Formal Synthesis of the Asbestinin Family of Marine Natural Products

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Abstract

The asbestinins are a sub-class of the ether bridged 2,11-cyclised cembranoid family of marine natural products that have been isolated from octocoral species *Briareum Asbestinum*. They are comprised of an unusual tetracyclic ring system consisting of conjoined cyclohexyl, hydroisobenzofuran, oxonene and oxapane ring units. They exhibit high structural complexity and a diverse range of bioactivities that include cytotoxicity against tumour cell lines, potent anti-bacterial properties and antagonism of both histamine and acetylcholine receptors. These biological properties lend support to the common belief that the natural role of this family of compounds is in predation deterrence.

The Clark group has been prolific in the total synthesis of members of the ether bridged 2,11-cyclised cembranoids, culminating in the enantioselective total syntheses of nine members of the cladiellin (also known as eunicellin) sub-class. They include; (−)-vigulariol, (−)-cladiella-6,7-diene-3-ol, (−)-cladiell-11-ene-3,6,7-triol, (−)-3-acetoxycladiella-6,7-diene, (−)-3-acetoxycladiellin-11-ene-6,7-diol, (−)-sclerophytin A, (−)-sclerophytin B, (+)-deacetylpolyanthellin A and (+)-polyanthillin A.

The key synthetic steps to construct the tetracyclic ring system include; a samarium diiodide reductive cyclisation to generate 2,6-*syn*-5,6-*anti* tetrahydropyranol motif, oxonium ylide formation with subsequent [2,3]-sigmatropic rearrangement of a functionalised diazoketone, an intermolecular Diels-Alder cycloaddition to construct the cyclohexyl ring and an intramolecular triflate displacement to form the final oxapane ring.

Herein, is presented the continued efforts in developing an efficient synthetic route to the asbestinins which will be general enough to enable the synthesis of virtually every member of this family of compounds.

Declaration

I hereby declare that the substance of this thesis has not been submitted, nor is currently being submitted in candidature for any other degree.

I also declare that the work embodied in this thesis is the result of my own investigations. Where work of other investigators has been used, this has been fully acknowledged in the text.

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Ralph Clark Sigerson

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Prof. J. Stephen Clark

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Finally, to my mother Anastasia, my greatest thanks of all.

Abbreviations

Ac	acetyl
acac	acetylacetonate
Ac_2O	acetic anhydride
aq.	aqueous
Ar	aryl
atm	1 atmosphere
ax	axial
Bn	benzyl
BOM	(benzyloxy)methyl
b.p.	boiling point
Bn	benzyl
brsm	based on recovered starting material
BTEAC	benzyltriethylammonium chloride
Bu	butyl
Bz	benzoyl
°C	degrees Celsius
CBS	Corey-Bakshi-Shibata
CI	chemical ionisation
CIDNP	chemically induced dynamic nuclear polarisation
COSY	correlation spectroscopy
CSA	10-camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCDT	dicylododecyl tartrate
DCE	1,2-dichloroethane
DCHT	dicyclohexyl tartrate
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement of polarisation transfer
DET	diethyl tartrate
DIBAL-H	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DIPT	diisopropyl tartrate

DMAP	*N*,*N*-4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMM	dimethoxymethane
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
EI	electron ionisation
eq	equatorial
ES	electrospray ionisation
Et	ethyl
Et_3N	triethylamine
EtOAc	ethyl acetate
Et_2O	diethyl ether
FAB	fast atom bombardment
FT	fourier transform
g	gram(s)
h	hour(s)
hfacac	hexafluoroacetylacetonate
HMDS	1,1,1,3,3,3-hexamethyldisilazide
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HPLC	high-pressure liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
hv	irradiation with light
i	iso
IC_{50}	half minimal inhibition concentration
Im	imidazolyl
imid.	imidazole
Ipc	isopinocamphenyl
IR	infrared spectrometry
IUPAC	international union of pure and applied chemistry
L.A.	Lewis acid
LDA	lithium diisopropylamide

liq.	liquid
LRMS	low resolution mass spectrometry
LUMO	lowest unoccupied molecular orbital
M	mole(s) per litre of solvent
m	meta
m-CPBA	meta-chloroperbenzoic acid
Me	methyl
MEM	(2-methoxyethoxy)methyl
MeOH	methanol
mg	milligramme(s)
mL	millilitre(s)
MLn	transition metal with ligands
mmol	millimole(s)
MOM	(methoxy)methyl
m.p.	melting point
Ms	methanesulfonyl
MS	mass spectrometry
MS	molecular sieves
MVK	methyl vinyl ketone
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOBA	3-nitrobenzaldehyde
o	ortho
OAc	acetate
p	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
Piv	pivaloyl
PMB	para-methoxybenzyl
ppm	parts per million
PPTS	pyridinium para-toluenesulfonate
Pr	propyl
p-TSA	para-toluenesulfonic acid
pyr	pyridine
quant.	quantitative

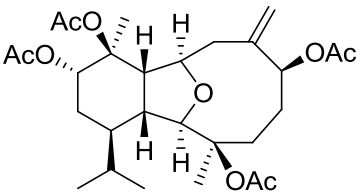
RCM	ring closing metathesis
R_f	retention factor in chromatography
rt	room temperature
t	*tert*
TBAB	tetra-*n*-butylammonium bromide
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
Temp	temperature
TEMPO	2,2,6,6,-tetramethyl-1-piperidinyloxy
TES	triethylsilyl
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMCDA	*N*,*N*,*N'*,*N'*-tetramethyl-1,2-diaminocyclohexane
TMEDA	*N*,*N*,*N'*,*N*'-tetramethylethylenediamine
TMP	tetramethylpiperidide
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammonium perruthenate
tr	triphenylmethyl (trityl)
Ts	para-toluenesulfonyl
TS	transition state
Δ	heat
µL	microlitre(s)
Å	Ångstrom

Table of Contents

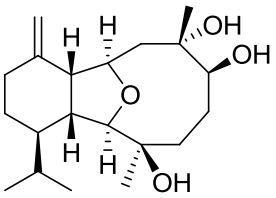
1 Introduction

1.1 The Ether-Bridged 2,11-Cyclised Cembranoid Family of Marine Natural Products

In the 44 years since the isolation of eunicellin (**1**, **Figure 1**), many other ether-bridged 2,11-cyclised cembranoids have been isolated and characterised.[1] They are exclusive to marine environments and have been found in a range of invertebrates, such as soft corals and gorgonians; and possess formidable structural complexity. They also exhibit a variety of biological activities, such as anti-inflammatory, anti-malarial, anti-bacterial, anti-fungal and cytotoxic activities.[2] One of the most potent cytotoxic members isolated to date is (−)-sclerophytin A (**2**, **Figure 1**), which exhibits growth inhibition activity against the murine L1210 leukaemia cell line in high potency (IC_{50} = 1.0 ng/mL).[3] As a result, this family of natural products has received a great deal of attention from the synthetic chemistry community over the last 20 years.



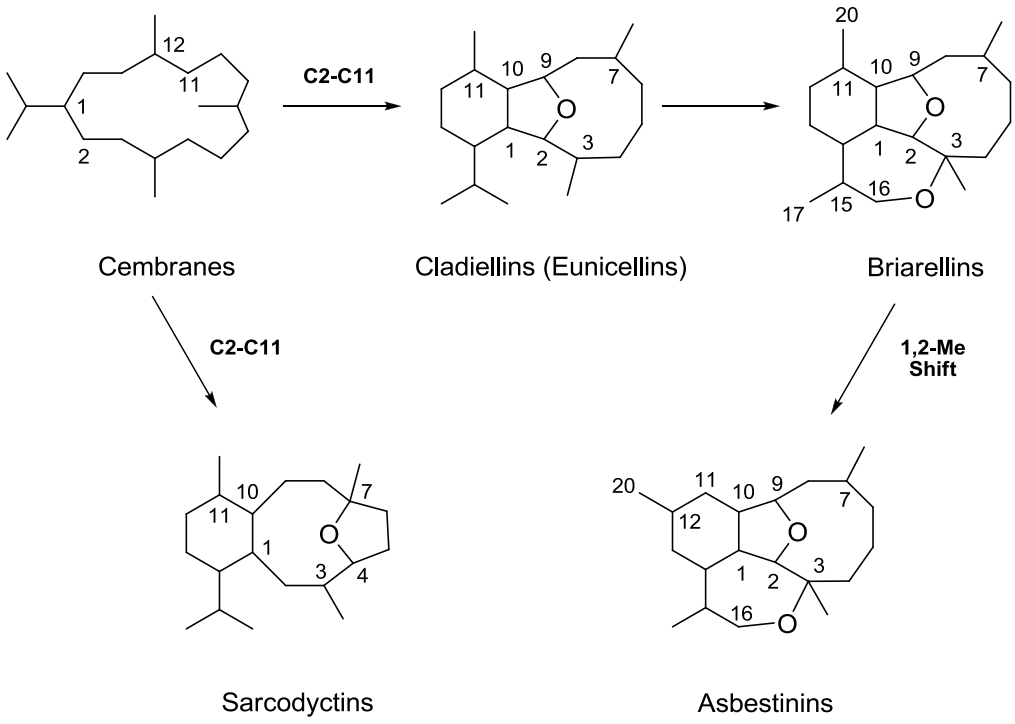
Eunicellin (**1**)



Sclerophytin A (**2**)

Figure 1

The ether-bridged 2,11-cyclised cembranoids have been classified into four distinct categories based on their conserved tricyclic core.[2] They include the cladiellins (also known as the eunicellins), briarellins, asbestinins and sarcodictyins (**Scheme 1**). The cladiellins, briarellins and asbestinins contain a novel diterpenoid structure associated with an unusual ether bridge between C-2 and C-9 (cladiellin nomenclature). In addition to this, the briarellins and asbestinins also contain an additional seven-membered ether ring between C-3 and C-16. The sarcodictyins contain a slightly different tricyclic core with a single ether bridge between C-4 and C-7.



Scheme 1

1.1.1 Proposed Biosynthesis

Insight into the proposed biosynthesis of the ether-bridged 2,11-cyclised cembranoids was obtained following the isolation of the first members of the asbestinin sub-class by Faulkner and co-workers in 1980.[4] In this publication, Faulkner disclosed the structures of the first five members of the asbestinin family, following their isolation by flash chromatography of extracts obtained from the gorgonian invertebrate *Briareum Asbestinum*, collected off the coast of Belize (**Figure 2**). Faulkner and co-workers concluded that the general asbestinin carbon scaffold was related to that of eunicellin (**1**); they concluded that the four sub-classes (the cladiellins, the briarellins, the asbestinins and the sarcodictyins) were derived from the same cembrane skeleton (**Scheme 1**). Cyclisation of this general cembrane skeleton between C-2 and C-11 (cembrane nomenclature) and differential ether ring formation would afford both the cladiellins (C-2 to C9 ether bridge, cladiellin numbering convention) and sarcodictyins (C-4 to C7 ether bridge). Subsequent ether ring formation between C-3 and C-16 would deliver the briarellins, followed by a 1,2-methyl shift between C-11 and C-12 to give the asbestinin skeleton. Although there has been no definitive study of this proposed biosysthesis to date, the discovery of metabolites from the gorgonian *Steckii*

(asbestinin) and *Alcyonium molle* (cladiellin) in combination with other cembrane metabolites has given credibility to this hypothesis.[5]

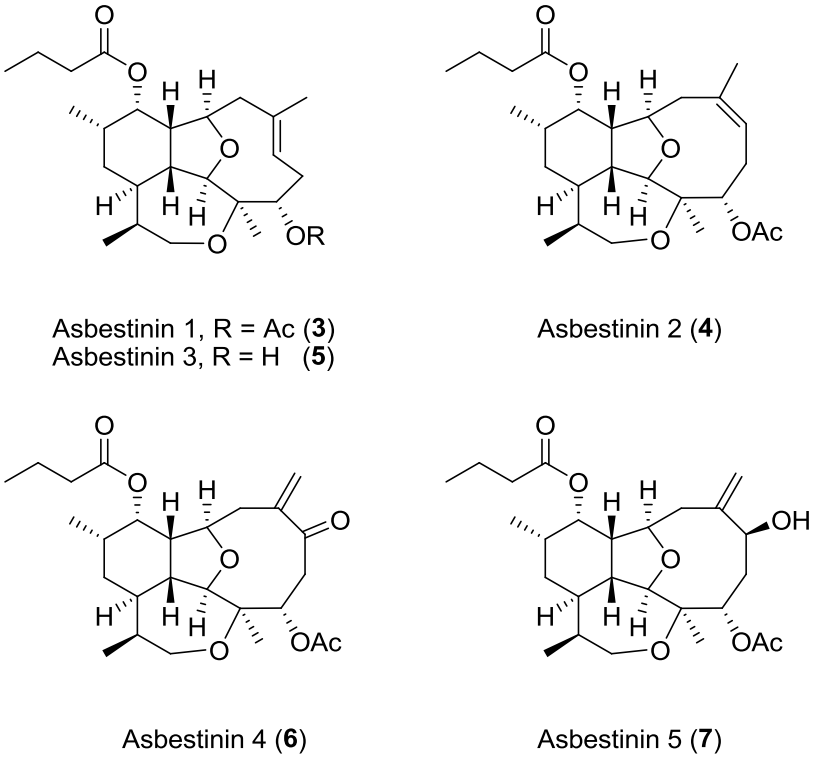
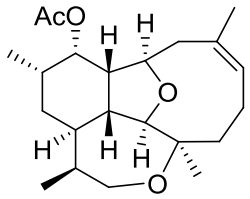


Figure 2

1.1.2 The Asbestinin Family of Natural Products

Over 30 members of the asbestinin class of natural product have been isolated from the gorgonian octocoral species *Briareum Asbestinum*. Many of them possess interesting bioactive properties such as cytotoxicity against tumour cell lines, potent anti-bacterial activity and antagonism of histamine and acetylcholine receptors.[2] As a result of their low natural abundance, the full bioactivity profiles have yet to be established for many compounds within the class. As stated above, the first members of the asbestinin sub-class were isolated by Faulkner and co-workers (**Figure 2**).[4] The structure of asbestinin-1 (**3**) was determined from a single X-ray diffraction study on the corresponding diol, which was obtained by lithium aluminium hydride reduction and recrystallisation. The structures of asbestinins-2,-3,-4 and -5 were deduced by NMR analysis and confirmed by chemical interconversions and comparison with data from asbestinin-1. The absolute configuration of the asbestinins was not confirmed until the total synthesis of

11-acetoxy-4-deoxyasbestinin D (**8**, **Figure 3**) was completed in 2005.[6] First isolated by Rodríguez and co-workers in 1991, this compound exhibits cytotoxicity against CHO-K1 cells (ED_{50} = 4.82 μg/mL) and has strong antimicrobial activity against *Klebsiella pneumoniae*,[7] Crimmins and co-workers disclosed the enantioselective total synthesis of this defining diterpene in a total of 26 steps.



11-Acetoxy-4-deoxyasbestinin D (**8**)

Figure 3

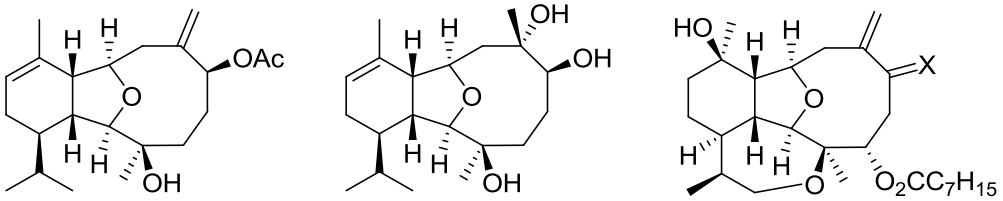
1.2 Previous Syntheses of Members of the Ether-Bridged 2,11-Cyclised Cembranoid Family of Marine Natural Products

Much research has been carried out towards the isolation, characterisation and total synthesis of the various members of the ether-bridged 2,11-cyclised cembranoid family. Several synthetic strategies have been employed to synthesise the challenging tricyclic cores present in these compounds. This section will focus on the total syntheses that have been completed by the leading research groups and published to date.

1.2.1 The Overman Group Approach

The first reported total synthesis of an ether-bridged 2,11-cyclised cembranoid was published by Overman and MacMillan in 1995.[8] This publication disclosed the complete total synthesis of (−)-7-deacetoxyalcyonin acetate (**9**), a compound that belongs to the cladiellin sub-class. The key synthetic steps included a chromium promoted Nozaki-Hiyama-Kishi coupling reaction and a Prins-pinacol condensation-rearrangement to produce the required hydroisobenzofuran ring, with the latter reaction having been developed by the Overman group for the stereoselective synthesis of tetrahydrofurans.[9]

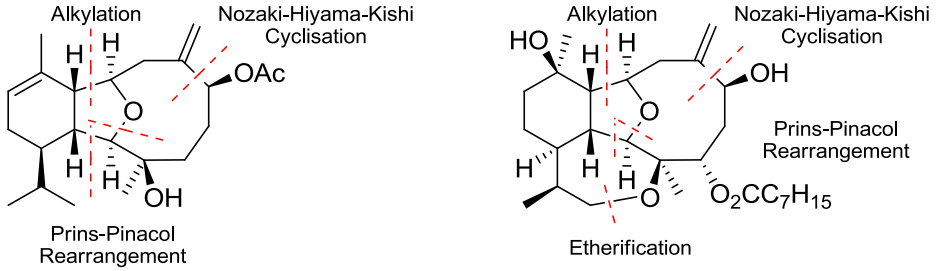
They have used this strategy for the synthesis of many ether-bridged 2,11-cyclised cembranoids since, including cladelli-11-ene-3,6,7-triol (**10**), (−)-sclerophytin A (**2, Figure 1**),[10] briarellin E (**11**) and briarellin F (**12**), shown in **Figure 4**.[11]



(-)-7-deacetoxyalcyonin acetate (**9**) | Cladielli-11-ene-3,6,7-triol (**10**) | Briarellin E, X = OH, ß-H (**11**) Briarellin F, X = O (**12**)

Figure 4

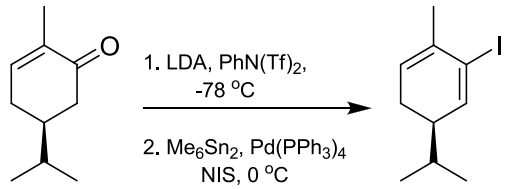
A summary of the overall strategy employed by Overman and co-workers is illustrated in **Figure 5**. A Prins-pinacol cyclisation reaction was used to incorporate the cyclohexyl ring and form the furan ring, followed by the closure of the medium ring using the Nozaki-Hiyama-Kishi coupling reaction.



Overman 1995-2003 **Overman 2003**

Figure 5

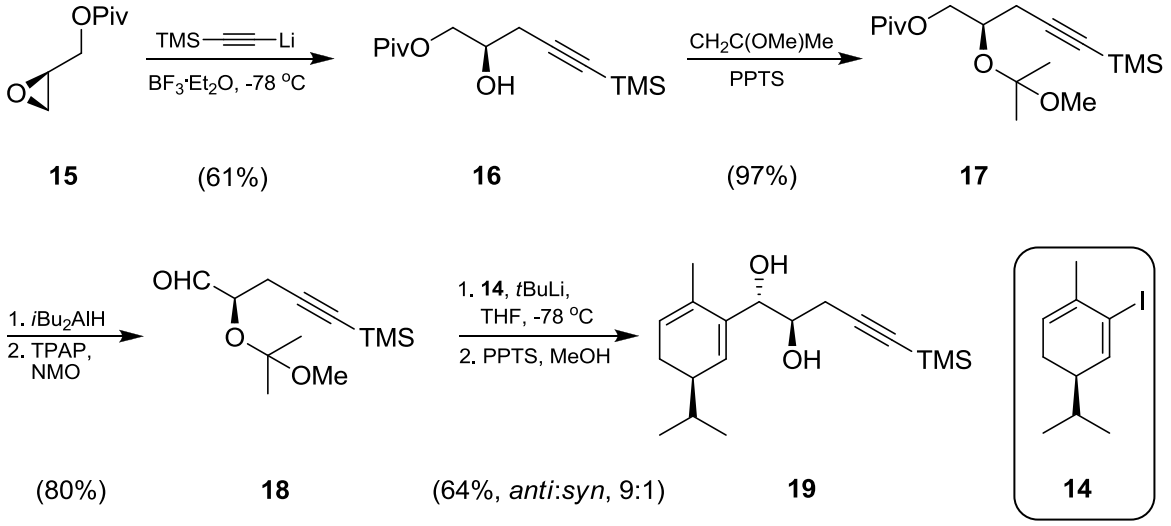
The synthesis of (−)-7-deacetoxyalcyonin acetate (**9**) began with the formation of the iodide **14**. This starting material was prepared by conversion of (*S*)-dihydrocarvone (**13**) into the kinetic enol triflate, which underwent palladium-catalysed coupling with hexamethylditin, followed by *in situ* iodination of the vinylic tin intermediate with *N*-iodosuccinimide (NIS) (**Scheme 2**).



13 (78%) **14**

Scheme 2

The next step involved the regioselective opening of (*S*)-glycidyl pivalate **15** using lithium (trimethylsilyl)acetylide in the presence of $BF_3{\cdot}Et_2O$, affording alcohol **16**, which was then protected as the 2-methoxypropyl (MOP) ether (**17**) upon exposure to 2-methoxypropene and PPTS (**Scheme 3**).The pivalate group of **17** was removed using an excess of *i*Bu_2AlH and the primary alcohol oxidised to the aldehyde using tetra-*n*-propylammonium perruthenate/*N*-methylmorpholine *N*-oxide (TPAP-NMO) to afford aldehyde **18** in 80% yield. Next, the previously synthesised iodide **14** was subjected to lithium-halogen exchange using *t*BuLi to form the corresponding vinyl lithium intermediate, to which aldehyde **18** was added at −78 ˚C. This was followed by mild acidic cleavage of the MOP group affording the Prins-pinacol rearrangement precursor **19** in a 64% yield as a 9:1 mixture of *anti* and *syn* stereoisomers.



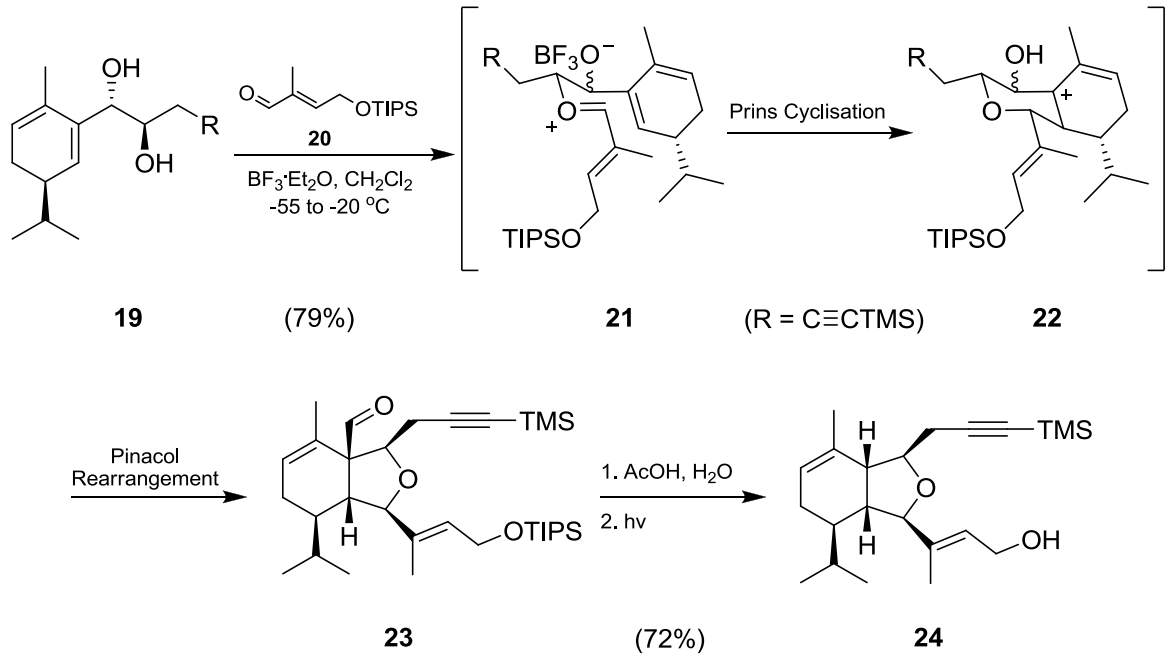
15 (61%) **16** (97%) **17**

(80%) **18** (64%, *anti*:*syn*, 9:1) **19** **14**

Scheme 3

The key Prins-pinacol condensation-rearrangement step was then performed by reacting diol **19** with an excess of enal **20** in the presence of $BF_3{\cdot}Et_2O$, in methylene chloride at low temperature. This reaction had been extensively studied by Overman and co-workers and consequently they had postulated a reaction mechanism.[12,13] The diol **19**

combines with the enal **20** in the presence of $BF_3{\cdot}Et_2O$ to form the more stable (*E*)-oxocarbenium ion **21**. This intermediate adopts the chair-like conformation required for the 6-*endo* cyclisation, with the substituents orientated in a pseudoequatorial position in the resulting transition state. This allows the oxocarbenium ion to approach the diene from the less sterically hindered side, affording the desired hexahydroisobenzofuran **23** as a single stereoisomer in 79% (**Scheme 4**). Cleavage of the triisopropylsilyl (TIPS) ether **23** under acidic conditions and photochemical decarbonylation to remove the formyl group gave bicyclic alcohol **24** in 72%.

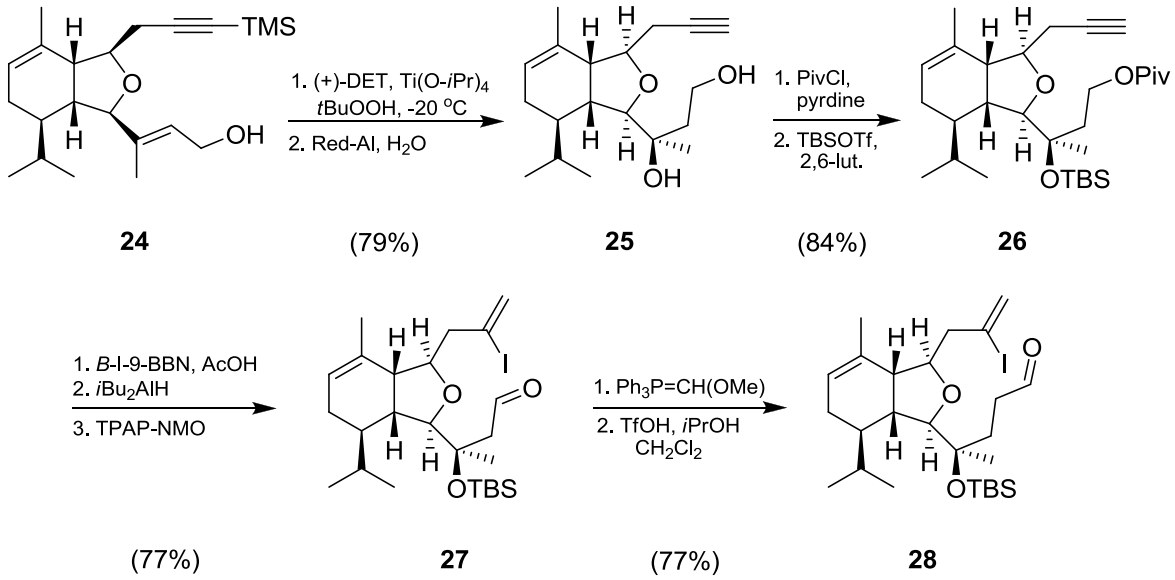


Scheme 4

To this point, intermediate **24** had been synthesised in 9 steps from (*S*)-glycidyl pivalate **15** with an overall yield of 17%, containing the full bicyclic core of (−)-7-deacetoxyalcyonin acetate (**9**, **Figure 4**).

The allylic alcohol functionality revealed by deprotection of the silyl ether was then utilised in a Sharpless asymmetric epoxidation of the alkene. The resulting epoxide was reduced regioselectively using bis(2-methoxy)ethoxyaluminium hydride (Red-Al), generating a tertiary alcohol stereoselectively. The *in situ* generation of NaOH effected concomitant cleavage of the trimethylsilyl (TMS) group to give the required diol **25** in 79% yield (**Scheme 5**). Differential protection of the primary and tertiary alcohols of diol **25** was performed in preparation for medium-ring closure, generating silyl ether

26. Selective iodoboration of the alkyne group of **26** with *B*-iodo-9-borabicyclo[3.3.1]nonane (*B*-I-9-BBN), followed by reductive cleavage of the pivaloyl group and TPAP-NMO oxidation, afforded aldehyde **27** in 77% yield. One carbon homologation of aldehyde **27**, by sequential treatment with (methoxymethylene) triphenylphosphorane and triflic acid, gave aldehyde **28** in 77% yield.

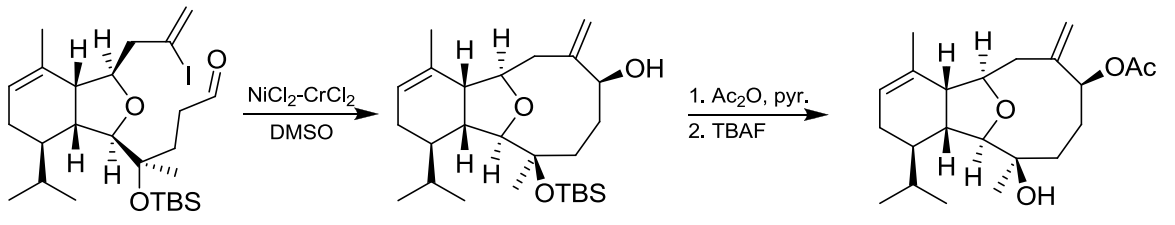


24 (79%) **25** (84%) **26**

(77%) **27** (77%) **28**

Scheme 5

The final ring was formed by an intramolecular Nozaki-Hiyama-Kishi coupling reaction using $NiCl_2$-$CrCl_2$ in DMSO, which afforded tricyclic ether **29** in 65% yield with high diastereoselectivity (>20:1 dr, **Scheme 6**). Finally, acetylation of alcohol **29** using acetic anhydride, and cleavage of the silyl ether with TBAF, gave (−)-7-deacetoxyalcyonin acetate (**9**) in 88% yield, completing the first total synthesis of a member of the ether-bridged 2,11-cyclised cembranoid family in 25 steps.[8]

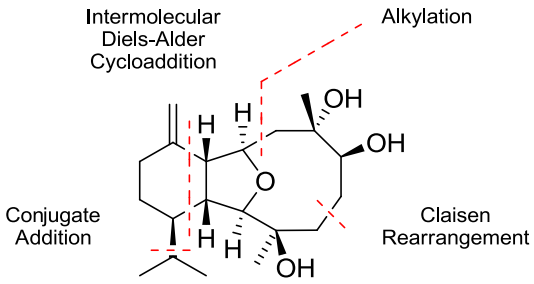


28 (65%) **29** (88%) (-)-Deacetoxyalcyonin acetate **9**

Scheme 6

1.2.2 The Paquette Group Approach

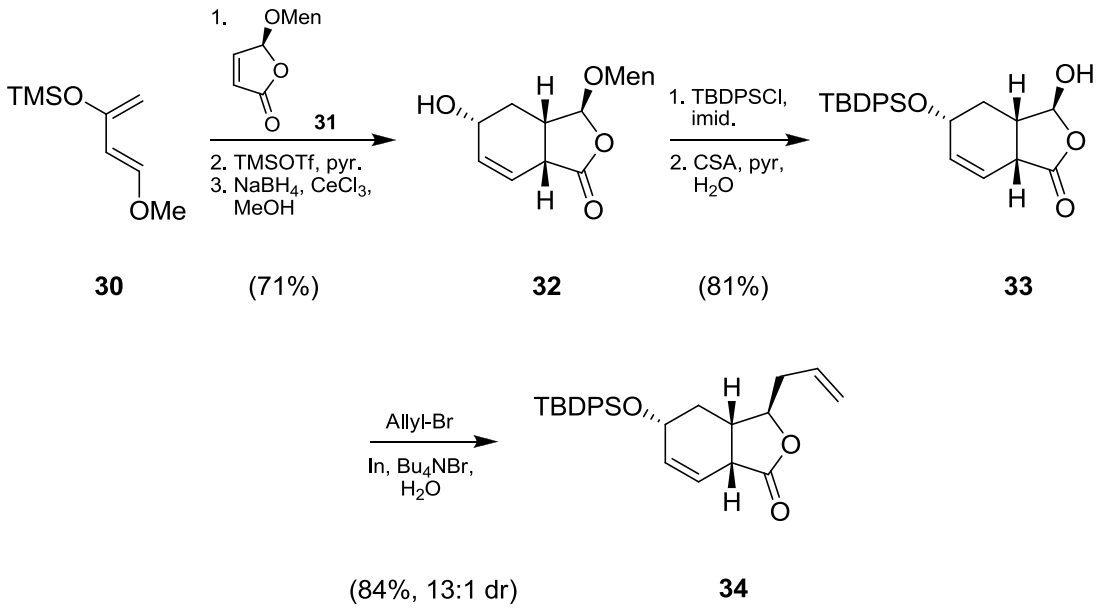
At the same time as the Overman group, Paquette and co-workers undertook the total synthesis of (−)-sclerophytin A (**2**, **Figure 1**) and disclosed their findings in 2001.[14] Their strategy was based upon a unique route utilising a Claisen rearrangement reaction as the key synthetic transformation to provide the required oxonane core of the cladiellins. This work resulted in the first total synthesis of (−)-sclerophytin A, which, to date, is the most cytotoxic cladiellin that has been isolated. A summary of the overall strategy employed by Paquette and co-workers is illustrated in **Figure 6**.



Paquette 2000-2001

Figure 6

The synthesis began with intermolecular Diels-Alder cycloaddition between Danishefsky's diene **30** and (5*S*)-5-(D-menthyloxy)-2-(5*H*)-furanone **31** (**Scheme 7**). The Diels-Alder adduct contained a labile silyl enol ether that was hydrolysed with concomitant loss of methoxide to give the corresponding enone. This ketone was then reduced under Luche conditions[15] to afford the desired allylic alcohol **32** in 71% yield. The secondary alcohol was protected as *t*-butyldiphenylsilyl (TBDPS) ether and the menthyl ether was cleaved to give hemiacetal **33**. The masked aldehyde of **33** then underwent an indium catalysed allylation to afford a mixture of diastereomers with a 13:1 ratio in favour of the desired bicycle **34**.

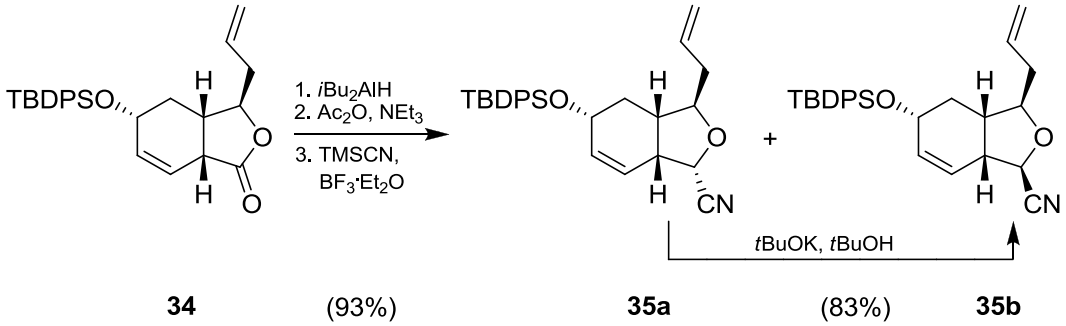


30 (71%) **32** (81%) **33**

(84%, 13:1 dr) **34**

Scheme 7

The lactone functionality of **34** was reduced to give a hemiacetal that was subsequently acetylated. The acetate was treated with trimethylsilyl cyanide to give a 1:1 mixture of nitriles **35a** and **35b** in excellent yield. Conversion of nitrile **35a** into **35b** was accomplished by thermodynamic equilibration using *t*BuOK in *t*BuOH (**Scheme 8**).

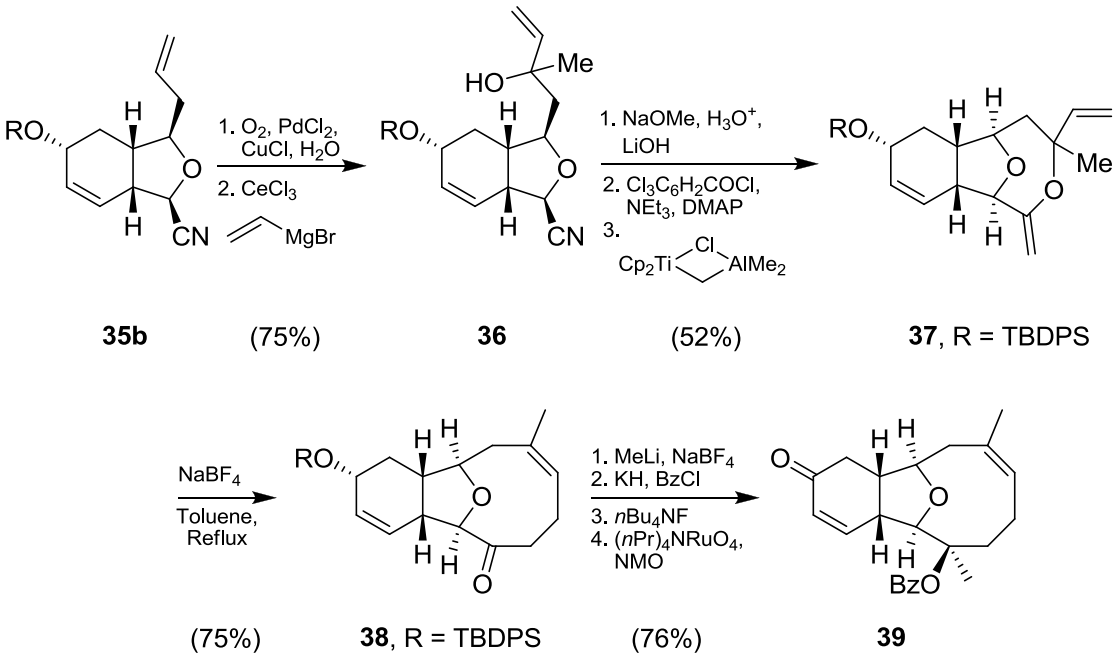


34 (93%) **35a** (83%) **35b**

Scheme 8

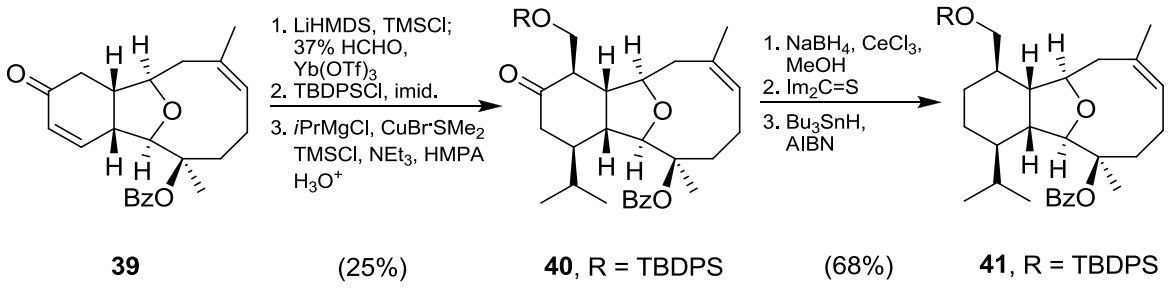
Wacker oxidation was performed on the terminal alkene of **35b** and the resulting ketone treated with vinyl magnesium bromide to provide tertiary alcohol **36** in 75% yield over two steps.[16] Hydrolysis of the nitrile gave the acid, which was subjected to Yamaguchi macrolactonisation to afford the corresponding lactone.[17,18] The lactone carbonyl group was methylenated using Tebbe conditions,[19] giving diene **37** in 52% yield (**Scheme 9**). With the required substrate for the Claisen rearrangement prepared, diene **37** was heated at reflux in toluene with sodium tetrafluoroborate ($NaBF_4$) to afford the required

oxonene **38** in 75% yield. Diastereoselective addition of methyllithium to ketone **38**, protection of the resulting tertiary alcohol, removal of the silyl ether and oxidation of the derived secondary alcohol produced enone **39** in 76% yield over four steps.



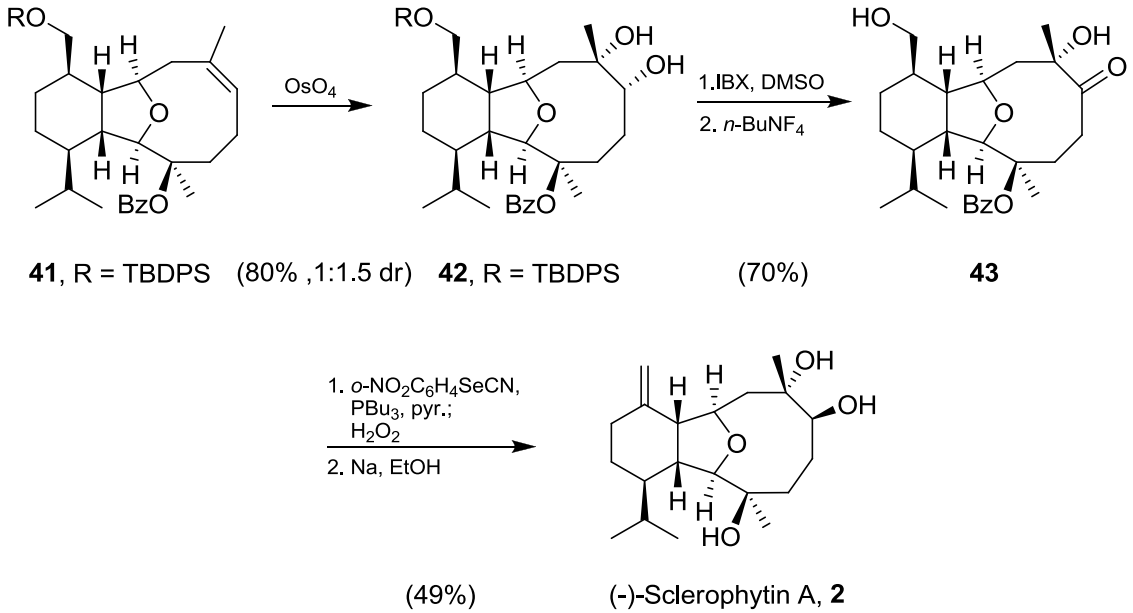
Scheme 9

Enone **39** was then hydroxymethylated by aldol condensation with formaldehyde, promoted by ytterbium triflate,[20] and the resulting alcohol protected as a silyl ether. Subsequent diastereoselective conjugate addition of the Gilman reagent[21] derived from isopropylmagnesium chloride, afforded ketone **40** in low yield (25% over 3 steps). Next, the three-step removal of the carbonyl functionality proceeded in 68% yield to give tricyclic ether **41** (**Scheme 10**).



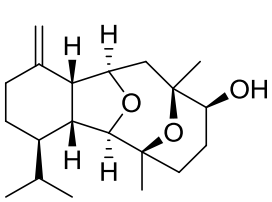
Scheme 10

Dihydroxylation of alkene **41** using osmium tetroxide resulted in a 1:1.5 mixture of the desired diol **42** and diastereomeric *syn*-1,2-diol. The C-6 hydroxyl was then oxidised to the ketone and the silyl ether cleaved using TBAF to give keto-alcohol **43** in 70% yield (**Scheme 11**). Finally, elimination of the primary alcohol of diol **43** using Grieco conditions[22] and concomitant cleavage of the benzoate ester was followed by ketone reduction using metallic sodium in ethanol, affording (−)-sclerophytin A (**2**) in 49% yield.



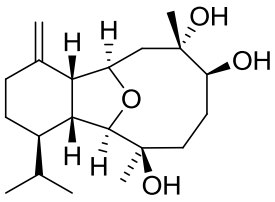
Scheme 11

The Overman group published their own synthesis of (−)-sclerophytin A (**2**) at almost the same time as the Paquette group and reduced the number of synthetic steps required to reach the target (from 35 to 27 steps). Although the Paquette synthesis was lengthy in comparison, it confirmed that the originally proposed structure of (−)-sclerophytin A (**44**) was incorrect (**Figure 7**). Both the Overman and Paquette groups had synthesised **44** and had found that its spectroscopic data differed significantly from that of the natural product. The Paquette group performed extensive NMR studies and a comprehensive literature investigation to elucidate the actual structure of (−)-sclerophytin A (**2**), which was in fact that shown in **Figure 7** (**2**).



Originally Proposed Structure of Sclerophytin A

44



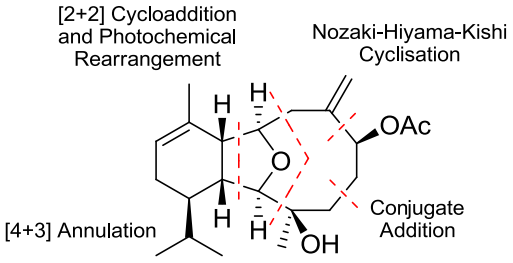
Authentic Structure of Sclerophytin A

2

Figure 7

1.2.3 The Molander Group Approach

The next researchers to publish in this field were Molander and co-workers, completing the total synthesis of (−)-7-deacetoxyalcyonin acetate (**8**) in 20 steps from the commercially available α-phellandrene (**45**).[23] The key synthetic transformations included; a [2+2]-cycloaddition and subsequent photochemical rearrangement to furnish the required hydroisobenzfuran ring, a Lewis acid mediated [4 + 3] annulation and a Nozaki-Hiyama-Kishi coupling reaction, which had previously been employed by the Overman group to close the medium ring (**Figure 8**).

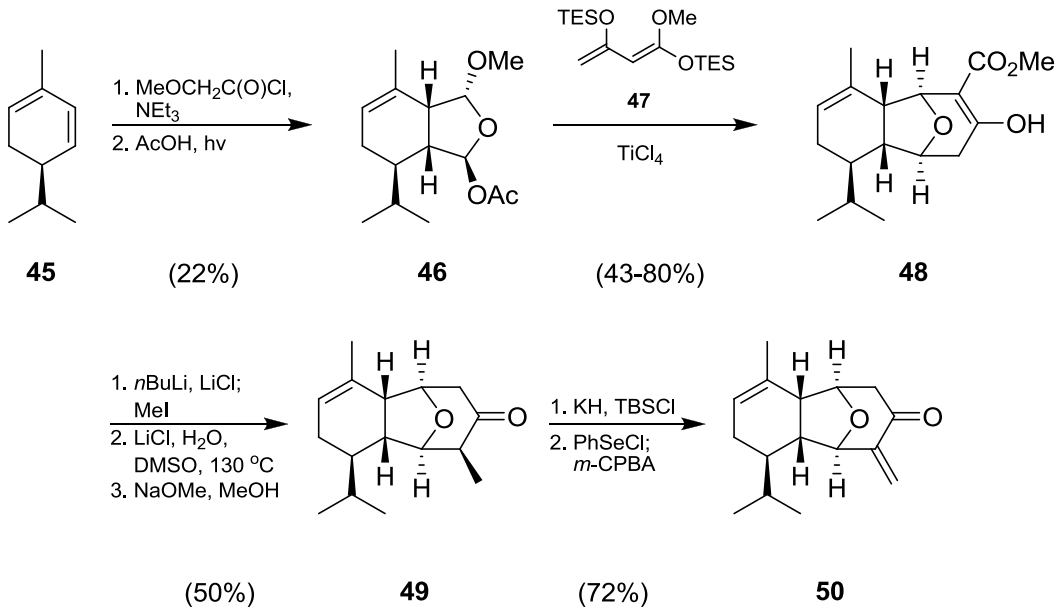


Molander 2004

Figure 8

The synthesis commenced with the formation of bisacetal **46** by the [2+2] cycloaddition of methoxyketene and α-phellandrene (**45**), followed by photochemical rearrangement (**Scheme 12**). Next, the [4+3] annulation reaction was performed by treatment of **46** with alkoxydiene **47** in the presence of titanium tetrachloride, affording tricycle **48** in yields ranging from 43-80%. In these first three steps, four of the stereocentres present in the target molecule were generated. Then, ester **48** underwent a diastereoselective

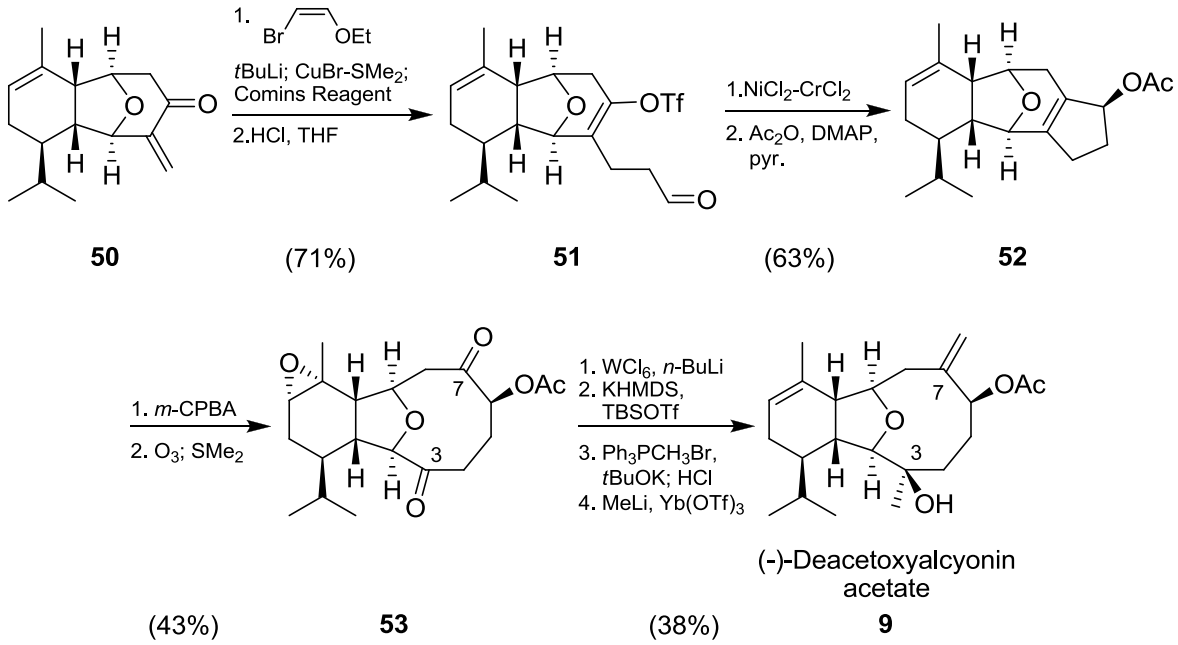
methylation using *n*-butyllithium, lithium chloride and methyl iodide. This was followed by a decarboxylation of the methyl ester using Krapcho conditions,[24] which unfortunately partially epimerised the newly formed methyl-bearing stereocentre (3.5:1 dr in favour of ketone **49**). This was corrected under basic conditions to afford ketone **49** in moderate yield. Next, ketone **49** was treated with potassium hydride and *tert*-butyldimethylchlorosilane (TBSCl) to form the tetrasubstituted silyl enol ether, after which, selenation and selenoxide elimination afforded enone **50** in 72% yield.



Scheme 12

Conjugate addition of the cuprate derived from *cis*-2-ethoxyvinyl bromide, followed by *in situ* formation of the vinyl triflate and hydrolysis of the ethyl enol ether, gave aldehyde **51** in 71% yield (**Scheme 13**). With the appropriate substituents now in place, the Nozaki-Hiyama-Kishi cyclisation reaction was performed and the resulting cyclopentenol acetylated to give ester **52** in 63% overall yield. Protection of the trisubstituted alkene as an epoxide was then performed in preparation for the ozonolysis reaction needed to generate the medium ring. These steps proceeded uneventfully, affording diketone **53** in 43% yield. The Sharpless tungsten reagent[25] was used to restore the trisubstituted alkene motif and the C-3 ketone was then selectively protected as a silyl enol ether using potassium hexamethyldisilazide (KHMDS) and *t*-butyldimethylsilyl triflate. This was followed by methylenation of the C-7 ketone, hydrolysis of the enol silane back to the C-3 ketone, and finally, selective methylation

of this carbonyl group using ytterbium triflate and methyl lithium to afford (−)-7-deacetoxyalcyonin acetate (**9**) as a single detectable diastereomer.



Scheme 13

The synthesis was completed in 20 steps with an overall yield of 0.4%. Fortunately, the low yielding steps contained within this synthesis were primarily at the start, enabling scale-up of these transformations to overcome the problem.

1.2.4 The Crimmins Group Approach

In 2004, the Crimmins group published a new approach to the synthesis of 2,11-cyclised cembranoids that involved formation of the medium ring followed by the construction of the hydroisobenzofuran and cyclohexyl rings. The keys steps involved using a ring-closing metathesis (RCM) reaction to form the medium ether ring, with completion of the final two rings by an intramolecular Diels-Alder reaction that would also generate three or four of the stereocentres required. A summary of the overall strategy employed by Crimmins and co-workers is illustrated in **Figure 9**.

Figure 9

The targets selected for the application of this strategy were ophirin B[26] (**54**), astrogorgin[27] (**55**) and 11-acetoxy-4-deoxyasbestinin D[6] (**8**), the first member of the asbestinin sub-class to be synthesised (**Figure 10**).

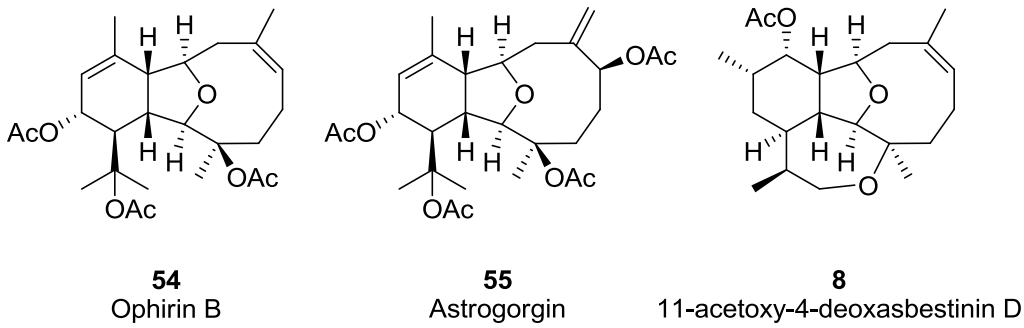
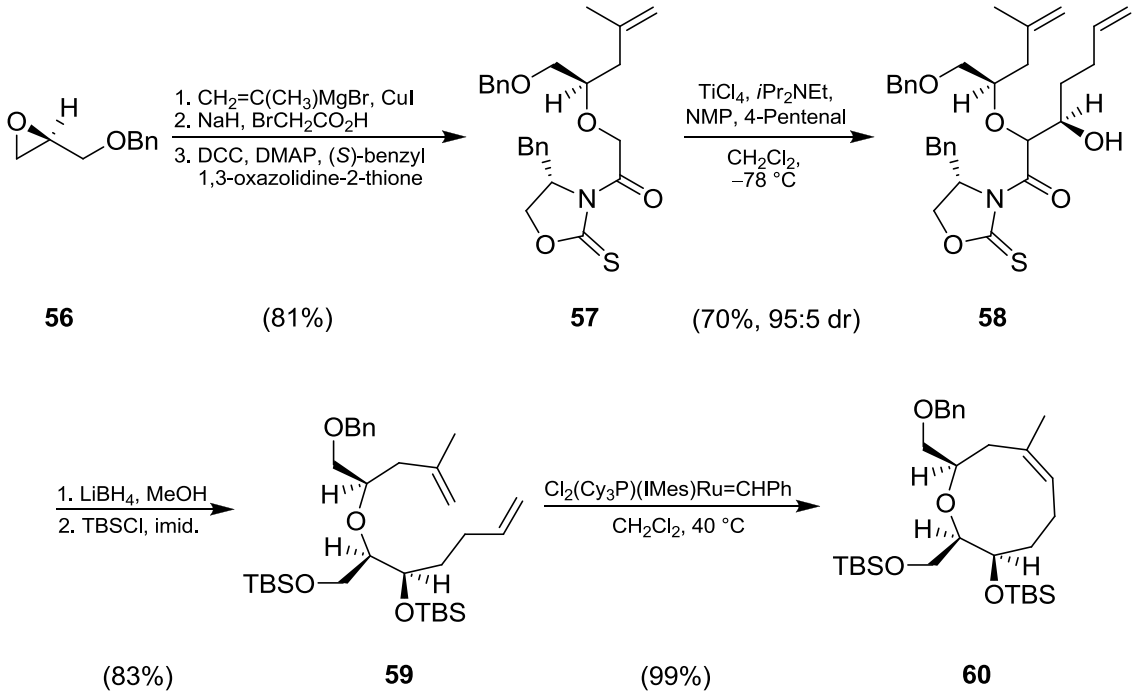


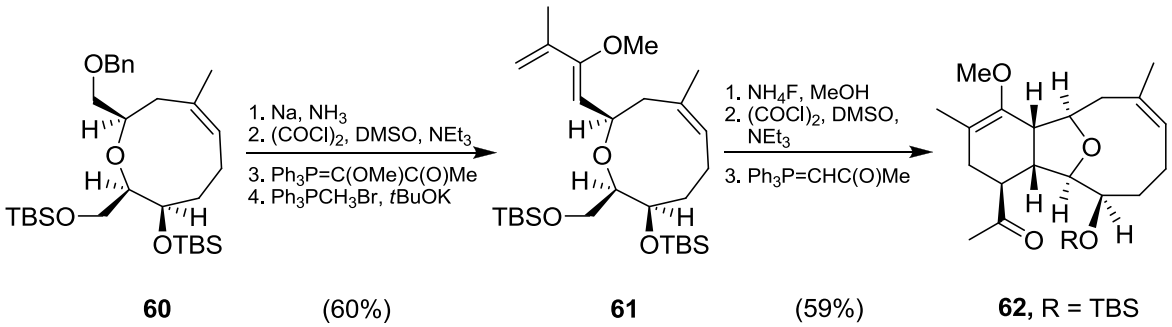
Figure 10

The synthesis of 11-acetoxy-4-deoxyasbestinin D (**8**) began with the opening of (*R*)-benzyl glycidyl ether (**56**) using 2-propenylmagnesium bromide and copper iodide (**Scheme 14**). The resulting alcohol was converted into oxazolidinethione **57** with the appropriate chiral auxiliary and coupling conditions. The titanium enolate of **57**, generated using the combination of $TiCl_4$ and Hünig's base, was reacted with 4-pentenal to form the glycolate aldol adduct **58** in good yield and high diastereoselectivity (95:5 dr). The chiral auxiliary was removed by lithium borohydride reduction and the resulting diol protected as its bis-TBS ether, generating the substrate required for the ring-closing metathesis (RCM) reaction. Treatment of diene **59** with Grubbs 2nd generation catalyst gave oxonene **60** in near quantitative yield.



Scheme 14

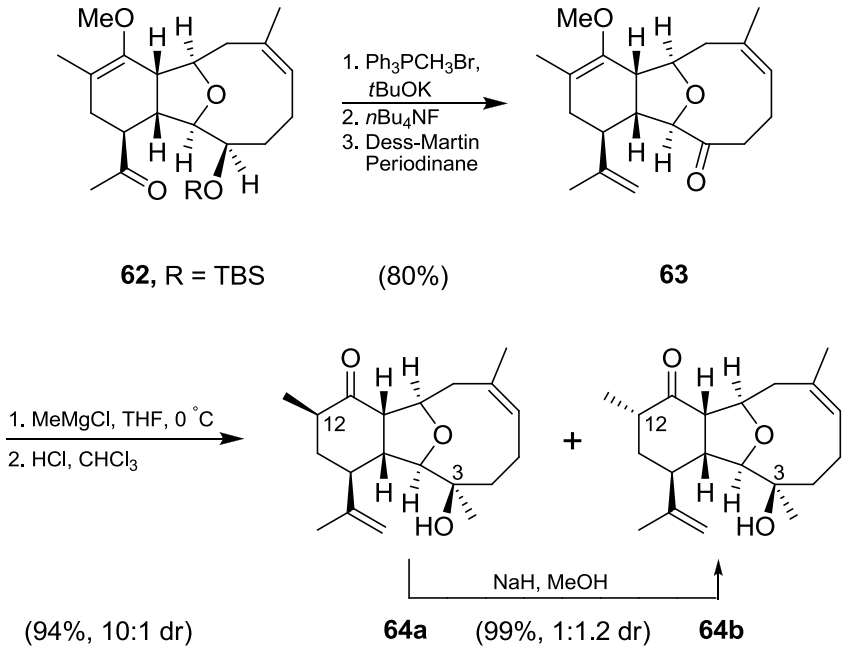
Dissolving metal reduction (Na/NH_3) removed the benzyl ether and subsequent Swern oxidation afforded the corresponding aldehyde. This compound was then subjected to two consecutive Wittig reactions to give diene **61** in 60% overall yield (**Scheme 15**). Removal of the primary silyl ether using ammonium fluoride and subsequent Swern oxidation gave the aldehyde in moderate yield. Wittig olefination with the required stabilised ylide resulted in a spontaneous *exo*-Diels-Alder cycloaddition to afford the desired tricyclic ketone **62** as a single diastereomer.



Scheme 15

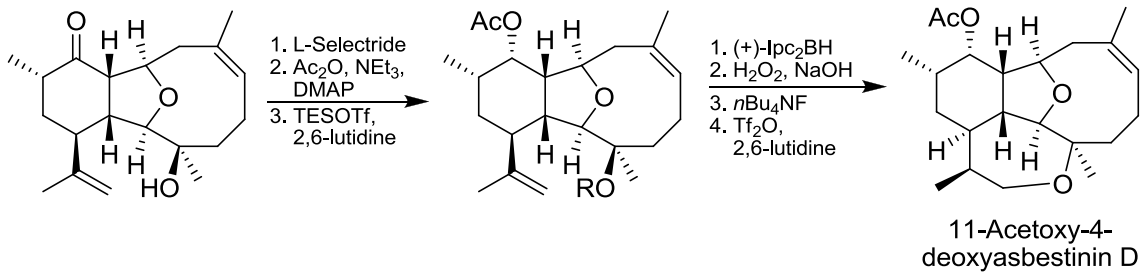
With construction of the diterpene skeleton complete, attention was turned to the functionalisation of the oxonene ring. Methylenation of the exocyclic ketone gave the alkene needed to generate the final ether ring (**Scheme 16**). This was followed by silyl

ether cleavage and subsequent oxidation, using Dess-Martin conditions,[28] to furnish ketone **63** in good yield. Diastereoselective methylation of the C-3 ketone using methylmagnesium chloride was followed by hydrolysis of the enol ether to give the α-methyl ketone, which unfortunately produced a 10:1 mixture of C-12 epimers favouring the wrong diastereomer. Separation of the diastereomers by chromatography and base-catalysed epimerisation of ketone **64a** afforded the required C-12 product (**64b**) in good yield after a two recycles.



Scheme 16

Stereoselective reduction of ketone **64b** was performed using L-Selectride and the resulting secondary alcohol was acetylated. Subsequent silyl ether protection of tertiary alcohol using triethylsilyl triflate and 2,6-lutidine afforded diene **65** in 75% over the three steps (**Scheme 17**). To complete the synthesis, chemoselective hydroboration of the 1,1-disubstituted alkene using (+)-diisopinocampheylborane followed by oxidation with hydrogen peroxide and sodium hydroxide afforded the required primary alcohol as a single diastereomer. The silyl ether was then removed using TBAF and selective formation of the primary triflate under basic conditions resulted in a spontaneous intramolecular etherification to close the final ring and give 11-acetoxy-4-deoxyasbestinin D (**8**).



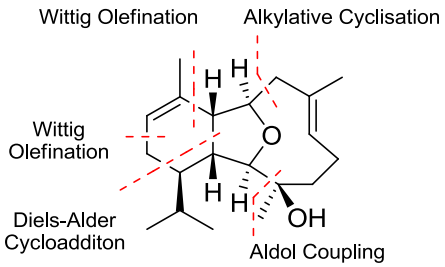
64b (75%) **65**, R = TES (43%) **8**

Scheme 17

The total synthesis of 11-acetoxy-4-deoxyasbestinin D (**8**) by the Crimmins group represented the first total synthesis of a natural product from the asbestinin sub-class. As a result, it served to confirm the absolute configuration of molecules within this sub-family of ether-bridged 2,11-cyclised cembranoids.

1.2.5 The Kim Group Approach

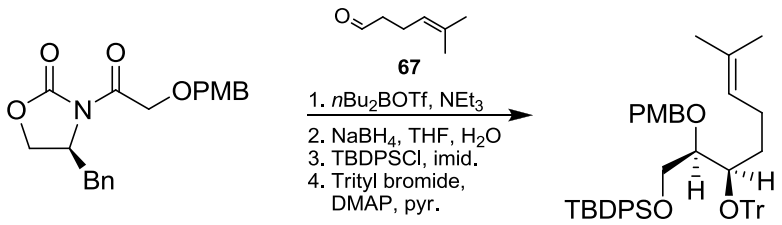
The next academic group to publish a complete total synthesis in this field was that of Kim in 2006.[29] The unique strategy adopted by the Kim group enabled the synthesis of (*E*)-alkene containing cladiellins for the first time, making it complementary to earlier research and enabling the synthesis of numerous members of the cladiellin family that had been inaccessible using previous strategies. The approach of Kim and co-workers involved the use of an intramolecular amide enolate alkylation, previously employed within the Kim group, and an intramolecular Diels-Alder cycloaddition to form the cyclohexyl and hydroisobenzofuran rings, analogous to the approach used by the Crimmins laboratory (**Figure 11**).



Kim 2006

Figure 11

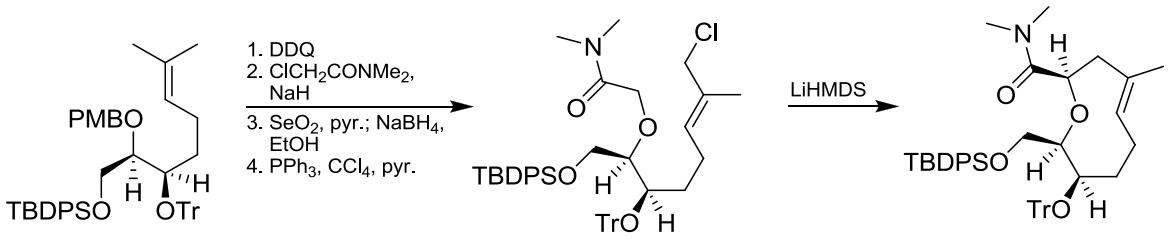
The synthesis of cladiella-6,11-dien-3-ol (**74**) started with an asymmetric glycolate aldol reaction between aldehyde **67** and the imide **66** using Evans dibutylboron triflate conditions.[30] Reductive removal of the chiral auxiliary using sodium borohydride was followed by the sequential protection of the primary alcohol as a silyl ether and the tertiary alcohol as a trityl ether, affording alkene **68** in 58% yield (**Scheme 18**).



66 (58%) **68**

Scheme 18

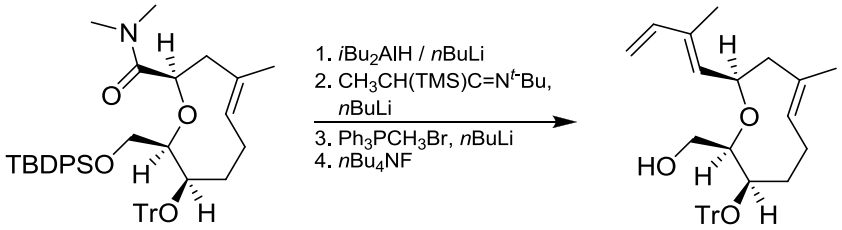
The *p*-methoxybenzyl (PMB) ether was removed by oxidation and the resulting alcohol was alkylated with *N*,*N*-dimethyl-2-chloroacetamide. Selective allylic oxidation and chloride displacement of the resulting alcohol gave the amide **69** (**Scheme 19**). Construction of the required (*E*)-oxonene **70** was completed by treatment of amide **69** with lithium hexamethyldisilazide (LiHMDS), affording a single detectable diastereomer in excellent yield.



68 (55%) **69** (92%) **70**

Scheme 19

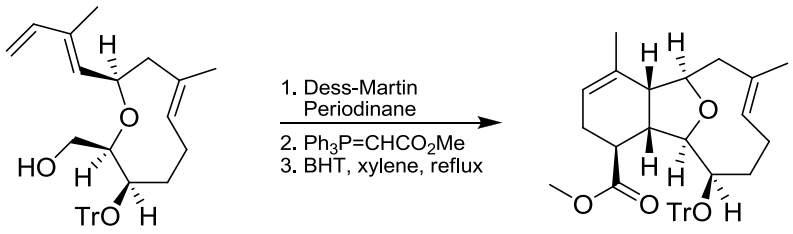
With the (*E*)-oxonene ether ring (**70**) completed, attention was turned to the generation of a suitable Diels-Alder substrate. The amide was reduced to the corresponding aldehyde using *i*Bu_2AlH/*n*BuLi, and subsequent olefination using Corey conditions[31] gave the required enal. Methylenation of the aldehyde carbonyl group, followed by silyl ether cleavage using TBAF afforded triene **71** in 62% yield (**Scheme 20**).



