C*
116.0	115.9	−0.1	CH=*C*H$_2$
80.9	80.7	−0.2	*C*HCH$_2$OSi
79.4	79.3	−0.1	*C*HCH=CH$_2$
74.1	74.0	−0.1	*C*HOH
63.4	63.3	−0.1	*C*H$_2$OSi
42.1	41.9	−0.2	CH$_2$CHOH
26.9	26.7	−0.2	SiC(*C*H$_3$)$_3$
19.3	19.1	−0.2	Si*C*(CH$_3$)$_3$

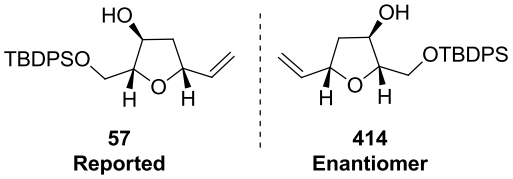
*Table **13**: Comparison of ^{13}C NMR data (125 MHz, CDCl$_3$) of **55** with that reported in the literature (125 MHz, CDCl$_3$).[19]*

The comparison of ^{1}H and ^{13}C NMR spectroscopic data gave a very good match. To rule out the possibility of having the corresponding *cis*-THF it was very desirable to compare the data to a *cis*-THF as well (*Scheme **131***).



*Scheme **131**: Possible cis-THF **413**.*

In the same communication, Roulland also reported the spectroscopic data for the enantiomer of the corresponding *cis*-THF **414** (*Scheme **132***).



*Scheme **132**: Reported compound **57**.*

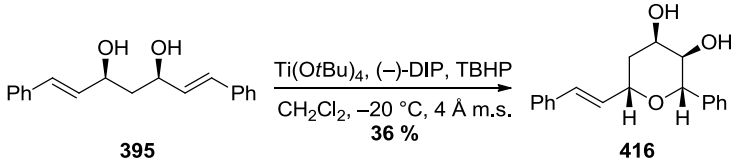
Using the spectroscopic information published for **57** and considering the fact that enantiomers possess the same NMR spectroscopic data, a comparison between the two sets of data was carried out (*Table **14***).

Lit. 57[19]	Compound 412	Δ ppm	Assignment
138.4	138.5	+0.1	*C*H=CH_2
135.7	135.6	−0.1	Ar*C*
133.4	135.5	+2.1	Ar*C*
129.9	130.0	+0.1	Ar*C*
127.9	127.8	−0.1	Ar*C*
116.4	115.9	−0.5	CH=*C*H_2
87.1	80.7	−6.4	*C*HCH_2OSi
79.7	79.3	−0.4	*C*HCH=CH_2
74.6	74.0	−0.6	*C*HOH
64.9	63.3	−1.6	*C*H_2OSi
41.3	41.9	+0.6	CH_2CHOH
26.8	26.7	−0.1	SiC(*C*H_3)$_3$
19.3	19.1	−0.1	Si*C*(CH_3)$_3$

*Table **14**: Comparison of ^{13}C NMR data (125 MHz, $CDCl_3$) of **414** with that reported in the literature (125 MHz, $CDCl_3$).[19]*

The ^{13}C NMR data did not match as well as in the previous case. In particular the chemical shifts of the peaks assigned to *C*HCH$_2$OSi and *C*H$_2$OSi are significantly different. This comparison strongly suggests the *trans*-THF **55** was obtained.

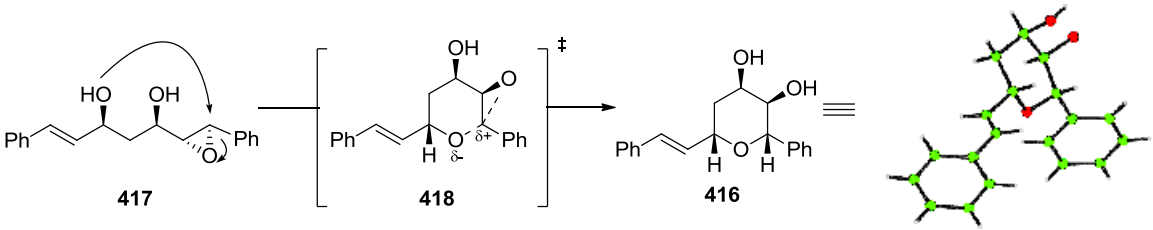
Additional evidence for the formation of an anti epoxide and ring opening to form a *trans*-THF also arises from analysing similar work carried out by James Neuhaus on desymmetrising **395** to give THP **416** (*Scheme **133***).[85]



395 **416**

*Scheme **133**: Work carried out by James Neuhaus on forming THP.*[85]

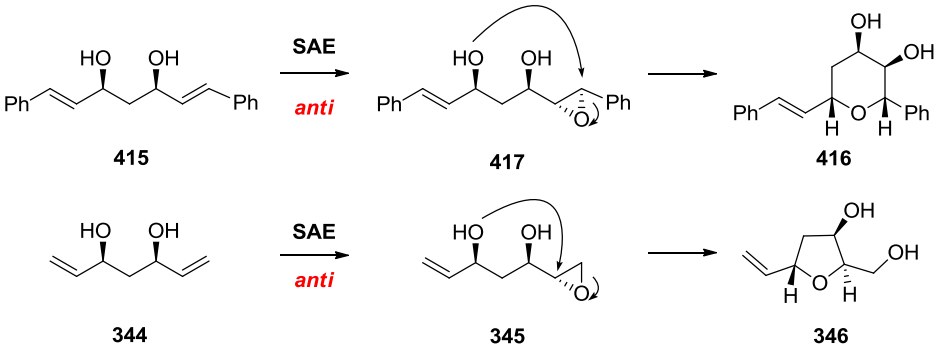
The interesting aspect of this work is the formation of the THP over a THF ring. The favoured 6-*endo*-tet cyclisation over the 5-*exo*-tet (*See Chapter **1.2.3.3***) was rationalised as a result of transition state stabilisation by the Ph group (*Scheme **134***).[35]



417 **418** **416**

*Scheme **134**: 6-endo-tet cyclisation to form **416** reported by James Neuhaus.*[85]

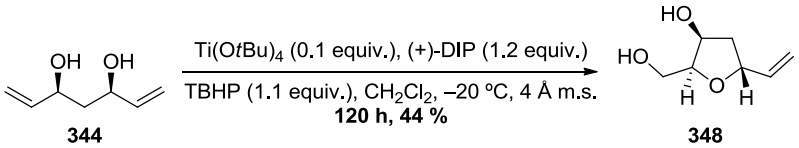
The X-ray crystal structure obtained proved the formation of the THP **416**. More importantly, the stereochemistry of the SAE is transferred to the product and the alkene had been epoxidised *anti* to the alcohol in accordance with general predictions for the SAE.[27] This finding strongly suggests the epoxidation of **344** occurs in a similar (*Scheme **135***).



*Scheme **135**: Comparison of the relative stereochemistry formed.*

It was decided to carry on with further work, as it was deemed worthwhile to obtain a crystal structure to confirm the formation of *trans*-THF **346** as well as to determine the absolute configuration. Efforts were made to grow a single crystal to determine the structure whilst exploration of the synthetic strategy continued.

Use of the other enantiomer of the corresponding tartrate, under the same conditions, successfully gave access to the THF **348** (*Scheme **136***).



*Scheme **136**: SAE using (+)-DIP.*

The spectroscopic data of **348** matched **346** and the specific rotation of both products ($[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +3.9 (c = 1.0, CH_2Cl_2) for **346**, $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ −2.7 (c = 1.0, CH_2Cl_2) for **348**) indicated successful formation of the enantiomer.

2.2.4 The Absolute Stereochemistry of 346

The absolute stereochemistry of the product THF **346** shown throughout assumes the stereochemistry formed arises from the SAE (*Figure **6***).[33]

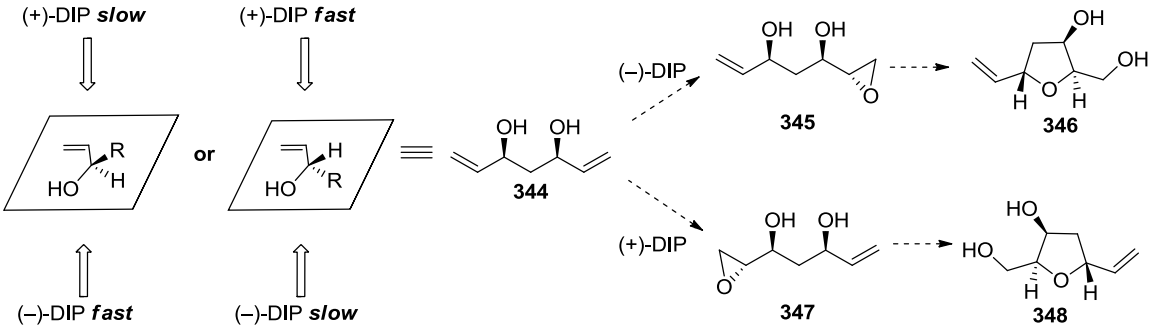
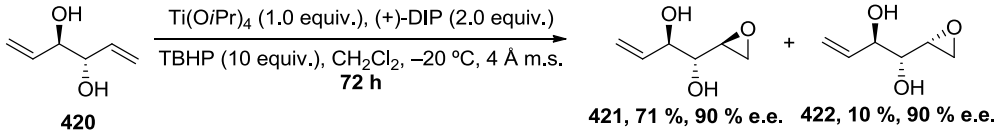


*Figure **6**: Mnemonic for the Sharpless asymmetric epoxidation applied on meso diol **344**.*

It was hoped that a comparison of the specific rotation obtained for the derivatised THF **55** with that reported by Roulland and co-workers would confirm which enantiomer was obtained, but the specific rotation was not reported in the literature supporting information.[19] It is noteworthy to mention work carried out by Takano and co-workers on the SAE of 1,2-meso diol **344**, which gave the opposite enantiomer expected from the SAE mnemonic (*Scheme **137***).



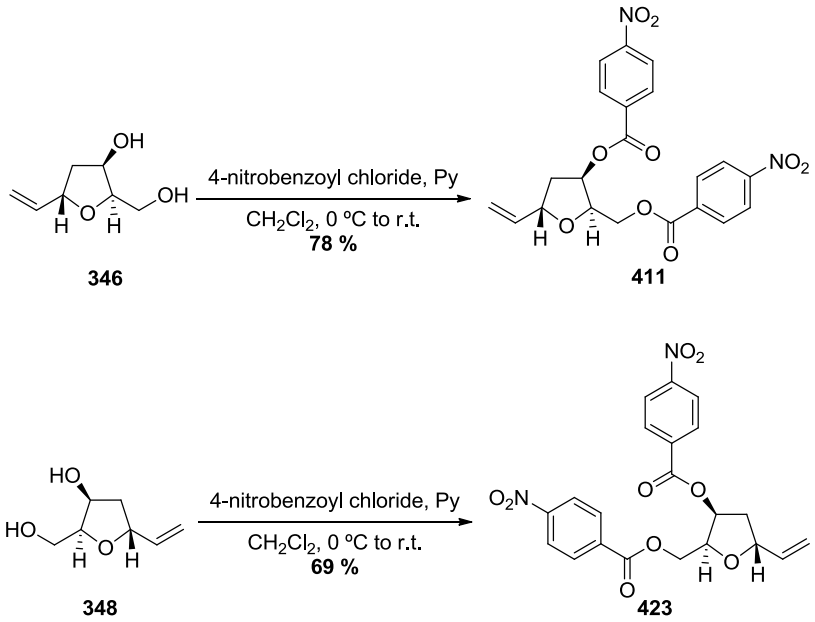
*Scheme **137**: SAE on **420** carried out by Takano and co-workers.*

The authors hypothesise that chelation of both the hydroxy groups of the 1,2-diol **420** to the titanium metal complex alters the SAE reaction. It also interesting that the diastereomeric ratio formed is ~7:1 where the *syn* epoxy alcohol is formed as the minor diastereoisomer; in our case an ~8:1 mixture of diastereoisomers was formed hinting that the *syn* epoxide gave the *cis* THF as the minor diastereoisomer. Work is currently underway to confirm the absolute stereochemistry.

2.2.5 Measurement of e.e.

The data reported from Ali Jahanshahi in the Donohoe group did not include an optical rotation to compare,[74] hence it was necessary to measure the e.e. of the THF formed to ensure

complete enantioselectivity. The use of HPLC was deemed fit to serve this purpose. A chromophore was required to allow for the detection of both compounds *via* UV/VIS spectroscopy. Thus both enantiomers of the THF formed were converted to the corresponding diesters (*Scheme **138***).

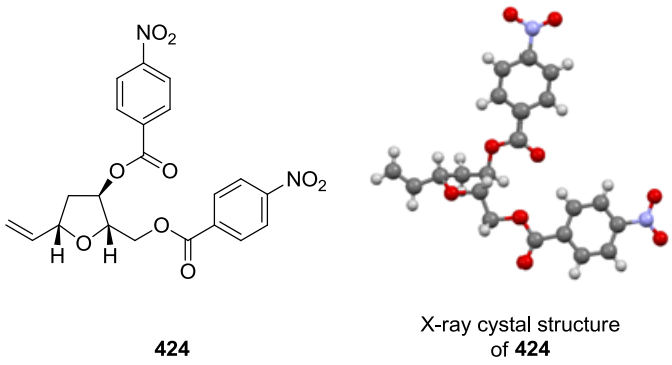


*Scheme **138**: Conversion to diesters **411** and **423**.*

With both enantiomers (each containing approximately 12% impurity) in hand the e.e. was obtained from the HPLC chromatograms (*See Appendix **1.2.1***). Thus it was found diester **411** was formed with an e.e. value of 97% whilst the diester **423** was generated in 99% e.e. assuming the minor impurity did not affect the HPLC trace.

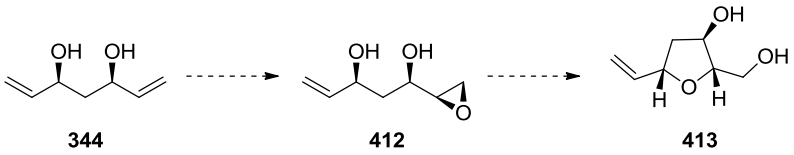
2.2.6 Recent Developments

At a very late stage of the project, crystals were formed in a sufficiently high quality for X-ray crystallography. Astonishingly the crystal submitted showed the structure of a *cis*-THF (*Scheme **139***).



*Scheme **139**: Crystal structure **424**.*

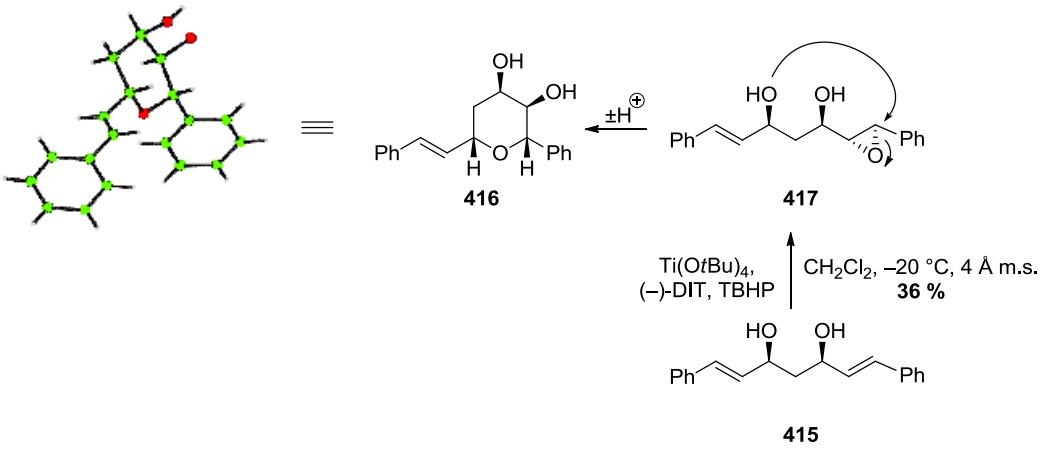
For this THF to form, the facial selectivity of the SAE epoxidation would have to be inverted giving the *syn* epoxy alcohol **412** (*Scheme **140***). The neighbouring hydroxyl group would then cyclise onto the epoxide formed giving *cis*-THF **413**.



*Scheme **140**: Reversed SAE epoxidation.*

Standard SAE conditions have been established to yield the *anti* epoxy alcohol.[27] The presence of an additional alcohol has been reported to affect the enantiofacial selectivity of epoxidation,[128,129] but would still yield the *anti* epoxy alcohol as discussed in the work reported by Takano and co-workers (see *Chapter **2.3.4***).

This X-ray crystal structure also contradicts previous data obtained. The X-ray crystal structure obtained by a co-worker working on a similar *meso*-1,3-diol system gave the expected structure resulting from an *anti* epoxidation (*Scheme **141***).[85]



*Scheme **141**: Crystal structure reported by James Neuhaus.*[85]

Although the cyclisation occurred in a 6-*endo*-tet fashion yielding a THP, by examining the relative stereochemistry of the X-ray crystal structure it can be concluded that the epoxy alcohol formed previously must be *anti*. Also the comparison of NMR data with the literature reported THF analogues (see *Chapter **2.2.3***) strongly suggested the formation of a *trans*-THF. Both of these pieces of data support the formation of a *trans*-THF.

It is possible that the crystal submitted for examination was the minor diastereomer formed. The sample used for recrystallisation contained a trace amount of impurity which could correspond to the *cis*-THF observed. From the ^{1}H NMR it was determined that the ratio of diastereoisomers present was 8.1:1 in the crude, before crystallisation (*Figure 7*). Due to the tiny mass of the crystal used for X-ray analysis it was impossible to obtain a ^{1}H NMR and determine whether the minor diastereisomer was submitted. However the crystal chosen for analysis was taken from the very top of the vial used. Thus ^{1}H NMR analysis of the remaining sample at the bottom of the vial used for recrystallisation showed the minor diastereoisomer had been removed (*Figure 7*).

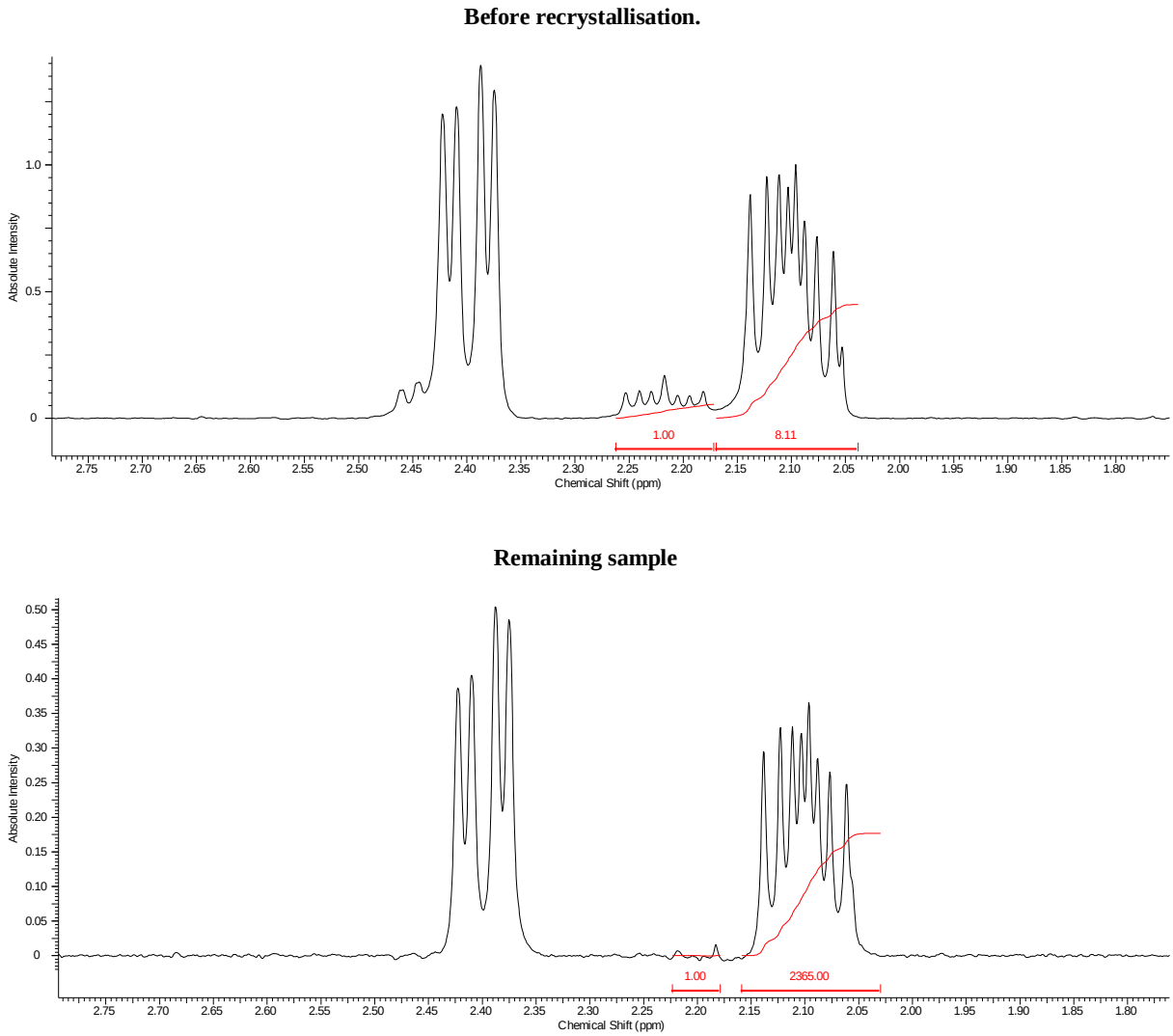


Figure 7: Selected regions to show removal of minor diastereoisomer.

Although possible, this relies on the assumption that the minor diastereoisomer crystallised at the top of the vial whilst the major diastereoisomer remained at the bottom. Thus study of the diastereomerically pure sample for crystal analysis would give a certain answer that the crystal previously analysed was the major or minor diastereoisomer. Further work to recystallise a diastereomerically pure sample is currently underway.

2.2.7 Conclusion

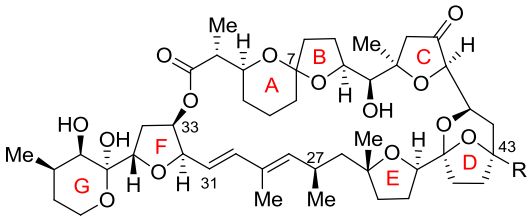
An efficient synthesis of *meso*-diol **344** was devised and successfully implemented. The use of the SAE was deemed successful in desymmetrising the *meso*-diol **344**. By derivatising the

THF **346** and comparing the spectroscopic data to reported literature compounds, the structural identity was supported as the desired *trans*-THF. Also it has been shown that the reaction proceeded with a high level of enantioselectivity. At this stage of the development of the synthetic route it was decided enough data was obtained to assume the formation of THF **346**. Moreover, the application of the methodology towards the synthesis of the FG fragment of pectenotoxin-4 was carried out and endeavours towards confirming the absolute stereochemistry of **411** were continued during the course of the following work.

2.3 Application Towards the FG fragment of Pectenotoxin-4

2.3.1 The Family of Pectenotoxins

The pectenotoxins are a family of macrocyclic polyether toxins, initially isolated by Yasumoto and co-workers in 1985 from the digestive glands of the toxic scallops *Patinopecten yessoensis* from the north-eastern coast of Japan.[93] It was later discovered that the producers of pectenotoxins are the toxic plankton species *Dinophysis fortii* and *D. acuminate*, ingested by scallops.[94] The structure of pectenotoxin-1 was determined by Yasumoto and co-workers using x-ray crystallography and NMR spectroscopy. However it was not until 1997 that the absolute configuration of pectenotoxin-1 was elucidated through further studies conducted on pectenotoxin-6.[95] More than twenty pectenotoxins have been isolated since 1985, their structures being determined largely by comparing NMR spectroscopy data. The pectenotoxins tend to differ in terms of absolute configuration at the AB spiroketal ring and structurally in the oxidation state of the carbon atom attached to the D ring (*Figure **8***).[96]



PTX-1 (7*R*, R = CH_2OH)
PTX-2 (7*R*, R = CH_3)
PTX-3 (7*R*, R = CHO)
PTX-4 (7*S*, R = CH_2OH)
PTX-6 (7*R*, R = CO_2H)
PTX-7 (7*S*, R = CO_2H)

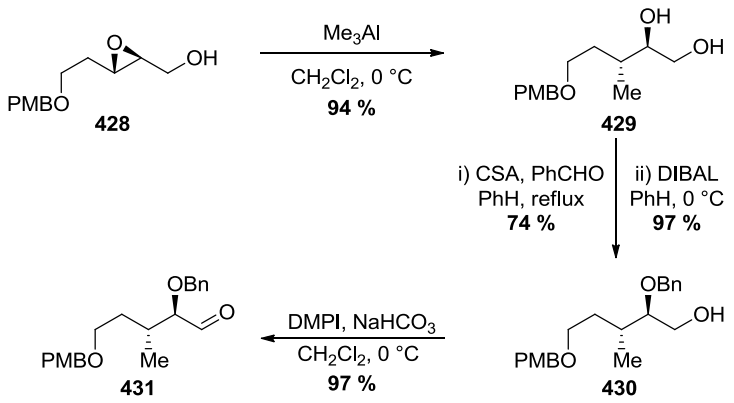
*Figure **8**: Structure of the pectenotoxins.*

2.3.2 Previous Synthesis of Pectenotoxin-4

2.3.2.1 Murai's Synthesis of the $C_{31\text{-}40}$ Segement

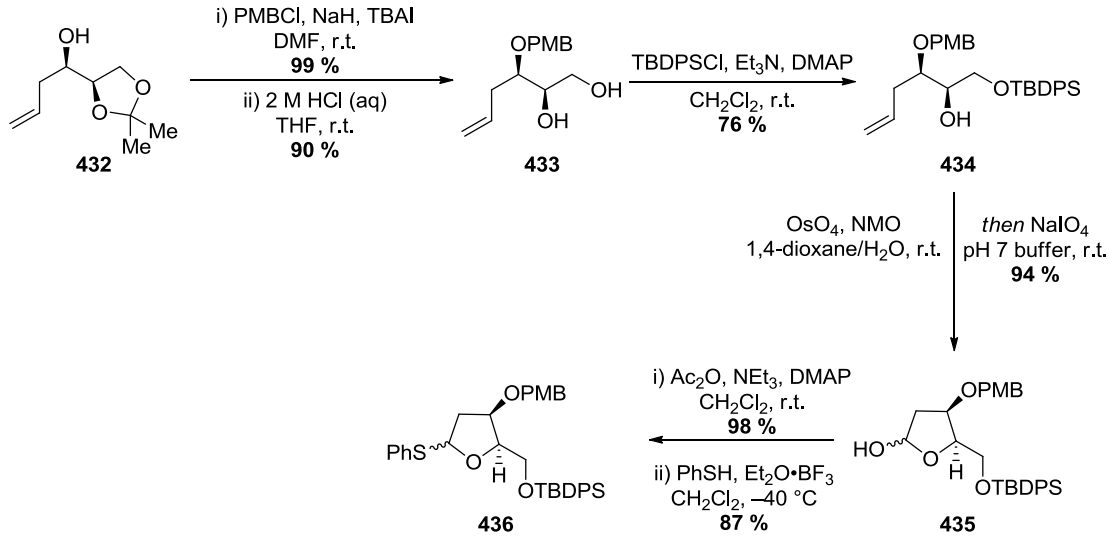
The synthesis of the FG rings was first reported in 1997 by Murai and co-workers in their work towards pectenotoxin-2.[97] It was later shown in 2005 that the synthesis published in 1997 yielded the opposite enantiomer.[98] Thus, Murai established an alternative convergent

synthesis, using a key reductive lithiation coupling step, providing the $C_{31\text{-}40}$ segment with the correct absolute stereochemistry The $C_{36\text{-}40}$ portion **431** was synthesised in four steps from known epoxide **428** (*Scheme **142***).[99]



*Scheme **142**: Synthesis of $C_{36\text{-}40}$ segment **431**.*

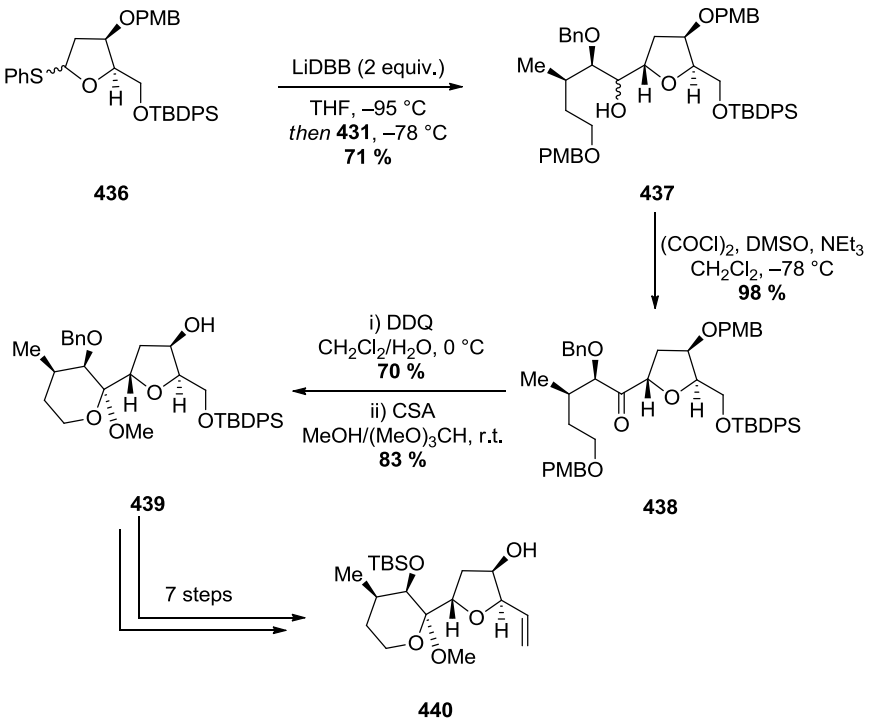
The $C_{31\text{-}35}$ portion **436** was synthesised from known *homo*-allylic alcohol **432** in 5 steps (*Scheme **143***).[100] Initial PMB protection followed by acetonide deprotection yielded the diol **433**. The use of TBDPS, a bulky silyl protecting group, allowed selective protection of the primary alcohol giving TBDPS silyl ether **434** in 76% yield. The key oxidative cleavage of the olefin **434** formed the cyclic hemiacetal **435** in 94%.



*Scheme **143**: Synthesis of fragment **436** $C_{31\text{-}35}$.*

Transformation to the monothioacetal **436** (as a mixture of anomers) was achieved *via* acylating the hemiacetal followed by treatment with thiophenol and boron trifluoride etherate.

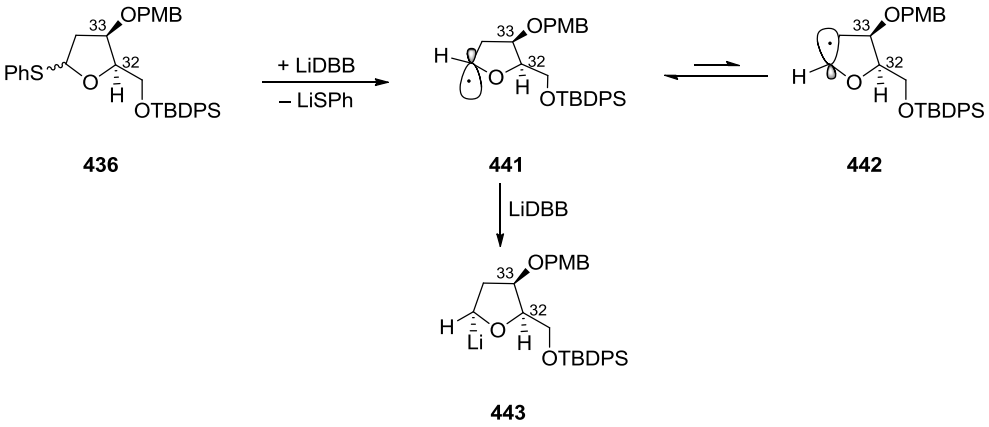
With both fragments in hand, the focus was directed towards the reductive coupling of these two segments **431** and **436** using LiDBB. Treatment of monothioacetal **436** with two equivalents of LiDBB resulted in the generation of the corresponding lithium anion, which was followed by addition of aldehyde **431** yielding the alcohol **437** as a mixture of diastereoisomers (*Scheme **141***).[68] Swern oxidation of the secondary alcohol **437** to the ketone **438** revealed a 4.2:1 mixture of diastereoisomers, with the major diastereomer possessing the desired stereochemistry.[101]



*Scheme **144**: Reductive coupling and final steps.*

Deprotection of both PMB groups of **438** was followed by conversion to the cyclic methyl acetal **439**. Further elaboration of the protecting group pattern and conversion of the primary TBDPS protected alcohol to a terminal alkene furnished the $C_{31\text{-}40}$ fragment **440** of PTX in 21 steps from known homo-allylic alcohol **432**.[98]

The key reductive coupling step was further explored and it was discovered that the *cis*-configuration of the substituents in 3 and 4 position (C_{33} and C_{32}) of the cyclic aldopentose derivative **436** were essential for the stereoselective generation of alkyl lithium species **443** (*Scheme **145***).[102]

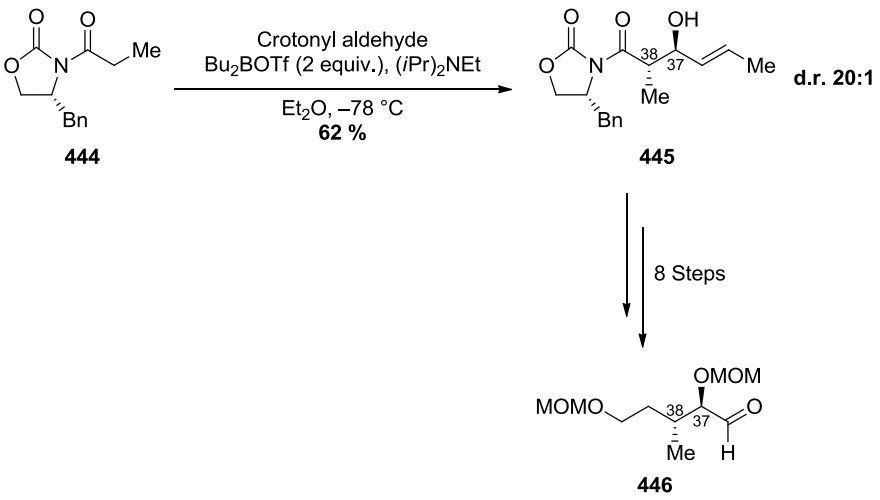


*Scheme **145**: Proposed mechanism for the generation of the Li species **443**.*

Also, it was proposed that the OPMB substituent at C_{33} leading to the unpaired electron preferentially being located on the opposite face to minimise electrostatic repulsion with the aromatic ring of the PMB group. This favours the generation of the lithium anion on the opposite face to the C_{33} substituent.

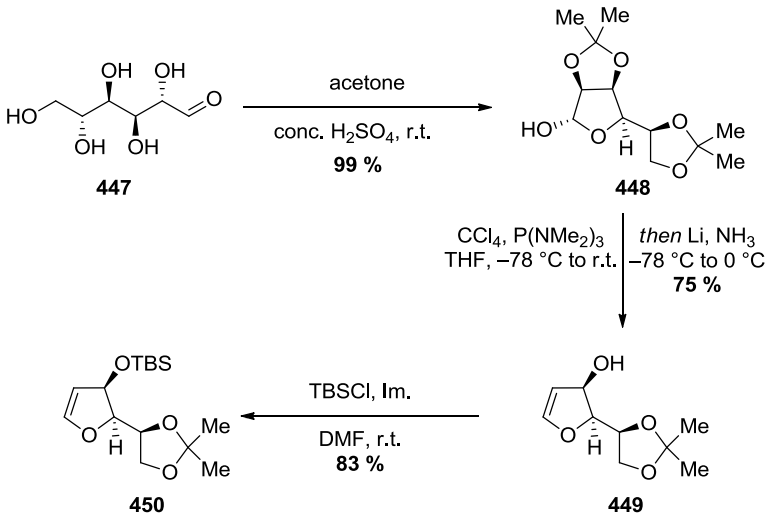
2.3.2.2 Paquette's Synthesis of the $C_{29\text{-}40}$ Fragment

Paquette and co-workers reported the synthesis of the $C_{29\text{-}40}$ fragment of pectenotoxin-2 overall in 21 steps using an alkoxide directed hydrogenation of the dihydrofuran **453**.[103] Initially, aldehyde **446** was synthesised in 9 steps from oxazolidinone **444** (*Scheme **146***).[104,105] The stereocenters at C_{37} and C_{38} were selectively generated by an *anti*-aldol reaction which employed the Heathcock modification to the Evans' aldol procedure.[106]



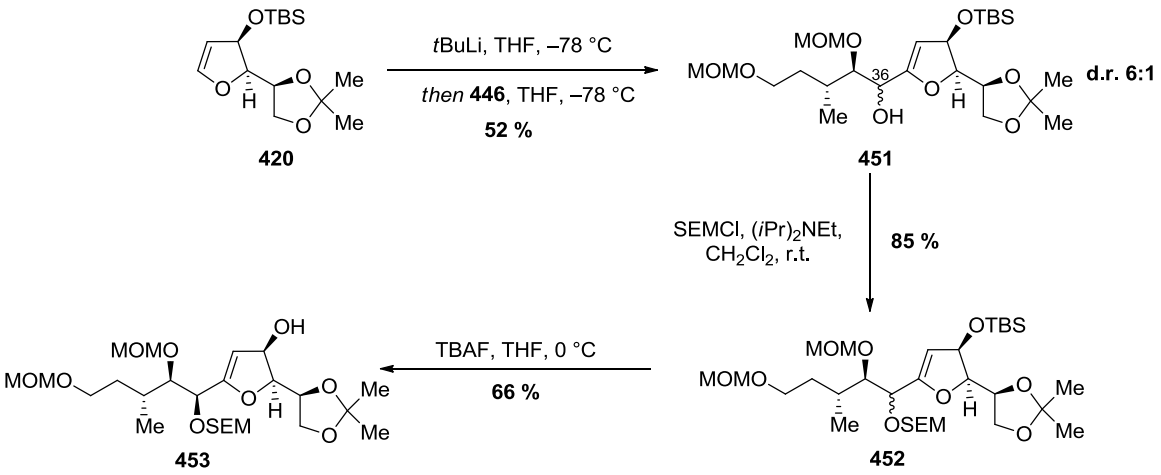
*Scheme **146**: Formation of aldehyde **446**.*

The dihydrofuran segment **450** was synthesised from D-mannose **447** in 3 steps (*Scheme* **147**).



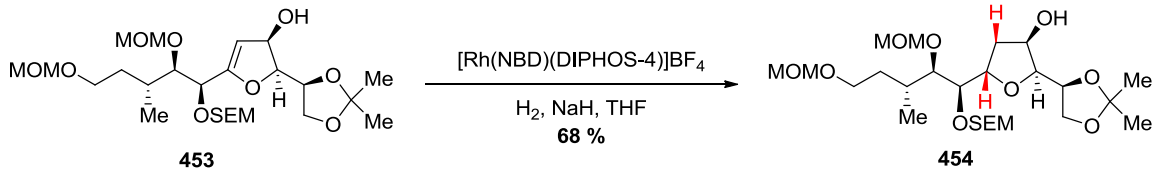
*Scheme **147**: Formation of dihydrofuran **450**.*

Treatment of dihydrofuran **450** with *tert*-butyllithium gave the corresponding vinyl anion which was reacted with aldehyde **446** (*Scheme **148***). A mixture of diastereoisomers at the C_{36} position resulted which were separated by forming the SEM ether at the secondary alcohol yielding **452**, followed by deprotection of the TBS group of the secondary alcohol on the dihydrofuran ring.[107]



*Scheme **148**: Coupling of dihydrofuran **420** and aldehyde **446**.*

The tetrahydrofuran **454** was obtained using an alkoxide-directed hydrogenation (*Scheme **149***). The propensity for the dihydrofuran to form the corresponding furan caused difficulties. The Lewis acidity of the catalyst was thought to be the cause of this elimination reaction. The addition of a base was not only vital to prevent elimination but also to favour complexation of the corresponding alkoxide of dihydrofuran **453** and the catalyst, resulting in the desired stereochemical outcome.[108]

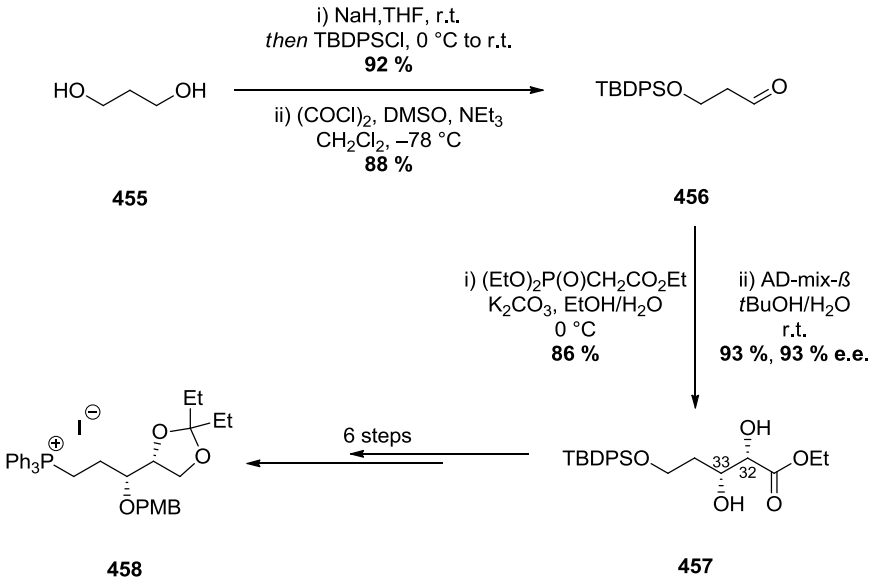


*Scheme **149**: Hydrogenation of dihydrofuran **453**.*

2.3.2.3 Brimble's Synthesis of the $C_{31\text{-}40}$ Fragment

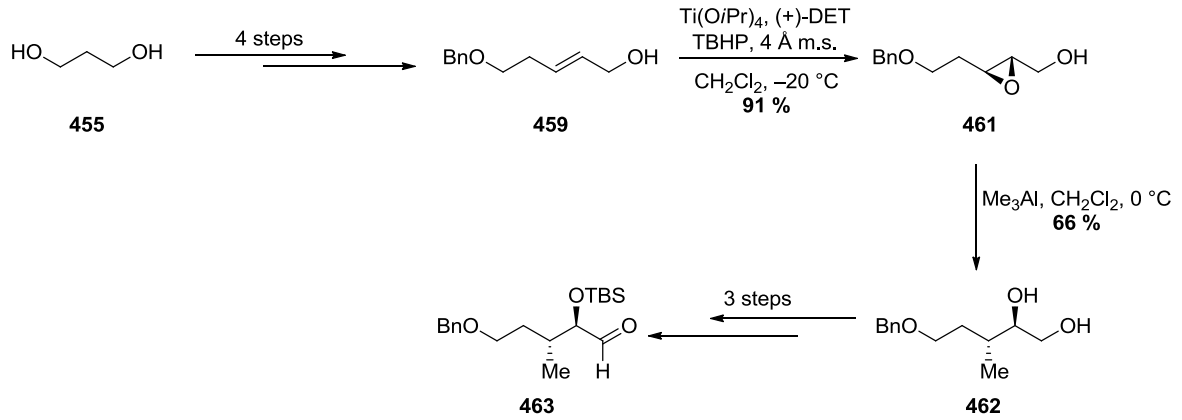
In 2010, Brimble *et al.* synthesised the FG rings using a convergent synthesis which centered on a *Z*-selective Wittig olefination.[109] The phosphonium species **458** was synthesised in 10 steps from diol **455** (*Scheme **150***). Initial TBDPS protection and oxidation yielded the aldehyde **456** in 81% yield over two steps. Olefination of the aldehyde **456** followed by Sharpless asymmetric dihydroxylation of the resulting alkene gave the diol **457** in 80% yield over two steps.[110,36] Within the dihydroxylation step the stereocentres at the C_{32} and C_{33} were

formed selectively. This diol **457** was further converted to the phosphonium salt **458** in 6 steps.



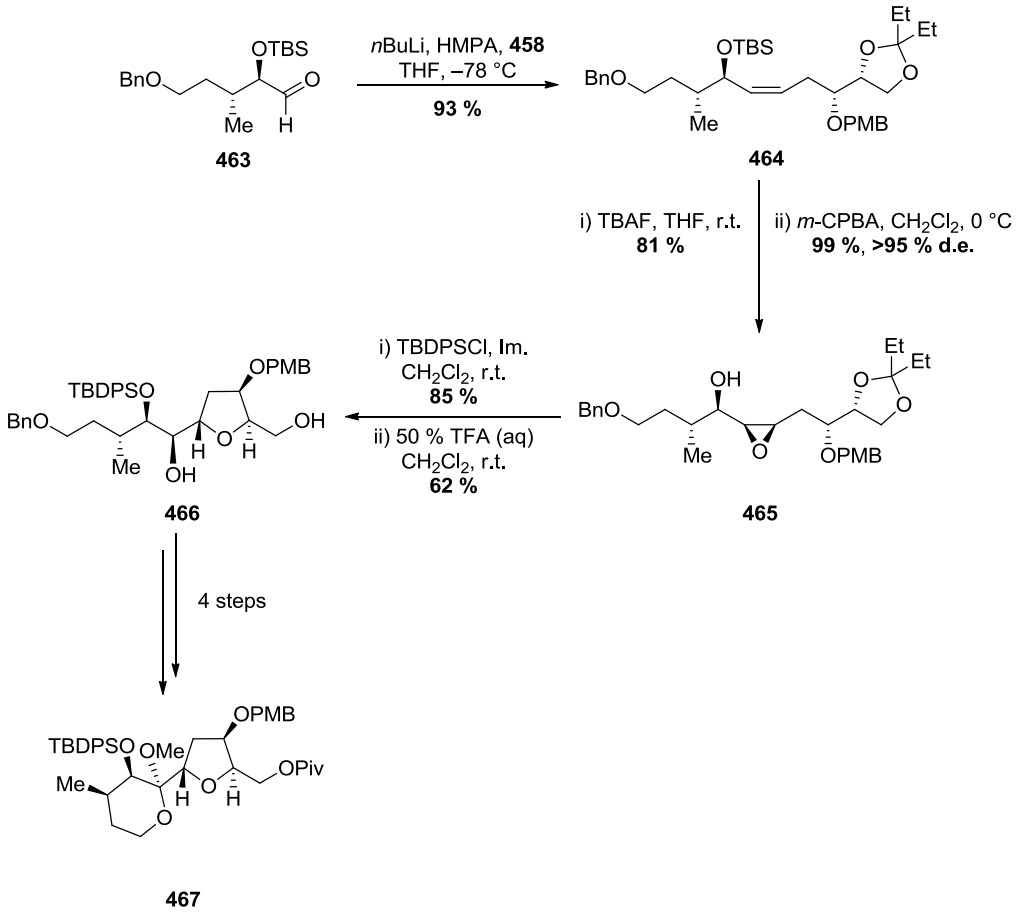
*Scheme **150**: Synthesis of phosphonium salt **458**.*

The aldehyde component **463** was formed from the same starting material, propane-1,3-diol **455**, in 9 steps (*Scheme **151***). Diol **455** was converted to allylic alcohol **459** in 4 steps which was epoxidised under Sharpless asymmetric conditions to yield alcohol **461** in 91% yield.[32] Regioselective epoxide opening using trimethylaluminium afforded 1,2-diol **462** in 66%. A further three steps, involving bis-silyl protection, selective deprotection and oxidation yielded aldehyde **463**.[111]



*Scheme **151**: Synthesis of aldehyde **463**.*

Wittig olefination of aldehyde **463** with the phosphonium salt **458** using *n*-butyl lithium gave the required linear backbone **464** (*Scheme **152***). Silyl deprotection using TBAF followed by stereoselective epoxidation, using *m*-CPBA, afforded epoxy alcohol **465** taking advantage of the intrinsic stereocontrol of the chiral substrate. The secondary alcohol **465** was protected using the TBDPS protecting group, which was proven to be stable under the acid catalysed cyclisation invoked by aqueous TFA.



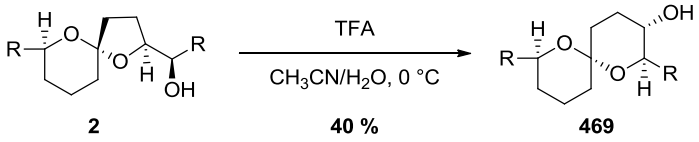
*Scheme **152**: Wittig olefination of **458** and aldehyde **463** and subsequent manipulation to **467**.*

A further 4 step manipulation, involving an oxidation of the secondary alcohol **466** and a series of protection and deprotection reactions, yielded the desired FG-ring fragment **467**.

2.3.2.4 Evans's Synthesis of Segment $C_{31\text{-}40}$

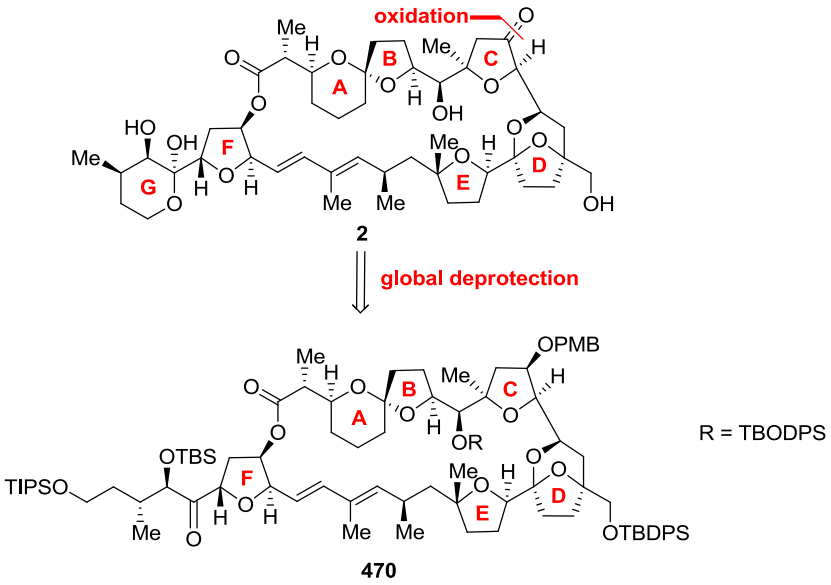
Only one total synthesis of pectenotoxin-4 has been reported,[112,92] even though multiple research groups have reported synthesising specific fragments, reflecting the challenges

associated with synthesising such a complex natural product. Evans and co-workers have published the only total synthesis of pectenotoxin-4 to date in 36 linear steps with an overall yield of 0.3%.[92,112] Evans also demonstrated the isomerisation of pectenotoxin-4 to pectenotoxin-8 (*Scheme **153***).



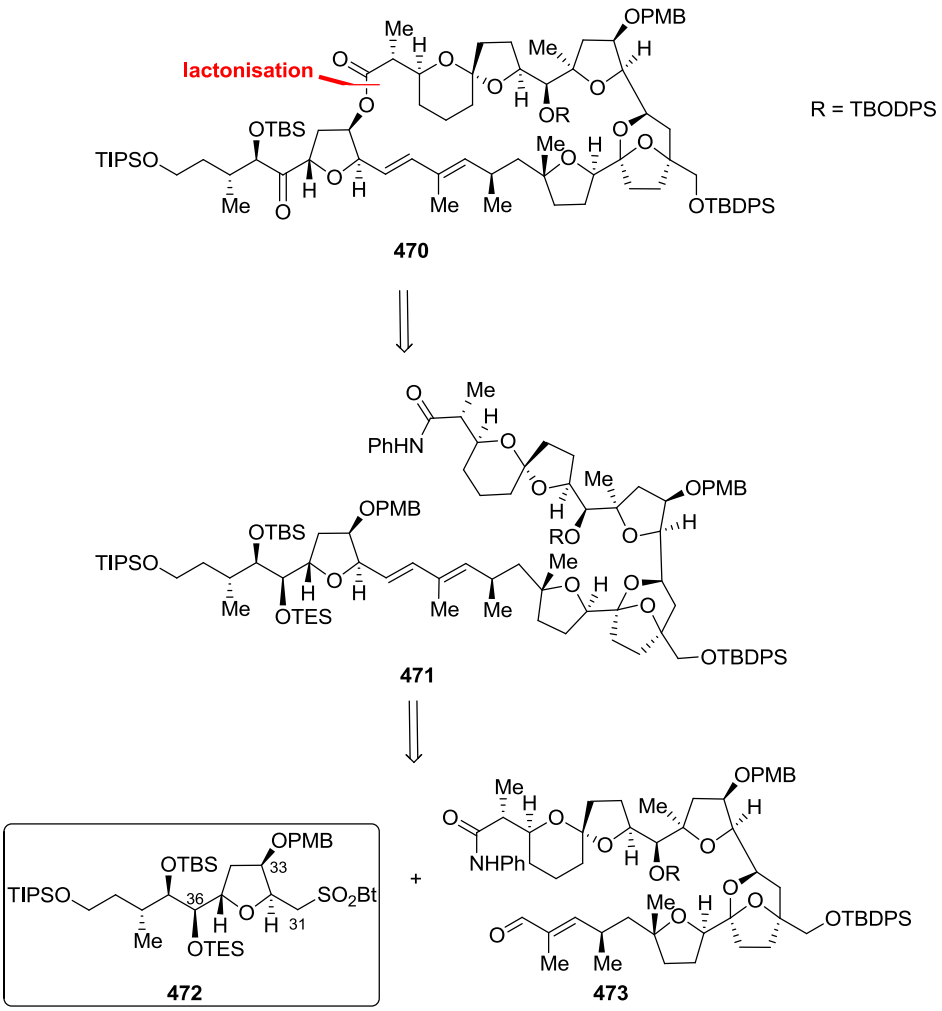
*Scheme **153**: Evans's interconversion of PTX-4, **2** to PTX-8, **469**.*

The retrosynthetic approach adopted by Evans involves an oxidation and a final global deprotection which also forms the G-ring (*Scheme **154***).



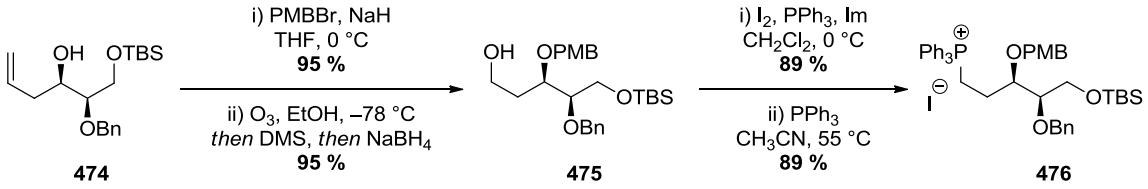
*Scheme **154**: Retrosynthesis of Evans's approach to pectenotoxin-4, **2**.*

The macrocycle of pectenotoxin-4 is formed *via* a macrolactonisation of **471** and homologation of aldehyde **473** and sulfone **472** (*Scheme **155***).



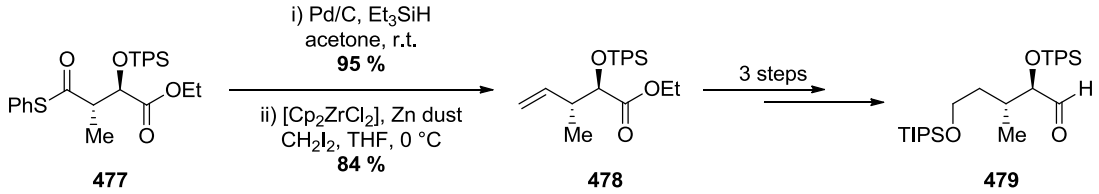
*Scheme **155**: Evans's retrosynthesis to fragments **472** and **473**.*

Evans and co-workers used a similar approach to Brimble in which a Wittig reaction was used to form the carbon backbone. Starting from known triol derivative **474** (available in 2 steps),[113] PMB protection followed by reductive ozonoloysis finally afforded alcohol **475** (*Scheme **156***). Conversion of alcohol **475** to the corresponding iodide, followed by reaction with triphenyl phosphene gave the desired phosphonium salt **476**.



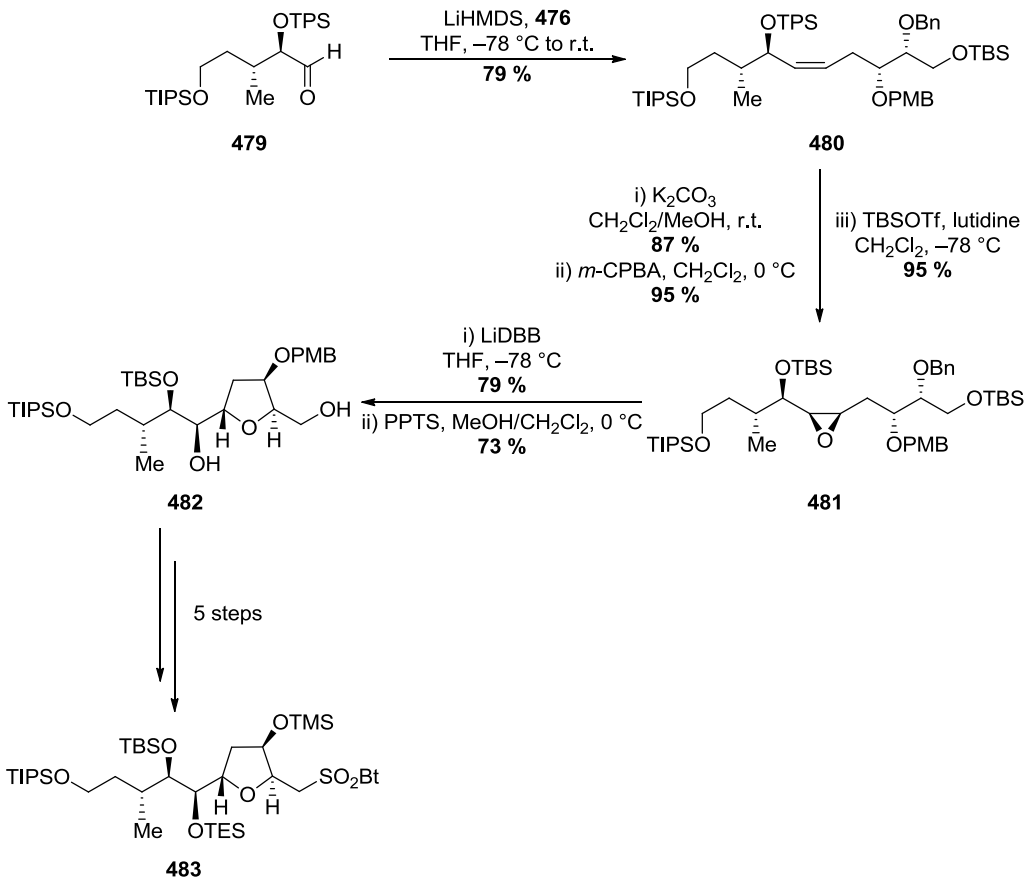
*Scheme **156**: Synthesis of phosphonium salt **476**.*

The synthesis of the aldehyde partner began with selective reduction of the thioester **477** (available in 4 steps)[114] followed by olefination under Lombardo conditions to give terminal alkene **478** (*Scheme **157***).[115] A further three step manipulation of **478**, involving a hydroboration, TPS protection and reduction completed the synthesis of the aldehyde component **479**.



*Scheme **157**: Synthesis of aldehyde **479**.*

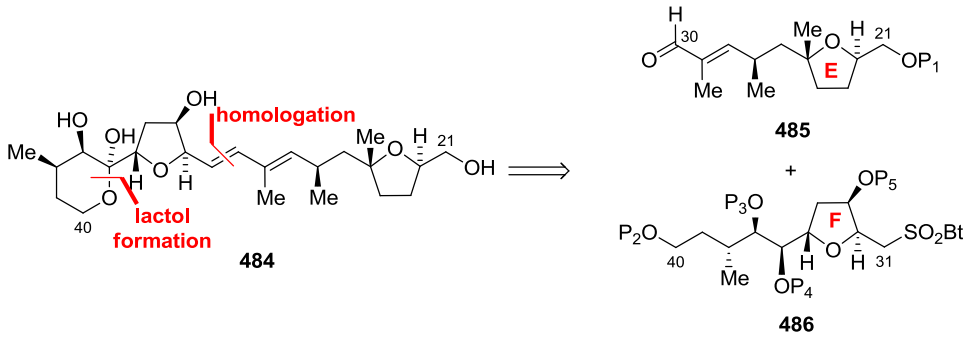
Using lithium bis(trimethylsilyl)amide to form the phosphorus ylide from salt **476**, and reacting with aldehyde **479** gave the desired olefin **480** in 79% yield (*Scheme **158***). Selective deprotection of the TPS group under basic conditions, directed stereoselective epoxidation using *m*-CPBA and reprotection of the epoxy alcohol gave the epoxide **481** as a single diastereomer. LiDBB allowed the removal of the benzyl protected alcohol in the presence of the other protecting groups. The following acid catalysed cyclisation gave THF **483**, which was further converted to yield the $C_{31\text{-}40}$ component for the total synthesis of pectenotoxin-4, **2**.



*Scheme **158**: Synthesis of fragment **483**.*

2.3.3 Aim and Retrosynthesis Analysis

Work in the Donohoe group is currently underway to form the southern hemisphere of pectenotoxin-4 ($C_{21\text{-}40}$). The retrosynthetic analysis described in *Scheme **159*** disconnects the C_{31}-C_{32} bond to give E ring THF **485** and F-ring THF **486**.



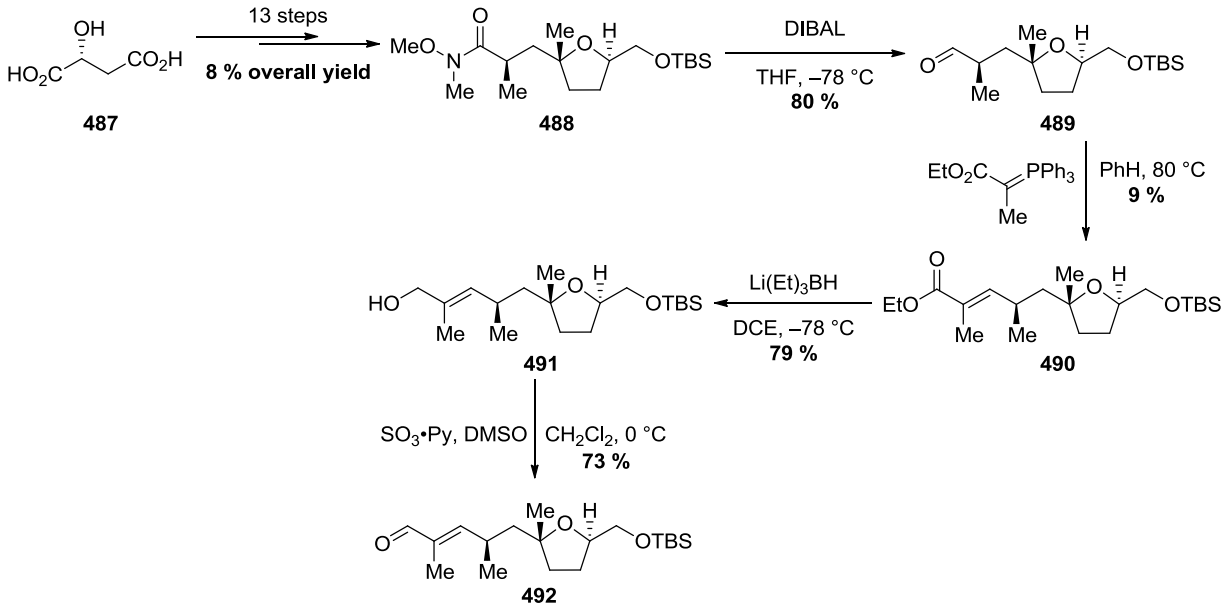
*Scheme **159**: Proposed retrosynthesis of the southern hemisphere of pectenotoxin-4, **2**.*

This disconnection approach is similar to Evans's route in which he reported using the Julia olefination to couple the E and F ring together.[92,116,117] The aim was to form analogous

portions of $C_{21\text{-}30}$ **485** and $C_{31\text{-}40}$ **486** in a more efficient method which could then be successfully coupled to yield the southern hemisphere of pectenotoxin-4, **2**.

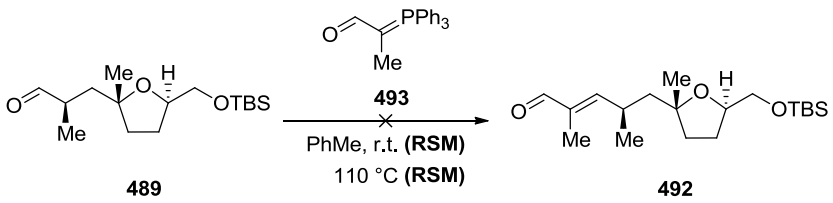
2.3.4 Synthesis of the E ring $C_{21\text{-}30}$

Co-workers in the Donohoe group completed the synthesis of the E ring in 16 steps (*Scheme **160***).[118] The low yielding Wittig step was attributed to the difficult olefination on aldehyde **489** as the stereogenic centre *α* to the carbonyl was susceptible to epimerisation under these conditions. Thus, under these conditions starting material was recovered as a mixture of epimers.



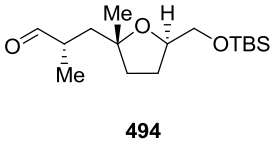
*Scheme **160**: Summary of the synthesis of E ring **492** performed by co-worker.*[118]

It was necessary to improve the yield of the Wittig reaction to ensure an efficient route to **492**. Thus the olefination of aldehyde **489** was investigated further. It was thought that the overall number of steps could be reduced by using 2-(triphenylphosphoranylidene)propionaldehyde **493**, as this would avoid the subsequent reduction and oxidation to **492** (*Scheme **161***).



*Scheme **161**: Attempted homologation of aldehyde **489**.*

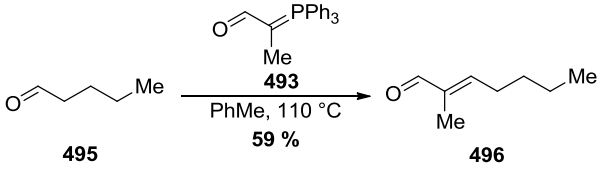
The reaction was attempted at room temperature as well as at 110 °C. In both cases, the reaction was terminated after 12 hours and no product was isolated or observed by TLC, only starting material was recovered from the reaction mixtures. The aldehyde proton in the ^{1}H NMR spectrum of the starting material was observed at δ 9.41 ppm (1H, d, J = 4.0 Hz). Studying the ^{1}H NMR data of the crude reaction material revealed an additional peak at δ 9.62 ppm (1H, d, J = 3.1 Hz) suggested the formation of a diastereomer indicating that the basic conditions resulted in epimerisation of the stereogenic centre α to the aldehyde (*Scheme **162***).



494

*Scheme **162**: Suggested diastereoisomer formed.*

To enable the optimisation of this step, the reaction of ylide **493** with valeraldehyde **495** was explored as a model system (*Scheme **163***).

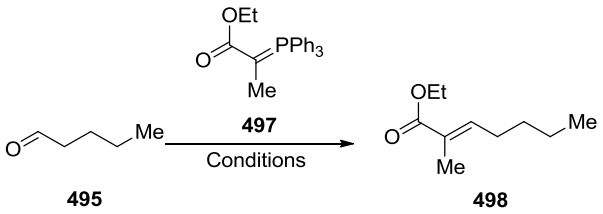


*Scheme **163**: Homologation of valeraldehyde **495**.*

The transformation appeared to proceed well, giving the conjugated aldehyde **495** in 59% yield. The structure was confirmed by comparison of the spectroscopic data that Tan and co-workers had reported for aldehyde **496**.[119] For the case of valeraldehyde **495** it was assumed the lack of a methyl group in the α-position to the aldehyde increased the reactivity of the

carbonyl moiety due to reduced steric hindrance. Thus, within the context of the described model system an alternative, ideally more reactive, Wittig reagent was then sought.

Using the initial synthesis route laid out in *Scheme* **160**, attempts to optimise the original olefination step were pursued. Again valeraldehyde was used, and treated to different conditions with (carbethoxyethylidene)triphenylphosphorane **497** (*Table **15***).

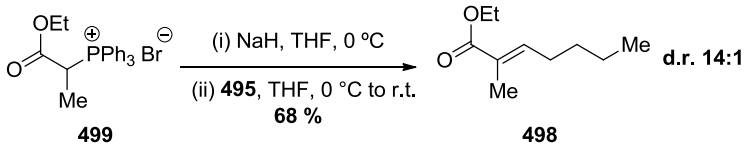


Entry	Solvent	Temperature	Yield of 498
1	PhH	80 °C	RSM
2	PhMe	110 °C	RSM
3	THF	65 °C	RSM

*Table **15**: Conditions screened for olefination of valeraldehyde **495**.*

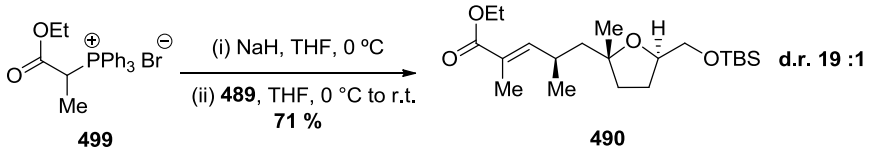
Heating the reaction mixture at 80 °C in benzene gave only recovered starting material (Entry 1). To enable heating at higher temperature, the solvent was replaced with toluene, yet still yielded only starting material (Entry 2). Finally using the polar solvent tetrahydrofuran also gave no indication of product formation (Entry 3).

The recovery of starting material **495** suggested the ylide **497** was not reactive enough and a more nucleophilic analogue was required. Using the precursor (1-(ethoxycarbonyl)ethyl)triphenylphosphonium bromide (1.20 equiv.) and a base (1.1 equiv.) to form the desired ylide, it was assumed this would be reactive enough. An initial attempt with valeraldehyde proved successful, giving the conjugated ester **498** in 68% yield (*Scheme **164***).



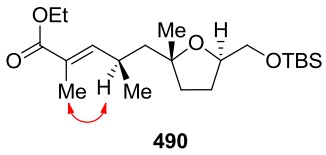
*Scheme **164**: Formation of **498**.*

The diastereoisomeric ratio was determined from examining the ^{1}H NMR spectrum of the crude reaction mixture and integrating the vinylic proton of alkene **498** relative to the vinylic proton of the minor diastereoisomer. The major diastereoisomer was confirmed to have the desired *trans*-stereochemistry by comparing the spectroscopic data with the literature data for **498** whose configuration was initially confirmed by NOE analysis.[120] Attention was turned to the THF **489** olefination using these conditions (*Scheme **165***).



*Scheme **165**: Formation of conjugated aldehyde **490**.*

The lack of the aldehyde proton in the ^{1}H NMR spectrum at δ 9.41 ppm and the presence of a vinylic proton at δ 6.64 ppm indicated the olefination of the aldehyde **489**. Matching the spectroscopic data with the previous synthesis by a coworker in the Donohoe group and NOE based NMR studies on the ester **490** provided evidence towards the alkene stereochemistry to be *trans* (*Scheme **166***).[118]

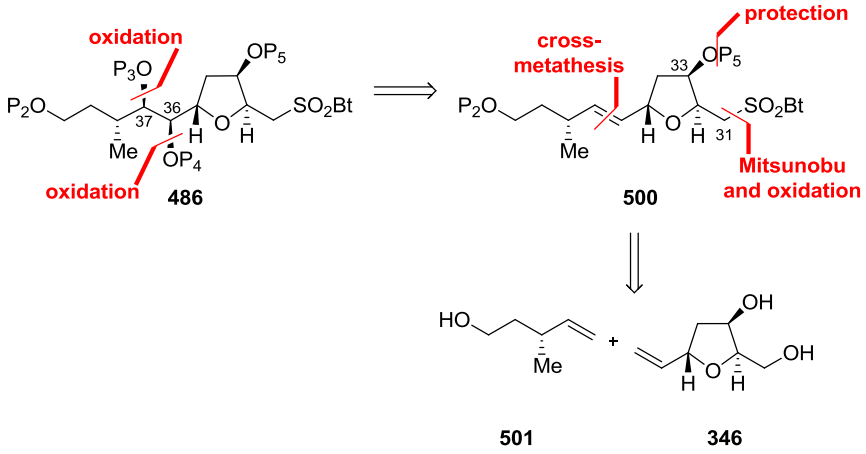


*Scheme **166**: Confirmation of stereochemistry by NOE studies.[118]*

Forming the ylide and then immediately reacting it with **489**, instead of using commercially available ylide suggests the preformed ylide may not be reactive enough to form **490**. With a reliable route now in place to synthesise the aldehyde segment, work turned to the formation of the F-ring **486**.

2.3.5 Synthesis of the F ring $C_{31\text{-}40}$

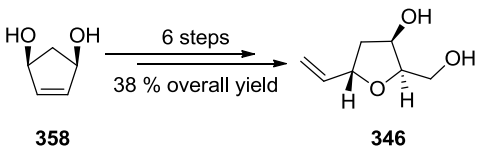
The retrosynthetic analysis shown in *Scheme **167*** outlines the major disconnections of the F-ring **486** of pectenotoxin-4. It was proposed that the stereochemistry at $C_{36\text{-}37}$ could be installed *via* Sharpless asymmetric dihydroxylation of alkene **500**.[36] The THF **346** discussed in *Chapter **2.2*** was believed to be a suitable starting material for the selective protection of the oxygen at C_{33} and subsequent Mitsunobu displacement followed by oxidation to the sulfone.[92]



*Scheme **167**: Retrosynthesis of the desired F-ring **486**.*

2.3.5.1 Protection of the C_{33} hydroxy group

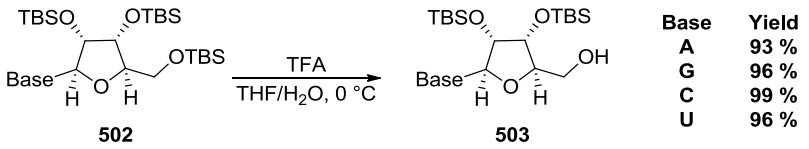
As discussed previously (*See Chapter **2.2***), THF **346** can be accessed from the commercially available cyclopentene diol **358** in 6 steps and 38% overall yield (*Scheme **168***).



*Scheme **168**: Summary of the synthesis of THF **346**.*

To selectively transform the primary alcohol into a sulfone in the presence of the secondary hydroxyl group, a protecting group strategy was required.

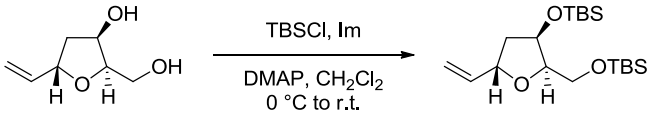
Work by Scott *et al.* showed the selective deprotection of a primary TBS group in the presence of secondary TBS groups (*Scheme **169***).[121]



502 **503**

*Scheme **169**: Selective TBS deprotection.*

It was proposed that treating *bis*-TBS THF **504** with these conditions would deprotect the primary TBS group, leaving the secondary TBS intact. Thus THF **504** was formed in 83% from diol **346** by reaction with an excess of TBSCl (*Scheme **170***).

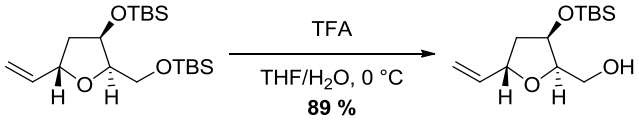


346 **83 %** **504**

*Scheme **170**: Bis-protection of diol **346**.*

Mass spectrometry indicated the *bis*-protection of the THF **504** ($[M + Na]^+$ = 281 *m/z*). The I.R. spectrum of **504** showed the lack of an O-H stretch suggesting protection of both hydroxyl groups. The ^{1}H NMR spectrum showed the minor impurity associated with **346** to be no longer present (*See Chapter **2.2.3***).

Pleasingly treatment of the THF **504** with TFA gave the desired primary alcohol THF **505** in 89% yield (*Scheme **171***).

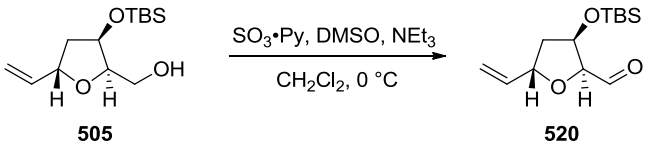


504 **505**

*Scheme **171**: Selective deprotection of **504**.*

The analysis of the product obtained indicated the loss of a TBS group ($[M + Na]^+$ = 281 *m/z*), showing the successful removal of one TBS group. To provide evidence that the major product was indeed the unprotected primary alcohol, the product was oxidised to the

corresponding aldehyde **520** to indicate the presence of an unprotected primary alcohol (*Scheme **172***).

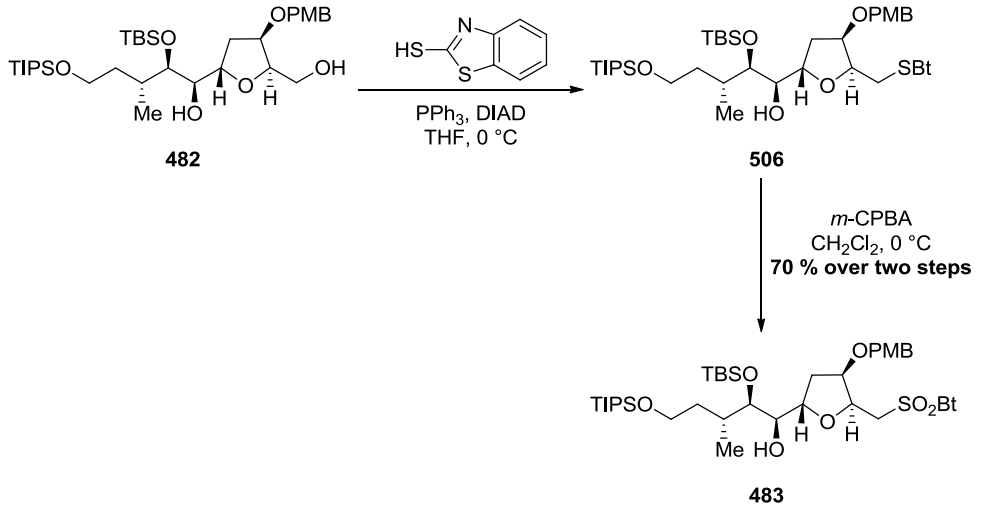


*Scheme **172**: Oxidation of **505**.*

Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed the requisite aldehyde chemical shift at δ_H 9.58 ppm, however the product decomposed upon purification. A 2-dimensional TLC of the crude reaction mixture highlighted the lack of stability of the product towards silica. To acquire further confirmation of **505**, work turned to functionalising the primary alcohol.

2.3.5.2 Formation of C_{31} sulfone

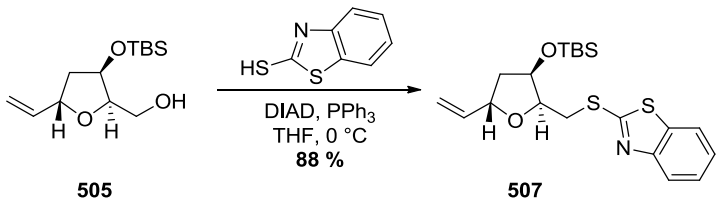
Evans *et al.* installed a benzthiazolyl sulfone using Mitsunobu displacement/substitution conditions followed by oxidation with *m*-CPBA (*Scheme **173***).[92]



*Scheme **173**: Formation of sulfone **483**.*

It was assumed that these conditions would still work for **505**, even though the presence of a TBS instead of a PMB group at C_{33} could affect the reaction. Repeating the Mitsunobu

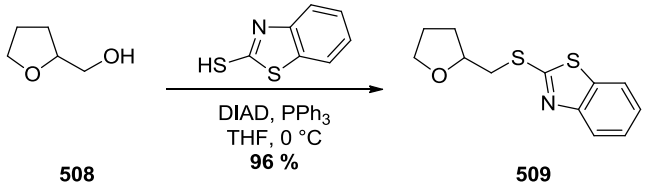
conditions on alcohol **505**, benzthiazole sulfide **507** was obtained in a very good 88% yield (*Scheme **174***).



*Scheme **174**: Formation of benzthiazole sulphide **507**.*

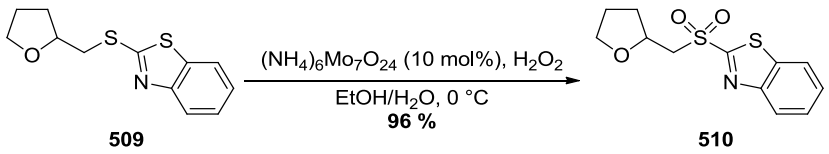
The chemical shift in the ^{13}C NMR spectrum of the methylene carbon adjacent to the heteroatom from O to S changed from δ 64.3 ppm to δ 36.2 ppm in the product sulfide **507**, providing good evidence that the primary hydroxy group had been displaced by the thiol nucleophile.

Evans then treated sulfide **506** with *m*-CPBA to obtain the sulfone **483**. Due to the presence of a terminal olefin in sulfide **507**, it was reasoned that a side reaction involving epoxidation of **507** with *m*-CPBA was likely to occur. Thus an alternative oxidising agent was required. It was believed that the oxidation of thioether **507** could take place using hydrogen peroxide in the presence of a transition metal catalyst. Masuyama and co-workers showed that catalytic ammonium molybdate in the presence of hydrogen peroxide could be used to oxidise sulfides to sulfones in the presence of alkenes.[122] It was deemed prudent to test these conditions in a model system first, thus sulfide **509** was formed from tetrahydrofurfuryl alcohol in 96% yield in an analogous method to before (*Scheme **175***).



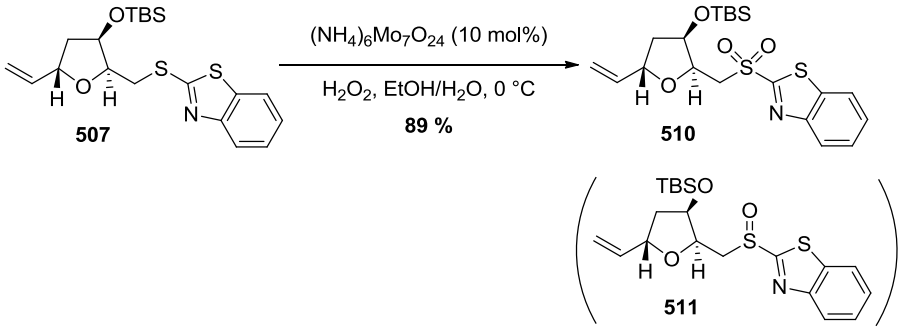
*Scheme **175**: Synthesis of model sulfide **509**.*

With model sulfide **509** in hand, oxidation using the conditions developed by Masuyama was attempted (*Scheme **176***).



*Scheme **176**: Oxidation of sulfide **509** to sulfone **510**.*

Gratifyingly the oxidation occurred in a high yield of 96%. During the course of the reaction, TLC analysis showed a polar spot initially formed, but could not be isolated. It was presumed that this was the intermediate sulfoxide because, as the reaction progressed, a new product spot formed as the initial polar spot diminished. These conditions seemed promising to apply to **507** (*Scheme **177***).

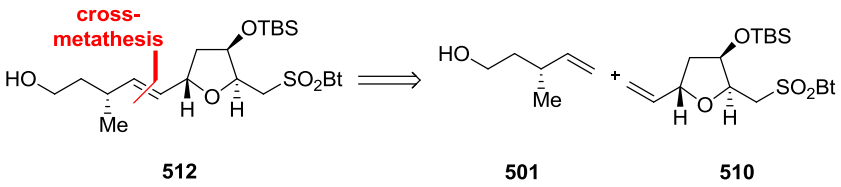


*Scheme **177**: Oxidation of sulfide ether **507**.*

The sulfone **510** was isolated in 89% yield, with no epoxide observed. Formation of the sulfone was apparent form the I.R. spectrum, with the absorptions at 1473 and 1261 cm^{-1}, typical for sulfone-containing moieties.[123] The I.R. stretching frequencies for sulfoxides are typically 1000-1100 cm^{-1}. Further evidence arises from the mass peak at 463 *m*/*z* $[M + Na]^+$ indicating sulfone was formed. In an analogous manner to the oxidation of the test substrate **509**, TLC analysis of this reaction showed the initial formation of a polar spot. This was again thought to be the intermediate sulfoxide **511** because as the reaction proceeded the spot disappeared.

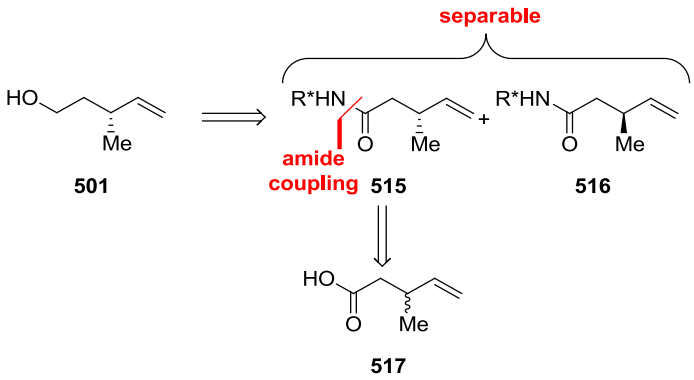
2.3.5.3 Synthesis of alcohol **501**

After successfully forming the desired sulfoxide **510**, attention turned to the synthesis of alcohol **501**, the precursor for cross metathesis (*Scheme **178***).



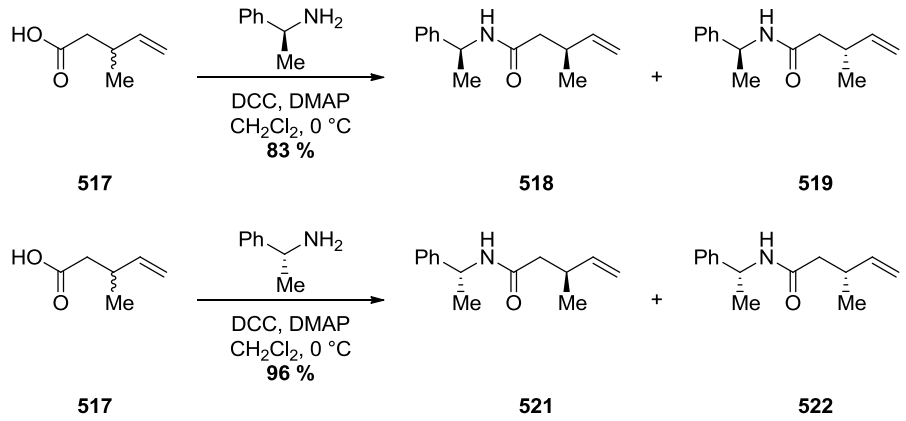
*Scheme **178**: Retrosynthesis of alkene **512**.*

Cross metathesis on unprotected alcohols, as well as sulfones, is well known in the literature.[124,82] The synthesis of alcohol **501** has been reported, albeit in a longer sequence involving an Ireland-Claisen rearrangement.[125] This method seemed to be an inefficient to form alcohol **501** and studies began into researching a shorter sequence. It was postulated that by converting the commercially available carboxylic acid **517** into its corresponding amide, with a chiral amine, the resulting diastereomers formed could be separated (*Scheme **179***).



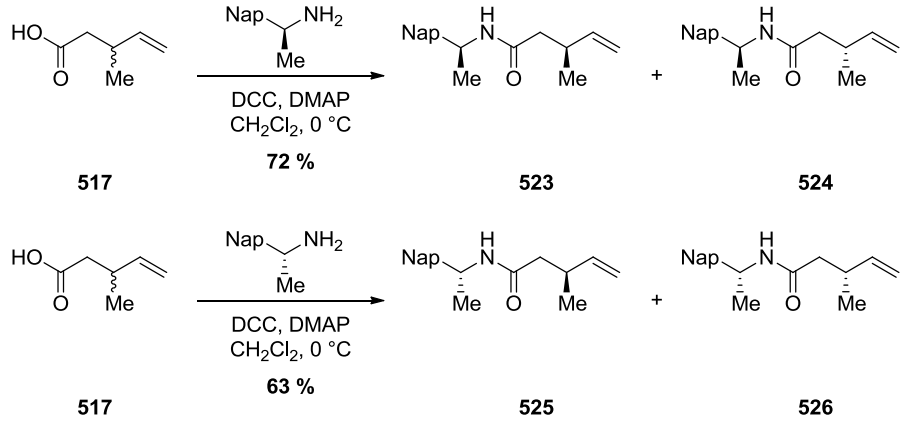
*Scheme **179**: Retrosynthesis of alcohol **501**.*

By taking the carboxylic acid **517** and subjecting it to amide coupling conditions (DCC, DMAP, CH_2Cl_2) with both enantiomers separately of methyl benzylamine, the resulting amides were formed in high yields (*Scheme **180***).



*Scheme **180**: Formation of amides **518-522**.*

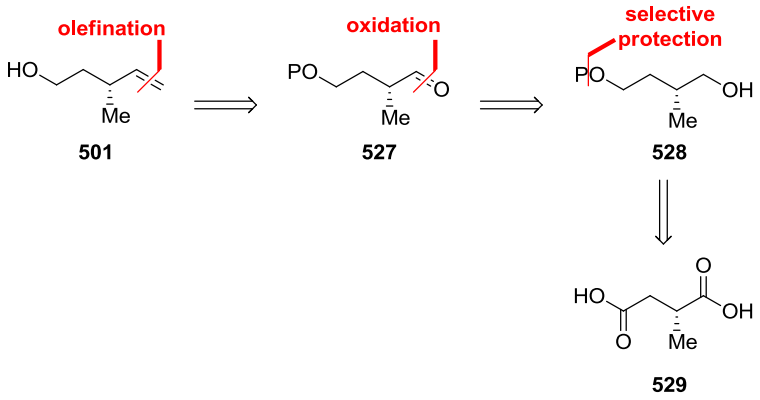
The I.R. data obtained for the pair of amides formed show the appropriate absorption frequencies corresponding to an amide carbonyl group (1637 cm^{-1} for **518** and **519**, 1636 cm^{-1} for **521** and **522**), indicative of the desired products. Disappointingly although coupling the amines with the carboxylic acid **517** gave the resulting amides in high yields, it was not possible to separate the diastereomers. In both cases, the two diastereoisomers co-eluted and it was not possible to separate them by column chromatography. The amides formed were also oils, therefore recrystallisation was not an option. Persisting with this strategy, another attempt was made using the enantiomers of 1-(naphthalen-1-yl)ethanamine (*Scheme **181***).



*Scheme **181**: Formation of amides **523-526**.*

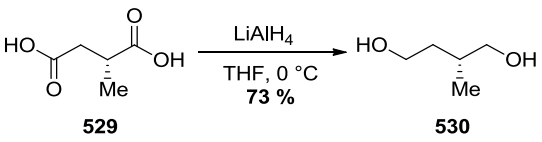
In both cases, coupling occurred reliably to give amides **523** and **524** in 72% yield and amides **525** and **526** in 63%. Frustratingly, once again both sets of diastereomers co-eluted and were oils. An alternative method was designed using material in which the desired

stereochemistry was pre-installed so as to avoid the need to separate diastereomers. *Scheme **182*** outlines a different route to the desired alcohol by disconnecting the alkene to the carbonyl precursor, which would be obtained from oxidation of **528**. This in turn could be accessed from commercially available bis-acid **529**.



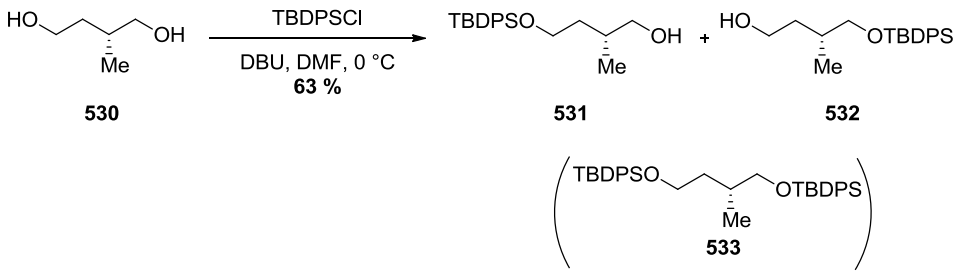
*Scheme **182**: Alternative retrosynthesis of alcohol **501**.*

The synthesis commenced with the reduction of commercially available (*R*)-(+)-methylsuccinic acid **529** to the corresponding diol **530** in 73% using lithium aluminum hydride (*Scheme **183***).