70 (62%) **71**

Scheme 20

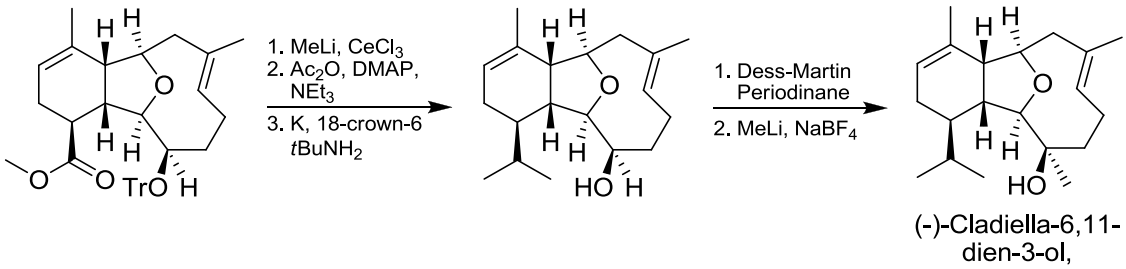
Oxidation of the primary alcohol gave the corresponding aldehyde, and construction of the dienophile by Wittig olefination gave the required Diels-Alder substrate. This compound was treated with 2,6-di-*t*-butyl-4-methylphenol (BHT), in refluxing xylene, to give the tricyclic ester **72** as a single diastereomer by an *exo*-cycloaddition (**Scheme 21**).



71 (67%) **72**

Scheme 21

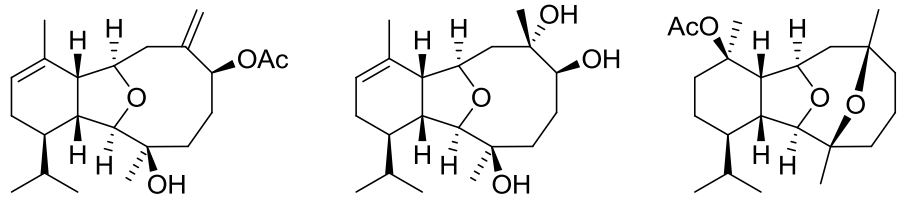
Addition of two equivalents of methylmagnesium chloride to ester **72**, followed by acetylation of the resulting tertiary alcohol, gave the required acetate. This ester was subjected to dissolving metal reduction which deoxygenated the ester and removed the trityl ether, giving diene **73** in 56% yield (**Scheme 22**). Oxidation of the C-3 alcohol to give the ketone and subsequent diastereoselective addition of methyllithium gave (−)-cladiella-6,11-dien-3-ol (**74**) as a single diastereomer, completing the total synthesis with an overall yield of 5.3%.



72 (56%) **73** (82%) **74**

Scheme 22

To further illustrate the flexibility of their strategy, Kim and co-workers synthesised three other cladiellins in a minimal number of steps using (−)-cladiella-6,11-dien-3-ol (**74**) as a starting material. These included; polyanthellin A (**75**), (−)-cladiell-11-ene-3,6,7-triol (**10**) and (−)-7-deacetoxyalcyonin acetate (**9**) (**Figure 12**).



(-)-7-deacetoxyalcyonin acetate, **9**

Cladielli-11-ene-3,6,7-triol, **10**

Polyanthellin A, **75**

Figure 12

The Kim group strategy was distinctive in comparison to approaches adopted by other groups because it enabled the synthesis of both *E* and *Z* cladiellin isomers, thus making it the only truly general approach up to this point. The availability of the *E*-oxonene ring (**70**) enables the direct introduction of the *anti*-1,2-diol functionality present in many of the cladiellins, and the complete construction of all three rings illustrated its synthetic utility.

1.2.6 The Clark Group Approach

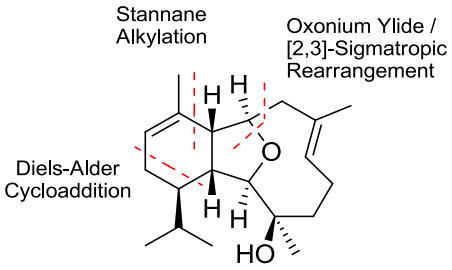
In 2007, the Clark group published the first total synthesis of (±)-vigulariol (**76**), a member of the cladiellin sub-class, which was completed in 20 steps with an overall yield of 4% (**Figure 13**).[32] Isolated from the octocoral *Vigularia juncea* by Sheu and co-workers, this target diterpenoid exhibits *in vitro* cytotoxicity against A 549 (human-lung adenocarcinoma) cell line with an IC_{50} = 18 μM.[33]

Vigulariol, **76**

R = H (–)-cladiella-6,11-dien-3-ol **74**
R = Ac (–)-3-Acetoxycladiella-6,11-diene **77**

Figure 13

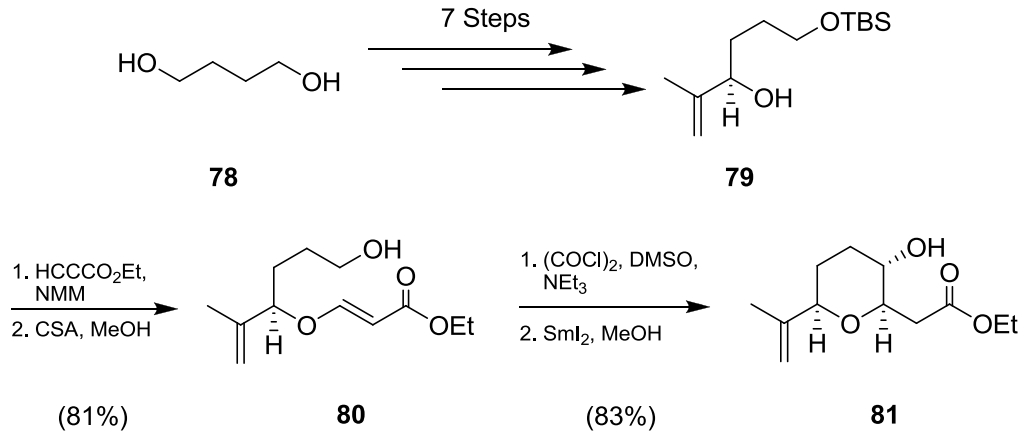
The Clark group followed this publication in 2010 with the optimisation of their key tandem oxonium ylide formation and [2,3]-sigmatropic rearrangement sequence.[34] It was found that this cyclisation reaction could be used to access cembranoids containing an *E*-oxonene by the use of a rhodium(II) catalyst, complimenting the copper-catalysed reaction used in the total synthesis of (±)-vigulariol (**76**). They disclosed the total syntheses of (−)-cladiell-11-ene-3,6,7-tiol (**10**, **Figure 12**), (−)-3-acetoxycladiella-6,11-diene (**77**, **Figure 13**) and (−)-cladiella-6,11-dien-3-ol (**74**), the latter of which had been shown by Kim and co-workers to be a versatile late-stage intermediate in the synthesis of several other cladiellin targets (**Figure 14**).



Clark 2007-2010

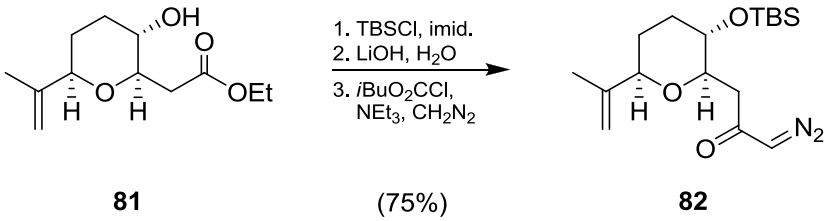
Figure 14

The synthesis of (−)-cladiella-6,11-dien-3-ol (**74**) hinged on the formation of the enantioenriched allylic alcohol (**79**). This was accessed using a known literature procedure in which Sharpless asymmetric epoxidation was used to afford an epoxide with high ee that was then converted into the enantioenriched alcohol in multi-gram quantities (>94% *ee*).[35] *O*-Alkylation using ethyl propiolate and silyl ether cleavage afforded the vinylogous carbonate **80** in good yield (**Scheme 23**). Swern oxidation[36] of alcohol **80** gave the corresponding aldehyde, which then underwent the key stereoselective reductive cyclisation mediated by samarium(II) iodide, affording tetrahydropyranol **81** in good yield.



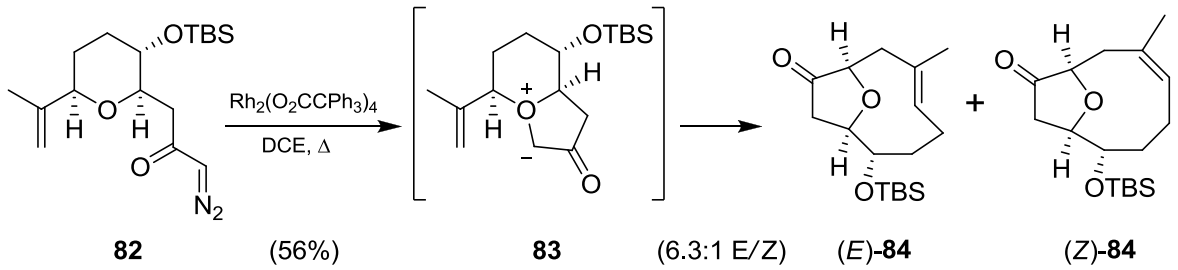
Scheme 23

Silyl ether protection was followed by saponification of the ester using lithium hydroxide. The resulting carboxylic acid was treated with *iso*-butylchloroformate to produce a mixed anhydride, which was then treated with diazomethane to give diazoketone **82** (**Scheme 24**).



Scheme 24

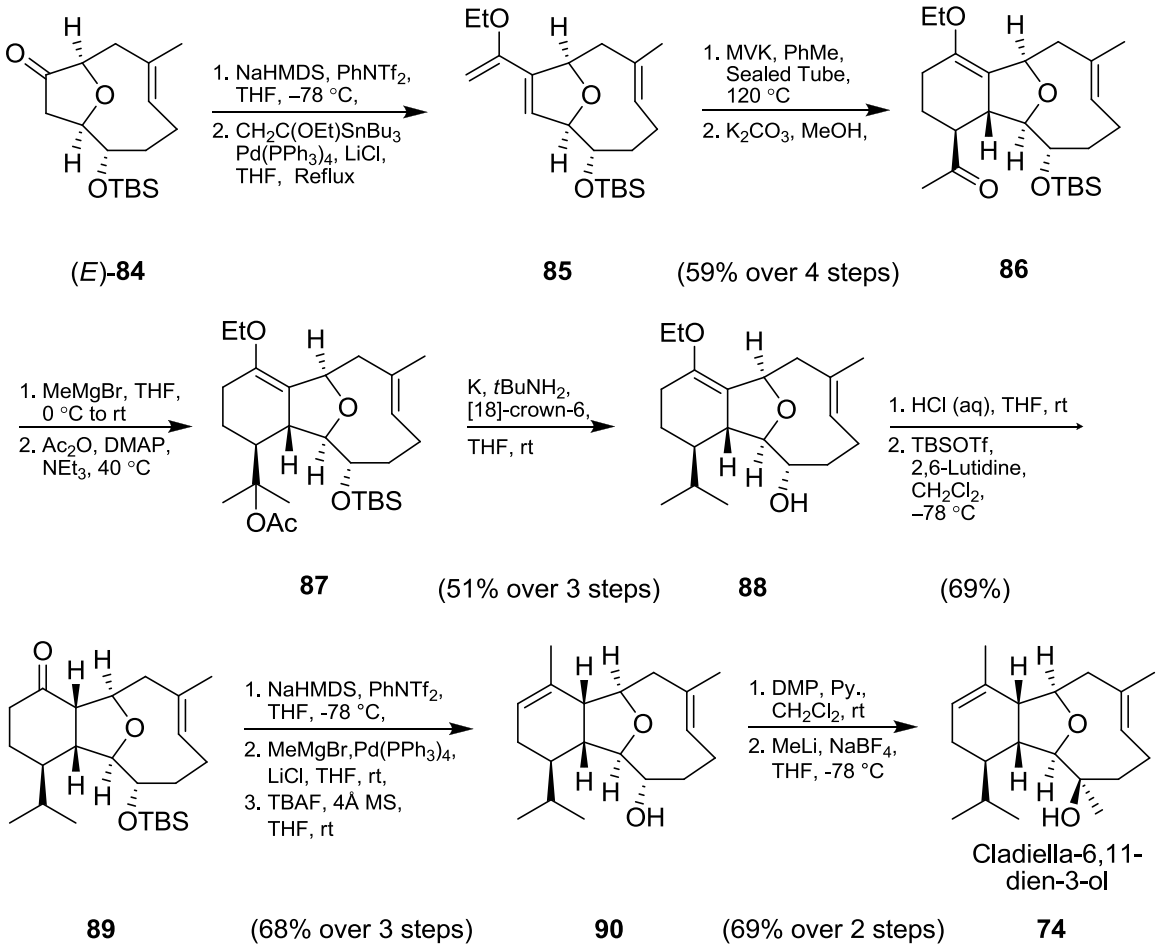
Treatment of diazoketone **82** with $Rh_2(O_2CCPh_3)_4$ generated the rhodium carbenoid, which cascaded through formation of the oxonium ylide (**83**) and subsequent [2,3]-sigmatropic rearrangement (**Scheme 25**), generating the conjoined (*E*)-oxonene and hydroisobenzofuranone ring [(*E*)-**84**] in moderate yield. The reaction generated a 6.3:1 mixture of *E*/*Z* oxonene stereoisomers, which contrasted with the copper-catalysed reaction reported in the group's 2007 publication [$Cu(hfacac)_2$ (5 mol%), CH_2Cl_2, reflux (96%, 5:1 Z/E)].[32]



82 (56%) **83** (6.3:1 E/Z) (*E*)-**84** (*Z*)-**84**

Scheme 25

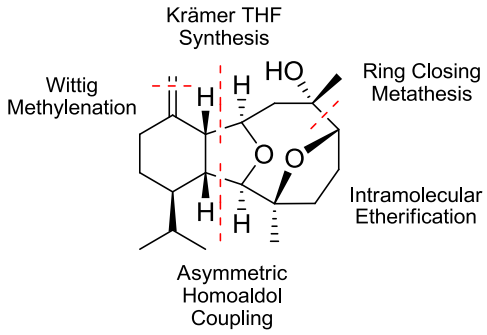
Ketone (*E*)-**84** was then converted into the enol triflate, which was followed by Stille coupling[37] with (1-ethoxyvinyl)tributylstannane to give diene **85**. Diels–Alder cycloaddition between diene **85** and methyl vinyl ketone (MVK), performed in a sealed tube, afforded tricyclic ketone **86** as a mixture of isomers (1.6:1, *endo*/*exo*). Treatment of the mixture of isomers with potassium carbonate in methanol delivered the thermodynamically favoured epimer, *exo*-(**86**), in 59% yield over four steps (**Scheme 26**). Ketone **86** was then treated with methylmagnesium bromide and the resulting tertiary alcohol acetylated to afford ester **87**. Removal of the acetate group was achieved by reductive elimination of the ester using metallic potassium and [18]-crown-6 in a *t*$BuNH_2$/tetrahydrofuran solvent system, analogous to that described by Kim and co-workers during their synthesis of (−)-cladiella-6,11-dien-3-ol (**74**, **Scheme 22**).[29] Unfortunately this reduction led to the removal of the silyl ether, and so reprotection of the hydroxyl group was necessary. Aqueous acidic hydrolysis of the enol ether followed by TBS-protection of the alcohol afforded ketone **89** in good yield. Ketone **89** was converted into the enol triflate and then subjected to a palladium(0)-mediated cross-coupling reaction to introduce the C-11 methyl substituent. This was followed by silyl ether cleavage to furnish alcohol **90** in 68% over the three steps. Finally, Dess–Martin oxidation[28] of alcohol **90** followed by addition of methyllithium, in the presence of $NaBF_4$, completed the synthesis of (−)-cladiella-6,11-dien-3-ol (**74**) .



Scheme 26

1.2.7 The Hoppe Group Approach

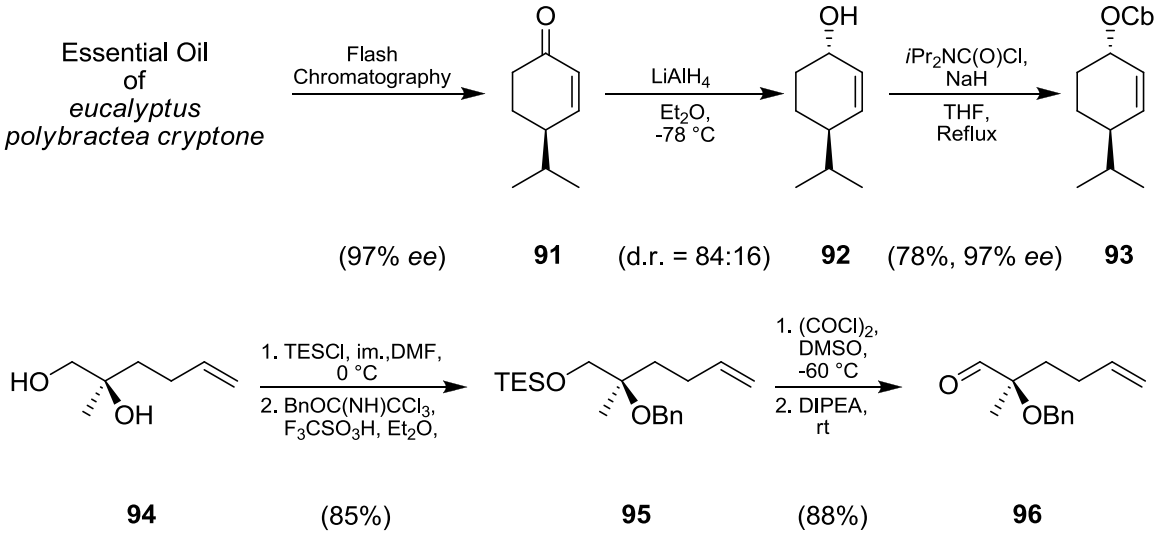
To date, the shortest total synthesis of a cladiellin natural product has been carried out by Hoppe and co-workers, completing the total synthesis of (+)-vigulariol in ten steps with an overall yield of 5%.[38] Their strategy for the construction of the tricyclic core centred around three key reactions: an asymmetric homoaldol reaction of a carbamate with an α-stereogenic enal, subsequent Krämer tetrahydrofuran synthesis with an appropriate acetal and finally a ring-closing metathesis reaction to construct the oxonene ring, analogous to the approach used by Crimmins (**Figure 15**).[39-41]



Hoppe 2008

Figure 15

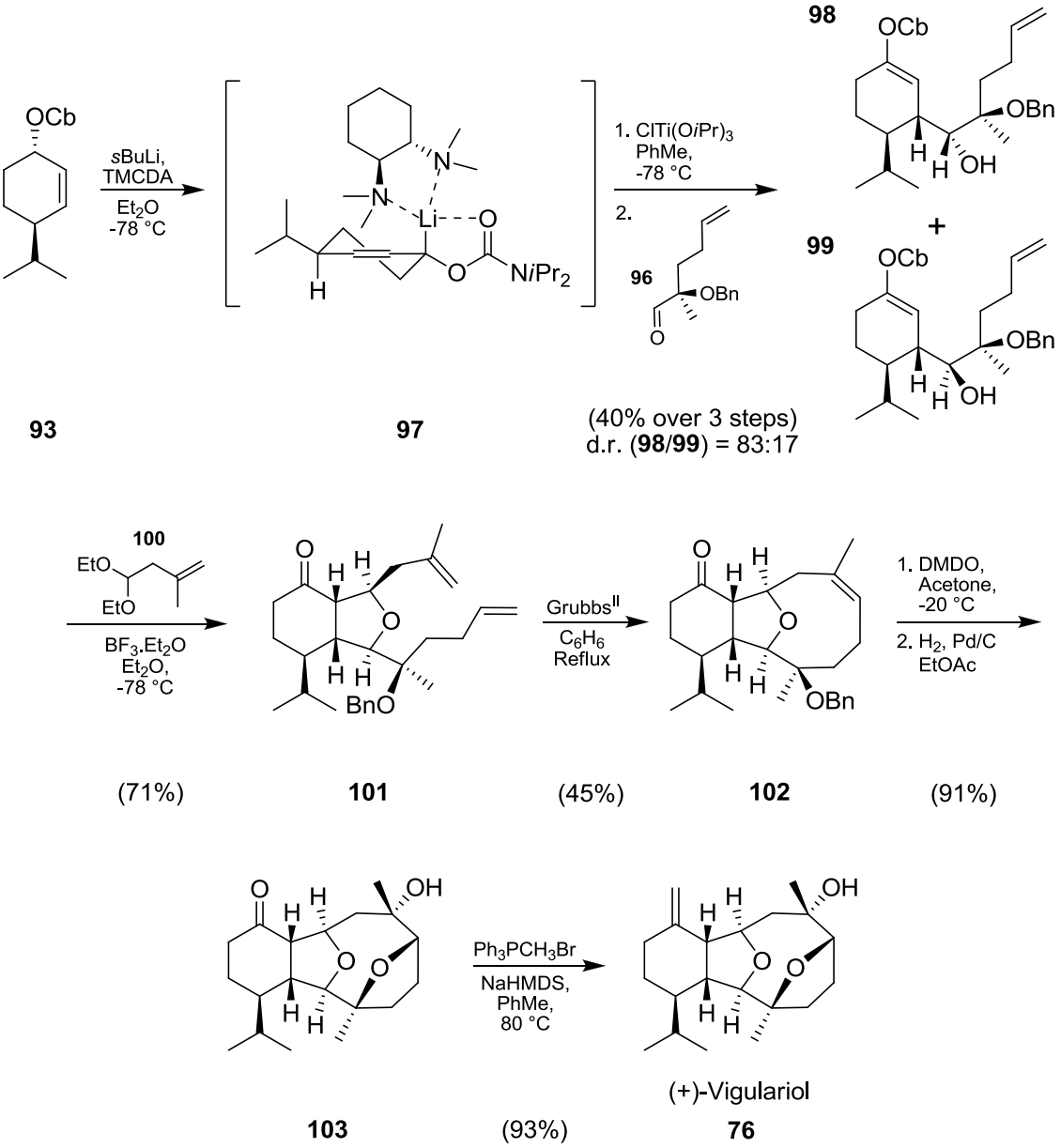
The synthesis began with the flash chromatography of commercially available eucalyptus oil which contained approximately 5% of the required (*R*)-(−)-cryptone (**91**) in 97% *ee*. This ketone was then reduced using $LiAlH_4$ to afford cyclohexanol **92** (d.r. = 84:16) which, after carbamoylation, gave cyclohexene **93** in good yield (**Scheme 27**). The required homoaldol coupling partner was generated from enantiopure diol **94** by a sequence of selective protections and direct oxidation of the silyl ether to the corresponding aldehyde **96**.[42]



Scheme 27

The asymmetric homoaldol reaction between coupling partners **93** and **96** was achieved by deprotonation of **93** using *s*-BuLi and TMCDA, subsequent lithium-titanium exchange using $ClTi(O\textit{i}\text{-}Pr)_3$ and trapping of the resultant anion with aldehyde **96** to give the required diastereomer **98** (40%, d.r. = 83:17). Lewis acid mediated tetrahydrofuran

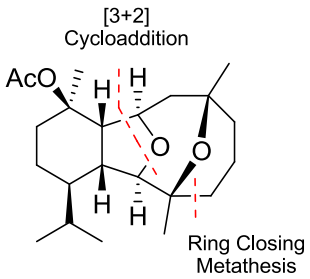
formation with acetal **100** provided RCM precursor **101** in 71% yield.[43,44] The (*Z*)-oxonene ring was formed in moderate yield using Grubbs 2nd generation catalyst. The resulting alkene **102** then underwent epoxidation, followed by removal of the benzyl protecting group and concomitant stereospecific attack of the epoxide, to construct the final cyclic ether (91%). Finally, (+)-vigulariol (**76**) was obtained by Wittig methylenation of ketone **103** in excellent yield.



Scheme 28

1.2.8 The Johnson Group Approach

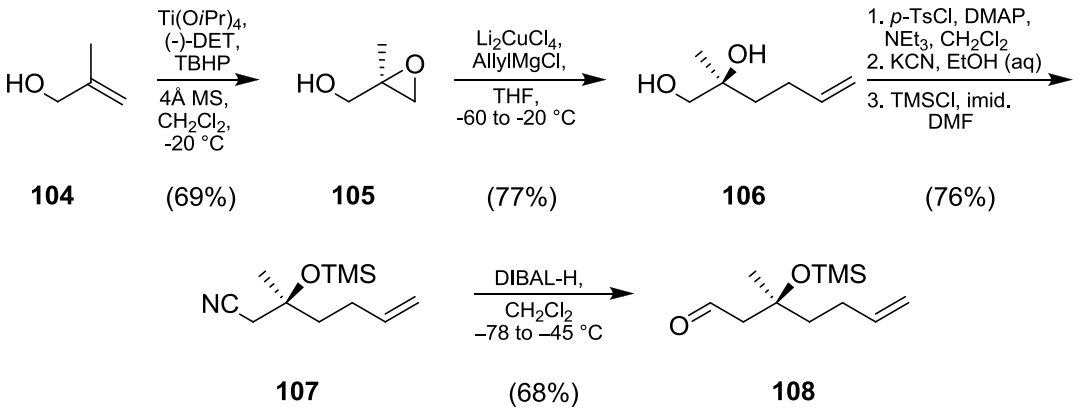
The next academic group to publish in this field was that of Johnson in 2009.[45] They reported a convergent total synthesis of polyanthellin A (**75**, **Figure 12**) with a longest linear sequence of 14 steps in 2% overall yield. Their strategy relied on a formal [3+2] cycloaddition reaction to construct the required hydroisobenzofuran core, as well as a ring-closing metathesis reaction to generate the oxonene ring (**Figure 16**).



Johnson 2009

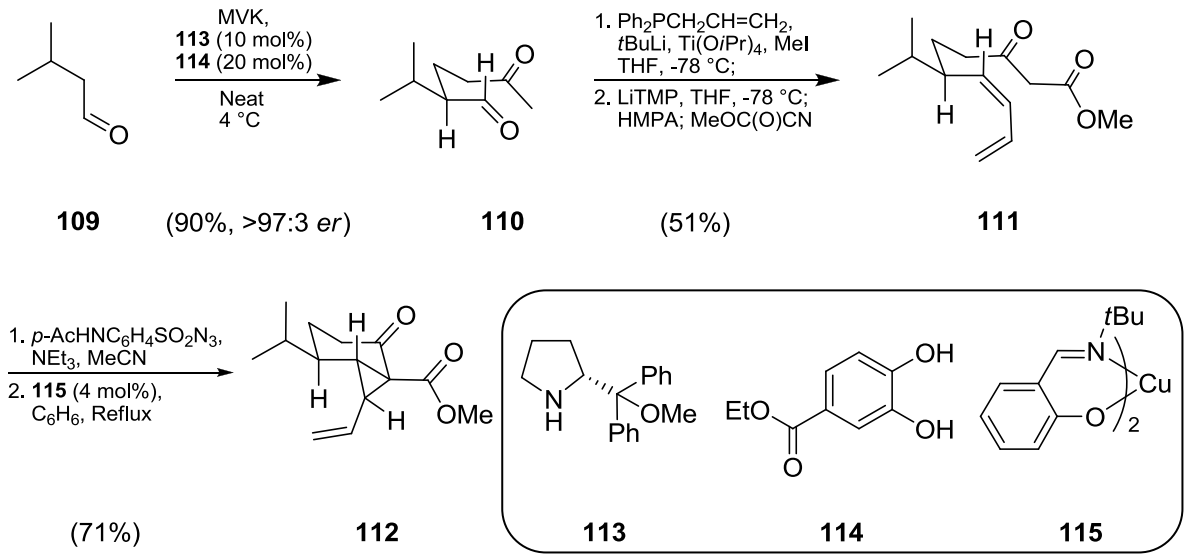
Figure 16

Their synthesis converged at the key [3+2] cycloaddition step, and so the aldehyde coupling partner **108** was required (**Scheme 29**). Sharpless asymmetric epoxidation of crotyl alcohol **104** followed by allyl cuprate addition afforded diol **106** in moderate yield. The primary alcohol of **106** was converted to the nitrile **107** *via* a tosylate displacement reaction and subsequent silyl protection of the tertiary hydroxyl group. Finally, DIBAL-H reduction of the nitrile furnished the required aldehyde **108** in 68% yield.



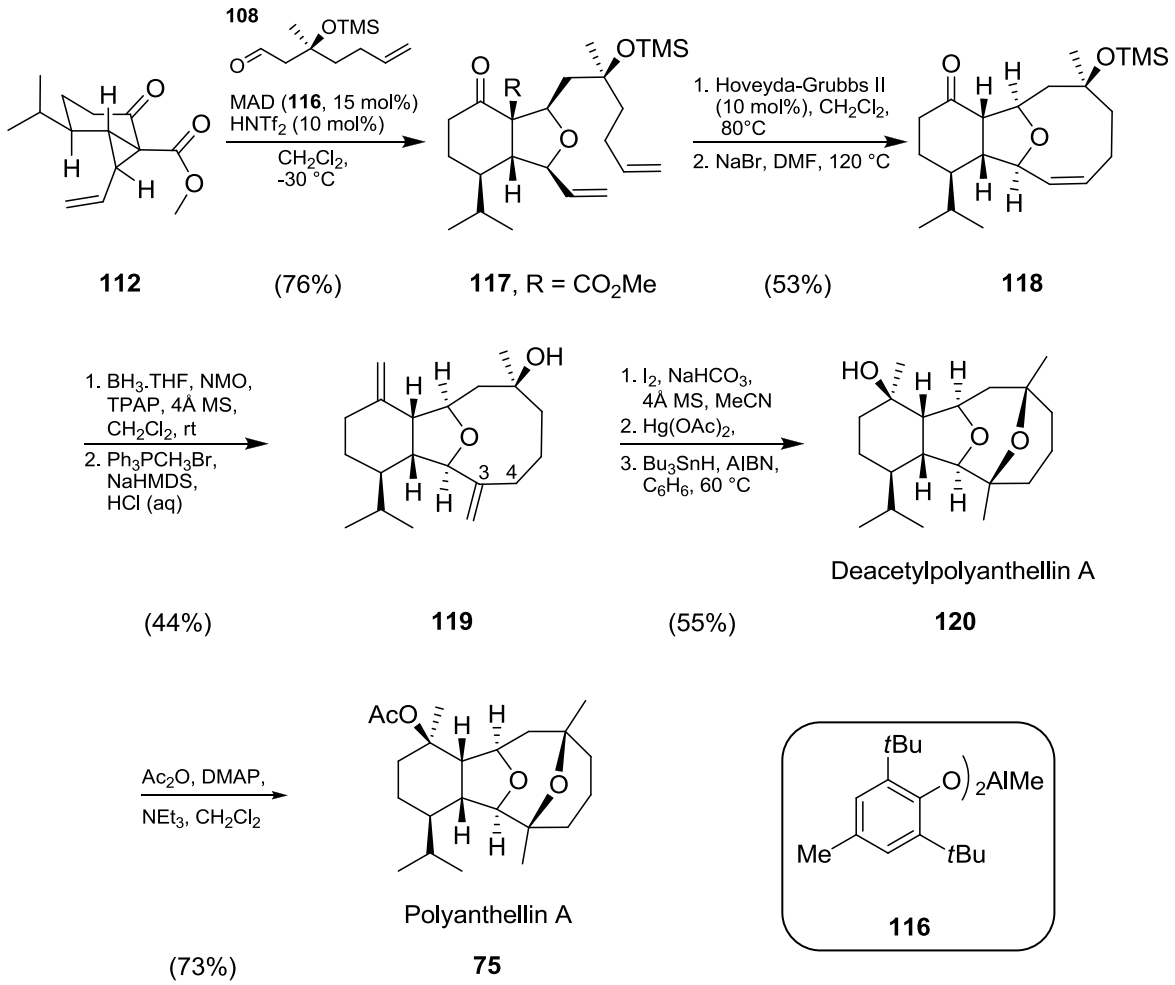
Scheme 29

Enantioselective organocatalytic conjugate addition of isovaleraldehyde (**109**) to methyl vinyl ketone, mediated by prolinol methyl ether **113**, afforded keto-aldehyde **110** in excellent yield and enantiomeric excess (>94 *ee*, **Scheme 30**). Conversion to the dienyl ß-keto-ester **111** was achieved *via* Wittig reaction with a titanated allyldiphenylphosphine reagent, generating the (*Z*)-terminal diene, followed by carboalkoxylation using LiTMP and Mander's reagent. Formation of furan precursor **112** required the formation of an intermediate diazo compound which then underwent intramolecular cyclopropanation, catalysed by Cu(*t*BuSal)$_2$ (**115**).



Scheme 30

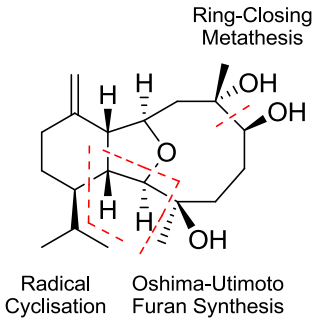
After extensive screening of Lewis acids, Johnson and co-workers discovered a potent MADNTf$_2$ catalyst system for the [3+2] cycloaddition of aldehyde **108** with cyclopropane **112**. This catalytic system was formed *in situ* from the protonolysis of HNTf$_2$ by a sterically encumbered and Lewis acidic alumino BHT reagent, affording cycloadduct **117** in 76% yield. Ring-closing metathesis, conducted under high dilution conditions, was performed using Hoveyda-Grubbs 2nd generation catalyst, furnishing the final (*Z*)-oxonene ring in good yield (70%). This was followed by thermal decarboxylation using Krapcho conditions to give tricyclic ketone **118** (**Scheme 31**). Direct hydroboration of alkene **118** and TPAP oxidation[46] afforded the corresponding diketone in modest yield (49%), and subsequent bis-methylenation afforded the diene **119**. A three-step sequence comprising iodoetherification, oxymercuration and Bu$_3$SnH/AIBN reduction then delivered deacetylpolyanthellin A (**120**) as a 6:1 mixture of diastereomers. Finally, acetylation under standard conditions afforded polyanthellin A (**75**) in 73% yield.



Scheme 31

1.2.9 The Morken Group Approach

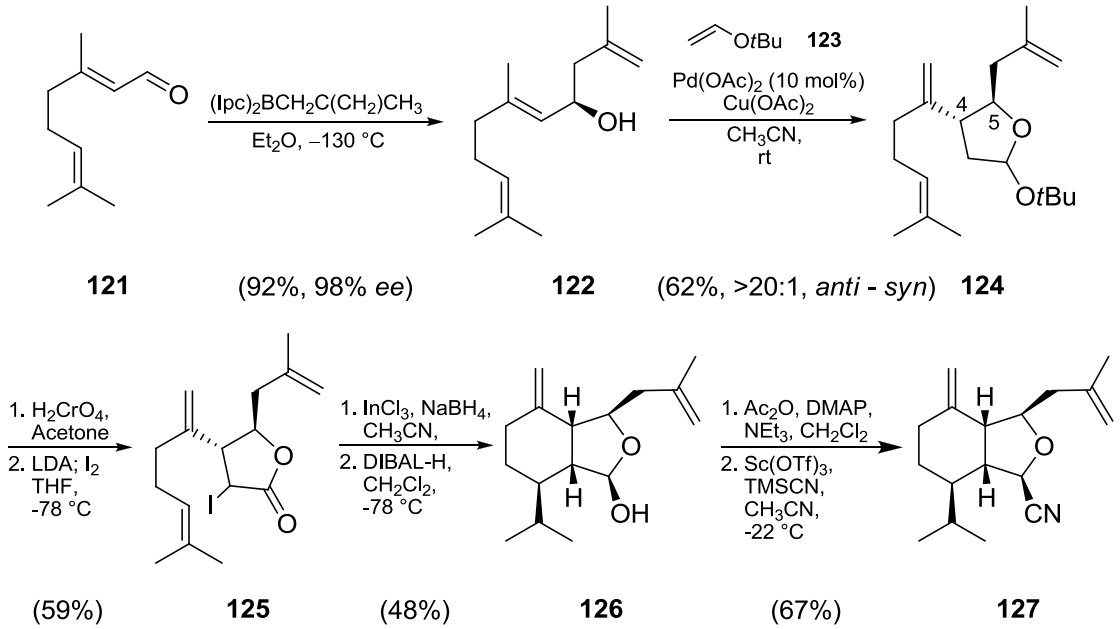
The latest researchers to publish a synthesis of a cladiellin natural product were Morken and co-workers in 2010.[47] They reported a linear total synthesis of (−)-sclerophytin A (**2**, **Figure 1**), in 13 steps and 3% overall yield. Their strategy was unique in that the hydroisobenzofuran core was constructed first using an Oshima-Utimoto protocol.[48-50] This was followed by a tin-free 6-*exo*-trig radical cyclisation reaction to form the cyclohexyl ring and a ring-closing metathesis reaction to generate the oxonene ring (**Figure 16**).



Morken 2010

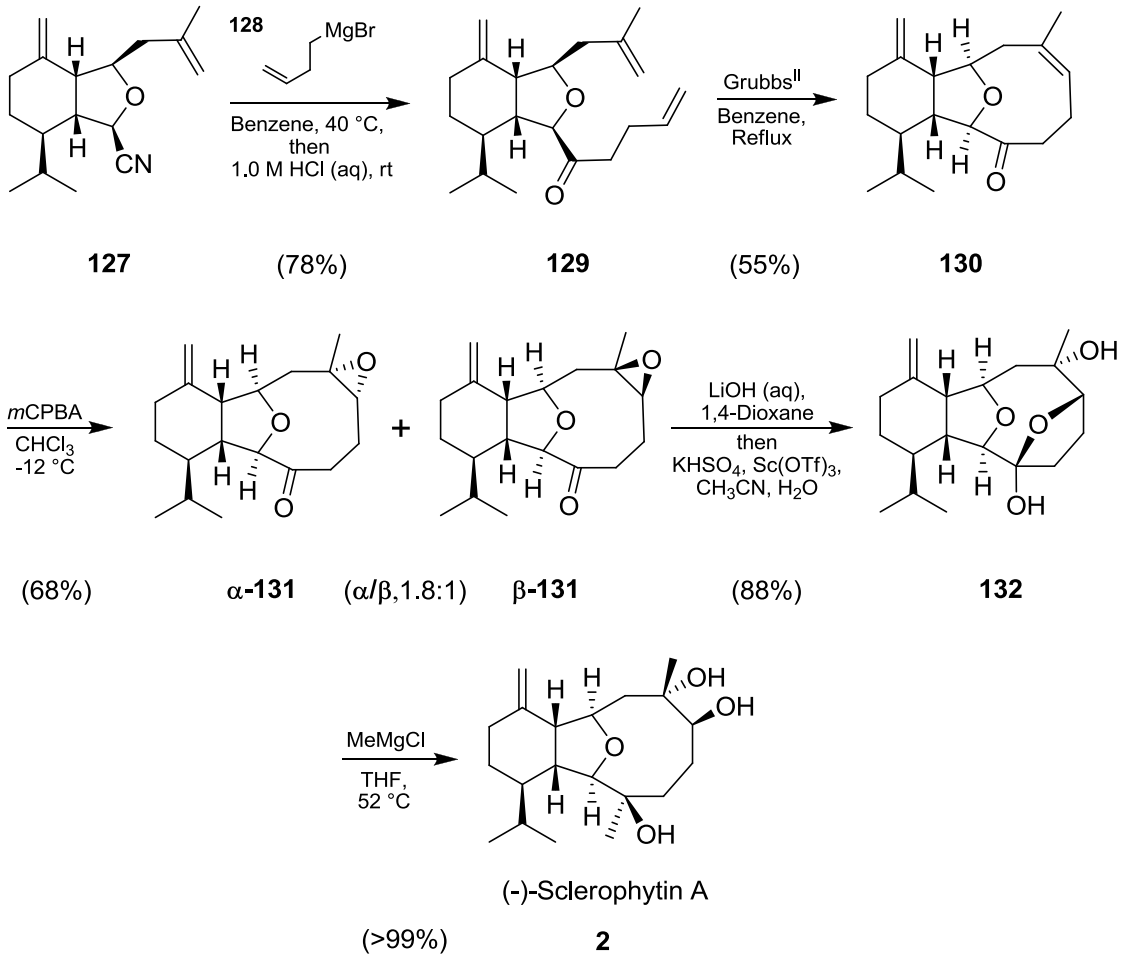
Figure 17

The synthesis began with the formation of allylic alcohol **122** from geranial (**121**) in one step by means of Brown's methallylation procedure (**Scheme 32**).[51-53] Next, an Oshima-Utimoto reaction using vinyl *t*-butoxide was employed to construct the tetrahydrofuran **124** as a mixture of epimers in moderate yield (62%). Jones oxidation of **124** to the corresponding lactone revealed that the key ring-forming reaction had proceeded to give a mixture of isomers with >20:1 *anti*/*syn* (C4:C5) ratio. α-Iodination of the lactone afforded the radical cyclisation precursor **125** in 59% over the two steps. Treatment of **125** with $InCl_3$ and $NaBH_4$ generated the cyclohexyl ring and subsequent DIBAL-H reduction of the lactone gave the hemiketal **126** in moderate yield. The hydroxyl group of **126** was then converted into a nitrile with retention of configuration by means standard transformations to give bicycle **127** in 67% yield.



Scheme 34

Formation of RCM precursor **129** was achieved in good yield by treatment of nitrile **127** with butenylmagnesium bromide followed by an acidic aqueous work-up (**Scheme 33**). Exposure to Grubbs 2nd generation catalyst afforded (*Z*)-oxonene **130** in moderate yield, the alkene of which was epoxidised under standard conditions in a highly regioselective manner, but with poor diastereoselectivity (68%, α-**131**/β-**131**, 1.8:1). It was found that treatment of the mixture under basic conditions resulted in selective hydrolysis of α-**131** to give the hemiketal **132** and that subsequent addition of a Lewis acid converted β-**131** into the same hemiketal with a total yield of 88%. Finally, treatment of **132** with methylmagnesium chloride afforded (−)-sclerophtyin A (**2**) quantitatively (>99%).



127 (78%) **129** (55%) **130**

(68%) **α-131** (α/β,1.8:1) **β-131** (88%) **132**

(>99%) **2**

Scheme 33

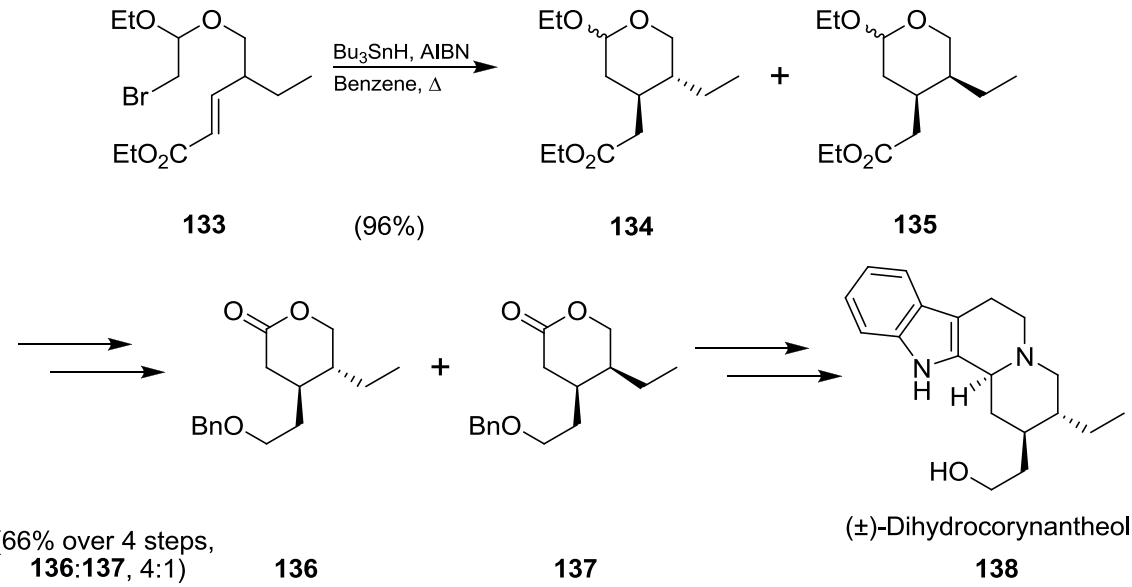
As can be seen from the extensive research outlined above, the total syntheses of members of the ether bridged 2,11-cyclised cembranoid family has provided a variety of interesting synthetic approaches. Herein, I outline the mechanistic and historical development of the key reactions utilised in our synthetic approach for the construction of this family of diterpenes.

1.3 Radical Cyclisation Reactions

Radical-mediated reactions have received extensive attention from the synthetic chemical community for many years. As a result, the scope of these reactions is too diverse to be covered within this text. The focus of this section will be on the formation of cyclic ethers by intramolecular radical capture using ß-alkoxyacrylate acceptors. This

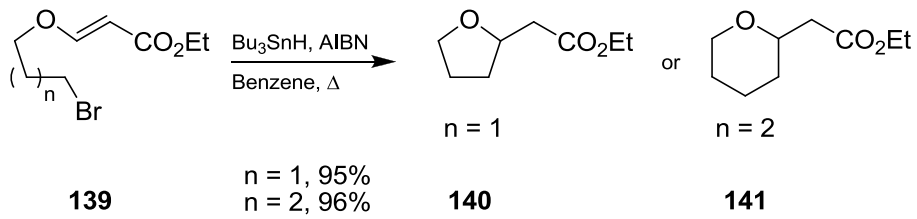
methodology has been developed over the past 25 years or so as an effective tool for the stereoselective formation of functionalised cyclic ethers. As a result, it has been successfully employed by various research groups for the total synthesis of numerous heterocyclic targets.

The first example of a completed total synthesis that utilised a radical-mediated cyclisation of this type was reported by Ihara and co-workers in 1987 (**Scheme 34**).[54] They performed the cyclisation of alkyl bromide **133** onto the β-alkoxyacrylate acceptor to generate a mixture of the four possible hemi-ketals **134** and **135**. After reduction of the ester, benzyl protection of the resulting alcohol and conversion of the hemi-acetal to the corresponding lactone, a 4:1 mixture of products was obtained favouring the required lactone **137**. The synthesis of (±)-dihydrocorynatheol (**138**) was completed using a linear sequence of 16 steps and an overall yield of 16%.



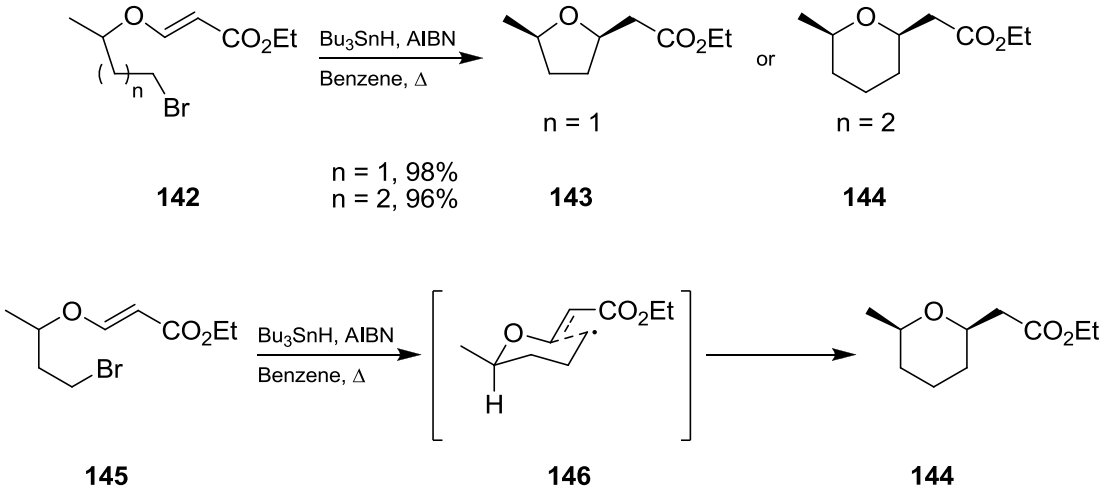
Scheme 34

In later work, Lee and co-workers disclosed their findings regarding the radical cyclisation of alkyl bromides (**139**) with internal ß-alkoxyacrylate functionality to give tetrahydrofuran **140** and tetrahydropyran **141** in excellent yields and with complete preference for the *exo* mode of cyclisation (**Scheme 35**).[55] The reactivity and *exo* selectivity were attributed to the large orbital coefficient present on the ß-carbon in the LUMO of the ß-alkoxyacrylate, which was expected to interact with the relatively high energy SOMO of the newly formed alkyl radical.



Scheme 35

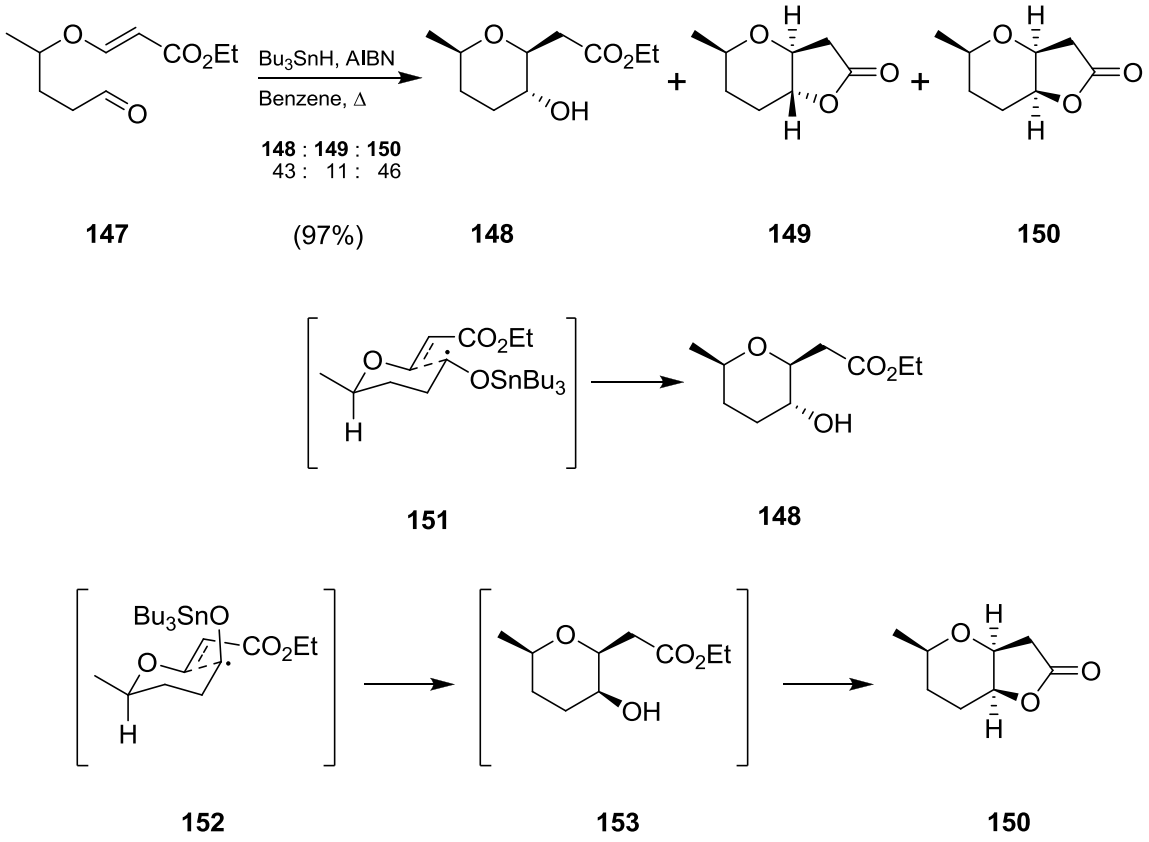
During the course of their investigation, a noteworthy stereochemical outcome was observed by Lee and co-workers, in that, with the appropriate cyclisation precursor **142**, formation of *cis*-2,5-disubstituted tetrahydrofuran **143** and *cis*-2,6-disubstituted tetrahydropyran **144** could be achieved in excellent yield and with complete diastereocontrol (**Scheme 36**).[55] This *cis*-selectivity was explained by the conformation adopted in chair-like intermediate **146**, with the radical acceptor orientated in the more favourable pseudoequatorial position prior to radical cyclisation.



Scheme 36

Lee and co-workers extended their findings to include the use of alternative radical initiators in a publication the following year (**Scheme 37**).[56] They showed that radical cyclisations between ß-alkoxyacrylates and stannyloxyalkyl radicals, formed from the treatment of an appropriate aldehyde, such as **147**, with tri-*n*-butyltin hydride and AIBN, could form cyclic ethers functionalised with a secondary alcohol. The resulting tetrahydropyranols were formed in excellent yield and with complete stereocontrol for the 2,6-*cis* configuration, analogous to that seen during their previous work.[55] However, two diastereomers did arise from the orientation of the stannyloxyalkyl radical in

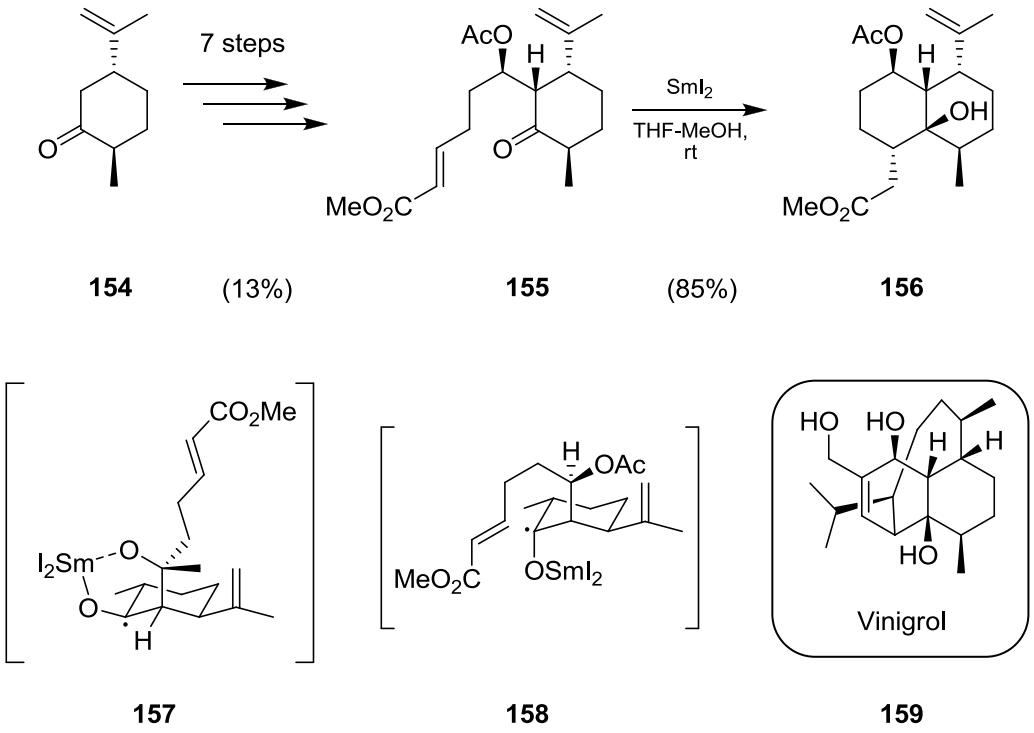
transition states **151** and **152**, giving rise to 2,3-*trans*-tetrahydropyranol **148** and 2,3-*cis*-tetrahydropyranol **153**, respectively, the latter of which underwent lactonisation to form lactone **150**.



Scheme 37

In 1996, Matsuda disclosed a samarium(II) iodide mediated 6-*exo*-trig ketyl-olefin cyclisation to generate the *cis*-decalin skeleton of vinigrol (**159**) from (+)-dihydrocarvone (**154**, **Scheme 38**).[57] Although the acceptor was not a ß-alkoxyacrylate, the cyclisation reaction did illustrate the synthetic potential of samarium to mediate such transformations. The cyclisation precursor **155** underwent a single-electron transfer from samarium(II) iodide to generate the ketyl radical intermediate **158**, which proceeded with *anti*-selectivity across the new C-C bond, generating the required stereochemistry present in the natural product. A second electron transfer reaction formed the anion at the α-position of the resulting ester which was then protonated by methanol, giving the bicyclic alcohol **156** in excellent yield (85%). Crucially, this approach required acetyl protection of the latent hydroxyl group present in **155**. When this was left unprotected, chelation of the samarium(III)

ketyl radical and this free hydroxyl group led to transition state **157**, which positioned the olefinic radical acceptor at too great a distance for cyclisation to occur.



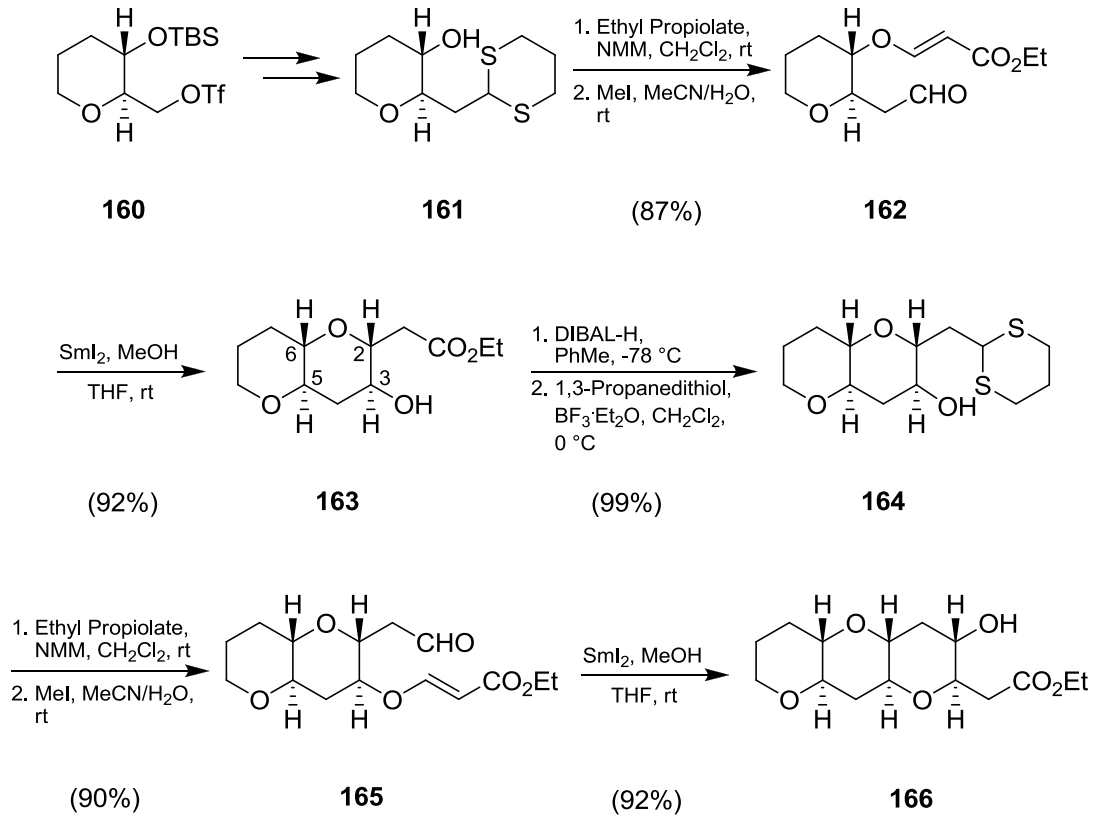
154 (13%) **155** (85%) **156**

157 **158** **159**

Scheme 38

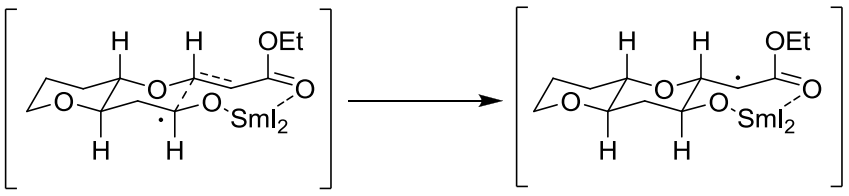
In 1999, Nakata and co-workers disclosed their development of a samarium(II) iodide induced reductive cyclisation reaction for the formation of *trans*-fused polytetrahydropyran ring systems (**Scheme 39**).[58] Their iterative approach enabled them to construct these systems using a sequence of simple, high yielding steps that generated the *trans*-fused tetrahydropyrans with complete diastereocontrol. The synthesis began with the formation of tetrahydropyranol **161**, which could be easily synthesised by a known literature procedure *via* triflate **160**.[59] Hetero-Michael addition of **161** with ethyl propiolate was followed by removal of the thioacetal by iodomethane, affording cyclisation precursor **162** in excellent yield over the two steps. Treatment of **162** with samarium(II) iodide and methanol in THF elicited the radical-mediated reductive cyclisation to give the 2,6-*syn*-3,5-*syn*-2,3-*trans*-tetrahyropyranol **163** in 92% yield and as a single diastereomer. The structure of **163** was confirmed by ^{1}H, ^{13}C, NOE and HMBC NMR analyses. Reduction of the ester and protection of the resulting aldehyde as a thioacetal gave alcohol **164** in effectively quantitative yield. Repetition of these synthetic transformations gave alcohol **166** in 66% yield over eight steps from

thioacetal **161**. In principle, the sequence could be used to construct *trans*-fused polycyclic tetrahydropyran ladder compounds of even greater size.



Scheme 39

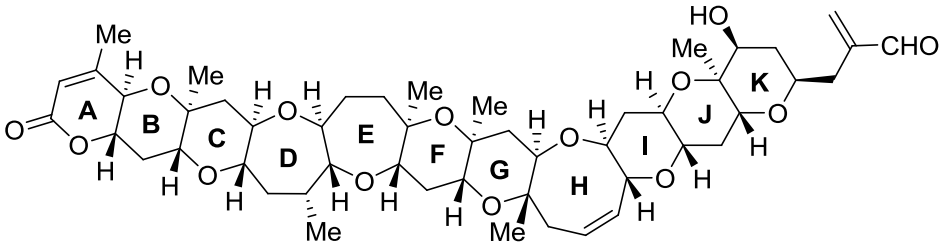
Nakata proposed a mechanism to explain the observed stereoselectivity during formation of these *trans*-fused polytetrahydropyran ring systems (**Scheme 40**).[58] Single-electron reduction of aldehyde **162** (**Scheme 39**) by samarium(II) iodide would give ketyl radical imtermediate **167**. Chelation by samarium (III) to the ester carbonyl group would lock the conformation of the six-membered transition state, orientating both the ketyl radical and the ß-alkoxyacrylate groups in an equatorial position. Cyclisation would occur forming intermediate **168**, which would then be reduced by another equivalent of samarium(II) iodide and protonation of the resulting anion by methanol would give adduct **163** (**Scheme 39**).



167 **168**

Scheme 40

Nakata and co-workers quickly followed this initial disclosure with a publication in the same year, extending the scope of their radical cyclisation to generate *trans*-fused tetrahydropyrans incorporating oxepane systems diastereoselectively.[60] This development would enable construction of ring systems comprising of six-seven-six-, six-seven-seven- and six-seven-seven-six-membered polycyclic ethers, the latter of which is present in the natural product, brevetoxin B (**Figure 18**).

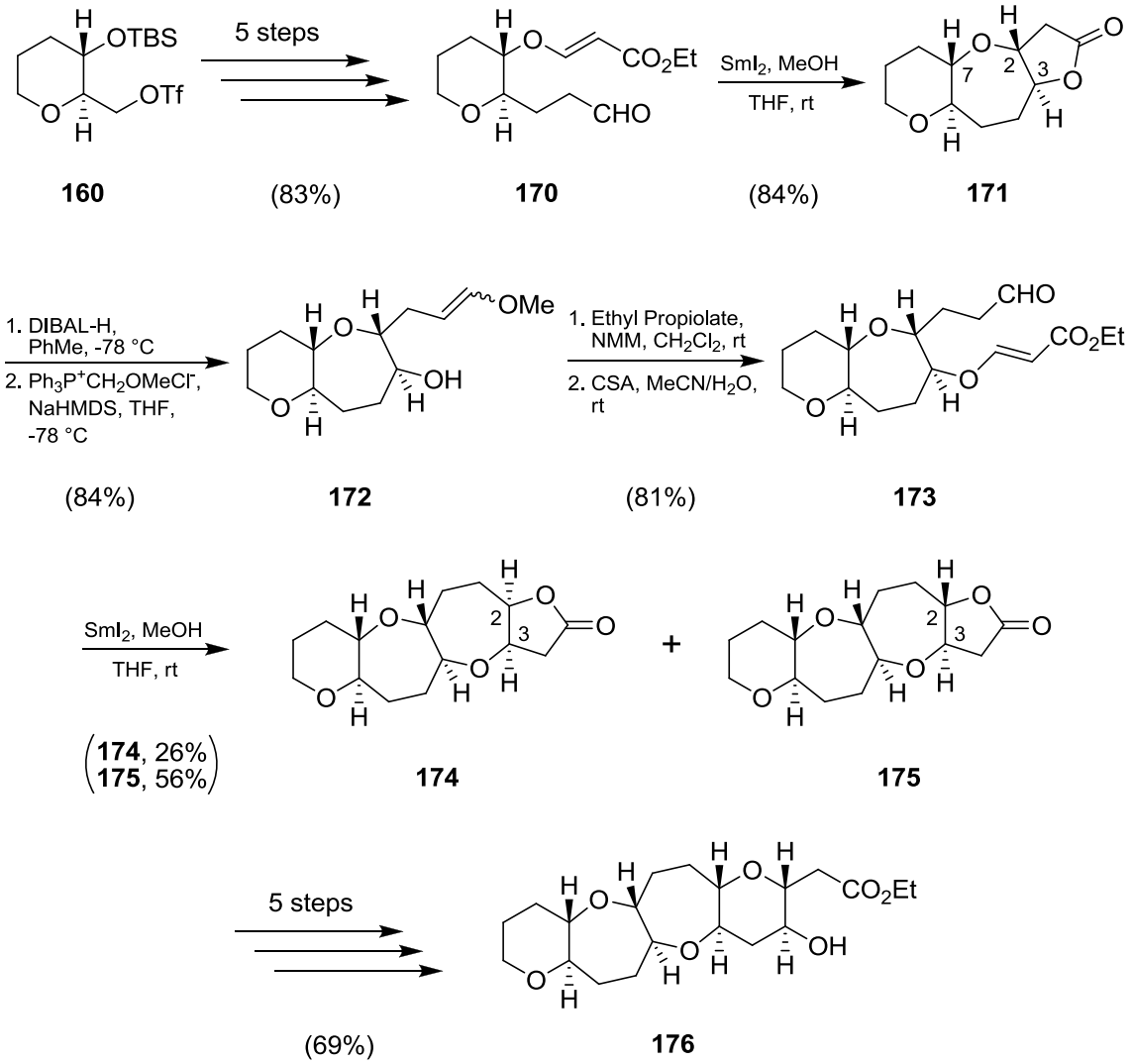


Brevetoxin-B (**169**)

Figure 18

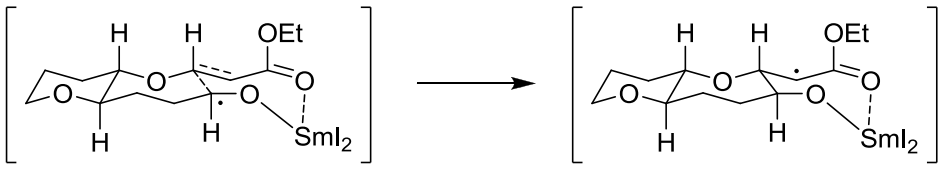
The cyclisation precursor **170** was generated from triflate **160** using a five-step sequence to generate the required aldehyde in 83% yield (**Scheme 41**). With **170** in hand, samarium(II) iodide mediated reductive cyclisation proceeded smoothly to furnish the 2,7-*cis*-2,3-*trans*-oxepane, *via* transition state **177**; subsequent lactonisation afforded the tricyclic lactone **171** (**Scheme 42**).[60] Reduction of lactone **171** using DIBAL-H followed by Wittig homologation generated the enol ether **172**. This was followed by *O*-alkylation with ethyl propiolate and acid-catalysed cleavage of the enol ether to give the corresponding aldehyde **173**. The second reductive cyclisation reaction generated a diastereomeric mixture of the 2,3-*cis*- (**174**) and 2,3-*trans*-oxepanes (**175**), in 26% and 56% yield, respectively. The oxepane **175** then underwent the same five-step sequence to generate the final 2,6-*syn*-2,3-*trans*-tetrahydropyran ring shown previously

(**Scheme 39,** tricyclic alcohol **166** from **163**), giving tetracyclic alcohol **176** in 69% yield over the five steps.