*Scheme **183**: Reduction of **529**.*

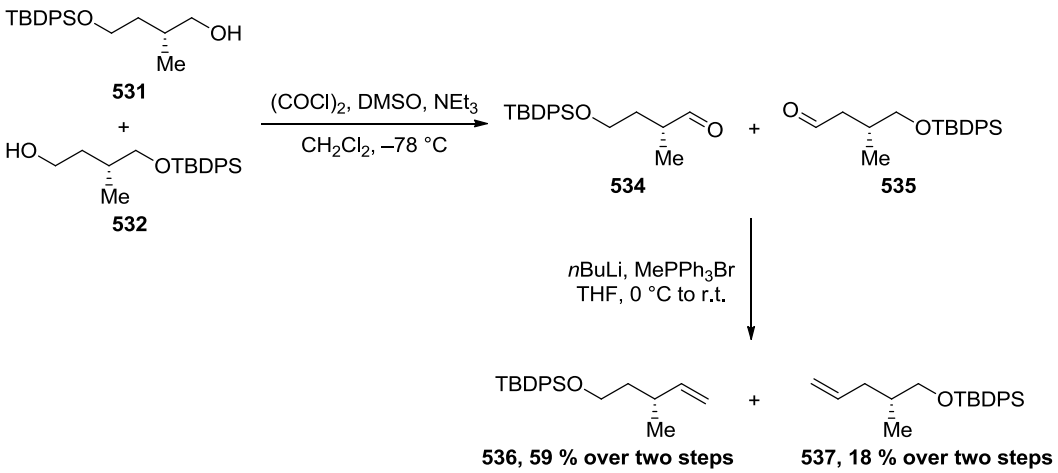
The diol **530** was elucidated from the lack of a chemical shift in the region δ_H 11-12 ppm, typical for a carboxylic acid, and the presence of chemical shifts from methylene protons (2 × C*H*$_2$OH) at δ_H 3.73-3.39 ppm. Selective protection of the less hindered primary alcohol of **530** was thought to be possible using a bulky silyl reagent such as TBDPSCl (*Scheme **184***).[126] It was not possible to identify the ratio of isomers **531** and **532** at this stage from the ^{1}H NMR spectrum as the two mono-silylated alcohols **531** and **532** have overlapping chemical shifts.



*Scheme **184**: TBDPS protection of diol **530**.*

Another by-product was also formed which contained no O-H stretching frequency in the I.R. Using this information as well as integrating the chemical shifts corresponding to aromatic protons at δ_H 7.56 ppm and δ_H 7.35-7.19 ppm in the ^{1}H NMR spectrum indicated bis-protected **533** had also been formed.

To perform a Wittig olefination, the alcohol must be oxidised to the corresponding aldehyde. The Swern oxidation has been shown to successfully oxidise alcohols with α stereocentres to the aldehyde without loss of enantiopurity.[126] The mixture of inseparablemono-protected alcohols **531** and **532** was submitted to Swern oxidation conditions (*Scheme **185***). Examining the ^{1}H NMR spectrum of the crude reaction mixture gave an indication of the proportion of isomers formed as the chemical shifts of the aldehyde protons of each isomer were distinguishable.

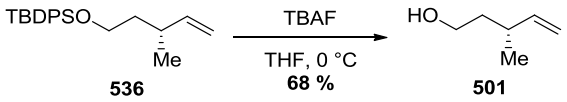


*Scheme **185**: Oxidation and subsequent olefination of alcohols **531** and **532**.*

By integrating the major peak at δ 9.60 ppm (1 H, d, *J* = 1.5 Hz) of the ^{1}H NMR spectrum of the inseparable mixture of isomers (assigned as the aldehyde proton of **534** due to the multiplicity of the coupling) relative to the chemical shift at δ 9.71 ppm (1 H, t, *J* = 1.5 Hz), (assigned as the aldehyde proton of **535**), the ratio of isomers has shown to be 6.5:1 **534**:**535**.

Due to the risk of epimerisation of the stereogenic centre *α* to the aldehyde in **534**, the mixture of aldehydes was taken on without further purification. Exposing the aldehyde to Wittig olefination conditions resulted in the formation of terminal alkenes **536** and **537** which were now separable by column chromatography. The major product was the desired alkene **536**, confirmed by examining the COSY spectra of both alkenes. Alkene **536** showed coupling between the allylic proton (C*H*CH_3) and the vinylic proton (C*H*=CH_2). Conversely, the allylic proton (C*H*CH_3) of **537** did not posses any coupling with the vinylic proton (C*H*=CH_2) and showed coupling with the methylene protons (CH_2OSi) in place.

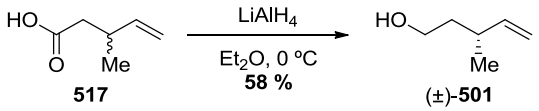
Treatment of silyl ether **536** with the fluoride source TBAF provided the alcohol **501** (*Scheme **186***).



*Scheme **186**: Deprotection of silyl ether **536**.*

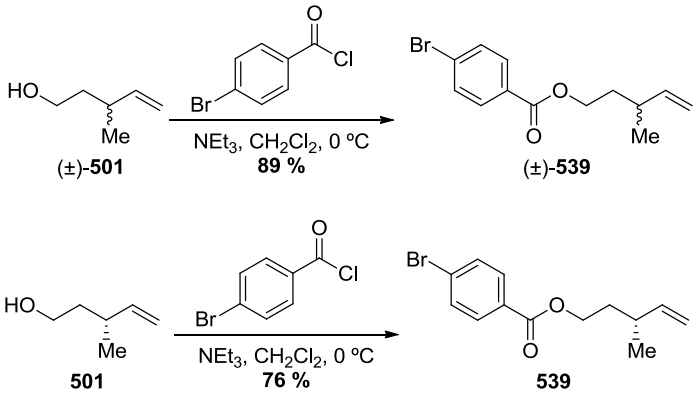
Due to the volatility of alcohol **501**, the yield obtained was lower than anticipated. The spectroscopic data and the specific rotation ($[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ −27.9 (c = 1.0, CH_2Cl_2), *literature* $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ −28.92 (c = 1.0, CH_2Cl_2))[125] of **501** matched that reported in the literature indicating the correct structure.

To confirm that no erosion of enantiopurity had occurred, it was decided to measure the e.e. through HPLC. The racemic analogue of (±)-**501** was formed by reducing the commercially available 3-methyl-4-pentenoic acid **517** (*Scheme **187***).



*Scheme **187**: Reduction of acid **517**.*

A chromophore was required to give a successful U.V. trace for the HPLC. Thus both **501** and (±)-**501** were esterified with 4-bromobenzoyl chloride (*Scheme **188***).



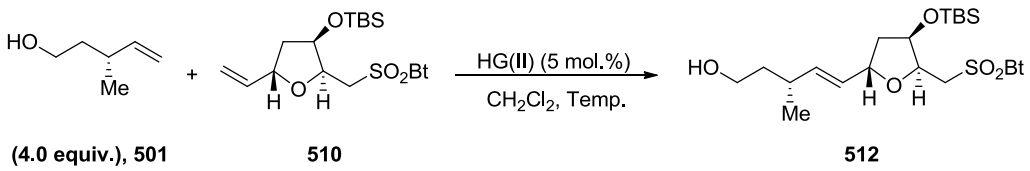
*Scheme **188**: Esterification of alcohols (±)-**501** and **501**.*

With both racemic and non-racemic esters in hand, attention was drawn to the enantiopurity of the **501**. The enantiomeric excess of the starting material bis-acid **529** was 95%. Pleasingly the HPLC trace showed that the alcohol **501** was formed in 91% e.e.

2.3.5.4 Formation of the C_{36} and C_{37} olefin by cross-metathesis

With a successful synthesis of both the alcohol **501** and sulfone **510** attention was now drawn towards the olefin cross-metathesis of alcohol **501** and THF **510**. Grubbs and co-workers have provided a general model to determine which olefin cross metathesis catalyst is required for the types of alkene undergoing cross-metathesis.[82] Using this model it was found that the most promising catalyst would be HG(II). Both terminal alkenes are considered to be Type 1 olefins and would homodimerise rapidly under these metathesis conditions. An excess of the less precious alcohol **501** should disfavour homodimerisation of **510**, favouring the formation of the desired product **512**. A similar case was explored by Donohoe and co-workers as part of the synthesis of (+)-sylvaticin.[56] It was reported that the optimum yield was obtained by

using 4.0 equivalents of the less precious cross metathesis partner. These conditions were implemented for forming **512** (*Table **16***).



(4.0 equiv.), 501 **510** **512**

Entry	Temperature	Yield
1	r.t.	13%
2	40 °C	53%
3	40 °C	78%[a]

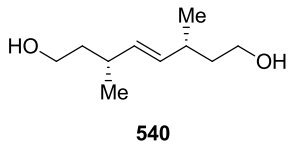
a) *Reaction was carried out in a sealed tube.*

*Table **16**: Screening of cross-metathesis conditions.*

In each of the cases examined, the reaction was stopped after 16 hours. Carrying out the reaction at room temperature gave a small amount of product **512** and the remaining material isolated was starting material (Entry 1). It was decided that heating the reaction would favour cross metathesis and a yield of 58% of the product was obtained. Surprisingly the mass of the starting material **501** recovered was lower than expected. It was presumed the volatility of the alcohol **501** prevented full conversion due to the system not being fully sealed. Thus using a sealed tube instead of a reflux condenser attached to a round bottom flask prevented the loss of alcohol and gave a very good yield of 78% (Entry 3). The THF was identified as the desired cross metathesis product from the lack of terminal olefin peaks in the ^{1}H NMR spectrum. The ratio of *E/Z* isomers formed was found to be 10:1 from the ^{1}H NMR spectrum of the crude reaction material, but the product was isolated as a single diastereoisomer after chromatography on silica. The magnitude of the coupling constant across the alkene was found to be J = 15.5 Hz, typical for a *trans*-alkene.

The formation of a by-product was also observed and this was subsequently isolated. The lack of peaks corresponding to terminal alkene protons in the ^{1}H NMR spectrum suggested it was a cross metathesis product. The lack of absorption peaks corresponding to sulfoxide

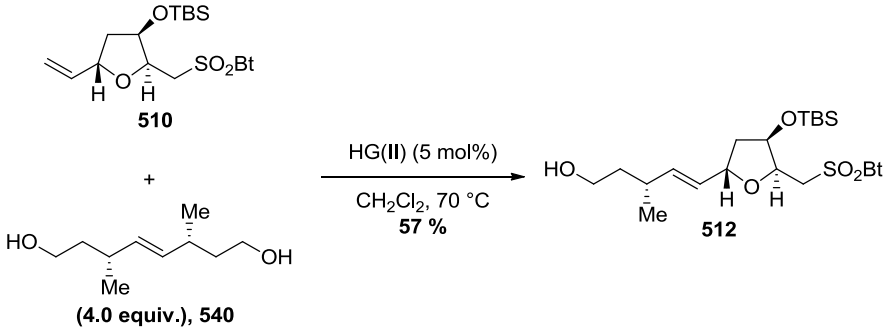
groups in the I.R. spectrum, and analysis of the NMR spectrum suggested the formation of **540**. This is expected due to the excess of alcohol **501** used to prevent formation of a homo dimer **540** (*Scheme **189***).



540

*Scheme **189**: Side product **540**.*

Although this alkene side product is undesirable, it was successfully recycled into the cross-metathesis reaction to form the THF **512**, albeit in a lower yield of 57% (*Scheme **190***).



*Scheme **190**: Cross metathesis using alkene **540**.*

2.3.5.5 Installation of hydroxyl groups at C_{36} and C_{37}

With a successful route to **512** now in place, the next stage involves oxidising the olefin to the corresponding diol. An investigation into the Sharpless asymmetric dihydroxylation was required to install the stereocentres at C_{36} and C_{37}. Sharpless developed a mnemonic that can be used to predict the stereochemical outcome of oxidising an alkene to the diol (*Figure **9***).

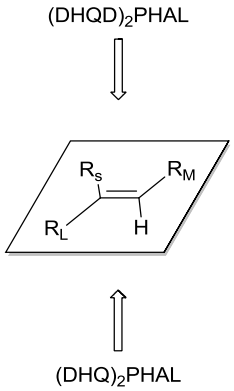
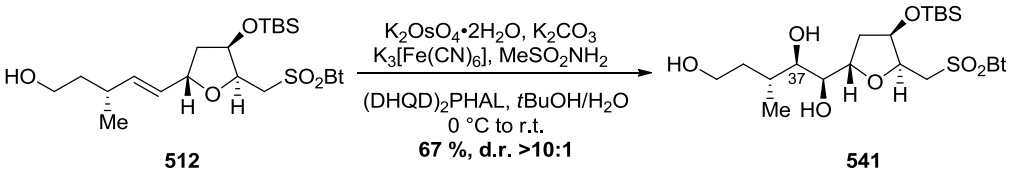


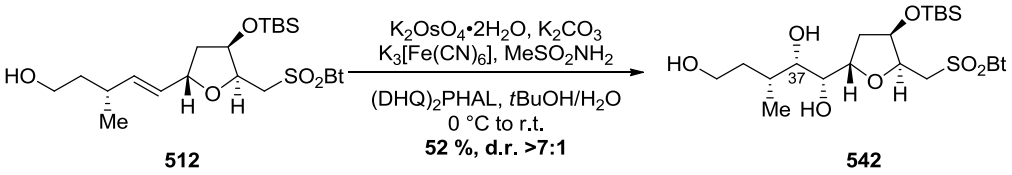
*Figure **9**: Mnemonic used to predict stereochemical outcome of oxidation.*

According to this mnemonic, using $(DHQD)_2PHAL$ as the quinidine ligand should provide the desired (*R*)-alcohol at C_{37} as a result of oxidation across the top face of the *trans*-disubstituted alkene. Subjecting alkene **512** to the dihydroxylation conditions, using $(DHQD)_2PHAL$, delivered the desired diol **541** in 67% yield and as a >10:1 mixture of diastereomers (*Scheme **191***).



*Scheme **191**: Oxidation of the alkene **510** using $(DHQD)_2PHAL$.*

Oxidation of the lower face of the alkene **512** was achieved by using $(DHQ)_2PHAL$ as the chiral ligand. The syn diol **542** was formed in 52% and the ^1H NMR spectrum of this isolated product showed the material obtained was not as pure as in the previous case though a 7:1 ratio of diastereomers was measured (*Scheme **192***).



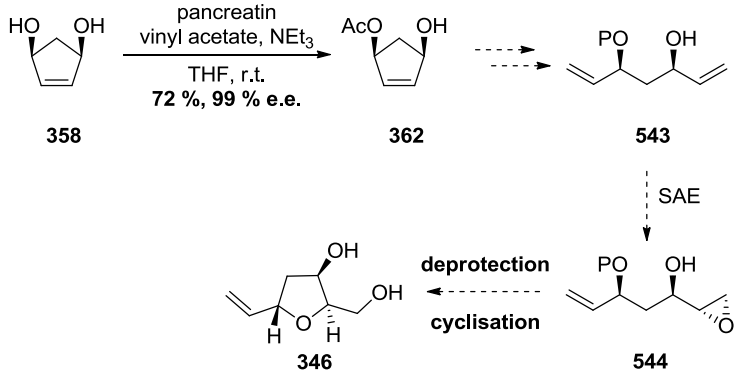
*Scheme **192**: Oxidation of alkene **512** using $(DHQ)_2PHAL$.*

The asymmetric dihydroxylations were found to proceed slowly at 0 ºC, despite the presence of methane sulfonamide in the asymmetric variant, which has been demonstrated to

accelerate the rate of dihydroxylation of non-terminal alkenes by enhancing the hydrolysis of the intermediate osmate ester.[127] Consequently the reactions were allowed to warm to room temperature. The diastereomeric ratio was determined by identifying the C_{37} chemical shift in the ^{1}H NMR spectra for each dihydroxylated product (δ_H 3.01-2.99 for **541**, δ_H 3.43-3.36 for **542**) and integrating this peak relative to the minor peak. The stereoselectivity of the asymmetric dihydroxylations have been assumed to conform to the Sharpless mnemonic.

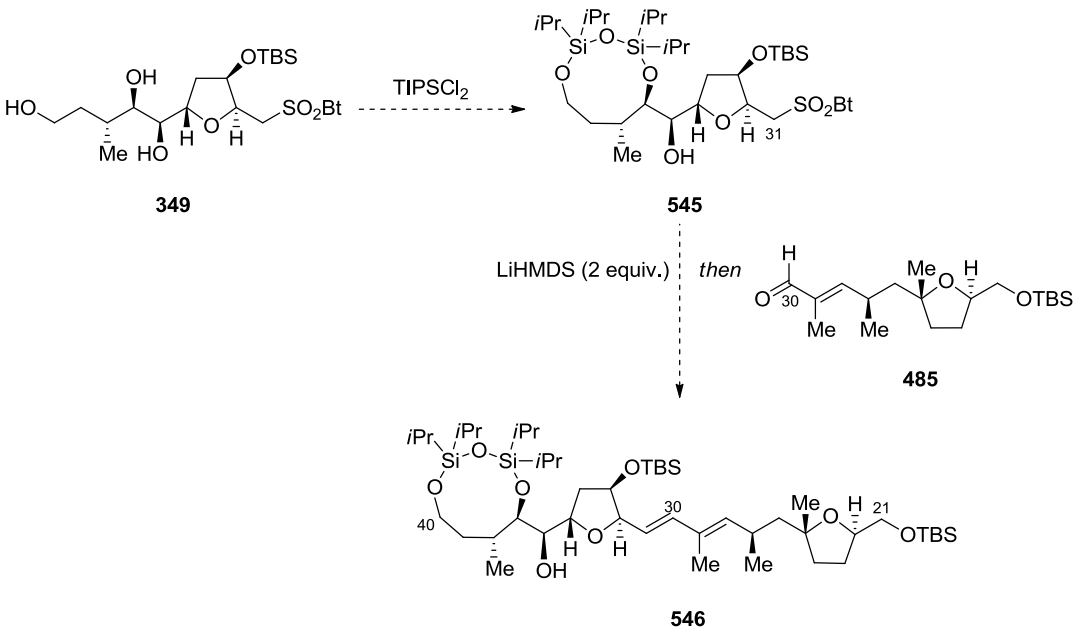
2.3.7 Conclusion and Future Work

The uncertainty of not knowing if the X-ray crystal structure obtained was of the major diastereoisomer leads to two possible outcomes of this research. If the *cis*-THF crystal structure obtained was the major isomer, then a rare example has been discovered in which the relative stereochemistry of the SAE has been inverted. The presence of an additional hydroxyl group must be affecting the SAE and would need to be protected to access the desired *trans*-THF. An alternative synthetic route would then need to be undertaken to reach **543** whereby the additional hydroxyl group is protected. A different approach could involve the desymmetrisation of the cyclopentene diol **362**, shown to be possible by Tietze and co-workers (*Scheme **193***).[130]



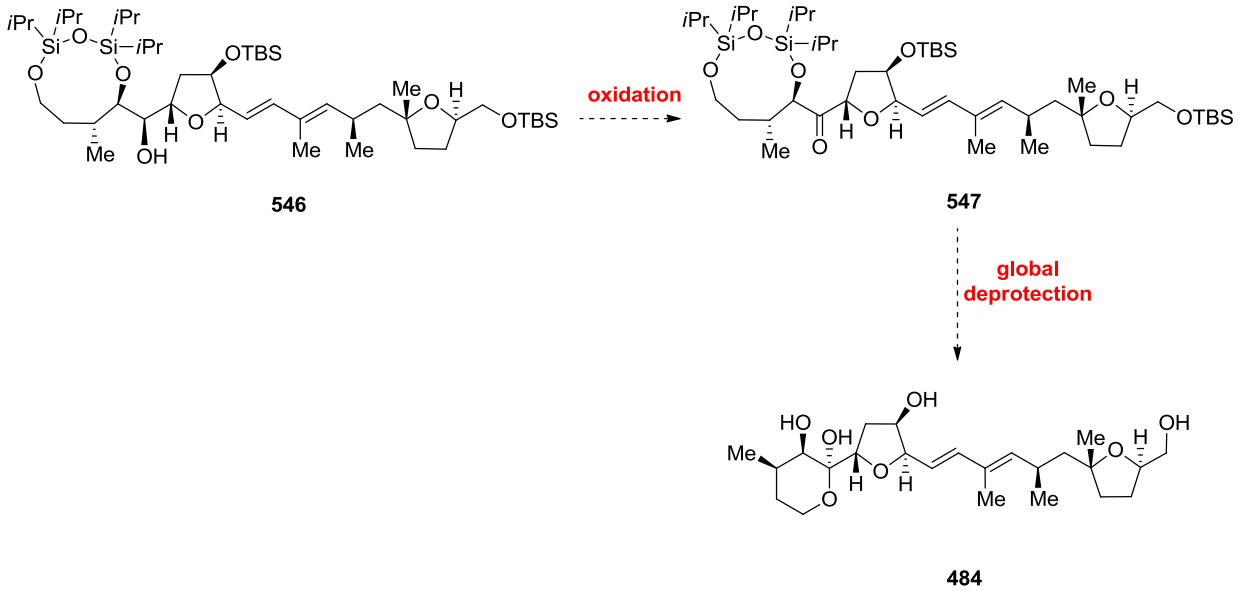
*Scheme **193**: Proposed alternative desymmetrisation of diol **358** and subsequent route to THF **346**.*

If the desired *trans*-THF is formed preferentially, meaning the X-ray crystal structure obtained was of the minor *cis*-THF, then the route towards the southern hemisphere of pectenotoxin-4 can progress. Performing a selective 1,4-diol protection using the Markiewicz reagent, known to disfavor protection of secondary 1,2-diols,[131] would give access to **545**. To complete the carbon skeleton of the lower hemisphere, a modified Julia Kocienski olefination[92] using two equivalents of base, to account for the free hydroxyl group, should yield **546** (*Scheme **194***).



*Scheme **194**: Extension to the $C_{21\text{-}40}$.*

A subsequent oxidation of alcohol **546** to give the corresponding ketone **547**, followed by a global deprotection would deliver the southern hemisphere of pectenotoxin-4 **484** (*Scheme **195***).



*Scheme **195**: Final steps to the southern hemisphere of pectenotoxin-4, **2**.*

Chapter 3: Experimental

General experimental techniques

^{1}H NMR spectra were recorded on a Bruker Avance AV400 (400 MHz) spectrometer, a Bruker AC200 (200 MHz) or a Bruker Avance DRX500 (500 MHz) spectrometer in $CDCl_3$, DMSO-d_6, C_6D_6 and CD_3OD referenced to residual solvent peaks or to $Si(CH_3)_4$ as an internal standard. Chemical shifts are quoted in ppm and signal splittings are recorded as singlet (s), doublet (d), triplet (t), quartet (q), septet (spt) and multiplet (m). Coupling constants, *J*, are quoted in Hz. ^{13}C NMR spectra were recorded on a Bruker Avance AV400 spectrometer at 100 MHz or on a Bruker Avance DRX500 at 125 MHz and were referenced to $CDCl_3$, DMSO-d_6, C_6D_6 or CD_3OD. ^{1}H and ^{13}C NMR spectra were recorded at room temperature.

Infra-red spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Spectra were analysed as thin films between NaCl plates. Selected absorption peaks are given in cm^{-1} and refer to stretching vibrations unless otherwise stated.

Mass spectra (LRMS) and accurate mass (HRMS) were recorded on a Bruker Micro ToF spectrometer under conditions of electrospray ionisation (ESI) unless otherwise stated. Values are reported as a ratio of mass to charge in Daltons. The lock-mass used for calibration was tetraoctylammonium bromide in positive ion mode and sodium dodecyl sulfate in negative ion mode.

Melting points were determined using a Leica VMTG heated-stage apparatus and are uncorrected.

Flash column chromatography was performed using silica gel 60 (0.033-0.070 mm, BDH) using head pressure by means of head bellows, employing the method of Still *et al.* TLC analyses were performed on Merck Kiesegel 60 F254 0.25 mm precoated aluminium-backed plates. Product spots were visualised under UV light (λ_{max}=254nm) and/or by staining with a potassium permanganate solution.

Reagents obtained from Acros, Aldrich, Avocado and Fluka fine chemicals suppliers were used directly as supplied or following purification according to procedures described by Armarego and Chai.

Anhydrous reactions were carried out under an inert atmosphere of argon. Flasks were dried in a flame then cooled under a stream of nitrogen or argon.

Toluene, dichloromethane, diethylether, tetrahydrofuran, methanol, pentane and benzene were dried by filtration through two activated alumina, purification columns. Petrol refers to petroleum ether boiling in the range 40-60 ^{o}C. Brine refers to a saturated aqueous solution of sodium chloride.

Compounds are numbered according to a *Scheme* which may differ from IUPAC recommendations.

Experimental details

General Procedure A: Mono-esterification of 2-exo-3-bicyclo[2.2.1]heptandiol

The corresponding acid chloride (1.00 equiv.) was dissolved in dichloromethane (0.20 M) and added *via* syringe pump (14.0 mL/h) to a solution of 2-exo-3-bicyclo[2.2.1]heptandiol (1.50 equiv.) in dichloromethane (0.20 M) at 0 ^{o}C. After leaving the reaction for 16 hours it was quenched with a saturated aqueous solution of sodium bicarbonate (0.10 M) and the phases were separated. The aqueous layer was extracted with dichloromethane (3 × 0.10 M) and the combined organic layers washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The crude esters were purified by flash column chromatography.

General Procedure B: Acid chloride esterification of racemic hydroxy esters

The corresponding acid chloride (2.00 equiv.) was added dropwise to a solution of racemic hydroxy ester (1.00 equiv.), 4-dimethylaminopyridine (0.10 equiv.) and pyridine (2.00 equiv.) in dichloromethane (0.18 M). The resulting solution was stirred at room temperature for 2 hours then quenched with a saturated solution of sodium bicarbonate (0.18 M) and the phases were separated. The aqueous layer was extracted with dichloromethane (3 × 0.18 M) and the combined organic layers washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The crude ester was purified by flash column chromatography.

General Procedure C: Aldol reaction of benzylic esters

Potassium carbonate (0.90 equiv.) was added to a solution of the corresponding ester (1.00 equiv.) and formaldehyde (0.90 equiv.) in dimethyl sulfoxide (0.30 M) at room temperature. After heating to 50 ^{o}C for 16 h, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (0.15 M), washed with water (0.10 M), dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

General Procedure D: Methylation of primary alcohols

Silver(I) oxide (4.00 equiv.) was added to a solution of the corresponding alcohol (1.00 equiv.) and iodomethane (12.0 equiv.) in diethyl ether (0.14 M) at room temperature. After 3 days the reaction mixture was filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

General Procedure E: Carboxylic acid esterification of racemic hydroxy esters

Dicyclohexylcarbodiimide (1.10 equiv.) was added to a solution of the corresponding racemic hydroxy ester (1.00 equiv.), the corresponding acid (1.10 equiv.) and 4-dimethylaminopyridine (0.10 equiv.) in dichloromethane (0.10 M) at 0 ^{o}C. After stirring for 16 hours at room temperature, the reaction mixture was filtered, washed sequentially with a saturated aqueous solution of citric acid (0.10 M) and a saturated aqueous solution of sodium bicarbonate (0.10 M). The organic layer was dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

General Procedure F: Preparation of LiDBB solution

A flame dried Schlenk tube under Argon, fitted with a magnetic follower, was charged with 4,4'-di-*tert*-butyl-1,1'-biphenyl (2.00 equiv.). Argon sparged tetrahydrofuran (0.10 M) was added *via* syringe and the solution was cooled to 0 ^{o}C. Lithium wire (40.0 equiv.) was finely chopped and added to the solution under a stream of argon. After 2 hours the reaction mixture was cooled to −78 ^{o}C.

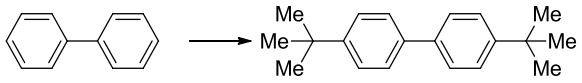
General Procedure G: Esterification using Mosher's acid

Dicyclohexylcarbodiimide (2.00 equiv.) was added to a solution of the corresponding alcohol (1.00 eq.), (*R*)-(+)-alpha-methoxy-alpha-trifluoromethylphenylacetic acid (2.00 equiv.) dimethylaminopyridine (0.10 equiv.), in dichloromethane (0.10 M) at 0 ^{o}C. After stirring for 16 hours at room temperature, the reaction mixture was filtered through a pad of celite, dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

Preparation of Silica Gel supported sodium periodate reagent

Prepared using the method by Shing.[86] Sodium periodate (10.0 g) was dissolved in water (20 mL), and heated to 70 °C. Silica gel (40.0 g) was then added to the solution and vigorously stirred for 16 hours to obtain a free flowing powder (60.0 g).

4,4'-Di-tert-butyl-1,1'-biphenyl, 251



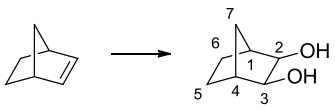
251

A solution of 2-chloro-2-methylpropane (65.0 mL, 600 mmol) in nitromethane (20.0 mL) was added to a solution of biphenyl (50.0 g, 325 mmol) and anhydrous aluminium chloride (30.0 g, 97.3 mmol) in nitromethane (70.0 mL) over 30 minutes under vigorous stirring. After 2 hours the crude mixture was poured onto crushed ice. The phases were separated and the aqueous layer was extracted with petrol (3 × 100 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by re-crystallisation from ethanol to give the title compound **251** (55.3 g, 64%) as a white crystalline solid.

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.70-7.42 (8 H, m, 8 × Ar*H*), 1.40 (18 H, s, 2 × C(CH_3)$_3$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 149.9 (2 × quat. Ar*C*), 138.2 (2 × quat. Ar*C*), 126.7 (2 × Ar*C*), 125.6 (2 × Ar*C*), 34.5 (2 × *C*(CH_3)$_3$), 31.4 (2 × C(*C*H_3)$_3$); **m.p.** 126-131 ^{o}C (lit. 126-130 ^{o}C).

The spectral data were consistent with those in the literature.[132]

(1*R*,2*S*,3*R*,4*S*)-Bicyclo[2.2.1]heptane-2,3-diol, 263



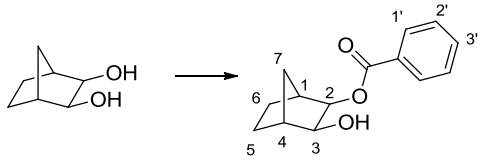
263

A solution of potassium permanganate (12.0 g, 76.0 mmol) and sodium hydroxide (2.61 g, 65.3 mmol) in water (250 mL) was added dropwise to a stirred solution of norbornene (5.00 g, 53.1 mmol) in *tert*-butanol (200 mL) and water (50.0 mL) at 0 ^{o}C over 30 minutes. Sodium metabisulphite was then added until the solution turned colourless. The mixture was filtered and the *tert*-butanol was removed from the filtrate *in vacuo*. The aqueous solution was extracted using ethyl acetate (4 × 300 mL) and the organic layers were combined and concentrated *in vacuo*. The crude product was purified by re-crystallisation from toluene to give (1*R*,2*S*,3*R*,4*S*)-bicyclo[2.2.1]heptane-2,3-diol **263** (4.97 g, 73%) as a white crystalline solid.

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 3.66 (2 H, s, C*H*OH), 3.26 (2 H, br s, O*H*), 2.12 (2 H, s, C(2)*H* and C(3)*H*), 1.74 (1 H, m, C(7)H_AH_B), 1.45 (2 H, m, C(5 and 6)H_AH_B), 1.13-0.99 (3 H, m, C(5 and 6)H_AH_B and C(7)H_AH_B); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 74.7 (*C*(2) and *C*(3)), 43.0 (*C*(1) and *C*(4)), 31.6 (*C*(7)), 24.5 (*C*(5) and *C*(6)); **m.p.** 139-142 ^{o}C (lit. 141-142 ^{o}C).

The spectral data were consistent with those in the literature.[72]

((±)-(1*S*,2*R*,3*S*,4*R*))-3-Hydroxybicyclo[2.2.1]heptan-2-yl benzoate, (±)-295

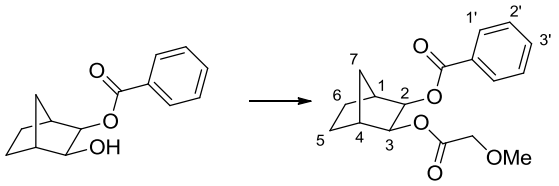


263 (±)-**295**

(1*R*,2*S*,6*R*,7*S*)-bicyclo[2.2.1]heptane-2,3-diol **263** (4.21 g, 32.9 mmol) and benzoyl chloride were subjected to general procedure A. Flash column chromatography (9:1 petrol:ethyl acetate) yielded the title ester (±)-**295** as a white solid (6.41 g, 84%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 8.02 (2 H, d, *J* = 7.8 Hz, C(1')*H*), 7.58-7.48 (1 H, m, C(3')*H*), 7.46-7.34 (2 H, m, C(2')*H*), 4.75 (1 H, d, *J* = 5.6 Hz, C(2)*H*), 3.93 (1 H, d, *J* = 5.6 Hz, C(3)*H*), 2.51 (1 H, br s, O*H*), 2.37 (1 H, s, C(1)*H*), 2.23 (1 H, s, C(4)*H*), 1.97 (1 H, d, *J* = 10.4 Hz, C(7)H_AH_B), 1.62-1.42 (2 H, m, C(5)H_AH_B and C(6)H_AH_B), 1.24-1.08 (3 H, m, C(5)H_AH_B and C(6)H_AH_B and C(7)H_AH_B); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 166.7 (*C*=O), 133.0 (Ar*C*), 130.0 (quat. Ar*C*), 129.6 (Ar*C*), 128.4 (Ar*C*), 78.9 (*C*(2)), 75.8 (*C*(3)), 43.3 (*C*(1)), 40.8 (*C*(4)), 33.0 (*C*(7)), 24.5 (*C*(6)), 24.4 (*C*(5)); **IR** (ν_{max}/cm^{-1}): 3489, 2963, 2876, 1717; **LRMS** (ESI$^+$, *m/z*): 255 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$, *m/z*): Calculated 255.0992 ($C_{14}H_{16}NaO_3$), Found 255.0988 (Δ+1.08 ppm); **m.p.** 61-64 ^{o}C.

((±)-(1*S*,2*R*,3*S*,4*R*))-3-(2-Methoxyacetoxy)bicyclo[2.2.1]heptan-2-yl benzoate, (±)-296



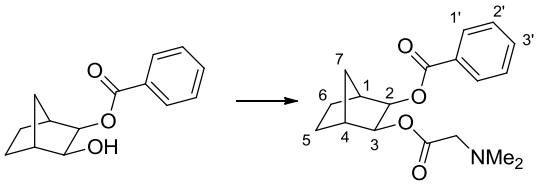
(±)-**295** (±)-**296**

((±)-(1*S*,2*R*,3*S*,4*R*))-3-Hydroxybicyclo[2.2.1]heptan-2-yl benzoate (±)-**295** (300 mg, 1.29 mmol) and 2-methoxyacetyl chloride were subjected to general procedure B. Flash column chromatography (9:1 petrol:diethyl ether) yielded the title diester (±)-**296** as a white solid (306 mg, 78%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 8.01 (2 H, d, *J* = 7.3 Hz, C(1')*H*), 7.60-7.52 (1 H, m, C(3')*H*), 7.49-7.39 (2 H, m, C(2')*H*), 5.05 (1 H, d, *J* = 5.8 Hz, C(3)H), 4.96 (1 H, d, *J* = 5.8 Hz, C(2)*H*), 3.92 (1 H, d, *J* = 16.4 Hz, CH_AH_BCO), 3.75 (1 H, d, *J* = 16.4 Hz, CH$_A$$H_B$CO), 3.23 (3 H, s, OC$H_3$), 2.44 (1 H, s, C(4)*H*), 2.36 (1 H, s, C(1)*H*), 2.01 (1 H, d, *J* = 10.4 Hz, C(7)H_AH_B), 1.64-1.61 (2 H, m, C(5)H_AH_B and C(6)H_AH_B), 1.33-1.30 (3 H, m, C(5)H$_A$$H_B$,

C(6)H$_A$*H*$_B$ and C(7)H$_A$*H*$_B$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 169.4 (Ph*C*O$_2$), 165.6 (*C*O$_2$), 133.0 (Ar*C*), 130.1 (quat. Ar*C*), 129.5 (Ar*C*), 128.4 (Ar*C*), 76.9 (*C*(2) and *C*(3)), 69.5 (*C*H$_2$OCH$_3$), 59.2 (OCH$_3$), 41.0 (*C*(1) and *C*(4)), 33.8 (*C*(7)), 24.4 (*C*(6)), 24.2 (*C*(5)); **IR** (ν_{max}/cm^{-1}): 2972, 1759, 1716; **LRMS** (ESI$^+$, *m/z*): 327 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$, *m/z*): Calculated 327.1203 ($C_{17}H_{20}NaO_5$), Found 327.1203 (Δ+0.1 ppm); **m.p.** 70-73 ^{o}C.

((±)-(1*S*,2*R*,3*S*,4*R*))-3-(2-(Dimethylamino)acetoxy)bicyclo[2.2.1]heptan-2-yl benzoate, (±)-297



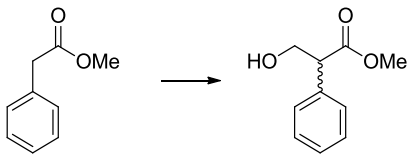
(±)-**295** (±)-**297**

N,*N*'-Dicyclohexylcarbodiimide (693 mg, 3.36 mmol) was added to a stirred solution of ((±)-(1*S*,2*R*,3*S*,4*R*))-3-hydroxybicyclo[2.2.1]heptan-2-yl benzoate (±)-**295** (500 mg, 3.05 mmol), *N*,*N*-dimethylpyridin-4-amine (38.0 mg, 0.31 mmol) and 2-(dimethylamino)acetic acid hydrochloride (467 mg, 3.36 mmol) in dichloromethane (30.5 mL) at 0 °C and the reaction mixture was warmed to room temperature. After 16 hours, the reaction mixture was filtered, washed with a saturated aqueous solution of citric acid (30.0 mL) and then a saturated aqueous solution of sodium bicarbonate (30.0 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (6:1 petrol:ethyl acetate) yielded the title diester (±)-**297** as a white solid (657 mg, 68%).

^{1}H NMR δ_H (400 MHz, CD_3OD): 8.01 (2 H, d, *J* = 7.3 Hz, C(1')*H*), 7.63 (1 H, t, *J* = 7.3 Hz, C(3')*H*), 7.51 (2 H, t, *J* = 7.8 Hz, C(2')*H*), 5.02 (1 H, d, *J* = 5.3 Hz, C(2)*H*), 4.91 (1 H, d, *J* = 5.8 Hz, C(3)*H*), 3.16 (1 H, d, *J* = 16.9 Hz, C*H*$_A$H$_B$N(CH$_3$)$_2$), 2.87 (1 H, d, *J* = 16.9 Hz,

$CH_AH_BN(CH_3)_2$), 2.41 (1 H, s, C(4)*H*), 2.32 (1 H, s, C(1)*H*), 2.12 (6 H, s, $N(CH_3)_2$), 2.05 (1 H, d, *J* = 10.4 Hz, $C(7)H_AH_B$), 1.64 (2 H, d, *J* = 7.8 Hz, $C(5)H_AH_B$ and $C(6)H_AH_B$), 1.41-1.27 (3 H, m, $C(5)H_AH_B$ and $C(6)H_AH_B$ and $C(7)H_AH_B$); **^{13}C NMR** δ_H (100 MHz, CD_3OD): 169.7 ($PhCO_2$), 166.0 (CO_2), 133.5 (Ar*C*), 130.4 (quat. Ar*C*), 129.6 (Ar*C*), 128.7 (Ar*C*), 77.3 (*C*(2)), 77.1 (*C*(3)), 59.2 ($CH_2N(CH_3)_2$), 44.1 ($N(CH_3)_2$), 41.5 (*C*(1)), 41.4 (*C*(4)), 33.6 (C(7)), 24.3 (*C*(5)), 24.1 (*C*(6)); **IR** (ν_{max}/cm^{-1}): 2975, 1715, 1275; **LRMS** (ESI^+, *m/z*): 318 ($[M+Na]^+$, 100%); **HRMS** (ESI^+, *m/z*): Calculated 318.1701 ($C_{18}H_{24}NO_4$), Found 318.1700 ($\Delta -0.2$ ppm); **m.p.** 34-37 °C.

(±)-Methyl 3-hydroxy-2-phenylpropanoate, (±)-305



304 (±)-**305**

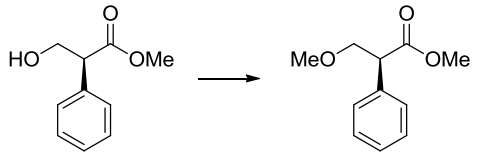
Potassium carbonate (882 mg, 6.39 mmol) was added to a stirred solution of methyl 2-phenylacetate **304** (1.00 mL, 7.10 mmol) and *para*-formaldehyde (192 mg, 6.39 mmol) in dimethyl sulphoxide (24.0 mL) at room temperature and then heated to 50 °C. After 16 hours, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (47.0 mL), washed with water (70.0 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (4:1 petrol:ethyl acetate) yielded the title compound (±)-**305** as a colourless oil (819 mg, 64%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.44-7.11 (5 H, m, Ar*H*), 4.15 (1 H, dd, *J* = 9.9, 7.8 Hz, CH_AH_BOH), 3.93-3.79 (2 H, m, CH_AH_BOH and $CHCH_2OH$), 3.72 (3 H, s, CO_2CH_3), 2.01 (1

H, br s, O*H*); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 173.6 (*C*O_2), 135.6 (Ar*C*), 128.9 (quat. Ar*C*), 128.2 (Ar*C*), 127.8 (Ar*C*), 64.6 (*C*H_2OH), 53.9 (*C*HCO_2), 52.2 (*C*H_3).

The spectral data were consistent with those in the literature.[133]

(±)-Methyl 3-methoxy-2-phenylpropanoate, (±)-306



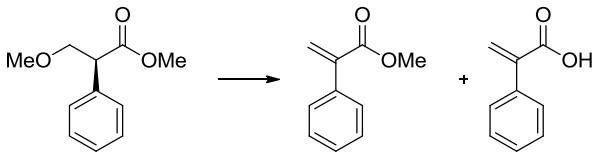
(±)-**305** (±)-**306**

Silver(I) oxide (1.02 g, 4.44 mmol) was added to a solution of methyl 3-hydroxy-2-phenylpropanoate (±)-**305** (200 mg, 1.11 mmol) and methyl iodide (1.89 g, 13.3 mmol) in diethyl ether (8.00 mL) at room temperature. After 3 days the reaction mixture was filtered and concentrated *in vacuo*. Flash column chromatography (9:1 petrol:diethyl ether) yielded the title ester (±)-**306** as a colourless oil (194 mg, 90%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.42-7.23 (5 H, m, Ar*H*), 4.02 (1 H, dd, *J* = 10.9, 7.9 Hz, CHC$H_A$$H_B$), 3.91 (1 H, dd, *J* = 9.8, 7.7 Hz, CHC$H_A$$H_B$), 3.70 (3 H, s, CO_2CH_3), 3.60 (1 H, dd, *J* = 8.8, 5.1 Hz, C*H*CH_2), 3.38 (3 H, s, CH_2OCH_3); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 172.8 (*C*O_2), 135.7 (Ar*C*), 128.7 (quat. Ar*C*), 128.1 (Ar*C*), 127.7 (Ar*C*), 74.3 (*C*H_3), 68.3 (*C*H_2OH), 52.3 (*C*HCO_2), 51.9 (*C*H_3).

The spectral data were consistent with those in the literature.[134]

Methyl 2-phenylacrylate, 307 and 2-Phenylacrylic acid, 308



(±)-**306** **307** **308**

Lithium hydroxide monohydrate (420 mg, 2.16 mmol) was added to a stirred solution of methyl 3-methoxy-2-phenylpropanoate (±)-**306** (168 mg, 0.864 mmol) in a 4:2:1 mixture of tetrahydrofuran (4.00 mL), water (2.00 mL) and methanol (1.00 mL) at room temperature. After stirring for 16 hours the reaction mixture was diluted with ethyl acetate (7.00 mL) and the phases were separated. The aqueous layer was extracted with ethyl acetate (3 × 7.00 mL) and the combined organic layers washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (4:1 petrol:diethyl ether → 3:2 petrol:ethyl acetate) to yield the title ester **307** as a yellow oil (17 mg, 12%) and the title acid **308** as a yellow oil (68 mg, 53%).

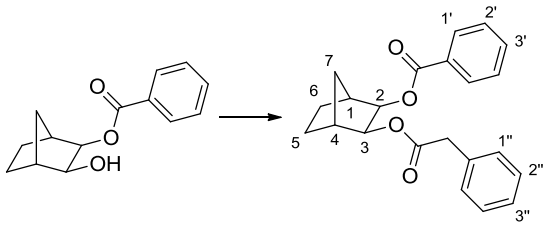
Spectroscopic data for methyl 2-phenylacrylate **307**: **^{1}H NMR** δ_H (400 MHz, $CDCl_3$): 7.79-7.32 (5 H, m, Ar*H*), 6.39 (1 H, s, C*H*$_A$H$_B$), 5.91 (1 H, s, CH$_A$*H*$_B$), 3.84 (3 H, s, CO_2CH_3); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 167.3 (*C*O_2), 141.3 (*C*H=CH$_2$), 136.7 (Ar*C*), 128.3 (quat. Ar*C*), 128.2 (Ar*C*), 128.1(Ar*C*), 126.9 (CH=*C*H$_2$), 52.2 (*C*H$_3$).

The spectral data were consistent with those in the literature.[135]

Spectroscopic data for 2-phenylacrylic acid **308**: **^{1}H NMR** δ_H (400 MHz, $CDCl_3$): 10.05 (1 H, br s, CO_2*H*), 7.45-7.37 (5 H, m, Ar*H*), 6.54 (1 H, s, C*H*$_A$H$_B$), 6.02 (1 H, s, CH$_A$*H*$_B$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 172.0 (*C*O_2), 140.6 (*C*=CH$_2$), 136.1 (quat. Ar*C*), 129.4 (Ar*C*), 128.4 (Ar*C*), 128.3 (Ar*C*), 128.2 (C=*C*H$_2$).

The spectral data were consistent with those in the literature.[136]

((±)-(1*S*,2*R*,3*S*,4*R*))-3-(2-Phenylacetoxy)bicyclo[2.2.1]heptan-2-yl benzoate, (±)-309

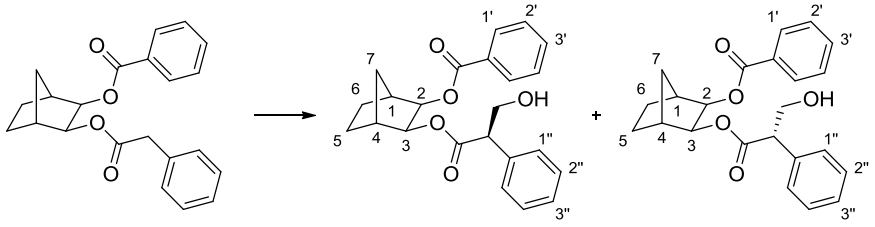


(±)-**295** (±)-**309**

((±)--(1*S*,2*R*,3*S*,4*R*))-3-Hydroxybicyclo[2.2.1]heptan-2-yl benzoate (±)-**295** (1.00 g. 4.31 mmol) and 2-phenylacetyl chloride were subjected to general procedure B. Flash column chromatography (9:1 petrol:diethyl ether) yielded the title diester (±)-**309** as a white solid (1.51 g, 91%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 8.00 (2 H, d, *J* = 7.6 Hz, C(1')*H*), 7.68-7.52 (1 H, m, C(3')*H*), 7.50-7.36 (2 H, m, C(2')*H*), 7.23-7.14 (3 H, m, C(1'')*H* and C(3'')*H*), 7.12-7.01 (2 H, m, C(2'')*H*), 5.01 (1 H, d, *J* = 5.8 Hz, C(3)*H*), 4.89 (1 H, d, *J* = 5.8 Hz, C(2)*H*), 3.51-3.39 (2 H, m, ArCH_2), 2.43 (1 H, s, C(4)*H*), 2.32 (1 H, s, C(1)*H*), 1.97 (1 H, d, *J* = 10.1 Hz, C(7)H_AH_B), 1.69-1.50 (2 H, m, C(5)H_AH_B and C(6)H_AH_B), 1.35-1.20 (3 H, m, C(5)H_AH_B, C(6)H_AH_B and C(7)H_AH_B); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 170.6 (PhCO_2), 165.6 (CO_2), 133.7 (quat. Ar*C*), 132.9 (Ar*C*), 130.2 (quat. Ar*C* and Ar*C*), 129.6 (Ar*C*), 129.2 (Ar*C*), 128.4 (Ar*C*), 126.9 (Ar*C*), 77.0 (*C*(2) and C(3)), 41.2 (*C*(1) and *C*(4)), 41.0 (PhCH_2), 33.7 (*C*(7)), 24.4 (*C*(6)), 24.2 (*C*(5)); **IR** (ν_{max}/cm^{-1}): 3064, 2969, 2877, 1721, 1715; **LRMS** (ESI$^+$, *m/z*): 373 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$, *m/z*): Calculated 373.1410 ($C_{22}H_{22}NaO_4$), Found 373.1415 (Δ−0.2 ppm); **m.p.** 43-47 ^{o}C.

((±)-(1*S*,2*R*,3*S*,4*R*))-3-(((*S*)-3-Hydroxy-2-phenylpropanoyl)oxy)bicyclo[2.2.1]heptan-2-yl benzoate, (±)-312 and ((±)-(1*S*,2*R*,3*S*,4*R*))-3-(((*R*)-3-Hydroxy-2-phenylpropanoyl)oxy)bicyclo[2.2.1]heptan-2-yl benzoate, (±)-314



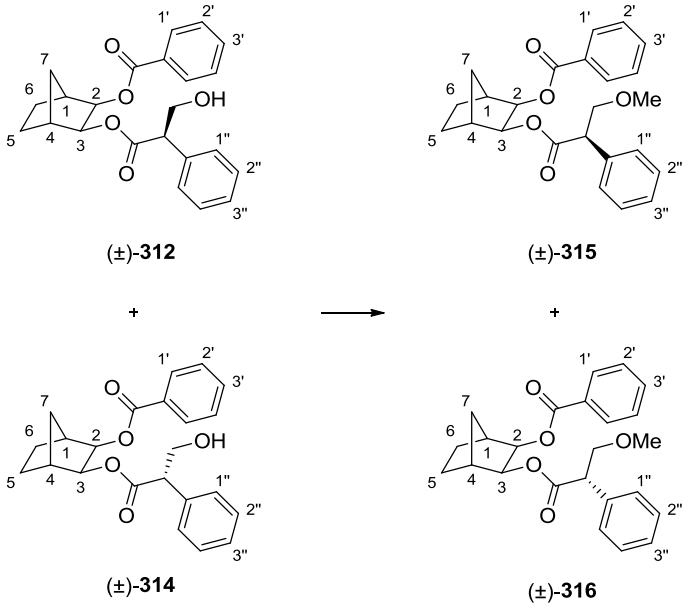
((±)-(1*S*,2*R*,3*S*,4*R*))-3-(2-phenylacetoxy)bicyclo[2.2.1]heptan-2-yl benzoate (±)-**309** (110 mg, 0.31 mmol) was subjected to general procedure C. Purification by flash column chromatography (9:1 petrol:ethyl acetate) gave the title compounds (±)-**312** and (±)-**314** as a white solid (79 mg, 67%) and as a 3.3:1 mixture of diastereomers.

Spectroscopic data for 3.3:1 mixture of diastereomers:

^{1}H NMR δ_H (400 MHz, $CDCl_3$): Major diastereomer: 7.82 (2 H, d, *J* = 7.4 Hz, C(1')*H*), 7.55-7.50 (1 H, m, C(3')*H*), 7.41-7.31 (2 H, m, C(2')*H*), 7.13-6.96 (5 H, m, Ar''*H*), 4.96-4.86 (2 H, m, C(2)*H* and C(3)*H*), 3.89 (1 H, dd, *J* = 10.9, 9.1 Hz, C*H*CH_2O), 3.72 (1 H, dd, *J* = 8.9, 5.4 Hz, CH_AH_BOH), 3.66-3.51 (1 H, dd, *J* = 8.9, 5.3 Hz, CH_AH_BOH), 2.49-2.32 (2 H, m, C(1)*H* and C(4)*H*), 2.17 (1 H, br s, CH_2OH), 1.98 (1 H, d, *J* = 10.4 Hz, C(7)H_AH_B), 1.67-1.48 (2 H, m, C(5)H_AH_B and C(6)H_AH_B), 1.36-1.15 (3H, m, C(5)H_AH_B and C(6)H_AH_B and C(7)H_AH_B); Minor diastereomer: 7.99 (2 H, d, *J* = 7.3 Hz, C(1')*H*), 7.64-7.56 (1 H, m, C(3')*H*), 7.49-7.42 (2 H, m, C(2')*H*), 7.25-7.19 (3 H, m, C(1'')*H* and C(3'')*H*), 7.13-6.96 (2 H, m, C(2'')*H*), 4.98 (1 H, d, *J* = 5.8 Hz, C(2)*H*), 4.96-4.86 (1H, m, C(3)*H*), 3.94 (1H, dd, *J* = 8.3, 4.4 Hz, C*H*CH_2OH), 3.66-3.51 (2 H, m, CH_2OH), 2.49-2.32 (2 H, m, C(1)*H* and C(4)*H*), 2.23 (1 H, br s, CH_2OH), 1.79 (1 H, d, *J* = 10.4 Hz, C(7)H_AH_B), 1.67-1.48 (2 H, m, C(5)H_AH_B and C(6)H_AH_B), 1.36-1.15 (3 H, m, C(5)H_AH_B and C(6)H_AH_B and C(7)H_AH_B); **^{13}C**

NMR δ_C (100 MHz, $CDCl_3$): 172.3 (Ph*C*O_2), 171.8(Ph*C*O_2), 166.0 (2 × *C*O_2), 135.8 (2 × quaternary Ar*C*), 134.8 (2 × quaternary Ar*C*), 133.1 (Ar*C*), 132.8 (Ar*C*), 129.8 (Ar*C*), 129.6 (Ar*C*), 129.5 (Ar*C*), 128.6 (Ar*C*), 128.5 (Ar*C*), 128.4 (Ar*C*), 128.2 (Ar*C*), 128.1 (Ar*C*), 127.9 (Ar*C*), 127.5 (Ar*C*), 77.3 (2 × *C*(2)), 77.2 (C(3), 77.1 (C(3)), 64.7 (*C*H_2OH), 64.3 (*C*H_2OH), 54.6 (*C*HCH$_2$OH), 53.8 (*C*HCH$_2$OH), 41.5 (*C*(1)), 41.1 (*C*(1) and *C*(4)), 41.0 (*C*(4)), 33.7 (C(7)), 33.6 (C(7)), 24.4 (*C*(6)), 24.3 (*C*(6)), 24.2 (2 × *C*(5)); **IR** (ν_{max}/cm^{-1}): 3507, 2968, 1722, 1452; **LRMS** (ESI$^+$, *m/z*): 403 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$, *m/z*): Calculated 403.1516 ($C_{23}H_{24}NaO_5$), Found 403.1510 (Δ -0.7ppm); **m.p.** 36-40 ^oC

((±)-(1*S*,2*R*,3*S*,4*4*))-3-(((*R*)-3-methoxy-2-phenylpropanoyl)oxy)bicyclo[2.2.1]heptan-2-yl benzoate, (±)-315 and ((±)-(1*S*,2*R*,3*S*,4*R*))-3-(((*S*)-3-methoxy-2-phenylpropanoyl)oxy)bicyclo[2.2.1]heptan-2-yl benzoate, (±)-316



Silver(I) oxide (1.693 g, 7.36 mmol) was added to a stirred solution of a 3.3:1 diastereomeric mixture of ((±)-(1*S*,2*R*,3*S*,4*R*))-3-(((*S*)-3-hydroxy-2-phenylpropanoyl)oxy)bicyclo[2.2.1]heptan-2-yl benzoate (±)-**312** and ((±)-(1*S*,2*R*,3*S*,4*R*))-3-(((*R*)-3-Hydroxy-2-

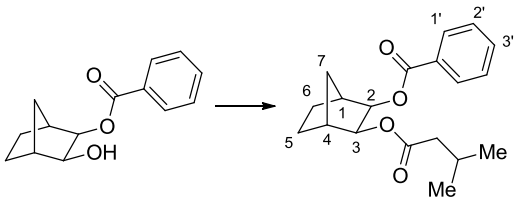
phenylpropanoyl)oxy)bicyclo[2.2.1]heptan-2-yl benzoate (±)-**314** (700 mg, 1.84 mmol) and iodomethane (3.14 g, 22.1 mmol) in diethyl ether (13.0 mL) at room temperature. After 3 days the reaction mixture was filtered and concentrated *in vacuo*. Flash column chromatography (4:1 petrol-diethyl ether) yielded the title esters (±)-**315** and (±)-**316** as a colourless oil (616 mg, 85%) and as a 3.3:1 mixture of diastereomers.

Spectroscopic data for 3.3:1 mixture of diastereomers

^{1}H NMR δ_H (400 MHz, $CDCl_3$): Major diastereomer: 7.83 (2 H, d, *J* = 7.4 Hz, C(1')*H*), 7.54-7.49 (1 H, m, C(3')*H*), 7.40-7.31 (2 H, m, C(2')*H*), 7.12-7.02 (5 H, m, Ar''*H*), 4.96 (1H, d, *J* = 5.8 Hz, C(2)*H*), 4.91 (1 H, d, *J* = 5.8 Hz, C(3)*H*), 3.81-3.68 (2 H, m, CH_2OCH_3), 3.43 (1 H, dd, *J* = 8.6 Hz and 5.3 Hz, C*H*CH_2OH), 3.22 (3 H, s, OCH_3), 2.40 (1 H, br s, C(1)*H*), 2.36 (1 H, br s, C(4)*H*), 1.99 (1 H, d, *J* = 10.4 Hz, C(7)H_AH$_B$), 1.66-1.47 (2 H, m, C(5)H_AH$_B$ and C(6)H_AH$_B$), 1.36-1.18 (3 H, m, C(5)H$_A$$H_B$ and C(6)H$_A$$H_B$ and C(7)H$_A$$H_B$); Minor diastereomer: 8.02 (2 H, d, *J* = 7.3 Hz, C(1')*H*), 7.62-7.55 (1 H, m, C(3')*H*), 7.48-7.42 (2 H, m, C(2')*H*), 7.25-7.21 (3 H, m, C(1'')*H* and C(3'')*H*), 7.12-7.02 (2 H, m, C(2'')*H*), 5.02 (1 H, d, *J* = 5.8 Hz, C(2)*H*), 4.83 (1 H, d, *J* = 5.8 Hz, C(3)*H*), 3.81-3.68 (2 H, m, CH_2OCH_3), 3.48 (1 H, dd, *J* = 6.8 Hz and *J* = 4.2 Hz, C*H*CH_2OCH_3), 3.09 (3 H, s, OCH_3), 2.40 (1 H, br s, C(1)*H*), 2.36 (1 H, br s, C(4)*H*), 1.87 (1 H, d, *J* = 10.1 Hz, C(7)H_AH$_B$), 1.66-1.47 (2 H, m, C(5)H_AH$_B$ and C(6)H_AH$_B$), 1.36-1.18 (3 H, m, C(5)H$_A$$H_B$ and C(6)H$_A$$H_B$ and C(7)H$_A$$H_B$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 171.3 (Ph*C*O$_2$), 171.2 (Ph*C*O$_2$), 165.6 (2 × *C*O$_2$), 135.3 (2 × quat. Ar*C*), 132.9 (Ar*C*), 132.6 (Ar*C*), 130.1 (2 × quat. Ar*C*), 129.7 (Ar*C*), 129.6 (Ar*C*), 128.6 (Ar*C*), 128.5 (Ar*C*), 128.4 (Ar*C*), 128.3 (Ar*C*), 128.2 (Ar*C*), 128.0 (Ar*C*), 127.8 (Ar*C*), 127.4 (Ar*C*), 77.2 (*C*(2)), 77.1 (*C*(2), 77.0 (*C*(3)), 76.9 (*C*(3)), 74.3 (*C*H$_3$), 73.6 (*C*H$_3$), 58.8 (*C*H$_2$OCH$_3$), 58.7 (*C*H$_2$OCH$_3$), 52.2 (*C*HCH$_2$OH), 51.9 (*C*HCH$_2$OH), 41.5 (*C*(1)), 41.2 (*C*(1) and *C*(4)), 41.1 (*C*(4)), 33.7 (*C*(7)), 33.6 (*C*(7)), 24.3 (*C*(5) and *C*(6)); **IR** (ν_{max}/cm^{-1}): 2968,

2878, 1722, 1602; **LRMS** (ESI^+, *m/z*): 417 ($[M+Na]^+$, 100%); **HRMS** (ESI^+, *m/z*): Calculated 417.1672 ($C_{23}H_{24}NaO_5$), Found 417.1671 (Δ−0.2ppm);

((±)-(1*S*,2*R*,3*S*,4*R*))-3-((3-Methylbutanoyl)oxy)bicyclo[2.2.1]heptan-2-yl benzoate, (±)-318

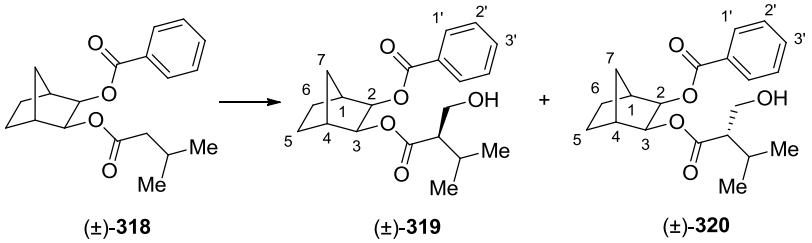


(±)-**295** (±)-**318**

((±)-(1*S*,2*R*,3*S*,4*R*))-3-Hydroxybicyclo[2.2.1]heptan-2-yl benzoate (±)-**295** (600 mg. 3.66 mmol) and 3-methylbutanoyl chloride were subjected to general procedure B. Flash column chromatography (19:1 petrol:ethyl acetate) yielded the title diester (±)-**318** as a white solid (1.20 g, 94%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 8.02 (2 H, d, *J* = 7.3 Hz, C(1')*H*), 7.60-7.51 (1 H, m, C(3')*H*), 7.48-7.38 (2 H, m, C(2')*H*), 5.00 (1 H, d, *J* = 5.6 Hz, C(2)*H*), 4.86 (1 H, d, *J* = 5.6 Hz, C(3)*H*), 2.43 (1 H, s, C(1)*H*), 2.32 (1 H, s, C(4)*H*), 1.99-1.93 (3 H, m, CH_2CH and C*H*(CH_3)$_2$), 1.92-1.82 (1 H, m, C(7)H_AH_B), 1.62-1.56 (2 H, m, C(5)H_AH_B and C(6)H_AH_B), 1.31-1.27 (3 H, m, *C*(5)H_AH_B and *C*(6)H_AH_B and *C*(7)H_AH_B), 0.86 (3 H, d, *J* = 6.6 Hz, CH(CH_3)$_A$(CH_3)), 0.75 (3 H, d, *J* = 6.6 Hz, CH(CH_3)$_A$(CH_3)$_B$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 172.1 (Ph*C*O_2), 165.7 (*C*O_2), 132.9 (quat. Ar*C*), 130.3 (Ar*C*), 129.5 (Ar*C*), 128.2 (Ar*C*), 77.0 (*C*(2)), 76.3 (*C*(3)), 43.2 (*C*H_2CO_2), 41.3 (*C*(1)), 41.1 (*C*(4)), 33.7 (*C*(7)), 25.4 (*C*H(CH_3)$_2$), 24.4 (*C*(5)), 24.3 (*C*(6)), 22.3 (2 ×*C*H_3); **IR** (ν_{max}/cm^{-1}): 2955, 1720, 1715; **LRMS** (ESI^+, *m/z*): 339 ($[M+Na]^+$, 100%); **HRMS** (ESI^+, *m/z*): Calculated 339.1567 ($C_{17}H_{20}NaO_5$), Found 339.1573 (Δ −1.8 ppm); **m.p.** 40-44 °C.

((±)-(1*S*,2*R*,3*S*,4*R*))-3-(((*R*)-2-(hydroxymethyl)-3-methylbutanoyl)oxy)bicyclo[2.2.1]heptan-2-yl benzoate, (±)-319 and ((±)-(1*S*,2*R*,3*S*,4*R*))-3-(((*S*)-2-(hydroxymethyl)-3-methylbutanoyl)oxy)bicyclo[2.2.1]heptan-2-yl benzoate, (±)-320



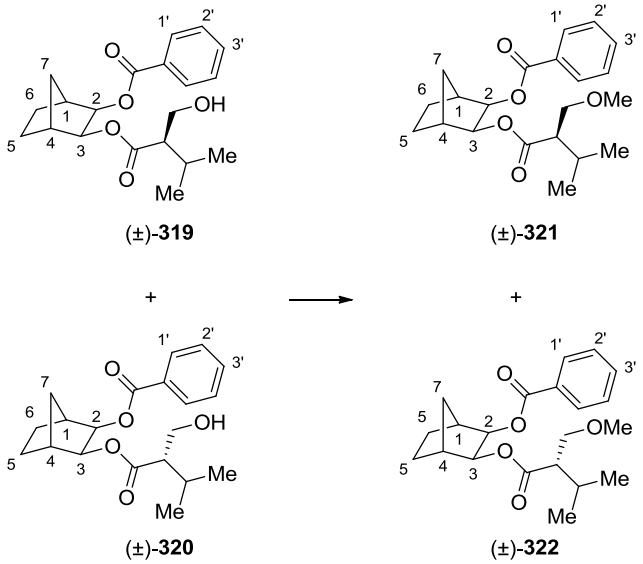
n-Butyl lithium in hexanes (1.6 M, 0.38 mL, 0.61 mmol) was added dropwise to a solution of diisopropylamine (0.09 mL, 0.61 mmol) in tetrahydrofuran (2.60 mL) at −78 °C. After 30 minutes, a solution of ((±)-(1*S*,2*R*,3*S*,4*R*))-3-((3-methylbutanoyl)oxy)bicyclo[2.2.1]heptan-2-yl benzoate, (±)-**318** (160 mg, 0.51 mmol) in tetrahydrofuran (2.60 mL) was added dropwise to the reaction mixture at −78 °C. After an additional 30 minutes, *para*-formaldehyde (18.2 mg, 0.61 mmol) was added to the reaction mixture at −78 °C. The resulting solution was stirred at room temperature for 16 h, then quenched with water (3.00 mL) and the phases were separated. The aqueous layer was extracted with diethyl ether (3 × 3.00 mL) and the combined organic layers washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by flash column chromatography (4:1 petrol:ethyl acetate) yielding the title diesters (±)-**319** and (±)-**320** as a colourless oil (116 mg, 66%) and as a >25:1 mixture of diastereoisomers.

Spectroscopic data for major diastereomer:

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.96 (2 H, d, *J* = 7.6 Hz, C(1')*H*), 7.62-7.53 (1 H, m, C(3')*H*), 7.52-7.43 (2 H, m, C(2')*H*), 4.52 (2 H, br s, C(2)*H* and C(3)*H*), 4.06 (1 H, dd, *J* = 10.9, 3.6 Hz, CH_AH$_B$OH), 3.83 (1 H, dd, *J* = 11.0, 3.4 Hz, CH$_A$$H_B$OH), 3.47 (1 H, d, *J* = 13.3

Hz, CH_2CO_2), 2.52 (2 H, br s, C(1)*H* and C(4)*H*), 2.19 (1 H, dq, *J* = 13.8, 6.9 Hz, C*H*$(CH_3)_2$), 1.74 (1 H, d, *J* = 11.6 Hz, C(7)H_AH_B), 1.60 (2 H, d, *J* = 8.3 Hz, C(5)H_AH_B and C(6)H_AH_B), 1.39 (1 H, d, *J* = 11.6 Hz, C(7)H_AH_B), 1.11 (2 H, d, *J* = 8.1 Hz, C(5)H_AH_B and C(6)H_AH_B), 0.95 (6 H, 2 × d, *J* = 6.8 Hz, CH(C$H_3)_2$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 205.2 (Ph*C*O_2), 155.7 (*C*O_2), 137.8 (quat. Ar*C*), 133.2 (Ar*C*), 128.7 (Ar*C*), 128.3 (Ar*C*), 82.2 (*C*(2) and *C*(3)), 61.3 (*C*H_2OH), 54.1, 40.2 (*C*(1) and *C*(4)), 30.8 (*C*(7)), 28.6 (*C*H$(CH_3)_2$) , 22.7 (*C*(5) and *C*(6)), 21.4 (2 × *C*H_3); **IR** (ν_{max}/cm^{-1}): 3504, 2964, 1722, 1677; **LRMS** (ESI$^+$, *m/z*): 369 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$, *m/z*): Calculated 369.1672 ($C_{20}H_{26}NaO_5$), Found 369.1672 (Δ+0.6 ppm).

((±)-(1*S*,2*R*,3*S*,4*R*))-3-(((*R*)-2-(Methoxymethyl)-3-methylbutanoyl)oxy)bicyclo[2.2.1]heptan-2-yl benzoate, (±)-321 and ((±)-(1*S*,2*R*,3*S*,4*R*))-3-(((*S*)-2-(Methoxymethyl)-3-methylbutanoyl)oxy)bicyclo[2.2.1]heptan-2-yl benzoate, (±)-322



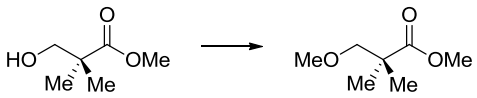
A solution of (±)-(1*S*,2*R*,3*S*,4*R*)-3-(((*R*)-2-(hydroxymethyl)-3-methylbutanoyl)oxy)bicyclo[2.2.1]heptan-2-yl benzoate (±)-**319** and (±)-(1*S*,2*R*,3*S*,4*R*)-3-

(((*S*)-2-(hydroxymethyl)-3-methylbutanoyl)oxy)bicyclo[2.2.1]heptan-2-yl benzoate (±)-**320** (100 mg, 2.88 mmol) was subjected to general procedure D. Flash column chromatography (9:1 petrol:diethyl ether) yielded the title esters (±)-**321** and (±)-**322** as a colourless oil (85.0 mg, 82%) and as a >25:1 mixture of diastereoisomers.

Spectroscopic data for major diastereomer:

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 8.05 (2 H, d, *J* = 7.3 Hz, C(1')*H*), 7.61-7.51 (1 H, m, C(3')*H*), 7.50-7.38 (2 H, m, C(2')*H*), 5.00 (1 H, d, *J* = 5.8 Hz, C(2)*H*), 4.89 (1 H, d, *J* = 6.1 Hz, C(3)*H*), 3.42-3.34 (2 H, m, CH_2OCH_3), 3.17 (3 H, s, OCH_3), 2.44 (1 H, s, C(1)*H*), 2.36 (1 H, s, C(4)*H*), 2.33-2.22 (1 H, m, C*H*CO_2), 2.08-1.93 (1 H, m, C*H*$(CH_3)_2$), 1.84-1.64 (1 H, m, C(7)H_AH_B), 1.63-1.50 (2 H, m, C(5)H_AH_B and C(6)H_AH_B), 1.41-1.20 (3 H, m, C(5)H_AH_B, C(6)H_AH_B and C(7)H_AH_B), 0.85-0.68 (6 H, m, CH(CH_3)$_2$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 173.0 (2 × Ph*C*O_2), 165.8 (2 × *C*O_2), 132.9 (Ar*C*), 130.4 (quat. Ar*C*), 129.6 (Ar*C*), 128.2 (Ar*C*), 77.1 (*C*(2)), 76.4 (*C*(3)), 71.6 (*C*H_2OH), 58.7 (*C*H_3), 52.5 (*C*HCO_2), 41.5 (*C*(1)), 41.4 (*C*(4)), 33.6 (*C*(7)), 24.4 (*CH*$(CH_3)_2$), 20.3 (*C*(5) and *C*(6)), 20.0 (*C*H_3); **IR** (ν_{max}/cm^{-1}): 2968, 1722, 1316; **LRMS** (ESI$^+$, *m/z*): 383 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$, *m/z*): Calculated 383.1829 ($C_{21}H_{28}NaO_5$), Found 383.1829 (Δ −0.9 ppm);

Methyl 3-methoxy-2,2-dimethylpropanoate, 326



325 **326**

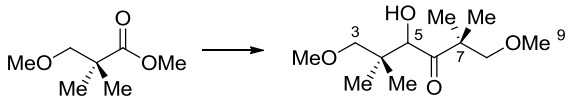
Sodium hydride (303 mg, 7.58 mmol, 60% dispersion in mineral oil) was added to a stirred solution of methyl 3-hydroxy-2,2-dimethylpropanoate **325** (500 mg, 3.79 mmol) and iodomethane (2.78 g, 19.0 mmol) in tetrahydrofuran (40 mL) at 0 ^{o}C. The resulting solution was stirred at room temperature for 16 hours then quenched with water (40 mL) and the

phases were separated. The aqueous layer was extracted with diethyl ether (3 × 40 mL) and the combined organic layers washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by flash column chromatography (19:1 petrol:ethyl acetate) yielding the title ester **326** as a colourless oil (553 mg, 100%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 3.69 (3 H, s, OC*H*$_3$), 3.38 (2 H, s, C*H*$_2$), 3.34 (3 H, s, CO_2CH_3), 1.19 (6 H, s, C(C*H*$_3$)$_2$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 177.0 (*C*O$_2$), 79.7 (*C*H$_2$), 59.3 (CO_2CH_3), 51.9 (CH_2OCH_3), 43.6 (*C*(CH$_3$), 22.4 (*C*H$_3$).

The spectral data were consistent with those in the literature.[137]

3-Hydroxy-1,6-dimethoxy-2,2,6-trimethylheptan-4-one, 327

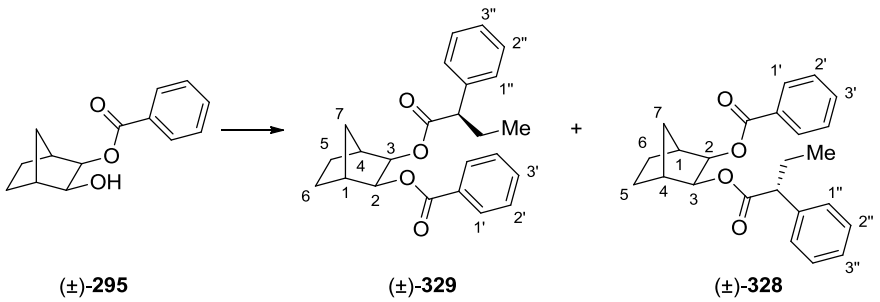


326 **327**

The LiDBB solution was prepared by general procedure F. A solution of methyl 3-methoxy-2,2-dimethylpropanoate **326** (50.0 mg, 0.34 mmol) in tetrahydrofuran (1.71 mL) was added to the LiDBB solution at −78 ^{o}C *via* syringe pump over 2 hours. After leaving the reaction to stir for an additional 2 hours, the solution was transferred, *via* cannular, to a saturated solution of aqueous ammonium chloride, (5.00 mL) washing the Schlenk tube with tetrahydrofuran (5 mL), and the phases were separated. The aqueous layer was extracted with diethyl ether (3 × 5.00 mL) and the combined organic layers washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by flash column chromatography (9:1 petrol:ethyl acetate) yielding the title hydroxy ketone **327** as a colourless oil (30 mg, 75%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 4.28 (1 H, d, *J* = 7.8 Hz, C*H*OH), 4.03 (1 H, d, *J* = 7.8 Hz, CHO*H*), 3.74 (1 H, d, *J* = 8.8 Hz, C(8)H_AH_B), 3.45 (1 H, d, *J* = 8.8 Hz, C(3)H_AH_B), 3.39 (1 H, d, *J* = 8.8 Hz, C(3)H_AH_B), 3.34 (3 H, s, OCH_3), 3.33 (3 H, s, OCH_3), 3.11 (1 H, d, *J* = 8.6 Hz, C(8)H_AH_B), 1.21 (3 H, s, C(CH_3)$_A$(CH$_3$)$_B$), 1.19 (3 H, s, C(CH$_3$)$_A$(CH_3)$_B$), 1.10 (3 H, s, C(CH_3)$_A$(CH$_3$)$_B$), 0.89 (3 H, s, C(CH$_3$)$_A$(CH_3)$_B$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 214.9 (*C*=O), 80.7 (*C*HOH), 79.6 (*C*H$_2$OCH$_3$), 75.6 (*C*H$_2$OCH$_3$), 59.2 (*C*(10)), 59.1 (*C*(1)), 37.9 (2 × *C*(CH$_3$)$_2$), 23.2 (*C*H$_3$), 22.1 (*C*H$_3$), 21.7 (*C*H$_3$), 21.2 (*C*H$_3$); **IR** (ν_{max}/cm^{-1}): 3455, 2964, 1712, 1478; **LRMS** (ESI$^+$, *m/z*): 255 ([M + Na]$^+$, 100%), **HRMS** (ESI$^+$, *m/z*): Calculated 255.1567 ($C_{12}H_{24}NaO_4$), Found 255.1567 (Δ −0.1 ppm).

(1*R*,2*S*,3*R*,4*S*)-3-((2-Phenylbutanoyl)oxy)bicyclo[2.2.1]heptan-2-yl benzoate, (±)-329 and (1*S*,2*R*,3*S*,4*R*)-3-((2-Phenylbutanoyl)oxy)bicyclo[2.2.1]heptan-2-yl benzoate, (±)-328



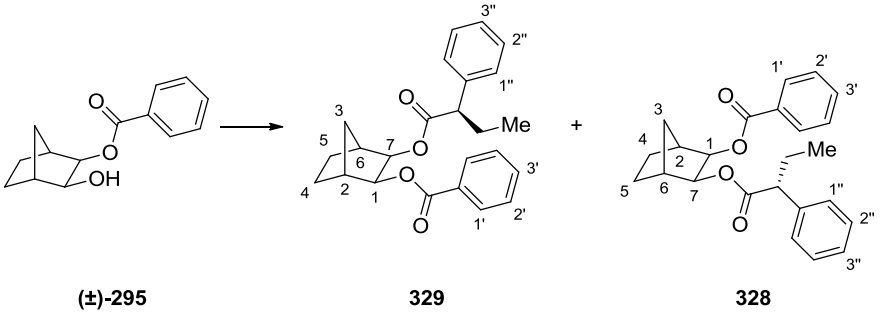
(±)-**295** (±)-**329** (±)-**328**

((±)-(1*R*,2*S*,6*R*,7*S*))-7-Hydroxybicyclo[2.2.1]heptan-1-yl benzoate (±)-**295** (2.00 g. 12.2 mmol) and 2-phenylbutanoyl chloride were subjected to general procedure B. Flash column chromatography (19:1 petrol:diethyl ether) yielded the title diesters (±)-**329** and(±)-**328** as a white solid (1.51 g, 91%) and as a 1:1 mixture of diastereoisomers.

Spectroscopic data for 1:1 mixture of diastereomers:

^{1}H NMR δ_H (400 MHz, $CDCl_3$): Diastereomer A: 8.02 (2 H, d, *J* = 7.6 Hz, C(1')*H*), 7.64-7.51 (1 H, m, C(3')*H*), 7.50-7.44 (2 H, m, C(2')*H*), 7.25-7.17 (3 H, m, C(1'')*H* and C(3'')*H*), 7.16-7.09 (2 H, m, C(2'')*H*), 5.00 (1 H, d, *J* = 5.8 Hz, C(2)*H*), 4.91-4.81 (1 H, m, C(3)*H*), 3.28 (1 H, t, *J* = 7.7 Hz, C*H*CO_2), 2.41 (1 H, m, C(1)*H*), 2.28 (1 H, s, C(4)*H*), 2.01-1.81 (3 H, m, C*H*$_2$$CH_3$ and C(7)H_AH_B), 1.67-1.47 (2 H, m, C(5)H_AH_B and C(6)H_AH_B), 1.33-1.16 (3 H, m, C(5)H_AH_B, C(6)H_AH_B and C(7)H_AH_B), 0.75 (3 H, t, *J* = 7.3 Hz, CH_2C*H*$_3$); Diastereomer B: 7.91 (2 H, d, *J* = 7.6 Hz, C(1')*H*), 7.64-7.51 (1 H, m, C(3')*H*), 7.43-7.36 (2 H, m, C(2')*H*), 7.16-7.09 (3 H, m, C(1'')*H* and C(3'')*H*), 7.08-7.02 (2 H, m, C(2'')*H*), 4.95 (1 H, d, *J* = 5.8 Hz, C(2)*H*), 4.91-4.81 (1 H, m, C(3)*H*), 3.17 (1 H, t, *J* = 7.7 Hz, C*H*CO_2), 2.41 (1 H, m, C(1)*H*), 2.18 (1 H, s, C(4)*H*), 2.01-1.81 (1 H, m, C(7)H_AH_B), 1.67-1.47 (4 H, m, C*H*$_2$$CH_3$ and C(5)H_AH_B and C(6)H_AH_B), 1.33-1.16 (3 H, m, C(5)H_AH_B and C(6)H_AH_B and C(7)H_AH_B), 0.65 (3 H, t, *J* = 7.5 Hz, CH_2C*H*$_3$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 173.0 (Ph*C*O_2), 165.7 (*C*O_2), 165.6 (*C*O_2), 139.0 (quat. Ar*C*), 138.5 (quat. Ar*C*), 132.9 (Ar*C*), 132.7 (Ar*C*), 130.3 (quat. Ar*C*), 130.1 (quat. Ar*C*), 129.7 (Ar*C*), 129.6 (Ar*C*), 128.4 (Ar*C*), 128.3 (Ar*C*), 128.2 (Ar*C*), 127.9 (Ar*C*), 127.8 (Ar*C*), 126.9 (2 × Ar*C*), 77.1 (2 × *C*(2)), 76.7 (2 × *C*(3)), 53.8 (*C*HCO_2), 53.3 (*C*HCO_2), 41.5 (2 × *C*(1)), 41.1 (2 × *C*(4)), 33.7 (*C*(7)), 33.6 (*C*(7)), 26.9 (*C*$H_2$$CH_3$), 26.3 (*C*$H_2$$CH_3$), 24.4 (2 × *C*(5)), 24.3 (2 × *C*(6)), 12.0 (*C*H_3), 11.9 (*C*H_3); **IR** (ν_{max}/cm^{-1}): 1715, 1452; **LRMS** (ESI^+, *m/z*): 401 (M+Na^+, 100%); **HRMS** (ESI^+, *m/z*): Calculated 401.1723 ($C_{24}H_{26}NaO_4$), Found 401.1721 (Δ+0.3 ppm); **m.p.** 58-60 ^{o}C.

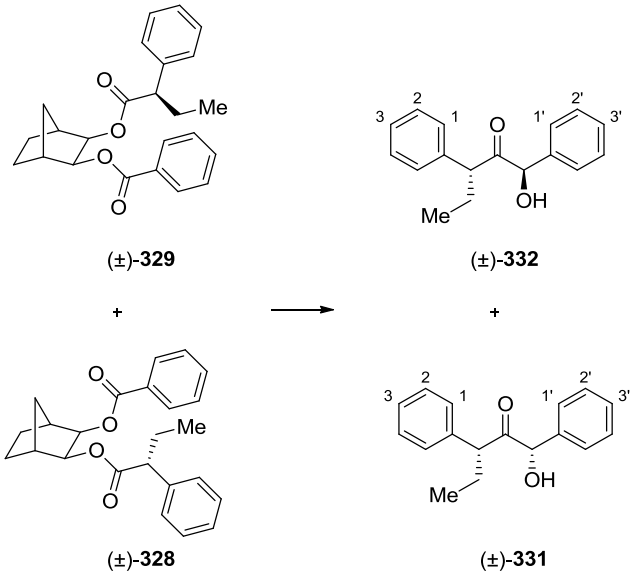
(1*R*,2*S*,6*R*,7*S*))-7-(((*R*)-2-phenylbutanoyl)oxy)bicyclo[2.2.1]heptan-2-yl benzoate, 329 and (1*S*,2*R*,6*S*,7*R*))-7-(((*R*)-2-phenylbutanoyl)oxy)bicyclo[2.2.1]heptan-2-yl benzoate, 328



((±)-1*R*,2*S*,6*R*,7*S*)-7-Hydroxybicyclo[2.2.1]heptan-1-yl benzoate (±)-**295** (700 mg, 3.02 mmol) and (*R*)-2-phenylbutanoic acid were subjected to general procedure E. Flash column chromatography (19:1 petrol:diethyl ether) yielded the title diester **329** and **328** as a white solid (1.14 g, 82%) as a 1:1 mixture of diastereoisomers.

The spectroscopic data is identical to the 1:1 diastereomeric mixture of (±)-**329** and (±)-**328**. $[\alpha]_D^{25}$ +3.3 (c = 1.0, CH_2Cl_2).

((±)-(1*S*,3*R*))-1-hydroxy-1,3-diphenylpentan-2-one, (±)-331 and ((±)-1*R*,3*R*)-1-hydroxy-1,3-diphenylpentan-2-one, (±)-332

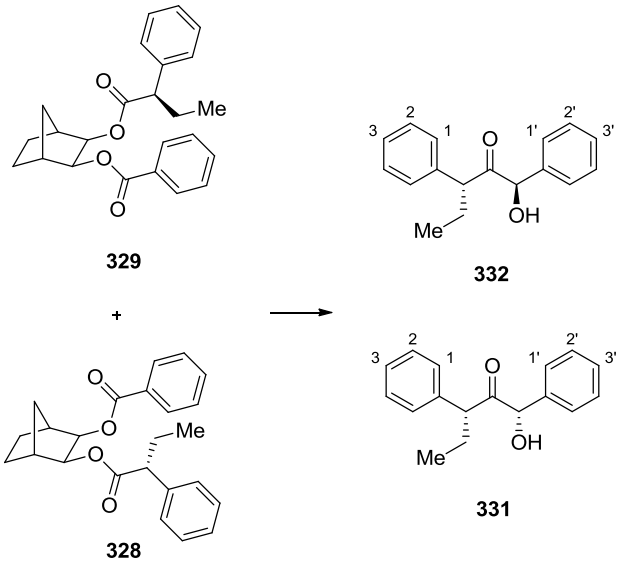


The LiDBB solution was prepared using general procedure F. A 1:1 mixture of (1*R*,2*S*,6*R*,7*S*))-7-(((±)-2-phenylbutanoyl)oxy)bicyclo[2.2.1]heptan-2-yl benzoate (±)-**329** and (1*S*,2*R*,6*S*,7*R*))-7-(((±)-2-phenylbutanoyl)oxy)bicyclo[2.2.1]heptan-2-yl benzoate (±)-**328** (100 mg, 0.26 mmol) in tetrahydrofuran (6.60 mL) was added to the LiDBB solution at −78 ^{o}C *via* syringe pump over 1.5 hours. After leaving the reaction mixture to stir for 2 hours, it was transferred to a solution of 2,6-di-*tert*-butyl-4-methylpyridine hydrogen chloride (295 mg, 1.22 mmol) in THF (10.0 mL) *via* cannular at −78 ^{o}C, washing the Schelnk tube with tetrahydrofuran (5.00 mL). After 15 minutes, the resulting solution was quenched with a saturated aqueous solution of ammonium chloride (10.0 mL) and warmed to room temperature. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 10.0 mL) and the combined organic layers washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by flash column chromatography (19:1 petrol:diethyl ether) yielding diastereomer (±)-**331** as a white solid (38 mg, 58%) and diastereomer (±)-**332** as a white solid (5 mg, 8%).

(1*S*,3*R*))-1-hydroxy-1,3-diphenylpentan-2-one, (±)-**331**: **^{1}H NMR** δ_H (400 MHz, $CDCl_3$): 7.25-7.16 (3 H, m, C(1')*H* and C(3')*H*), 7.15-6.99 (5 H, m, C(2')*H* and C(1)*H* and C(3)*H*), 6.83-6.66 (2 H, m, C(2)*H*), 5.14 (1 H, s, C*H*OH), 4.30 (1 H, br. s, O*H*), 3.65 (1 H, t, *J* = 7.6 Hz, C*H*CH_2CH_3), 2.05 (1 H, ddt, *J* = 13.9, 7.3, 7.2 Hz, CHC$H_AH_BCH_3$), 1.80 (1 H, ddt, *J* = 14.1, 7.2, 7.1 Hz, CHC$H_AH_BCH_3$), 0.84 (3 H, t, *J* = 7.5 Hz, CH_3); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 210.2 (*C*=O), 137.5 (quat. Ar*C*), 136.7 (quat. Ar*C*), 128.6 (2 × Ar*C*), 128.2 (Ar*C*), 128.1 (Ar*C*), 127.8 (Ar*C*), 126.8 (Ar*C*), 80.9 (*C*HOH), 55.6 (*C*HCH_2CH_3), 27.5 (CH*C*H_2CH_3), 12.2 (CHCH_2*C*H_3); **IR** (ν_{max}/cm^{-1}): 3442, 1715, 1452; **LRMS** (ESI^{+}, *m/z*): 277 ([M + Na]$^{+}$, 100%); **HRMS** (ESI^{+}, *m/z*): Calculated 277.1199 ($C_{17}H_{18}NaO_2$), Found 277.1203 (Δ -1.1 ppm); **m.p.** 59-63 ^{o}C.

(1*R*,3*R*)-1-hydroxy-1,3-diphenylpentan-2-one, (±)-**332**: **^{1}H NMR** δ_H (400 MHz, $CDCl_3$): 7.47-7.27 (8 H, m, Ar*H*); 7.18 (2 H, d, *J* = 7.1 Hz, Ar*H*), 5.06 (1 H, d, *J* = 4.6 Hz, C*H*OH), 4.28 (1 H, d, *J* = 4.8 Hz, O*H*), 3.57 (1 H, t, *J* = 7.3 Hz, C*H*CH_2CH_3), 1.95 (1 H, ddt, *J* = 14.1, 7.3, 7.2 Hz, C$H_AH_BCH_3$), 1.65 (1 H, ddt, *J* = 14.3, 7.3, 7.2 Hz, $CH_AH_BCH_3$), 0.55 (3 H, t, *J* = 7.5 Hz, CH_2CH_3); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 209.0 (*C*=O), 138.0 (quat. Ar*C*), 137.8 (quat. Ar*C*), 129.2 (Ar*C*), 129.0 (Ar*C*), 128.9 (Ar*C*), 128.8 (Ar*C*), 127.8 (Ar*C*), 127.7 (Ar*C*), 78.0 (*C*HOH), 55.2 (*C*HCH_2CH_3), 25.4 (CH*C*H_2CH_3), 11.6 ($CHCH_2CH_3$); **IR** (ν_{max}/cm^{-1}): 3442, 1715, 1649; **LRMS** (ESI^+, *m/z*): 277 ($[M + Na]^+$, 100%); **HRMS** (ESI^+, *m/z*): 277.1199 ($C_{17}H_{18}NaO_2$) Calculated, Found 277.1211 (Δ −4.4 ppm); **m.p.** 60-63 °C.

(1*S*,3*R*)-1-Hydroxy-1,3-diphenylpentan-2-one, 331, and (1*R*,3*R*)-1-hydroxy-1,3-diphenylpentan-2-one, 332



The LiDBB solution was prepared using general procedure F. A 1:1 mixture of (1*R*,2*S*,6*R*,7*S*))-7-(((±)-2-phenylbutanoyl)oxy)bicyclo[2.2.1]heptan-2-yl benzoate **329** and (1*S*,2*R*,6*S*,7*R*))-7-(((±)-2-phenylbutanoyl)oxy)bicyclo[2.2.1]heptan-2-yl benzoate **328** (100 mg, 0.26 mmol) in tetrahydrofuran (6.60 mL) was added to the LiDBB solution at −78 °C *via* syringe pump over 1.5 hours. After leaving the reaction mixture to stir for 2 hours it was

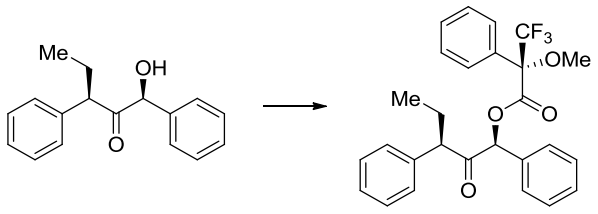
transferred to a solution of 2,6-di-*tert*-butyl-4-methylpyridine hydrogen chloride (295 mg, 1.22 mmol) in THF (10.0 mL) *via* cannula at −78 °C, washing the Schelnk tube with tetrahydrofuran (5.00 mL). After 15 minutes, the resulting solution was quenched with a saturated aqueous solution of ammonium chloride (10.0 mL) and warmed to room temperature. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 10.0 mL) and the combined organic layers washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The crude products were purified by flash column chromatography (19:1 petrol:diethyl ether), yielding diastereomer **331** as a white solid (39 mg, 59%) and diastereomer **332** as a white solid (5 mg, 6%).

The spectroscopic data was identical to (±)-**331** and (±)-**332**.

(1*S*,3*R*))-1-hydroxy-1,3-diphenylpentan-2-one, **331**: $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: −97.8 (c = 1.0, CH_2Cl_2).

(1*R*,3*R*)-1-hydroxy-1,3-diphenylpentan-2-one, **332**: $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: −81.1 (*c* = 0.3, CH_2Cl_2).