Scheme 41

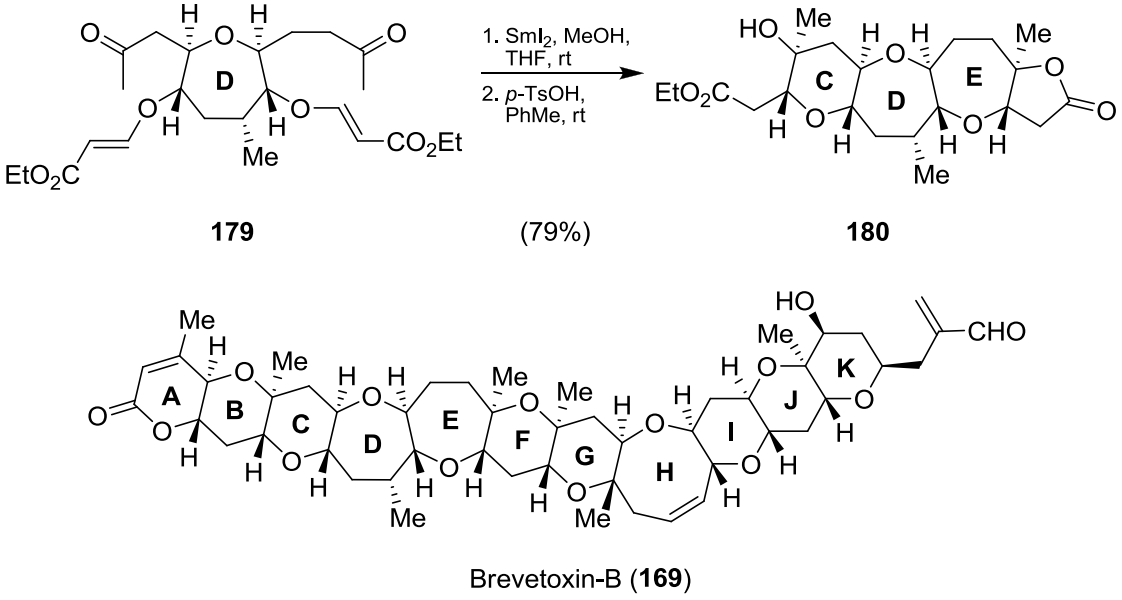
Nakata proposed transition state **177** to account for the observed stereochemistry for 2,7-*cis*-2,3-*trans*-oxepane ring formation (**Scheme 42**).[60] Both the ketyl radical and ß-alkoxyacrylate acceptor are equatorially orientated in the augmented chair-like 7-membered transition state, analogous to that shown in **Scheme 40**, prior to radical cyclisation.



177 **178**

Scheme 42

The culmination of Nakata and co-workers efforts was demonstrated in 2004 with the total synthesis of brevetoxin B which was completed in 59 linear steps (**169**, **Scheme 43**).[61] The extended used of samarium(II) iodide mediated radical cyclisation reactions throughout the synthesis demonstrates the chemoselectivity of this reagent. Construction of the C, D, and E rings of brevetoxin B (**169**) utilising tandem radical cyclisation is noteworthy and illustrates the versatility of this methodology for the construction of polycyclic ether natural products.



179 (79%) **180**

Brevetoxin-B (**169**)

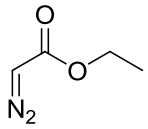
Scheme 43

1.4 Reactions of Metal Carbenoids derived from α-Diazo Carbonyl Compounds

As a result of the highly reactive and unstable nature of "free" carbenes, their use in synthetic transformations generally results in poor yields and selectivities. By using transition metals to form metal carbenoids, the reactivity of these carbenes can be efficiently tempered, increasing their synthetic value.[62-65] Metal carbenoids are generally formed by the decomposition of diazo compounds, resulting in the formation of transition metal complexes that have been utilised in a variety of catalytic reactions and frequently display high chemo-, regio- and stereoselectivity. Such metal carbenoids are usually formed from late transitions metal complexes, the most commonly used of which are complexes of copper and rhodium, and differ significantly in their stability and reactivity from transition metal carbene complexes obtained from early transition metals.[64] In addition, the incorporation of chiral ligands into catalytically generated metal carbenoid systems has further increased the potential of α-diazo carbonyl compounds in asymmetric synthesis.

1.4.1 Formation of α-Diazo Carbonyl Compounds

The first synthesis of an α-diazo carbonyl compound was reported by Curtius in 1883 and involved the diazotisation of glycine ethyl ester, affording ethyl diazoacetate (**181**, **Figure 19**).[66] Since then, interest has grown in this type of compound due to its synthetic versatility and, as a result, more efficient methods for its preparation have followed.

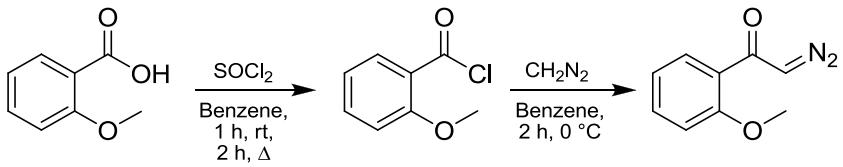


181

Figure 19

1.4.1.1 Acylation of Diazomethane

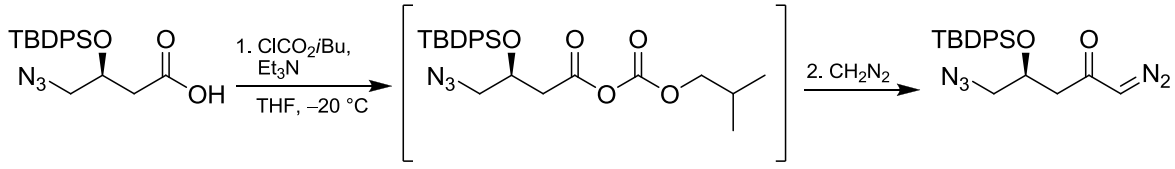
The most commonly used method for the preparation of acyclic terminal α-diazo carbonyl compounds involves the acylation of diazomethane with an appropriate acyl chloride. The synthesis of diazoketones by this method involves an excess of at least two equivalents of diazomethane to quench the hydrogen chloride that is formed *in situ* and would otherwise decompose the product. As a result, formation of diazoketones by this method is generally used for robust starting materials that do not contain acid-sensitive functionality, but if need be a buffer such as triethylamine can be employed to protect such compounds (**Scheme 44**).[67]



182 **183** (98% over 2 steps) **184**

Scheme 44

When an α-diazo carbonyl compound that contains sensitive functionality is required, acylation of diazomethane *via* the formation of a mixed anhydride, such as **186**, is often the method of choice, especially in natural product synthesis (**Scheme 45**).[68]



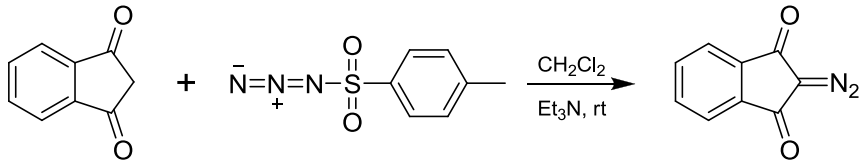
185 **186** (90%) **187**

Scheme 45

1.4.1.2 Diazo Group Transfer

Developed for the synthesis of cyclic α-diazo carbonyl compounds that were unattainable by acylation protocols, diazo group transfer is a versatile method that enables the transfer of a complete diazo group from a donor, such as an arylsulfonyl azide, to an acceptor containing a suitably activated α-methylene unit. These acceptors

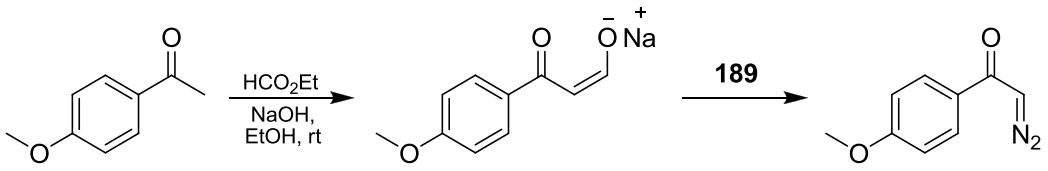
include a variety of carboxylic acid and ketone derivatives that can be categorised as either containing a sufficiently activated α-methylene unit for diazo transfer, or one that requires activation prior to diazo transfer. Sufficiently activated acceptors include; malonic esters, ß-ketoesters, ß-ketoamides, ß-ketoaldehydes and ß-diketones, which can all react directly with diazo group donors using a relatively weak base such as piperidine or triethylamine (**Scheme 46**).[69]



188 **189** (80%) **190**

Scheme 46

One method used to activate α-methylene groups with insufficient reactivity is the Regitz deformylating diazo transfer reaction (**Scheme 47**).[70] This procedure temporarily installs a formyl group *via* Claisen condensation, which activates the methylene group prior to the diazo transfer step, and is then readily released as part of the aryl sulfonamide after diazo transfer.



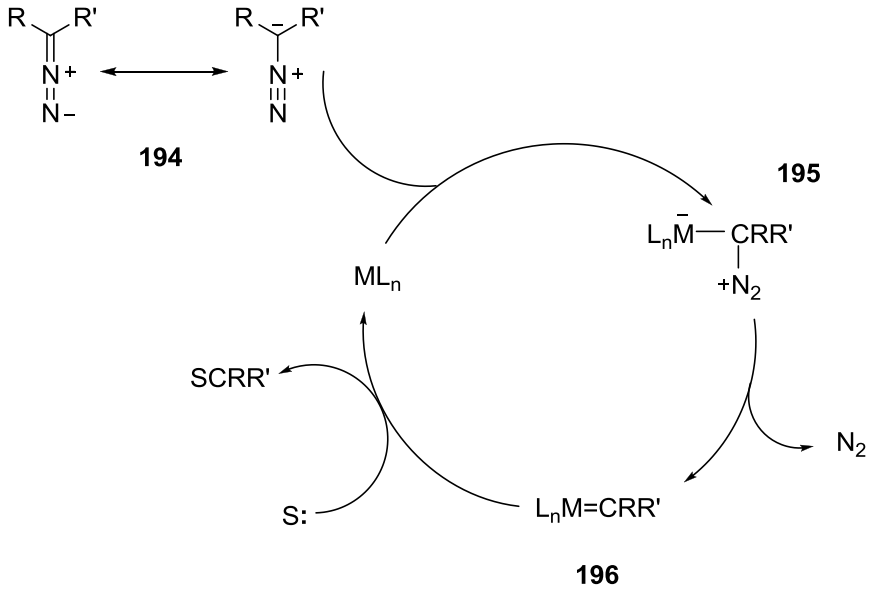
191 **192** (75%) **193**

Scheme 47

1.4.2 Metal Carbenoid Formation

The transition metal-mediated decomposition of diazo compounds to form transient electrophilic metal carbenes has been developed into a robust carbon-carbon bond forming process. The catalytic activity of such transition metal complexes depends on the Lewis acidic nature of the metal, as well as the coordinative unsaturation of the complex, allowing them to act as electrophiles with diazo compounds.[62] Originally

proposed by Yates,[71] the commonly accepted mechanism for the catalytic decomposition of diazo compounds is shown in **Scheme 48**.



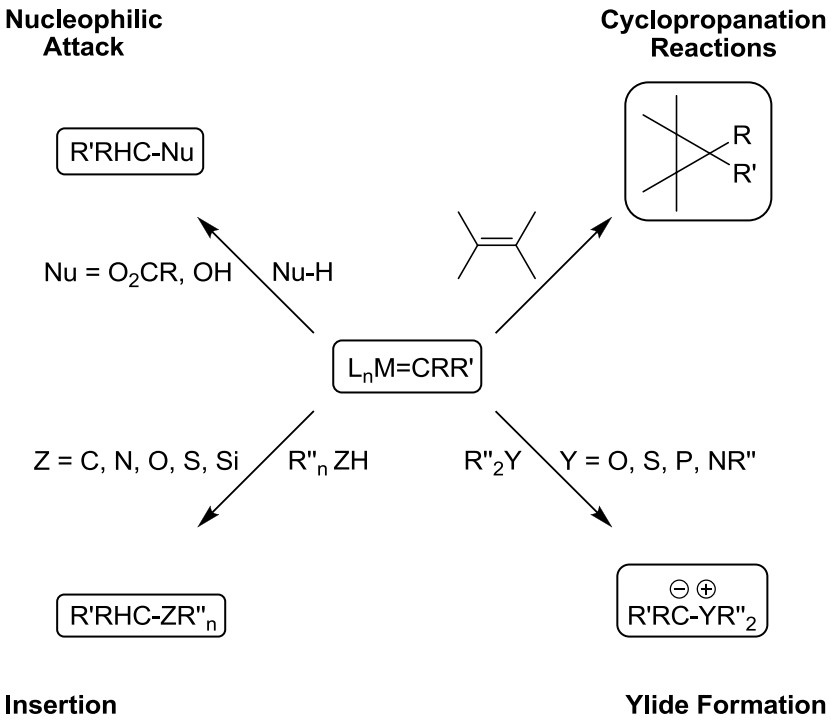
Scheme 48

Nucleophilic addition of diazo compound **194** to the transition metal complex generates the diazonium adduct **195**. Loss of dinitrogen gas occurs to give the metal-stabilised carbene **196**, which then undergoes transfer to the electron-rich substrate (S:), regenerating the catalyst and completing the catalytic cycle. Evidence for this catalytic cycle came from decomposition studies of diazo compounds with iodorhodium(III) tetra-*p*-tolylporphyrin. This generated a spectroscopically stable (porphyrinatorhodium)-diaminocarbene complex, analogous to the generic structure **195**.[72,73]

1.4.3 Metal Carbenoid Transformations

The chemical stability of metal carbenoids has enabled the development of a vast array of synthetically useful transformations (**Scheme 49**). These range from dipolar additions used to construct functionalised heterocycles, to aromatic cycloadditions and rearrangement reactions utilised in the formation of larger carbon scaffolds.[64] The most common transformation performed by a metal-stabilised carbene is cyclopropanation, in which the metal carbenoid reacts with an alkene, installing its electrophilic carbon tether, and generating a new cyclopropyl group that could be challenging to construct

by other means. Asymmetric inter- and intra-molecular cyclopropanation reactions have been investigated extensively and have found wide-ranging uses within the synthetic community. Transformations such as insertions and attack of nucleophiles are also of synthetic importance when metal carbenoids are employed. Insertion reactions often predominate when groups such as C-H, N-H, O-H, S-H and Si-H are present in the substrate, enabling the construction of heteroatom carbon scaffolds present in many synthetic targets. Nucleophilic attack on electrophilic metal carbenoids by carboxylic acids, water or halides enables the introduction of ester, hydroxyl or alkyl halide groups. When aprotic nucleophiles are employed, such as ethers, thioethers or tertiary amines, an oxonium, sulfonium or ammonium ylide is generated, respectively. These ylides are of a transient nature and rearrange to give numerous products, typically *via* a [1,2]-Stevens shift or [2,3]-sigmatropic rearrangement.



Scheme 49

The scope of metal carbenoid transformations is too great to cover within this review and so will not be covered in further detail. However, the chemistry of oxonium ylides and their subsequent rearrangements will be discussed in detail.

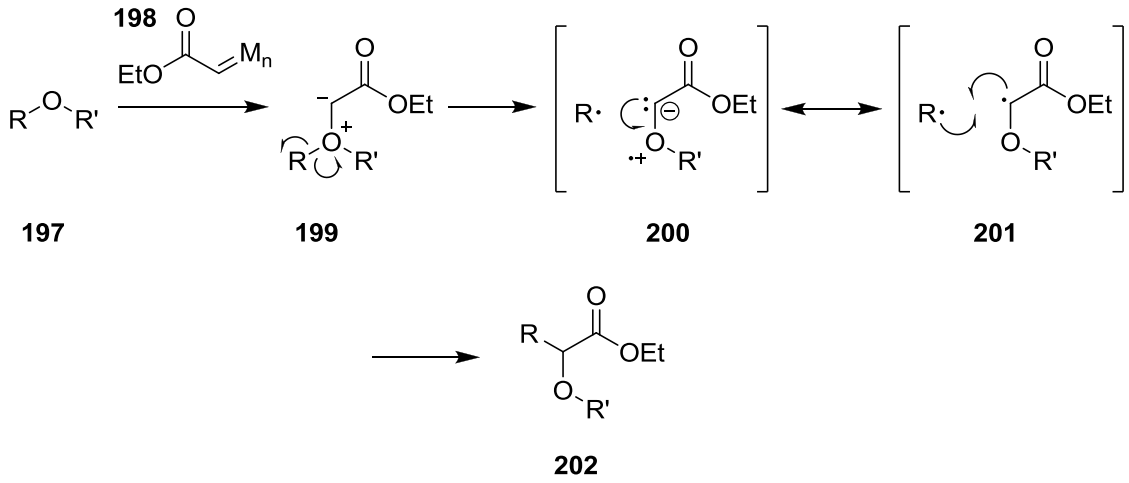
1.5 Oxonium Ylide Formation and Subsequent Rearrangement

The formation of sulfur, nitrogen and phosphorus ylides by metal-stabilised carbenes with has seen extensive investigation over the years. In the case of sulfur ylides, this is largely due to the synthetic ease with which they are formed due to the ease of removal of a proton from a sulfonium salt and the stabilising effect of having access to their d orbitals.[74] For many years, reactions involving α-diazo carbonyl compounds and ethers were thought to proceed by direct C-O insertion, as the products derived from the formation and subsequent rearrangement of oxonium ylides were indistinguishable in many cases. Oxonium ylides, unlike their sulfonium and ammonium counterparts, are not isolable intermediates because they lack the aforementioned p_{π}-d_{π} orbital interactions as seen for sulfur. Irrefutable evidence for the formation and rearrangement of oxonium ylides was found by analogy. The isolation of [2,3]-sigmatropic rearrangement products observed for allylic substrates derived from sulfur, nitrogen and phosphorous were akin to that attained for oxygen, which could only be possible *via* the generation of an oxonium ylide. Once an oxonium ylide has been generated, there are two predominant rearrangement pathways; the [1,2]-Stevens rearrangement and the [2,3]-sigmatropic rearrangement. Other less common and competing transformations include; the [1,4]-Shift, ß-elimination and reactions with nucleophiles.

1.5.1 The [1,2]-Stevens Rearrangement

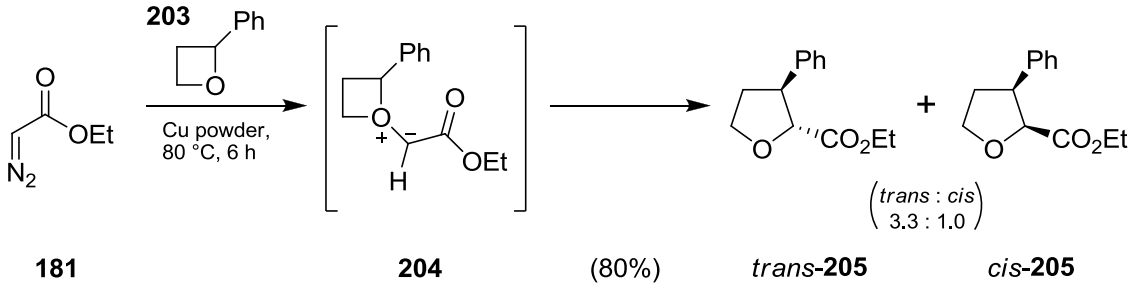
An oxonium ylide, formed by nucleophilic attack of an ethereal oxygen lone pair on an electrophilic metal carbenoid, can undergo a reorganisation reaction known as a [1,2]-Stevens rearrangement, in which one of the alkyl groups migrates.[74] This migration cannot occur by a direct concerted [1,2]-shift because this is a symmetry-forbidden process that contravenes the Woodward-Hoffmann rules,[75] and so must occur by some other mechanism. Extensive mechanistic studies established that, on the basis of CIDNP NMR data, the oxonium ylide rearranges through a homolysis-recombination pathway (**Scheme 50**).[76] After the formation of oxonium ylide **199**, homolytic cleavage of the carbon-oxygen bond generates a singlet radical pair (**200**), which then undergoes a

electron transfer to quench the oxonium cation. Finally, recombination within the solvent cage generates the [1,2]-shift product **202**.



Scheme 50

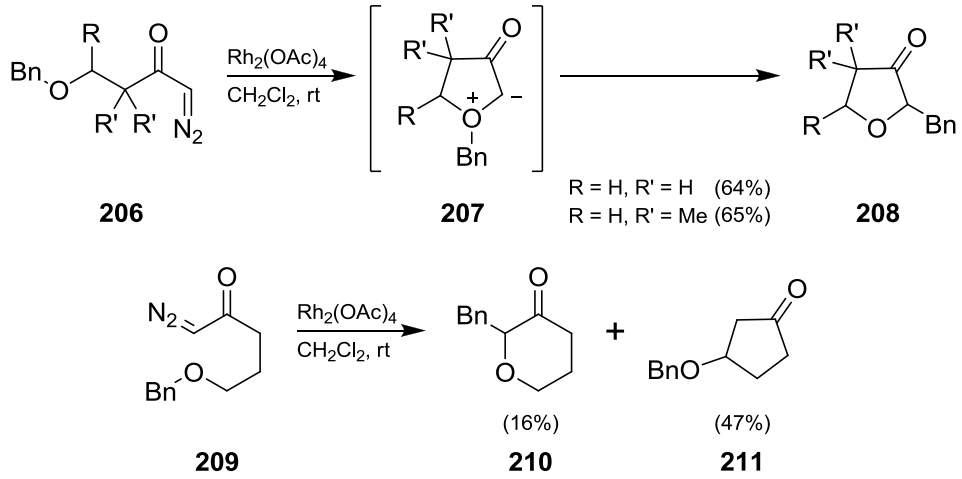
One of the earliest examples of cyclic oxonium ylide formation and subsequent [1,2]-Stevens rearrangement was disclosed by Nozaki and co-workers in 1966.[77] In this case, the copper-catalysed decomposition of ethyl diazoacetate (**181**) was performed in neat 2-phenyloxetane (**203**) at 80 °C, generating the oxonium ylide which then rearranged to give a mixture of both the *cis*- and *trans*-tetrahydrofuran **205** in good yield (**Scheme 51**).



Scheme 51

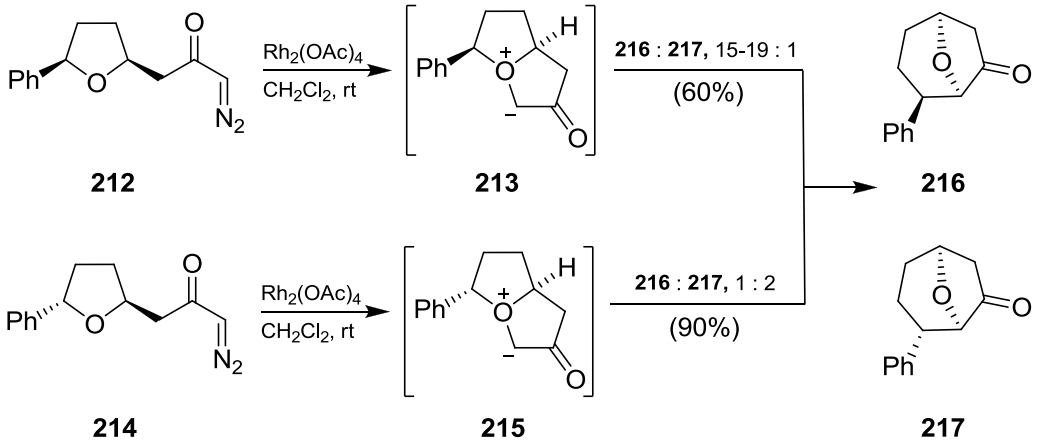
Later, West and co-workers disclosed an operationally simple approach to the construction of functionalised tetrahydrofuranones and tetrahydropyranones.[78] Their approach employed the [1,2]-Stevens rearrangement of oxonium ylide **207**, affording product **208** in moderate yield (**Scheme 52**). Interestingly, they found that in certain cases carbenoid C-H insertion would compete with ylide formation, depending on the

size of ring formed. When the choice between formation of a five-membered ring *via* insertion, or a six-membered oxonium ylide was present, the insertion reaction predominated, affording cyclopentanone **211** in higher yield than the [1,2]-shift product **210**.



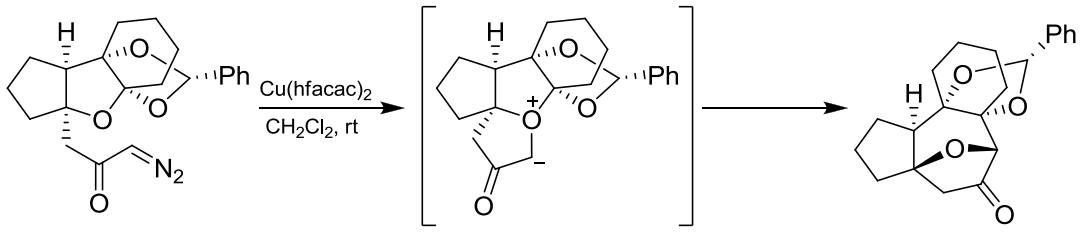
Scheme 52

Next, West and co-workers applied oxonium ylide formation and subsequent [1,2]-Stevens rearrangement to the synthesis of bridged bicyclic ethers (**Scheme 53**).[79] In both cases, complete group regioselectivity was observed for the [1,2]-Stevens shift, consistent with the carbon bearing the best radical stabilising substituent migrating preferentially. The major diastereomer that arose from migration in each case did so with retention of configuration, but that derived from the *cis*-substrate **212** showed a much higher degree of retention than that generated from the *trans*-substrate **214**.



Scheme 53

Recently, West has applied the oxonium ylide formation and [1,2]-Stevens rearrangement protocol to the synthesis of the skeleton found in the tigliane class of natural product, constructing the fused tricyclic core with complete regioselectivity and in excellent yield (**Scheme 54**).[80]



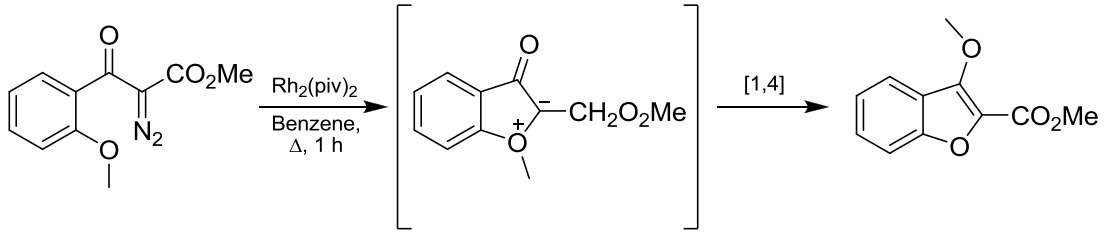
218 (81%) **219** **220**

Scheme 54

1.5.2 The [1,4]-Shift

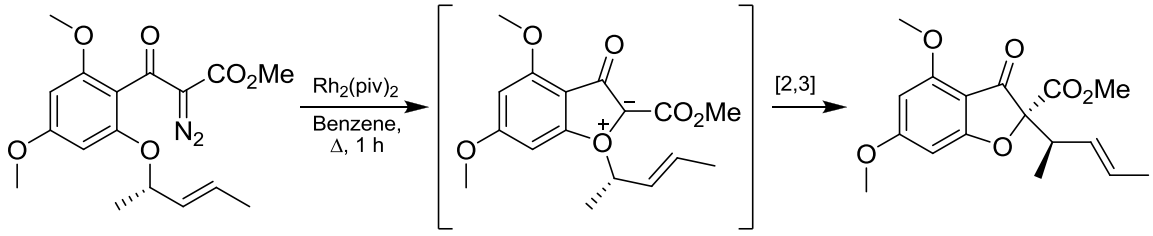
The formation of an oxonium ylide will usually be followed by one of three major reaction pathways: C-H insertion, [1,2]-Stevens shift or [2,3]-sigmatropic rearrangement. In certain cases, another minor reaction pathway can be observed that gives rise to products attained by an apparent [1,4]-shift.[81] A product of this type was disclosed by Pirrung and co-workers during their total synthesis of (+)-griseofulvin, in which the key step involved [2,3]-sigmatropic rearrangement of the ylide derived from the diazoketone **224** (**Scheme 55**).[82] As the presence of the *o*-methoxy substituent in **224** could give rise to an alternative oxonium ylide, they sought to discern the possible fate of such a transformation. Model diazoketone **221** was prepared from *o*-anisic acid and subjected to rhodium(II)-mediated reaction, giving rise to the previously unseen product resulting from apparent [1,4]-shift of the allyl group in the oxonium ylide **222**. When these conditions were applied to the more complex fully-functionalised system, no *o*-methyl ylide formation was detected and only the symmetry allowed [2,3]-sigmatropic rearrangement product **226** was isolated.

Model System



221 (41%) **222** **223**

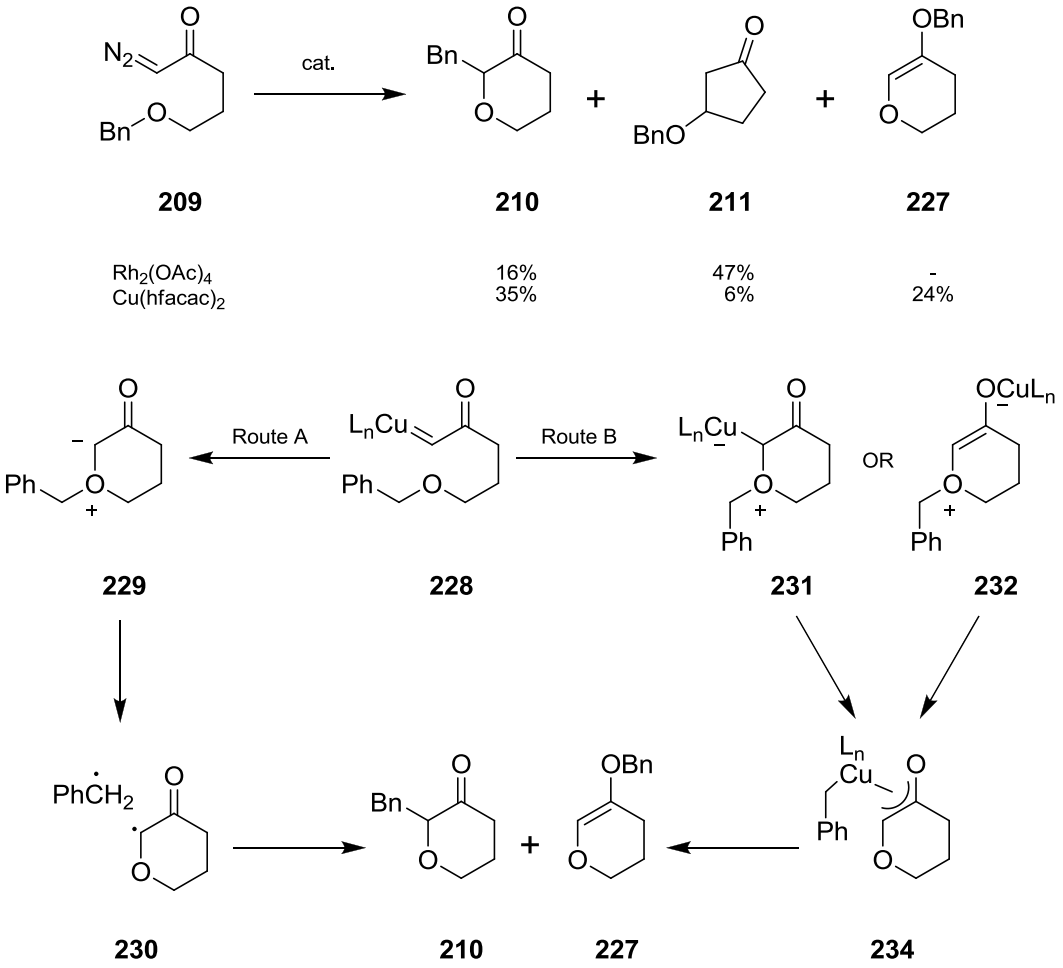
Real System



224 (62%) **225** **226**

Scheme 55

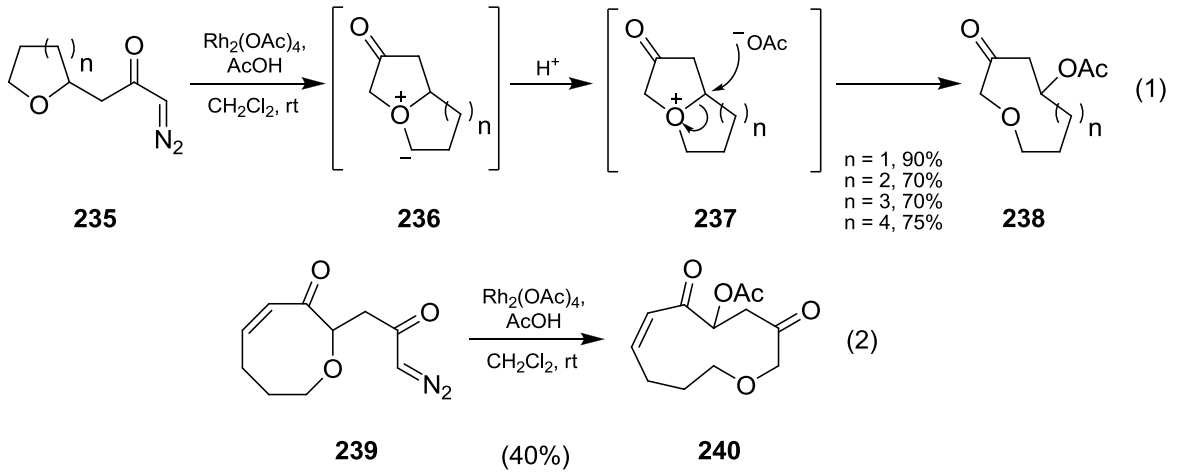
Next, West and co-workers extended their investigations concerning ylide formation from α-diazo carbonyl compounds (**Scheme 52**).[83] When diazoketone **209** was reacted under rhodium(II)-mediated conditions, the C-H insertion reaction predominated, forming cyclopentanone **211** in preference to the [1,2]-shift product **210**. When they employed copper(II)-mediated conditions ($Cu[hfacac]_2$, CH_2Cl_2, reflux) to the same substrate (**209**), only minimal formation of **211** was seen, with the [1,2]-shift product **210** now predominating (**211** [6%], **210** [34%], **Scheme 56**). In addition to this reversal in product distribution, a new compound (**227**), which was the result of a [1,4]-shift, was isolated in 24% yield. This profound difference between the outcomes of reactions mediated by rhodium and copper complexes led West to postulate a mechanism to account for the [1,2]- and [1,4]-shift products. He concluded that the [1,4]-shift product was the result of the recombination of radical pair **230** at oxygen rather than at the carbon (Route A). Importantly, no homodimers of radical pair **230** were isolated for the copper(II)-mediated reaction. As a consequence, West and co-workers gave an alternative metal-assisted mechanism (Route B) in which the metal-bound ylides **231** and **232** could rearrange to give coordinated intermediate **234**. From this enolate, the formation of the [1,2]- and [1,4]-shift products could arise without the formation of any radical intermediates, accounting for the lack of any homodimerisation side-products.



Scheme 56

1.5.3 Nucleophilic Attack of Oxonium Ylides

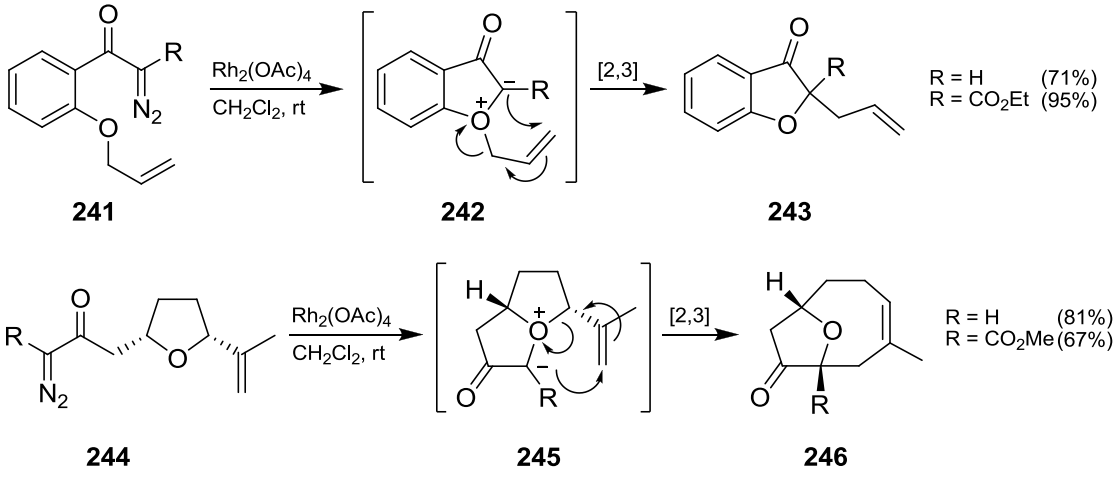
Another reaction pathway available to oxonium ylides is protonation to form an oxonium ion and then attack of a nucleophile. This transformation has been used for the formation of medium-sized ether ring systems from bicyclic oxonium ylides.[84] The rhodium(II)-mediated decomposition of diazoketone **235** generated the required oxonium ylide **236**, which was swiftly protonated by acetic acid. Subsequent nucleophilic attack by the acetate counter ion at the bridge-head carbon then delivered cyclic ether **238** in good to excellent yield (eq 1, **Scheme 57**). Oku and co-workers have developed this protocol as a tandem [*p* + 6] ring expansion method, as can be seen from ether **240** (eq 2, *p* = initial ring size).[85]



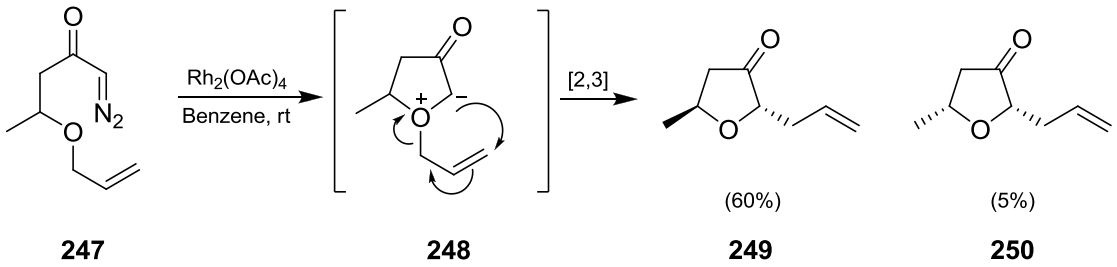
Scheme 57

1.5.4 The [2,3]-Sigmatropic Rearrangement

The first reported examples of an intramolecular oxonium ylide formation and subsequent [2,3]-sigmatropic rearrangement were disclosed independently by Pirrung[86] and Roskamp[87] in 1986. Pirrung generated allylic oxonium ylides **242** and **245** which rapidly underwent [2,3]-sigmatropic rearrangement to generate the functionalised tetrahydrofuran-3-one bicycles **243** and **246**, respectively (**Scheme 58**). In the case of **246**, a three-carbon ring expansion of the original cyclic ether occurred as a result of the bridged bicyclic positioning of oxonium ylide **245**. Roskamp disclosed the generation of functionalised tetrahydrofuran-3-ones by [2,3]-sigmatropic rearrangement of ylide **248**, preferentially affording the 2,5-*trans* product **249** (**Scheme 59**).



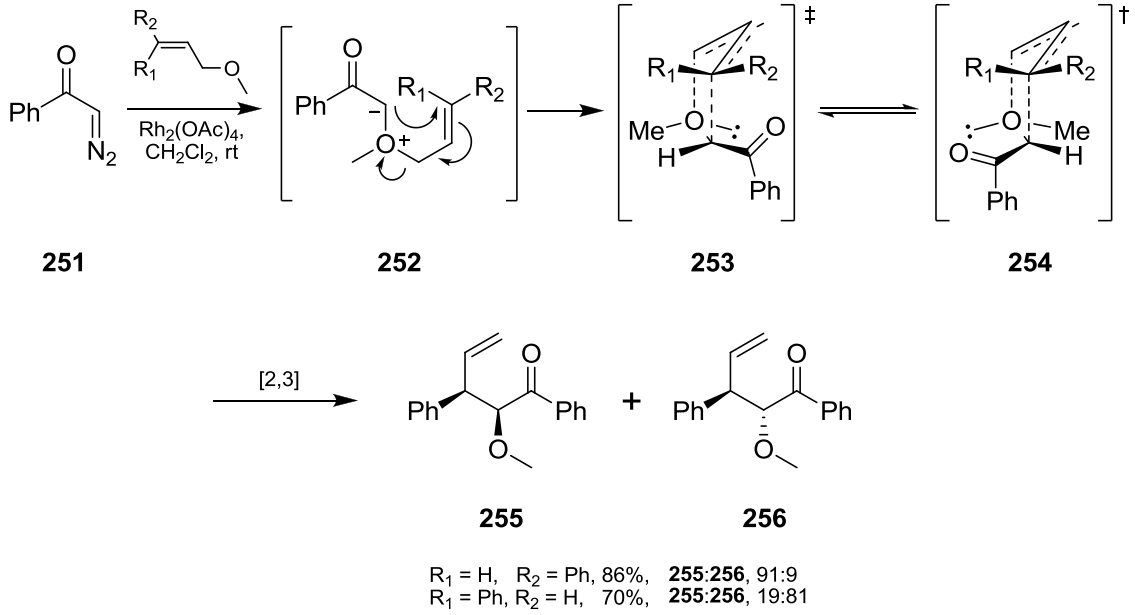
Scheme 58



247 **248** **249** **250**

Scheme 59

Doyle and co-workers reported the intermolecular formation of oxonium ylides from allylic ethers which, up to this point, had been elusive due to their propensity to undergo cyclopropanation (**Scheme 60**).[88] Gratifyingly, they found that oxonium ylide formation predominated, with only minimal cyclopropanation side products. Doyle rationalised the product distribution arising from oxonium ylide **252** *via* an envelope transition state in which the *O*-methyl group was orientated preferentially *trans* to the chain bearing the carbonyl group, thus minimising steric repulsion. With the positioning of these groups set in the transition state, the relative configuration of the alkene tether determined the stereochemical outcome of the product.



251 **252** **253** **254**

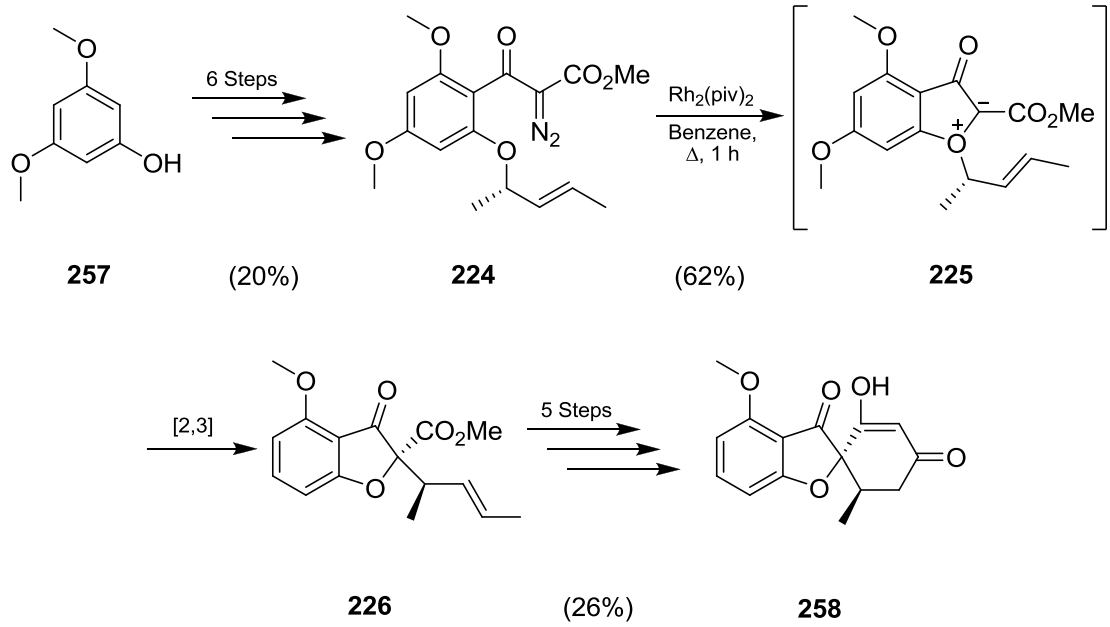
255 **256**

Scheme 60

The first total synthesis of a natural product utilising an oxonium ylide formation and subsequent [2,3]-sigmatropic rearrangement was reported by Pirrung and co-workers in 1991.[82] The anti-fungal agent (+)-griseofulvin was chosen to showcase the asymmetric capability of the oxonium ylide formation / [2,3]-sigmatropic rearrangement

methodology because its spirocyclic structure and vicinal stereogenic centres make it a challenging target to construct using a concise route. Up to this point, an enantioselective synthesis of the natural product had not been reported and all previous syntheses reported had delivered racemic material.

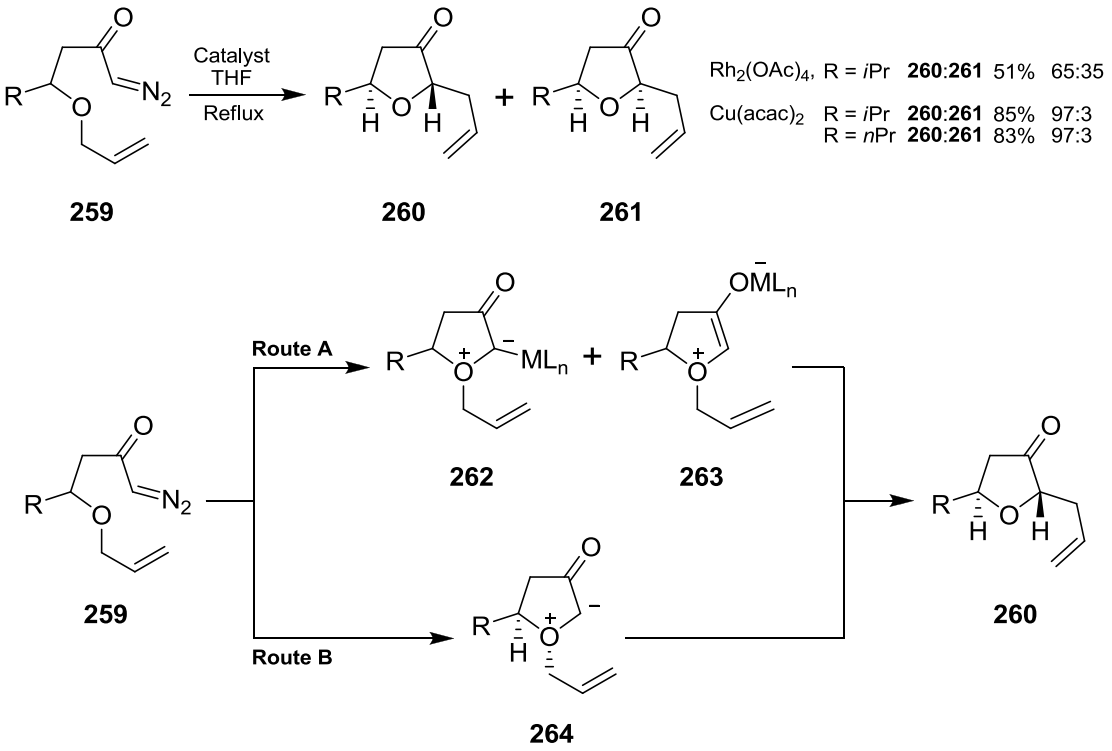
The synthesis of (+)-griseofulvin (**258**) began with the commercially available phenol **257**, which, after a few routine transformations, gave α-diazo-β-ketoester **224** in good yield (**Scheme 61**). The rhodium(II)-mediated decomposition of **224** and subsequent formation and rearrangement of the oxonium ylide afforded benzofuranone **226** in 62% yield. The inherent chirality within **224** enabled the [2,3]-sigmatropic rearrangement to proceed in a stereospecific manner, affording benzofuranone **226** as a single detectable diastereomer. The natural product was completed in a further five steps, the highlight of which was a Dieckmann cyclisation to construct the spirocyclic core, furnishing (+)-griseofulvin (**258**) in 12 linear steps with an overall 5% yield.



Scheme 61

Clark disclosed his investigations into the diastereoselective formation of tetrahydrofuran-3-ones,[89] and developed new conditions that were superior to those reported by Roskamp and Johnson (**Scheme 62**).[87] He found that the outcome of the reaction was heavily dependent on the reaction conditions and the nature of the catalyst used, and that yield and stereoselectivity greatly increased on using a copper

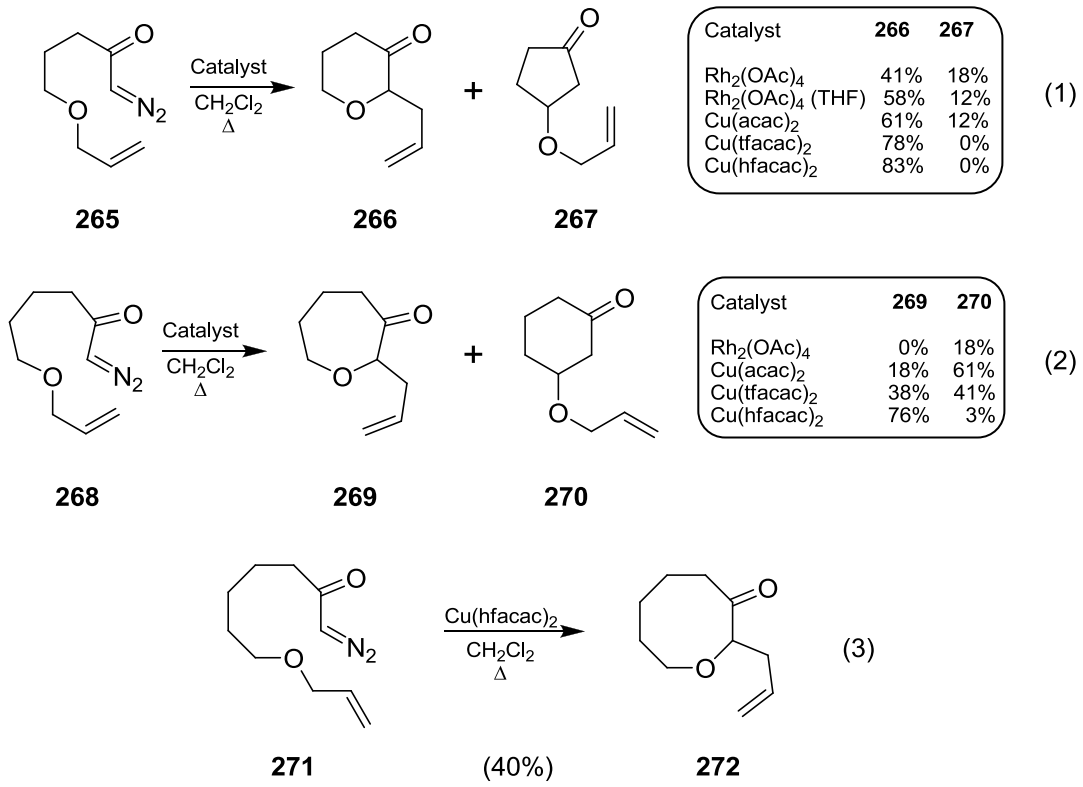
complex instead of a rhodium complex as the catalyst. This pronounced effect on the diastereoselective outcome of the reaction suggested that the rearrangement occurred *via* a metal-bound ylide species, such as **262** or **263** (**route A**), or that oxonium ylide formation occurred *via* a selective trapping of one of the diastereotopic oxygen lone pairs, affording intermediate **264** (**route B**). For the latter mechanism to be feasible, it would be essential for the rate of oxonium ylide rearrangement to be rapid in comparison to inversion at the oxonium centre, which seems unlikely.



Scheme 62

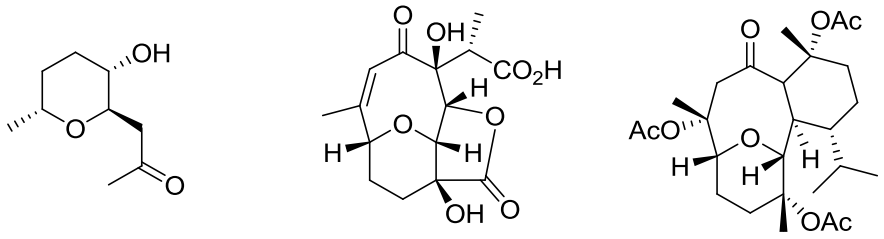
Clark extended his investigations to the construction of six- to eight-membered ether ring systems in a publication the following year (**Scheme 63**).[90] Once again, it was found that formation of the product was dependent on the reaction conditions and catalyst used, with copper(II) catalysts outperforming their rhodium counterparts. The [2,3]-sigmatropic rearrangement products **266** and **269** were obtained in good yield, with copper(II) catalysts favouring ylide formation over C-H insertion. The exact role of the catalyst in these transformations was unclear, but by increasing the electron demand of the catalyst ligands, ylide formation was favoured. Clark postulated that the high yields attained with the use of $Cu(hfacac)_2$ were the result of a greater stabilising effect on the metal-bound ylide intermediate, which would either suppress the reformation of the

original metal carbenoid or reduce the energy difference between the metal-bound ylide and the transition state for the [2,3]-sigmatropic rearrangement



Scheme 63

The Clark group has successfully applied this methodology to the total synthesis of several natural products over the last two decades, constructing a variety of *O*-heterocyclic ring systems in a highly stereoselective manner in the course of this work. The first of these syntheses, that of decarestrictine L (**273, Figure 20**),[91] was accomplished using a concise ten step sequence in 1994. Other completed targets include the aforementioned (+)-vigulariol (**76**),[32] (−)-3-acetoxycladiella-6,11-diene (**77**) and (−)-cladiella-6,11-dien-3-ol (**74**, **Figure 13**).[34] Currently within the group, ongoing investigations toward neoliacinic acid (**274**)[92] and labiatin A (**275**) also utilise this methodology.[93]



Decarestrictine L
273

Neoliacinic Acid
274

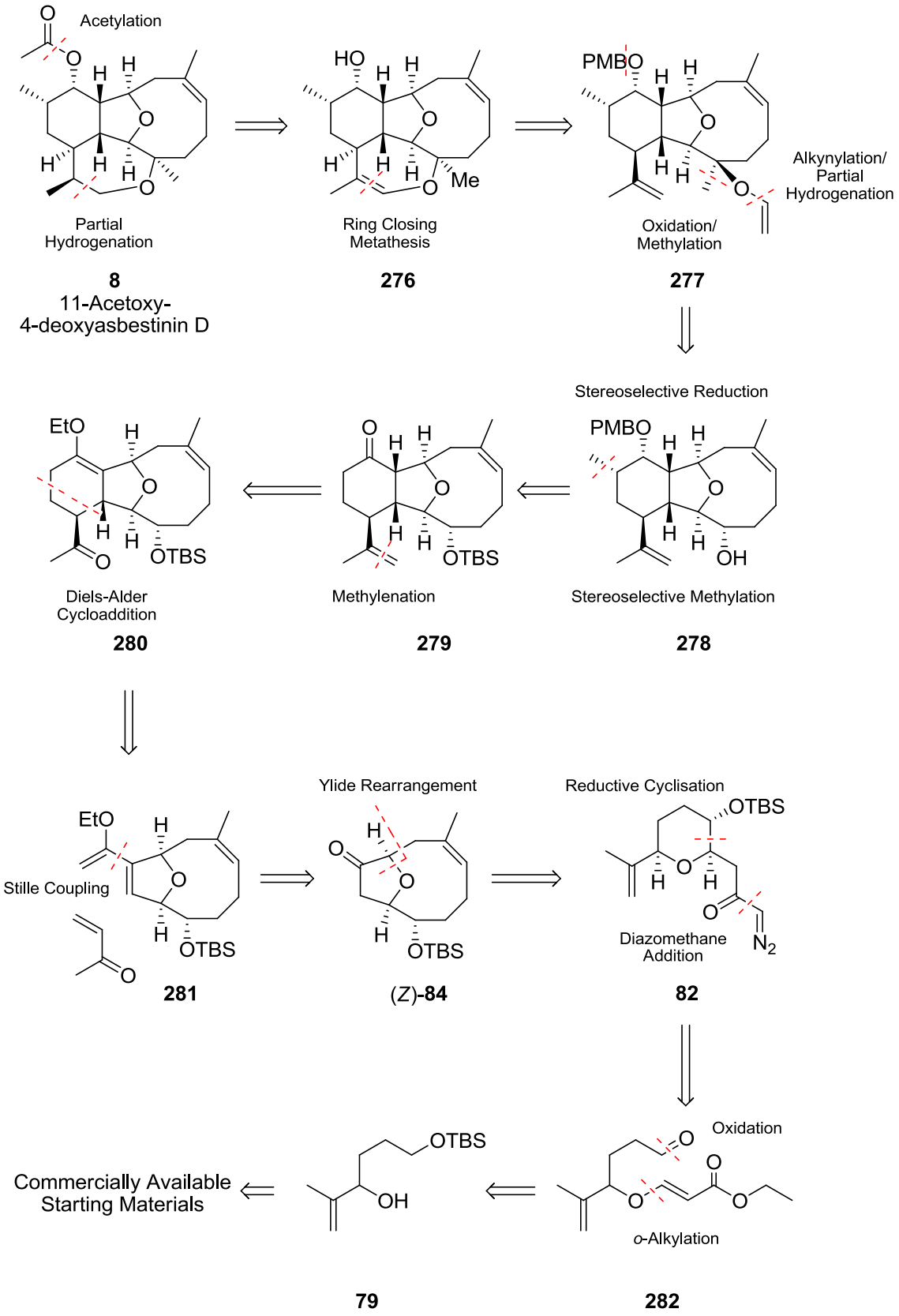
Labiatin A
275

Figure 20

1.6 Retrosynthetic Analysis

11-Acetoxy-4-deoxasbestinin D (**8**) is a complex tetracyclic natural product with nine stereocentres, all of which are contiguous. It was proposed that the total synthesis could be completed in a concise manner and that a general approach to the synthesis of the entire asbestinin sub-class of ether bridged 2,11-cyclised cembranoids could be developed. From previous research, it was known that the construction of the bridged bicyclic core present in these natural products could be accomplished by the decomposition of an appropriate α-diazoketone, forming the corresponding oxonium ylide, which would undergo a [2,3]-sigmatropic rearrangement.[32,94]

The proposed retrosynthesis of 11-acetoxy-4-deoxasbestinin D (**8**) is shown in **Scheme 64**. Removal of the acetyl group and introduction of a C=C bond gives alcohol **276**. Cleavage of this alkene forms the required RCM precursor **277**. A series of disconnections and functional group manipulations affords enol ether **280** and retro Diels-Alder cycloaddition of the cyclohexyl ring then gives triene **281**. This bicyclic triene would be formed from ketone (*Z*)-**84** via enol triflate formation and Stille cross-coupling. The bicyclic ketone (*Z*)-**84** would be formed from the key oxonium ylide formation and [2,3]-sigmatropic rearrangement sequence starting from the functionalised diazoketone **82**. Formation of this precursor would be performed by reductive cyclisation of aldehyde **282**, which in turn would be obtained by *O*-alkylation of allylic alcohol **79**. Prior to this, simple intermediates would be obtained from commercially available starting materials.

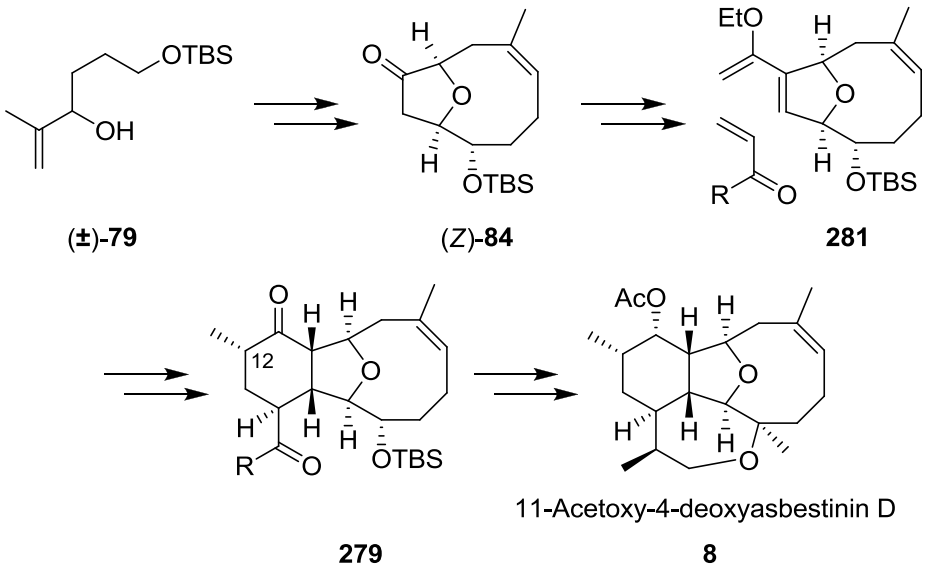

Acetylation
Partial Hydrogenation
8
11-Acetoxy-4-deoxyasbestinin D
Ring Closing Metathesis
276
Oxidation/ Methylation
277
Alkynylation/ Partial Hydrogenation
Stereoselective Reduction
Stereoselective Methylation
278
Methylenation
279
Diels-Alder Cycloaddition
280
Stille Coupling
281
Ylide Rearrangement
(Z)-84
Reductive Cyclisation
Diazomethane Addition
82
Oxidation
o-Alkylation
282
Commercially Available Starting Materials
79

Scheme 64

2 Results and Discussion

2.1 Introduction

Following the successful total synthesis of various members of the cladiellin sub-class of ether bridged 2,11-cyclised cembranoids,[32,34] the synthesis of the asbestinin family was undertaken (**Scheme 65**). The initial challenge was the development of an efficient synthesis of (±)-11-acetoxy-4-deoxyasbestinin D (**8**), a compound first synthesised in an enantioselective fashion by Crimmins in 2005.[6] The proposed synthetic route incorporated enough versatility in its latter steps to access virtually every member within this family of compounds. It also proceeded in a highly diastereoselective manner to the tricyclic core **280** (**Scheme 64**), with the single stereocentre in allylic alcohol **79** controlling the formation of the other stereocentres to this point. With the bicyclic ketone (*Z*)-**84** already accessible using the route developed for the synthesis of vigulariol,[32] the next challenge was to accomplish the proposed Diels-Alder cycloaddition reaction. It would be necessary to establish whether a dienophile, containing an appropriately functionalised tether, could be used to deliver a cycloadduct that would simplify the construction of the final oxepane ring. The completion of 11-acetoxy-4-deoxyasbestinin D (**8**) would also require the functionalisation of the tricyclic core by the introduction of a C-12 methyl group in a diastereoselective fashion.

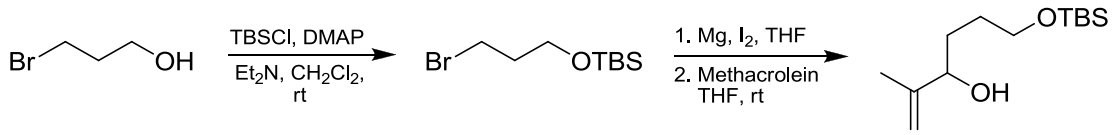


Scheme 65

2.2 Synthesis of Allylic Alcohol 79

2.2.1 Initial Synthetic Route to Allylic Alcohol (±)-79

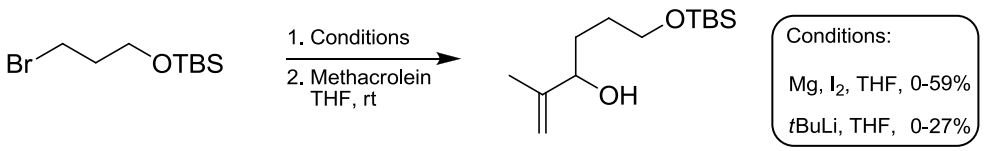
The formation of allylic alcohol (±)-**79** had been developed within the group during the synthesis of the cladiellins in racemic form (**Scheme 66**).[95] The synthesis commenced with the protection of commercially available 3-bromopropan-1-ol (**283**) to give the silyl ether **284** in good yield. Subsequent treatment with magnesium afforded the corresponding Grignard reagent, which was then reacted with methacrolein to generate allylic alcohol **(±)-79**. It was found that the yield of this reaction was dependent on the number of equivalents of the Grignard reagent used, and that optimal conditions required 2 equivalents relative to methacrolein.



283 (86%) **284** (93%) (±)-**79**

Scheme 66

When these conditions were applied to the synthesis of the asbestinins it was found that the formation of allylic alcohol **(±)-79** was poor with variable yields. A variety of conditions were explored, focusing on the duration and temperature during Grignard formation, as well as the activation of the magnesium turnings, but all variations of the reaction conditions failed to give a satisfactory outcome (**Scheme 67**). Treatment of bromide **284** with *t*-butyllithium generated the corresponding organolithium reagent, but when this was reacted with methacrolein, allylic alcohol **(±)-79** was again formed in poor yield.

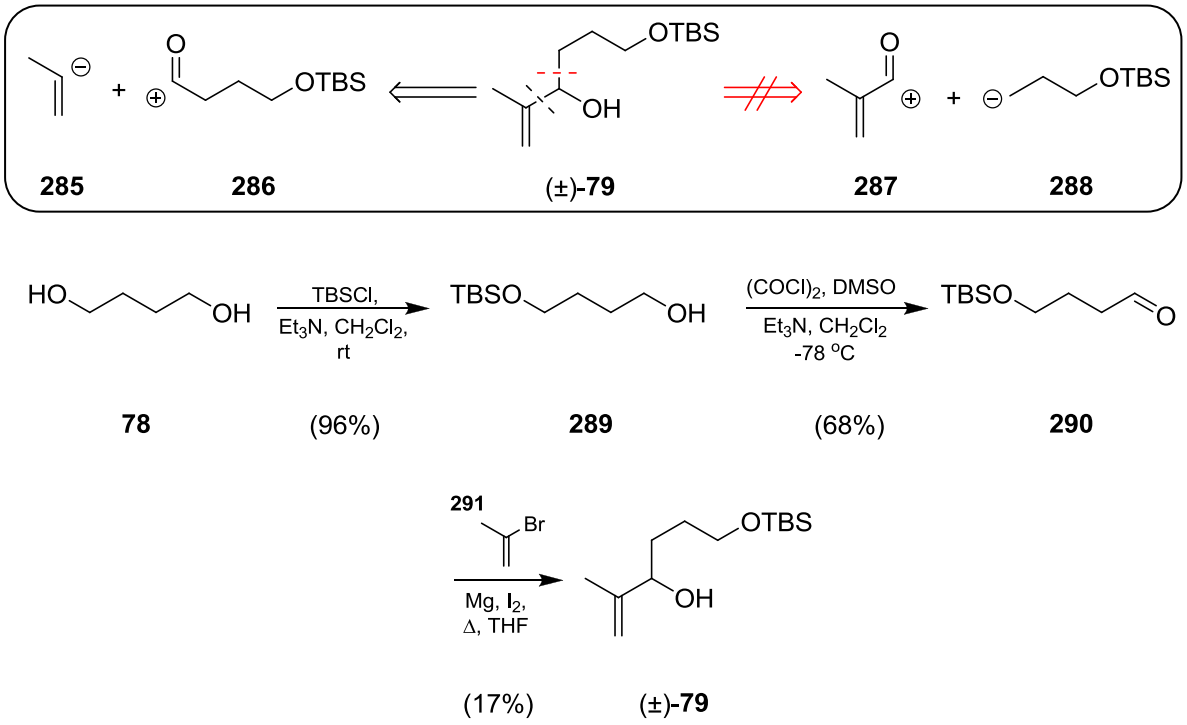


284 (±)-**79**

Scheme 67

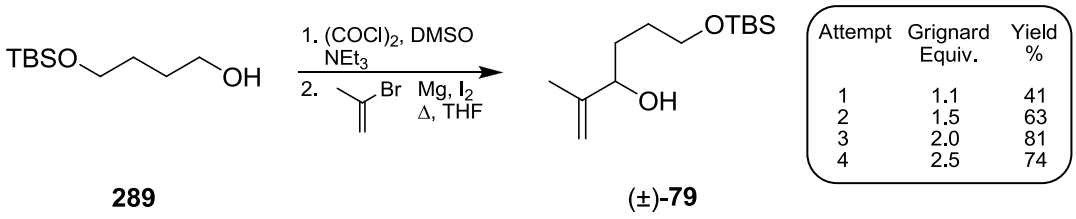
2.2.2 Revised Synthetic Route to Allylic Alcohol (±)-79

The failure of the initial route to generate sufficient quantities of allylic alcohol **(±)-79** meant that an alternative route was required (**Scheme 68**). Synthons **285** and **286** were proposed as suitable alternatives and could be accessed from the corresponding bromide and aldehyde, respectively. First, commercially available 1,4-butandiol **78** was mono-protected using *t*-butyldimethylsilyl chloride (TBSCl) to afford silyloxy alcohol **289** in excellent yield. Next, Swern oxidation[36] of primary alcohol **289** gave aldehyde **290** in a modest 68% yield. When aldehyde **290** was treated with the Grignard reagent derived from 1.1 equivalents of *i*-propenyl bromide (**291**), only a 17% yield of allylic alcohol **(±)-79** was obtained.