(*S*)-(1*S*,3*R*)-2-oxo-1,3-diphenylpentyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate, E1

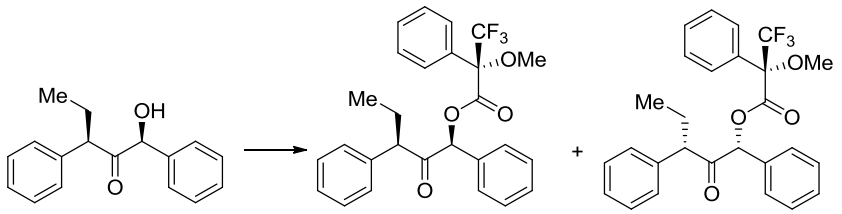


331 **E1**

(1*S*,3*R*)-1-hydroxy-1,3-diphenylpentan-2-one **331** (24.0 mg, 0.09 mmol) was subjected to general procedure G. Purification by flash column chromatography (4:1 petrol-dichloromethane) yielded the title compound **E1** as a colourless oil (41 mg, 96%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.69-7.50 (2 H, m, Ar*H*), 7.46-7.32 (3 H, m, Ar*H*), 7.31-7.22 (2 H, m, Ar*H*), 7.21-6.99 (6 H, m, Ar*H*), 6.94-6.71 (2 H, m, Ar*H*), 6.16 (1H, s, *H*CO), 3.75 (1 H, t, *J* = 7.5 Hz, C*H*CH_2CH_3), 3.66 (3 H, s, OCH_3), 2.17 (1 H, dt, *J* = 13.9, 7.0 Hz, C$H_A$$H_B$$CH_3$), 1.77 (1 H, dt, *J* = 14.2, 7.4 Hz, $CH_A$$H_B$$CH_3$), 0.87 (3 H, t, *J* = 7.3 Hz, CH_2CH_3); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 203.3 (*C*=O), 129.6 (Ar*C*), 129.4 (Ar*C*), 128.7, 128.6, 128.3, 127.5, 127.0 (Ar*C*), 82.7 (*C*HOH), 57.4 (*C*HCH_2CH_3), 26.7 (*C*H_2CH_3), 12.0 (CH_2*C*H_3); **^{19}F NMR** δ_F (377 MHz, $CDCl_3$): −71.74; **IR** (ν_{max}/cm^{-1}): 2966, 1753, 1730, 1455; **LRMS** (ESI^+, *m/z*): 493 ($[M + Na]^+$, 100%); **HRMS** (ESI^+, *m/z*): Calculated 493.1597 ($C_{27}H_{25}F_3NaO_4$), Found 493.1597 (Δ -1.1 ppm); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: +10.9 (c = 1.0, CH_2Cl_2).

(*S*)-(1*S*,3*R*)-2-oxo-1,3-diphenylpentyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate, E1 and (*S*)-(1*R*,3*R*)-2-oxo-1,3-diphenylpentyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate, E2

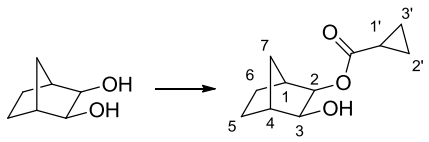


(1*S*,3*R*)-1-hydroxy-1,3-diphenylpentan-2-one (±)-**331** (36 mg, 0.14 mmol) was subjected to general procedure G. Purification by flash column chromatography (4:1 petrol:dichloromethane) yielded the title compounds **E1** and **E2** as a 1:1 inseparable mixture of diastereoisomers colourless oil (66 mg, 92%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): Diastereomer A: 7.71-7.55 (2 H, m, Ar*H*), 7.48-7.35 (3 H, m, Ar*H*), 7.33-7.04 (8 H, m , Ar*H*), 6.87 (2 H, dd, *J* = 4.8, 2.3 Hz, Ar*H*), 6.20 (1 H, s, C*H*CO), 3.76 (1 H, t, *J* = 7.3 Hz, C*H*CH_2CH_3), 3.68 (3 H, s, OCH_3), 2.22-2.13 (1 H, m, C$H_A$$H_B$$CH_3$), 1.77 (1 H, tq, *J* = 14.2, 7.3 Hz, $CH_A$$H_B$$CH_3$), 0.88 (3 H, td, *J* = 7.3, 3.3 Hz,

CH_2CH_3); Diastereomer B: 7.71-7.55 (2 H, m, Ar*H*), 7.48-7.35 (3 H, m, Ar*H*), 7.33-7.04 (8 H, m , Ar*H*), 6.87 (2 H, dd, *J* = 4.8, 2.3 Hz, Ar*H*), 6.17 (1 H, s, C*H*CO), 3.76 (1 H, t, *J* = 7.3 Hz, C*H*CH_2CH_3), 3.52 (3 H, s, OCH_3), 2.22-2.13 (1 H, m, $CH_AH_BCH_3$), 1.77 (1 H, tq, *J* = 14.2, 7.3 Hz, $CH_AH_BCH_3$), 0.88 (3 H, td, *J* = 7.3, 3.3 Hz, CH_2CH_3); **^{13}C NMR** $\delta_{C:}$ 203.3 (*C*=O), 203.0 (*C*=O), 131.7 (2 × quat. Ar*C*), 131.6 (quart Ar*C*), 131.5 (quat. Ar*C*), 129.7 (Ar*C*), 129.6 (Ar*C*), 129.4 (2 × Ar*C*), 128.8 (Ar*C*), 128.7 (2 × Ar*C*), 128.6 (Ar*C*), 128.3 (Ar*C*), 127.8 (Ar*C*), 127.5 (Ar*C*), 127.0 (Ar*C*), 82.7 (*C*HOH), 82.5 (*C*HOH), 57.4 (*C*HCH_2CH_3), 57.3 (*C*HCH_2CH_3), 55.7 (*C*HCH_2CH_3), 55.5 (*C*HCH_2CH_3), 26.7 (2 × *C*H_2CH_3), 12.0 (2 ×*C*H_3; **IR** (ν_{max}/cm^{-1}): 3065, 3032, 2966, 2877, 1752; **^{19}F NMR** δ_F (377 MHz, $CDCl_3$): −71.72, −72.13; **LRMS** (ESI$^+$, *m/z*): 493 ([M + Na]$^+$, 100%); **HRMS** (ESI$^+$, *m/z*): Calculated 493.1597 ($C_{27}H_{25}F_3NaO_4$), Found 493.1586 (Δ+2.2 ppm); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +24.7 (c = 1.0, CH_2Cl_2).

((±)-(1*S*,2*R*,3*S*,4*R*))-3-Hydroxybicyclo[2.2.1]heptan-2-yl cyclopropanecarboxylate, (±)-341



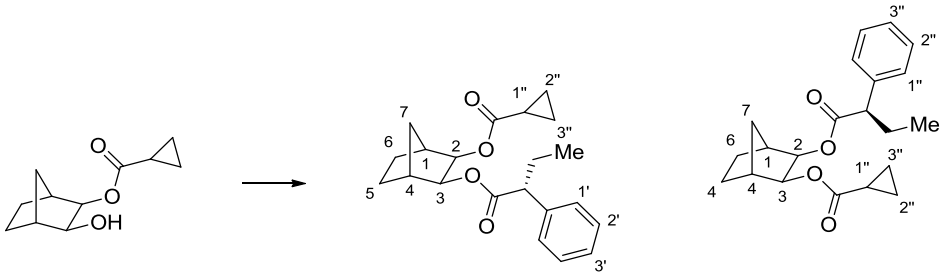
263 **(±)-341**

(1*S*,2*R*,3*S*,4*R*)-bicyclo[2.2.1]heptane-2,3-diol **263** (900 mg, 7.03 mmol) and cyclopropanecarbonyl chloride were subjected to general procedure A. Flash column chromatography (9:1 petrol:ethyl acetate) yielded the title ester (±)-**341** as a colourless oil (1.30 g, 94%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 4.53 (1 H, d, *J* = 5.6 Hz, C(2)*H*), 3.82 (1 H, d, *J* = 5.8 Hz, C(3)*H*), 2.20 (3 H, m, C(1)*H*, C(4)*H* and O*H*), 1.82 (1 H, d, *J* = 10.4 Hz, C(7)H_AH_B), 1.70-

1.58 (1 H, m, C(1')*H*), 1.55-1.33 (2 H, m, C(5)H_AH_B and C(6)H_AH_B), 1.21-1.04 (3 H, m, C(5)H_AH_B, C(6)H_AH_B and C(7)H_AH_B), 1.05-0.93 (2 H, m, C(2')H_AH_B and C(3')H_AH_B), 0.91-0.80 (2 H, m, C(2')H_AH_B and C(3')H_AH_B); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 175.0 (*C*O_2), 78.2 (*C*(2)), 75.7 (*C*(3)), 43.2 (*C*(1)), 40.7 (*C*(4)), 32.7 (*C*(7)), 24.4 (*C*(5) and *C*(6)), 12.8 (*C*(1')), 8.8 (*C*(2')), 8.6 (*C*(3')); **IR** (ν_{max}/cm^{-1}): 3479, 2966, 2876, 1714 **LRMS** (ESI$^+$, *m/z*): 219 (M+Na$^+$, 100%); **HRMS** (ESI$^+$, *m/z*): Calculated 219.0992 ($C_{11}H_{16}NaO_3$), Found 219.0994 (Δ −1.1ppm).

(1*S*,2*R*,3*S*,4*R*))-3-(((±)-2-phenylbutanoyl)oxy)bicyclo[2.2.1]heptan-2-yl cyclopropanecarboxylate, (±)-337 and (1*R*,2*S*,3*R*,4*S*))-3-(((±)-2-phenylbutanoyl)oxy)bicyclo[2.2.1]heptan-2-yl cyclopropanecarboxylate, (±)-338

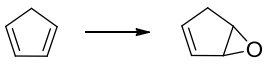


((±)-(1*S*,2*R*,3*S*,4*R*))-3-Hydroxybicyclo[2.2.1]heptan-2-yl cyclopropanecarboxylate (±)-**341** (1.50 g, 7.65 mmol) and 2-phenylbutanoyl chloride were subjected to general procedure B. Flash column chromatography (19:1 petrol:diethyl ether) yielded the title diesters **337** and **338** as a white solid (2.17 g, 83%) as a 1:1 mixture of diastereoisomers.

^{1}H NMR δ_H (400 MHz, $CDCl_3$): Diastereoisomer A: 7.43-7.08 (5 H, m, Ar*H*), 4.81-4.60 (2 H, m, C(2)*H* and C(3)*H*), 3.46 (1 H, t, *J* = 7.7 Hz, C*H*CO_2), 2.24 (2 H, app. s, C(1)*H* and C(4)*H*), 2.18-2.01 (1 H, m, C(7)H_AH_B), 1.90-1.70 (3 H, m, C(1')*H* and CH_2CH_3), 1.58-1.35 (2 H, C(5)H_AH_B and C(6)H_AH_B), 1.24-1.10 (3 H, m, C(5)H_AH_B and C(6)H_AH_B and

C(7)H$_A$*H*$_B$), 1.07-0.96 (2 H, m, C(2'')*H*$_A$H$_B$ and C(3'')*H*$_A$H$_B$), 0.90 (3 H, t, *J* = 8.2 Hz, CH$_2$C*H*$_3$), 0.84-0.57 (2 H, m, C(2'')H$_A$*H*$_B$ and C(3'')H$_A$*H*$_B$); Diastereoisomer B: 7.43-7.08 (5 H, m, Ar*H*), 4.81-4.60 (2 H, m, C(2)*H* and C(3)*H*), 3.42 (1 H, t, *J* = 7.7 Hz, C*H*CO$_2$), 2.24 (1 H, app. s, C(4)*H*), 2.18-2.01 (2 H, m, C(1)*H* and C(7)*H*$_A$H$_B$), 1.90-1.70 (1 H, m, C(1')*H*), 1.58-1.35 (4 H, m, C*H*$_2$CH$_3$ and C(5)*H*$_A$H$_B$ and C(6)*H*$_A$H$_B$), 1.24-1.10 (3 H, m, C(5)H$_A$*H*$_B$ and C(6)H$_A$*H*$_B$ and C(7)H$_A$*H*$_B$), 1.07-0.96 (2 H, m, C(2'')*H*$_A$H$_B$ and C(3'')*H*$_A$H$_B$), 0.90 (3 H, t, *J* = 8.2 Hz, CH$_2$C*H*$_3$), 0.84-0.57 (2 H, m, C(2'')H$_A$*H*$_B$ and C(3'')H$_A$*H*$_B$); **^{13}C NMR** δ_C (100 MHz, CDCl$_3$): 173.9 (2 × Ph*C*=O), 173.1 (*C*O$_2$), 173.0 (*C*O$_2$), 139.2 (quat. Ar*C*), 139.0 (quat. Ar*C*), 128.4 (2 × Ar*C*), 128.1 (3 × Ar*C*), 127.0 (Ar*C*), 76.8 (*C*(2)), 76.7 (*C*(2)), 76.5 (*C*(3)), 76.4 (*C*(3)), 53.7 (*C*(7)), 53.3 (*C*(7)), 41.2 (*C*(1)), 41.1 (*C*(1) and *C*(4)), 40.9 (*C*(1'')), 33.5 (2 × *C*(7)), 27.1 (*C*H$_2$CH$_3$), 26.7 (*C*H$_2$CH$_3$), 24.4 (*C*(5)), 24.3 (*C*(5)), 24.2 (2 × *C*(6)), 12.4 (2 × *C*H$_3$), 12.2 (2 × *C*H$_3$), 8.5 (2 × *C*(2'')), 8.4 (2 × *C*(1'')); **IR** (ν_{max}/cm^{-1}): 3063, 2968, 2877, 1734; **LRMS** (ESI$^+$, *m/z*): 365 (M+Na$^+$, 100%); **HRMS** (ESI$^+$, *m/z*): Calculated 365.1723 (C$_{21}$H$_{26}$NaO$_4$), Found 365.1723 (Δ+0.4 ppm); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +24.7 (c = 1.0, CH$_2$Cl$_2$).

6-Oxabicyclo[3.1.0]hex-2-ene, 361



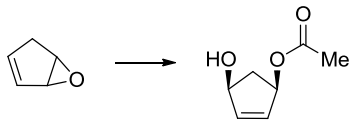
360 **361**

To a solution of freshly cracked cyclopentadiene (6.00 g, 90.8 mmol) in dichloromethane (56.0 mL) was added sodium carbonate (12.0 g, 113 mmol). A solution of sodium acetate (228 mg, 2.78 mmol) in peracetic acid (39% in acetic acid, 8.00 mL, 45.4 mmol) was added dropwise at 0 ºC. After 16 hours, the reaction mixture was filtered and concentrated at 300 mbar, 25 °C. The residue was distilled at 16-18 mbar at 110 ºC. The title compound **361** was obtained in 48% yield (1.79 g, 21.8 mmol).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 6.08-6.04 (1 H, m, CH=C*H*CO), 5.94-5.85 (1 H, m, C*H*=CH), 3.83-3.76 (1 H, m, C*H*OCH), 3.73-3.68 (1 H, m, CHOC*H*), 2.58-2.48 (1 H, m, CH_AH$_B$), 2.34-2.20 (1 H, m, CH$_A$$H_B$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 137.5 (CH=*C*HCHOC), 131.0 (*C*H=CHCHOC), 58.6 (CH=CH*C*HOC), 56.9 (CHO*C*H), 35.2 (*C*H$_2$).

The spectral data were consistent with those in the literature.[77]

(±)-(1*S*,4*R*)-4-Hydroxycyclopent-2-en-1-yl acetate, (±)-362



361 (±)-**362**

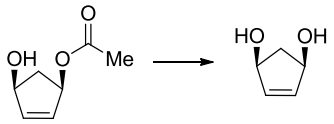
A suspension of tetrakis(triphenylphosphine)palladium (8.0 mg, 0.67 mmol, 0.20 mol%) in tetrahydrofuran (4.40 mL) was stirred at room temperature until a yellow solution was obtained. The solution was then cooled to 0 ºC and acetic acid (222 mg, 3.33 mmol) was added dropwise over 10 minutes. A solution of epoxide **361** (300 mg, 3.65 mmol) in tetrahydrofuran (4.40 mL) was then added dropwise over 10 minutes. The reaction mixture was then stirred for a further 10 minutes at 0 ºC and filtered through a plug of silica eluting with diethyl ether (10.0 mL). The filtrate was then dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (9:1 petrol:ethyl acetate) yielded the title compound (±)-**362** as a colourless oil (399 mg, 73%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 6.07-6.01 (1 H, m, C(OCOCH$_3$)C*H*=CH), 5.96-5.93 (1 H, m, C(OCOCH$_3$)CH=C*H*), 5.46-5.39 (1 H, m, C*H*OCOCH$_3$), 4.58 (1 H, d, *J* = 6.0 Hz, C*H*OH), 2.74 (1 H, dt, *J* = 14.7, 7.3 Hz, CH_AH$_B$), 1.99 (3 H, s, OCOCH_3), 1.59 (1 H, dt, *J* = 14.6, 11.1 Hz, CH$_A$$H_B$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 170.9 (quat. *C*=O), 138.5

(C(OCOCH$_3$)*C*H=CH), 132.6 (C(OCOCH$_3$)CH=*C*H), 77.1 (*C*HOCOCH$_3$), 74.8 (*C*HOH), 40.5 (*C*H$_2$), 21.1 (OCO*C*H$_3$).

The spectral data were consistent with those in the literature.[77]

(±)-(1*R*,3*S*)-Cyclopent-4-ene-1,3-diol, 358



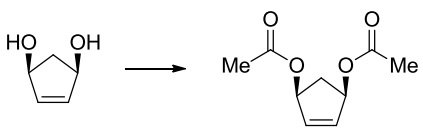
(±)-**362** **358**

Potassium carbonate (195 mg, 1.40 mmol) was added to a stirred solution of alcohol (±)-**362** (200 mg, 1.41 mmol) in methanol (14.0 mL) at 0 °C. After stirring at room temperature for 16 hours the reaction mixture was concentrated *in vacuo*. Flash column chromatography (4:1 petrol:ethyl acetate) yielded the title compound **358** as a white solid (58.8 mg, 42%).

^{1}H NMR δ_H (400 MHz, CD$_3$OD): 5.92 (2 H, s, C*H*=C*H*), 4.61 (2 H, dd, *J* = 7.1, 5.4 Hz, 2 × C*H*OH), 2.75 (1 H, dt, *J* = 13.6, 7.3 Hz, C*H*$_A$H$_B$), 1.44 (1 H, dt, *J* = 13.5, 5.4 Hz, CH$_A$*H*$_B$); **^{13}C NMR** δ_C (100 MHz, CDCl$_3$): 135.7 (*C*H=*C*H), 73.9 (*C*HOH), 43.1 (*C*H$_2$); **m.p.** 52-54 ^{o}C (lit. 55-59 ^{o}C).

The spectral data were consistent with those in the literature.[78]

(1*R*,3*S*)-Cyclopent-4-ene-1,3-diyl diacetate, 371



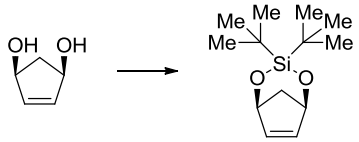
358 **371**

Acetic anhydride (0.50 mL, 5.29 mmol) was added dropwise to a stirred solution of *cis*-4-cyclopentene-1,3-diol **358** (20.0 mg, 0.20 mmol) in pyridine (0.50 mL, 6.21 mmol) at 0 °C and warmed to room temperature. After 1 hour the reaction mixture was concentrated *in vacuo*. Flash column chromatography (19:1 petrol:ethyl acetate) yielded the title compound **371** as a colourless oil (36.0 mg, 97%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 6.12 (2 H, s, C*H*=C*H*), 5.58 (2 H, dd, *J* = 7.5, 3.8 Hz, C*H*OAc), 2.91 (1 H, dt, *J* = 15.0, 7.6 Hz, CH_AH_B), 2.09 (6 H, s, CH_3CO_2), 1.77 (1 H, dt, *J* = 15.0, 3.9 Hz, CH_AH_B); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 170.7 (*C*=O), 134.6 (*C*=*C*), 76.6 (C*H*OAc), 37.1 (CH_2), 21.1 (CH_3).

The spectral data were consistent with those in the literature.[138]

(1*R*,5*S*)-3,3-Di-*tert*-butyl-2,4-dioxa-3-silabicyclo[3.2.1]oct-6-ene, 372



358 **372**

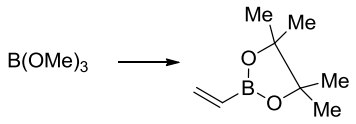
Di-*tert*-butylsilyl bis trifluoromethanesulfonate (6.35 mL, 19.5 mmol) was added dropwise to a solution of *cis*-4-cyclopentene-1,3-diol **358** (1.77 g, 17.7 mmol) and 2,6-lutidine (6.18 mL, 53.1 mmol) in dichloromethane (40.0 mL) over 10 minutes at 0 °C. After stirring for a further 10 minutes at room temperature the reaction was concentrated *in vacuo*. Flash column chromatography (4:1 petrol:dichloromethane) yielded the title compound **372** as a colourless oil (4.26 g, 91%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 6.39 (2 H, s, C*H*=C*H*), 4.73 (2 H, br. s, 2 × C*H*OSi), 2.42 (1 H, d, *J* = 12.5 Hz, CH_AH_B), 1.74 (1 H, dt, *J* = 12.4 Hz, 3.1, CH_AH_B), 0.97 (9 H, s,

Si(C(CH_3)$_A$(C(CH_3)$_B$), 0.89 (9 H, s, Si(C(CH_3)$_A$(C(CH_3)$_B$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 140.0 (*C*=*C*), 76.2 (*C*HOSi), 44.5 (*C*H_2), 28.8 (Si(C(*C*H_3)$_A$(C(CH_3)$_B$), 28.0 (Si(C(CH_3)$_A$(C(*C*H_3)$_B$), 21.3 (Si(*C*(CH_3)$_A$(C(CH_3)$_B$), 20.7 (Si(C(CH_3)$_A$(*C*(CH_3)$_B$).

The spectral data were consistent with those in the literature.[139]

4,4,5,5-Tetramethyl-2-vinyl-1,3,2-dioxaborolane, 389



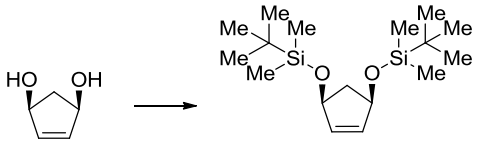
391 **389**

A solution of vinylmagnesium bromide (10.9 mL, 10.9 mmol, 1.0 M in THF) was added to a solution trimethyl borate **391** (1.00 ml, 8.70 mmol) in Et_2O (3.00 mL) dropwise over a period of 5 minutes at −78 ^oC. After 1 hour the reaction was warmed to 0 ^oC and quenched with dropwise addition of 30% aqueous solution of HCl (3.00 mL). After 30 minutes, the mixture was separated and the aqueous layer was extracted with Et_2O (3 × 3.00 mL). The combined organic extracts were dried over Na_2SO_4, filtered and partially concentrated under reduced pressure. The resulting solution was then added to a mixture of pinacol (1.51 g, 12.8 mmol) and 4 Å molecular sieves and stried at room temperature for 12 hours. The mixture was then filtered and concentrated *in vacuo*. Flash column chromatography (19:1 petrol:diethyl ether) yielded the title compound **389** as a colourless oil (751 mg, 56%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 6.16-5.78 (3 H, m, C*H*=CH_2), 1.29 (12 H, s, 2 x (CH_3)$_2$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 137.0 (CH=*C*H_2), 83.3 (*C*(CH_3)$_2$), 24.8 (*C*H_3).

The spectral data were consistent with those in the literature, also missing corresponding δ_C (*C*H=CH_2).[84]

(3*R*,5*S*)-3,5-Bis((*tert*-butyldimethylsilyl)oxy)cyclopent-1-ene, 370



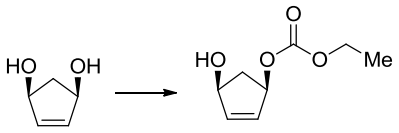
358 **370**

tert-Butyldimethylsilyl chloride (826 mg, 5.50 mmol) was added to a solution of *cis*-4-cyclopentene-1,3-diol **358** (250 mg, 2.50 mmol), imidazole (374 mg, 5.50 mmol) and 4-dimethylaminopyridine (30.5 mg, 0.25 mmol) in dichloromethane (25.0 mL) at 0 °C. The reaction was warmed to room temperature and stirred for 16 hours. The reaction was quenched with a saturated aqueous solution of ammonium chloride (25.0 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 25.0 mL) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (19:1 petrol:dichloromethane) yielded the title compound **370** as a colourless oil (755 mg, 92%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 5.72 (2 H, s, C*H*=C*H*), 4.54 (2 H, t, *J* = 6.6 Hz, C*H*OSi), 2.75-2.43 (1 H, m, CH_AH_B), 1.66-1.33 (1 H, m, CH_AH_B), 0.82 (18 H, s, 2 × SiC(CH_3)$_3$), 0.01 (6 H, s, 2 × Si(CH_3)$_A$(CH_3)$_B$), −0.01 (6 H, s, 2 × Si(CH_3)$_A$(CH_3)$_B$) ; **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 135.9 (*C*H=*C*H), 74.9 (*C*HOSi), 45.2 (*C*H_2), 25.9 (SiC(*C*H_3)$_3$), 25.7 (SiC(*C*H_3)$_3$), 18.2 (Si*C*(CH$_3$)$_3$), −4.6 (2 × Si(*C*H_3)$_3$).

The spectral data were consistent with those in the literature.[140]

(±)-Ethyl ((1*R*,4*S*)-4-hydroxycyclopent-2-en-1-yl) carbonate, (±)-373



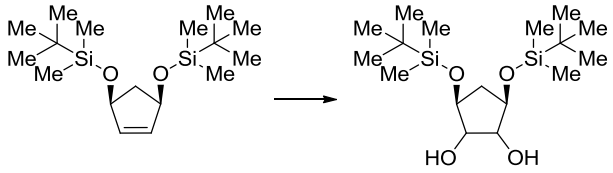
358 (±)-**373**

Dichloromethane (3.00 mL) was added to *cis*-4-cyclopentene-1,3-diol **358** (200 mg, 2.00 mmol) and cooled to 0 °C. Triethylamine (0.84 mL, 5.99 mmol) was then added, followed by dropwise addition of ethyl chloroformate (0.38 mL, 4.00 mmol). The reaction was warmed to room temperature and stirred for 16 hours. The reaction mixture was cooled to 0 °C and water (3.00 mL) was then added followed by an aqueous solution of 1 M HCl (6.00 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 9.00 mL) and the combined layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (4:1 petrol:diethyl ether) yielded the title compound (±)-**373** as a colourless oil (172 mg, 68%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 6.09 (1 H, dq, *J* = 5.5, 1.1 Hz, CH=C*H*CHOCO), 5.97 (1 H, dq, *J* = 5.5, 1.1 Hz, C*H*=CHCHOCO), 5.34-5.32 (1 H, m, C*H*OCO), 4.68-4.65 (1 H, m, C*H*OH), 4.15 (2 H, q, *J* = 7.3 Hz, $CO_2CH_2CH_3$), 2.79 (1 H, dt, *J* = 14.6, 7.3 Hz, CH_AH_B), 1.68 (1 H, dt, *J* = 14.6, 4.0 Hz, CH_AH_B), 1.27 (3 H, t, *J* = 7.3 Hz, $CO_2CH_2CH_3$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 154.5 (*C*=O), 139.0 (CH=*C*HCHOCO), 131.5 (*C*H=CHCHOCO), 80.2 ($CO_2CH_2CH_3$), 74.3 (*C*HOCO), 63.8 (*C*HOH), 40.0 (CH_2), 14.0 ($CO_2CH_2CH_3$).

The spectral data were consistent with those in the literature.[141]

(3*R*,5*S*)-3,5-Bis((*tert*-butyldimethylsilyl)oxy)cyclopentane-1,2-diol, 398

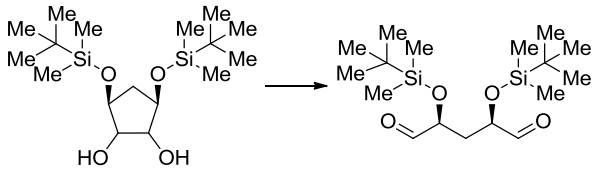


370 **398**

Potassium osmate dihydrate (14.0 mg, 0.037 mmol) was added to a solution of alkene **370** (400 mg, 1.22 mmol) and 4-methylmorpholine *N*-oxide (429 mg, 3.66 mmol) in a 10:9:1 mixture of tetrahydrofuran (6.00 mL), *tert*-butanol (5.40 mL) and water (0.60 mL) and stirred at room temperature for 16 hours. The reaction was quenched with sodium sulphite (1.00 g) and diluted with water (10.0 mL). The mixture was extracted with ethyl acetate (3 × 12.0 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (4:1 petrol:dichloromethane) yielded the title compound **398** as a crystaline solid (300 mg, 68%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 3.97-3.87 (2 H, m, 2 × C*H*OH), 3.84 (2 H, br.s, 2 × C*H*OSi), 2.44 (2 H, br.s, 2 × O*H*), 2.34-2.23 (1 H, m, CH_AH_B), 1.36 (1 H, dt, J = 13.5, 6.8 Hz, CH_AH_B), 0.81 (18 H, s, 2 × SiC(CH_3)$_3$), 0.00 (6 H, s, 2 × Si(CH_3)$_A$(CH_3)$_B$), −0.02 (6 H, s, 2 × Si(CH_3)$_A$(CH_3)$_B$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 78.1 (*C*HOSi), 75.5 (*C*HOH), 40.2 (CH_2), 25.8 (SiC(*C*H_3)$_3$), 25.6 (SiC(*C*H_3)$_3$), 18.0 (Si*C*(CH_3)$_3$), −4.7 (Si(*C*H_3)$_2$), −4.8 (Si(*C*H_3)$_2$); **IR** (ν_{max}/cm^{-1}): 3340, 2929, 2857, 1472, 1251; **LRMS** (ESI$^+$, *m/z*): 385.3 (M+Na$^+$, 100%); **HRMS** (ESI$^+$, *m/z*): Calculated 385.2201 ($C_{17}H_{38}NaO_4Si_2$), Found 385.2189 (Δ +3.1 ppm); **m.p.** 93-95 ^{o}C.

(2*R*,4*S*)-2,4-Bis((*tert*-butyldimethylsilyl)oxy)pentanedial, 399

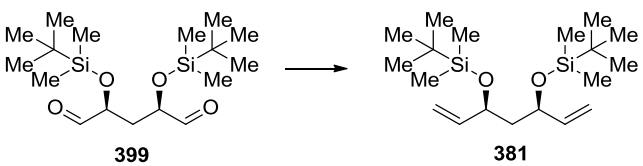


398 **399**

Silica-supported sodium periodate (1.17 mmol/g, 1.00 g, 1.17 mmol) was added to a solution of compound **398** (150 mg, 0.41 mmol) in diethyl ether (4.00 mL) at room temperature and stirred for 4 hours. The reaction mixture was filtered, washing the filter cake with diethyl ether (3 × 10.0 mL), dried over magnesium sulfate and concentrated *in vacuo*. The title compound **399** was used without further purification.

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 9.55 (2 H, d, *J* = 1.0 Hz, 2 × C*H*O), 4.15 (2 H, m, C*H*OSi), 2.05-1.89 (2 H, m, CH_2), 0.83 (18 H, s, 2 × SiC(CH_3)$_3$), 0.00 (12 H, s, 2 ×Si(CH_3)$_2$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 203.6 (*C*=O), 73.7 (*C*HOSi), 36.7 (*C*H_2), 25.8 (SiC(*C*H_3)$_A$(CH$_3$)$_B$), 25.7 (SiC(CH$_3$)$_A$(*C*H$_3$)$_B$), 18.1 (Si*C*(CH$_3$)$_2$), −4.6 (Si(*C*H$_3$)$_A$(CH$_3$)$_B$), −4.9 (Si(CH$_3$)$_A$(*C*H$_3$)$_B$); **IR** (ν_{max}/cm^{-1}): 1770, 1709, 1636, 1384; **LRMS** (ESI$^+$, *m/z*): 361 (M+H$^+$, 100%); **HRMS** (ESI$^+$, *m/z*): Calculated 383.2044 ($C_{17}H_{36}NaO_4Si_2$), Found 383.2058 (Δ −3.2 ppm).

(5*R*,7*S*)-2,2,3,3,9,9,10,10-Octamethyl-5,7-divinyl-4,8-dioxa-3,9-disilaundecane, 381



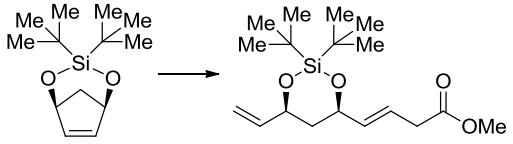
399 **381**

*n*Butyl lithium (1.6 M in hexanes, 1.17 mL, 1.87 mmol) was added dropwise to a solution of triphenylmethylphosphonium bromide (740 mg, 2.08 mmol) in tetrahydrofuran (4.20 mL) at

0 °C. After 15 min a solution of dialdehyde **399** (150 mg, 0.416 mmol) in tetrahydrofuran (4.20 mL) was added and the reaction stirred for a further 15 minutes then warmed to room temperature. After 16 hours the reaction was quenched with saturated aqueous ammonium chloride (10.0 mL), the layers separated and the aqueous layer extracted with diethyl ether (3 × 10.0 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (19:1 petrol:dichloromethane) yielded the title compound **381** as colourless oil (85.0 mg, 53% over two steps).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 5.79 (2 H, ddd, *J* = 17.2, 10.5, 6.6 Hz, 2 × C*H*=CH_2), 5.12 (2 H, d, *J* = 17.1 Hz, 2 × CH=C*H*$_A$H$_B$), 5.01 (2 H, d, *J* = 10.5 Hz, 2 × CH=CH$_A$*H*$_B$), 4.16 (2 H, q, *J* 6.6 Hz, 2 × C*H*OSi), 1.80 (1 H, dt, *J* = 13.5, 6.8 Hz, C*H*$_A$H$_B$), 1.58-1.46 (1 H, m, CH$_A$*H*$_B$), 0.86 (18 H, s, 2 × SiC(C*H*$_3$)$_3$), 0.03 (6 H, s, 2 × Si(C*H*$_3$)$_A$(CH$_3$)$_B$), 0.01 ((6 H, s, 2 × Si(CH$_3$)$_A$(C*H*$_3$)$_B$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 141.5 (*C*H=CH_2), 114.1 (CH=*C*H$_2$), 71.1 (C*H*OSi), 47.0 (*C*H$_2$), 25.9 (SiC(*C*H$_3$)$_3$), 18.2 (Si*C*(CH$_3$)), 14.2 (Si*C*(CH$_3$)$_3$), −4.1 (Si(*C*H$_3$)$_2$), −4.8 (Si(*C*H$_3$); **IR** (ν_{max}/cm^{-1}): 2361, 2342, 669 ; **LRMS** (ESI$^+$, *m/z*): 379 (M+Na$^+$, 100%); **HRMS** (ESI$^+$, *m/z*): Calculated 379.2465 ($C_{19}H_{40}NaO_2Si_2$), Found 379.2466 (Δ +1.0 ppm).

(*E*)-Methyl 4-((4*R*,6*S*)-2,2-Di-*tert*-butyl-6-vinyl-1,3,2-dioxasilinan-4-yl)but-3-enoate, 394



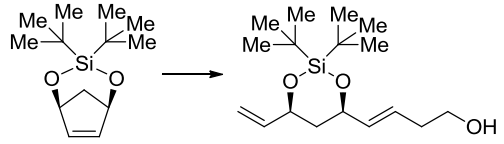
354 **(±)-394**

Hoveyda-Grubbs second generation catalyst (24.0 mg, 0.04 mmol) was added to a stirred solution of cyclopentene **354** (300 mg, 1.25 mmol) and methyl but-3-enolate (0.59 mL, 5.49 mmol) in dichloromethane (8.00 mL) at room temperature. After 16 hours the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride and the

layers were separated. The aqueous layer was extracted with dichloromethane (3 × 8.00 mL) and the combined organic layers dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (4:1 Heptane-diethyl ether) yielded the title compound (±)-**394** as colourless oil (306 mg, 81%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 5.83 (2 H, dddd, *J* = 15.0, 10.7, 3.6, 1.7 Hz, C*H*=CH_2 and C*H*=$CHCH_2CO_2CH_3$), 5.68-5.49 (1 H, m, CH=C*H*$CH_2CO_2CH_3$), 5.31 (1 H, ddd, *J* = 17.0, 3.6, 1.9 Hz, CH=CH_AH_B), 5.06 (1 H, ddd, *J* = 10.4, 3.6, 2.0 Hz, CH=CH_AH_B), 4.76-4.45 (2 H, m, 2 × C*H*OSi), 3.69 (3 H, s, CO_2CH_3), 3.10-2.99 (2 H, m, $CH_2CO_2CH_3$), 1.72 (1 H, ddd, 14.3, 8.3, 6.0 Hz, CH_AH_BCHOSi), 1.56-1.46 (1 H, m, CH_AH_BCHOSi), 1.08-0.98 (18 H, m, Si(C(CH_3)$_3$)$_2$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 172.0 (*C*=O), 140.1 (*C*H=CH_2), 125.9 (*C*H=$CHCH_2CO_2$), 124.5 (CH=*C*HCH_2CO_2), 113.2 (CH=*C*H_2); 73.4 (*C*HOSi), 73.2 (*C*HOSi), 42.4 (*C*H_2CHOSi), 37.9 (*C*H_2CO_2), 27.5 (C(*C*H_3)$_3$), 27.2 (C(*C*H_3)$_3$), 29.5 (CO_2*C*H_3), 22.5 (*C*(CH_3)$_3$), 21.7 (*C*(CH_3); **IR** (ν_{max}/cm^{-1}): 2954, 1737, 1436, 1253, 1160, 971; **LRMS** (ESI$^+$, *m/z*): 363.2 ([M + Na]$^+$, 100%); **HRMS** (ESI$^+$, *m/z*): Calculated 363.1968 ($C_{18}H_{32}NaO_4Si$), Found 363.1863 (Δ +0.3 ppm).

(±)-(*E*)-4-((4*R*,6*S*)-2,2-Di-*tert*-butyl-6-vinyl-1,3,2-dioxasilinan-4-yl)but-3-en-1-ol, (±)-393



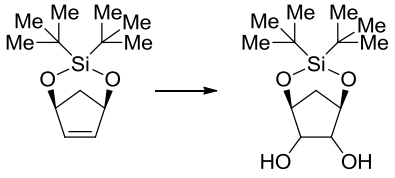
354 (±)-**393**

Hoveyda-Grubbs second generation catalyst (24.0 mg, 0.04 mmol) was added to a stirred solution of cyclopentene **372** (300 mg, 1.25 mmol) and but-3-en-1-ol (0.47 mL, 5.49 mmol) in dichloromethane (8.00 mL) at room temperature. After 16 hours the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride and the layers were

separated. The aqueous layer was extracted with dichloromethane (3 × 8.00 mL) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (7:3 Heptane-ethyl acetate) yielded the title compound (±)-**393** as colourless oil (306 mg, 69%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 6.06-5.64 (1 H, m, C*H*=CH_2), 5.62-5.48 (1 H, m, CH=C*H*CH_2CH_2OH), 5.42-5.22 (1 H, m, C*H*=$CHCH_2CH_2OH$), 5.12-4.87 (2 H, m, CH=CH_2), 3.94-3.55 (2 H, m, CH_2OH), 2.34 (2 H, ddd, *J* = 18.0, 9.5, 6.2 Hz, CH_2CH_2OH), 1.75-1.25 (2 H, m, CH_2COSi), 1.23-0.85 (18 H, m, SiC(CH_3)$_3$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 140.5 (*C*H=CH_2), 133.8 (*C*H=$CHCH_2OH$), 128.3 (CH=*C*HCH_2OH), 113.2 (CH=*C*H_2), 73.3 (2 × *C*HOSi), 63.0 (*C*H_2OH), 42.3 (*C*H_2CHOSi), 36.3 (*C*H_2CH_2OH), 27.5 (C(*C*H_3)$_3$), 27.2 (C(*C*H_3)$_3$), 22.7 (*C*(CH_3)$_3$, 21.9 (*C*(CH_3); **IR** (ν_{max}/cm^{-1}): 3325, 2933, 1473, 1370, 1265, 1100, 1026; **LRMS** (ESI$^+$, *m/z*): 335.2 (M+Na$^+$, 100%); **HRMS** (ESI$^+$, *m/z*): Calculated 335.2019 ($C_{17}H_{32}NaO_3Si$), Found 335.2016 (Δ +2.1ppm).

(1*R*,5*S*)-3,3-Di-*tert*-butyl-2,4-dioxa-3-silabicyclo[3.2.1]octane-6,7-diol, 401



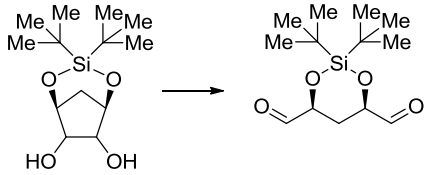
354 **401**

Potassium osmate dihydrate (59.0 mg, 0.16 mmol) was added to a solution of alkene **354** (1.25 g, 5.20 mmol) in a 10:9:1 mixture of tetrahydrofuran (25.0 mL), *tert*-butanol (22.5 mL) and water (2.50 mL) and stirred at room temperature for 16 hours. The reaction was quenched with sodium sulphite (1.00 g) and diluted with water (20.0 mL). The mixture was extracted with ethyl acetate (3 × 20.0 mL), dried over magnesium sulfate, filtered and

concentrated *in vacuo*. Flash column chromatography (4:1 petrol:ethyl acetate) yielded the title compound **401** as colourless oil (879 mg, 65%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 4.41 (2 H, d, *J* = 2.2 Hz, 2 x C*H*OH), 4.22 (2 H, d, *J* = 2.7 Hz, 2 x C*H*OSi), 2.23 (1 H, d, *J* = 14.4 Hz, CH_AH$_B$), 1.76 (1 H, dt, *J* = 14.2, 3.2 Hz, CH$_A$$H_B$), 0.97 (9 H, s, Si(C(C$H_3$)$_3$)$_A$(C(CH$_3$)$_3$)$_B$), 0.94 (9 H, s, Si(C(CH$_3$)$_3$)$_A$(C(C$H_3$)$_3$)$_B$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 80.1 (*C*HOH), 75.7 (C*H*OSi), 34.8 (*C*H$_2$), 28.4 (C(*C*H$_3$)$_3$)$_A$(C(CH$_3$)$_3$)$_B$), 27.7 (Si(C(CH$_3$)$_3$)$_A$(C(*C*H$_3$)$_3$)$_B$), 20.6 (2 x *C*(CH$_3$)$_3$); **IR** (ν_{max}/cm^{-1}): 3286, 2939, 2860, 1477, 1110; **LRMS** (ESI$^+$, *m/z*): 297 (M+Na$^+$, 100%); **HRMS** (ESI$^+$, *m/z*): Calculated 297.1493 ($_{13}$H$_{26}$NaO$_4$Si), Found 297.1497 (Δ −1.3 ppm); **m.p.** 89-96 ^{o}C.

(1*R*,5*S*)-3,3-Di-*tert*-butyl-2,4-dioxa-3-silabicyclo[3.2.1]octane-6,7-diol, 402



401 **402**

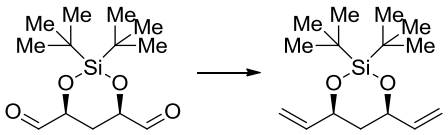
Silica-supported sodium periodate (1.17mmol/g, 1.58 g, 1.85 mmol) was added to a solution of compound **401** (100 mg, 0.365 mmol) in diethyl ether (4.00 mL) at room temperature and stirred for 4 hours. The reaction mixture was filtered, washing the filter cake with diethyl ether (3 × 4.00 mL) and concentrated *in vacuo*. The title compound **402** was used without further purification.

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 9.64 (2 H, s, 2 x C*H*O), 4.48 (2 H, dd, *J* = 11.9, 2.3 Hz, 2 x C*H*OSi), 2.17 (2 H, dt, *J* = 14.2, 2.5 Hz, CH_AH$_B$), 1.62 (2 H, dt, *J* = 14.2, 11.9 Hz, CH$_A$$H_B$), 1.07 (9 H, s, (C(C$H_3$)$_3$)$_A$(C(CH$_3$)$_3$)$_B$), 1.04 (9 H, s, Si(C(CH$_3$)$_3$)$_A$(C(C$H_3$)$_3$)$_B$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 201.90 (*C*HO), 76.9 (*C*HOSi), 30.8 (*C*H$_2$), 28.4 (C(*C*H$_3$)$_3$)$_A$(C(CH$_3$)$_3$)$_B$),

22.7 ($Si(C(CH_3)_3)_A(C(\mathit{C}H_3)_3)_B$), 20.6 ($Si(\mathit{C}(CH_3)_3)_A(C(CH_3)_3)_B$), 19.8 ($Si(C(CH_3)_3)_A(\mathit{C}(CH_3)_3)_B$); **IR** ($\nu_{max}/cm^{-1}$): 3456, 2936, 2861, 1742, 1475, 1144; **LRMS** (ESI^+, *m/z*): 295 ($[M + Na]^+$, 100%); **HRMS** (ESI^+, *m/z*): Calculated 273.1517 ($C_{13}H_{25}O_4Si$), Found 273.1520 (Δ +0.7 ppm).

(4*R*,6*S*)-2,2-Di-*tert*-butyl-4,6-divinyl-1,3,2-dioxasilinane, 354

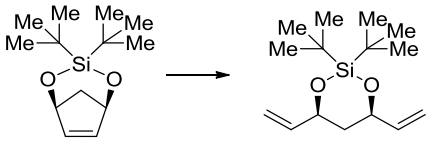
Method A:



402 **354**

*n*Butyl lithium (1.6 M in hexanes, 3.10 mL, 4.96 mmol) was added dropwise to a solution of triphenylmethylphosphonium bromide (1.85 g, 5.19 mmol) in tetrahydrofuran (12.0 mL) at 0 °C. After 15 minutes a solution of dialdehyde **402** (321 mg, 1.18 mmol) in tetrahydrofuran (2.00 mL) was added and stirred for a further 15 minutes then warmed to room temperature. After 16 hours the reaction was quenched with saturated aqueous ammonium chloride (15.0 mL), the layers separated and the aqueous layer extracted with diethyl ether (3 × 15.0 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (19:1 petrol:dichloromethane) yielded the title compound **354** as colourless oil (199 mg, 63%).

Method B:



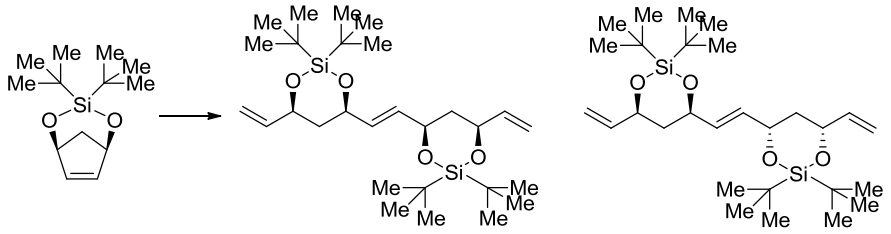
372 **354**

Ethylene gas was bubbled through a solution of Hoveyda-Grubbs second generation catalyst (8.1 mg, 0.013 mmol) in dichloromethane (21.0 mL) at −78 °C. A solution of alkene **372** (100 mg, 0.42 mmol) in dichloromethane (21.0 mL) was added dropwise using a syinge pump over 42 minutes (0.5 mL/h), followed by addition of a saturated aqueous solution of ammonium chloride (20.0 mL). The layers were separated and the aqueous layer extracted with dichloromethane (3 × 20.0 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (19:1 petrol:dichloromethane) yielded the title compound **354** as a colourless oil (99.6 mg, 89%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 5.87 (2 H, ddd, J = 17.0, 10.4, 4.7 Hz, 2 x C*H*=CH_2), 5.48-5.25 (2 H, m, CH=CH_AH_B), 5.10 (2 H, d, J = 10.5 Hz, 2 x CH=CH_AH_B), 4.82-4.45 (2 H, m, 2 x C*H*OSi), 1.78 (1 H, dt, J = 14.2, 2.2 Hz, CH_AH_B), 1.67-1.43 (1 H, m, CH_AH_B), 1.08 (9 H, s, $(C(CH_3)_3)_A(C(CH_3)_3)_B$), 1.04 (9 H, s, $Si(C(CH_3)_3)_A(C(CH_3)_3)_B$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 140.6 (*C*H=CH_2), 113.2 (CH=*C*H_2), 74.0 (*C*HOSi), 42.2 (*C*H_2), 27.4 ($SiC(CH_3)_3)_A(C(CH_3)_3)_B$), 27.2 ($Si(C(CH_3)_3)_A(C(CH_3)_3)_B$), 22.7 ($Si(C(CH_3)_3)_A(C(CH_3)_3)_B$), 19.9 ($Si(C(CH_3)_3)_A(C(CH_3)_3)_B$).

The spectral data were consistent with those in the literature.[142]

(±)-(*E*)-1,2-Bis((4*R*,6*S*)-2,2-di-*tert*-butyl-6-vinyl-1,3,2-dioxasilinan-4-yl)ethane, (±)-384 and (*E*)-1,2-Bis((4*R*,6*S*)-2,2-di-*tert*-butyl-6-vinyl-1,3,2-dioxasilinan-4-yl)ethane, 385



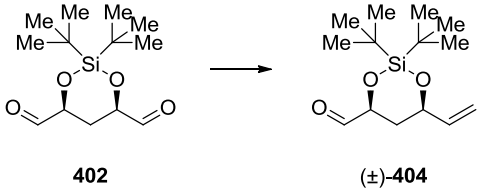
372 **(±)-384** **385**

An inseparable 1:1 mixture of compounds (±)-**384** and **385** were isolated as a colourless oil in the synthesis of diene **354** *via Method B* in a ratio of 10:1 *trans:cis* isomers.

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 5.84 (4 H, dddd, *J* = 16.6, 10.4, 4.6, 1.5 Hz, 4 × C*H*=CH_2), 5.73 (4 H, ddd, *J*= 8.9, 2.1, 0.7 Hz, 2 × C*H*=C*H*), 5.42-5.19 (4 H, m, 4 × CH=CH_AH_B), 5.07 (4 H, ddd, *J* = 10.4, 3.5, 1.8 Hz, 4 × CH=CH_AH_B), 4.75-4.30 (8 H, m, 8 × C*H*OSi), 1.89-1.67 (4 H, m, 4 × CH_AH_B), 1.60-1.45 (4 H, m, 4 × CH_AH_B), 1.05-0.99 (36 H, m, 4 × SiC(CH_3)$_3$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 140.6 (*C*H=CH_2), 131.4 (*C*H=*C*H), 113.2 (CH=*C*H_2), 76.7 (2 × *CH*OSi), 74.0 (2 × C*H*OSi), 42.6 (*C*H_2), 42.2 (C*H*$_2$), 27.4 (SiC(*C*H_3)$_3$), 27.2 (2 × SiC(*C*H_3)), 22.7 (Si*C*(CH_3)$_3$), 19.9 (Si*C*(CH_3)$_3$).

The spectral data were consistent with those in the literature.[142]

(±)-(4*S*,6*R*)-2,2-Di-*tert*-butyl-6-vinyl-1,3,2-dioxasilinane-4-carbaldehyde, 404

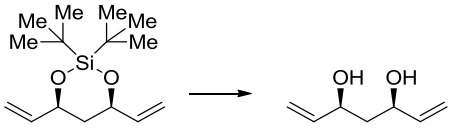


402 **(±)-404**

Compound (±)-**404** was isolated as a colourless oil in the synthesis of bis-alkene **354** *via Method A.*

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 9.59 (1 H, s, C*H*O), 5.77 (1 H, ddd, *J* = 17.0. 10.4, 4.4 Hz, C*H*=CH_2), 5.33-5.22 (1 H, m, CH=CH_AH_B), 5.05 (1 H, d, *J* = 10.5 Hz, CH=CH_AH_B), 4.57 (1 H, t, *J* = 9.4 Hz, C*H*CHO), 4.40 (1 H, dd, *J* = 17.0, 1.5 Hz, C*H*CH=CH_2), 1.87 (1 H, dt, *J* = 14.1, 2.4 Hz, CH_AH_B), 1.56-1.44 (1 H, m, CH_AH_B), 0.99 (9 H, s, Si(C(CH_3)$_A$(CH_3)$_B$)), 0.97 (9 H, s, Si(C(CH_3)$_A$(CH_3)$_B$)); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 201.4 (*C*=O), 139.7 (*C*H=CH_2), 114.0 (CH=*C*H_2), 77.9 (*C*HOSi), 73.3 (*C*HOSi), 36.4 (*C*H_2), 27.3 (Si(C(*C*H_3)$_3$)$_A$(C(CH_3)$_3$)$_B$), 27.1 (Si(C(CH_3)$_3$)$_A$(C(*C*H_3)$_3$)$_B$), 22.0 (Si(*C*(CH_3)$_3$)$_A$(C(CH_3)$_3$)$_B$), 19.9 (Si(C(CH_3)$_3$)$_A$(*C*(CH_3)$_3$)$_B$); **IR** (ν_{max}/cm^{-1}): 2956, 2930, 2858, 2360, 1739, 1363; **LRMS** (ESI$^+$, *m/z*): 293 (M+Na$^+$, 100%); **HRMS** (ESI$^+$, *m/z*): Calculated 293.1549 ($C_{14}H_{26}NaO_3Si$), Found 293.1552 (Δ +1.9 ppm).

(3*R*,5*S*)-Hepta-1,6-diene-3,5-diol, 344



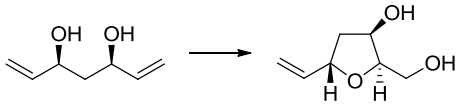
354 **344**

Tetrabutylammonium fluoride solution (1.0 M in tetrahydrofuran, 1.00 mL, 1.00 mmol) was added dropwise to a stirred solution of compound **354** (127 mg, 0.474 mmol) in tetrahydrofuran (5.00 mL) at room temperature. The reaction mixture was then heated to reflux, stirred for 5 hours then cooled to room temperature. A saturated aqueous solution of ammonium chloride (5.00 mL) was added to the reaction mixture and the layers separated. The aqueous layer was extracted with diethyl ether (5 × 5.00 mL), the combined organic layers dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column

chromatography (7:3 petrol:diethyl ether) yielded the title compound **344** as a colourless oil (57.0 mg, 94%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 5.90 (2 H, ddd, *J* = 17.0, 10.7, 5.9 Hz, 2 x C*H*=CH_2), 5.29 (2 H, d, *J* = 17.2 Hz, 2 x C$H_A$$H_B$=CH), 5.13 (2 H, d, *J* = 10.4 Hz, 2 x $CH_A$$H_B$=CH), 4.51-4.30 (2 H, m, 2 x C*H*OH), 2.72 (2 H, br.s, 2 x O*H*), 1.80-1.66 (2 H, m, CH_2CHOH); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 140.5 (*C*H=*C*H_2), 114.7 (CH=*C*H_2), 73.2 (*C*HOH), 43.0 (*C*H_2CHOH); **IR** (ν_{max}/cm^{-1}): 3347, 2936, 2859, 1424, 1311; **LRMS** (ESI^+, *m/z*): 151.1 (M+Na^+, 100%); **HRMS** (ESI^+, *m/z*): Calculated 151.0730 ($C_7H_{12}NaO_2$), Found 151.0727 (Δ +1.7 ppm).

(2*R*,3*R*,5*S*)-2-(Hydroxymethyl)-5-vinyltetrahydrofuran-3-ol, 346



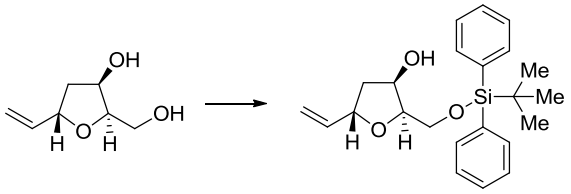
344 **346**

Dichloromethane (6.00 mL) was added to a flame dried schlenk tube with 4 Å molecular sieves (50% weight, 110 mg) at room temperature. Titanium(IV) *tert*-butoxide (70 μL, 0.17 mmol) was then added and the mixture cooled to −30 °C. (−)-Diisopropyl D-tartrate (0.43 mL, 2.04 mmol) was added dropwise and the mixture was stirred for 30 minutes. A solution of diol **344** (220 mg, 1.72 mmol) in dichloromethane (2.00 mL) was added dropwise and stirred for a further 30 minutes. A solution of *tert*-butyl hydrogen peroxide (5.5 M in hexanes, 0.34 mL, 1.89 mmol) was added dropwise and the reaction was warmed to −20 °C and stirred for 5 days. Pyridinium *para*-toulenesulfonate (22.6 mg, 0.09 mmol) was added and the reaction was stirred for a further 1.5 hours. The reaction was poured into a stirred solution of iron (II) sulfate heptahydrate (200 mg) in water (8.00 mL) and stirred for 30 minutes at 0 °C before the layers were separated. The aqueous layer was extracted with ethyl acetate (5 ×

10.0 mL) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (ethyl acetate) yielded the title compound **346** as colourless oil (144 mg, 58%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 5.77 (1 H, dd, *J* = 17.1, 10.3, 6.9 Hz, C*H*=CH_2), 5.24 (1 H, d, *J* = 17.1 Hz, CH=C$H_A$$H_B$), 5.10 (1 H, d, *J* = 10.0 Hz, CH=C$H_A$$H_B$), 4.54 (1 H, dt, *J* = 9.7, 6.3 Hz, C*H*CH=CH_2), 4.32-4.20 (1 H, m, C*H*OH), 3.86-3.78 (1 H, m, C*H*CH_2OH), 3.68-3.52 (2 H, m, CH_2OH), 2.57-2.20 (2 H, br. s, CH_2O*H* and CHO*H*), 1.98 (1 H, ddd, *J* = 13.2, 5.8, 2.1 Hz, C$H_A$$H_B$CHOH), 1.78 (1 H, ddd, *J* = 13.3, 9.7, 6.1 Hz, $CH_A$$H_B$CHOH); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 137.9 (*C*H=CH_2), 116.8 (CH=*C*H_2), 87.0 (*C*HCH_2OH), 79.6 (*C*HCH=CH_2), 73.6 (*C*HOH), 63.3 (*C*H_2OH), 41.8 (CH_2CHOH); **IR** (ν_{max}/cm^{-1}): 3381, 2931, 1737, 1427; **LRMS** (ESI^+, *m/z*): 167 ($[M + Na]^+$, 100%); **HRMS** (ESI^+, *m/z*): Calculated 167.0679 ($C_7H_{12}NaO_3$), Found 167.0681 (Δ −1.4ppm); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +3.9 (c = 1.0, CH_2Cl_2).

(2*R*,3*R*,5*S*)-2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-5-vinyltetrahydrofuran-3-ol, 55



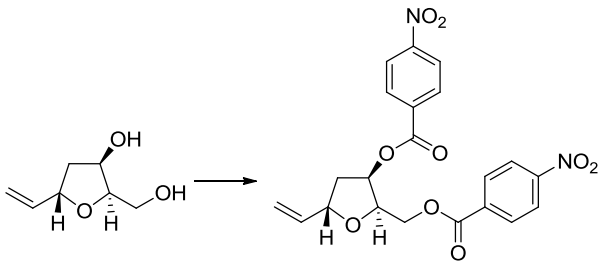
346 **55**

tert-Butyldiphenylchlorosilane (10 μL, 0.04 mmol) was added to a stirred solution of THF **346** (5.0 mg, 0.04 mmol) and imidazole (3.0 mg, 0.04 mmol) in dichloromethane (0.50 mL) at 0 °C and the reaction mixture warmed to room temperature. After stirring for 3 hours, the reaction was quenched with a saturated aqueous solution of ammonium chloride (0.5 mL) and the layers separated. The aqueous layer was extracted with dichloromethane (3 × 1.00 mL), the combined organic layers dried over magnesium sulfate, filtered and concentrated *in*

vacuo. Flash column chromatography (4:1 petrol:ethyl acetate) yielded the title compound **55** as colourless oil (7.9 mg, 52%).

^{1}H NMR δ_H (500 MHz, $CDCl_3$): 7.74 (4 H, m, Ar*H*), 7.49-7.36 (6 H, m, Ar*H*), 5.84 (1 H, ddd, *J* = 17.1, 10.3, 6.6, C*H*=CH_2), 5.27 (1 H, d, *J* = 17.1, CH=CH_AH_B), 5.13 (1 H, d, *J* = 10.3 Hz, CH=CH_AH_B), 4.75-4.67 (1 H, m, C*H*CH=CH_2), 4.62 (1 H, t, *J* = 3.9, C*H*OH), 4.04-4.01 (1 H, m, C*H*CH_2OSi), 4.00-3.97 (2 H, m, CH_2OSi), 2.20 (1 H, m, CH_AH_BCHOH), 1.91-1.79 (1 H, m, CH_AH_BCHOH), 1.07 (9 H, s, SiC(CH_3)$_3$); **^{13}C NMR** δ_C (125 MHz, $CDCl_3$): 138.5 (*C*H=CH_2), 135.6 (Ar*C*), 135.5 (Ar*C*), 130.0 (quat. Ar*C*), 127.8 (Ar*C*), 115.9 (CH=*C*H_2), 80.7 (*C*HCH_2OSi), 79.3 (*C*CH=CH_2), 74.0 (*C*HOH), 63.3 (*C*H_2OSi), 41.9 (*C*H_2CHOH), 26.7 (SiC(*C*H_3)$_3$), 19.1 (Si*C*(CH_3)$_3$); **IR** (ν_{max}/cm^{-1}): 3444, 2930, 2856, 2661, 1472, 1428, 1113; **LRMS** (ESI$^+$, *m/z*): 405 ([M + Na]$^+$, 100%); **HRMS** (ESI$^+$, *m/z*): Calculated 405.1856 ($C_{23}H_{30}NaO_3Si$), Found 405.1856 (Δ −3.5 ppm); $[\alpha]_D^{25}$ +0.8 (c = 0.4, CH_2Cl_2).

((2*R*,3*R*,5*S*)-3-((4-Nitrobenzoyl)oxy)-5-vinyltetrahydrofuran-2-yl)methyl 4-nitrobenzoate, 411



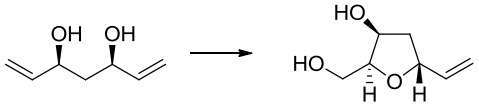
346 **411**

4-Nitrobenzoyl chloride (49.0 mg, 0.26 mmol) was added to a stirred solution of diol **346** (17.0 mg, 0.12 mmol) and pyridine (0.02 ml, 0.26 mmol) in dichloromethane (1.20 mL) at 0 °C and then warmed to room temperature. After 16 hours the reaction was quenched with a

saturated aqueous solution of sodium hydrogencarbonate (1.20 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 1.20 mL) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (4:1 petrol:ethyl acetate) yielded the title compound **411** as colourless oil (194 mg, 78%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 8.38-8.20 (8 H, m, Ar*H*), 5.90 (1 H, ddd, *J* = 17.1, 10.3, 6.6 Hz, C*H*=CH_2), 5.55 (1 H, d, *J* = 6.1 Hz, C*H*OCOAr), 5.41 (1 H, d, *J* = 17.1 Hz, CH=CH_AH_B), 5.25 (1 H, d, *J* = 10.5 Hz, CH=CH_AH_B), 4.72 (1 H, dt, *J* = 10.9, 5.6 Hz, C*H*CH=CH_2), 4.59 (2 H, td, *J* = 4.4, 1.9 Hz, CH_2OCOAr), 4.44 (1 H, td, *J* = 4.7, 2.1 Hz, C*H*CH_2OCOAr), 2.40 (1 H, dd, *J* = 14.1, 5.3 Hz, CH_AH_BCHOCOAr), 2.16-2.03 (1 H, m, CH_AH_BCHOCOAr); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 164.4 (*C*=O), 164.2 (*C*=O), 150.8 (quat. Ar*C*), 150.7 (quat. Ar*C*), 136.7 (*C*H=CH_2), 135.1 (quat. Ar*C*), 134.9 (quat. Ar*C*), 130.9 (Ar*C*), 123.7 (Ar*C*), 117.7 (CH=*C*H_2), 82.3 (*C*HCH_2OCOAr), 80.3 (*C*HCH=CH_2), 78.0 (*C*HOAr), 65.4 (*C*H_2OAr), 38.7 (*C*H_2CHOAr); **IR** (ν_{max}/cm^{-1}): 2361, 1723, 1608, 1526, 1349, 1270, 1103; **LRMS** (ESI^+, *m/z*): 465 (M+Na^+, 100%); **HRMS** (ESI^+, *m/z*): Calculated 465.0905 ($C_{21}H_{18}N_2NaO_9$), Found 465.0888 (Δ +3.6 ppm); **m.p.** 69-73 ^{o}C; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +22.3 (c = 1.0, CH_2Cl_2).

(2*S*,3*S*,5*R*)-2-(Hydroxymethyl)-5-vinyltetrahydrofuran-3-ol, 348



344 **348**

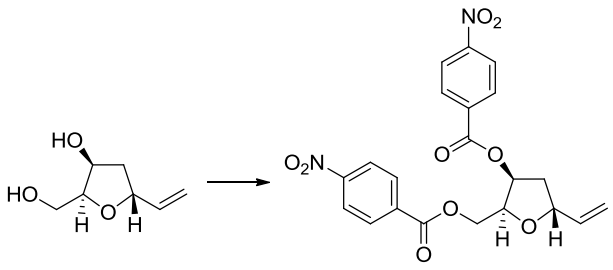
Dichloromethane (2.00 mL) was added to a flame dried schleck tube with 4 Å molecular sieves (50% weight, 10 mg) at room temperature. Titanium(IV) *tert*-butoxide (10 μL, 0.03

mmol) was then added and the mixture cooled to −30 °C. (+)-Diisopropyl L-tartrate (0.08 mL, 0.374 mmol) was added dropwise and the mixture was stirred for 30 minutes. A solution of diol **344** (40 mg, 0.31 mmol) in dichloromethane (1 mL) was added dropwise and stirred for a further 30 minutes. A solution of *tert*-butyl hydrogen peroxide (5.5 M in hexanes, 0.06 mL, 0.33 mmol) was added dropwise and the reaction was warmed to −20 °C and stirred for 5 days. Pyridinium *para*-toulenesulfonate (22 mg, 0.088 mmol) was added and the reaction was stirred for a further 1.5 hours. The reaction was poured into a stirred solution of iron (II) sulfate heptahydrate (30 mg) in water (3 ml) for 30 minutes at 0 °C before the layers were separated. The aqueous layer was extracted with ethyl acetate (5 × 5 mL) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (Ethyl acetate) yielded the title compound **348** as colourless oil (19 mg, 44%).

The spectroscopic data was identical to **346**.

$[\alpha]_D^{25}$ −2.7 (c = 1.0, CH_2Cl_2).

((2*S*,3*S*,5*R*)-3-((4-Nitrobenzoyl)oxy)-5-vinyltetrahydrofuran-2-yl)methyl 4-nitrobenzoate, 423



348 **423**

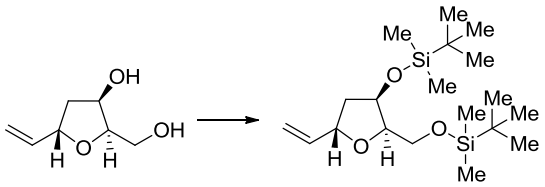
4-Nitrobenzoyl chloride (16.0 mg, 0.09 mmol) was added to a stirred solution of diol **348** (6.0 mg, 0.04 mmol) and pyridine (7.0 µl, 0.09 mmol) in dichloromethane (0.40 mL) at 0 °C and

then warmed to room temperature. After 16 hours the reaction was quenched with a saturated aqueous solution of sodium hydrogencarbonate (0.04 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 0.04 mL) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (4:1 petrol:ethyl acetate) yielded the title compound **423** as colourless oil (57.0 mg, 69%).

The spectroscopic data was identical to **411**.

$[\alpha]_D^{25}$ −20.7 (c = 1.0, CH_2Cl_2).

tert-Butyl(((2*R*,3*R*,5*S*)-3-((_tert_-Butyldimethylsilyl)oxy)-5-vinyltetrahydrofuran-2-yl)methoxy)dimethylsilane, 504

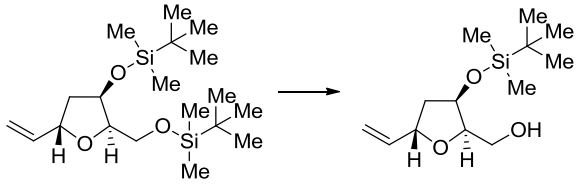


346 **504**

tert-Butyldimethylsilyl chloride (209 mg, 1.39 mmol) was added to a stirred solution of THF **346** (90.0 mg, 0.63 mmol), imidazole (95.0 mg, 1.39 mmol) and 4-dimethylaminopyridine (7.0 mg, 0.06 mmol) in dichloromethane (6.00 mL) at 0 °C and the reaction mixture was warmed to room temperature. After stirring for 2 hours the reaction was quenched with saturated aqueous ammonium chloride solution (6.00 mL) and the layers separated. The aqueous layer was extracted with dichloromethane (3 × 6.00 mL), the combined organic layers dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (7:3 petrol:dichloromethane) yielded the title compound **504** as colourless oil (195 mg, 83%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 5.74 (1 H, ddd, *J* = 17.2, 10.2, 7.1 Hz, C*H*=CH_2), 5.29-5.15 (1 H, m, CH=C*H*$_A$H$_B$), 5.03 (1 H, d, *J* = 10.5 Hz, CH=CH$_A$*H*$_B$), 4.56-4.39 (1 H, m, C*H*CH=C*H*$_2$), 4.25 (1 H, d, *J* = 5.1 Hz, C*H*OSi), 3.77 (1 H, ddd, *J* = 6.2, 4.1, 1.7 Hz, C*H*CH$_2$OSi), 3.59 (1 H, dd, *J* = 10.6, 4.0 Hz, C*H*$_A$H$_B$OSi), 3.36 (1 H, dd, *J* = 10.6, 6.5, CH$_A$*H*$_B$OSi), 1.82 (1 H, ddd, *J* = 12.6, 5.3, 1.5 Hz, C*H*$_A$H$_B$CHOSi), 1.64 (1 H, ddd, *J* = 12.6, 10.3, 5.3 Hz, CH$_A$*H*$_B$CHOSi), 0.90-0.75 (18 H, m, 2 × SiC(C*H*$_3$)$_3$), 0.06-−0.06 (12 H, m, 2 × Si(C*H*$_3$)$_2$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 138.7 (*C*H=CH_2), 116.1 (CH=*C*H$_2$), 87.8 (*C*HCH$_2$OSi), 79.6 (*C*HCH=CH_2), 74.3 (*C*HOSi), 63.9 (*C*H$_2$OSi), 41.6 (*C*H$_2$CHOSi), 25.9 (SiC(*C*H$_3$)$_3$), 25.8 (SiC(*C*H$_3$)$_3$), 18.4 (Si*C*(CH$_3$)$_3$), 18.0 (Si*C*(CH$_3$)$_3$), −5.3 (Si(*C*H$_3$)$_2$, −5.4 (Si(*C*H$_3$)$_2$); **IR** (ν_{max}/cm^{-1}): 2361, 2341, 2031; **LRMS** (ESI$^+$, *m/z*): 281 ([M + Na]$^+$, 100%); **HRMS** (ESI$^+$, *m/z*): Calculated 281.1543 ($C_{13}H_{26}O_3NaSi_2$), Found 281.1538 (Δ +1.8 ppm); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ −63.0 (c = 1.0, CH_2Cl_2).

((2*R*,3*R*,5*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-5-vinyltetrahydrofuran-2-yl)methanol, 505



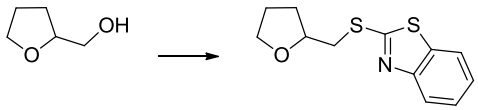
504 **505**

Aqueous trifluoroacetic acid (0.76 mL, TFA-H_2O 1:1) was added to a solution of alkene **504** (50.0 mg, 0.13 mmol) in tetrahydrofuran (1.52 mL) at 0 °C. After 1 hour the reaction was neutralised with a saturated aqueous solution of sodium hydrogen carbonate (2.00 mL), diluted with ethyl acetate (30.0 mL) and the layers separated. The organic phase was washed sequentially with water (4.00 mL), then brine (4.00 mL) and dried over magnesium sulfate,

filtered and concentrated *in vacuo*. Flash column chromatography (4:1 petrol:ethyl acetate) yielded the title compound **505** as colourless oil (30.0 mg, 89%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 5.83-5.66 (1 H, m, C*H*=CH_2), 5.27-5.16 (1 H, m, CH=CH_AH_B), 5.06 (1 H, d, *J* = 10.3 Hz, CH=CH_AH_B), 4.57-4.44 (1 H, m, C*H*CH=CH_2), 4.33-4.24 (1 H, m, C*H*OSi), 3.77 (1 H, dt, *J* = 6.6, 3.3 Hz, C*H*CH_2OH), 3.74-3.67 (1 H, m, CH_AH_BOH),), 3.45 (1 H, dd, *J* = 10.3, 6.6 Hz, CH_AH_BOH), 2.01-1.89 (1 H, m, CH_AH_BCHOSi), 1.81 (1 H, ddd, *J* = 13.0, 9.5, 6.1 Hz, CH_AH_BCHOSi), −0.03 (6 H, s, Si(CH_3)$_2$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 138.9 (*C*H=CH_2), 116.3 (CH=*C*H_2), 86.8 (*C*HCH_2OH), 79.5, 74.8, 64.3, 40.9 (*C*H_2CHOSi), 25.9 (SiC(*C*H_3)$_3$), 17.9 (Si*C*$(CH_3)_3$), −5.4 (Si*C*H_3); **IR** (ν_{max}/cm^{-1}): 3434, 2930, 1255, 1046; **LRMS** (ESI$^+$, *m/z*): 281 ([M + Na]$^+$, 100%); **HRMS** (ESI$^+$, *m/z*): Calculated 281.1543 ($C_{13}H_{26}O_3NaSi_2$), Found 281.1541 (Δ +0.7 ppm); $[\alpha]_D^{25}$ +3.2 (c = 1.0, CH_2Cl_2).

2-(((Tetrahydrofuran-2-yl)methyl)thio)benzo[d]thiazole, 509



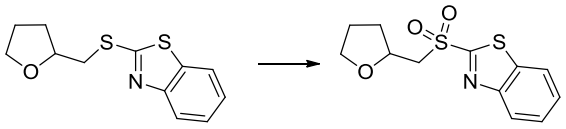
508 **509**

Diisorpropyl azodicarboxylate (3.23 mL, 15.5 mmol) was added dropwise to a solution of tetrahydrofurfuryl alcohol **508** (0.75 mL, 7.75 mmol) and triphenylphosphine (4.06 g, 15.5 mmol) in tetrahydrofuran (150 mL) at 0 °C. The reaction mixture was stirred for 3.5 hours at room temperature and concentrated *in vacuo*. Flash column chromatography (9:1 petrol:ethyl acetate) yielded the title compound **509** as colourless oil (1.88 g, 96%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.86 (1 H, d, *J* = 8.1 Hz, Ar*H*), 7.74 (1 H, d, *J* = 7.8 Hz, Ar*H*), 7.40 (1 H, t, *J* = 7.7 Hz, Ar*H*), 7.34-7.22 (1 H, m, Ar*H*), 4.28 (1 H, quin, *J* = 6.4 Hz,

C*H*CH_2S), 3.96-3.93 (1 H, m, C$H_A$$H_B$O), 3.87-3.73 (1 H, m, C$H_A$$H_B$O), 3.64-3.50 (2 H, 2 × dd, *J* = 13.2, 5.9 Hz, CH_2S), 2.20-2.07 (1 H, m, C$H_A$$H_B$CH), 2.06-1.85 (2 H, m, C$H_2$$CH_2$CH), 1.81-1.66 (1 H, m, C$H_A$$H_B$CH); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 166.9 (quat. Ar*C*), 153.1 (quat. Ar*C*), 135.3 (quat. Ar*C*), 126.0 (Ar*C*), 124.2 (Ar*C*), 121.4 (Ar*C*), 121.0 (Ar*C*), 77.3 (*C*HCH_2S), 68.5 (*C*H_2O), 38.1 (*C*H_2S), 30.8 (*C*H_2CH), 25.9 (*C*$H_2$$CH_2$CH); **IR** ($\nu_{max}$/$cm^{-1}$): 1630, 1514, 1463, 1426, 1241; **LRMS** (ESI^+, *m/z*): 274 ($[M + Na]^+$, 100%); **HRMS** (ESI^+, *m/z*): Calculated 274.0331 ($C_{12}H_{13}NNaOS_2$), Found 274.0335 (Δ−1.4 ppm).

2-(((Tetrahydrofuran-2-yl)methyl)sulfonyl)benzo[d]thiazole, 510



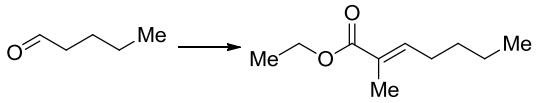
509 **510**

Ammonium molybdate (49.2 mg, 0.0398 mmol) was added to hydrogen peroxide (30 wt% in H_2O, 162 μL, 1.60 mmol) at 0 °C to give a bright yellow solution. In a separate flask, compound **509** (100 mg, 0.40 mmol) was dissolved in ethanol (2.40 mL), cooled to 0 °C and the molybdate solution was then added *via* stirred for 16 hours at room temperature. The reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate (2.00 mL) and the aqueous layer extracted with diethyl ether (3 × 4.00 mL). The combined organic layers were washed with brine (12.0 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (7:3 petrol:ethyl acetate) yielded the title compound **510** as colourless oil (101 mg, 89%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 8.22 (1 H, d, *J* = 8.1 Hz, Ar*H*), 8.02 (1 H, d, *J* = 7.8 Hz, Ar*H*), 7.72-7.54 (2 H, m, Ar*H*), 4.58-4.41 (1 H, m, C*H*CH_2S), 3.88 (1 H, dd, *J* = 14.5, 7.2 Hz, C$H_A$$H_B$S), 3.79-3.56 (3 H, m, C$H_2$O and C$H_A$$H_B$S), 2.20 (1 H, dd, *J* = 13.1, 5.8 Hz, CH_2CH_A-H_B), 2.00-1.83 (2 H, m, C$H_2$$CH_2$), 1.75 (1 H, dd, *J* = 12.3, 8.5 Hz, $CH_2$$CH_A$$H_B$); **^{13}C NMR**

δ_C (100 MHz, $CDCl_3$): 166.5 (quat. Ar*C*), 152.6 (quat. Ar*C*), 136.8 (quat. Ar*C*), 127.9 (Ar*C*), 127.6 (Ar*C*), 125.4 (Ar*C*), 122.4 (Ar*C*), 73.6 (*C*HCH_2S), 68.2 (*C*H_2O), 59.4 (*C*H_2S), 31.5 (*C*H_2CH), 25.3 (*C*$H_2$$CH_2$CH); **IR** ($\nu_{max}$/$cm^{-1}$): 2970, 2870, 1472, 1314, 1142, 1049, 946, 763; **LRMS** (ESI^+, *m/z*): 306 ($[M + Na]^+$, 100%); **HRMS** (ESI^+, *m/z*): Calculated 306.0229 ($C_{12}H_{13}NNaO_3S_2$), Found 306.0238 (Δ −2.9 ppm).

(*E*)-Ethyl 2-methylhept-2-enoate, 498



495 **498**

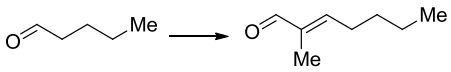
Ethyl 2-(diethoxyphosphoryl)propanoate (5.11 g, 11.6 mmol) was added to a solution of sodium hydride (462 mg, 11.6 mmol, 60% dispersion in mineral oil) in tetrahydrofuran (132 mL) at 0 °C then warmed to room temperature. After 1.5 hours, a solution of valeraldehyde **495** (1.00 g, 11.6 mmol) in tetrahydrofuran (50.0 mL) was then added dropwise to the reaction mixture and stirred for 5 hours. Water (50.0 mL) and diethyl ether (50.0 mL) was added and the mixture was extracted with diethyl ether (3 × 50.0 mL). The organic layers were combined, washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (2:1 Hexane-toluene) yielded the title compound **498** as colourless oil (1.34 g, 68%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 6.75 (1 H, t, *J* = 7.1 Hz, C(CH_3)=C*H*), 4.17 (2 H, q, *J* = 7.1 Hz, CO_2C*H*$_2CH_3$), 2.16 (2 H, q, *J* = 7.2 Hz, CO_2C*H*CH_3), 1.81 (3 H, s, C(C*H*$_3$)=CH), 1.47 (7 H, m, CO_2CH_2C*H*$_3$ and C*H*$_2C$*H*$_2CH_3$), 0.89 (3 H, t, *J* = 7.0 Hz, CH_2CH_2C*H*$_3$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 168.3 (*C*=O), 142.4 (C(CH_3)=*C*H), 127.6 (*C*(CH_3)=CH), 60.3

($CO_2CH_2CH_3$), 30.7 ($C(CH_3)=CHCH_2CH_2$), 28.3 ($C(CH_3)=CH$), 22.4 ($CH_2CH_2CH_3$), 14.3 ($CH_2CH_2CH_3$), 14.0 ($CO_2CH_2CH_3$), 12.3 ($CH_2CH_2CH_3$).

The spectral data were consistent with those in the literature.[120]

(*E*)-2-Methylhept-2-enal, 496



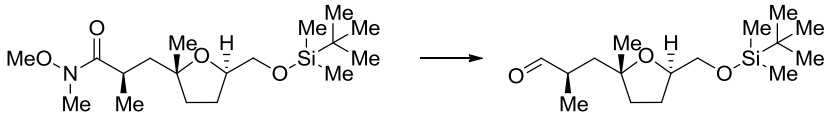
495 **496**

2-(triphenylphosphoranylidene)propanal (1.22 g, 3.83 mmol) was added to a solution of valeraldehyde **495** (0.12 mL, 3.48 mmol) in toluene (35.0 mL) at room temperature and the reaction mixture was heated to 110 °C . After 16 hours the reaction was cooled to room temperature and concentrated *in vacuo.* Flash column chromatography (9:1 petrol:ethyl acetate) yielded the title compound **496** as a colourless oil (285 mg, 59%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 9.43 (1 H, s, C*H*O), 6.43 (1 H, t, *J* = 7.5 Hz, C*H*=C(CH_3)), 2.29 (2 H, q, *J* = 7.3 Hz, CH_2CH=C(CH_3)), 1.68 (3 H, s, CH=C(CH_3)), 1.48-1.36 (4 H, m, CH_2C$H_2$$CH_3$), 0.87 (3 H, t, *J* = 7.3 Hz, $CH_2CH_2CH_3$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 195.4 (*C*=O), 155.0 (*C*H=C(CH_3)), 139.3 (CH=*C*(CH_3)), 30.5 (*C*H_2CH=C(CH_3)), 28.7 (CH=C(CH_3)), 22.4 (*C*$H_2CH_2CH_3$), 13.9 (CH_2*C*H_2CH_3), 9.1 (CH_2CH_2*C*H_3).

The spectral data were consistent with those in the literature. [119]

(*R*)-3-((2*R*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-methyltetrahydrofuran-2-yl)-2-methylpropanal, 489

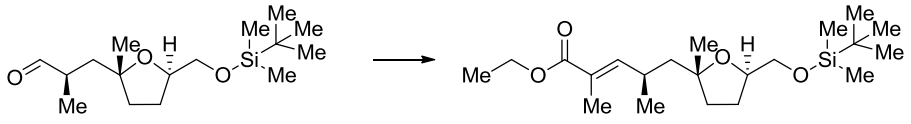


488 **489**

A solution of diisobutylaluminium hydride (1.80 mL, 1.80 mmol, 1.0 M in heptane) was added to a stirred solution of weinreb amide **488**[118] (300 mg, 0.90 mmol) in tetrahydrofuran (18.0 mL) at −78 °C. The resulting solution was stirred at −78 °C for 3 hours before being quenched with ethyl acetate (18.0 mL) and warmed to room temperature. A saturated aqueous solution of potassium sodium tartrate (18.0 mL) was added, the layers were separated and the aqueous layer extracted with ethyl acetate (3 × 18.0 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (9:1 petrol:ethyl acetate) yielded the title compound **489** as colourless oil (216 mg, 80%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 9.41 (1 H, d, *J* = 4.2 Hz, C*H*O), 3.91-3.70 (1 H, m, C*H*CH_2OSi), 3.55 (2 H, dd, *J* = 4.5, 4.3, Hz, C*H*$_2$OSi), 2.57-2.29 (1 H, m, C*H*(CH_3)), 2.09 (2 H, dd, *J* = 14.5, 9.5 Hz, C*H*$_A$H$_B$CH(CH_3)), 1.96-1.75 (4 H, m, C*H*$_2$C*H*$_2$C(CH_3)), 1.56 (1 H, dd, *J* = 14.6, 3.8 Hz, CH$_A$*H*$_B$CH(CH_3)), 1.21 (3 H, s, CC*H*$_3$), 1.10 (3 H, d, *J* = 7.1 Hz, CH(C*H*$_3$)), 0.89 (9 H, s, SiC(C*H*$_3$)$_3$), 0.05 (6 H, s, Si(C*H*$_3$)$_2$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 204.0 (*C*=O), 82.6 (*C*(CH_3)), 79.6 (*C*HCH_2OSi), 65.6 (*C*H$_2$OSi), 43.2 (*C*H$_2$CH(CH_3)), 42.7 (*C*H(CH_3), 36.1 (*C*H$_2$CH$_2$C(CH_3)), 28.4 (C(*C*H$_3$)), 28.0 (CH$_2$*C*H$_2$C(CH_3)), 26.0 (SiC(*C*H$_3$)$_3$), 18.4 (Si*C*(CH_3)$_3$), 15.4 (CH*C*H$_3$), −5.3 (Si*C*H$_3$), −5.4 (Si*C*H$_3$); **IR** (ν_{max}/cm^{-1}): 2958, 2935, 2853, 1725, 1462, 1375; **LRMS** (ESI$^+$, *m/z*): 323 ([M + Na]$^+$, 100%); **HRMS** (ESI$^+$, *m/z*): 323.2013 ($C_{16}H_{32}NaO_3Si$), Found 323.2006 (Δ +2.2 ppm); $[\alpha]_D^{25}$ +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, 490



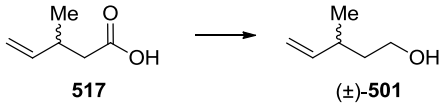
489 **490**

(1-(Ethoxycarbonyl)ethyl)triphenylphosphonium bromide (922 mg, 2.08 mmol) was added to a stirred solution of sodium hydride (30.0 mg, 2.08 mmol, 60% in mineral oil) in tetrahydrofuran (15.0 mL) at 0 °C. After 10 minutes a solution of aldehyde **489** (520 mg, 1.73 mmol) in tetrahydrofuran (6.00 mL) was added dropwise and heated to reflux. After 16 hours the reaction was quenched with a saturated aqueous solution of ammonium chloride (21.0 mL), diluted with ethyl acetate (21.0 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 21.0 mL) and the combined organic layers dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (19:1 petrol:ethyl acetate) yielded the title compound **490** as colourless oil (799 mg, 71%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 6.62 (1 H, dd, *J* = 9.8, 1.2 Hz, C=C*H*), 4.20 (2 H, q, *J* = 7.2 Hz, CH_3CH_2O), 3.98-3.88 (2 H, m, OC*H* and CH_AH_BOSi), 3.62 (1 H, dd, *J* = 10.4, 5.5 Hz, CH_AH_BOSi), 2.74-2.60 (1 H, m, C*H*CH_3), 1.90-1.75 (5 H, m, C=C(CH_3)CO_2 and THF-CH_2), 1.73-1.55 (4 H, m, THF-CH_2 and $CH(CH_3)CH_2$), 1.28 (3 H, t, *J* = 7.2 Hz, CH_3CH_2O), 1.16 (3 H, s, CCH_3), 1.06 (3 H, d, *J* = 7.2 Hz, $CH(CH_3)$), 0.89 (9 H, s, $SiC(CH_3)_3$), 0.05 (6 H, s, $Si(CH_3)_2$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 168.5 (*C*=O), 149.1 (C=C*H*), 124.2 (*C*=CH), 82.9 ($C(CH_3)$), 79.6 (*C*HCH_2OSi), 66.1 (*C*H_2OSi), 60.6 ($CO_2CH_2CH_3$), 48.1 (*C*HCH_3) , 37.5 ($CH_2CH_2C(CH_3)$), 30.1 (*C*$H_2CH(CH_3)$), 28.4 ($C(CH_3)$=CH), 26.9 ($CH_2CH_2C(CH_3)$, 26.0 ($SiC(CH_3)_3$), 21.5 ($C(CH_3)$), 18.5 ($SiC(CH_3)_3$), 14.3 ($CHCH_3$), 12.3 ($CO_2CH_2CH_3$), −5.3

(Si*C*H$_3$), −5.4 (Si*C*H$_3$); **IR** (ν_{max}/cm^{-1}): 2959, 2930, 2856, 1710, 1466, 1366, 1252; **LRMS** (ESI$^+$, *m/z*): 407 ([M + Na]$^+$, 100%); **HRMS** (ESI$^+$, *m/z*): 407.2588 ($C_{21}H_{40}NaO_4Si$), Found 407.22692 (Δ +1.2 ppm); $[\alpha]_D^{25}$ −9.8 (c = 1.0, CH_2Cl_2).

(*R*)-3-Methylpent-4-en-1-ol, (±)-501



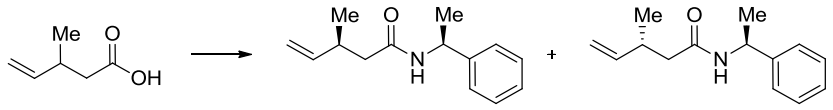
517 (±)-**501**

A solution of 3-methyl-4-pentenoic acid **517** (1.00 g, 8.77 mmol) in diethyl ether (4.00 mL) was added dropwise to a suspension of lithium aluminium hydride (4.00 g, 11.4 mmol) in diethyl ether (12.0 mL) at 0 °C. After 15 minutes the reaction mixture was warmed to room temperature and stirred for 2 hours. The reaction was then cooled to 0 °C and cautiously quenched by the addition of water (10.0 mL) and concentrated hydrochloric acid (2.00 mL) until the aqueous layer was pH 3. The two layers were separated and the aqueous layer extracted with diethyl ether (3 × 10.0 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (9:1 petrol:diethyl ether) yielded the title compound (±)-**501** as a colourless oil (509 mg, 58%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 5.71 (1 H, ddd, *J* = 17.4, 9.9, 8.1 Hz, C*H*=CH$_2$), 5.14-4.84 (2 H, m, CH=C*H*$_2$), 3.65 (2 H, t, *J* = 6.4 Hz, C*H*$_2$OH), 2.30 (1 H, dt, *J* = 14.1, 7.0 Hz, C*H*CH$_3$), 1.64-1.46 (2 H, m, C*H*$_2$CH$_2$OH), 1.02 (3 H, d, *J* = 6.8 Hz, CHC*H*$_3$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 144.2 (*C*H=CH$_2$), 113.1 (CH=*C*H$_2$), 61.1 (*C*H$_2$OH), 39.3 (*C*HCH$_3$), 34.8 (*C*H$_2$CH$_2$OH), 20.4 (CH*C*H$_3$).

The spectral data were consistent with those in the literature.[143]

(*S*)-3-Methyl-*N*-((*S*)-1-phenylethyl)pent-4-enamide, 518 and (*R*)-3-Methyl-*N*-((*S*)-1-phenylethyl)pent-4-enamide, 519



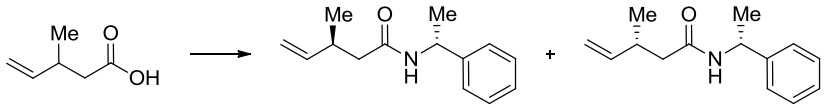
517 **518** **519**

N,*N'*-Dicyclohexylcarbodiimide (497 mg, 2.41 mmol) was added to a stirred solution of 3-methyl-4-pentenoic acid **517** (250 mg, 2.19 mmol), (*S*)-(-)-*alpha*-methylbenzylamine (0.28 mL, 2.41 mmol) and *N*,*N*-dimethylpyridin-4-amine (27.0 mg, 0.22 mmol) in dichloromethane (22.0 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 hours. The reaction was quenched with a saturated aqueous solution of ammonium chloride (22.0 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 22.0 mL), combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (4:1 petrol:ethyl acetate) yielded the title compounds **518** and **519** as a colourless oil and as an inseparable 1:1 mixture of diastereoisomers (456 mg, 96%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.35-7.10 (10 H, m, Ar*H*), 5.69 (2 H, ddt, *J* = 17.0, 10.4, 6.6 Hz, 2 × C*H*CH_2), 5.07 (2 H, quin, *J* = 7.2 Hz, 2 × NC*H*Ph), 5.00-4.82 (4 H, m, 2 × CH=CH_2), 2.66-2.57 (2 H, m, 2 × C*H*CH=CH_2), 2.22-1.96 (4 H, m, 2 × CH_2C=O), 1.41 (6 H, 2 × d, *J* = 6.9 Hz, 2 × NHCHCH_3), 0.97 (6 H, 2 × d, *J* = 6.7 Hz, 2 × CH_2CHCH_3); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 170.8 (C=O), 143.2 (2 × quat. Ar*C*), 142.8 (*C*H=CH_2), 128.7 (Ar*C*), 128.6 (Ar*C*), 127.4 (Ar*C*), 126.3 (Ar*C*), 126.2 (Ar*C*), 113.6 (CH=*C*H_2), 48.7 (NH*C*HCH$_3$), 48.6 (NH*C*HCH$_3$), 43.9 (2 × *C*H_2C=O), 35.0 (*C*HCH=CH_2), 34.9 (*C*HCH=CH_2), 21.7 (NHCH*C*H$_3$), 19.7 (CH_2CH*C*H$_3$); **IR** (ν_{max}/cm^{-1}): 3281, 2971, 1636, 1542, 1495, 1451, 1375,

1211, 1135, 995, 913; **LRMS** (ESI^+, *m/z*): 240 ([M + Na]$^+$, 100%); **HRMS** (ESI^+, *m/z*): Calculated 240.1359 ($C_{14}H_{19}ONa$), Found 240.1359 (Δ −0.1 ppm); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +12.2 (c = 1.0, CH_2Cl_2).