Scheme 68

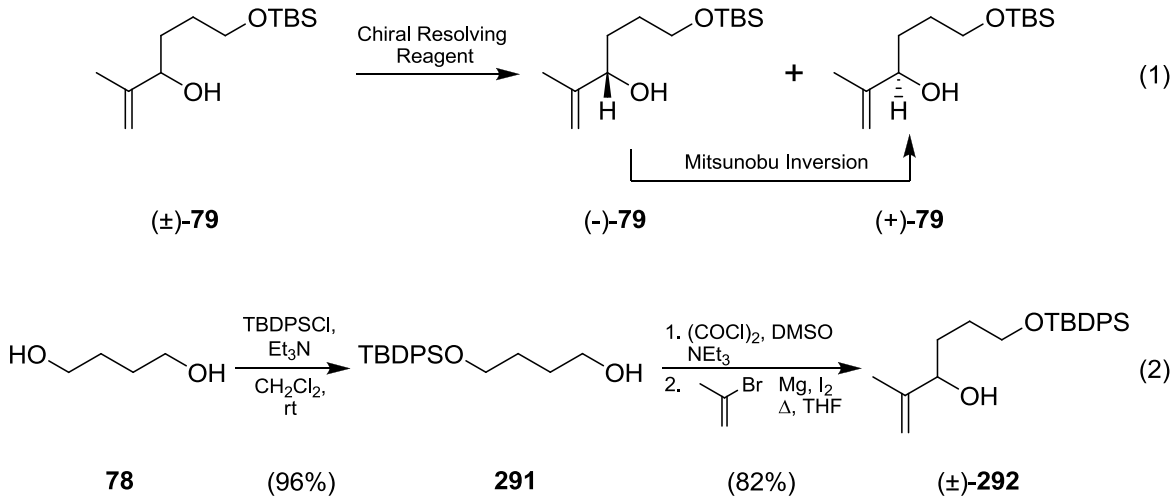
The poor yield was thought to have arisen due to the instability of the aldehyde **290**, and that this problem could be circumvented by treatment of the crude aldehyde with the Grignard reagent, without chromatographic purification (**Scheme 69**). Gratifyingly, this proved to be the case, with allylic alcohol **(±)-79** generated in 41% yield (over two steps) upon treatment of the crude aldehyde with 1.1 equivalents of the Grignard reagent. Further investigation revealed that the optimum conditions for the formation of the allylic alcohol **(±)-79** required 2.0 equivalents of 2-propenylmagnesium bromide, affording 81% yield.



Scheme 69

2.2.3 Resolution of Allylic Alcohol (±)-79

With an efficient large scale route to allylic alcohol **(±)-79** available, attention then turned to the enantiomeric resolution of this material. As stated earlier, the configuration of the carbinol stereocentre present in allylic alcohol **(±)-79** held great importance as it directly controlled the outcome of each stereochemical transformation up to the construction of the tricyclic core **280** (**Scheme 64**). The resolution of this racemic material into its constituent enantiomers and Mitsunobu-mediated inversion of the carbinol stereocentre present in the undesired alcohol (−)-**79**, offered an inexpensive route into the synthesis of the asbestinins with high ee (eq.1, **Scheme 70**). As the resolved allylic alcohols would have to be measured for enantiopurity by HPLC analysis, the starting material would require a UV chromophore to enable detection. To facilitate UV detection, the TBS ether present in alcohol **(±)-79** was replaced with the *t*-butyldiphenylsilyl analogue (TBDPS), and the synthesis of allylic alcohol **(±)-292** was performed in an analogous manner to the newly developed route (eq. 2).



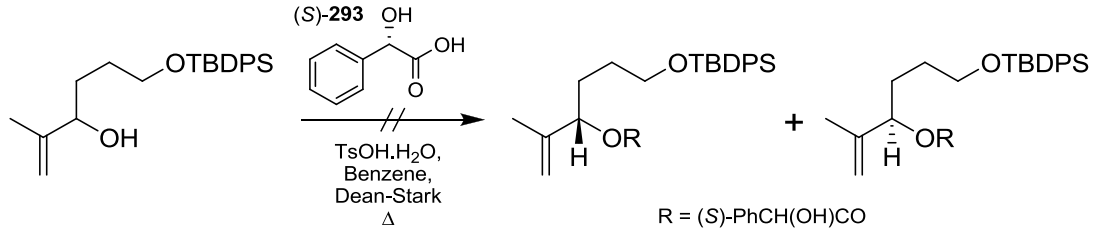
Scheme 70

2.2.3.1 Diastereomeric Separation of Allylic Alcohol (±)-292

First, we considered resolution of the allylic alcohol (±)-**292** *via* the formation and separation of a diastereomeric mixture. Separation of the resulting diastereomers by chromatography or preferential recrystallisation in a given solvent system would be followed by saponification of the separated esters to give the enantiopure alcohols.

Acid Catalysed Esterification

Whitesell and Reynolds disclosed a method for the resolution of a variety of structurally simple, racemic secondary alcohols by the acid catalysed esterification with (−)-(*S*)-mandelic acid **293**, driven by the azeotropic removal of water (**Scheme 71**).[96] After chromatographic separation of the resulting esters, saponification afforded the requisite alcohols in excellent yield and with optical purities ranging between 92 and 98%. When these conditions were applied to allylic alcohol (±)-**292**, only decomposition of the starting material was observed.

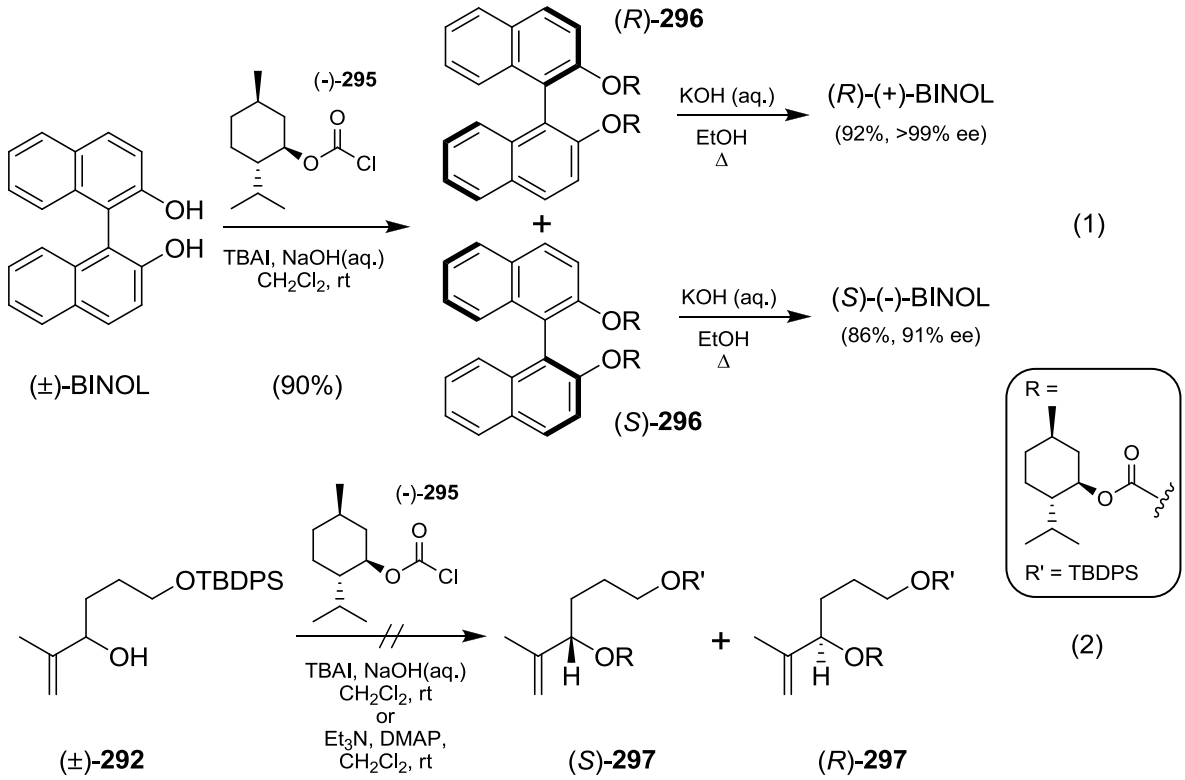


(±)-**292** (*S*)-**294** (*R*)-**294**

Scheme 71

Acid Chloride Carbonylation

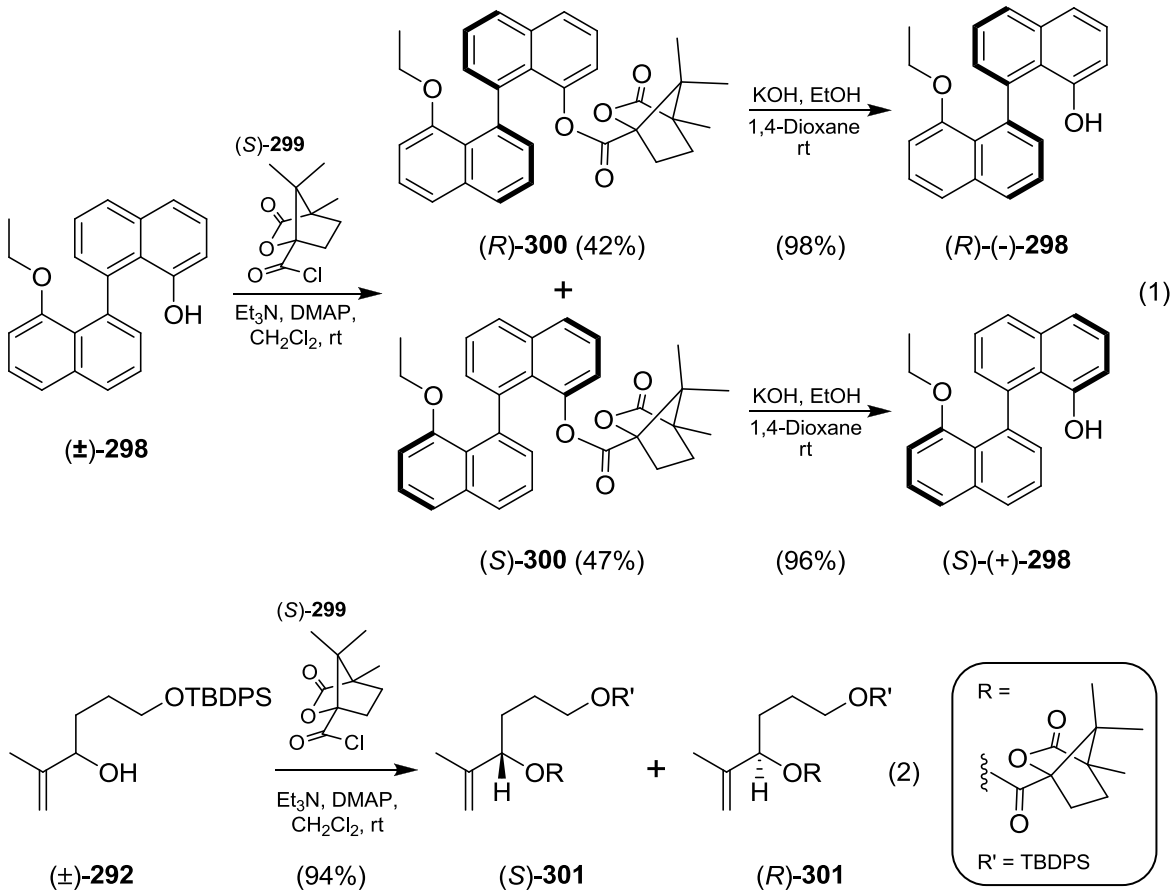
Wan and co-workers published a convenient method for the separation of racemic 1,1'-binaphthols using menthyl chloroformate [(−)-**295**] as the resolving reagent (eq. 1, **Scheme 72**).[97] The reactions were performed in a biphasic solution, with phase transfer catalysis mediated by tetra-*n*-butylammonium iodide (TBAI), generating enantiopure naphthols in excellent yields (91-99% ee). When these conditions were applied to allylic alcohol (±)-**292**, no esterification occurred. Standard acylation conditions using triethylamine and DMAP also failed to deliver the diastereomeric carbonates.



Scheme 72

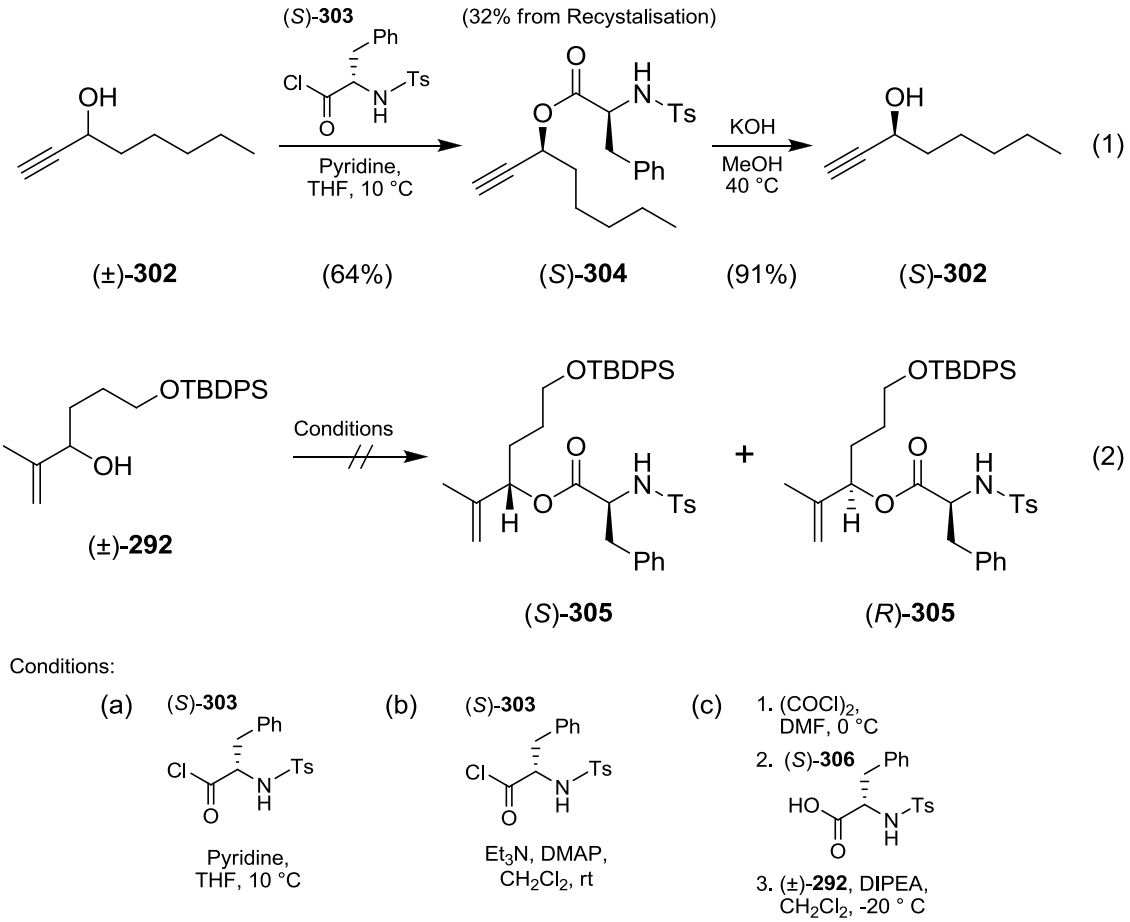
Acid Chloride Esterification

Hua and co-workers studies concerning asymmetric catalysis had led them to develop an effective method for the resolution of 8'-alkoxy-1,1'-binaphthalene-8-ols.[98] This involved esterification of the racemic alcohol with (−)-(*S*)-camphanic chloride [(−)-**299**] and separation of the resulting esters *via* a combination of recrystallisation and chromatography (eq. 1, **Scheme 73**). When these conditions were applied to allylic alcohol (**±**)-**292**, esterification occurred affording the diastereomeric esters (*S*)-**301** and (*R*)-**301** in 94% yield. Unfortunately, the diastereomeric mixture was inseparable by either preferential recrystallisation or chromatography, as both esters (*S*)-**301** and (*R*)-**301** exhibited the same R_f value in every solvent system investigated (eq. 2).



Scheme 73

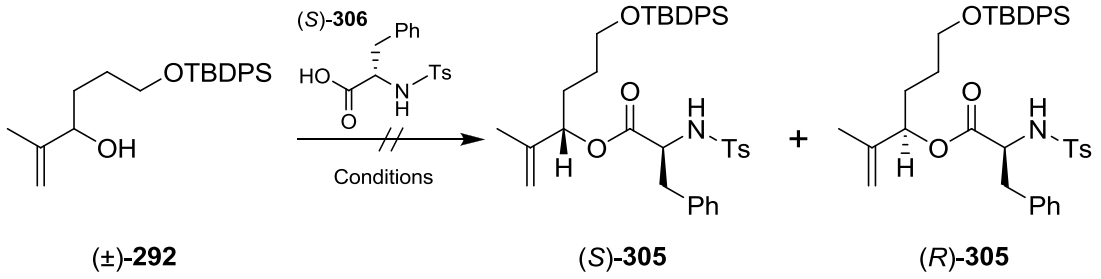
Ikegami and co-workers disclosed a convenient method for the resolution of racemic octyn-3-ols using *N*-(*p*-tosyl)-(L)-phenylalanyl chloride [(*S*)-**303**] as the resolving reagent, with the chiral auxiliary itself being easily accessed in two steps from (L)-phenylalanine.[99] Their facile method was developed to enable access to (*S*)-1-octyn-3-ol (S)-**302** for use in the synthesis of arachidonic acid metabolites (eq. 1, **Scheme 74**). When these conditions were applied to allylic alcohol (**±**)-**292**, no esterification was observed (eq. 2a). With the handling of the acid chloride (S)-**303** being a potential source of experimental error, the *in situ* formation was then attempted (eq. 2c). Treatment of *N*-(*p*-tosyl)-(L)-phenylalanine (*S*)-**306** with the Vilsmeier reagent was followed by addition of the allylic alcohol (**±**)-**292**. Unfortunately, this procedure also proved to be ineffective for the esterification of the allylic alcohol (**±**)-**292**.



Scheme 74

Carbodiimide Activated Esterification

Künstler and co-workers investigations into oligomerisation catalysed by metal complexes led them to develop an effective method for the preparation of optically pure 1-alkyn-3-ols (**Scheme 75**).[100] Their method relied on the activation of *N*-(*p*-tosyl)-(L)-phenylalanine (*S*)-**306** with dicyclohexylcarbodiimide (DCC) and subsequent displacement by the alcohol. These conditions proved to be ineffective for resolution of allylic alcohol (±)-**292**, with slight decomposition of the starting alcohol the only reaction observed. Alternative coupling conditions also failed to deliver the required esterification products.



(±)-**292** (*S*)-**305** (*R*)-**305**

(a) DCC, DMAP, CH_2Cl_2, rt (b) EDCi, DMAP, CH_2Cl_2, rt (c) EDCi, DMAP, DMF, 50 °C

Scheme 75

Due to the poor results obtained and the inability to effectively separate the diastereomers resulting from the coupling with (−)-(*S*)-camphanic chloride [(−)-**299**] (**Scheme 73**), no further investigation into the resolution of allylic alcohol (±)-**292** by means of diastereomer separation was performed.

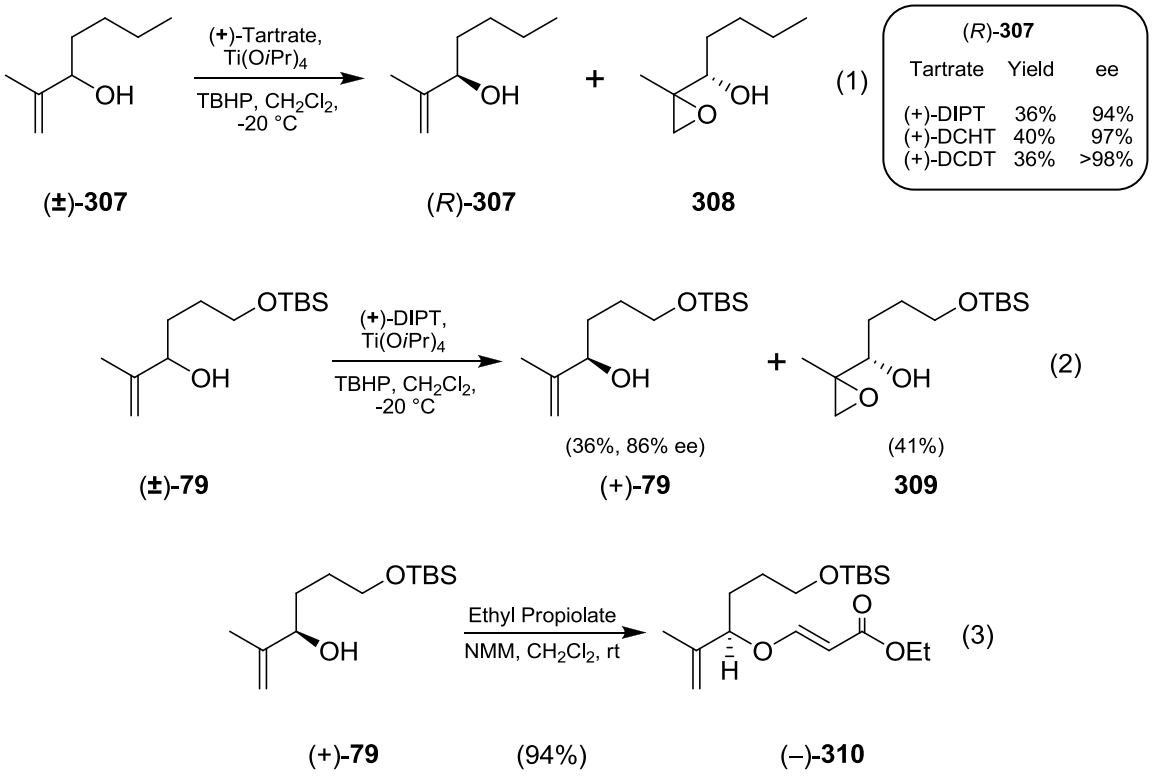
2.2.3.2 Kinetic Resolution of Allylic Alcohol (±)-292

The kinetic resolution of the allylic alcohol (±)-**292** as a means to separate the constituent enantiomers was also explored. The separation of the kinetically more reactive enantiomer would give facile access to the required alcohol (±)-**292**. Where possible, recovery of the undesired enantiomer and inversion of the carbinol stereocentre by Mitsunobu-mediated conditions would enable complete conversion of all the material to the required allylic alcohol (+)-**292**.

Kinetic Resolution of Allylic Alcohol (±)-79

Previously within the Clark group, the Sharpless kinetic resolution procedure had been investigated as a means of resolving allylic alcohol **(±)-79**.[94,95] This method utilises the differing reactivity of the enantiomers of an allylic alcohol towards a catalytic system comprised of a chiral tartrate ester and titanium(IV) isopropoxide, with *t*-butyl hydrogen peroxide (TBHP) as the stoichiometric oxidant.[101] Sharpless and co-workers disclosed the kinetic resolution of allylic alcohol (±)-**307** using a variety of (+)-tartrate ligands (diisopropyl, DIPT, dicyclohexyl, DCHT, and dicyclododecyl, DCDT) and isolated the *R*-enantiomer in up to 40% yield with enantiomeric excesses between 94-98% (eq. 1,

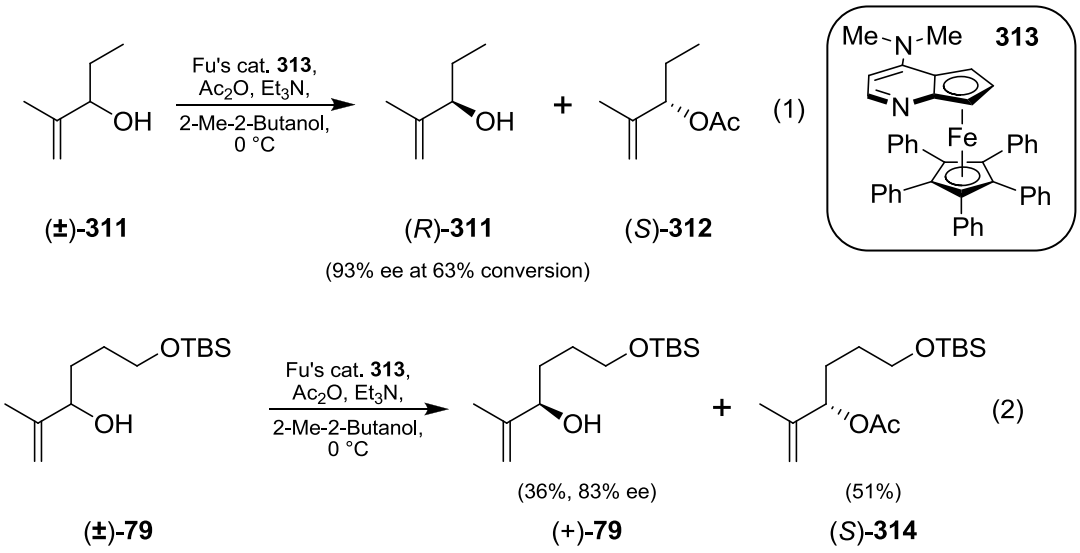
Scheme 76). When the (+)-diisopropyl tartrate system was applied to allylic alcohol (±)-**79** on a small scale (250 mg), it was found that the *R*-allylic alcohol (+)-**79** was isolated in 36% yield (eq. 2). With no UV chromophore present in allylic alcohol (+)-**79**, the vinylogous carbonate (−)-**310** was generated by treatment of allylic alcohol (+)-**79** with ethyl propiolate and *N*-methylmorpholine (NMM, eq.3, 94% yield). Normal phase chiral HPLC analysis[102] of (−)-**310** indicated an 86% enantiomeric excess of the (*R*)-isomer. Unfortunately, when the kinetic resolution of allylic alcohol (±)-**79** was attempted on a larger scale (5 g), none of the epoxy alcohol **309** was obtained, presumably due to the fact that the reaction was performed without stirring in the freezer at −20 °C. As a result, no further investigation of this method was performed.



Scheme 76

A second kinetic resolution previously investigated within the Clark group was developed by Fu and co-workers.[95] Catalysed by the chiral ferrocenyl DMAP derivative **313** in combination with acetic anhydride, the reaction resulted in preferential acetylation of the (*S*)-enantiomer of (±)-**311**, resolving allylic alcohol (*R*)-**311** in 93% enantiomeric excess (eq. 1, **Scheme 77**).[103] However, when these conditions were applied to allylic alcohol (±)-**79**, only 83% enantiomeric excess was obtained (eq. 2). Furthermore, the reaction required 12 days to reach 60% conversion on a small scale

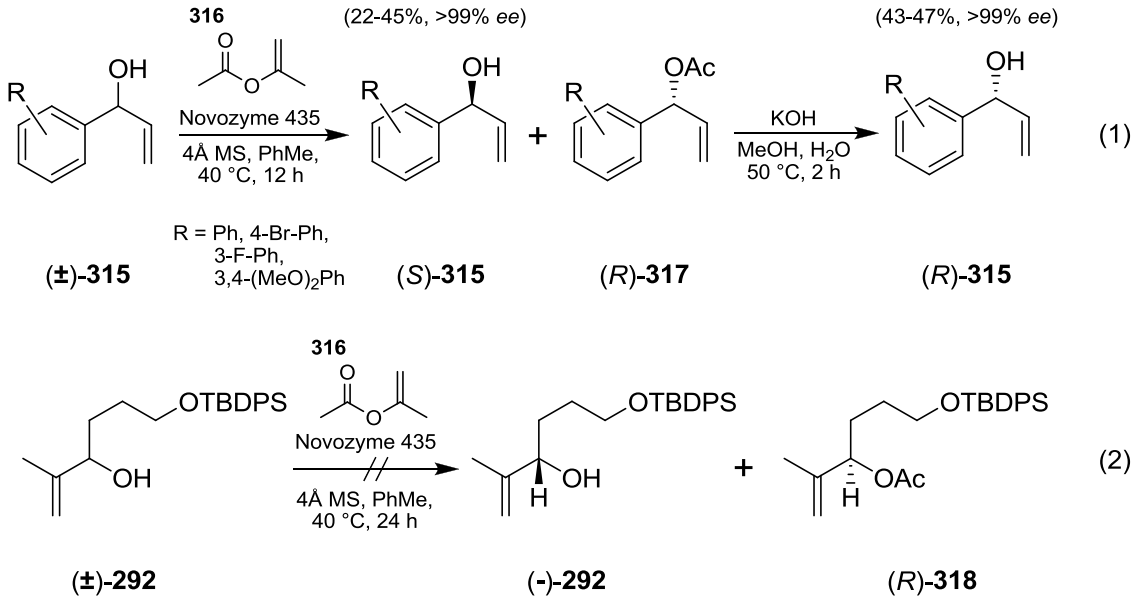
(120 mg), and so the method was unsuitable for preparation of the quantities of allylic alcohol (+)-**79** required to complete a synthesis of one of the natural products.



Scheme 77

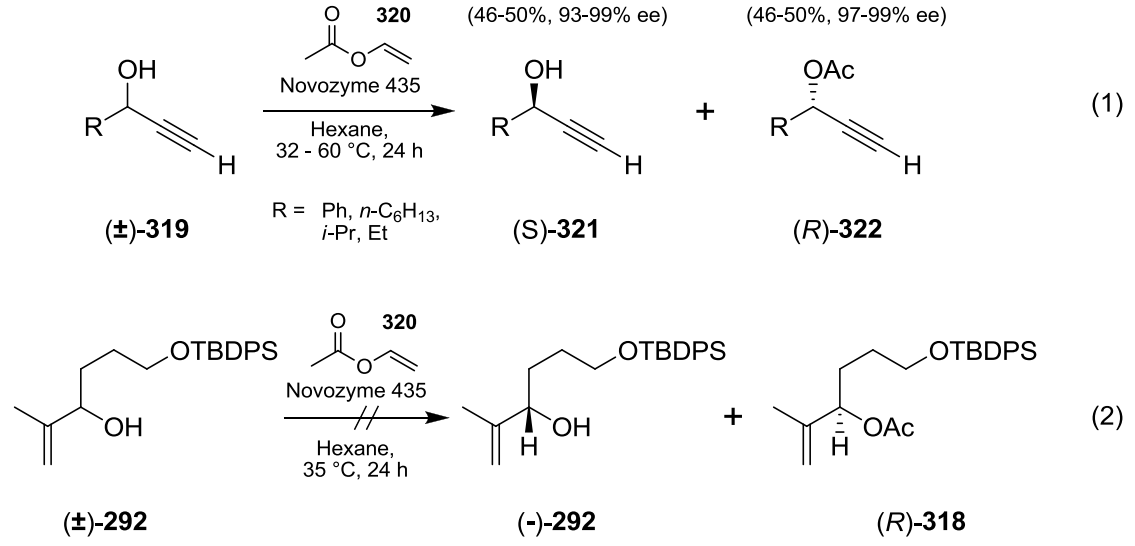
Enzymatic Kinetic Resolution of Allylic Alcohol (±)-292

In a publication from Kočovsky and co-workers, enantiomerically pure 1-arylpropenols were generated using resin bound lipase formulation Novozyme 435, which, in the presence of 2-propenyl acetate (**316**), acetylated only the (*R*)-enantiomer (eq. 1, **Scheme 78**).[104] The alcohol (*S*)-**315** and ester (*R*)-**317** could be easily separated and the ester saponified to give the enantiopure alcohol (*R*)-**315**. Unfortunately, when these conditions were applied to allylic alcohol **(±)-292**, even after prolonged exposure, only the starting material was observed (eq. 2).



Scheme 78

Continuing with this strategy, conditions were cited in a publication by Raminelli and co-workers, in which racemic aryl and alkyl propargylic alcohols were resolved in excellent yield and with high enantiopurity. Again, lipase formulation Novozyme 435 was used, this time in conjunction with hexane and vinyl acetate, to elicit preferential acetylation of the *R*-enantiomer (eq. 1, **Scheme 79**).[105] Unfortunately this reaction also proved ineffective for the resolution of allylic alcohol **(±)-292**, and so no further investigations into the enzymatic kinetic resolution of the material was performed (eq. 2).



Scheme 79

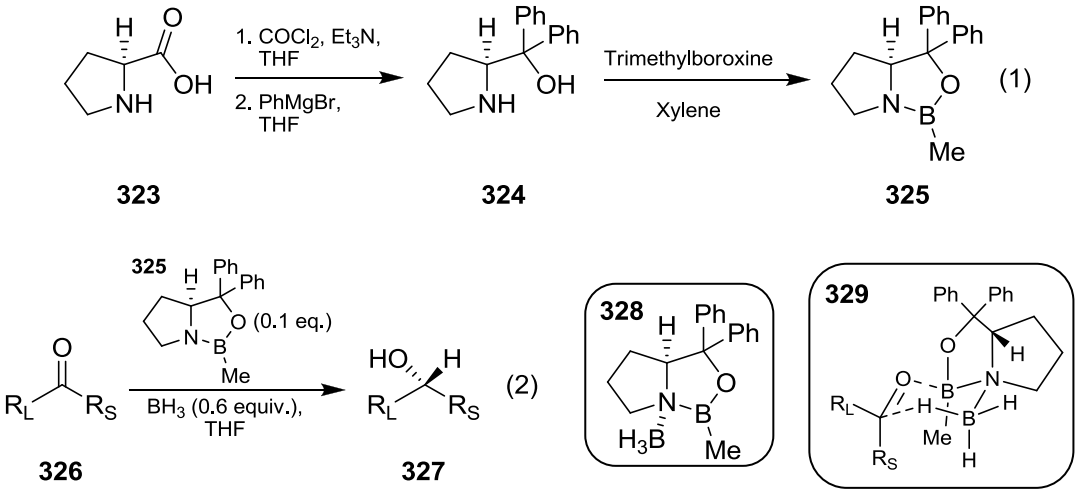
With the limited yields and enantioenrichment attained for the kinetic resolution of allylic alcohol (±)-**79**, coupled with failure of the aforementioned enzymatic protocols for the kinetic resolution of allylic alcohol (±)-**292**, no further investigation into the resolution of these alcohols was performed.

2.2.4 Synthesis of Allylic Alcohol (+)-79

As a consequence of the inability to effectively resolve allylic alcohol (±)-**79** or its UV active analogue (±)-**292**, an alternative strategy was sought for the synthesis of the enantioenriched alcohol. In this section, previous efforts for the construction of allylic alcohol (+)-**79** within the Clark group are summarised.

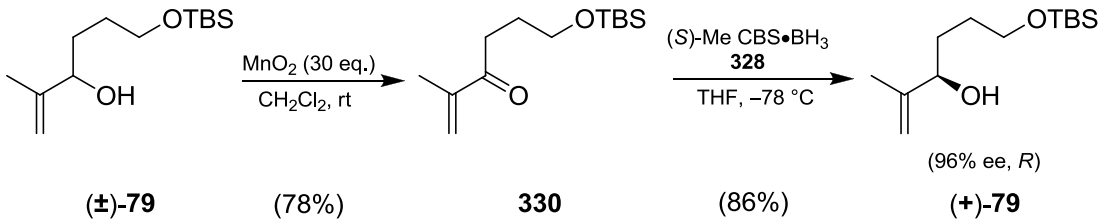
2.2.4.1 Asymmetric Reduction of Enone 330

The asymmetric reduction of enone **330** had been investigated within the group as a potential route to enantioenriched allylic alcohol (+)-**79**.[94] The chiral oxazaborolidine reduction of prochiral ketones developed by Corey, Bakshi and Shibata (CBS) was selected due to the predictable outcome of the reduction and the catalytic nature of oxazaborolidine **325**, which itself could be synthesised in a few steps from L-proline (**323**, eq. 1, **Scheme 80**). The observed stereochemical outcome of the CBS reduction can be rationalised by proposed transition state **329**, in which the six-membered transition state orientates the larger of the two ketone substituents (R_L) away from both the pyrrolidine and geminal diphenyl groups, enabling differentiation between the *Re* and *Si* faces of the prochiral ketone on the basis of minimised steric interactions (eq.2).[106,107]



Scheme 80

The synthesis began with the allylic oxidation of racemic alcohol (**±**)-**79**, which required a large excess of manganese(IV) oxide to generate the enone **330** in 78% yield (**Scheme 81**). The CBS reduction was performed catalytically (20 mol%) with catecholborane as the stoichiometric reductant, but this afforded alcohol (**+**)-**79** with low enantiopurity (14-40% ee). Only when the reduction was performed using a stoichiometric quantity (1.2 equiv.) of active species **328** was allylic alcohol (**+**)-**79** attained in good yield and high enantiopurity (86%, 96% ee, *R*). The enantiomeric purity was determined by conversion of allylic alcohol (**+**)-**79** into the corresponding vinylogous carbonate (−)-**310**, analogous to that shown in **Scheme 76**.[108] Unfortunately, the inability to perform the reduction under catalytic conditions meant that the route was deemed too expensive due to the substantial quantities of the oxazaborolidine **325** required.



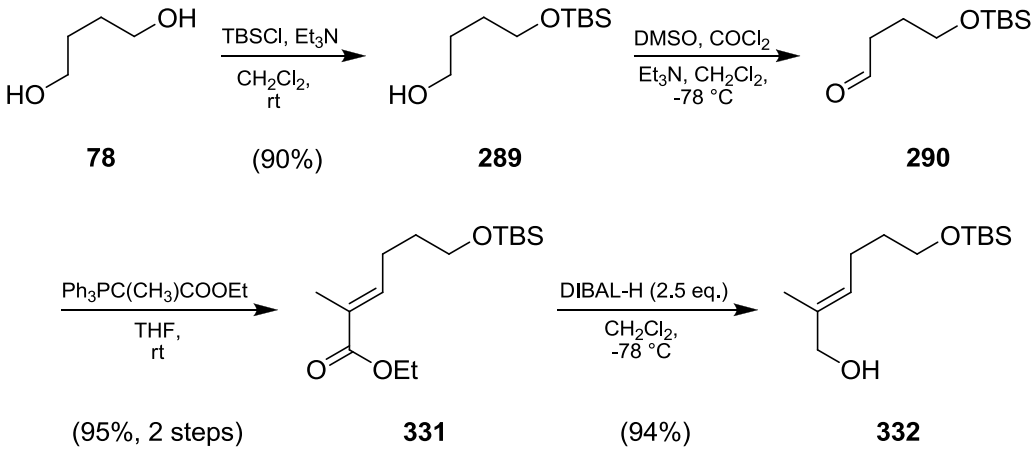
Scheme 81

2.2.4.2 Sharpless Asymmetric Epoxidation Route to Allylic Alcohol (+)-79

It was found from a review of the literature that allylic alcohol (**+**)-**79** was a known compound. It had been synthesised by Williams and co-workers in four steps from 4-(*t*-butyldimethylsilyloxy)butanal **290** in 61% yield and 97% enantiomeric excess.

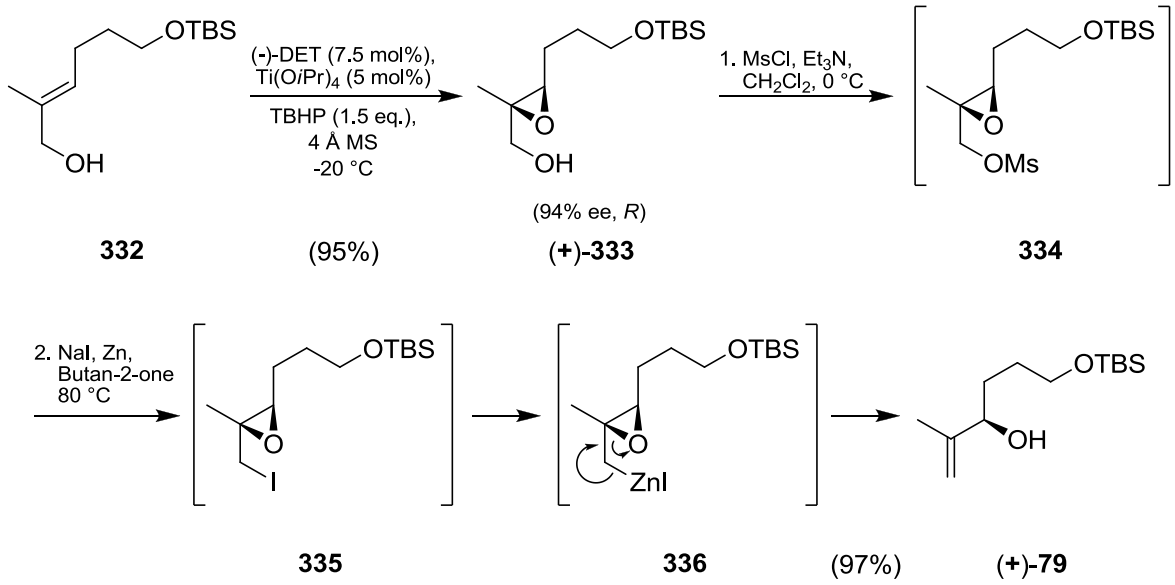
However, no experimental procedures were available from the original paper, and so efforts were directed towards the deduction of the optimal conditions.[95] The stereochemical induction required to form allylic alcohol (+)-**79** was elicited *via* a highly enantioselective Sharpless asymmetric epoxidation reaction of the allylic alcohol **332.**[35,109]

The synthesis commenced with the mono-protection of 1,4-butanediol (**78**) with TBS chloride in good yield (**Scheme 82**). Next, Swern oxidation[36] of silyloxy alcohol **289** was followed by immediate use of the resulting aldehyde **290** in a Wittig olefination reaction with (carbethoxyethylidene)triphenylphosphorane, affording ester **331** in 95% yield over the two steps. The reduction of ester **331** was performed using 2.5 equivalents of DIBAL-H at −78 °C to generate allylic alcohol **332** in near quantitative yield (94%). However, the outcome of the reaction was heavily dependent on the temperature and number of equivalents of the reductant used.



Scheme 82

With the allylic alcohol **332** in hand, the subsequent Sharpless asymmetric epoxidation was then investigated. Various conditions were explored, but epoxide (+)-**333** was obtained in 95% yield with 94% enantiomeric excess (*R*) when low reagent loading was employed (**Scheme 83**).[110] Next, the epoxy alcohol (+)-**333** was then converted into allylic alcohol (+)-**79** using a three step process. First, the treatment of alcohol (+)-**333** with mesyl chloride afforded the epoxy mesylate **334**, which was then immediately converted into the epoxy iodide **335** *in situ* using sodium iodide at reflux. After 1 h, zinc powder was added to form the organozinc intermediate **336** which concomitantly opened the epoxide ring delivering allylic alcohol (+)-**79** in 97% yield.



332 (95%) **(+)-333** **334**

335 **336** (97%) **(+)-79**

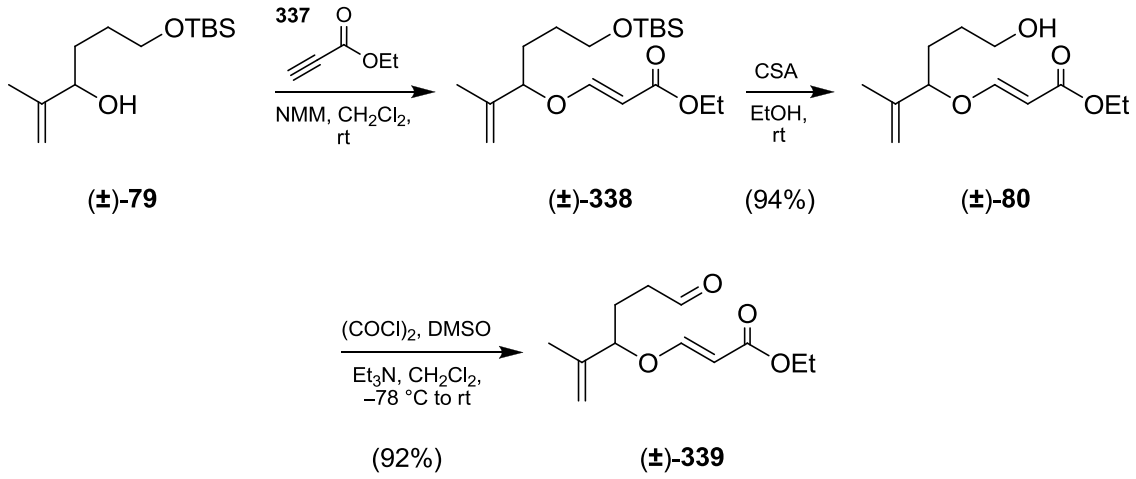
Scheme 83

2.3 Synthesis of Diazoketone (±)-82

With the racemic allylic alcohol (±)-**79** now available on large scale and a viable route to the enantioenriched counterpart (+)-**79** established, attention returned to the development of a route to the asbestinins in racemic form. The initial challenge was the synthesis of diazoketone (±)-**82**, which had been developed during the synthesis of vigulariol.[94] To do so would involve the construction of a tetrahydropyranol (±)-**81** *via* a signature reaction of the designed route: intramolecular reductive cyclisation.

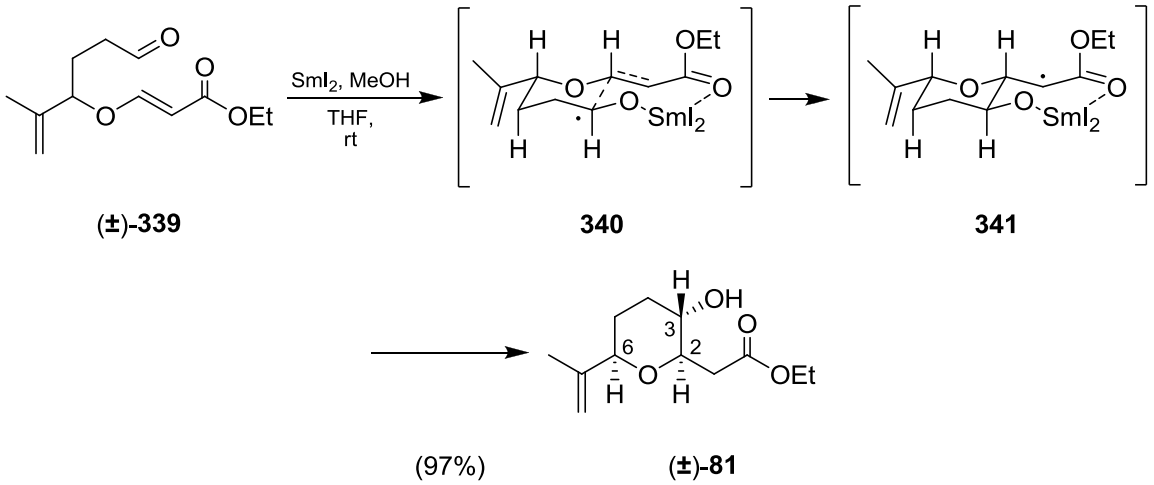
2.3.1 Construction of Tetrahydropyranol (±)-81

The synthesis commenced with the hetero-Michael addition of allylic alcohol (±)-**79** to ethyl propiolate (**337**), affording the *E*-vinylogous carbonate (±)-**338**.[111] This was followed by acidic cleavage of the TBS ether, affording alcohol (±)-**80** in 94% over the two steps (**Scheme 84**). It was found that chromatographic isolation of vinylogous carbonate (±)-**338** prior to CSA deprotection resulted in substantially reduced yields; the best results were obtained when the crude TBS ether (±)-**338** was filtered through a silica plug to remove the more polar impurities and then directly reacted with CSA in ethanol. The primary alcohol (±)-**80** was then oxidised using Swern conditions[36] to afford aldehyde (±)-**339** in excellent yield.



Scheme 84

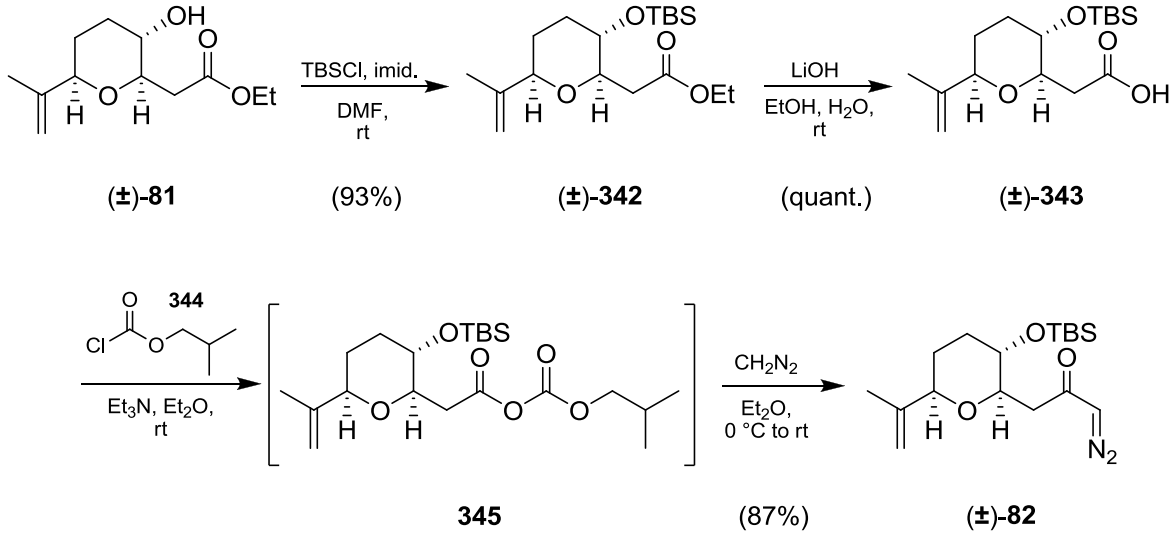
With the ß-alkoxyacrylate (±)-**339** in hand, the reductive cyclisation reaction was then performed using the conditions developed by Nakata and co-workers.[60,112] The aldehyde (±)-**339** was treated with a freshly prepared solution of samarium(II) iodide and methanol, initially forming the ketyl radical **340**, which subsequently underwent cyclisation (**Scheme 85**). Single electron reduction of radical **341** and protonation of the resulting carbanion by methanol afforded the tetrahydropyranol (±)-**81** in 97% yield. The tetrahydropyranol (±)-**81** exhibited the 2,6-*syn*-2,3-*trans* geometry, as confirmed by the large coupling constant between H-2 and H-3 (9.2 Hz), an outcome that is consistent with the findings of Nakata and co-workers when performing cyclisation reactions of related substrates.[112]



Scheme 85

2.3.2 Construction of Diazoketone (±)-82

Next, the secondary alcohol (±)-**81** was protected as a TBS ether in excellent yield. This was followed by lithium hydroxide mediated saponification of the ester (±)-**342**, quantitatively generating the carboxylic acid (±)-**343** (**Scheme 86**). Next, construction of the diazoketone (±)-**82** was achieved by a two-step process that first involved the activation of the carboxylic acid (±)-**343**. In previous efforts within the group activation had been performed by the formation of the corresponding acid chloride, but this had led to poor yields of the required diazoketone (±)-**82**, presumably due to the *in situ* formation of hydrogen chloride.[94] Formation of the mixed anhydride, generated from carboxylic acid (±)-**343** and *iso*-butylchloroformate, was followed by addition to an ethereal solution of diazomethane at 0 °C. This reaction required a large excess of diazomethane (10 equiv.) to elicit effective formation of diazoketone (±)-**82**, but the required product was obtained in very good yield.



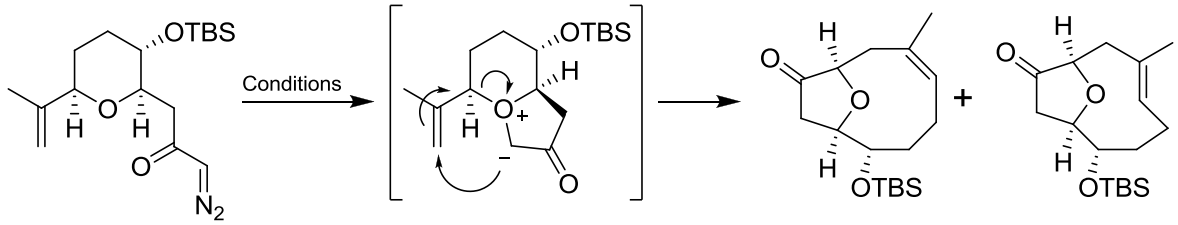
Scheme 86

2.4 Bicyclic Ketone Formation *via* Tandem Oxonium Ylide Generation and [2,3]-Sigmatropic Rearrangement

With the formation of diazoketone (±)-**82** secured, the next step to be investigated was the key step of the synthetic route: the oxonium ylide formation and subsequent [2,3]-sigmatropic rearrangement. This transformation would deliver the bicyclic ketone

(±)-**84**, containing the required (*Z*)-oxonene and dihydrofuranone rings, along with three of the stereocentres found in 11-acetoxy-4-deoxyasbestinin D (**8**, **Figure 3**).

Generation of an oxonium ylide and its subsequent rearrangement is known to be significantly influenced by the nature of the metal complex employed as the catalyst for the reaction, with the metal and its associated ligands, as well as the reaction conditions, playing a decisive role. Previous work performed during the total synthesis of vigulariol (**76**, **Figure 13**) had been directed towards the optimisation of the reaction (**Scheme 87** and **Table 1**).[94] It is known that copper catalysis generally delivers higher yields of the products resulting from oxonium ylide formation and subsequent [2,3]-sigmatropic rearrangement than the rhodium-mediated processes, and so copper complexes were investigated first.[113,114] The electrophilic nature of the metal was probed by modifying the electron demand of its ligands (entries 1-3). Upon increasing the electrophilic nature of the catalytic complex, both the isolated yields and isomer ratios (*Z*:*E*) increased dramatically, with copper(II) hexafluoroacetylacetonate [$Cu(hfacac)_2$] providing bicyclic ketones (+)-(***Z***)-**84** and (−)-(***E***)-**84** in 95% yield with a 5:1 isomer ratio (entry 3). Employing a rhodium catalyst under analogous conditions resulted in a considerable drop in product yield and afforded the isomeric bicyclic ketones in a near equimolar ratio, indicating that the metal plays an important role in the rearrangement reaction and that a metal-bound ylide might be involved (entry 4). Lower temperatures had little effect on the overall yield but did improve the product distribution slightly, although at the expense of reaction time (entries 5 and 6). Investigations into the reaction solvent indicated that there was not a direct and simple correlation between the solvent polarity and the outcome of the reaction (entries 3, 7-11). All the solvents tested afforded the bicyclic ketones in good to excellent yields, with reactions performed in methylene chloride still delivering the best results (entry 3). The distribution of isomers varied considerably, with THF affording the highest *Z*:*E* isomer ratio (6.9:1) and acetonitrile the lowest (1.3:1).



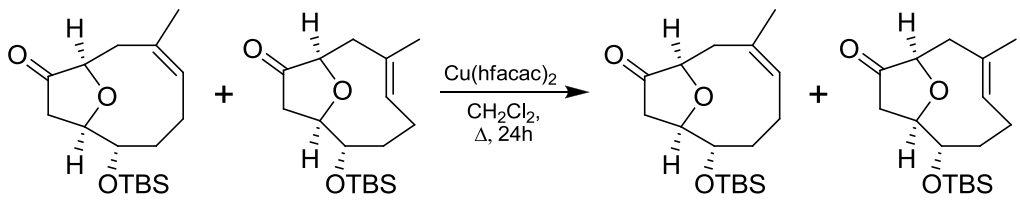
(+)-**82** **83** (+)-(***Z***)-**84** (−)-(***E***)-**84**

Scheme 87

Entry	Catalyst	Solvent	Temperature	Duration	Ratio *Z*:*E*	Yield
1	$Cu(acac)_2$	CH_2Cl_2	Reflux	3 h	3.5:1	30%
2	$Cu(tfacac)_2$	CH_2Cl_2	Reflux	3 h	3.6:1	70%
3	$Cu(hfacac)_2$	CH_2Cl_2	Reflux	15 min	5:1	95%
4	$Rh_2(OAc)_4$	CH_2Cl_2	Reflux	1 h	1.2:1	52%
5	$Cu(hfacac)_2$	CH_2Cl_2	0 °C	7 h	5.5:1	96%
6	$Cu(hfacac)_2$	CH_2Cl_2	rt	3 h	5.9:1	94%
7	$Cu(hfacac)_2$	DCE	Reflux	15 min	3.9:1	85%
8	$Cu(hfacac)_2$	THF	Reflux	45 min	6.9:1	74%
9	$Cu(hfacac)_2$	Et_2O	Reflux	15 min	3.1:1	93%
10	$Cu(hfacac)_2$	C_6H_6	Reflux	30 min	4.8:1	94%
11	$Cu(hfacac)_2$	MeCN	Reflux	2 h	1.3:1	78%

Table 1[94]

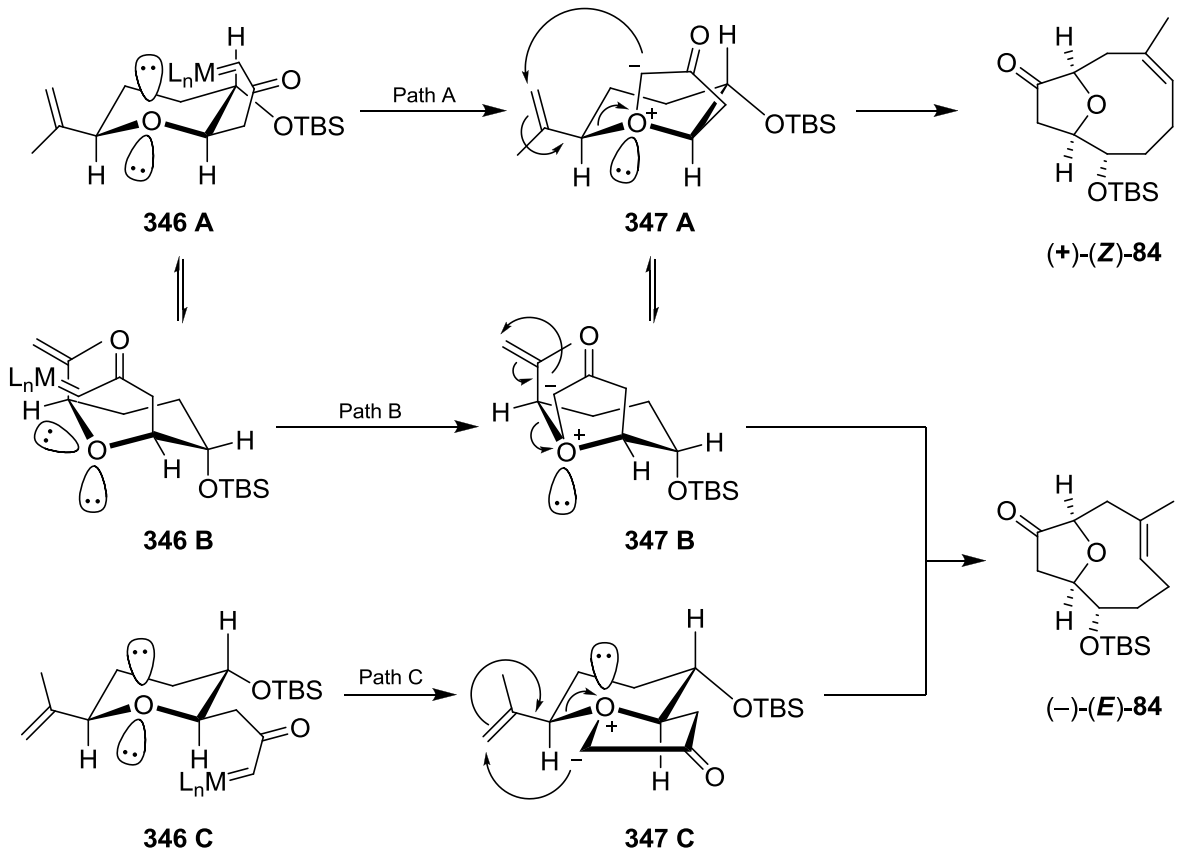
The dramatic differences in the outcome of the reaction when employing different catalysts, temperatures and solvents suggest that it is unlikely that the transformation involves a free oxonium ylide as a common intermediate, as this would be expected to deliver similar product distributions. To account for this observation it was concluded that the [2,3]-sigmatropic rearrangement involved a metal-bound ylide intermediate. However, the potential existed for the catalytic system to be causing product isomerisation and so altering the product distribution after the fact. To discover whether isomerisation was an issue, a control experiment was performed in which the bicyclic ketones (+)-(***Z***)-**84** and (−)-(***E***)-**84** were heated to reflux in methylene chloride using 10 mol% $Cu(hfacac)_2$ (**Scheme 88**).[94] After 24 h, the ratio of bicyclic ketones remained unchanged and isomerisation of the double bond was not observed, suggesting that the *Z*:*E* isomer distribution was the true kinetic ratio.



(+)-(***Z***)-**84** (−)-(***E***)-**84** (quant.) (+)-(***Z***)-**84** (−)-(***E***)-**84**

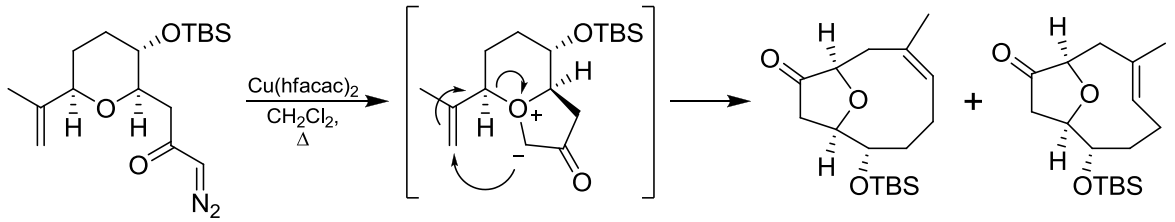
Scheme 88

An explanation of how the isomers are formed can be deduced from the various metal carbenoid conformers the molecule can adopt (**Scheme 89**). From the most stable metal carbenoid conformer **346 A**, the formation of the oxonium ylide **347 A** will occur at the "axial" lone pair of the oxygen, generating the five-membered ring under the least strain, which then undergoes the [2,3]-sigmatropic rearrangement to give the bicyclic ketone (**+**)-(***Z***)-**84** (**Path A**). Ring flipping of conformer **346 A** will orientate the bulky substituents into an axial position, affording conformer **346 B**, which although higher in energy to conformer **346 A**, does allow formation of the five-membered ring in a *syn*-fashion (**347 B**), minimising ring strain and concomitantly forming bicyclic ketone (−)-(***E***)-**84** (**Path B**). While the final conformer (**346 C**) adopts the favoured equatorial disposition of its bulky substituents, oxonium ylide formation occurs at the "equatorial" lone pair of the oxygen, generating an *anti*-configuration for the five-membered ring, creating the greatest ring strain. Computational calculations for the energies of oxonium ylide intermediates **347 A**, **B** and **C** indicate a relatively small difference between them (22 kJ mol^{-1}), meaning that all conformers should exist in equilibrium.[115] This "free" oxonium ylide representation does not concur with diverse range of results observed, meaning that the transition states of the [2,3]-sigmatropic rearrangement need to be considered in the context of a hypothesis invoking a metal-bound ylide intermediate.



Scheme 89

Following identification of the optimum catalyst, solvent and temperature for the formation of the bicyclic ketone (***Z***)-**84**, the synthesis of the asbestinins was used to investigate what effect that duration of the reaction played in the oxonium ylide formation and [2,3]-sigmatropic rearrangement (**Scheme 90** and **Table 2**). Initially, replicating the optimal conditions attained during the synthesis of vigulariol (**76**, entry 3, **Table 1**) afforded the bicyclic ketones with a similar *Z*:*E* isomer ratio but in poor yield (entry 1, **Table 2**). When the time taken for addition of the diazoketone (±)-**82** was extended to 40-45 min, there was a significant increase in the product yield and in the product ratio favouring the ***Z***-isomer (entries 2 and 3). Optimal conditions were seen when the addition was performed over a 90 min period, giving the bicyclic ketone in near quantitative yield and with a *Z*:*E* isomer ratio of 6.5:1 (entry 4). Extending the duration of the addition further, to 120 min, resulted in a marginal decrease in both the yield and product distribution. Clearly, the duration of the addition plays an important role in determining both the overall yield and the ratio of product obtained, with the optimal conditions being performed on large scale (2.6 g).



(±)-82 **83** **(±)-(*Z*)-84** **(±)-(*E*)-84**

Scheme 90

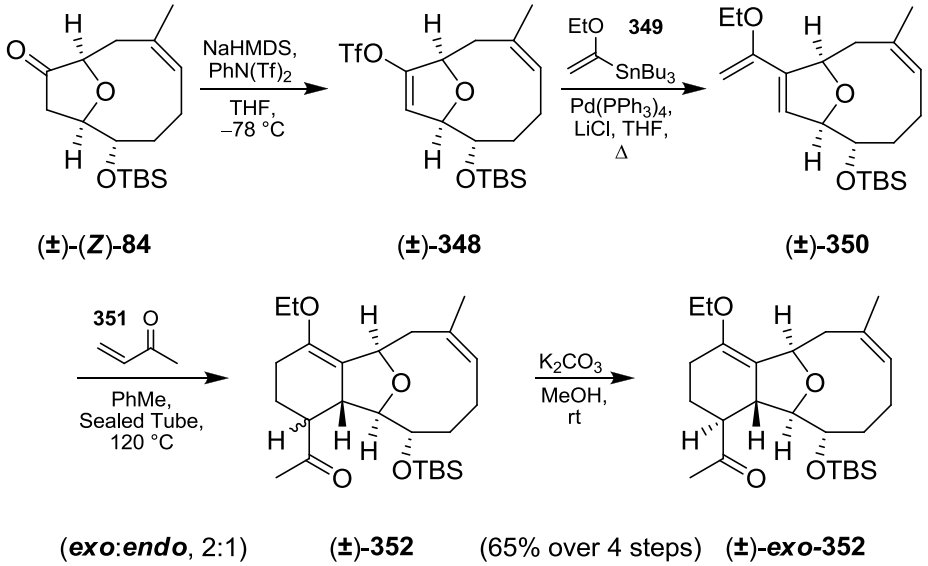
Entry	Duration	Ratio *Z*:*E*	Yield
1	15 min	4.8:1	64%
2	40 min	6.1:1	85%
3	45 min	5.9:1	90%
4	**90 min**	**6.5:1**	**97%**
5	120 min	6.2:1	94%

Table 2

2.5 Investigations into the Diels-Alder Cycloaddition to Construct the Tricyclic Core

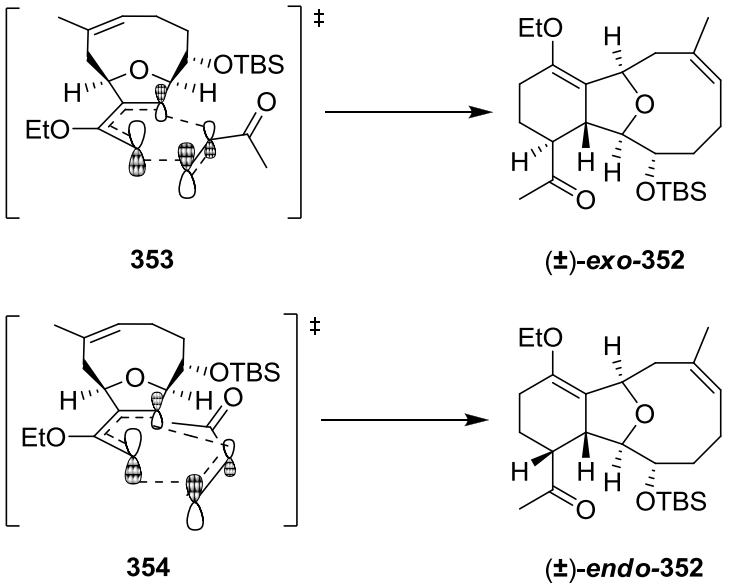
Successful formation of the bicyclic ketone (±)-(*Z*)-**84** meant that the next stage of the synthesis - construction of the cyclohexyl ring - could be investigated. In previous work within the Clark group, an intermolecular Diels-Alder strategy had been utilised to construct the ring, and this formed the initial route for the synthesis of the asbestinins.[94] Kinetic deprotonation of bicyclic ketone (±)-(*Z*)-**84** and trapping of the resulting sodium enolate with *N*-phenyl-*bis*-trifluoromethanesulfonamide generated the corresponding enol triflate (±)-**348**, which was used in the next step after filtration through a plug of silica gel (**Scheme 91**).[116] Next, the crude enol triflate (±)-**348** was subjected to a Stille cross coupling[37] with the commercially available stannane tributyl(ethoxyvinyl)tin **349**, generating the required Diels-Alder diene (±)-**350**.[117] The diene (±)-**350** proved to be very unstable to silica gel chromatography, and so filtration of the crude reaction mixture through a pad of Celite®535 followed by immediate use in the next step was performed to give optimum results. The thermally mediated intermolecular Diels-Alder cycloaddition with methyl vinyl ketone **351** was performed in a sealed tube at 120 °C for 3 days, generating a 2:1 mixture of the ***exo***:***endo***

cycloadducts (±)-**352**. Finally, base catalysed epimerisation of the mixture of cycloadducts afforded the required tricyclic ketone (±)-***exo*-352** as a single diastereomer in 65% yield over the four steps.



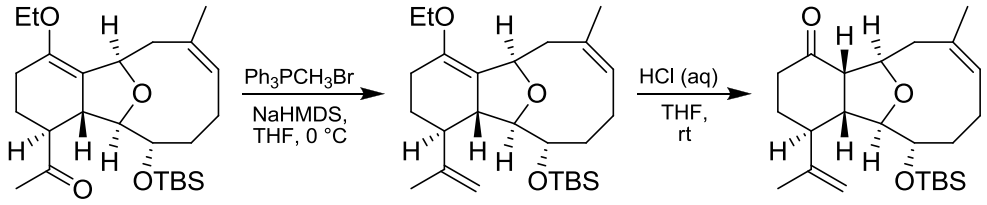
Scheme 91

The stereochemical outcome of the Diels-Alder cycloaddition reaction can be rationalised by the transition states **353** and **354**. The complete regioselectivity that is observed from the reaction is the result of the matched electronics of the electron rich diene and electron deficient dienophile (**Scheme 92**). The complete facial selectivity (diene component) that is observed from the reaction is the result of the bowl-like topography of the substrate that shields the inner face of the diene, with attack by the dienophile only possible from the convex face of the diene.



Scheme 92

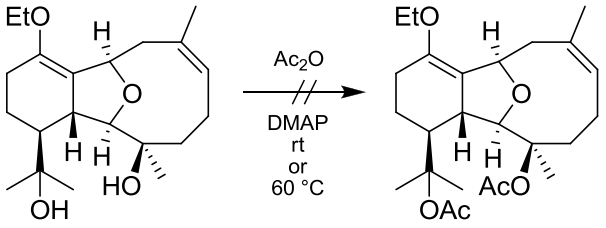
The tricyclic ketone (±)-***exo*-352** was then converted to the terminal alkene (±)-**355** by means of a Wittig methylenation reaction using a four-fold excess of the phosphorus ylide derived from methyltriphenylphosphonium bromide (**Scheme 93**).[6] This reaction was followed by the acid-mediated hydrolysis of enol ether (±)-**355** which afforded tricyclic ketone (±)-**356** in excellent yield.



(±)-***exo*-352** (75%) **(±)-355** (92%) **(±)-356**

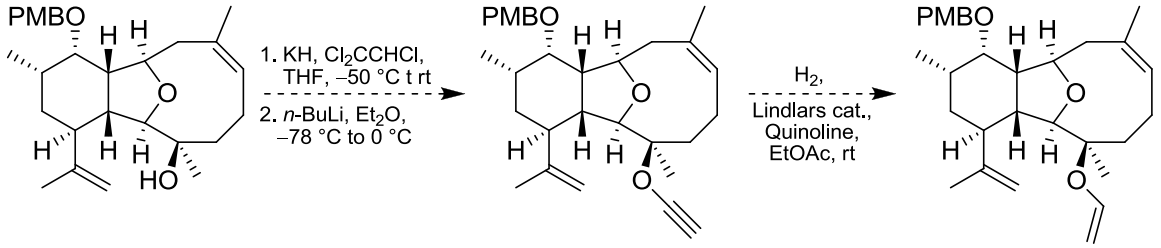
Scheme 93

At this point, related work that had been carried out within the Clark group on the total synthesis of orphirin B had shown that it was difficult to perform alkylation of the tertiary alcohol (+)-**357** (**Scheme 94**).[95] The proposed synthetic route for the asbestinins required the alkylation of an analogous tertiary alcohol **359**, which was an essential intermediate in the planned ring closing metathesis (RCM) route (**Scheme 95**). In the absence of a viable route to the *bis*-terminal diene **277**, construction of the final oxepane ring by means of a RCM reaction would not be achievable. Consequently, an alternative approach to construction of the final ring was required.

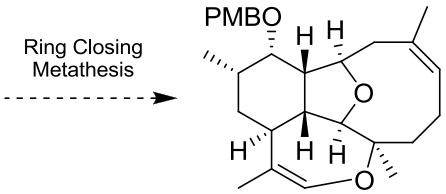


(+)-357 **358**

Scheme 94[95]



359 **360** **277**

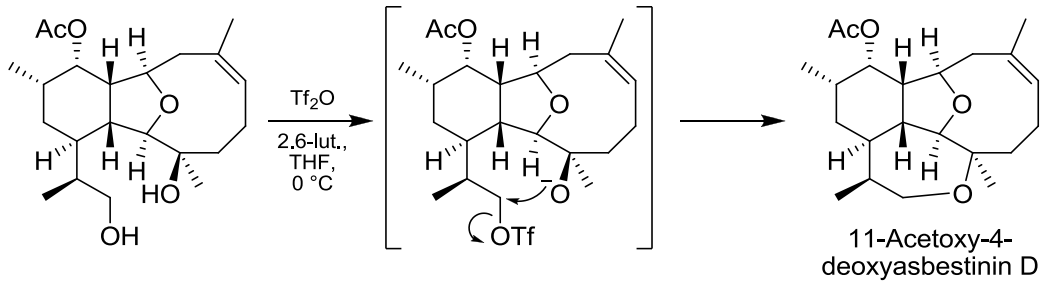


276

Scheme 95

2.5.1 Diels-Alder Cycloaddition of α-Alkoxy Functionalised Enones in the Construction of the Tricyclic Core

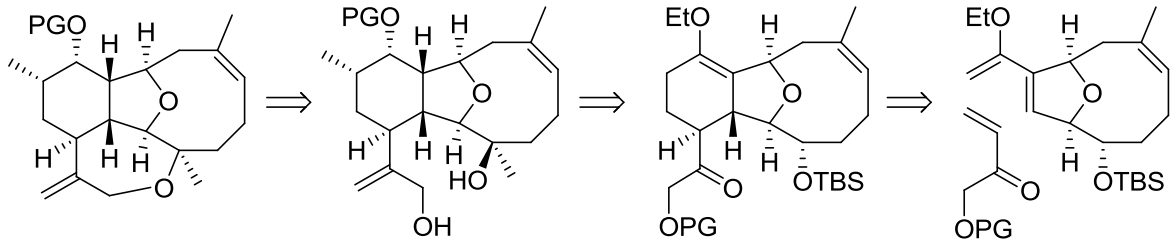
With the problems that had arisen during the total synthesis of orphirin B, and the implications that these presented for the RCM route to the asbestinins, a new method for the construction of the final oxepane ring was required. Insight was drawn from the final step in the total synthesis of 11-acetoxy-4-deoxyasbestinin D, reported by Crimmins and co-workers (**Scheme 96**).[6] These workers utilised intramolecular displacement of the triflate **362** by an analogous tertiary alcohol to that which had caused problems during the total synthesis of orphirin B, closing the final oxepane ring in 66% yield and completing the natural product.



361 (66%) **362** **8**

Scheme 96[6]

It was expected that an appropriately functionalised dienophile **366** could be used for the construction of the cyclohexenyl ring **365**, and that the closure of the oxepane ring could be achieved by an analogous transformation (**Scheme 97**).



363 **364** **365** **366** **(±)-350**

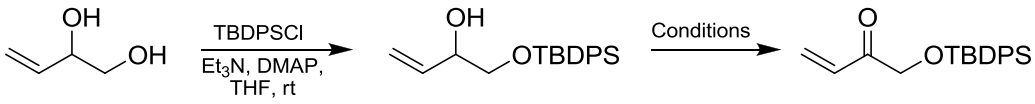
Scheme 97

2.5.1.1 Diels-Alder Cycloaddition of the α-Silyloxy Enone 369

The bicyclic ketone (±)-(*Z*)-**84** already contained a TBS ether protecting group and so orthogonal protection of the latent hydroxyl group present in the required dienophile was necessary. The first protecting group employed for the synthesis of the α-hydroxy dienophile was the *t*-butyldiphenylsilyl group (TBDPS).

The synthesis commenced with the protection of the primary alcohol of racemic 3-butene-1,2-diol (±)-**367** with TBDPSCl in good yield (**Scheme 98**). Next, oxidation of the allylic alcohol (±)-**368** was then explored using a variety of conditions (**Table 3**). The manganese-mediated oxidation reactions of the allylic alcohol (±)-**368** at both rt and reflux were explored first but these proved to be ineffective and only starting material was recovered (entries 1, 2).[118] Chromium-mediated reactions were employed for the allylic oxidation of (±)-**368**, in both methylene chloride[119] and also in the absence of any solvent,[120] but neither afforded the desired product (entries 3, 4). The

TPAP/NMO oxidation protocol was also attempted, delivering enone **369** in 10% yield (entry 5). Finally, Swern oxidation[36] for the allylic oxidation of alcohol (±)-**368** gave the desired enone **369** in a modest 54% yield (entry 6). The enone **369** proved to be unstable and chromatographic purification led to partial decomposition of the product. Upon large scale implementation of the Swern conditions (4.8 g of alcohol (±)-**368**), the oxidation proved to be even less effective and the enone **369** was obtained in just 22% yield. In light of these results, an alternative route for the construction of enone **369** was required.



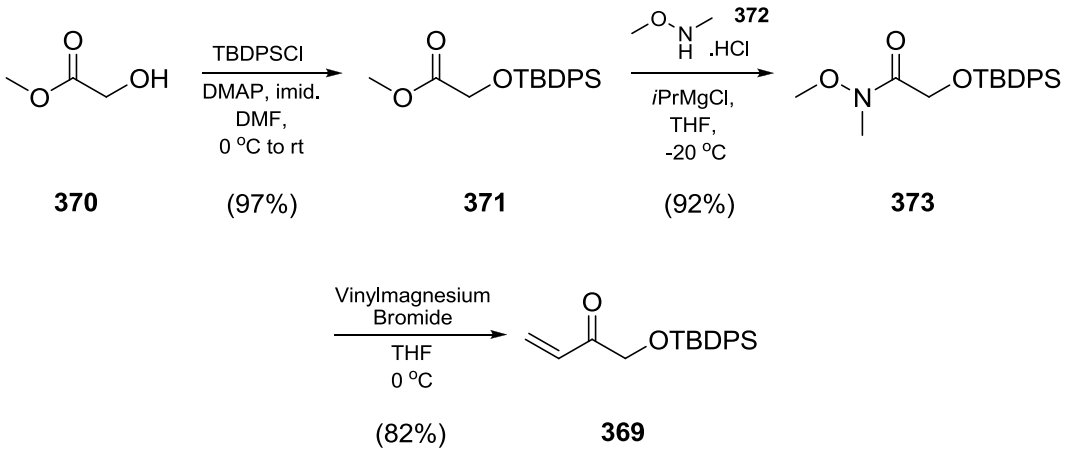
(±)-**367** (86%) (±)-**368** **369**

Scheme 98

Entry	Conditions	Solvent	Temperature	Yield
1	MnO_2	Acetone	Reflux	SM
2[118]	$KMnO_4/MnO_2$	CH_2Cl_2	rt	SM
3[119]	PDC, 4 Å MS	CH_2Cl_2	rt	Decomp.
4[120]	$K_2Cr_2O_7$	neat	rt	Decomp.
5	TPAP/NMO	CH_2Cl_2	rt	10%
6[36]	$(COCl)_2$, DMSO, Et_3N	CH_2Cl_2	−78 °C	54%

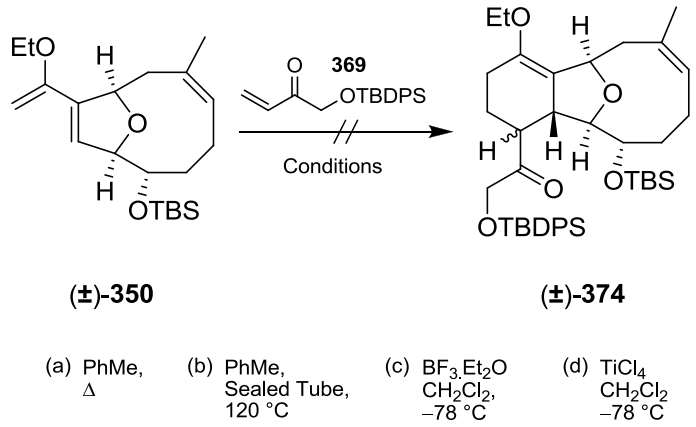
Table 3

The alternative route to the enone **369** started with the TBDPS protection of methyl glycolate **370** in near quantitative yield (**Scheme 99**).[121] The construction of the Weinreb amide **373** was achieved in excellent yield by treatment of ester **371** with *N*,*O*-dimethylhydroxylamine hydrochloride (**372**) and *iso*-propylmagnesium chloride at −20 °C.[122] Finally, treatment of Weinreb amide **373** with vinylmagnesium bromide followed by an acidic aqueous work-up afforded the required enone **369** in 82% yield.[123]



Scheme 99

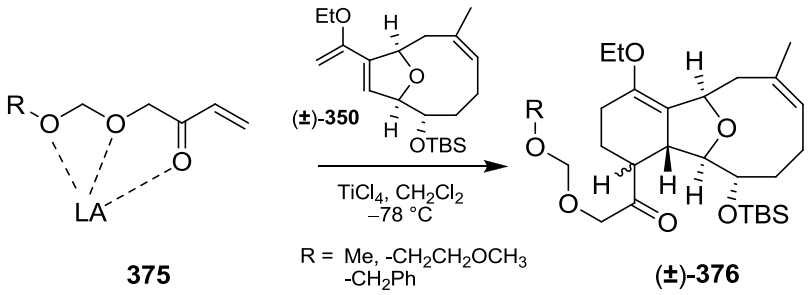
Following preparation of the required dienophile **369**, attention was directed towards construction of the tricyclic core. The Diels-Alder diene (±)-**350** was generated from the bicyclic ketone (±)-(***Z***)-**84** by the same two-step enol triflate / Stille coupling procedure previously used for the construction of the tricyclic ketone (±)-***exo*-352** (**Scheme 91**). Initial investigation of thermal conditions at both atmospheric pressure and in a sealed tube, resulted in partial decomposition of both enone **369** and diene (±)-**350** (conditions a and b, **Scheme 100**). Next, Diels-Alder cycloaddition was attempted using Lewis acid mediated conditions, with treatment with $BF_3{\cdot}Et_2O$ and $TiCl_4$ in methylene chloride at −78 °C resulting in complete decomposition of both the enone **369** and diene (±)-**350** within 15 min (conditions c and d). Following the failure of both the thermal and Lewis acid mediated reactions, no further work was performed using the α-silyloxy enone **369**.



Scheme 100

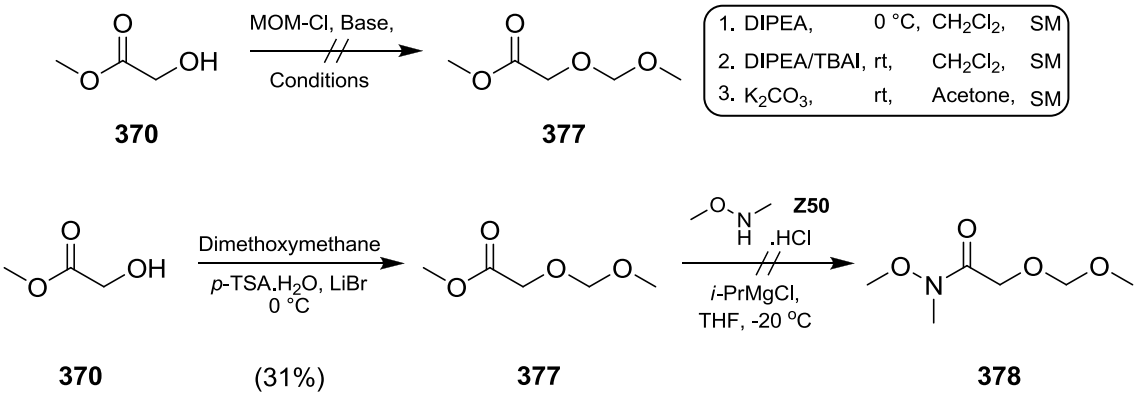
2.5.1.2 Diels-Alder Cycloaddition of the Ether Protected α-Hydroxy Enone Dienophiles

Failure of the thermal Diels-Alder reaction of α-silyloxy enone **369** implied that the coupling partners were not activated enough with respect to each other for cycloaddition to occur. The Lewis acid mediated Diels-Alder reactions of enone **369** resulted in total decomposition of both coupling partners at −78 °C, a near 200 degree negative reversal in temperature to the thermal conditions. It was thought that cycloaddition could be accomplished if the reactivity of the Lewis acid could be tempered, but to an extent that still enabled activation of the dienophile. To address this issue, it was thought that by incorporating a Lewis basic ether-type protecting group in the dienophile that could coordinate the Lewis acidic metal might temper its reactivity, enabling the cycloaddition to proceed (**Scheme 101**).



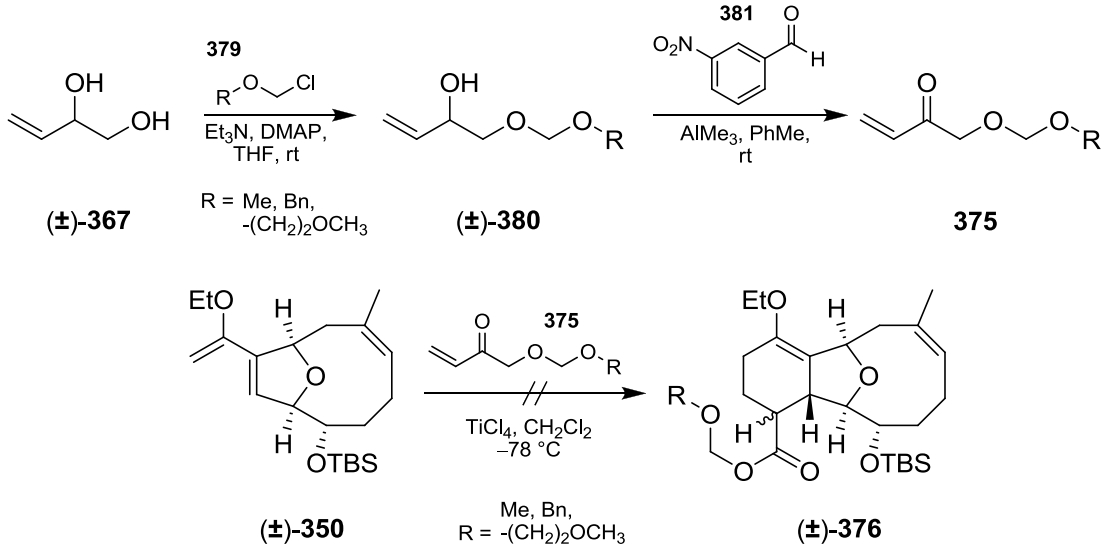
Scheme 101

The synthesis of the methoxymethyl (MOM) protected dienophile was first attempted using a Weinreb amide route that was analogous to that employed for the synthesis of the silyloxy enone **369**.[119,122] Unfortunately, after employing a variety of conditions to protect the alcohol of methyl glycolate **370**, which was accomplished in a poor 31% yield, this route failed at the stage at which the Weinreb amide **378** was to be formed (**Scheme 102**).



Scheme 102

Further research into the synthesis of ether-protected enones (**375**) returned to the allylic oxidation reaction that had been investigated during the synthesis of the silyloxy enone **369** (**Scheme 98**). Ether protection of 3-butene-1,2-diol (±)-**367** afforded the corresponding allylic alcohols (±)-**380** in poor to moderate yields (30-53% yield, **Scheme 103** and **Table 4**). Next, each of the allylic alcohols was subjected to an Oppenauer oxidation. Reaction of the MOM allylic alcohol (±)-**380** afforded only starting material, but both the methoxyethoxymethyl (MEM) and benzyloxy methyl (BOM) enones [(±)-**375**] were obtained in moderate yield (51-53%). The titanium tetrachloride mediated Diels-Alder cycloadditions for both the MEM- and BOM-enones [(±)-**375**] again resulted in complete decomposition of both the diene and dienophile, analogous to that seen with the silyloxy enone **369**. The inability to effectively temper the reactivity of the Lewis acidic metal coupled with the poor yields obtained for the synthesis of the required dienophiles, meant that no further investigations were performed using the ether protected α-hydroxy enone dienophiles.



Scheme 103

Entry	Protecting Group	Alkylation Yield	Oppenauer Ox. Yield	Diels-Alder Cycloaddition Yield
1	**MOM**	30%	SM	-
2	**MEM**	51%	31%	Decomp.
3	**BOM**	53%	25%	Decomp.

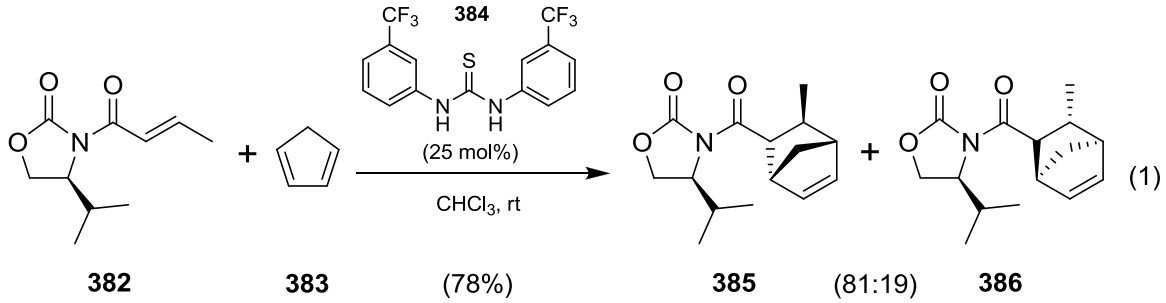
Table 4

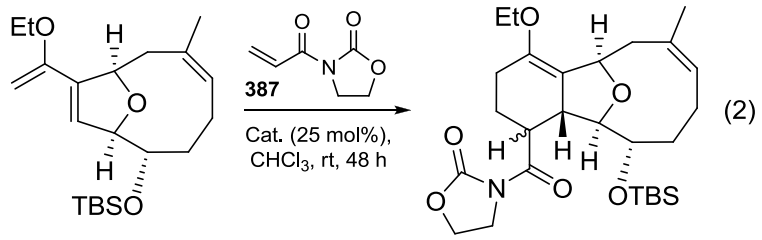
2.5.1.3 Hydrogen Bonding / Brønsted Base Mediated Diels-Alder Cycloaddition for the Construction of the Tricyclic Core

At this stage it was necessary to find an effective additive that could promote the Diels-Alder cycloaddition reaction but without the decomposition that had been encountered when Lewis acid mediated conditions had been employed. This requirement led us to consider the use of metal-free catalysis. A vast range of organocatalysts, containing hydrogen-bonding/Brønsted base functionality, have been reported in the literature for the promotion of Diels-Alder and hetero-Diels-Alder type cycloadditions.[124-126] It was decided to screen a selection of easily synthesised or commercially available additives against the oxazolidinone-derived dienophile **387** because 1,3-dicarbonyl compounds of this type had been used as model dienophiles in many publications. Schreiner and Wittkopp disclosed a publication in which they activated an *N*-acyloxazolidinone dienophile **382** using H-bond formation with an *N*,*N'*-diaryl electron-poor thiourea **384**, promoting the *endo*-Diels-Alder cycloaddition with cyclopentadiene in good yield at rt (eq 1, **Scheme 104**).[127] These conditions were chosen as those under which the various hydrogen-bonding/Brønsted base catalysts that had been selected would be tested.

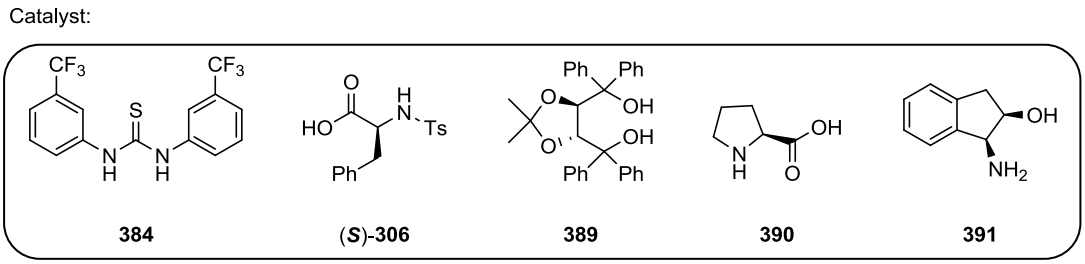
Initial investigations into the cycloaddition of diene (**±**)-**350** and *N*-propenoyl oxazolidinone **387**, promoted by H-bond catalysis with thiourea **384**, afforded only starting material after 48 h at rt in chloroform (eq 2, **Scheme 104**). Next, *N*-tosyl-(L)-phenylalanine [(***S***)-**306**] was tested, but this additive resulted in complete decomposition of the diene (**±**)-**350**, leaving the enone **382** intact. The commercially available TADDOL **389** afforded the first positive result for the Diels-Alder cycloaddition reaction; the tricyclic ketone (**±**)-**388** was obtained in 6% yield. When (L)-proline was used as the catalyst it was found to promote the cycloaddition with the formation of

tricyclic ketone (±)-**388** in 7% yield. Finally, aminoindanol **391** proved to be ineffective in promoting the cycloaddition reaction, affording only starting material.





Catalyst	Result
384	SM
(***S***)-**306**	Decomp.
389	6% Yield
390	7% Yield
391	SM



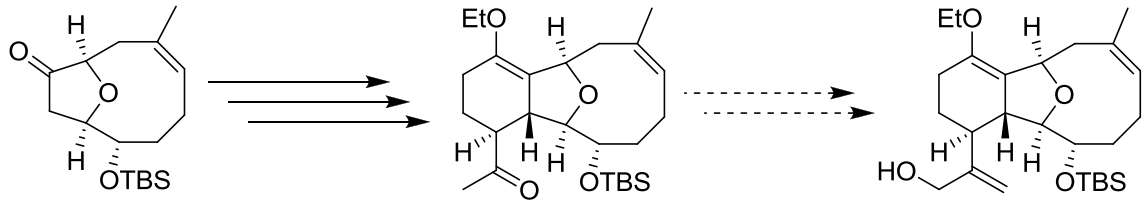
Scheme 104

As a consequence of the inability to identify effective conditions for the Diels-Alder reaction of diene (±)-**350** with various α-hydroxy protected enones, no further investigations into this potential cycloaddition were performed. Instead, attention was directed toward the manipulation of the tricyclic ketone (±)-***exo*-352**, with a view to constructing the allylic alcohol tether present in diol **364** (**Scheme 97**).

2.6 Functionalisation of the Tricyclic Ketone (±)-*exo*-352

The tricyclic ketone (±)-***exo*-352** was generated from the bicyclic ketone (±)-(***Z*)-84** by the same four step sequence discussed previously (**Scheme 91** and **105**). It was postulated that following transformation of the terminal ketone (±)-***exo*-352** into the allylic alcohol (±)-**392**, the intramolecular triflate displacement method developed by

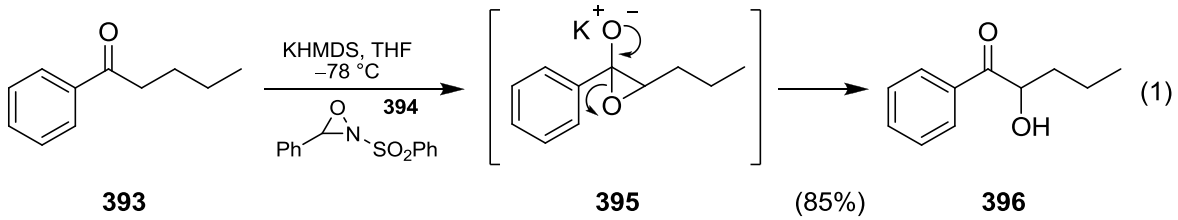
Crimmins and co-workers could be implemented for the closure of the oxepane ring (**Scheme 96** and **97**).[6]



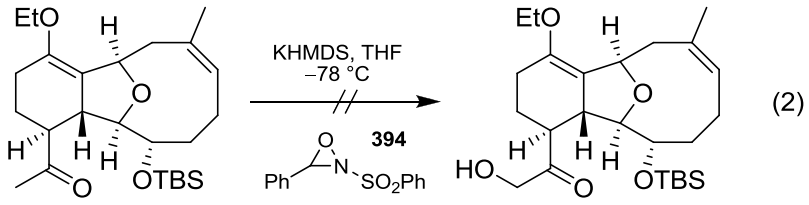
(±)-(***Z***)-**84** (65% over 4 steps) (±)-***exo*-352** (±)-**392**

Scheme 105

Davis and co-workers disclosed the synthesis of a variety α-hydroxy carbonyl compounds by formation of the corresponding epoxide **395** using the sulfonyloxaziridine **394** (eq 1, **Scheme 106**).[128] Unfortunately, when the tricyclic ketone (±)-***exo*-352** was subjected to literature conditions - formation of the corresponding potassium enolate at −78 °C followed by the addition of the sulfonyloxaziridine **394** – only decomposition of the starting material was observed (eq 2).



393 **395** (85%) **396**

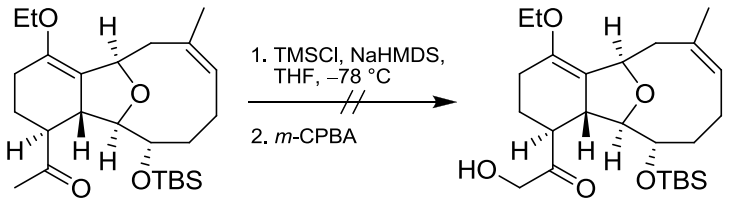


(±)-***exo*-352** (±)-**392**

Scheme 106

The formation of the required α-hydroxy ketone (±)-**392** was also attempted using Rubottom oxidation conditions (**Scheme 107**).[129] In this case, a mixture of the tricyclic ketone (±)-***exo*-352** and trimethylsilyl chloride (TMSCl) was treated with NaHMDS at −78 °C, but the required silyl ether was not formed and partial decomposition of the tricyclic ketone (±)-***exo*-352** was observed. This result suggested that generation of the

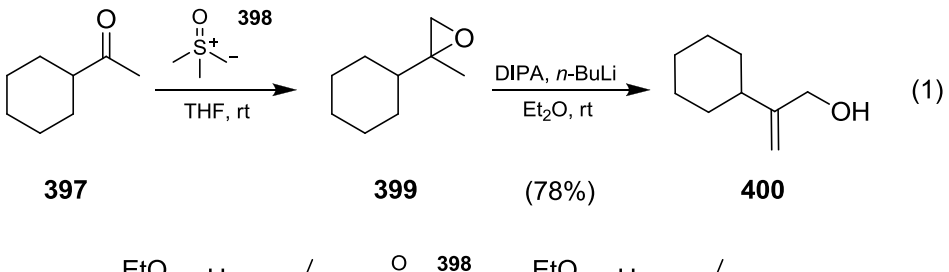
kinetic enolate required for the oxidation would be difficult to achieve and so an alternative route was investigated.



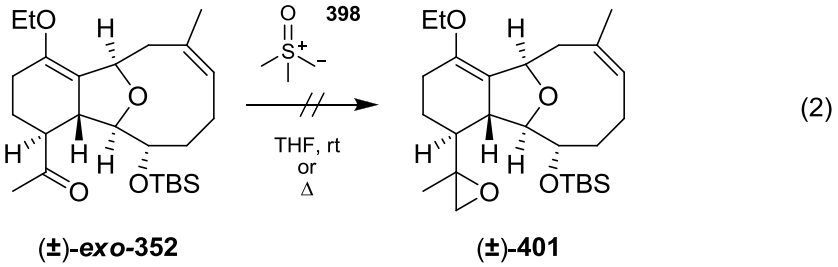
(±)-*exo*-352 **(±)-392**

Scheme 107

A two-step protocol involving a Corey-Chaykovsky epoxidation followed by base-mediated ring opening of the resulting epoxide was proposed as an alternative to the route described above. Model studies were performed prior to the application of this sequence to the real system (**Scheme 108**). Cyclohexylketone **397** was treated with a single equivalent of dimethyloxosulfonium methylide **398**, which was easily prepared from trimethylsulfoxonium iodide and sodium hydride (eq 1). The resulting epoxide **399** was found to be volatile and so after chromatographic purification it was carefully concentrated *in vacuo*. Treatment of the epoxide **399** with a single equivalent of lithium di-*iso*-propylamide (LDA) afforded the allylic alcohol **400** in 78% yield over the two steps.[130] When the Corey-Chaykovsky epoxidation procedure was applied to the tricyclic ketone (±)-***exo*-352** at both rt and at reflux, the epoxide (±)-**401** was not obtained and only partial decomposition of the starting ketone (±)-***exo*-352** was observed.



397 **399** (78%) **400**



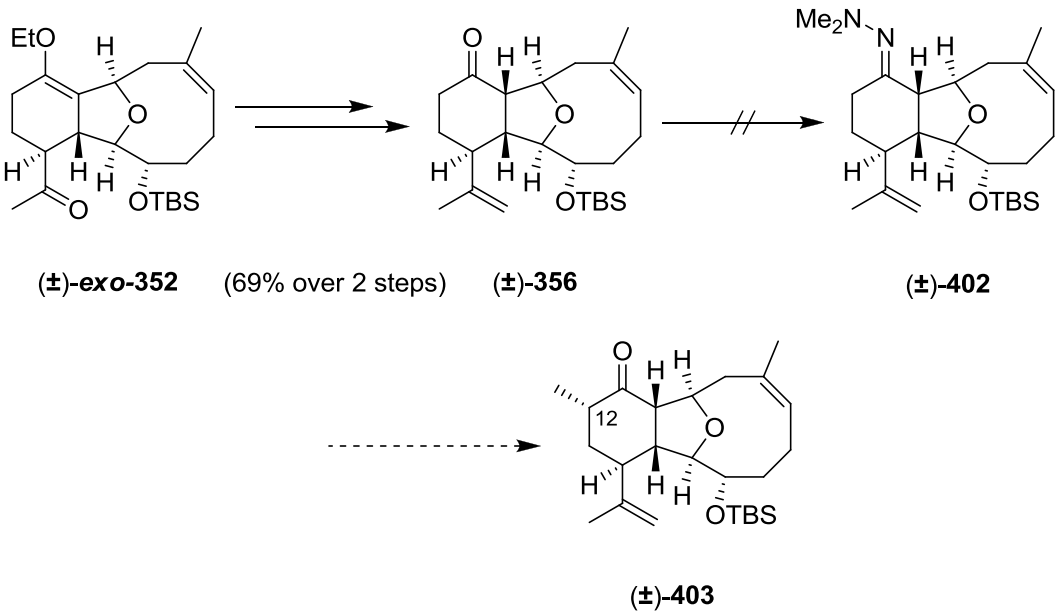
(±)-*exo*-352 **(±)-401**

Scheme 108

The inability to form the Corey-Chaykovsky epoxide (±)-**401** or generate the kinetic enolate required for the Rubottom oxidation, suggested the carbonyl group of tricyclic ketone (±)-***exo*-352** was too sterically hindered for these transformations to proceed. Models of the tricyclic ketone (±)-***exo*-352** place the ketone inside the bowl-like topography of the molecule that the favoured configuration dictates, making access for sterically demanding reagents less favourable. Consequently, further investigations into the manipulation of this carbonyl group were not performed.

2.7 C-12 Methylation of Tricyclic Ketone (±)-356

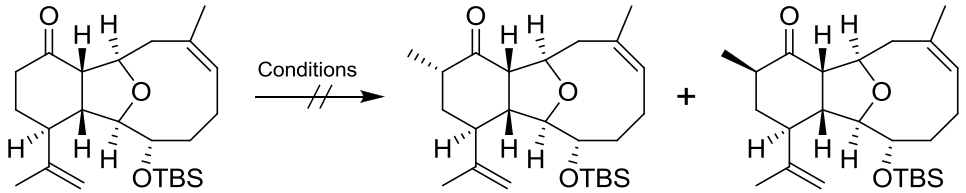
The next transformation to be investigated was introduction of the C-12 methyl substituent into the tricyclic ketone (±)-**356**. Initial attempts to do this *via* the formation and subsequent α-methylation of a hydrazone derivative had failed at the hydrazone formation step (**Scheme 109**).[131,132]



Scheme 109

Thus, generation of the kinetic enolate by a sterically demanding base, followed by the nucleophilic attack of this enolate on iodomethane was proposed as a viable route to introduce the required C-12 methyl group. It was hoped that the resulting α-methyl diastereomers would be separable by chromatography and that the undesired diastereomer could be epimerised to give to the diastereomer with the required C-12 configuration.

Initial investigations focused on the formation of the kinetic enolate at low temperature followed by the addition of the electrophile (**Scheme 110**). In every case, partial decomposition of ketone (±)-**356** was observed without product formation.[133-135]

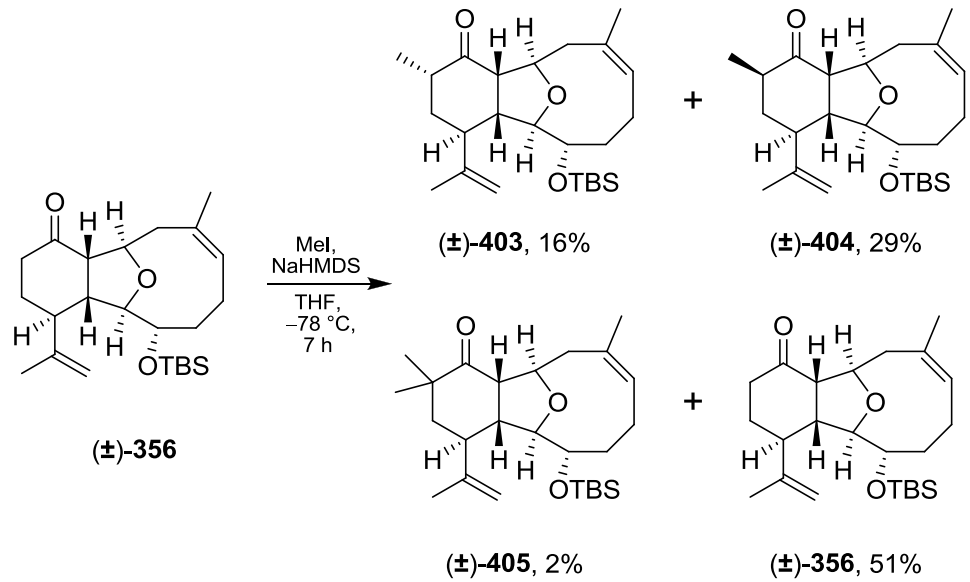


(±)-**356** (±)-**403** (±)-**404**

(a) 1. DIPA, *n*-BuLi, THF, –10 °C; 2. DMPU, MeI, –50 °C (b) 1. TMSCl, NaHMDS, THF, –78 °C; 2. MeI, –78 °C to rt (c) 1. NaHMDS, THF, –78 °C; 2. MeI, –78 °C to rt (d) 1. KHMDS, HMPA, THF, –78 °C; 2. MeI, –78 °C to rt (e) 1. $NaNH_2$, THF, –78 °C; 2. MeI, –78 °C

Scheme 110

Successful introduction of the C-12 methyl group was achieved when a mixture of the ketone (±)-**356** and iodomethane was cooled to −78 °C and then treated with the base (**Scheme 111**). Optimal conditions required 6 equivalents of both iodomethane and NaHMDS (1.0 M in THF, added dropwise over 10 min) to afford the best results. Unreacted ketone (±)-**356** was recycled through the transformation.



(±)-**356**

(±)-**403**, 16% (±)-**404**, 29%

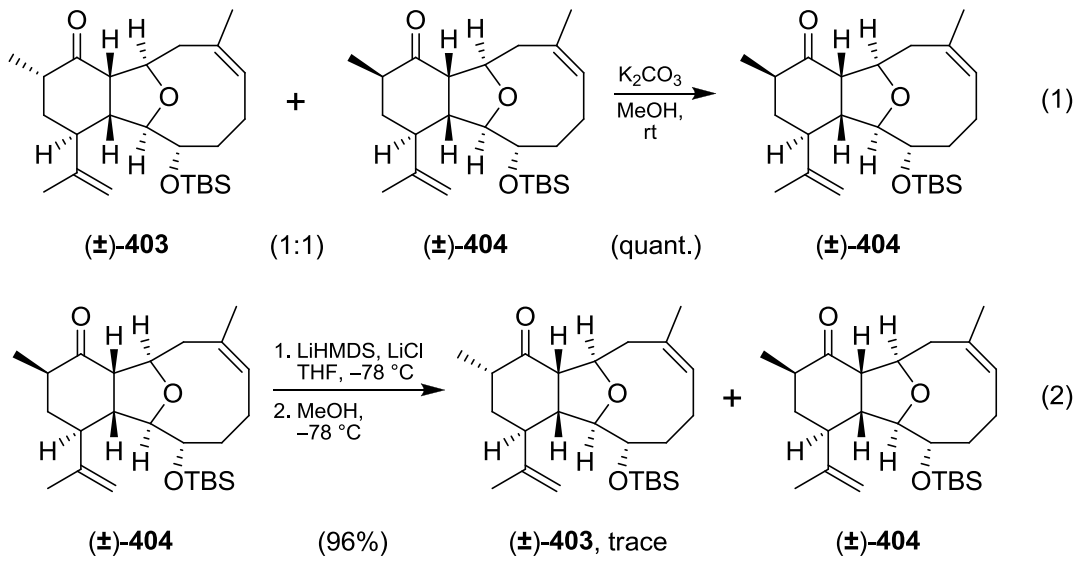
(±)-**405**, 2% (±)-**356**, 51%

Scheme 111

At this point, both α-methyl diastereomers (±)-**403** and (±)-**404** were separable by chromatography and subjected to Nuclear Overhauser analysis (NOESY), which

unfortunately failed to establish the configuration of either compound unambiguously. The assigned stereochemistry for each of the diastereomers is done so on a retrospective basis from the completion of the formal target (±)-**417** and comparison with the published data.[6]

Epimerisation of the diastereomers was investigated next. An equimolar mixture of tricyclic ketones (±)-**403** and (±)-**404** was subjected to epimerisation under basic conditions, resulting in the quantitative formation of ketone (±)-**404** having the undesired configuration (eq 1, **Scheme 112**). This result was completely contrary to what was expected, as it placed the methyl group in a more sterically demanding position compared to the ketone (±)-**403**. When kinetic conditions were applied to the epimerisation of ketone (±)-**404**, followed by low temperature quenching with methanol, minimal formation of the desired ketone (±)-**403** was observed (> 1%, eq 2).

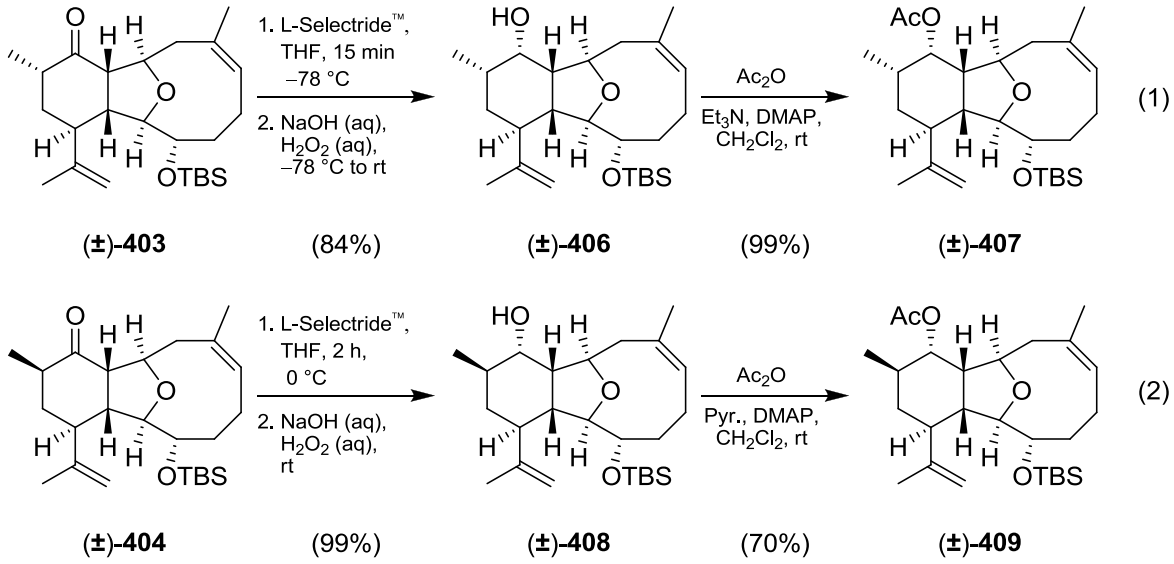


Scheme 112

2.8 Construction of the Formal Targets (±)-417 and (±)-418

The inability to conclusively assign the configuration of either of the α-methyl ketones (±)-**403** and (±)-**404** meant that it was necessary to progress both diastereomers through the transformations needed to construct the formal target (±)-**417**. First, ketone (±)-**403** was subjected to reduction with a sterically encumbered borohydride reagent. In this case, the stereochemical outcome was controlled by the configuration of the adjacent α-methyl group, affording alcohol (±)-**406** in good yield within 15 min at −78 °C (eq 1, **Scheme 113**). Next, acylation of the alcohol (±)-**406** afforded ester

(±)-**407** in near quantitative yield.[6] When these conditions were applied to the undesired diastereomer, the borohydride reduction of ketone (±)-**404** required 2 h for completion at 0 °C. In addition, acylation of alcohol (±)-**408** proved to be less effective than in the case of its isomeric counterpart, probably as a result of the steric environment.[136]

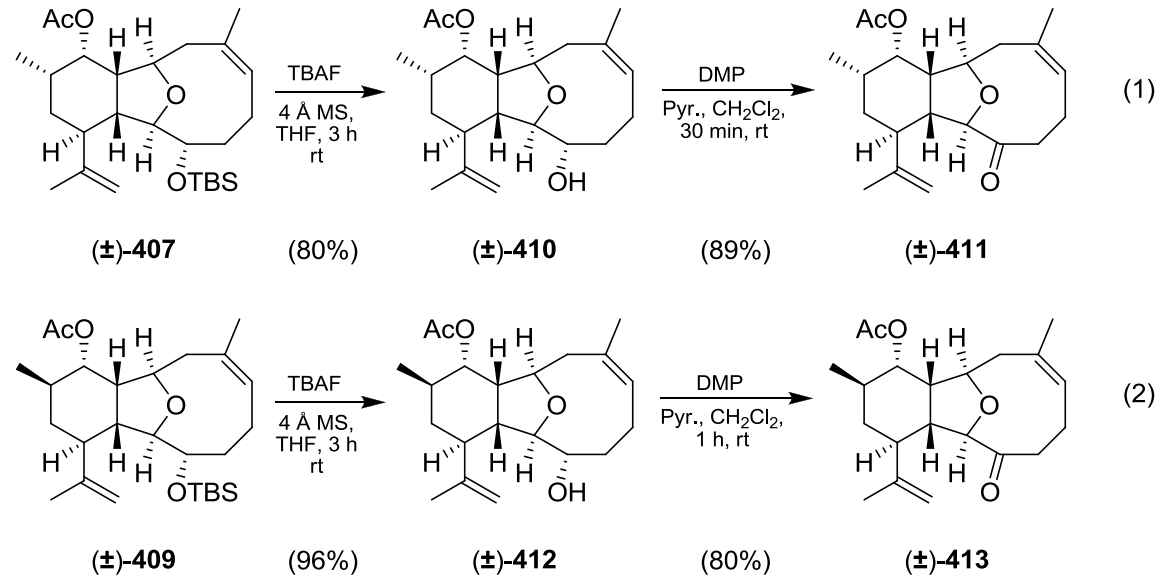


(±)-**403** (84%) (±)-**406** (99%) (±)-**407** (1)

(±)-**404** (99%) (±)-**408** (70%) (±)-**409** (2)

Scheme 113

Next, silyl ether deprotection[95] followed by DMP oxidation[28] afforded both ketones (±)-**411** and (±)-**413** in good to excellent yields (**Scheme 114**).

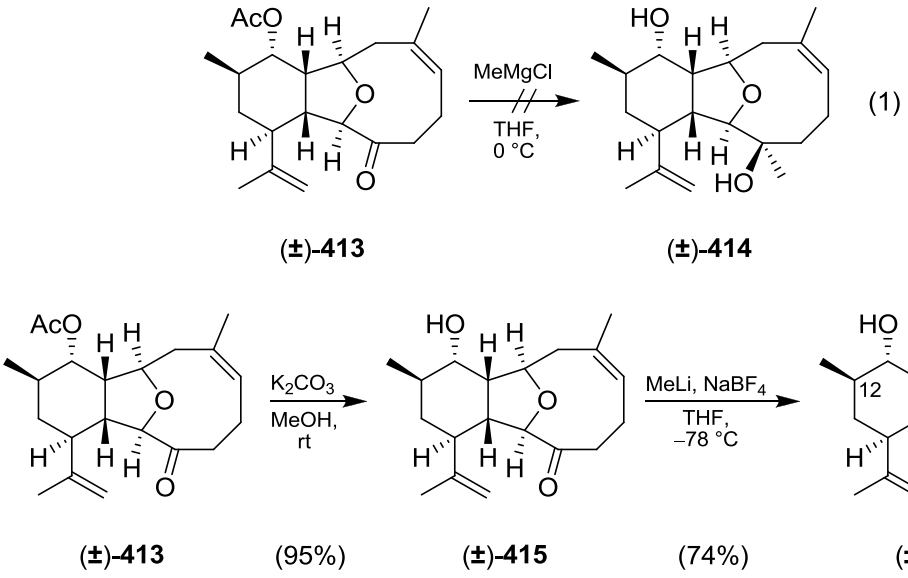


(±)-**407** (80%) (±)-**410** (89%) (±)-**411** (1)

(±)-**409** (96%) (±)-**412** (80%) (±)-**413** (2)

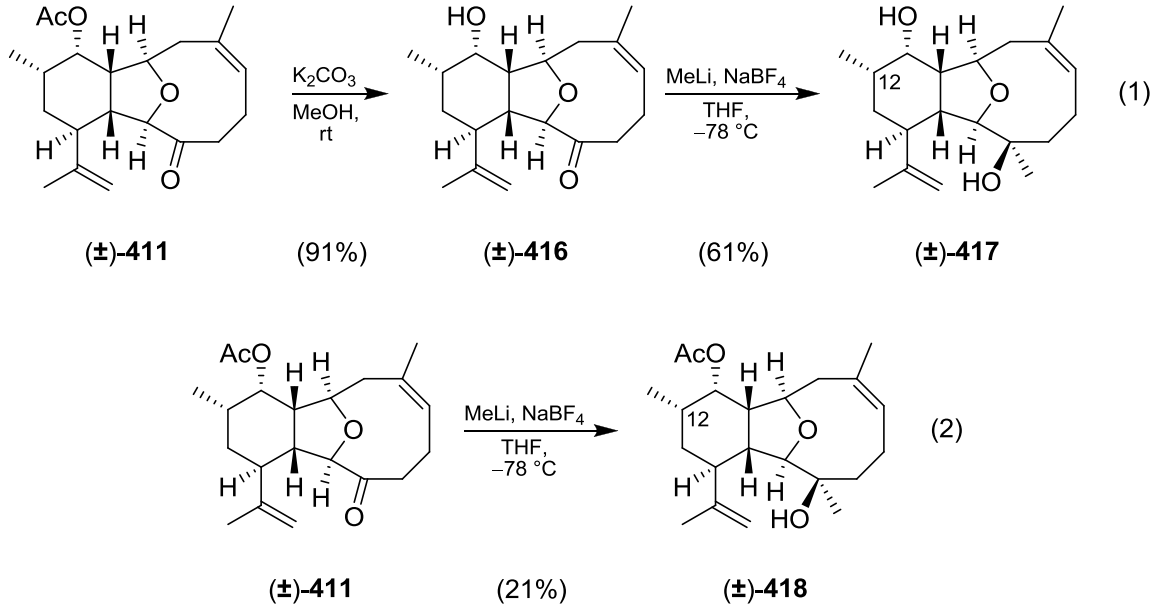
Scheme 114

The undesired ketoester (±)-**413** was treated with excess methylmagnesium chloride at 0 °C, in an attempt to form the tertiary alcohol and cleave the ester simultaneously to afford the diol (±)-**414**. Unfortunately, this reaction resulted in decomposition of the starting material (eq 1, **Scheme 115**). Saponification of ketoester (±)-**413** was followed by stereoselective methyl addition under modified reaction conditions, affording diol (±)-**414** in good yield (eq 2). At this point, the spectra published by Crimmins[6] did not match those of diol (±)-**414**, suggesting that the thermodynamic product from the epimerisation of the α-methyl ketones (±)-**403** and (±)-**404** did indeed have the undesired configuration at C-12.



Scheme 115

The ketoester (±)-**411** was then saponified in excellent yield using conditions reported previously (eq 1, **Scheme 116**). This reaction was followed by stereoselective methylation of ketoalcohol (±)-**416** which proceeded in moderate yield and afforded the formal target (±)-**417**, for which its data correlated with that published by Crimmins and co-workers.[6] In addition, direct methylation of ketoester (±)-**411** generated alcohol (±)-**418**, another formal target, although the yield was rather low in this case (eq 2).


AcO
H
H
O
H
H
H
O
K_2CO_3
MeOH,
rt
HO
MeLi, $NaBF_4$
THF,
–78 °C
12
(1)
(±)-411
(91%)
(±)-416
(61%)
(±)-417
(2)
(±)-411
(21%)
(±)-418

Scheme 116

3 Summary and Future Work

3.1 Summary

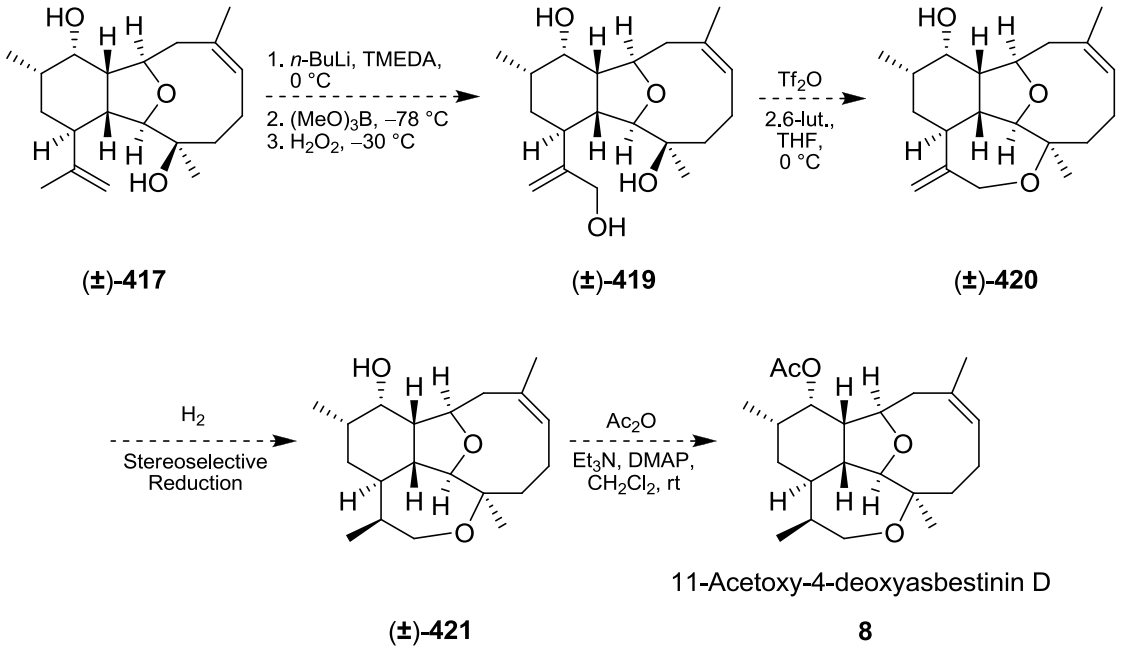
The successful racemic synthesis of the formal target (±)-**417** was completed in 23 steps with an overall yield of 1%. The poor yield obtained during introduction of the C-12 methyl group drastically reduced the overall yield, with the synthesis of the precursor to this step, tricyclic ketone (±)-**356**, having been constructed in a total of 16 steps with an overall yield of 19%. Construction of the tricyclic core (±)-***exo*-352** featured three pivotal ring-forming transformations. First, the construction of the tetrahydropyranol (±)-**81** was achieved using a samarium(II) iodide mediated reductive cyclisation in 97% yield. Next, the signature reaction of the synthesis, the copper-catalysed decomposition of the diazoketone (±)-**82** to form the oxonium ylide **83** and its subsequent [2,3]-sigmatropic rearrangement to form the bicyclic ketones (±)-(***Z***)-**84** and (±)-(***E***)-**85**, proceeded in 97% overall yield and an *Z*:*E* isomer ratio of 6.5:1. Finally, an intermolecular Diels-Alder cycloaddition reaction was used to construct the tricyclic core (±)-***exo*-352** from the bicyclic ketone (±)-(***Z***)-**84** in 65% yield over four steps.

The resolution of the allylic alcohol **(±)-79** was investigated as a means to access the enantioenriched precursors of the asbestinins but was found to be an ineffective procedure. Following the development of a scalable route to the enantioenriched allylic alcohol **(+)-79**, the synthesis of multiple members of the asbestinin family is accessible using our methodology.

Investigations into the potential use of protected α-hydroxy enones as suitable Diels-Alder dienophiles for the construction of the tricyclic core **365**, has uncovered two issues. Firstly, the dienophiles themselves tend to be highly unstable and so are difficult to construct. Secondly, Lewis acidic catalysis of these cycloadditions results in decomposition of the dienophiles and the diene **(±)-350**, implying that attempts to utilise this diene in Lewis acid mediated cycloaddition reactions is likely to fail.

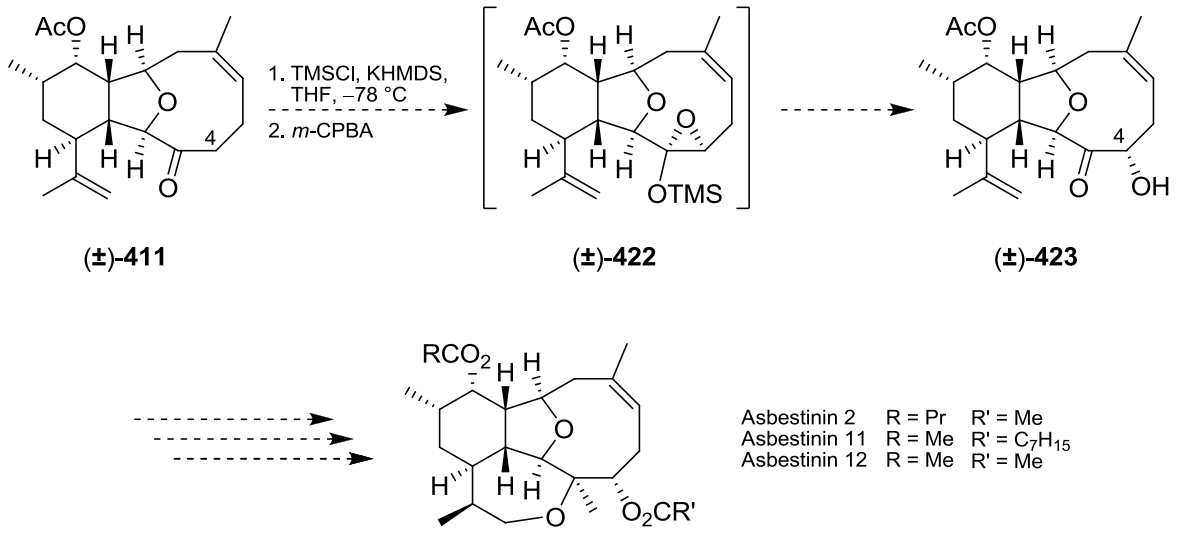
3.2 Future Work

Future work should focus on three main areas. Firstly, completion of the racemic synthesis to 11-acetoxy-4-deoxyasbestinin D (**8**) is envisioned *via* the formation of the allyllithium species using the *n*-butyllithium/TMEDA complex, followed by treatment with trimethylborate and *in situ* oxidation to the allylic alcohol **(±)-419** (**Scheme 117**).[137] Secondly, use of Crimmins's intramolecular triflate displacement methodology to close the final oxepane ring, followed by stereoselective reduction of the exocyclic alkene which should be controlled by the topology of the molecule. Finally, esterification of alcohol **(±)-421** with acetic anhydride to complete the synthesis of 11-acetoxy-4-deoxyasbestinin D (**8**).



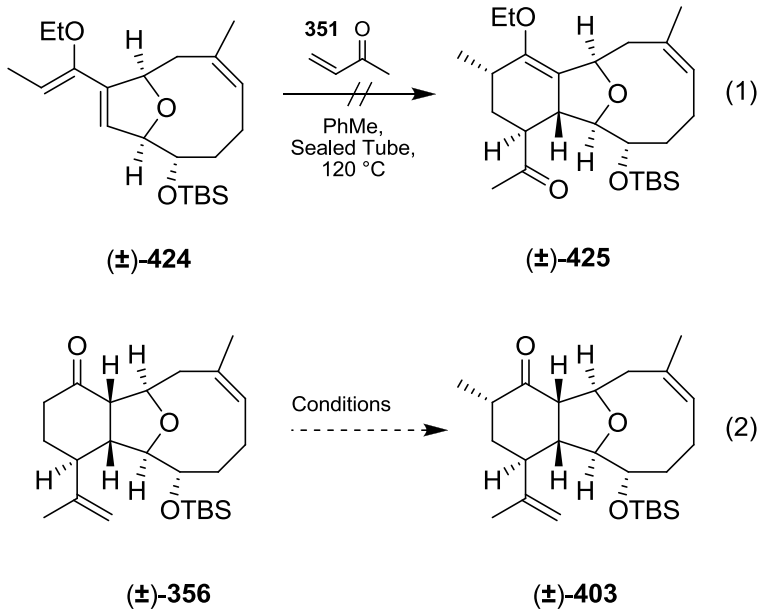
Scheme 117

Another area of future work to be explored is installation of the C-4 oxygen unit *via* Rubottom oxidation of ketone **(±)-411** (**Scheme 118**). Again the topology of the molecule should only allow epoxidation of the silyl enol ether from the concave face, delivering the required configuration needed for keto alcohol **(±)-423**.



Scheme 118

The final area requiring investigation is the introduction of the C-12 methyl group. Previous work within the group had envisioned achieving this transformation by cycloaddition of an appropriate Diels-Alder diene with MVK, but the reaction afforded a complex mixture (eq 1, **Scheme 119**).[94] Improvement of the enolate alkylation conditions utilised during the synthesis of the asbestinins offers another possible route (eq. 2).



Scheme 119

4 Experimental

General Comments

Air and/or moisture sensitive reactions were performed under an atmosphere of argon in apparatus that had been flame dried under vacuum. Organic solvents were dried using a Pure Solv™ solvent purification system. All reagents were purchased from commercial suppliers and used without further purification, unless otherwise stated.

All reactions were monitored by thin layer chromatography (TLC) using Merck silica 60 covered plates. TLC plates were viewed under UV light or were visualised using either potassium permanganate solution or acidic ethanolic anisaldehyde solution. Flash chromatography was performed using silica gel (LC60A, 35–70 micron, 60A). Petroleum ether used for chromatography was the 40–60 °C fraction.

IR spectra were measured on a Shimadzu FTIR–8400 instrument using a type 11a diamond single reflection element. The IR spectrum of each compound was directly detected as a thin layer at ambient temperature from a chloroform solution, unless otherwise stated.

^{1}H NMR spectra were measured on a Bruker 400 MHz or Spectrospin 500 MHz spectrometer at ambient temperature, unless otherwise stated. The carbon numbering drawn on the molecule corresponds to the conventional asbestinin numbering used for the NMR signal assignment. IUPAC numbering was used for the molecule names. Data are reported as follows: chemical shift δ in ppm relative to $CHCl_3$ (7.26), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad or a combination of these), coupling constant(s) *J* (Hz) and assignment. ^{13}C NMR spectra were measured at ambient temperature on a Bruker 400 MHz or Spectrospin 500 MHz spectrometer at 100 MHz or 125 MHz, respectively. Multiplicities were obtained using a DEPT sequence. Data are reported as follows: chemical shift δ in ppm relative to $CHCl_3$ (77.16) and assignment.

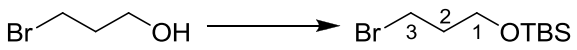
High resolution mass spectrometry (HRMS) measurements were performed by the analytical services of the University of Glasgow on a Jeol MStation JMS–700 instrument. Low resolution mass spectrometry (LRMS) measurements were performed on the same instrument; the intensity of each peak is quoted as a percentage of the largest, where this information is available. Ionisation techniques used include electron impact (EI),

chemical ionisation (CI), fast atom bombardment (FAB) and electron spray ionisation (ESI).

Elemental analyses were measured on an Exeter Analytical Elemental Analyser EA 440.

Melting points were measured using an Electrothermal IA 9100 apparatus.

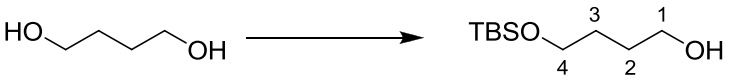
(3-Bromopropoxy)(*tert*-butyl)dimethylsilane, (284).[95]



283 **284**

To a stirred solution of 3-bromompropan-1-ol **283** (3.00 g, 21.6 mmol) in anhydrous CH_2Cl_2 (45 mL) was added triethylamine (5.41 mL, 38.8 mmol). After 5 min *tert*-butyldimethylsilyl chloride (3.90 g, 25.9 mmol) and DMAP (422 mg, 3.45 mmol) was added and the resulting solution stirred for 17 h. The reaction was diluted with CH_2Cl_2 (50 mL) and water (50 mL). The organic phase was separated and washed with water (50mL), aqueous 1.0 M HCl (50 mL) and brine (50 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Vacuum distillation (b.p. 85-95 °C at 14 mmHg) {Lit.[138] 182 °C at 760 mmHg} afforded the bromide **284** as a colourless oil (5.24 g, 96%): R_f = 0.80 (methylene chloride – methanol, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (2H, t, *J* = 5.7 Hz, CH_2-C1 or CH_2-C3), 3.52 (2H, t, *J* = 6.4 Hz, CH_2-C1 or CH_2-C3), 2.03 (2H, tt, *J* = 6.4, 5.7 Hz, CH_2-C2), 0.89 (9H, s, 3 × CH_3-*t*Bu), 0.07 (6H, s, CH_3-Si). ^{13}C NMR (100 MHz, $CDCl_3$) δ 60.6 (CH_2-C3), 35.7 (CH_2-C1), 30.8 (CH_2-C2), 26.1 (3 × CH_3-*t*Bu), 18.4 (C-*t*Bu), −5.2 (CH_3-Si).

4-(*tert*-Butyldimethylsilyloxy)butan-1-ol, (289).[139]

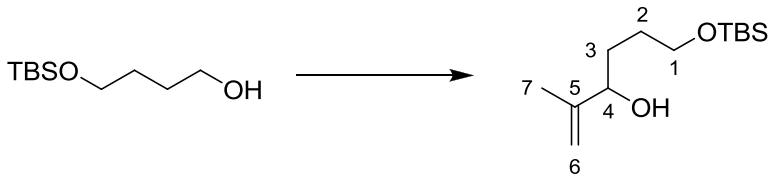


78 **289**

To a stirred solution of 1,4-butandiol **78** (15.0 g, 166 mmol) and triethylamine (23.1 mL, 166 mmol) in anhydrous CH_2Cl_2 (400 mL) at rt was added *tert*-butyldimethylsilyl chloride (16.7 g, 111 mmol) portion-wise over 5 min. The resulting solution was stirred for 24 h. The reaction was diluted with water (200 mL). The organic phase separated, washed sequentially with saturated aqueous NH_4Cl (2 × 100 mL), water (2 × 100 mL) and brine (100 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – ethyl acetate, 5:1) afforded the alcohol

289 as a colourless oil (21.9g, 96%): R_f = 0.40 (petroleum ether – ethyl acetate, 4:1); ν_{max} 3325, 2932, 2862, 2361, 1466, 1389, 1258, 1103, 1065 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.70–3.60 (4H, m, CH_2-C1,CH_2-C4), 2.57 (1H, t, *J* = 5.7 Hz, OH), 1.68–1.61 (4H, m, CH_2-C2, CH_2-C3), 0.90 (9H, s, 3 × CH_3-*t*Bu), 0.07 (6H, s, CH_3-Si); ^{13}C NMR (100 MHz, $CDCl_3$) δ 63.5 (CH_2-C1 or CH_2-C4), 62.9 (CH_2-C1 or CH_2-C4), 30.4 (CH_2-C2), 30.1 (CH_2-C3), 26.1 (3 × CH_3-*t*Bu), 18.4(C-*t*Bu), −5.3 (CH_3-Si); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{10}H_{25}O_2Si$ 205.1624, found 205.1621, Δ −1.6 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 69.1 (26%), 81.2 (26%), 113.3 (12%), 205.3 (100%); Anal. Calcd for $C_{10}H_{24}O_2Si$: C, 58.75%; H, 11.86%; Found: C, 58.38%; H, 11.99%.