(*S*)-3-Methyl-*N*-((*R*)-1-phenylethyl)pent-4-enamide, 521 and (*R*)-3-Methyl-*N*-((*R*)-1-phenylethyl)pent-4-enamide, 522



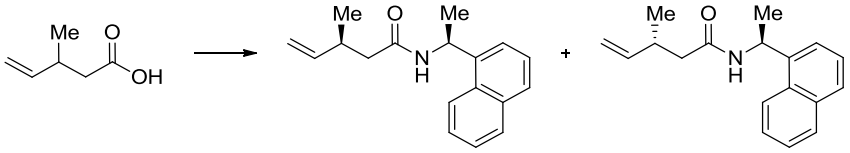
517 **521** **522**

N,*N'*-Dicyclohexylcarbodiimide (497 mg, 2.41 mmol) was added to a stirred solution of 3-methyl-4-pentenoic acid (250 mg, 2.19 mmol), (*R*)-(+)-*alpha*-methylbenzylamine (0.28 mL, 2.41 mmol) and *N*,*N*-dimethylpyridin-4-amine (27.0 mg, 122 mmol) in dichloromethane (22.0 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 hours. The reaction was quenched with a saturated aqueous solution of ammonium chloride (22.0 mL) and the layers were separated. The aqueous layer was then extracted with dichloromethane (3 × 22.0 mL) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (4:1 petrol:ethyl acetate) yielded the title compounds **521** and **522** as a colourless oil and as an inseparable 1:1 mixture of diastereoisomers (394 mg, 83%).

The spectroscopic data was identical to 1:1 mixture of **519**:**520**.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +4.9 (c = 1.0, CH_2Cl_2).

(*R*)-3-Methyl-*N*-((*S*)-1-(naphthalen-1-yl)ethyl)pent-4-enamide, 523 and (*S*)-3-Methyl-*N*-((*S*)-1-(naphthalen-1-yl)ethyl)pent-4-enamide, 524



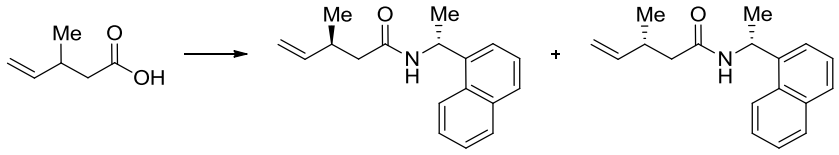
517 **523** **524**

N,*N'*-Dicyclohexylcarbodiimide (497 mg, 2.41 mmol) was added to a stirred solution of 3-methyl-4-pentenoic acid **517** (250 mg, 2.19 mmol), (*S*)-(+)-1-(1-naphthyl)ethylamine (412 mg, 2.41 mmol) and *N*,*N*-dimethylpyridin-4-amine (27.0 mg, 122 mmol) in dichloromethane (22.0 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 hours. The reaction was quenched with a saturated aqueous solution of ammonium chloride (22.0 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 22.0 mL) and the combined organic layers dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (9:1 petrol:ethyl acetate) yielded the title compounds **523** and **524** as a colourless oil and as an inseparable 1:1 mixture of diastereoisomers (369 mg, 63%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 8.16 (2 H, d, *J* = 8.3 Hz, 2 × Ar*H*), 7.92 (2 H, d, *J* = 7.8 Hz, 2 × Ar*H*), 7.81 (2 H, d, *J* = 8.1 Hz, 2 × Ar*H*), 7.64-7.51 (4 H, m, 2 × Ar*H*), 7.50-7.39 (2 H, m, 2 × Ar*H*), 5.81 (2 H, ddd, *J* = 17.2, 10.3, 7.0 Hz, 2 × C*H*=CH_2), 5.09-5.05 (2 H, m, 2 × CH=C$H_A$$H_B$), 5.05-4.95 (2 H, m, 2 × CH=$CH_A$$H_B$), 2.74-2.69 (2 H, m, 2 × C*H*(CH_3)CH_2), 2.47-2.26 (4 H, m, 2 × CH(CH_3)CH_2), 1.09 (6 H, d, *J* = 6.6 Hz, 2 × NHCH(CH_3)); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 172.5 (2 × *C*=O), 142.8 (*C*H=CH_2), 142.7 (*C*H=CH_2), 138.1 (quat. Ar*C*), 133.9 (quat. Ar*C*), 131.2 (quat. Ar*C*), 128.7 (Ar*C*), 128.4 (Ar*C*), 126.6 (Ar*C*), 125.9 (Ar*C*), 125.1 (Ar*C*), 123.7 (Ar*C*), 123.6 (Ar*C*), 113.6 (CH=*C*H_2), 44.5 (2 × N*C*HCH_3), 43.9 (2 × *C*H_2CON), 34.9 (2 × C*H*CH=CH_2), 20.6 (2 × NCH(*C*H_3)), 19.7 (2 × CH(*C*H_3)CH=CH_2);

IR (ν_{max}/cm^{-1}): 3283, 2970, 1632, 1534, 1451, 1372, 1207, 996; **LRMS** (ESI$^+$, *m/z*): 268 ([M + H]$^+$, 100%); **HRMS** (ESI$^+$, *m/z*): Calculated 290.1515 ($C_{18}H_{21}NNaO$), Found 290.1515 (Δ−0.0 ppm); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +27.1 (c = 1.0, CH_2Cl_2).

(*R*)-3-Methyl-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)pent-4-enamide, 525 and (*S*)-3-Methyl-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)pent-4-enamide, 526



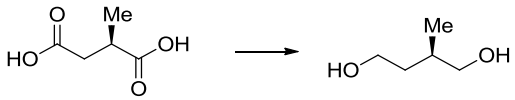
517 **525** **526**

N,*N*'-Dicyclohexylcarbodiimide (497 mg, 2.41 mmol) was added to a stirred solution of 3-methyl-4-pentenoic acid **517** (250 mg, 2.19 mmol), (*R*)-(+)-1-(1-naphthyl)ethylamine (412 mg, 2.41 mmol) and *N*,*N*-dimethylpyridin-4-amine (27.0 mg, 122 mmol) in dichloromethane (22 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 hours. The reaction was quenched with a saturated aqueous solution of ammonium chloride (22.0 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 22.0 mL), combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (9:1 petrol:ethyl acetate) yielded the title compounds **525** and **526** as a colourless oil and as an inseparable 1:1 mixture of diastereoisomers (369 mg, 63%).

The spectroscopic data was identical to 1:1 mixture of **523**:**524**.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ −1.5 (c = 1.0, CH_2Cl_2).

(*R*)-2-Methylbutane-1,4-diol, 530



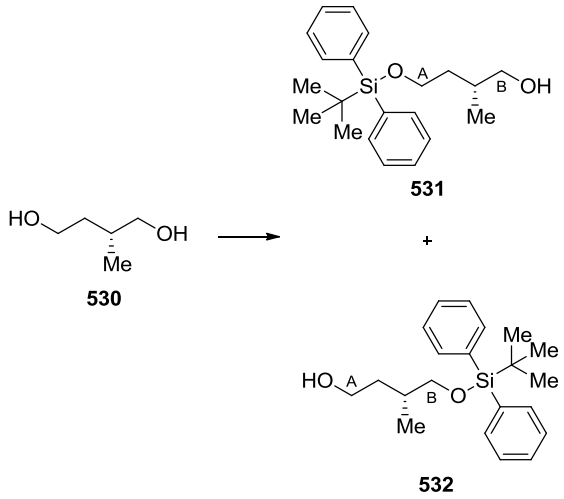
529 **530**

A solution of (*R*)-2-methylsuccinic acid **529** (1.00 g, 7.58 mmol) in diethyl ether (4.00 mL) was added dropwise to a suspension of lithium aluminium hydride (4.00 g, 11.4 mmol) in diethyl ether (12.0 mL) at 0 °C. After 15 minutes the reaction mixture was warmed to room temperature and stirred for 2 hours. The reaction was then cooled to 0 °C and cautiously quenched with water (10.0 mL) and concentrated hydrochloric acid (2.00 mL) until the aqueous layer was pH 3 and the two layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 10.0 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (7:3 petrol:ethyl acetate) yielded the title compound **530** as a colourless oil (418 mg, 53%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 3.73 (1 H, dt, *J* = 10.8, 5.5 Hz, $CH_2CH_AH_BOH$), 3.67-3.57 (1 H, m, $CHCH_AH_BOH$), 3.52 (1 H, dd, *J* = 10.6, 4.5 Hz, $CHCH_AH_BOH$), 3.39 (1 H, dd, *J* = 10.6, 7.2 Hz, $CHCH_AH_BOH$), 2.28 (2 H, br.s, 2 × OH), 1.84-1.68 (1 H, m, $CHCH_3$), 1.64-1.42 (2 H, m, CH_2CH_2OH), 0.88 (3 H, d, *J* = 6.9 Hz, $CHCH_3$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 68.3 (CH_2OH), 61.2 (CH_2OH), 37.5 (CH_2CH_2OH), 34.1 ($CHCH_3$), 17.3 ($CHCH_3$); $[\alpha]_D^{25}$ −27.9 (c = 1, CH_2Cl_2).

The spectral data were consistent with those in the literature.[126]

(*R*)-4-((*tert*-Butyldiphenylsilyl)oxy)-2-methylbutan-1-ol, 531 and (*R*)-4-((*tert*-Butyldiphenylsilyl)oxy)-3-methylbutan-1-ol, 532



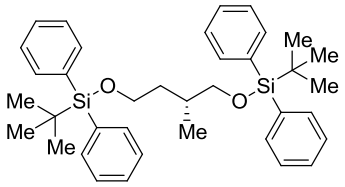
tert-Butyl(chloro)diphenylsilane (164.0 mg, 1.58 mmol) was added to a stirred solution of diol **530** (150 mg, 1.44 mmol), imidazole (107 mg, 1.58 mmol) and 4-dimethylaminopyridine (17.0 mg, 0.14 mmol) in dichloromethane (14.0 mL) at 0 °C. After stirring for 16 hours at room temperature, the reaction was quenched with saturated aqueous solution of ammonium chloride (14.0 mL) at 0 °C and the layers separated. The aqueous layer was extracted with dichloromethane (3 × 14.0 mL) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (9:1 petrol:dichloromethane) yielded an inseparable unknown mixture of the title compounds **531** and **532** as colourless oil (310 mg, 63%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): Major isomer: 7.60 (8 H, 2 × d, *J* = 7.8 Hz, Ar*H*), 7.42-7.21(12 H, m, Ar*H*), 3.76-3.55 (4 H, m, 2 × C_AH_2O), 3.51-3.31 (4 H, m, 2 × C_BH_2O), 1.85-1.70 (2 H, m, 2 × C*H*CH_3), 1.63-1.49 (2 H, m, 2 × CH_AH_BCHCH_3), 1.48-1.34 (2 H, m, 2 × CH_AH_BCHCH_3), 0.98 (18 H, s, 2 × SiC(CH_3)$_3$), 0.82 (6 H, d, *J* = 6.9, 2 × CH_3); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 135.6 (quat. Ar*C*), 133.5 (quat. Ar*C*), 129.8 (Ar*C*), 127.7 (Ar*C*), 68.3

(*C*H_2OSi), 62.5 (*C*H_2OSi), 36.8 (*C*H_2CH_2OH), 33.9 (*C*HCH$_3$) , 26.8 (SiC(*C*H$_3$)), 19.1 (Si*C*(CH$_3$)$_3$), 17.2 (CH*C*H$_3$); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +6.3 (c = 1.0, CH_2Cl_2).

The spectral data were consistent with those in the literature.[126]

(*R*)-2,2,6,11,11-Pentamethyl-3,3,10,10-tetraphenyl-4,9-dioxa-3,10-disiladodecane, 533

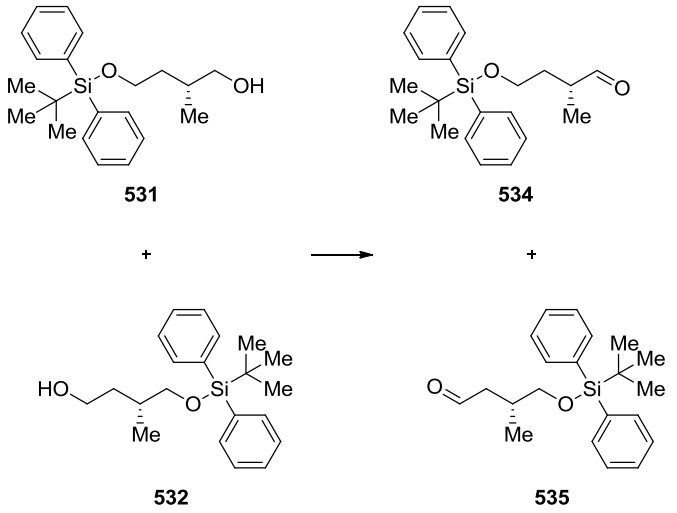


533

Compound **533** was isolated as a byproduct in the synthesis of alcohols **531** and **532**.

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.56 (8 H, dd, *J* = 6.2, 1.6 Hz, Ar*H*), 7.35-7.19 (12 H, m, Ar*H*), 3.61 (2 H, t, *J* = 6.5 Hz, CHC*H*$_2$OSi), 3.46-3.32 (2H, m, CH$_2$C*H*$_2$OSi), 1.85-1.76 (1 H, m, C*H*$_A$H$_B$CH$_2$OSi), 1.70 (1 H, dd, *J* = 13.1, 6.0 Hz, CH$_A$*H*$_B$CH$_2$OSi), 1.33-1.21 (1 H, m, C*H*CH$_3$), 0.95 (18 H, d, *J* = 2.7 Hz, 2 × SiC(C*H*$_3$)$_3$), 0.80 (3 H, d, *J* = 6.6 Hz, C*H*$_3$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 136.0 (4 × Ar*C*), 135.0 (4 × quat. Ar*C*), 129.7 (4 ×Ar*C*), 127.8 (4 × Ar*C*), 69.1 (CH(CH$_3$)*C*H$_2$OSi), 62.2 (CH$_2$*C*H$_2$OSi), 36.3 (*C*H$_2$CH$_2$OSi), 32.7 (*C*H(CH$_3$)), 27.1 (SiC(*C*H$_3$)$_3$), 27.1 (SiC(*C*H$_3$)$_3$), 19.4 (Si*C*(CH$_3$)$_3$), 19.3 (Si*C*(CH$_3$)$_3$), 16.9 (CH(*C*H$_3$)); **IR** (ν_{max}/cm^{-1}): 2858, 1472, 1428, 1265, 1110, 823; **LRMS** (ESI$^+$, *m/z*): 603 ([M + Na]$^+$, 100%); **HRMS** (ESI$^+$, *m/z*): Calculated 603.3091 ($C_{37}H_{48}NaO_2Si_2$), Found 603.3088 (Δ +2.3 ppm); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ −12.1 (c = 1.0, CH_2Cl_2).

(*R*)-4-((*tert*-Butyldiphenylsilyl)oxy)-2-methylbutanal, 534 and (*R*)-4-((*tert*-Butyldiphenylsilyl)oxy)-3-methylbutanal, 535



Dimethyl sulphoxide (0.06 mL, 0.87 mmol) was added dropwise to a stirred solution of oxally chloride (0.04 mL, 0.44 mmol) in dichloromethane (6.00 mL) at −78 °C. After 30 minutes, a solution of an unknown mixture of alcohols **531** and **532** (100 mg, 0.29 mmol) in dichloromethane (2.00 mL) was added dropwise to the reaction mixture. After a further 30 minutes, triethylamine (0.20 ml, 1.45 mmol) was added dropwise. The reaction mixture was stirred for an additional 30 minutes, warmed to 0 °C and quenched with a saturated aqueous ammonium chloride solution (10.0 mL). The layers were separated and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo* to yield a 6.5:1 mixture of the title compounds **534** and **535** as colourless oil

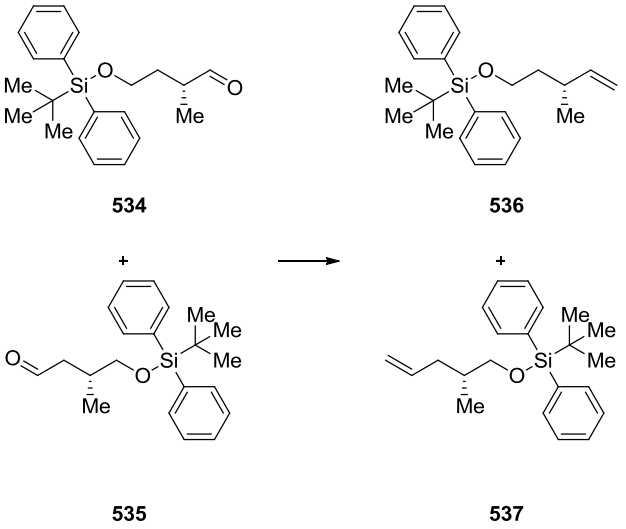
Major isomer **534***:*

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 9.60 (1 H, d, *J* = 1.5 Hz), 7.63-7.52 (4 H, m, Ar*H*), 7.39-7.26 (6 H, m, Ar*H*), 3.71-3.56 (2 H, m, CH_2OSi), 2.53-2.47 (1 H, m, CHCH$_3$), 2.03-1.82 (1 H, m, CH_AH$_B$CH$_2$OSi), 1.61-1.48 (1 H, m, CH$_A$$H_BCH_2$OSi), 1.01 (3 H, d, *J* = 7.1 Hz,

CHC*H*$_3$), 0.98-0.95 (9 H, m, SiC(C*H*$_3$)$_3$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 204.9 (*C*HO), 135.6 (Ar*C*), 133.5 (quat. Ar*C*), 129.7 (Ar*C*), 127.7 (Ar*C*), 61.2 (*C*H$_2$OSi), 43.5 (*C*HCH$_3$), 33.4 (*C*H$_2$CH$_2$OSi), 26.8 (SiC(*C*H$_3$)$_3$), 19.2 (Si*C*(CH$_3$)$_3$), 13.1 (CH*C*H$_3$); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +35.6 (c = 1.0, CH_2Cl_2).

The spectral data were consistent with those in the literature.[126]

(*R*)-*tert*-Butyl((3-methylpent-4-en-1-yl)oxy)diphenylsilane, 536 and (*R*)-*tert*-Butyl((2-methylpent-4-en-1-yl)oxy)diphenylsilane, 537



*n*Butyl lithium (1.6 M in hexanes, 1.48 mL, 2.36 mmol) was added dropwise to a solution of triphenylmethylphosphonium bromide (929 mg, 2.60 mmol) in tetrahydrofuran (12.0 mL) at 0 °C. After 15 minutes a solution of 6.5:1 mixture of aldehydes **534** and **535** (400 mg, 1.18 mmol) in tetrahydrofuran (2.00 mL) was added dropwise and stirred for 15 minutes, then warmed to room temperature. After 16 hours the reaction was quenched with saturated aqueous ammonium chloride (14.0 mL), the layers separated and the aqueous layer extracted with diethyl ether (3 × 14.0 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (19:1

petrol:dichloromethane) yielded the title compound **536** as a colourless oil (116 mg, 58%) and the title compound **537** as a colourless oil (36 mg, 18%).

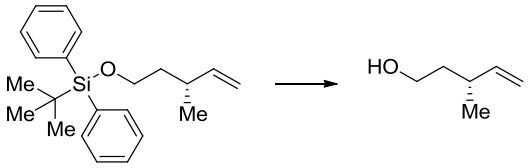
*Compound **536**:*

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.68-7.54 (4H, m, PhH), 7.44-7.25 (6H, m, PhH), 5.59 (1H, ddd, *J* = 17.5, 10.2, 7.6 Hz, C*H*=CH_2), 4.95-4.73 (2H, m, CH=CH_2), 3.60 (2H, t, *J* = 6.6 Hz, CH_2OSi), 2.29 (1H, dt, *J* = 13.9, 7.0 Hz, C*H*CH_3), 1.56-1.38 (2H, m, CH_2CH_2O), 0.97 (9H, s, C(CH_3)$_3$), 0.90 (3H, d, *J* = 6.9 Hz, CHCH_3) ; **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 144.4 (Ph*C*), 135.6 (*C*H=CH_2), 134.1 (quat. Ph*C*), 129.5 (Ph*C*), 127.6 (Ph*C*), 112.6 (CH=*C*H_2), 62.0 (*C*H_2OSi), 39.3 (*C*H_2CH_2O), 34.2 (*C*HCH_3), 26.9 (C(*C*H_3)), 20.1 (CH*C*H_3), 19.2 (*C*(CH_3)), **IR** (ν_{max}/cm^{-1}): 2930, 1472, 1428, 1108; **LRMS** (ESI^+, *m/z*): 361 ([M + Na]$^+$, 100%); **HRMS** (ESI^+, *m/z*): Calculated 361.1958 ($C_{22}H_{30}NaOSi$), Found 361.1948 (Δ +2.8 ppm); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +55.5 (c = 1.0, CH_2Cl_2).

*Compound **537**:*

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.71-7.49 (4H, m, Ar*H*), 7.39-7.25 (6H, m, Ar*H*), 5.68 (1H, ddt, *J* = 17.1, 10.0, 7.1, 7.1 Hz, C*H*=CH_2), 4.99-4.86 (2H, m, CH=CH_2), 3.42 (2H, t, *J* = 6.8 Hz, CH_2OSi), 2.24-2.11 (1H, m, C*H*(CH_3)), 1.92-1.76 (1H, m, CH_AH_BCH(CH_3)), 1.74-1.62 (1H, m, CH_AH_BCH(CH_3)), 0.98 (9H, s, SiC(CH_3)$_3$), 0.83 (3H, d, *J* = 6.6 Hz, CH(CH_3)); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 137.3 (Ar*C*), 135.6 (*C*H=CH_2), 134.0 (quat. Ar*C*), 129.5 (Ar*C*), 127.6 (Ar*C*), 115.7 (CH=*C*H_2), 68.4 (*C*H_2OSi), 37.7 (*C*H_2CH(CH_3)), 26.9 (SiC(*C*H_3)$_3$), 19.4 (Si*C*(CH_3)$_3$), 16.4 (CH(*C*H_3)); **IR** (ν_{max}/cm^{-1}): 3405, 2963, 2877, 1652, 1488, 1383, 1109; **LRMS** (ESI^+, *m/z*): 361 ([M + Na]$^+$, 100%); **HRMS** (ESI^+, *m/z*): Calculated 361.1958 ($C_{22}H_{30}NaOSi$), Found 361.1941 (Δ+4.6 ppm); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +70.6 (c = 1.0, CH_2Cl_2).

(*R*)-3-Methylpent-4-en-1-ol, 501



536 **501**

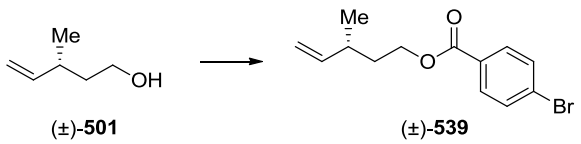
A solution of tetrabutylammonium fluoride (1 M in tetrahydrofuran, 1.4 mL, 1.4 mmol) was added to a solution of alkene **536** (300 mg, 0.89 mmol) in tetrahydrofuran (9.00 mL) at room temperature. After 16 hours the reaction was quenched with a saturated solution of ammonium chloride (9.00 mL), the layers were separated and the aqueous solution was extracted with diethyl ether (3 × 9.00 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (7:3 petrol:diethyl ether) yielded the title compound **501** as colourless oil (61.0 mg, 68%).

The spectroscopic data was identical to (±)-**501**.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ **−**27.9 (c = 1, CH_2Cl_2).

The spectral data were consistent with those in the literature.[125]

3-Methylpent-4-en-1-yl benzoate, (±)-539



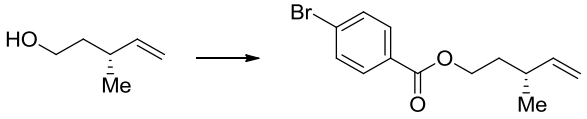
(±)-**501** (±)-**539**

4-Bromobenzoyl chloride (120 mg, 0.55 mmol) was added to a stirred solution of alcohol (±)-**501** (50.0 mg, 0.50 mmol) and triethylamine (0.08 mL, 0.55 mmol) in dichloromethane (5.00 mL) at 0 °C and then warmed to room temperature. After 2 hours the reaction was quenched

with a saturated aqueous solution of ammonium chloride (5.00 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 5.00 mL), the combined organic layers dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (4:1 petrol:dichloromethane) yielded the title compound (±)-**539** as a colourless oil (124 mg, 88%)

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.83 (2 H, d, *J* = 8.6 Hz, Ar*H*), 7.51 (2 H, d, *J* = 8.6 Hz, Ar*H*), 5.65 (1 H, ddd, *J* = 17.4, 10.0, 7.6 Hz, C*H*=CH_2), 5.03-4.82 (2 H, m, CH=CH_2), 4.34-4.16 (2 H, m, CH_2O_2Ar), 2.28 (1 H, dt, *J* = 14.0, 7.1 Hz, C*H*CH=CH_2), 1.71 (2 H, tq, *J* = 13.7, 7.0 Hz, CH_2CH(CH_3)), 1.01 (3 H, d, *J* = 6.9 Hz, CH(CH_3)); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 165.9 (Ar*C*O_2), 143.2 (*C*H=CH_2), 131.7 (Ar*C*), 131.1 (Ar*C*), 129.4 (quat. Ar*C*), 128.0 (quat. Ar*C*), 113.7 (CH=*C*H_2), 63.6 (*C*H_2OCOAr), 35.1 (*C*H(CH_3), 34.9 (*C*H_2CH(CH_3)), 20.3 (CH(*C*H_3)); **IR** (ν_{max}/cm^{-1}): 2932, 1707, 1463, 1428, 1111; **LRMS** (ESI$^+$, *m/z*): 305.0 ([M + Na]$^+$, 100%); **HRMS** (ESI$^+$, *m/z*): Calculated 305.0153 ($C_{13}H_{15}BrO_2Na$), Found 305.0148 (Δ +0.9 ppm).

(*R*)-3-Methylpent-4-en-1-yl 4-bromobenzoate, 539



501 **539**

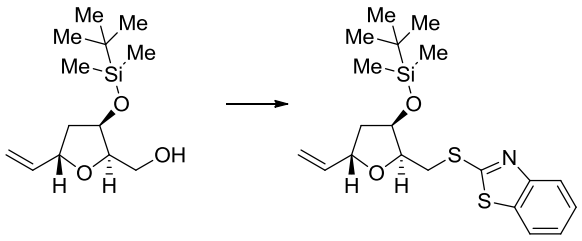
4-Bromobenzoyl chloride (61.0 mg, 0.28 mmol) was added to a stirred solution of alcohol **501** (25.0 mg, 0.25 mmol) and triethylamine (0.04 mL, 0.28 mmol) in dichloromethane (3.00 mL) at 0 °C and then warmed to room temperature. After 2 hours the reaction was quenched with a saturated aqueous solution of ammonium chloride (3.00 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 3.00 mL), the

combined organic layers dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (4:1 petrol:dichloromethane) yielded the title compound **539** as a colourless oil (53.6 mg, 76%).

The spectroscopic data was identical to (±)-**539**.

$[\alpha]_D^{25}$ +29.4 (c = 1, CH_2Cl_2).

2-((((2*S*,3*R*,5*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-5-vinyltetrahydrofuran-2-yl)methyl)thio)benzo[d]thiazole, 507



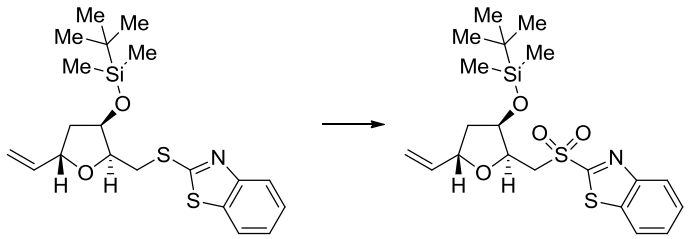
505 **507**

Diisorpropyl azodicarboxylate (0.04 mL, 0.23 mmol) was added dropwise to a solution of alcohol **505** (50 mg, 0.19 mmol), 2-benzothiazolethiol (38.4 mg, 0.23 mmol) and triphenylphosphine (60.0 mg, 0.23 mmol) in tetrahydrofuran (2 mL) at 0 °C. The reaction mixture was stirred for 3.5 hours at room temperature and concentrated *in vacuo*. Flash column chromatography (3:2 petrol:dichloromethane) yielded the title compound **507** as colourless oil (68.0 mg, 88%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 7.77 (1 H, d, *J* = 8.1 Hz, Ar*H*), 7.67 (1 H, d, *J* = 7.8 Hz, Ar*H*), 7.38-7.28 (1 H, m, Ar*H*), 7.25-7.15 (1 H, m, Ar*H*), 5.79 (1 H, ddd, *J* = 17.1, 10.3, 6.9 Hz, C*H*=CH_2), 5.24 (1 H, d, *J* = 17.1 Hz, CH=CH_AH_B), 5.07 (1 H, d, *J* = 10.5 Hz, CH=CH_AH_B), 4.53 (1 H, dt, *J* = 9.7, 6.1 Hz, C*H*CH=CH_2), 4.31-4.19 (1 H, m, C*H*OSi), 4.10 (1 H, td, *J* = 5.9, 2.5 Hz, C*H*CH_2S), 3.48 (2 H, d, *J* = 5.9 Hz, CH_2S), 2.00-1.85 (1 H, m, CH_AH_BCHOSi), 1.83-1.71 (1 H, m, CH_AH_BCHOSi), 0.80 (9 H, s, SiC(CH_3)$_3$), 0.00 (3 H, s,

$Si(CH_3)_A(CH_3)_B$) −0.02 (3 H, s, $Si(CH_3)_A(CH_3)_B$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 166.5 (quat. Ar*C*), 153.1 (quat. Ar*C*), 138.3 (*C*H=CH_2), 135.4 (quat. Ar*C*), 126.0 (Ar*C*), 124.2 (Ar*C*), 121.5 (Ar*C*), 121.1 (Ar*C*), 116.3 (CH=*C*H_2), 85.5 (*C*HCH_2S), 79.9 (*C*HCH=CH_2), 76.0 (*C*HOSi), 41.9 (*C*H_2CHOSi), 36.2 (*C*H_2S), 25.8 ($SiC(CH_3)_3$), 18.0 ($SiC(CH_3)_3$), −4.7 ($Si(CH_3)_2$); **IR** (ν_{max}/cm^{-1}): 1613, 1510, 1460, 1426, 1248; **LRMS** (ESI^+, *m/z*): 430 ([M + Na]$^+$, 100%); **HRMS** (ESI^+, *m/z*): Calculated 430.1301 ($C_{20}H_{29}NO_2S_2SiNa$), Found 430.1286 (Δ +3.7 ppm); $[\alpha]_D^{25}$ +36.2 (c = 1.0, CH_2Cl_2).

2-((((2*S*,3*R*,5*S*)-3-((*tert*-butyldimethylsilyl)oxy)-5-vinyltetrahydrofuran-2-yl)methyl)sulfonyl)benzo[d]thiazole, 510



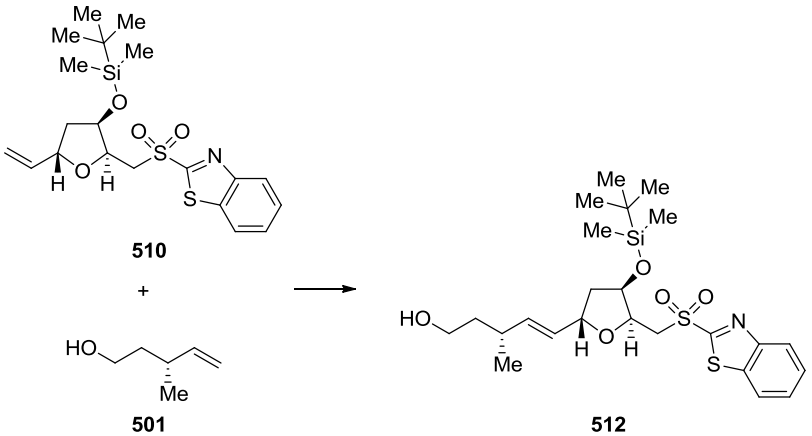
Ammonium molybdate (17.0 mg, 0.015 mmol) was added to hydrogen peroxide (30 wt% in H_2O, 162 μL, 1.60 mmol) at 0 °C to give a bright yellow solution. In a separate flask, sulfide **507** (60.0 mg, 0.147 mmol) was dissolved in ethanol (0.90 mL), cooled to 0 °C and the molybdate solution was added and the reaction mixture stirred for 16 hours at room temperature. The reaction mixture was diluted with a saturated aqueous solution of sodium bicarbonate (2.00 mL) and the aqueous layer extracted with diethyl ether (3 × 4.00 mL). The combined organic layers were washed with brine (2.00 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (7:3 petrol:ethyl acetate) yielded the title compound **510** as colourless oil (57.4 mg, 89%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 8.12 (1 H, d, *J* = 7.8 Hz, Ar*H*), 7.92 (1 H, d, *J* = 7.6 Hz, Ar*H*), 7.59-7.42 (2 H, m, Ar*H*), 5.40 (1 H, ddd, *J* = 17.1, 10.5, 6.2 Hz, C*H*=CH_2), 4.88 (1 H,

d, *J* = 17.1 Hz, CH=C$H_A$$H_B$), 4.74 (1 H, d, *J* = 10.5 Hz, CH=CH$_A$$H_B$), 4.39 (1 H, dt, *J* = 9.1, 6.2 Hz, C*H*=CH$_2$), 4.29-4.18 (2 H, m, C*H*CH$_2$S and C*H*OSi), 3.74 (1 H, dd, *J* = 14.7, 7.3 Hz, CH_AH$_B$S), 3.57-3.46 (1 H, m, CH$_A$$H_B$S), 1.86 (1 H, ddd, *J* = 12.8, 5.9, 2.3 Hz, CH_AH$_B$CHOSi), 1.66 (1 H, ddd, *J* = 12.9, 9.4, 5.4 Hz, CH$_A$$H_B$CHOSi), 0.79 (9 H, s, SiC(CH_3)$_3$), 0.02 (3 H, s, Si(CH_3)$_A$(CH$_3$)$_B$), 0.01 (3 H, s, Si(CH$_3$)$_A$(CH_3)$_B$) ; **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 166.4 (quat. Ar*C*), 152.6 (quat. Ar*C*), 137.6 (*C*H=CH$_2$), 137.0 (quat. Ar*C*), 127.9 (Ar*C*), 127.5 (Ar*C*), 125.4 (Ar*C*), 122.3 (Ar*C*), 115.9 (CH=*C*H$_2$), 80.5 (*C*HCH$_2$S), 79.7 (*C*HCH=CH$_2$), 76.1 (*C*HOSi), 58.2 (*C*H$_2$S), 40.6 (*C*H$_2$CHOSi), 25.7 (SiC(*C*H$_3$)$_3$), 17.9 (Si*C*(CH$_3$)$_3$), −4.7 (Si*C*H$_3$), −4.8 (Si*C*H$_3$); **IR** (ν_{max}/cm^{-1}): 2929, 2857, 2360, 2360, 1473, 1261; **LRMS** (ESI$^+$, *m/z*): 462 ([M + Na]$^+$, 100%); **HRMS** (ESI$^+$, *m/z*): Calculated 462.1199 ($C_{24}H_{38}NO_5S_2Si$), Found 462.1180 (Δ +4.3 ppm), $[\alpha]_D^{25}$ −4.5 (c = 1.0, CH_2Cl_2).

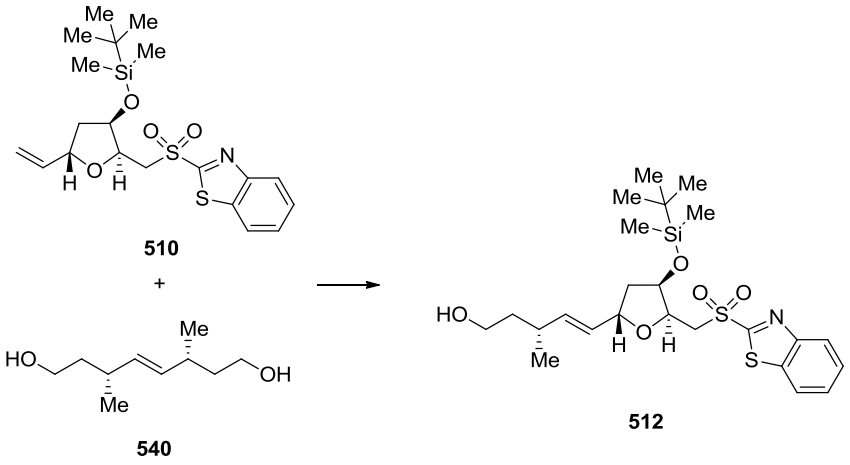
(*R*, *E*)-5-((2*S*, 4*R*, 5*S*)-5-((Benzo[d]thiazol-2-ylsulfonyl)methyl)-4-((*tert*-butyldimethylsilyl)oxy)tetrahydrofuran-2-yl)-3-methylpent-4-en-1-ol, 512

Method A:



A solution of Hoveyda-Grubbs second generation catalyst (2.0 mg, 0.003 mmol) in dichloromethane (1.00 mL) was added dropwise to a solution of alcohol **501** (26.0 mg, 0.256 mmol) and tetrahydrofuran **510** (30.0 mg, 0.064 mmol) in dichloromethane (7.00 mL) at room temperature and the reaction mixture was heated to reflux. After 16 hours at reflux the reaction was cooled and immobilised on silica. Flash column chromatography (7:3 petrol:diethyl ether) yielded the title compound **512** as colourless oil (23 mg, 71%).

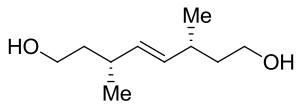
Method B:



A solution of Hoveyda-Grubbs second generation catalyst (1.2 mg, 1.70 μmol) in dichloromethane (0.60 mL) was added dropwise to a solution of diol **540** (23.0 mg, 0.136 mmol) and tetrahydrofuran **510** (15.0 mg, 0.034 mmol) in dichloromethane (3.40 mL) at room temperature and the reaction mixture was heated to reflux. After 16 hours at reflux the reaction was cooled and immobilised on silica. Flash column chromatography (7:3 petrol:ethyl acetate) yielded the title compound **512** as colourless oil (8.7 mg, 57%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 8.14 (1 H, d, *J* = 8.1 Hz, Ar*H*), 7.93 (1 H, d, *J* = 7.8 Hz, Ar*H*), 7.63-7.44 (2 H, m, Ar*H*), 5.20 (1 H, dd, *J* = 15.5, 8.2 Hz, CH(CH_3)C*H*=CH), 4.90 (1 H, dd, *J* = 15.3, 7.2 Hz, CH=C*H*CHOC), 4.34 (1 H, dt, *J* = 9.3, 6.5 Hz, CH=CHC*H*OC), 4.26-4.17 (2 H, m, C*H*OSi & C*H*CH_2Si), 3.75 (1 H, dd, *J* = 14.7, 7.6 Hz, CH_AH_BS), 3.56-3.47 (1 H, m, CH_AH_BS), 3.46-3.34 (2 H, m, CH_2OH), 1.95-1.85 (1 H, m, C*H*CH_3), 1.80 (1 H, ddd, *J* = 12.8, 5.7, 1.8 Hz, CH_AH_BCHOSi), 1.62 (1 H, ddd, *J* = 12.9, 9.7, 5.5 Hz, CH_AH_BCHOSi) 1.39-1.28 (2 H, m, CH_2CH(CH_3)), 0.80 (9 H, s, SiC(CH_3)$_3$), 0.02 (3 H, s, Si(CH_3)$_A$(CH_3)$_B$), 0.00 (3 H, s, Si(CH_3)$_A$(CH_3)$_B$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 164.4 (quat. Ar*C*), 152.7 (quat. Ar*C*), 138.5 (quat. Ar*C*), 128.0 (2 × Ar*C*), 127.9 (Ar*C*), 127.5 (Ar*C*), 125.4 (CH=*C*HCHOC), 122.3 (*C*H=CHCHOC), 80.6 (*C*HOSi), 79.7 (*C*H=CHCHOC), 76.2 (*C*HCH_2S), 60.9 (*C*H_2S), 58.2 (*C*H_2OH), 41.1 (*C*$H_2$$CH_2$OH), 39.2 (*C*$H_2$CHOSi), 33.1 (*C*H($CH_3$)), 25.7 (SiC(*C*$H_3$)$_3$), 20.2 (CH(C*H*$_3$)), 17.9 (Si*C*($CH_3$)$_3$), −4.7 (Si*C*$H_3$), −4.8 (Si*C*$H_3$); **IR** ($\nu_{max}$/cm^{-1}): 2928, 2857, 2360, 1722, 1472, 1332, 1253, 1147, 1075, 836; **LRMS** (ESI$^+$, *m/z*): 512 ([M + H]$^+$, 100%); **HRMS** (ESI$^+$, *m/z*): Calculated 512.1955 ($C_{24}H_{38}NO_5S_2Si$), Found 512.1943 (Δ+2.4 ppm); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +74.2 (c = 1.0, CH_2Cl_2).

(3*R*,6*R*,*E*)-3,6-Dimethyloct-4-ene-1,8-diol, 540



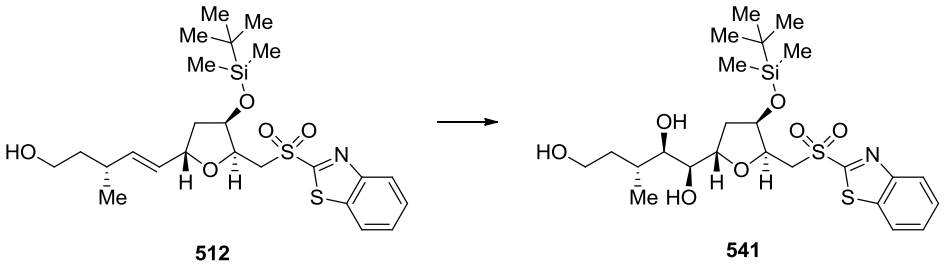
540

Compound **540** was isolated as a side product in the synthesis of alcohol **512** *via Method A.*

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 5.23 (2 H, d, *J* = 4.7 Hz, C*H*=C*H*), 3.58 (2 H, t, *J* = 6.4 Hz, 2 × O*H*), 1.61-1.45 (6 H, m, 2 × C$H_2$$CH_2$OH and 2 × C*H*$CH_3$), 0.93 (6 H, d, *J* = 6.6, 2 × CHCH_3); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 134.7 (*C*H=*C*H), 61.4 (*C*H_2OH), 39.8

(*C*H_2CH$_2$OH), 34.0 (*C*HCH$_3$), 21.3 (CH*C*H$_3$); **IR** (ν_{max}/cm^{-1}): 3351, 2957, 2361, 2342, 1456; **LRMS** (ESI$^+$, *m/z*): 195 ([M +Na]$^+$, 100%); **HRMS** (ESI$^+$, *m/z*): Calculated 195.1356 ($C_{10}H_{20}NaO_2$), Found 195.1949 (Δ +3.4 ppm); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ −11.2 (c = 1.0, CH_2Cl_2).

(1*S*,2*R*,3*R*)-1-((2*S*,4*R*,5*S*)-5-((Benzo[d]thiazol-2-ylsulfonyl)methyl)-4-((*tert*-butyldimethylsilyl)oxy)tetrahydrofuran-2-yl)-3-methylpentane-1,2,5-triol, 541

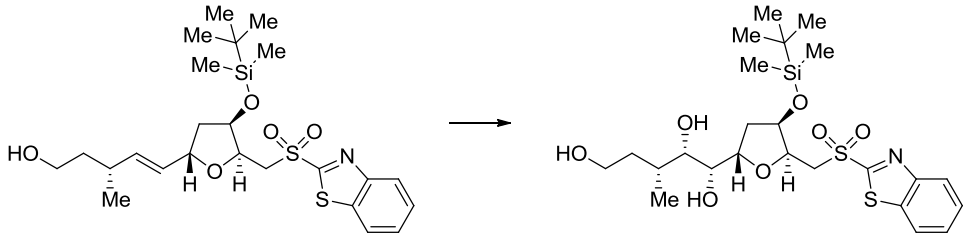


Potassium ferricyanide (33.0 mg, 0.099 mmol), potassium carbonate (14.0 mg, 0.099 mmol), methanesulfonamide (3.0 mg, 0.033 mmol), and $(DHQD)_2PHAL$ (2.0 mg, 0.003 mmol) was added to a stirred solution of alkene **512** (17 mg, 0.033 mmol) in *tert*-butanol (0.20 mL) and water (0.20 mL) and cooled to 0 °C. A solution of potassium osmate (1.2 mg, 0.002 mmol) in water (0.05 mL) was to the reaction mixture and stirred for 3 days. The reaction mixture was quenched sodium sulphite (10.0 mg), diluted with water (2.00 mL), warmed to room temperature and stirred vigorously. Ethyl acetate (2.00 mL) was added, the layers separated and the aqueous layer was extracted with ethyl acetate (3 × 2.00 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (Ethyl acetate) yielded the title compound **541** as colourless oil (18 mg, 81%).