6-(*tert*-Butyldimethylsilyloxy)-2-methylhex-1-en-3-ol, (±)-79.



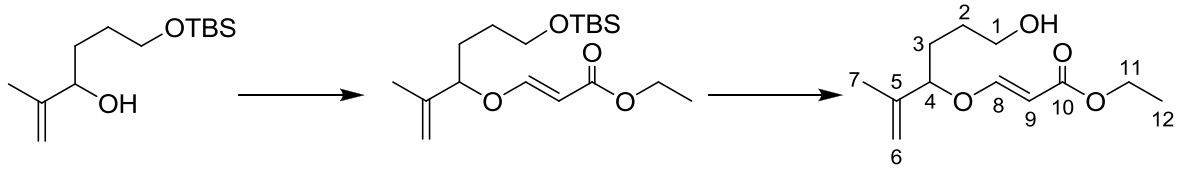
289 **(±)-79**

To a stirred solution of oxalyl chloride (3.02 mL, 35.2 mmol) in anhydrous CH_2Cl_2 (40 mL) at −78 °C was added a solution of anhydrous DMSO (2.75 g, 35.2mmol) in anhydrous CH_2Cl_2 (40 mL) dropwise. After 15 min a solution of alcohol **289** (6.00 g, 29.4 mmol) in anhydrous CH_2Cl_2 (40 mL) was added dropwise and the resulting solution stirred at −78 °C. After 1.5 h, triethylamine (20.5 mL, 147 mmol) was added and the reaction allowed to warm to rt over a period of 1 h. The reaction was diluted with CH_2Cl_2 (125 mL) and saturated aqueous NH_4Cl (125 mL). The organic phase was separated and washed with brine (150 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo* (The crude aldehyde was used without further purification).

To a slurry of magnesium turnings (1.43 g, 58.7 mmol) and iodine (trace) in anhydrous THF (29 mL) at reflux was added dropwise a solution of 2-bromopropene (7.10 g, 58.7 mmol) in anhydrous THF (20 mL), maintaining constant reflux throughout. The resulting suspension was stirred at rt for 2 h and then cooled to 0 °C. A solution of the crude aldehyde in anhydrous THF (39 mL) was added dropwise and the reaction stirred at 0 °C for 15 min. The reaction was quenched with saturated aqueous NH_4Cl (100 mL). The

aqueous phase was separated and extracted with Et_2O (2 × 50 mL). The organic phases were combined and washed with brine (100 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – ethyl acetate, 19:1 to 9:1) afforded the allylic alcohol (±)-**79** as a colourless oil (5.82 g, 81%): R_f = 0.55 (petroleum ether – ethyl acetate, 5:1); ν_{max} 3341, 2932, 2862, 1466, 1389, 1258,1096, 1003 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.96 (1H, br s, CH_2-C6), 4.83 (1H, br s, CH_2-C6), 4.10–4.04 (1H, m, CH-C4), 3.66 (2H, t, *J* = 5.5 Hz, CH_2-C1), 2.55 (1H, br d, *J* = 3.5 Hz, OH), 1.72 (3H, br s, CH_3-C7), 1.70–1.55 (4H, m, CH_2-C2, CH_2-C3), 0.90 (9H, s, 3 × CH_3-*t*Bu), 0.06 (6H, s, CH_3-Si); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7 (C-C5), 110.9 (CH_2-C6), 75.6 (CH-C4), 63.5 (CH_2-C1), 32.5 (CH_2-C3), 29.0 (CH_2-C2), 26.1 (3 × CH_3-*t*Bu), 18.5 (C-*t*Bu), 18.0 (CH_3-C7), −5.2 (CH_3-Si); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{13}H_{29}O_2Si$ 245.1937, found 245.1935, Δ −0.9 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 69.1 (80%), 95.2 (100%), 227.4 (45%), 245.4 (30%); Anal. Calcd for $C_{13}H_{28}O_2Si$: C, 63.86%; H, 11.57%; Found: C, 63.76%; H, 11.70%.

Ethyl (*E*)-3-(6-hydroxy-2-methyl-1-hexen-3-yl)oxypropenoate, (±)-80.[94]



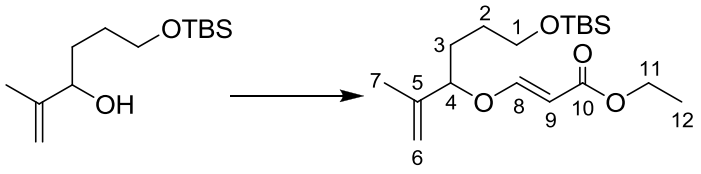
(±)-79 (±)-338 (±)-80

To a stirred solution of allylic alcohol (±)-**79** (1.50 g, 6.13 mmol) in anhydrous CH_2Cl_2 (16 mL) was added ethyl propiolate (1.21 g, 12.3 mmol) and *N*-methylmorpholine (1.24 g, 12.3 mmol) and the resulting brown solution stirred for 24 h. The reaction mixture was concentrated *in vacuo*, giving a dark brown oil, and the crude vinylogous carbonate was then passed through a small plug of silica gel (petroleum ether – ethyl acetate, 4:1) to remove the polar impurities. The crude vinylogous carbonate was then dissolved in ethanol (64 mL) and to this was added CSA (286 mg, 1.23 mmol) and the reaction stirred for 30 min. The remaining solids were removed and the filtrate concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – ethyl acetate, 4:1) afforded the alcohol (±)-**80** as a colourless oil (1.31 g, 94%): R_f = 0.10 (petroleum ether – ethyl acetate, 5:1); ν_{max} 3433, 2980, 2947, 2874, 1705, 1694, 1638, 1620, 1447, 1371,

1325, 1285, 1231, 1200, 1173, 1128, 1045 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (1H, d, *J* = 12.4 Hz, CH-C8), 5.26 (1H, d, *J* = 12.4 Hz, CH-C9), 5.05–4.98 (1H, m, CH_2-C6), 4.97 (1H, s, CH_2-C6), 4.27 (1H, dd, *J* = 7.7, 5.4 Hz, CH-C4), 4.14 (2H, dq, *J* = 7.1, 1.4 Hz, CH_2-C11), 3.67 (2H, br t, *J* = 5.7 Hz, CH_2-C1), 1.87–1.69 (2H, m, CH_2-C2), 1.67 (3H, s, CH_3-C7), 1.65–1.51 (2H, m, CH_2-C3), 1.26 (3H, t, *J* = 7.1 Hz, CH_3-C12); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2 (C-C10), 161.5 (CH-C8), 142.8 (C-C5), 114.8 (CH_2-C6), 98.2 (CH-C9), 86.5 (CH-C4), 62.5 (CH_2-C1), 59.9 (CH_2-C11), 29.6 (CH_2-C3), 28.7 (CH_2-C2), 17.1 (CH_3-C7), 14.5 (CH_3-C12); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{12}H_{21}O_4$ 229.1440, found 229.1437, Δ = −1.2 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 69.1 (20%), 89.1 (100%), 117.1 (20%), 229.2 (60%); Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.12%; H, 8.85%; Found: C, 63.02%; H, 9.03%.

In addition to this reaction, vinylogous carbonate (±)-**338** was isolated and characterised as follows:

Ethyl (*E*)-3-[6-(*tert*-butyldimethylsiloxy)-2-methyl-1-hexen-3-yl] oxypropenoate, (±)-338.[111,140]

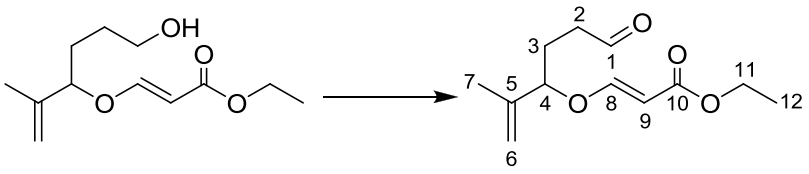


(±)-79 (±)-338

R_f = 0.70 (petroleum ether – ethyl acetate, 9:1); ν_{max} 2955, 2862, 1713, 1643, 1466, 1373, 1319, 1250, 1196, 1134, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (1H, d, *J* = 12.4 Hz, CH-C8), 5.25 (1H, d, *J* = 12.4 Hz, CH-C9), 4.98 (1H, br s, CH_2-C6), 4.96 (1H, br s, CH_2-C6), 4.26 (1H , br t, *J* = 6.6 Hz, CH-C4), 4.14 (2H, dq, *J* = 7.1, 1.4 Hz, CH_2-C11), 3.68–3.58 (2H, m, CH_2-C1), 1.82–1.70 (2H, m, CH_2-C2), 1.68 (3H, br s, CH_3-C7), 1.63–1.43 (2H, m, CH_2-C3), 1.26 (3H, t, *J* = 7.1 Hz, CH_3-C12), 0.89 (9H, s, 3 × CH_3-*t*Bu), 0.04 (6H, s, CH_3-Si); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2 (C-C10), 161.6 (CH-C8), 142.9 (C-C5), 114.8 (CH_2-C6), 98.0 (CH-C9), 86.7 (CH-C4), 62.7 (CH_2-C1), 59.8 (CH_2-C11), 29.6 (CH_2-C2), 28.6 (CH_2-C3), 26.1 (3 × CH_3-*t*Bu), 18.5 (C-*t*Bu), 17.0 (CH_3-C7), 14.5 (CH_3-C12), −5.2 (CH_3-Si); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{18}H_{35}O_4Si$ 343.2305, found 343.2295, Δ = −2.9 ppm;

LRMS (CI, Me_3CH) *m/z* (intensity) 69.1 (48%), 95.2 (42%), 227.4 (100%), 343.4 (20%); Anal. Calcd for $C_{18}H_{34}O_4Si$: C, 63.10%; H, 10.02%; Found: C, 63.15%; H, 10.02%.

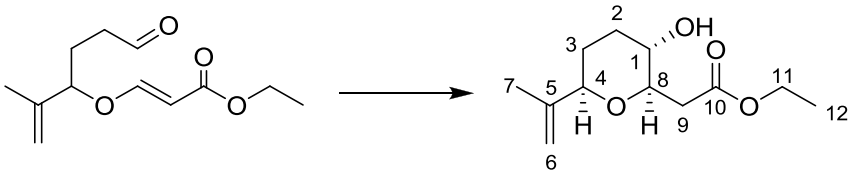
Ethyl (*E*)-3-(5-methyl-5-hexenal-4-yl)oxypropenoate, (±)-339.[36]



(±)-80 **(±)-339**

To a stirred solution of oxalyl chloride (5.4 mL, 63 mmol) in anhydrous CH_2Cl_2 (160 mL) at −78 °C was added a solution of anhydrous DMSO (10.1 g, 130 mmol) in anhydrous CH_2Cl_2 (55 mL) dropwise by cannula. The resulting solution was stirred for 30 min followed by the addition of a solution of alcohol **(±)-80** (8.0 g, 35 mmol) in anhydrous CH_2Cl_2 (110 mL). The resulting solution was stirred for 3 h. To this was added triethylamine (24.4 mL, 175 mmol) and the reaction allowed to warm to rt over 1 h. The reaction was diluted with CH_2Cl_2 (150 mL) and water (100 mL). The aqueous phase was separated and extracted using CH_2Cl_2 (2 × 50 mL). The organic phases were combined and washed with brine (150 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – ethyl acetate, 9:1 to 2:1) afforded the aldehyde **(±)-339** as a colourless oil (7.32 g, 92 %): R_f = 0.31 (petroleum ether – ethyl acetate, 2:1); ν_{max} 2978, 1705, 1643, 1451, 1373, 1327, 1281, 1196, 1134, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (1H, s, CH-C1), 7.44 (1H, d, *J* = 12.4 Hz, CH-C8), 5.26 (1H, d, *J* = 12.4 Hz, CH-C9), 5.02 (1H, br s, CH_2-C6), 4.98 (1H, br s, CH_2-C6), 4.29 (1H, dd, *J* = 7.4, 5.7 Hz, CH-C4), 4.14 (2H, dq, *J* = 7.1, 1.5 Hz, CH_2-C11), 2.55 (2H, br t, *J* = 7.1 Hz, CH_2-C2), 2.10–1.92 (2H, m, CH_2-C3), 1.68 (3H, s, CH_3-C7), 1.26 (3H, t, *J* = 7.1 Hz, CH_3-C12); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2 (CH-C1), 168.0 (C-C10), 161.0 (CH-C8), 142.2 (C-C5), 115.2 (CH_2-C6), 98.6 (CH-C9), 85.1 (CH-C4), 60.0 (CH_2-C11), 39.8 (CH_2-C2), 25.7 (CH_2-C3), 17.2 (CH_3-C7), 14.5 (CH_3-C12); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{12}H_{19}O_4$ 227.1283, found 227.1279, Δ = −1.9 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 111.2 (85%), 117.1 (40%), 227.2 (100%).

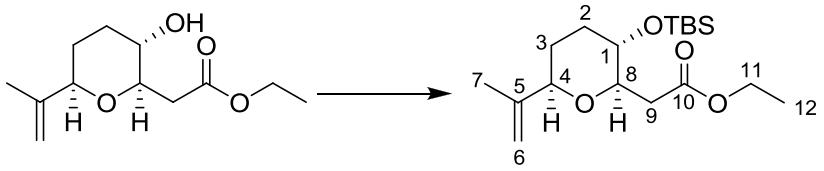
Ethyl [(2*R**,3*S**,6*R**)-3-hydroxy-6-isopropenyltetrahydropyran-2-yl] acetate, (±)-81 [58]



(±)-339 (±)-81

To a stirred solution of aldehyde (±)-**339** (3.00 g, 13.3 mmol) and anhydrous MeOH (2.15 mL, 1.70 g, 53.0 mmol) in anhydrous THF (135mL) at rt was added a freshly prepared solution of SmI_2 (0.1 M in THF) until the solution remained deep blue in colour (approx. 4 equiv.). The resulting solution was stirred for 15 min and the reaction was then quenched using EtOAc (60 mL) and saturated aqueous $Na_2S_2O_3$ (150 mL). The aqueous phase was separated and extracted with EtOAc (3 × 40 mL). The organic phases were combined and washed with brine (50 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – ethyl acetate, 4:1 to 1:1) afforded the pyranol (±)-**81** as a colourless oil (2.93 g, 97%): R_f = 0.21 (petroleum ether – ethyl acetate, 2:1); ν_{max} 3480, 3426, 2978, 2940, 2862, 1736, 1443, 1373, 1304, 1258, 1188, 1157, 1072 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.93 (1H, s, CH_2-C6), 4.81 (1H, s, CH_2-C6), 4.16 (2H, q, *J* = 7.2 Hz, CH_2-C11), 3.74 (1H, br d, *J* = 9.9 Hz, CH-C4), 3.60 (1H, ddd, *J* = 9.2, 7.0, 5.1 Hz, CH-C8), 3.43–3.37 (1H, m, CH-C1), 2.82 (1H, dd, *J* = 15.1, 5.1 Hz, CH_2-C9), 2.58 (1H, dd, *J* = 15.1, 7.0 Hz, CH_2-C9), 2.20–2.12 (1H, m, CH_2-C2), 1.94 (1H, d, *J* = 5.9 Hz, OH), 1.87–1.79 (1H, m, CH_2-C3), 1.72 (3H, s, CH_3-C7), 1.59–1.50 (2H, m, CH_2-C2, CH_2-C3), 1.26 (3H, t, *J* = 7.2 Hz, CH_3-C12); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4 (C-C10), 145.1 (C-C5), 110.7 (CH_2-C6), 80.3 (CH-C4), 79.0 (CH-C8), 70.7 (CH-C1), 60.8 (CH_2-C11), 39.0 (CH_2-C9), 33.3 (CH_2-C2), 29.8 (CH_2-C3), 19.3 (CH_3-C7), 14.4 (CH_3-C12); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{12}H_{21}O_4$ 229.1440, found 229.1441, Δ = −0.7 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 73.1 (73%), 85.2 (75%), 183.3 (25%), 229.3 (100%); Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.13%; H, 8.85%; Found: C, 63.16%; H, 8.95%.

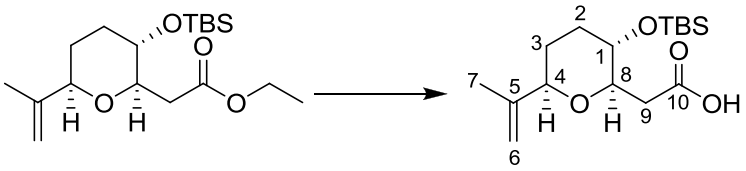
Ethyl [(2*R**,3*S**,6*R**)-3-(*tert*-butyldimethylsiloxy)-6-isopropenyl tetrahydropyran-2-yl]acetate, (±)-342.[94]



(±)-81 **(±)-342**

To a stirred solution of pyranol (±)-**81** (4.50 g, 19.8 mmol) and imidazole (2.68 g, 39.4 mmol) in anhydrous DMF (45 mL) at rt was added *tert*–butyldimethylsilyl chloride (5.35 g, 35.5 mmol). The resulting solution was stirred for 22 h and then quenched using Et_2O (100mL) and water (100 mL). The organic phase was separated and washed sequentially with saturated aqueous NH_4Cl (2 × 50 mL), water (2 × 50 mL) and brine (100 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – diethyl ether, 98:2) afforded the silyl ether (±)-**342** as a colourless oil (6.30 g, 93%): R_f = 0.67 (petroleum ether – diethyl ether, 9:1); v_{max} 2940, 2862, 1744, 1466, 1258, 1188, 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.91 (1H, s, CH_2-C6), 4.78 (1H, s, CH_2-C6), 4.14 (2H, q, *J* = 7.1 Hz, CH_2-C11), 3.73 (1H, br d, *J* = 10.0 Hz, CH-C4), 3.68–3.60 (1H, m, CH-C8), 3.41–3.33 (1H, m, CH-C1), 2.80 (1H, d, *J* = 14.8 Hz, CH_2-C9), 2.37 (1H, dd, *J* = 14.8, 9.2 Hz, CH_2-C9), 2.05–1.97 (1H, m, CH_2-C2), 1.86–1.78 (1H, m, CH_2-C3), 1.70 (3H, s, CH_3-C7), 1.61–1.44 (2H, m, CH_2-C2, CH_2-C3), 1.25 (3H, t, *J* = 7.1 Hz, CH_3-C12), 0.87 (9H, s, 3 × CH_3–*t*Bu), 0.06 (6H, s, CH_3–Si); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0 (C-C10), 145.3 (C-C5), 110.3 (CH_2-C6), 80.0 (CH-C4), 79.6 (CH-C8), 70.9 (CH-C1), 60.4 (CH_2-C11), 38.4 (CH_2-C9), 33.5 (CH_2-C2), 29.7 (CH_2-C3), 25.9 (3 × CH_3–*t*Bu), 19.4 (CH_3-C7), 18.1 (C–*t*Bu), 14.4 (CH_3-C12), −3.9 (CH_3–Si), −4.6 (CH_3–Si); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{18}H_{35}O_4Si$ 343.2305, found 343.2307, Δ = −0.5 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 69.1 (100%), 85.1 (72%), 343.1 (25%); Anal. Calcd for $C_{18}H_{34}O_4Si$: C, 63.10%; H, 10.02%; Found: C, 63.07%; H, 10.01%.

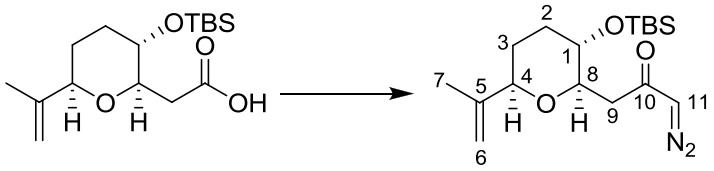
[(2*R,3*S**,6*R**)-3-(*tert*-Butyldimethylsilyloxy)-6-isopropenyltetrahydropyran-2-yl] acetic acid, (±)-343.**



(±)-342 **(±)-343**

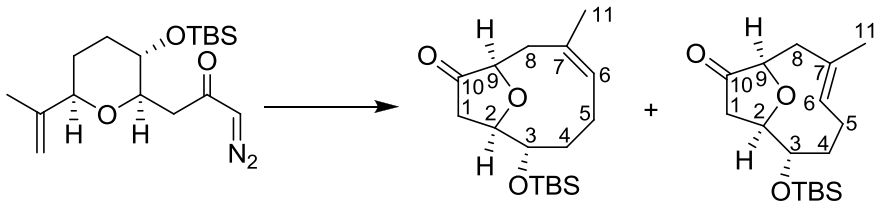
To a stirred solution of ester **(±)-342** (3.50 g, 10.2 mmol) in ethanol (50 mL) and water (17 mL) was added LiOH (734 mg, 30.7 mmol) and the resulting solution stirred for 20 h. The reaction was then acidified to pH 2~3 using 1 M HCl (aq.) and diluted with EtOAc (75 mL) and water (40 mL). The aqueous phase was separated and extracted using EtOAc (3 × 25 mL). The organic phases were combined and washed with brine (30 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. No further purification was required affording the acid **(±)-343** as a colourless solid (3.21 g, quant.): R_f = 0.24 (petroleum ether – ethyl acetate, 9:1); m.p. 72–74 °C; ν_{max} 2940, 2862, 1713, 1435, 1304, 1258, 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.94 (1H, s, CH_2-C6), 4.84 (1H, s, CH_2-C6), 3.82 (1H, br d, *J* = 9.4 Hz, CH-C4), 3.62 (1H, dt, *J* = 8.9, 3.2 Hz, CH-C8), 3.40-3.32 (1H, m, CH-C1), 2.87 (1H, dd, *J* = 15.7, 3.2 Hz, CH_2-C9), 2.48 (1H, dd, *J* = 15.7, 9.0 Hz, CH_2-C9), 2.11–2.02 (1H, m, CH_2-C2), 1.86–1.78 (1H, m, CH_2-C3), 1.73 (3H, s, CH_3-C7), 1.62–1.48 (2H, m, CH_2-C2, CH_2-C3), 0.88 (9H, s, 3 × CH_3-*t*Bu), 0.07 (6H, s, CH_3-Si); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3 (C-C10), 144.6 (C-C5), 111.3 (CH_2-C6), 80.8 (CH-C4), 79.0 (CH-C8), 70.7 (CH-C1), 37.7 (CH_2-C9), 33.3 (CH_2-C2), 29.6 (CH_2-C3), 25.9 (3 × CH_3-*t*Bu), 19.2 (CH_3-C7), 18.0 (C-*t*Bu), −3.9 (CH_3-Si), −4.6 (CH_3-Si); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{16}H_{31}O_4Si$ 315.1992, found 315.1989, Δ = −0.7 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 69.1 (100%), 85.1 (73%), 257.1 (18%), 315.1 (15%); Anal. Calcd for $C_{16}H_{30}O_4Si$: C, 61.08%; H, 9.63%; Found: C, 60.98; H, 9.63%.

1-Diazo-3-[(2*R,3*S**,6*R**)-3-(*tert*-butyldimethylsilyloxy)-6-isopropenyltetrahydropyran-2-yl]-propan-2-one, (±)-82.**[93,114,141]



To a stirred solution of acid (±)-**343** (3.00 g, 9.54 mmol) and anhydrous triethylamine (1.86 mL, 13.4 mmol) in anhydrous Et_2O (120 mL) was added isobutyl chloroformate (1.55 mL, 1.63 g, 11.9 mmol) dropwise and the resulting solution stirred for 2.5 h. The solution of the anhydride was filtered under reduced pressure, under an argon atmosphere, to remove the polar salt precipitate and the filtrate was added immediately to a freshly prepared ethereal solution of diazomethane (~95 mmol) dropwise. The solution was stirred for 66 h in the absence of light and the reaction was then quenched using glacial acetic acid (3–4 drops) and poured into saturated aqueous NH_4Cl (250 mL) and stirred vigorously for 15 min. The aqueous phase was separated and extracted using Et_2O (3 × 70 mL). The organic phases were combined and washed with brine (100 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – diethyl ether, 99:1 to 9:1) afforded the diazoketone (±)-**82** as a yellow oil (2.82 g, 87%): R_f = 0.91 (petroleum ether – ethyl acetate, 5:1); ν_{max} 2955, 2929, 2858, 2100, 1641, 1347, 1251, 1122, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.39 (1H, br s, CH-C11), 4.92 (1H, br s, CH_2-C6), 4.80 (1H, br s, CH_2-C6), 3.72 (1H, br d, *J* = 10.0 Hz, CH-C4), 3.61–3.54 (1H, m, CH-C8), 3.39–3.29 (1H, m, CH-C1), 2.77 (1H, br d, *J* = 13.9 Hz, CH_2-C9), 2.45–2.35 (1H, m, CH_2-C9), 2.08–2.01 (1H, m, CH_2-C2), 1.84–1.77 (1H, m, CH_2-C3), 1.71 (3H, s, CH_3-C7), 1.55–1.46 (2H, m, CH_2-C2, CH_2-C3), 0.87 (9H, s, 3 × CH_3-*t*Bu), 0.06 (6H, s, CH_3-Si); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8 (C-C10), 145.3 (C-C5), 110.5 (CH_2-C6), 80.2 (CH-C4), 79.9 (CH-C8), 70.8 (CH-C1), 55.3 (CH-C11) , 44.3 (CH_2-C9) , 33.5 (CH_2-C2), 29.8 (CH_2-C3), 25.9 (3 × CH_3-*t*Bu), 19.4 (CH_3-C7), 18.1 (C-*t*Bu), −3.8 (CH_3-Si), −4.6 (CH_3-Si).

(1*R,2*S**,5*Z*,8*R**)-2-(*tert*-Butyldimethylsilyloxy)-6-methyl-11-oxabicyclo[6.2.1]-5-undecen-9-one, (±)-(*Z*)-84, and (1*R**,2*S**,5*E*,8*R**)-2-(*tert*-Butyldimethylsilyloxy)-6-methyl-11-oxabicyclo[6.2.1]-5-undecen-9-one, (±)-(*E*)-84.**[93,114,141]



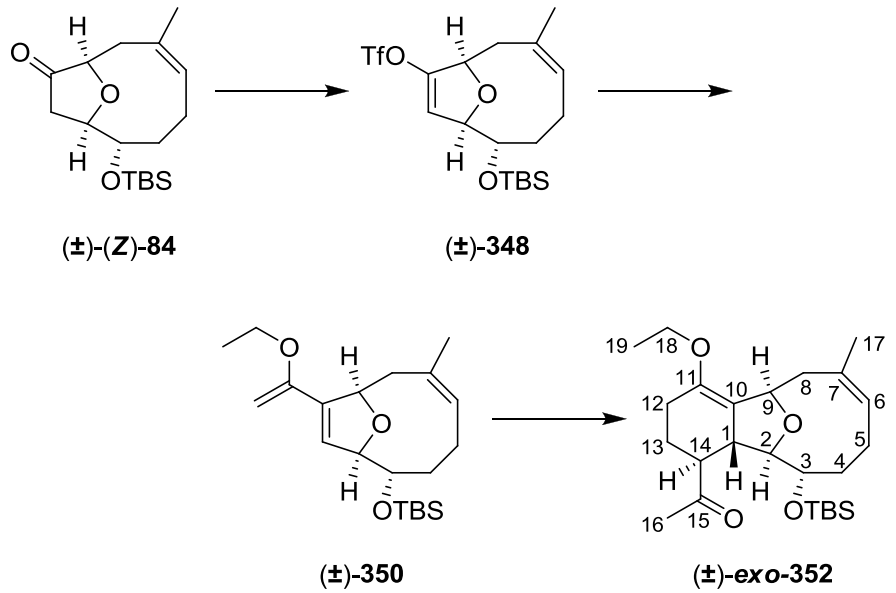
(±)-82 **(±)-(*Z*)-84** **(±)-(*E*)-84**

To a stirred solution of $Cu(hfacac)_2$ (198 mg, 399 μmol) in anhydrous CH_2Cl_2 (150 mL) at reflux was added a solution of diazoketone (±)-**82** (2.70 g, 7.97 mmol) in anhydrous CH_2Cl_2 (400 mL) over 2 h while maintaining reflux. The resulting solution was stirred for a further 30 min at reflux, allowed to cool to rt and then concentrated *in vacuo*. Flash column chromatography on $AgNO_3$ (10% w/w) impregnated silica gel (petroleum ether – diethyl ether, 19:1 to 1:1) afforded the *Z*-alkene (±)-(*Z*)-**84** (2.01 g, 81%) as a colourless crystalline solid and the *E*-alkene (±)-(*E*)-**84** (322 mg, 13%) as a colourless crystalline solid.

(±)-(*Z*)-84: R_f = 0.53 (petroleum ether – diethyl ether, 9:1); m.p. 68–70 °C; ν_{max} 2932, 2855, 1759, 1466, 1412, 1373, 1258, 1165, 1134, 1096, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.41 (1H, dd, *J* = 11.6, 5.8 Hz, CH-C6), 4.24 (1H, t, *J* = 4.4 Hz, CH-C9), 4.17 (1H, d, *J* = 8.7 Hz, CH-C2), 3.41 (1H, ddd, *J* = 11.1, 8.7, 2.7 Hz, CH-C3), 2.81–2.68 (3H, m, CH_2-C1, CH_2-C5, CH_2-C8), 2.29 (1H, d, *J* = 17.7 Hz, CH_2-C1), 2.21 (1H, dd, *J* = 14.6, 4.4, CH_2-C8), 2.02–1.93 (1H, m, CH_2-C5), 1.91–1.81 (1H, m, CH_2-C4), 1.75 (3H, s, CH_3-C11), 1.69–1.59 (1H, m, CH_2-C4), 0.85 (9H, s, 3 × CH_3-*t*Bu), 0.05 (3H, s, CH_3-Si), 0.01 (3H, s, CH_3-Si); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.0 (C-C10), 132.5 (C-C7), 127.7 (CH-C6), 80.4 (CH-C2), 78.9 (CH-C9), 75.4 (CH-C3), 42.4 (CH_2-C1), 33.5 (CH_2-C8), 33.2 (CH_2-C4), 26.9 (CH_3-C11), 25.9 (CH_2-C5, CH_3-*t*Bu), 18.0 (C-*t*Bu), −3.7 (CH_3-Si), −4.4 (CH_3-Si); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{17}H_{31}O_3Si$ 311.2042, found 311.2044, Δ = −0.5 ppm; LRMS (CI, Me_3CH) *m*/*z* (intensity) 73.1 (13%), 179.2 (15%), 311.2 (100%).

(±)-(*E*)-84: R_f = 0.53 (petroleum ether – diethyl ether, 9:1); m.p. 53–55 °C; ν_{max} 2932, 2862, 1751, 1466, 1443, 1412, 1366, 1250, 1157, 1111, 1065, 1011 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.36 (1H, dd, *J* = 12.1, 4.6 Hz, CH-C6), 4.16–4.11 (2H, m, CH-C2, CH-C9), 3.02 (1H, dd, *J* = 8.9, 7.5 Hz, CH-C3), 2.78 (1H, ddd, *J* = 18.1, 9.1, 1.4 Hz, CH_2-C1), 2.55–2.51 (2H, m, CH_2-C8), 2.29–2.21 (1H, m, CH_2-C5), 2.28 (1H, br d, *J* = 18.0 Hz, CH_2-C1), 2.20–2.21 (1H, m, CH_2-C5), 1.97 (1H, dddd, *J* = 14.2, 11.8, 7.7, 3.7 Hz, CH_2-C4), 1.71 (1H, td, *J* = 14.1, 3.7 Hz, CH_2-C4), 1.57 (3H, s, CH_3-C11), 0.86 (9H, s, 3 × CH_3-*t*Bu), 0.08 (3H, s, CH_3-Si), 0.03 (3H, s, CH_3-Si); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.5 (C-C10), 133.4 (CH-C6), 124.9 (C-C7), 80.9 (CH-C2), 78.5 (CH-C9), 76.6 (CH-C3), 42.1 (CH_2-C1), 40.4 (CH_2-C8), 35.9 (CH_2-C4), 27.0 (CH_2-C5), 25.9 (3 × CH_3-*t*Bu), 18.9 (CH_3-C11), 18.0 (C-*t*Bu), −3.7 (CH_3-Si), −4.6 (CH_3-Si); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{17}H_{31}O_3Si$ 311.2042, found 311.2046, Δ = −1.0 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 69.1 (22%), 253.2 (22%), 311.2 (100%).

1-{(1'*R**,2'*Z*,6'*S**,7'*R**,8'*R**,9'*S**,12'*Z*)-9-(*tert*-Butyldimethylsilyloxy)-3-ethoxy-13-methyl-15-oxatricyclo[6.6.1.$0^{2,7}$]-2,12-pentadecadien-6-yl}ethanone, (±)-(*exo*)-352.[37]



To a stirred solution of ketone (±)-(*Z*)-**84** (2.00 g, 6.44 mmol) and $PhN(Tf)_2$ (4.60 g, 12.9 mmol) in anhydrous THF (140 mL) at −78 °C was added NaHMDS (16.1 mL of a 1.0 M

solution in THF, 16.1 mmol) dropwise over 20 min. The resulting solution was stirred at −78 °C for 4 h, and the reaction was quenched using water (40 mL) and allowed to warm to rt. The aqueous phase was separated and extracted using Et_2O (3 × 40 mL). The organic phases were combined and washed with brine (50 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude enol triflate (±)-**348** was passed through a small plug of silica gel (petroleum ether – diethyl ether, 19:1) to remove the polar impurities and then concentrated *in vacuo* to afford a yellow oil which was used in the next step without further purification.

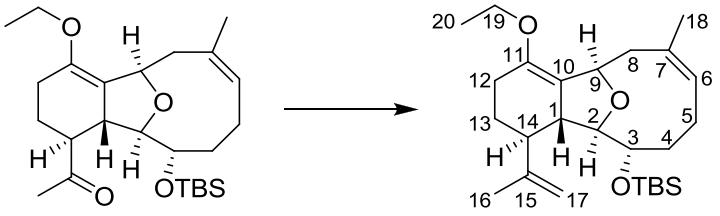
A two neck round bottom flask equipped with magnetic stirrer bar and condenser was flame dried under vacuum, filled with argon, evacuated and filled with argon once more. To this was flask was added lithium chloride (819 mg, 19.3 mmol) and the apparatus flame dried under vacuum once again. After cooling to rt under an argon atmosphere the flask was charged with a solution of the crude enol triflate in anhydrous THF (140 mL). To this solution was added $CH_2C(OEt)SnBu_3$ (6.98 g, 19.3 mmol) and $Pd(PPh_3)_4$ (1.12 g, 966 μmmol) and the resulting mixture heated to reflux for 20 h. After cooling to rt the reaction mixture was diluted with water (40 mL) and Et_2O (100 mL). The aqueous phase was separated and extracted using Et_2O (3 × 40 mL). The organic phases were combined and then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude diene (±)-**350** was passed through a pad of Celite®535, eluting with Et_2O (50 mL) and the filtrate concentrated *in vacuo* and used in the next step without further purification.

The crude diene and methyl vinyl ketone (5.22 mL, 4.51 g, 64.4 mmol) were dissolved in anhydrous toluene (180 mL) and heated to 120 °C in a sealed tube for 72 h. After cooling to rt the volatiles were removed *in vacuo* to give a yellow oil. Flash column chromatography on silica gel (petroleum ether – diethyl ether, 19:1, 1% Et_3N) afforded an *endo*-*exo* mixture of Diels–Alder cycloadducts (±)-**352**.

To a stirred solution of the *endo*-*exo* mixture of Diels–Alder cycloadducts (±)-**352** in methanol (60 mL) at rt was added potassium carbonate (1.07 g, 7.73 mmol) and the solution stirred for 22 h. The reaction was diluted with saturated aqueous NH_4Cl (30 mL) and EtOAc (75 mL). The aqueous phase was separated and extracted using EtOAc (3 × 30 mL). The organic phases were combined and then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – diethyl ether, 19:1, 1% Et_3N) afforded the ***exo***–Diels-Alder cycloadduct (±)-(***exo***)-**352** as

a colourless oil (1.82 g, 65% over 4 steps): R_f = 0.58 (petroleum ether – diethyl ether, 4:1); ν_{max} 2932, 2855, 1713, 1443, 1358, 1258, 1188, 1065, 1011 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.37 (1H, dd, *J* = 11.3, 5.4 Hz, CH-C6), 4.89–4.85 (1H, m, CH-C9), 3.79 (2H, q, *J* = 7.0 Hz, CH_2-C18), 3.71 (1H, dd, *J* = 9.1, 2.8 Hz, CH-C2), 3.59 (1H, q, *J* = 2.8 Hz, CH-C3), 3.17–3.06 (1H, m, CH-C5), 2.96–2.88 (1H, m, CH-C1), 2.84 (1H, br d, *J* = 13.9 Hz, CH_2-C8), 2.35–2.12 (3H, m, CH-C14, CH_2-C12), 2.16 (3H, s, CH_3-C16), 2.07–1.99 (1H, m, CH_2-C13), 1.93 (1H, dd, *J* = 13.9, 4.0 Hz, CH_2-C8), 1.89–1.75 (3H, m, CH_2-C4, CH_2-C5), 1.69–1.57 (1H, m, CH_2-C13), 1.67 (3H, s, CH_3-C17), 1.24 (3H, t, *J* = 7.0 Hz, CH_3-C19), 0.88 (9H, s, 3 × CH_3-*t*Bu), 0.04 (3H, s, CH_3-Si), 0.03 (3H, s, CH_3-Si); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.3 (C-C15), 143.8 (C-C11), 130.6 (C-C7), 130.2 (CH-C6), 119.3 (C-C10), 88.2 (CH-C2), 75.3 (CH-C9), 72.0 (CH-C3), 63.2 (CH_2-C18), 52.4 (CH-C14), 43.6 (CH-C1), 37.5 (CH_2-C8), 33.0 (CH_2-C4), 29.8 (CH_3-C16), 28.5 (CH_3-C17), 27.2 (CH_2-C13), 26.3 (3 × CH_3-*t*Bu), 24.6 (CH_2-C12), 22.1 (CH_2-C5), 18.7 (C-*t*Bu), 15.9 (CH_3-C19), −4.3 (CH_3-Si), −4.4 (CH_3-Si); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{25}H_{43}O_4Si$ 435.2931, found 435.2932, Δ = −0.3 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 69.1 (9%), 89.2 (100%), 435.5 (50%).

(1*R**,2*Z*,6*S**,7*R**,8*R**,9*S**,12*Z*)-9-(*tert*-Butyldimethylsilyloxy)-3-ethoxy-6-isopropenyl-13-methyl-15-oxatricyclo[6.6.1.$0^{2,7}$]-2,12-pentadecadiene, (±)-355.[6]

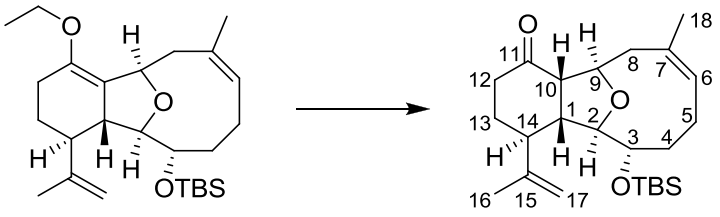


(±)-*exo*-352 (±)-355

To a stirred slurry of Ph_3PCH_3Br (2.86 g, 8.05 mmol) in anhydrous THF (38 mL) at 0°C was added NaHMDS (6.44 mL of a 1.0 M solution in THF, 6.44 mmol) dropwise over 10 min and the resulting bright yellow mixture stirred 0°C for 1 h. To this was added a solution of ketone (±)-(*exo*)-**352** (700 mg, 1.61 mmol) in anhydrous THF (19 mL) and the reaction stirred at rt for 2.5 h. The reaction was quenched using saturated aqueous NH_4Cl (15 mL) and diluted with Et_2O (40 mL). The aqueous phase was separated and

extracted using Et_2O (3 × 20 mL). The organic phases were combined and then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – diethyl ether, 98:2) afforded the triene (±)-**355** as a colourless solid (522 mg, 75%): R_f = 0.69 (petroleum ether – diethyl ether, 9:1); m.p. 109–113 °C; ν_{max} 2924, 2855, 1443, 1381, 1358, 1249, 1188, 1142, 1119, 1065, 1011 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.30 (1H, dd, *J* = 11.5, 5.6 Hz, CH-C6), 4.88–4.84 (1H, m, CH-C9), 4.73 (1H, br s, CH_2-C17), 4.71 (1H, br, s, CH_2-C17), 3.81–3.76 (2H, m, CH_2-C19), 3.75–3.69 (2H, m, CH-C2, CH-C3), 3.17 (1H, ddd, *J* = 12.5, 11.5, 8.8 Hz, CH_2-C5), 2.83 (1H, br d, *J* = 13.9 Hz, CH_2-C8), 2.56–2.49 (1H, m, CH-C14), 2.30–2.15 (2H, m, CH_2-C13), 1.94 (1H, dd, *J* = 13.9, 4.0 Hz, CH_2-C8), 1.91–1.82 (2H, m, CH-C1, CH_2-C12), 1.79–1.71 (2H, m, CH_2-C5, CH_2-C12), 1.70–1.60 (2H, m, CH_2-C4), 1.68 (3H, s, CH_3-C18), 1.63 (3H, s, CH_3-C16), 1.23 (3H, t, *J* = 7.0 Hz, CH_3-C20), 0.89 (9H, s, 3 × CH_3-*t*Bu), 0.03 (3H, s, CH_3-Si), 0.02 (3H, s, CH_3-Si); ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.6 (C-C15), 144.3 (C-C11), 131.2 (C-C7), 129.8 (CH-C6), 120.1 (C-C10), 111.7 (CH_2-C17), 88.4 (CH-C2), 75.4 (CH-C9), 71.8 (CH-C3), 62.9 (CH_2-C19), 48.1 (CH-C1), 44.7 (CH-C14), 37.6 (CH_2-C8), 33.7 (CH_2-C12), 29.4 (CH_2-C4), 28.5 (CH_3-C18), 26.3 (3 × CH_3-*t*Bu), 24.9 (CH_2-C13), 22.0 (CH_2-C5), 18.8 (CH_3-C16), 18.6 (C-*t*Bu), 15.9 (CH_3-C20), −4.2 (CH_3-Si), −4.4 (CH_3-Si); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{26}H_{45}O_3Si$ 433.3138, found 433.3145, Δ = −1.7 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 89.1 (100%), 158.2 (20%), 433.5 (65%).

(1*R**,2*S**,6*S**,7*R**,8*R**,9*S**,12*Z*)-9-(*tert*-Butyldimethylsilyloxy)-6-isopropenyl-13-methyl-15-oxatricyclo[6.6.1.$0^{2,7}$]-12-pentadecen-3-one, (±)-356.

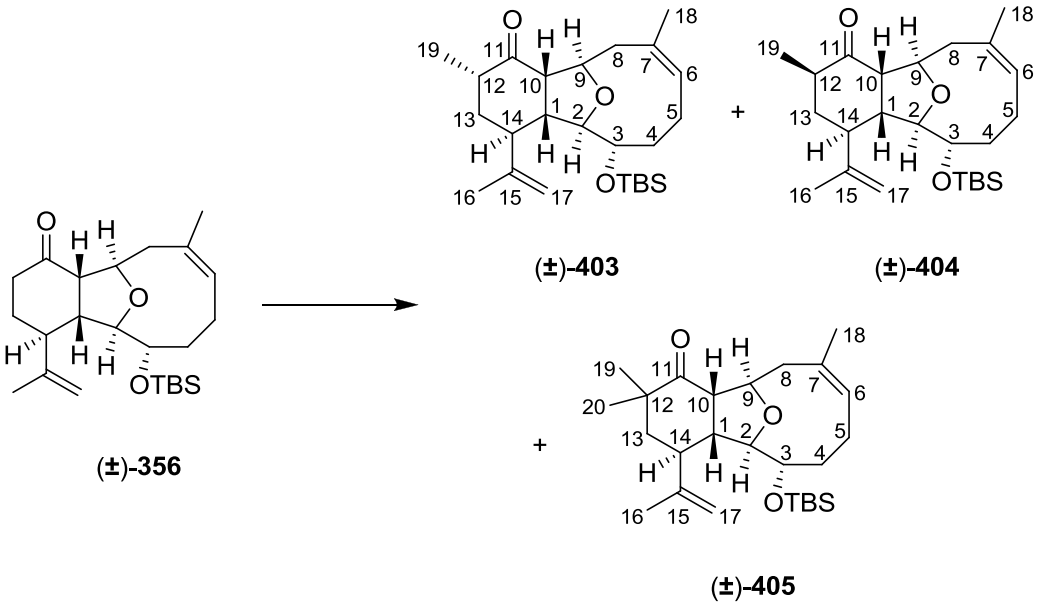


(±)-355 (±)-356

To a stirred solution of enol ether (±)-**355** (190 mg, 439 μmol) in anhydrous THF (20 mL) was added aq. 1.0 M HCl (430 μL, 430 μmol) and the resulting solution stirred at rt for 1 h. The reaction was diluted with water (8 mL) and CH_2Cl_2 (40 mL). The aqueous phase was separated and extracted using CH_2Cl_2 (3 × 10 mL). The organic phases were

combined and then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – diethyl ether, 98:2) afforded the ketone (±)-**356** as a colourless solid (164 mg, 92%): R_f = 0.58 (petroleum ether – diethyl ether, 4:1); m.p. 106–109 °C; ν_{max} 2922, 2862, 1705, 1458, 1250, 1072 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.48 (1H, dd, *J* = 11.7, 5.7 Hz, CH-C6), 4.87 (1H, s, CH_2-C17), 4.86 (1H, s, CH_2-C17), 4.34 (1H, ddd, *J* = 9.9, 3.2, 3.1 Hz, CH-C9), 3.73 (1H, d, *J* = 9.0 Hz, CH-C2), 3.32 (1H, ddd, *J* = 11.0, 9.0, 3.3 Hz, CH-C3), 2.84 (1H, br d, *J* = 14.8 Hz, CH_2-C8), 2.77–2.68 (2H, m, CH-C10, CH_2-C5), 2.54 (1H, ddd, *J* = 15.9, 13.8, 5.8 Hz, CH_2-C12), 2.45–2.40 (1H, m, CH_2-C12), 2.39–2.32 (2H, m, CH-C1, CH-C14), 2.00–1.88 (2H, m, CH_2-C5, CH_2-C13), 1.92 (3H, s, CH_3-C18), 1.81 (1H, dd, *J* = 14.8, 3.2 Hz, CH_2-C8), 1.78–1.59 (3H, m, CH_2-C4, CH_2-C13), 1.68 (3H, s, CH_3-C16), 0.85 (9H, s, 3 × CH_3-*t*Bu), 0.04 (3H, s, CH_3-Si), 0.01 (3H, s, CH_3-Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.7 (C-C11), 145.9 (C-C15), 132.8 (C-C7), 127.4 (CH-C6), 113.5 (CH_2-C17), 87.4 (CH-C2), 80.6 (CH-C9), 71.9 (CH-C3), 52.5 (CH-C10), 49.6 (CH-C14), 44.4 (CH-C1), 38.7 (CH_2-C12), 35.0 (CH_2-C8), 33.8 (CH_2-C4), 30.7 (CH_2-C13), 28.2 (CH_3-C18), 26.4 (CH_2-C5), 26.0 (3 × CH_3-*t*Bu), 19.2 (CH_3-C16), 18.0 (C-*t*Bu), −3.90 (CH_3-Si), −3.93 (CH_3-Si); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{24}H_{41}O_3Si$ 405.2825, found 405.2821, Δ = −1.0 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 69.1 (100%), 73.1 (85), 113.2 (30%), 405.4 (10%).

(1*R,2*S**,4*S**,6*S**,7*R**,8*R**,9*S**,12*Z*)-9-(*tert*-Butyldimethylsilyloxy)-4-methyl-6-isopropenyl-13-methyl-15-oxatricyclo[6.6.1.$0^{2,7}$]-12-pentdecen-3-one, (±)-403, (1*R**,2*S**,4*R**,6*S**,7*R**,8*R**,9*S**,12*Z*)-9-(*tert*-Butyldimethylsilyloxy)-4-methyl-6-isopropenyl-13-methyl-15-oxatricyclo[6.6.1.$0^{2,7}$]-12-pentdecen-3-one, (±)-404 and (1*R**,2*S**,6*S**,7*R**,8*R**,9*S**,12*Z*)-9-(*tert*-Butyldimethylsilyloxy)-4,4-dimethyl-6-isopropenyl-13-methyl-15-oxatricyclo[6.6.1.$0^{2,7}$]-12-pentdecen-3-one, (±)-405.**



(The above reaction was run in quadruplicate until quenched, at which point reaction mixtures were combined for the aqueous work-up, as larger scale attempts resulted in drastically poorer conversion and product yield)

To a stirred solution of ketone (±)-**356** (4 × 190 mg, 4 × 470 μmol) in anhydrous THF (4 × 6 mL) at −78 °C was added iodomethane (4 × 102 μL, 4 × 1.63 mmol) and the resulting solution stirred for 5 min. To this was added NaHMDS (4 × 1.63 mL of a 1.0 M solution in THF, 4 × 1.63 mmol) dropwise over 10 min and the reaction stirred at −78 °C for 7 h. The reaction was quenched using water (4 × 6 mL) and diluted with Et_2O (4 × 15 mL) and allowed to warm to rt, at which point the four individual quenched reactions were combined. The aqueous phase was separated and extracted using Et_2O (3 × 20 mL). The organic phases were combined, then washed with brine (25 mL), then dried (Mg_2SO_2), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – diethyl ether, 98:2) afforded the starting ketone (±)-**356** (385 mg,

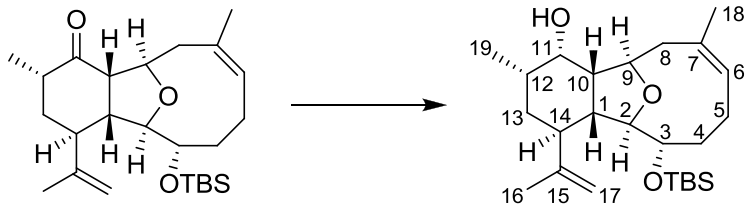
51%), the geminal α-dimethyl ketone (±)-**405** (16.3 mg, 2%), the α-methyl ketone (±)-**404** (234 mg, 30%), and the product, (±)-**403** (123 mg, 16%), each as a colourless solid.

(±)-**403**: R_f = 0.77 (petroleum ether – diethyl ether, 4:1); m.p. 91–94 °C; ν_{max} 2932, 2862, 1713, 1458, 1381, 1250, 1088, 1072 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.48 (1H, dd, *J* = 11.6, 5.8 Hz, CH-C6), 4.84 (2H, s, CH_2-C17), 4.31 (1H, dt, *J* = 9.1, 3.2 Hz, CH-C9), 3.66 (1H, d, *J* = 9.1 Hz, CH-C2), 3.35 (1H, ddd, *J* = 11.9, 9.1, 3.1 Hz, CH-C3), 2.86 (1H, d, *J* = 14.5 Hz, CH-C8), 2.77–2.61 (3H, m, CH-C10, CH-C12, CH_2-C5), 2.48 (1H, dd, *J* = 12.1, 6.6 Hz, CH-C1), 2.34-2.26 (1H, m, CH-C14), 2.11–2.01 (2H, m, CH_2-C8, CH_2-C13), 1.95–1.90 (1H, m, CH_2-C5), 1.86 (3H, s, CH_3-C18), 1.74–1.57 (3H, m, CH_2-C4, CH_2-C13), 1.71 (3H, s, CH_3-C16), 1.15 (3H, d, *J* = 7.1 Hz, CH_3C19), 0.88 (9H, s, 3 × CH_3-*t*Bu), 0.06 (3H, s, CH_3-Si), 0.04 (3H, s, CH_3-Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.2 (C-C11), 145.9 (C-C15), 133.0 (C-C7), 127.6 (CH-C6), 113.5 (CH_2-C17), 86.6 (CH-C2), 80.0 (CH-C9), 72.7 (CH-C3), 51.6 (CH-C10), 47.3 (CH-C1), 41.9 (CH-C12), 41.0 (CH-C14), 36.0 (CH_2-C8, CH_2-C13), 33.8 (CH_2-C4), 28.1 (CH_3-C18), 26.3 (CH_2-C5), 26.0 (3 × CH_3-*t*Bu), 18.7 (CH_3-C16), 18.1 (C-*t*Bu), 16.6 (CH_3-C19), −3.8 (CH_3-Si), −4.0 (CH_3-Si); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{25}H_{43}O_3Si$ 419.2981, found 419.2977, Δ = −1.1 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 73.1 (100%), 85.2 (62%), 287.3 (28%), 419.4 (60%).

(±)-**404**: R_f = 0.70 (petroleum ether – diethyl ether, 4:1); m.p. 97–99 °C; ν_{max} 2932, 2862, 1705, 1458, 1381, 1258, 1180, 1080, 1003 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.48 (1H, dd, *J* = 11.7, 5.5 Hz, CH-C6), 4.87 (1H, br s, CH_2-C17), 4.85 (1H, br s, CH_2-C17), 4.39 (1H, dt, *J* = 9.8, 3.0 Hz, CH-C9), 3.72 (1H, d, *J* = 9.1 Hz, CH-C2), 3.31 (1H, ddd, *J* = 12.1, 9.1, 3.3 Hz, CH-C3), 2.83 (1H, br d, *J* = 14.9 Hz, CH_2-C8), 2.75 (1H, dd, *J* = 9.8, 6.5 Hz, CH-C10), 2.74–2.68 (1H, m, CH_2-C5), 2.67–2.60 (1H, m, CH-C12), 2.51 (1H, dt, *J* = 12.3, 2.7 Hz, CH-C14), 2.37 (1H, dd, *J* = 11.8, 6.5 Hz, CH-C1), 1.99–1.89 (2H, m, CH_2-C5, CH_2-C13), 1.92 (3H, s, CH_3-C18), 1.79 (1H, dd, *J* = 14.9, 3.0 Hz, CH_2-C8), 1.74–1.59 (2H, m, CH_2-C4), 1.67 (3H, s, CH_3-C16), 1.52 (1H, ddd, *J* = 13.0, 13.0, 13.0 Hz, CH_2-C13), 1.07 (3H, d, *J* = 6.6 Hz, CH_3-C19), 0.85 (9H, s, 3 × CH_3-*t*Bu), 0.04 (3H, s, CH_3-Si), 0.00 (3H, s, CH_3-Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.2 (C-C11), 145.7 (C-C15), 132.8 (C-C7), 127.4 (CH-C6), 113.4 (CH_2-C17), 87.5 (CH-C2), 81.2 (CH-C9), 72.0 (CH-C3), 52.9 (CH-C10), 50.7 (CH-C1), 44.8 (CH-C14), 41.9 (CH-C12), 39.8 (CH_2-C13), 35.0 (CH_2-C8), 33.9 (CH_2-C4), 28.1 (CH_3-C18), 26.4 (CH_2-C5), 26.0 (3 × CH_3-*t*Bu), 19.2 (CH_3-C16), 18.0 (C-*t*Bu), 14.5 (CH_3-C19), −3.90 (CH_3-Si), −3.93 (CH_3-Si); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{25}H_{43}O_3Si$ 419.2981, found 419.2979, Δ = −0.6 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 69.1 (58%), 287.4 (68%), 361.4 (25%), 419.5 (100%).

(±)-**405**: R_f = 0.60 (petroleum ether – diethyl ether, 9:1); m.p. 108–111 °C; ν_{max} 2932, 2862, 1697, 1458, 1381, 1250, 1088, 1057 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.48 (1H, dd, *J* = 11.5, 5.3 Hz, CH-C6), 4.88 (1H, s, CH-C17), 4.86 (1H, s, CH-C17), 4.34 (1H, dt, *J* = 9.8, 3.1 Hz, CH-C9), 3.72 (1H, d, *J* = 9.2 Hz, CH-C2), 3.31 (1H, ddd, *J* = 11.2, 9.2, 3.1 Hz, CH-C3), 2.81 (1H, br d, *J* = 14.9 Hz, CH_2-C8), 2.76–2.66 (1H, m, CH_2-C5), 2.71 (1H, dd, *J* = 9.8, 6.7 Hz, CH-C10), 2.49 (1H, td, *J* = 12.0, 3.4 Hz, CH-C14), 2.32 (1H, dd, *J* = 12.0, 6.7 Hz, CH-C1), 1.96–1.88 (2H, m, CH_2-C5, CH_2-C8), 1.93 (3H, s, CH_3-C18), 1.75–1.58 (4H, m, CH_2-C4, CH_2-C13), 1.69 (3H, s, CH_3-C16), 1.23 (3H, s, CH_3-C19/C20), 1.13 (3H, s, CH_3-C19/C20), 0.86 (9H, s, 3 × CH_3-*t*Bu), 0.05 (3H, s, CH_3-Si), 0.02 (3H, s, CH_3-Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.6 (C-C11), 146.1 (C-C15), 132.9 (C-C7), 127.5 (CH-C6), 113.2 (CH_2-C17), 86.9 (CH-C2), 81.3 (CH-C9), 72.4 (CH-C3), 51.3 (CH-C10), 48.9 (CH-C1), 44.5 (C-C12), 44.47 (CH_2-C13), 40.6 (CH-C14), 35.1 (CH_2-C8), 33.8 (CH_2-C4), 28.0 (CH_3-C18), 27.9 (CH_3-C19/C20), 27.4 (CH_3-C19/C20), 26.4 (CH_2-C5), 26.0 (3 × CH_3-*t*Bu), 19.3 (CH_3-C16), 18.1 (C-*t*Bu), −3.8 (CH_3-Si), −4.0 (CH_3-Si); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{26}H_{45}O_3Si$ 433.3138, found 433.3137, Δ = −0.3 ppm; LRMS (CI, Me_3CH) *m*/*z* (intensity) 69.1 (28%), 232.3 (100%), 433.4 (65%).

(1*R**,2*S**,3*S**, 4*S**,6*S**,7*R**,8*R**,9*S**,12*Z*)-9-(*tert*-Butyldimethylsilyloxy)-4-methyl-6-isopropenyl-13-methyl-15-oxatricyclo[6.6.1.$0^{2,7}$]-12-pentdecen-3-ol, (±)-406.[6]

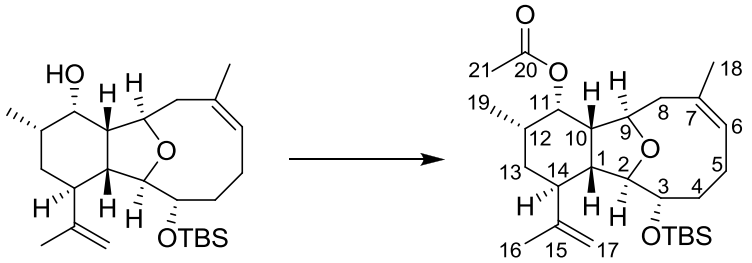


(±)-403 (±)-406

To a stirred solution of ketone (±)-**403** (150 mg, 358 μmol) in anhydrous THF (4 mL) at −78 °C was added L-Selectride™ (430 μL of a1.0 M solution in THF, 430 μmol) dropwise and the resulting solution stirred for 15 min. The reaction was quenched using aqueous 3.0 M NaOH (215 μL, 644 μmol) and aqueous hydrogen peroxide (446 μL of a 30% w/v solution, 3.94 mmol) and stirred at rt for 3 h. The reaction mixture was diluted with

water (3 mL) and Et_2O (10 mL). The aqueous phase was separated and extracted using Et_2O (3 × 10 mL). The organic phases were combined and then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (*n*–hexane – diethyl ether, 9:1) afforded the alcohol (±)-**406** as a colourless solid (126 mg, 84%): R_f = 0.24 (petroleum ether – diethyl ether, 9:1); m.p. 182–184 °C; ν_{max} 3364, 2932, 2855, 1458, 1381, 1250, 1088, 1042 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.47 (1H, dd, *J* = 11.5, 5.7 Hz, CH-C6), 4.80 (1H, br s, CH_2-C17), 4.80–4.78 (1H, m, CH_2-C17), 4.49 (1H, dt, *J* = 9.5, 3.0 Hz, CH-C9), 4.12 (1H, ddd, *J* = 6.1, 4.8, 4.8 Hz, CH-C11), 3.56 (1H, d, *J* = 9.0 Hz, CH-C2), 3.41 (1H, ddd, *J* = 11.1, 9.0, 3.1 Hz, CH-C3), 2.84–2.68 (2H, m, CH_2-C5, CH_2-C8), 2.37 (1H, ddd, *J* = 9.5, 6.3, 6.1 Hz, CH-C10), 2.26 (1H, td, *J* = 11.6, 4.5 Hz, CH-C14), 2.16–2.07 (1H, m, CH-C12), 2.02 (1H, dd, *J* = 14.4, 3.0 Hz, CH_2-C8), 1.94 (1H, dd, *J* = 11.6, 6.3 Hz, CH-C1), 1.91 (1H, dd, *J* = 11.9, 5.7 Hz, CH_2-C5), 1.87 (3H, s, CH_3-C18), 1.72–1.50 (4H, m, CH_2-C4, CH_2-C13), 1.65 (3H, s, CH_3-C16), 1.41 (1H, d, *J* = 4.8 Hz, OH), 1.12 (3H, d, *J* = 7.4 Hz, CH_3-C19), 0.86 (9H, s, 3 × CH_3–*t*Bu), 0.05 (3H, s, CH_3–Si), 0.02 (3H, s, CH_3–Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.3 (C-C15), 133.4 (C-C7), 127.1 (CH-C6), 112.5 (CH_2-C17), 86.2 (CH-C2), 79.8 (CH-C9), 72.4 (CH-C3), 71.4 (CH-C11), 46.5 (CH-C1), 43.0 (CH-C10), 38.4 (CH-C14), 37.7 (CH_2-C8), 35.2 (CH_2-C13), 34.3 (CH-C12), 34.0 (CH_2-C4), 28.3 (CH_3-C18), 26.3 (CH_2-C5), 26.0 (3 × CH_3–*t*Bu), 19.5 (CH_2-C16), 18.1 (C–*t*Bu), 14.1 (CH_3-C19), −3.8 (CH_3–Si), −4.0 (CH_3–Si); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{25}H_{45}O_3Si$ 421.3138, found 421.3137, Δ = −0.2 ppm; LRMS (CI, Me_3CH) *m*/*z* (intensity) 212.3 (10%), 289.4 (35%), 421.5 (100%).

(1*R,2*S**,3*S**, 4*S**,6*S**,7*R**,8*R**,9*S**,12*Z*)-9-(*tert*-Butyldimethylsilyloxy)-3-acetoxy-4-methyl-6-isopropenyl-13-methyl-15-oxatricyclo[6.6.1.$0^{2,7}$]-12-pentdecene, (±)-407.[6]**

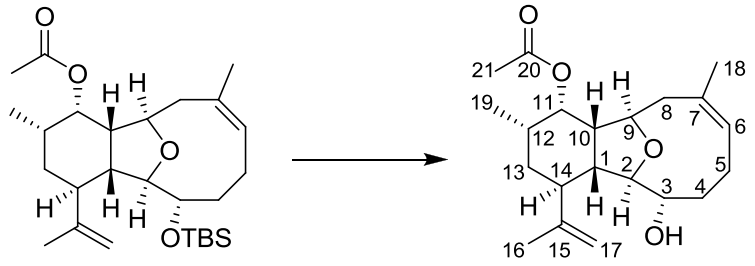


(±)-406 **(±)-407**

To a stirred solution of alcohol (±)-**406** (120 mg, 285 μmol) in anhydrous CH_2Cl_2 (5 mL) at rt was added triethylamine (159 μL, 1.14 mmol) and DMAP (3.5 mg, 29 μmol) and the resulting solution stirred at rt for 5 min. To this was added acetic anhydride (54.0 μL, 58.2 mg, 570 μmol) dropwise and the reaction stirred at rt for 18 h. The reaction was quenched using saturated aqueous NH_4Cl (5 mL). The aqueous phase was separated and extracted using CH_2Cl_2 (3 × 10 mL). The organic phases were combined and then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (*n*-hexane – diethyl ether, 9:1) afforded the ester (±)-**407** as a colourless solid (130 mg, 99%): R_f = 0.41 (petroleum ether – diethyl ether, 9:1); m.p. 82–85 °C; ν_{max} 2932, 2855, 1744, 1458, 1373, 1234, 1088, 1034 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.46 (1H, dd, *J* = 11.6, 5.7 Hz, CH-C6), 5.27 (1H, dd, *J* = 6.5, 6.5 Hz, CH-C11), 4.81 (1H, s, CH_2-C17), 4.80 (1H, s, CH_2-C17), 4.56–4.51 (1H, m, CH-C9), 3.57 (1H, d, *J* = 9.0 Hz, CH-C2), 3.38–3.32 (1H, m, CH-C3), 2.83 (1H, br d, *J* = 14.6 Hz, CH_2-C8), 2.80–2.69 (1H, m, CH_2-C5), 2.38–2.25 (3H, m, CH-C10, CH-C12, CH-C14), 2.11 (3H, s, CH_3-C21), 2.01 (1H, dd, *J* = 11.7, 6.0 Hz, CH-C1), 1.95 (1H, dd, *J* = 14.6, 3.1 Hz, CH-C8), 1.93–1.87 (1H, m, CH_2-C5), 1.74 (3H, s, CH_3-C18), 1.72–1.55 (4H, m, CH_2-C4, CH_2-C13), 1.64 (3H, s, CH_3-C16), 1.09 (3H, d, *J* = 7.4 Hz, CH_3-C19), 0.85 (9H, s, 3 × CH_3-*t*Bu), 0.04 (3H, s, CH_3-Si), 0.01 (3H, s, CH_3-Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4 (C-C20), 146.8 (C-C15), 132.6 (C-C7), 127.7 (CH-C6), 112.8 (CH_2-C17), 86.2 (CH-C2), 79.9 (CH-C9), 73.5 (CH-C11), 72.1 (CH-C3), 46.8 (CH-C1), 40.8 (CH-C10), 38.2 (CH-C14), 36.8 (CH_2-C8), 35.1 (CH_2-C13), 33.9 (CH_2-C4), 31.0 (CH-C12), 28.2 (CH_3-C18), 26.3 (CH_2-C5), 26.0 (3 × CH_3-*t*Bu), 21.3 (CH_3-C21), 19.4 (CH_3-C16), 18.1 (CH_3-C19), 14.5 (C-*t*Bu), −3.8 (CH_3-Si), −4.0 (CH_3-Si); HRMS (CI, Me_3CH)

$[M+H]^+$ calcd for $C_{27}H_{47}O_4Si$ 463.3244, found 463.3247, Δ = −0.7 ppm; LRMS (CI, Me_3CH) *m*/*z* (intensity) 271.4 (25%), 331.4 (25%), 403.5 (80%), 463.6 (100%).

(1*R,2*S**,3*S**, 4*S**,6*S**,7*R**,8*R**,9*S**,12*Z*)-3-Acetoxy-4-methyl-6-isopropenyl-9-hydroxyl-13-methyl-15-oxatricyclo[6.6.1.$0^{2,7}$]-12-pentdecene, (±)-410.**

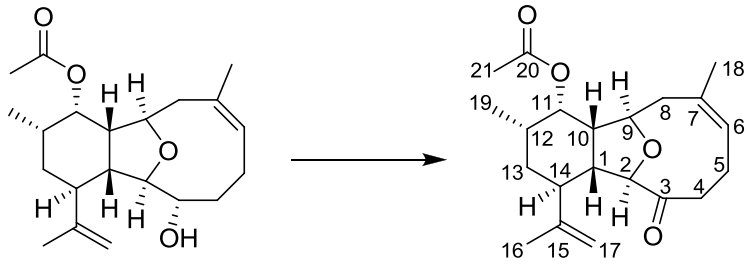


(±)-407 **(±)-410**

To a round bottom flask that had been flame dried under vacuum and then placed under an argon atmosphere was added 4 Å molecular sieves and the flask flame dried under vacuum once more. After cooling to rt under an argon atmosphere, a solution of silyl ether (±)-**407** (130 mg, 281 μmol) in anhydrous THF (7 mL) was added and the resulting slurry stirred at rt for 5 min. To this mixture was added tetrabutylammonium fluoride (562 μL of a 1.0 M solution in THF, 562 μmol) dropwise and the reaction stirred at rt for 3 h. The reaction was quenched using saturated aqueous NH_4Cl (5 mL). The aqueous phase was separated and extracted using EtOAc (3 × 10 mL). The organic phases were combined and washed with brine (15 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (*n*-hexane – diethyl ether, 4:1) afforded the alcohol (±)-**410** as a colourless solid (79.1 mg, 80%): R_f = 0.38 (petroleum ether – diethyl ether, 2:1); m.p. 168–170 °C; ν_{max} 3449, 2932, 2855, 1736, 1443, 1373, 1234, 1088, 1026 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.48 (1H, dd, *J* = 11.6, 5.7 Hz, CH-C6), 5.27 (1H, dd, *J* = 6.4, 6.4 Hz, CH-C11), 4.85–4.81 (2H, m, CH_2-C17), 4.53 (1H, td, *J* = 9.1, 2.7 Hz, CH-C9), 3.52 (1H, d, *J* = 9.1 Hz, CH-C2), 3.31 (1H, ddd, *J* = 14.5, 9.1, 7.7 Hz, CH-C3), 2.86–2.72 (2H, m, CH_2-C5, CH_2-C8), 2.38 (1H, ddd, *J* = 9.1, 6.5, 6.4 Hz, CH-C10), 2.34–2.28 (1H, m, CH-C12), 2.30 (1H, td, *J* = 11.4, 6.4 Hz, CH-C14), 2.19 (1H, dd, *J* = 11.4, 6.5 Hz, CH-C1), 2.11 (3H, s, CH_3-C21), 1.97–1.90 (2H, m, CH_2-C5, CH_2-C8), 1.75–1.71 (1H, m, CH_2-C4), 1.73 (3H, s, CH_3-C18), 1.68 (3H, s, CH_3-C16), 1.65–1.57 (2H,

m, CH_2-C13), 1.09 (3H, d, *J* = 7.4 Hz, CH_3-C19), 1.07–1.04 (1H, m, CH_2-C4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3 (C-C20), 147.4 (C-C15), 132.5 (C-C7), 127.9 (CH-C6), 112.6 (CH_2-C17), 86.6 (CH-C2), 80.2 (CH-C9), 73.3 (CH-C11), 71.8 (CH-C3), 47.1 (CH-C1), 40.8 (CH-C10), 38.4 (CH-C14), 37.0 (CH_2-C8), 34.8 (CH_2-C13), 34.3 (CH_2-C4), 31.0 (CH-C12), 28.3 (CH_3-C18), 26.0 (CH_2-C5), 21.3 (CH_3-C21), 19.3 (CH_3-C16), 14.6 (CH_3-C19); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{21}H_{33}O_4$ 349.2379, found 349.2374, Δ = −1.4 ppm; LRMS (CI, Me_3CH) *m*/*z* (intensity) 61.1 (25%), 289.4 (95%), 349.4 (100%).

(1*R**,2*S**,3*S**, 4*S**,6*S**,7*R**,8*R**,12*Z*)-3-Acetoxy-4-methyl-6-isopropenyl-13-methyl-15-oxatricyclo[6.6.1.$0^{2,7}$]-12-pentadecen-9-one, (±)-411.[28]

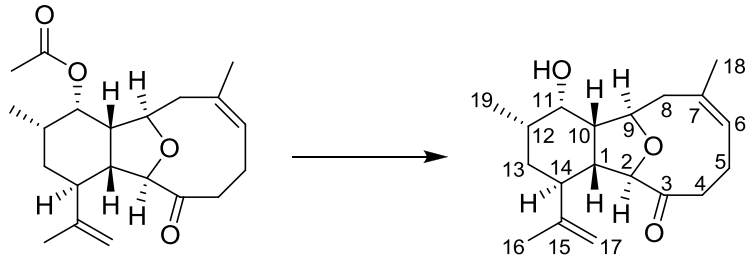


(±)-410 (±)-411

To a stirred solution of alcohol (±)-**410** (75.0 mg, 215 μmol) in anhydrous CH_2Cl_2 (7 mL) was added pyridine (70.1 μL, 68.1 mg, 861 μmol) dropwise and the resulting solution stirred at rt for 5 min. To this was added Dess–Martin periodinane (137 mg, 323 μmol) and the reaction mixture was stirred for 30 min. The reaction was quenched using saturated aqueous $Na_2S_2O_3$/saturated aqueous $NaHCO_3$ (5:1, 6 mL) and mixture was stirred vigorously for 20 min. The aqueous phase was separated and extracted using CH_2Cl_2 (3 × 10 mL). The organic phases were combined and washed with brine (15 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (*n*–hexane – diethyl ether, 4:1) afforded the ketone (±)-**411** as a colourless solid (66.2 mg, 89%): R_f = 0.59 (petroleum ether – diethyl ether, 2:1); m.p. 89–91 °C; ν_{max} 2932, 1736, 1705, 1451, 1373, 1234, 1026 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.53 (1H, dd, *J* = 10.4, 6.4 Hz, CH-C6), 5.21 (1H, dd, *J* = 6.0, 4.7 Hz, CH-C11), 4.79 (1H, s, CH_2-C17), 4.76 (1H, s, CH_2-C17), 4.52–4.45 (1H, m, CH-C9), 4.05 (1H, d, *J* = 3.1 Hz, CH-C2), 3.20–2.95 (1H, m, CH_2-C5), 2.84–2.77 (2H, m, CH-C1, CH_2-C4), 2.75–2.61 (1H, m, CH_2-

C8), 2.46–2.35 (2H, m, CH-C14, CH_2-C4), 2.25 (1H, ddd, *J* = 6.6, 6.6, 6.0 Hz, CH-C10), 2.17–2.04 (2H, m, CH-C12, CH_2-C5), 2.09 (3H, s, CH_3-C21), 1.96 (1H, dd, *J* = 14.3, 5.3 Hz, CH_2-C8), 1.70 (3H, s, CH_3-C18), 1.69 (3H, s, CH_3-C16), 1.61–1.57 (2H, m, CH_2-C13), 0.99 (3H, d, *J* = 7.2 Hz, CH-C19); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.5 (C-C3), 170.6 (C-C20), 147.7 (C-C15), 133.9 (C-C7), 127.7 (CH-C6), 112.1 (CH_2-C17), 88.1 (CH-C2), 81.9 (CH-C9), 73.0 (CH-C11), 42.7 (CH-C1, CH-C10), 42.5 (CH_2-C4), 38.7 (CH-C14), 37.6 (CH_2-C8), 31.9 (CH_2-C13), 30.4 (CH-C12), 26.7 (CH_3-C18), 25.6 (CH_2-C5), 21.3 (CH_3-C21), 20.1 (CH_3-C16), 15.7 (CH_3-C19); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{21}H_{31}O_4$ 347.2222, found 347.2219, Δ = −1.1 ppm; LRMS (CI, Me_3CH) *m*/*z* (intensity) 269.3 (15%), 287.3 (80%), 347.3 (100%)

(1*R**,2*S**,3*S**, 4*S**,6*S**,7*R**,8*R**,12*Z*)-3-Hydroxy-4-methyl-6-isopropenyl-13-methyl-15-oxatricyclo[6.6.1.0^{2,7}]-12-pentdecen-9-one, (±)-416.

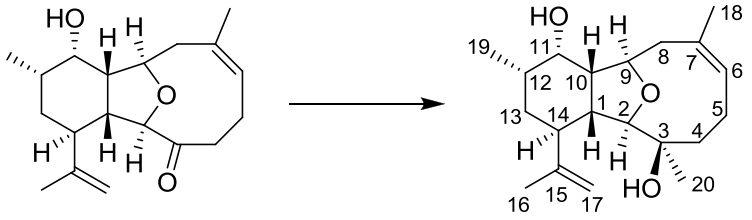


(±)-411 (±)-416

To a stirred solution of keto–ester (±)-**411** (58.0 mg, 167 μmol) in methanol (10 mL) was added potassium carbonate (69.4 mg, 502 μmol) and the resulting solution stirred at rt for 18 h. The reaction was quenched using saturated aqueous NH_4Cl (10 mL). The aqueous phase was separated and extracted using CH_2Cl_2 (3 × 10 mL). The organic phases were combined and then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (*n*–hexane – diethyl ether, 4:1) afforded the keto–alcohol (±)-**416** as a colourless solid (46.2 mg, 91%): R_f = 0.41 (petroleum ether – diethyl ether, 2:1); m.p. 108–110 °C; ν_{max} 3480, 2924, 2878, 1697, 1451, 1381, 1327, 1258, 1234, 1211, 1173, 1103, 1049 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.60–5.53 (1H, m, CH-C6), 4.79 (1H, s, CH_2-C17), 4.76 (1H, s, CH_2-C17), 4.58–4.53 (1H, m, CH-C9), 4.04 (1H, d, *J* = 4.6 Hz, CH-C2), 3.93–3.89 (1H, m, CH-C11), 3.00–2.86 (1H, m, CH_2-C5), 2.85

(1H, td, *J* = 12.7, 4.8 Hz, CH_2-C4), 2.76 (1H, ddd, *J* = 7.5, 7.3, 4.6 Hz, CH-C1), 2.65–2.47 (1H, m, CH-C14), 2.50 (1H, dd, *J* = 12.2, 7.2 Hz, CH_2-C8), 2.38 (1H, dt, *J* = 12.2, 4.8 Hz, CH_2-C4), 2.22 (1H, ddd, *J* = 7.3, 5.0, 5.0 Hz, CH-C10), 2.12–2.02 (2H, m, CH_2-C5, CH_2-C8), 1.89–1.77 (2H, m, CH-C12, OH), 1.80 (3H, s, CH_3-C18), 1.72 (3H, s, CH_3-C16), 1.64 (1H, ddd, *J* = 13.7, 7.6, 5.2 Hz, CH_2-C13), 1.47 (1H, ddd, *J* = 13.7, 8.3, 4.9 Hz, CH_2-C13), 1.04 (3H, d, *J* = 7.1 Hz, CH_3-C19); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.6 (C-C3), 148.4 (C-C15), 134.4 (C-C7), 127.4 (CH-C6), 111.4 (CH_2-C17), 87.8 (CH-C2), 82.1 (CH-C9), 71.5 (CH-C11), 45.6 (CH-C10), 42.4 (CH_2-C4), 42.1 (CH-C1), 39.6 (CH-C14), 37.7 (CH_2-C8), 32.1 (CH-C12), 30.0 (CH_2-C13), 26.0 (CH_3-C18), 25.1 (CH_2-C5), 20.8 (CH_3-C16), 16.5 (CH_3-C19); HRMS (FAB/NOBA) $[M+H]^+$ calcd for $C_{19}H_{29}O_3$ 305.2117, found 305.2119, Δ = −0.9 ppm; LRMS (FAB/NOBA) *m/z* (intensity) 69.8 (48%), 193.1 (20%), 305.2 (100%).

(1*R**,2*S**,3*S**, 4*S**,6*S**,7*R**,8*R**,9R*,12Z)-3-Hydroxy-4-methyl-6-isopropenyl-9-methyl-13-methyl-15-oxatricyclo[6.6.1.0^{2,7}]-12-pentdecen-9-ol, (±)-417.[95]

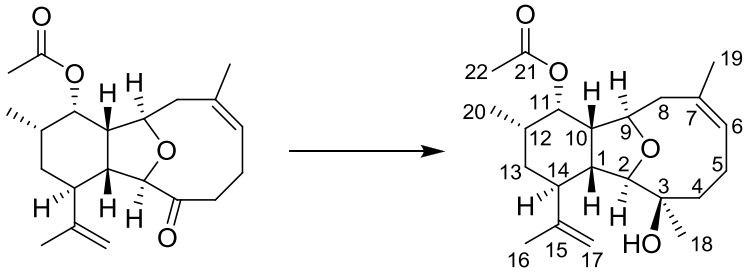


(±)-416 **(±)-417**

To a stirred solution of keto-alcohol (±)-**416** (35.8 mg, 118 μmol) in anhydrous THF (8 mL) at rt was added $NaBF_4$ (129 mg, 1.18 mmol) and the resulting mixture stirred for 10 min. After cooling to −78 °C, methyl lithium (294 μL of a 1.6 M solution in Et_2O, 470 μmol) was added dropwise and the reaction stirred at −78 °C for 1 h. The reaction was quenched using saturated aqueous $NaHCO_3$ (5 mL), diluted with Et_2O (10 mL) and allowed to warm to rt. The aqueous phase was separated and extracted using Et_2O (3 × 10 mL). The organic phases were combined and washed with brine (10 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (*n*-hexane – diethyl ether, 1:3) afforded the starting keto-alcohol (±)-**416** (7.3 mg, 20%) and the diol (±)-**417** as a colourless solid (22.5 mg, 61%): R_f = 0.20 (petroleum ether – diethyl ether, 1:2); m.p. 186–189 °C; ν_{max} 3364, 2916, 1443, 1373, 1296, 1227, 1150,

1111, 1088, 1042, 1003 cm^{-1}; ^1H NMR (500 MHz, C_6D_6, 60 °C) δ 5.53 (1H, dd, *J* = 10.9, 6.2 Hz, CH-C6), 4.88 (1H, s, CH_2-C17), 4.86 (1H, s, CH_2-C17), 4.27 (1H, dd, *J* = 6.8, 3.6 Hz, CH-C9), 3.90 (1H, d, *J* = 7.5 Hz, CH-C2), 3.48–3.45 (1H, m, CH-C11), 2.90–2.68 (4H, m, CH-C1, CH-C14, CH_2-C5, CH_2-C8), 2.23–2.18 (1H, m, CH-C10), 1.94–1.86 (1H, m, CH_2-C5), 1.86–1.81 (1H, m, CH_2-C8), 1.80–1.73 (1H, m, CH_2-C13), 1.76 (3H, s, CH_3-C19), 1.71 (3H, s, CH_3-C16), 1.71–1.66 (2H, m, CH_2-C4), 1.63–1.56 (1H, m, CH-C12), 1.38–1.31 (2H, m, CH_2-C13, OH), 1.28 (3H, s, CH_3-C18), 1.23–1.17 (1H, m, OH), 0.96 (3H, d, *J* = 7.0 Hz, CH_3-C20); ^{13}C NMR (125 MHz, C_6D_6, 60 °C) δ 150.3 (C-C15), 132.7 (C-C7), 130.4 (CH-C6), 111.0 (CH_2-C17), 90.1 (CH-C2), 80.4 (CH-C9), 75.1 (C-C3), 72.7 (CH-C11), 46.5 (CH-C10), 43.1 (CH-C1), 40.4 (CH-C14), 39.1 (CH_2-C4), 39.0 (CH_2-C8), 32.3 (CH-C12), 30.1 (CH_3-C18), 29.4 (CH_2-C13), 28.7 (CH_3-C19), 25.0 (CH_2-C5), 22.3 (CH_3-C16), 17.6 (CH_3-C20);HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{20}H_{33}O_3$ 321.2430, found 321.2427, Δ = −0.8 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 285.3 (15%), 303.3 (100%), 321.3 (65%).

(1*R**,2*S**,3*S**, 4*S**,6*S**,7*R**,8*R**,9R*,12Z)-3-Acetoxy-4-methyl-6-isopropenyl-9-methyl-13-methyl-15-oxatricyclo[6.6.1.$0^{2,7}$]-12-pentdecen-9-ol, (±)-418.[95]

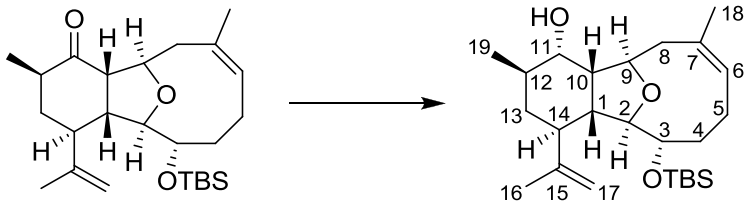


(±)-411 (±)-418

To a stirred solution of keto-ester (±)-**411** (8.0 mg, 23 μmol) in anhydrous THF (3 mL) at rt was added $NaBF_4$ (25.4 mg, 231 μmol), and the resulting mixture stirred at rt for 10 min. After cooling to −78 °C, methyl lithium (58 μL of a 1.0 M solution in Et_2O, 92 μmol) was added dropwise and the reaction stirred at −78 °C for 1 h. The reaction was quenched at −78 °C using saturated aqueous $NaHCO_3$ (5 mL) and then diluted with Et_2O (10 mL). After warming to rt the aqueous phase was separated and extracted using Et_2O (3 × 10 mL). The organic phases were combined and washed with brine (15 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on

silica gel (*n*–hexane – diethyl ether, 2:1) afforded the keto–alcohol (±)-**418** as a colourless oil (1.8 mg, 21%): R_f = 0.45 (petroleum ether – diethyl ether, 1:1); ν_{max} 3464, 2963, 2925, 1736, 1451, 1373, 1242, 1111, 1080, 1034 cm $^{-1}$; ^{1}H NMR (500 MHz, C_6D_6, 60 °C) δ 5.53 (1H, dd, *J* = 11.1, 6.2 Hz, CH-C6), 5.24 (1H, dd, *J* = 5.1, 3.8 Hz, CH-C11), 4.87-4.83 (2H, m, CH_2-C17), 4.28 (1H, dd, *J* = 7.1, 4.0 Hz, CH-C9), 3.88 (1H, d, *J* = 6.6 Hz, CH-C2), 2.94-2.86 (1H, m, CH_2-C5), 2.78-2.67 (3H, m, CH-C1, CH-C14, CH_2-C8), 2.35 (1H, ddd, *J* = 7.1, 5.1, 5.0 Hz, CH-C10), 1.93-1.84 (2H, m, CH-C12, CH_2-C5), 1.83 (3H, s, CH_3-C22), 1.78 (1H, dd, *J* = 14.4, 4.0 Hz, CH_2-C8), 1.70 (3H, s, CH_3-C19), 1.68 (3H, s, CH_3-C16), 1.67-1.59 (3H, m, CH_2-C4, CH_2-C13), 1.42-1.37 (1H, m, CH_2-C13), 1.26 (3H, s, CH_2-C18), 0.89 (3H, d, *J* = 7.0 Hz, CH_3-C20); ^{13}C NMR (125 MHz, C_6D_6, 60 °C) δ 170.0 (C-C21), 149.4 (C-C15), 132.7 (C-C7), 130.1 (CH-C6), 111.1 (CH_2-C17), 89.6 (CH-C2), 79.8 (CH-C9), 74.7 (C-C3), 73.9 (CH-C11), 44.5 (CH-C10), 43.2 (CH-C1), 40.0 (CH-C14), 39.0 (CH_2-C4), 38.3 (CH_2-C8), 30.7 (CH_2-C13), 30.5 (CH-C12), 29.8 (CH_3-C18), 25.0 (CH_2-C5), 21.5 (CH_3-C16), 20.6 (CH_3-C22), 16.8 (CH_3-C20); HRMS (EI) $[M]^+$ calcd for $C_{22}H_{34}O_4$ 362.2457, found 362.2455, Δ = −0.7 ppm; LRMS (EI) *m*/*z* (intensity) 43.0 (82%), 108.1 (55%), 176.1 (98%), 237.2 (100%), 362.3 (20%).

(1*R**,2*S**,3*R**, 4*R**,6*S**,7*R**,8*R**,9*S**,12*Z*)-9-(*tert*-Butyldimethylsilyloxy)-4-methyl-6-isopropenyl-13-methyl-15-oxatricyclo[6.6.1.0^{2,7}]-12-pentdecen-3-ol, (±)-408.[6]

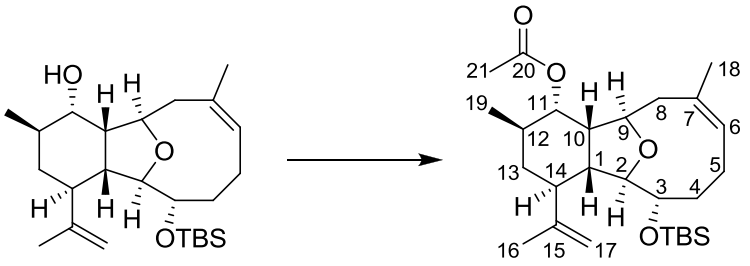


(±)-404 (±)-408

To a stirred solution of ketone (±)-**404** (8.0 mg, 19 μmol) in anhydrous THF (2 mL) at 0 °C was added L–Selectride™ (38 μL of a 1.0 M solution in THF, 38 μmol) dropwise and the resulting solution stirred at 0 °C for 2 h. The reaction was quenched using aqueous 3.0 M NaOH (19 μL, 57 μmol) and aqueous hydrogen peroxide (4 μL of a 30% w/v solution, 38 μmol) and stirred at rt for 2 h. The reaction was diluted with water (3 mL)

and Et_2O (10 mL). The aqueous phase was separated and extracted using Et_2O (3 × 20 mL). The organic phases were combined and then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – diethyl ether, 9:1) afforded the alcohol (±)-**408** as a colourless solid (8.0 mg, 99%): R_f = 0.33 (petroleum ether – diethyl ether, 4:1); m.p. 176–179 °C; ν_{max} 3410, 2924, 2856, 1458, 1250, 1080, 1042 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.47 (1H, dd, *J* = 11.6, 5.6 Hz, CH-C6), 4.78–4.76 (2H, m, CH_2-C17), 4.36–4.34 (1H, m, CH-C9), 3.59 (1H, dd, *J* = 10.3, 6.0 Hz, CH-C11), 3.53 (1H, d, *J* = 9.0 Hz, CH-C2), 3.43 (1H, ddd, *J* = 12.2, 9.0, 3.2 Hz, CH-C3), 2.89–2.74 (2H, m, CH_2-C5, CH_2-C8), 2.40 (1H, ddd, 11.6, 9.9, 6.0 Hz, CH-C10), 2.10 (1H, ddd, *J* = 12.7, 11.9, 3.2 Hz, CH-C14), 2.04 (1H, dd, *J* = 14.4, 3.1 Hz, CH_2-C8), 2.00 (1H, dd, *J* = 11.8, 5.7 Hz, CH-C1), 1.95–1.88 (1H, m, CH_2-C5), 1.87 (3H, s, CH_3-C18), 1.77–1.59 (4H, m, CH-C12, CH_2-C4, CH_2-C13), 1.63 (3H, s, CH_3-C16), 1.07 (1H, ddd, *J* = 12.8, 12.7, 12.7 Hz, CH_2-C13), 1.02 (3H, d, *J* = 6.4 Hz, CH_3-C19), 0.86 (9H, s, 3 × CH_3–*t*Bu), 0.05 (3H, s, CH_3–Si), 0.02 (3H, s, CH_3–Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.0 (C-C15), 133.7 (C-C7), 127.1 (CH-C6), 112.5 (CH_2-C17), 86.5 (CH-C2), 78.8 (CH-C9), 76.5 (CH-C11), 72.0 (CH-C3), 46.7 (CH-C1), 44.9 (CH-C14), 43.0 (CH-C10), 38.4 (CH_2-C13), 37.0 (CH_2-C8), 34.6 (CH-C12), 34.0 (CH_2-C4), 26.4 (CH_2-C5), 26.0 (CH_3-C18, 3 × CH_3–*t*Bu), 19.4 (CH_3-C16), 18.4 (CH_3-C19), 18.1 (C–*t*Bu), −3.90 (CH_3–Si), −3.94 (CH_3–Si); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{25}H_{45}O_3Si$ 421.3138, found 421.3133, Δ = −1.1 ppm; LRMS (CI, Me_3CH) *m*/*z* (intensity) 73.1 (55%), 121.2 (100%), 289.4 (20%), 421.5 (30%).

(1*R,2*S**,3*R**, 4*R**,6*S**,7*R**,8*R**,9*S**,12*Z*)-9-(*tert*-Butyldimethylsilyloxy)-3-acetoxy-4-methyl-6-isopropenyl-13-methyl-15-oxatricyclo[6.6.1.$0^{2,7}$]-12-pentdecene, (±)-409.[136]**

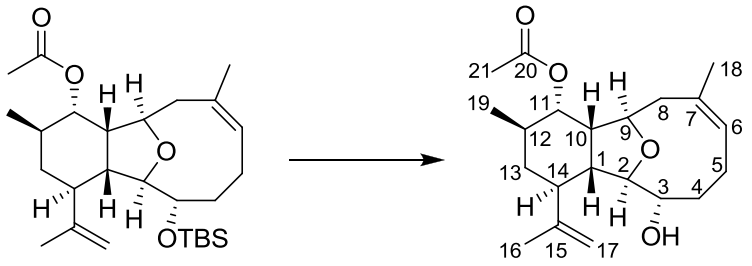


(±)-408 **(±)-409**

To a solution of alcohol (±)-**408** (33 mg, 78 µmol), DMAP (2.8 mg, 32 µmol) and pyridine (18.6 mg, 235 µmol) at 0 °C in anhydrous CH_2Cl_2 (2 mL) was added acetyl chloride (18.5 µmol, 235 µmol) and the resulting solution stirred at rt for 21 h. The reaction was quenched using saturated aqueous NH_4Cl (4 mL) and diluted with water (10 mL) and CH_2Cl_2 (20 mL). The aqueous phase was separated and extracted using CH_2Cl_2 (3 × 10 mL). The organic phases were combined and then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – diethyl ether, 19:1) afforded the starting alcohol (±)-**408** (3.5 mg, 11%) and the ester (±)-**409** as a colourless solid (25 mg, 70%): R_f = 0.79 (petroleum ether – diethyl ether, 4:1); m.p. 122–125 °C; ν_{max} 2932, 2855, 1744, 1458, 1373, 1234, 1080, 1026 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.46 (1H, dd, *J* = 11.6, 5.6 Hz, CH-C6), 5.02 (1H, dd, *J* = 11.1, 6.1 Hz, CH-C11), 4.78 (2H, m, CH_2-C17), 4.43–4.38 (1H, m, CH-C9), 3.54 (1H, d, *J* = 9.1 Hz, CH-C2), 3.36 (1H, dt, *J* = 10.8, 3.3 Hz, CH-C3), 2.88 (1H, d, *J* = 14.7 Hz, CH_2-C8), 2.83–2.72 (1H, m, CH_2-C5), 2.34 (1H, ddd, *J* = 9.7, 6.1, 5.5 Hz, CH-C10), 2.14–2.04 (2H, m, CH-C1, CH-C14), 2.11 (3H, s, CH_3-C21), 1.94–1.82 (2H, m, CH-C12, CH_2-C5), 1.88 (1H, dd, *J* = 14.7, 2.7 Hz, CH_2-C8), 1.74–1.58 (3H, m, CH_2-C4, CH_2-C13), 1.70 (3H, s, CH_3-C18), 1.63 (3H, s, CH_3-C16), 1.18 (1H, ddd, *J* = 12.4, 12.4, 12.3 Hz, CH_2-C13), 0.88 (3H, d, *J* = 6.4 Hz, CH_3-C19), 0.85 (9H, s, 3 × CH_3-*t*Bu), 0.03 (3H, s, CH_3-Si), 0.02 (3H, s, CH_3-Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8 (C-C20), 146.6 (C-C15), 132.4 (C-C7), 127.9 (CH-C6), 112.8 (CH_2-C17), 86.7 (CH-C2), 78.7 (CH-C9), 77.3 (CH-C11), 71.7 (CH-C3), 46.8 (CH-C1), 45.0 (CH-C14), 41.1 (CH-C10), 38.2 (CH_2-C13), 36.7 (CH_2-C8), 34.0 (CH_2-C4), 32.7 (CH-C12), 28.3 (CH_3-C18), 26.3 (CH_2-C5), 26.0 (3 × CH_3-*t*Bu), 21.4 (CH_3-C21), 19.3

(CH_3-C16), 18.2 (CH_3-C19), 18.0 (C-*t*Bu), −3.94 (2 × CH_3-Si); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{27}H_{47}O_4Si$ 463.3244, found 463.3239, Δ = −1.0 ppm; LRMS (CI, Me_3CH) *m*/*z* (intensity) 69.1 (100%), 97.1 (25%), 463.2 (20%).

(1*R**,2*S**,3*R**, 4*R**,6*S**,7*R**,8*R**,9*S**,12*Z*)-3-Acetoxy-4-methyl-6-isopropenyl-9-hydroxyl-13-methyl-15-oxatricyclo[6.6.1.$0^{2,7}$]-12-pentdecene, (±)-412.[95]

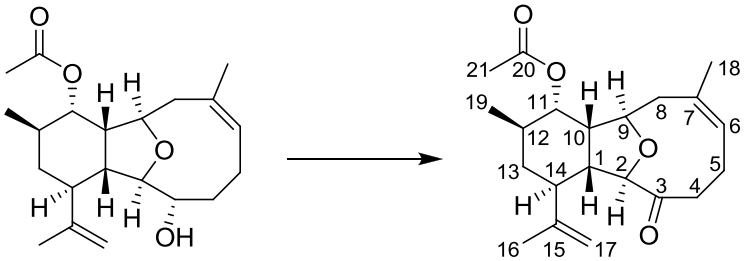


(±)-409 (±)-412

To a stirred solution of silyl ether (±)-**409** (18 mg, 39 μmol) in anhydrous THF (3 mL) at rt was added 4 Å molecular sieves and the resulting mixture stirred for 5 min. To this was added TBAF (78 μL of a 1.0 M solution in THF, 78 μmol) and the reaction stirred for 2.5 h. The reaction was quenched using saturated aqueous NH_4Cl (4 mL) and diluted with EtOAc (10 mL). The aqueous phase was separated and extracted using EtOAc (3 × 10 mL). The organic phases were combined and washed with brine (10 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – diethyl ether, 4:1) afforded the alcohol (±)-**412** as a colourless solid (13 mg, 96%): R_f = 0.32 (petroleum ether – diethyl ether, 2:1); m.p. 129–132 °C; ν_{max} 3457, 2924, 2855, 1736, 1451, 1373, 1234, 1196, 1080, 1026 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.48 (1H, dd, *J* = 11.6, 5.7 Hz,CH-C6), 5.01 (1H, dd, *J* = 11.1, 6.2 Hz, CH-C11), 4.82–4.79 (2H, m, CH_2-C17), 4.44–4.39 (1H, m, CH-C9), 3.45 (1H, d, *J* = 9.8 Hz, CH-C2), 3.32 (1H, dt, *J* = 9.9, 4.0 Hz, CH-C3), 2.91–2.75 (2H, m, CH_2-C5, CH_2-C8), 2.41 (1H, ddd, *J* = 9.6, 6.2, 6.0 Hz, CH-C10), 2.23 (1H, dd, *J* = 11.7, 5.9 Hz, CH-C1), 2.14–2.08 (1H, m, CH-C14), 2.10 (3H, s, CH_3-C21), 1.97–1.83 (3H, m, CH-C12, CH_2-C5, CH_2-C13), 1.77–1.65 (3H, m, CH_2-C4, CH_2-C13), 1.69 (3H, s, CH_3-C18), 1.66 (3H, s, CH_3-C16), 1.60 (1H, br s, OH), 1.18 (1H, ddd, *J* = 12.8, 12.8, 12.8 Hz, CH_2-C13), 0.88 (3H, d, *J* = 6.4 Hz, CH_3-C19); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7 (C-C20), 147.1 (C-C15), 132.4 (C-C7), 128.0 (CH-C6),

112.7 (CH_2-C17), 86.9 (CH-C2), 78.9 (CH-C9), 77.1 (CH-C11), 71.3 (CH-C3), 47.1 (CH-C1), 45.2 (CH-C14), 41.0 (CH-C10), 38.2 (CH_2-C13), 36.8 (CH_2-C8), 34.5 (CH_2-C4), 32.6 (CH-C12), 28.3 (CH_3-C18), 26.2 (CH_2-C5), 21.3 (CH_3-C21), 19.1 (CH_3-C16), 18.1 (CH_3-C19); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{21}H_{33}O_4$ 349.2379, found 349.2373, Δ = −1.7 ppm; LRMS (CI, Me_3CH) *m*/*z* (intensity) 113.2 (58%), 289.2 (100%), 331.2 (50%), 349.2 (60%).

(1*R**,2*S**,3*R**, 4*R**,6*S**,7*R**,8*R**,12*Z*)-3-Acetoxy-4-methyl-6-isopropenyl-13-methyl-15-oxatricyclo[6.6.1.$0^{2,7}$]-12-pentdecen-9-one, (±)-413.[28]

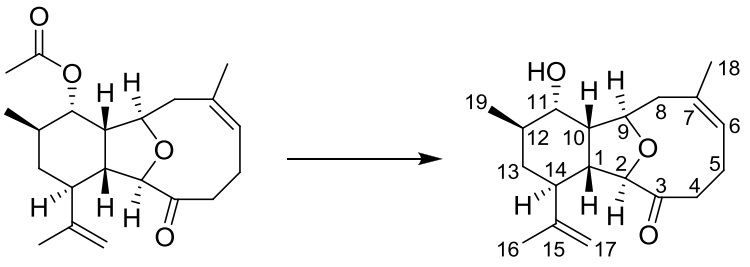


(±)-412 (±)-413

To a stirred solution of alcohol (±)-**412** (28.0 mg, 80.3 μmol) in anhydrous CH_2Cl_2 (3 mL) was added pyridine (25.4 mg, 321 μmol) dropwise and the resulting solution stirred at rt for 5 min. To this was added Dess–Martin periodinane (52.1 mg, 121 μmol) and the reaction stirred for 1h. The reaction was quenched using saturated aqueous $Na_2S_2O_3$/saturated aqueous $NaHCO_3$ (5:1, 3 mL) and then stirred vigorously for 1 h. The aqueous phase was separated and extracted using Et_2O (3 × 10 mL). The organic phases were combined and washed with brine (10 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – ethyl acetate, 4:1) afforded the ketone (±)-**413** as a colourless solid (22.3 mg, 80%): R_f = 0.46 (petroleum ether – diethyl ether, 4:1); m.p. 103–105 °C; ν_{max} 2924, 1744, 1705, 1451, 1373, 1234, 1188, 1119, 1072, 1026 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.50 (1H, dd, *J* = 11.6, 5.9 Hz, CH-C6), 5.00 (1H, dd, *J* = 11.1, 6.3 Hz, CH-C11), 4.76 (1H, s, CH_2-C17), 4.75 (1H, s, CH_2-C17), 4.54 (1H, td, *J* = 9.6, 3.4 Hz, CH-C9), 4.00 (1H, s, CH-C2), 3.32 (1H, ddt, *J* = 12.4, 12.2, 6.0 Hz, CH_2-C5), 2.97 (1H, d, *J* = 14.8 Hz, CH_2-C8), 2.81 (1H, dd, *J* = 12.0, 6.2 Hz, CH-C1), 2.80 (1H, ddd, *J* = 12.2, 6.1, 2.8 Hz, CH_2-C4), 2.38 (1H, dt, *J* = 12.4, 6.7 Hz, CH_2-C4), 2.26 (1H, ddd, *J* = 9.6, 6.3, 6.3 Hz, CH-C10), 2.14–2.05 (2H,

m, CH-C14, CH_2-C5), 2.07 (3H, s, CH_3-C21), 1.88 (1H, dd, *J* = 14.8, 3.4 Hz, CH_2-C8), 1.87–1.78 (1H, m, CH-C12), 1.69 (1H, ddd, *J* = 13.4, 3.3, 3.3 Hz, CH_2-C13), 1.65 (3H, s, CH_3-C16), 1.60 (3H, s, CH_3-C18), 1.22 (1H, ddd, *J* = 12.9, 12.6, 12.6 Hz, CH_2-C13), 0.88 (3H, d, *J* = 6.4 Hz, CH_3-C19); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.9 (C-C3), 170.4 (C-C20), 146.8 (C-C15), 133.3 (C-C7), 127.9 (CH-C6), 112.8 (CH_2-C17), 88.7 (CH-C2), 81.0 (CH-C9), 76.4 (CH-C11), 44.7 (CH-C14), 43.8 (CH-C1), 42.6 (CH_2-C4), 41.5 (CH-C10), 37.7 (CH_2-C13), 36.8 (CH_2-C8), 33.0 (CH-C12), 27.7 (CH_3-C18), 26.5 (CH_2-C5), 21.3 (CH_3-C21), 19.0 (CH_3-C16), 18.1 (CH_3-C19); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{21}H_{31}O_4$ 347.2222, found 347.2223, Δ = +0.2 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 73.1 (20%), 287.3 (80%), 347.3 (100%).

(1*R**,2*S**,3*R**, 4*R**,6*S**,7*R**,8*R**,12*Z*)-3-Hydroxy-4-methyl-6-isopropenyl-13-methyl-15-oxatricyclo[6.6.1.$0^{2,7}$]-12-pentdecen-9-one, (±)-415.

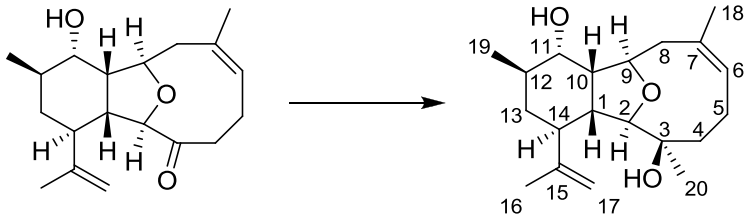


(±)-413 **(±)-415**

To a stirred solution of keto–ester (±)-**413** (22.3 mg, 64.4 μmol) in methanol (5 mL) at rt was added potassium carbonate (26.7 mg, 193 μmol) and the resulting solution stirred at rt for 96 h. The reaction was quenched using saturated aqueous NH_4Cl (5 mL) and diluted with CH_2Cl_2 (10 mL). The aqueous phase was separated and extracted using CH_2Cl_2 (3 × 10 mL). The organic phases were combined and then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – diethyl ether, 3:1) afforded the alcohol (±)-**415** as a colourless solid (18.6 mg, 95%): R_f = 0.22 (petroleum ether – diethyl ether, 4:1); m.p. 171–173 °C; ν_{max} 3472, 2916, 1697, 1451, 1373, 1319, 1258, 1234, 1211, 1180, 1119, 1042 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.50 (1H, dd, *J* = 11.5, 5.7 Hz, CH-C6), 4.74 (2H, s, CH_2-C17), 4.49 (1H, td, *J* = 3.3, 9.7 Hz, CH-C9), 3.99 (1H, s, CH-C2), 3.56 (1H, ddd, *J* = 10.4, 6.1, 4.4 Hz, CH-C11), 3.34 (1H, ddt, *J* = 12.4, 12.3, 6.3 Hz, CH_2-C5), 2.95 (1H, d, *J* = 14.4 Hz, CH_2-C8), 2.81 (1H, ddd, *J*

= 12.7, 6.3, 2.5 Hz,CH_2-C4), 2.74 (1H, dd, *J* = 12.0, 6.1 Hz, CH-C1), 2.39 (1H, dt, *J* = 12.4, 6.7 Hz, CH_2-C4), 2.31 (1H, ddd, *J* = 9.7, 6.2, 6.1 Hz, CH-C10), 2.12–2.02 (3H, m, CH-C14, CH_2-C5, CH_2-C8), 1.76 (3H, s, CH_3-C18), 1.72 (1H, d, *J* = 4.4 Hz, OH), 1.71–1.60 (2H, m, CH-C12, CH_2-C13), 1.64 (3H, s, CH_3-C16), 1.09 (1H, ddd, *J* = 12.8, 12.8, 12.8 Hz, CH_2-C13), 1.01 (3H, d, *J* = 6.4 Hz, CH_3-C19); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.9 (C-C3), 147.2 (C-C15), 134.7 (C-C7), 126.9 (CH-C6), 112.4 (CH_2-C17), 88.6 (CH-C2), 81.3 (CH-C9), 75.7 (CH-C11), 44.6 (CH-C14), 43.9 (CH-C1), 43.3 (CH-C10), 42.8 (CH_2-C4), 37.8 (CH_2-C13), 37.0 (CH_2-C8), 34.8 (CH-C12), 27.7 (CH_3-C18), 26.5 (CH_2-C5), 19.1 (CH_3-C16), 18.4 (CH_3-C19); HRMS (FAB/NOBA) $[M+H]^+$ calcd for $C_{19}H_{29}O_3$ 305.2117, found 305.2114, Δ = −1.0 ppm; LRMS (FAB/NOBA) *m*/*z* (intensity) 69.8 (55%), 305.2 (45%), 368.2 (100%).

(1*R**,2*S**,3*R**, 4*R**,6*S**,7*R**,8*R**,9R*,12Z)-3-Hydroxy-4-methyl-6-isopropenyl-9-methyl-13-methyl-15-oxatricyclo[6.6.1.0^{2,7}]-12-pentdecen-9-ol, (±)-414.[95]

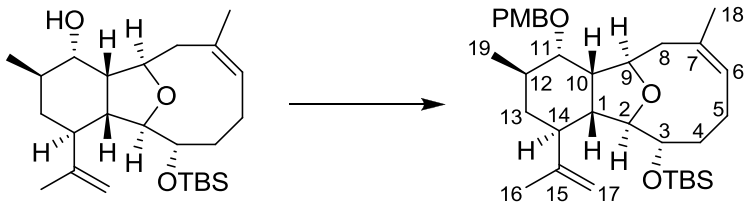


(±)-415 **(±)-414**

To a stirred solution of keto–alcohol (±)-**415** (8.00 mg, 26.3 μmol) in anhydrous THF (3 mL) at rt was added $NaBF_4$ (28.9 mg, 263 μmol) and the resulting mixture stirred at rt for 10 min. After cooling to −78 °C, methyl lithium (65.7 μL of a 1.6 M solution in Et_2O, 105 μmol) was added dropwise and the reaction stirred at −78 °C for 1 h. The reaction was quenched at −78 °C using saturated aqueous NH_4Cl (4 mL) and diluted with Et_2O (15 mL). After warming to rt the aqueous phase was separated and extracted using Et_2O (3 × 10 mL). The organic phases were combined and washed with brine (10 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (*n*–hexane – diethyl ether, 2:1) afforded the starting keto–alcohol (1.1 mg, 4%) and the diol (±)-**414** as a colourless solid (6.9 mg, 82%): R_f = 0.37 (petroleum ether – diethyl ether, 2:1); m.p. 195–198 °C; ν_{max} 3511, 3395, 2916, 2862, 1451, 1373, 1312, 1258, 1188, 1150, 1126, 1049 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (1H, dd, *J* = 11.2, 5.6 Hz,

CH-C6), 4.80–4.73 (2H, m, CH_2-C17), 4.37 (1H, td, *J* = 2.7, 9.9 Hz, CH-C9), 3.75 (1H, s, CH-C2), 3.59 (1H, dd, *J* = 10.0, 6.4 Hz, CH-C11), 3.35 (1H, br s, OH-C11), 3.29–3.15 (1H, m, CH_2-C5), 2.97 (1H, br d, *J* = 13.7 Hz, CH_2-C8), 2.62 (1H, ddd, *J* = 9.9, 6.4, 6.2 Hz, CH-C10), 2.28 (1H, dd, *J* = 11.8, 6.2 Hz, CH-C1), 2.20–2.15 (1H, m, CH_2-C8), 2.08 (1H, dt, *J* = 12.4, 3.3 Hz, CH-C14), 2.03–1.95 (1H, m, CH_2-C5), 1.91–1.85 (1H, m, CH_2-C4), 1.88 (3H, s, CH_3-C18), 1.76–1.69 (1H, m, CH-C12), 1.75 (1H, ddd, *J* = 14.7, 11.8, 6.9 Hz, CH_2-C4), 1.66 (1H, br s, OH-C3), 1.65 (3H, s, CH_3-C16), 1.62–1.56 (1H, m, CH_2-C13), 1.12 (1H, ddd, *J* = 12.9, 12.8, 12.8 Hz, CH_2-C13), 1.01 (3H, d, *J* = 6.4 Hz, CH_3-C19), 0.87 (3H, s, CH_3-C20); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.5 (C-C15), 137.9 (C-C7), 128.1 (CH-C6), 112.7 (CH_2-C17), 90.3 (CH-C2), 78.5 (CH-C9), 76.2 (CH-C11), 75.4 (C-C3), 46.5 (CH-C14), 45.8 (CH-C1), 44.4 (CH-C10), 38.7 (CH_2-C4), 38.0 (CH_2-C13), 37.4 (CH_2-C8), 34.4 (CH-C12), 28.9 (CH_3-C20), 28.6 (CH_3-C18), 27.6 (CH_2-C5), 18.8 (CH_3-C16), 18.4 (CH_3-C19); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{20}H_{33}O_3$ 321.2430, found 321.2433, Δ = +0.9 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 69.1 (62%), 262.2 (100%), 303.4 (50%), 321.4 (30%).

(1*R**,2*S**,3*R**, 4*R**,6*S**,7*R**,8*R**,9*S**,12*Z*)-9-(*tert*-Butyldimethylsilyloxy)-3-(*para*-methoxybenzyloxy)-4-methyl-6-isopropenyl-13-methyl-15-oxatricyclo[6.6.1.0^{2,7}]-12-pentdecene, PMB-(±)-409.[142]

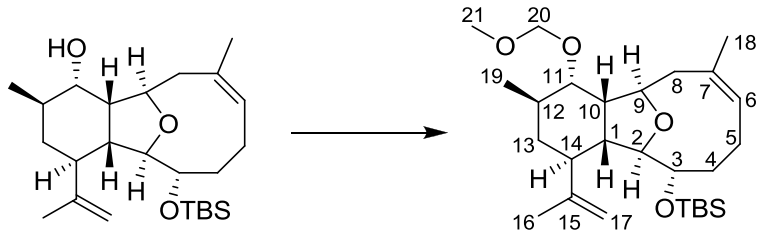


(±)-408 **PMB-(±)-409**

To a solution of alcohol (±)-**408** (12.0 mg, 28.5 μmol) in anhydrous DMF (2 mL) at rt was added sodium hydride (2.1 mg, 86 μmol) and the resulting mixture stirred for 30 min. To this was added *para*-methoxybenzyl chloride (13.4 mg, 85.6 μmol) and the reaction stirred at rt for 18h. The reaction was quenched using saturated aqueous NH_4Cl (5 mL) and diluted with water (10 mL) and EtOAc (20 mL). The organic phase was separated and sequentially washed with water (2 × 10 mL), saturated aqueous NH_4Cl (2 × 10 mL) and brine (15 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column

chromatography on silica gel (petroleum ether – diethyl ether, 19:1) afforded the PMB-ether **PMB-(±)-409** as a colourless oil (7.6 mg, 49%): R_f = 0.66 (petroleum ether – diethyl ether, 4:1); ν_{max} 2932, 2855, 1512, 1458, 1250, 1080, 1042 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31–7.27 (2H, m, CH–Ar), 6.90–6.87 (2H, m, CH–Ar), 5.47 (1H, d, *J* = 9.4, 5.0 Hz, CH-C6), 4.77 (1H, s, CH_2-C17), 4.76 (1H, s, CH_2-C17), 4.71 (1H, d, *J* = 10.3 Hz, CH_2-PMB), 4.46 (1H, d, *J* = 10.3 Hz,CH_2-PMB), 4.41–4.34 (1H, m, CH-C9), 3.81 (3H, s, CH_3-PMB), 3.52 (1H, d, *J* = 9.1 Hz, CH-C2), 3.49–3.43 (1H, m, CH-C3), 3.30 (1H, dd, *J* = 10.6, 5.9 Hz, CH-C11), 2.87–2.73 (2H, m, CH_2-C5, CH_2-C8), 2.51 (1H, ddd, *J* = 8.6, 5.9, 5.8 Hz, CH-C10), 2.12–1.98 (3H, m, CH-C1, CH-C14, CH_2-C8), 1.95–1.86 (1H, m, CH_2-C5), 1.86-1.77 (1H, m, CH-C12), 1.81 (3H, s, CH_3-C18), 1.73–1.57 (3H, m, CH_2-C4, CH_2-C13), 1.63 (3H, s, CH_3-C16), 1.08 (1H, ddd, *J* = 12.4, 12.4, 12.4 Hz, CH_2-C13), 1.00 (3H, dd, *J* = 6.5 Hz, CH_3-C19), 0.87 (9H, s, 3 × CH_3-*t*Bu), 0.07 (3H, s, CH_3-Si), 0.05 (3H, s, CH_3-Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.1 (C-C15), 133.4 (C-C7, C–Ar), 130.7 (C–Ar), 129.6 (CH–Ar), 129.4 (CH–Ar), 127.5 (CH-C6), 113.9 (CH–Ar), 113.86 (CH–Ar), 112.5 (CH_2-C17), 86.8 (CH-C2), 84.6 (CH-C11), 77.4 (CH-C9), 74.0 (CH_2-PMB), 71.6 (CH-C3), 55.4 (CH_3-PMB), 46.6 (CH-C14), 45.3 (CH-C1), 41.6 (CH-C10), 38.9 (CH_2-C13), 36.9 (CH_2-C8), 34.4 (CH-C12), 34.1 (CH_2-C4), 28.9 (CH_3-C18), 26.4 (CH_2-C5), 26.0 (3 × CH_3-*t*Bu), 19.4 (CH_3-C16), 19.0 (CH_3-C19), 18.1 (C-*t*Bu), −3.9 (2 × CH_3-Si); HRMS (FAB/NOBA) $[M+H]^+$ calcd for $C_{33}H_{53}O_4Si$ 541.3713, found 541.3705, Δ = −1.4 ppm; LRMS (FAB/NOBA) *m/z* (intensity) 121.1 (100%), 307.1 (35%), 541.3 (10%).

(1*R,2*S**,3*R**, 4*R**,6*S**,7*R**,8*R**,9*S**,12*Z*)-9-(*tert*-Butyldimethylsilyloxy)-3-(methoxymethyloxy)-4-methyl-6-isopropenyl-13-methyl-15-oxatricyclo[6.6.1.$0^{2,7}$]-12-pentdecene, MOM-(±)-409.[143]**

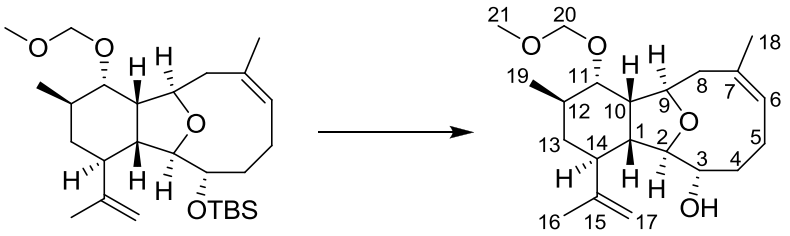


(±)-408 **MOM-(±)-409**

To a stirred solution of alcohol (±)-**408** (30.0 mg, 71.3 μmol) in anhydrous CH_2Cl_2 (2 mL) at rt was added sodium iodide (1.1 mg, 7.1 μmol), DIPEA (55.3 mg, 428 μmol) and chloromethyl methyl ether (17.2 mg, 214 μmol), sequentially, and the resulting orange solution stirred at reflux for 20 h. The reaction was quenched using saturated aqueous $NaHCO_3$ (3 mL) and stirred vigorously for 15 min. The aqueous phase was separated and extracted using CH_2Cl_2 (3 × 10 mL). The organic phases were combined and then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – diethyl ether, 9:1) afforded the ether **MOM**-(±)-**409** as a colourless solid (32.9 mg, 99%): R_f = 0.68 (petroleum ether – diethyl ether, 4:1); m.p. 115–117 °C; ν_{max} 2932, 2855, 1458, 1373, 1250, 1150, 1080, 1034 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.49 (1H, dd, *J* = 10.9, 5.6 Hz, CH-C6), 4.82 (1H, d, *J* = 6.7 Hz, CH_2-C20), 4.78–4.75 (2H, m, CH_2-C17), 4.59 (1H, d, *J* = 6.7 Hz, CH_2-C20), 4.40–4.32 (1H, m, CH-C9), 3.52 (1H, d, *J* = 9.2 Hz, CH-C2), 3.48–3.39 (2H, m, CH-C3, CH-C11), 3.44 (3H, s, CH_3-C21), 2.91–2.71 (2H, m, CH_2-C5, CH_2-C8), 2.44–2.35 (1H, m, CH-C10), 2.09 (1H, ddd, *J* = 12.6, 12.2, 3.2 Hz, CH-C14), 2.04–1.97 (2H, m, CH-C1, CH_2-C8), 1.90 (1H, td, *J* = 12.5, 6.3 Hz, CH_2-C5), 1.83 (3H, s, CH_3-C18), 1.82–1.75 (1H, m, CH-C12), 1.72–1.57 (3H, m, CH_2-C4, CH_2-C13), 1.62 (3H, s, CH_3-C16), 1.09 (1H, ddd, *J* = 12.9, 12.8, 12.6 Hz, CH_2-C13), 1.04 (3H, d, *J* = 6.4 Hz, CH_3-C19), 0.86 (9H, s, 3 × CH_3–*t*Bu), 0.04 (3H, s, CH_3–Si), 0.01 (3H, s, CH_3–Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.0 (C-C15), 133.0 (C-C7), 127.8 (CH-C6), 112.6 (CH_2-C17), 97.2 (CH_2-C20), 86.9 (CH-C2), 83.6 (CH-C11), 79.1 (CH-C9), 71.4 (CH-C3), 56.5 (CH_3-C21), 46.4 (CH-C1), 45.4 (CH-C14), 41.7 (CH-C10), 39.0 (CH_2-C13), 37.1 (CH_2-C8), 34.2 (CH_2-C4), 33.4 (CH-C12), 28.5 (CH_3-C18), 26.5 (CH_2-C5), 26.0 (3 × CH_3–*t*Bu), 19.3 (CH_3-C16), 19.1 (CH_3-C19), 18.1 (C–*t*Bu), −3.9 (2 × CH_3–Si); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for

$C_{27}H_{49}O_4Si$ 465.3400, found 465.3405, Δ = +0.9 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 81.1 (75%), 403.3 (55%), 465.3 (100%).

(1*R,2*S**,3*R**, 4*R**,6*S**,7*R**,8*R**,9*S**,12*Z*)-3-(Methoxymethyloxy)-4-methyl-6-isopropenyl-9-hydroxy-13-methyl-15-oxatricyclo[6.6.1.0^{2,7}]-12-pentdecene, MOM-(±)-412.[95]**

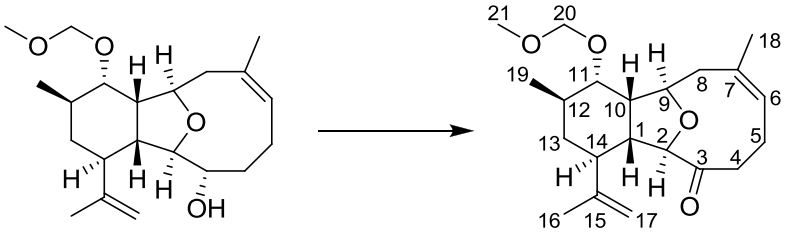


MOM-(±)-409 **MOM-(±)-412**

A round bottom flask containing a magnetic stirrer bar was flame dried under vacuum. After being placed under an atmosphere of argon, 4 Å molecular sieves were added and the flask allowed to cool to rt. To this was added a solution of silyl ether **MOM-(±)-409** (27 mg, 58 μmol) in anhydrous THF (3 mL) and the resulting slurry stirred at rt for 5 min. This was followed by the addition of TBAF (1.0 M in THF, 117 μl, 117 μmol) dropwise and the reaction stirred at rt for 4 h. The reaction was quenched using saturated aqueous NH_4Cl (3 mL). The aqueous phase was separated and extracted using EtOAc (3 × 10 mL). The organic phases were combined and washed with brine (10 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – diethyl ether, 4:1 to 1:1) afforded the alcohol **MOM-(±)-412** as a colourless solid (19.5 mg, 96%): R_f = 0.16 (petroleum ether – diethyl ether, 4:1); m.p. 107–109 °C; ν_{max} 3418, 2924, 1451, 1373, 1188, 1150, 1088, 1072, 1026 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.49 (1H, dd, *J* = 11.3, 5.9 Hz, CH-C6), 4.80–4.77 (2H, m, CH_2-C17), 4.78 (1H, d, *J* = 6.5 Hz, CH_2-C20), 4.58 (1H, d, *J* = 6.5 Hz, CH_2-C20), 4.40–4.33 (1H, m, CH-C9), 3.45–3.33 (3H, m, CH-C2, CH-C3, CH-C11), 3.42 (3H, s, CH_3-C21), 2.90–2.75 (2H, m, CH_2-C5, CH_2-C8), 2.50–2.43 (1H, m, CH-C10), 2.17 (1H, dd, *J* = 11.9, 5.9 Hz, CH-C1), 2.08 (1H, ddd, *J* = 12.5, 11.9, 3.3 Hz, CH-C14), 2.00 (1H, d, *J* = 14.2 Hz, CH_2-C8), 1.97–1.90 (1H, m, CH_2-C5), 1.84–1.62 (4H, m, CH-C12, CH_2-C4, CH_2-C13), 1.81 (3H, s, CH_3-C18), 1.65 (3H, s, CH_3-C16), 1.09 (1H, ddd, *J* = 12.7, 12.7, 12.5 Hz, CH_2-

C13), 1.04 (3H, d, *J* = 6.4 Hz, CH_3-C19); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.6 (C-C15), 133.0 (C-C7), 127.9 (CH-C6), 112.3 (CH_2-C17), 97.4 (CH_2-C20), 87.2 (CH-C11), 83.6 (CH-C9), 71.1 (CH-C3), 56.5 (CH_3-C21), 46.8 (CH-C1), 45.6 (CH-C14), 41.7 (CH-C10), 39.0 (CH_2-C13), 37.2 (CH_2-C8), 34.7 (CH_2-C4), 33.4 (CH-C12), 28.6 (CH_3-C18), 26.3 (CH_2-C5), 19.2 (CH_3-C16), 19.0 (CH_3-C19); HRMS (FAB/NOBA) $[M+H]^+$ calcd for $C_{21}H_{35}O_4$ 351.2535, found 351.2534, Δ = −0.4 ppm; LRMS (FAB/NOBA) *m/z* (intensity) 73.7 (100%), 147.0 (35%), 351.2 (13%).

(1*R**,2*S**,3*R**, 4*R**,6*S**,7*R**,8*R**,12*Z*)-3-(Methoxymethyloxy)-4-methyl-6-isopropenyl-13-methyl-15-oxatricyclo[6.6.1.0^{2,7}]-12-pentdecen-9-one, MOM-(±)-413.[28]

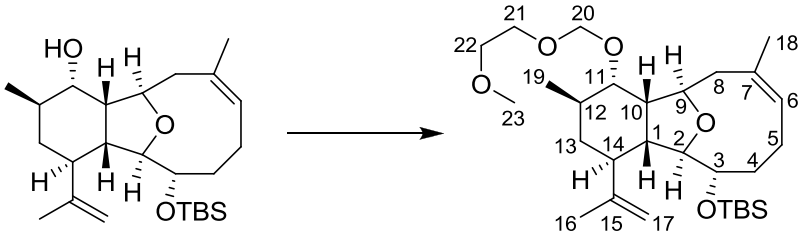


MOM-(±)-412 **MOM-(±)-413**

To a solution of alcohol **MOM-(±)-412** (18.0 mg, 51.4 μmol) in anhydrous CH_2Cl_2 (3 mL) at rt was added pyridine (16.3 mg, 205 μmol) and Dess–Martin periodinane (32.7 mg, 77.1 μmol) and the resulting solution stirred at rt for 45 min. The reaction was quenched using saturated aqueous $Na_2S_2O_3$/saturated aqueous $NaHCO_3$ (5:1, 2 mL), diluted with Et_2O (10 mL) and stirred vigorously for 1 h. The aqueous phase was separated and extracted using Et_2O (3 × 10 mL). The organic phases were combined and washed with brine (10 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – diethyl ether, 9:1, 1% Et_3N) afforded the ketone **MOM-(±)-413** as a colourless oil (14.5 mg, 81%): R_f = 0.70 (petroleum ether – ethyl acetate, 4:1); ν_{max} 2916, 1705, 1451, 1150, 1119, 1096, 1034 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60–5.53 (1H, m, CH-C6), 4.74–4.71 (2H, m, CH_2-C17), 4.70 (1H, d, *J* = 6.6 Hz, CH_2-C20), 4.54 (1H, d, *J* = 6.6 Hz, CH_2-C20), 4.47–4.40 (1H, m, CH-C9), 3.96 (1H, s, CH-C2), 3.43 (1H, dd, *J* = 10.7, 6.1 Hz, CH-C11), 3.39 (3H, s, CH_3-C21), 3.10–2.95 (1H, m, CH_2-C5), 2.78 (1H, ddd, *J* = 12.0, 4.8, 4.8 Hz, CH_2-C4), 2.72 (1H,

dd, *J* = 11.8, 6.3 Hz, CH-C1), 2.68–2.61 (1H, m, CH_2-C8), 2.40–2.26 (2H, m, CH-C10, CH_2-C4), 2.15–2.03 (2H, m, CH-C14, CH_2-C5), 2.00 (1H, dd, *J* = 14.2, 5.9 Hz, CH_2-C8), 1.79–1.69 (1H, m, CH-C12), 1.75 (3H, s, CH_3-C18), 1.67–1.61 (1H, m, CH_2-C13), 1.63 (3H, s, CH_3-C16), 1.12 (1H, ddd, *J* = 13.0, 13.0, 13.0 Hz, CH_2-C13), 1.03 (3H, d, *J* = 6.4 Hz, CH_3-C19); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.8 (C-C3), 147.2 (C-C15), 134.6 (C-C7), 127.3 (CH-C6), 112.5 (CH_2-C17), 97.0 (CH_2-C20), 88.0 (CH-C2), 82.5 (CH-C11), 80.1 (CH-C9), 56.4 (CH_3-C21), 45.2 (CH-C14), 44.2 (CH-C10), 42.8 (CH-C1), 42.1 (CH_2-C4), 38.6 (CH_2-C8), 38.3 (CH_2-C13), 33.7 (CH-C12), 26.6 (CH_3-C18), 26.3 (CH_2-C5), 19.0 (CH_3-C16), 18.9 (CH_3-C19); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{21}H_{33}O_4$ 349.2379, found 349.2377, Δ = −0.4 ppm; LRMS (CI, Me_3CH) *m*/*z* (intensity) 287.4 (50%), 317.3 (100%), 349.4 (88%).

(1*R**,2*S**,3*R**, 4*R**,6*S**,7*R**,8*R**,9*S**,12*Z*)-9-(*tert*-Butyldimethylsilyloxy)-3-(methoxyethoxymethyloxy)-4-methyl-6-isopropenyl-13-methyl-15-oxatricyclo[6.6.1.0^{2,7}]-12-pentdecene, MEM-(±)-409.[143]

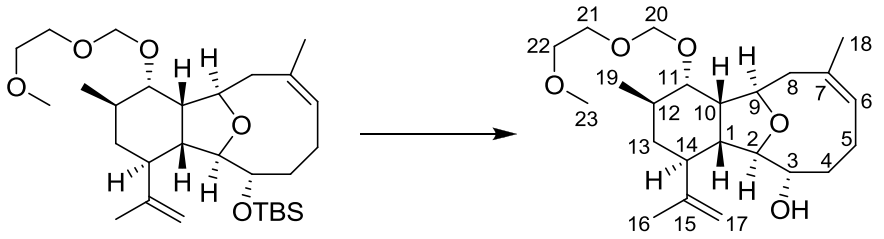


(±)-408 **MEM-(±)-409**

To a stirred solution of alcohol (±)-**408** (40.0 mg, 95.1 μmol) in anhydrous CH_2Cl_2 (3 mL) at rt was added sodium iodide (1.4 mg, 9.5 μmol), DIPEA (73.7 mg, 571 μmol) and 2-methoxyethoxymethyl chloride (35.5 mg, 285 μmol), sequentially, and the resulting orange solution stirred at reflux for 22 h. The reaction was quenched using saturated aqueous $NaHCO_3$ (3 mL) and stirred vigorously for 10 min. The aqueous phase was separated and extracted using CH_2Cl_2 (3 × 10 mL). The organic phases were combined and then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – diethyl ether, 9:1) afforded the ether **MEM**-(±)-**409** as a colourless solid (39 mg, 80%): R_f = 0.35 (petroleum ether – diethyl ether, 4:1); m.p. 74–76 °C; ν_{max} 2932, 1458, 1373, 1250, 1196, 1080, 1034 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.49 (1H, dd, *J* = 10.5, 5.8 Hz, CH-C6), 4.90 (1H, d, *J* = 7.0 Hz, CH_2-

C20), 4.77–4.74 (2H, m, CH_2-C17), 4.71 (1H, d, *J* = 7.0 Hz, CH_2-C20), 4.38–4.30 (1H, m, CH-C9), 3.92 (1H, ddd, *J* = 10.4, 4.6, 3.3 Hz, CH_2-C21), 3.66–3.60 (1H, m, CH_2-C21), 3.59–3.48 (4H, m, CH-C2, CH-C11, CH_2-C22), 3.45–3.41 (1H, m, CH-C3), 3.40 (3H, s, CH_3-C23), 2.90–2.73 (2H, m, CH_2-C5, CH_2-C8), 2.44–2.35 (1H, m, CH-C10), 2.08 (1H, dt, *J* = 12.5, 3.2 Hz, CH-C14), 2.04–1.94 (2H, m, CH-C1, CH_2-C8), 1.90 (1H, td, *J* = 12.0, 5.8 Hz, CH_2-C5), 1.85–1.76 (1H, m, CH-C12), 1.81 (3H, s, CH_3-C18), 1.72–1.57 (3H, m, CH_2-C4, CH_2-C13), 1.62 (3H, s, CH_3-C16), 1.10 (1H, ddd, *J* = 12.7, 12.7, 12.5 Hz, CH_2-C13), 1.03 (3H, d, *J* = 6.5 Hz, CH_3-C19), 0.83 (9H, s, 3 × CH_3-*t*Bu), 0.03 (3H, s, CH_3–Si), 0.00 (3H, s, CH_3–Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.0 (C-C15), 132.9 (C-C7), 127.9 (CH-C6), 112.6 (CH_2-C17), 95.9 (CH_2-C20), 86.9 (CH-C2), 83.1 (CH-C11), 79.0 (CH-C9), 71.9 (CH_2-C22), 71.3 (CH-C3), 68.1 (CH_2-C21), 59.2 (CH_3-C23), 46.3 (CH-C1), 45.4 (CH-C14), 41.5 (CH-C10), 39.0 (CH_2-C13), 37.1 (CH_2-C8), 34.2 (CH_2-C4), 33.3 (CH-C12), 28.5 (CH_3-C18), 26.5 (CH_2-C5), 26.0 (3 × CH_3-*t*Bu), 19.3 (CH_3-C16), 19.1 (CH_3-C19), 18.1 (C-*t*Bu), −4.0 (2 × CH_3–Si); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{29}H_{53}O_5Si$ 509.3662, found 509.3660, Δ = −0.5 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 212.3 (30%), 273.4 (28%), 509.5 (100%).

(1*R**,2*S**,3*R**, 4*R**,6*S**,7*R**,8*R**,9*S**,12*Z*)-3-(Methoxyethoxymethyloxy)-4-methyl-6-isopropenyl-13-methyl-15-oxatricyclo[6.6.1.0^{2,7}]-12-pentdecen-9-ol, MEM-(±)-412.[95]

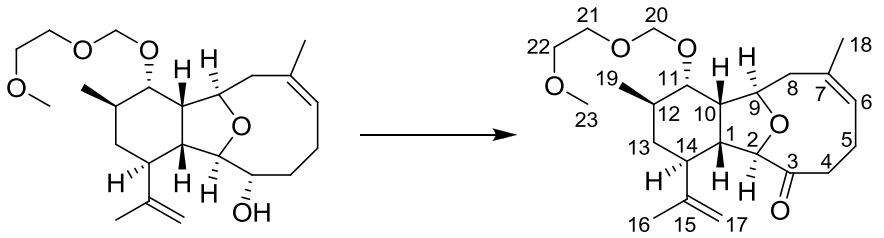


MEM-(±)-409 **MEM-(±)-412**

To a stirred solution of silyl ether **MEM**-(±)-**409** (35.0 mg, 68.8 μmol) in anhydrous THF (3 mL) at rt was added 4 Å molecular sieves and the resulting mixture stirred for 10 min. To this was added TBAF (137 μL of a 1.0 M solution in THF, 137 μmol) and the mixture stirred at rt for 1 h. The reaction was quenched using saturated aqueous NH_4Cl (3 mL). The aqueous phase was separated and extracted using EtOAc (3 × 10 mL). The organic phases were combined and washed with brine (10 mL), then dried ($MgSO_4$), filtered and

concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – diethyl ether, 2:1) afforded the alcohol **MEM**-(±)-**412** as a colourless solid (27 mg, 99%): R_f = 0.21 (petroleum ether – diethyl ether, 1:1); m.p. 83–85 °C; ν_{max} 3426, 2916, 1451, 1373, 1273, 1196, 1072, 1026 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.48 (1H, dd, *J* = 11.1, 5.8 Hz, CH-C6), 4.85 (1H, d, *J* = 6.8 Hz, CH_2-C20), 4.78 (1H, s, CH_2-C17), 4.77 (1H, s, CH_2-C17), 4.71 (1H, d, *J* = 6.8 Hz, CH_2-C20), 4.39–4.31 (1H, m, CH_2-C9), 3.88 (1H, ddd, *J* = 10.4, 4.8, 3.4 Hz, CH_2-C21), 3.65–3.59 (1H, m, CH_2-C21), 3.58–3.50 (2H, m, CH_2-C22), 3.48 (1H, dd, *J* = 10.6, 5.9 Hz, CH-C11), 3.43–3.32 (2H, m, CH-C2, CH-C3), 3.38 (3H, s, CH_3-C23), 2.90–2.71 (2H, m, CH_2-C5, CH_2-C8), 2.50–2.41 (1H, m, CH-C10), 2.19–2.13 (1H, m, CH-C1), 2.07 (1H, dt, *J* = 12.4, 3.2 Hz, CH-C14), 1.98 (1H, d, *J* = 14.8 Hz, CH_2-C8), 1.95–1.89 (1H, m, CH_2-C5), 1.84–1.74 (1H, m, CH-C12), 1.80 (3H, s, CH_3-C18), 1.74–1.60 (3H, m, CH_2-C4, CH_2-C13), 1.65 (3H, s, CH_3-C16), 1.09 (1H, ddd, *J* = 12.6, 12.6, 12.4 Hz, CH_2-C13), 10.2 (3H, d, *J* = 6.4 Hz, CH_3-C19); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.5 (C-C15), 132.9 (C-C7), 127.9 (CH-C6), 112.3 (CH_2-C17), 96.2 (CH_2-C20), 87.2 (CH-C2), 83.4 (CH-C11), 79.4 (CH-C9), 71.9 (CH_2-C22), 71.1 (CH-C3), 68.1 (CH_2-C21), 59.2 (CH_3-C23), 46.8 (CH-C1), 45.6 (CH-C14), 41.6 (CH-C10), 38.9 (CH_2-C13), 37.2 (CH_2-C8), 34.7 (CH_2-C4), 33.5 (CH-C12), 28.6 (CH_3-C18), 26.3 (CH_2-C5), 19.2 (CH_3-C16), 19.1 (CH_3-C19); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{23}H_{39}O_5$ 395.2797, found 395.2800, Δ = +0.7 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 163.2 (20%), 289.4 (100%), 395.4 (90%).