^{1}H NMR δ_H (400 MHz, $CDCl_3$): 8.14 (1 H, d, *J* = 7.8 Hz, Ar*H*), 7.96 (1 H, d, *J* = 7.6 Hz, Ar*H*), 7.64-7.48 (2 H, m, Ar*H*), 4.25 (1 H, dt, *J* = 9.1, 2.7 Hz, C*H*CH$_2$SO$_2$), 4.21-4.15 (1 H,

m, COC*H*CHOH), 4.08 (1 H, ddd, *J* = 9.5, 5.9, 3.9 Hz, C*H*OSi), 3.76-3.60 (2 H, m, CH_2OH), 3.59-3.48 (2 H, m, CH_2SO_2), 3.39 (1 H, t, *J* = 3.3 Hz, COCHC*H*OH), 3.01-2.99 (1 H, m, CH(CH_3)C*H*OH), 2.10-1.98 (1 H, m, C$H_A$$H_B$CHOSi), 1.76 (1 H, ddd, *J* = 13.2, 6.1, 2.2 Hz, $CH_A$$H_B$CHOSi), 1.72-1.62 (1 H, m, C*H*CH_3), 1.59-1.39 (2 H, m, CH_2CH_2OH), 0.79 (9 H, s, C(CH_3)$_3$), 0.75 (3 H, d, *J* = 6.9 Hz, CHCH_3) 0.01 (3 H, s, Si(CH_3)$_A$(CH_3)$_B$), −0.01 (3 H, s, Si(CH_3)$_A$(CH_3)$_B$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$): 167.1 (quat. Ar*C*), 152.5 (quat. Ar*C*), 136.7 (quat. Ar*C*), 128.2 (Ar*C*), 127.9 (Ar*C*), 125.2 (Ar*C*), 122.5 (Ar*C*), 81.8 (*C*HOSi), 80.2 (CO*C*HCHOH), 76.5 (*C*H_2CSO_2), 74.4 (CO*C*HCHOH), 71.1 (CH(CH_3)*C*HOH), 60.4 (*C*H_2SO_2), 57.9 (*C*H_2OH), 35.2 (*C*H_2CH_2OH), 34.5 (*C*H_2CHOSi), 33.8 (*C*HCH_3), 25.7 (SiC(*C*H_3)$_3$), 17.9 (Si*C*(CH_3)$_3$), 16.9 (CH*C*H_3), −4.6 (Si*C*H_3), −4.8(Si*C*H_3); **IR** (ν_{max}/cm^{-1}): 3481, 2929, 2857, 2362, 2341, 1472, 1332, 1253, 1148; **LRMS** (ESI$^+$, *m/z*): 568.2 ([M + Na]$^+$, 100%); **HRMS** (ESI$^+$, *m/z*): Calculated 568.1829 ($C_{24}H_{39}NO_7S_2SiNa$), Found 568.1826 (Δ +0.7 ppm); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ −3.6 (c = 0.8, CH_2Cl_2).

(1*R*,2*S*,3*R*)-1-((2*S*,4*R*,5*S*)-5-((benzo[d]thiazol-2-ylsulfonyl)methyl)-4-((*tert*-butyldimethylsilyl)oxy)tetrahydrofuran-2-yl)-3-methylpentane-1,2,5-triol, 542



540 **542**

Potassium ferricyanide (16.0 mg, 0.05 mmol), potassium carbonate (7.0 mg, 0.05 mmol), methanesulfonamide (1.6 mg, 0.02 mmol), and $(DHQ)_2$PHAL (1 mg, 1.28 μmol) was added to a stirred solution of alkene **540** (10.0 mg, 0.02 mmol) in *tert*-butanol (0.10 mL) and water (0.10 mL) and cooled to 0 °C. A solution of potassium osmate (1.0 mg, 2.71 μmol) in water

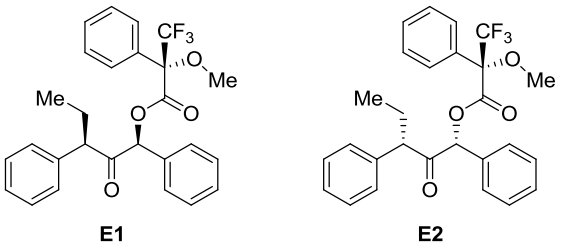
(0.10 mL) was to the reaction mixture and stirred for 3 days. The reaction mixture was quenched sodium sulphite (320 mg), diluted with water (0.50 mL), warmed to room temperature and stirred vigorously. Ethyl acetate (1.00 mL) was added, the layers separated and the aqueous layer was extracted with ethyl acetate (3 × 2.00 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (Ethyl acetate) yielded the title compound **542** as colourless oil (5.7 mg, 52%).

^{1}H NMR δ_H (500 MHz, $CDCl_3$): 8.23 (1 H, d, *J* = 8.5 Hz, Ar*H*), 8.04 (1 H, d, *J* = 7.9 Hz, Ar*H*), 7.70-7.58 (2 H, m, Ar*H*), 4.43-4.35 (1 H, m, C*H*CH_2SO_2), 4.34-4.21 (2 H, m, COC*H*CHOH and C*H*OSi), 3.75-3.66 (2 H, m, CH_2OH), 3.65-3.55 (2 H, m, CH_2SO_2), 3.43-3.36 (1 H, m, CH(CH_3)C*H*OH), 3.12-3.08 (1 H, m, COCHC*H*OH), 2.30-2.16 (1 H, m, C$H_A$$H_B$CHOSi), 1.84 (1H, ddd, *J* = 12.8, 6.5, 2.8, $CH_A$$H_B$CHOSi), 1.73-1.56 (1 H, C*H*CH_3), 1.50-1.36 (2 H, m C$H_2$$CH_2$OH), 0.91 (3 H, d, *J* = 6.9 Hz, CHCH_3), 0.89-0.83 (9 H, m, SiC(CH_3)$_3$), 0.10-0.04 (6 H, m, Si(CH_3)$_2$); **^{13}C NMR** δ_C (125 MHz, $CDCl_3$): 166.3 (quat. Ar*C*), 152.5 (quat. Ar*C*), 136.7 (quat. Ar*C*), 128.2 (Ar*C*), 127.8 (Ar*C*), 125.4 (Ar*C*), 122.5 (Ar*C*), 82.7 (*C*HOSi), 80.2 (CO*C*HCHOH), 76.2 (*C*H_2CSO_2), 70.4 (CH(CH_3)*C*HOH), 60.5 (*C*H_2SO_2), 57.6 (*C*H_2OH), 36.5 (*C*$H_2$$CH_2$OH), 35.9 (*C*$H_2$CHOSi), 33.5 (*C*H$CH_3$), 26.7 (SiC(*C*$H_3$)$_3$), 17.9 (Si*C*($CH_3$)$_3$), 14.8 (CH*C*$H_3$), −4.7 (Si*C*$H_3$), −4.8 (Si*C*$H_3$); **IR** ($\nu_{max}$/cm^{-1}): 3481, 2929, 2857, 2362, 2341, 1472, 1332, 1148; **LRMS** (ESI$^+$, *m/z*): 568.2 ([M + Na]$^+$, 100%); **HRMS** (ESI$^+$, *m/z*): Calculated 568.1829 ($C_{24}H_{39}NO_7S_2SiNa$), Found 568.1823 (Δ +1.1 ppm); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ **+0.6** (c = 0.3, CH_2Cl_2).

Appendix 1: Mosher's Esters and HPLC Data

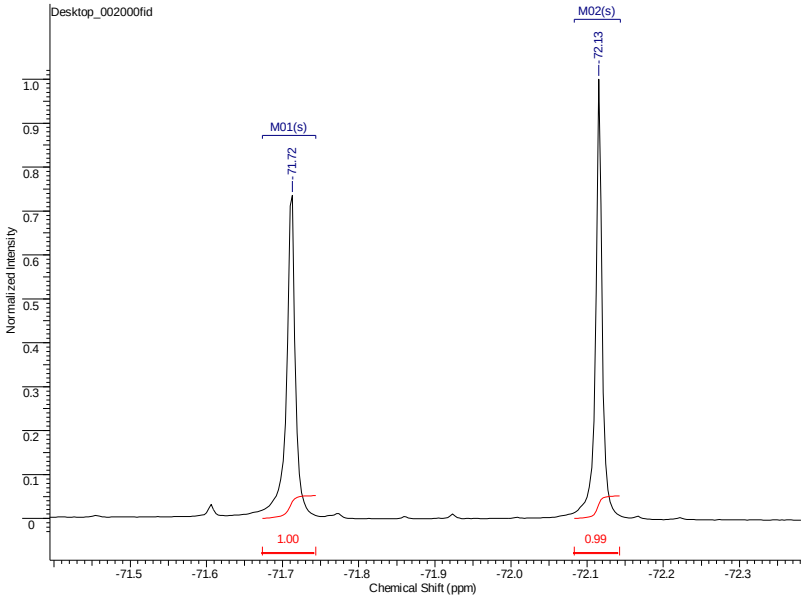
A 1.1 Mosher's Esters

^{19}F NMR (377 MHz, $CDCl_3$):

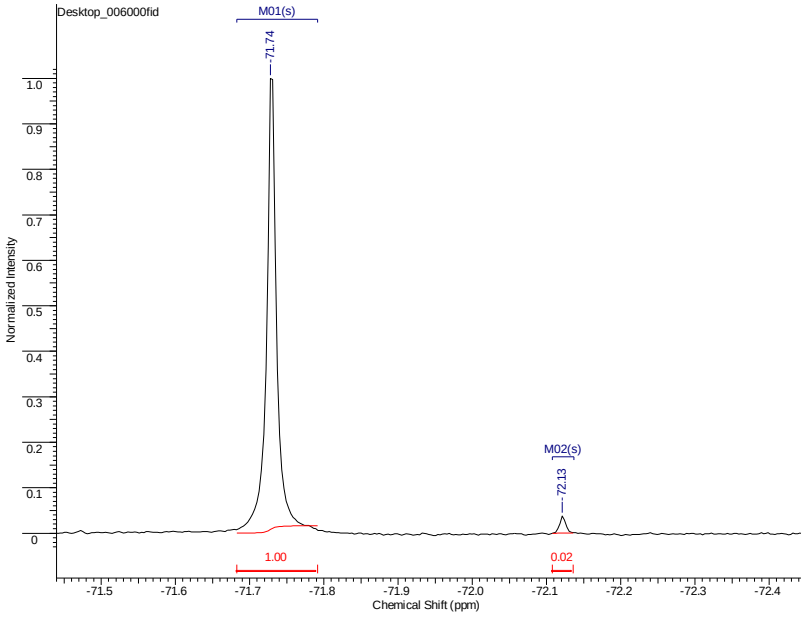


E1 **E2**

1:1 mixture of diastereomers E1 and E2

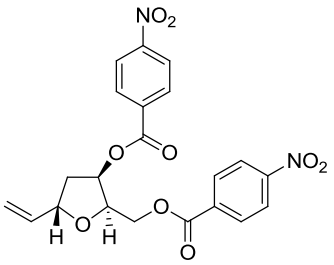


98:2 mixture of diastereomers E1 and E2

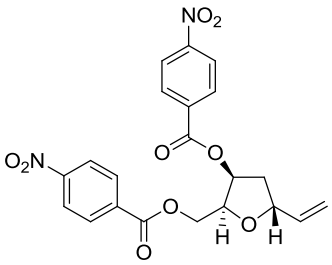


A 1.2 HPLC Data

A 1.2.1 Compounds 411 and 423

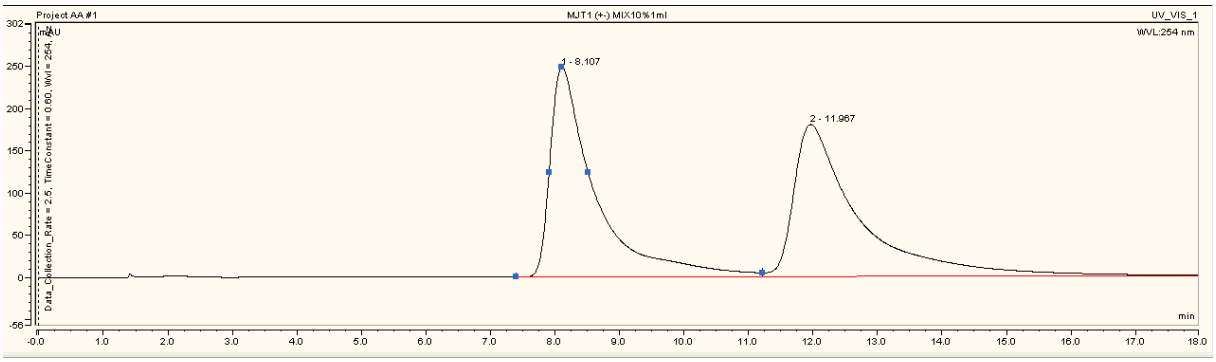


411



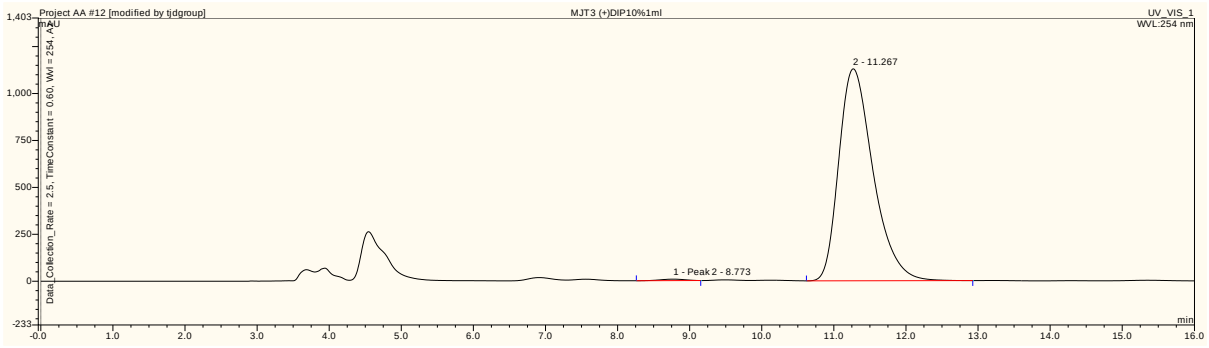
423

1:1 Mixture of **411** and **423**



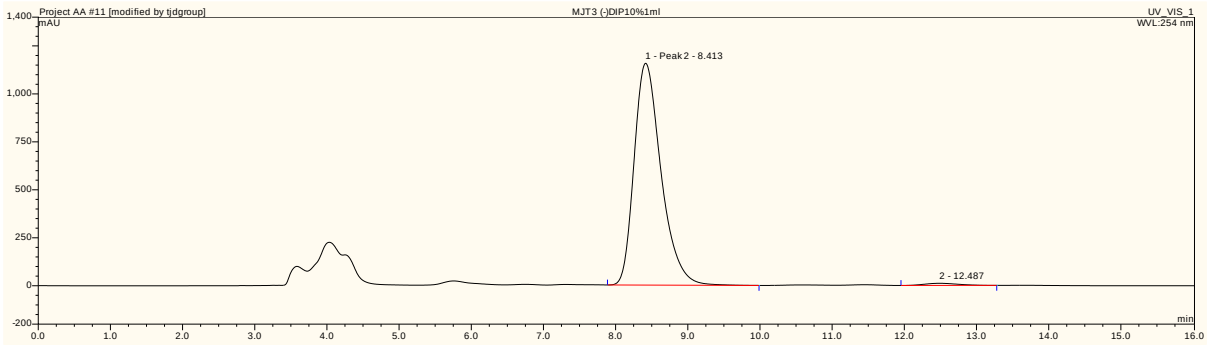
No.	Ret.Time/min	Area/mAU*min	Rel.Area/%	Type
1	8.107	202.007	48.85	BMB
2	11.967	211.5406	51.15	BMB
Total:		413.5475	100	1.3 % e.e.

Compound **423**



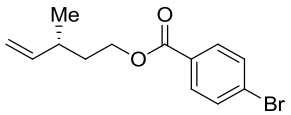
No.	Ret.Time/min	Area/mAU*min	Rel.Area/%	Type
1	8.773	3.099	0.5	BMB*
2	11.267	622.7653	99.5	BMB
Total:		625.8642	100	99% e.e.

Compound **411**



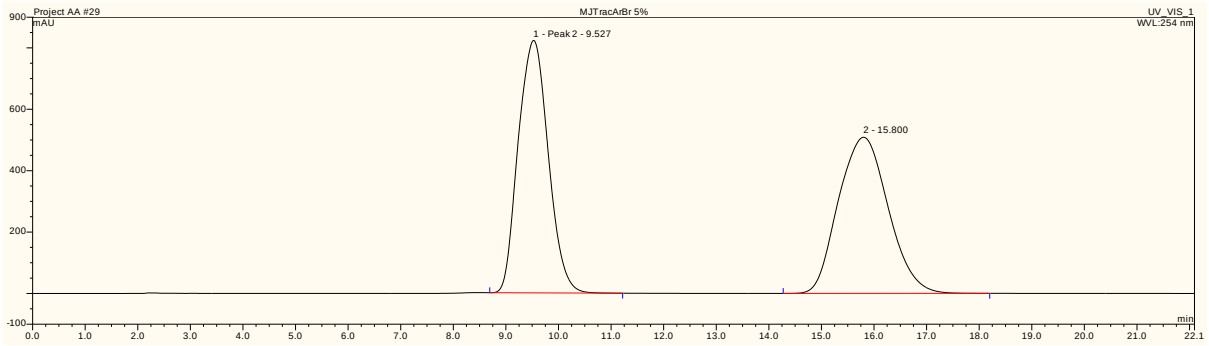
No.	Ret.Time/min	Area/mAU*min	Rel.Area/%	Type
1	8.413	499.6135	98.79	BMB
2	12.487	6.1023	1.21	BMB
Total:		505.7158	100	97.5% e.e.

A 1.2.2 Compounds (±)-539 and 539



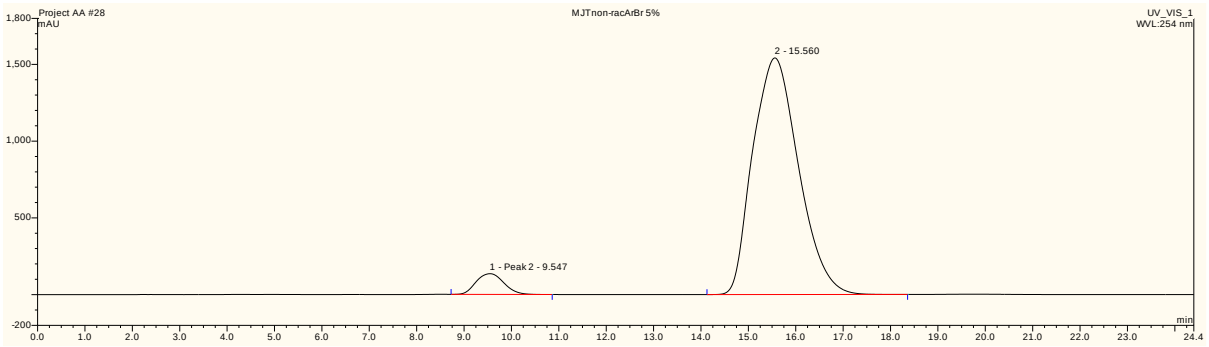
539

Compound (±)-**539**



No.	Ret.Time/min	Area/mAU*min	Rel.Area/%	Type
1	9.527	544.9619	49.43	BMB
2	15.8	557.5391	50.57	BMB
Total:		1102.501	100	0% e.e.

Compound **539**



No.	Ret.Time/min	Area/mAU*min	Rel.Area/%	Type
1	9.547	91.6077	4.05	BMB
2	15.56	1723.9529	95.95	BMB
Total:		1815.5605	100	90.9% e.e.

Appendix 2: Single Crystal X-ray Diffraction

A 2.1 Single-Crystal X-ray Diffraction Report for Compound 331

(Datablock: 0540510)

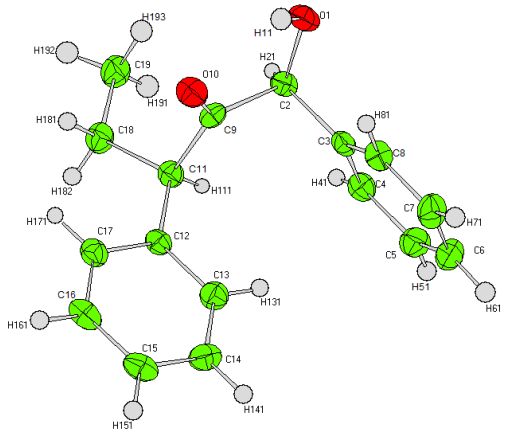


*Figure **A1:** X-ray crystal structure of **331**.*

Crystals of **331** were grown by Michael Tucker and run by Callens Cédric from diethylether and pentane. A single crystal having dimensions approximately ***0.30 x 0.28 x 0.50 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 KappaCCD diffractometer (graphite-monochromated MoK_α radiation, λ = 0.71073 Å). Intensity data were processed using the DENZO-SMN package.[1]

Examination of the systematic absences of the intensity data showed the space group to be ***P 1 2/1 1.*** The structure was solved in this space group using the direct-methods program SIR92,[2] 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.[3] 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 = 0.0294, wR = 0.0679.***

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.

References

1 Otwinowski, Z.; Minor, W. *Methods Enzymol.* **1997**, *276*, 307-326.

2 Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. *J. Appl. Crystallogr.* **1994**, *27*, 435.

3 Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

Crystal identification	CCK 0540510
Chemical formula	C_{17} H_{18} O_2
Formula weight	254.33
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	P 1 2/1 1
a (Å)	5.5958(1)
b (Å)	7.7292(2)
c (Å)	15.7357(5)
α (°)	90
β (°)	96.7613(12)
γ (°)	90
Cell volume (Å^3)	675.85(3)
Z	2
Calculated density (Mg/m^3)	1.250
Absorption coefficient (mm^{-1})	0.080
F_{000}	272
Crystal size (mm)	0.30 × 0.28 × 0.50
Description of crystal	Colourless block
Absorption correction	multi-scan
Transmission coefficients (min,max)	0.96, 0.98
θ range for data collection (°)	5.43≤ θ ≤ 27.51
Index ranges	−7≤ h ≤ 7, -10≤ k ≤ 8, -20≤ l ≤ 20
Reflections measured	2806
Unique reflections	1825
R_{int}	0.029
Observed reflections (I > -3σ(I))	1825
Refinement method	Full-matrix least-squares on Fsqd
Parameters refined	173
Weighting scheme	Modified Sheldrick
Goodness of fit	0.9788
R	0.0294
wR	0.0679
Residual electron density (min,max) (eÅ^{-3})	−0.36, 0.28

*Table **A1**: Crystal data and refinement details.*

Atom	*x*	*y*	*z*	U_{equiv}
O(1)	0.2321(2)	0.87588(18)	0.14368(7)	0.0321
C(2)	0.3172(3)	0.7151(2)	0.17615(10)	0.0241
C(3)	0.3849(3)	0.7173(2)	0.27283(10)	0.0222
C(4)	0.5924(3)	0.6357(3)	0.31025(10)	0.0266
C(5)	0.6471(3)	0.6354(3)	0.39870(11)	0.0330
C(6)	0.4964(3)	0.7154(3)	0.44972(11)	0.0358
C(7)	0.2900(3)	0.7976(3)	0.41257(11)	0.0352
C(8)	0.2332(3)	0.7985(2)	0.32416(10)	0.0283
C(9)	0.1247(3)	0.5758(2)	0.15527(9)	0.0223
O(10)	0.08186(19)	0.62013(19)	0.13251(7)	0.0309
C(11)	0.1997(3)	0.3875(2)	0.16354(10)	0.0234
C(12)	0.0454(3)	0.2918(2)	0.22146(10)	0.0223
C(13)	0.1071(3)	0.2976(2)	0.31012(10)	0.0275
C(14)	-0.0338(3)	0.2154(3)	0.36461(11)	0.0314
C(15)	-0.2385(3)	0.1259(3)	0.33229(11)	0.0316
C(16)	-0.3030(3)	0.1196(3)	0.24468(11)	0.0319
C(17)	-0.1616(3)	0.2016(2)	0.18984(11)	0.0268
C(18)	0.1944(3)	0.3127(3)	0.07240(10)	0.0302

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

Atom	*x*	*y*	*z*	U_{iso}
H(21)	0.4575	0.6820	0.1456	0.0256
H(41)	0.6998	0.5790	0.2743	0.0312
H(51)	0.7911	0.5802	0.4244	0.0374
H(61)	0.5363	0.7134	0.5109	0.0418
H(71)	0.1834	0.8549	0.4466	0.0414
H(81)	0.0920	0.8574	0.2977	0.0321
H(111)	0.3668	0.3895	0.1897	0.0248
H(131)	0.2519	0.3627	0.3336	0.0312
H(141)	0.0106	0.2183	0.4263	0.0364
H(151)	-0.3324	0.0647	0.3701	0.0376
H(161)	-0.4489	0.0577	0.2218	0.0369
H(171)	-0.2076	0.1987	0.1295	0.0297
H(181)	0.0267	0.3163	0.0441	0.0343
H(182)	0.2470	0.1887	0.0788	0.0344
H(192)	0.3592	0.3494	-0.0384	0.0504
H(193)	0.3046	0.5345	0.0107	0.0487
H(191)	0.5225	0.4091	0.0469	0.0489
H(11)	0.0796	0.8664	0.1373	0.0467

*Table **A3**: Atomic coordinates and isotropic thermal parameters (Å^2) of hydrogen atom.*

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	0.0363(7)	0.0223(7)	0.0368(7)	0.0065(6)	0.0007(5)	-0.0020(6)
C(2)	0.0262(8)	0.0211(9)	0.0254(8)	0.0024(7)	0.0051(6)	-0.0008(7)
C(3)	0.0246(8)	0.0181(9)	0.0245(8)	-0.0008(7)	0.0052(7)	-0.0050(7)
C(4)	0.0234(8)	0.0257(10)	0.0309(9)	-0.0002(8)	0.0040(6)	-0.0012(8)
C(5)	0.0309(9)	0.0345(11)	0.0320(9)	0.0045(8)	0.0022(7)	-0.0035(9)
C(6)	0.0396(10)	0.0411(12)	0.0260(9)	-0.0012(8)	0.0016(8)	-0.0103(9)
C(7)	0.0372(10)	0.0388(12)	0.0311(10)	-0.0085(8)	0.0112(8)	0.0049(10)
C(8)	0.0271(9)	0.0261(10)	0.0317(9)	-0.0021(8)	0.0034(7)	-0.0012(8)
C(9)	0.0231(9)	0.0280(11)	0.0164(7)	0.0006(6)	0.0040(6)	0.0011(7)
O(10)	0.0244(6)	0.0294(7)	0.0380(7)	0.0034(6)	0.0001(5)	0.0020(6)
C(11)	0.0208(8)	0.0229(10)	0.0260(8)	0.0006(7)	0.0004(6)	-0.0004(7)
C(12)	0.0231(8)	0.0171(9)	0.0267(9)	0.0008(7)	0.0028(6)	0.0039(7)
C(13)	0.0271(8)	0.0270(10)	0.0282(9)	0.0004(8)	0.0033(7)	0.0002(8)
C(14)	0.0371(10)	0.0312(11)	0.0267(8)	0.0042(8)	0.0069(7)	0.0046(9)
C(15)	0.0304(9)	0.0253(10)	0.0413(10)	0.0060(9)	0.0135(7)	0.0012(9)
C(16)	0.0259(8)	0.0225(10)	0.0474(11)	0.0034(9)	0.0053(7)	-0.0007(8)
C(17)	0.0271(9)	0.0213(10)	0.0313(9)	0.0000(8)	0.0006(7)	0.0016(8)
C(18)	0.0339(9)	0.0298(11)	0.0273(9)	-0.0043(8)	0.0054(7)	-0.0003(8)
C(19)	0.0404(10)	0.0355(12)	0.0275(9)	-0.0050(8)	0.0094(7)	-0.0030(9)

*Table **A5**: Anisotropic thermal parameters (Å^2).*

O(1) . C(2)	1.406(2)	C(9). C(11)	1.516(3)
O(1) . H(11)	0.850	C(11) . C(12)	1.519(2)
C(2). C(3)	1.524(2)	C(11). C(18)	1.543(2)
C(2). C(9)	1.531(2)	C(12). C(13)	1.398(2)
C(3). C(4)	1.390(2)	C(12). C(17)	1.393(2)
C(3). C(8)	1.389(2)	C(13). C(14)	1.385(3)
C(4). C(5)	1.389(2)	C(14). C(15).	1.383(3)
C(5). C(6)	1.377(3)	C(15). C(16)	1.384(2)
C(6). C(7)	1.386(3)	C(16). C(17)	1.390(2)
C(7). C(8)	1.390(2)	C(18). C(19)	1.526(2)
C(9). O(10)	1.2184(18)		

Note – C-H atoms have been excluded

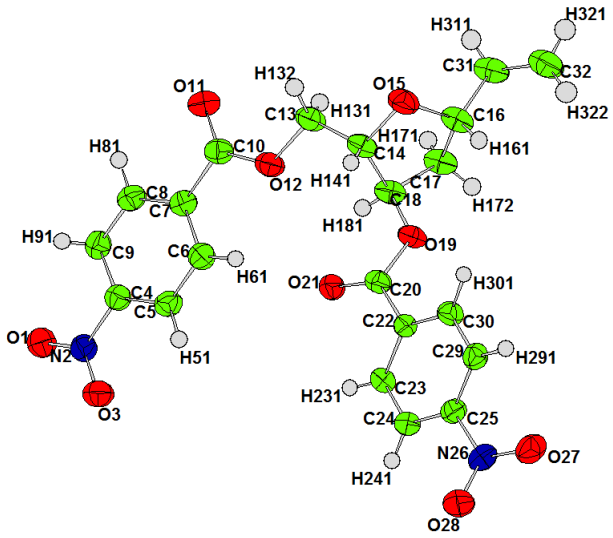
*Table **A6**: Bond lengths (Å).*

C(2). O(1) . H(11)	105.0	O(10) . C(9) . C(11)	122.59(15)
O(1). C(2) . C(3)	112.76(14)	C(9). C(11) . C(12)	110.34(13)
O(1). C(2) . C(9)	110.12(12)	C(9) . C(11) . C(18)	107.76(13)

C(3 .) C(2) . C(9) .	107.96(13)	C(12) . C(11) . C(18)	115.15(14)
C(2). C(3) . C(4) .	121.00(14)	C(11) . C(12) . C(13)	119.50(14)
C(2). C(3) . C(8) .	119.22(14)	C(11) . C(12) . C(17)	122.47(14)
C(4). C(3) . C(8) .	119.75(15)	C(13). C(12). C(17) .	118.00(15)
C(3). C(4) . C(5) .	119.96(15)	C(12). C(13) . C(14)	120.77(16)
C(4). C(5) . C(6) .	120.38(16)	C(13) . C(14) . C(15)	120.59(16)
C(5). C(6) . C(7) .	119.80(16)	C(14). C(15) . C(16)	119.43(16)
C(6). C(7) . C(8) .	120.38(17)	C(15) . C(16) . C(17) .	120.11(16)
C(7). C(8) . C(3) .	119.73(16)	C(12). C(17) . C(16) .	121.10(15)
C(2). C(9) . O(10)	118.99(15)	C(11) . C(18) . C(19)	112.98(15)
C(2). C(9) . C(11) .	118.41(13)	O(10) . C(9) . C(11)	122.59(15)

**Note – H atoms have been excluded*
*Table **A7**: Bond angles (°)*

A 2.2 Single-Crystal X-ray Diffreaction Report for Compound 424



Crystals of **424** were grown by Michael Tucker and run by Matthew Tatton from dichloromethane and pentane. A single crystal having dimensions approximately ***0.34 x 0.24 x 0.04 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 KappaCCD diffractometer (graphite-monochromated MoK_α radiation, λ = 0.71073 Å). Intensity data were processed using the DENZO-SMN package.[1]

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.

Computing details

Data collection: *COLLECT* (Nonius, 2001).; cell refinement: *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: Superflip (Palatinus & Chapuis, 2007); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *CAMERON* (Watkin *et al.*, 1996); software used to prepare material for publication: *CRYSTALS* (Betteridge*et al.*, 2003).

$C_{21}H_{18}N_2O_9$	$F(000) = 460$
$M_r = 442.38$	$D_x = 1.450$ Mg m^{-3}
Monoclinic, $P2_1$	Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
$a = 5.7169$ (3) Å	Cell parameters from 2319 reflections
$b = 11.3774$ (5) Å	$\theta = 5$–$27°$
c = 15.6559 (8) Å	$\mu = 0.12$ mm^{-1}
$\beta = 95.882$ (2)°	$T = 150$ K
$V = 1012.95$ (9) Å^3	Block, colourless
$Z = 2$	0.32 × 0.24 × 0.04 mm

*Table **A8**: Crystal data.*

Nonius KappaCCD diffractometer	2098 reflections with $I > 2.0\sigma(I)$
Graphite monochromator	$R_{int} = 0.026$
ω scans	$\theta_{max} = 27.5°$, $\theta_{min} = 5.3°$
Absorption correction: multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)	$h = -7 \rightarrow 7$
$T_{min} = 0.82$, $T_{max} = 1.00$	$k = -14 \rightarrow 14$
37923 measured reflections	$l = -20 \rightarrow 20$
2402 independent reflections	

*Table **A9**: Data collection.*

Refinement on F^2	Primary atom site location: Other
Least-squares matrix: full	Hydrogen site location: difference Fourier map
$R[F^2 > 2\sigma(F^2)] = 0.042$	H-atom parameters constrained
$wR(F^2) = 0.104$	Method, part 1, Chebychev polynomial, (Watkin, 1994, *P*rince, 1982) [*w*eight] = $1.0/[A_0*T_0(x) + A_1*T_1(x) \cdots + A_{n-1}]*T_{n-1}(x)]$ where A_i are the Chebychev coefficients listed below and x = *F* /*F*max Method = Robust Weighting (*P*rince, 1982) W = [*w*eight] * [1-(delta*F*/6*sigma*F*)^2]^2 A_i are: 94.5 154. 92.5 37.9 8.04
$S = 0.91$	$(\Delta/\sigma)_{max} = 0.0002$
2401 reflections	$\Delta\rho_{max} = 0.24$ e Å^{-3}
289 parameters	$\Delta\rho_{min} = -0.21$ e Å^{-3}
1 restraint	

*Table **A10**:.Refinement*

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	−0.3769 (4)	−0.0844 (2)	0.71060 (16)	0.0526
N2	−0.3430 (4)	0.0139 (2)	0.68293 (16)	0.0425
O3	−0.4769 (4)	0.0615 (2)	0.62676 (16)	0.0538
C4	−0.1323 (5)	0.0779 (3)	0.71837 (19)	0.0391
C5	−0.1038 (6)	0.1932 (3)	0.69470 (19)	0.0429
C6	0.0904 (6)	0.2545 (3)	0.7309 (2)	0.0431
C7	0.2543 (5)	0.1985 (3)	0.78971 (18)	0.0401
C8	0.2230 (5)	0.0814 (3)	0.8113 (2)	0.0431
C9	0.0299 (6)	0.0195 (3)	0.77621 (19)	0.0435
C10	0.4630 (5)	0.2633 (3)	0.83142 (19)	0.0420
O11	0.6191 (4)	0.2186 (2)	0.87824 (15)	0.0509
O12	0.4509 (4)	0.3772 (2)	0.81218 (16)	0.0504
C13	0.6321 (6)	0.4528 (3)	0.8537 (2)	0.0485
C14	0.5804 (5)	0.5739 (3)	0.8167 (2)	0.0419
O15	0.7576 (4)	0.6512 (2)	0.85673 (15)	0.0500
C16	0.6466 (5)	0.7527 (3)	0.89118 (19)	0.0462
C17	0.4076 (5)	0.7077 (4)	0.91040 (19)	0.0475
C18	0.3420 (5)	0.6236 (3)	0.83702 (19)	0.0426
O19	0.2407 (3)	0.6930 (2)	0.76446 (12)	0.0405
C20	0.0859 (5)	0.6368 (3)	0.70818 (18)	0.0367
O21	0.0288 (4)	0.5357 (2)	0.71436 (13)	0.0437
C22	−0.0120 (5)	0.7159 (3)	0.63734 (17)	0.0346
C23	−0.2217 (5)	0.6809 (3)	0.59105 (18)	0.0392
C24	−0.3273 (5)	0.7526 (3)	0.52650 (18)	0.0400
C25	−0.2197 (5)	0.8574 (3)	0.51015 (18)	0.0380
N26	−0.3409 (5)	0.9383 (3)	0.44712 (17)	0.0440
O27	−0.2766 (4)	1.0413 (2)	0.44822 (16)	0.0538
O28	−0.5027 (5)	0.9013 (3)	0.39750 (17)	0.0635
C29	−0.0064 (5)	0.8926 (3)	0.55309 (19)	0.0394
C30	0.0977 (5)	0.8200 (3)	0.61723 (19)	0.0390
C31	0.7981 (6)	0.8030 (4)	0.9649 (2)	0.0559
C32	0.8362 (6)	0.9156 (4)	0.9777 (2)	0.0622
H51	−0.2172	0.2287	0.6547	0.0516*
H61	0.1130	0.3334	0.7164	0.0524*
H81	0.3412	0.0446	0.8503	0.0521*
H91	0.0055	−0.0614	0.7911	0.0524*
H131	0.6236	0.4529	0.9159	0.0580*
H132	0.7906	0.4256	0.8419	0.0583*
H141	0.5806	0.5725	0.7531	0.0491*
H161	0.6188	0.8139	0.8462	0.0551*
H171	0.4256	0.6652	0.9644	0.0586*
H172	0.2953	0.7734	0.9134	0.0583*
H181	0.2297	0.5610	0.8508	0.0510*
H231	−0.2948	0.6074	0.6036	0.0457*
H241	−0.4697	0.7302	0.4937	0.0483*
H291	0.0636	0.9642	0.5389	0.0482*
H301	0.2471	0.8413	0.6471	0.0469*
H311	0.8731	0.7492	1.0057	0.0686*
H321	0.9372	0.9425	1.0269	0.0784*
H322	0.7619	0.9718	0.9389	0.0790*

*Table **A11**: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($Å^2$).*

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0491 (12)	0.0468 (14)	0.0615 (14)	−0.0069 (10)	0.0046 (10)	0.0069 (11)
N2	0.0400 (13)	0.0410 (15)	0.0468 (13)	0.0005 (11)	0.0060 (11)	−0.0020 (12)
O3	0.0470 (12)	0.0554 (15)	0.0563 (13)	−0.0009 (11)	−0.0074 (10)	0.0051 (12)
C4	0.0375 (13)	0.0415 (15)	0.0386 (14)	0.0007 (12)	0.0046 (11)	−0.0019 (13)
C5	0.0443 (15)	0.0451 (17)	0.0381 (14)	0.0045 (13)	−0.0011 (11)	0.0044 (13)
C6	0.0453 (15)	0.0411 (16)	0.0424 (15)	−0.0005 (13)	0.0018 (12)	0.0025 (14)
C7	0.0397 (14)	0.0448 (17)	0.0359 (13)	0.0035 (13)	0.0050 (11)	0.0005 (13)
C8	0.0421 (15)	0.0472 (17)	0.0396 (14)	0.0059 (14)	0.0016 (12)	0.0034 (13)
C9	0.0491 (16)	0.0392 (16)	0.0424 (15)	0.0020 (14)	0.0054 (12)	0.0013 (13)
C10	0.0389 (15)	0.0514 (18)	0.0355 (14)	0.0011 (13)	0.0033 (12)	0.0010 (13)
O11	0.0431 (11)	0.0595 (15)	0.0490 (12)	0.0047 (11)	−0.0013 (9)	0.0051 (11)
O12	0.0448 (12)	0.0482 (13)	0.0544 (13)	−0.0066 (10)	−0.0127 (9)	0.0063 (11)
C13	0.0389 (15)	0.054 (2)	0.0497 (17)	−0.0082 (15)	−0.0071 (13)	−0.0007 (15)
C14	0.0321 (13)	0.0538 (18)	0.0392 (14)	−0.0101 (13)	0.0006 (11)	−0.0006 (14)
O15	0.0323 (10)	0.0598 (15)	0.0575 (13)	−0.0079 (10)	0.0023 (9)	−0.0078 (12)
C16	0.0375 (14)	0.063 (2)	0.0371 (14)	−0.0100 (15)	0.0018 (12)	−0.0044 (15)
C17	0.0369 (14)	0.068 (2)	0.0371 (14)	−0.0061 (15)	0.0025 (11)	−0.0015 (15)
C18	0.0347 (14)	0.0561 (19)	0.0360 (14)	−0.0064 (13)	−0.0012 (11)	0.0063 (13)
O19	0.0329 (9)	0.0484 (12)	0.0384 (10)	−0.0091 (9)	−0.0052 (8)	0.0039 (9)
C20	0.0290 (12)	0.0442 (17)	0.0368 (14)	−0.0024 (12)	0.0022 (10)	−0.0040 (12)
O21	0.0437 (11)	0.0367 (11)	0.0485 (12)	−0.0034 (9)	−0.0053 (9)	0.0037 (10)
C22	0.0330 (12)	0.0334 (14)	0.0365 (13)	0.0016 (11)	−0.0008 (10)	−0.0046 (11)
C23	0.0370 (13)	0.0382 (16)	0.0414 (14)	−0.0042 (12)	−0.0009 (11)	−0.0040 (13)
C24	0.0380 (14)	0.0407 (16)	0.0395 (14)	0.0007 (12)	−0.0040 (11)	−0.0014 (13)
C25	0.0367 (13)	0.0401 (15)	0.0368 (13)	0.0059 (12)	0.0016 (11)	−0.0015 (12)
N26	0.0436 (13)	0.0460 (15)	0.0424 (13)	0.0090 (12)	0.0050 (11)	0.0071 (12)
O27	0.0477 (12)	0.0462 (14)	0.0676 (15)	0.0023 (11)	0.0066 (11)	0.0174 (12)
O28	0.0677 (16)	0.0561 (16)	0.0608 (14)	0.0051 (13)	−0.0231 (12)	0.0036 (13)
C29	0.0385 (14)	0.0336 (15)	0.0467 (15)	−0.0001 (12)	0.0070 (12)	0.0031 (13)
C30	0.0313 (12)	0.0414 (16)	0.0441 (14)	−0.0025 (12)	0.0029 (11)	−0.0033 (13)
C31	0.0390 (16)	0.079 (3)	0.0484 (18)	−0.0036 (17)	−0.0028 (13)	−0.0074 (18)
C32	0.0436 (17)	0.084 (3)	0.058 (2)	−0.0038 (18)	−0.0004 (15)	−0.024 (2)

*Table **A12**: Atomic displacement parameters (Å2).*

O1—N2	1.222 (4)	C16—H161	0.992
N2—O3	1.231 (3)	C17—C18	1.513 (5)
N2—C4	1.467 (4)	C17—H171	0.970
C4—C5	1.378 (5)	C17—H172	0.989
C4—C9	1.396 (4)	C18—O19	1.455 (4)
C5—C6	1.383 (5)	C18—H181	0.996
C5—H51	0.944	O19—C20	1.345 (3)
C6—C7	1.398 (4)	C20—O21	1.202 (4)
C6—H61	0.937	C20—C22	1.492 (4)
C7—C8	1.391 (5)	C22—C23	1.393 (4)
C7—C10	1.495 (4)	C22—C30	1.391 (4)
C8—C9	1.375 (5)	C23—C24	1.388 (4)
C8—H81	0.959	C23—H231	0.964
C9—H91	0.963	C24—C25	1.377 (4)
C10—O11	1.208 (4)	C24—H241	0.952
C10—O12	1.331 (4)	C25—N26	1.470 (4)
O12—C13	1.449 (4)	C25—C29	1.390 (4)
C13—C14	1.512 (5)	N26—O27	1.228 (4)
C13—H131	0.979	N26—O28	1.221 (4)
C13—H132	0.993	C29—C30	1.386 (4)
C14—O15	1.436 (4)	C29—H291	0.944
C14—C18	1.538 (4)	C30—H301	0.962
C14—H141	0.997	C31—C32	1.312 (6)
O15—C16	1.448 (4)	C31—H311	0.954
C16—C17	1.518 (4)	C32—H321	0.964

C16—C31	1.485 (5)	C32—H322	0.951
O1—N2—O3	123.1 (3)	C16—C17—C18	102.8 (2)
O1—N2—C4	118.3 (3)	C16—C17—H171	108.9
O3—N2—C4	118.6 (3)	C18—C17—H171	110.0
N2—C4—C5	119.1 (3)	C16—C17—H172	110.9
N2—C4—C9	118.3 (3)	C18—C17—H172	113.7
C5—C4—C9	122.6 (3)	H171—C17—H172	110.3
C4—C5—C6	118.9 (3)	C14—C18—C17	103.5 (2)
C4—C5—H51	119.5	C14—C18—O19	109.2 (2)
C6—C5—H51	121.6	C17—C18—O19	107.3 (3)
C5—C6—C7	119.7 (3)	C14—C18—H181	112.7
C5—C6—H61	120.6	C17—C18—H181	113.7
C7—C6—H61	119.7	O19—C18—H181	110.1
C6—C7—C8	120.2 (3)	C18—O19—C20	115.8 (2)
C6—C7—C10	120.9 (3)	O19—C20—O21	124.6 (3)
C8—C7—C10	118.9 (3)	O19—C20—C22	111.8 (3)
C7—C8—C9	120.7 (3)	O21—C20—C22	123.5 (3)
C7—C8—H81	118.2	C20—C22—C23	116.9 (3)
C9—C8—H81	121.0	C20—C22—C30	122.5 (2)
C4—C9—C8	117.9 (3)	C23—C22—C30	120.6 (3)
C4—C9—H91	120.6	C22—C23—C24	119.9 (3)
C8—C9—H91	121.5	C22—C23—H231	120.6
C7—C10—O11	124.4 (3)	C24—C23—H231	119.5
C7—C10—O12	111.1 (3)	C23—C24—C25	118.3 (3)
O11—C10—O12	124.5 (3)	C23—C24—H241	121.3
C10—O12—C13	117.3 (2)	C25—C24—H241	120.4
O12—C13—C14	105.4 (2)	C24—C25—N26	118.6 (2)
O12—C13—H131	109.9	C24—C25—C29	123.1 (3)
C14—C13—H131	110.6	N26—C25—C29	118.3 (3)
O12—C13—H132	110.8	C25—N26—O27	117.9 (3)
C14—C13—H132	111.1	C25—N26—O28	119.0 (3)
H131—C13—H132	109.0	O27—N26—O28	123.0 (3)
C13—C14—O15	106.8 (2)	C25—C29—C30	118.0 (3)
C13—C14—C18	113.5 (3)	C25—C29—H291	120.4
O15—C14—C18	106.6 (3)	C30—C29—H291	121.6
C13—C14—H141	110.4	C22—C30—C29	120.1 (3)
O15—C14—H141	111.9	C22—C30—H301	120.2
C18—C14—H141	107.7	C29—C30—H301	119.7
C14—O15—C16	109.5 (2)	C16—C31—C32	124.7 (4)
O15—C16—C17	104.0 (3)	C16—C31—H311	117.4
O15—C16—C31	110.7 (3)	C32—C31—H311	117.8
C17—C16—C31	116.2 (3)	C31—C32—H321	120.6
O15—C16—H161	109.9	C31—C32—H322	120.2
C17—C16—H161	107.2	H321—C32—H322	119.2
C31—C16—H161	108.6		

*Table **A13**: Geometric parameters (Å, º).*

B

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C6—H61···O21	0.94	2.35	3.225 (4)	155 (1)
C16—H161···O1^{i}	0.99	2.42	3.372 (4)	161 (1)
C17—H171···O11^{ii}	0.97	2.58	3.330 (4)	135 (1)
C30—H301···O1^{i}	0.96	2.43	3.383 (4)	173 (1)

*Table **A14**: Hydrogen-bond geometry (Å, º).*

Symmetry codes: (i) *x*+1, *y*+1, *z*; (ii) −*x*+1, *y*+1/2, −*z*+2.

Appendix 3: References

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