(1*R,2*S**,3*R**, 4*R**,6*S**,7*R**,8*R**,12*Z*)-3-(Methoxyethoxymethyloxy)-4-methyl-6-isopropenyl-13-methyl-15-oxatricyclo[6.6.1.0^{2,7}]-12-pentdecen-9-one, MEM-(±)-413.[28]**

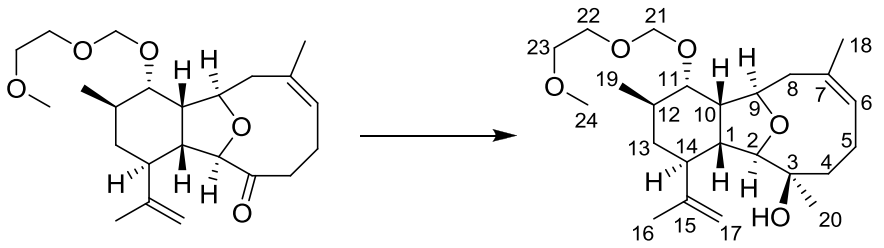


MEM-(±)-412 **MEM-(±)-413**

To a stirred solution of alcohol **MEM-(±)-412** (27.0 mg, 68.4 μmol) in anhydrous CH_2Cl_2 (3 mL) at rt was added pyridine (21.7 mg, 274 μmol) and the resulting solution stirred for 10 min. To this was added Dess–Martin periodinane (43.7 mg, 103 μmol) and the reaction stirred at rt for 30 min. The reaction was quenched using saturated aqueous $Na_2S_2O_3$/saturated aqueous $NaHCO_3$ (5:1, 3 mL) and stirred vigorously for 1 h. The aqueous phase was separated and extracted using CH_2Cl_2 (3 × 15 mL). The organic phases were combined and washed with brine (15 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – diethyl ether, 4:1) afforded the ketone **MEM-(±)-413** as a colourless oil (24 mg, 89%): R_f = 0.74 (petroleum ether – diethyl ether, 1:1); ν_{max} 2916, 2886, 1705, 1451, 1196, 1111, 1080, 1026 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.56 (1H, dd, *J* = 10.2, 6.7 Hz, CH-C6), 4.77 (1H, d, *J* = 6.8 Hz, CH_2-C20), 4.72 (2H, br s, CH_2-C17), 4.67 (1H, d, *J* = 6.8 Hz, CH_2-C20), 4.44–4.39 (1H, m, CH-C9), 3.95 (1H, s, CH-C2), 3.83 (1H, ddd, *J* = 10.7, 4.9, 3.7 Hz, CH_2-C21), 3.64–3.58 (1H, m, CH_2-C21), 3.57–3.49 (2H, m, CH_2-C22), 3.46 (1H, dd, *J* = 10.7, 6.3 Hz, CH-C11), 3.38 (3H, s, CH_3-C23), 3.08–2.94 (1H, m, CH_2-C5), 2.77 (1H, td, *J* = 12.0, 4.8 Hz, CH_2-C4), 2.72 (1H, dd, *J* = 11.8, 6.3 Hz, CH-C1), 2.63 (1H, br d, *J* = 13.2 Hz, CH_2-C8), 2.36 (1H, td, *J* = 8.5, 6.3 Hz, CH-C10), 2.30 (1H, dt, *J* = 12.0, 5.0 Hz, CH_2-C4), 2.14–2.03 (2H, m, CH-C14, CH_2-C5), 1.99 (1H, dd, *J* = 13.2, 5.9 Hz, CH_2-C8), 1.79–1.69 (1H, m, CH-C12), 1.74 (3H, s, CH_3-C18), 1.66–1.60 (1H, m, CH_2-C13), 1.62 (3H, s, CH_3-C16), 1.12 (1H, ddd, *J* = 12.9, 12.9, 12.9 Hz, CH_2-C13), 1.02 (3H, d, *J* = 6.4 Hz, CH_3-C19); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.7 (C-C3), 147.2 (C-C15), 134.6 (C-C7), 127.3 (CH-C6), 112.5 (CH_2-C17), 96.0 (CH_2-C20), 88.0 (CH-C2), 82.4 (CH-C11), 80.1 (CH-C9), 71.9 (CH_2-C22), 68.0 (CH_2-C21), 59.2 (CH_3-C23), 45.3 (CH-C14), 44.2 (CH-C10), 42.9 (CH-C1),

42.1 (CH_2-C4), 38.7 (CH_2-C8), 38.3 (CH_2-C13), 33.8 (CH-C12), 26.6 (CH_3-C18), 26.3 (CH_2-C5), 19.01 (CH_3-C16), 18.99 (CH_3-C19); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{23}H_{37}O_5$ 393.2641, found 393.2634, Δ = −1.9 ppm; LRMS (CI, Me_3CH) *m*/*z* (intensity) 287.3 (100%), 317.4 (85%), 393.4 (10%).

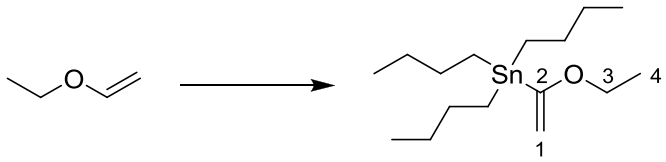
1*R,2*S**,3*R**, 4*R**,6*S**,7*R**,8*R**,9R*,12Z)-3-(Methoxyethoxymethyloxy)-4-methyl-6-isopropenyl-9-methyl-13-methyl-15-oxatricyclo[6.6.1.0^{2,7}]-12-pentdecen-9-ol, MEM-(±)-414.[95]**



To a stirred solution of ketone **MEM-(±)-413** (24.0 mg, 61.1 μmol) in anhydrous THF (3 mL) at −78 °C was added methylmagnesium chloride (204 μL of a 3.0 M solution in THF, 611 μmol) dropwise and the resulting solution stirred at −78 °C for 45 min. The reaction was allowed to warm to 0 °C over 1.5 h and then quenched using saturated aqueous $NaHCO_3$ (3 mL). The aqueous phase was separated and extracted using Et_2O (3 × 10 mL). The organic phases were combined and washed with brine (10 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – diethyl ether, 2:1) afforded the alcohol **MEM-(±)-414** as a colourless oil (22.7 mg, 91%): R_f = 0.26 (petroleum ether – diethyl ether, 2:1); ν_{max} 3511, 2916, 2886, 1451, 1373, 1188, 1103, 1034 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.89–5.79 (1H, m, CH-C6), 4.83 (1H, d, *J* = 6.8 Hz, CH_2-C21), 4.74 (2H, s, CH_2-C17), 4.69 (1H, d, *J* = 6.8 Hz, CH_2-C21), 4.41–4.29 (1H, m, CH-C9), 3.88 (1H, ddd, *J* = 10.6, 4.9, 3.4 Hz, CH_2-C22), 3.76–3.69 (1H, m, CH-C2), 3.61 (1H, ddd, *J* = 10.5, 6.2, 3.9 Hz, CH_2-C22), 3.56–3.52 (2H, m, CH_2-C23), 3.48 (1H, dd, *J* = 10.1, 6.5 Hz, CH-C11), 3.38 (3H, s, CH_3-C24), 3.31–3.16 (1H, m, CH_2-C5), 3.06–2.90 (1H, m, CH_2-C8), 2.72–2.58 (1H, m, CH-C10), 2.25 (1H, dd, *J* = 12.0, 6.3 Hz, CH-C1), 2.16–1.92 (2H, m, CH_2-C5, CH_2-C8), 2.06 (1H, ddd, *J* = 12.7, 12.0, 3.4 Hz, CH-C14), 1.88–1.68 (3H, m, CH-C12, CH_2-C4), 1.82 (3H, s, CH_3-C18), 1.66–

1.56 (1H, m, CH_2-C13), 1.63 (3H, s, CH_3-C16), 1.14 (1H, ddd, *J* = 13.0, 12.9, 12.7 Hz, CH_2-C13), 1.01 (3H, d, *J* = 6.4 Hz, CH_3-C19), 0.85 (3H, s, CH_3-C20); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.6 (C-C15), 136.6 (C-C7), 129.3 (CH-C6), 112.7 (CH_2-C17), 95.9 (CH_2-C21), 90.7 (CH-C2), 83.1 (CH-C11), 78.8 (CH-C9), 75.2 (CH-C3), 71.9 (CH_2-C23), 68.0 (CH_2-C22), 59.2 (CH_3-C24), 46.9 (CH-C14), 45.7 (CH-C1), 42.9 (CH-C10), 38.8 (CH_2-C4), 38.6 (CH_2-C13), 37.4 (CH_2-C8), 33.2 (CH-C12), 28.8 (CH_3-C18, CH_3-C20), 27.6 (CH_2-C5), 19.1 (CH_3-C19), 18.7 (CH_3-C16). HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{24}H_{41}O_5$ 409.2954, found 409.2960, Δ = +1.4 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 303.4 (100%), 333.4 (80%), 409.4 (48%).

2-(Ethoxy)-2-(tributylstannyl)ethene, 349.[117]

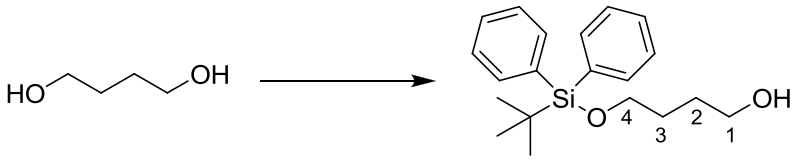


426 **349**

To a solution of ethyl vinyl ether **426** (5.77 g, 80.0 mmol) in anhydrous THF (55 mL) at −78 °C was added *tert*-butyl lithium (25.0 mL of a 1.6 M solution in pentanes, 40.0 mmol) dropwise over 10 min. The resulting bright yellow solution was stirred at −78 °C for 1.5 h and then allowed to warm to 0 °C over 50 min (the solution turned colourless). The reaction was stirred for a further 30 min at 0 °C and then cooled to −78 °C. To this was added tributyltin chloride (8.68g, 26.6 mmol) dropwise over 10 min and the resulting solution stirred at −78 °C for 20 min, then allowed to warm to rt. The reaction was quenched using water 15 mL) and the organic phase was separated and washed with water (3 × 20 mL) and brine (30 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Vacuum distillation (b.p. 125–130 °C at 12 mmHg) afforded the stannane **349** as a colourless oil (7.9 g, 82%): R_f = 0.86 (petroleum ether – diethyl ether, 9:1); ν_{max} 2955, 2924, 2870, 2855, 1566, 1456, 1373, 1180, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.67 (1H, br d, *J* = 1.6 Hz, CH-C1), 4.04 (1H, d, *J* = 1.6 Hz, CH-C1), 3.69 (2H, q, *J* = 7.0 Hz, CH_2-C3), 1.56–1.48 (6H, m, CH_2- *n*Bu), 1.36–1.29 (6H, m, CH_2- *n*Bu), 1.25 (3H, t, *J* = 7.0 Hz, CH_3-C4), 0.96–0.87 (15H, m, CH_2/CH_3- *n*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1 (C-

C2), 95.5 (CH_2-C1), 62.2 (CH_2-C3), 29.1 (CH_2– *n*Bu), 27.4 (CH_2– *n*Bu), 14.7 (CH_3-C4), 13.9 (CH_3–*n*Bu), 9.9 (CH_2–*n*Bu).

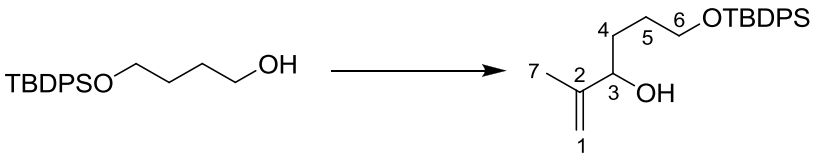
4-(*tert*-butyldiphenylsilyloxy)butan-1-ol, 291.



78 **291**

To a stirred solution of 1,4–butandiol **78** (1.00 g, 11.1 mmol) and triethylamine (1.54 mL, 11.1 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 °C was added a solution of *tert*–butyl(chloro)diphenylsilane (2.0 g, 7.4 mmol) in anhydrous CH_2Cl_2 (5 mL) dropwise and the resulting solution stirred at rt for 19 h. The reaction was quenched using water (50 mL). The organic phase was separated, washed with saturated aqueous NH_4Cl (30 mL), water (30 mL), brine (30 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. No further purification was required and the silyl–alcohol **291** was obtained as a colourless oil (2.33 g, 96%): R_f = 0.65 (petroleum ether – ethyl acetate, 4:1); ν_{max} 3356, 2940, 2862, 1466, 1427, 1389, 1111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68–7.66 (4H, m, CH–Ar), 7.45–7.37 (6H, m, CH–Ar), 3.71–3.67 (4H, CH_2-C1, CH_2-C4), 2.04 (1H, s, OH), 1.71–1.63 (4H, m, CH_2-C2, CH_2-C3), 1.06 (9H, s, 3 × CH_3–*t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7 (CH–Ar), 133.7 (C–Ar), 129.8 (CH–Ar), 127.8 (CH–Ar), 64.2 (CH_2-C1 or CH_2-C4), 63. 0 (CH_2-C1 or CH_2-C4), 30.0 (CH_2-C2 or CH_2-C3), 29.4 (CH_2-C2 or CH_2-C3), 27.0 (3 × CH_3–*t*Bu), 19.3 (C–*t*Bu); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{20}H_{29}O_2Si$ 329.1937, found 329.1938, Δ = +0.4 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 89.3 (55%), 251.3 (30%), 329.3 (100%); Anal. Calcd for $C_{20}H_{28}O_2Si$: C, 73.12%; H, 8.59%; Found: C, 73.06; H, 8.60%.

6-(*tert*-butyldiphenylsilyloxy)-2-methylhex-1-en-3-ol, (±)-292.



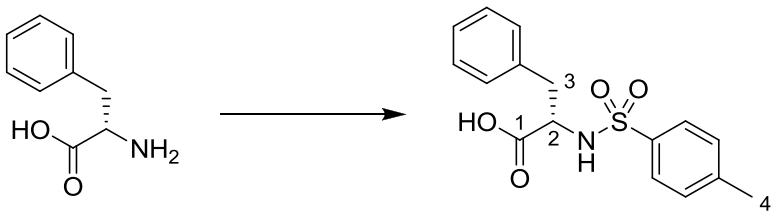
291 **(±)-292**

To a stirred solution of oxalyl chloride (407 µL, 4.75 mmol) in anhydrous CH_2Cl_2 (6mL) at −78 °C was added a solution of DMSO (371 mg, 5.74 mmol) in anhydrous CH_2Cl_2 (6 mL) dropwise and the resulting solution stirred at −78 °C for 15 min. To this was added a solution of alcohol **291** (1.30 g, 3.96 mmol) in anhydrous CH_2Cl_2 (6 mL) dropwise and the reaction stirred at −78 °C for 1 h. This was followed by the addition of triethylamine (2.75 mL, 19.8 mmol) and the resulting mixture stirred at rt for 1 h. The reaction was diluted with CH_2Cl_2 (20 mL) and saturated aqueous NH_4Cl (40 mL). The organic phase was separated and washed with brine (25 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude aldehyde was used without further purification.

To a slurry of magnesium turnings (192 mg, 7.91 mmol) and iodine (trace) in anhydrous THF (4 mL) at reflux was added a solution of 2-bromopropene (957 mg, 7.92 mmol) in anhydrous THF (16 mL) dropwise (1~2 mL of the solution added to initiate the reaction which was indicated by decolourisation of the reaction from dark brown to a cloudy colourless metallic white, followed by completion of the addition over 10 min). The reaction was stirred at rt for 1.5 h and then cooled to 0 °C. To this was added a solution of the crude aldehyde in anhydrous THF (6 mL) dropwise and the reaction stirred at 0 °C for 30 min. The reaction was quenched using saturated aqueous NH_4Cl (50 mL) and the aqueous phase was then separated and extracted using Et_2O (2 × 30 mL). The organic phases were combined and washed with brine (50 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – ethyl acetate, 19:1 to 9:1) afforded the allylic alcohol (±)-**292** as a cloudy white oil (1.20 g, 82%): R_f = 0.50 (petroleum ether – ethyl acetate, 9:1); ν_{max} 3356, 3071, 2932, 2862, 1458, 1427, 1389, 1111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (4H, d, *J* = 6.5 Hz, CH–Ar), 7.43–7.37 (6H, m, CH–Ar), 4.95 (1H, br s, CH_2-C1), 4.84 (1H, br, s, CH_2-C1), 4.09 (1H, s, CH-C3), 3.68 (2H, t, *J* = 5.8 Hz, CH_2-C6), 2.04 (1H, d, *J* = 3.8 Hz, OH), 1.73 (3H, s, CH_3-C7), 1.68–1.61 (4H, m, CH_2-C4, CH_2-C5), 1.05 (9H, s, 3 × CH_3-*t*Bu); ^{13}C NMR (100

MHz, $CDCl_3$) δ 147.6 (C-C2), 135.7 (CH–Ar), 133.9 (C–Ar), 129.8 (CH–Ar), 127.8 (CH–Ar), 111.1 (CH_2-C1), 75.7 (CH-C3), 64.1 (CH_2-C6), 31.9 (CH_2-4 or CH_2-C5), 28.7 (CH_2-4 or CH_2-C5), 27.0 (3 × CH_3-*t*Bu), 19.3 (C-*t*Bu), 17.9 (CH_3-C7); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{23}H_{33}O_2Si$ 369.2250, found 369.3348, Δ = −0.6 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 95.1 (100%), 351.1 (67%), 369.1 (60%); Anal. Calcd for $C_{23}H_{32}O_2Si$: C, 74.95%; H, 8.75%; Found: C, 74.55%; H, 8.98%.

(*S*)-2-(4-Methylphenylsulfonamido)-3-phenylpropanoic acid, (*S*)-306.[144]

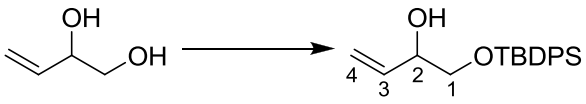


427 (***S***)-**306**

To a stirred solution of (L)-phenylalanine **427** (2.00 g, 12.1 mmol) and sodium hydroxide (484 mg, 12.1 mmol) in water (20 mL) was added a solution of *para*-toluenesulfonyl chloride (2.54 g, 13.3 mmol) in Et_2O (10 mL). The biphasic solution was stirred vigorously for 4 h with the addition of aqueous 5.0 M sodium hydroxide (1 mL per hour). The reaction was acidified using conc. HCl (37% w/v, 2.5 mL) and the aqueous phase separated and extracted using Et_2O (3 × 20 mL). The organic phases were combined and washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was dissolved in Et_2O (100 mL) and water (100 mL) and neutralised to pH 7 using $NaHCO_3$ (s). The aqueous phase was separated and extracted using Et_2O (3 × 50 mL). The organic phases were combined and washed with brine (50 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo* affording the carboxylic acid (***S***)-**306** as a colourless solid (3.62 g, 94%): R_f = 0.60 (dichloromethane – methanol, 9:1); ν_{max} 3403, 1597, 1404, 1304, 1157, 1096, 1026 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.60 (2H, d, *J* = 8.3 Hz, CH-tolyl), 7.26 (2H, d, *J* = 8.0 Hz, CH-tolyl), 7.21–7.11 (5H, m, CH-Ph), 3.77 (1H, dd, *J* = 6.5, 5.0 Hz, CH-C2), 3.02 (1H, dd, *J* = 13.6, 5.0 Hz, CH_2-C3), 2.92 (1H, dd, *J* = 13.6, 6.5 Hz, CH_2-C3), 2.39 (3H, s, CH_3-C4); ^{13}C NMR (100 MHz, CD_3OD) δ 177.0 (C-C1),

144.3 (C–Ar), 139.0 (C–Ar), 138.8 (C–Ar), 131.0 (CH–Ar), 130.6 (CH–Ar), 128.9 (CH–Ar), 128.2 (CH–Ar), 127.2 (CH–Ar), 60.5 (CH-C2), 40.7 (CH_2-C3), 21.4 (CH_3-C4).

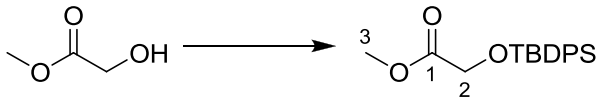
1-(*tert*-Butyldiphenylsilyloxy)but-3-en-2-ol, (±)-368.[145]



(±)-367 **(±)-368**

To a stirred solution of (±)-3-butene-1,2-diol (±)-**367** (4.00 g, 45.4 mmol), triethylamine (12.7 mL, 91.0 mmol) and DMAP (555 mg, 4.54 mmol) in anhydrous THF (300 mL) at rt was added a solution of *tert*-butylcholordiphenylsilane (13.7 g, 49.9 mmol) in anhydrous THF (100 mL) via cannula. The reaction was stirred at rt for 66 h, filtered under reduced pressure to remove the salt precipitate and the resulting filtrate concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – diethyl ether, 9:1) afforded the allylic alcohol (±)-**368** as a colourless oil (12.8 g, 86%): R_f = 0.49 (petroleum ether – diethyl ether, 4:1); ν_{max} 3410, 3071, 2932, 2862, 1466, 1427, 1111, 1065 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74–7.65 (4H, m, CH–Ar), 7.47–7.36 (6H, m, CH-Ar), 5.79 (1H, ddd, *J* = 17.2, 10.6, 5.6 Hz, CH-C3), 5.32 (1H, td, *J* = 17.2, 1.4 Hz, CH_2-C4), 5.17 (1H, td, *J* = 10.6, 1.3 Hz, CH_2-C4), 4.27–4.22 (1H, m, CH-C2), 3.70 (1H, dd, *J* = 10.2, 3.7 Hz, CH_2-C1), 3.55 (1H, dd, *J* = 10.2, 7.5 Hz, CH_2-C1), 2.62 (1H, d, *J* = 3.8 Hz, OH), 1.08 (9H, s, 3 × CH_3-*t*Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8 (CH-C3), 135.73 (CH-Ar), 135.69 (CH–Ar), 133.3 (C–Ar), 133.2 (C–Ar), 130.0 (CH–Ar), 127.9 (CH–Ar), 116.7 (CH_2-C4), 73.2 (CH-C2), 67.9 (CH_2-C1), 27.0 (3 × CH_3-*t*Bu), 19.4 (C-*t*Bu); HRMS (CI, Me_3CH) $[M-H_2O+H]^+$ calcd for $C_{20}H_{25}OSi$ 309.1675, found 309.1681, Δ = +1.9 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 199.2 (40%), 249.3 (100%), 309.3 (45%).

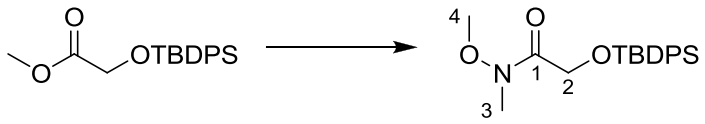
Methyl 2-(*tert*-butyldiphenylsilyloxy)acetate, 371.[121]



370 **371**

To a stirred solution of methyl glycolate **370** (2.00 g, 11.1 mmol), imidazole (907 mg, 13.3 mmol) and DMAP (271 mg, 2.22 mmol) in anhydrous DMF (18 mL) at 0 °C was added *tert*-butylchlorodiphenylsilane (3.36 g, 12.2 mmol) dropwise. The resulting solution was stirred at rt for 18 h. The reaction was quenched using water (50 mL) and diluted with Et_2O (60 mL). The organic phase was separated and washed with saturated aqueous NH_4Cl (50 mL) and water (50 mL). The combined aqueous phase was extracted using Et_2O (3 × 25 mL). The organic phases were combined and washed with brine (50 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – diethyl ether, 49:1 to 9:1) afforded the ester **371** as a colourless oil (3.52 g, 97%): R_f = 0.53 (petroleum ether – diethyl ether, 9:1); ν_{max} 3071, 2932, 2855, 1767, 1427, 1288, 1211, 1111, 1003 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71–7.68 (4H, m, CH–Ph), 7.46–7.37 (6H, m, CH–Ph), 4.25 (2H, s, CH_2-C2), 3.69 (3H, s, CH_3-C1), 1.09 (9H, s, 3 × CH_3–*t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8 (C-C1), 135.7 (CH–Ph), 133.0 (C–Ph), 130.0 (CH–Ph), 127.9 (CH–Ph), 62.3 (CH_2-C2), 51.8 (CH_3-C3), 26.1 (3 × CH_3–*t*Bu), 19.4 (C–*t*Bu); Anal. Calcd for $C_{19}H_{24}O_3Si$: C, 69.46%; H, 7.38%; Found: C, 69.49%; H, 7.38%.

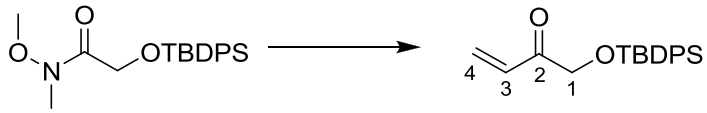
2-(*tert*-Butyldiphenylsilyloxy)-*N*-methoxy-*N*-methylacetamide, 373.[122]



371 **373**

To a stirred slurry of ester **371** (2.3 g, 7.0 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (1.06 g, 10.9 mmol) in anhydrous THF (14 mL) at −20 °C was added isopropylmagnesium chloride (10.5 mL of a 2.0 M solution in THF, 21.0 mmol) dropwise over 10 min. The resulting solution was stirred at −20 °C for 20 min and then quenched using saturated aqueous NH_4Cl (10 mL). The reaction was allowed to warm to rt and diluted with water (50 mL) and Et_2O (100 mL). The aqueous phase was separated and extracted using Et_2O (2 × 30 mL). The organic phases were combined and washed with brine (50 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – diethyl ether, 19:1 to 0:1) afforded the Weinreb amide **373** as a colourless crystalline solid (2.30 g, 92%): R_f = 0.61 (petroleum ether – ethyl acetate, 2:1); m.p. 49–51 °C; ν_{max} 3048, 2932, 2855, 1690, 1427, 1327, 1157, 1111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74–7.71 (4H, m, CH–Ar), 7.45–7.37 (6H, m, CH–Ar), 4.42 (2H, s, CH_2-C2), 3.44 (3H, s, CH_3-C4), 3.13 (3H, s, CH_3-C3), 1.10 (9H, s, 3 × CH_3–*t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.6 (C-C1),135.8 (CH–Ph), 133.3 (C–Ph), 129.9 (CH–Ph), 127.9 (CH–Ph), 62.2 (CH_2-C2), 61.3 (CH_3-C4), 32.6 (CH_3-C3), 26.9 (3 × CH_3–*t*Bu), 19.5 (C–*t*Bu); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{20}H_{28}NO_3Si$ 358.1838, found 358.1840, Δ = +0.4 ppm; LRMS (CI, Me_3CH) *m*/*z* (intensity) 250.3 (80%), 301.3 (100%), 322.3 (55%), 358.3 (60%); Anal. Calcd for $C_{20}H_{27}NO_3Si$: C, 67.18%; H, 7.63%; N, 3.92%; Found: C, 67.35%; H, 7.72%, N, 4.05%.

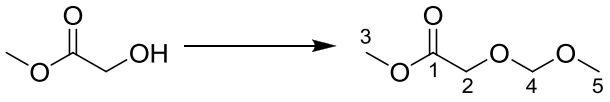
1-(*tert*-Butyldiphenylsilyloxy)but-3-en-2-one, 369.[123]



373 **369**

To a stirred solution of Weinreb amide **373** (230 mg, 640 μmol) in anhydrous THF (3 mL) at rt was added vinylmagnesium bromide (2.57 mL of a 1.0 M solution in THF, 2.57 mmol) dropwise over 5 min. The resulting yellow solution was stirred at rt for 16 h. The reaction was diluted with EtOAc (30 mL) and washed vigorously with aqueous HCl (1.0 M, 20 mL), followed by saturated aqueous $NaHCO_3$ (20 mL). The aqueous phase was separated and extracted using EtOAc (2 × 20 mL). The organic phases were combined and washed with brine (30 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – diethyl ether, 19:1) afforded the enone **369** as a colourless oil (107 mg, 82%): R_f = 0.51 (petroleum ether – ethyl acetate, 9:1); ν_{max} 3071, 2955, 2932, 2893, 2862, 1705, 1466, 1427, 1397, 1111, 1065 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67–7.65 (4H, m, CH–Ar), 7.46–7.37 (6H, m, CH–Ar), 6.70 (1H, dd, *J* = 17.5, 10.6 Hz, CH-C3), 6.32 (1H, dd, *J* = 17.5, 1.6 Hz, CH_2-C4), 5.77 (1H, dd, *J* = 10.6, 1.6 Hz, CH_2-C4), 4.38 (2H, s, CH_2-C1), 1.10 (9H, s, 3 × CH_3–*t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0 (C-C2), 135.9 (CH–Ar), 132.8 (C–Ar), 131.9 (CH-C3), 130.1 (CH–Ar), 129.1 (CH_2-C4), 128.0 (CH–Ar), 69.1 (CH_2-C1), 26.9 (3 × CH_3–*t*Bu), 19.4 (C–*t*Bu); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{20}H_{25}O_2Si$ 325.1624, found 325.1627, Δ = +0.9 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 71.1 (38%), 247.3 (100%), 257.3 (30%), 325.4 (5%); Anal. Calcd for $C_{20}H_{24}O_2Si$: C, 74.02%; H, 7.47%; Found: C, 75.82%; H, 7.97%.

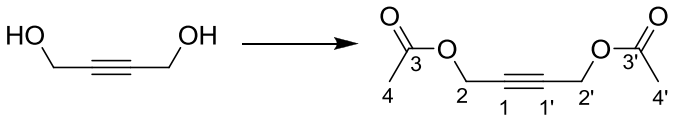
Methyl 2-{[(methoxy)methyl]oxy}acetate, 377.[146]



370 **377**

To a stirred solution of methyl glycolate **370** (2.00 g, 22.2 mmol) and lithium bromide (386 mg, 4.44 mmol) in dimethoxymethane (42 mL) was added *para*–toluenesulfonic acid monohydrate (422 mg, 2.22 mmol) and the resulting mixture stirred at rt for 64 h. The reaction was diluted with brine (50 mL) and Et_2O (50 mL). The aqueous phase was separated and extracted using Et_2O (3 × 25 mL). The organic phases were combined and then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (cyclohexane – ethyl acetate, 1:0 to 0:1) afforded the ester **377** as a colourless oil (970 mg, 31%): R_f = 0.22 (cyclohexane – ethyl acetate, 9:1); ν_{max} 2924, 1759, 1443, 1265, 1211, 1150, 1119, 1057 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.70 (2H, s, CH_2-C4), 4.17 (2H, s, CH_2-C2), 3.76 (3H, s, CH_3-C5), 3.39 (3H, s, CH_3-C3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7 (C-C1), 96.6 (CH_2-C4), 64.4 (CH_2-C2), 55.9 (CH_3-C3), 52.0 (CH_3C5); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_5H_{11}O_4$ 135.0657, found 135.0657, Δ = −0.4 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 69.1 (17%), 103.2 (100%), 135.2 (78%).

But-2-yne-1,4-diyl diacetate, 429.[147]

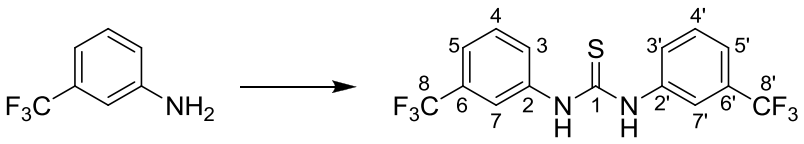


428 **429**

A round bottom flask was charged with 2–butyne–1,4–diol **428** (2.00 g, 23.2 mmol) and acetic anhydride (5.34 g, 52.3 mmol) and heated to 100 °C for 2 h with stirring. The reaction was allowed to cool to rt. Vacuum distillation (b.p. 135–140 °C at 4 mmHg) afforded the diacetate **429** as a colourless oil (3.71 g, 94%): R_f = 0.44 (petroleum ether –

diethyl ether, 9:1); ν_{max} 1743, 1435, 1373, 1211, 1150, 1026 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71 (4H, s, CH_2-C2, CH_2-C2'), 2.10 (6H, s, CH_3-C4, CH_3-C4'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3 (C-C3, C-C3'), 80.9 (C-C1, C-C1'), 52.2 (CH_3-C4, CH_3-C4'), 20.8 (CH_2-C2, CH_2-C2'); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_8H_{11}O_4$ 171.0657, found 171.0660, Δ = +1.4 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 69.1 (15%), 111.2 (100%), 171.3 (50%); Anal. Calcd for $C_8H_{10}O_4$: C, 56.46%; H, 5.93%; Found: C, 56.38%; H, 5.97%.

1,3-bis(3-(Trifluoromethyl)phenyl)thiourea, 384.[148]

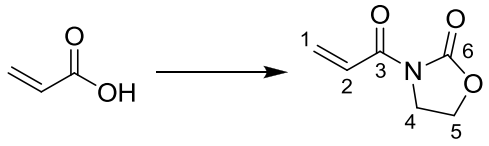


430 **384**

To a stirred solution of 3-(trifluoromethyl)aniline **430** (2.00 g, 12.4 mmol) and triethylamine (2.08 mL, 14.9 mmol) in anhydrous THF (90 mL) at 0 °C was added a solution of thiophosgene (614 mg, 5.34 mmol) in anhydrous THF (10 mL) dropwise. The resulting solution was stirred at rt for 18 h. The reaction was concentrated *in vacuo* and the resulting residue was partitioned between in water (70 mL) and Et_2O (50 mL). The aqueous phase was separated and extracted using Et_2O (2 × 50 mL). The organic phases were combined and washed with brine (50 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was recrystalised from $CHCl_3$ (20 mL) and collected by filtration. The resulting yellow/orange solid was dissolved in a minimum volume of Et_2O, precipitated out of solution using *n*-hexane and collected by vacuum filtration. The resulting solid was placed under high vacuum for 18 h, affording the thiourea **384** as a yellow solid (1.49 g, 77%): m.p. = thermal decomp. at >200 °C; ν_{max} 3210, 3048, 1535, 1497, 1451, 1327, 1165, 1126, 1072 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.89 (2H, s, CH-C7, CH-C7'), 7.72 (2H, d, *J* = 8.0 Hz, CH-C5, CH-C5'), 7.53 (2H, t, *J* = 7.9 Hz, CH-C4, CH-C4'), 7.45 (2H, d, *J* = 7.7 Hz, CH-C3, CH-C3'), 3.31 (2H, s, NH); ^{13}C NMR (100 MHz, CD_3OD) δ 182.5 (C-C1), 141.3 (CH-Ar), 132.0 (CF_3, q, $J_{C\text{-}F}$ = 32.5 Hz, CF_3-C8, CF_3-C8'), 130.5 (CH-Ar), 128.7 (CH-Ar), 126.8 (C-Ar), 124.1 (C-Ar), 122.7 (CH-Ar), 121.9 (CH-Ar); LRMS (CI, Me_3CH) $[M+H]^+$ *m/z* (intensity) 162.1 (25%), 331.2 (100%),

365.4 (8%); Anal. Calcd for $C_{15}H_{10}F_6N_2S$: C, 49.45%; H, 2.77%; N, 7.69%; Found: C, 49.28%; H, 2.80%; N, 7.68%.

3-Acryloyloxazolidin-2-one, 387.[149]



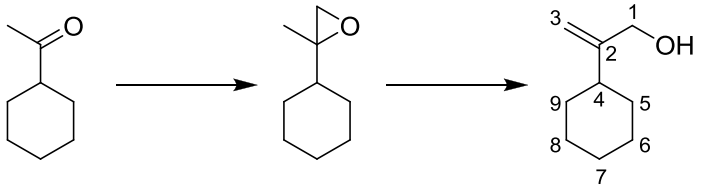
431 **387**

To a stirred solution of freshly distilled acrylic acid **431** (721 mg, 10.0 mmol) in anhydrous Et_2O (50 mL) was added triethylamine (1.39 mL, 10.0 mmol) at 0 °C and the resulting solution stirred for 5 min. To this was added acryloyl chloride (905 mg, 10.0 mmol) dropwise over 2 min with the immediate formation of a colourless precipitate. The resulting mixture was stirred at 0 °C for 40 min, followed by 30 min at rt. The reaction mixture was filtered under reduced pressure, washing the salt precipitate cake with Et_2O (100 mL). The filtrate was concentrated *in vacuo* and the resulting residue dissolved in THF (20 mL).

To a suspension of 2–oxazolidinone (697 mg, 8.00 mmol) and lithium chloride (424 mg, 10.0 mmol) in anhydrous THF (20 mL) was added the solution of the anhydride. The resulting mixture was stirred at rt for 3 h. The reaction was concentrated *in vacuo* and the resulting residue dissolved in CH_2Cl_2 (50 mL) and diluted with aqueous HCl (1.0 M, 50 mL). The aqueous phase was separated and extracted using CH_2Cl_2 (3 × 50 mL). The organic phases were combined and washed with a mixture of saturated aqueous $NaHCO_3$ solution and water (1:1, 50 mL), followed by brine (50 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – diethyl ether, 4:1 to 1:1) afforded the enone **387** as a yellow crystalline solid (450 mg, 40%): R_f = 0.50 (diethyl ether – petroleum ether, 4:1); m.p. 79–81 °C; ν_{max} 1775, 1690, 1412, 1397, 1319, 1234, 1126, 1065, 1026 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (1H, dd, *J* = 17.0, 10.5 Hz, CH-C2), 6.57 (1H, dd, *J* = 17.0, 1.8 Hz, CH_2-C1), 5.91 (1H, dd, *J* = 10.5, 1.8 Hz, CH_2-C1), 4.45 (2H, t, *J* = 8.3 Hz, CH_2-C5), 4.09 (2H, t, *J* = 8.3 Hz, CH_2-C4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2 (C-C6), 153.5 (C-C3), 132.0 (CH_2-C1), 127.1 (CH-C2),

62.3 (CH_2-C5), 42.7 (CH_2-C4); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_6H_8NO_3$ 142.0504, found 142.0507, Δ = +1.7 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 69.1 (15%), 85.2 (10%), 142.2 (100%); Anal. Calcd for $C_6H_7NO_3$: C, 51.06%; H, 5.01%; N, 9.92%; Found: C, 51.15%; H, 5.00%; N, 9.77%.

2-Cyclohexylprop-2-en-1-ol, 400.[130]



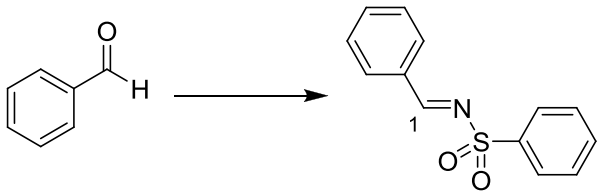
397 **399** **400**

To a stirred solution of cyclohexylmethyl ketone **397** (253 mg, 2.00 mmol) in anhydrous THF (8 mL) at rt was added dimethylsulfoniummethyl ylide (1.50 mL of a 0.67 M solution in THF, 1.00 mmol) dropwise and the resulting solution stirred rt for 72 h. The reaction was diluted with water (10 mL) and EtOAc (20 mL). The aqueous phase was separated and extracted using EtOAc (3 × 10 mL). The organic phases were combined and washed with brine (20 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – diethyl ether, 19:1) afforded the epoxide **399** as a colourless oil that was found to be volatile.

To a stirred solution of diisopropylamine (506 mg, 5.00 mmol) in anhydrous Et_2O (60 mL) at rt was added *n*-butyl lithium (2.0 mL of a 2.5 M solution in hexanes, 5.0 mmol) dropwise and the resulting solution stirred at rt for 30 min. To this was added a solution of epoxide **399** in anhydrous Et_2O (10 mL) and the resulting solution stirred at rt for 19 h. The reaction was quenched using water (10 mL). The aqueous phase was separated and extracted using Et_2O (3 × 110 mL). The organic phases were combined and washed with brine (20 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether – diethyl ether, 9:1) afforded the allylic alcohol **400** as a colourless oil (109 mg, 78%): R_f = 0.18 (petroleum ether – diethyl ether, 9:1); ν_{max} 3318, 2924, 2855, 1651, 1451, 1065, 1026 cm^{-1}; ^1H NMR (500 MHz,

$CDCl_3$) δ 5.05–4.95 (1H, m, CH_2-C3), 4.88–4.86 (1H, m, CH_2-C3), 4.12 (2H, d, *J* = 5.7 Hz, CH_2-C1), 1.98–1.90 (1H, m, CH-C4), 1.81–1.74 (4H, m, CH_2-C5, CH_2-C6, CH_2-C7, CH_2-C9), 1.71–1.65 (1H, m, CH_2-C7), 1.38 (1H, t, *J* = 6.0 Hz, OH), 1.34–1.12 (5H, m, CH_2-C5, CH_2-C6, CH_2-C8, CH_2-C9); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6 (C-C2), 107.5 (CH_2-C3), 65.2 (CH_2-C1), 41.3 (CH-C4), 32.5 (CH_2-C5, CH_2-C9), 26.7 (CH_2-C6, CH_2-C8), 26.3 (CH_2-C7); Anal. Calcd for $C_9H_{16}O$: C, 77.07%; H, 11.52%; Found: C, 76.98; H, 11.61%.

(E)-*N*-benzylidenebenzenesulfonamide, 433.[150]

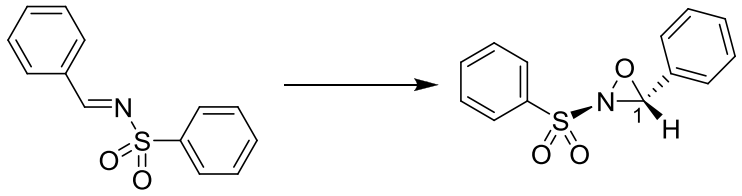


432 **433**

To a flame dried 100 mL round bottom flask equipped with a magnetic stirrer bar, Dean-Stark adaptor and condenser, under an argon atmosphere was added 4 Å molecular sieves, Amberlite IR-200(PLUS) ion-exchange resin$^{(TM)}$ (100 mg), benzenesulfonamide (3.00 g, 19.1 mmol), freshly distilled benzaldehyde **432** (2.03 g, 19.1 mmol) and toluene (50 mL) and the resulting mixture heated to reflux for 17 h. The reaction was allowed to cool to rt, filtered under reduced pressure and the solid rinsed using toluene. The filtrate was concentrated *in vacuo* and triturated using *n*-hexane. The resulting solid was filtered off and the product was recrystalised by dissolving the solid in EtOAc (10mL) with gentle warming (>40 °C), allowing to cool to rt and diluting with *n*-hexane (100mL). The precipitated solids were broken up over 2 h, filtered off and placed under high vacuum for 17 h affording the product **433** as colourless crystalline solid (3.00 g, 64%): R_f = 0.40 (petroleum ether – diethyl ether, 2:1); m.p. 75–79 °C; ν_{max} 1605, 1574, 1451, 1319, 1157, 1088 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (1H, s, CH-C1), 8.04–8.00 (2H, m, CH-Ph), 7.97–7.93 (2H, m, CH-Ph), 7.67–7.47 (6H, m, CH-Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8 (CH-C1), 138.4 (C-Ph), 135.2 (CH-Ph), 133.7 (CH-Ph), 132.5 (C-Ph), 131.5 (CH-Ph), 129.3 (CH-Ph), 128.8 (CH-Ph), 128.2 (CH-Ph), 126.6 (CH-Ph); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{13}H_{12}NO_2S$ 246.0589, found 246.0592, Δ = +1.3 ppm; LRMS (CI, Me_3CH)

m/*z* (intensity) 69.1 (20%), 158.2 (15%), 246.2 (100%); Anal. Calcd for $C_{13}H_{11}NO_2S$: C, 63.65%; H, 4.53%; N, 5.71%; Found: C, 62.19%; H, 4.48%; N, 5.90%.

(±)-trans-2-(Phenylsulfonyl)-3-phenyloxaziridine, 394.[150]



433 **394**

A mixture of *N*-benzylidenebenzenesulfonamide **433** (1.00 g, 4.08 mmol) and BTEAC (103 mg, 450 μmol) in saturated aqueous $NaHCO_3$ (10 mL) and $CHCl_3$ (10 mL) was stirred vigorously at 0 °C for 5 min. To this was added a solution of *m*-CPBA (1.03 g, 4.48 mmol) in $CHCl_3$ (20 mL) dropwise over 10 min and the biphasic solution stirred at 0 °C for 1 h. The reaction was diluted with water (20 mL). The organic phase was separated and washed with aqueous Na_2SO_3 (10% w/v, 15 mL), water (15 mL) and brine (20 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo* (<40 °C). The resulting residue was triturated using *n*-hexane, dissolved in a minimal volume of EtOAc, filtered, diluted with *n*-hexane (100 mL) and stored at −18 °C for 20 h. Filtration of the resulting precipitate afforded the oxaziridine **394** as a colourless solid (712 mg, 67%): ν_{max} 2353, 2338, 1451, 1350, 1242, 1173, 1088 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08–8.05 (2H, m, CH–Ar), 7.79–7.75 (1H, m, CH–Ar), 7.66–7.63 (2H, m, CH–Ar), 7.49–7.37 (5H, m, CH–Ar), 5.49 (1H, s, CH-C1); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.2 (C–Ar), 131.6 (C–Ar), 129.54 (CH-Ar), 129.53 (CH–Ar), 128.9 (CH–Ar), 128.4 (CH–Ar), 76.5 (CH-C1); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{13}H_{12}NO_3S$ 262.0538, found 262.0536, Δ = −0.8 ppm; LRMS (CI, Me_3CH) *m*/*z* (intensity).

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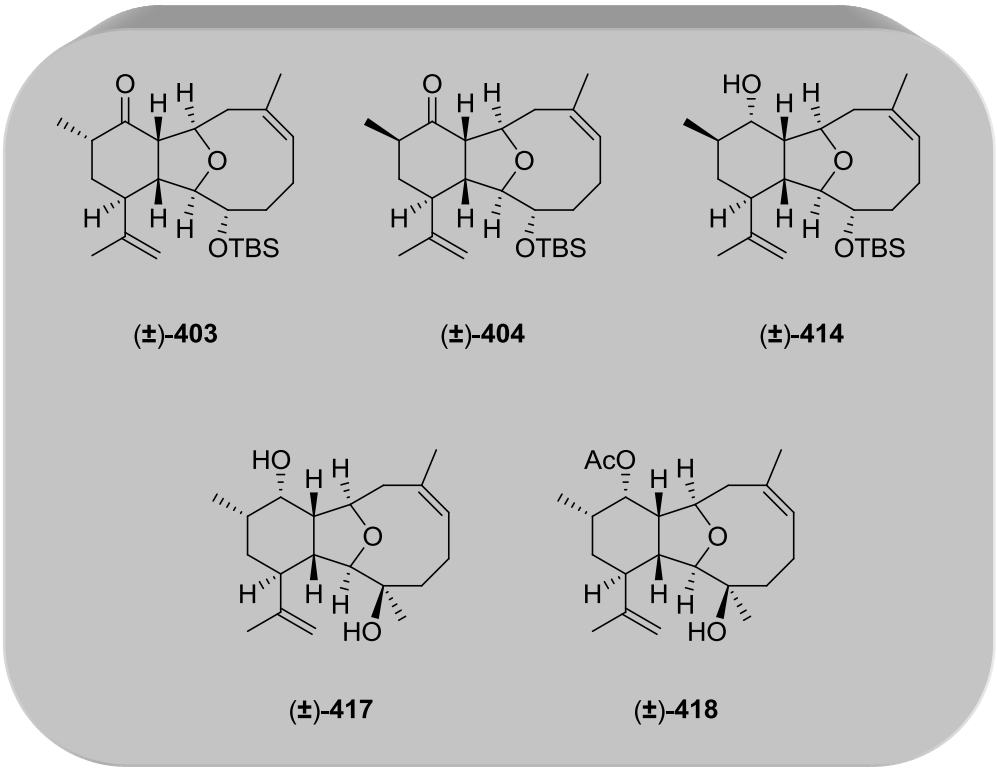
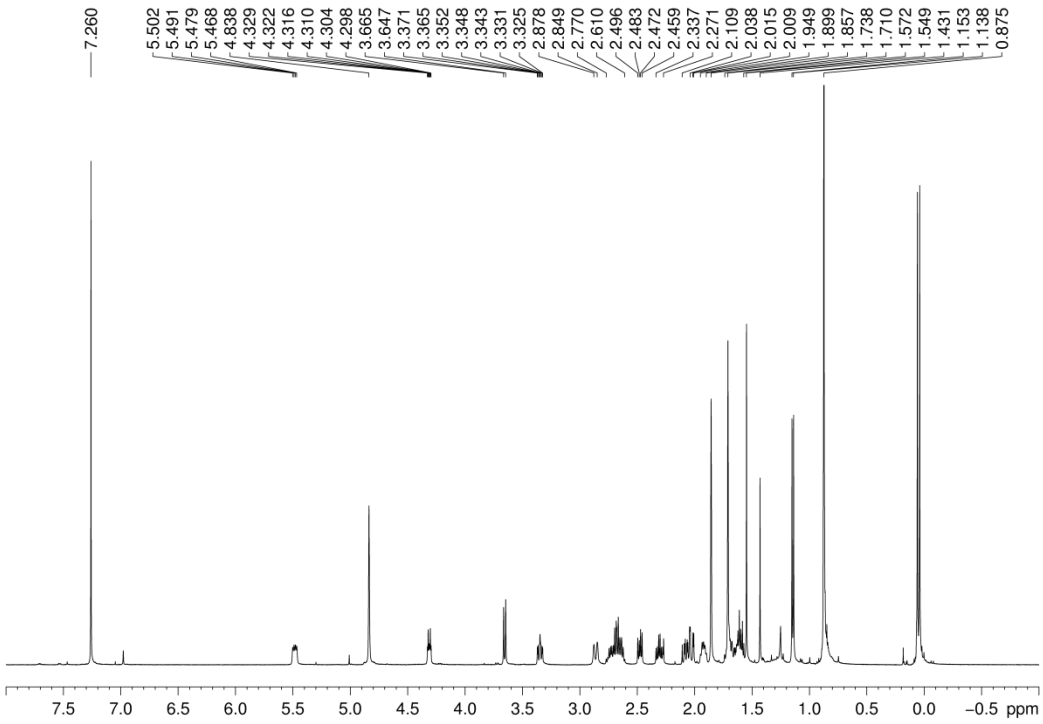
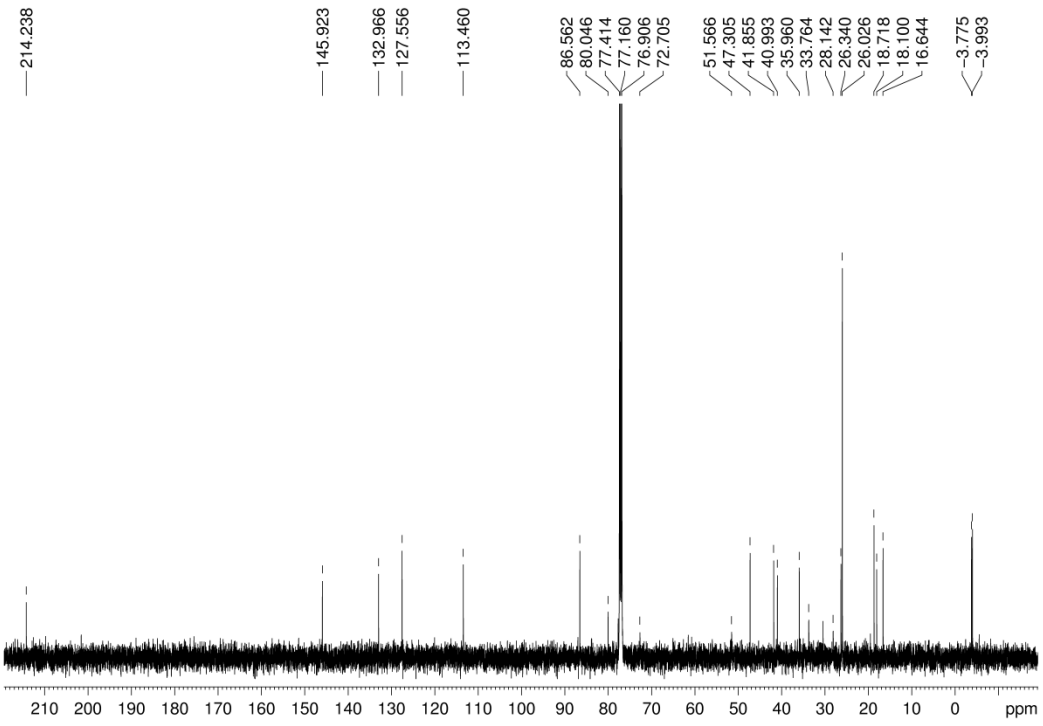
6 Appendices

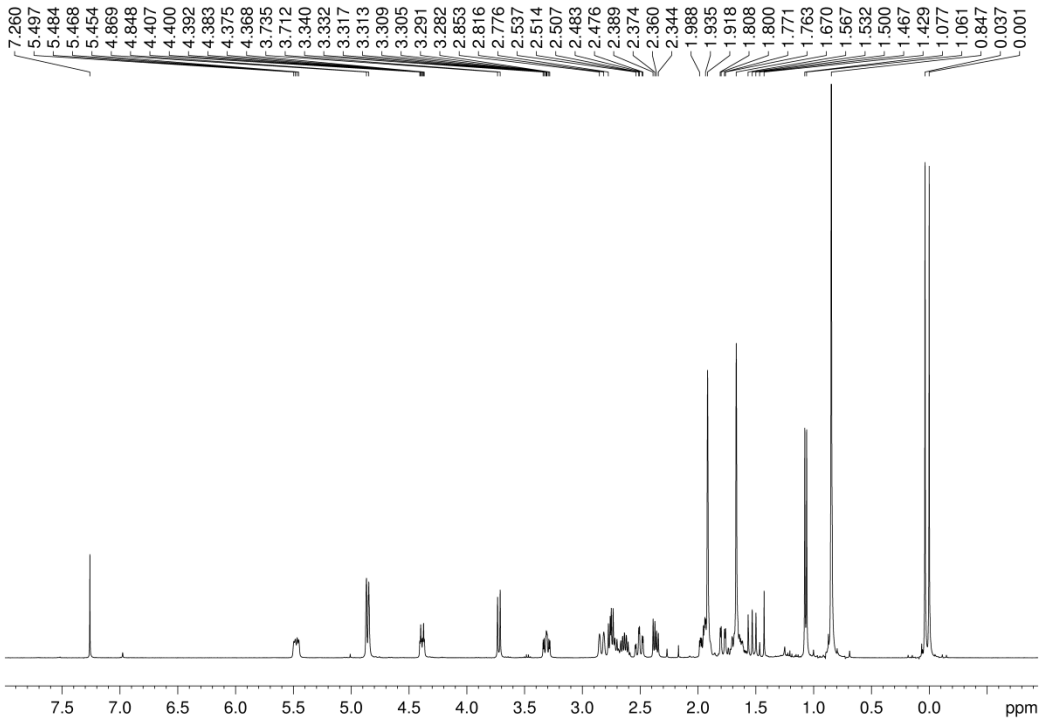


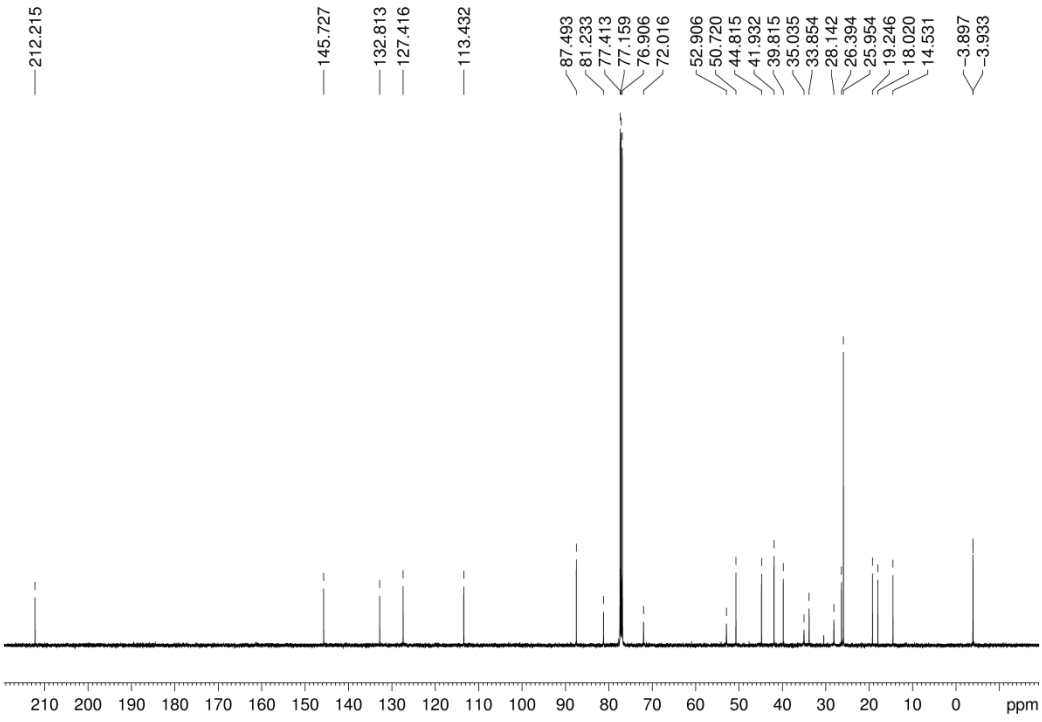
Appendix 1: ^{1}H and ^{13}C NMR of Compound (±)-**403**



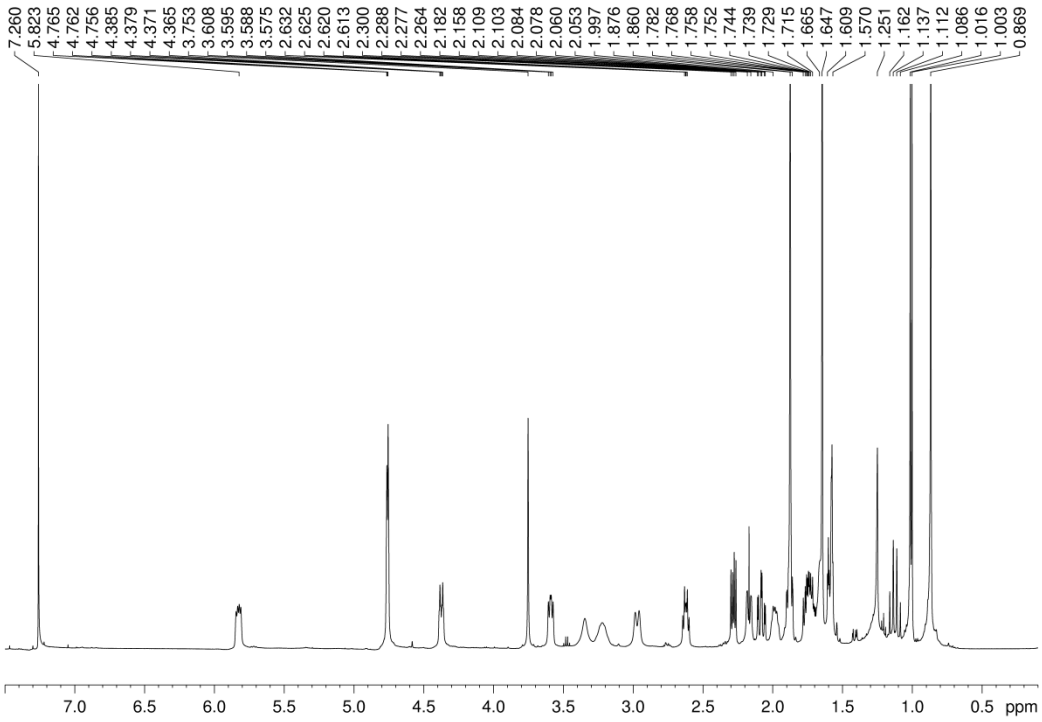


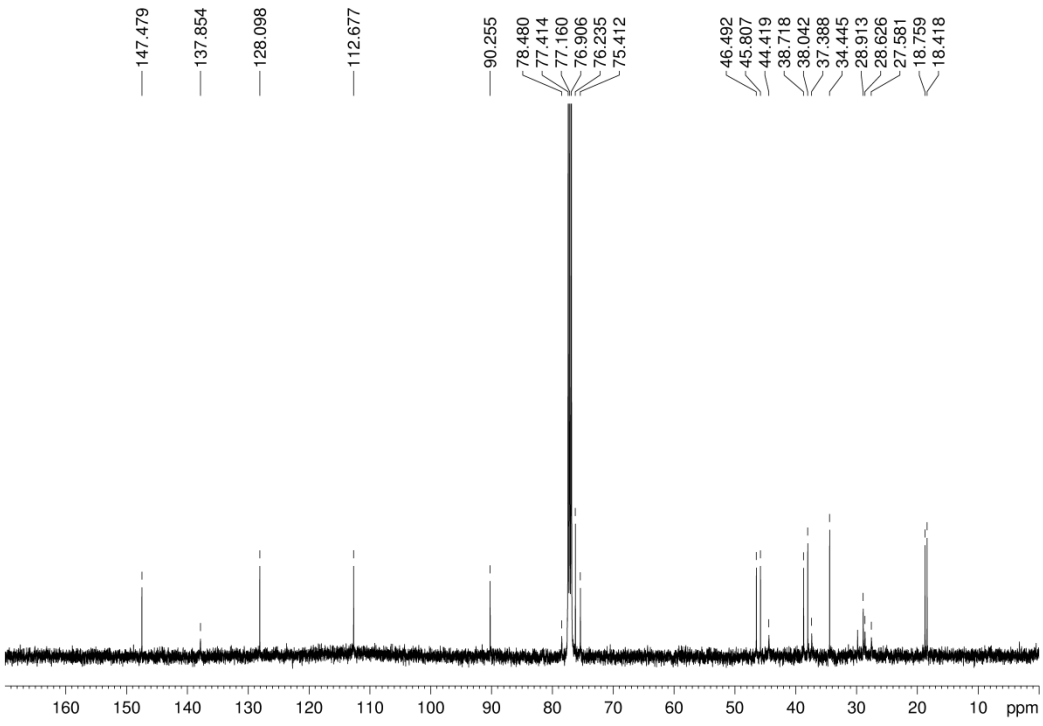
Appendix 2: ^{1}H and ^{13}C NMR of Compound (±)-**404**



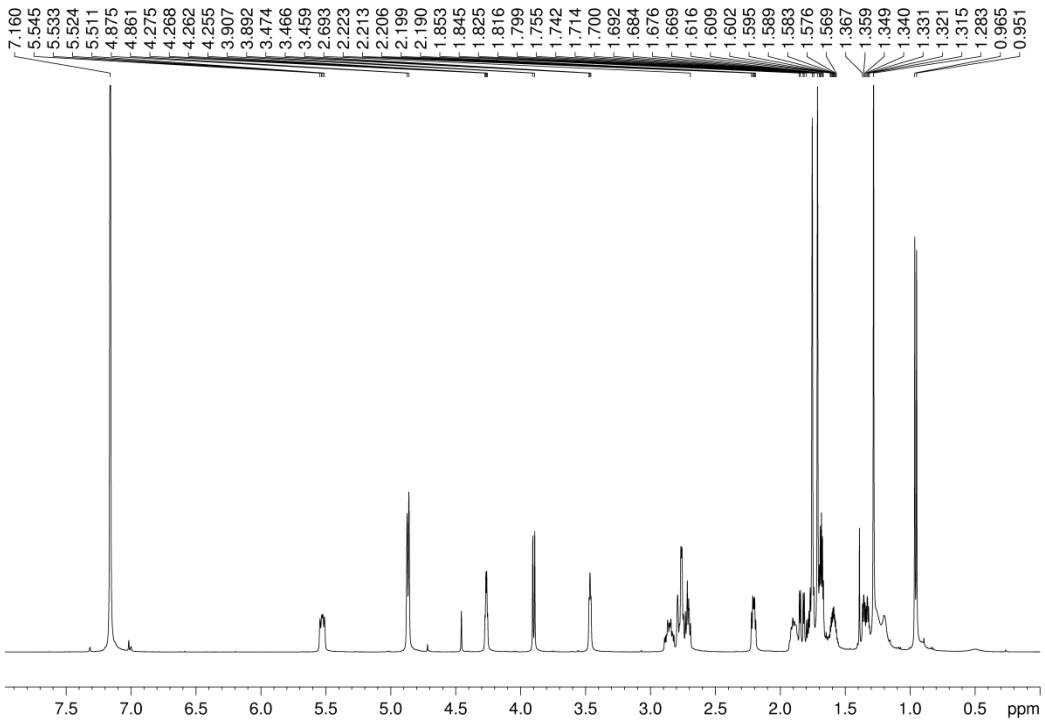


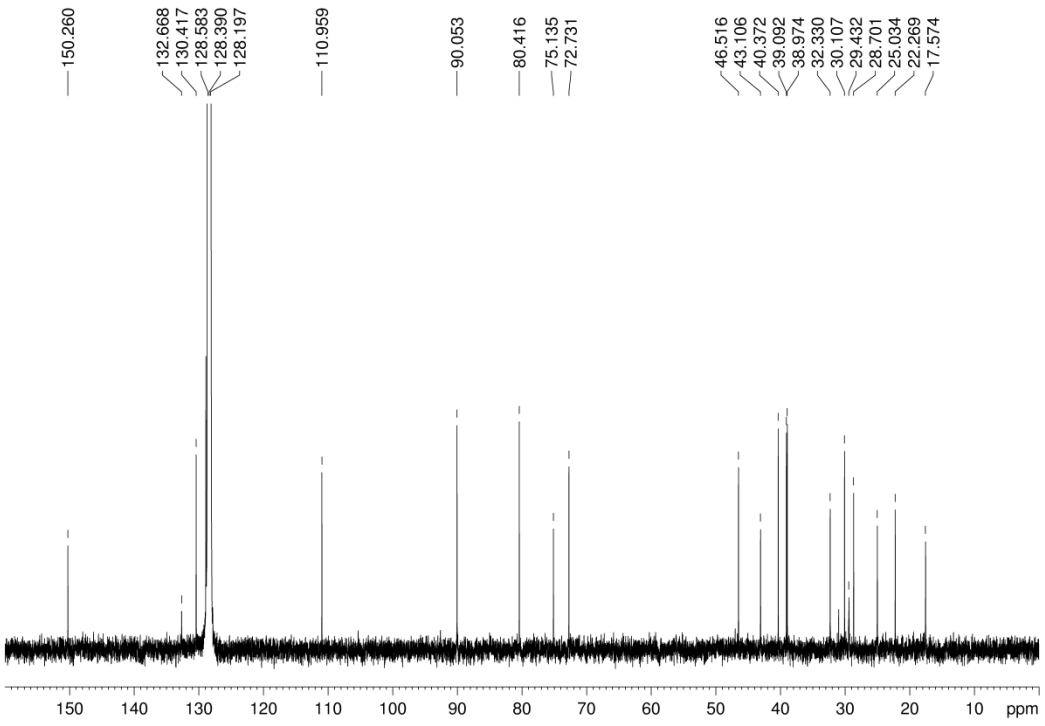
Appendix 3: ^{1}H and ^{13}C NMR of Compound (±)-**414**





Appendix 4: ^{1}H and ^{13}C NMR of Formal Target (±)-**417**





Appendix 5: ^{1}H and ^{13}C NMR of Formal Target (±)-**418**